Organocatalytic Asymmetric Biomimetic Transfer Hydrogenations of Olefins

New Catalytic Routes to Saturated *β*-Branched Ketones, *β*,*β*-Disubstituted Nitroalkanes as well as *β*-Nitroesters as Precursors of *β*-Amino Acids

I n a u g u r a l - D i s s e r t a t i o n

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Abstract

This work describes the successful development of highly efficient and enantioselective organocatalytic approaches to the synthesis of chiral *β*-substituted ketones, *β*,*β*-disubstituted nitroalkanes as well as *β*-nitroesters. The latter could be efficiently converted to the corresponding β^2-amino acids. Inspired by the *in vivo* enzymatic conjugate reductions with NAD(P)H cofactors, we established biomimetic transfer hydrogenations, for which dihydropyridines and organocatalysts were employed as NAD(P)H and enzyme analogues, respectively.

The asymmetric conjugate reduction of enones was achieved *via* iminium catalysis using a salt composed of a protonated valine *tert*-butyl ester and a chiral BINOL phosphate counteranion. The process was particularly well-suited for cyclic *α*,*β*-unsaturated ketones. Acyclic enones could also be successfully used, although yielding the products with slightly lower enantioselectivities.

A *Jacobsen*-type thiourea efficiently catalyzed the transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes *via* hydrogen bonding catalysis. The reaction had a broad substrate scope and a number of aromatic and aliphatic nitroalkenes could be utilized.

Moreover, we successfully established a concise new strategy to enantioenriched β^2-amino acids. The key step in this process was a highly enantioselective and efficient thiourea-catalyzed conjugate reduction of *β*-nitroacrylates to the saturated analogues. The nitroesters were then easily and efficiently converted into the corresponding β^2-amino acids. In addition, a convenient synthesis of the required *β*-nitroacrylates *via* a Henry reaction–dehydration process was developed.

Kurzzusammenfassung

Diese Arbeit beschreibt die erfolgreiche Entwicklung hocheffizienter and enantioselektiver organokatalytischer Verfahren zur Synthese chiraler β-substituierter Ketone, β,β-disubstituierter Nitroalkane sowie β-Nitroester. Die letzteren konnten direkt zu den entsprechenden β^2-Aminosäuren umgesetzt werden. In Anlehnung an die enzymatischen konjugierten Reduktionen mit dem NAD(P)H-Cofaktor *in vivo* wurden biomimetische Transferhydrierungen unter Verwendung von Dihydropyridinen und Organokatalysatoren als NAD(P)H- und Enzymanaloga entwickelt.

Die asymmetrische konjugierte Reduktion α,β-ungesättigter Ketone wurde mit Hilfe von Iminiumkatalyse unter Einsatz eines Salzes des protonierten Valin-*tert*-butylesters in Kombination mit einem chiralen BINOL-phosphat-Gegenion erreicht. Diese Methode erwies sich für zyklische Ketone als besonders geeignet. Auch azyklische α,β-ungesättigte Ketone konnten erfolgreich verwendet werden, aber lieferten die Produkte mit leicht geringeren Enantioselektivitäten.

Ein *Jacobsen*-artiges Thioharnstoffderivat katalysierte die Transferhydrierung β,β-disubstituierter Nitroalkene über die Ausbildung von Wasserstoffbrückenbindungen. Eine Vielzahl aromatischer und aliphatischer Substrate wurde mit hohen Ausbeuten und Enantioselektivitäten zu den entsprechenden Nitroalkanen reduziert.

Außerdem wurde eine neue Strategie für den schnellen Zugang zur enantiomerenangereicherten β^2-Aminosäuren erfolgreich entwickelt. Den zentralen Schritt dieses Prozesses stellte eine hochenantioselektive und vielseitige Thioharnstoff-katalysierte konjugierte Reduktion von β-Nitroacrylaten dar. Die erhaltenen β-Nitroester konnten anschließend leicht zu den entsprechenden β^2-Aminosäuren umgesetzt werden. Zusätzlich wurde eine praktische Methode zur Herstellung der β-Nitroacrylate über eine Henry-Reaktion gefolgt von einer Dehydrierung entwickelt.

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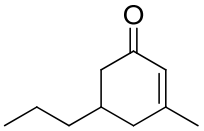
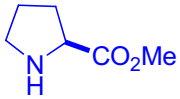
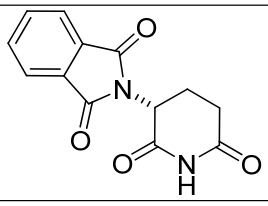
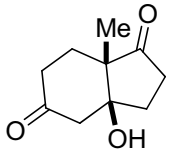
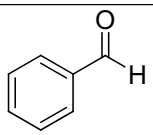
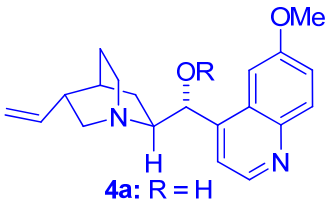
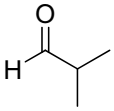
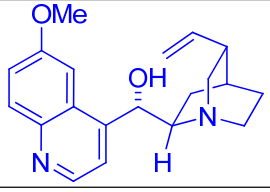
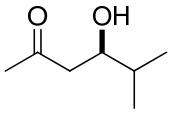
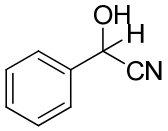
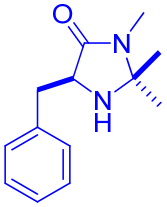
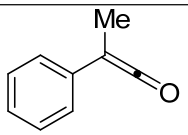
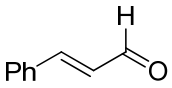
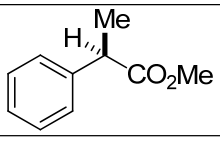
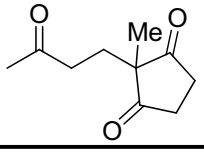
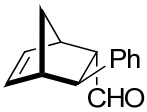
1		10	
2		11	
3		12	
4	 **4a:** R = H **4b:** R = Ac	13	
5		14	
6		15	
7		16	
8		17	
9		18	

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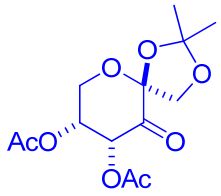
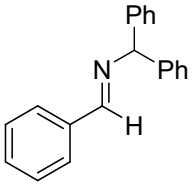
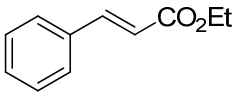
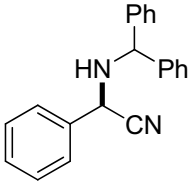
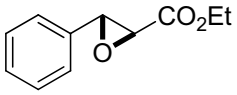
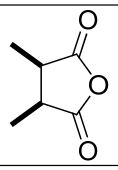
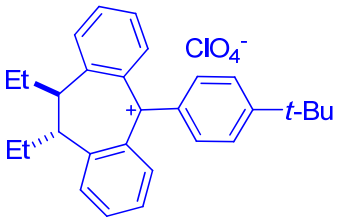
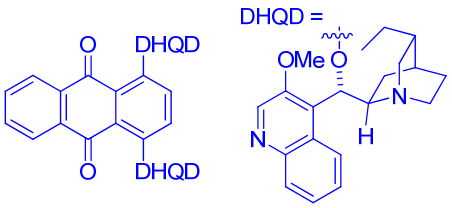
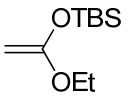
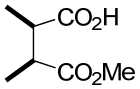
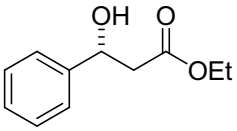
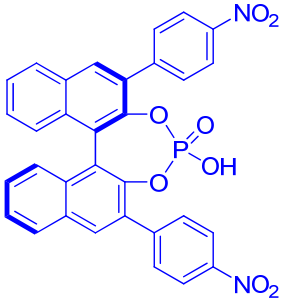
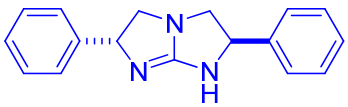
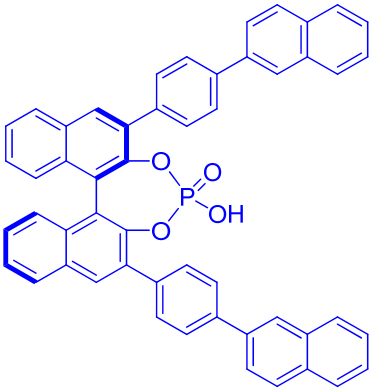
19		26	
20		27	
21		28	
22		29	
23		30	
24		31	
25		32	

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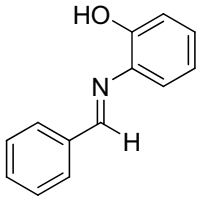
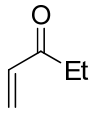
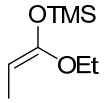
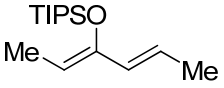
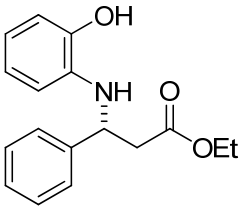
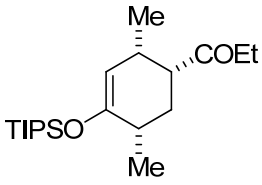
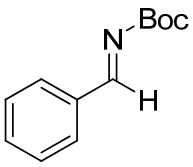
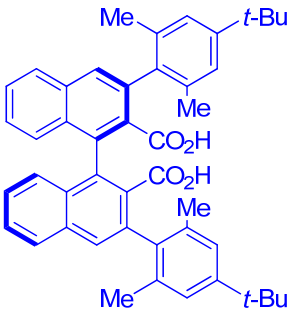
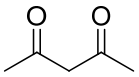
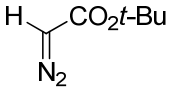
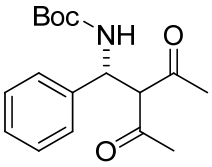
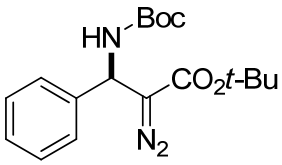
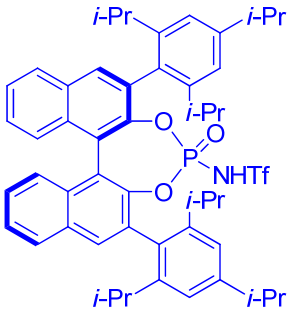
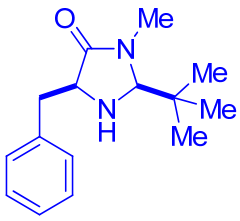
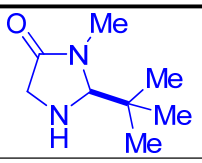
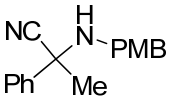
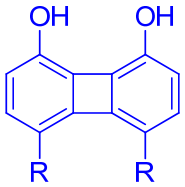
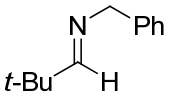
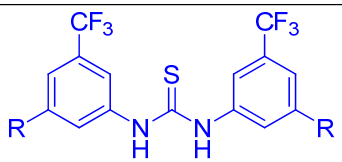
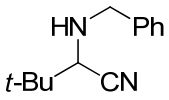
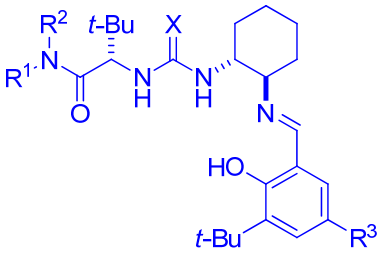
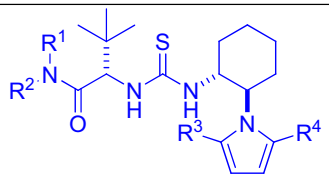
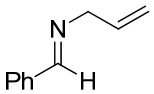
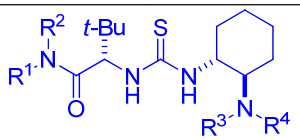
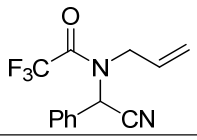
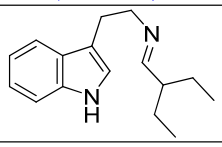
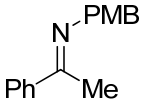
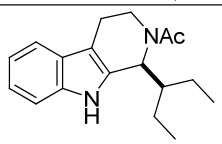
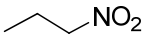
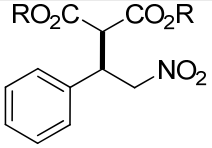
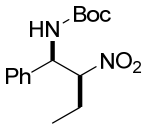
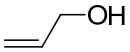
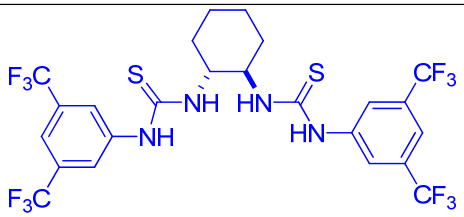
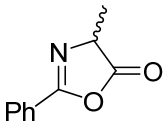
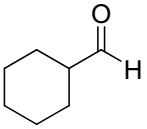
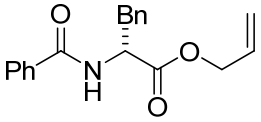
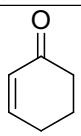
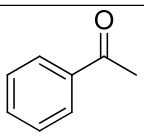
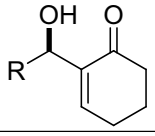
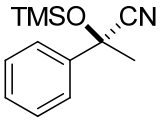
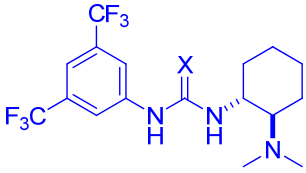
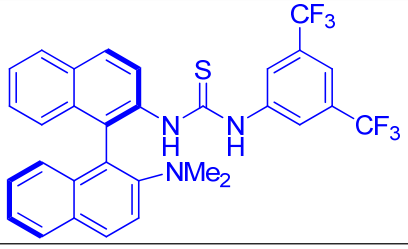
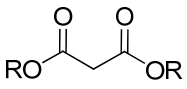
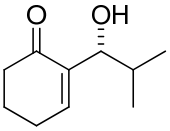
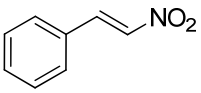
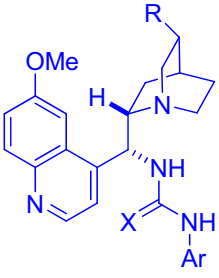
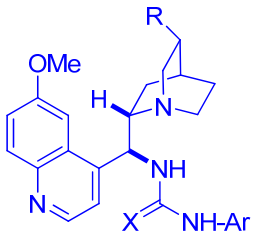
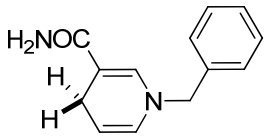
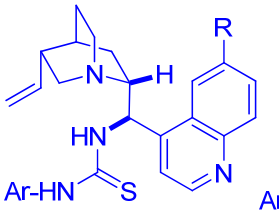
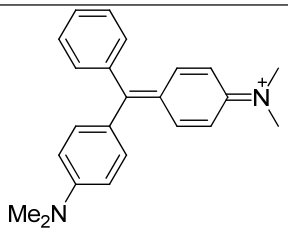
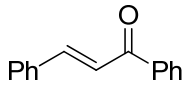
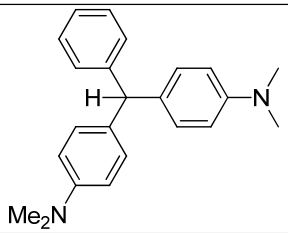
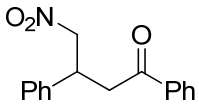
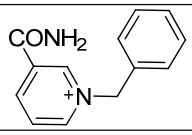
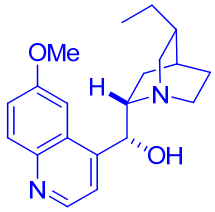
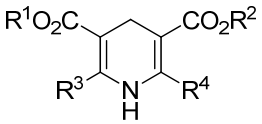
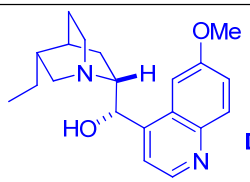
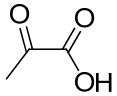
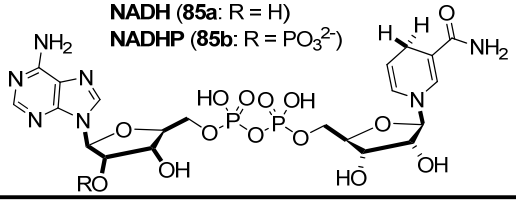
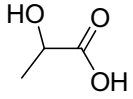
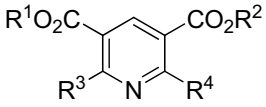
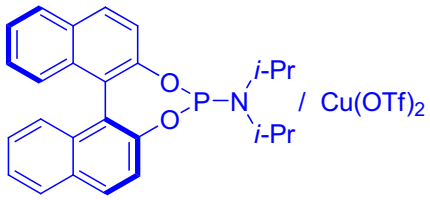
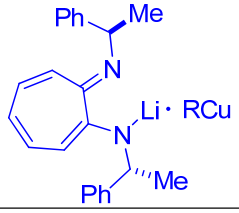
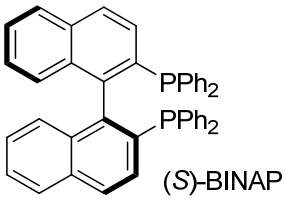
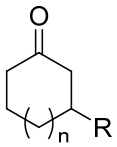
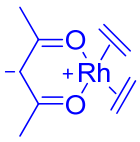
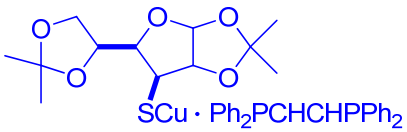
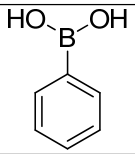
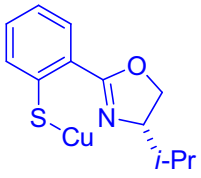
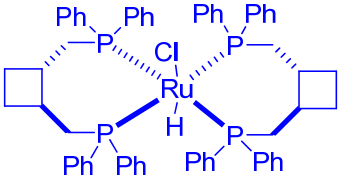
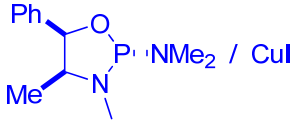
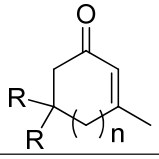
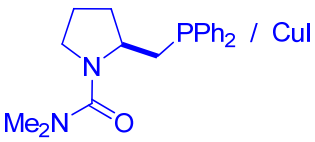
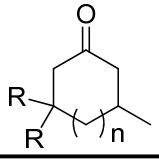
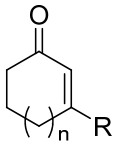
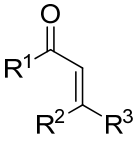
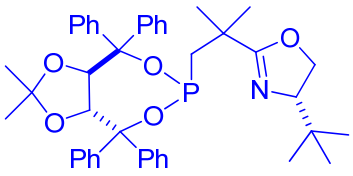
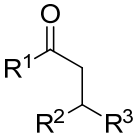
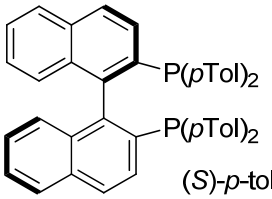
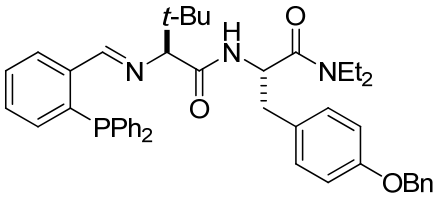
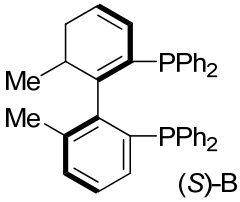
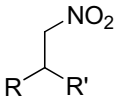
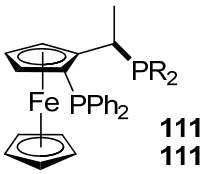
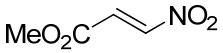
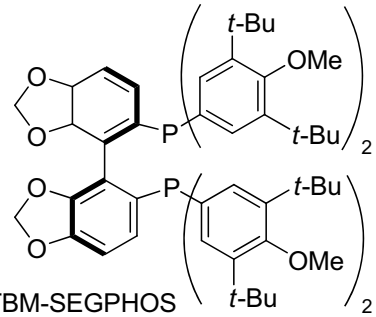
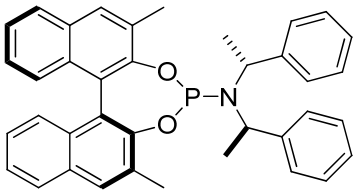
33		**40**	
34		**41**	
35		**42**	
36		**43**	
37		**44**	
38		**45**	
39		**46**	

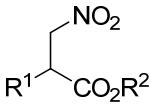
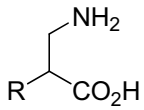
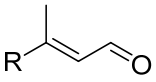
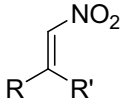
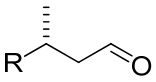
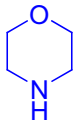
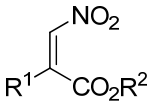
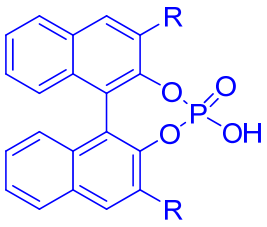
N°	Corresponding Compound	N°	Corresponding Compound
47		**54**	
48	 **48a**: R = H **48b**: R = NO_2	**55**	
49	 **49a**: R = $CO_2C_8H_{17}$ **49b**: R = CF_3	**56**	
50	 **50a**: X = S, R^1 = Bn, R^2 = H, R^3 = OMe **50b**: X = S, R^1 = Bn, R^2 = H, R^3 = OPiv **50c**: X = O, R^1 = Bn, R^2 = H, R^3 = OPiv **50d**: X = S, R^1 = R^2 = Me, R^3 = OPiv **50e**: X = S, R^1 = Bn, R^2 = Me, R^3 = *t*-Bu **50g**: X = S, R^1 = R^2 = Et, R^3 = OPiv	**57**	 **57a**: R^1 = R^2 = R^3 = R^4 = Me **57b**: R^1 = R^2 = Et, R^3 = R^4 = Me **57c**: R^1 = R^2 = Bn, R^3 = R^4 = Me **57d**: R^1 = R^2 = *n*-Pr, R^3 = R^4 = Me **57e**: R^1 = Bn, R^2 = Me, R^3 = R^4 = Me **57f**: R^1 = Bn, R^2 = H, R^3 = R^4 = Me **57g**: R^1 = R^2 = Et, R^3 = R^4 = Et **57h**: R^1 = R^2 = Et, R^3 = Me, R^4 = Ph **57i**: R^1 = R^2 = Et, R^3 = R^4 = Ph **57j**: R^1 = R^2 = Bn, R^3 = R^4 = Et **57k**: R^1 = R^2 = Bn, R^3 = Me, R^4 = Ph **57l**: R^1 = R^2 = Bn, R^3 = R^4 = Ph
51		**58**	 **58a**: R^1 = R^2 = Me, R^3 = Ac, R^4 = H **58b**: R^1 = Me, R^2 = H, R^3 = R^4 = *n*-Pr **58c**: R^1 = Bn, R^2 = H, R^3 = R^4 = H **58d**: R^1 = Bn, R^2 = Me, R^3 = R^4 = H
52		**59**	
53		**60**	

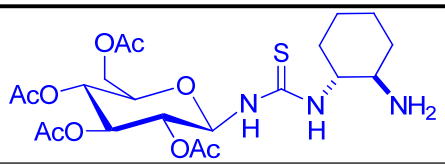
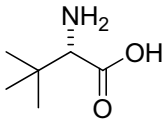
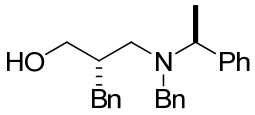
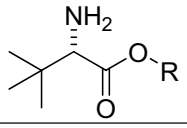
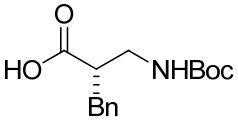
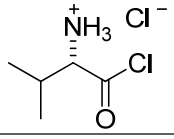
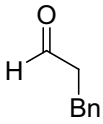
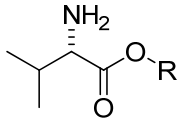
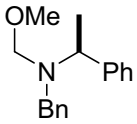
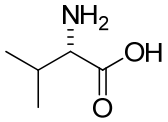
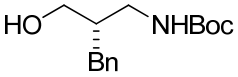
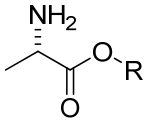
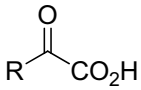
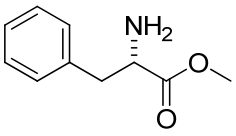
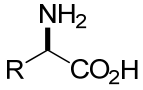
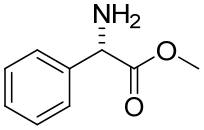
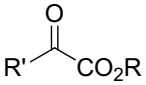
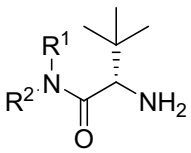
N°	Corresponding Compound	N°	Corresponding Compound
61		**70**	 **70a**: R = Et **70b**: R = Me
62		**71**	
63		**72**	
64		**73**	
65		**74**	
66	 **66a**: R = Ph **66b**: R = Cy	**75**	
67	 **67a**: X = S **67b**: X = O	**76**	
68	 **68a**: R = Et **68b**: R = Me	**77**	
69		**78**	 **78a**: R = CH=CH$_2$ X = S **78b**: R = CH$_2$CH$_3$ X = O Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$

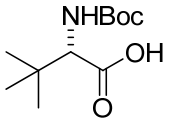
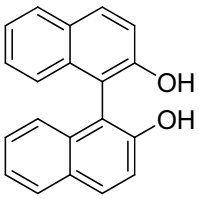
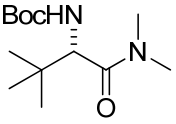
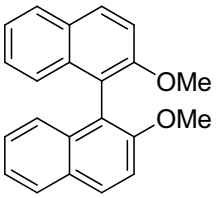
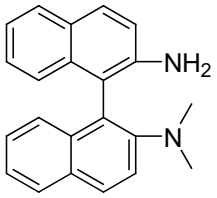
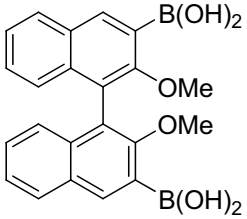
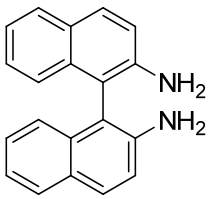
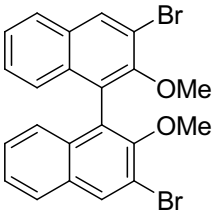
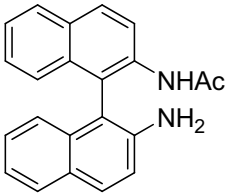
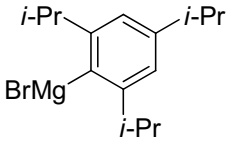
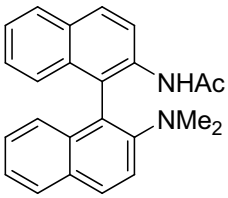
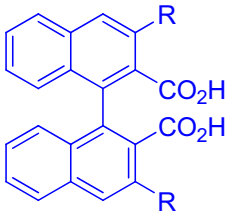
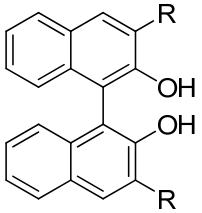
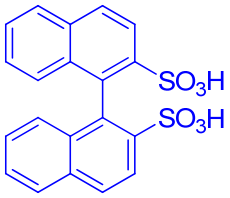
N°	Corresponding Compound	N°	Corresponding Compound
79	 **79a**: R = CH=CH$_2$, X = S **79b**: R = CH$_2$CH$_3$, X = S **79c**: R = CH$_2$CH$_3$, X = O Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$	86	
80	 **80a**: R = OMe **80b**: R = H Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$	87	
81		88	
82		89	
83	 **Dihydroquinine (DHQ)**	90	 **95a**: R^1 = R^2 = Et, R^3 = R^4 = Me **95b**: R^1 = R^2 = Et, R^3 = Me, R^4 = *i*-Pr **95c**: R^1 = R^2 = *t*-Bu, R^3 = R^4 = Me **95d**: R^1 = R^2 = *i*-Bu, R^3 = R^4 = Me **95e**: R^1 = R^2 = *neo*-pent, R^3 = R^4 = Me **95f**: R^1 = R^2 = Me, R^3 = R^4 = Me **95g**: R^1 = Me, R^2 = *t*-Bu, R^3 = R^4 = Me **95h**: R^1 = R^2 = Me, R^3 = R^4 = Et **95i**: R^1 = R^2 = Me, R^3 = R^4 = *n*-Pr **95j**: R^1 = R^2 = Me, R^3 = R^4 = Ph
84	 **Dihydroquinidine (DHQD)**	91	
85	**NADH** (**85a**: R = H) **NADHP** (**85b**: R = PO$_3^{2-}$) 	92	

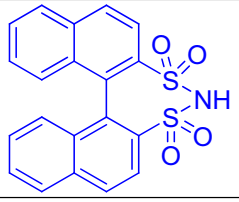
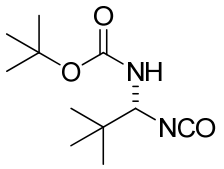
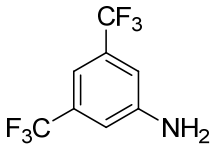
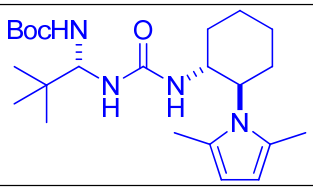
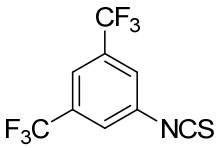
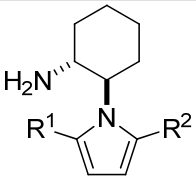
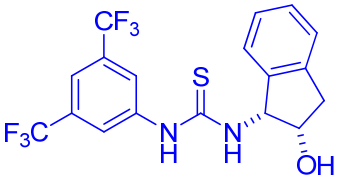
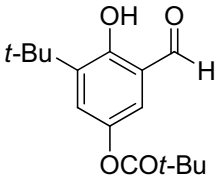
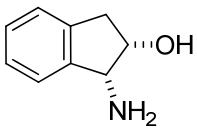
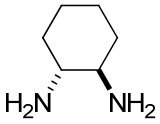
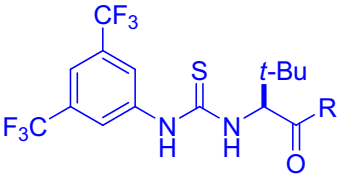
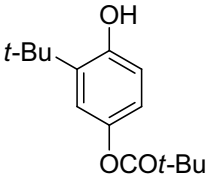
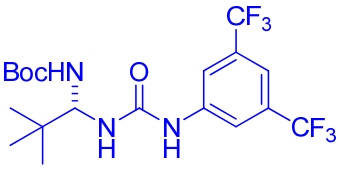
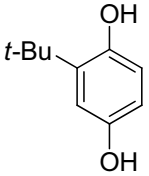
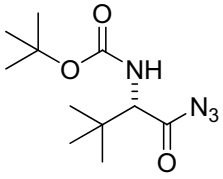
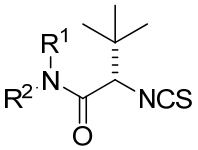
N°	Corresponding Compound	N°	Corresponding Compound
93	 **93a**: $R^1 = R^2 = Et$, $R^3 = R^4 = Me$ **93b**: $R^1 = R^2 = Et$, $R^3 = Me$, $R^4 = i$-Pr **93c**: $R^1 = R^2 = t$-Bu, $R^3 = R^4 = Me$ **93d**: $R^1 = R^2 = i$-Bu, $R^3 = R^4 = Me$ **93e**: $R^1 = R^2 = neo$-pent, $R^3 = R^4 = Me$ **93f**: $R^1 = R^2 = Me$, $R^3 = R^4 = Me$ **93g**: $R^1 = Me$, $R^2 = t$-Bu, $R^3 = R^4 = Me$ **93h**: $R^1 = R^2 = Me$, $R^3 = R^4 = Et$ **93i**: $R^1 = R^2 = Me$, $R^3 = R^4 = n$-Pr **93j**: $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$	**100**	
94		**101**	
95	 **95a**: n = 1, R = Ph **95b**: n = 1, R = Me **95c**: n = 0, R = Me **95d**: n = 1, R = Et **95e**: n = 1, R = *i*-Bu **95f**: n = 1, R = *i*-Pr **95g**: n = 1, R = CH_2CH_2Ph **95h**: n = 0, R = Et **95i**: n = 0, R = CH_2CH_2Ph **95j**: n = 2, R = Me	**102**	
96		**103**	
97		**104**	
98		**105**	 **105a**: n = 1, R = Me
99		**106**	 **106a**: n = 1, R = Me

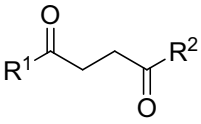
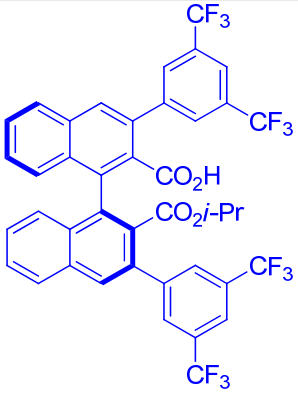
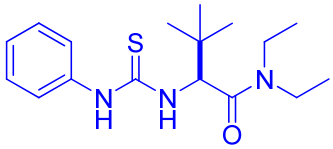
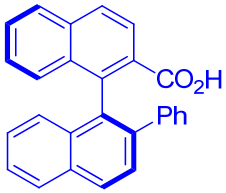
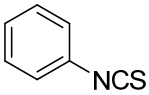
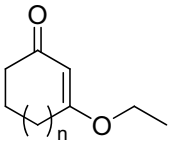
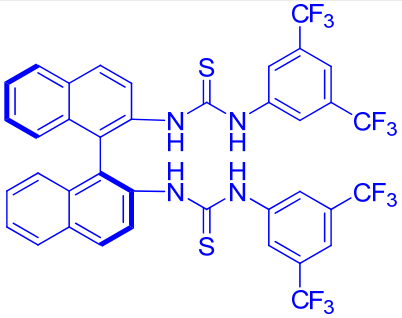
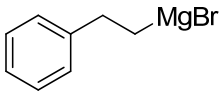
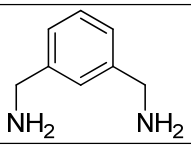
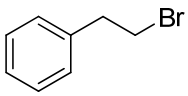
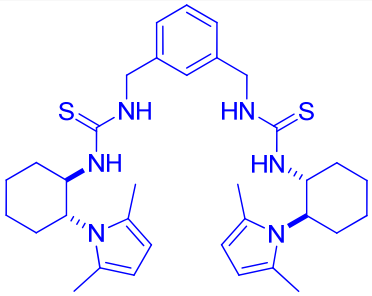
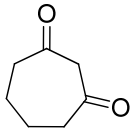
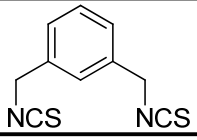
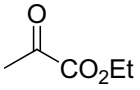
N°	Corresponding Compound	N°	Corresponding Compound
107	 **107a**: n = 1, R = Ph **107b**: n = 1, R = Me **107c**: n = 0, R = Me **107d**: n = 1, R = Et **107e**: n = 1, R = *i*-Bu **107f**: n = 1, R = *i*-Pr **107g**: n = 1, R = CH_2CH_2Ph **107h**: n = 0, R = Et **107i**: n = 0, R = CH_2CH_2Ph **107j**: n = 2, R = Me	113	 **113a**: R^1=R^2=Me, R^3=Ph **113b**: R^1=R^2=Me, R^3=CO_2Et **113c**: R^1=R^2=Me, R^3=*n*-Pent
108		114	 **114a**: R^1=R^2=Me, R^3=Ph **114b**: R^1=R^2=Me, R^3=CO_2Et **114c**: R^1=R^2=Me, R^3=*n*-Pent
109	 (*S*)-*p*-tol-BINAP	115	
110	 (*S*)-BIPHEMP	116	 **116a**: R = C_6H_5, R' = Me **116b**: R = C_6H_5, R' = *i*-Pr **116c**: R = C_6H_5, R' = Et **116d**: R = C_6H_5, R' = *n*-Pr **116e**: R = 2-naphthyl, R' = Me **116f**: R = *p*-Me-C_6H_5, R' = Me **116g**: R = *p*-CN-C_6H_5, R' = Me **116h**: R = *p*-F-C_6H_5, R' = Me **116i**: R = *p*-Cl-C_6H_5, R' = Me **116j**: R = *m*-Cl-C_6H_5, R' = Me **116k**: R = *o*-Cl-C_6H_5, R' = Me **116l**: R = *t*-Bu, R' = Me **116m**: R = Et, R' = Me **116n**: R = 2-furyl, R' = Me
111	 **111a**: R = *t*-Bu **111b**: R = Cy	117	
112	 (*R*)-DTBM-SEGPHOS	118	

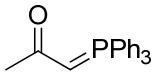
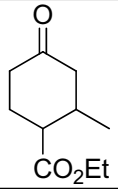
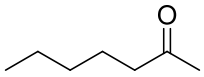
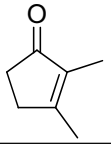
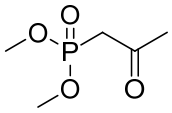
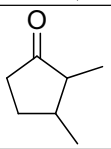
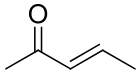
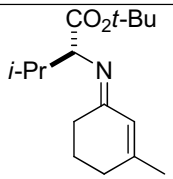
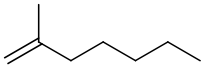
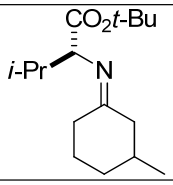
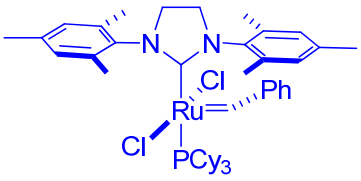
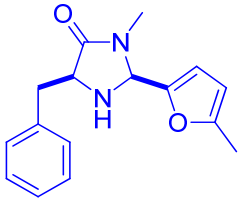
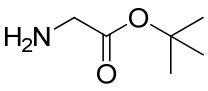
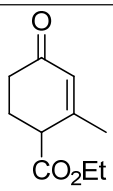
N°	Corresponding Compound	N°	Corresponding Compound
119	 **119a**: R = Me; R' = Et **119b**: R = C_6H_5; R' = *i*-Pr **119c**: R = C_6H_5; R' = Me **119d**: R = C_6H_5; R' = Et **119e**: R = C_6H_5; R' = *t*-Bu **119f**: R = C_6H_5; R' = Bn **119g**: R = *p*-Me-C_6H_4; R' = Et **119h**: R = *p*-MeO-C_6H_4; R' = Et **119i**: R = *p*-F-C_6H_4; R' = Et **119j**: R = *p*-Cl-C_6H_4; R' = Et **119k**: R = *p*-MeO-C_6H_4; R' = *t*-Bu **119l**: R = *p*-F-C_6H_4; R' = *t*-Bu **119m**: R = 2-thienyl; R' = Et **119n**: R = *n*-Pent; R' = Et **119o**: R = *i*-Pr; R' = Et	**122**	 **122a**: R = Me **12b-f**: R = Ph
		123	
120	 **120a**: R = C_6H_5, R' = Me **120b**: R = C_6H_5, R' = *i*-Pr **120c**: R = C_6H_5, R' = Et **120d**: R = C_6H_5, R' = *n*-Pr **120e**: R = 2-naphthyl, R' = Me **120f**: R = *p*-Me-C_6H_5, R' = Me **120g**: R = *p*-CN-C_6H_5, R' = Me **120h**: R = *p*-F-C_6H_5, R' = Me **120i**: R = *p*-Cl-C_6H_5, R' = Me **120j**: R = *m*-Cl-C_6H_5, R' = Me **120k**: R = *o*-Cl-C_6H_5, R' = Me **120l**: R = *t*-Bu, R' = Me **120m**: R = Et, R' = Me **120n**: R = 2-furyl, R' = Me	**124**	
		125	
121	 **121a**: R = Me; R' = Et **121b**: R = C_6H_5; R' = *i*-Pr **121c**: R = C_6H_5; R' = Me **121d**: R = C_6H_5; R' = Et **121e**: R = C_6H_5; R' = *t*-Bu **121f**: R = C_6H_5; R' = Bn **121g**: R = *p*-Me-C_6H_4; R' = Et **121h**: R = *p*-MeO-C_6H_4; R' = Et **121i**: R = *p*-F-C_6H_4; R' = Et **121j**: R = *p*-Cl-C_6H_4; R' = Et **121k**: R = *p*-MeO-C_6H_4; R' = *t*-Bu **121l**: R = *p*-F-C_6H_4; R' = *t*-Bu **121m**: R = 2-thienyl; R' = Et **121n**: R = *n*-Pent; R' = Et **121o**: R = *i*-Pr; R' = Et	**126**	 **155a**: R = 2,4,6-*i*-Pr-C_6H_2 **155b**: R = C_6H_5 **155c**: R = 2,6-Me-C_6H_3 **155d**: R = 3,5-Me-C_6H_3 **155e**: R = 2-naphthyl **155f**: R = 4-biphenyl **155g**: R = CO_2Me **155h**: R = H **155i**: R = $SiPh_3$

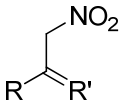
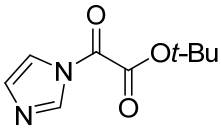
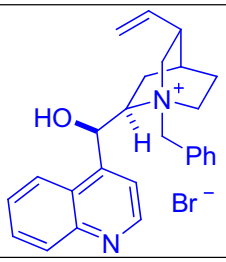
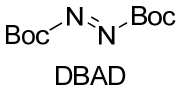
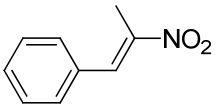
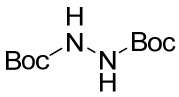
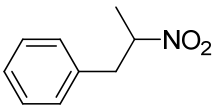
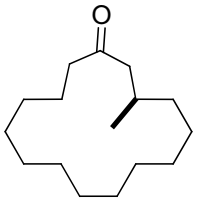
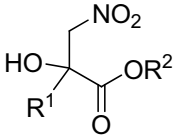
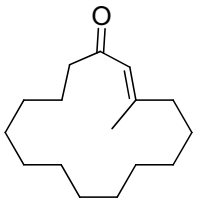
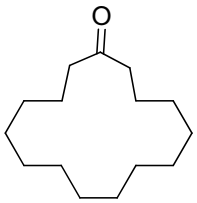
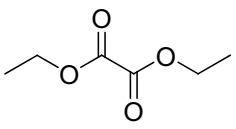
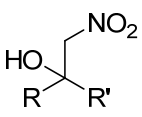
N°	Corresponding Compound	N°	Corresponding Compound
127		**136**	
128		**137**	 **137a**: R = Me **137b**: R = *t*-Bu
129		**138**	
130		**139**	 **139a**: R = *t*-Bu **139b**: R = Me
131		**140**	
132		**141**	 **141a**: R = Me **141b**: R = *t*-Bu
133		**142**	
134		**143**	
135	 **139a:** R = Me; R' = Et **139b:** R = C_6H_5; R' = *i*-Pr **139c:** R = C_6H_5; R' = Me **139d:** R = C_6H_5; R' = Et **139e:** R = C_6H_5; R' = *t*-Bu **139f:** R = C_6H_5; R' = Bn **139g:** R = *p*-Me-C_6H_4; R' = Et **139h:** R = *p*-MeO-C_6H_4; R' = Et **139i:** R = *p*-F-C_6H_4; R' = Et **139g:** R = *p*-Cl-C_6H_4; R' = Et **139k:** R = *p*-MeO-C_6H_4; R' = *t*-Bu **139l:** R = *p*-F-C_6H_4; R' = *t*-Bu **139m:** R = 2-thienyl; R' = Et **139n:** R = *n*-Pent; R' = Et **139o:** R = *i*-Pr; R' = Et	**144**	 **144a**: $R^1 = R^2$ = Me **144b**: $R^1 = R^2$ = Et **144c**: $R^1 = R^2$ = Bn **144d**: $R^1 = R^2$ = *n*-Pr **144e**: R^1 = Bn, R^2 = Me **144f**: R^1 = Bn, R^2 = H

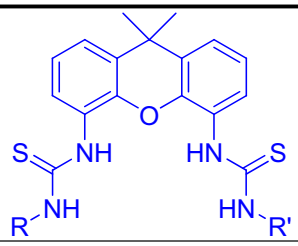
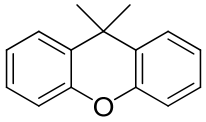
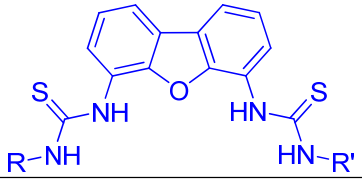
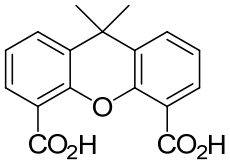
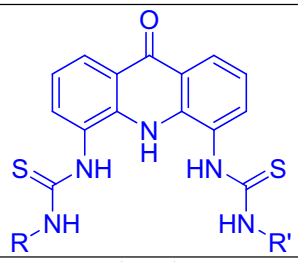
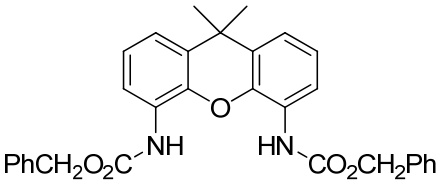
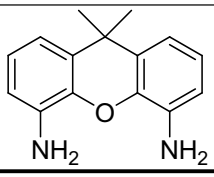
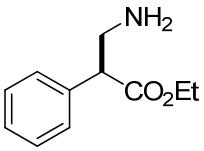
N°	Corresponding Compound	N°	Corresponding Compound
145		**152**	
146		**153**	
147		**154**	
148		**155**	
149		**156**	
150		**157**	 **157a**: R = H **157b**: R = 3,5-$(CF_3)_2$-C_6H_3
151		**158**	

N°	Corresponding Compound	N°	Corresponding Compound
159		**167**	
160		**168**	
161		**169**	 **169a**: $R^1 = R^2$ = Me **169b**: $R^1 = R^2$ = Et **169c**: R^1 = Me, R^2 = Ph **169d**: $R^1 = R^2$ = Ph
162		**170**	
163		**171**	
164	 **164a**: R = NMe_2 **164b**: R = OH	**172**	
165		**173**	
166		**174**	 **174a**: $R^1 = R^2$ = Me **174b**: $R^1 = R^2$ = Et **174c**: $R^1 = R^2$ = Bn **174d**: $R^1 = R^2$ = *n*-Pr **174e**: R^1 = Bn, R^2 = Me **174f**: R^1 = Bn, R^2 = H

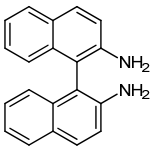
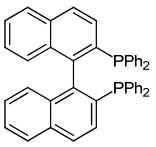
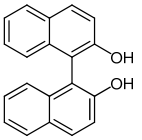
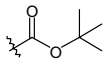
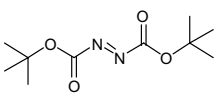
N°	Corresponding Compound	N°	Corresponding Compound
175	 **175a**: $R^1 = R^2$ = Me **175b**: $R^1 = R^2$ = Et **175c**: R^1 = Me, R^2 = Ph **175d**: $R^1 = R^2$ = Ph	182	
176		183	
177		184	 **184a**: n = 1 **184b**: n = 0 **184c**: n = 2
178		185	
179		186	
180		187	
181		188	

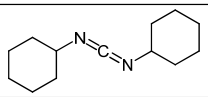
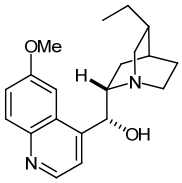
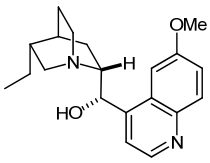
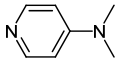
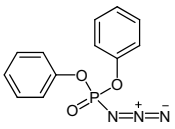
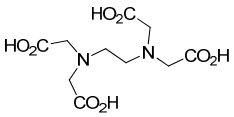
N°	Corresponding Compound	N°	Corresponding Compound
189		**197**	
190		**198**	
191		**199**	
192		**200**	
193		**201**	
194		**202**	
195		**203**	 **203a**: R = C_6H_5, R' = Me **203b**: R = C_6H_5, R' = *i*-Pr **203c**: R = C_6H_5, R' = Et **203d**: R = C_6H_5, R' = *n*-Pr **203e**: R = 2-naphthyl, R' = Me **203f**: R = *p*-Me-C_6H_5, R' = Me **203g**: R = *p*-CN-C_6H_5, R' = Me **203h**: R = *p*-F-C_6H_5, R' = Me **203i**: R = *p*-Cl-C_6H_5, R' = Me **203j**: R = *m*-Cl-C_6H_5, R' = Me **203k**: R = *o*-Cl-C_6H_5, R' = Me **203l**: R = *t*-Bu, R' = Me **203m**: R = Et, R' = Me
196		**204**	 **204a-n** (for R- and R' substituents, see the corresponding compounds **203a-n**)

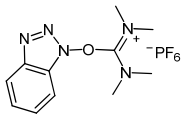
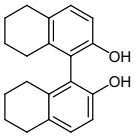
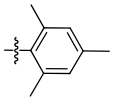
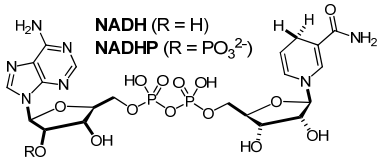
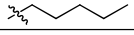
N°	Corresponding Compound	N°	Corresponding Compound
205	 **205a-n** (for R- and R' substituents, see the corresponding compounds **203a-n**)	**211**	
206		**212**	 DBAD
207		**213**	
208		**214**	
209	 **209a**: R = Me; R' = Et **209b**: R = C_6H_5; R' = *i*-Pr **209c**: R = C_6H_5; R' = Me **209d**: R = C_6H_5; R' = Et **209e**: R = C_6H_5; R' = *t*-Bu **209f**: R = C_6H_5; R' = Bn **209g**: R = *p*-Me-C_6H_4; R' = Et **209h**: R = *p*-MeO-C_6H_4; R' = Et **209i**: R = *p*-F-C_6H_4; R' = Et **209j**: R = *p*-Cl-C_6H_4; R' = Et **209k**: R = *p*-MeO-C_6H_4; R' = *t*-Bu **209l**: R = *p*-F-C_6H_4; R' = *t*-Bu **209m**: R = 2-thienyl; R' = Et **209n**: R = *n*-Pent; R' = Et **209o**: R = *i*-Pr; R' = Et	**215**	
		216	
210		**217**	 **217a-n** (for R- and R' substitutents, see the corresponding compounds **203a-n**)

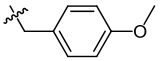
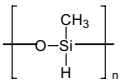
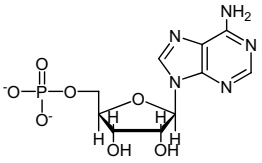
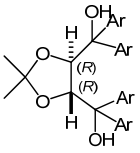
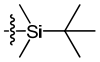
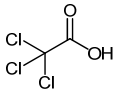
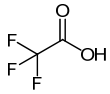
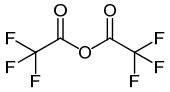
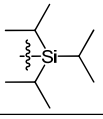
N°	Corresponding Compound	N°	Corresponding Compound
218		222	
219		223	
220		224	
221		225	

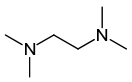
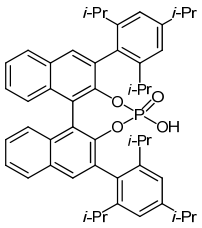
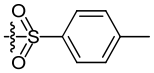
Abbreviations

A(-H)	Lewis acid (Brønsted acid)	-
abs.	absolute (distilled and dried)	-
Ac	acetyl	
ACDC	asymmetric counteranion directed catalysis	-
Alk	alkyl	-
aq.	aqueous	-
Ar	aryl (substituted aromatic ring)	-
B	Brønsted/Lewis base	-
BINAM	1,1'-binaphthyl-2,2'-diamine	
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	
BINOL	1,1'-binaphthyl-2,2'-diol	
Boc	*tert*-butoxycarbonyl	
Bn	benzyl	
Bu	butyl	
c	concentration	
ca.	circa (approximately)	-
c.a.	commercially available	
calcd	calculated	
cat.	catalyst	-
COD	1,5-cyclooctadiene	
conv.	conversion	-
cy	cyclohexyl	
d	day	-
DBAD	di-*tert*-butylazodicarboxylate	

DCC	dicyclohexylcarbodiimide	
DHQ	dihydroquinine	
DHQD	dihydroquinidine	
diast.	diastereoisomer	
DKR	dynamic kinetic resolution	-
DMAP	*N*,*N*,-4-dimethylaminopyridine	
DMF	*N,N*-dimethylformamide	
DMSO	dimethylsulfoxide	
DNA	deoxyribonucleic acid	-
DPPA	diphenylphosphoryl azide	
dr	diastereomeric ratio	-
E^+	electrophile	-
EDTA	ethylenediamine tetraacetic acid	
ee	enantiomeric excess	-
EI	electron ionization	
ent	enantiomer	-
equiv	equivalent	-
er	enantiomeric ration	-
ESI-MS	electro-spray-ionization mass spectroscopy	-
Et	ethyl	
EM	exact mass	-
eq.	equation	
GC	gas chromatography	-
GEBC	gel entrapped base catalyst	
h	hour (length of reaction time)	-
HMPA	hexamethylphosphoric acid triamide (hexamethylphosphoramide)	

HPLC	high performance liquid chromatography	-
HOMO	highest occupied molecular orbital	-
HR-MS	high resolution mass spectroscopy	-
HTBU	*O*-benz-*O*-triazole-1-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate	
Hz	hertz	-
H_8-BINOL	5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol	
i	iso	-
LUMO	lowest unoccupied molecular orbital	-
m	meta	-
M	metal	
M	molar (concentration)	-
M	mass (mass spectroscopy)	-
Me	methyl	
Mes	mesityl	
min	minute	-
m.p.	melting point	-
MS	mass spectroscopy	-
MS	molecular sieves	-
MTBE	methyl *tert*-butyl ether	
MW	molecular weight	-
m/*z*	Mass to charge ratio	
n	normal (e.g. unbranched alkyl chain)	-
N	normal (concentration)	-
NAD(P)H	nicotinamide adenine dinucleotide (phosphate)	
n.d.	non-determined	-
NMM	*N*-methylmorpholine	
NMR	nuclear magnetic resonance	-
Nu^-	nucleophile	-
o	ortho	-
Oxone	potassium peroxymonosulfate	$KHSO_5$
p	para	-
P	product	-
Pent	pentyl	

Ph	phenyl	
Piv	pivaloyl	
PMB	*p*-methoxybenzyl	
PMHS	polymethylhydrogensilane	
ppm	parts per million	-
Pr	propyl	
quant.	quantitative	-
rac.	racemic	-
RNA	ribonucleic acid	e.g. 
rt	room temperature	-
S	substrate	-
s.m.	starting material	
t	*tert*	-
TADDOL	2,2-dimethyl-α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol	
TBS	*tert*-butyldimethylsilyl	
TCA	trichloroacetic acid	
Tf	trifluoromethanesulfonyl	
TFA	trifluoroacetic acid	
TFAA	trifluoroacetic anhydride	
THF	tetrahydrofuran	
TIPS	triisopropylsilyl	
TLC	thin-layer chromatography	-

TMEDA	*N*,*N*,*N'*,*N*'-tetramethylenediamine	
TMS	trimethylsilyl	
TMS	tetramethylsilane	
Tol	*p*-tolyl	
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate	
Ts	*p*-toluenesulfonyl	
τ_R	retention time	-
UV	ultraviolet	-
vs.	versus	-
[α]	specific optical rotation	
*	stereogenic center	-

Acknowledgements

The entire work embodied in this thesis is the result of investigations that I carried out from January 2005 to December 2008 at the Department of Homogeneous Catalysis of the *Max-Planck-Institut (MPI) für Kohlenforschung* under the supervision of *Prof. Dr. Benjamin List*.

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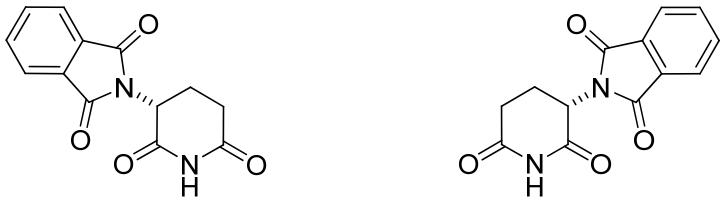
1 Introduction

Chirality is an intrinsic universal feature of various levels of matter.[1] Molecular chirality plays a key role in science and technology. In particular, life depends on molecular chirality, in that many biological functions are inherently dissymmetric. Most physiological phenomena arise from highly precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways. There are numerous examples of enantiomer effects which are frequently dramatic. Enantiomers often smell and taste different. This smell difference can be illustrated by the example of (*R*)-celery ketone **1** (also called (*R*)-livescone), a synthetic fragrance material with typical lovage and celery character.[2] The enantiomers of **1** differ as strikingly in their olfactory properties as in the rare case of carvone.[3] Only the stronger (*R*)-enantiomer is responsible for the characteristic celery note of the racemate, whereas the (*S*)-enantiomer, which is five times weaker has an aniseed-like liquorice smell with minty facets (Figure 1.1).[4] Thus for fragrance and perfume manufacturers the distinction between two enantiomers of the same molecule is of great importance.

1 (*R*)-**Celery ketone** | *ent*-**1** (*S*)-**Celery ketone**

Figure 1.1: The enantiomers of the celery ketone (i.e. livescone).

The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs. Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration, which results in marked differences in the pharmacological activities of enantiomers. A compelling example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide **2** to pregnant women in the 1960s (Figure 1.2).[5] (*R*)-Thalidomide has desirable sedative properties, while its (*S*)-enantiomer is teratogenic and induces fetal malformations.[6,7]



2 (*R*)-(+)-**Thalidomide** | *ent*-**2** (*S*)-(−)-**Thalidomide**

Figure 1.2: The drug (*R*)-thalidomide **2** and its enantiomer *ent*-**2**.

Such problems arising from inappropriate molecular recognition should be avoided at all costs. Nevertheless, even in the early 1990s, about 90% of the synthetic chemical drugs were still racemic, which reflects the difficulty in the practical synthesis of enantiopure compounds.[8] Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals and flavors is a very significant endeavor.

The discovery of truly efficient methods to achieve this has been a substantial challenge for chemists in both academia and the industry. Earlier, enantiomerically pure compounds were obtained by the classical resolution of a racemate or by transformations of readily accessible, naturally occurring chiral compounds such as amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids. However, stereoselective conversion of an unsaturated compound to a chiral product, namely through an asymmetric reaction, is the most attractive approach. In practice, access to pure enantiomers has largely relied on biochemical or biological methods. However, the scope of such methods using enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts. On the other hand, a chemical approach allows for the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors.

Chemical synthesis is nowadays one of the key technologies underlying modern drug discovery and development. As the number of chiral drugs is increasing,[9] asymmetric synthesis[10] and efficient chiral separation technologies[11] are steadily gaining importance. With respect to the first, asymmetric syntheses,[12] the application of chiral auxiliaries or chiral pool strategies has become well established in industrial processes. Regarding asymmetric catalysis, enzymatic transformations[13] and the reactions employing metal catalysts are important tools for organic synthesis and are invaluable to the pharmaceutical industry.[14,15]

Recent developments in the field of asymmetric catalysis point to a third class of catalysts, so called organocatalysts, which are low-molecular weight organic molecules that can even contain a metal possibly playing a structure-defining but not a catalytic role. Organocatalysts have also been regarded as small molecule enzymes.[16,17]

Despite its rich historical past, the use of small organic molecules as chiral catalysts has only recently been recognized as a valuable addition or alternative to the existing, well-established, often metal-based methodologies in asymmetric synthesis. The question must be asked, however, as to why it has taken so long for chemists to appreciate and exploit the potential of chiral organocatalysts.

Principally, asymmetric organocatalytic reactions were, for a long time, considered to be inefficient and limited in scope. In parallel, metal catalysts provided a flexible ground for all

types of reactions and thus received a disproportionate emphasis. Although today the majority of reactions in asymmetric catalysis continue to rely on metal-containing complexes, this picture is changing and organocatalysis is becoming an increasingly important segment of organic chemistry, offering even advantages over metal-based and biocatalytic methods.[16b] Organocatalytic reactions can be performed under an aerobic atmosphere, with wet solvents; indeed, the presence of water is often beneficial to the rate and selectivity of the reaction.[17j] The operational simplicity and availability of these mostly inexpensive bench-stable catalysts – which are incomparably more robust than enzymes or other biocatalysts – make organocatalysis an attractive method for the synthesis of complex structures.[16b,17r] In addition, they provide a rich platform for multicomponent, tandem, or domino-type multistep reactions,[18] allowing increases in the structural complexity of products in a highly stereocontrolled manner. The absence of transition metals makes organocatalytic methods especially attractive for the preparation of compounds that do not tolerate metal contamination such as pharmaceutical and agrochemical products.[19] Nowadays, increasing numbers of industrial application are based on asymmetric organocatalytic reactions, and the environmentally friendly "green" aspect of this chemistry is widely considered for replacing standard, metal-based reactions.[20,21]

Numerous research groups around the world are now working on the development of the field of organocatalysis and exploiting the power of this method.[16,17] The current potential and objectives in asymmetric organocatalysis are shown in Figure 1.3.[17r]

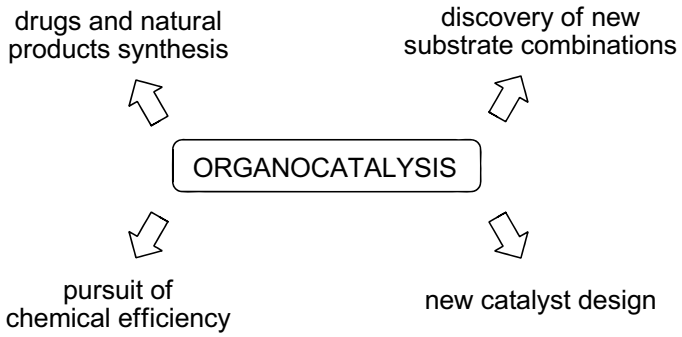


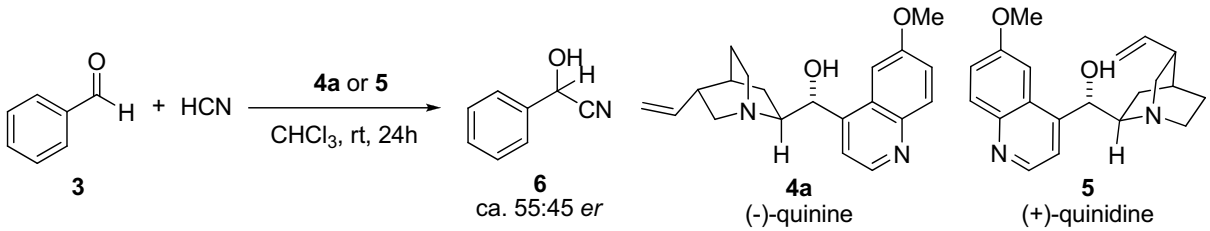
Figure 1.3: Current objectives in asymmetric organocatalysis.

2 Background

2.1 Asymmetric Organocatalysis

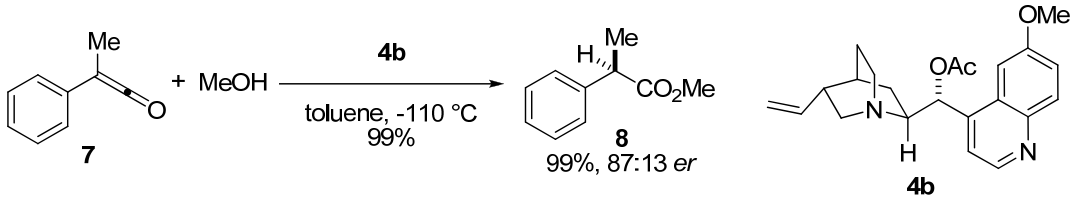
The history of organocatalytic reactions has a rich background as it is suggested that organocatalysts played a determinant role in the prebiotic formation of key building blocks such as sugars. In this way, the reactions might have led to the introduction and widespread use of homochirality in the living word.[22] The discovery of the first organocatalytic reaction is attributed to *von Liebig*, who found – accidentally – that dicyan is transformed into oxamide in the presence of an aqueous solution of acetaldehyde.[23]

In the early 1900s, *Bredig* was motivated to find the chemical origin of enzyme activity observed in living organisms. In his early experiments he showed enantiomeric enrichment in the thermal decarboxylation of optically active camphorcarboxylic acid to D- and L-limonenes, respectively.[24] He also developed the first asymmetric carbon-carbon bond forming reaction by adding hydrogen cyanide to benzaldehyde **3** in the presence of a catalytic amount of quinine **4a** or quinidine **5** (Scheme 2.1).[25] It should be noted that, although these studies were considered as conceptually groundbreaking, the enantiomeric ratio of the reaction was lower than 55:45.



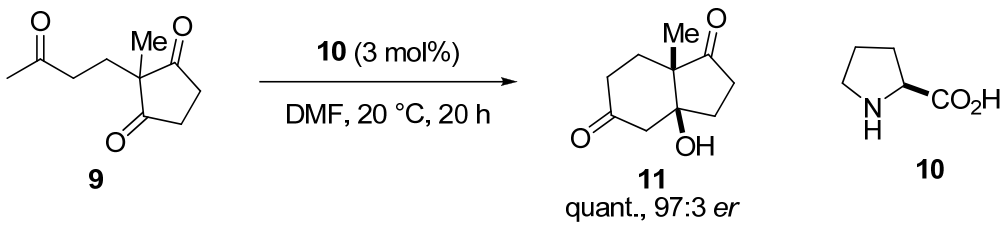
Scheme 2.1: First asymmetric organocatalytic reaction.[25]

The advent of synthetically useful levels of enantioselectivity can be dated to the late 1950s, when *Pracejus* reported that methyl phenyl ketene **7** could be converted to (–)-*α*-phenyl methylpropionate **8** in 87:13 *er* by using *O*-acetylquinine **4b** as catalyst (Scheme 2.2). [26]



Scheme 2.2: *Pracejus*'s enantioselective ester synthesis from phenyl methyl ketene.[26]

Another key event in the history of organocatalytic reactions was the discovery of an efficient L-proline-mediated asymmetric Robinson annulation reported during the early 1970s, the so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction (an intramolecular aldol reaction, Scheme 2.3).[27] It is pertinent to note, that this chemistry is rooted in the early studies of *Knoevenagel* and *Langenbeck*.[28,29]



Scheme 2.3: The L-proline-mediated Robinson annulation.[27]

Although this reaction was discovered in the early 1970s, its potential has not been realized until recently. A revival of this chemistry was initiated at the beginning of this century with the discovery of the L-proline-catalyzed direct asymmetric intermolecular aldol reaction and the conceptualization of enamine catalysis in 2000 by *List et al.*[30] Shortly after, the first highly enantioselective example of iminium catalysis for the Diels-Alder reaction was described by *MacMillan et al.*[31]

The area of asymmetric organocatalysis then became a main focus of research for an increasing number of research groups around the world. In the next chapter a short overview of this exciting and rapidly growing field is presented.

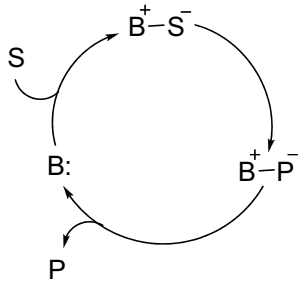
2.1.1 Types of Organocatalysis

Organocatalysts are usually classified, when a classification is possible, as either Lewis base, Lewis acid, Brønsted base, or Brønsted acid catalysts.[17e] The corresponding organocatalytic reactions will be described accordingly.

2.1.1.1 Lewis base catalysis

Lewis bases (B:) are atoms or molecules possessing a lone pair of electrons; by donating this pair of electrons they can form a new covalent bond. They can initiate a catalytic cycle *via*

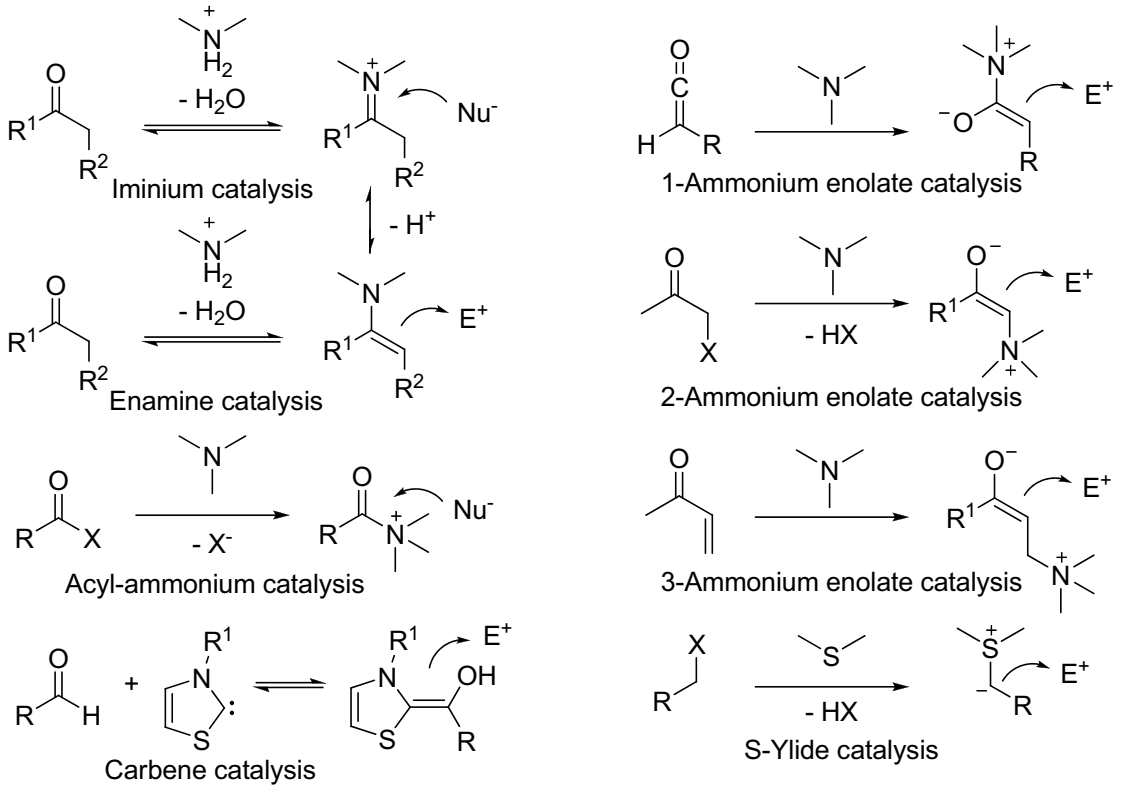
nucleophilic addition to the substrate (S). The activated substrate can possess electrophilic or nucleophilic properties and react further to form to the desired product (P). The resulting product is then released and the catalyst regenerated for further turnover (Scheme 2.4).



Scheme 2.4: Simplified catalytic cycle of Lewis base catalysis. (B: Lewis base catalyst, S: substrate, P: product)

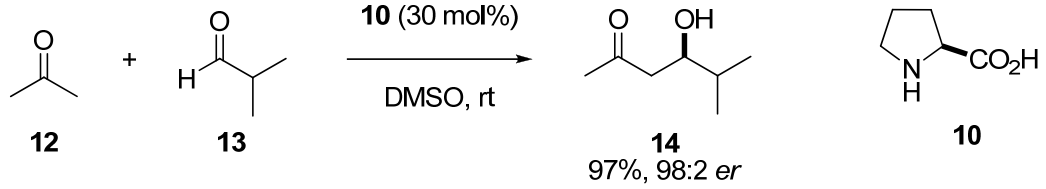
The majority of organocatalysts are nitrogen-, carbon-, oxygen-, phosphorus-, and sulfur-based Lewis bases such as amines, carbenes, phosphines, phosphoramides, formamides and sulfites. Among these catalysts, the nitrogen- and phosphorus-based ones are the most studied, with amine catalysts being more easily available than their phosphorus-containing counterparts, due mainly to their natural abundance.[32]

Due to their various modes of activation, they can catalyze an array of different enantioselective reactions (Scheme 2.5). Thus, Lewis bases are the most used catalysts in organocatalysis.[16,17,33,34]



Scheme 2.5: Examples of Lewis base organocatalysis (Nu^-: nucleophile, E^+: electrophile).

In 2000, *List et al.* discovered that a simple amino acid, L-proline (**10**), can efficiently catalyze a direct asymmetric intermolecular aldol reaction of acetone **12** with a variety of aromatic and α-branched aliphatic aldehydes. The highest enantioselectivity was obtained with isobutyraldehyde **13** as electrophile (Scheme 2.6).[30a]

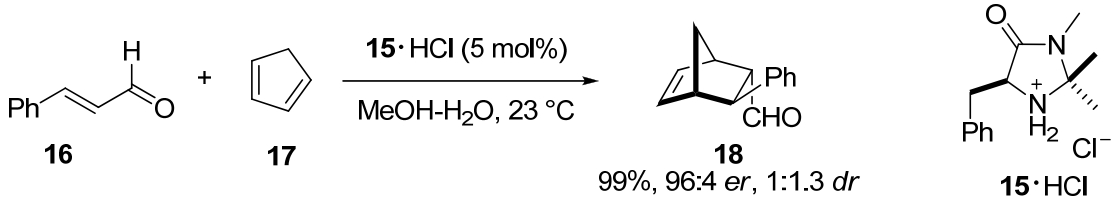


Scheme 2.6: L-Proline-catalyzed direct intermolecular asymmetric aldol reaction.[30a]

The authors suggested that the reaction proceeds *via* an enamine-based mechanism.[30a,35] A key intermediate is an iminium ion, which is formed between acetone **12** and proline **10**. The generation of this iminium ion lowers the lowest unoccupied molecular orbital (LUMO) energy of the system and thus facilitates α-deprotonation leading to the enamine, which is the actual nucleophilic carbanion equivalent. The reaction of the enamine intermediate with the aldehyde then provides, after hydrolysis, the enantiomerically enriched aldol product.

In the same year, *MacMillan et al.* described the first highly enantioselective example of iminium catalysis. In iminium catalysis, the active species is an iminium ion formed by the reversible reaction of an amine catalyst with the carbonyl substrate. The higher reactivity of the iminium ion compared to the carbonyl species is utilized to facilitate the reactions. Early examples of non-asymmetric and asymmetric iminium catalysis were the amine-catalyzed Knoevenagel condensation and proline- or proline-derivative-catalyzed Michael additions.[36,37,38]

The pioneering example of modern iminium catalysis was *MacMillan*'s asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes with dienes using chiral imidazolidinone catalyst [**15**·HCl] (Scheme 2.7).[31,39]



Scheme 2.7: Imidazolidinone-catalyzed enantioselective Diels–Alder reaction.[31]

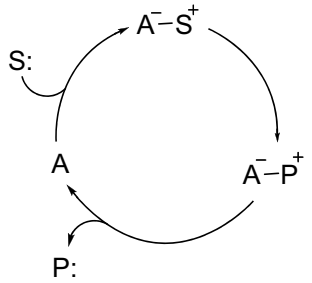
The authors suggested that the condensation of the α,β-unsaturated aldehyde **16** with the enantiopure amine catalyst [**15**·HCl] forms an activated iminium ion with a lowered LUMO energy, which then reacts with the diene **17** in a Diels-Alder reaction. This concept has been

further extended to other reactions of α,β-unsaturated aldehydes, such as 1,3-dipolar cycloadditions, alkylations, and conjugate additions.[34]

As iminium catalysis is one of the main focuses of this Ph.D. work, a more detailed overview of this concept is presented in chapter 2.1.2.

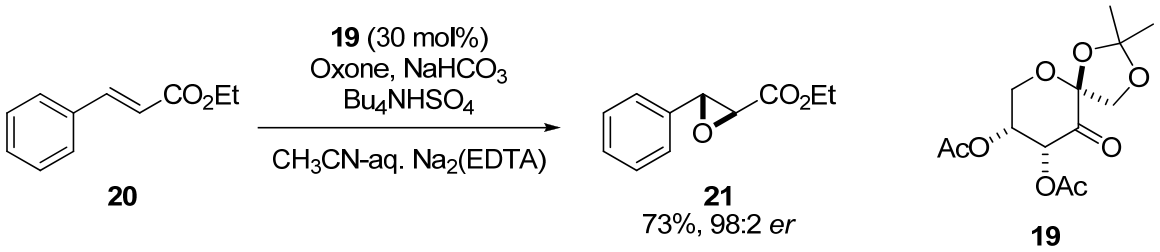
2.1.1.2 Lewis acid catalysis

Lewis acids (A) are atoms or molecules that can accept a pair of electrons and form ionic interactions or hydrogen bonds. They can initiate a catalytic cycle by activating a nucleophilic substrate (S:) *via* electrophilic coordination or addition reaction, thus increasing the substrate electrophilicity or stabilizing an ionic nucleophilic substrate. The activated substrate reacts further, followed by the release of the product (P) and regeneration of the catalyst (Scheme 2.8).



Scheme 2.8: Simplified catalytic cycle of Lewis acid catalysis. (A: Lewis acid catalyst , S: substrate, P: product).

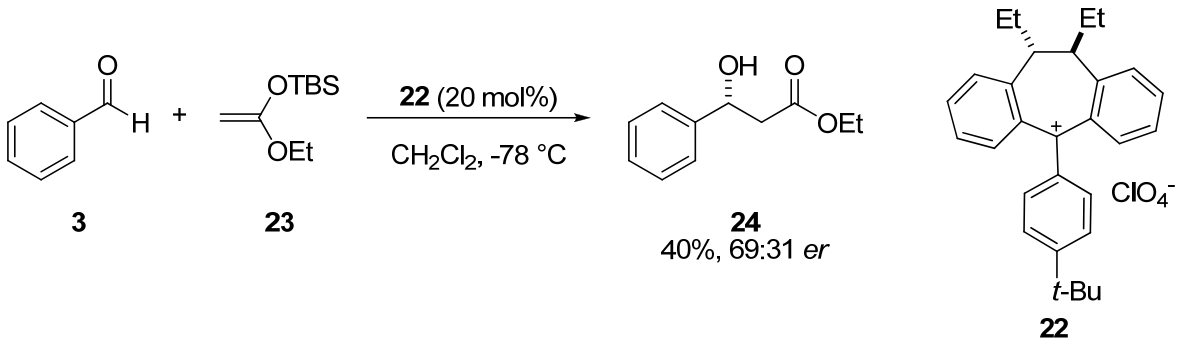
An example of Lewis acid catalysis is the epoxidation of olefins using chiral dioxiranes generated *in situ* from chiral ketone catalysts and Oxone as the stoichiometric oxidant.[40] *Shi et al.* developed the elegant D-fructose-derived ketone catalyst **19** for the enantioselective epoxidation of olefins (Scheme 2.9).[41]



20 → **21** 73%, 98:2 *er*; **19**

Scheme 2.9: A ketone-catalyzed enantioselective epoxidation of olefins.[41]

Mukaiyama et al. showed that trityl salts are efficient catalysts for aldol reaction.[42] Shortly after, *Chen et al.* developed triarylcarbenium ions (e.g. **22**) to catalyze a Mukaiyama aldol reaction (Scheme 2.10).[43]



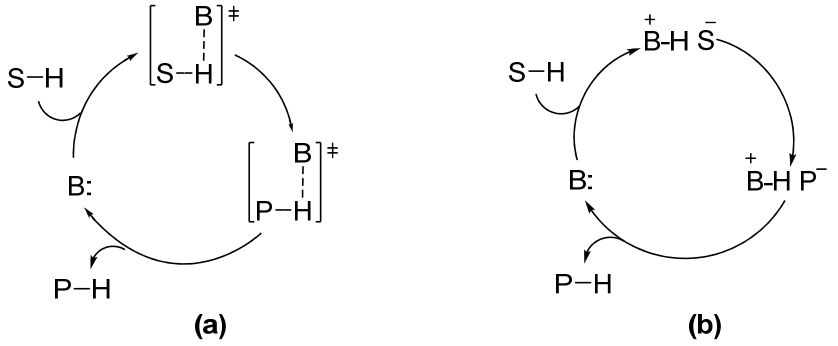
3 **23** **24** 40%, 69:31 *er* **22**

Scheme 2.10: Chiral triarylcarbenium ion-catalyzed Mukaiyama aldol reaction.[43]

It should be noted that, in comparison to other types of organocatalysis there are only a few Lewis acid organocatalyzed reactions. The area of Lewis acid catalysis is still dominated by transition metal catalysts.

2.1.1.3 Brønsted base catalysis

Brønsted bases (B:) are defined as chemical species (molecules or ions) that are able to gain, or "accept" a proton. They can initiate a catalytic cycle *via* activation of a nucleophilic substrate through (partial) deprotonation (Scheme 2.11).



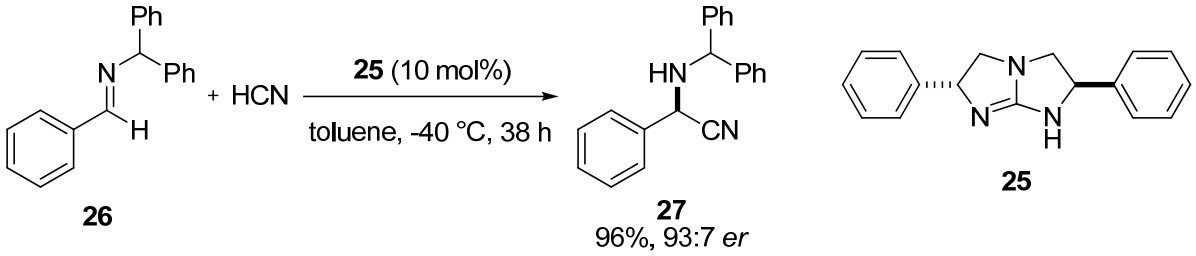
Scheme 2.11: Simplified catalytic cycles of Brønsted base catalysis with a Brønsted base acting as a (a) hydrogen bonding acceptor ("general Brønsted base") or a (b) proton acceptor ("specific Brønsted base"). (B: Brønsted base catalyst, S: substrate, H: hydrogen, P: product).

Depending of the substrate acidity the Brønsted base acts as a hydrogen bonding acceptor (Scheme 2.11a) or a proton acceptor (Scheme 2.11b). Hydrogen bonding acceptors are generally called "general Brønsted bases" and proton acceptors "specific Brønsted bases".

The first asymmetric Brønsted base-catalyzed reaction was reported by *Bredig et al.* who employed catalytic quinine **4a** or quinidine **5** (Scheme 2.1).[25] Further pioneering work on this area was reported by *Pracejus et al.*,[26] *Bergson et al.*,[44] *Wynberg et al.*,[45] *Inoue et al.*,[46] and *Oda et al.*[47] between 1960 and 1985.

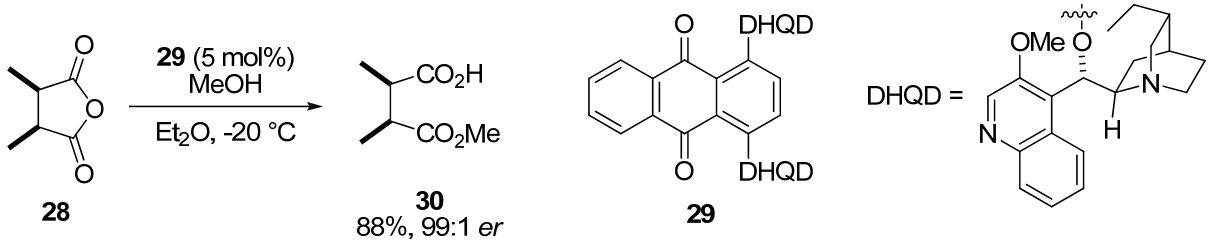
Typical organic Brønsted base catalyses in asymmetric synthesis are hydrocyanations, Strecker reactions, Michael reactions and desymmetrization of *meso*-anhydrides.[17e,48]

Corey and *Grogan* reported a Strecker reaction using the synthetic chiral C_2-symmetric guanidine **25** (Scheme 2.12).[49] The catalyst is believed to function *via* hydrogen bonding activation of the aryl imine through a protonated guanidium-cyanide complex to afford adduct **27**.



Scheme 2.12: Brønsted base-catalyzed Strecker reaction.[49]

Deng et al. reported the desymmetrization of cyclic *meso*-anhydrides such as **28** by alcoholysis using commercially available cinchona alkaloids **29** (Scheme 2.13).[50] Mechanistic studies suggested that the amine catalyst operates by general base catalysis, activating methanol *via* hydrogen bonding for nucleophilic attack on the anhydride.

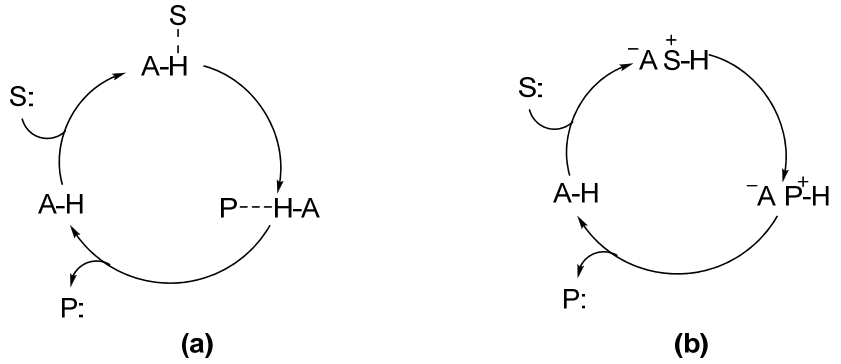


Scheme 2.13: Brønsted base-catalyzed desymmetrization of cyclic *meso*-anhydrides.[50]

2.1.1.4 Brønsted acid catalysis

The fundamental role of metal containing Lewis-acid catalysts lies in the activation of the "C=X" bond (X = O, NR, CR_2), decreasing its LUMO energy and promoting nucleophilic addition to the "C=X" group. Complementary to this catalyst class are metal-free Brønsted acid catalysts,[51] which have recently emerged as a new type of organocatalysts for a number of enantioselective carbon-carbon bond-forming reactions.[52] Brønsted acids (A-H) are defined as chemical species (molecules or ions) that are able to lose, or "donate" a proton and can initiate a catalytic cycle *via* activation through (partial) protonation of an electrophilic substrate (Scheme 2.14)

Chiral Brønsted acid catalysis is classified into two categories: "general Brønsted acid catalysis" when the catalyst partially protonates the transition state of the reaction *via* hydrogen bonding interactions (Scheme 2.14a) and "specific Brønsted acid catalysis" when the Brønsted acid is strong enough to protonate the substrate (Scheme 2.14b).



Scheme 2.14: Simplified catalytic cycles of Brønsted acid catalysis with a Brønsted acid acting as a (a) hydrogen bonding donor ("general Brønsted acid") or a (b) proton donor ("specific Brønsted acid"). (A-H: Brønsted acid catalyst, S: substrate, H: hydrogen, P: product).

Even though it is not always possible to clearly distinguish between these two mechanisms (Figure 2.1),[51f] the pK_a value of the Brønsted acid gives an indication on the nature of the catalyst (Figure 2.2).[17p]

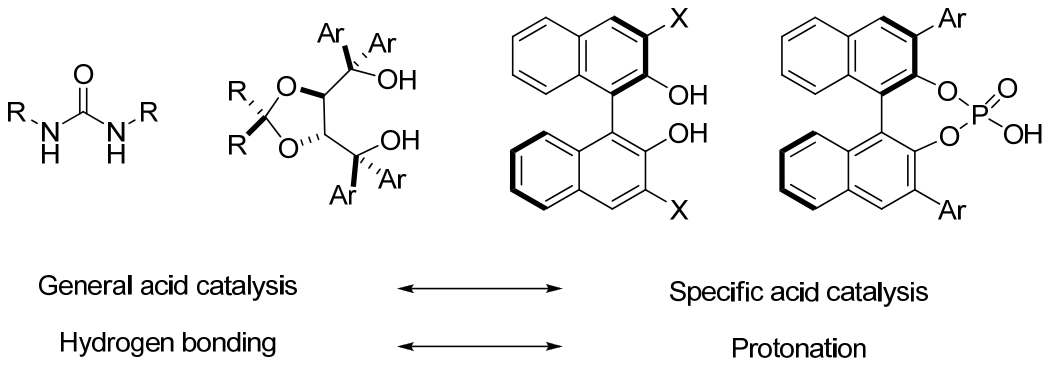


Figure 2.1: Chiral Brønsted acids.

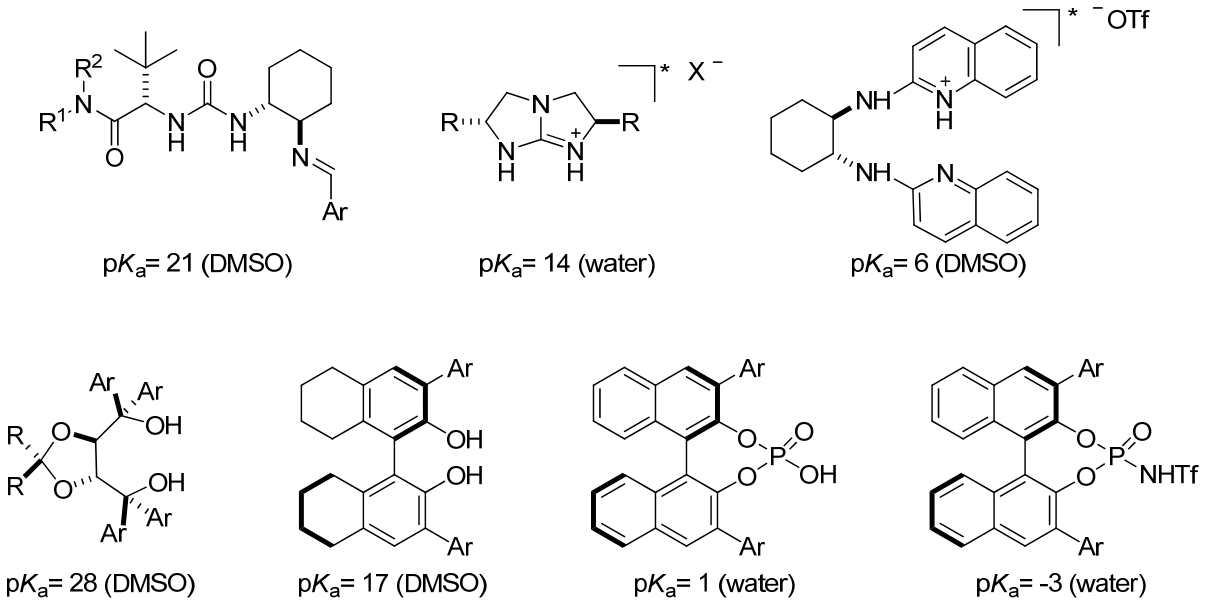


Figure 2.2: Approximate pK_a values of Brønsted acid organocatalysts.

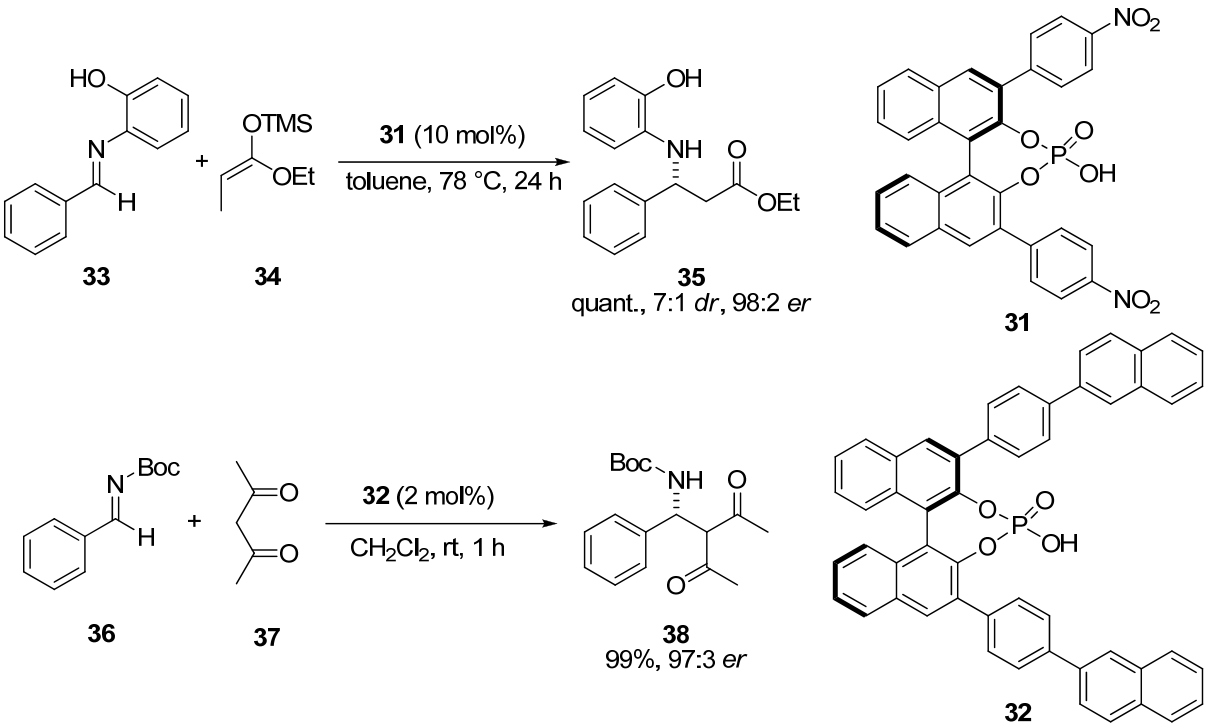
General Brønsted acid catalysis

Catalysis through hydrogen bonding[17p,57a,e,53] has been recently introduced as a powerful methodology for asymmetric catalysis. Similar to enzymatic catalysis where hydrogen bonding to a transition state occurs, this type of catalysis may be described as general Brønsted acid catalysis. As this concept is one of the main focuses of this Ph.D.work, a separate chapter will be dedicated to hydrogen bonding catalysis (see chapter 2.1.3).

Specific Brønsted acid catalysis

In contrast to general Brønsted acid catalysis, stronger acids are used in specific Brønsted acid catalysis allowing the full protonation of the substrate.

The potential of using relatively strong Brønsted acid catalysts has been essentially ignored over the last decades. In 2004 *Akiyama et al.*[54] and *Terada et al.*[55] demonstrated in pioneering studies that relatively strong chiral BINOL-derived phosphoric acids such as **31** and **32** are efficient and highly enantioselective catalysts for Mannich reactions of aldimines (Scheme 2.15).



Scheme 2.15: Mannich reactions catalyzed by BINOL-derived phosphoric acids.[54,55]

After those findings, chiral phosphoric acids were acknowledged as novel chiral catalysts[53] and attracted the attention of synthetic organic chemists. It was observed that they are bifunctional catalysts[56] bearing both a Brønsted-acidic site and a Lewis-basic site and the 3,3'-substituents play a crucial role in attaining excellent enantioselectivities (Figure 2.3).[52]

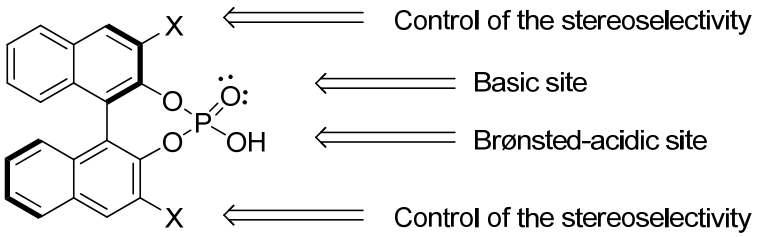
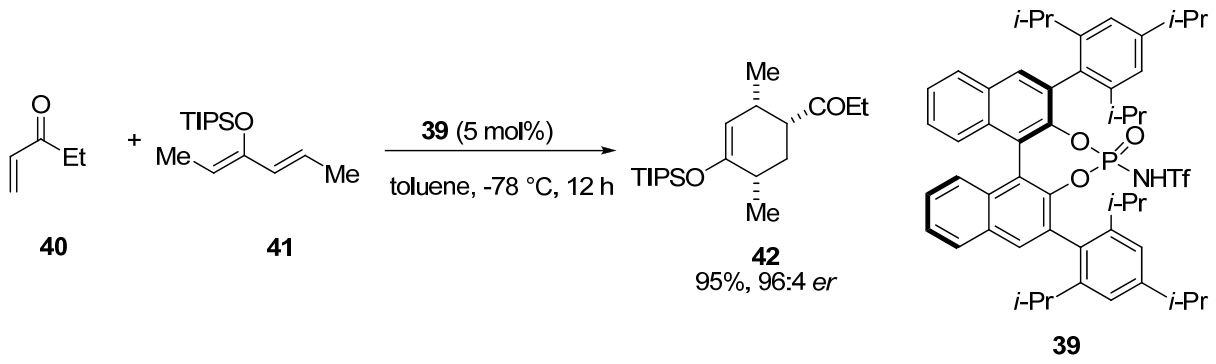


Figure 2.3: Bifunctional chiral Brønsted acid.

Such chiral phosphoric acids have been recently used as efficient enantioselective catalysts for different organic transformations including Friedel-Crafts alkylation of furan, Diels-Alder, Pictet-Spengler, and Strecker reactions as well as transfer hydrogenation of imines.[51f,52]

Yamamoto et al. designed a stronger chiral Brønsted acid in an effort to expand the substrate scope of enantioselective Brønsted acid-catalyzed reactions. For example, BINOL-derived *N*-triflyl phosphoramide **39** catalyzes the Diels-Alder reaction of *α,β*-unsaturated ketone **40** with

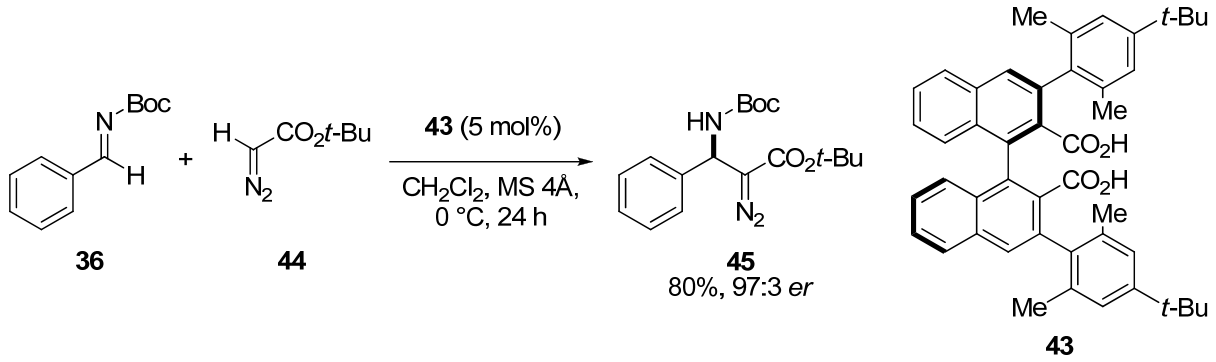
electron-rich diene **41** to give cyclohexene derivatives **42** with high enantioselectivities (Scheme 2.16).[57]



40 **41** **42** 95%, 96:4 *er* **39**

Scheme 2.16: *N*-triflyl phosphoramide-catalyzed enantioselective Diels-Alder reaction.[57]

Maruoka et al. prepared the chiral catalyst **43** containing two carboxylic acids and an axially chiral binaphthyl moiety, and applied them to highly enantioselective Mannich reaction of *N*-Boc-imines with diazo compounds (Scheme 2.17).[58]



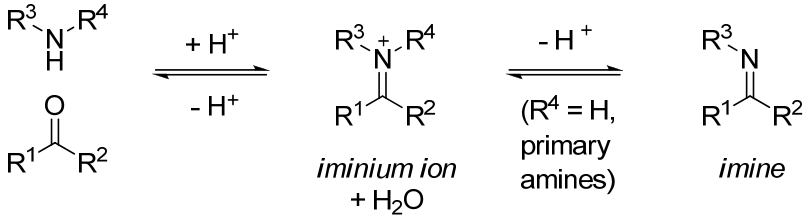
36 **44** **45** 80%, 97:3 *er* **43**

Scheme 2.17: Dicarboxylic acid-catalyzed enantioselective Mannich reaction.[58]

2.1.2 Iminium Catalysis

No specific date can be given for the introduction of the concept of iminium catalysis. The earliest recorded example of an iminium-catalyzed process is probably the Knoevenagel condensation mediated by primary and secondary amines.[59] In the early 1900s iminium ions where postulated for the first time as active intermediates for the decarboxylation of *β*-ketocarboxylic acids[60,61,62] and in 1937 *Langenbeck et al.* reported the first iminium-catalyzed conjugate addition reaction.[63] A landmark in the history of iminium catalysis is the discovery of the iminium-catalyzed transimination by *Cordes* and *Jencks* in 1962.[64] Cycloadditions *via* iminium catalysis were not discovered until the turn of the century. In 1976, *Baum* and *Viehe* reported that iminium salts provide significant acceleration in Diels-Alder reactions.[65] However, it was not until 2000 that *MacMillan et al.* disclosed a more general strategy for the Diels-Alder reaction using enantioselective iminium catalysis (Scheme 2.7).[31]

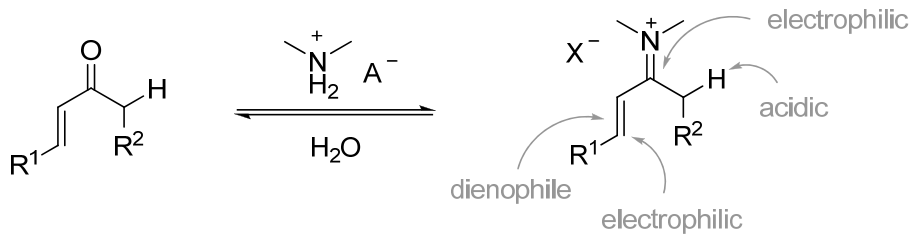
The condensation of aldehydes or ketones with primary amines typically results in an equilibrium where a considerable amount of the imine is present (Scheme 2.18).[66] This reaction was discovered in 1864 by *Schiff*.[67] These primary amine-derived imines are basic (pK_a ca. 7),[68] and they readily exist as iminium ions in an acidic solution.



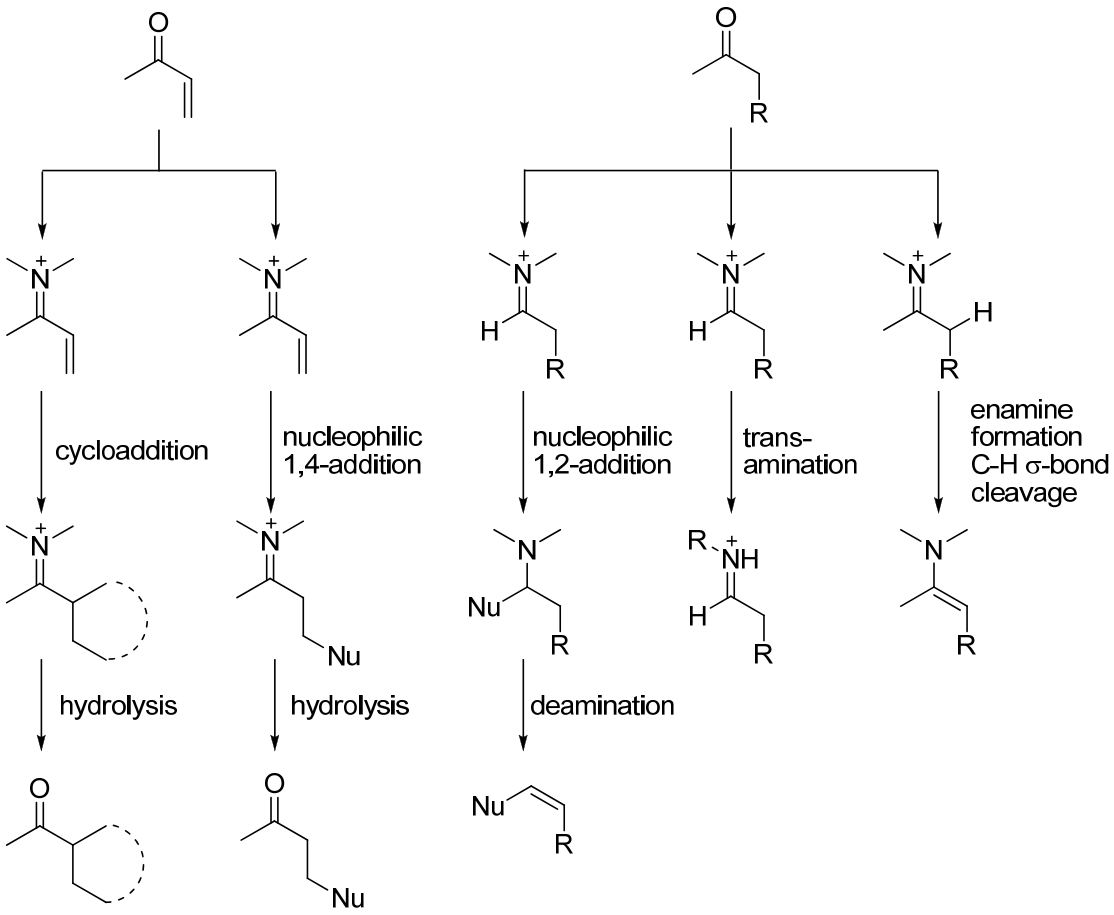
Scheme 2.18: Formation of iminium ions and imines.

With secondary amines, aldehydes and ketones may also condense to form iminium cations. In this case, deprotonation to form imines is impossible, and as such, these iminium cations can only be isolated as salts of strong acids. For iminium catalysis, both primary and secondary amines can be used, although secondary amines tend to dominate this field. Primary amines always require an external acid cocatalyst, but the use of an acid cocatalyst is also very common with secondary amines.

Iminium ions are more electrophilic than the corresponding aldehydes or ketones. For this reason, the reversible formation of the iminium salt activates the carbonyl component for the attack of a nucleophile (Scheme 2.19).[17g] Examples of possible modes of iminium activation are depicted in Scheme 2.20.[34]

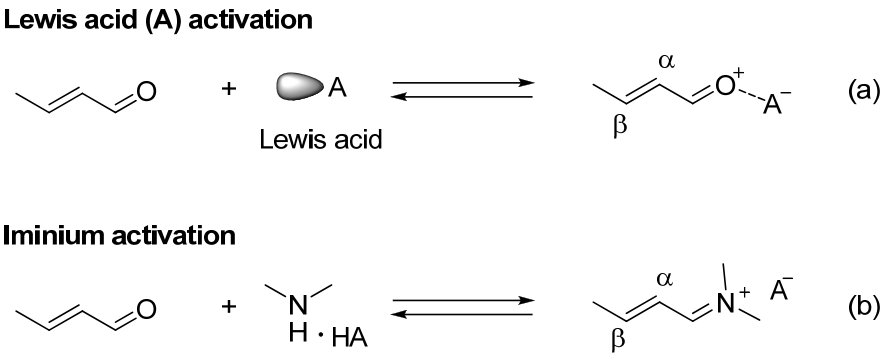


Scheme 2.19: Iminium catalysis.



Scheme 2.20: Different activation modes in iminium catalysis.

MacMillan et al. introduced with their iminium-catalyzed Diels-Alder reaction[31] a new strategy for asymmetric synthesis based upon design criteria borrowed from the area of Lewis acid catalysis. This catalytic concept – also termed iminium activation – was based on the mechanistic postulate that: (1) the electronic principle underpinning Lewis acid activation (LUMO-lowering activation); and (2) the kinetic lability toward ligand substitution enabling Lewis acid-catalyst turnover (Scheme 2.21a) might also be available with an organic compound existing in a rapid equilibrium between an electron deficient and a relatively electron-rich state (Scheme 2.21b).[16b,17k]



Scheme 2.21: Activation of carbonyl compounds.[16b]

Guided by these postulates, *MacMillan et al.* developed different imidazolidinone catalysts (Figure 2.4), which have been successfully applied to catalyze cycloaddition reactions, 1,4-addition reactions, transfer hydrogenations as well as cascade reactions.[16b]

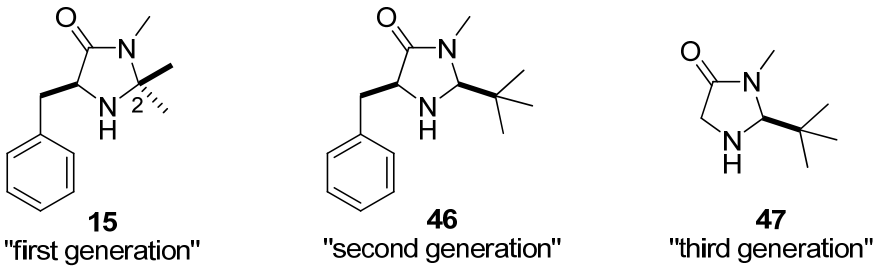


Figure 2.4: Examples of *MacMillan* imidazolidinone catalysts.

Imidazolidinone catalyst **15** ("first generation" *MacMillan* catalyst) was successfully applied to several transformations such as enantioselective Diels-Alder reaction, nitrone additions,[69] and Friedel-Crafts alkylations of pyrrole nucleophiles.[70] However low reactivity was observed in many reactions due to the diminished nucleophilicity of catalyst **15** toward carbonyl additions as the participating nitrogen lone pair is positioned adjacent to an eclipsing methyl group. In order to overcome this unfavorable interaction and enable a rapid iminium ion formation, the geminal dimethyl functionality was replaced with a *tert*-butyl group which eliminated steric crowding at the carbon *C*-2 and allowed for an increased iminium geometry control. These changes lead to the imidazolidinone catalyst **46** ("second generation" *MacMillan* catalyst).[71] The reactivity of this catalyst could be further increased by replacing the benzyl substituent adjacent to the participating nitrogen lone pair with a hydrogen atom, giving the "third generation" imidazolidinone catalyst **47**.

2.1.3 Hydrogen Bonding Catalysis and (Thio)urea Catalysts

Whereas individual hydrogen bonds are relatively weak compared to covalent bonds, collectively they can be of enormous importance. They are for example essential for the organization and the base pairing of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA),[72] small molecule recognition,[73] and the catalytic cycle of various enzymes.[74,75] Despite the many vital functions that hydrogen bonds fulfill in biological systems, they had, until recently been little utilized for the promotion of chemical reactions. Nevertheless, over the past decade, this situation has changed dramatically, and many enantioselective reactions have been developed, in which a chiral hydrogen bond donor serves as the catalyst.

Unlike covalent bonds, the nature of hydrogen bonds can vary dramatically. Countless variations can be found in bond strengths and geometric orientations of the hydrogen bonds, even within the same bonding partners. To simplify the matter, hydrogen bonds have been grouped into three different categories: strong, moderate, and weak (Table 2.1).[16b]

Table 2.1: *Jeffrey*'s classification of strong, moderate and weak, hydrogen bonds[76]

Bonding strength	**Strong**	**Moderate**	**Weak**
A–H ···B interaction	mostly covalent	mostly electrostatic	electrostatic
Length of H-bond (Å)	~1.2-1.5	~1.5-2.2	~2.2-3.2
Bond angle AHB (°)	175-180	130-180	90-150
Bond energy (kcal/mol)	14-40	4-15	<4
Typical example	intermolecular NH ···N bond in conjugate acid proton sponge	NH ···O=C bonds in peptide helices and sheets	bonds involving CH donors to N or O acceptors

The strength of the hydrogen bond donor is best correlated to its pK_a-value, although environmental factors, such as solvation, temperature, and dielectric constants, can also affect the nature of a hydrogen bond.

Given the infinite variations in bonding patterns, hydrogen bonding is best considered as a continuum of bonding interactions, from weak to strong. Moving further along this spectrum, past the strong hydrogen bonds, there is the further possibility of full proton transfer between the hydrogen bond donor and the acceptor, with the donor now being considered as a Brønsted acid (Figure 2.5).[16b]

Figure 2.5: Hydrogen bonding continuum.

The wide variability observed in the strength and bonding geometries of hydrogen bonds not only provides unique challenges for catalyst design but also offers opportunities for the discovery and development of new concepts in catalysis.

2.1.3.1 Early Successes: From Biphenylenediols to Efficient *N,N'-D*iaryl(thio)urea Catalysts

The systematic use of hydrogen bonding for the promotion of racemic organic reactions began most noticeably during the 1980s. In a seminal investigation, *Hine et al.* showed that hydrogen bonding with 1,8-biphenylenediols **48a** (Figure 2.6) could effectively activate a substrate for nucleophilic attack.[77] *Kelly et al.* found that achiral biphenylenediols **48b** (40-50 mol%) significantly accelerated the Diels-Alder reaction of cyclopentadiene with various acroleins[78] and proposed double hydrogen bond donation to the dienophile (**A**; Figure 2.6).[53]

At around the same time, *Etter et al.* observed hydrogen bond-directed co-crystallization of *N*,*N'*-diarylureas (**B**; Figure 2.6) with compounds incorporating a wide variety of Lewis basic functional groups, such as nitroaromatics, ethers, ketones, and sulfoxides.[79] In each case the donation of two hydrogen bonds by a single urea molecule to the Lewis base was implicated. This demonstration provided the basis for the development of urea-based organocatalysts.

The first report on the application of *Etter*'s concept of using ureas as Lewis acids was proposed by *Curran et al.*, who showed that the outcome of radical allylation reactions and Claisen rearrangements can be altered by the presence of ureas and thioureas (e.g. diarylurea **49a**).[80] In 2002, a thorough study on the use of *Etter*-type ureas (e.g. **49b**) for the promotion of Diels-Alder reactions has been described by *Schreiner et al.*[81] Several other classes of hydrogen bond donors, such as guanidinium ions, alcohols, and phenols, have also been used as catalysts to promote organic reactions.[82,83,84]

The early reports provide clear demonstration of the ability of hydrogen bond donors to function as Lewis acids and thereby promote organic reactions. The formation of a hydrogen bond to the electrophile (typically carbonyl or imine), through either a one-point or two-point

interaction, increases its electrophilicity and lowers its LUMO energy, thereby making it more reactive to the second reactant, such as a nucleophile or a diene.

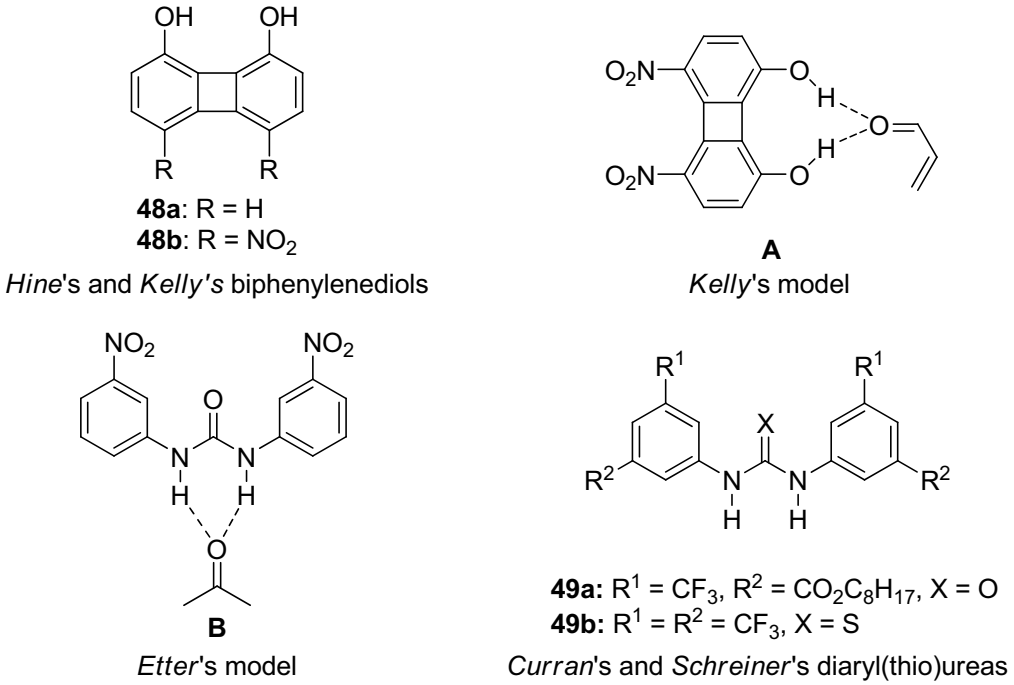


Figure 2.6: *Hine*'s and *Kelly*'s biphenylenediol catalysts (**48a** and **48b**, respectively); rationale for the catalysis of the Diels-Alder reaction by **48b** through double hydrogen-bond donation (**A**, Kelly); a representation of the binding between *m*-nitrocarbanilide and acetone (**B**) and *Curran*'s and *Schreiner*'s (thio)urea catalysts (**49a** and **49b**, respectively).

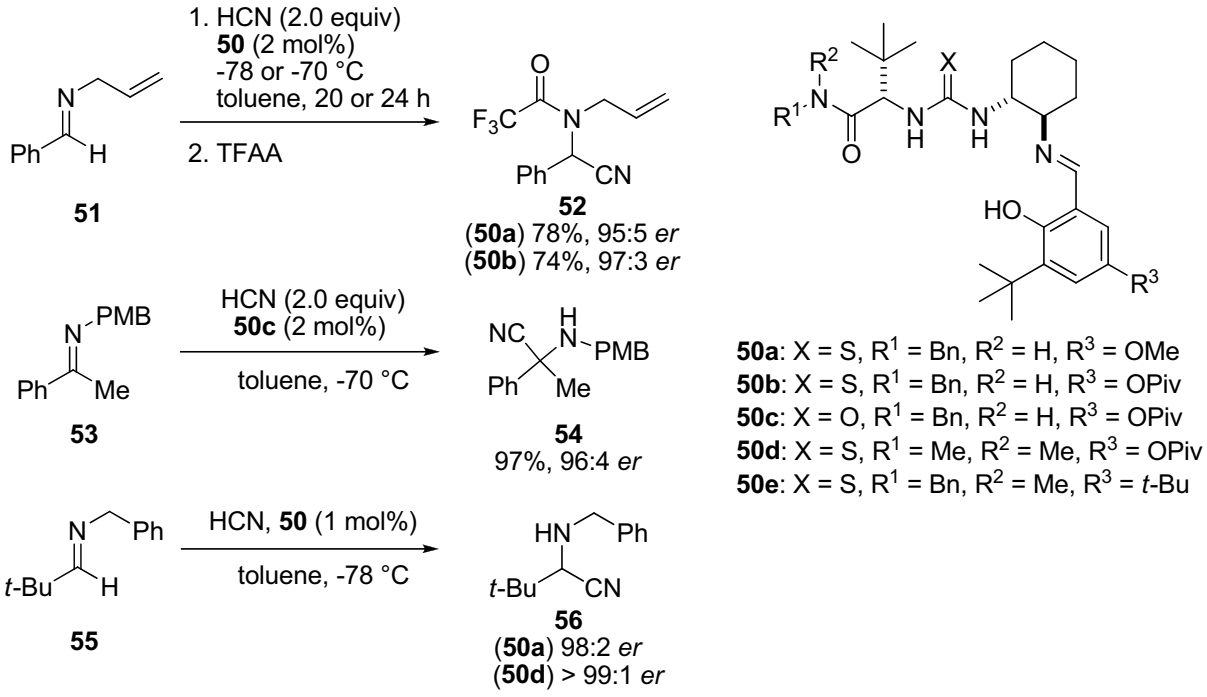
Over the past six years, many laboratories have focused their efforts on the development of chiral hydrogen bond donors to catalyze enantioselective organic reactions. One of the earliest successes in this area came from *Jacobsen et al.*, who reported the use of peptide-like chiral urea-based catalysts for the hydrocyanation of aldimines and ketimines.[85,86]

2.1.3.2 Chiral (Thio)ureas for Asymmetric Organocatalysis

The availability of enantiopure chiral building blocks bearing primary amino functionalities from the chiral pool and other sources greatly facilitates the synthesis of asymmetric (thio)ureas. Taking into account the excellent general stability, high conformational rigidity,[87] and Lewis-base binding properties[79] of (thio)urea derivatives, it is not surprising that chiral analogs are rapidly emerging as versatile, functional group tolerant, and easily prepared and modified catalyst templates for the promotion of a wide range of synthetically useful asymmetric carbon–carbon bond forming processes.[53]

Schiff base-derived catalysts

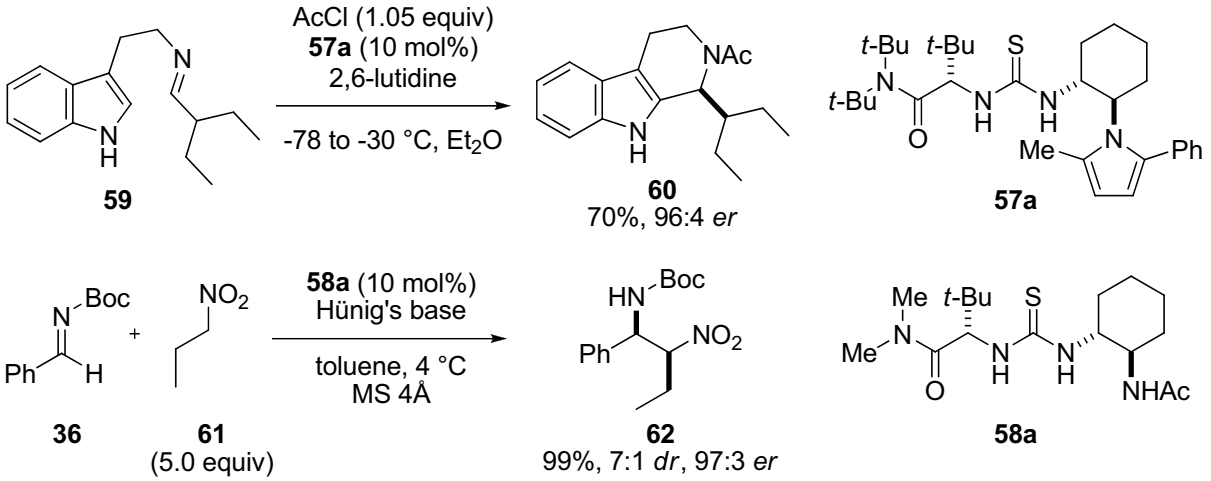
In the course of studies involving a combinatorial approach to the design of catalysts for metal-ion-promoted asymmetric Strecker reaction, *Jacobsen et al.* observed that in the case of one particular urea-derived ligand the control reaction in absence of metal ion furnished the product with the highest enantioselectivity. After optimization, **50a** (Scheme 2.22) was identified as an efficient and highly enantioselective catalyst for the addition of hydrogen cyanide to *N*-allyl amines **51**.[85] Further optimization[88] led to the development of **50b** and its robust and readily synthesized[89] urea-derivative **50c**, which is compatible with a broad range of imine substrates including traditionally challenging ketimine derivatives (Scheme 2.22).[86] Mechanistic and binding studies determined that the catalyst binds the imine (*Z*)-isomer preferentially through double hydrogen bond donation to the imine lone pair, in a fashion directed by the minimization of steric interactions between the catalyst and large imine substituents. This insight guided the design of an improved catalyst (**50d**), possessing remarkable reactivity and selectivity profiles (Scheme 2.22).[90] That the (thio)urea-catalyzed Strecker reaction is not another isolated example of an organocatalyzed transformation, but that asymmetric hydrogen bonding catalysis is generalizable was shown in 2002.[91-94]



Scheme 2.22: (Thio)urea-catalyzed asymmetric Strecker reactions (PMB = *p*-methoxybenzyl).[90]

Simplification of catalysts 50

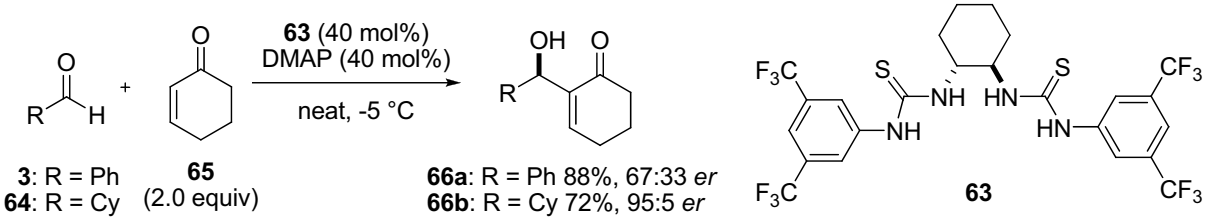
Interestingly, it has recently been shown that structural simplification of the catalysts **50a-e** is possible without loss of enantioselectivity.[92] This allows a certain latitude for the fine-tuning of catalyst structure to suit the requirements of individual reaction classes, and has led to the development of simplified (yet superior to **50a-e**) analogs **57a** and **58a** for the efficient promotion of the asymmetric acyl Pictet-Spengler,[95] acyl Mannich[96] (catalyst **57a**), and nitro Mannich (catalyst **58a**)[97] reactions (Scheme 2.23).



Scheme 2.23: Simplified (thio)urea derivatives for the asymmetric Pictet-Spengler and nitro Mannich reactions.[95,97] (Hünig's base: diisopropylethylamine)

Bisthiourea catalyst

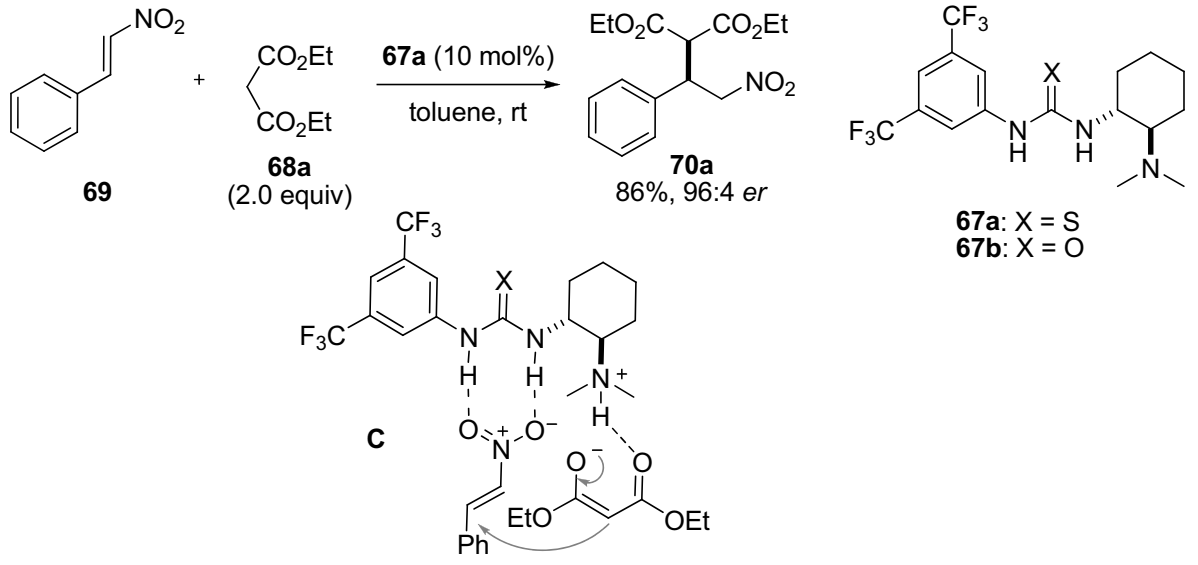
Nagasawa et al. have applied chiral diaryl thiourea to catalyze asymmetric Baylis-Hillman reactions.[98] *Trans*-1,2-Diaminocyclohexane-derived bisthiourea **63** promoted the *N*,*N*-4-dimethyl aminopyridine (DMAP)-mediated addition of cyclohexenone to a range of activated aldehydes. While aromatic aldehydes generally proved to be mediocre substrates in terms of selectivity, the analogous aliphatic electrophiles were converted to the Baylis-Hillman adducts with moderate to excellent enantioselectivities (Scheme 2.24). The high selectivity, sense of stereoinduction observed and superiority of **63** over mono-thiourea analogs prompted the authors to propose that both thiourea moieties are involved in the transition state of the rate-determining (and stereocenter-forming) step.[99,100]



Scheme 2.24: Bisthiourea-catalyzed enantioselective Baylis-Hillman reactions.[98]

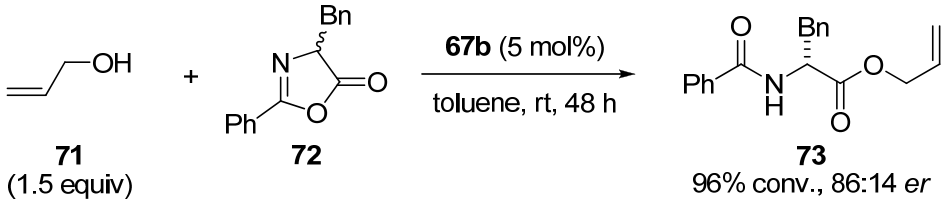
Chiral bifunctional (thio)urea catalysts

The excellent functional group tolerance of the (thio)urea catalysts stems from their relatively weak enthalpic binding with organic Lewis base nucleophiles, such as alcohols and amines. Recently the concept of exploiting the high functional group tolerance of these materials by incorporating a Lewis or Brønsted basic nucleophile-activating functionality into the catalyst structure has begun to be explored. Such bifunctional catalysts mimic natural enzymatic systems by activating both electrophile and nucleophile simultaneously,[101] allowing for a significantly improved catalytic activity and, perhaps more importantly, a greater degree of stereocontrol in the addition event. The majority of these prototype systems represent a hybrid strategy that borrows heavily from the design principles set down in the seminal work of *Curran*, *Jacobsen* and *Schreiner* outlined above. They involve the installation of readily tunable aromatic functionality (to maximize the catalyst's rigidity and hydrogen bond donating ability) at one (thio)urea nitrogen atom, and a chiral (in this case Lewis or Brønsted basic) functionality at the other. *Takemoto et al.* reported the first (thio)urea-based bifunctional catalyst, tertiary amine **67** (Scheme 2.25), which efficiently promotes the addition of malonate esters (e.g. **68a**) to *β*-nitrostyrenes (e.g. **69**) with excellent enantioselectivity.[102] The authors found that both the tertiary amine and the thiourea moieties were requisite for efficient and selective catalysis, and proposed a model to explain the sense of stereoinduction observed (**C**, Scheme 2.25). This model involves a deprotonation of the malonate pronucleophile by the tertiary amine followed by the addition of the resultant nucleophile to a single face of the thiourea-bound nitroolefin.



Scheme 2.25: *Takemoto*'s bifunctional catalysis of the addition of malonates to nitroolefins *via* a dual activation concept.[102]

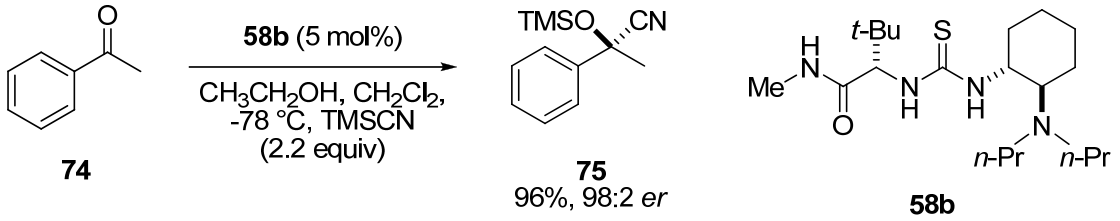
Berkessel et al. have successfully applied **67a** and its urea derivative **67b** to the dynamic kinetic resolution of racemic azlactones. For example, the addition of allyl alcohol **71** to the DL-phenylalanine-derived azlactone **72** catalyzed by **67b** gave amide **73** in good conversion and enantioselectivity (Scheme 2.26).[103]



71 (1.5 equiv) **72** **73** 96% conv., 86:14 *er*

Scheme 2.26: Dynamic kinetic resolution of azlactones-catalyzed by bifunctional catalyst **67b**.[103]

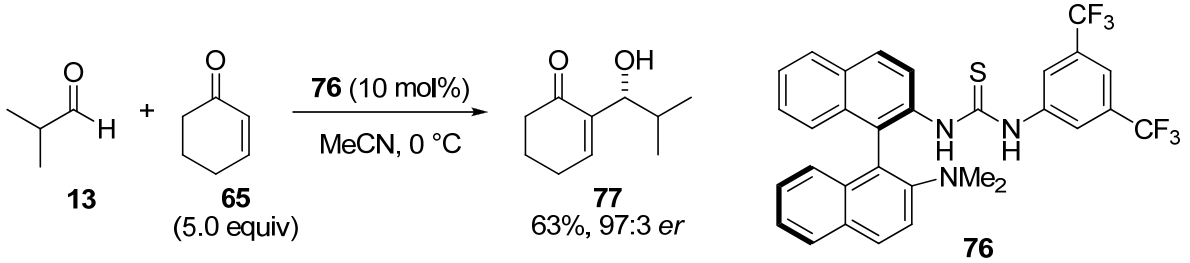
Very recently, *Jacobsen et al.* modified the structural backbone of Schiff-base catalysts **50a-e** (see Scheme 2.22) to incorporate a tertiary amino functionality. Thiourea **58b** was demonstrated to be optimal for the highly efficient and selective catalytic asymmetric cyanosilylation of ketones (Scheme 2.27).[104]



74 **75** 96%, 98:2 *er* **58b**

Scheme 2.27: Bifunctional organocatalytic cyanosilylation of ketones.[104]

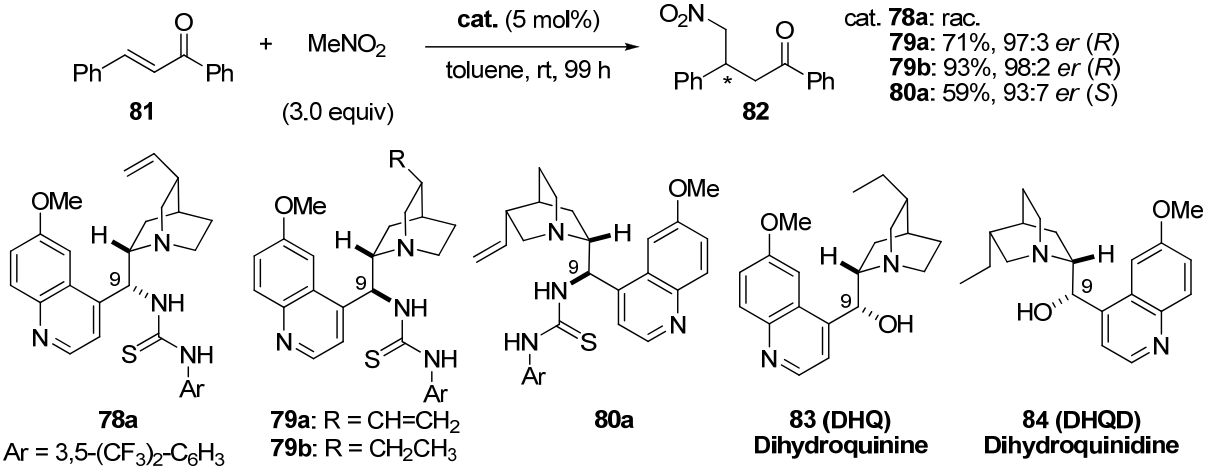
An axially chiral thiourea-based bifunctional catalyst has been recently developed by *Wang et al.* for the promotion of enantioselective Baylis–Hillman reactions.[105] Compound **76** was found to promote the addition of cyclohexenone **65** to a range of aromatic and aliphatic aldehydes with good to excellent yields and selectivities (Scheme 2.28). This catalyst was later found to be also effective for the addition of 2,4-pentadione to (*E*)-*β*-nitrostyrenes.[106]



13 **65** (5.0 equiv) **77** 63%, 97:3 *er* **76**

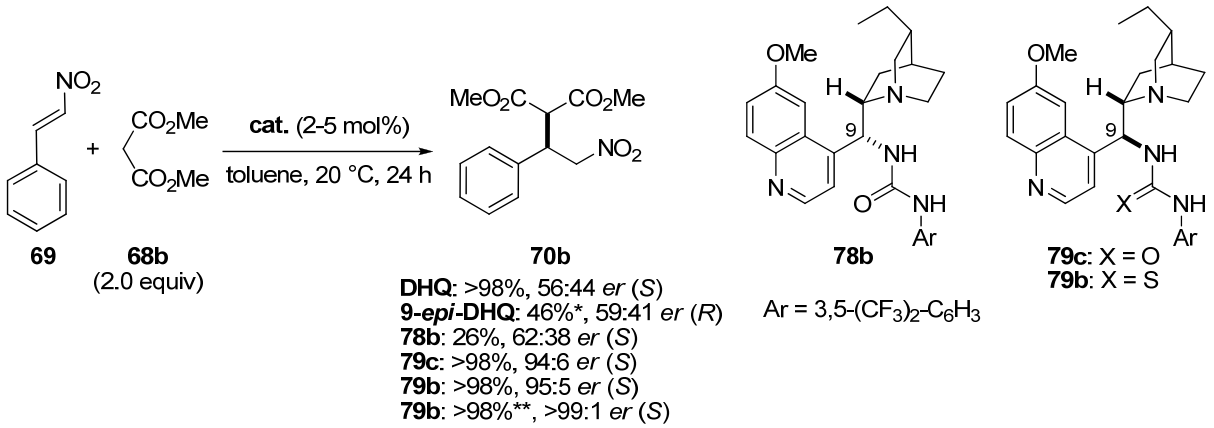
Scheme 2.28: Bifunctional catalysis of asymmetric Baylis-Hillman reactions.[105]

Soós et al. and *Connon et al.* have independently investigated the use of (thio)urea-substituted cinchona alkaloid derivatives as bifunctional catalysts.[53] *Soós* prepared four thiourea-substituted cinchona alkaloid catalysts **78a-80a** (Scheme 2.29) and evaluated their performance in the asymmetric addition of nitromethane to chalcones.[107] Surprisingly the thiourea derivative with the "natural" stereochemistry at the carbon *C*-9 (**78a**) was inactive in the addition of nitromethane to **81**. However analogs of **78a** with inverted stereochemistry at the carbon *C*-9 proved to be both active and highly selective bifunctional catalysts for the same reaction.[108] These results strongly indicate that a relative stereochemical arrangement of the catalyst Lewis/Brønsted acidic and basic groups conducive to their synergistic operation is a prerequisite for chiral bifunctional catalyst design.



Scheme 2.29: Asymmetric bifunctional catalysis of the addition of nitromethane to chalcone.[107]

Analogous results have been found for dihydro cinchona alkaloids. *Connon et al.* prepared a range of (thio)urea-substituted derivatives of dihydroquinine (DHQ, **83**) and dihydroquinidine (DHQD, **84**) for the asymmetric catalysis of the addition of diethylmalonate to nitroolefins (Scheme 2.30).[109] The authors found that while neither epimerization of DHQ at *C*-9 (9-*epi*-DHQ) nor a substitution of the carbon *C*-9 hydroxy group with an *N*-arylurea moiety (catalyst **78b**) improved the catalyst activity, a combination of both modifications resulted in an extremely active and selective catalyst with an "unnatural" stereochemistry at the carbon *C*-9 (**79c**).



Scheme 2.30: Bifunctional catalysis of the addition of dimethylmalonate to nitroolefins.[109] (* After 144 hours. ** After 30 hours at -20 °C)

Shortly after this report, *Dixon et al.* disclosed similar results using a cinchonine-derived analog of **80a** (at loadings of 10 mol%).[110]

2.2 Transfer Hydrogenation Using Hantzsch Esters: a Biomimetic Approach

2.2.1 Hydrogenation Processes of Unsaturated Compounds

Asymmetric hydrogenation of unsaturated organic compounds, such as olefins, carbonyls and imines, which is a standard procedure in both academic laboratories and industrial applications,[111,112] will be briefly overviewed in this Chapter. This process is arguably the single most important catalytic reaction for the synthesis of enantiomerically pure compounds and has reached a remarkable level of sophistication. This can be illustrated by the Nobel Prize in Chemistry awarded to Noyori and Knowles in 2001 for their studies of the transition metal-catalyzed asymmetric hydrogenation. [113] In principle hydrogenation can be accomplished in two ways: either *via* direct catalytic hydrogenation with molecular hydrogen gas, or indirectly by transfer hydrogenation from another reductant or *via* catalytic hydrosilylation followed by hydrolysis. The direct methodology has economic advantages because molecular hydrogen is inexpensive but is also less convenient and more dangerous because one has to deal with an explosive gas. Transfer hydrogenations (and hydrosilylations) are safer but are less favorable in terms of atom economy.

Until recently, all the methods developed for the reduction of organic compounds have been dominated by the use of metal catalysts surrounded by proper stereo-discriminating chiral ligands. Highly efficient catalysts based on rhodium(I) or ruthenium(II) complexes with chiral diphosphine ligands have been introduced for the enantioselective olefin reduction of enamines and unsaturated carboxylic acids with molecular hydrogen.[111,113b] More recently, iridium complexes with chiral phosphorus/nitrogen containing ligands have been used for the enantioselective reduction of nonfunctionalized olefins.[114,115] The asymmetric reduction of ketones and imines is commonly performed by using molecular hydrogen and chiral ruthenium(II) catalysts.[113b] A mild alternative for the latter reductions is to perform the reactions under hydrogen transfer conditions.[116] The hydrogen donors most commonly used for the transfer hydrogenation of ketones are propan-2-ol (generally used with sodium or potassium hydroxide as a base) and formic acid (generally used as an azeotrope with triethylamine).[117] Highly enantioselective processes, in particular for the reduction of ketones, have been established using catalysts based on vicinal amino alcohols, diamines, or pseudodipeptides in combination with ruthenium(II)–arene precursors.[117,118,119]

The common element in the systems described above is that the principal center of reactivity is positioned on a (transition) metal hydride or dihydride. However, a shift of this paradigm was recently made by the discovery that simple ammonium salts of secondary amines were able to catalyze the chemoselective reduction of α,β-unsaturated aldehydes in the presence of a dihydropyridine as the hydride donor.[120]

2.2.2 Nature's Enantioselective Hydrogenation Strategies

Nature's biological systems perform stereoselective hydrogenations using transform-specific oxidoreductases.[121] These enzymes are comprised of cofactors that play the vital role of "Nature's reducing agents". The dihydropyridine-based nucleotides NADH (**85a**, reduced nicotinamide adenine dinucleotide) and the closely related NADPH (**85b**, reduced nicotinamide adenine dinucleotide phosphate) are the most prevalent cofactors used for enantioselective biochemical hydrogenations. Based on this general transfer hydrogenation strategy, Nature's biosynthetic machines create important biomonomer building blocks, including chiral alcohols and amines, required for other essential metabolic processes.[121] From a chemical perspective, it is important to consider that molecules such as NADH incorporate two architectural components that function in concert to enable a highly selective delivery of hydride to electrophilic biochemical species. First, the nucleosidic element enables molecular recognition by a specific enzymatic environment wherein selective reduction might occur. Second, the dihydropyridine ring system (once positioned in the vicinity of a specific electrophile) has the capacity to deliver a hydride species from its 4-position to a carbonyl or imine group to create an enantiopure carbon-nitrogen or carbon-oxygen stereogenic center (Figure 2.7 and Scheme 2.31).[122,123]

Depending of the reaction conditions, two possible mechanisms are suggested for the reduction reaction mediated by NAD(P)H analogs: a one-step hydride ion transfer *via* a transition state, in which the migrating hydrogen atom carries some fractional negative charge (Scheme 2.32a), or a multistep hydride transfer. The latter process can occur in two steps, where an initial electron transfer is followed by the migration of a hydrogen atom (Scheme 2.32b), or in three steps involving an electron-proton-electron transfer (Scheme 2.32c).[123]

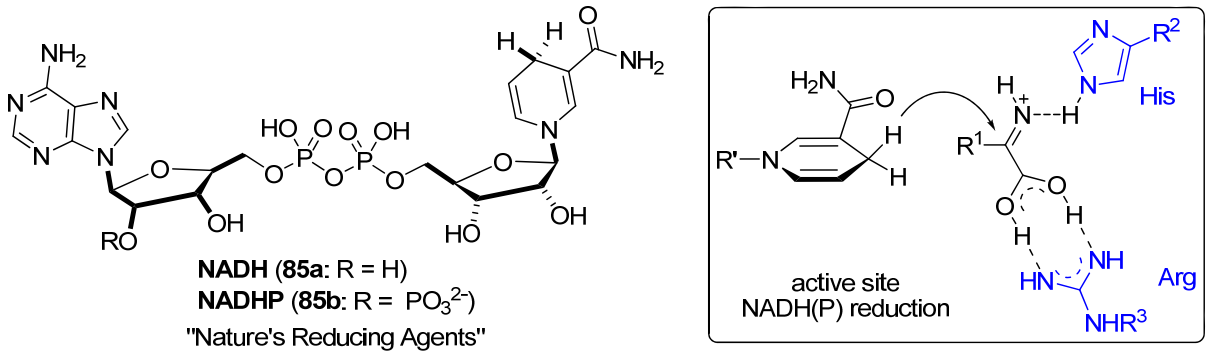
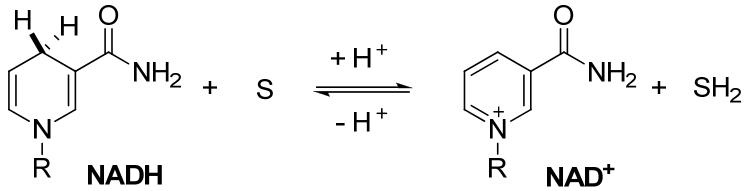
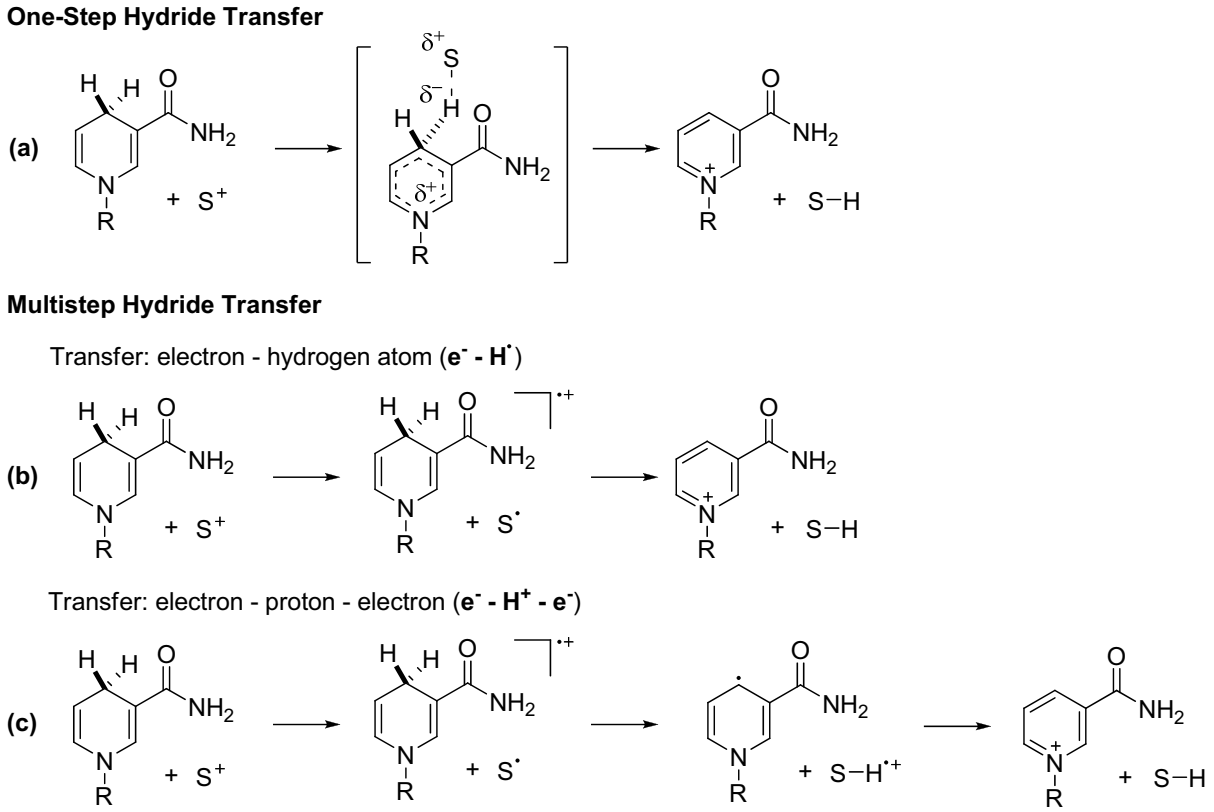


Figure 2.7: Organocatalyzed reductions in biological systems (Arg: arginine, His: histidine).



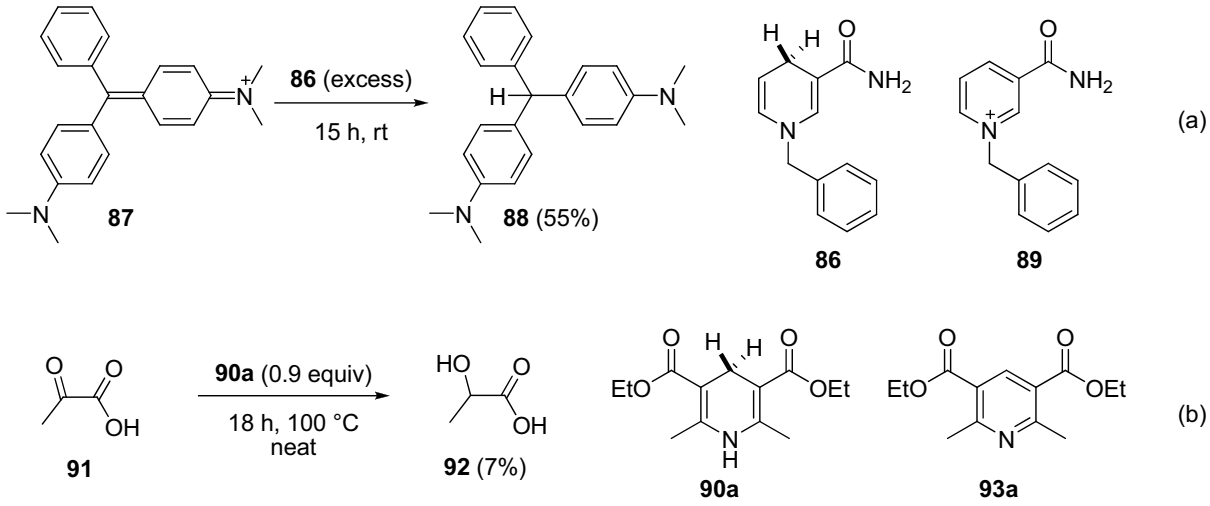
Scheme 2.31: NADH's dihydropyridine ring as Nature's reducing agent (S: Substrate).[122,123]



Scheme 2.32: Mechanism of reduction reactions mediated by NADH analogs (S: Substrate).[123]

2.2.3 Hantzsch Esters as Biomimetic Reducing Agents

Westheimer and *Mauzerall* were the first to demonstrate that synthetic dihydropyridine analogs of NADH could be used to mediate hydrogen transfer.[124,125] It was found that 1-benzyldihydronicotinamide (**86**) reduced dyestuff **87** to its leuco base **88** with a concomitant formation of pyridinium ion **89** in aqueous solvent (Scheme 2.33a). Deuterium labeling experiments demonstrated that only a 4-deuterio-analog of the reductant (and not 2- or 6-deuterated variants) transferred deuterium to the product. While **86** could not reduce pyruvic acid (**91**), hydrogen transfer from Hantzsch dihydropyridine **90a**[126] did occur at higher temperature, albeit in low yield (Scheme 2.33b).[127]

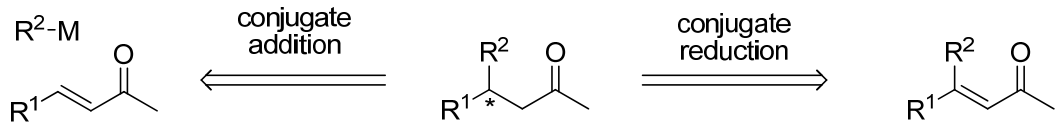


Scheme 2.33: *Westheimer*'s reduction of **87** and **91** with **86** and **90a**, respectively.[127]

In the years following *Westheimer*'s work, dihydropyridines[128] were found to serve as mild, useful reagents capable of reducing organic substrates such as *α,β*-unsaturated electrophiles,[129] imines,[130] iminium ions,[131] aldehydes,[132] and ketones[133] in the absence of metal ions under either thermal or organocatalyzed conditions.

2.3 Enantioselective Synthesis of *β,β*-Disubstituted Saturated Ketones

Currently, there are few catalysts that can reduce carbon–carbon double bonds with high enantioselectivity to generate products with stereocenters *β* to carbonyls. These products are usually synthesized *via* asymmetric conjugate additions of nucleophiles to *α,β*-unsaturated ketones (usually referred to as Michael addition, Scheme 2.34).[134] The best catalysts (rhodium, ruthenium or iridium catalysts) for these reactions work well for a limited number of substrates and nucleophiles.[135] In some cases, catalytic asymmetric conjugate reductions of an *α,β*-unsaturated carbonyl compound *via* direct hydrogenations (using molecular hydrogen)[136] or *via* indirect hydrogenations (from another hydrogen source)[137] can also generate a stereocenter *β* to the carbonyl (Scheme 2.34).



Scheme 2.34: Catalytic processes for the synthesis of enantiomerically pure *β,β*-disubstituted saturated ketones.

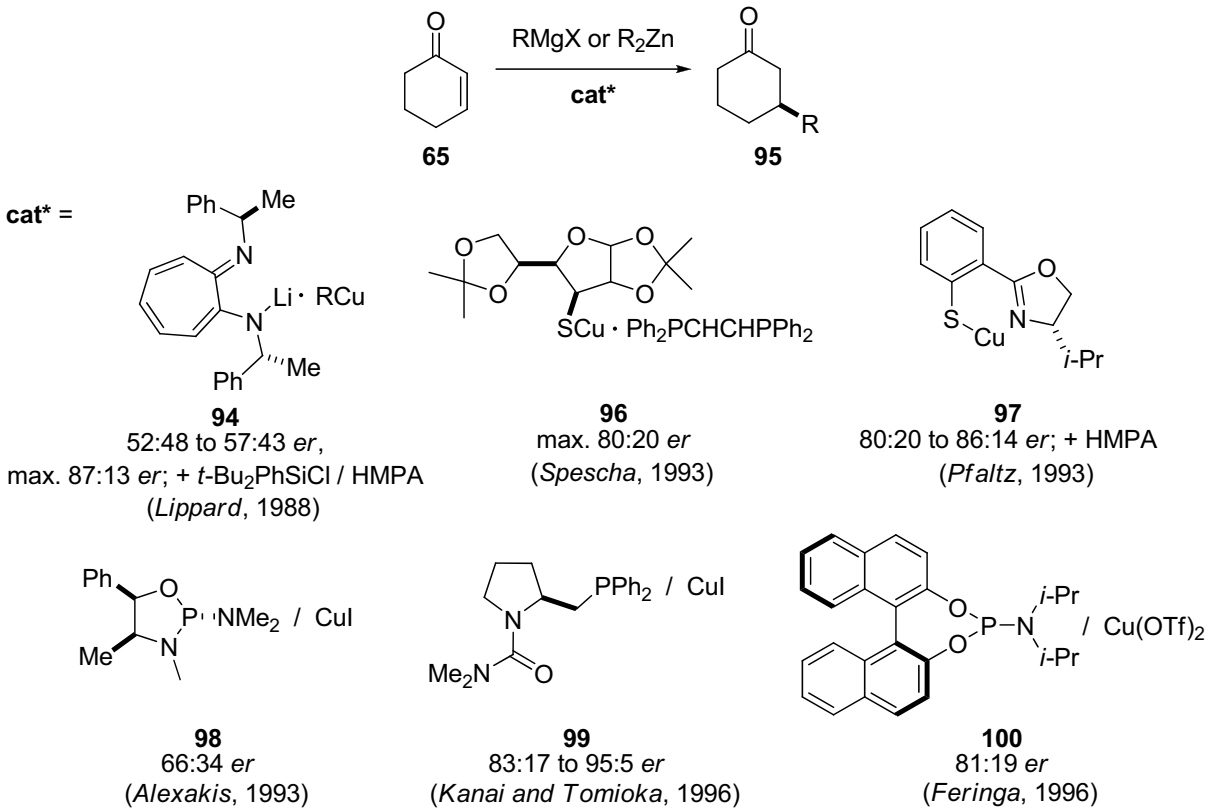
2.3.1 Asymmetric Conjugate Addition to *β*-Branched Enones

The transition metal-catalyzed asymmetric Michael addition is an efficient synthetic tool for making carbon–carbon bonds and creating a center of chirality in an organic molecule.[138] Michael additions of nucleophiles such as organolithium, Grignard, diorganozinc, or trialkylaluminium reagents to enones are catalyzed *inter alia* by copper, nickel and cobalt salts. The best results are obtained with copper(I) catalysts, especially those in which copper is bonded to a "soft", readily polarizable center (sulfur or phosphorus).

The first reaction of this type was reported by *Lippard et al.* in 1988.[139a] The authors reacted 2-cyclohexenone (**65**) with Grignard reagents in the presence of the chiral aminotroponeimine copper complex **94** as catalyst to obtain the 1,4-adducts **95** with 52:48 to 57:43 *er*.

Inspired by these results, several research groups worked on the development of new ligands for the asymmetric conjugate addition to the enone **65** (Scheme 2.35); enantioselectivities of

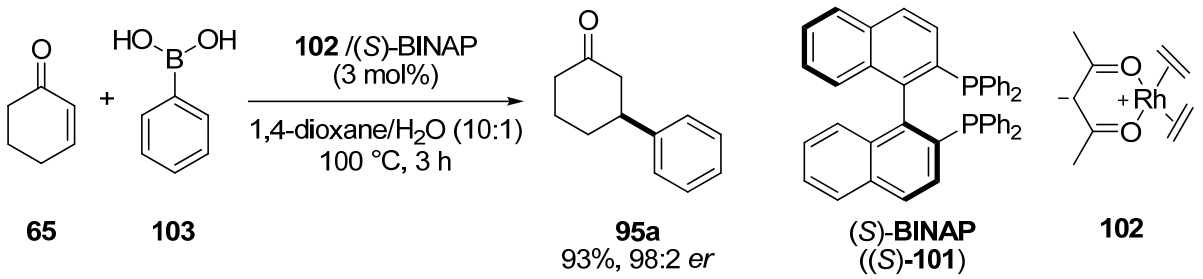
up to 95:5 *er* could be obtained. In all these cases, the regioselectivities (1,4- vs. 1,2-addition) and chemical yields were acceptable to good.[140-146]



Scheme 2.35: Early examples of copper-catalyzed enantioselective 1,4-additions to cyclic enones.[139-146] (HMPA: hexamethylphosphoric acid triamide).

Cyclic enones are normally used as substrates for copper-catalyzed enantioselective Michael addition. In some cases, however, good enantioselectivities were also attained with acyclic enones.[147] A drawback of these systems is that they are limited to (functionalized) aliphatic dialkyzinc reagents, whereby the introduction of an aryl group *via* arylzinc halides gives racemic mixtures.

In 1997, *Miyaura et al.*[148] showed that arylboronic acids can add efficiently to Michael acceptors in the presence of a rhodium(I) catalyst and water as cosolvent. With the use of a 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **101**) as chiral ligand associated with rhodium(I) **102**, the *Hayashi* and *Miyaura* groups have developed an asymmetric version of the Michael addition of organoboron compounds (Scheme 2.36).[149,150,151] One drawback of this process is the use of a large excess of boronic acids (generally five equivalents) to achieve high yields due to an undesirable side reaction, the reduction of the organoboron reagent.[149, 152 , 153] Moreover, the preparation and purification of some boronic acids is tremendously difficult[154] and many of them are air and moisture sensitive.



Scheme 2.36: Rhodium(I)-catalyzed asymmetric 1,4-addition of phenylboronic acid to cyclohexenone.[149-151]

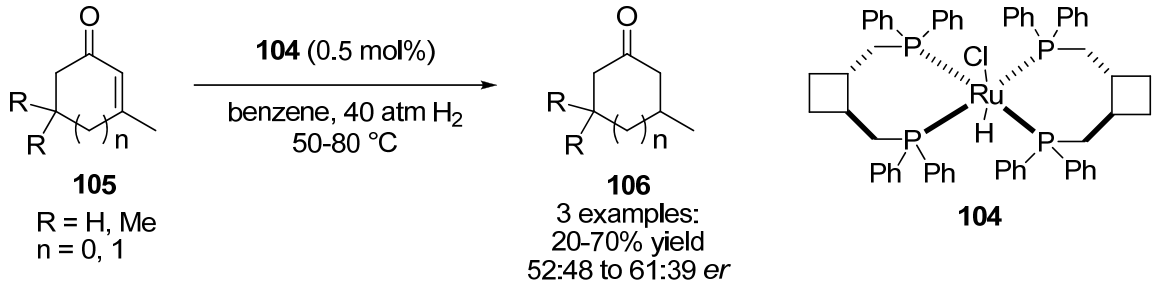
2.3.2 Asymmetric Conjugate Reduction of *β,β*-Disubstituted Enones

Most synthetic routes to chiral *β*-substituted cyclic ketones are based on the asymmetric conjugate addition of nucleophiles to cyclic *α,β*-unsaturated ketones. Excellent catalysts have been discovered for the conjugate addition to 6- or 7-membered ring. However catalytic asymmetric conjugate addition to cyclopentenone typically yields products with lower enantioselectivities.[155]An alternative and complementary approach can be envisaged for the synthesis of chiral *β*-substituted ketones: the asymmetric conjugate reduction of *β*-branched enones.

2.3.2.1 Asymmetric Hydrogenation

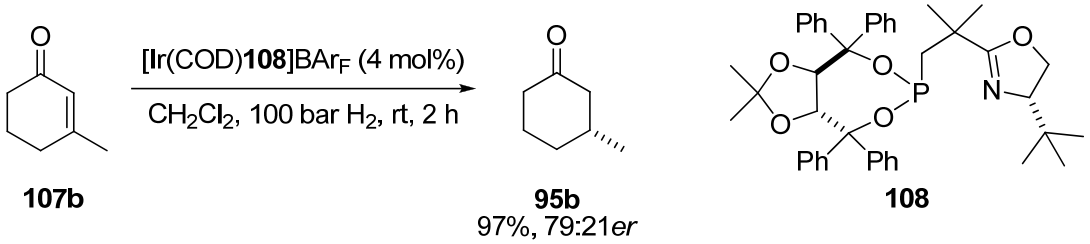
Asymmetric hydrogenation in the presence of chiral rhodium or ruthenium phosphines has been developed into an impressive number of alkene reduction methodologies during the last 20 years.[156,157] Despite the tremendous progress in this area, high stereoselectivities nearly always depend on the olefin proximity to highly polar functional groups such as amides, acids and alcohols. Attempts to generalize these procedures to alkenes conjugated with less polar groups such as aldehydes, ketones, esters or nitro groups have been much less successful.

An early example of hydrogenations of *α,β*-unsaturated ketones by molecular hydrogen has been reported by *Simonneaux et a.*[158] In the presence of chiral ruthenium complexes **104** cyclic enones **105** could be reduced under high pressure to the corresponding saturated ketones **106** with low to moderate yields (Scheme 2.37).



Scheme 2.37: *Simonneaux*'s asymmetric hydrogenation of cyclohexenone derivatives.[158]

In 2005, *Pfaltz et al*. reported an efficient iridium-catalyzed hydrogenation of 3-methyl-2-cyclohexenone (**107b**) in the presence of the phosphine ligand **108** (Scheme 2.38).[159,160] Under these reaction conditions 3-methyl-2-cyclohexanone (**95b**) was obtained almost quantitatively but with moderate enantioselectivity.



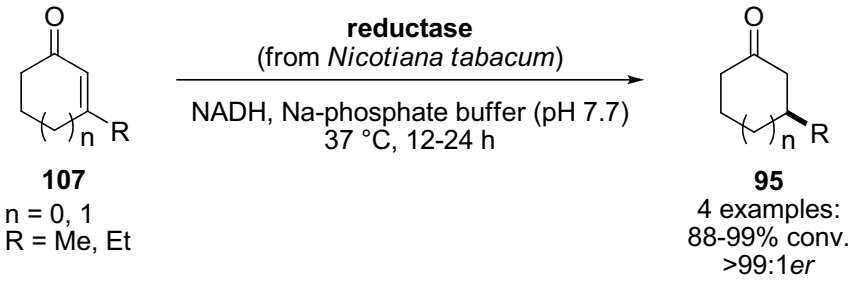
Scheme 2.38: Enantioselective iridium-catalyzed hydrogenation of 3-methyl-2-cyclohexanone.[159]

The lack of generally applicable hydrogenation catalysts for "difficult" alkenes (like *α,β*-unsaturated ketones), the need to prepare complex ligands and the requirement for high pressures have encouraged the development of bio- and metal-catalyzed indirect hydrogenations of enones (transfer hydrogenation, hydrosilylation).

2.3.2.2 Asymmetric Transfer Hydrogenation

Asymmetric transfer hydrogenations of *β*-substituted *α,β*-unsaturated cyclic ketones have been developed in the presence of a biocatalyst and NADH (**85a**) as cofactor.[161,162]

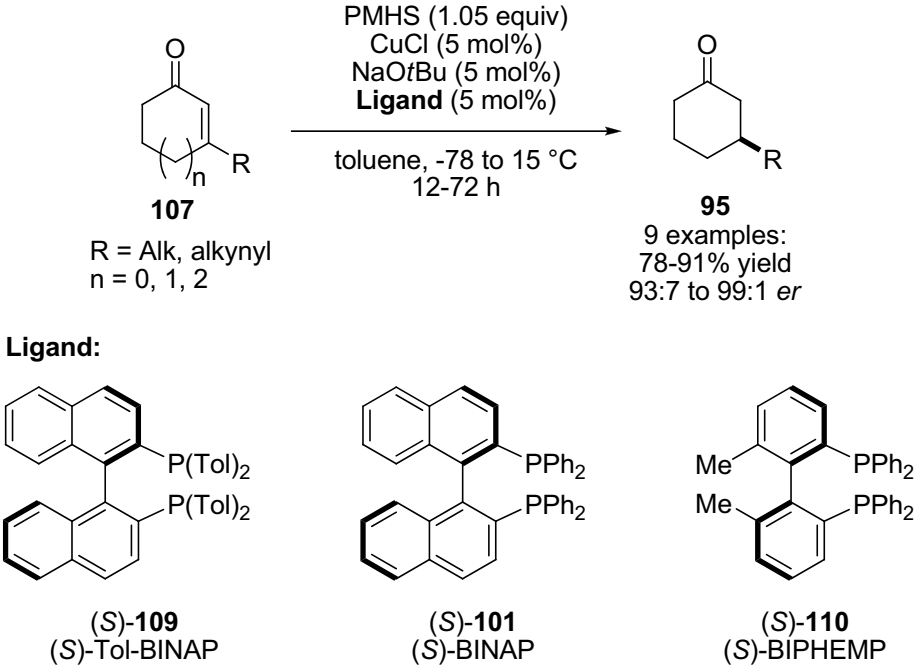
Shimoda et al. found that reductase isolated from *Nicotiana tabacum* is an efficient and highly enantioselective biocatalyst for the conjugate reduction of some cyclic enones (5- or 6-membered) **107** in the presence of NADH (Scheme 2.39).[161]



Scheme 2.39: Biocatalyzed enantioselective conjugate reduction of α,β-unsaturated cyclic ketones.[161]

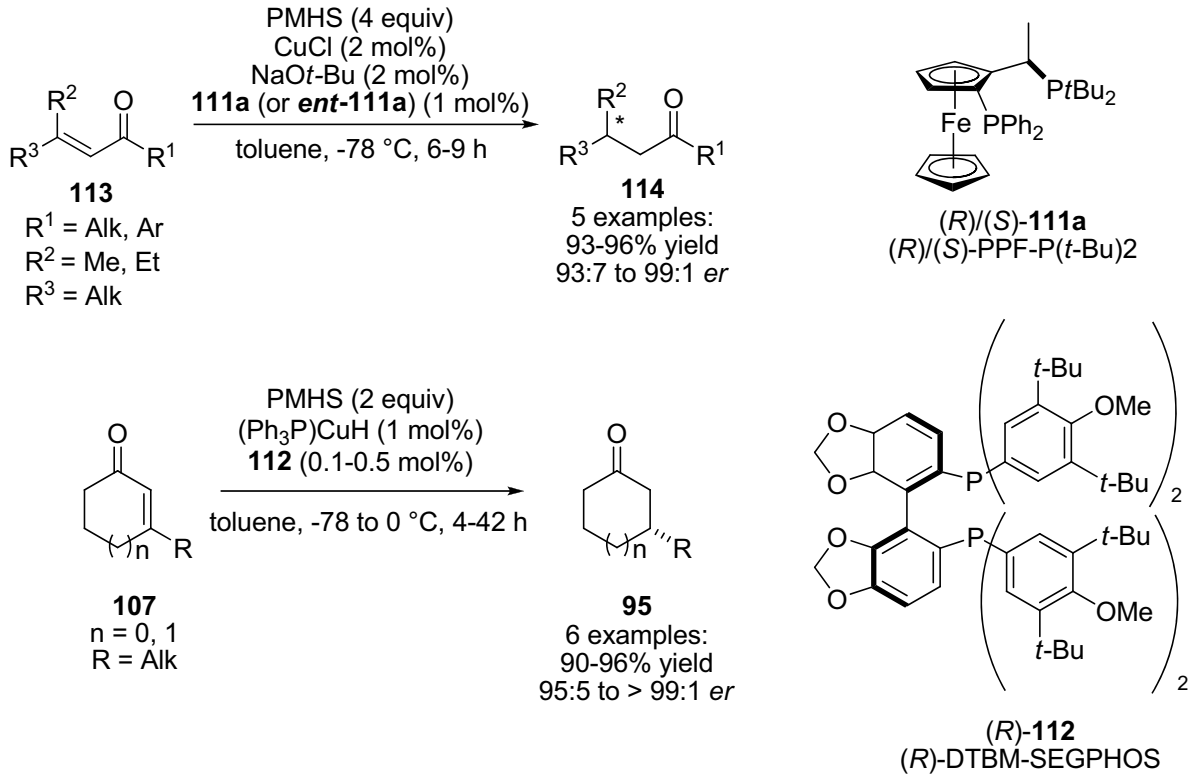
2.3.2.3 Asymmetric Hydrosilylation

The use of silanes such as polymethylhydrogensilane (PMHS), a safe and inexpensive polymer, as stoichiometric reductant is a well established process for conjugate reduction (hydrosilylation followed by hydrolytic work-up) of olefins. The use of this process for the asymmetric conjugate reduction of α,β-unsaturated cyclic ketones was reported in 2000 by *Buchwald et a.*[163] The combination of catalytic amounts of copper chloride, sodium *tert*-butoxide and a chiral bisphosphine ((*S*)-**109**, (*S*)-**101** and (*S*)-**110** for 5-, 6- and 7-membered rings, respectively) generated a highly enantioselective catalyst for the asymmetric conjugate reduction of cyclic enones (Scheme 2.40).



Scheme 2.40: Copper-catalyzed asymmetric conjugate reduction of α,β-unsaturated cyclic ketones.[163]

Around the same time, *Lipshutz et al.* also reported that copper catalysts bearing chiral bisphosphine **111a** or **112** were effective toward asymmetric conjugate reduction of cycloalkenones or acyclic enones, respectively, in the presence of PMHS (Scheme 2.41).[164] Recently, an efficient asymmetric rhodium-catalyzed conjugate reduction of *β*,*β*-disubstituted *α*,*β*-unsaturated ketones with alkoxylhydrosilanes has been described.[165]

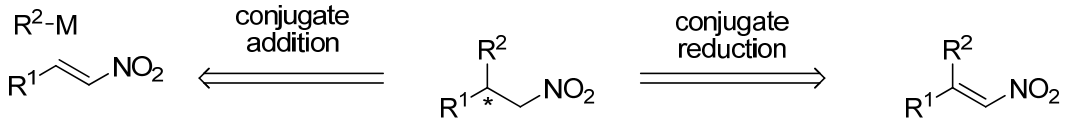


Scheme 2.41: *Lipshutz*'s copper-catalyzed asymmetric reductions of enones.[164]

2.4 Enantioselective Synthesis of β,β-Disubstituted Nitroalkanes and β-Nitroesters

Nitroalkanes are important intermediates in organic synthesis, mainly due to the ease of their conversion into the corresponding amines, aldehydes, carboxylic acids, or denitrated compounds.[166, 167] For this reason, optically pure nitro compounds, and particularly β-nitroesters that are precursors of valuable β²-amino acids (see Chapter 2.4.3), are valuable chiral building blocks for asymmetric synthesis.

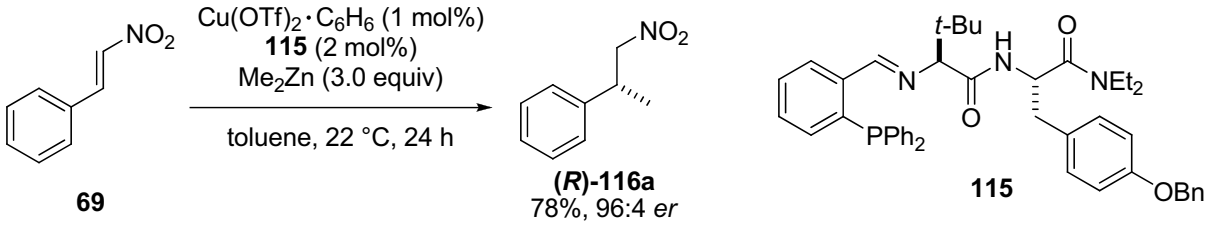
Similar to the enantiomerically pure saturated ketones (chapter 2.3), chiral β,β-disubstituted nitroalkanes can be obtained by asymmetric conjugated addition to nitroalkenes or enantioselective conjugate reduction of β,β-disubstituted nitroalkenes using chiral transition metal catalysts or biocatalyst (Scheme 2.42).



Scheme 2.42: Catalytic processes for the synthesis of enantiomerically pure β,β-disubstituted nitroalkanes.

2.4.1 Asymmetric Conjugate Addition to β-Branched Nitroolefins

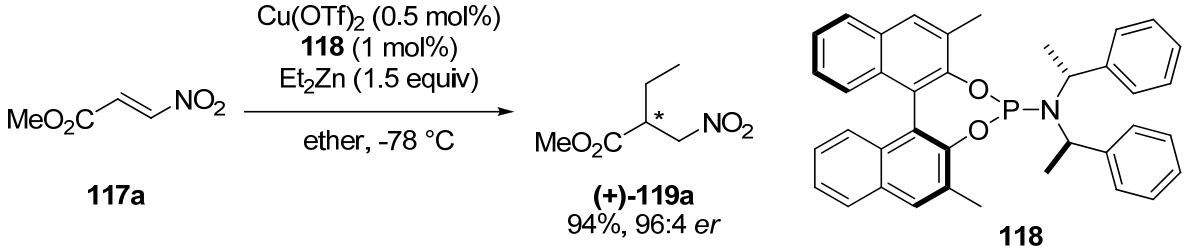
Seebach et al. reported that the enantioselective addition of primary dialkylzinc reagents to aryl substituted nitroolefins could be achieved using an excess of titanium TADDOLates.[168] The first catalytic ligand accelerated addition of diethylzinc to nitrostyrene was described by *Alexakis et al.*[169] In the last years there has been considerable effort toward catalytic asymmetric conjugate addition of organozinc compounds to nitroolefins. More recently, *Hoveyda et al.* reported an efficient and highly enantioselective copper-catalyzed asymmetric conjugated addition of alkylzinc reagents to acyclic nitroalkenes **69** in the presence of chiral dipeptide phosphine ligand **115** (Scheme 2.43).[170,171]



69 **(*R*)-116a** 78%, 96:4 *er* **115**

Scheme 2.43: *Hoveyda*'s asymmetric copper-catalyzed conjugate addition to nitrostyrene.[170]

Stereoselective conjugate additions to 3-nitroacrylates **117**, which are valuable substrates for the synthesis of β^2-amino acids, have also been investigated.[172] *Sewald et al.* reported a copper-catalyzed process in the presence of phosphine ligand **118** yielding the corresponding nitroesters **119** with high enantioselectivities (Scheme 2.44).[172b]

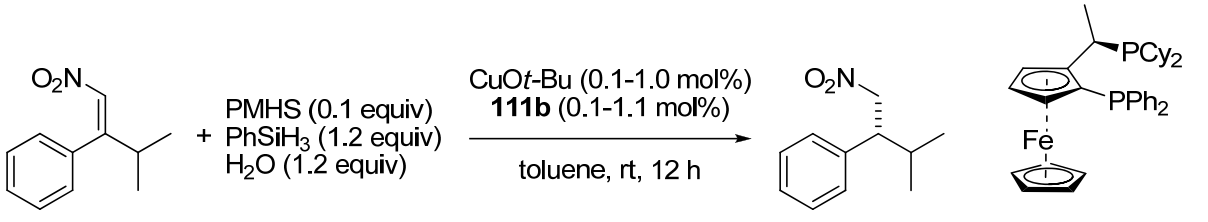


117a **(+)-119a** 94%, 96:4 *er* **118**

Scheme 2.44: Enantioselective copper-catalyzed conjugate addition to methyl 3-nitroacrylate.[172b]

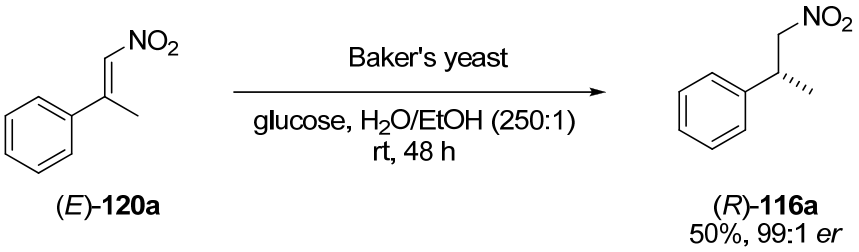
2.4.2 Asymmetric Conjugate Reduction of *β,β*-Disubstituted Nitroolefins

Catalytic enantioselective conjugate reduction of *β,β*-disubstituted nitroolefins **120** is another approach for the synthesis of chiral *β*-branched nitroalkanes **116**. At the beginning of this Ph.D. thesis only one biocatalytic and one transition-metal-catalyzed variant had been reported. *Carreira et al.* developed an elegant chiral copper complex-catalyzed version using a silane as stoichiometric reductant (Scheme 2.45)[173] and *Ohto et al.* used fermenting bakers' yeast in the presence of glucose (Scheme 2.46).[174,175]



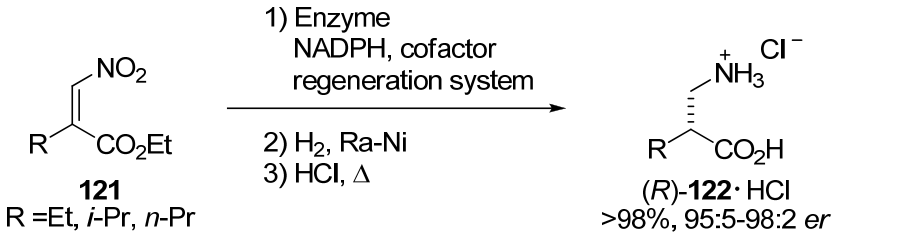
(*Z*)-**120b** (*R*)-**116b** 83%, 97:3 *er* **111b** (*S,R*)-JOSIPHOS

Scheme 2.45: Enantioselective copper(I)-catalyzed conjugate reduction of *β,β*-disubstituted nitroalkenes.[173]



Scheme 2.46: Enantioselective biocatalyzed conjugate reduction of β,β-disubstituted nitroalkenes.[174]

Asymmetric bioreductions of some aliphatic β-nitroacrylates **121**, as a route to chiral β^2-amino acids **122**, have been reported during the course of this Ph.D. thesis (Scheme 2.47).[175a] This process, however, was not applicable to aromatic substrates which were not soluble enough in the aqueous media needed for optimal enzymatic activity.



Enzyme = *Saccharomyces carlsbergensis* old yellow enzyme
Regeneration system: glucose-6-phosphate/baker's yeast glucose-6-phosphate dehydrogenase

Scheme 2.47: Enantioselective bioreduction of β-nitroacrylates as a route to chiral β^2-amino acids.[175a]

2.4.3 β-Nitroacrylates as Precursors of β^2-Amino Acids

β-Nitroacrylates are interesting starting materials for the preparation of β^2-amino acids. At this point it is appropriate to say a few words about β^2-amino acids, in order to demonstrate the utility of these compounds and thus the importance of developing versatile, practical, and efficient enantioselective processes to synthesize them.

α-Substituted-β-amino acids (β^2-amino acids), like their β-substituted-β-amino acid counterparts (β^3-amino acids, Figure 2.8),[176] are of immense chemical and biological interest.[177]

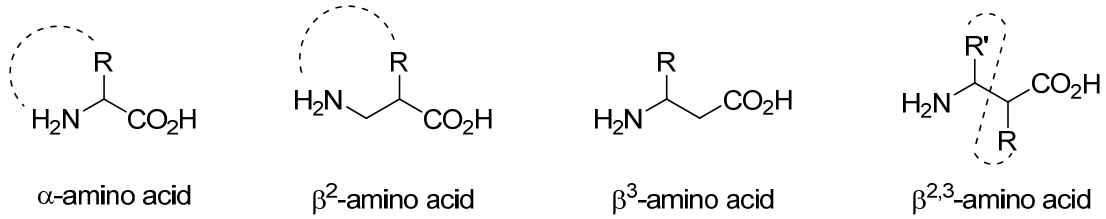


Figure 2.8: General structure of *α*- and *β*-amino acids.

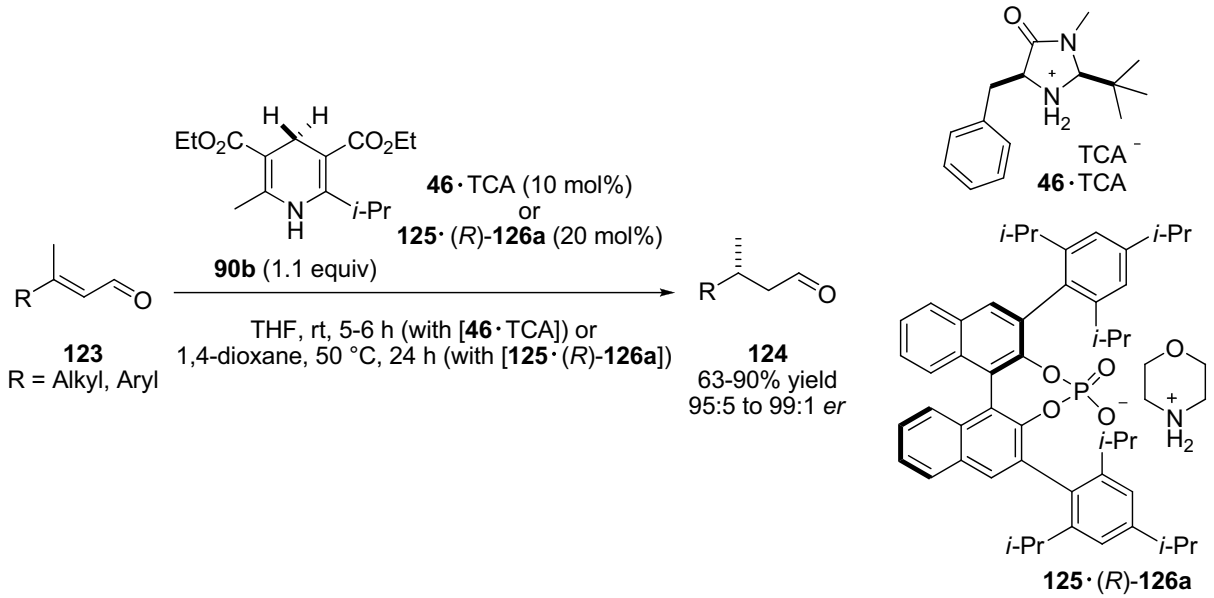
They occur naturally within pseudopeptides [178] and highly potent biological effects are observed with both naturally occurring and synthetic derivatives.[179] They have also been shown to display interesting structural properties as constituents of *β*-peptides[180] which are stable to cleavage by peptidase and to metabolic transformations, and can mimic *α*-peptides in peptide–protein and protein–protein interactions.[176] Despite the importance of *β*-amino acids in biology and peptide chemistry, the synthesis of *β*²-amino acids has received little attention when compared to their *β*³-amino acid counterparts.[177,181] To date the stereoselective Mannich reaction[182] and the asymmetric alkylation of chiral *β*-alanine derivatives[183,184] have received most attention as synthetic routes to *β*²-amino acids. Other routes based upon conjugate addition, [185 , 186] Curtius rearrangement, [187] catalytic C–H insertion, [188] dynamic kinetic resolution,[189] enantioselective hydrogenation,[190] and catalytic asymmetric addition of cyanide to *α*,*β*-unsaturated imides[191] among others[192] have also proved successful.

3 Background and Objectives of this Ph.D. Work

Hydrogenation is among the most important catalytic reactions for the synthesis of enantiomerically pure chemicals and pharmaceuticals but is also a biological process all living organisms use. Remarkably, both in nature, as well as in chemical synthesis, metals have generally been required to bring about this reaction. In the synthesis of pharmaceuticals however, this can be a significant problem because the removal of potentially toxic metal-impurities from the reaction product is often difficult to achieve. As an attractive alternative to metal catalysis, organocatalysis has recently emerged as a powerful tool of organic synthesis.

The goal of this Ph.D.-work was to develop an organocatalytic approach to the synthesis of enantiomerically pure saturated ketones and also for the preparation of chiral β,β-disubstituted nitroalkanes and β-nitroesters, which can be used to access optically pure primary amines and β²-amino acids, respectively.

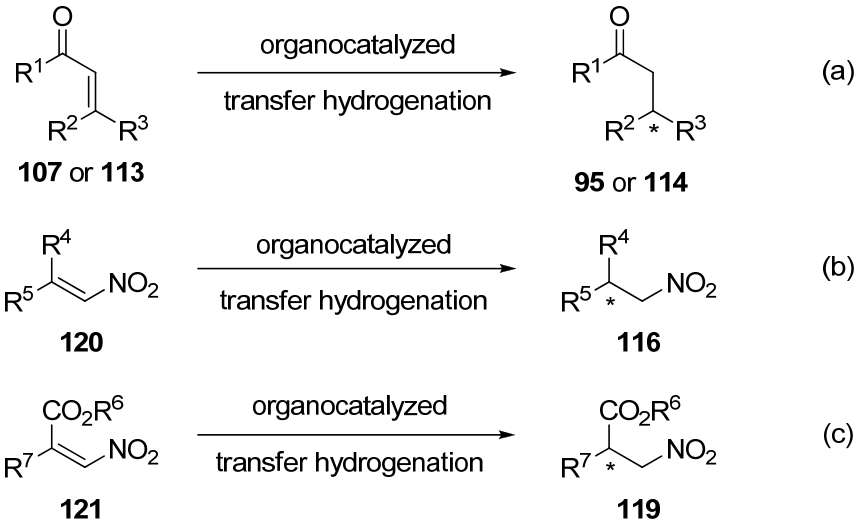
Recent studies undertaken in our laboratory have led to the development of highly enantioselective organocatalytic biomimetic transfer hydrogenations of α,β-unsaturated aldehydes **123**, wherein enzymes and expensive NADH cofactors generally used in biochemical reductions are replaced by low molecular weight amine catalysts (**46** or **125**) and Hantzsch esters **90b** as the hydrogen source (Scheme 3.1).[120b,c]



Scheme 3.1: Enantioselective biomimetic metal-free transfer hydrogenations of α,β-unsaturated aldehydes.[120b,c]

The reaction proceeds *via* iminium catalysis (see chapter 2.1.2) and was first catalyzed by the trichloroacetate salt of *MacMillan* imidazolidinium **46** giving the saturated aldehydes **124** in high yield and with excellent enantioselectivities.[120b] Intrigued by the observation of a strong counteranion effect on the yield and enantioselectivity of the reaction, and inspired by the recent introduction of chiral phosphates as asymmetric Brønsted acid catalysts (see chapter 2.1.1.4), a new catalytic salt was subsequently developed in our laboratory that consists of an achiral ammonium cation and a chiral phosphate anion (**125** and (*R*)-**126a**). This ion pair effectively catalyzed the transfer hydrogenation, constituting the beginning of a new highly enantioselective catalysis strategy: asymmetric counteranion-directed catalysis (ACDC).[120c,193]

Taking advantage of the knowledge gained in our laboratory in the field of metal-free catalytic asymmetric transfer hydrogenation of unsaturated aldehydes in the presence of Hantzsch esters, we intended to develop a practical and highly enantioselective organocatalytic process for the conjugate reduction of enones (Scheme 3.2a) and nitroolefins (Scheme 3.2b-c). The success of such investigations would not only offer a new approach to valuable enantioenriched molecules such as β^2-amino acids **122** (Scheme 3.2c) but also a complementary one to the metal- and biocatalyzed variants that have already been reported in the literature (see chapters 2.3 and 2.4).



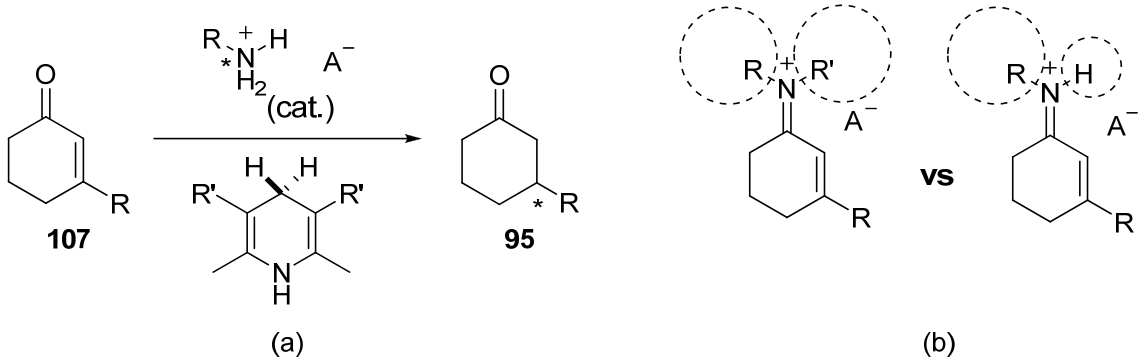
Scheme 3.2: Planned organocatalytic transfer hydrogenations of β,β-disubstituted enones (a), nitroalkenes (b) and β-nitroacrylates (c).

Our strategy for the transfer hydrogenation of enones **107** and **113** (Scheme 3.2a), nitroalkenes **120** (Scheme 3.2b) and β-nitroacrylates **121** (Scheme 3.2c) is explained in Chapters 3.1, 3.2 and 3.3, respectively. The results of these investigations are reported in Chapters 4.3, 4.4 and 4.5, respectively.

3.1 Enantioselective Transfer Hydrogenation of *α,β*-Unsaturated Ketones

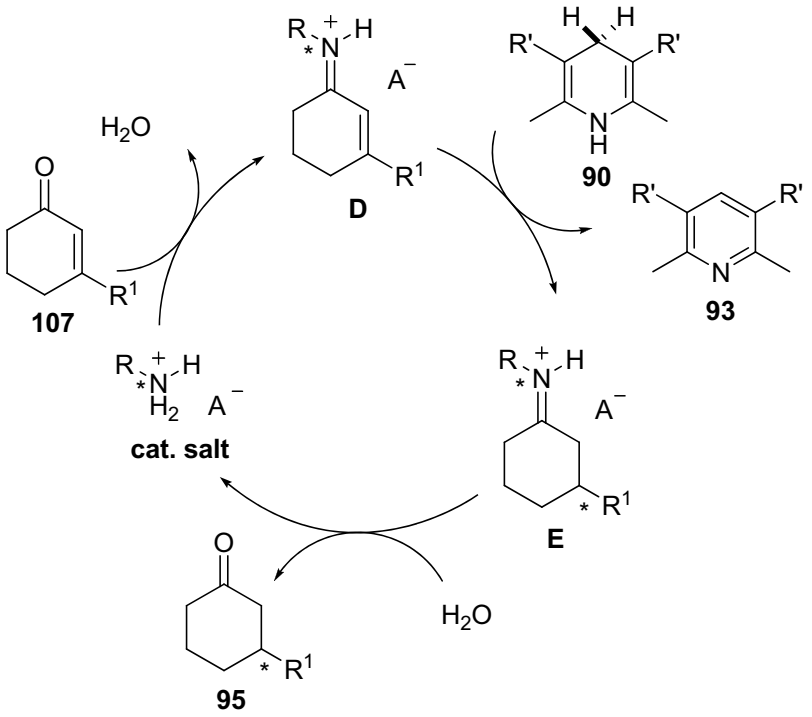
Since stereogenically complex carbocycles are among the most widely found synthons in natural products and medicinal agents, their preparation in enantiomerically pure form is of interest. We intended to develop an organocatalytic enantioselective conjugate reduction of enones (see Scheme 3.2a), a reaction that was previously only possible in the presence of metal catalysts (mostly air and moisture sensitive copper catalysts, see Chapter 2.3.2.3) or, for some cyclic enones, in the presence of biocatalysts (see Chapter 2.3.2.2).

Inspired by the asymmetric catalytic transfer hydrogenation of *α,β*-unsaturated aldehydes (see Scheme 3.1), we reasoned that it should be possible to develop an enantioselective amine-catalyzed transfer hydrogenation of enones **107** in the presence of the commercially available Hantzsch ester **90** (Scheme 3.3a). We hypothesized that due to the more demanding steric requirements of *α,β*-unsaturated ketones in comparison to *α,β*-unsaturated aldehydes **123**, chiral primary amine catalysts, which are less sterically hindered than secondary ones might be more suitable for the activation of enones **107** (Scheme 3.3b).



Scheme 3.3: (a) Envisaged enantioselective iminium-catalyzed transfer hydrogenations of *α,β*-unsaturated ketones and (b) comparison of the steric requirement of an iminium ion formed between an ketone and a secondary amine versus a primary amine.

Mechanistically, the reaction was envisaged to proceed *via* a special form of iminium catalysis (Scheme 3.4). Accordingly, after an initial reversible iminium ion formation (**D**), which effectively lowers the LUMO energy of the substrate, follows conjugate hydride transfer from dihydropyridine **90**. This step generates pyridine **93** along with iminium ion **E**. Hydrolysis then releases the saturated ketone **95** and regenerates the catalyst.



Scheme 3.4: Hypothetical catalytic cycle for the primary amine-catalyzed transfer hydrogenation of *β*-substituted cyclohexenone in the presence of Hantzsch ester.

Based on these considerations, our goal was to develop an appropriate catalyst, which would be able to catalyze the desired conjugate reduction in high yields and with high enantioselectivities. To reach these objectives, four points had to be taken into account in the design of a broadly useful iminium-activation catalyst: (1) the catalyst should undergo efficient and reversible iminium ion formation; (2) high level of iminium geometry control and (3) selective π-facial discrimination of the iminium ion should be achieved in order to control the enantioselectivity of the reaction, and (4) the ease of catalyst preparation and implementation would be essential for the widespread adoption of the catalytic process.

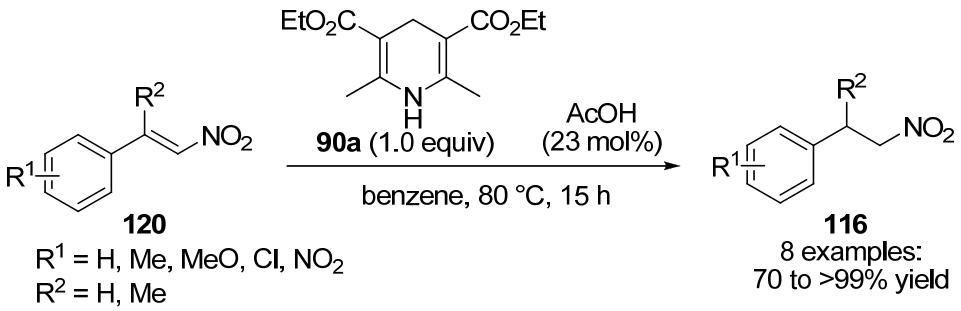
3.2 Enantioselective Transfer Hydrogenation of *β*,*β*-Disubstituted Nitroolefins

Catalytic enantioselective conjugate reductions of *β*,*β*-disubstituted nitroolefins are useful for the synthesis of chiral *β*-branched nitroalkanes.[194] The approach is particularly attractive because nitroolefins are relatively easy to synthesize either by condensing ketones with nitroalkanes or *via* nitration of olefins. Furthermore, the resulting nitroalkanes are valuable intermediates e.g. for further reduction to chiral amines.

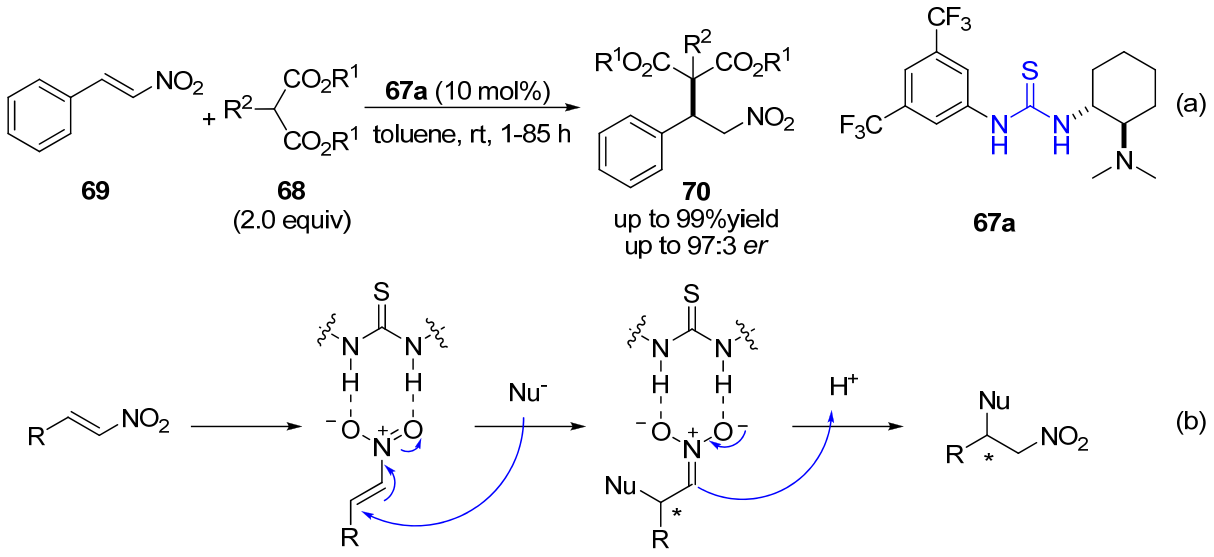
With these considerations in mind and since only one biocatalytic[174] and one transition metal-catalyzed[173] variant had previously been reported (see chapter 2.4.2), we intented to develop a metal-free transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes **120** to corresponding nitroalkanes **116** (see Scheme 3.2b).

It is worth to note that *Carreira*'s copper-catalyzed variant is highly effective and enantioselective. However, this approach is laborious.[173c] This consideration strengthened the idea that the development of a more practical and also metal-free variant of this conjugate reduction would be of great interest.

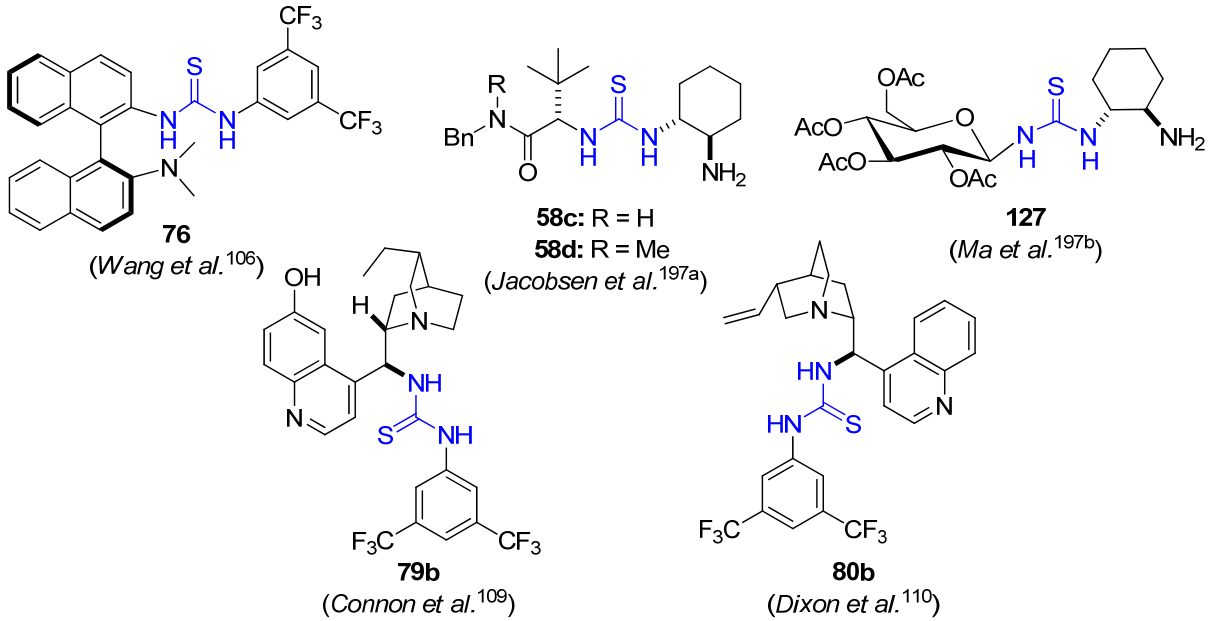
Acetic acid is a known catalyst for the Hantzsch ester-mediated conjugate reductions of nitroolefins (Scheme 3.5),[129c] and chiral thiourea derivatives have recently been used to activate nitroolefins (Scheme 3.6[102,195,196] and Scheme 3.7[106,109,110,197]). We thus reasoned that hydrogen bonding catalysts would be particularly promising for the development of an organocatalytic stereoselective transfer hydrogenation of nitroolefins **120** in the presence of Hantzsch ester **90** as the hydrogen source (Scheme 3.8a).



Scheme 3.5: Acetic acid-catalyzed transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes in the presence of Hantzsch ester.[129c]

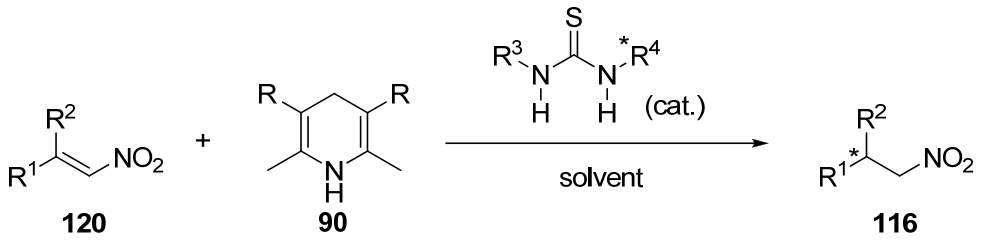


Scheme 3.6: *Takemoto*'s Michael addition of 1,3-dicarbonyl compounds to nitroolefins catalyzed by a bifunctional thiourea (a) and proposed mechanism for the nitroolefin activation (b).[102]

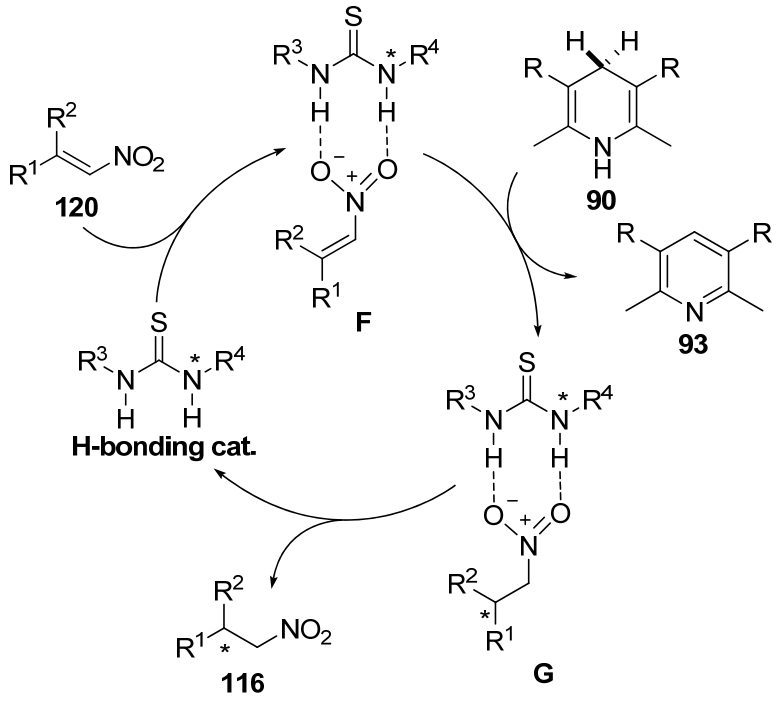


Scheme 3.7: Examples of thiourea catalysts used for the Michael addition of 1,3-dicarbonyl compounds to nitroolefins.

According to the model proposed by *Takemoto et al.*[102] (Scheme 3.6b), we hypothesized that it would be possible to activate the nitroolefin **120** *via* hydrogen bonding interactions in the presence of a thiourea catalyst, allowing a hydride transfer from the Hantzsch ester **90** to occur (Scheme 3.8). After hydride and proton transfer from the hydrogen source the enantiomerically pure nitroalkane **116** would be released, allowing the thiourea catalyst to participate in further catalytic cycles (Scheme 3.9).



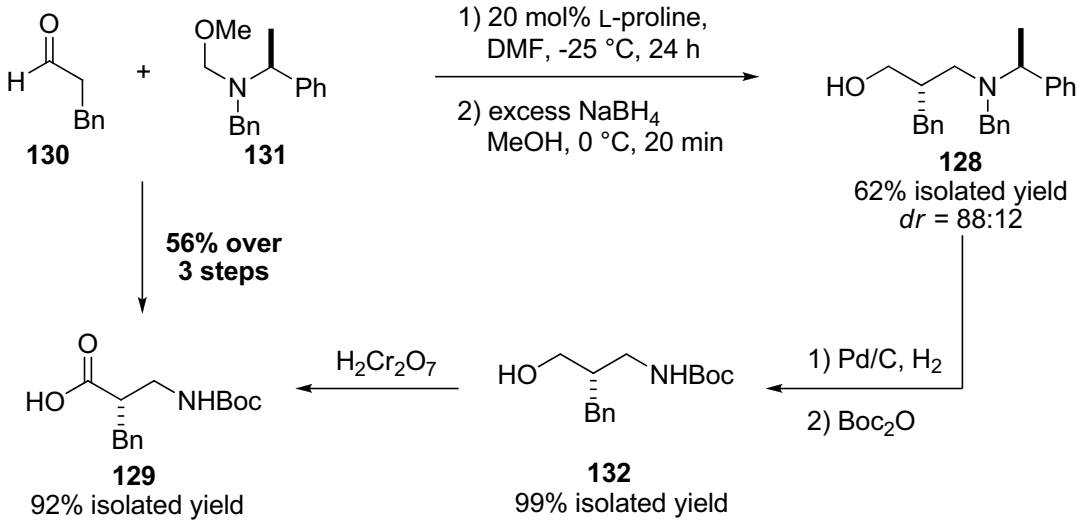
Scheme 3.8: Planned enantioselective hydrogen-bonding-catalyzed transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes.



Scheme 3.9: Hypothetical catalytic cycle for the hydrogen bonding-catalyzed transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes.

3.3 Enantioselective Transfer Hydrogenation of *β*-Nitroacrylates: A Route to *β*²-Amino Acids

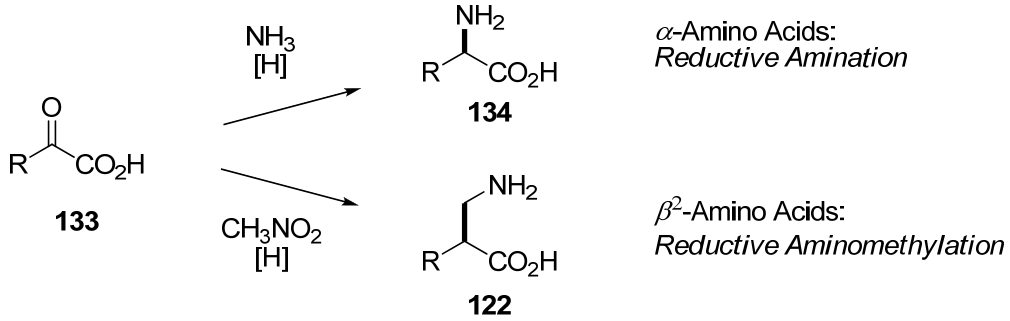
Pioneered by *Seebach et al.* and *Gellmann et al*., *β*-peptides recently emerged as a new class of peptidomimetics with potentially widespread biological and medicinal applications. [198,199] As a consequence, synthesis of *β*-amino acids has attracted considerable attention.[177,200] While *β*³-amino acids, which are branched in the *β*-position, are now commercially available with most natural substituents, the analogous *β*²-amino acids, branched in the *α*-position, although particularly promising, are more difficult to obtain (see chapter 2.5).[176] During the course of this Ph.D. project, *Gellmann et al*. reported an elegant organocatalytic Mannich reaction that furnishes *β*-amino alcohols **128**, after reduction of the generated *β*-amino aldehyde upon treatment with sodium borohydride, in high yields and enantioselectivities.[182b, 201] The products of this reaction can be readily converted into *β*²-amino acids **129** (Scheme 3.10).



Scheme 3.10: *Gellman*'s synthesis of pure β^2-amino acid *via* proline-catalyzed diastereoselective aminomethylation of aldehydes.[182b]

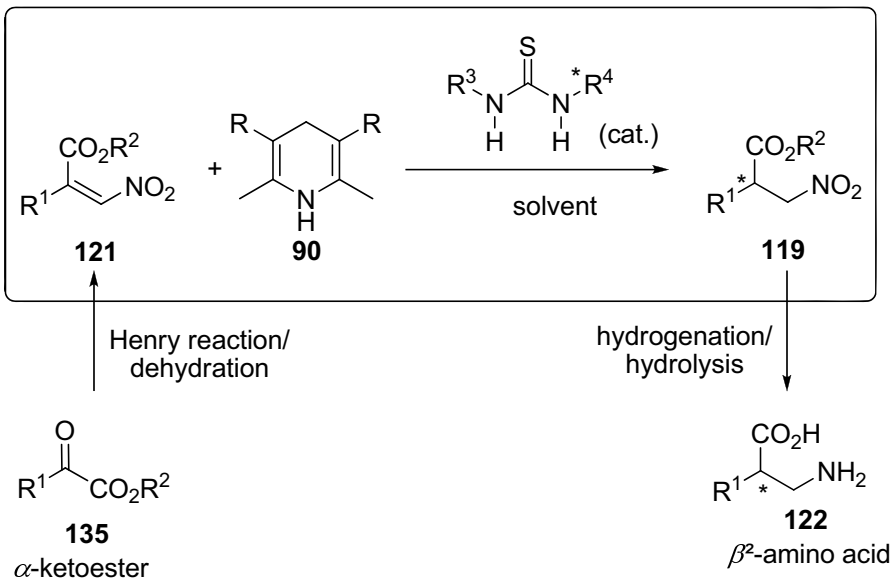
Because of the growing importance of β^2-amino acids, the development of an alternative approach that relies on a catalytic asymmetric Hantzsch ester-mediated conjugate reduction of readily available β-nitroacrylates **121** to the corresponding β-nitroesters **119** (see Scheme 3.2c),[202] which are easily converted into β^2-amino acids **122** *via* hydrogenation is of great interest.[203,204]

This approach to β^2-amino acids took its inspiration from Nature. We envisioned that in analogy to an enzymatic reductive amination of α-ketoacids **133** with ammonia,[205] a hypothetic reductive aminomethylation with nitromethane should lead to the corresponding β^2-amino acids **122** (Scheme 3.11).



Scheme 3.11: Envisioned synthesis of β^2-amino acids *via* reductive aminomethylation in analogy to Nature's preparation of α-amino acids through reductive amination.[205]

Like for the conjugate reduction of nitroolefins **120**, we hypothesized that it would be possible to activate β-nitroacrylates **121**, which are easily accessible from α-ketoesters **135**, with hydrogen bonding catalysts such as a thiourea catalyst (Scheme 3.12).

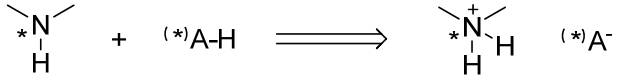


Scheme 3.12: Planned enantioselective hydrogen bonding-catalyzed transfer hydrogenation of *β*-nitroacrylates as a key step for the synthesis of chiral *β*²-amino acids.

4 Results and Discussions

4.1 Synthesis of Ammonium Salt Organocatalysts

In this chapter the syntheses of the different chiral amines as well as the chiral Brønsted acids used to form the ammonium salts (Scheme 4.1) screened as catalysts for the transfer hydrogenation of enones **107** and **113** (see Chapter 4.3) are reported.



Scheme 4.1: Formation of the catalytic salts consisting of a chiral ammonium ion and a (chiral) counteranion.

4.1.1 Synthesis of Amino Acid Derivatives

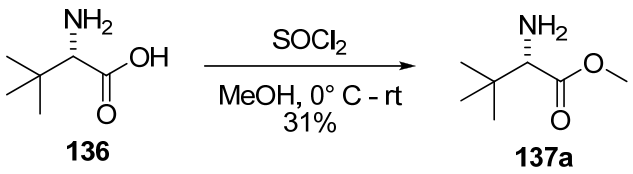
4.1.1.1 Synthesis of Amino Esters

Some amino esters were prepared from their corresponding amino acids whereas others were directly obtained after basification and extraction of their corresponding commercially available amino ester hydrochloride salts.

As only few milligrams of each primary amine were required for a first evaluation of their catalytic activity in the transfer hydrogenation of 3-methylcyclohex-2-enone (**107b**), most of the processes used to synthesize them (and that are presented in this chapter) have not been optimized.

Synthesis of amino esters from their corresponding amino acids

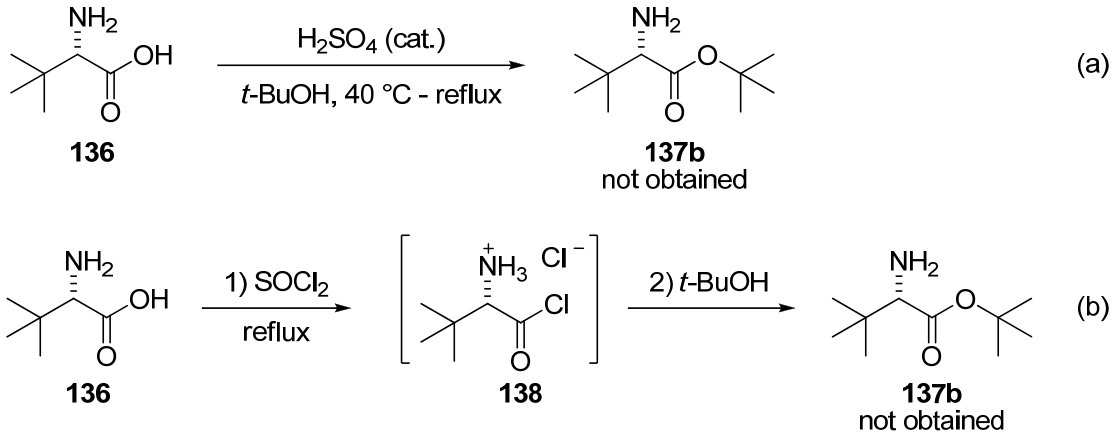
Esterification of commercially available L-*tert*-leucine (**136**, provided by Degussa) in the presence of thionyl chloride[206] and methanol afforded the corresponding L-*tert*-leucine methyl ester (**137a**) in 31% yield (Scheme 4.2).



Scheme 4.2: Synthesis of L-*tert*-leucine methyl ester (**137a**) from L-*tert*-leucine (**136**).[206]

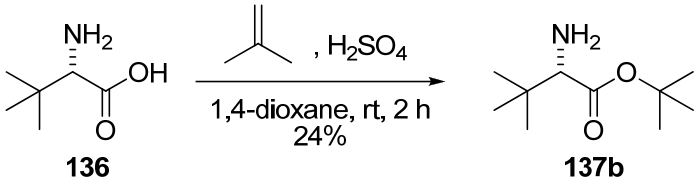
To be able to analyze the effect of the ester group bulkiness on the activity and enantioselectivity of the catalyst, the corresponding *tert*-butyl ester was also prepared (**137b**). To this purpose esterification of amino acid **136** in the presence of *tert*-butyl alcohol and a catalytic amount of concentrated sulfuric acid[207] was first tried (Scheme 4.3a). This reaction failed, probably (partially) due to the poor solubility of L-*tert*-leucine (**136**) in *tert*-butyl alcohol leading to the formation of a highly viscous mixture under reflux conditions, which could not be stirred anymore.

Another synthetic pathway was then followed, starting with the preparation of L-*tert*-leucine chloride (**138**) from L-*tert*-leucine (**136**) and thionyl chloride,[206] followed by the reaction of **138** with *tert*-butyl alcohol (Scheme 4.3b). This process did not lead to the formation of the desired amino ester either.



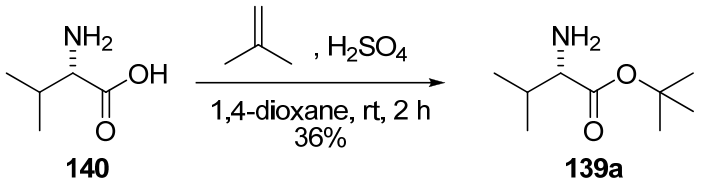
Scheme 4.3: Initial attempts toward the esterification of L-*tert*-leucine (**136**) to L-*tert*-leucine *tert*-butyl ester (**137b**).

By following *Roeske*'s methodology[208] and reacting amino acid **136** with isobutene in the presence of concentrated sulfuric acid, L-*tert*-leucine *tert*-butyl ester (**137b**) was formed in 24% yield (Scheme 4.4).



Scheme 4.4: Synthesis of L-*tert*-leucine *tert*-butyl ester (**137b**) from L-*tert*-leucine (**136**).[208]

Using the same procedure L-valine *tert*-butyl ester (**139a**) was easily prepared from commercially available L-valine (**140**) in 36% yield (Scheme 4.5).



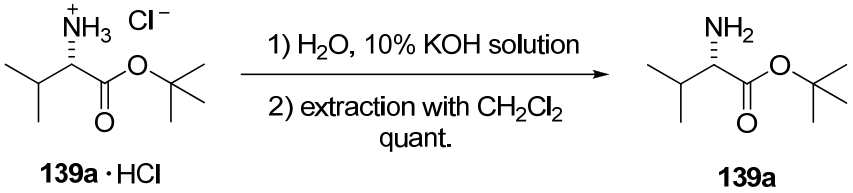
140 **139a**

Scheme 4.5: Synthesis of free L-valine *tert*-butyl ester (**139a**) from L-valine (**140**).

Preparation of free amino esters from their corresponding hydrochloride salt

Some amino esters were purchased from commercial suppliers as hydrochloric salts. The free amino esters were then easily obtained by dissolving the corresponding salt in water and adding a potassium hydroxide solution until a basic pH was reached. By extraction with dichloromethane the free amino esters were released quantitatively. However, in the case of very volatile amino esters some of the product was lost while removing the solvent under reduced pressure.

Using this extraction process the preparation of L-valine *tert*-butyl ester (**139a**) could be achieved in quantitative yield (Scheme 4.6).



139a·HCl **139a**

Scheme 4.6: Synthesis of L-valine *tert*-butyl ester (**139a**) from L-valine *tert*-butyl ester hydrochloride (**139a**·HCl).

Other free amino esters that were prepared from their corresponding hydrochloride salts are shown in Figure 4.1.

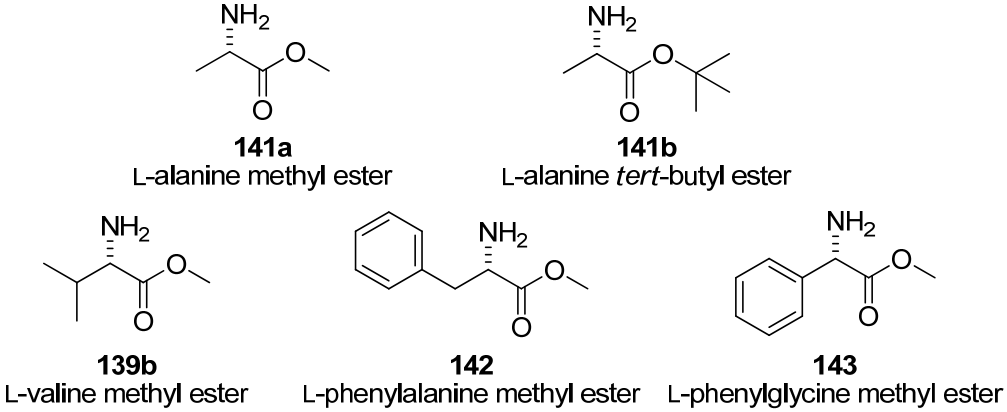
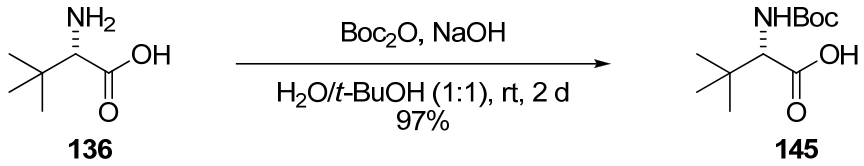


Figure 4.1: Amino esters prepared by extraction from their corresponding hydrochloride salt.

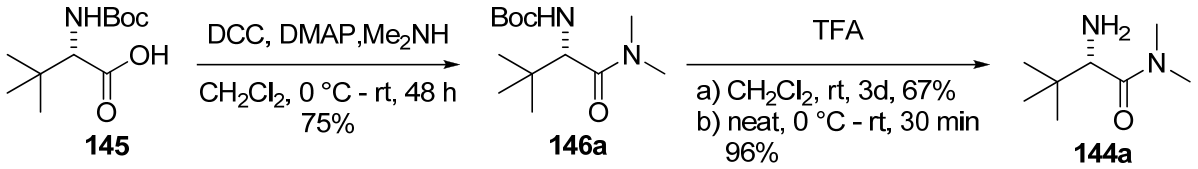
4.1.1.2 Synthesis of Amino Amides

L-*tert*-Leucine-*N,N*-dimethylamide (**144a**, Scheme 4.8) was obtained in several steps from the corresponding L-*tert*-leucine (**136**). The amino function in **136** had to be protected prior to amide formation. For this purpose we chose the *tert*-butoxycarbonyl (Boc) protection. This was done by reacting amino acid **136** with *tert*-butoxycarbonyl anhydride (Boc_2O) and sodium hydroxide in a mixture of water and *tert*-butanol as solvent.[209] After acidification and extraction *N*-Boc-protected amino acid **145** was isolated in 97% yield (Scheme 4.7).



Scheme 4.7: *N*-Boc-Protection of L-*tert*-leucine (**136**).[209]

N-Boc-L-*tert*-leucine (**145**, prepared according to the procedure reported in Scheme 4.7 or purchase from Sigma-Aldrich) was then activated with dicyclohexylcarbodiimide (DCC)[210] and a catalytic amount of DMAP and converted with dimethylamine to the corresponding amide (**146a**, Scheme 4.8). According to the literature[210] we deprotected *N*-Boc-amide **146a** with trifluoroacetic acid (TFA) in dichloromethane affording L-*tert*-leucine-*N,N*-dimethylamide (**144a**) in 67% yield after three days at room temperature. The deprotection reaction could be accelerated and optimized by stirring **146a** in neat TFA at room temperature for about 30 minutes, giving the desired amide in 96% yield (Scheme 4.8).

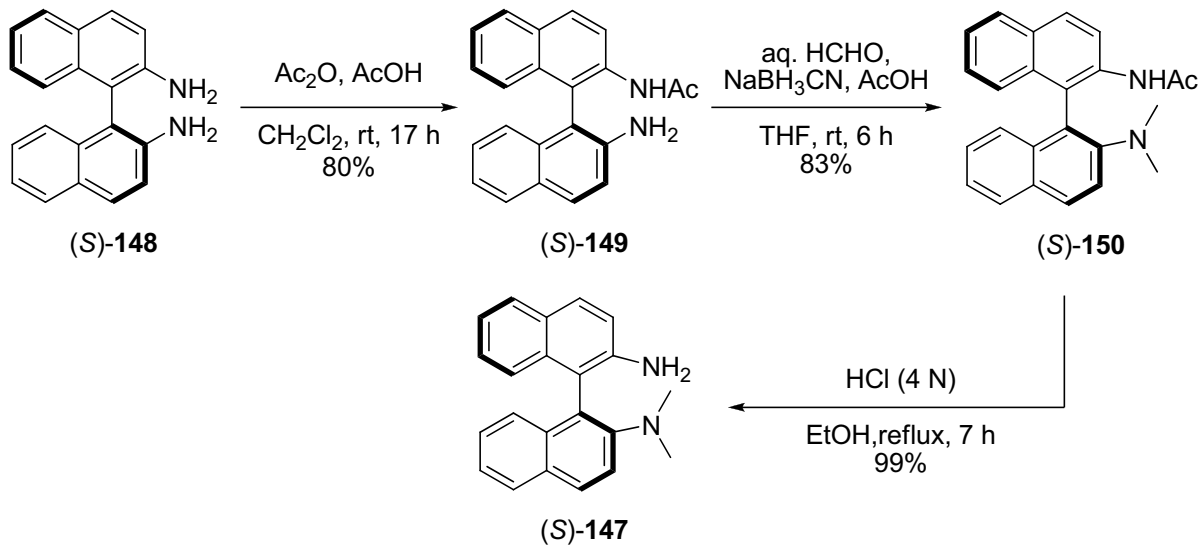


Scheme 4.8: Synthesis of L-*tert*-leucine-*N,N*-dimethylamide (**144a**) from *N*-Boc-L-*tert*-leucine (**145**).[210]

4.1.2 Synthesis of Other Primary Amines

(*S*)-N^2,N^2-dimethyl-1,1'-binaphthyl-2,2'-diamine ((*S*)-**147**) was prepared from binaphthyl-diamine (*S*)-**148** ((*S*)-BINAM) according to the procedure reported by *Wang et al.* (Scheme 4.9).[106]

The synthesis started with the protection of one amine group of (*S*)-BINAM) ((*S*)-**148**) using acetic anhydride in the presence of acetic acid to yield amino acetamide (*S*)-**149** (80%). (*S*)-*N*-(2'-(dimethylamino)-1,1'-binaphthyl-2-yl)acetamide (*S*)-**150** was easily obtained by reacting amino acetamide (*S*)-**149** with aqueous formaldehyde in the presence of sodium cyanoborohydride. After a basic work-up dimethylamino acetamide (*S*)-**150** was isolated in 83% yield. The acetamide functionality of (*S*)-**150** was then hydrolyzed with hydrochloric acid to release almost quantitatively free dimethylamino amine (*S*)-**147**.

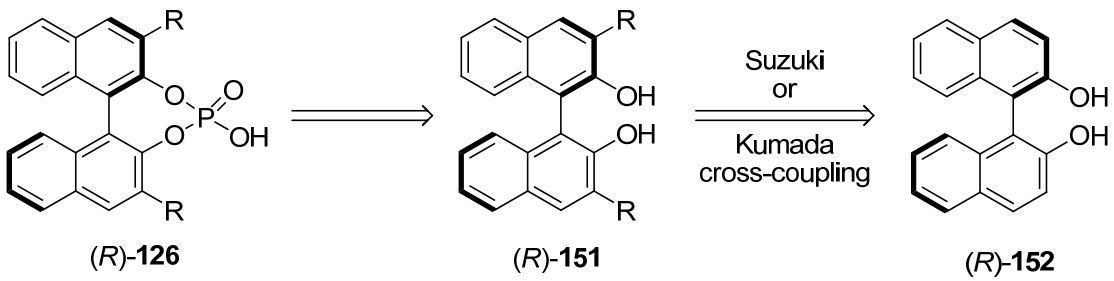


(*S*)-**148** (*S*)-**149** (*S*)-**150** (*S*)-**147**

Scheme 4.9: Synthesis of dimethylamino amine (*S*)-**147** from diamine (*S*)-**148**.[106]

4.1.3 Synthesis of BINOL-Derived Phosphates

Brønsted-acid BINOL-derived phosphoric acids **126** could be synthesized from 3,3'-disubstituted BINOL **151**, that was readily prepared from commercially available enantiomerically pure BINOL **152** (Scheme 4.10).



(*R*)-**126** (*R*)-**151** (*R*)-**152**

Scheme 4.10: Retrosynthetic approach to the preparation of 3,3'-disubstituted BINOL-derived phosphates **126**.

Depending on the nature of the substituents R that was introduced on the BINOL, two different synthetic pathways could be used. Aromatic substituents that are not too sterically hindered were introduced at the 3- and 3'-position of BINOL **152** *via* Suzuki cross-coupling reaction. For highly sterically hindered substituents a Kumada cross-coupling reaction had to be used.

3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP, **126a**) as well as octahydro-BINOL phosphates H_8-**126a** were synthesized *via* Kumada cross-coupling from the corresponding commercially available (H_8-)BINOL ((H_8-)**152**, see chapter 4.1.3.1). The other phosphoric acids screened in the course of this Ph.D. work ((*R*)-**126b-g**, Figure 4.2) were prepared *via* Suzuki cross-coupling reaction.[211] Hydrogen phosphate (*R*)-**126h** was commercially available.

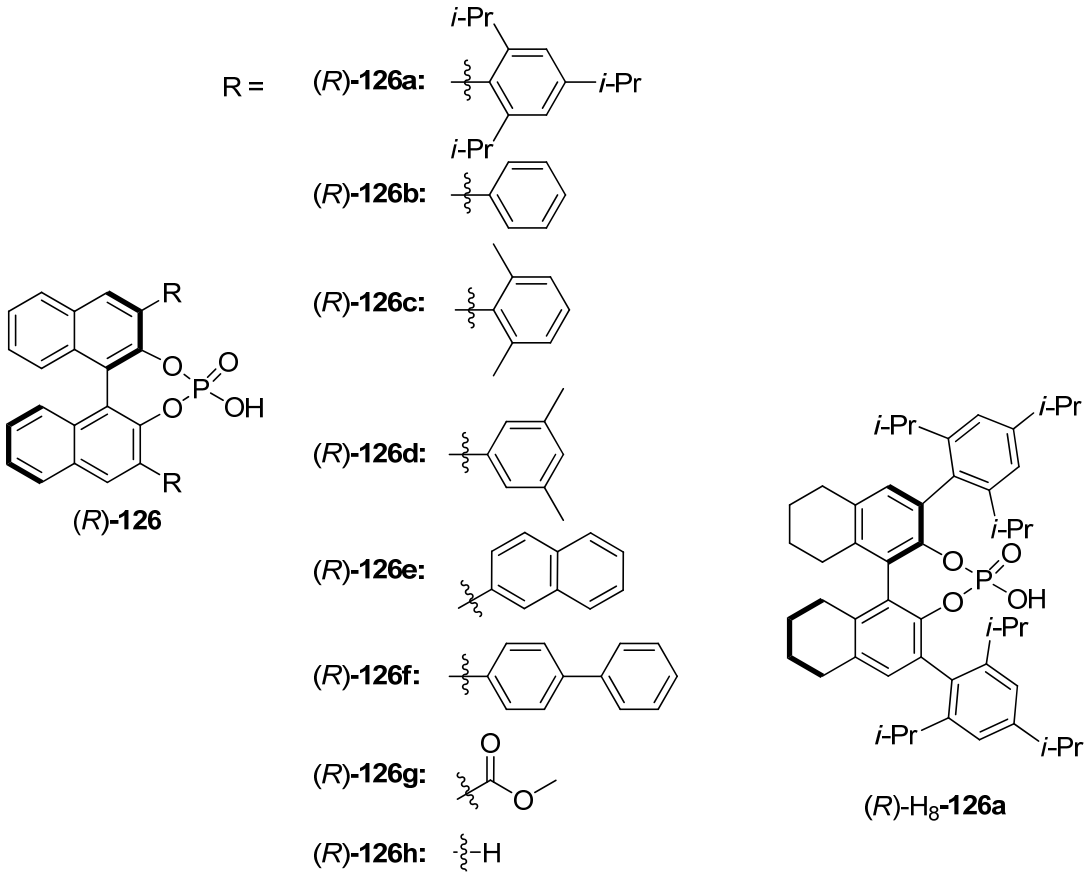
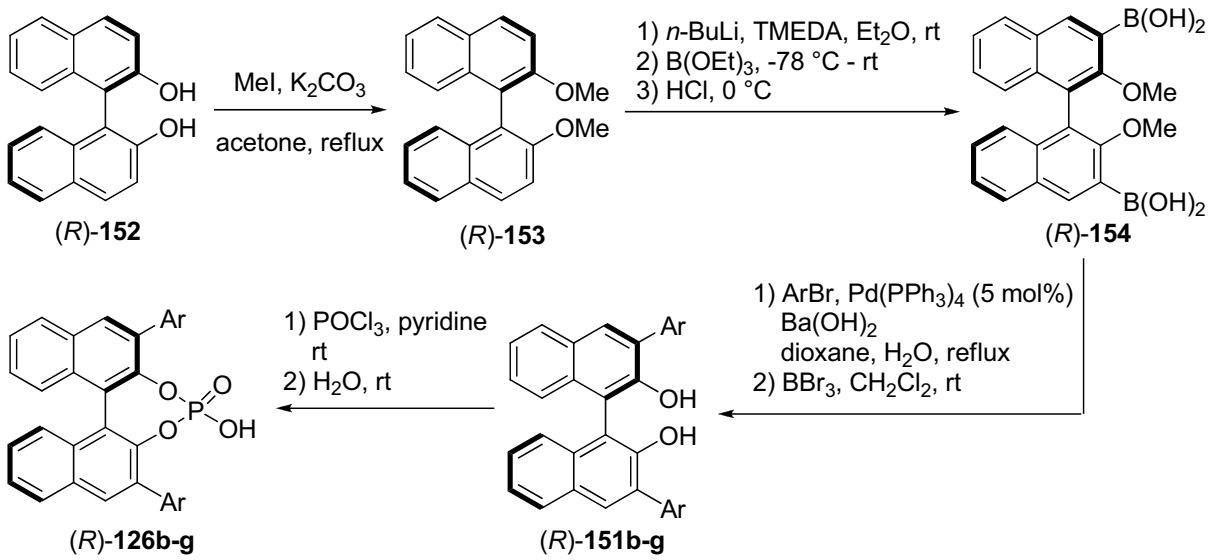


Figure 4.2: Overview of the screened chiral phosphoric acids.[211]

4.1.3.1 Synthesis of BINOL-Derived Phosphates *via* Suzuki Cross-Coupling

The phosphoric acids bearing aromatic substituents that are not very sterically hindered ((*R*)-**126b-g**) were prepared *via* Suzuki cross-coupling reaction according to the procedure of

Jørgensen et al.[212] and *Wipf et al.*[213] (Scheme 4.11). The key step involved a palladium-catalyzed cross coupling of boronic diacid (*R*)-**154** and the respective aryl halide to generate the BINOL (*R*)-**151**. The boronic acid **154** needed for this Suzuki cross-coupling process was synthesized by *ortho*-lithiation of the compound (*R*)-**153**, followed by treatment with triethylborate. During an acidic work-up, hydrolysis of the borate gave the desired boronic acid ((*R*)-**154**). Subsequent phenol deprotection and phosphorylation of (*R*)-**151** afforded (*R*)-**126**.



Scheme 4.11: General procedure for the synthesis of BINOL phosphates (*R*)-**126** *via* Suzuki cross-coupling process.[211]

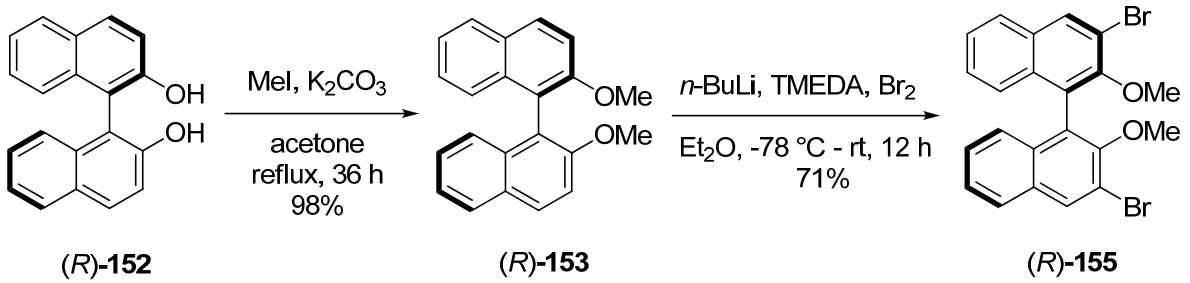
4.1.3.2 Synthesis of BINOL-Derived Phosphates *via* Kumada Cross-Coupling

As TRIP and other phosphoric acids bearing highly sterically hindered aromatic substituents were obtained in poor yields using Suzuki cross-coupling process, they were prepared *via* Kumada cross-coupling reaction. The key step of this process is a nickel-catalyzed cross coupling of a dibromide compound and the respective aryl magnesium bromide (see the following TRIP synthesis, Schemes 4.12-4.14).

(R)-TRIP ((R)-126a) synthesis

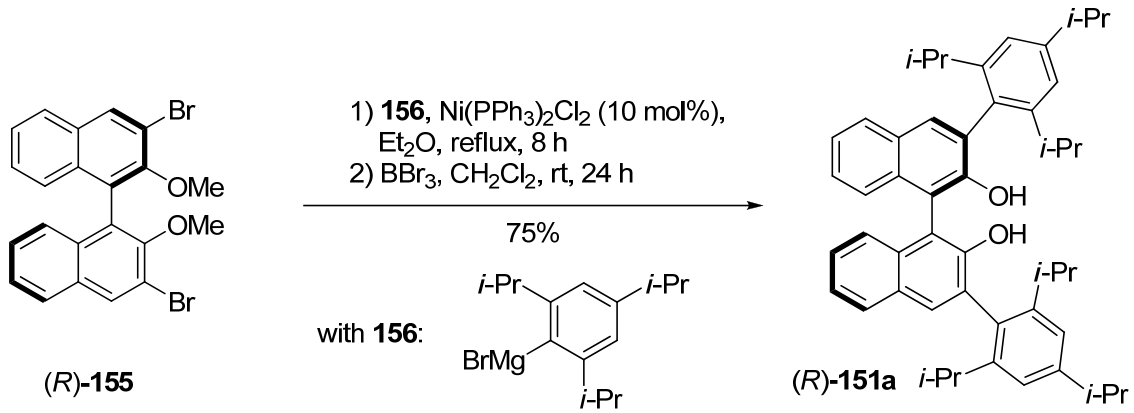
The preparation of the phosphoric acid **126a** was developed and optimized by *A. M. Seayad* according to the procedure of *Schrock et al.*[214] and *Akiyama et al.*[215] (Schemes 4.12-4.14).[216] This is now a well established process in our laboratory.

(*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl ((*R*)-**155**) needed for the Kumada cross-coupling reaction was prepared from commercially available BINOL ((*R*)-**152**). Methylation with methyl iodide provided dimethoxybinaphthyl (*R*)-**153**, which was then *ortho*-lithiated in the presence of *n*-butyl lithium and *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) followed by quenching with bromide (Scheme 4.12). The dibromide (*R*)-**155** was obtained in 70% yield over two steps.



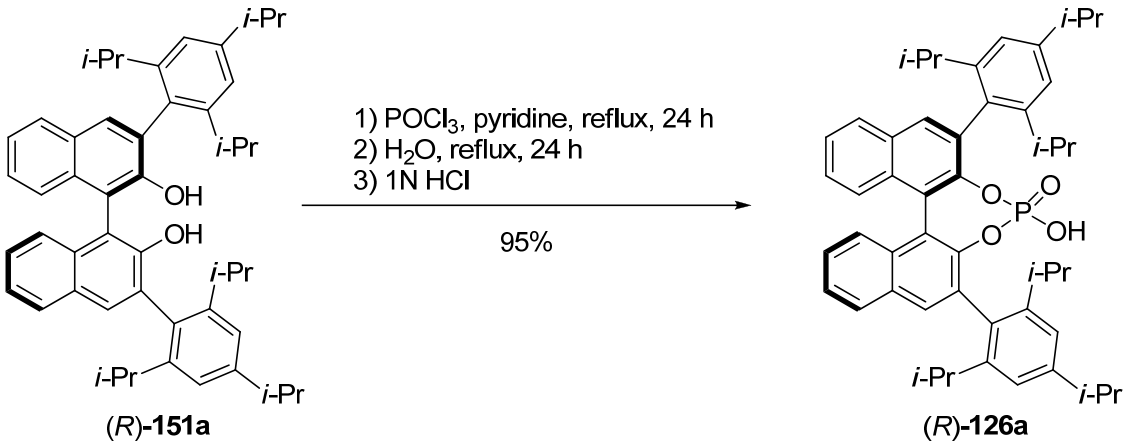
Scheme 4.12: Preparation of the dibromide (*R*)-**155** from BINOL (*R*)-**152**.

The nickel-catalyzed Kumada cross-coupling of (*R*)-3,3'-dibrom-2,2'-dimethoxy-1,1'-binaphthyl ((*R*)-**155**) with 2,4,6-triisopropylphenyl magnesium bromide **156** allowed the introduction of highly sterically hindered 2,4,6-triisopropylphenyl substituents in the 3- and 3'-positions of the BINOL derivative (*R*)-**155**. After deprotection of the methyl groups using boron tribromide (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol ((*R*)-**151a**) was formed in 75% yield (Scheme 4.13)



Scheme 4.13: Diarylation of the dibromide (*R*)-**153** *via* Kumada cross-coupling.

Phosphorylation of (*R*)-**151a** was achieved using phosphoryl trichloride in pyridine at reflux. Finally, hydrolysis with water at reflux followed by a treatment with hydrochloric acid (1 N) afforded the phosphoric acid catalyst (*R*)-**126a** in 95% yield (Scheme 4.14).



Scheme 4.14: Synthesis of BINOL phosphate (*R*)-**126a**.

BINOL phosphate (*R*)-**126a** was recrystallized by *S. Hoffmann* using acetonitrile as solvent. The obtained crystals could be examined by X-ray structure analysis (Figure 4.3).

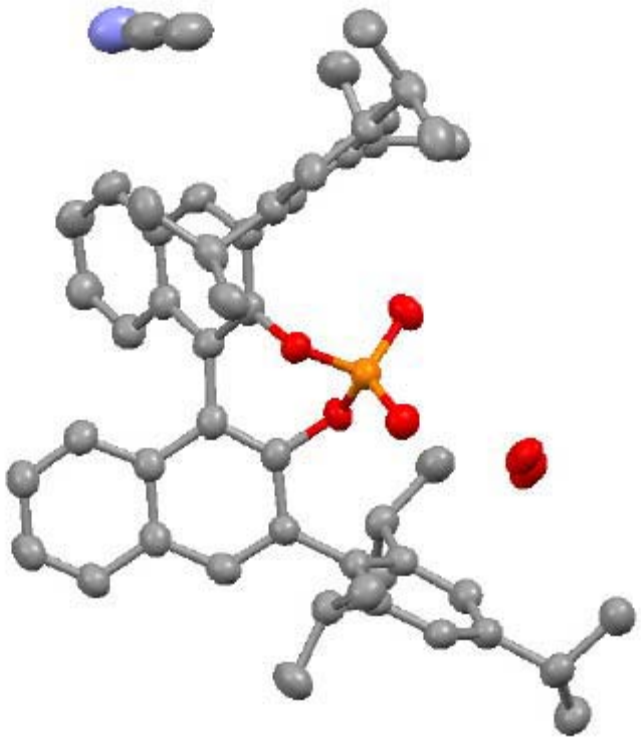
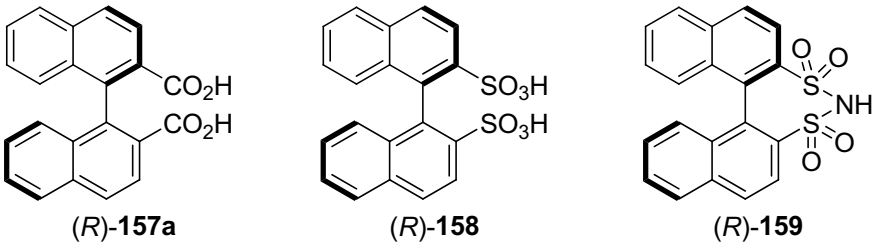


Figure 4.3: X-Ray structure analysis of BINOL phosphate (*R*)-**126a** (from *S. Hoffmann*'s Ph.D. thesis; the structure contains acetonitrile and water; carbon atoms: grey, oxygen atones: red, phosphorus atom: orange, nitrogen atom: blue. The hydrogen atoms of the molecule are omitted for clarity).

4.1.4 Other Chiral Amines and Chiral acids

We tested the *MacMillan* imidazolidinones **46** and **47** (see Chapter 2.1.2, Figure 2.4) for the conjugate reduction of enones **107**.

We also analyzed the catalytic activity of dicarboxylic acid (*R*)-**157a** as well as disulfonic acid (*R*)-**158** and disulfonimide (*R*)-**159**, which were used as chiral counteranions in iminium catalysis or as Brønsted acids involving hydrogen bonding catalysis (Figure 4.4).[217]



(*R*)-**157a** (*R*)-**158** (*R*)-**159**

Figure 4.4: Some chiral acids tested as counteranions or Brønsted acids to catalyze the transfer hydrogenation of enones **107**.[218]

4.1.5 Preparation of the Amino Acid-Derived Salts

The ammonium salts were prepared by mixing an amine and an acid (one equivalent of each, see Scheme 4.1) in a small volume of diethyl ether. The mixture was then stirred for a few minutes and the solvent removed under reduced pressure, leading to the formation of the desired ammonium salt. In some cases ammonium salts directly precipitated in diethyl ether solution and were filtered and washed with cold pentane.

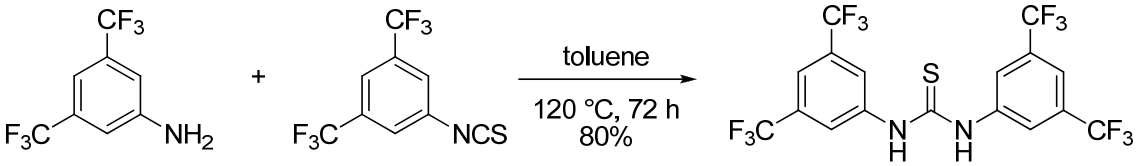
Note: for the catalyst screening process we prepared the ammonium salts *in situ* in order to save material and time.

4.2 Synthesis of (Thio)urea Organocatalysts

In this chapter the syntheses of the different mono- and bis(thio)urea derivatives screened as catalysts for the transfer hydrogenation of nitroolefins **120** and **121** (see Chapters 4.4 and 4.5, respectively) are reported.

4.2.1 Preparation of Mono(thio)urea Catalysts

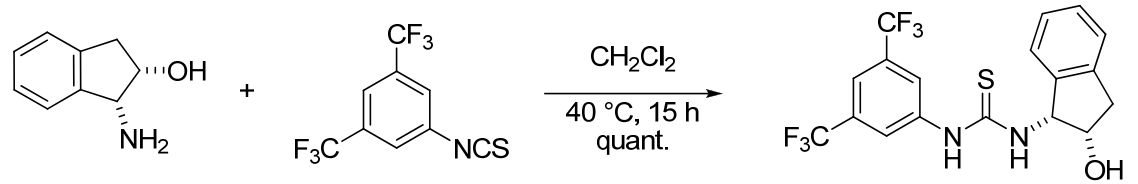
Achiral thiourea catalyst **49b**, *N*,*N*′-bis(3,5-bis(trifluoromethyl)phenyl)thiourea, was prepared according to a modified procedure reported by *Schreiner et al.*[218] 3,5-Bis(trifluoromethyl)-aniline (**160**) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**) were stirred in toluene at 120 °C for 72 hours, affording the thiourea catalyst **49b** in 80% yield (Scheme 4.15).



160 **161** **49b**

Scheme 4.15: Preparation of achiral *Schreiner* thiourea catalyst **49b**.

According to *Ricci et al.*'s methodology[219] 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)thiourea **162** was formed by stirring (1*R*,2*S*)-*cis*-1-amino-2-indanol (**163**) with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**) in dichloromethane (Scheme 4.16). Because of the poor solubility of amino alcohol **163** in dichloromethane at room temperature the reaction was run at 40 °C for 15 hours, affording bifunctional catalyst **162** in quantitative yield.

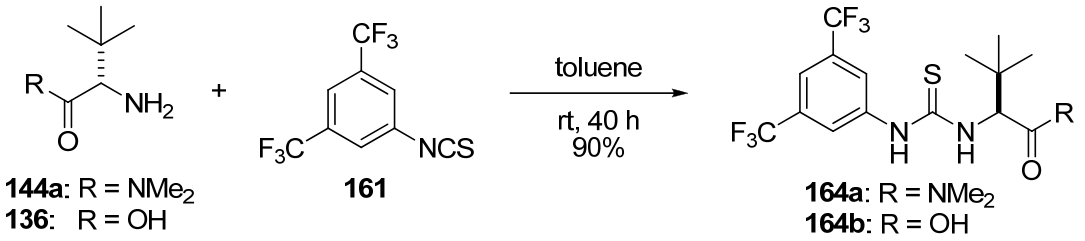


163 **161** **162**

Scheme 4.16: Synthesis of bifunctional thiourea catalyst **162**.

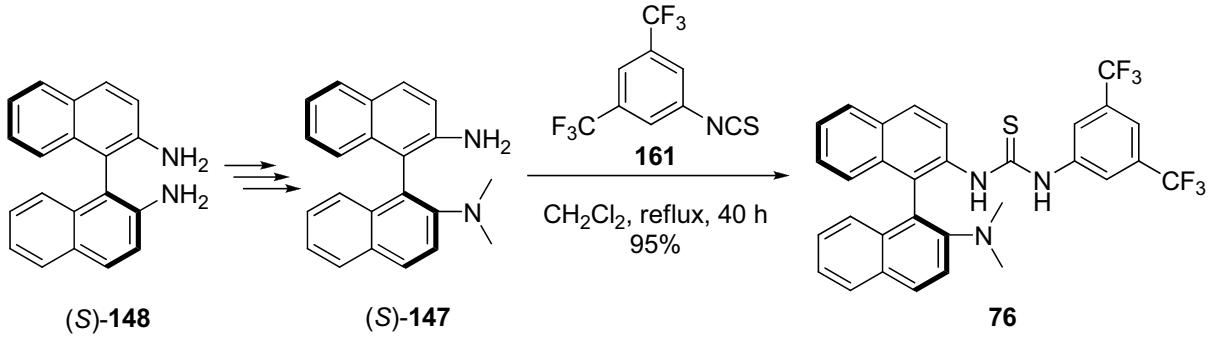
Bifunctional catalyst **164a** was generated in high yield (90%) by reacting L-*tert*-leucine-*N,N*-dimethylamide (**144a**) (see its preparation Chapter 4.1.1.2, Scheme 4.8) with 3,5-

bis(trifluoromethyl)phenyl isothiocyanate (**161**) in toluene at room temperature (Scheme 4.17). Thiourea **164b** was prepared following the same method (Scheme 4.17).[220]



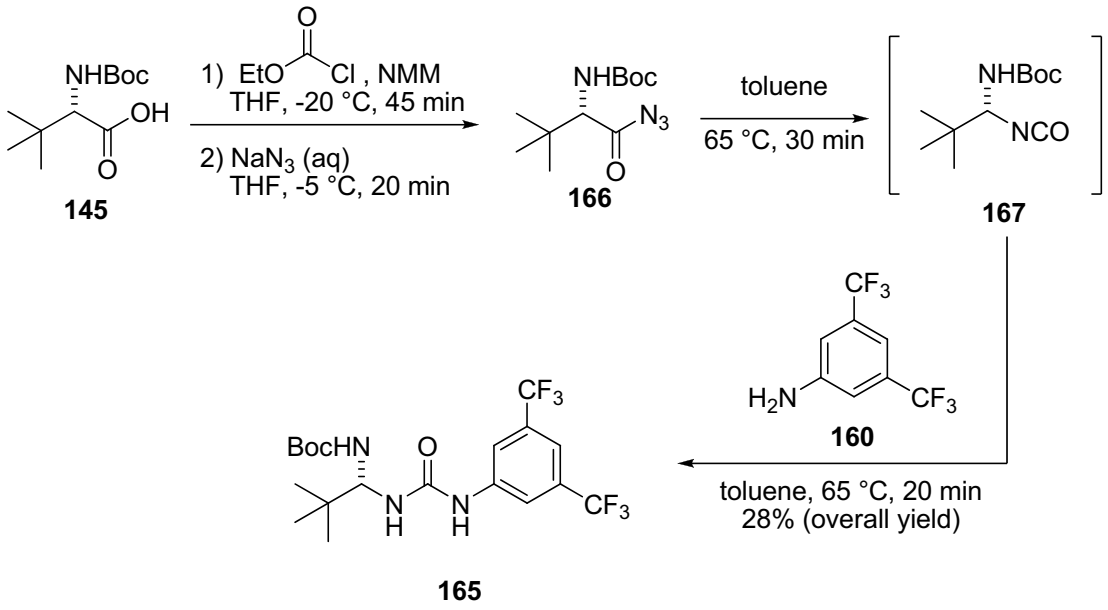
Scheme 4.17: Preparation of thiourea catalysts **164a** and **164b**.[220]

Catalyst **76** was obtained according to *Wang et al.*'s procedure.[106]. Amino amide (*S*)-**147** was synthesized in three steps from (*S*)-1,1'-binaphthyl-2,2'-diamine ((*S*)-BINAM, (*S*)-**148**) as reported in chapter 4.1.2 (see Scheme 4.9). It was then stirred with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**) in dichloromethane for 40 hours at reflux, affording **76** in excellent yield (95%, Scheme 4.18).



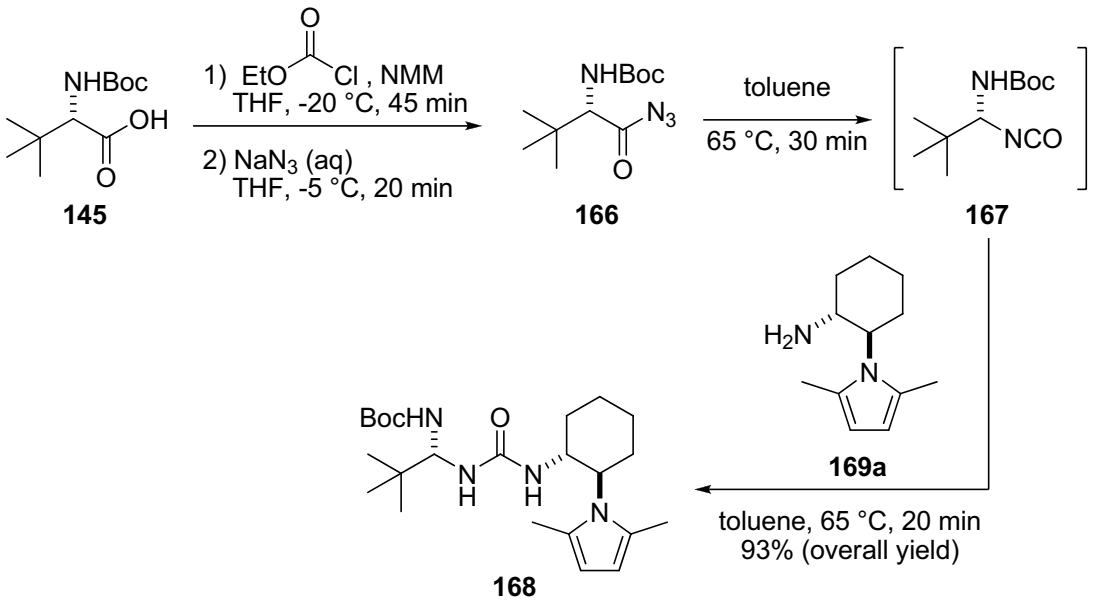
Scheme 4.18: Preparation of bifunctional BINAM-derived thiourea catalyst **76**.

Starting from commercially available *N*-Boc-L-*tert*-leucine **145**[221] urea **165** was prepared by a Curtius rearrangement process.[222] *N*-Boc-Protected amino acid **145** was first converted to its corresponding acyl azide **166** by reaction of its mixed anhydride (formed with ethylchloroformate and *N*-methylmorpholine (NMM)) with sodium azide. After work-up acyl azide **166** was used in the next step without further purification. Isocyanate **167** was generated *in situ via* Curtius rearrangement upon heating acyl azide **166** in toluene at 65 °C and then trapped with 3,5-bis(trifluoromethyl)aniline (**160**) to give urea **165** with an overall yield of 28% (Scheme 4.19). Catalyst **165** crystallized directly from the toluene solution at 65 °C and was recovered by a simple filtration.



Scheme 4.19: Preparation of urea catalyst **165** by a Curtius rearrangement process.

Using the same procedure the urea catalyst **168** was obtained in 93% overall yield. In this case isocyanate **167,** prepared from *N*-Boc-L-*tert*-leucine **145**,[225] was trapped with (1*R*,2*R*)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclohexanamine **169a** (Scheme 4.20). (The synthesis of **169a** is reported in Chapter 4.2.2.2, Scheme 4.27). In comparison with compound **165**, urea **168** was more soluble in toluene. Indeed it did not crystallize in the reaction mixture (even at room temperature) and was isolated by column chromatography after solvent removal under reduced pressure.



Scheme 4.20: Synthesis of urea catalyst **168** from *N*-Boc-L-*tert*-leucine **145**.

4.2.2 Preparation of *Jacobsen*-Type Monothiourea Catalysts

We tested different *Jacobsen* thiourea motifs (e.g. **50**, **57** and **58**) to catalyze the transfer hydrogenations of nitroolefins (see Chapter 4.4.2). Among these *Jacobsen* catalysts, thiourea **57a** was the most promising in terms of reactivity and enantioselectivity (see Chapter 4.4.2.3) and was further optimized by varying the substituents on the tertiary amine and the pyrrolyl groups.

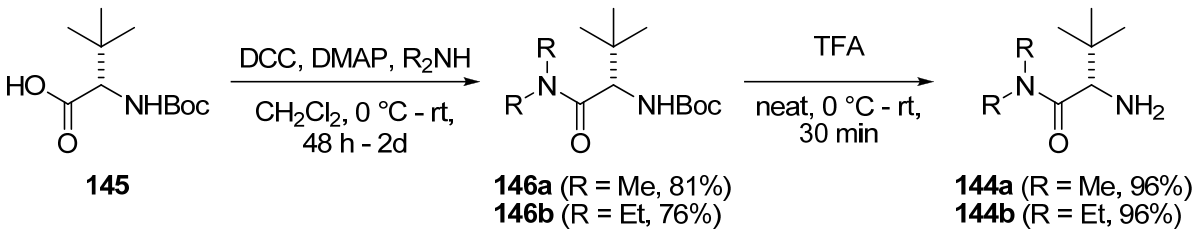
Jacobsen and *Jacobsen*-type catalysts were all prepared according or in analogy to the reported procedures.[90,95]

4.2.2.1 Synthesis of *Jacobsen*(-Type) Thioureas 58e and 50g

Compound **50d** (see Chapter 2.1.3.2, Scheme 2.22) was prepared by other group members[223] according to the procedure reported by *Jacobsen et al.*[95] Using a similar procedure diethylamino thiourea analog **50g** was synthesized from thiourea **58e** and pivalate **170** (Schemes 4.21-4.24).

Preparation of thiourea catalyst 58e

L-*tert*-Leucine diethylamide (**144b**) was formed from *N*-Boc-L-*tert*-leucine (**145**) (Scheme 4.21) using the same procedure as that reported for the preparation of L-*tert*-leucine dimethylamide (**144a**, see Chapter 4.1.1.1, Scheme 4.8).



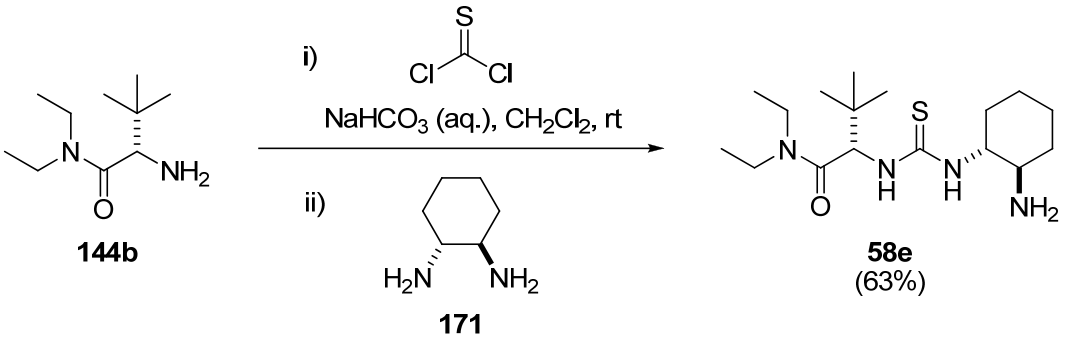
145

146a (R = Me, 81%)
146b (R = Et, 76%)

144a (R = Me, 96%)
144b (R = Et, 96%)

Scheme 4.21: Synthesis of L-*tert*-leucine dimethylamide (**144a**) and diethylamide (**144b**) from Boc-L-*tert*-leucine (**145**).

Thiourea **58e** was obtained by *in situ* conversion of L-*tert*-leucine diethylamide (**144b**) to its corresponding isothiocyanate derivative with thiophosgene in an aqueous solution of sodium bicarbonate. The isothiocyanate was then trapped with (*R*,*R*)-1,2-diaminocyclohexane (**171**), leading to the formation of thiourea **58e** in 63% yield (Scheme 4.22).

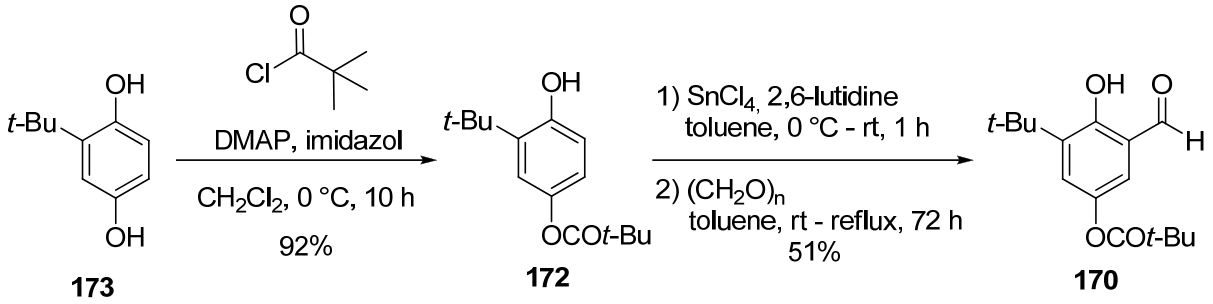


Scheme 4.22: Synthesis of thiourea catalyst **58e** from L-*tert*-leucine diethylamide (**144b**) and (*R*,*R*)-1,2-diaminocyclohexane (**171**).

Part of the prepared thiourea **58e** was kept to be later tested as hydrogen bonding catalyst and the rest was used for the preparation of catalyst **50g**.

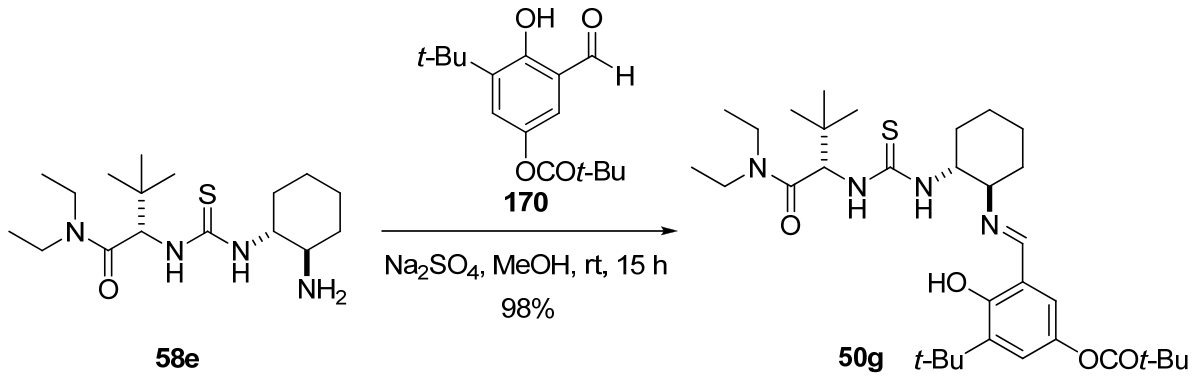
Preparation of thiourea catalyst 50g

3-*tert*-Butyl-5-formyl-4-hydroxyphenyl pivalate **170** was synthesized from 3-*tert*-butyl-4-hydroxyphenyl pivalate **172**. Compound **172** was prepared by *R. Rios* in 92% yield by reacting 2-*tert*-butylhydroquinone **173** with pivaloyl chloride in the presence of imidazole and a catalytic amount of DMAP at 0 °C (Scheme 4.23). Pivalate **172** was then treated with 2,6-lutidine and a catalytic amount of tin chloride, followed by paraformaldehyde addition. The reaction mixture was stirred at reflux for three days and after an acidic work-up pivalate **170** was obtained in 51% yield (Scheme 4.23).



Scheme 4.23: Synthesis of 3-*tert*-butyl-5-formyl-4-hydroxyphenyl pivalate **170**.

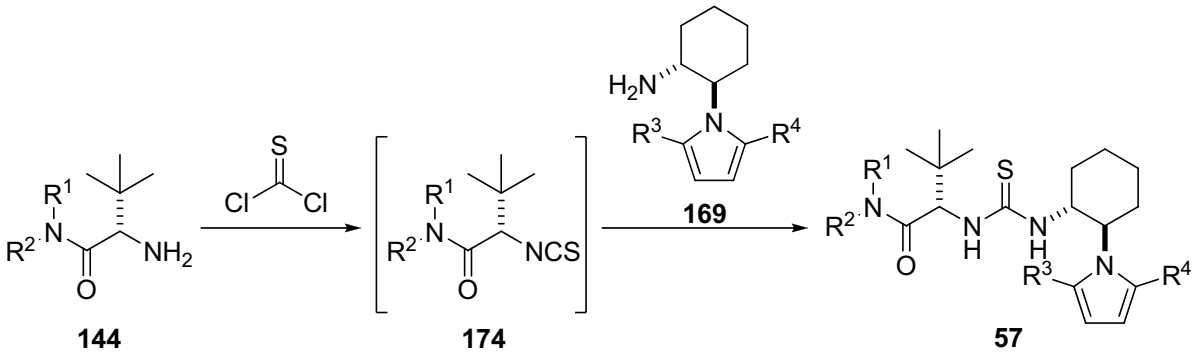
Compound **50g** was then easily obtained and in almost quantitative yield by mixing compound **58e** with pivalate **170** in methanol in the presence of sodium sulfate (Scheme 4.24).



Scheme 4.24: Preparation of *Jacobsen*-type thiourea catalyst **50g**.

4.2.2.2 Synthesis of *Jacobsen*(-Type) Thioureas 57a-l

Similar to the synthesis of *Jacobsen* catalyst **58e**, thioureas **57** were prepared from amino amides **144**, which were first converted *in situ* into their corresponding isothiocyanate **174** with thiophosgene. Isothiocyanates **174** were then trapped with appropriate (1*R*,2*R*)-2-(1*H*-pyrrol-1-yl)cyclohexanamine derivative **169** to generate the thiourea moiety of catalysts **57** (Scheme 4.25).[90]



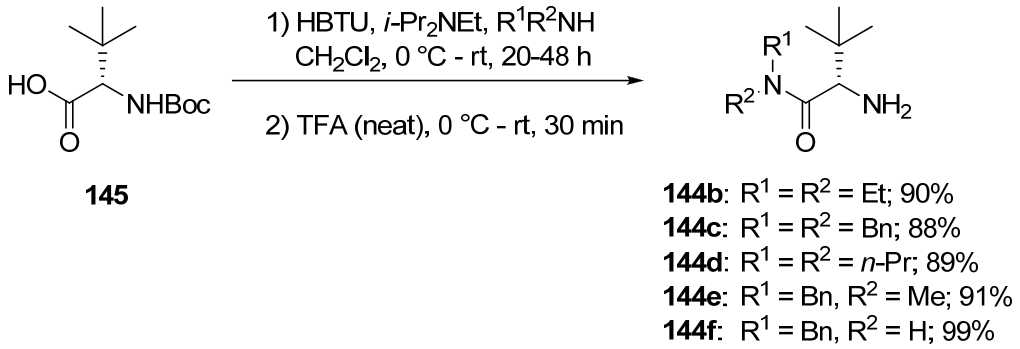
Scheme 4.25: General procedure for the formation of thiourea catalysts **57**.[90]

Preparation of L-tert-leucine-derived amides 144

To synthesize thioureas **57**, diethylamino amide **144b** as well as L-*tert*-leucine amides with bulkier substituents on the amide functionality (**144c-f**) had to be prepared. For this purpose the procedure reported by *Jacobsen et al*. was followed (Scheme 4.26)[95] as it was more efficient for coupling *N*-Boc-L-*tert*-leucine **145** with bulky amines than the method previously reported (see Chapter 4.1.1.1, Scheme 4.8 and Chapter 4.2.2.1, Scheme 4.21).

N-Boc-L-*tert*-leucine (**145**) was reacted at room temperature with *O*-benzotriazole-1-*N*,*N*,*N*′,*N*′-tetraethyluronium hexafluorophosphate (HBTU) and diisopropylethylamine, followed by the coupling with amine of choice. After an acidic work-up and removal of the

solvent, crude *N*-Boc-L-*tert*-leucine amide was obtained and without further purification treated with TFA (neat) to deprotect the amine group and afford L-*tert*-leucine amides **144b-f** in high to excellent yields (Scheme 4.26).[224]



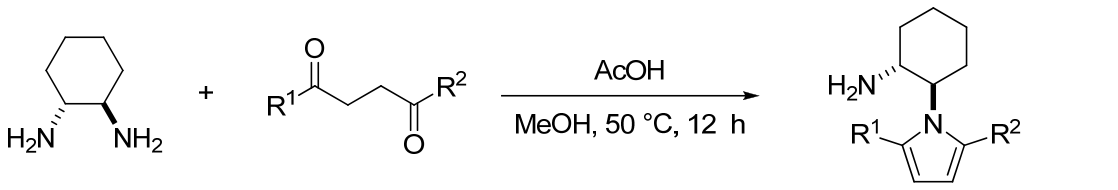
145

144b: $R^1 = R^2$ = Et; 90%
144c: $R^1 = R^2$ = Bn; 88%
144d: $R^1 = R^2$ = *n*-Pr; 89%
144e: R^1 = Bn, R^2 = Me; 91%
144f: R^1 = Bn, R^2 = H; 99%

Scheme 4.26: Synthesis of L-*tert*-leucine-derived amides **144b-f**.

Preparation of pyrrolylcyclohexanamines 169

To prepare (1*R*,2*R*)-2-(1H-pyrrol-1-yl)cyclohexylamine derivatives **169**, (*R*,*R*)-1,2-diaminocyclohexane (**171**) was treated with appropriate diones **175** in methanol in the presence of a stoichiometric amount of acetic acid. The mixture was stirred overnight at 50 °C, leading to the formation of 2,5-substituted pyrrolyl-cyclohexylamines **169** in high yields (Scheme 4.27).



171

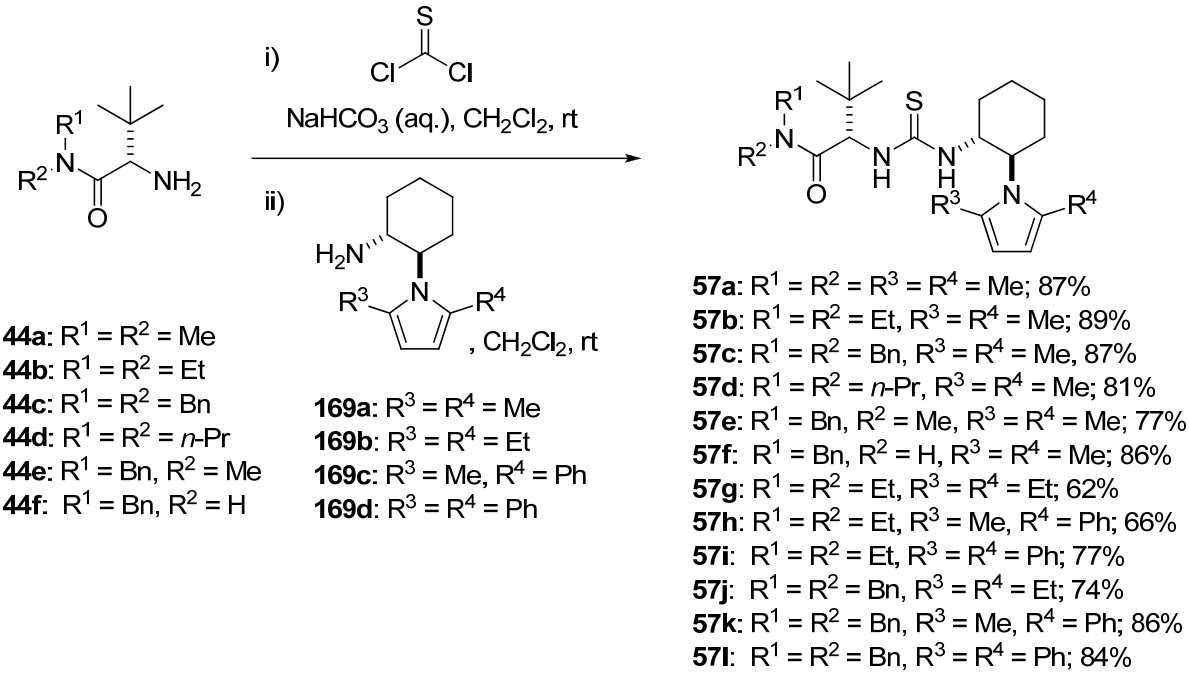
175a: $R^1 = R^2$ = Me
175b: $R^1 = R^2$ = Et
175c: R^1 = Me, R^2 = Ph
175d: $R^1 = R^2$ = Ph

169a: $R^1 = R^2$ = Me; 87%
169b: $R^1 = R^2$ = Et; 95%
169c: R^1 = Me, R^2 = Ph; 92%
169d: $R^1 = R^2$ = Ph; 76%

Scheme 4.27: Synthesis of amines **169**.

Generation of thiourea catalysts 57

According to the general procedure reported in Scheme 4.25, catalysts **57** were easily formed by trapping the *in situ* generated isothiocyanate (derived from amino amides **144**) with the appropriate amine **169**. This process afforded a variety of thioureas (**57a-l**) in moderate to good yields (Scheme 4.28).



144a: $R^1 = R^2$ = Me
144b: $R^1 = R^2$ = Et
144c: $R^1 = R^2$ = Bn
144d: $R^1 = R^2$ = *n*-Pr
144e: R^1 = Bn, R^2 = Me
144f: R^1 = Bn, R^2 = H

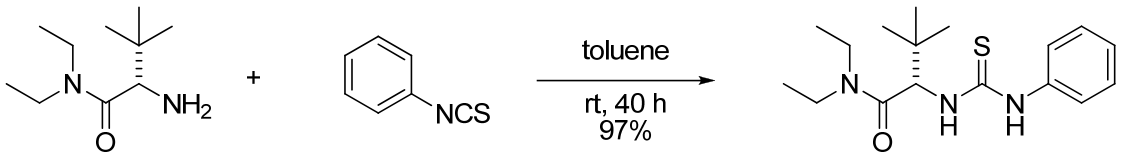
169a: $R^3 = R^4$ = Me
169b: $R^3 = R^4$ = Et
169c: R^3 = Me, R^4 = Ph
169d: $R^3 = R^4$ = Ph

57a: $R^1 = R^2 = R^3 = R^4$ = Me; 87%
57b: $R^1 = R^2$ = Et, $R^3 = R^4$ = Me; 89%
57c: $R^1 = R^2$ = Bn, $R^3 = R^4$ = Me, 87%
57d: $R^1 = R^2$ = *n*-Pr, $R^3 = R^4$ = Me; 81%
57e: R^1 = Bn, R^2 = Me, $R^3 = R^4$ = Me; 77%
57f: R^1 = Bn, R^2 = H, $R^3 = R^4$ = Me; 86%
57g: $R^1 = R^2$ = Et, $R^3 = R^4$ = Et; 62%
57h: $R^1 = R^2$ = Et, R^3 = Me, R^4 = Ph; 66%
57i: $R^1 = R^2$ = Et, $R^3 = R^4$ = Ph; 77%
57j: $R^1 = R^2$ = Bn, $R^3 = R^4$ = Et; 74%
57k: $R^1 = R^2$ = Bn, R^3 = Me, R^4 = Ph; 86%
57l: $R^1 = R^2$ = Bn, $R^3 = R^4$ = Ph; 84%

Scheme 4.28: Preparation of thiourea catalysts **57a-l**.

4.2.2.3 Synthesis of *Jacobsen*-Type Thiourea 176

Thiourea **176** was prepared using a similar process as the one followed for the synthesis of catalyst **164a** (see Chapter 4.2.1, Scheme 4.16). Thiourea **176** was obtained in excellent yield from L-*tert*-leucine-*N,N*-diethylamide (**144b**) and phenyl isothiocyanate (**177**, Scheme 4.29).



144b **177** **176**

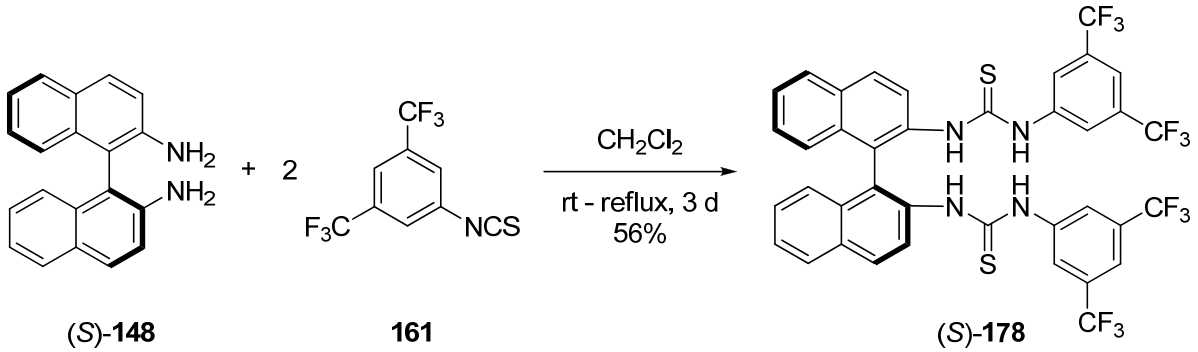
Scheme 4.29: Preparation of *Jacobsen* thiourea catalyst **176**.

4.2.3 Preparation of Bisthiourea Catalysts

Bisthiourea catalysts were also synthesized in order to test if an increase of the hydrogen bonding concentration has a positive influence on the catalyst reactivity.

These bisthioureas were prepared following the same strategy as the one used for the synthesis of monothioureas (see Chapter 4.2.1). This consisted of letting an amine and an

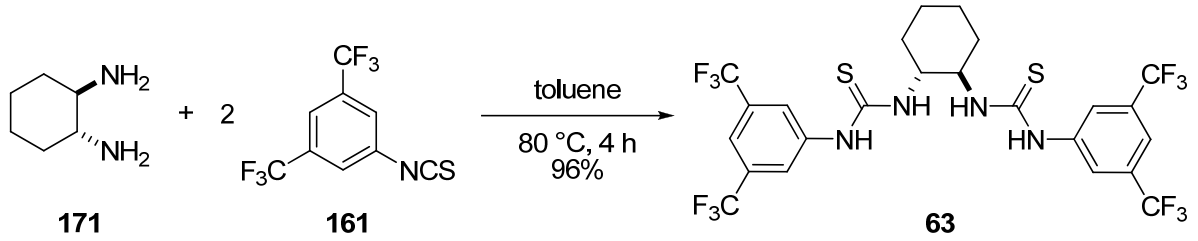
isothiocyanate react together in an appropriate solvent (dichloromethane or toluene) at room temperature or at reflux (Scheme 4.30-4.32).



(*S*)-**148** **161** (*S*)-**178**

Scheme 4.30: Preparation of BINAM-derived bisthiourea (*S*)-**178**.

Bisthioureas (*S*)-**178** and **63** were generated starting from chiral linkers (enantiomerically pure diamines **148** and **171**). Compound (*S*)-**178** was obtained in moderate yield (56%) by mixing (*S*)-BINAM ((*S*)-**148**) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**) for three days in dichloromethane (Scheme 4.30), whereas *Nagasawa* catalyst **63**[98] was formed within four hours in excellent yield starting from (*R*,*R*)-1,2-diaminocyclohexane (**171**) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**), using toluene as solvent (Scheme 4.31).

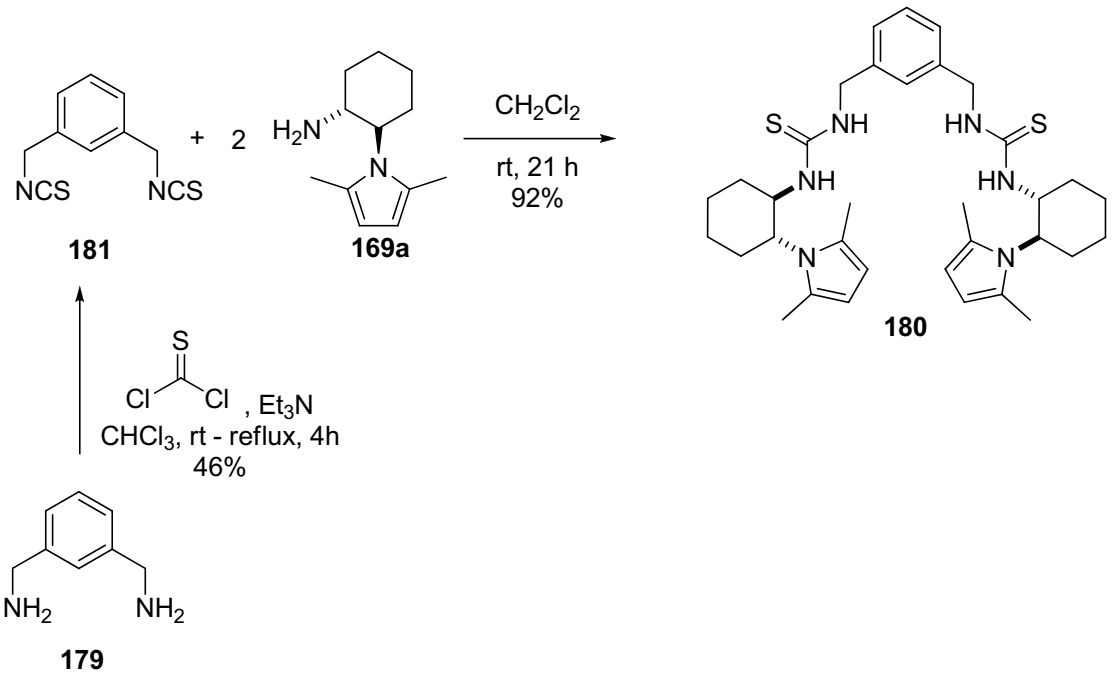


171 **161** **63**

Scheme 4.31: Synthesis of bisthiourea catalyst **63**.

Bisthioureas were also prepared from achiral linkers. As these hydrogen bonding catalysts were not efficient (neither in terms of reactivity nor enantioselectivity) in the catalysis of the studied conjugate reduction, just one motif (with 1,3-phenylenedimethanamine **179** as linker) is described in this Ph.D. thesis (Scheme 4.32).

For the preparation of bisthiourea **180**, bisisothiocyanate **181** was synthesized by reacting the corresponding diamine **179** with thiophosgene in the presence of triethylamine.[225] Bisisothiocyanate **181** was then trapped with (1*R*,2*R*)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclohexanamine **169a** (Scheme 4.32).



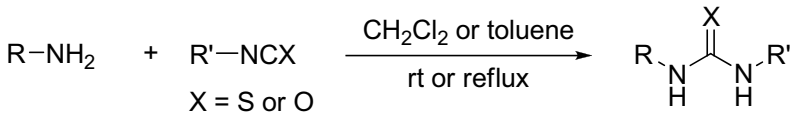
Scheme 4.32: Synthesis of chiral bisthiourea catalyst **180**.

4.2.4 Other Hydrogen Bonding Organocatalysts

Takemoto bifunctional catalyst **67a** as well BINOL-derived phosphoric acid **126i** and (di)carboxylic acids **157b**, **182** and **183** were prepared by other group members and tested as hydrogen bonding catalysts in the conjugate reductions of nitroolefins **120** (see Table 4.17, Chapter 4.4.2.1).[226]

4.2.5 Discussion of the Results

A variety of (thio)urea catalysts was successfully prepared using a simple strategy: letting an amine and an iso(thio)cyanate react together in an appropriate solvent and at the desired temperature (Scheme 4.33). The solvent (mostly toluene or dichloromethane) was mainly chosen depending on the solubility of the different starting materials. In the same way, some syntheses could be run at room temperature; whereas others were slow at this temperature, partially due to solubility problem of amines. In this case the reactions were run at higher temperatures. Using this simple and versatile process mono- and bis(thio)ureas were formed in mostly high yields.



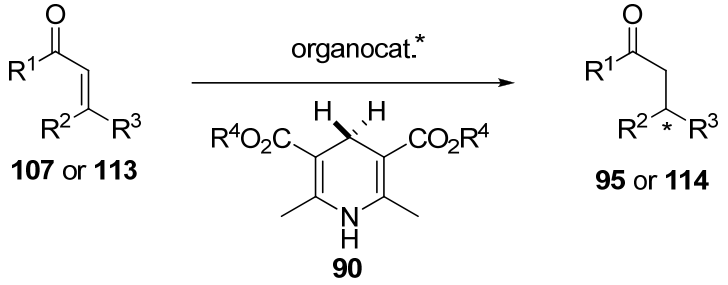
Scheme 4.33: General procedure for the formation of (thio)urea compounds.

When the isothiocyanates were not commercially available, they were easily prepared by reacting the corresponding amine with thiophosgene under basic conditions (Scheme 4.25 and Scheme 4.32). Isocyanate **167** was synthesized by Curtius rearrangement (Scheme 4.19). In most of the cases the (thio)isocyanates were generated *in situ* and then trapped with the amine of choice to generate the thiourea moiety (e. g. Scheme 4.28).

It should be noted that the preparation of urea compounds was more difficult than the one of thioureas, mostly due to their lower solubility in organic solvents.

4.3 Enantioselective Transfer Hydrogenation of *α,β*-Unsaturated Ketones

The aim of the following experiments was to develop an organocatalytic process for the synthesis of enantiomerically pure *β,β*-disubstituted ketones. For this purpose we focused our work on the development of a highly enantioselective dihydropyridine-mediated transfer hydrogenation of *β,β*-disubstituted unsaturated ketones **107** and **113** (Scheme 4.34).[227]



Scheme 4.34: Planned organocatalytic transfer hydrogenation of enones.

4.3.1 Synthesis of the Starting Materials and Racemic Products

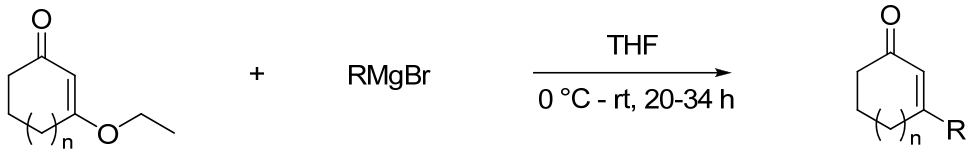
3-Methylcyclohexenone (**107b**) and 3-methylcyclopentenone (**107c**) are commercially available substrates and were purchased from Sigma-Aldrich. Enones **107a** and **113a** were prepared by *J. Zhou* and kindly shared.

4.3.1.1 Synthesis of the *α,β*-Unsaturated Cyclic Ketones

β-Branched *α,β*-unsaturated 5- and 6-membered cyclic ketones were easily prepared according to the procedure reported by *Buchwald et a.*[163]

β-Substituted cyclohexenone and cyclopentenone derivatives were synthesized by reacting their corresponding vinylogous ester **184** (commercially available 3-ethoxycyclohexenone (**184a**) and 3-ethoxycyclopentenone (**184b**), respectively) with two equivalents of the appropriate Grignard reagent in tetrahydrofurane (THF). The Grignard reagents were added at 0 °C. Afterwards the reaction mixture was stirred at room temperature until full conversion

was reached; leading to the formation of the desired cyclic enones in generally high yields (Scheme 4.35). The yields reported in Scheme 4.35 correspond to the isolated yields after column chromatography. Their low values, especially for the 3-ethyl substituted cyclic enones **107d** and **107h**, are due to the loss of product while removing the solvent residues in high vacuum. In the case of non-volatile products (3-phenethyl substituted enones **107g** and **107i**) no loss of product was observed during the solvent removal and the isolated yields remained very high (> 90%).

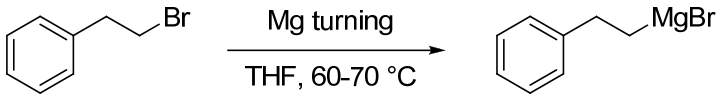


184a: n = 1
184b: n = 0

107a: n = 1, R = Ph; 76%
107d: n = 1, R = Et; 53%*
107e: n = 1, R = *i*-Bu; 77%*
107f: n = 1, R = *i*-Pr; 68%*
107g: n = 1, R = CH_2CH_2Ph; 91%
107h: n = 0, R = Et; 34%*
107i: n = 0, R = CH_2CH_2Ph; 91%

Scheme 4.35: General procedure for the preparation of 5- and 6-membered cyclic enones **107**. (*Volatile compounds).

It should be noted that the phenethylmagnesium bromide (**185**) could not be obtained from commercial suppliers. It was thus prepared by treating (2-bromoethyl)benzene (**186**) with activated magnesium turnings in anhydrous THF at 60-70 °C overnight (Scheme 4.36). The solution was then cooled to 40 °C (as a precipitate formed when the reaction was cooled to room temperature) and the Grignard reagent directly transferred to the solution of vinylogous esters **184a** or **184b** in THF for the synthesis of cyclic enones **107g** and **107i** (see Scheme 4.35).

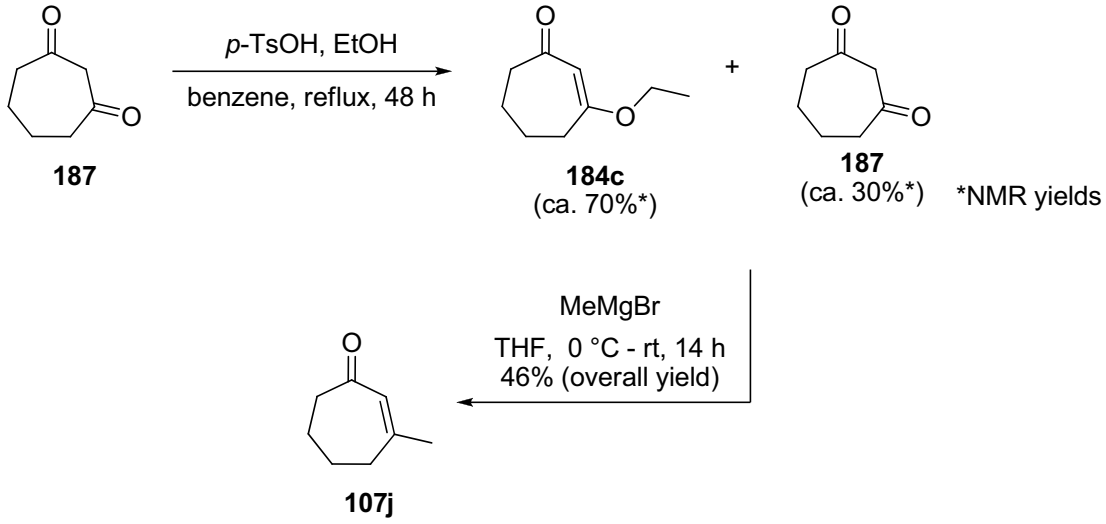


186 **185**

Scheme 4.36: Preparation of phenethylmagnesium bromide (**185**).

7-Membered cyclic vinylogous ester **184c** was prepared following the procedure reported by *de Meijere et al.*[228] Cycloheptane-1,3-dione (**187**) was reacted with ethanol and a catalytic amount (1 mol%) of *para*-toluene sulfonic acid (*p*-TsOH) in benzene. The reaction mixture was then stirred at reflux (Scheme 4.37). After two days the reaction was stopped even though some of the starting material was still unreacted. After purification by flash chromatography a

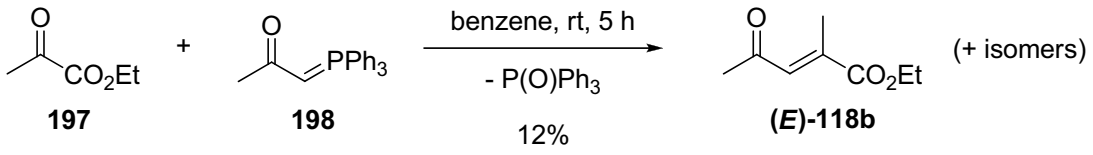
mixture of 3-ethoxycyclohept-2-enone (**184c**) and starting material **187** was isolated. As it was supposed that the presence of cycloheptane-1,3-dione (**187**) would not disturb the preparation of the 3-methylcycloheptenone (**107j**) the mixture of compounds **184c** and **187** was used in the next step without further purification. This mixture was reacted with methylmagnesium bromide in THF affording cycloheptenone **107j**, which could be easily separated from remaining cycloheptane-1,3-dione (**187**) by flash chromatography and was isolated with an overall yield of 46% (Scheme 4.37).



Scheme 4.37: Preparation of vinylogous ester **184c** and further transformation to enone **107j**.

4.3.1.2 Synthesis of the α,β-Unsaturated Acyclic Ketones

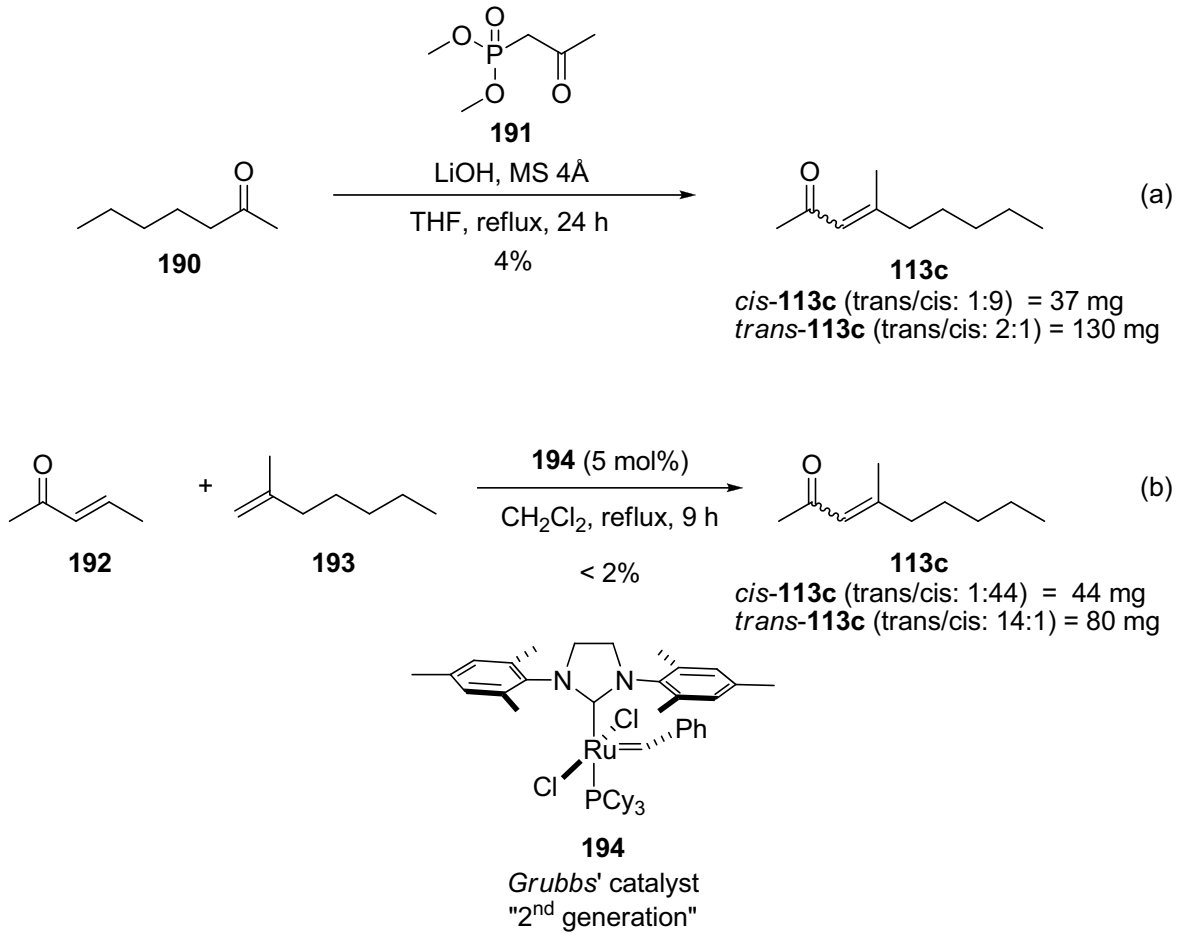
Acyclic enones were prepared following different procedures than the ones used for the formation of cyclic enones. (*E*)-Ethyl 2-methyl-4-oxopent-2-enoate ((*E*)-**113b**) [229] was synthesized through a Wittig reaction according to the literature.[230] Ethyl pyruvate (**188**) was added to a suspension of 1-(triphenylphosphoranylidene)-2-propanone (**189**) in benzene. The reaction was stirred at room temperature for five hours, during which time it became homogeneous, leading to the formation of the desired product ((*E*)-**113b**) in 12% yield (Scheme 4.38) as well as isomers (*Z*)-**113b** and ethyl 2-methylene-4-oxopentanoate).



Scheme 4.38: Synthesis of (*E*)-ethyl 2-methyl-4-oxopent-2-enoate (**113b**).

To further explore the substrate scope in the planned catalytic reaction (see Scheme 4.34), an acyclic enone with a long aliphatic chain, 4-methylnon-3-en-2-one (**113c**) was also synthesized. This unsaturated ketone (**113c**) was first prepared through Horner-Wadsworth-Emmons olefination, a reaction that is widely employed in organic synthesis for the preparation of acrylic esters (Scheme 4.39a).[231] Heptan-2-one (**190**) was treated in THF with a phophonate carbanion, which was generated *in situ* from the reaction of dimethyl-2-oxopropylphosphonate (**191**) with lithium hydroxide in the presence of activated 4 Å molecular sieves. After 24 hours at reflux most of the starting ketone **190** remained unreacted and the desired product **113c** was formed in only 4% yield as a mixture of (*E*)- and (*Z*)-isomers. Separation of the two isomers was difficult to achieve even by a careful column chromatography and only fractions of *enriched cis*- or *enriched trans*-**113c** could be isolated (Scheme 4.39a).

As only few milligrams of 4-methylnon-3-en-2-one (**113c**) were formed using this Horner-Wadsworth-Emmons olefination procedure (Scheme 4.39a), we looked for another strategy for the generation of *α,β*-unsaturated ketone **113c** and chose the ruthenium-catalyzed olefin cross-metathesis described by *Grubbs et a.*[232] (*E*)-Pent-3-en-2-one (**192**) and 2-methylhept-1-ene (**193**) were reacted together in dichloromethane at reflux in the presence of a catalytic amount (5 mol%) of *Grubbs*' second generation ruthenium catalyst (**194**) (Scheme 4.39b). Under these conditions 4-methylnon-3-en-2-one (**113c**) was obtained in poor yield (<2%) and as a mixture of *trans*- and *cis*-isomers. Like in the previous case the separation of the two isomers by column chromatography allowed us to obtain *enriched cis*- and *enriched trans*-**113c** but no pure fractions of each isomer (Scheme 4.39b). This process was repeated several times to get enough starting material to investigate the organocatalytic conjugate reduction of this aliphatic acyclic enone (**113c**) under various reaction conditions.



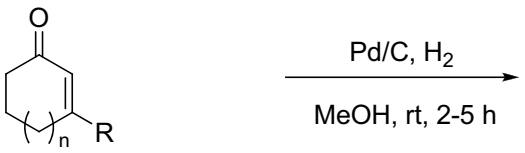
Scheme 4.39: Synthesis of 4-methylnon-3-en-2-one (**113c**) through (a) Horner-Wadsworth-Emmons Olefination or (b) ruthenium-catalyzed cross-metathesis.

4.3.1.3 Synthesis of the Racemic Products

Racemic samples of the enantiomerically enriched saturated ketones described in this Ph.D. thesis (**95a-j** and **114a-c**) were needed as reference substances not only to control the progress of the investigated organocatalyzed transfer hydrogenations but also to determine and optimize the separation conditions of the (*R*)- and (*S*)-enantiomers of each saturated ketone using gas chromatography (GC) or high performance liquid chromatography (HPLC) analysis on a chiral phase. Once the separation conditions were defined, product samples from our catalytic (test) reactions could be subjected to GC or HPLC analysis for the measurement of their enantiomeric ratio (*er*).

3-Methylcyclohexanone (**95b**) and 3-methylcyclopentanone (**95c**) were commercially available substrates and purchased from Sigma-Aldrich. The other racemic ketones were easily obtained in moderate to high yields (60-92%) through palladium-catalyzed conjugate reduction of the enones with molecular hydrogen (Scheme 4.40).[233] The reaction was usually

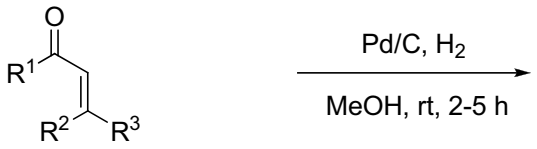
complete after about two hours and had to be stopped immediately after full conversion was observed to avoid the formation of over reduced compounds. In the case of volatile ketones (especially compound **95h**), loss of product occurred during the removal of solvents under reduced pressure; this explains the sometimes poor yields that are reported in Scheme 4.40.



(a)

107a: n = 1, R = Ph
107d: n = 1, R = Et
107e: n = 1, R = *i*-Bu
107f: n = 1, R = *i*-Pr
107g: n = 1, R = CH_2CH_2Ph
107h: n = 0, R = Et
107i: n = 0, R = CH_2CH_2Ph
107j: n = 2, R = Me

95a: n = 1, R = Ph; 61%
95d: n = 1, R = Et; 69%[a]
95e: n = 1, R = *i*-Bu; 69%[a]
95f: n = 1, R = *i*-Pr; 75%[a]
95g: n = 1, R = CH_2CH_2Ph; 80%
95h: n = 0, R = Et; 6%[a]
95i: n = 0, R = CH_2CH_2Ph; 92%
95j: n = 2, R = Me; 79%



(b)

113a: $R^1 = R^2$ = Me, R^3 = Ph
113b: $R^1 = R^2$ = Me, $R^3 = CO_2Et$
113c: $R^1 = R^2$ = Me, R^3 = *n*-Pent

114a: $R^1 = R^2$ = Me, R^3 = Ph; 92%
114b: $R^1 = R^2$ = Me, $R^3 = CO_2Et$; 87
114c: $R^1 = R^2$ = Me, R^3 = *n*-Pent; 60%

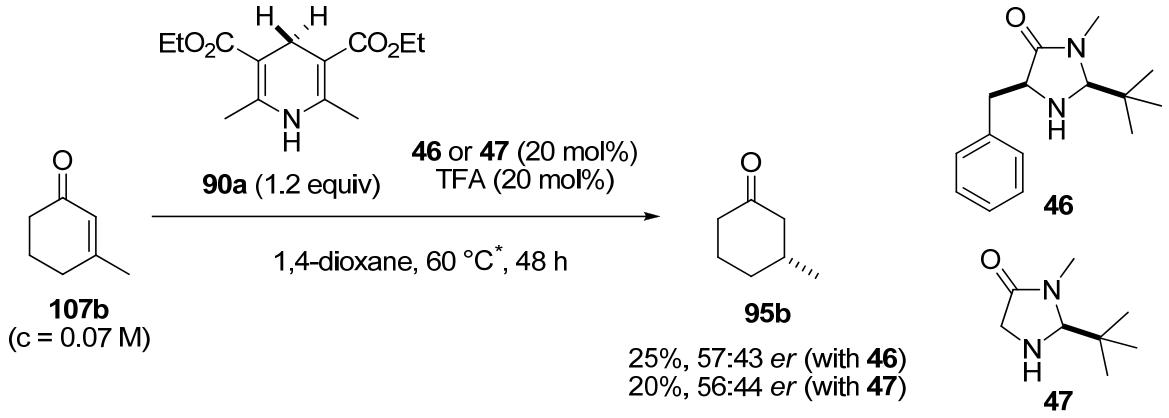
Scheme 4.40: Synthesis of racemic (a) cyclic ketones (**95**) and (b) acyclic ketones (**114**). ([*]Volatile ketones).

4.3.2 Development and Optimization of the Catalytic System

4.3.2.1 Identification of the Catalyst's Core Structural Motif

At the time this Ph.D.work started, the highly efficient metal-free asymmetric transfer hydrogenations of *α,β*-unsaturated aldehydes **123** catalyzed by *MacMillan* imidazolidinones (**46** or **47**) in the presence of Hantzsch ester **90** as hydrogen source had just been independently developed and reported by our laboratory[120b] and *MacMillan et al.*[120d] Inspired by this work, we first applied the reaction conditions of these conjugate reductions of enal **123** to the transfer hydrogenation of enones. 3-Methylcyclohexenone (**107b**), which is commercially available was chosen as the standard substrate for the development of the desired reaction and for the optimization process.

3-Methylcyclohexenone (**107b**) was first treated with commercially available Hantzsch ester **90a** (1.2 equivalents) in dioxane at room temperature in the presence of a catalytic amount (20 mol%) of catalyst **46** or **47** as TFA salt. Under these conditions no conversion was observed even after five days. The reaction mixtures were then warmed up to 60 °C. At this temperature 3-methylcyclohexanone (**95b**) was formed, but with low yield and enantioselectivity (Scheme 4.41).

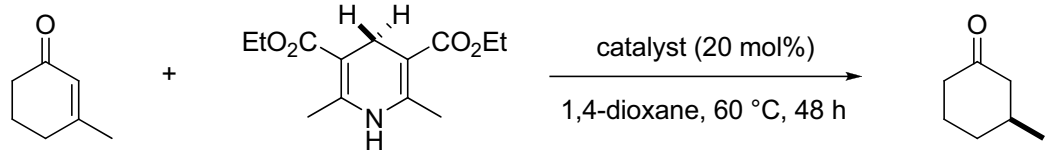


Scheme 4.41: First attempts of the conjugate reduction of 3-methylcyclohexenone (**107b**) using MacMillan secondary amines **46** and 47**.** (* No reaction took place at lower temperatures).

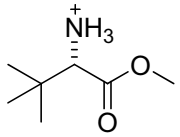
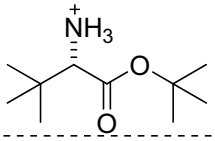
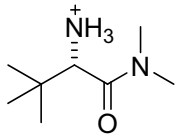
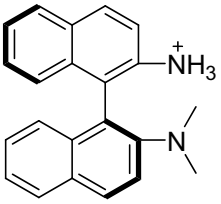
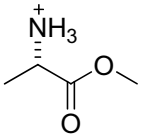
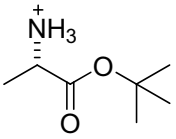
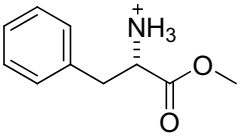
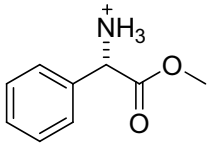
As expected, *MacMillan* imidazolidinium catalysts, which are highly effective for the transfer hydrogenation of *α,β*-unsaturated aldehydes in the presence Hantzsch ester, proved to be much less efficient with ketone substrates. Hypothesizing that primary amine catalysts, due to their reduced steric requirements, might be suitable for the activation of ketones (see Chapter 3.1, Scheme 3.3), we investigated the development of a new ammonium salt motif made of a primary amine and an acid.

After various catalytic systems made of a primary amine and TFA were screened in the transfer hydrogenation of 3-methylcyclohexenone (**107b**) using dioxane as solvent, the first promising results in terms of enantioselectivity (64:36 *er*) were observed with L-*tert*-leucine methyl ester-derived salt [**137a**•TFA]. Inspired by these results the catalytic activity of other L-*tert*-leucine derivatives was evaluated as shown in Table 4.1. The conversions and enantiomeric excesses were determined by GC measurements with a chiral stationary phase. It is worth specifying that the transfer hydrogenations were at first run at room temperature without any success. Only by increasing the temperature to 60 °C ketone **95b** could be generated in good yields.

Table 4.1: Initial results using primary amines to catalyze the transfer hydrogenation of enone **107b**



107b (c = 0.1M) | **90a** (1.2 equiv) | (*S*)-**95b**

Entry	Catalytic salt: Ammonium ion	Counteranion		conv. [%][a]	*er*[a]
1	-	-		< 5	-
2		$CF_3CO_2^-$	**137a**·TFA	42	64:36
3		$CF_3CO_2^-$	**137b**·TFA	72	76:24
4		$CF_3CO_2^-$	**144a**·TFA	20	53:47
5		$CF_3CO_2^-$	(*S*)-**147**·TFA	41	66:34
6		$CF_3CO_2^-$	**141a**·TFA	1	51:49
7		$CF_3CO_2^-$	**141b**·TFA	23	75:25
8		$CF_3CO_2^-$	**142**·TFA	78	60:40
9		$CF_3CO_2^-$	**143**·TFA	74	57:43

[a] Determined by chiral GC.

It has to be noted that prior to screening different catalytic systems, one experiment was done without any catalyst to examine the background reaction. As expected, the transfer

hydrogenation of cyclic enone **107b** was extremely slow when no catalyst was present to activate the substrate (Table 4.1, entry 1).

By running the conjugate reduction in dioxane at 60 °C for two days in the presence of commercially available Hantzsch ester **90a** (1.2 equivalents), we observed that L-*tert*-leucine methyl ester salt [**137a**·TFA] could effectively activate the substrate (83% conversion), leading to the formation of the desired product with moderate enantioselectivity (Table 4.1, entry 2). Starting from this observation, we sought to optimize the catalyst structure using the L-*tert*-leucine derivatives as the catalyst core. Trifluoroacetate salt of L-*tert*-leucine *tert*-butyl ester [**137b**·TFA] proved to be more active and enantioselective than its methyl ester analog, reaching an enantiomeric ratio of 76:24 (entry 3). These results demonstrated that activity and enantioselectivity increased with the bulkiness of the ester group. Ammonium salt made of L-*tert*-leucine dimethylamide (**144a**) and TFA was much less active and enantioselective than its amino ester derivatives (entry 4). It has to be noted that trifluoroacetate salt of (*S*)-BINAM-derived primary amine (*S*)-**147** also gave encouraging results as it afforded (*S*)-3-methylcyclohexanone (**95b**) with 41% conversion and moderate enantioselectivity (66:34 *er*, entry 5). Considering all these results amino ester salt bearing a bulky ester group (entry 3) appeared to be the most promising catalytic system for the conjugate reduction of 3-methylcyclohexanone (**107b**). We then intended to optimize the amino ester structure to improve the catalyst efficiency.

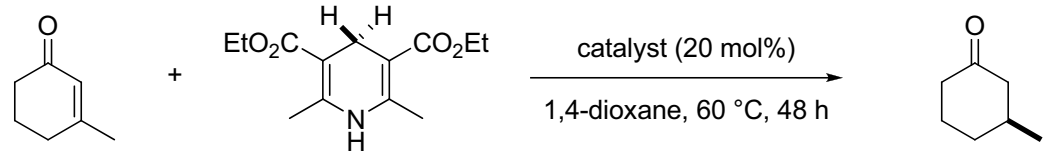
For this purpose the efficiency of amino acid derivatives **141**, **146** and **143** was also evaluated. L-Alanine methyl ester-based catalyst [**141a**·TFA] was not suitable to activate the enone **107b** (entry 6). However the activity and enantioselectivity of the ammonium salt could be increased from 51:49 *er* up to 75:25 *er* by replacing the methyl substituent of the ester group by a *tert*-butyl group (entry 7 vs. entry 6). These results are in agreement with the ones observed with trifluoroacetate salt of L-*tert*-leucine methyl and *tert*-butyl esters (entry 3 vs. entry 2); whereby the activity of the catalyst increased with the bulkiness of the ester group. By comparing the conversions and enantioselectivities obtained with L-alanine esters and their corresponding L-*tert*-leucine esters (entries 2 vs. 6 and entries 3 vs. 7), it appeared that a more bulky *α*-substituent led to a significant increase of the catalytic efficiency. With this idea in mind, we analyzed the behavior of trifluoroacetate salt of different amino methyl esters (L-phenylalanine and L-phenylglycine methyl esters, **142** and **143**, respectively, entries 8 and 9). With both catalytic systems good conversions (74-78%) were reached. They proved to be more active than their L-*tert*-leucine methyl ester analog [**137a**·TFA], however the desired saturated ketone (*S*)-**95b** was formed with lower enantioselectivities (entries 8 and 9 vs. 2).

Based on these observations, we intended to continue our investigation using L-*tert*-leucine *tert*-butyl ester [**137b**·TFA]. Once the amine structure was determined, our objective was then to define the basic structure of the counteranion.

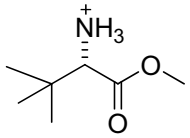
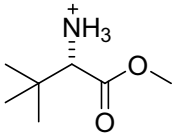
4.3.2.2 Determination of the Counteranion Effect and Motif

It has to be noted that all the amino esters presented in Table 4.1 (except **137b**) were purchased as hydrochloride salts. These commercially available salts (i.e. with chloride as counteranion) were also tested as catalysts in the conjugate reduction of 3-methylcyclohexenone (**107b**). It is worth underlining that not only the structure of the amino acid had an effect on the reactivity and enantioselectivity of the catalytic salt, but also the counteranion. This is illustrated in Table 4.2 with the comparison of the efficiency of trifluoroacetate and hydrochloride salts of L-*tert*-leucine methyl ester (**137a**). The hydrochloride salt proved to be less reactive than trifluoroacetate one, however it was more enantioselective. This tendency proved to be general and was also observed by comparing trifluoroacetate and hydrochloride salts of other amino esters.

Table 4.2: Counteranion-effect on the transfer hydrogenation of enone **107b**



107b (c = 0.1 M) + **90a** (1.2 equiv) → (*S*)-**95b**

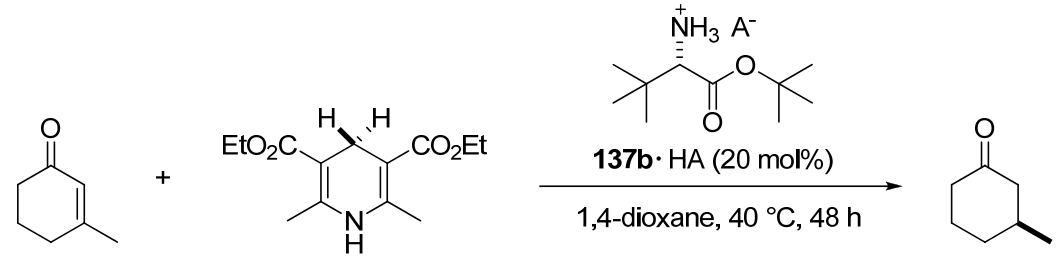
Entry	Catalytic salt: Ammonium ion	Counteranion		conv. [%][a]	*er*[a]
1		$CF_3CO_2^-$	**137a**·TFA	42	64:36
2		Cl^-	**137a**·HCl	11	78:22

[a] Determined by chiral GC.

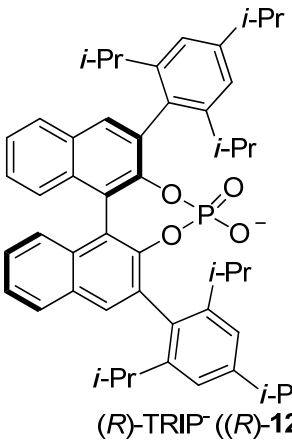
Considering these last results it was obvious that not only the structure of the amine played a role in the catalyst efficiency, but also that of the counteranion. We then decided to optimize the catalytic salt by screening different counteranions.

At this time *S. Mayer* was working in our laboratory on the development of a new organocatalytic concept for the transfer hydrogenation of α,β-unsaturated aldehydes **123**: the asymmetric counteranion-directed catalysis (ACDC, see Chapter 3).[120c] Encouraged by these studies, we also investigated chiral counteranions and in particular chiral BINOL-derived phosphate counteranions. A variety of these chiral BINOL-derived phosphoric acids, used mostly as Brønsted acid organocatalysts, were available in our laboratory and could be tested. The first attempt was done using TRIP (**126a**) as a counteranion, as this BINOL-derived phosphate proved to be the most efficient for numerous catalyses undertaken in our laboratory (Table 4.3).[120c,214,234]

Table 4.3: Use of TRIP as chiral counteranion and analysis of the matched/mismatched catalyst–ion pair combination



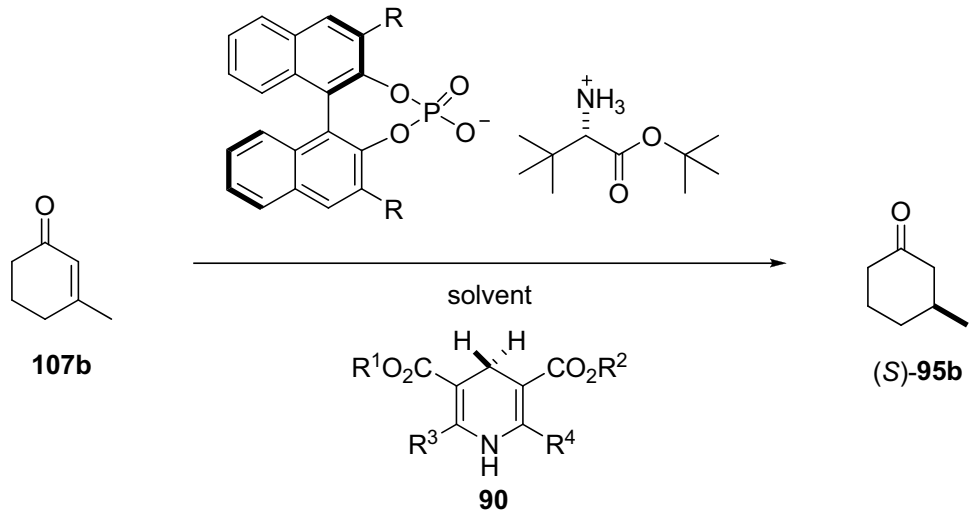
107b (c = 0.1 M) + **90a** (1.2 equiv) → (*S*)-**95b**

Entry	Counteranion (A^-)	conv. [%][a]	*er*[a]
1	 (*R*)-TRIP$^-$ ((*R*)-**126a**$^-$)	42	94:6
2	(*S*)-TRIP$^-$ ((*S*)-**126a**$^-$)	12	52:48

[a] Determined by chiral GC.

The combination of L-*tert*-leucine *tert*-butyl ester (**137b**) with (*R*)-TRIP ((*R*)-**126a**) to form the catalytic salt proved to be a real success and furnished (*S*)-3-methycyclohexanone ((*S*)-**95b**) with high enantioselectivity (94:6 *er*, entry 1). Under the reaction conditions (in dioxane at 40°C) the activity of the catalyst remained moderate after two days. Interestingly, with the other enantiomer of the counteranion ((*S*)-TRIP), nearly racemic product was formed (52:48 *er*, entry 2), illustrating a dramatic matched/mismatched case.

Considering the high enantioselectivity achieved in the presence of (*R*)-TRIP, the ground structure of the catalyst for the transfer hydrogenation of *α,β*-unsaturated ketone **107** was determined. We decided to optimize the reaction conditions and counteranion structure using chiral L-*tert*-leucine *tert*-butyl ester (**137b**) as amine and chiral (*R*)-BINOL-derived (phosphate) counteranions to form our catalytic system (Scheme 4.42).



Scheme 4.42: New catalytic system consisting of a chiral ammonium ion and a chiral (*R*)-BINOL-derived phosphate counteranion for the transfer hydrogenation of enones.

4.3.2.3 First Solvent Screening

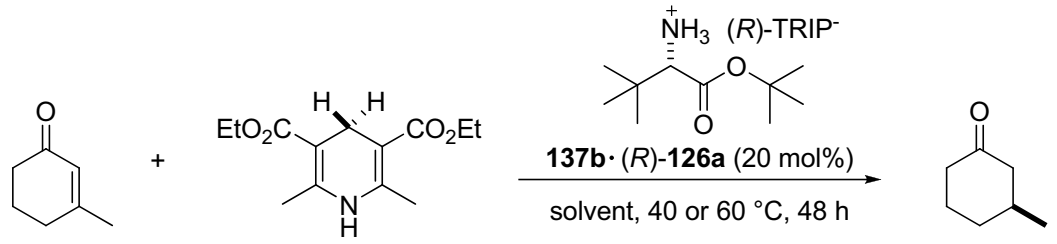
The Hantzsch ester-mediated transfer hydrogenation of 3-methylcyclohexenone (**107b**) in the presence of catalyst prepared from amino ester **137b** and (*R*)-TRIP (20 mol%) was performed in different solvents (Table 4.4).

In apolar aromatic solvents like toluene and benzene high conversions (85% and 76%, respectively) were reached without loss of enantioselectivity when the reactions were run at 60 °C (entries 2 and 6). As expected, a decrease of the temperature to 40 °C led to a slight increase of the enantioselectivity but in parallel a significant decrease of the activity (entries 3 and 7). In the presence of diethyl ether the reaction could not be heated over 40 °C (due to the low bowling point of the solvent), but even under these conditions very high conversion and

excellent enantioselectivity were achieved (entry 9). The use of THF (entry 8) as well as chlorinated (entries 4 and 5) and (di)polar solvents (entries 10 and 11) was not suitable for the studied conjugate reduction and led to a drop in reactivity.

Optimal enantioselectivity and reactivity were obtained in diethyl ether. Accordingly, this solvent was used for further optimization.

Table 4.4: Solvent effect on the transfer hydrogenation of enone **107b**



107b (c = 0.1 M) + **90a** (1.2 equiv) → (*S*)-**95b**

Entry	Solvent	Temperature [°C]	conv. [%][a]	*er*[a]
1	dioxane	60	27	94:6
2	toluene	**60**	**85**	**95:5**
3	toluene	40	31	97:3
4	CH_2Cl_2	60	29	85:15
5	$CHCl_3$	60	30	91:9
6	**benzene**	**60**	**76**	**95:5**
7	benzene	40	26	96:4
8	THF	60	12	90:10
9	**Et_2O**	**40**	**80**	**98:2**
10	MeOH	60	4	76:24
11	MeCN	60	16	77:23

[a] Determined by chiral GC.

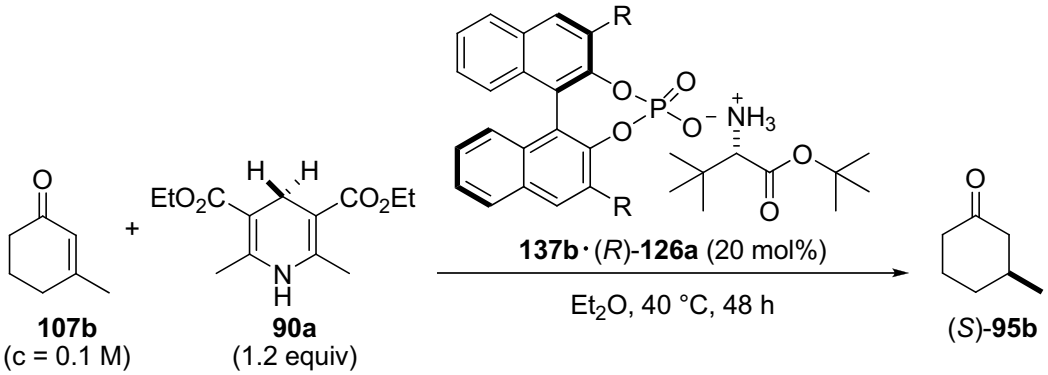
4.3.2.4 Optimization of the Chiral Counteranion

Optimization of the (R)-BINOL-derived phosphate (R)-126a

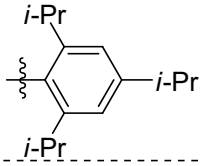
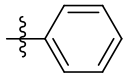
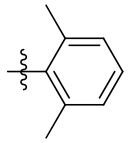
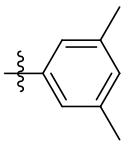
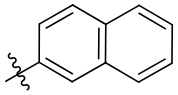
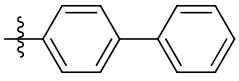
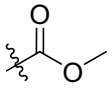
The catalyst salt prepared from L-*tert*-leucine *tert*-butyl ester (**137b**) and (*R*)-BINOL-derived (*R*)-**126a** was very active and enantioselective for the transfer hydrogenation of enone **107b**. To determine if the catalyst efficiency could be further improved, chiral (*R*)-BINOL-derived

phosphates (*R*)-**126b-g** bearing various substituents at the 3- and 3'-positions were screened (Table 4.5).

Table 4.5: Screening of chiral (*R*)-BINOL-derived phosphates



107b (c = 0.1 M) + **90a** (1.2 equiv) → (*S*)-**95b**

Entry	R =	conv. [%][a]	*er*[a]
1	(*R*)-**126a**: 	**80**	**98:2**
2	(*R*)-**126b**: 	51	83:17
3	(*R*)-**126c**: 	50	94:6
4	(*R*)-**126d**: 	62	95:5
5	(*R*)-**126e**: 	49	89:11
6	(*R*)-**126f**: 	48	95:5
7	(*R*)-**126g**: 	49	90:10

[a] Determined by chiral GC.

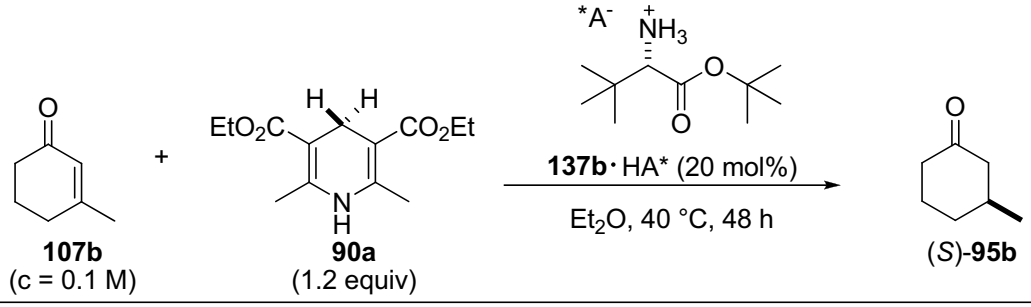
Surprisingly, in the presence of all these other BINOL-derived phosphates, the transfer hydrogenation was much slower (entries 2-7). A loss of enantioselectivity was also observed when (*R*)-**126a** was replaced by its analog compounds (*R*)-**126b-f**, all bearing less sterically demanding aromatic substituents at the 3- and 3'-positions (entries 1-6). By replacing the aromatic substituents of (*R*)-**126a-f** with ester groups ((*R*)-**126g**, entry 7 vs. entries 1-6), we

could not improve the catalyst reactivity and enantioselectivity, which were still lower than those obtained using (*R*)-**126a**.

Evaluation of further (R)-BINOL-derived counteranions

Other (*R*)-BINOL-derived acids, which were available in our laboratory, were used to form catalytic salts (Table 4.6).

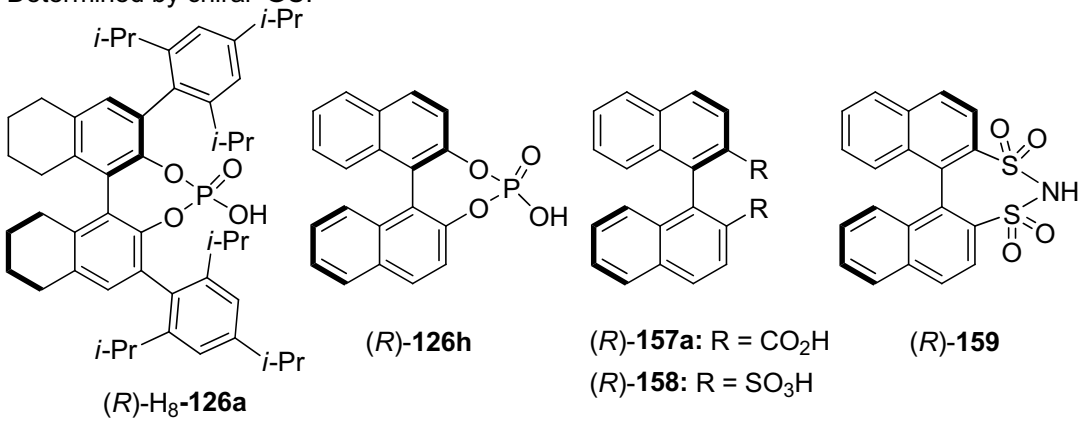
Table 4.6: Evaluation of further (*R*)-BINOL-derived counteranions



107b (c = 0.1 M) + **90a** (1.2 equiv) → (*S*)-**95b**

Entry	HA* =	conv. [%][a]	*er*[a]
1	(*R*)-**126a**	**80**	**98:2**
2	(*R*)-H_8-**126a**	95	95:5
3	(*S*)-H_8-**126a**	30	58:42
4	(*R*)-**126h**	70	89:11
5	(*R*)-**157a**	33	74:26
6	(*R*)-**158**	16	77:23
7	(*R*)-**159**	9	86:14

[a] Determined by chiral GC.



(*R*)-H_8-**126a** (*R*)-**126h** (*R*)-**157a:** R = CO_2H (*R*)-**158:** R = SO_3H (*R*)-**159**

Octahydro-BINOL phosphate (*R*)-H_8-**126a** proved to be more reactive than its saturated analog (*R*)-**126a**. However, it was slightly less enantioselective (entries 1-2). A strong matched/mismatched effect was once again illustrated by running the transfer hydrogenation in the presence of the opposite enantiomeric counteranion ((*S*)-H_8-**126a**) (entries 2-3).

L-*tert*-Leucine *tert*-butyl ester (**137b**) was also treated with chiral non-substituted (*R*)-BINOL-derived phosphoric acid (*R*)-**126h**, dicarboxylic acid (*R*)-**157a**, disulfonic acid (*R*)-**158** and disulfonimide (*R*)-**159** to form new catalytic salts. As expected, the phosphoric acid (*R*)-**126h** bearing only hydrogen atoms at the 3- and 3'-positions was less enantioselective than its TRIP analog (*R*)-**126a** (entry 4 vs. entry 1). The amine salt prepared with dicarboxylic acid (*R*)-**157a** had moderate activity and enantioselectivity (entry 5). The enantiomeric ratio obtained in entry 5 (74:26 *er*) could be slightly or significantly increased by replacing dicarboxylic acid (*R*)-**157a** with disulfonic acid (*R*)-**158** or disulfonimide (*R*)-**159**, respectively, though with a resulting loss of catalyst reactivity (entries 6-7 vs. entry 5).

From all the non-substituted (*R*)-BINOL-derived counteranions evaluated for the transfer hydrogenation of 3-methylcyclohexenone (**107b**, entries 4-7), (*R*)-BINOL-derived phosphate motif (*R*)-**126h** was the most efficient and could be optimized by incorporating substituents at the 3- and 3'-positions to generate (*R*)-**126a**, which proved to be the most enantioselective counteranion tested. Accordingly, we favored the use of (*R*)-TRIP ((*R*)-**126a**) in combination with L-*tert*-leucine *tert*-butyl ester (**137b**) to form our catalytic system for the conjugate reduction of enones.

4.3.3 Optimization of the Reaction Conditions

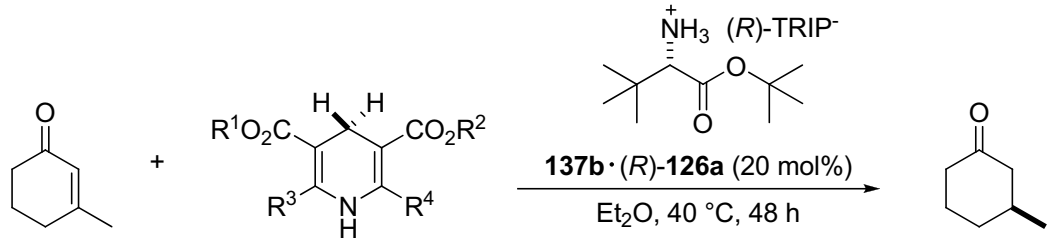
Once an efficient catalytic system was found, our objective became to optimize the reaction conditions further in order to improve the reaction conversion and, if possible, to reduce the catalyst loading (at this stage a conversion of 80% was reached after two days using 20 mol% of catalyst).

4.3.3.1 Hantzsch Ester Structure and Concentration

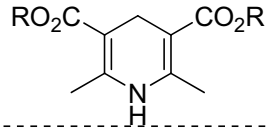
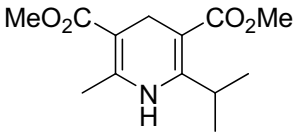
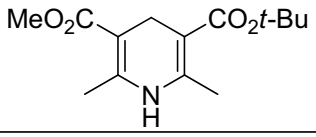
We first examined the effect of the Hantzsch ester structure on the efficiency (reactivity and enantioselectivity) of the transfer hydrogenation (Table 4.7).[120]

Hantzsch esters **90a** and **90c** are commercially available and were purchased from Sigma-Aldrich. Other dihydropyridines (**90b** and **90d-g**) were prepared by other group members.[235]

Table 4.7: Optimization of dihydropyridine structure for the transfer hydrogenation of enone **107b**



107b (c = 0.1 M) + **90** (1.2 equiv) → (*S*)-**95b**

Entry	Hantzsch ester		conv. [%][a]	*er*[a]
				
1	**90a**:	**R = Et**	**80**	**98:2**
2	**90c**:	R = *t*-Bu	58	97:3
3	**90d**:	R = *neo*-pent	85	96:4
4	**90e**:	R = *i*-Bu	50	95:5
5	**90f**:	R = Me	69	94:6
6	**90b**:		76	95:5
7	**90g**:		65	96:4

[a] Determined by chiral GC.

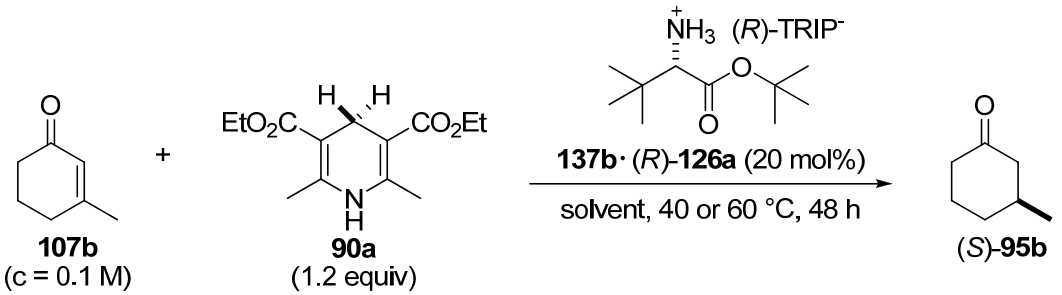
By modifying the ester groups of dihydropyridine **90** we did not observe very significant variations in the enantioselectivity, although diethyl ester derivative **90a** was slightly more enantioselective than its analogs (entries 1-5). On the contrary, the reactivity was much more strongly affected by the structure of the Hantzsch ester, with the highest conversion observed using **90a** (entry 1). The use of non-symmetrical dihydropyridines **90b** and **90g** led to a slight loss of enantioselectivity and a decrease of the reactivity (entries 6-7). According to these results, commercially available diethyl ester Hantzsch ester **90a** was the optimal hydrogen source in terms of enantioselectivity. Moreover its use allowed us to obtain high conversions. It was therefore chosen as the hydrogen source for the transfer hydrogenation of 3-methylcyclohexenone **107b**.

It has to be specified that the increase in the dihydropyridine **90a** concentration had no effect on the catalysis efficiency, so we continued our optimization processes using 1.2 equivalents of this Hantzsch ester.

4.3.3.2 Solvent and Temperature

As previously described (see Chapter 4.3.2.3, Table 4.4), the reactivity increased significantly with increased temperature. However, the positive effect of the temperature on the reaction conversion was counterbalanced by a slight loss of enantioselectivity. A good compromise was to run the transfer hydrogenation at 60 °C (instead of 40 °C). Since such a temperature could not be reached using volatile diethyl ether as solvent, other ethereal solvents were tested (Table 4.8).

Table 4.8: Screening of ethereal solvents for the transfer hydrogenation of enone **107b**



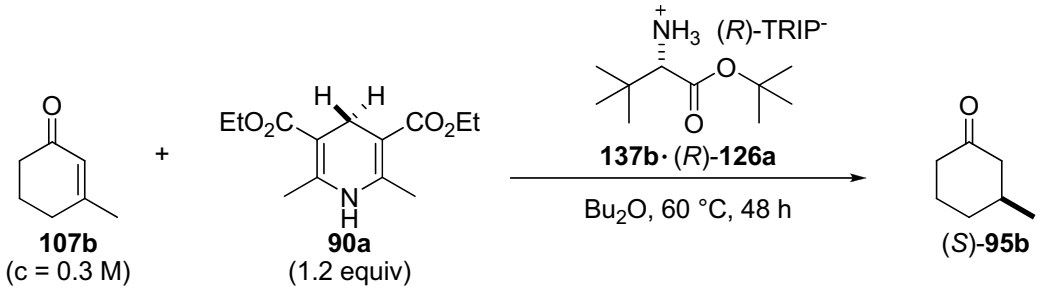
Entry	Solvent	Temperature [°C]	conv. [%][a]	*er*[a]
1	Et_2O	40	80	98:2
2	MTBE	60	24	98:2
3	Bu_2O	40	47	98:2
4	**Bu_2O**	**60**	**90**	**97:3**

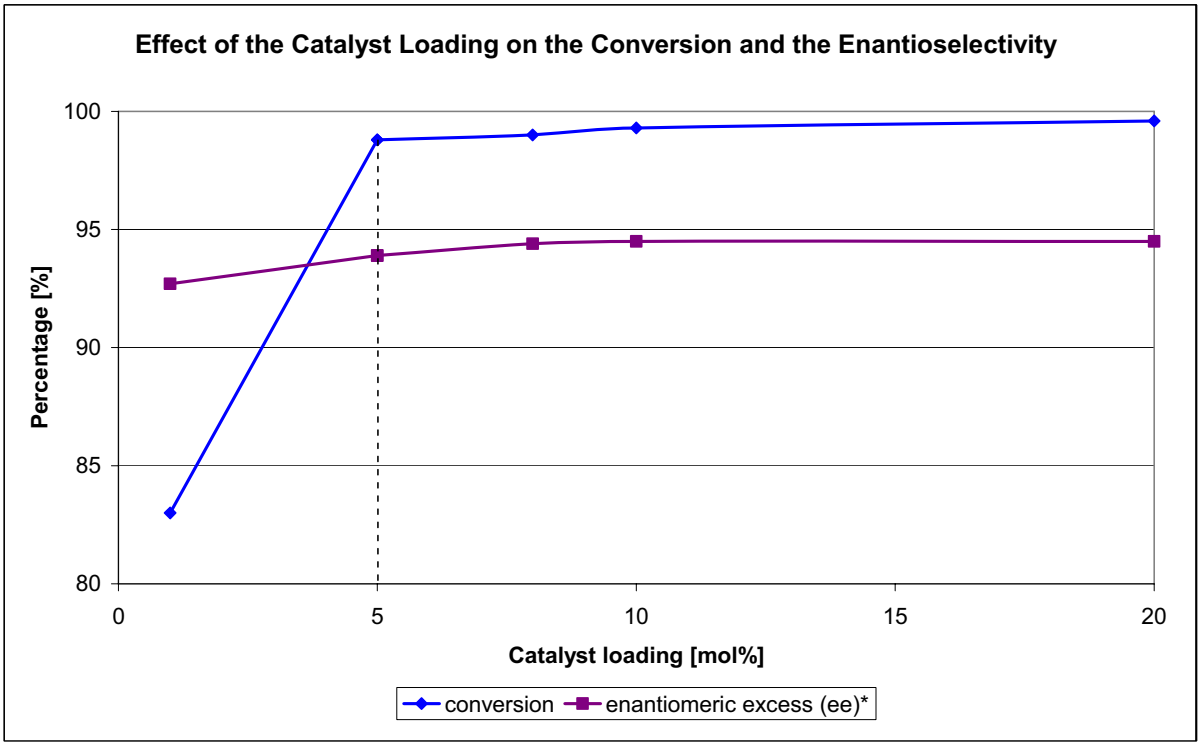
[a] Determined by chiral GC.

Methyl *tert*-butyl ether (MTBE) was not a suitable solvent for the reaction as its use led to a dramatic decrease of the reactivity, even at 60 °C (entry 2). On the contrary, in the presence of dibutyl ether a conversion of 90 % was reached after 48 hours at 60°C, without significant loss of enantioselectivity (97:3 *er*, entry 4). This solvent was therefore selected for further investigations.

4.3.3.3 Catalyst Loading

In the previous optimization processes a relatively high catalyst loading (20 mol%) was used in order to obtain a catalytic efficiency that was high enough to detect reactivity and enantioselectivity variations while modifying the reaction conditions. To make this catalytic conjugate reduction more attractive, the use of a lower amount of catalyst was required. It should be noted that these investigations were done after an initial small screening of the substrate concentration (0.02-0.50 molar) during which the higher catalytic efficiency was obtained at a concentration of 0.3 molar. Consequently, this concentration was used for the screening of the catalyst loading (Scheme 4.43)





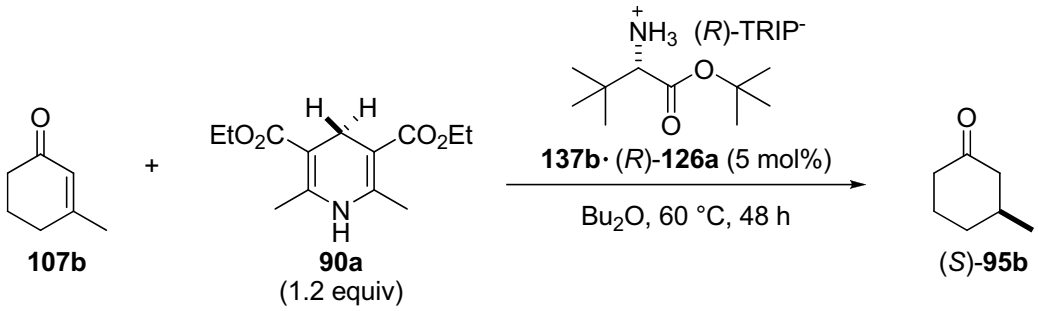
Scheme 4.43: Screening of the catalyst loading for the transfer hydrogenation of enone **107b** (*To facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

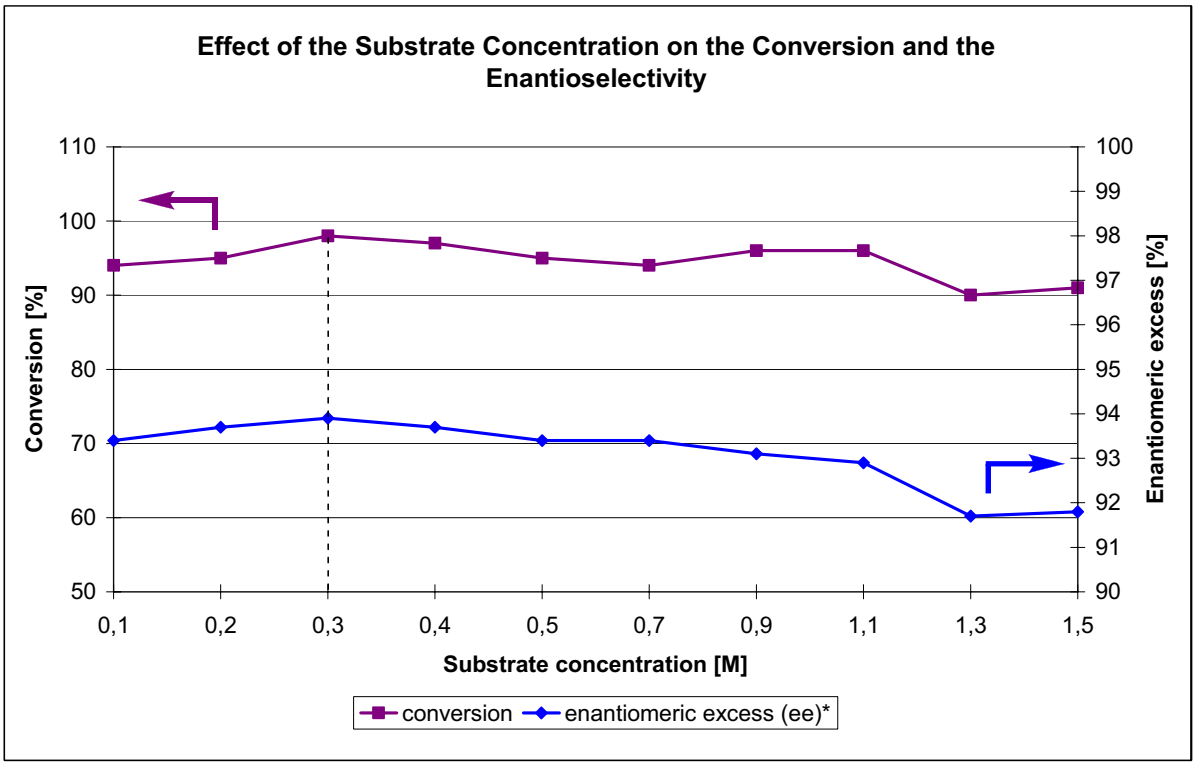
A reduction of the catalyst loading from 20 to 5 mol% had no significant effect on reactivity and enantioselectivity of the reaction. However, a further decrease resulted in decreased

conversion of the enone (Scheme 4.43). Based on this screening, 5 mol% of catalyst were used for further optimizations.

4.3.3.4 Substrate Concentration

Since chemical processes are usually economically and ecologically more attractive when they are highly concentrated (i.e. use minimum solvent), we intended to raise the enone concentration as long as no loss of catalytic efficiency was noticeable (Scheme 4.44).





Scheme 4.44: Optimization of the substrate concentration for the catalytic transfer hydrogenation of **107b**. (*To facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

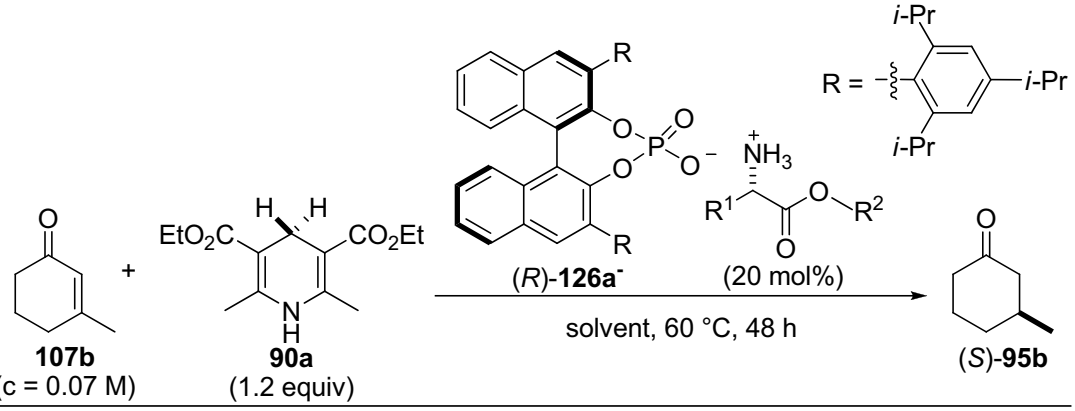
An increase of the substrate concentration from 0.1 until 0.3 molar had a positive effect on the reactivity of the catalysis without affecting the enantioselectivity. At higher substrate concentrations (and consequently higher concentrations of the Hantzsch ester **90a**) a loss of

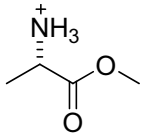
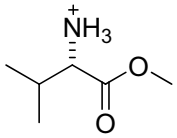
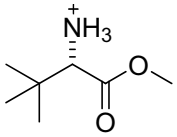
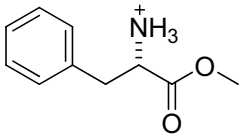
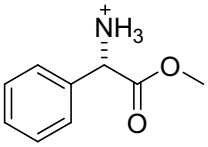
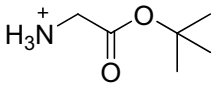
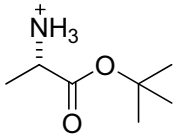
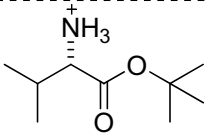
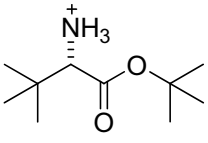
efficiency was observed. This phenomenon could be explained by the low solubility of dihydropyridine **90a** in dibutyl ether.
The concentration of 0.3 molar was thus used to examine the reaction scope (see Chapter 4.3.4).

4.3.3.5 Final Catalyst Optimization

Despite optimizing the reaction conditions and reducing the catalyst loading, we were still not fully satisfied with the enantioselectivity of the catalytic system. We then rescreened amino esters (Table 4.9), including some that were missing in the previous amine structure investigation (see Chapter 4.3.2.1). For this screening, salts prepared with BINOL-derived phosphate **126a** were tested under the same reaction conditions as those used in the initial screening (reactions run in dioxane at 60 °C, see Table 4.1).
As with the amino ester trifluoroacetate salts (see Chapter 4.3.2.1), we observed the *tert*-butyl ester derivatives were more suitable for the studied catalysis than their methyl ester analogs. Interesting results of this new catalyst structure investigation can be summarized as follows; the phosphoric acid derivative alone ((*R*)-**126a**) was much less active than the amino acid ester salts and generated the product in only 60:40 *er* (entry 1). Moreover the chirality of the amino acid seemed to be important, as achiral glycine-derived salt [**195**·(*R*)-**126a**] gave significantly reduced enantioselectivity (entry 7 vs. entries 2-6 and 8-10). Accordingly, catalyst salts consisting of a chiral ammonium ion and a chiral counteranion were favored. Among this salts, it appeared that the one made of L-valine ester derivatives **139** (entries 3 and 9) were more reactive and slightly more enantioselective than their L-*tert*-leucine ester analogs **137** (entries 4 and 10). L-Valine *tert*-butyl ester-based salt (**139a.** (*R*)- **126a**) was chosen for further studies as it proved superior in comparison with other amino acid esters with regard to catalytic efficiency and enantioselectivity.
Using this optimized catalytic salt ([**139a**·(*R*)-**126a**]) all the screenings previously reported (screenings of the solvent, temperature, Hantzsch ester, substrate concentration and catalyst loading) were repeated, leading to the same results as those obtained with L-*tert*-leucine *tert*-butyl ester salt ([**137b**·(*R*)-**126a**]).

Table 4.9: Finer optimization of the amino ester structure for the transfer hydrogenation of enone **107b**



Entry		Ammonium ion	Solvent	conv. [%][a]	*er* (*ee* [%])[a]
1	(*R*)-**126a**:	-	Bu_2O	25	60:40 (21)
2	**141a**·(*R*)-**126a**:		dioxane	14	80:20 (61)
3	**139b**·(*R*)-**126a**:		dioxane Bu_2O	23 75	92:8 (84) 94:6 (89)
4	**137a**·(*R*)-**126a**:		dioxane Bu_2O	12 66	88:12 (76) 94:8 (88)
5	**142**·(*R*)-**126a**:		dioxane	17	88:12 (76)
6	**143**·(*R*)-**126a**:		dioxane	10	80:20 (59)
7	**195**·(*R*)-**126a**:		dioxane	66	74:26 (47)
8	**141b**·(*R*)-**126a**:		dioxane	27	91:9 (82)
9	**139a**·(*R*)-**126a**:		**dioxane** **Bu_2O**	**24** **81**	**95:5 (91)** **97:3 (95)**
10	**137b**·(*R*)-**126a**:		dioxane Bu_2O	18 73	95:5 (90) 97:3 (94)

[a] Determined by chiral GC.

4.3.4 Investigation of the Reaction Scope

4.3.4.1 Scope of the Catalytic Reaction

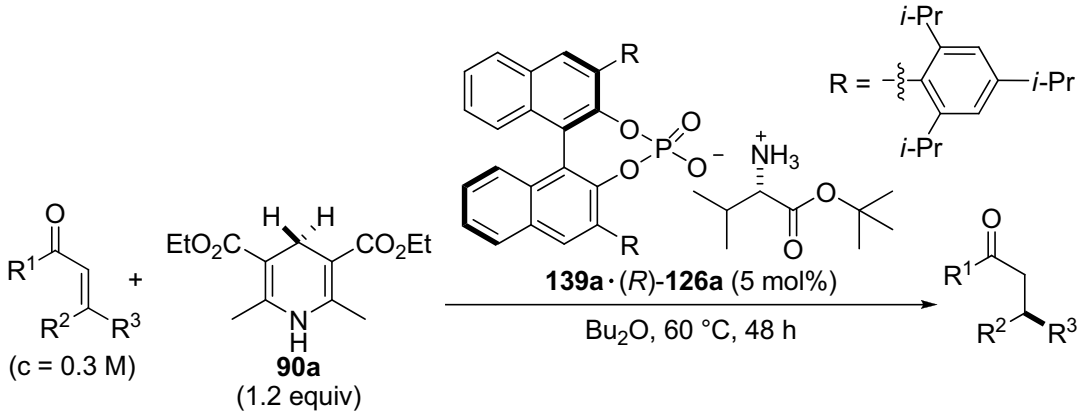
According to the screenings of catalytic system, solvent, temperature, substrate concentration, Hantzsch ester structure, and catalyst loading reported in Chapter 4.3.3, we identified the following protocol as optimal: Treating the enone (0.3 molar) with commercially available Hantzsch ester **90a** (1.2 equivalents) in the presence of catalytic salt [**139a** • (*R*)-**126a**] (5 mol%) at 60 °C in dibutyl ether for 48 hours gave the saturated ketones in high yields and enantioselectivities (Table 4.10).

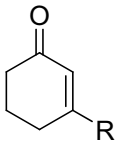
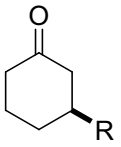
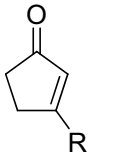
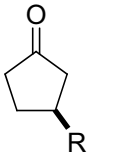
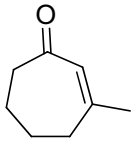
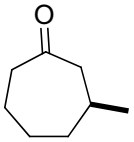
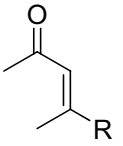
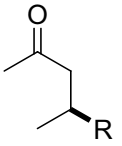
After having developed an efficient and highly enantioselective transfer hydrogenation of 3-methylcylohexenone **107b** to (*S*)-3-methylcyclohexanone **95b** *via* iminium catalysis in the presence of Hantzsch ester **90a**, we were interested to extend the methodology to other *β*,*β*-disubstituted *α*,*β*-unsaturated ketones (cyclic and also acyclic), and thus, evaluate the scope of the catalysis (Table 4.10). Since most of the generated ketones (**95** and **114**) are volatile, yields were measured by GC or HPLC analysis. Less volatile products like **95g** and **95i** (Table 4.10, entries 5 and 9) were also isolated by column chromatography. In these cases chromatographically determined and isolated yields were nearly identical. The absolute configuration of the products **95b** and **95c** was determined by using chiral-GC analysis and comparing the retention times measured for the enriched compounds with their corresponding commercially available (*R*)- or (*S*)-enantiomers. The other absolute configurations were assigned by analogy.

The developed transfer hydrogenation was particularly well suited for *β*-alkyl substituted cyclohexenones (entries 1-5), in which case the products were generally formed in very high yields and good to excellent enantioselectivities. A lower enantioselectivity was reached with phenyl substituted enone **107a**, although the corresponding saturated ketone **95a** was obtained almost quantitatively (entry 6). Unfavorable steric and electronic environments of **107a** might explain this loss of selectivity. Cyclopentenones were slightly less reactive than cyclohexenones but provided the products in equally high enantioselectivities (entries 7-9). In those cases a higher catalyst loading (10 mol%) was used to improve the substrate reactivity. Cycloheptenones were also suitable substrates, and 3-methylcyclohept-2-enone (**107j**) gave the desired product **95j** with excellent yield and enantioselectivity (entry 10). Not only cyclic enones **107** were suitable substrates for the developed conjugate reduction, acyclic ketones

113 could also be used. However they were reduced to the corresponding saturated ketones **114** with slightly lower enantioselectivities (entries 11 and 12).

Table 4.10: Preliminary scope of the catalytic transfer hydrogenation



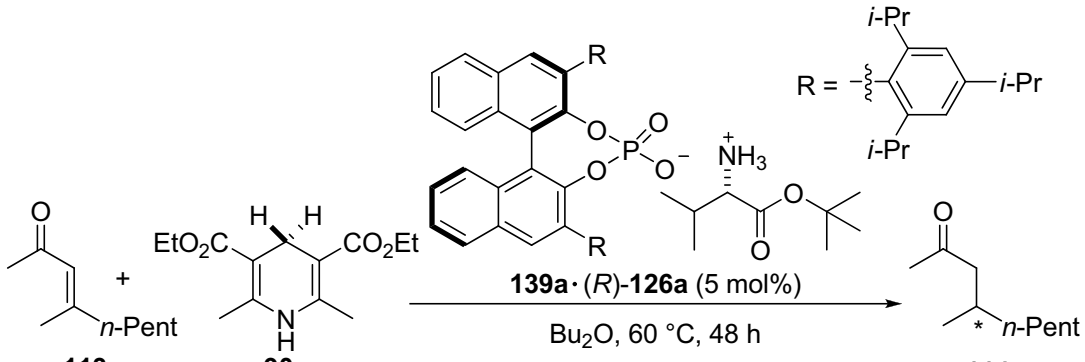
Entry	Enone	Product	Yield [%][a]	*er*[a]
				
1	R = Me (**107b**)	**95b**	99	97:3
2	R = Et (**107d**)	**95d**	98	98:2
3	R = *i*-Bu (**107e**)	**95e**	89	98:2
4	R = *i*-Pr (**107f**)	**95f**	94	99:1
5	R = CH_2CH_2Ph (**107g**)	**95g**	99[b]	98:2[c]
6	R = Ph (**107a**)	**95a**	99	92:8
				
7[d]	R = Me (**107c**)	**95c**	78	99:1
8[d]	R = Et (**107h**)	**95h**	71	98:2
9[d]	R = CH_2CH_2Ph (**107i**)	**95i**	68[c]	98:2[c]
10	 **107j**	 **95j**	>99	98:2
				
11	R = Ph (**113a**)	**114a**	81	15:85
12	R = CO_2Et (**113b**)	**114b**	>99	8:92

[a] Determined by chiral GC. [b] Isolated yield. [c] Determined by HPLC. [d] With 10 mol% of catalyst.

4.3.4.2 Effect of the Enone Geometry

Aliphatic acyclic ketone **113c** was prepared as *cis*-enriched and *trans*-enriched isomers and thus used for investigating the effect of the enone geometry on the conjugate reduction (Table 4.11). As expected, the reactivity of this acyclic *α,β*-unsaturated ketone was lower than with cyclic enones (especially starting from a *cis*-enriched substrate, entry 1). However, we were pleased to see that our catalytic system induced enantioselectivity (84:16 *er*, starting from *trans*-enriched isomer, entry 2). It has to be noted that we used *cis*- or *trans*-enriched (and not pure *cis*- or *trans*-) unsaturated ketone **113c** for these experimentations, as only a partial separation of both isomers could be achieved by column chromatography. The results reported in Table 4.11 point out that in contrast to the stereoconvergent enal transfer hydrogenations previously developed in our laboratory,[120b] the enantioselectivity of the enone conjugate reductions strongly depends on the geometry of the substrate (entries 1 and 2): *cis*- and *trans*-**113c** give opposite enantiomers of product **114c**. Obviously, only pure *cis*- or *trans*-enone should be employed to reach optimal enantioselectivities.

Table 4.11: Effect of the substrate geometry on the transfer hydrogenation of enones



113c (*c* = 0.3 M) + **90a** (1.2 equiv) → **114c**

Entry	Enone	Product	Yield [%][a]	*er*[a]
2	trans/**cis** = 1:44	(*S*)-**114c**	36	75:25
3	**trans**/cis = 14:1	(*R*)-**114c**	65	84:16

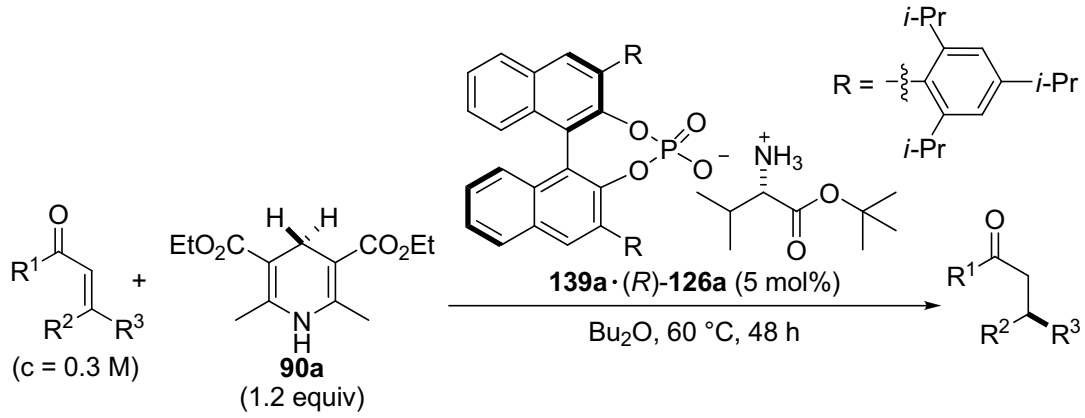
[a] Determined by chiral GC.

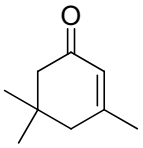
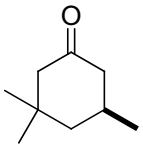
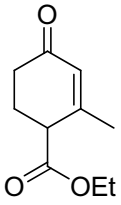
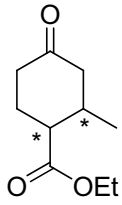
4.3.4.3 Extension to More Complex Substrates

We then intended to apply the developed catalytic conjugate reduction to isophorone (**105a**), a challenging test case given both *β*,*β*-disubstitution and the geminal methyl groups at the *β*'-position (i.e. at carbon *C*-5), and to Hagemann's ester (**196**, Table 4.12).

Although isophorone is a quite difficult substrate, it could be reduced to saturated ketone **106a** under our reaction conditions with high enantioselectivity, although with 5 mol% catalyst loading the product was generated in only 42% yield (entry 1). We were pleased to find that the conjugate reduction also worked to some extent even with Hagemann's ester (**196**), leading to the formation of cyclohexanecarboxylic acid derivative **197** with moderate yield and enantioselectivity (entry 2).

Table 4.12: Extension of the substrate scope of the catalytic transfer hydrogenation

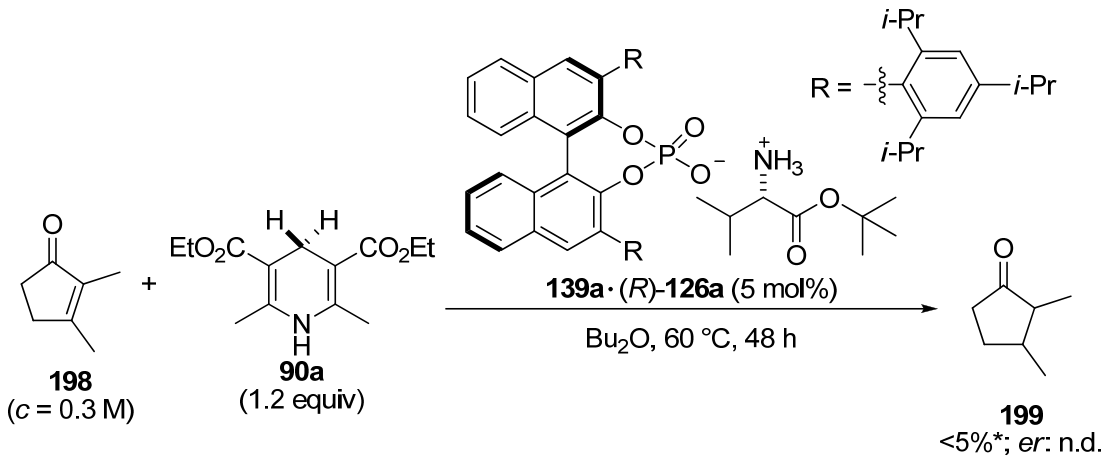


Entry	Enone	Product	Yield [%]	*er*[a]
1	 **105a**	 **106a**	42	94:6
2	 **196**	 **197** *dr* = 1:1	36	*diast. 1:* 75:25 *diast. 2:* 72:28

[a] Determined by chiral GC. (diast. = diastereoisomer).

4.3.4.4 Effect of an *α*-Substituent

After establishing that the developed catalytic process worked well with *β*-alkyl-substituted cyclic enones, we wished to determine if it could be applied to the conjugate reduction of cyclic enone **198**; a particularly challenging substrate due to increased steric demand at the *α*-position (Scheme 4.45). The result of this experiment showed that the introduction of a substituent at the *α*-position prevented the transfer hydrogenation from occurring, probably because the subtrate activation with catalyst [**139a**·(*R*)-**126a**] was hindered and thus the iminium ion formation could not take place.

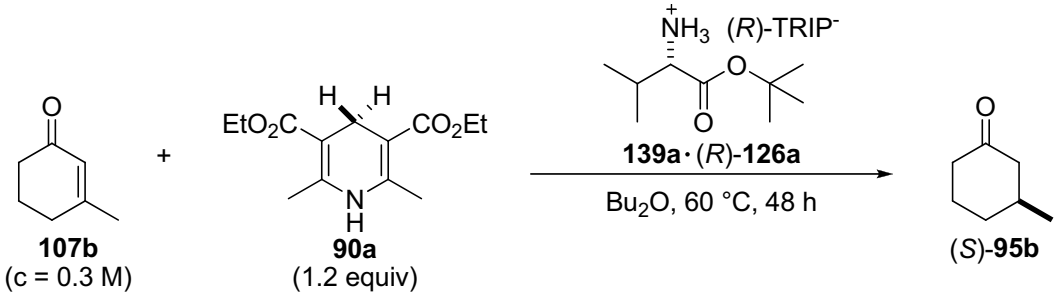


Scheme 4.45: Effect of an *α*-substituent on the efficiency of the transfer hydrogenation.

4.3.5 Scale-Up of the Transfer Hydrogenation

For the exploration of the reaction scope, the catalyses were done on a 10-40 milligram scale. After observing that the transfer hydrogenation was really effective on such a relatively small scale, we became interested in a scale up of the reaction. For this purpose we used commercially available 3-methylcyclohexenone **107b** as the substrate. Due to the high molecular weight of the phosphonate counteranion (**126a**$^-$), a further reduction in catalyst loading seemed desirable (see Table 4.13). It has to be specified that between the development of the catalytic conjugate reduction reported in Chapter 4.3.4 (see Tables 4.10-4.12) and this scale-up process, the method employed to purify the BINOL-derived phosphates **126** was improved by *M. Klußmann* and *S. Marcus* and our laboratory was then able to generate (*R*)-TRIP with higher purity and activity than the one previously used.

Table 4.13: Reduction of the catalyst loading



107b (c = 0.3 M) + **90a** (1.2 equiv) → (*S*)-**95b**

Entry	Catalyst loading [mol%] Amino ester (**139a**)	(*R*)-TRIP ((*R*)-**126a**)	conv. [%][a]	*er*[a]
1	5.0	5.0	> 99	97:3
2	3.0	3.0	95	97:3
3	2.0	2.0	95	97:3
4	1.0	1.0	93	96:4
5	5.0	4.0	99	97:3
6	5.0	3.0	99	97:3
7	5.0	2.0	98	97:3
8	5.0	1.0	93	97:3
9	5.0	0.1	94	97:3

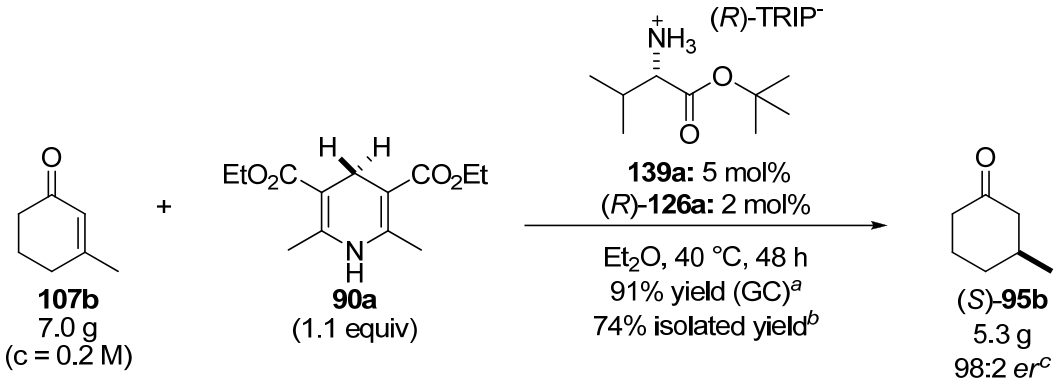
[a] Determined by chiral GC.

By decreasing the catalyst loading to 3 mol%, a slight drop in reactivity and enantioselectivity was observed (entry 1 vs. entry 2). This effect was amplified by further diminishing the amount of TRIP (entries 3-4). However, by keeping the concentration of the L-valine derivative **139a** at 5 mol%, the TRIP loading could be reduced to 2 mol% without loss of conversion or enantioselectivity (entries 5-7) and even to 0.1 mol% with just an insignificant decrease in the catalyst efficiency.

Once the problem of the high (*R*)-TRIP loading was solved, we met a new difficulty: the product isolation from dibutyl ether was difficult to achieve *via* distillation. This problem was overcome by using diethyl ether as the solvent, which could be separated from our product by very careful rotary evaporation under slightly reduced pressure at room temperature. As it was observed in the previous experiments (see solvent optimization, Chapter 4.3.3.2, Table 4.8) a lower reactivity was observed in the presence of diethyl ether.

After rescreening different (*R*)-TRIP loadings (from 0.1 to 2.0 mol%) and substrate concentrations using diethyl ether as solvent, we identified the following protocol as optimal: Treating the 3-methylcyclohexenone (**107b**, 0.2 molar) with commercially available Hantzsch ester **90a** (1.1 equivalents) in the presence of valine derivative **139a** (5 mol%) and TRIP ((*R*)-

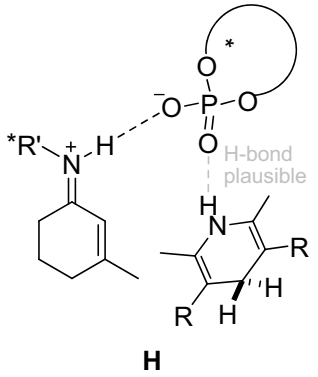
126a, 2 mol%) at 40 °C in diethyl ether for 48 hours gave the saturated ketones **95b** (5.3 g) in high yield and enantioselectivity (Scheme 4.46).



Scheme 4.46: Scale-up of the transfer hydrogenation of 3-methylcyclohexene. ([a] Determined by chiral GC before purification by column chromatography. [b] Volatile compound; loss of product during the evaporation of solvent and eluents. [c] Determined by GC).

4.3.6 Mechanistic Considerations

Mechanistically, we assume the reaction to proceed *via* a hydrogen bond assisted iminium phosphate ion pair. In addition to binding the iminium ion, the phosphate counteranion may also interact with the Hantzsch ester *via* an additional hydrogen bond (Scheme 4.47).

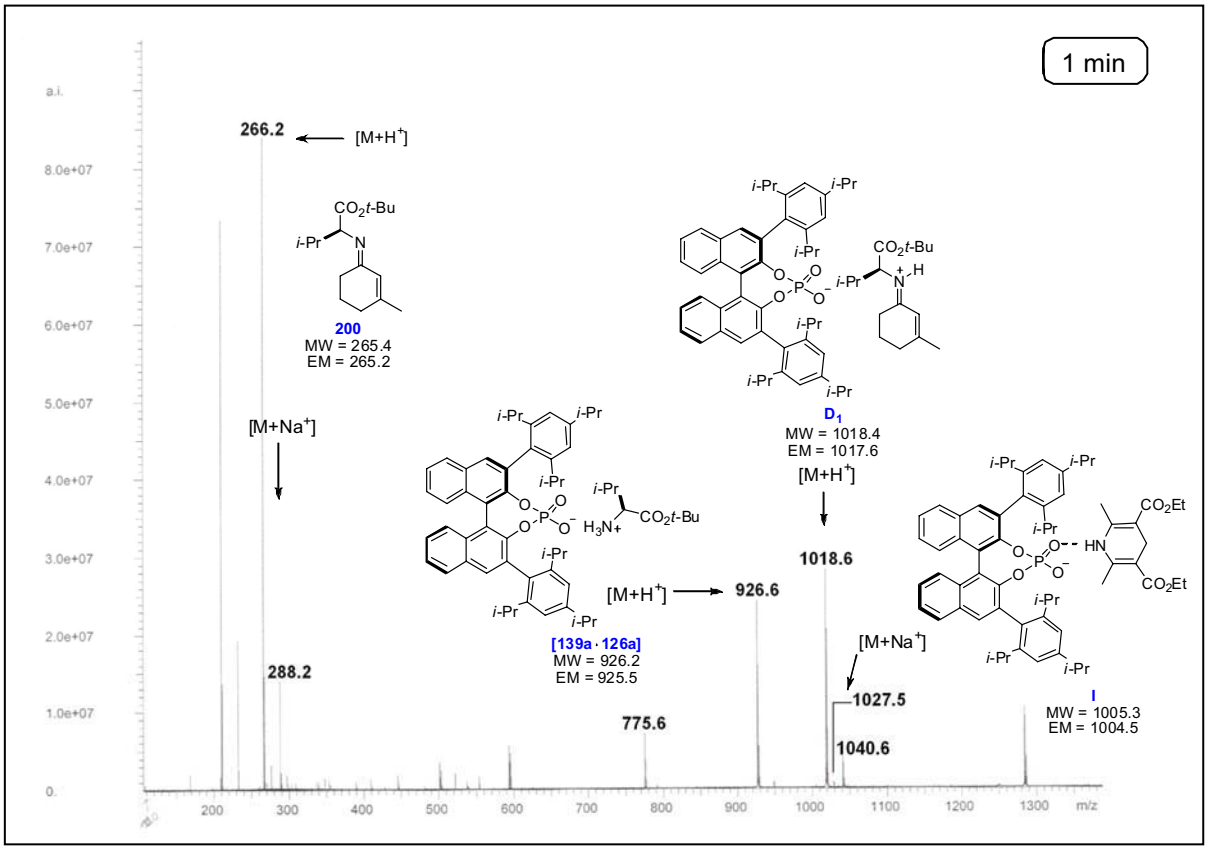


Scheme 4.47: Hypothetical transition state for the transfer hydrogenation of enone **107b**.

To test these assumptions and gain more insight into the mechanism of the reaction in solution we followed the progress of the reaction using Electrospray-Ionization Mass Spectroscopy (ESI-MS). For this purpose we carried out the transfer hydrogenation of enone **107b** (about 70 milligrams) under the reaction conditions used for the scaled up reaction (5 mol% of amino ester **139a**, 2 mol% of (*R*)-TRIP with 1.1 equivalents of dihydropyridine **90a** in diethyl ether

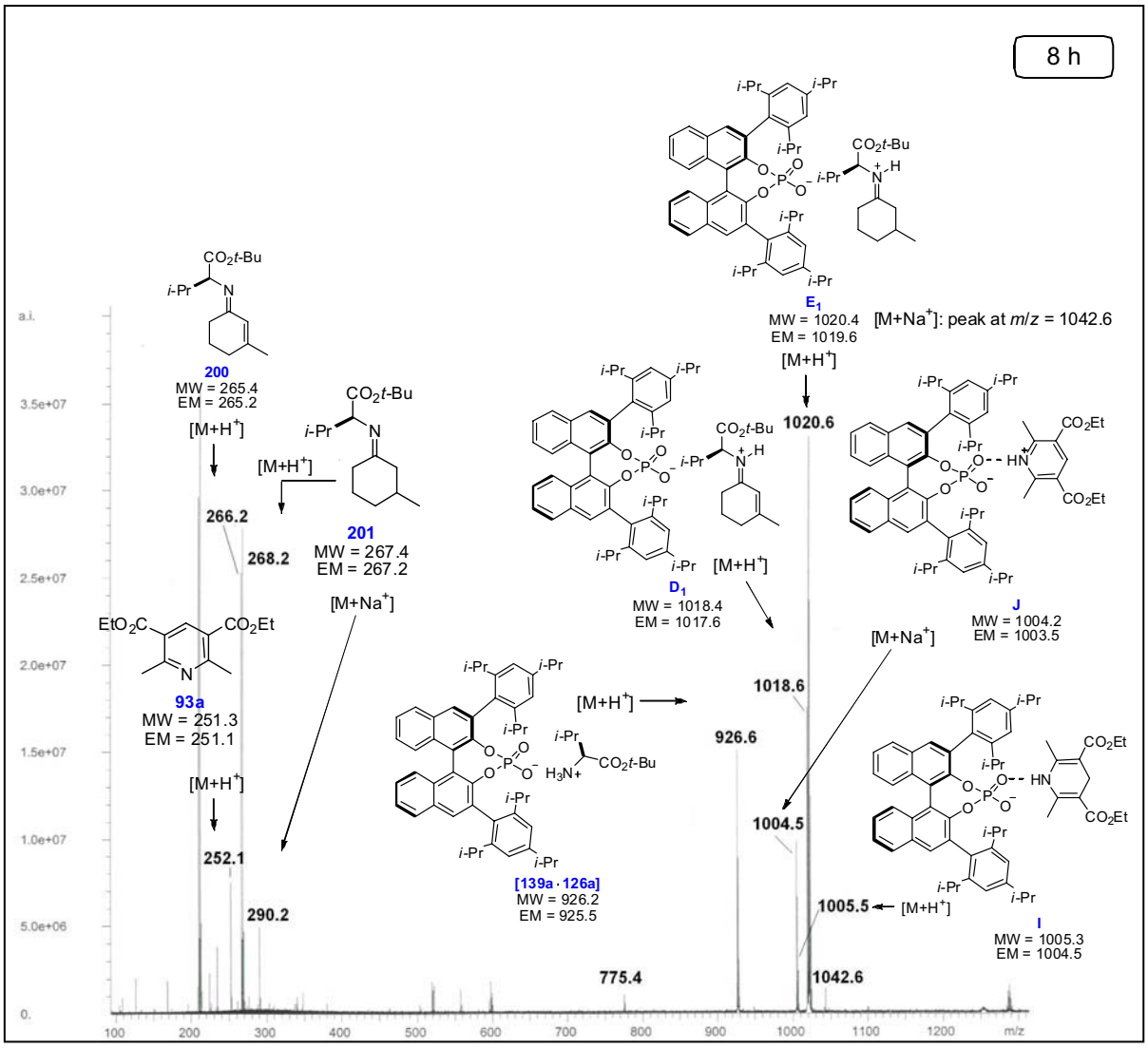
at 40 °C, see Chapter 4.3.5). Samples were taken from the reaction mixture at different time intervals over 24 hours and submitted to ESI-MS analysis.

Spectra obtained after one minute and eight hours are shown in the following schemes (Schemes 4.48-4.49). It has to be noted that the reaction mixture was not homogeneous as Hantzsch ester is only partially soluble in diethyl ether. For the ESI-MS measurements we only took an aliquot from homogeneous solution (obtained after stopping the stirring for a few seconds). For this reason, the peaks corresponding to the dihydropyridine **90a** have a low intensity since only a small amount of it was dissolved in the solvent and thus measured. Moreover because of the low mass of the substrate **107b** and its corresponding saturated ketone (**95b**), these compounds could not be detected using ESI-MS, as the utilized spectrometer could only detect molecules with molecular weight higher than 200-300 g/mol. For this reason no peaks corresponding to 3-methylcyclohexenone (**107b**) and 3-methylcycloxanone (**107b**) (exact mass (EM) = 110 g/mol and 107 g/mol, respectively) are present in the spectra.



Scheme 4.48: Spectrum corresponding to the ESI-MS measurement done after a reaction time of one minute. (MW: molecular weight. EM: exact mass).

In the ESI-MS spectrum after one minute (Scheme 4.48) we can clearly identify peaks at *m*/*z* = 266 and 288 ($[M+H]^+$ and $[M+Na]^+$, respectively) corresponding to the imine **200** formed by the condensation of the excess of valine derivative **139a** and enone **107b** (EM = 265 g/mol). We also observed the presence of the catalytic salt ([**139a**·(*R*)-**126a**], EM = 925 g/mol) at *m*/*z* = 926 ($[M+H]^+$) and more interestingly of the iminium phosphate ion pair $\mathbf{D_1}$ (EM = 1018 g/mol) at *m*/*z* = 1019 and 1041 ($[M+H]^+$ and $[M+Na]^+$, respectively). Our hypothesis that phosphate counteranion (*R*)-**126a** may also interact with the Hantzsch ester **90a** *via* an additional hydrogen bond (**I**, EM = 1005 g/mol) was supported by the presence of a peak at *m*/*z* = 1028 ($[M+Na]^+$), although a peak corresponding to [$\mathbf{D_1}$·**90a**] (EW = 1271 g/mol) was not detected.



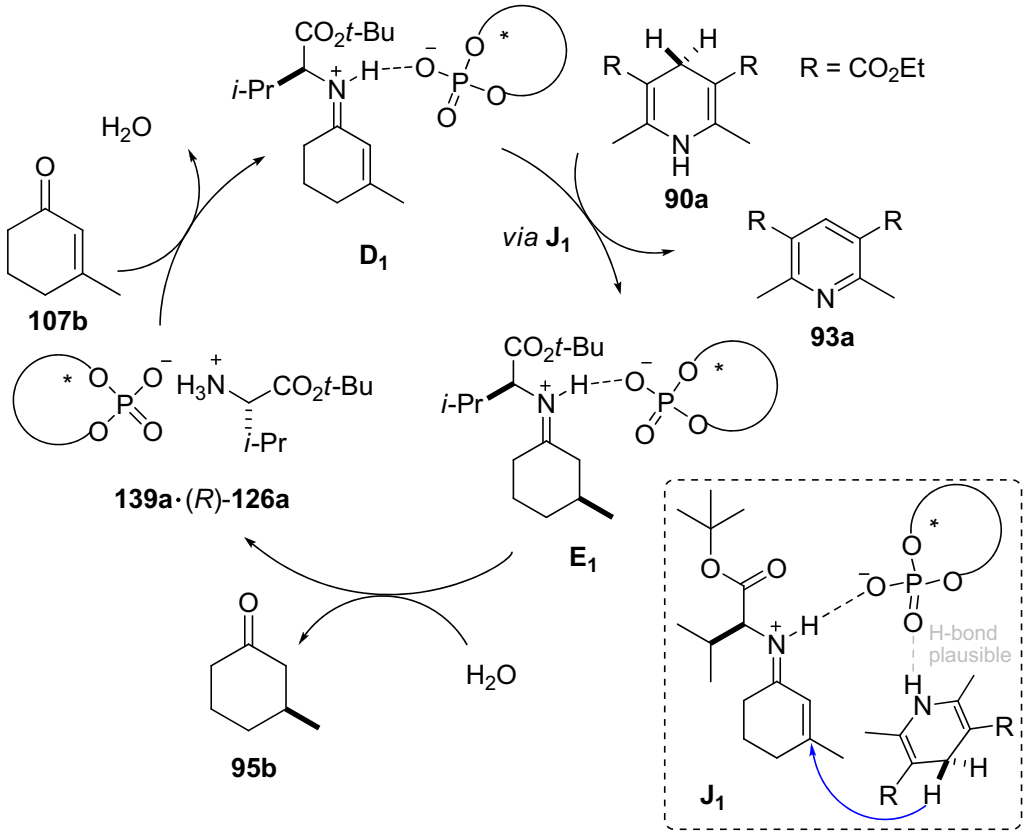
Scheme 4.49: Spectrum corresponding to the ESI-MS measurement done after a reaction time of eight hours. (MW: molecular weight. EM: exact mass).

Over time (after eight hours, Scheme 4.49) peaks appeared at *m*/*z* = 268 and 290 ($[M+H]^+$ and $[M+Na]^+$, respectively) showing that saturated ketone **95b** was formed and reacted with amino ester **139a** to form the saturated imine **2001** (EM = 267 g/mol). We also observed the presence of the iminium phosphate ion pair formed between the catalytic salt and the product (**E**$_1$, EM = 1020 g/mol) at *m*/*z* = 1021 and 1043 ($[M+H]^+$ and $[M+Na]^+$, respectively). During the course of the reaction, the intensity of the peaks corresponding to the saturated iminium phosphate ion pair **E**$_1$ (*m*/*z* = 1021 ($[M+H]^+$)) became higher than the intensity of the unsaturated iminium phosphate ion pair **D**$_1$ (*m*/*z* = 1019 ($[M+H]^+$), Scheme 4.49 vs. Scheme 4.48), indicating the progress of the reaction. A peak at *m*/*z* = 1005 ($[M+H]^+$) although appeared with the time, which would indicate the presence of pyridinium phosphate ion pair I (E = 1004 g/mol).

Consistent with our starting hypothesis (see Chapter 3.1) that the conjugate reduction of enone would proceed as in the conjugate reduction of enals[120b] *via* iminium catalysis seemed to be confirmed. A more precise catalytic cycle than the one given in Scheme 3.4 can thus be depicted (Scheme 4.50).

In this mechanism, ammonium phosphate ion [**139a**•(*R*)-**126a**] reversibly condenses with enone **107b** to form iminium phosphate ion pair **D**$_1$. This intermediate would be stabilized by hydrogen bonding interactions. Through this iminium ion formation (**D**$_1$), the LUMO energy of the substrate would decrease, allowing the conjugate hydride transfer from dihydropyridine **90a** to take place (from the *Re*-face of the iminium ion). This step generates the pyridine **93a** along with the saturated iminium phosphate ion pair **E**$_1$. Hydrolysis then releases the saturated ketone (*S*)-**95b** and regenerates the catalyst for further turnover.

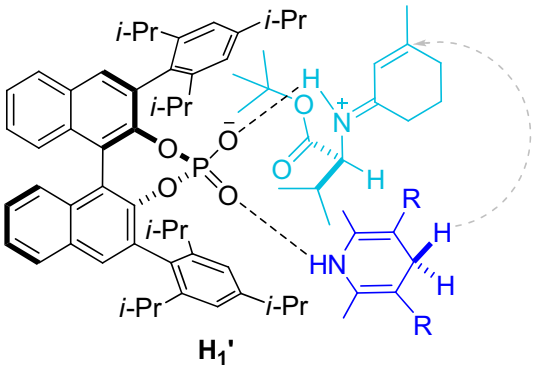
It is important to note that this catalysis with a primary amine salt is a special case of iminium catalysis that is actually a combination of iminium and Brønsted catalysis.



Scheme 4.50: Proposed mechanism for the transfer hydrogenation of enone **107b** with catalytic system [**139a**•(*R*)-**126a**].

The results obtained from these ESI-MS analyses are consistent with our assumption that the reaction proceeds *via* a hydrogen bond assisted iminium phosphate ion pair. Moreover the interactions of the counteranion with the Hantzsch ester *via* an additional hydrogen bond are plausible.

According to these observations we tried to establish a working model transition state (**H$_1$'**, Scheme 4.51) taking into account the hydrogen bonding interactions between the counteranion and the iminium ion, and between the counteranion and the dihydropyridine.



Scheme 4.51: Working model transition state for the transfer hydrogenation of enone **107b**.

To determine the structure of the transition state and the involved hydrogen bonding interactions with more accuracy, further mechanistic investigations and computational calculations would be required.

4.3.7 Conclusion and Discussion

We successfully developed a very efficient ammonium salt made of a chiral primary amine (**139a**) and a chiral phosphoric acid ((*R*)-**126a**) for the asymmetric transfer hydrogenation of enones. While the effect of the amino ester *α*-substituent on the enantioselectivity was not very pronounced, the catalysts incorporating the *tert*-butyl ester group had much higher efficiency compared to their methyl ester analogs. Accordingly, the valine *tert*-butyl ester **139a** was the amine of choice. Encouraged by previous studies on asymmetric counteranion-directed catalysis undertaken in our laboratory,[120c] we then investigated chiral BINOL-derived phosphates as counteranion. Among them (*R*)-TRIP ((*R*)-**126a**) counteranion gave the highest enantioselectivities. Interestingly, using the opposite enantiomer of the chiral phosphoric acid (i.e. using (*S*)-**126a**), the saturated ketone was generated in racemic form (see Chapter 3.2.2, Table 4.3), illustrating a strong case of a matched/mismatched ion pair combination. Accordingly, the catalytic system made of L-valine *tert*-butyl ester **139a** and BINOL-derived phosphate (*R*)-TRIP$^-$ ((*R*)-**126a**$^-$) was the most efficient and thus the favored one to catalyze the transfer hydrogenation of *α*,*β*-unsaturated ketones **107** and **113**.

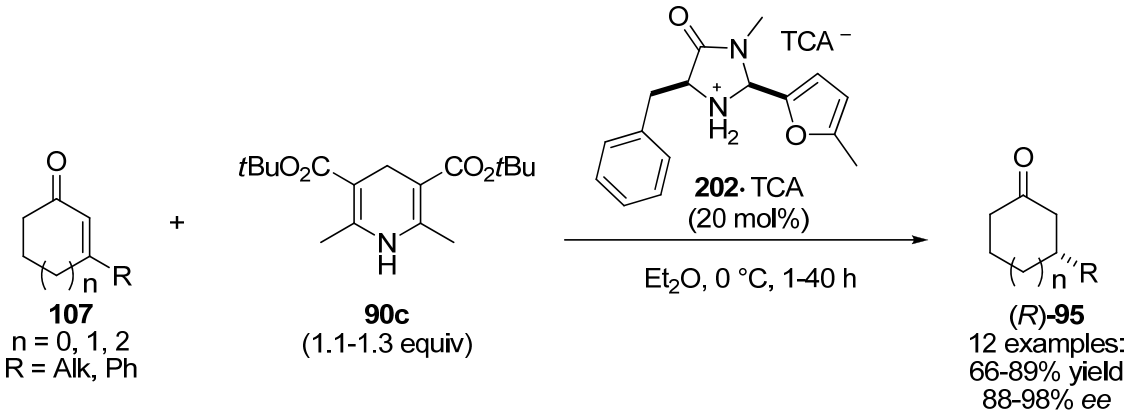
Using this catalytic salt we further optimized the reaction conditions (solvent, temperature, Hantzsch ester structure, catalyst loading and substrate concentration), leading to the development of a highly efficient and enantioselective transfer hydrogenation of enones *via* iminium catalysis at 5 mol% catalyst loading. The catalysis worked well not only with a range of *β*-substituted *α*,*β*-unsaturated cyclic ketones **107** but also with some *β*,*β*-disubstituted acyclic enones **113**, although the acyclic saturated ketones **114** were formed with slightly lower enantioselectivities. Even acyclic enone **113c** bearing a long aliphatic chain could be activated toward the reaction. However, because this catalytic process is not stereoconvergent and only (*E*)- or (*Z*)-enriched enone **113c** could be employed only moderate enantioselectivities were obtained. It would be interesting to examine, in future work, if stereoconvergence can be achieved by adding a catalytic amount of phosphine derivative (for example triphenylphosphine). We expect that the use of a phosphine derivative would create a

rapid equilibrium between (*E*)-**113** and (*Z*)-**113** *via* a conjugate addition/elimination pathway and if under our catalytic conditions one of the isomers reacts faster than the other, the corresponding saturated ketone would be preferentially formed and it would be possible to reach high enantiomeric ratios.

The catalytic transfer hydrogenation could be successfully scaled up to a multi-gram scale reaction (with a factor of about 700), without loss of reactivity or enantioselectivity, even by reducing the (*R*)-TRIP ((*R*)-**126a**) concentration to 2 mol%.

Mechanistically, we believe that the reaction proceeds *via* a special form of iminium catalysis (i.e. iminium and Brønsted acid catalysis), where an iminium phosphate ion pair is stabilized by hydrogen bonding interactions between the phosphate counteranion, the iminium ion and the Hantzsch ester. These assumptions were supported by monitoring the reaction with ESI-MS. Keeping in mind that hydride attack has to occur from the *Re*-face of the iminium ion to form the product with an (*S*)-configuration, led us to develop transition state $\mathbf{H_1'}$ (Scheme 4.51) as a working model.

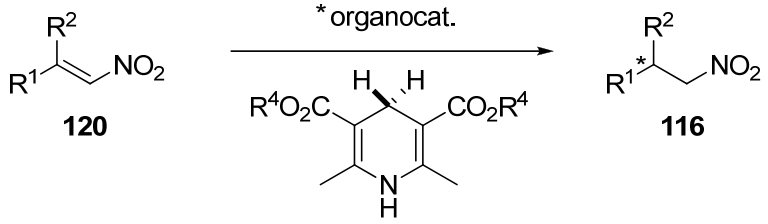
At this stage it is worth to note that after the acceptance of our manuscript describing these results, a related report appeared, in which catalyst [**202** · TCA] (20 mol%) had been successfully used for the transfer hydrogenation of cyclic ketones **107** (Scheme 4.52).[236] *MacMillan et al.* disclosed an alternative approach for the conjugate reduction of cyclic enones *via* iminium catalysis in the presence of chiral secondary amine **202** (*MacMillan* imidazolidinone) as a trichloroacetate salt to catalyze the reaction with the commercially available Hantzsch ester **90c** as the hydrogen source. The reaction proceeded in diethyl ether at 0 °C, leading to the formation of the saturated ketones ((*R*)-**95**) in moderate to high yields and with good to excellent enantioselectivities after only a few hours. Attractive features of this process were the use of a small and readily available catalyst – since free amine **202** is commercially available – as well as short reaction times, affording full conversion of the starting material after less than 10-15 h in most of the cases, even at 0 °C. However, high catalyst loading had to be used to achieve such reactivity (20 mol% against 5 mol% with our process) and even running the reaction at low temperature (0 °C) lower enantioselectivities than the ones obtained with our catalytic system were reached. Beside being more enantioselective, our methodology was not limited to the transfer hydrogenation of cyclic substrates as it was the case with *MacMillan*'s variant. Moreover since (*R*)-TRIP ((*R*)-**126a**) is now commercially available, our catalytic system can also be readily obtained.



Scheme 4.52: Alternative approach for the transfer hydrogenation of enones **107** *via* iminium catalysis.

4.4 Enantioselective Transfer Hydrogenation of *β*,*β*-Disubstituted Nitroalkenes

The objective of the following investigations was to develop an organocatalytic process for the synthesis of enantiomerically pure *β*,*β*-disubstituted nitroalkanes. To reach this target we focused our work on the development of a highly enantioselective catalytic transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes (Scheme 4.53). For this purpose an appropriate catalyst, which would allow efficient substrate activation with high level of stereocontrol and selective π-facial discrimination to control the enantioselectivity of the reaction had to be developed.[237]



Scheme 4.53: Planned Hantzsch ester-mediated organocatalytic asymmetric transfer hydrogenation of nitroalkenes **120**.

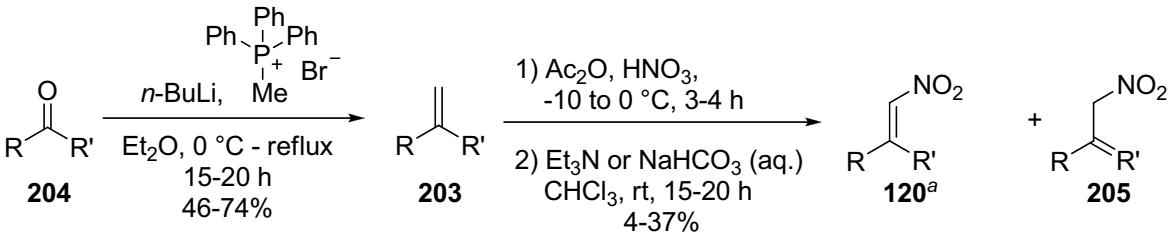
4.4.1 Synthesis of the Nitroolefins and Racemic Products

4.4.1.1 Synthesis of the Nitroolefins via Nitration

β,*β*-Disubstituted nitroalkenes **120a-n**[238], which were not commercially available, were synthesized from the corresponding alkenes **203** according to the procedure reported by *Ohta et al*. (Scheme 4.54).[239] The alkenes **203** that were not commercially available were prepared by Wittig olefination as described in Scheme 4.54.[241] After deprotonation of methyltriphenylphosphinium bromide with *n*-butyl lithium in diethyl ether at 0 °C, ketone **204** was added to the reaction mixture, which was then stirred overnight at reflux, affording the desired compounds **203** in moderate yields (46-74%).

Alkenes **203** were then slowly added to a solution of acetic anhydride and nitric acid at low temperature. After work-up, the corresponding crude nitro acetate was obtained and used in the next step without further purification. The elimination of acetic acid occurred in basic

media (using triethylamine or aqueous solution of sodium bicarbonate, depending on the substrate). After an acidic work-up and column chromatography β,β-disubstituted nitroalkenes **120a-m** were isolated (4-37% yield). The low yields of this reaction were due to the formation of initial ketone **204** *via* a retro-Henry reaction as well as the generation of the isomer **205** as by-product. Moreover, it is worth to specify that the full separation of isomers **120** and **205** by column chromatography was difficult to achieve. For this purpose, several separation processes were required for each nitroolefin **120**, running the column chromatographies very slowly using solvents with very low polarity. Under these conditions pure products could be isolated but with low yields.



204 **203** **120**[a] **205**

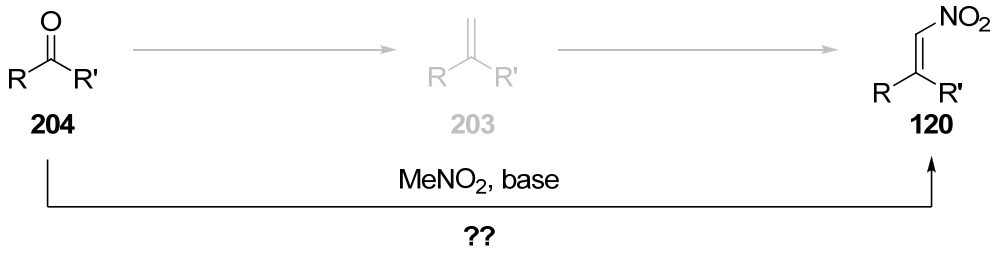
203a: R = C_6H_5, R' = Me; (c.a.)
203b: R = C_6H_5, R' = *i*-Pr; 74%
203c: R = C_6H_5, R' = Et; 74%
203d: R = C_6H_5, R' = *n*-Pr; 71%
203e: R = 2-naphthyl, R' = Me; 61%
203f: R = *p*-Me-C_6H_5, R' = Me; (c.a.)
203g: R = *p*-CN-C_6H_5, R' = Me; 51%
203h: R = *p*-F-C_6H_5, R' = Me; (c.a.)
203i: R = *p*-Cl-C_6H_5, R' = Me; (c.a.)
203j: R = *m*-Cl-C_6H_5, R' = Me; 46%
203k: R = *o*-Cl-C_6H_5, R' = Me; 65%
203l: R = *t*-Bu, R' = Me; (c. a.)
203m: R = Et, R' = Me; (c. a.)

120a: R = C_6H_5, R' = Me; 37%
120b: R = C_6H_5, R' = *i*-Pr; 13%[b]
120c: R = C_6H_5, R' = Et; 18%
120d: R = C_6H_5, R' = *n*-Pr; 17%
120e: R = 2-naphthyl, R' = Me; 14%
120f: R = *p*-Me-C_6H_5, R' = Me; 22%
120g: R = *p*-CN-C_6H_5, R' = Me; 19%
120h: R = *p*-F-C_6H_5, R' = Me; 23%
120i: R = *p*-Cl-C_6H_5, R' = Me; 8%
120j: R = *m*-Cl-C_6H_5, R' = Me; 6%
120k: R = *o*-Cl-C_6H_5, R' = Me; 4%
120l: R = *t*-Bu, R' = Me; 28%
120m: R = Et, R' = Me; 15%[c]

Scheme 4.54: General procedure for the preparation of nitroolefin **120a-n.** (c.a.: commercially available. [a] (*E*)-Isomer (*E*/*Z* > 98:2). [b] (*Z*)-Isomer. [c] Sum of the (*E*)- and (*Z*)-enriched isomers).

4.4.1.2 Investigations to Optimize the Nitroolefin Preparation

Because of the low nitroolefin yields obtained after the two-step-process described above (see Scheme 4.54), it was of interest to optimize our substrate synthesis. To reach this objective we oriented our investigations on the development of a one-step-procedure starting from ketones **204** and treating it with nitromethane in the presence of an appropriate base (Scheme 4.55).



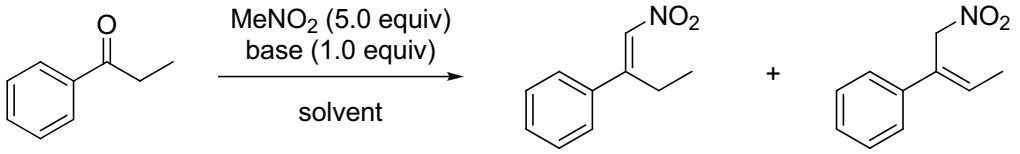
Scheme 4.55: Considered strategy to improve the synthesis of nitroolefins **120a-n.**

We tested different bases for the preparation of (*E*)-2-phenyl-1-nitro-1-butene **120c** (Table 4.14). We first used *N*,*N*-dimethyl (or diethyl)-aminoethylamine in the presence, or absence, of TFA in neat nitromethane or using benzene as a solvent (entries 1-3). As the reactions were very slow at low temperature, we then heated them up. However, under these conditions the desired product was not formed. Most of the starting material was recovered, along with some of the isomer **205c** (entries 1-2). The use of a Dean-Stark apparatus following *Barco et al.*'s procedure[240] did not improve the reaction conversion (entry 4 vs. entry 3). With butylamine, the desired product was observed but as a mixture of (*E*)- and (*Z*)-isomers, along with (*E*)- and (*Z*)-**205c**. Unreacted starting material remained as the main component (entry 5). According to the methodology reported by *Bandgar et al.*, [241] we run the reaction in presence of gel-entrapped base catalyst (GEBC, 20% agar-agar aqua gel), which led to the full recovery of the starting material (entry 6).

Through these experiments we could not improve the preparation of nitroolefin **120c**. However in the presence of butylamine the desired product could be synthesized to some extent as a (*E*)- and (*Z*) mixture. We then tried to apply these conditions to another ketone, 1-(furan-2-yl)ethanone **204n**, to see if its corresponding nitroolefin **120n** could be prepared in this way (Table 4.15)

We first tried *N*,*N*-diethylaminoethylamine in benzene. Once again no reaction was observed (entry 1). With butylamine no reaction occurred either in ethanol or in neat nitromethane (entries 2-3). However, by running the synthesis in toluene, we obtained the desired nitroolefin **120n** as well as its isomer **205n** with low conversion (entry 4).

Table 4.14: Attempted one-pot preparation of nitroolefin **120c** (s. m.: starting material)

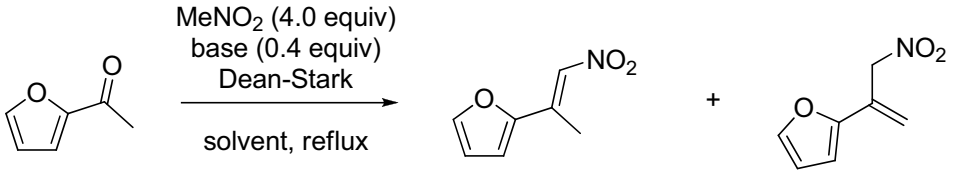


204c **120c** **205c**

Entry	Base	Solvent	Temperature	Main product(s)
1	$Me_2N(CH_2)_2NH_2$ + TFA	$MeNO_2$	0 °C - reflux	**205c** + s. m.
2	$Me_2N(CH_2)_2NH_2$ + TFA	benzene	0 °C - reflux	**205c** + s. m.
3	$Et_2N(CH_2)_2NH_2$	benzene	reflux	s. m.
4	$Et_2N(CH_2)_2NH_2$	benzene	reflux[a]	s. m.
5	*n*-$BuNH_2$	$MeNO_2$	0 °C - reflux	**120c** (*E*/*Z*) + **205c** (*E*/*Z*) + s. m.
6	GEBC[b]	MeCN	0 °C - reflux	s. m.

[a] Dean-Stark apparatus was used. [b] GEBC: Gel Entrapped Base Catalyst (20% agar-agar aqua gel containing 10% KOH).

Table 4.15: Attempted one-pot preparation of nitroolefin **120n** (s. m.: starting material)[242]

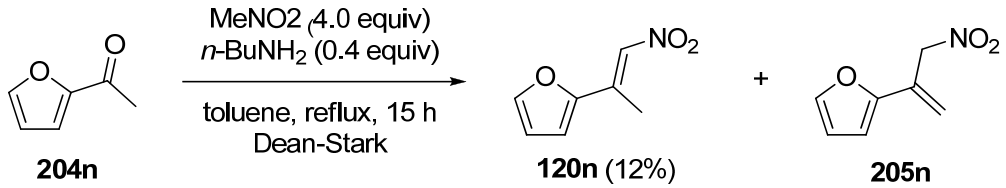


204n **120n** **205n**

Entry	Base	Solvent	Main product(s)
1[a]	$Et_2N(CH_2)_2NH_2$	benzene	s. m.
2	*n*-$BuNH_2$	EtOH	s. m.
3	*n*-$BuNH_2$	$MeNO_2$	s. m.
4	*n*-$BuNH_2$	toluene	s. m. + **120n** + **205n**

[a] 100 equivalents of base were used.

After optimization of the reaction conditions (*E*)-2-(furan-2-yl)-1-nitro-1-propene (**120n**) was generated in 12% yield from its corresponding ketone in the presence of nitromethane and butylamine (Scheme 4.56).



204n **120n** (12%) **205n**

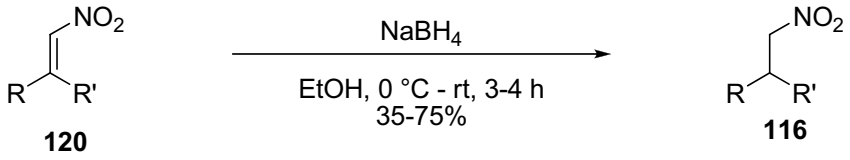
Scheme 4.56: One-step synthesis of nitroolefin **120n**.

This investigation did not lead to a significant improvement of the preparation of nitroolefins **120**. Nevertheless, at this point, we decided to stop these experiments and to focus our work on the development of an organocatalytic method for the transfer hydrogenation of the prepared *β*,*β*-disubstituted nitroalkenes **120a-n.**

4.4.1.3 Synthesis of the Racemic Nitroalkanes

Racemic products **116** were required to develop the GC conditions for the separation of both enantiomers in order to be able to determine the enantiomeric ratios of the chiral nitroalkanes prepared *via* organocatalytic transfer hydrogenation of nitroalkenes **120**.

For this purpose we first used sodium borohydride as the hydrogen source in ethanol for the non-asymmetric conjugate reduction of nitroolefins **120**. The racemates **116** were obtained in 35-75% yield after running the reaction for a few hours at 0 °C and then at room temperature (Scheme 4.57).



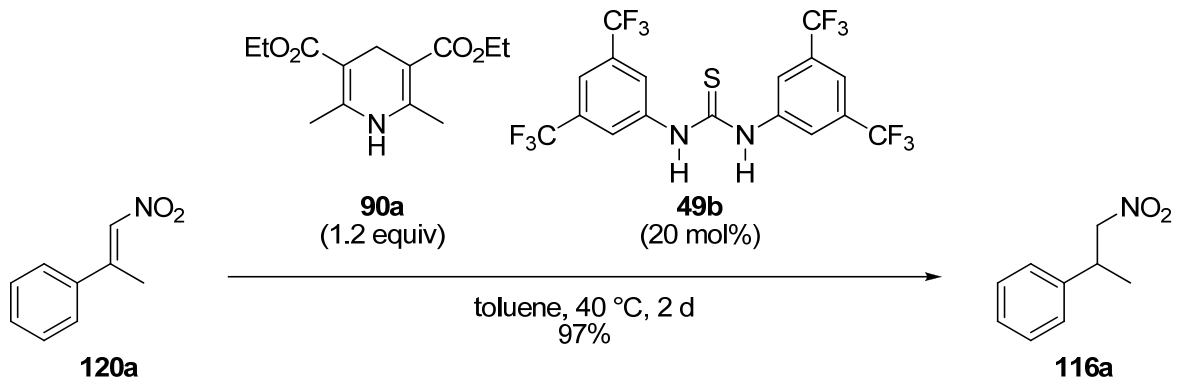
120a: R = C_6H_5, R' = Me
120b: R = C_6H_5, R' = *i*-Pr
120c: R = C_6H_5, R' = Et
120d: R = C_6H_5, R' = *n*-Pr
120e: R = 2-naphthyl, R' = Me
120f: R = *p*-Me-C_6H_5, R' = Me
120g: R = *p*-CN-C_6H_5, R' = Me
120h: R = *p*-F-C_6H_5, R' = Me
120i: R = *p*-Cl-C_6H_5, R' = Me
120j: R = *m*-Cl-C_6H_5, R' = Me
120k: R = *o*-Cl-C_6H_5, R' = Me
120l: R = *t*-Bu, R' = Me
120m: R = Et, R' = Me
120n: R = 2-furyl, R' = Me

116a: R = C_6H_5, R' = Me; 57%
116b: R = C_6H_5, R' = *i*-Pr; 45%
116c: R = C_6H_5, R' = Et; 58%
116d: R = C_6H_5, R' = *n*-Pr; 56%
116e: R = 2-naphthyl, R' = Me; 71%
116f: R = *p*-Me-C_6H_5, R' = Me; 75%
116g: R = *p*-CN-C_6H_5, R' = Me; 47%
116h: R = *p*-F-C_6H_5, R' = Me; 75%
116i: R = *p*-Cl-C_6H_5, R' = Me; 42%
116j: R = *m*-Cl-C_6H_5, R' = Me; 54%
116k: R = *o*-Cl-C_6H_5, R' = Me; 69%
116l: R = *t*-Bu, R' = Me; 35%*
116m: R = Et, R' = Me; 42%*
116n: R = 2-furyl, R' = Me; 66%

Scheme 4.57: Procedure for the preparation of the racemic nitroalkanes **116a-n.** (*NMR yield; because of the high volatility of the compound, the crude product was not isolated).

It is worth to comment, that after we successfully developed an organocatalytic enantioselective transfer hydrogenation of nitroalkenes **120a-n** using thiourea catalysts (see Chapter 4.4.4, Scheme 4.25), we found a more efficient way to prepare the racemic products **116** with yields higher than 90% using Hantzsch ester **90a** as the hydrogen source and stirring the reaction mixtures in toluene for two days in the presence of *Schreiner* catalyst **49b**

(20 mol%), as shown in Scheme 4.58 for the synthesis of racemic 2-phenyl-1-nitro-1-propane (**116a**).[243]



Scheme 4.58: Improved procedure for the preparation of racemic nitroalkanes **116a-n.**

4.4.2 Identification of the Catalyst's Core Structural Motif

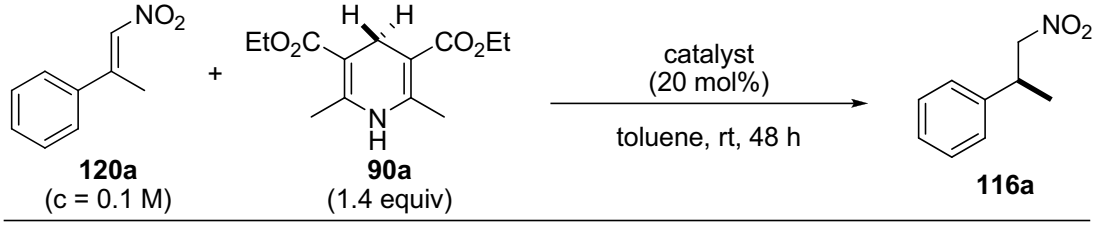
Our first objective in the development of an efficient catalytic transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes **120** was to find an appropriate organocatalyst.

Because acetic acid is a known catalyst for Hantzsch ester-mediated conjugate reductions of nitroolefins,[199c] and because chiral urea derivatives had been used to activate nitroolefins for conjugate additions[102] (see Chapter 3.2), we reasoned that chiral Brønsted acids and hydrogen-bonding catalysts would be particularly promising for the development of an organocatalytic transfer hydrogenation of nitroolefins in the presence of dihydropyridine. As a model reaction, we investigated the transfer hydrogenation of (*E*)-1-nitro-2-phenyl-1-propene (**120a**) to 2-phenyl-1-nitro-1-propane (**116a**) using commercially available Hantzsch ester **90a**.

4.4.2.1 Evaluation of the Catalyst Motif

We started our catalyst screening using different acid types (Lewis or Brønsted acids) with a relatively high catalyst loading (20 mol%). The reactions were run in toluene (**120a**: 0.1 molar) at room temperature for 48 hours in the presence of dihydropyridine **90a** (1.4 equivalents, Table 4.16).

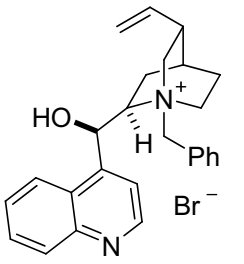
Table 4.16: Evaluation of various acids as catalysts for the transfer hydrogenation of nitroolefin **120a**



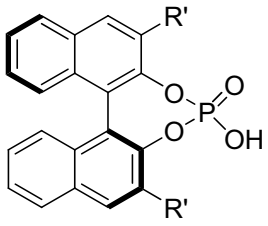
120a (c = 0.1 M) + **90a** (1.4 equiv) → **116a**

Entry	Catalyst	conv. [%][a]	*er*[a]
1	**-**	-	-
2	**206**	-	-
3	(*S*)-**126a**	85	45:55
4	(*S*)-**126i**	35	43:57
5	(*S*)-**157b**	**85**	**71:29**
6	(*S*)-**182**	9	48:52
7	(*S*)-**183**	11	50:50
8	**67a**	-	-
9	**50d**	**10**	**95:5**

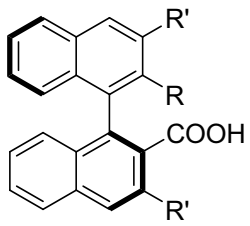
[a] Determined by chiral GC.



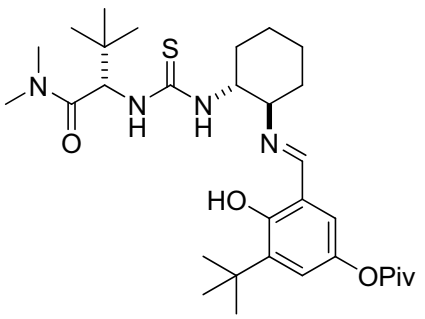
206



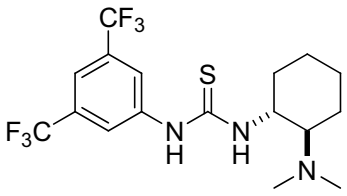
(*S*)-**126a**: R = 2,4,6-(*i*-Pr)$_3$-C$_6$H$_3$
(*S*)-**126i**: R = Si(Ph)$_3$



(*S*)-**157b:** R = CO_2H, R' = 3,5-$(CF_3)_2$-C_6H_4
(*S*)-**182:** R = CO_2*i*-Pr, R' = 3,5-$(CF_3)_2$-C_6H_4
(*S*)-**183:** R = Ph, R' = H



50d



67a

First the background reaction of the catalysis was tested in the absence of a catalyst. Under the reaction conditions no reaction took place (entry 1). The same result was obtained in the presence of *N*-benzylcinchonidinium salt **206** (entry 2). We then screened strong Brønsted acid catalysts, like (*S*)-BINOL-derived phosphoric acids ((*S*)-**126a** and (*S*)-**126i**) or dicarboxylic acids ((*S*)-**157b**, **182** and **183**, entries 3-7). Phosphoric acids (*S*)-TRIP ((*S*)-**126a**) and (*S*)-**126i**) could activate the substrate but afforded the product (*R*)-**116a** with very low

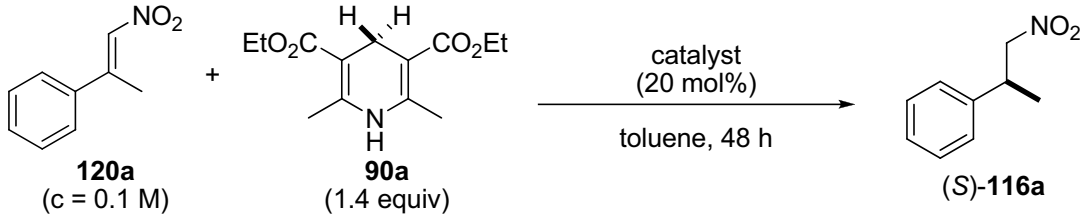
enantioselectivity (entries 3 and 4). Using dicarboxylic acid (*S*)-**157b** a high conversion (85%) as well as a promising enantiomeric ratio was reached (71:29, entry 5). Encouraged by this result we tested some binaphthyl dicarboxylic acid derivatives like (*S*)-2'-(isopropoxycarbonyl)-1,1'-binaphthyl-2-carboxylic acid ((*S*)-**182**) and 2'-phenyl-1,1'-binaphthyl-2-carboxylic acid ((*S*)-**183**), leading to a dramatic loss of reactivity and enantioselectivity (entries 6 and 7). As *Takemoto et al.*[102] had reported the activation of nitroolefins using bifunctional catalyst **67a**, we investigated the activity of this thiourea catalyst in our process (entry 8). Under our reaction conditions no conversion was observed. On the other hand, using *Jacobsen* thiourea catalyst **50d** the desired product ((*S*)-**116a**) was formed with low yield but excellent enantioselectivity (95:5, entry 9). According to these experiments two catalyst motifs seemed to be promising for the studied transfer hydrogenation: binaphthyl dicarboxylic acid ((*S*)-**157b**) and thiourea **50d**.

As a very high enantiomeric ratio was obtained using the thiourea **50d**, we decided to focus our work on the development of thiourea catalysts, which would be more active than **50d** while maintaining high enantioselectivity.

4.4.2.2 Effect of the Temperature on the Catalysis

Jacobsen and *Takemoto* thiourea catalysts (**67a** and **50d**, respectively) had a low (or no) activity. As suspected, an increase of the reaction temperature from room temperature to 40 °C led to an acceleration of the reaction (Table 4.17, entry 1 vs. 2 and entry 3 vs. 4), to reach very high conversions (higher than 80%) in the presence of catalyst **50d** (entry 2). At 40 °C a high enantiomeric ratio was obtained, even if it was slightly lower than the one reached at room temperature. On the contrary, *Takemoto* catalyst **67a** was not suitable to activate our substrate even at 40 °C, at which temperature nitroalkane **116a** was generated in very poor yield and enantioselectivity (entry 4).

Table 4.17: Evaluation of the temperature effect on the transfer hydrogenation of nitroolefin **120a**



120a (c = 0.1 M) + **90a** (1.4 equiv) → (*S*)-**116a**

Entry	Catalyst	Temperature [°C]	conv. [%][a]	*er*[a]
1	**50d**	rt	10	95:5
2	**50d**	**40**	**85**	**93:7**
3	**67a**	rt	-	-
4	**67a**	40	6	48:52

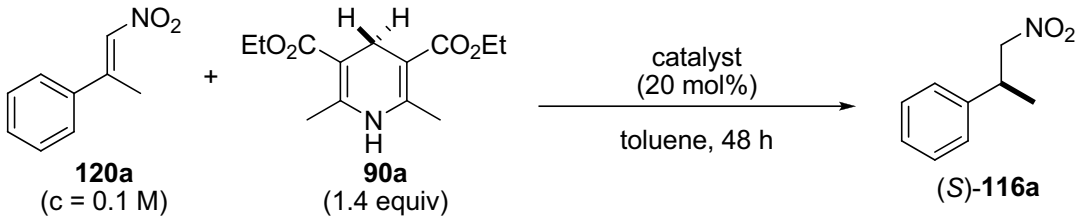
[a] Determined by chiral GC.

4.4.2.3 Screening of (Bis)thiourea Catalysts

Inspired by the high activity of *Jacobsen* thiourea catalyst **50d**, we synthesized several thiourea compounds with different motifs (see Chapter 4.2) and then tested their reactivity and enantioselectivity in the transfer hydrogenation of **120a** (Table 4.18). It has to be noted that most of the reactions presented in Table 4.18 were performed at room temperature prior to the investigation of the temperature effect reported in Table 4.17. As at that stage we were just interested in determining whether the tested hydrogen bonding thioureas were able to activate nitroolefin **120a** (at least to some extent) and since our research was mostly focused on the catalyst enantioselectivity, it was not necessary to rerun these reactions at higher temperatures.

Efficiency of L-*tert*-leucine-derived bifunctional catalysts **164a-b** was first evaluated (entries 3-4). In the cases of thiourea compound bearing an amide or an acid functionality the product could be generated to some extent and with moderate enantioselectivity (entries 3 and 4). While the use of bifunctional compound **162** allowed the reaction to reach higher conversion, this catalyst was less enantioselective than its L-*tert*-leucine-derived analogs **164** (entry 5 vs. entries 3 and 4). BINAM-derived catalyst **76** was not suitable for our reaction in terms of reactivity or enantioselectivity (entry 6). We then prepared *N*-Boc-L-*tert*-leucine-derived ureas **165** and **168**, assuming that intermolecular hydrogen bonding interactions between the hydrogen of the *N*-Boc-protected amine and the oxygen of the urea moiety could occur, which would fix the conformation of the catalyst. As the activity of these catalysts was tested at 40 °C, their high conversion can not directly be compared with the activity of the catalysts

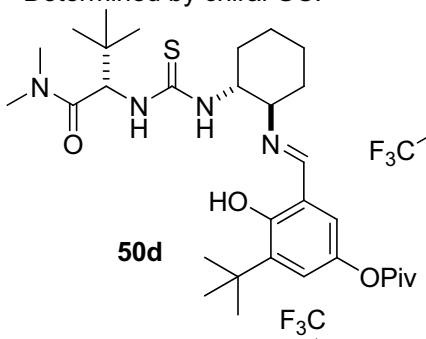
Table 4.18: Screening of thiourea catalysts for the transfer hydrogenation of nitroolefin **120a**



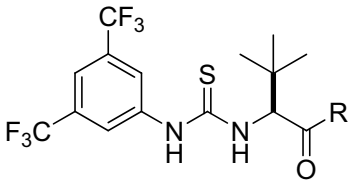
120a (c = 0.1 M) + **90a** (1.4 equiv) → (*S*)-**116a**

Entry	Catalyst	Temperature [°C]	conv. [%][a]	*er*[a]
1	**50d**	rt	10	95:5
2	**50d**	**40**	**85**	**93:7**
3	**164a**	40	50	81:19
4	**164b**	rt	9	78:22
5	**162**	rt	31	39:61
6	**76**	rt	9	51:49
7	**165**	40	67	45:55
8	**168**	40	77	33:67
9	**180**	40	-	-
10	**63**	rt	55	40:60
11	**178**	rt	45	71:29

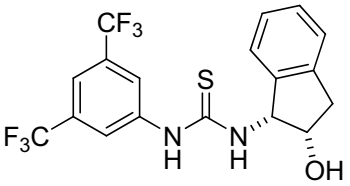
[a] Determined by chiral GC.



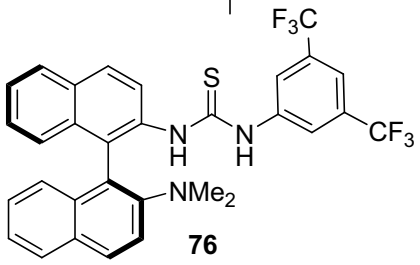
50d



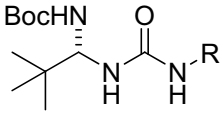
164a: R = NMe_2
164b: R = OH

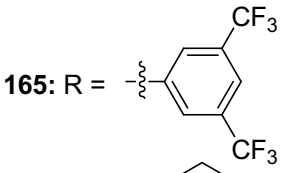


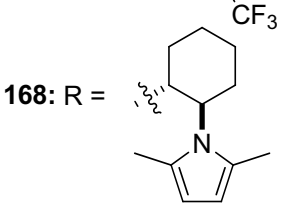
162

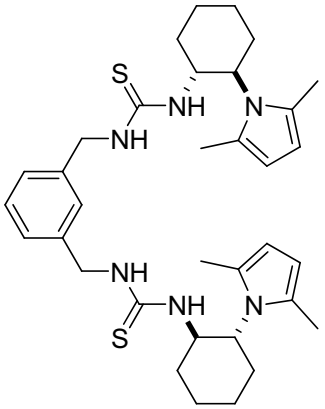


76

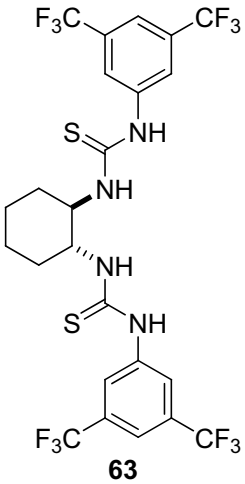




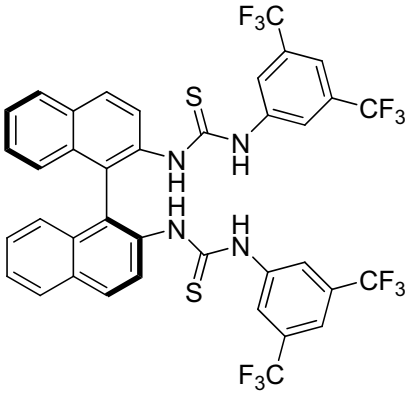




180



63



178

tested in the transfer hydrogenation of **120a** at room temperature. However, it is possible to comment on the enantiomeric ratio of the generated nitroalkane (*R*)-**116a**, which was low employing catalyst **165** but could be increased with catalyst **168**, in which the trifluoromethylphenyl substituent was replaced by a pyrrolyl derivative (entries 7 and 8). At this point we intended to develop more active catalysts and reasoned that bisthioureas would be more efficient than monothioureas in the activation of the nitroolefin **120a**, since the hydrogen bond concentration would be higher.

Catalyst **180** proved to be ineffective for the reaction, as it could not activate the substrate (entry 9). We explained this result in part by the fact that **180** did not have a sufficiently rigid enough structure to fix the two thiourea moieties close to each other to allow an increase of the concentration of the hydrogen bond interaction at only one place (i.e. the four hydrogen atoms of the bisthiourea catalyst activate the same nitroolefin molecule through hydrogen bonding interactions with the nitro functionality). Bisthioureas **63** and **178** have a more conformationally fixed structure, with both thiourea moieties oriented in such a way, that they can activate the same substrate molecule simultaneously, increasing the hydrogen bonding concentration and the strength of the interaction. This would allow for a stronger activation of the nitroolefin **120a**. Indeed, higher conversions (at room temperature) were reached using these two catalysts (**63** and **178**, entries 10 and 11). However, their enantioselectivity remained much lower than the one obtained using *Jacobsen* catalyst **50d**. We thus decided to pursue the development of the asymmetric conjugate reduction of nitroolefins using monothiourea catalyst **50d** and running the reaction at 40 °C.

4.4.3 Optimization of the Catalyst and Reaction Conditions

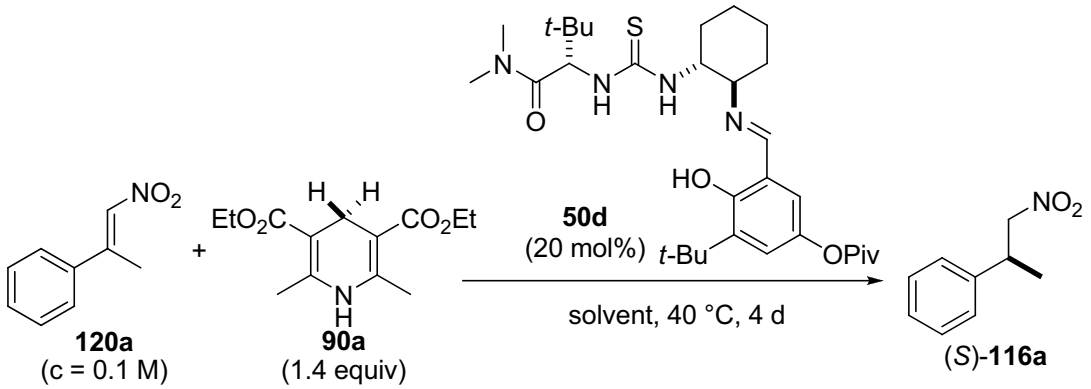
4.4.3.1 Optimization of the Solvent

We started to optimize our catalytic process by screening different solvents. It has to be noted that for the analysis of the general catalyst structure previously reported (see Chapter 4.4.2), we arbitrarily chose to run the reactions in toluene as this solvent was a commonly used one for thiourea-catalyzed reactions (see Chapter 2.1.3.2). For the following investigation of the solvents we performed the conjugate reductions of nitroalkene **120a** (0.1 molar) at 40 °C in

the presence of Hantzsch ester **90a** (1.4 equivalents) and thiourea catalyst **50d** (20 mol%) as shown in Table 4.19.

In apolar aromatic solvents like toluene and benzene high conversions (79% and 92%, respectively) and enantiomeric ratios (93:7 *er*) were reached (entries 1 and 2). THF was also an adequate solvent with regard to the reaction conversion. However, in this solvent the product was generated with much lower enantioselectivity (entry 3). High enantiomeric ratio could be obtained in diethyl ether, even though the reaction was slower (entry 4). The catalytic efficiency was only moderate in chlorinated solvents (entries 5 and 6). Using dioxane, methanol or acetonitrile poor conversions or/and enantioselectivities were reached (entries 7-9). Since the highest catalytic efficiency in terms of activity and selectivity was observed when toluene was used as solvent, it was employed for further investigations.

Table 4.19: Solvent effect on the transfer hydrogenation of nitroalkene **120a**



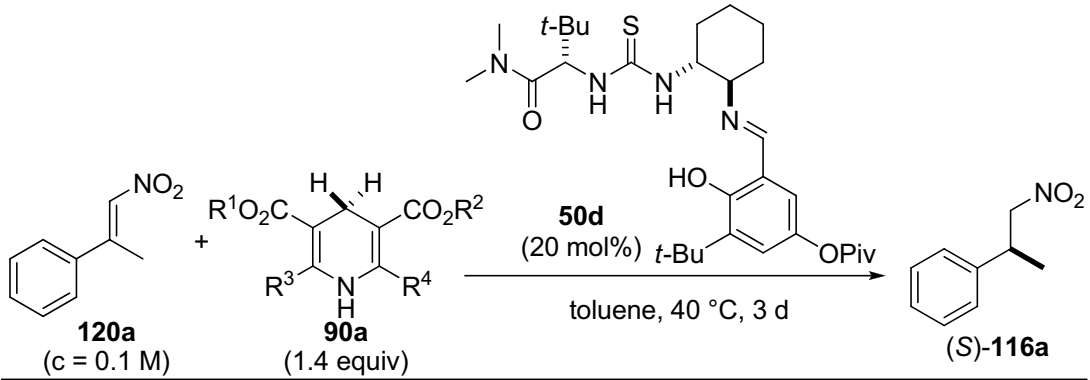
Entry	Solvent	conv. [%][a]	*er*[a]
1	**toluene**	**92**	**93:7**
2	**benzene**	**79**	**93:7**
3	THF	63	65:35
4	Et_2O	37	89:11
5	CH_2Cl_2	34	83:17
6	$CHCl_3$	30	66:34
7	dioxane	10	61:39
8	MeOH	92	50:50
9	MeCN	9	58:42

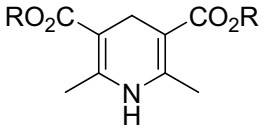
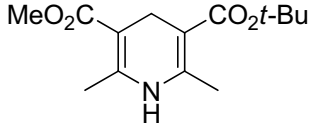
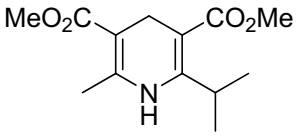
[a] Determined by chiral GC.

4.4.3.2 Hantzsch Ester Structure and Concentration

In order to optimize our catalytic process we then explored the effect of the Hantzsch ester structure on the product formation (Table 4.20). Modification of the ester groups of the dihydropyridine did not lead to significantly different reaction conversions. On the other hand, by increasing the bulkiness of the ester group, the enantiomeric ratios of the product were improved (entries 1-5). In the presence of Hantzsch ester **90c**, which bears *tert*-butyl ester functionalities, optimal conversion (94%) and enantioselectivity (97:3 *er*) was reached (entry 4). The use of non-symmetrical dihydropyridine **90b** induced a dramatic drop in the efficiency of the process (entry 6). According to these results, dihydropyridine **90c** was the favored hydrogen source for the conjugate reduction of nitroalkene **120a**. Gratifyingly, Hantzsch ester **90c** also had the advantage of being commercially available.

Table 4.20: Optimization of the dihydropyridine structure for the transfer hydrogenation of nitroolefin **120a**



Entry		Hantzsch ester	conv. [%][a]	*er*[a]
				
1	**90a**:	R = Et	89	93:7
2	**90d**:	R = *i*-Bu	92	96:4
3	**90e**:	R = *neo*-pent	75	96:4
4	**90c**:	**R = *t*-Bu**	**94**	**97:3**
5	**90g**:		85	96:4
6	**90b**:		10	54:46

[a] Determined by chiral GC.

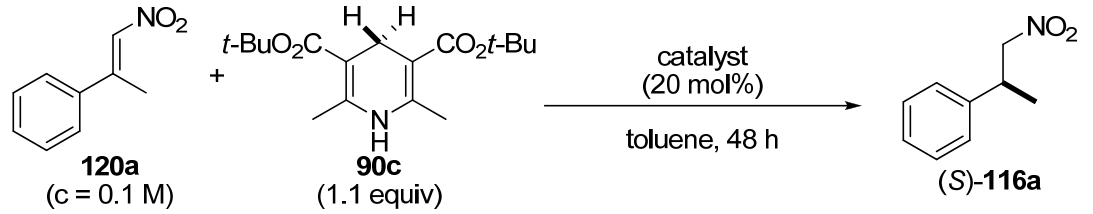
The Hantzsch ester concentration had no effect on the efficiency of the transfer hydrogenation of nitroolefin **120a**. For economical reasons we continued our optimization using 1.1 equivalents of **90c**.

4.4.3.3 Optimization of *Jacobsen*(-Type) Thiourea Catalyst

Screening of some Jacobsen thiourea motifs

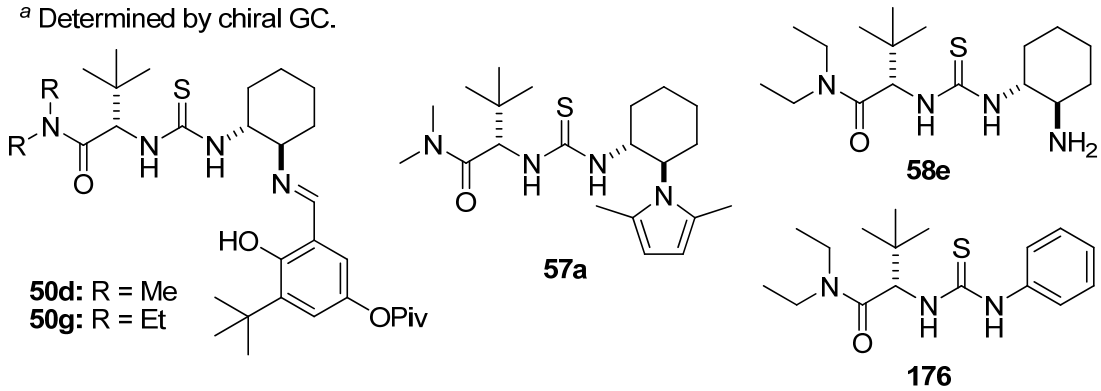
After having defined the adequate solvent and optimal dihydropyridine structure for our process, we intended to improve the catalyst efficiency further by modifying its structure and by screening other *Jacobsen*(-type) thioureas (Table 4.21).

Table 4.21: Screening of different *Jacobsen* thiourea motifs for the catalytic transfer hydrogenation of nitroolefin **120a**



Entry	Catalyst	Temperature [°C]	conv. [%][a]	*er*[a]
1	**50d**	40	94	97.0:3.0
2	**50d**	60	98	96.0:4.0
3	**50g**	40	93	97.0:3.0
4	**57a**	**40**	**95**	**97.5:2.5**
5	**58e**	40	61	82.5:17.5
6	**176**	40	69	83.0:17.0

[a] Determined by chiral GC.



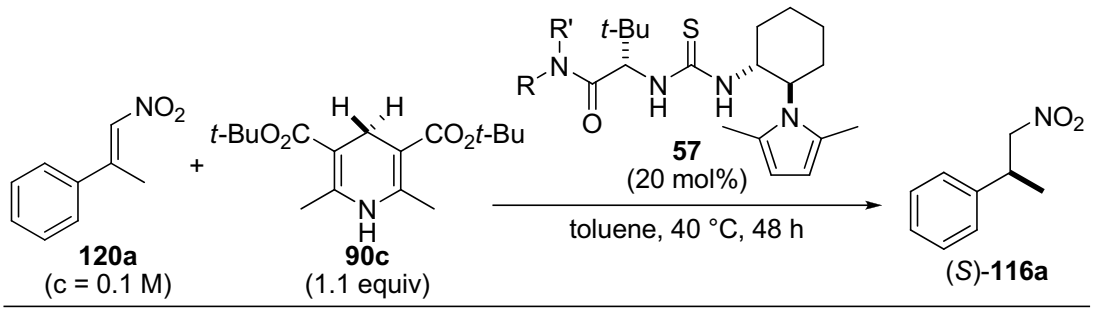
Before testing the activity of different catalysts, we first examined the effect of a temperature increase (from 40 to 60 °C) on the efficiency of the transfer hydrogenation. As expected the

reactivity was slightly improved but in parallel the enantioselectivity slightly decreased as a result of this modification (entry 1 vs. entry 2). Thus, we decided to run further reactions at 40 °C. We were then interested in investigating the influence of the susbtituent on the nitrogen atom of the amino amide functionality of **50d**. The replacement of *N*-methyl groups (in **50d**) by ethyl groups (in **50g**) did not have any influence on the catalyst efficiency (entries 1 and 3). On the other hand, an effect was observed by substituting the salicyl imine functionality of **50d** by a pyrrolyl group (thiourea **57a**) whereby the product was obtained with a slightly higher enantiomeric ratio than in the presence of its analog **50d** (entry 4). A significant loss of catalytic efficiency in terms of reactivity and selectivity was observed when using thioureas **58e** and **176**, which bear an aminocyclohexyl- or a phenyl-substituent, respectively (entries 5 and 6). According to these results, thiourea motif **57** was found to be the optimal one. Our objective was then to optimize the structure of this catalyst by varying the substituent on the amide functionality and on the pyrrolyl group.

Optimization of Jacobsen thiourea motif 57

We first studied the influence of the amide substituents on the catalyst efficiency (Table 4.22).

Table 4.22: Optimization of thiourea motif **57**: effect of the amide structure on the transfer hydrogenation of nitroolefin **120a**



120a (c = 0.1 M) + **90c** (1.1 equiv) → (*S*)-**116a**

Entry	Catalyst	R	R'	conv. [%][a]	*er*[a]
1	**57a**	Me	Me	95	97.5:2.5
2	**57b**	**Et**	**Et**	**96**	**98.5:1.5**
3	**57c**	**Bn**	**Bn**	**97**	**98.0:2.0**
4	**57d**	***n*-Pr**	***n*-Pr**	**96**	**98.0:2.0**
5	**57e**	Bn	Me	95	94.5:5.5
6	**57f**	Bn	H	90	91.5:8.5

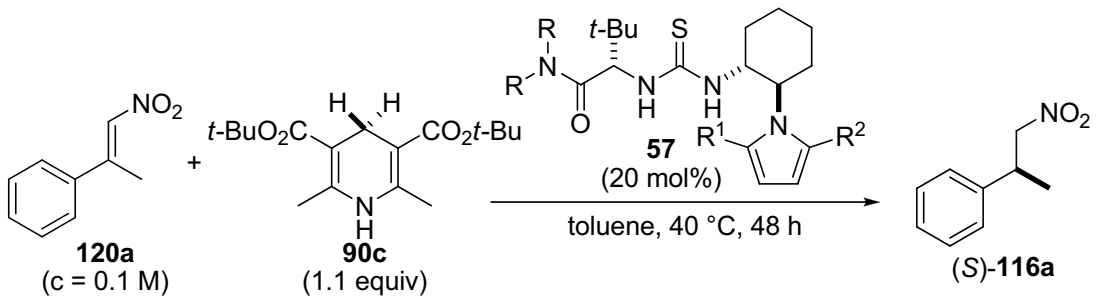
[a] Determined by chiral GC.

The increase of the length of the alkyl substituents (e. g. the replacement of dimethyl group by diethyl or dipropyl ones in **57b** and **57d**, respectively), led to a slight improvement of both reactivity and enantioselectivity (entries 2 and 4 vs. entry 1). Similar catalytic activity was

observed in the presence of *N*,*N*-dibenzyl-substituted thiourea **57c** (entry 3). Lower enantioselectivities were reached using *N*,*N*-benzylmethyl- or *N*-benzyl derivatives **57e** and **57f**, respectively (entries 5 and 6). From this screening it appeared that **57b** was slightly more enantioselective than other thioureas.

At this stage, it was difficult to favor one of these two catalysts (**57b** and **57c**). We decided to study the effect of the pyrrolyl substituents on the catalytic activity of both compounds (Table 4.23). This investigation clearly pointed out that reactivity and enantioselectivity of the catalyst decrease when the bulkiness of the substituent at the 2- and 5-positions of the pyrrolyl group is increased (entries 1-4 and entries 5-8). 2,5-Dimethylpyrrolyl-derived thioureas **57b** and **57c** appeared to have the optimal activity.

Table 4.23: Optimization of thiourea motif **57**: effect of the pyrrolyl structure on the transfer hydrogenation of nitroolefin **120a**



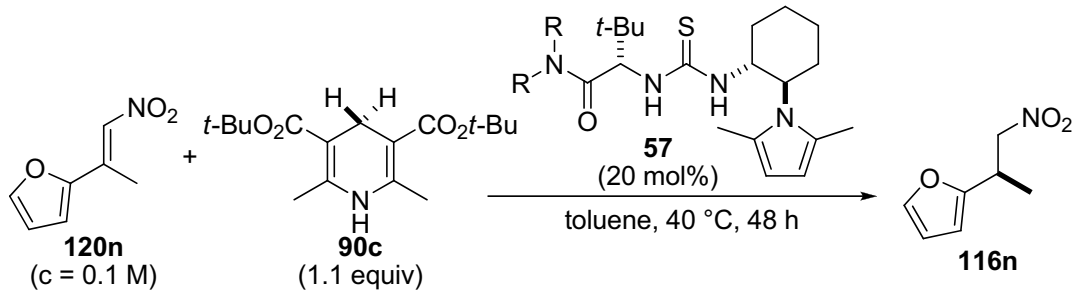
120a (c = 0.1 M) + **90c** (1.1 equiv) → (*S*)-**116a**

Entry	Catalyst:	R	R^1	R^2	conv. [%][a]	*er*[a]
1	**57b**	**Et**	**Me**	**Me**	**96**	**98.5:1.5**
2	**57g**	Et	Et	Et	87	96.0:4.0
3	**57h**	Et	Ph	Me	27	76.5:23.5
4	**57i**	Et	Ph	Ph	12	63.0:37.0
5	**57c**	**Bn**	**Me**	**Me**	**97**	**98.0:2.0**
6	**57j**	Bn	Et	Et	92	97.0:3.0
7	**57k**	Bn	Ph	Me	35	78.0:22:0
8	**57l**	Bn	Ph	Ph	19	56.0:44.0

[a] Determined by chiral GC.

To confirm the superiority of catalyst **57b**, a second reaction was investigated. We tested the catalytic activity of the thioureas **57a-f** in the transfer hydrogenation of (*E*)-2-(furan-2-yl)-1-nitro-1-propene (**120n**, Table 4.24). Once again, the optimal enantioselectivity was obtained using catalyst **57b**, bearing *N*,*N*-diethyl amino amide group (entry 2). According to these experiments, thiourea **57b** was favored and employed for the further optimization.

Table 4.24: Screening of *Jacobsen* thiourea motifs to catalyze the transfer hydrogenation of nitroolefin **120n**

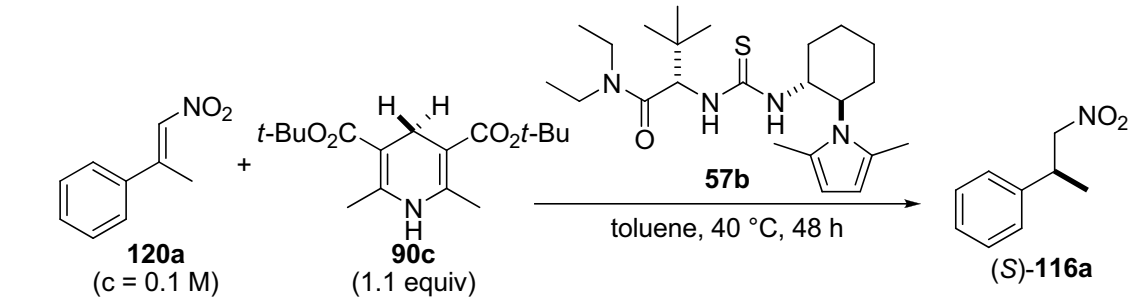


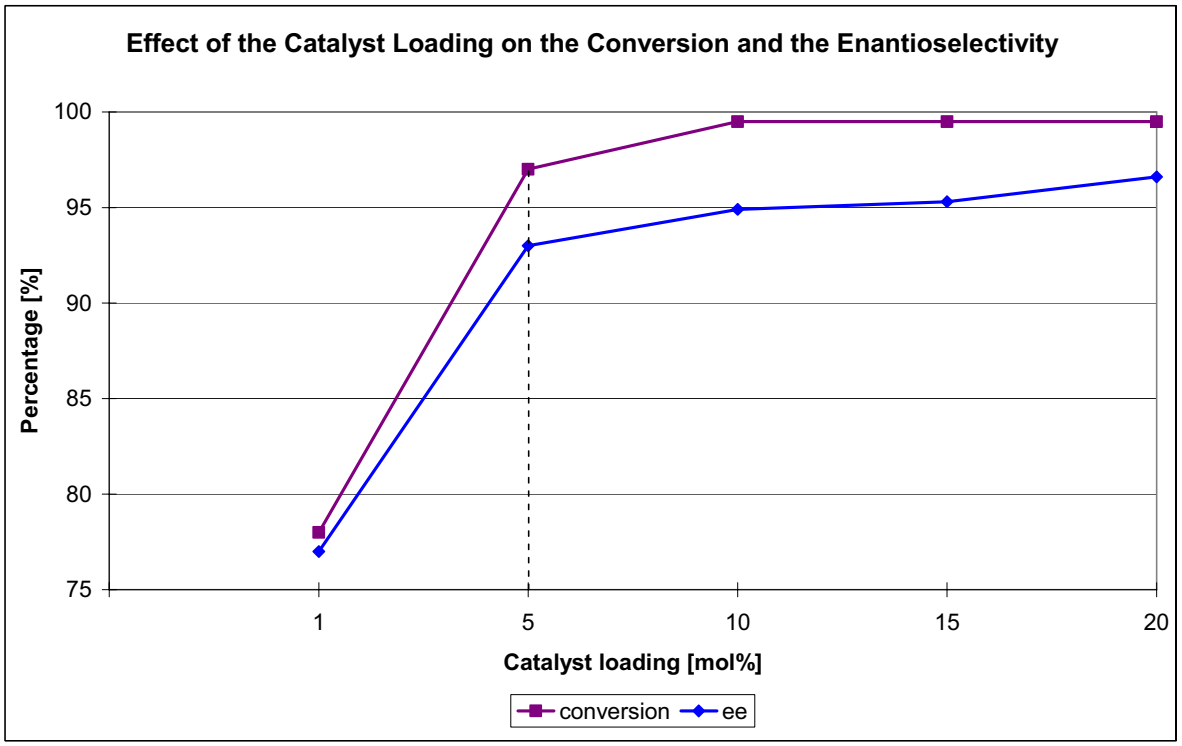
Entry	Catalyst:	R	R'	conv. [%][a]	*er*[a]
1	**57a**	Me	Me	72	94:6
2	**57b**	**Et**	**Et**	**74**	**97:3**
3	**57c**	Bn	Bn	64	95:5
4	**57d**	*n*-Pr	*n*-Pr	74	95:5
5	**57e**	Bn	Me	66	95:5
6	**57f**	Bn	H	74	91:9

[a] Determined by chiral GC.

4.4.3.4 Catalyst Loading

Once we had found the optimal catalyst (**57b**) for our process, we were interested in decreasing its relatively high catalyst loading (20 mol%) as much as possible, without loss of efficiency. The results of this investigation are reported in Scheme 4.59, which shows that no significant effect on the catalysis conversion and enantioselectivity after 48 hours reaction time was observed by lowering the thiourea amount from 20 to 5 mol%. However, a further decrease of the catalyst concentration led to a significant drop in activity and selectivity. Our objective was thus reached; thiourea **57b** could be used at a lower catalyst loading (5 mol %).

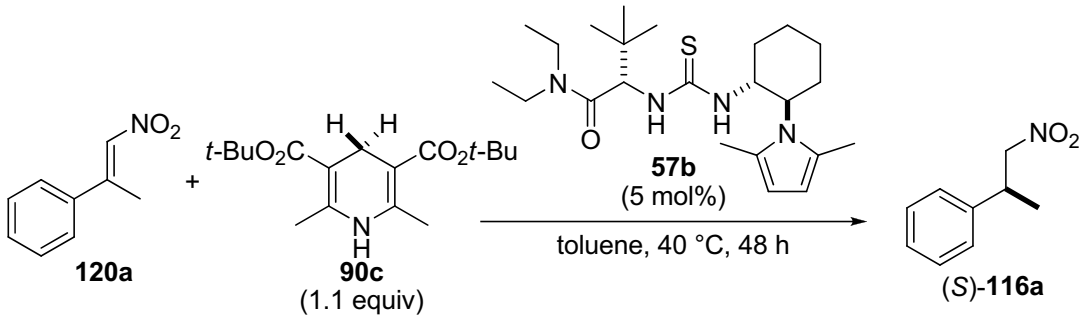


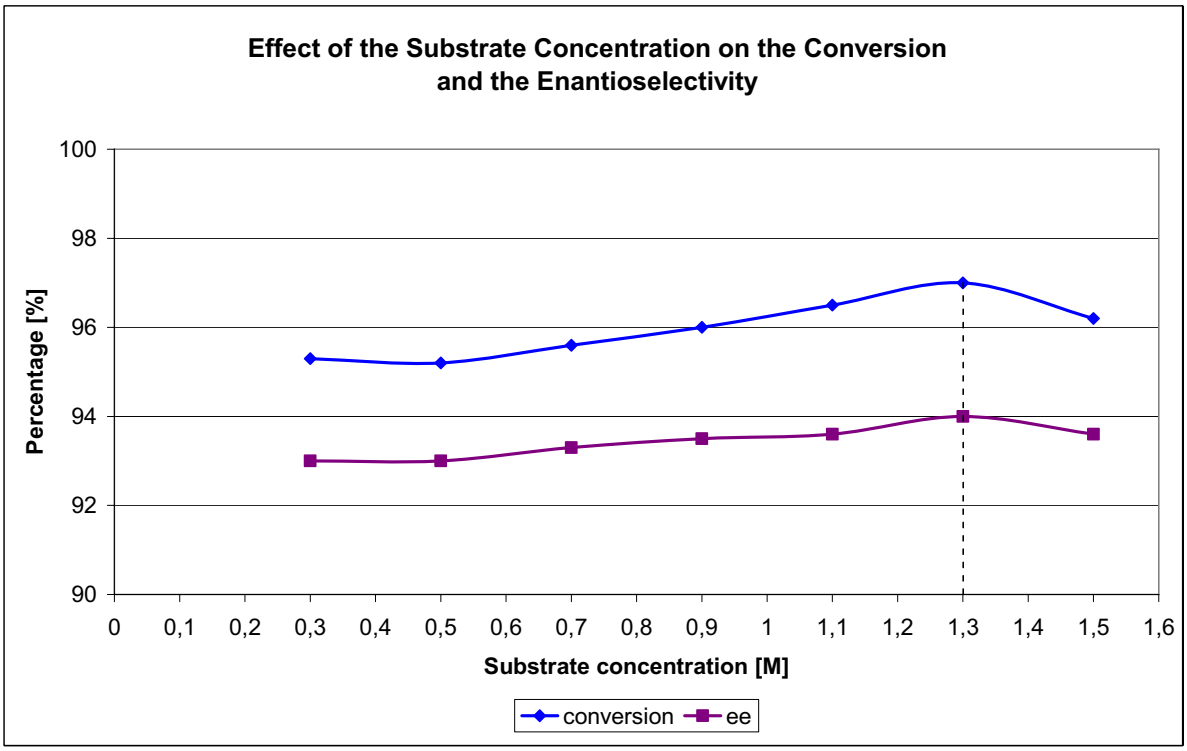


Scheme 4.59: Effect of the catalyst loading on the catalytic transfer hydrogenation of nitroolefin **120a**. (Note: to facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

4.4.3.5 Substrate Concentration

Before evaluating the scope of the reaction, we intended to increase the substrate concentration (i.e., use minimum solvent). For this purpose, we evaluated its (from 0.3 to 1.5 molar) on the efficiency of the catalysis (Scheme 4.60). As we already observed in the development of the conjugate reduction of α,β-unsaturated ketones (see Chapter 4.3.3.4, Scheme 4.44), an increase in the concentration of the nitroalkene **120a** slightly improved the conversion and enantioselectivity of the reaction. The maximal catalyst efficiency was obtained in a 1.3 molar solution. A further increase of the nitroolefin concentration caused a slight degradation of the yield and enantioselectivity of the reaction. For evaluating the scope of the reaction (see Chapter 4.4.4, Table 4.25), 1.3 molar solutions where thus used.





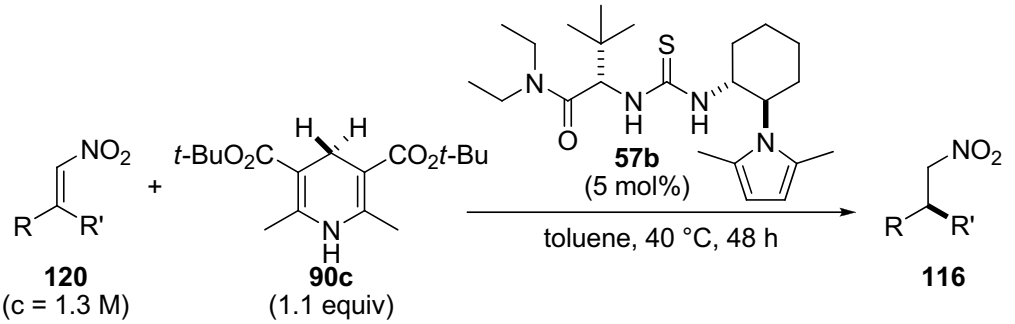
Scheme 4.60: Effect of the on the substrate concentration catalytic transfer hydrogenation of nitroolefin **120a**. (Note: to facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

4.4.4 Investigation of the Reaction Scope

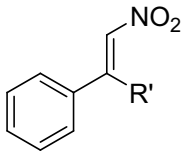
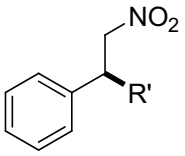
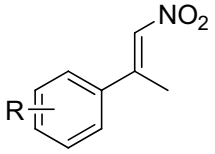
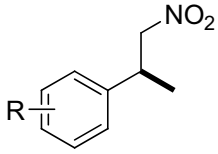
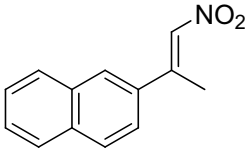
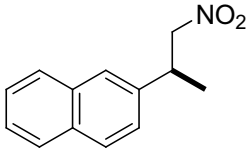
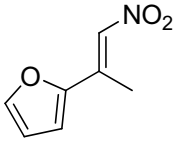
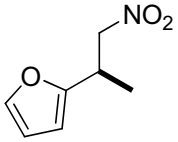
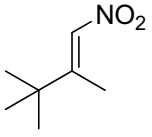
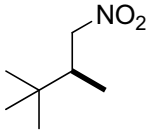
Based on the optimization of the catalyst, the solvent, the Hantzsch ester structure, the catalyst loading and the substrate concentration (see Chapters 4.4.2 and 4.4.3) in the transfer hydrogenation of (*E*)-1-nitro-2-phenyl-1-propene (**120a**), the following protocol was subsequently used for investigating the scope of the reaction: Treating nitroolefins **120** (1.3 molar) with commercially available Hantzsch ester **90c** (1.1 equivalents) in the presence of thiourea catalyst **57b** (5 or 10 mol%, depending on the substrate) at 40 °C in toluene for 24-48

hours afforded the saturated *β,β*-disubstituted nitroalkanes **116** in high yields and enantioselectivities (Table 4.25).

Table 4.25: Scope of the catalytic transfer hydrogenation of nitroolefins **120**



120 (c = 1.3 M) **90c** (1.1 equiv) **116**

Entry	Nitroalkene[a]	Nitroalkane	Yield [%][b]	*er*[c]
				
1	**120a:** R' = Me	**116a**	97	97:3
2	**120c:** R' = Et	**116c**	94	97:3
3	**120d:** R' = *n*-Pr	**116d**	>99	98:2
4[d]	(*Z*)-**120b:** R' = *i*-Pr	**116b**	92	8:92
				
5	**120f:** R = *p*-Me	**116f**	99	97:3
6[d]	**120g:** R = *p*-CN	**116g**	99	95:5
7	**120h:** R = *p*-F	**116h**	97	95:5
8	**120i:** R = *p*-Cl	**116i**	99	97:3
9	**120j:** R = *m*-Cl	**116j**	97	95:5
10	**120k:** R = *o*-Cl	**116k**	84	83:17
11[d]	 **120e**	 **116e**	>99	96:4
12[d]	 **120n**	 **116n**	84	96:4
13[d]	 **120l**	 **116l**	82	96:4

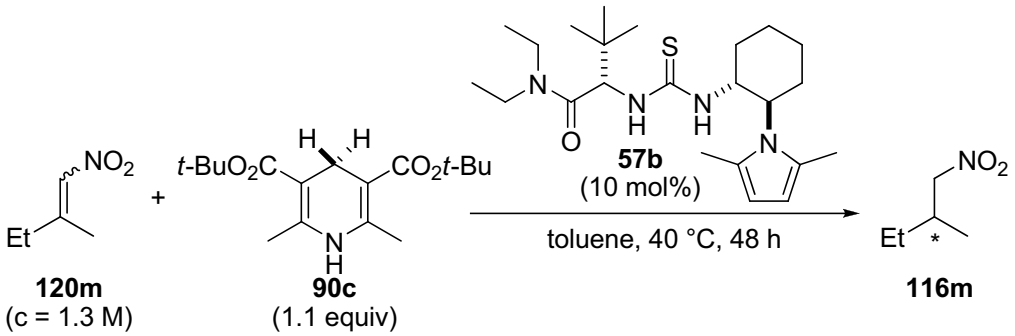
[a] (*E*)-Isomer (*E*/*Z* > 98:2). [b] Isolated yield. [c] Determined by chiral GC. [d] 10 mol% of catalyst **57b**.

The reaction proved to have a broad substrate scope and gave products with high yields and enantioselectivities with a number of *β*-alkylsubstituted nitrostyrenes (entries 1-3). In the presence of bulkier substituents such as an isopropyl group, however, lower reactivity and selectivity were observed (entry 4). Various electron-donating or withdrawing substituents at the phenyl ring were tolerated (entries 5-10). The nitroolefin **120g**, bearing an electron-withdrawing cyanide group, was slightly less reactive than the other substrates. In this case, we used 10 mol% of thiourea **57b** to achieve an equally high catalytic efficiency as with other *para*-substituted nitrostyrenes (entry 6). A substituent at the *ortho*-position of the phenyl ring led to a drop in reactivity and enantioselectivity (entry 10). Not only phenyl rings were appropriate but also other aromatic or heteroaromatic groups such as 2-naphthyl- and 2-furyl substituents (entries 11 and 12). Interestingly, aliphatic nitroalkenes were equally suitable substrates. *tert*-Butyl-substituted nitroolefin **120l** gave the corresponding product in good yield and excellent enantioselectivity (entry 11).

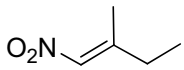
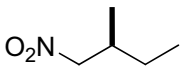
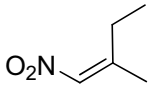
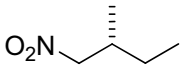
The absolute configuration of the compound **120d** was determined by measuring its optical rotation value and comparing it with the literature value.[173] The other absolute configurations were assigned by analogy.

We were pleased to see that our catalyst could even differentiate between the ethyl and methyl substituents of aliphatic 2-methyl-1-nitrobutenes (**120m**) as its corresponding nitroalkanes (**116m**) were formed in high yield and reasonable enantiomeric ratios (Table 4.26). Remarkably, the enantioselectivity is strongly dependent on the olefin geometry. We partially separated the two olefin diastereoisomers by preparative HPLC. It is worth noting that directly after the (partial) separation of the (*E*)- and (*Z*)-isomer by HPLC, nitroolefin **120m** isomerized again to some extent. We found that (*E*)-enriched-**120m** gave the nitroalkane (*S*)-**116m** with significantly higher enantioselectivity (entry 1). A sample enriched in the (*Z*)-isomer gave the opposite enantiomer but with much lower enantiomeric ratio (entry 2). Since the transfer hydrogenation is not stereoconvergent, optimal enantioselectivities can only be reached using pure (*E*)- or pure (*Z*)-nitroalkenes **120**.

Table 4.26: Catalytic transfer hydrogenation of 2-methyl-1-nitrobutene **120m**



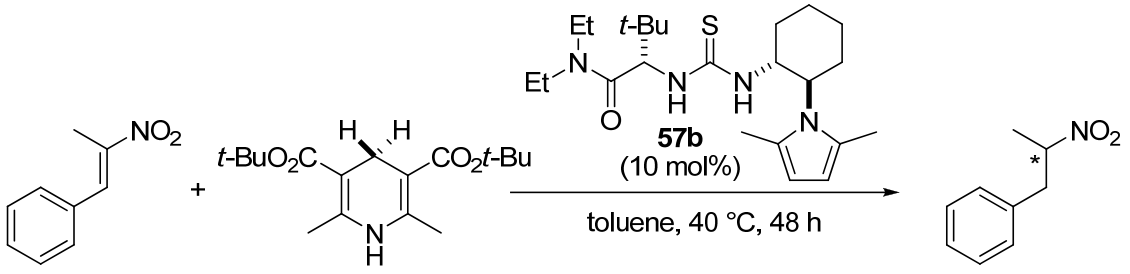
120m (c = 1.3 M) + **90c** (1.1 equiv) → **116m**

Entry	Nitroalkene	Nitroalkane	Yield [%][a]	*er*[a]
1			97	82:18
	(*E*)-**120m** (*E*/*Z* = 93:7)	(*S*)-**116m**		
2			95	44:56
	(*Z*)-**120m** (*E*/*Z* = 14:86)	(*R*)-**116m**		

[a] Yield and *er* of volatile product **116m** determined by chiral GC.

After having explored the scope of the reaction and realized that the catalytic conjugate reduction worked well with a variety of aromatic and aliphatic *β,β*-disubstituted nitroalkenes (**120**), we then wondered if we could apply it to other nitroolefin classes such as *α,β*-disubstituted nitroalkenes. For this purpose we investigated the catalytic transfer hydrogenation of commercially available (*E*)-(2-nitroprop-1-enyl)benzene (**207**) to 2-nitropropyl)benzene (**208** , Scheme 4.61). For this study, 20 mol% of thiourea **57b** were used, affording the desired nitroalkane **208** nearly racemic but in quantitative yield.

According to these results, we developed a very efficient process for the preparation of *β,β*-disubstituted nitroalkanes **116**. Another methodology has to be established for the synthesis of analogs *α,β*-disubstituted nitroalkane **208**.



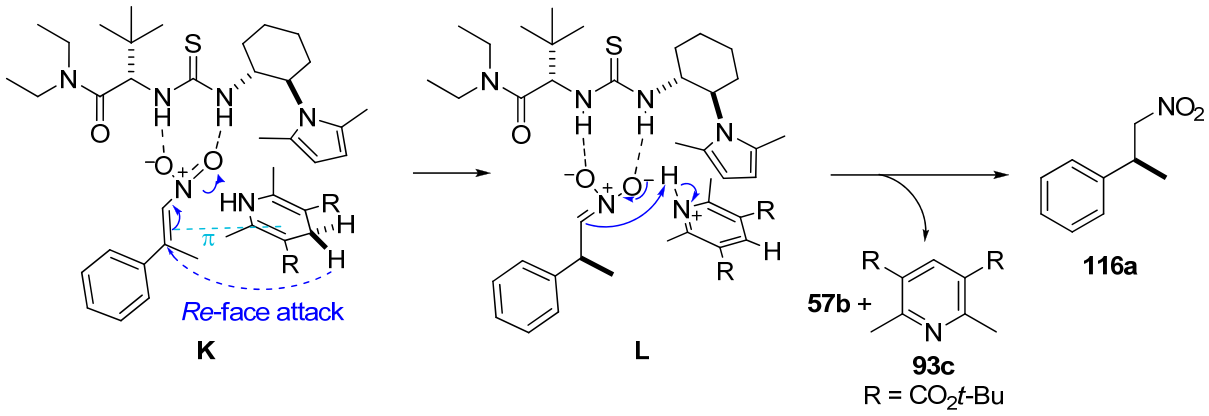
207 (c = 1.3 M) + **90c** (1.1 equiv) → **208** >99%, 52:48 *er*

Scheme 4.61: Extension of the process to the catalytic transfer hydrogenation of *α,β*-disubstituted nitroalkene **207**.

4.4.5 Mechanistic Considerations

Mechanistically, our first hypothesis was that the reaction proceeded *via* nitroolefin activation by the thiourea moiety of the catalyst through hydrogen bonding interactions, which is in accordance with the mechanism proposed by *Takemoto et al.* for the addition of malonates to nitroolefins (see Chapter 3, Scheme 3.6).[102]

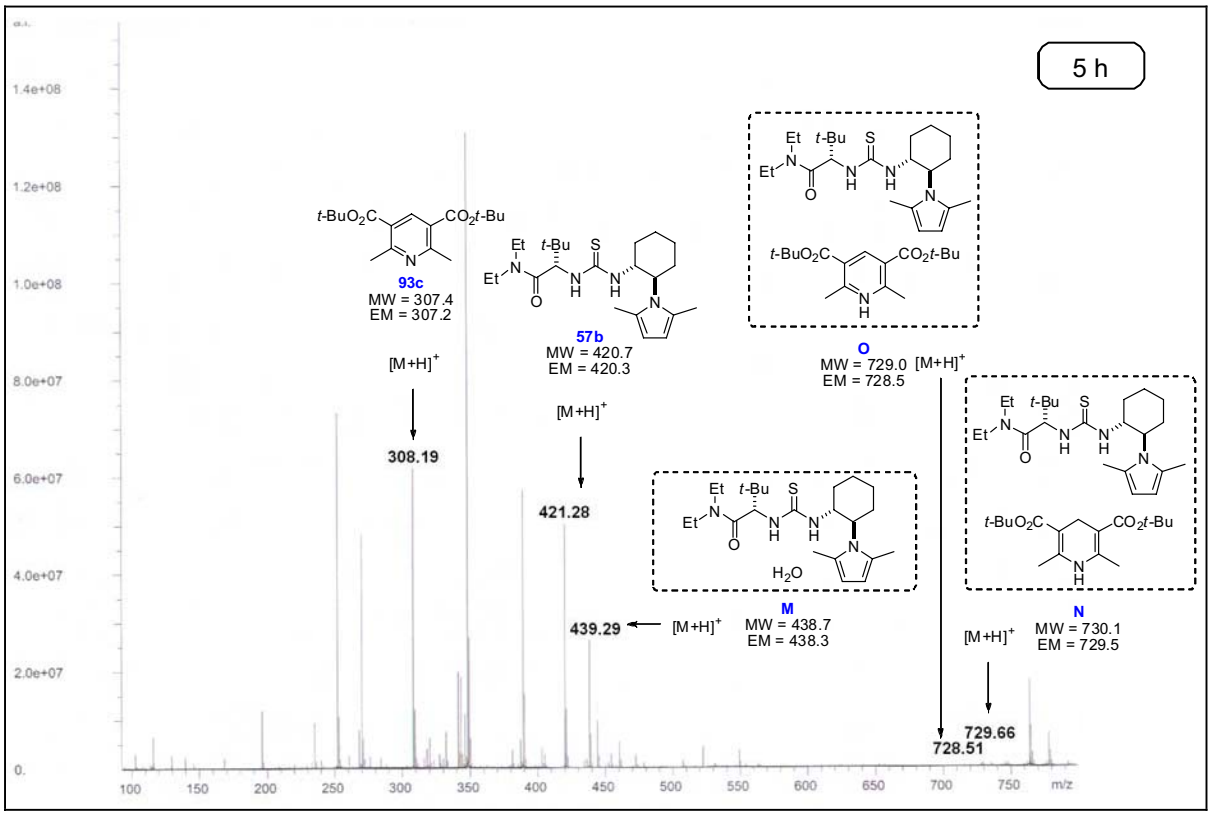
The results of the conjugate reduction (i.e. formation of the products with generally (*S*)-configuration) suggest that the hydride attack occurs from the *Re*-face of the nitroalkene **120a**. We then assumed that the reaction might occur through a transition state similar to the working model **K** (Scheme 4.62) with the hydride transfer from the Hantzsch ester taking place from the *Re*-face. This step would be followed by a proton transfer from the pyridinium ion in **L**, generating the desired product (**116a**) along with the pyridine derivative **93c**. Activation of the dihydropyridine might occur through interactions of its π-system with the nitroolefin π-system. Moreover interactions between the thiourea catalyt and water molecules that could be present in the reaction media, might take place. This would lead to the acidification of the water molecules, which might then play a role in the catalytic cycle. Mechanistic studies and computational calculations would be needed to gain more insight about the configuration of the plausible transitions states **K** and **L** (Scheme 4.62) and about the possible role played by water in the catalytic transfer hydrogenation of nitroalkenes **120**.



Scheme 4.62: First postulated mechanism: activation of nitroolefin **120a** *via* hydrogen bonds with the thiourea moiety of catalyst **57b** with additional interactions between the catalyst and the dihydropyridine **90c**.

In order to gain insight into the reaction mechanism we followed the progress of the reaction using ESI-MS analysis. For this purpose we carried out the transfer hydrogenation of nitroolefin **120a** under the reaction conditions reported in Table 4.25 (see Chapter 4.4.4). Samples were taken from the reaction mixture at different time intervals over 24 hours and submitted to ESI-MS analysis.

Unfortunately, this study did not furnish the expected information since it was not possible to detect compounds containing a nitro functionality using this analytical method. For this reason we could not observe if there were hydrogen bonding interactions between the catalyst and the nitroolefin. Based on the ESI-MS experiments we can only hypothesize that hydrogen bonding interactions between the catalyst and water (**M**, EW = 438 g/mol) and eventually between the catalyst and the Hantzsch ester **90c** (**N**, EW = 729 g/mol) or pyridinium ion (**O**, EW = 728 g/mol) occur (see the peaks at *m/z* = 439 ($[M+H]^+$), 730 ($[M+H]^+$, and 729 ($[M+H]^+$), respectively, in Scheme 4.63).



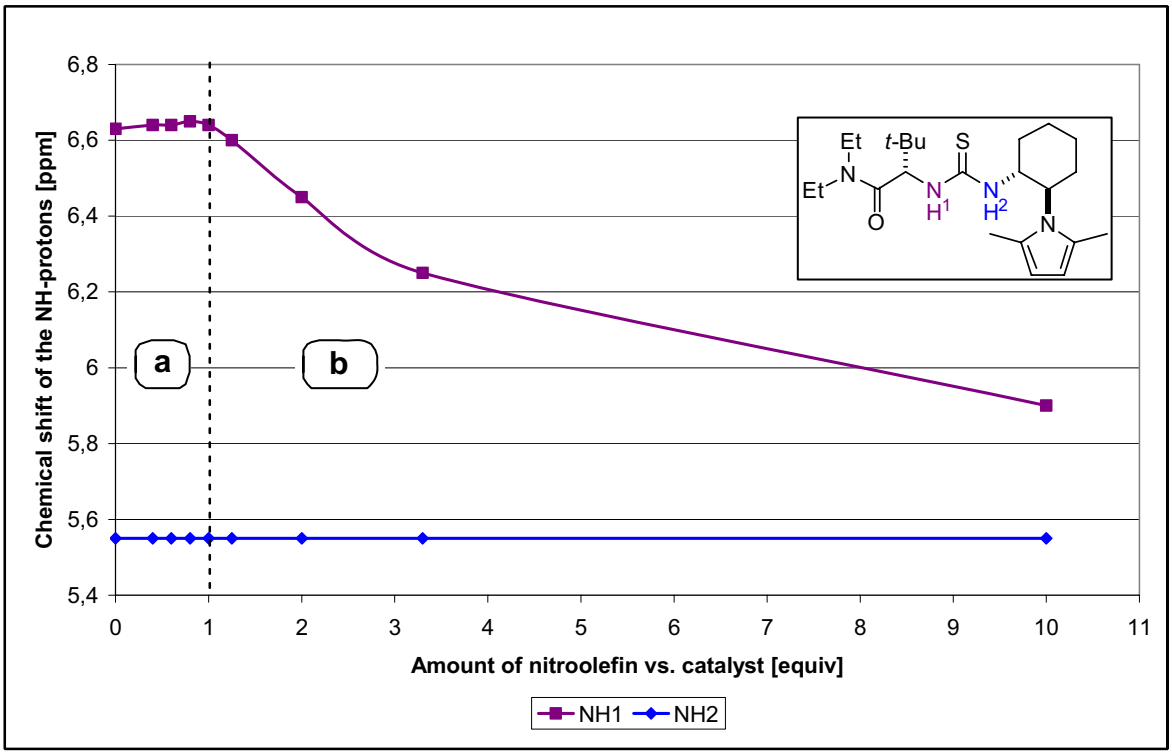
Scheme 4.63: Spectrum corresponding to the ESI-MS measurement done after a reaction time of five hours. (MW: molecular weight. EM: exact mass).

We then performed several nuclear magnetic resonance (NMR)-titrations to determine if hydrogen bonding interactions between the thiourea moiety and nitroolefin or/and between the catalyst and water took place (Schemes 4.64-4.65). This was done by monitoring the chemical shifts of the protons of the thiourea group in the catalyst **57b**.

We first investigated the possible interactions between the catalyst **57b** and the nitroolefin **120f** (chosen arbitrarily as the model substrate). For this purpose we analyzed solutions of the catalyst **57b** in deuterated toluene by NMR, which contained different amounts of the nitroolefin **120f** (from 0.4 to 1.5 equivalents). The analysis of the ^{1}H-NMR spectra of these

solutions did not provide direct evidence for nitro group binding to the catalyst since all the chemical shifts remained unchanged upon the nitroolefin addition (Scheme 4.64a).

We then assumed that it would be possible to observe a change of chemical shifts of the thiourea moiety of **57b** by using chemically more relevant conditions, i.e. catalytic amounts of the thiourea, by utilizing 1.0 to 10.0 equivalents of nitroolefin **120f** (Scheme 4.64b). Under these conditions, the addition of **57b** resulted in a pronounced upfield shift (from 6.63 to 5.90 ppm) of the resonance of one of the thiourea protons (proton N**H**^{1}, Scheme 4.64b). Although shifts as large as 0.2 part per million (ppm) occur as a result of simple medium effect, the observed upfield shift of 0.73 ppm with **57b** pointed to a direct interaction between the catalyst and the nitroolefin **120f** (through at least one proton of the thiourea moiety).

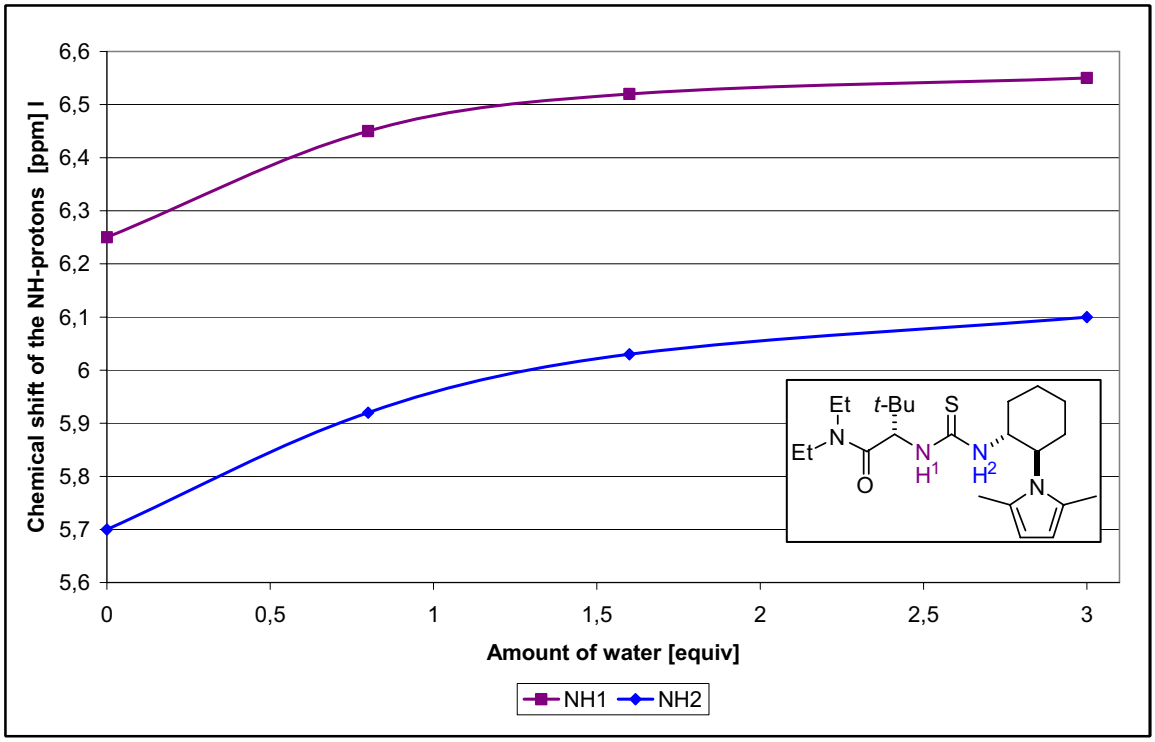


Scheme 4.64: Influence of the addition of nitroolefin **120f** to a catalyst solution on the chemical shift of the protons of the thiourea moiety of **57b**.

Furthermore, we evaluated the possible interactions between the catalyst **57b** and water. To this end, we measured by NMR solutions of thiourea **57b** in dried deuterated toluene containing different amounts of water (0.0, 0.8, 1.6 and 3.0 equivalents).

On the other hand, when the experiment was run in deuterated dried chloroform, the resonance of both thiourea protons was shifted downfield by about 0.3 and 0.4 ppm, respectively (Scheme 4.65). Accordingly, we reasoned that hydrogen bonding interactions between the catalyst and water molecules might also occur in the analyzed deuterated

chloroform solutions. Since such interactions were not observed running the NMR titrations in dried deuterated toluene, it is difficult to have a clear picture on the role of water in the reaction. Further investigations as well as computational calculations would be needed to gain more insight into the effect of water on the conjugate reduction of nitroolefins **120**.

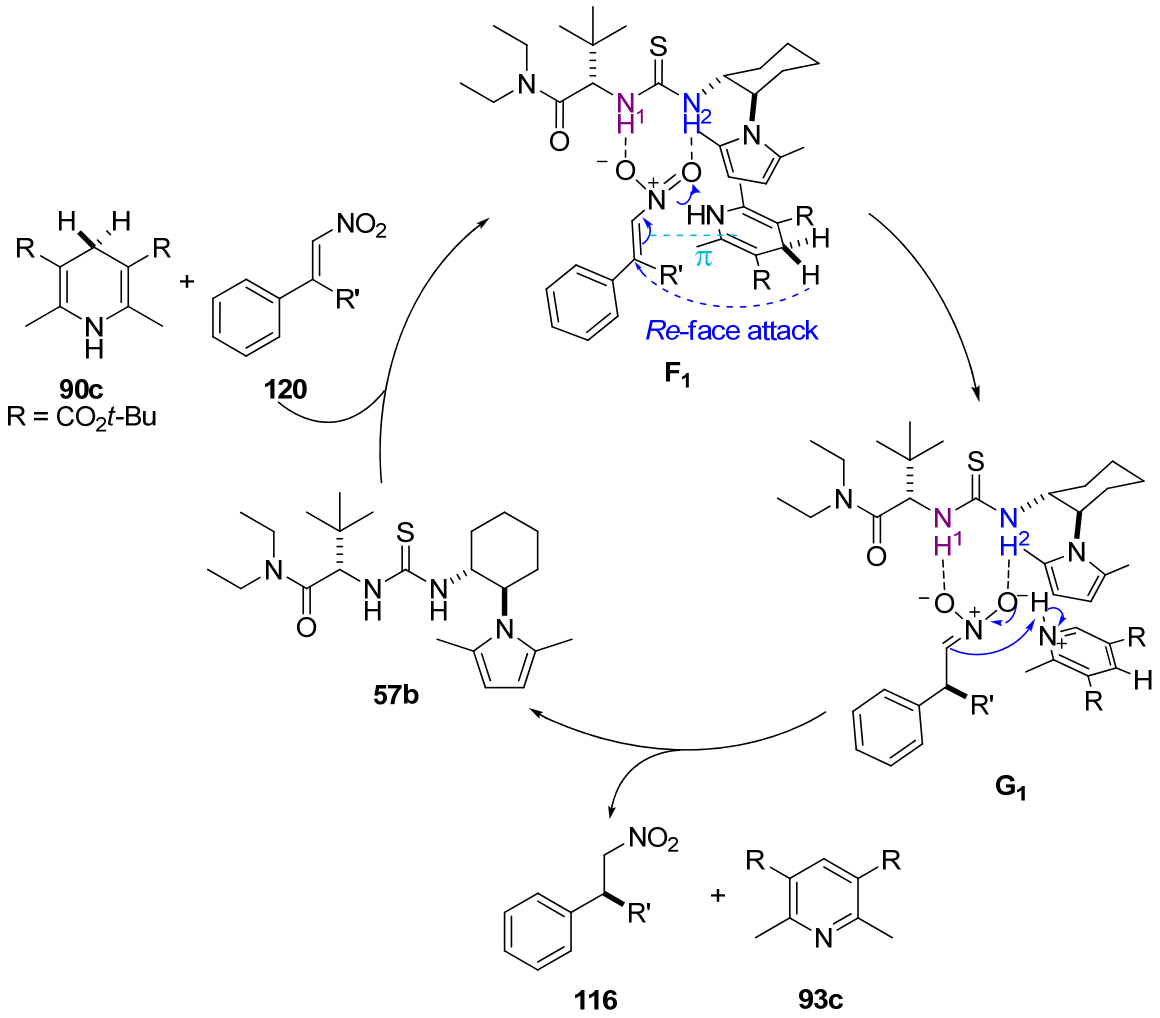


Scheme 4.65: Influence of the addition of water to a $CDCl_3$ solution of catalyst **57b** on the chemical shift of the protons of the thiourea moiety of **57b**.

Based on the results of the ESI-MS analyses and the NMR titrations, it was not possible to define which of the mechanisms we suggested was the most probable. Our investigations pointed out that hydrogen bonding interactions would occur between the thiourea **57b** and the nitroolefin **120f** and that the catalyst might eventually also interact with water. For the latter case, however, no evidences were found by NMR titration in deuterated toluene. At this stage of the mechanistic study, we could not determine if the catalyst would interact preferably with the nitroolefin or water, in case both were present in the reaction media, or if water really played a role in the catalytic cycle.

We then proposed the catalytic cycle represented in Scheme 4.66, neglecting the presence and/or action of water. We assumed that the nitroalkene **120** was activated through hydrogen bonding interactions (most probably directly) with the thiourea moiety of the catalyst **57b** as represented in the transition state $\mathbf{F_1}$ (Scheme 4.66). This would lead to a decrease of the LUMO energy of the olefin and allow the hydride transfer from the Hantzsch ester **90c**, which might itself be activated through π-stacking interaction with the nitroolefin and perhaps also

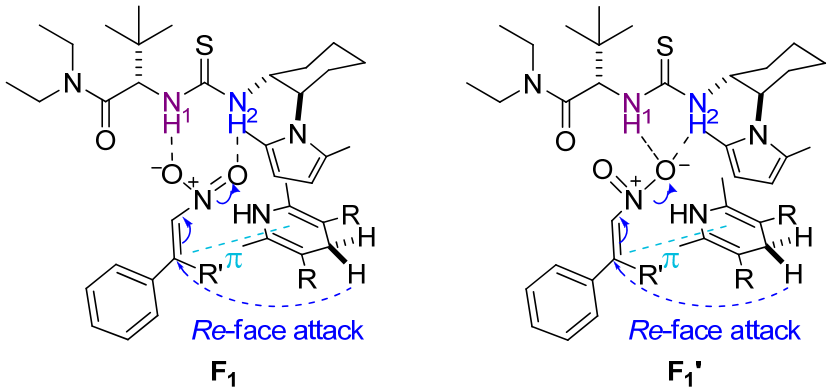
with the pyrrol function of the catalyst **57b**. A subsequent proton transfer from the pyridinium ion in **G_1** would afford the nitroalkane **116** along with the pyridine derivative **93c.**



Scheme 4.66: Proposed mechanism for hydrogen bonding-catalyzed transfer hydrogenation of the nitroolefin **120**. The possible role played by water in this catalytic cycle is neglected.

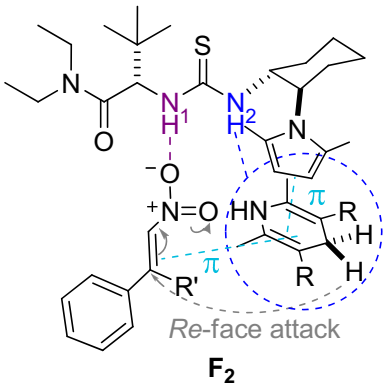
At this stage it is worth specifying that we previously only discussed the nitroolefin activation through hydrogen bonding interactions between the thiourea moiety of catalyst **57b** and the two oxygens of the nitro functionality in olefin **120a** (transition state **F_1**, Scheme 4.67). An alternative transition state would be **F_1'**, in which both hydrogen atoms of the thiourea moiety of **57b** interact with only one oxygen of the nitro group in substrate **120a**.

To support the catalytic cycle depicted in Scheme 4.66 and to gain more insight into the transition state (**F_1** or **F_1'**) and the mechanism of the reaction as well as the possible role that water could play in the activation of the nitroolefin, further mechanistic studies as well as computational calculations are required (see Outlook, Chapter 6).



Scheme 4.67: Activation of both oxygen of the nitroolefin through hydrogen activation (**F**$_1$) vs. double activation of only one oxygen of the nitro functionality (**F'**$_1$).

It would also be interesting to explore the interactions between the catalyst **57b** and the Hantzsch ester **90c**. Effectively, based on the results of the NMR titrations, the chemical shift of only one proton of the thiourea moiety (N**H**^{1} in Scheme 4.64) was shifted upfield while adding nitroolefin to the catalyst. This suggests that a single hydrogen bond is formed between the thiourea and the nitroolefin. We could thus envisage that the free hydrogen of the thiourea moiety (N**H**^{2} in Scheme 4.64) interacts with the dihydropyridine through hydrogen bonding interaction (Scheme 4.68). However, it is not clear with which atom of the Hantzsch ester is involved since hydrogen bond with the nitrogen of the hydrogen source would lead to the deactivation of the dihydropyridine. To explore this idea, it would be interesting to perform in a future work NMR titrations of deuterated toluene solutions of catalyst **57a** containing different amounts of Hantzsch ester **90c** to observe the influence of **90c** on the chemical shifts of the protons of the thiourea moiety (N**H**^{1} and N**H**^{2} in Scheme 4.64). To support this hypothesis computational calculations would also be needed.



Scheme 4.68: New hypothesis for the working model transition state of the Hantzsch ester-mediated asymmetric transfer hydrogenation of nitroolefins.

4.4.6 Conclusion and Discussion

We have successfully developed an efficient enantioselective hydrogen bonding-catalyzed transfer hydrogenation of *β*,*β*-disubstituted nitroolefins using the thiourea **57b** as a catalyst and the commercially available Hantzsch ester **90c** as the hydrogen source. This highly enantioselective process led to the synthesis of the chiral *β*,*β*-disubstituted nitroalkanes **116**, which are valuable intermediates such as for further reduction to chiral amines.

Before we undertook this investigation, only one biocatalytic and one transition-metal-catalyzed variant had been realized. *Carreira et al.* developed an elegant chiral copper complex-catalyzed version using a silane as the stoichiometric reductant.[173] However, the efficiency of this process was counterbalanced by its low practicability as it required a subsequential addition of the reactants/reagents over a period of 17 hours prior to adding the nitroolefin. On the other hand, *Ohto et al.* used fermenting bakers' yeast in the presence of glucose, which allowed for an effective conjugate reduction of a limited number of aliphatic *β*,*β*-disubstituted nitroalkenes.[174]

Our experiments pointed out that Brønsted acids, like chiral BINOL-derived phosphoric or dicarboxylic acids (**126a** and **157b**, respectively), were active catalysts for the transfer hydrogenation of nitroolefin **120** but gave the desired product with poor or moderate enantioselectivity, respectively. More promising results were obtained using hydrogen-bonding or general acid-type thiourea catalysts. Thiourea derivatives identical or similar to those pioneered by *Jacobsen et al.*, and in particular **50d** and **57a**, turned out to be reactive and highly enantioselective catalysts. Further structural fine-tuning of the thiourea **57a** afforded the catalyst **57b**, which proved to be optimal in terms of reactivity and enantioselectivity.

Maximal catalytic efficiency was obtained when the process was run in toluene (nitroolefin **120**: 1.3 molar) at 40 °C in the presence of the thiourea catalyst **57b** (5 mol%) and the commercially available Hantzsch ester **90c**. Under these reaction conditions, the transfer hydrogenation had a broad substrate scope and gave the *β*,*β*-disubstituted nitroalkanes **116** in high yields and enantioselectivities with a number of *β*-alkylsubstituted nitrostyrenes. Remarkably, aliphatic nitroalkenes were equally suitable as *tert*-butyl- and ethyl-substituted nitroolefins (**120l** and **120m**, respectively) generated the corresponding product in high yields and enantioselectivities. While investigating the latter substrate (**120m**) we realized that the reaction was not stereoconvergent, which means that the enantioselectivity was strongly dependent on the olefin geometry. For this reason, the nitroolefins have to be used as the pure

(*E*)- or (*Z*)-isomers to allow for the generation of the corresponding nitroalkanes with optimal enantiomeric ratios. As with the conjugate reduction of enones, it would be of interest to investigate the role of catalytic phosphine derivatives in inducing stereoconvergence by isomerizing the nitroolefin *in situ*.

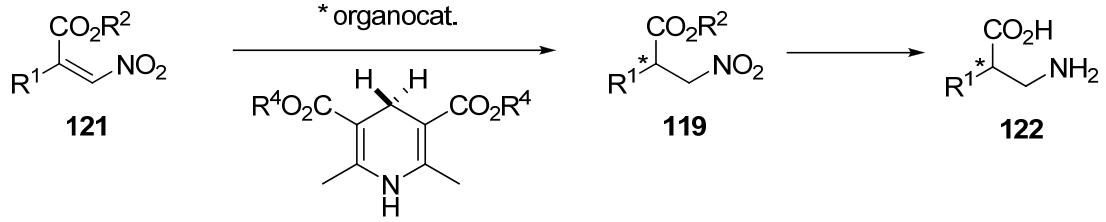
Mechanistically, we assumed that the reaction is catalyzed by hydrogen bonding interactions between the thiourea moiety of the catalyst **57b** and the nitroolefin **120** (see the proposed catalytic cycle in Scheme 4.66)**.** Possible interactions between Hantzsch ester **90c** and catalyst **57b** were supported by monitoring the reaction with ESI-MS (see Chapter 4.4.5). The activation of the Hantzsch ester could occur by π-stacking with the pyrrolyl group of the catalyst **57b**; eventually also through additional interactions by hydrogen bonding with one proton of the thiourea moiety of **57b** (N**H**^{2} in Scheme 4.64, Chapter 4.4.5). In this case the nitroolefin would be activated by only one proton of the thiourea (N**H**^{1} in Scheme 4.64, Chapter 4.4.5). To gain more insight into the mechanism of the transfer hydrogenation, further studies as well as computational calculations would be needed.

A drawback of this highly efficient conjugate reduction is the difficulty in obtaining pure nitroolefins **120**, which were in most case isolated in very low yields (See Chapter 4.4.1). The development of an efficient synthesis of *β*,*β*-disubstituted nitroalkenes **120** in a one-step process from the corresponding ketone **204** in the presence of nitromethane and a catalytic amount of a base would be of great interest and would make our catalytic methodology even more attractive.

To conclude, we can say that general Brønsted acid catalysis is highly useful for the Hantzsch ester-mediated enantioselective conjugate reduction of *β*,*β*-disubstituted nitroolefins. Our versatile organocatalytic approach adds to the previously developed transition metal[173] and biocatalyzed[174] versions. The modest atom economy of Hantzsch ester-mediated conjugate reductions may be counterbalanced by the practical and convenient use of bench-stable, crystalline Hantzsch esters.

4.5 Enantioselective Transfer Hydrogenation of *β*-Nitroacrylates: a Route to *β*²-Amino Acids

We were very interested in establishing a practical process for the preparation of valuable chiral *β*²-amino acids. For this purpose, we based our strategy on the elaboration of an effective organocatalytic approach to synthesize *β*-nitroesters **119**, which would be further converted to the corresponding chiral *β*²-amino acids **122**. Inspired by our transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes **120** (see Chapter 4.4), we assumed that it would be possible to generate *β*-nitroesters **119** through a catalytic Hantzsch ester-mediated conjugate reduction of the corresponding *β*-nitroacrylates **121** (Scheme 4.69).



Scheme 4.69: Planned Hantzsch ester-mediated organocatalytic asymmetric transfer hydrogenation of *β*-nitroacrylates **121**, as a route to *β*²-amino acids **122**.

Our objectives were: first to develop an efficient and highly enantioselective catalytic transfer hydrogenation of *β*-nitroacrylates **121** and then to find reaction conditions to convert the obtained *β*-nitroesters **119** to their corresponding *β*²-amino acids **122**.

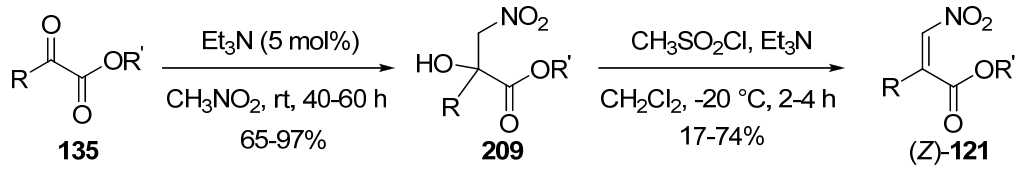
4.5.1 Synthesis of the Starting Materials and Racemic Products

4.5.1.1 Synthesis of the *β*-Nitroacrylates

The substrates (**121**) were synthesized from the corresponding *α*-ketoesters **135** in a two-step process *via* a Henry reaction followed by dehydration (Scheme 4.70).[244] First, the *α*-ketoesters **135** were reacted with nitromethane and a catalytic amount of triethylamine (5 mol%) to generate the corresponding *β*-nitro-*α*-hydroxyesters **209**[203] in good to excellent yields (65-97%). The dehydration step was performed in dry dichloromethane in the presence of three

equivalents of methanesulfonyl chloride and triethylamine.[245] After a basic work-up the *β*-nitroacrylates **121** were isolated in poor to moderate yields (17-74%).

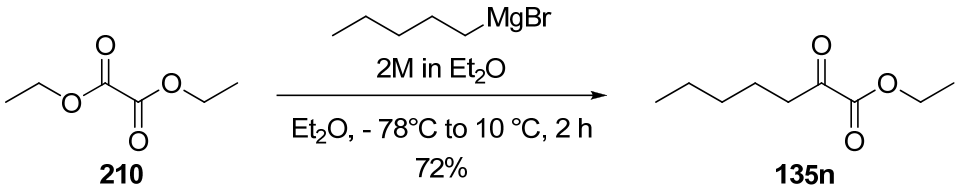
Most of the *α*-ketoesters **135** were commercially available. When it was not the case, they were prepared using one of the procedures reported in Schemes 4.71-4.74.[248-251]



135a: R = Me; R' = Et (c. a.)	**209a**: 96%	**121a**: R = Me; R' = Et; 74%*
135b: R = C_6H_5; R' = *i*-Pr	**209b**: 92%	**121b**: R = C_6H_5; R' = *i*-Pr; 72%
135c: R = C_6H_5; R' = Me (c. a.)	**209c**: 85%	**121c**: R = C_6H_5; R' = Me; 59%
135d: R = C_6H_5; R' = Et (c. a.)	**209d**: 92%	**121d**: R = C_6H_5; R' = Et; 63%
135e: R = C_6H_5; R' = *t*-Bu	**209e**: 77%	**121e**: R = C_6H_5; R' = *t*-Bu; 17%
135f: R = C_6H_5; R' = Bn	**209f**: 84%	**121f**: R = C_6H_5; R' = Bn; 21%
135g: R = *p*-Me-C_6H_4; R' = Et (c. a.)	**209g**: 82%	**121g**: R = *p*-Me-C_6H_4; R' = Et; 52%
135h: R = *p*-MeO-C_6H_4; R' = Et (c. a.)	**209h**: 81%	**121h**: R = *p*-MeO-C_6H_4; R' = Et; 34%
135i: R = *p*-F-C_6H_4; R' = Et (c. a.)	**209i**: 97%	**121i**: R = *p*-F-C_6H_4; R' = Et; 49%
135j: R = *p*-Cl-C_6H_4; R' = Et (c. a.)	**209j**: 82%	**121j**: R = *p*-Cl-C_6H_4; R' = Et; 53%
135k: R = *p*-MeO-C_6H_4; R' = *t*-Bu	**209k**: 69%	**121k**: R = *p*-MeO-C_6H_4; R' = *t*-Bu; 25%
135l: R = *p*-F-C_6H_4; R' = *t*-Bu	**209l**: 68%	**121l**: R = *p*-F-C_6H_4; R' = *t*-Bu; 27%
135m: R = 2-thienyl; R' = Et (c. a.)	**209m**: 65%	**121m**: R = 2-thienyl; R' = Et; 46%
135n: R = *n*-Pent; R' = Et	**209n**: 94%	**121n**: R = *n*-Pent; R' = Et; 66%**
135o: R = *i*-Pr; R' = Et (c. a.)	**209o**: 97%	**121o**: R = *i*-Pr; R' = Et; 30%

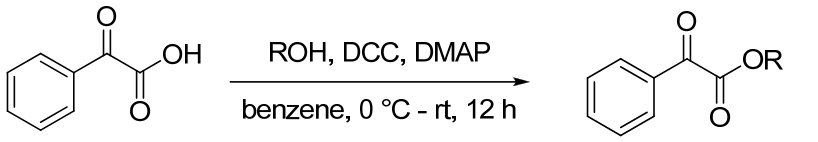
Scheme 4.70: Two-step process used to synthesize the *β*-nitroacrylates **121** from the corresponding *α*-ketoesters **135**. ([a] (*E*)-**121a**: 6% and (*Z*)-**121a**: 68%. [b] (*E*)-**121n**: 5% and (*Z*)-**121n**: 61%).

Ethyl 2-oxoheptanoate (**135n**) was generated by treating diethyloxalate **210** with pentylmagnesium bromide at -78 °C in diethylether, followed by an acidic work-up (Scheme 4.71).[246]



Scheme 4.71: Preparation of ethyl 2-oxoheptanoate (**135n**).

Isopropyl and *tert*-butyl 2-oxo-2-phenylacetate (**135b** and **135e**, respectively) were prepared from the corresponding 2-oxo-carboxylic acid **133a** according to the literature[247] (Scheme 4.72). To a solution of 2-oxo-2-phenylacetic acid (**133a**) in benzene a catalytic amount of DMAP (10 mol%) was added at 0 °C, followed by DCC and the alcohol of choice. Afterwards the reactions were stirred for twelve hours, the *α*-ketoesters **135b** and **135e** were obtained in moderate to good yields.

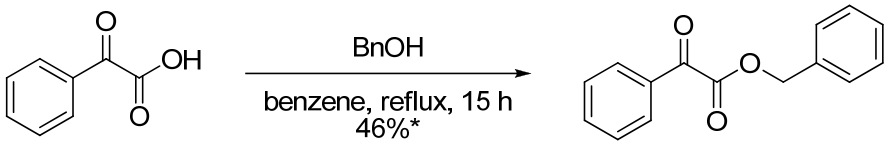


133a

135b: R = *i*-Pr; 88%*
135e: R = *t*-Bu; 25%*

Scheme 4.72: Synthesis of isopropyl- and *tert*-butyl-2-oxo-2-phenylacetate (**135b** and **135e**, respectively) from 2-oxo-2-phenylacetic acid (**133a**). (*NMR yield of the crude product after work-up).

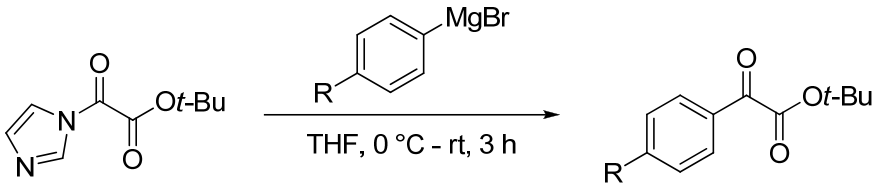
A slightly different procedure was used to generate benzyl-2-oxo-2-phenylacetate (**135f**).[248] In this case a mixture of 2-oxo-carboxylic acid **133a** and benzyl alcohol was stirred overnight at reflux, without the addition of DCC or DMAP (Scheme 4.73). After removal of the solvent under reduced pressure, the crude *α*-ketoester **135f** was obtained in moderate yield and used in the next step (Henry reaction, see Scheme 4.70) without further purification.



133a **135f**

Scheme 4.73: Synthesis of benzyl-2-oxo-2-phenylacetate (**135f**) from 2-oxo-2-phenylacetic acid (**133a**). (*NMR yield of the crude product after work-up).

tert-Butyl 2-oxo-2-phenylacetate derivatives (**135k** and **135l**), bearing a substituent on the phenyl ring, were synthesized from *tert*-butyl 2-(1H-imidazol-1-yl)-2-oxoacetate (**211**), following the procedure reported by *Mosher et a.*[249] The aryl Grignard reagent was added at 0 °C to a solution of **211** in THF. The mixture was then allowed to warm up to room temperature and stirred at this temperature for three hours (Scheme 4.74). After the work-up, the crude *α*-ketoesters **135** were obtained and used in the next step (Henry reaction, see Scheme 4.70) without further purification.



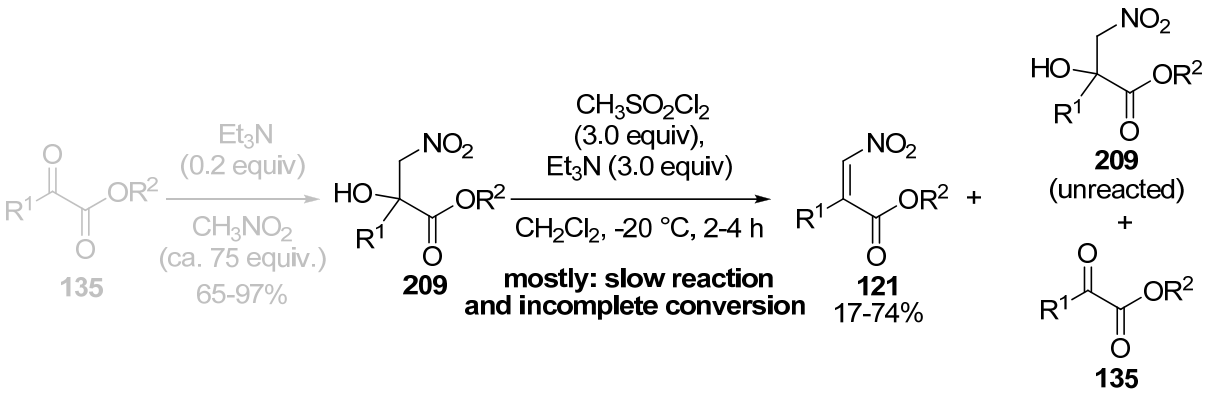
211

135k: R = OMe; 26%*
135l: R = F: 37%*

Scheme 4.74: Synthesis of *tert*-butyl 2-(4-methoxyphenyl)-2-oxoacetate (**135k**) and *tert*-butyl 2-(4-fluorophenyl)-2-oxoacetate (**135l**) from *tert*-butyl 2-(1H-imidazol-1-yl)-2-oxoacetate (**2011**). (*NMR yield of the crude product after work-up).

4.5.1.2 Investigations to Optimize the Preparation of *β*-Nitroacrylates

The strategy that we used for the substrate preparation led to the generation of the desired *β*-nitroacrylates **121** in mostly low yields (see Scheme 4.70). Looking at this two-step procedure we observed that the first step, the Henry reaction, generated the *β*-nitro-*α*-hydroxyesters **209** in good yields. However, the dehydration of the alcohol **209** afforded the corresponding *β*-nitroacrylates **121** in much lower yields, especially when the substrates **121** bore bulky ester functionalities. In this case, the reaction was really slow and the alcohol **209** could not be fully converted to the dehydrated product **121**. Another reason for the low efficiency of this dehydration was a retro-Henry reaction that took place under our reaction conditions, leading to the formation of the initial starting material **135** (Scheme 4.75).



Scheme 4.75: Synthesis of the *β*-nitroacrylates **121** and formation of the *α*-ketoesters **135** *via* a retro-Henry reaction.

Based on these observations we intended to improve the preparation of the substrate **121** focusing our work on the development of two different strategies. On the one hand, we wished to synthesize *β*-nitroacrylates **121** directly from the corresponding *α*-ketoesters **135** in one-pot, and, on the other hand, we sought to optimize the dehydration process. In the latter case, the objective was to find reaction conditions which would allow us to reach excellent conversions and, at the same time, would prevent the retro-Henry process from occurring. For these experiments we used ethyl 2-oxo-2-phenylacetate **135d** as the model starting material.

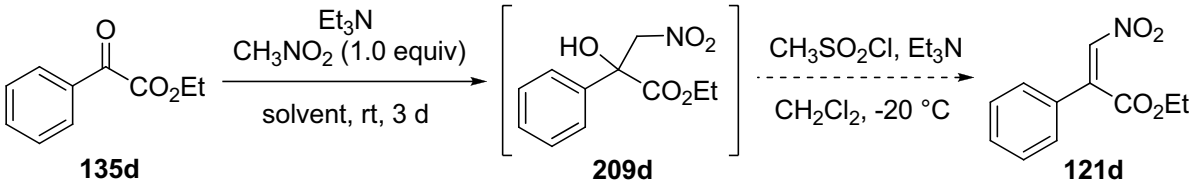
One-pot preparation of β-nitroacrylates 121

With regards to the two-step strategy that was employed for the preparation of the substrates **121** (see Scheme 4.70), we observed that for the Henry-reaction as well as for the dehydration step, the same base was used: triethylamine. We then wondered if we could perform the synthesis as a one-pot process, using only one equivalent of nitromethane and a catalytic amount of triethylamine for the Henry reaction, followed by addition of methanesulfonyl

chloride and some more triethylamine, after the α-ketoester **135** was fully converted to the corresponding alcohol **209** (Table 4.27).

We first investigated the Henry reaction running the reaction neat at room temperature in the presence of one equivalent of nitromethane and a catalytic amount of triethylamine (20 mol%, entry 1). Under these conditions, the conversion was poor even after three days. We then performed the reaction in dried dichloromethane, as this solvent had to be used in the dehydration step. This modification did not allow us to improve the conversion (entry 2), even using a stoichiometric amount of triethylamine (entry 3). No improvement was observed by running the reaction at 40 °C.

Table 4.27: Investigations toward the one-pot synthesis of the β-nitroacrylates **121**



135d **209d** **121d**

Entry	Solvent	Et_3N [equiv]	Conversion [%][a]
1	neat	0.2	13
2	CH_2Cl_2	0.2	9
3	CH_2Cl_2	1.0	11

[a] Determined by GC.

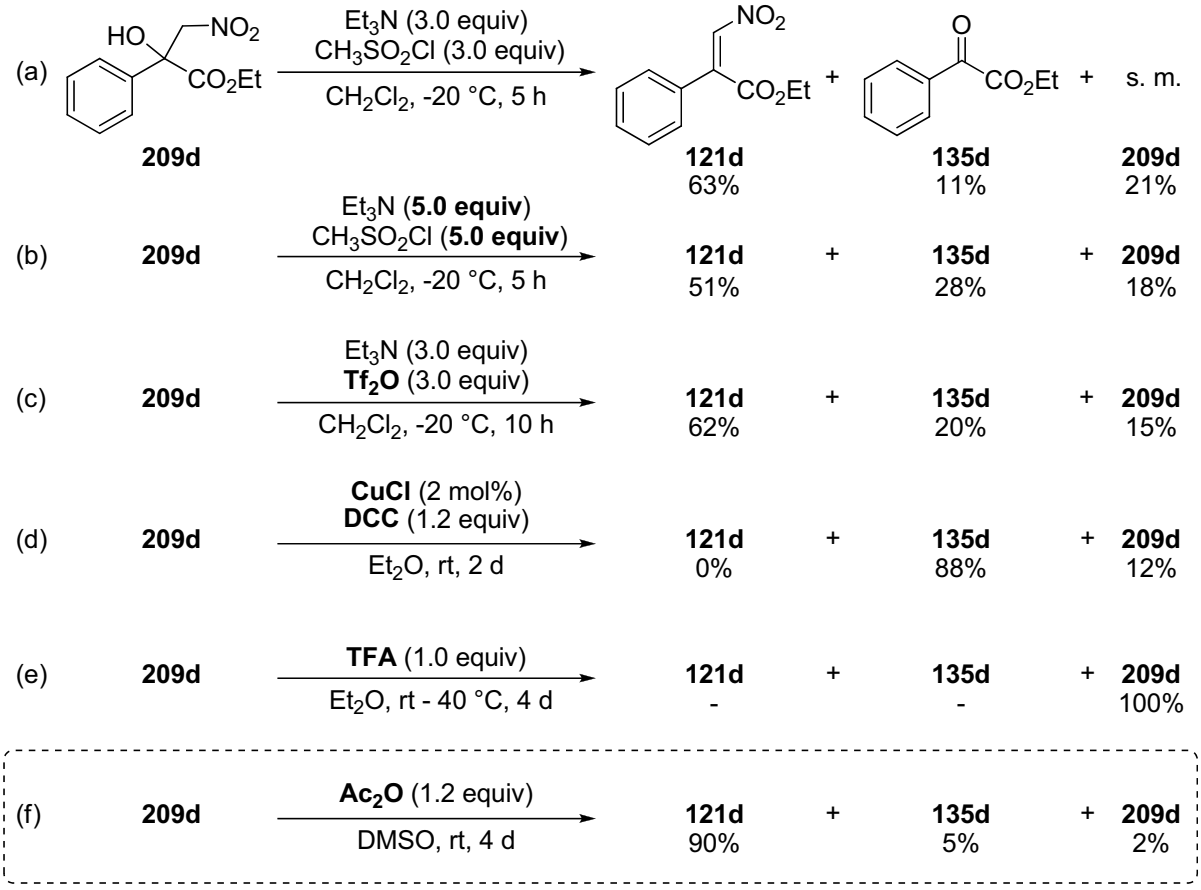
Since the Henry reaction afforded the β-nitro-α-hydroxyesters **209** in much higher yields (92% in the case of **209d**) under the reaction conditions reported in Scheme 4.67 (using about 75 equivalents of nitromethane), we decided to stop our efforts toward the development of a one-pot procedure, which only led to a dramatic decrease in the efficiency of the Henry reaction.

Optimization of the dehydration of the alcohol 209d

We then explored different reaction conditions for the dehydration of β-nitro-α-hydroxyester **209d** to ethyl 3-nitro-2-phenylacrylate (**121d**) as shown in Scheme 4.76.

Initially, we used methanesulfonyl chloride (3.0 equivalents) and triethylamine (3.0 equivalents) to achieve the dehydration of **209d**, obtaining the product **121d** in 63% yield after five hours (Scheme 4.76a). Under these conditions, 21% of the starting material remained unreacted and the α-ketoester **135d** was generated in 11% yield. In order to increase the reaction conversion we decided to increase the amount of methanesulfonyl chloride and

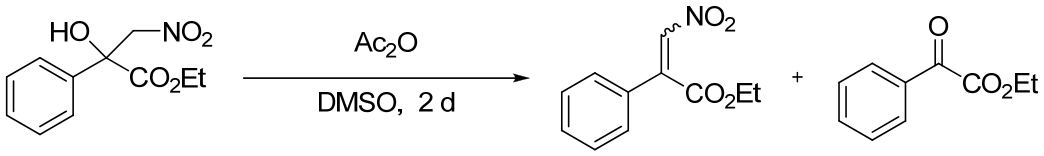
triethylamine up to five equivalents (Scheme 4.76b). This modification favored the retro-Henry reaction at the expense of the desired dehydration reaction. The replacement of methanesulfonyl chloride by the more reactive trifluoromethanesulfonic acid anhydride (triflic anhydride) led to a slight increase of the *α*-ketoester **135d** formation (Scheme 4.76c). According to the procedure reported by *Seebach et al.*,[250] we also tested the effect of DCC in the presence of catalytic copper(I) chloride (2 mol%) in diethyl ether on the dehydration reaction (Scheme 4.76d). We observed that after two days, the expected product **121d** was not formed. Instead, the *α*-ketoester **135d** was obtained in 88% yield. Using TFA to protonate the hydroxyl group and favor the elimination of a water molecule, no reaction took place after stirring the mixture for two days at room temperature. A temperature increase up to 40 °C did not improve the reactivity of the starting material, which remained unchanged (Scheme 4.76e). After all these unsuccessful attempts, we were pleased to see that running the reaction in dimethylsulfoxide (DMSO) with acetic anhydride (1.2 equivalents) for four days, we could obtain ethyl 3-nitro-2-phenylacrylate (**121d**) in excellent yield (90%, Scheme 4.76f). We then tried to further optimize the reaction conditions of this process to decrease the reaction time (see Table 4.28).



Scheme 4.76: Investigations to improve the yield of the dehydration reaction of *β*-nitro-*α*-hydroxyesters **209** to *β*-nitroacrylates **121**.

We repeated the reaction reported in Scheme 4.76f in the presence of 1.2 equivalents of acetic anhydride and stopped it after two days. Under these conditions, *β*-nitroacrylate **121d** was generated with 80% yield (Table 4.28, entry 1). An increase of the temperature up to 40 °C accelerated the retro-Henry process (entry 2). It was thus preferred to run the reaction at room temperature. We then tried to further increase the conversion of the reaction, and thus the yield of the desired product (**121d**), by using a higher amount of the relatively inexpensive acetic anhydride (3.0 equivalents, entry 3). This proved to be a success and led to the formation of ethyl 3-nitro-2-phenylacrylate (**121d**) in excellent yield (91%).

Table 4.28: Optimization of the dehydration of the alcohol **209d** by acetic anhydride.



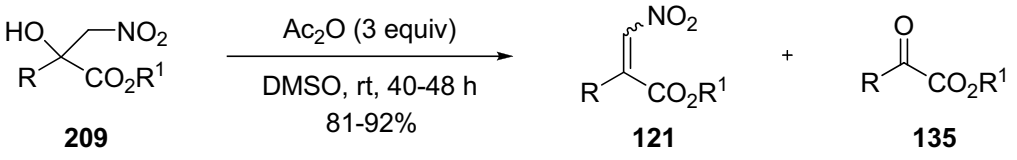
209d **121d** **135d**

Entry	Ac_2O [equiv]	Temperature [°C]	Yield of **121d** [%]	Yield of **135d** [%]
1	1.2	rt	80	5
2	1.2	40	84	12
3	**3.0**	**rt**	**91**	**7**

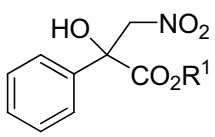
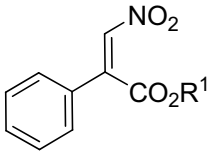
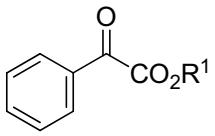
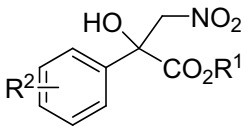
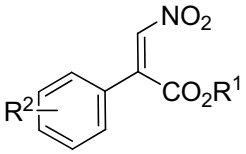
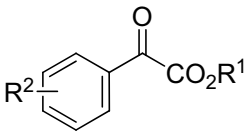
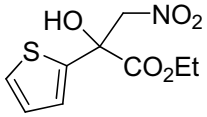
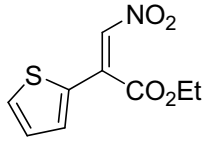
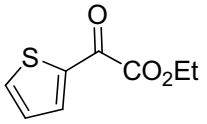
We then applied this process to the dehydration of other *β*-nitro-*α*-hydroxyesters **209** and in particular to the ones bearing bulky ester functionalities (i.e. the alcohols which were problematic under the conditions reported in Scheme 4.70, affording *β*-nitroacrylates **121** in very poor yields). These results are presented in Table 4.29.

For all the alcohols **209** tested, the dehydration step occurred with very high yields (81-92%, Table 4.29). Especially impressive improvements were observed in the syntheses of *tert*-butyl- and benzyl ester-derived *β*-nitroacrylates **121e** and **121f** (entries 2 and 3). In these cases the product was generated in only 17% and 21% yield, respectively, in the presence of methanesulfonyl chloride (see Scheme 4.70) and in 92% and 87% yield, respectively, using acetic anhydride (Table 4.29). Delighted by this success, we then decided to concentrate our work on the development of an organocatalytic transfer hydrogenation of the prepared *β*-nitroacrylates **121**.

Table 4.29: Scope for the dehydration of alcohols **209** in the presence of acetic anhydride



209 **121** **135**

Entry	Substrate[a]	Yield of **121** [%][b] (yield previously obtained [%])	Yield of **135** [%]
			
1	R^1 = Et (**209d**)	**121d**: 91 (63)	**135d**: 7
2	R^1 = *t*-Bu (**209e**)	**121e**: 92 (17)	**135e**: 4
3	R^1 = Bn (**209f**)	**121f**: 87 (21)	**135f**: 8
			
4	R^1 = Et, R^2= *p*-F, (**209i**)	**121i**: 88 (49)	**135i**: 10
5[c]	R^1 = *t*-Bu, R^2= *p*-OMe (**209k**)	**121k**: 86 (25)	**135k**: 9
6	R^1 = *t*-Bu, R^2= *p*-F (**209l**)	**121l**: 89 (27)	**135l**: 5
			
7[d]	**209m**	**121m**: 81 (46)	**135m**: 13

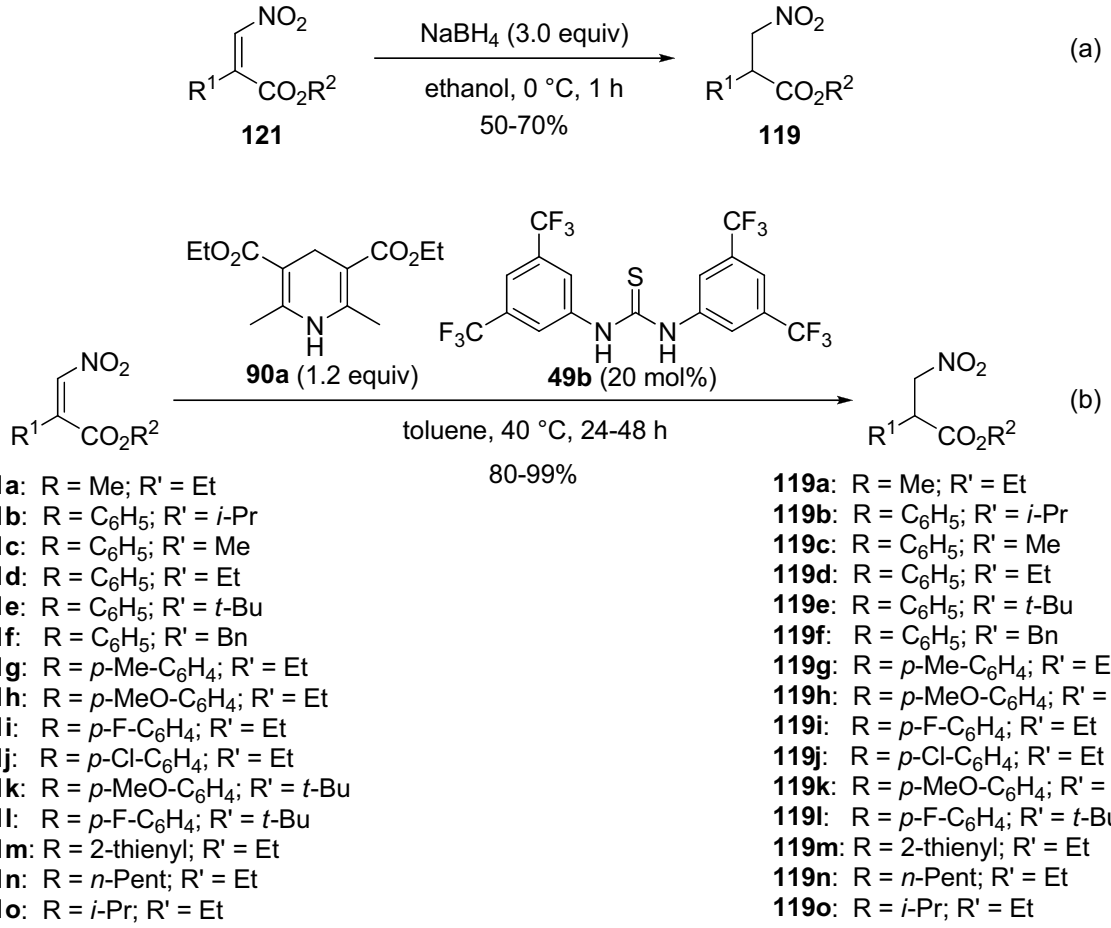
[a] After 40-48 h at rt, 1-4% of the substrate **209** still remained in the reaction mixture. [b] The given yields correspond to the total yield of the isolated isomers ((*E*)-isomer + (*Z*)-isomer). In each case the (*Z*)-isomer was the main product (yield of the (*E*)-isomer: 0-4%). [c] (*E*)-isomer: 11% and (*Z*)-isomer: 75%. [d] (*E*)-isomer: 78 % and (*E*)-isomer: 3%.

4.5.1.3 Synthesis of the Racemic *β*-Nitroesters

As already reported in the Chapters 4.3.1.3 and 4.4.1.3, the preparation of the racemic products was necessary to determine the separation conditions of the (*R*)- and (*S*)-enantiomers using GC with a chiral stationary phase. This allowed us, afterwards, to measure the enantiomeric ratios of the enantioenriched *β*-nitroesters **119**, which were synthesized through our organocatalytic conjugate reduction of the corresponding *β*-nitroacrylates **121**.

To generate the racemic compounds **119**, we could use both procedures reported in Scheme 4.77. Through the conjugate reduction of the *β*-nitroacrylates **121** with an excess of sodium

borohydride in ethanol we formed the racemic *β*-nitroesters **119** within about one hour in moderate to good yields (50-70%, Scheme 4.77a). Higher yields (about 80-99%) were obtained treating nitroolefin **121** with the Hantzsch ester **90a** in the presence of a catalytic amount of the *Schreiner* catalyst **49b** (Scheme 4.77b). However, to obtain such good yields the reactions had to be run for 24-48 hours. Accordingly, these two methods were complementary. As we just needed few milligrams of **119** for the chiral GC analysis, we did not intend to optimize their synthesis and prepared them by arbitrarily choosing one or the other process.



121a: R = Me; R' = Et
121b: R = C_6H_5; R' = *i*-Pr
121c: R = C_6H_5; R' = Me
121d: R = C_6H_5; R' = Et
121e: R = C_6H_5; R' = *t*-Bu
121f: R = C_6H_5; R' = Bn
121g: R = *p*-Me-C_6H_4; R' = Et
121h: R = *p*-MeO-C_6H_4; R' = Et
121i: R = *p*-F-C_6H_4; R' = Et
121j: R = *p*-Cl-C_6H_4; R' = Et
121k: R = *p*-MeO-C_6H_4; R' = *t*-Bu
121l: R = *p*-F-C_6H_4; R' = *t*-Bu
121m: R = 2-thienyl; R' = Et
121n: R = *n*-Pent; R' = Et
121o: R = *i*-Pr; R' = Et

119a: R = Me; R' = Et
119b: R = C_6H_5; R' = *i*-Pr
119c: R = C_6H_5; R' = Me
119d: R = C_6H_5; R' = Et
119e: R = C_6H_5; R' = *t*-Bu
119f: R = C_6H_5; R' = Bn
119g: R = *p*-Me-C_6H_4; R' = Et
119h: R = *p*-MeO-C_6H_4; R' = Et
119i: R = *p*-F-C_6H_4; R' = Et
119j: R = *p*-Cl-C_6H_4; R' = Et
119k: R = *p*-MeO-C_6H_4; R' = *t*-Bu
119l: R = *p*-F-C_6H_4; R' = *t*-Bu
119m: R = 2-thienyl; R' = Et
119n: R = *n*-Pent; R' = Et
119o: R = *i*-Pr; R' = Et

Scheme 4.77: Preparation of the racemic *β*-nitroesters **119** with sodium borohydride (a) or Hantzsch ester **90a** in the presence of *Schreiner* catalyst **49b** (b).

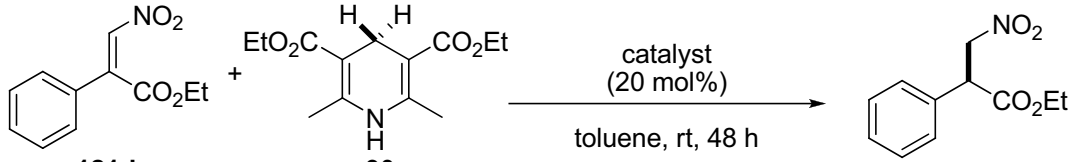
4.5.2 Determination and Optimization of the Catalyst Structure

Inspired by our thiourea-catalyzed transfer hydrogenation of nitroalkenes **120** to nitroalkanes **116** in the presence of Hantzsch ester **90c**, we assumed that it would be possible to synthesize the *β*-nitroesters **119** from their corresponding *β*-nitroacrylates **121** using similar conditions. To this end we tested most of the mono- and bisthioureas that we had previously screened for the conjugate reduction of nitroolefins **120** (see Chapter 4.4.2). For this investigation, we used (*Z*)-ethyl 3-nitro-2-phenylacrylate (**121d**) as a model substrate (0.2 molar in toluene). We arbitrarily chose the dihydropyridine **90a** as it was readily available in our laboratory, and performed the reaction at room temperature for 48 hours in the presence of 20 mol% of catalyst (Table 4.30).

We first ran the Hantzsch ester-mediated transfer hydrogenation of ethyl 3-nitro-2-phenylacrylate **121d** without a catalyst to evaluate the background reaction. The saturated product **119d** was generated in 22% yield (and in 53% yield by performing the reaction at 40 °C, Table 4.30, entries 1 and 2). These results pointed out that the studied conjugate reduction had a significant background reaction that we would need to take into account for the development of an efficient process. However, for the screening of the thiourea motifs (i.e. the investigation of their catalytic activity) we neglected this information and ran the reactions at room temperature. The bisthioureas **63** and **178** were found to activate the substrate (entries 3 and 4). Especially high conversion (99%) was reached using catalyst **63** (entry 3). However, in both cases the *β*-nitroester **119d** was obtained in only moderate enantioselectivity. The selectivity of the reaction could be increased by using thiourea motifs **164a**, **50d** and **57a** (entries 5-7). As we had already observed in the conjugate reduction of nitroalkenes **120** (see Chapters 4.4.2.3 and 4.4.3.3), the *Jacobsen* thiourea catalysts **50d** and **57a** were particularly efficient in terms of both reactivity and selectivity (entries 6 and 7). Once again, thiourea motif **57a** was the most enantioselective (entry 7).

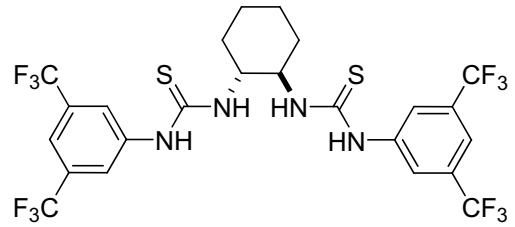
Based on the results reported in Table 4.30, we then intended to optimize the structure of the catalyst **57a** by modifying the substituent of the amide functionality (Table 4.31) and of the pyrrolyl group (Table 4.32).

Table 4.30: Screening of different thiourea motifs for the transfer hydrogenation of the *β*-nitroacrylate **121d**

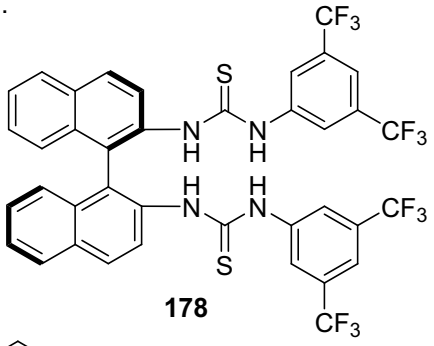


Entry	Catalyst	conv. [%][a]	*er*[a]
1	**-**	22	-
2[b]	**-**	53	-
3	**63**	99	29:71
4	**178**	39	63:37
5	**164a**	77	76:24
6	**50d**	99	89:11
7	**57a**	**94**	**92:8**

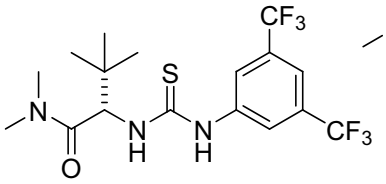
[a] Determined by chiral GC. [b] Reaction run at 40 °C.



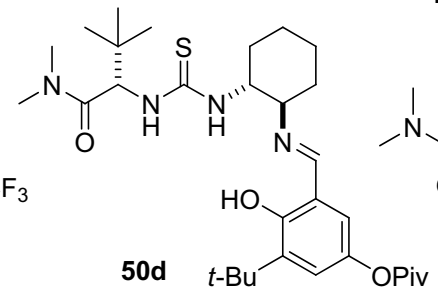
63



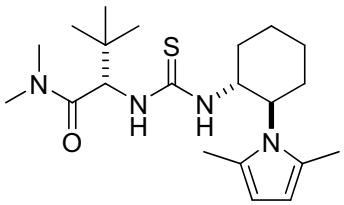
178



164a



50d



57a

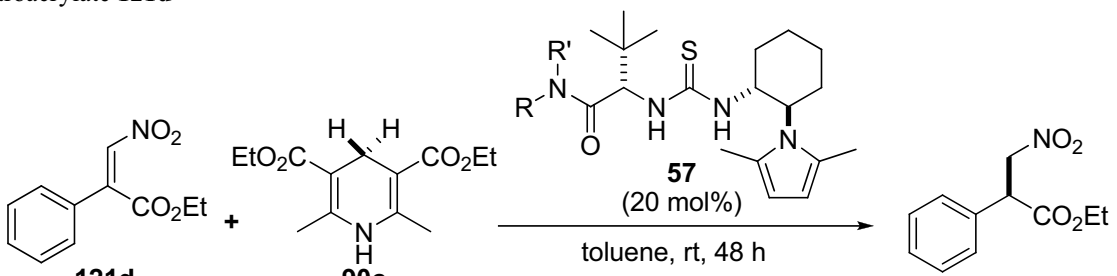
Optimization of the Jacobsen thiourea motif 57

Since an analogous catalyst optimization was done for the development of the transfer hydrogenation of nitroolefins **120** (see Chapter 4.4.3.3, Tables 4.22 and 4.23) and since in both cases, starting from the nitroalkenes **120** as well as the *β*-nitroacrylates **121**, similar tendencies were observed, the results reported in Tables 4.31 and 4.32 will be discussed only briefly.

By increasing the length of the alkyl substituents R and R' of the amide (compound **57**), we could slightly improve the reactivity of the catalyst (Table 4.31, entry 1 vs. entries 2 and 4). In the case of thiourea **57b**, even the enantioselectivity was increased (entry 1 vs. entry 2).

Surprisingly, for this catalytic transfer hydrogenation, the use of *N*,*N*-dibenzylamide-derived thiourea **57c** led to a significant decrease of the enantiomeric ratio (entry 3). Lower enantioselectivities were reached using *N*,*N*-benzylmethyl- or *N*-benzyl-derived catalyst **57e** and **57f**, respectively (entries 5 and 6). Accordingly, *N*,*N*-diethyl-substituted thiourea **57b** was the favored catalyst.

Table 4.31: Optimization of thiourea motif **57**: effect of the amide structure on the transfer hydrogenation of the *β*-nitroacrylate **121d**



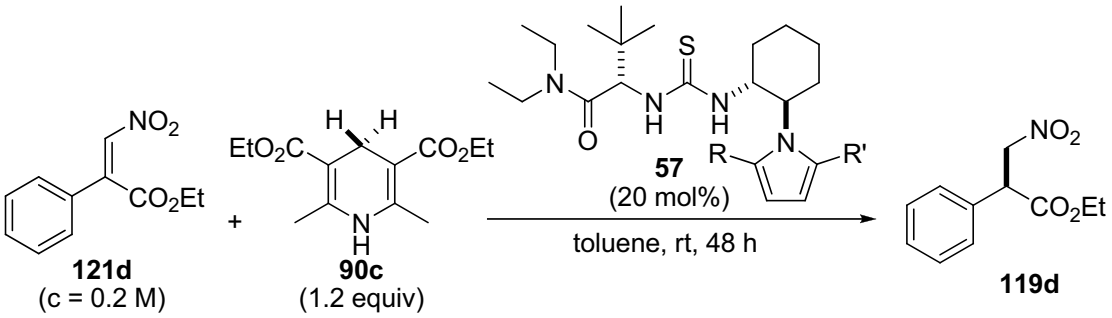
Entry	Catalyst:	R	R'	conv. [%][a]	*er* [a]
1	**57a**	Me	Me	94	92:8
2	**57b**	**Et**	**Et**	**98**	**96:6**
3	**57c**	Bn	Bn	89	86:14
4	**57d**	*n*-Pr	*n*-Pr	97	92:8
5	**57e**	Bn	Me	94	91:9
6	**57f**	Bn	H	85	83:17

[a] Determined by chiral GC.

We then studied the effect of changing the pyrrolyl structure of **57** on its catalytic efficiency (Table 4.32). Once again we noticed a decrease in the catalyst efficiency when we increased the bulkiness of the substituents at the 2- and 5-positions of the pyrrolyl group (entry 1 vs. entries 2-4).

Based on these experiments we realized that for the transfer hydrogenation of *β*-nitroacrylates **121** the *Jacobsen*-type thiourea **57b** was once again superior in terms of enantioselectivity and generated the saturated ester in excellent yield. This thiourea catalyst was thus used for further optimization.

Table 4.32: Optimization of the thiourea motif **57**: effect of the pyrrolyl structure on the transfer hydrogenation of the *β*-nitroacrylate **121d**



Entry	Catalyst:	R	R'	conv. [%][a]	*er*[a]
1	**57b**	**Me**	**Me**	**98**	**96:6**
2	**57g**	Et	Et	81	90:10
3	**57h**	Ph	Me	53	77:23
4	**57i**	Ph	Ph	35	66:34

[a] Determined by chiral GC.

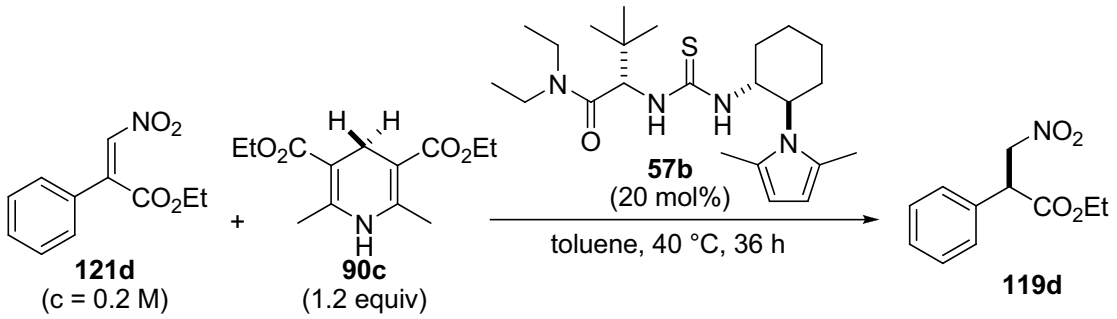
4.5.3 Optimization of the Reaction Conditions

4.5.3.1 Optimization of the Solvent

We started to optimize our thiourea-catalyzed process by investigating the effect of the solvent on the efficiency of the reaction. For this screening we performed the conjugate reduction of *β*-nitroacrylate **121d** (0.2 molar) at 40 °C in the presence of Hantzsch ester **90a** (1.2 equivalents) and thiourea catalyst **57b** (20 mol%) as shown in Table 4.33.

Under the reaction conditions, very good to excellent conversions were obtained in all the tested solvents (81% to over 99%, entries 1-9). We observed similar tendencies for this reaction as in the transfer hydrogenation of nitroalkenes **120** (see Chapter 4.4.3.1, Table 4.19). Very high enantioselectivities were obtained in apolar aromatic solvents such as toluene and benzene (entries 1 and 2). However, the catalyst selectivity was only moderate in diethyl ether or in chlorinated solvents (entries 3-5). On the other hand, the *β*-nitroester **119d** was generated nearly or completely racemic when running the reaction in THF, dioxane, methanol, or acetonitrile. According to this screening, toluene proved once again to be superior in terms of enantioselectivity. This solvent was thus favored.

Table 4.33: Effect of the solvent on the transfer hydrogenation of the *β*-nitroacrylate **121d**



Entry	Solvent	conv. [%][a]	*er*[a]
1	**toluene**	**>99**	**92:8**
2	**benzene**	**>99**	**90:10**
3	Et_2O	81	77:23
4	CH_2Cl_2	>99	78:22
5	$CHCl_3$	>99	79:21
6	THF	93	52:48
7	dioxane	99	53:47
8	MeOH	>99	50:50
9	MeCN	>99	50:50

[a] Determined by chiral GC.

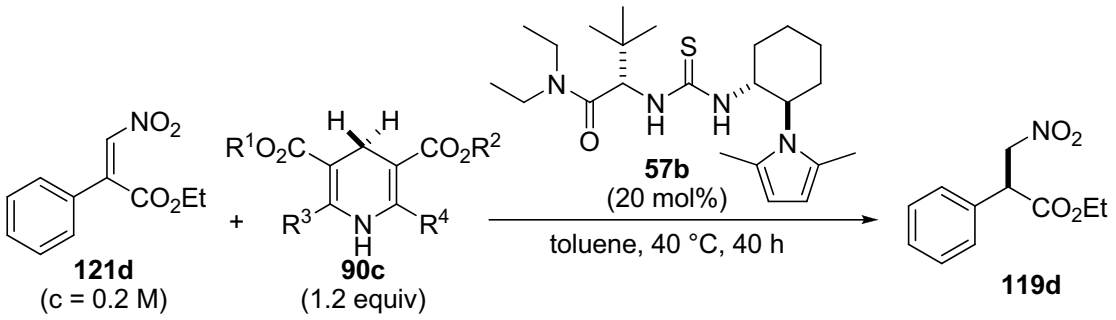
4.5.3.2 Optimization of the Hantzsch Ester Structure and Concentration

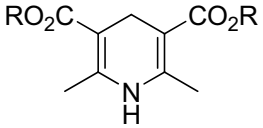
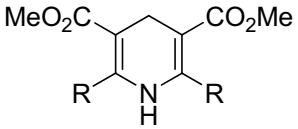
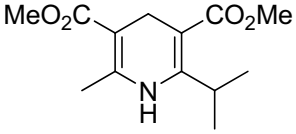
Once we had identified the optimal catalyst and solvent for the transfer hydrogenation of the *β*-nitroacrylate **121d**, we intended to optimize the structure of the Hantzsch ester **90**. For this purpose we investigated the effect that the ester groups and the substituents at the 2- and 6-positions of the dihydropyridine **90** had on the efficiency of the reaction (Table 4.34).[251]

The modification of the ester groups of the Hantzsch ester did not lead to very significant variations in the efficiency of the reaction. We obtained good to excellent conversions. However, the structure of the ester functionality had a more pronounced effect on the enantioselectivity of the conjugate reduction (entries 1-4). The *tert*-butyl ester functionalities appeared to be most suitable (entry 4). On the other hand, an increase in the length of the aliphatic chain and the bulkiness of the substituents at the 2- and 6-positions of the dihydropyridine **90** led to a loss of enantioselectivity (entries 5-7). Reactivity was also compromised in the presence of the diphenyl-derived Hantzsch ester **90j** (entry 7). The non-

symmetrical dihydropyridines **90b** were unsuitable for our process since their use induced a dramatic drop in the efficiency of the reaction (entry 8). According to these experiments, the commercially available di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate **90c** was the favored hydrogen source for the transfer hydrogenation of *β*-nitroacrylates **121**.

Table 4.34: Optimization of the dihydropyridine structure for the transfer hydrogenation of the *β*-nitroacrylate **121d**

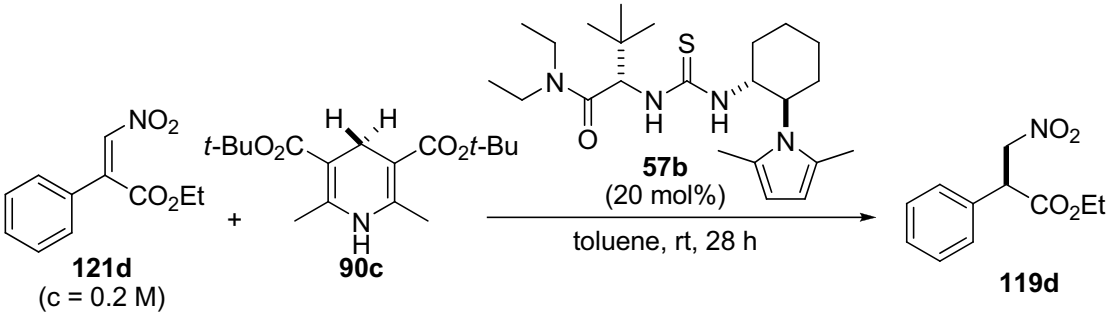


Entry		Hantzsch ester	conv. [%][a]	*er*[a]
				
1	**90a**:	R = Et	>99	92:8
2	**90f**:	R = Me	89	89:11
3	**90d**:	R = *i*-Bu	>99	90:10
4	**90c**:	**R = *t*-Bu**	**>99**	**94:6**
				
5	**90h**:	R = Et	>99	90:10
6	**90i**:	R = *n*-Pr	>99	89:10
7	**90j**:	R = Ph	81	81:19
				
8	**90b**:		>99	74:26

[a] Determined by chiral GC.

After we had defined the optimal Hantzsch ester, we were interested in evaluating the effect of its concentration on the efficiency of the process. To this end, we decided to run the reactions at lower temperatures (i.e. at room temperature instead of 40 °C), assuming that this would slow down the conjugate reduction and thus facilitate the study of the effect of the dihydropyridine concentration on the conversion of the reaction (Table 4.35).

Table 4.35: Optimization of dihydropyridine structure for the transfer hydrogenation of the *β*-nitroacrylate **121d**



Entry	Hantzsch ester **90c** [equiv]	conv. [%][a]	*er*[a]
1	**1.0**	**97**	**96:4**
2	**1.1**	**>99**	**95:5**
3	1.3	>99	94:6
4	1.5	>99	94:6
5	2.0	>99	94:6

[a] Determined by chiral GC.

An increase in the Hantzsch ester concentration from 1.1 to 2.0 equivalents had no influence on the conversion of the reaction (Table 4.35, entries 2-5). However this change led to a slight decrease of the enantioselectivity. It was then more favorable to keep the concentration of dihydropyridine low. Nevertheless, by using it in a stoichiometric amount, we observed a slight loss of reactivity (entry 1). At this point, we favored the use of 1.1 equivalents of **90c** for further optimizations.

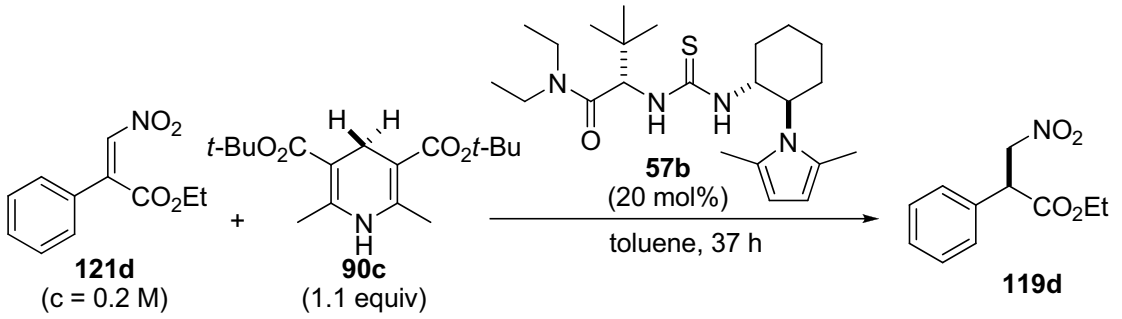
4.5.3.3 Effect of the Temperature on the Catalysis

Since we observed that the transformation suffered from a relatively strong background reaction, which increased with the reaction temperature (see Chapter 4.5.2, Scheme 4.30), we were interested in investigating the effect of the temperature on the catalysis, in order to further optimize the transfer hydrogenation (Table 4.36).

We were not surprised to find that a temperature increase led to a slight loss of enantioselectivity (entries 1-5) and were pleased to observe that excellent conversions were reached even when running the reaction at 0 °C (entry 1). At this point we assumed that a further decrease of the temperature would not significantly improve the enantioselectivity but

further decrease the reactivity of the reaction. We thus decided to perform the transfer hydrogenations at 0 °C.

Table 4.36: Optimization of the temperature for the transfer hydrogenation of the *β*-nitroacrylate **121d**



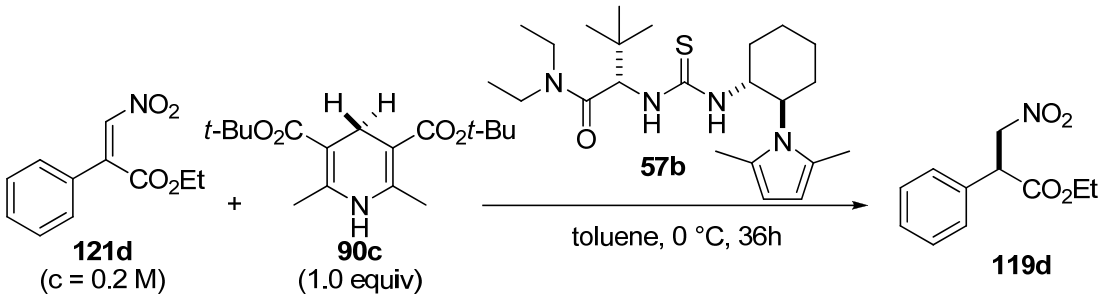
Entry	Temperature [°C]	conv. [%][a]	*er*[a]
1	**0**	**>99**	**96:4**
2[b]	23	>99	96:4
3	40	>99	95:5
4	50	>99	94:6
5	60	>99	94:6

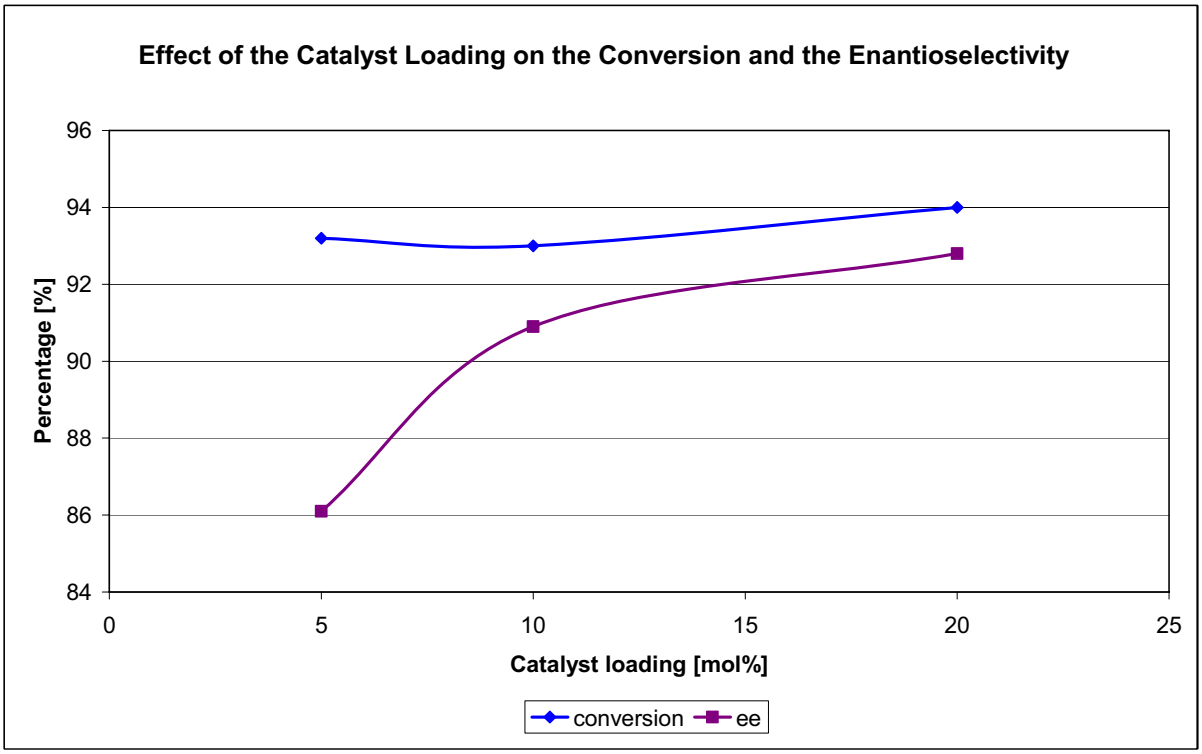
[a] Determined by chiral GC. [b] Reaction run at room temperature.

4.5.3.4 Optimization of the Catalyst Loading and the Substrate Concentration

Like for the development of the transfer hydrogenation of enones (see Chapter 4.3) and nitroalkenes (see Chapter 4.4), we used a relatively high catalyst loading (20 mol%) and diluted solutions (0.1-0.2 molar) during the optimization of the conjugate reduction of *β*-nitroacrylate **121d**. It was thus of interest to reduce the catalyst loading (Scheme 4.78) and increase the substrate concentration (Scheme 4.79).

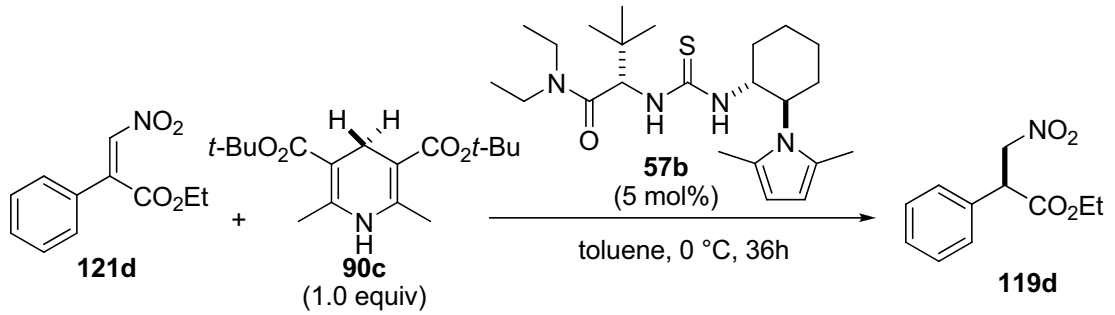
We decided to run the reactions with only 1.0 equivalent of the Hantzsch ester **90c**, to prevent the background reaction from taking place while doing the work-up of the reaction at room temperature (for more information, see Chapter 4.5.3.5), in case the conversions were not complete at a reduced catalyst loading.

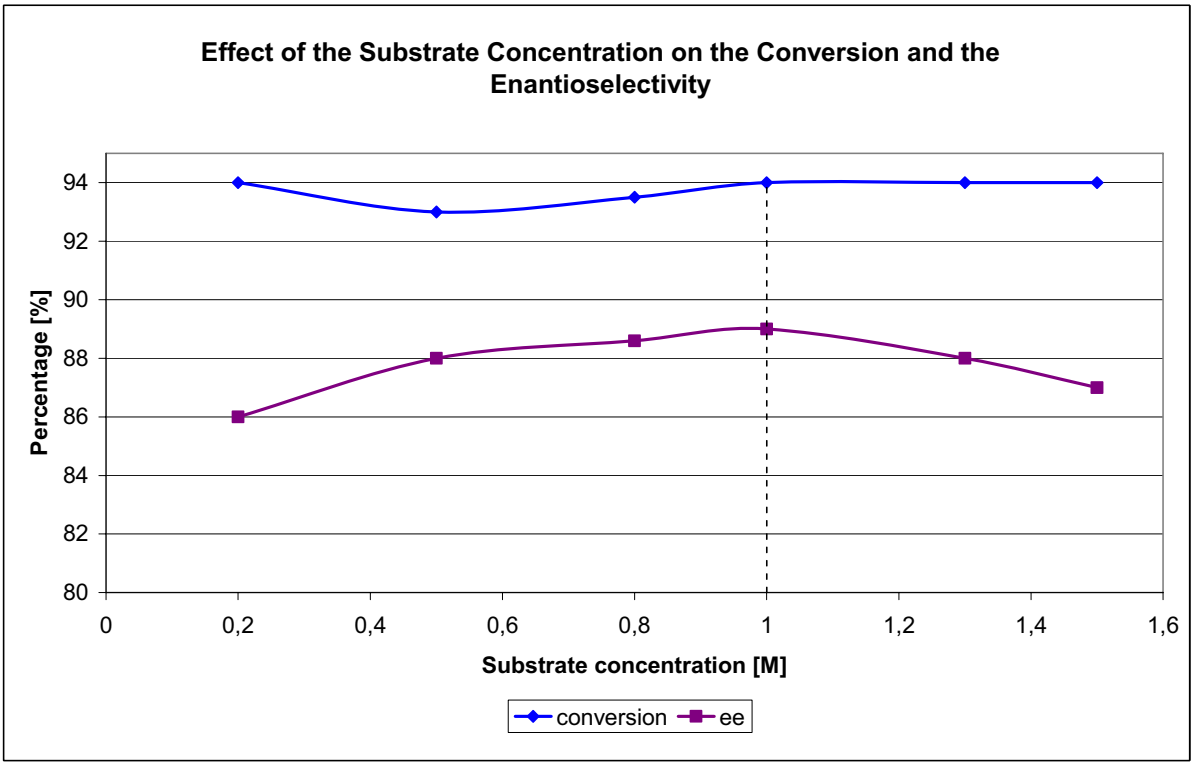




Scheme 4.78: Effect of the catalyst loading on the catalytic transfer hydrogenation of the *β*-nitroacrylate **121d**. (Note: to facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

By decreasing the catalyst loading we observed a significant loss of enantioselectivity, which was especially pronounced at catalyst loadings lower than 10 mol% (Scheme 4.78). On the other hand, the modification had no effect on the reaction conversion. We then wondered if we could improve the enantioselectivity of the transfer hydrogenation by increasing the concentration, while using a catalyst loading of 5 mol% (Scheme 4.79). We were pleased to find that the selectivity was increased by raising the concentration of the *β*-nitroacrylate **121d** from 0.2 to 1.0 molar. A further increase of the concentration led to a loss of enantioselectivity. Accordingly, we used 1.0 molar solutions in the subsequent experiments. Since under these conditions we could only obtain a maximal enantiomeric ratio of 95:5, we decided to increase the catalyst loading to 10 mol% for further investigations.



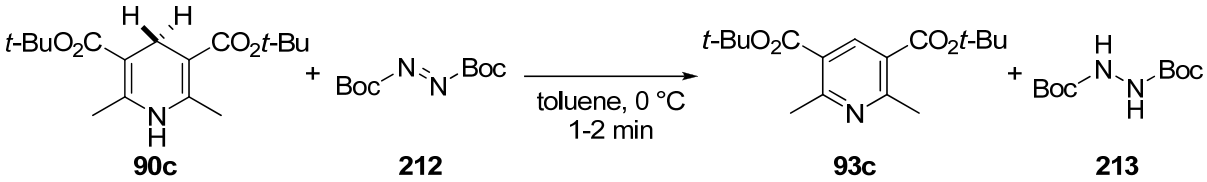


Scheme 4.79: Effect of the substrate concentration on the catalytic transfer hydrogenation of *β*-nitroacrylate **121d**. (Note: to facilitate the reading of this scheme, the enantioselectivities were expressed as enantiomeric excesses (*ee*) rather than enantiomeric ratios (*er*)).

4.5.3.5 Optimization of the Work-Up of the Reaction

Before extending our catalytic conjugate reduction to other *β*-nitroacrylates, we intended to optimize the work-up of the reaction, as we observed that the enantiopurity of the product was lost during this process to some extent. Effectively, in order to decrease the rate of the background reaction, we performed the transfer hydrogenations at 0 °C. However, the work-ups were done at room temperature, accelerating the background reaction, in cases where the conversion of the catalytic conjugate reduction was not complete and starting material as well as Hantzsch ester still remained in the reaction mixture.

When we were dealing with *β*-nitroacrylates that had a lower reactivity and thus could not be fully converted to the saturated esters **119**, we had to oxidize the remaining Hantzsch ester **90c** to the pyridine derivative **93c** to prevent it from reacting with the left over substrate during the work-up. For this purpose we chose di-*tert*-butyl-azodicarboxylate (DBAD, **212**), which was added to the reaction mixture at 0 °C. Under these conditions, DBAD is reduced to compound **213** through a transfer hydrogenation process by Hantzsch ester **90c** (Scheme 4.80). It should be specify that this process had been developed in our laboratory and allows the oxidation of dyhydropyridines **90** within only a few minutes.



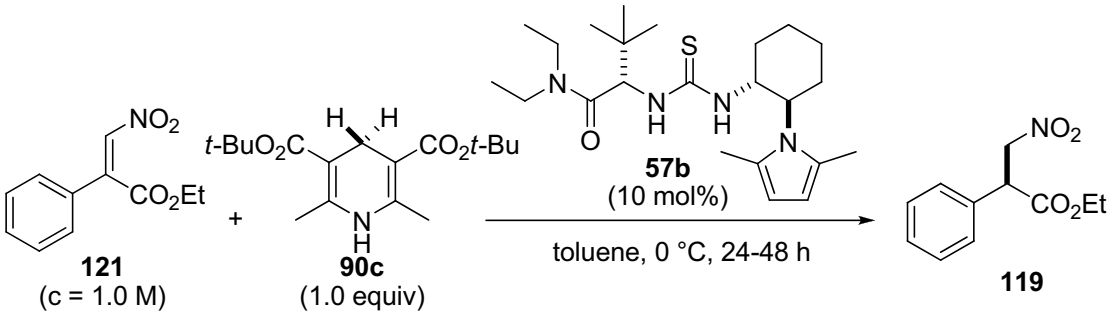
Scheme 4.80: Oxidation of the Hantzsch ester **90c** to the pyridine derivative **93c** in the presence of DBAD (**212**).

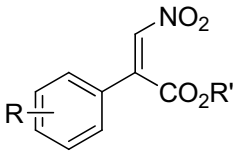
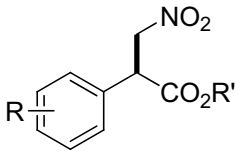
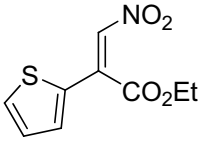
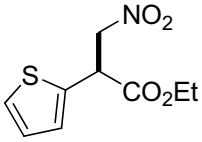
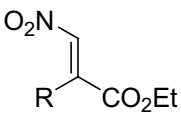
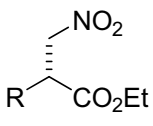
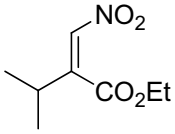
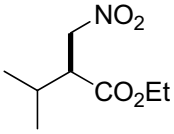
By oxidizing **90c**, we were able to prevent the undesired background reaction from occuring during the work-up of the reaction (at room temperature).

4.5.4 Investigation of the Reaction Scope

According to the optimization of the catalyst, the solvent, the Hantzsch ester structure and concentration, the catalyst loading and the substrate concentration (see Chapters 4.5.2 and 4.5.3) in the transfer hydrogenation of (*Z*)-ethyl 3-nitro-2-phenylacrylate (**121d**), the following protocol was subsequently used for investigating the scope of the reaction: Treating *β*-nitroacrylates **121** (1.0 molar) with the commercially available Hantzsch ester **90c** (1.0 equivalent) and thiourea catalyst **57b** (10 mol%) at 0 °C in toluene for 24-48 hours gave the saturated esters **119** in good yields and with high enantioselectivities (Table 4.37). These reaction conditions are almost identical to the ones we had previously developed for the analogous reductions of unfunctionalized trisubstituted nitroolefins **120** (see Chapter 4.4.4, Table 4.25).

Table 4.37: Scope of the catalytic transfer hydrogenation of *β*-nitroacrylates **121**



Entry	Nitroacrylate[a]			Nitroester	Yield [%]	*er*[b]
						
		R	R'			
1	**121c**:	H	Me	**119c**	86	94:6
2	**121d**:	H	Et	**119d**	95	96:4
3	**121b**:	H	*i*-Pr	**119b**	91	97:3
4	**121e**:	H	*t*-Bu	**119e**	92	97:3
5	**121f**:	H	Bn	**119f**	91	97:3
6	**121g**:	*p*-Me	Et	**119g**	92	96:4
7	**121h**:	*p*-MeO	Et	**119h**	87	95:5
8	**121i**:	*p*-F	Et	**119i**	97	94:6
9	**121j**:	*p*-Cl	Et	**119j**	96	94:6
10	**121k**:	*p*-MeO	*t*-Bu	**119k**	61	96:4
11	**121l**:	*p*-F	*t*-Bu	**119l**	85	97:3
12	 **121m**			 **119m**	83	96:4
						
		R				
13	**121a**:	Me		**119a**	97	97:3
14	**121n**:	*n*-Pent		**119n**	91	97:3
15	 **121o**			 **119o**	92	97:3

[a] Isomeric purity > 98:2. [b] Determined by chiral GC. [c] Yields determined by GC (volatile products).

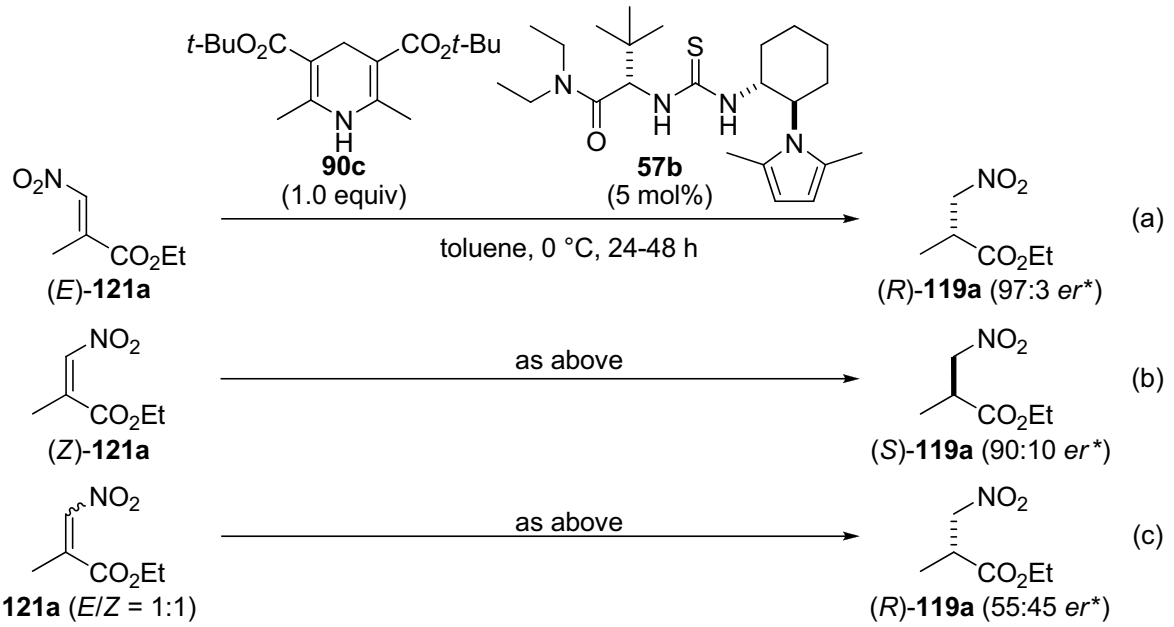
The thiourea-catalyzed conjugate reduction of the *β*-nitroacrylates **121** worked well with a variety of substrates. The ester functionality of the phenyl-substituted derivatives **121c-f** could

be varied significantly without affecting the yield of the product, which was high in all the cases (entries 1-5). Interestingly, the enantioselectivity of the reaction increased slightly with the size and bulkiness of the ester group (entries 1-5). Electron-donating and withdrawing-substituents at the *para*-position of the phenyl ring were well tolerated (entries 6-11), although a slight loss of reactivity was observed with a methoxy substituent, especially in the case of the *tert*-butyl ester-derived olefin **121k** (entry 10). Heteroaryl-derived **121m** was an equally suitable substrate (entry 12). Gratifyingly, branched as well as unbranched aliphatic *β*-nitroacrylates could be utilized as well, furnishing the corresponding *β*-nitroesters in similarly high yields and enantioselectivities (entries 13-15).

It is worth noting that the absolute configuration of compounds **121a**, **121c** and **121f** was determined by comparing the value of their optical rotation or the one of the corresponding β^2-amino acids to the values reported in the literature (see experimental part, Chapter 7.6). The configuration of the other compounds was assigned by analogy.

4.5.5 Development of a Stereoconvergent Process

After evaluating the scope of the reaction, we investigated the effect of the *β*-nitroacrylate geometry on the outcome of the catalysis (Scheme 4.81).

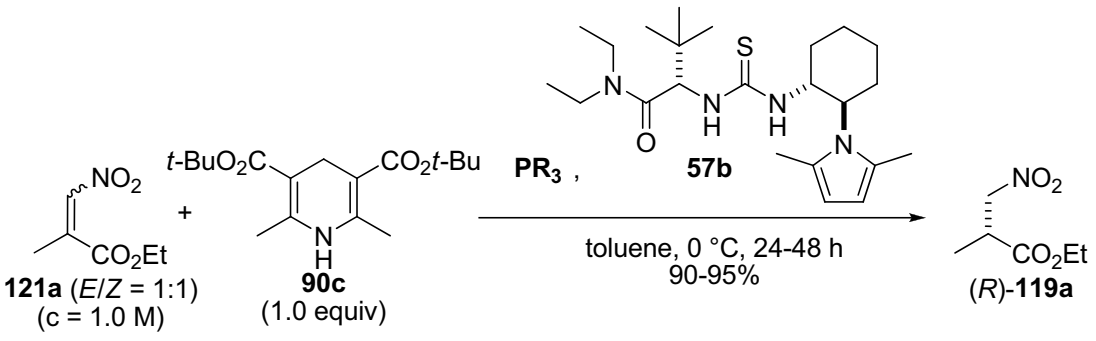


Scheme 4.81: Effect of the substrate geometry on the catalytic transfer hydrogenation of the *β*-nitroacrylate **121a**. (* Determined by chiral GC).

As already observed in the transfer hydrogenations of enones (see Chapter 4.3.4.2) and nitroalkenes (see Chapter 4.4.4), the conjugate reduction of *β*-nitroacrylates **121** was not stereoconvergent. As a result the enantioselectivity of the reaction strongly depended on the substrate geometry. Accordingly, nitroolefins (*E*)- and (*Z*)-**121a** afforded the product **119a** with (*R*)- and (*S*)-configuration, respectively (Scheme 4.81a,b). In both cases a high enantiomeric ratio was obtained. Accordingly, an equimolar mixture of the (*E*)- and (*Z*)-isomers gave an essentially racemic product **119a** (Scheme 4.81c).

We then intended to establish stereoconvergence by adding a catalytic amount of a phosphine derivative to the reaction with a 1:1 mixture of (*E*)- and (*Z*)-**121a** (Table 4.38). Remarkably, by using 5 mol% of triphenylphosphine, we could strongly increase the enantioselectivity of the reaction from 55:45 *er* to 88:12 *er* (entries 1 and 2). An increase of the amount of triphenylphosphine did not lead to a further improvement of the selectivity (entry 3), even in the presence of 10 mol% of the thiourea catalyst **57b** (entry 4). On the other hand, the process was not stereoconvergent in the presence of catalytic tributylphosphine (entry 5). At this point, we did not screen further phosphine derivatives. However, we assumed that it would be possible to establish a fully stereoconvergent system by optimizing further the reaction conditions and screening other phosphine derivatives.

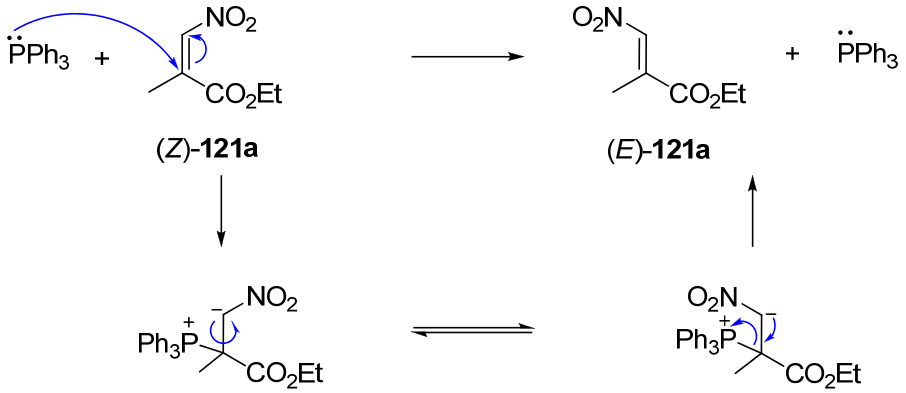
Table 4.38: Investigation to establish stereoconvergence



Entry	PR_3	PR_3 [mol%]	**62b** [mol%]	*er*[a]
1	-	-	5	55:45
2	**PPh_3**	**5**	**5**	**88:12**
3	PPh_3	10	5	86:14
4	PPh_3	10	10	87:13
5	PBu_3	5	5	57:43

[a] Determined by chiral GC.

As already mentioned in Chapters 4.3.7 and 4.4.6, we propose that the addition of a phosphine to our process creates a rapid equilibrium between (*E*)-**121a** and (*Z*)-**121a** via a conjugate addition/elimination pathway. Since the *β*-nitroester with the (*R*)-configuration ((*R*)-**119a**) was the major product under our reaction conditions, we can assume that the equilibrium favored the (*E*)-isomer of the *β*-nitroacrylate ((*E*)-**121a**, Scheme 4.82). However, when mixing the (*Z*)-isomer of the *β*-nitroacrylate ((*Z*)-**121a**) with triphenylphosphine in toluene at 0 °C without Hantzsch ester **90c** or catalyst **57b**, no strong evidence for the isomerization of (*Z*)-**121a** to (*E*)-**121a** was observed. This led us to assume that catalyst **57b** should also activate the *β*-nitroacrylate toward the Michael addition of triphenylphosphine. Further experiments would be required to support this hypothesis.



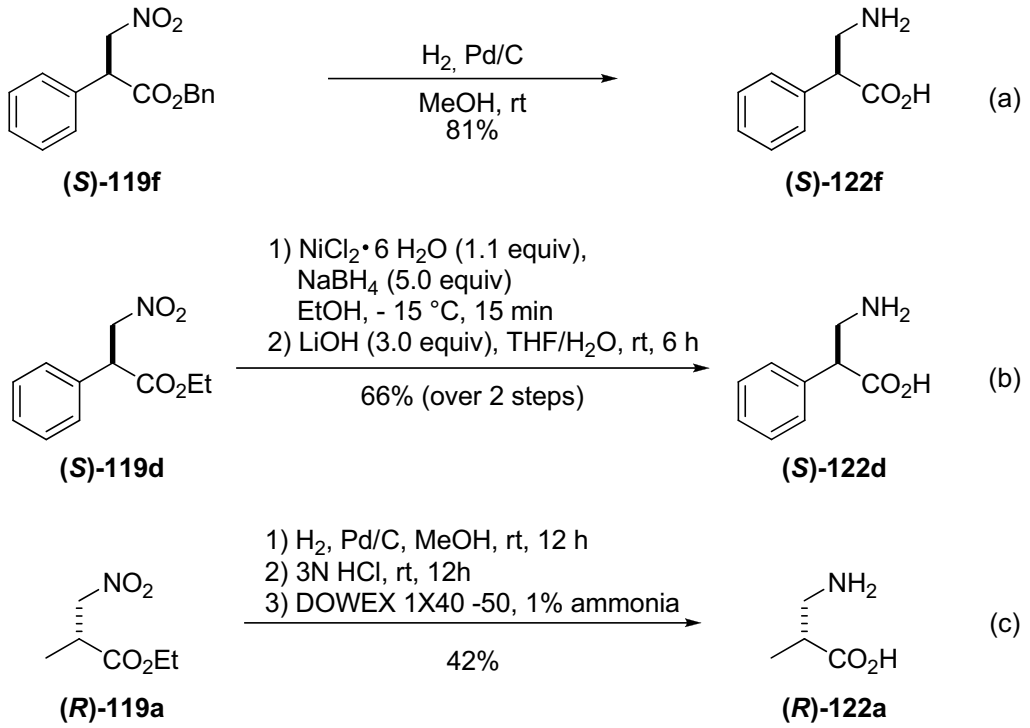
Scheme 4.82: Addition–elimination of triphenylphosphine on the *β*-nitroacrylate (*Z*)-**121a** through a Michael–retro-Michael pathway.

4.5.6 Transfer Hydrogenation of *β*-Nitroacrylates: a Route to *β*²-Amino Acids

When we developed an organocatalytic transfer hydrogenation of *β*-nitroacrylates **121** to the corresponding *β*-nitroesters **119**, we envisioned it as a route to valuable chiral *β*²-amino acids **122**. Once our first objective was reached (i.e. the successful development of an efficient organocatalytic conjugate reduction of *β*-nitroacrylates **121**), we focused our work on our second goal: establishing a process for the conversion of the generated chiral *β*-nitroesters **119** to their corresponding *β*²-amino acids **122** (Scheme 4.83).[252]

We were pleased to see that the hydrogenation of the benzylester-derived nitroester **119f** in the presence of palladium directly afforded the free *β*²-amino acid (*R*)-**122a** without any loss of enantioselectivity (Scheme 4.83a). Starting from aromatic and aliphatic nitroesters, which

bore ester functionalities other than benzyl, the conversion into the corresponding β^2-amino acids was successfully achieved through facile hydrogenation–hydrolysis sequences (Scheme 4.83b-c).



Scheme 4.83: Synthesis of β^2-amino acids **122** from their corresponding β-nitroesters **119** via (a) hydrogenation or (b) and (c) a hydrogenation–hydrolysis process.[253] (The absolute configuration of compounds **122** was determined by comparing their optical rotation to that reported in the literature (see Chapter 7.6)).

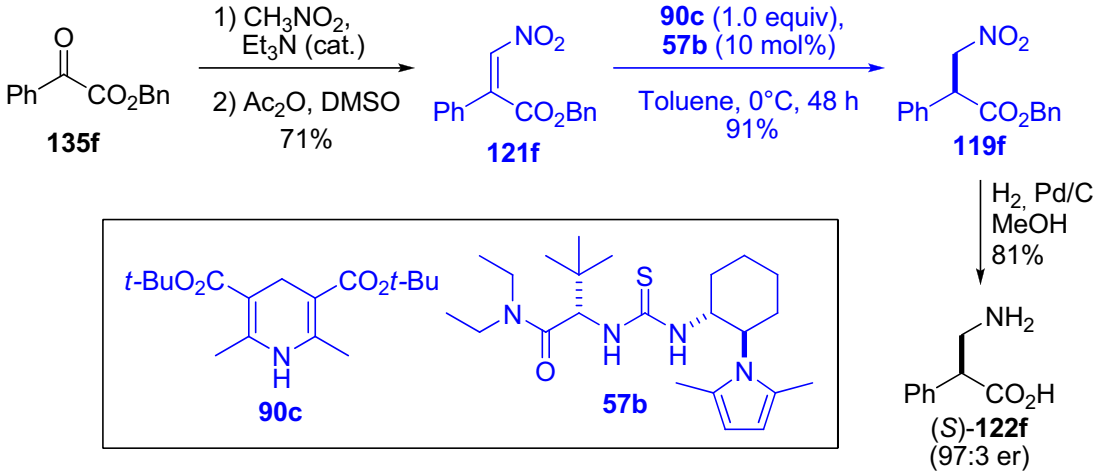
4.5.7 Mechanistic Considerations

We assumed that the transfer hydrogenation of β-nitroacrylates followed the same mechanism as the one involved in the conjugate reduction of nitroolefins **120**, involving similar transition states **K** and **L**, where the R'-substituent of the nitroolefin is an ester functionality (see Chapter 4.4.5, Scheme 4.66). The β-nitroacrylates **121** would be activated through hydrogen bonding interactions with the thiourea moiety of the catalyst **57b**, lowering the LUMO energy of the nitroolefin. This would allow the hydride transfer to occur from the *Re*-face according to the catalytic cycle reported in Chapter 4.4.5 (Scheme 4.66).

4.5.8 Conclusion and Discussion

Our approach to chiral *β*-nitroesters **119**, as an intermediate toward the synthesis of *β*²-amino acids **122**, took its inspiration from the *Jacobsen*-type thiourea-catalyzed *β*-nitroolefin **120** reductions that we had previously developed (see Chapter 4.4).

Based on our previous results and after screening different thiourea motifs, we once again identified the *Jacobsen*-type thiourea **57b** as the optimal catalyst (in terms of reactivity and enantioselectivity) for the highly enantioselective conjugate reduction of *β*-nitroacrylates **121**. Treating these olefins (1.0 molar) with the commercially available Hantzsch ester **90c** (1.0 equivalent) and thiourea catalyst **57b** (10 mol%) at 0°C in toluene gave the saturated ester **119f** in good yield and with high enantioselectivity (Scheme 4.84). By hydrogenating the *β*-nitroester **119f** in the presence of a catalytic amount of palladium, we could directly obtain the free *β*²-amino acid (*S*)-**122f**.



Scheme 4.84: Conjugate reduction of *β*-nitroacrylates **121** to *β*-nitroesters **119**, as a key step for the synthesis of *β*²-amino acids **122**.

It has to be specified that in the case of *β*-nitroesters with ester groups other than benzyl, the conversion into the corresponding *β*²-amino acids was facile too, involving a hydrogenation-hydrolysis sequence (see Scheme 4.83).

The key step of this process to chiral *β*²-amino acids was the asymmetric Hantzsch ester-mediated catalytic conjugate reduction of *β*-nitroacrylates **121** to *β*-nitroesters **119**. After the development and optimization of the transfer hydrogenation conditions (optimization of the catalyst structure and loading, solvent, substrate concentration, and Hantzsch ester structure and concentration, see Chapters 4.5.2 and 4.5.3), we were pleased to see that the reaction was rather general and worked well with a variety of substrates (see Table 4.37). The ester group

could be varied significantly as probed with phenyl-substituted derivatives **121b-f**. While the yield was high in all cases, the enantioselectivity increased slightly with size and bulkiness of the ester moiety. Other aryl and hetero aryl groups could be utilized as well (**121g-m**), leading to the corresponding products in similarly high yields and enantioselectivities. Interestingly, not only aromatic *β*-nitroacrylates were suitable, but also branched as well as unbranched aliphatic *β*-nitroacrylates.

We also investigated the effect of the *β*-nitroacrylate olefin geometry on the outcome of the reaction (see Scheme 4.81). Once again, we observed that the enantioselectivity of the nitroolefin reductions strongly depended on the substrate olefin geometry (also see Chapter 4.4.4). Accordingly, *β*-nitroacrylates (*E*)- and (*Z*)-**121a** gave the opposite enantiomers of product **119a**, each with high enantioselectivity, while an equimolar mixture of both isomers yielded essentially racemic **119a**. Remarkably though, stereoconvergence could be established upon adding a catalytic quantity of triphenylphosphine, probably through a rapid equilibrium between (*E*)-**121a** and (*Z*)-**121a** *via* a conjugate addition/elimination pathway. Under our reaction conditions the isomer dominating the reaction was found to be the (*E*)-olefin. It reacted with thiourea catalyst **57b** to afford the (*R*)-nitroester ((*R*)-**121a**) as the major product.

Moreover, we successfully developed a simple and practical process for the preparation of the *β*-nitroacrylates **121**, which was based on a Henry reaction–dehydration sequence. The *α*-ketoester **135** was first reacted with nitromethane in the presence of a catalytic amount of triethylamine, followed by dehydration of the resulting alcohol **209** with acetic anhydride. The desired *β*-nitroacrylates **121** were obtained in good yields and high (*Z*)-stereoselectivity, as reported in Scheme 4.84 for the formation of (*Z*)-benzyl 3-nitro-2-phenylacrylate (**121f**).

Our organocatalytic asymmetric *β*-nitroacrylates reduction achieves similar enantioselectivities as the recently developed biocatalytic version[175a] (see Chapter 2.4.2, Scheme 2.47) but has a significantly broader scope, since it is also suitable for aromatic *β*-nitroacrylates **121**. It is also an elegant and concise alternative to the methodology developed by *Gellmann et al.*[182b] (see Chapter 3.3, Scheme 3.10).

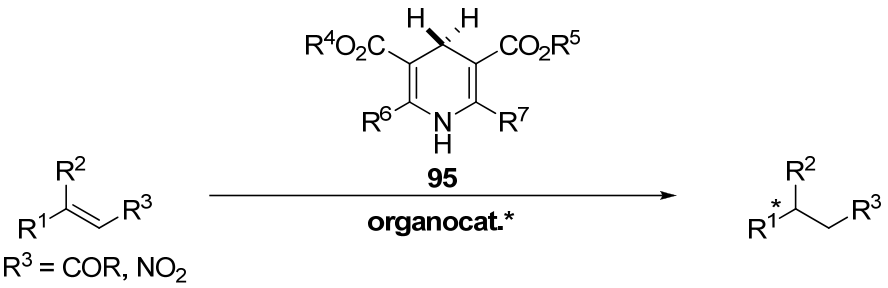
To summarize this project, we successfully developed a short new approach to enantiopure β^2-amino acids. The key step in our methodology is a highly enantioselective and versatile thiourea-catalyzed conjugate reduction of *β*-nitroacrylates **121** to their saturated derivatives **119**. In addition we have developed a convenient synthesis of the required *β*-nitroacrylates **121** *via* a Henry reaction followed by acetic anhydride-mediated dehydration. Moreover, the successful conversion of our reduction products into β^2-amino acids **122** through a

hydrogenation process or a hydrogenation–hydrolysis sequence was facile and efficient. As for the transfer hydrogenations that we reported in Chapters 4.3 and 4.4, the modest atom economy of this procedure is counterbalanced by the practical and convenient use of bench stable, crystalline Hantzsch esters and readily available reagents and catalysts.

5 Summary

This Ph.D. thesis describes the successful development of organocatalytic approaches to the synthesis of enantiomerically enriched saturated ketones as well as the preparation of chiral *β*,*β*-disubstituted nitroalkanes and also *β*-nitroesters, which could be efficiently converted to the corresponding *β*²-amino acids.

Inspired by Nature's transfer hydrogenations by enzymes and NAD(P)H cofactors, we based our work on the establishment of biomimetic catalytic conjugate reductions of enones (**107** and **113**) and nitroolefins (**120** and **121**) to generate the desired enantiomerically enriched product (i.e. the saturated ketones **95** and **114** as well as nitroalkanes **116** and nitroesters **119**). For this purpose, our strategy was to replace the relatively expensive NAD(P)H by dihydropyridine **90** and to find active organocatalysts as enzyme analogs (Scheme 5.1).



Scheme 5.1: Hantzsch ester-mediated organocatalytic transfer hydrogenation of enones or nitroolefins.

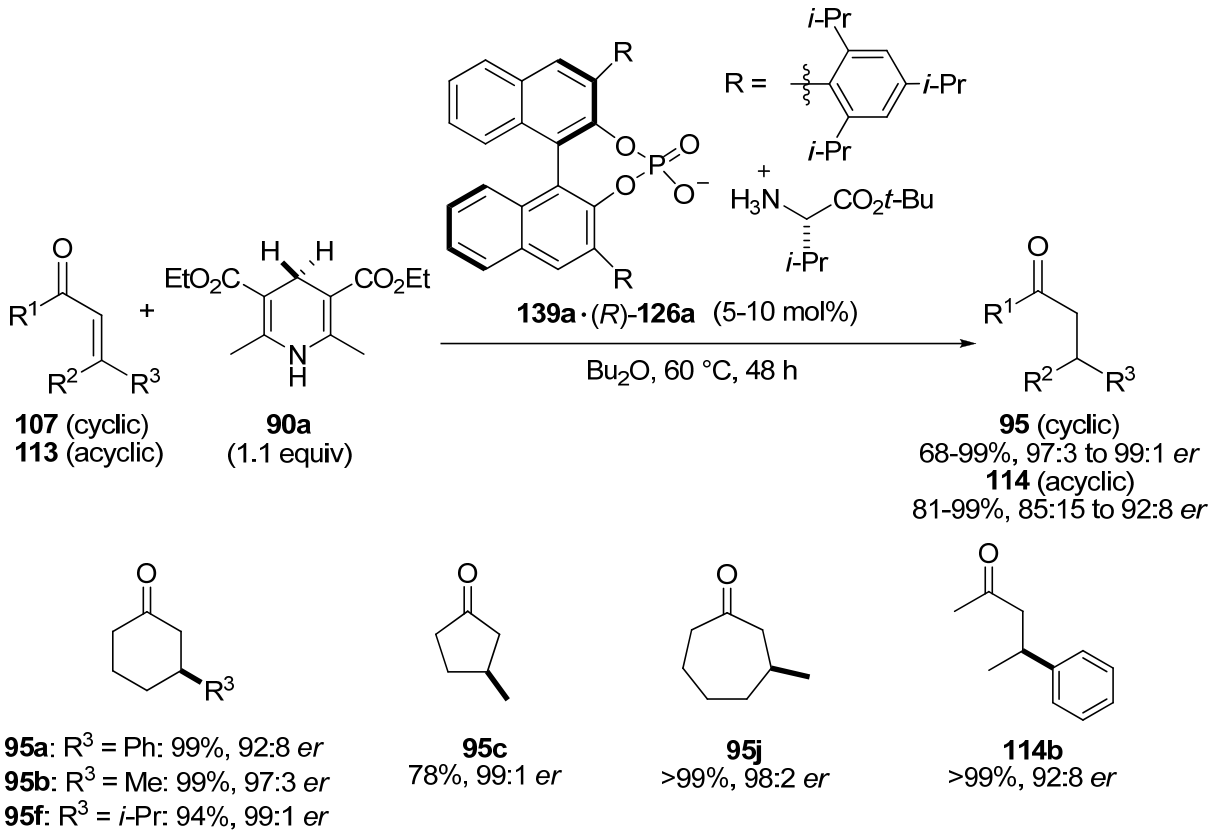
We first concentrated our work on the development of the Hantzsch ester-mediated transfer hydrogenation of *α*,*β*-unsaturated ketones **107** and **113**. Motivated by the conjugate reduction of enals *via* iminium catalysis that had been previously developed in our laboratory,[120b] we focused our study on the investigation of primary amine – in particular amino esters – derived salts to activate the enones through the formation of an iminium ion intermediate. Among all the amines tested, valine *tert*-butyl ester **139a** was superior in terms of reactivity and enantioselectivities (see Chapter 4.3.3.5, Table 4.9).

During our experiments we observed that not only the structure of the primary amine had an effect on the efficiency of the catalytic salt, but also the counteranion. We then investigated several counteranions and in particular chiral BINOL-derived phosphates. (*R*)-TRIP ((*R*)-**126a**) counteranion gave the highest enantioselectivities (see Chapter 4.3.2.4, Table 4.5).

The chirality present in the amino acid seemed to be required as glycine-derived catalyst [**195**· (*R*)-**126a**] gave significantly reduced enantioselectivity. Moreover, the phosphoric acid

derivative alone ((*R*)-**126a**, (*R*)-TRIP) was much less active than the amino acid ester salts and gave the product in only 40:60 *er* (see Chapter 4.3.3.5, Table 4.9). Interestingly, the product configuration was mainly determined by the amine geometry. Consequently, using the opposite enantiomeric counteranion ((*S*)-**126a**, (*S*)-TRIP), the same absolute configuration was generated in the product but with much lower enantioselectivity, illustrating a case of a matched/mismatched ion pair combination (see Chapter 4.3.2.2, Table 4.3). Accordingly, the catalytic system made of L-valine *tert*-butyl ester **139a** and BINOL-derived phosphate (*R*)-TRIP ((*R*)-**126a**) was chosen to catalyze the transfer hydrogenation of *α*,*β*-unsaturated ketones.

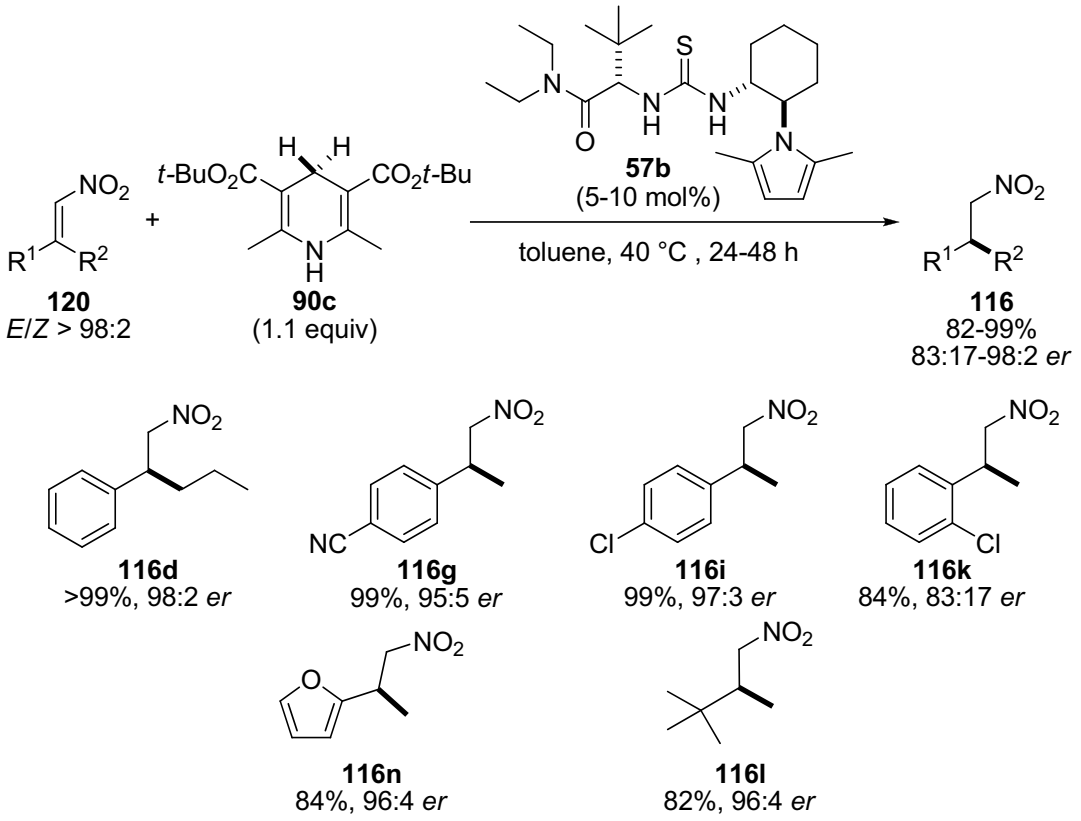
Using this catalytic salt at a loading of 5-10 mol%, we achieved an efficient and highly enantioselective transfer hydrogenation of enones through iminium catalysis in the presence of the commercially available Hantzsch ester **90a** (Scheme 5.2 and Chapter 4.3.4.1, Table 4.10). The reaction worked with a range of *β*-substituted *α*,*β*-unsaturated cyclic ketones **107** as well as with *β*,*β*-disubstituted acyclic enones **113**, although the acyclic saturated ketones **114** were formed with slightly lower enantioselectivities.



Scheme 5.2: Ammonium salt-catalyzed asymmetric transfer hydrogenation of enones.

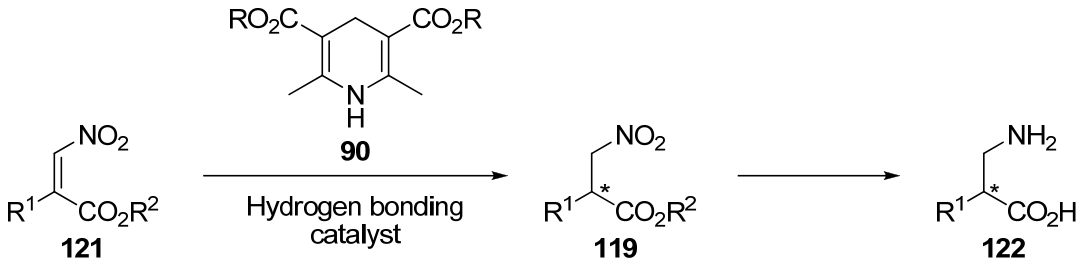
Remarkably, the catalytic conjugate reduction could be successfully scaled up to a multi-gram scale reaction, without loss of reactivity or enantioselectivity, even by reducing the amount of (*R*)-TRIP ((*R*)-**126a**) to 2 mol% (see Chapter 4.3.5).
Mechanistically, we believe that the reaction proceeds *via* an iminium phosphate ion pair stabilized by hydrogen bonding interactions with additional hydrogen bonding interactions between the phosphate counteranion and the Hantzsch ester. These assumptions were supported by monitoring the reaction with ESI-MS (see Chapter 4.3.6).

Besides the asymmetric conjugate reduction of *α*,*β*-unsaturated ketones, we investigated the transfer hydrogenation of *β*,*β*-disubstituted nitroalkenes **120** to synthesize enantiomerically enriched *β*,*β*-disubstituted nitroalkanes **116**.
For the development of this process, we evaluated the catalytic activity of various general or specific Brønsted acids. Thiourea derivatives identical or similar to those pioneered by *Jacobsen et al.*, and in particular **50d** and **57a**, turned out to be the most effective catalysts (see Chapter 4.4.3.3, Table 4.21). Further structural fine-tuning of the thiourea **57a** afforded the catalyst **57b**, which proved to be optimal in terms of reactivity and enantioselectivity (see Chapter 4.4.3.3, Tables 4.22 and 4.23).
Using this hydrogen bonding catalyst (**57b**, 5 mol%) and the commercially available Hantzsch ester **90c**, we successfully developed an efficient asymmetric transfer hydrogenation of nitroolefins **120**. The process had a broad substrate scope and afforded the *β*,*β*-disubstituted nitroalkanes **116** in high yields and enantioselectivities with a number of *β*-alkylsubstituted nitrostyrenes. Remarkably, aliphatic nitroalkenes were equally suitable substrates, even the ethylmethyl-disubstituted nitroolefin **120m** (Scheme 5.3, see also Chapter 4.4.4, Table 4.25).
The investigation of the aliphatic nitroolefin **120m** indicated that the enantioselectivity and the conformation of the product **116m** were strongly dependent on the olefin geometry (i.e. the reaction was not stereoconvergent (see Chapter 4.4.4, Table 4.26). For this reason, optimal enantiomeric ratios could only be reached by using the nitroolefins as a pure (*E*)- or (*Z*)-isomer.
Mechanistically, we assumed that the reaction proceeds *via* hydrogen bonding interactions between the thiourea moiety of the catalyst **57b** and the nitro group of the nitroolefin **120**.



Scheme 5.3: Hydrogen bond-catalyzed asymmetric transfer hydrogenation of nitroalkenes **120**.

This efficient, versatile, and practical hydrogen bonding-catalyzed transfer hydrogenation of nitroolefins **120** to the corresponding nitroalkanes **116** inspired us to try the reaction with *β*-nitroacrylates **121** to prepare enantiomerically enriched *β*-nitroesters **119**, as a key step for the synthesis of *β*²-amino acids **122** (Scheme 5.4).

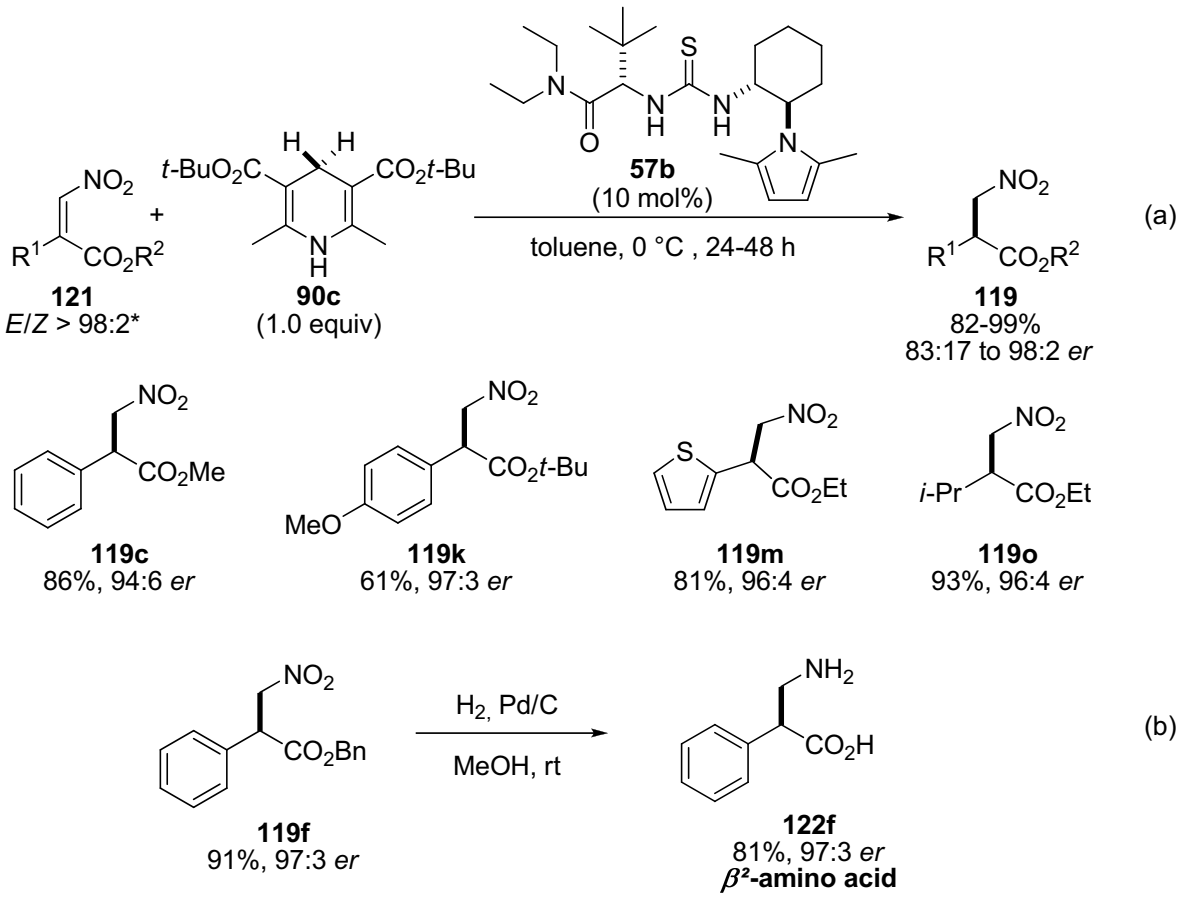


Scheme 5.4: Developed approach for the synthesis of *β*²-amino acids **122** with the hydrogen bonding-catalyzed transfer hydrogenation of *β*-nitroacrylates **121** as the key step.

Based on our previous results and after screening different thiourea motifs, we identified once again *Jacobsen*-type thiourea **57b** as the optimal catalyst (in terms of reactivity and enantioselectivity) for the highly enantioselective conjugate reduction of *β*-nitroacrylates **121** (see Chapter 4.5.2, Tables 4.30-4.32).

Employing this catalyst (10 mol%) and the commercially available dihydropyridine **90c**, we were able to prepare a variety of *β*-nitroesters **119** in high yields and enantioselectivities. The reaction was rather general and worked well with a broad range of substrates (Scheme 5.5 and see Chapter 4.5.4, Table 4.37). The ester group could be varied significantly and different aryl and hetero aryl groups could be utilized, leading in all the cases to the formation of the desired product with high enantiomeric ratios. Gratifyingly, branched as well as unbranched aliphatic *β*-nitroacrylates were equally suitable substrates.

The generated *β*-nitroesters **119** were then easily converted to the corresponding enantiomerically enriched *β²*-amino acids **122** *via* a facile and efficient hydrogenation-hydrolysis sequence (see Chapter 4.5.6, Scheme 4.81). In the case of the benzylester-derived *β*-nitroester **119f**, the free *β²*-amino acid (*S*)-**122f** was directly obtained by hydrogenation in the presence of a catalytic amount of palladium (Scheme 5.5).



Scheme 5.5: Conjugate reduction of *β*-nitroacrylates **121** to *β*-nitroesters **119**, as a key step for the synthesis of *β²*-amino acids **122**. (* In the case of **121m**: *Z*/*E* > 98:2).

We also investigated the effect of the *β*-nitroacrylate geometry on the outcome of the reaction. Once again, we observed that the enantioselectivity of the transfer hydrogenation strongly

depended on the substrate olefin geometry. Remarkably though, stereoconvergence could be established upon adding a catalytic amount of triphenylphosphine, which probably induces a rapid equilibrium between (*E*)-**121** and (*Z*)-**121** *via* a conjugate addition/elimination pathway (see Chapter 4.5.5).

Additionally, we successfully established a practical and efficient synthesis of the *β*-nitroacrylates **121** from the corresponding *α*-ketoesters **135**. This optimized preparation of the olefins **121** was based on a Henry reaction, followed by dehydration with acetic anhydride, affording the desired olefins **121** in good yields and with a high (*Z*)-stereoselectivity (see Chapter 4.5.1.2).

Mechanistically, we assumed that the reaction proceeded through a similar catalytic cycle as the one involved in the transfer hydrogenation of nitroolefin **120** (see Chapter 4.4.5, Scheme 4.64).

Part of this work has been published in scientific journals:

"*Highly Enantioselective Transfer Hydrogenation of α,β-Unsaturated Ketones*":
N. J. A. Martin, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13368.

"*Organocatalytic Asymmetric Transfer Hydrogenation of Nitroolefins*":
N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976.

"*Organocatalytic Asymmetric Transferhydrogenation of β-Nitroacrylates: Accessing β²-Amino Acids*":
N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862.

6 Outlook

To improve the atom economy of our organocatalytic approaches for the transfer hydrogenation of olefins it would be of interest to regenerate the Hantzsch ester after the conjugate reduction is finished. The immobilization of the dihydropyridine on a solid support would facilitate their regeneration since it would be possible to isolate the pyridine derivative at the end of the reaction directly by filtration. It would then be simple to reduce this oxidized species for example with sodium cyanoborohydride.[253] The immobilization of the Hantzsch esters at the 3-position should still allow hydrogen bonding interactions between the catalyst and the amine functionality of the dihydropyridine to occur (Figure 6.1).

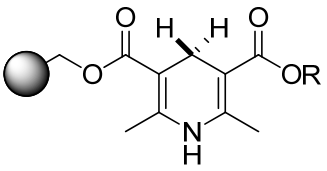
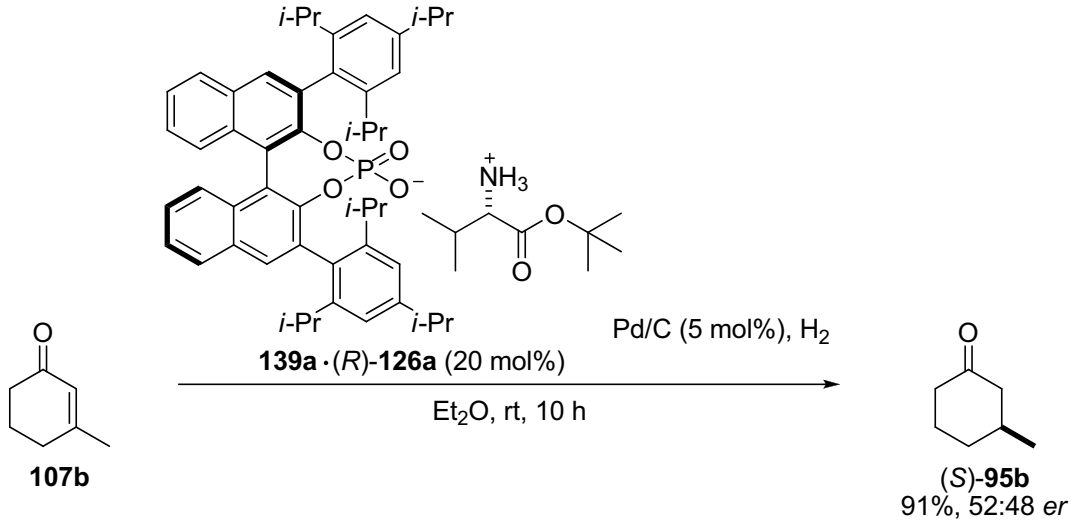


Figure 6.1: Immobilization of dihydropyridine on a solid support.

Another alternative to obtain more atom economic and thus more attractive processes would be to replace the Hantzsch ester by molecular hydrogen and perform the olefin hydrogenations in the presence of our organocatalysts in combination with a transition metal catalyst. We made a first attempt for the direct conjugate reduction of 3-methylcyclohexenone **107b** in the presence of our catalytic system ([**139a**·(*R*)-**126a**], 20 mol%) with palladium on charcoal (5 mol%). Since the activation of enone **107b** with palladium was faster than the activation of **107b** with the chiral ammonium salt [**139a** ·(*R*)-**126a**], predominantly non-asymmetric transfer hydrogenation took place, yielding saturated ketone **95b** in excellent yield but almost racemically (Scheme 6.1). An enantioselective reaction can in principle be developed, by varying the structure of the metal-catalyst until conditions are found for which the iminium catalysis is the faster reaction.



Scheme 6.1: First attempt toward the direct hydrogenation of 3-methylcyclohexenone.

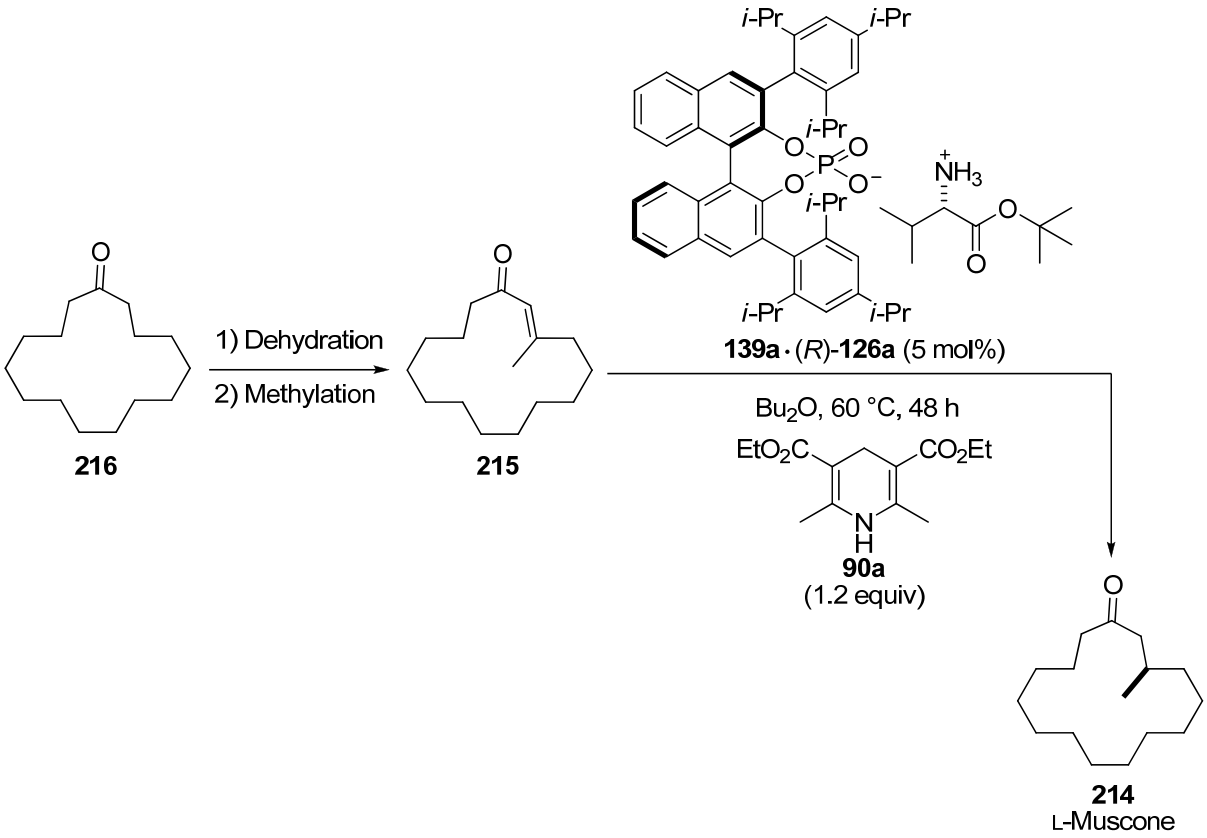
The transfer hydrogenations of olefins that we reported are not enantioconvergent. This means that the substrates have to be used as pure (*E*)- or (*Z*)-isomers to be able to reach high enantioselectivities. Since the separation of both isomers is sometimes difficult to achieve, it would be convenient to develop stereoconvergent processes, allowing the employment of pure isomers as well as mixtures of (*E*)- and (*Z*)-isomers without affecting the enantiomeric ratios of the products. As shown for the conjugate reduction of *β*-nitroacrylates, it is possible to induce stereoconvergence upon adding a catalytic amount of triphenylphosphine to the system (see Chapter 4.5.5). It would be of interest to first optimize this process by testing other phosphine derivatives and by varying the reaction conditions and to then apply it to the transfer hydrogenations of enones and nitroalkenes.

6.1 Transfer Hydrogenation of *α,β*-Unsaturated Ketones

In future work, experiments to improve the activity of our catalytic salt [**139a** · (*R*)-**126a**] should be done, in order to reduce the reaction time and catalyst loading. Since we limited our investigation to chiral BINOL-derived counteranions, and especially BINOL phosphates ones, other counteranions (with or without phosphate functionality), should be screened. For these tests smaller chiral as well as achiral counteranions can be envisaged (e.g. naphthyl-, phenyl- or alkyl-substituted phosphate, sulfate or carbonate compounds).

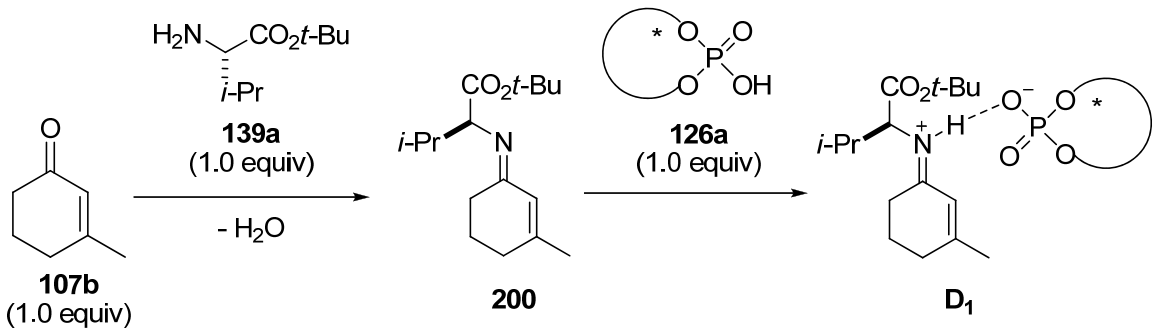
For the application of our methodology to the synthesis of an industrially relevant product, Muscone could serve as a target molecule. L-Muscone (**214**) is well-known as the pheromone

of the male musk deer and is considered as a very important musk because of its superior odor characteristics and environmental harmlessness. It is thus a fragrance of choice for the perfume industry. An asymmetric methylation of (*E*)-cyclopentadec-2-enone is one of the most effective routes to construct (*R*)-3-methylcyclopentadecanone (**214**, L-muscone).[254] Another strategy would be to prepare (*E*)-3-methylcyclopentadec-2-enone (**215**) from the commercially available cyclopentadecanone (**216**) *via* a dehydration–methylation sequence and then to apply the condition of our transfer hydrogenation of enones to convert **215** to (*R*)-3-methylcyclopentadecanone (**214**, L-muscone, Scheme 6.2).



Scheme 6.2: Transfer hydrogenation of enone **215** *via* iminium catalysis as a key step for the synthesis of L-muscone (**214**).

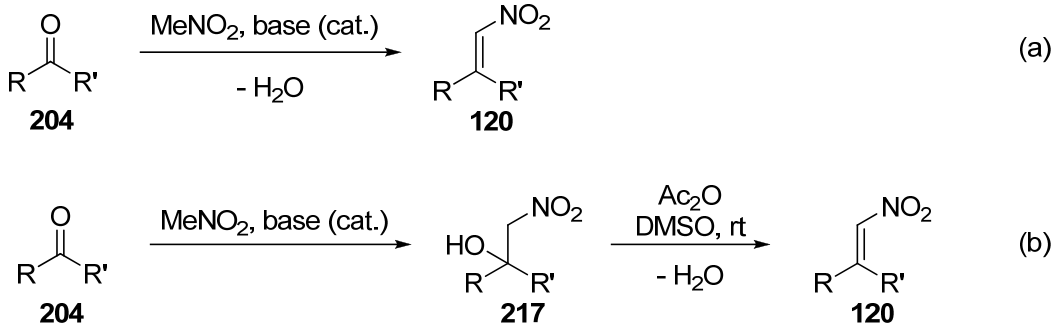
To have more precise information about the mechanism of the reaction and the structure of the intermediates species as well as the hydrogen bonding involved during the conjugate reduction of enones, more thorough mechanistic studies would be required. For example it would be useful to obtain a crystal structure of the iminium intermediate $\mathbf{D_1}$ (see Chapter 4.3.6, Scheme 4.48). To this end, the imine resulting from the condensation of 3-methyl-cyclohexenone (**107b**) and valine tert-butyl ester (**139a**) should be formed and isolated. A subsequent addition of an equimolar amount of (*R*)-TRIP ((*R*)-**126a**) would generate the iminium salt $\mathbf{D_1}$ (Scheme 6.3).



Scheme 6.3: Preparation of the intermediate $\mathbf{D_1}$ for X-ray analysis.

6.2 Transfer Hydrogenation of *β,β*-Disubstituted Nitroalkenes

The efficient strategy for the synthesis of *β,β*-disubstituted nitroalkanes would be even more attractive if an effective preparation of the nitroalkenes could be achieved. It would therefore be of interest to further investigate the base-catalyzed one-pot preparation of nitroolefins **120** from the corresponding ketones **204** in the presence of nitromethane *via* a nitroaldol (Henry) condensation (Scheme 6.4a). Another approach would be to apply the conditions established for the preparation of the *β*-nitroacrylates **121a** (i.e. a Henry reaction– dehydration sequence, see Chapter 4.5.1.2) to the formation of the nitroolefins **120** (Scheme 6.4b).



Scheme 6.4: Optimization of the preparation of nitroolefin **120** *via* (a) Henry condensation or (b) a Henry reaction–dehydration sequence.

We observed that the substituents at the 2- and 5-positions of the pyrrolyl group of thiourea **57b** have a strong influence on the catalyst efficiency and a decrase of the bulkyness of the substituents lead to an increase of the reactivity and enantioselectivity of the catalyst (see Chapters 4.4.3.3 and 4.5.2). It would the be interesting to prepared thioureas **57m** and **57n** (Figure 6.2) without susbtituents or with only one methyl substituent on the pyrrol

functionality and to test these catalysts in the transfer hydrogenation of nitroolefins, to see if the reaction conversions and enantiomeric excesses of the products could be further improved.

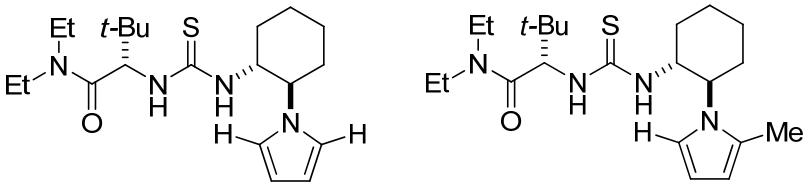


Figure 6.2: Possibilities to improve the efficiency of thiourea catalyst **57b**.

BINOL-derived dicarboxylic acid **157b** proved to be a reactive catalyst for the transfer hydrogenation of nitroalkene **120a**, leading to the formation of the corresponding nitroalkane in good yield (85%) and moderate enantioselectivity (71:29 *er*). This enantiomeric ratio could be improved by optimizing the substituents at the 3- and 3'-positions of the BINOL moiety of **157b** (Figure 6.3). In the same way, the bisthioureas **63** and **178** are suitable to activate the nitroolefin **120a** and they are generally more active than monothioureas (see Chapter 4.4.2.3, Scheme 4.18). However, in the presence of these catalysts, the product was generated with only moderate selectivity. It would thus be of interest to optimize the structure of these bisthiourea compounds, for example by replacing the 3,5-bis(trifluoromethyl)phenyl substituents by pyrrol-1-ylcyclohexyl derivatives and/or amino amide groups (Figure 6.3).
Since we observed that the bisthiourea catalysts with a fixed conformation were often more active than monothioureas, it would be interesting to prepare and test bisthioureas of type **218**, **219** and **220**, which are derived from 9,9-dimethyl-9*H*-xanthene, dibenzofuran and acridin-9(10*H*)-one, respectively (Figure 6.4).

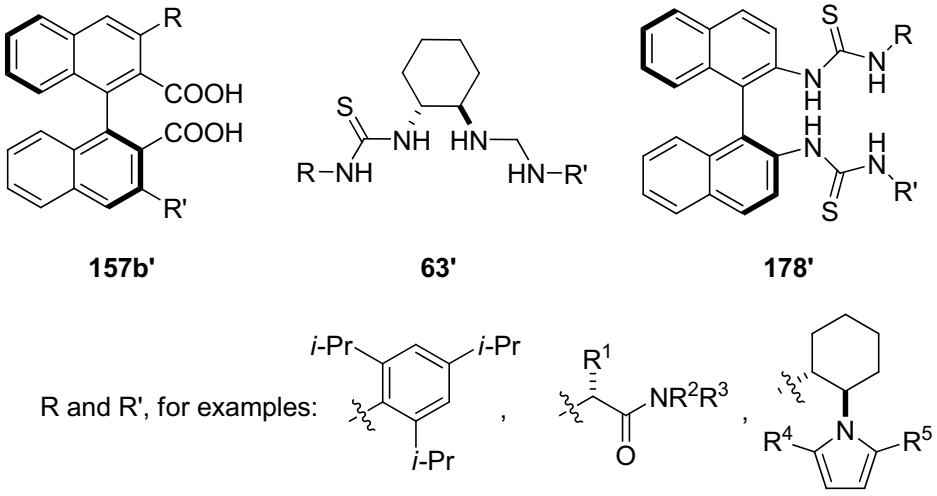


Figure 6.3: Possibilities for the optimization of the catalyst **157b**, **63** and **178**.

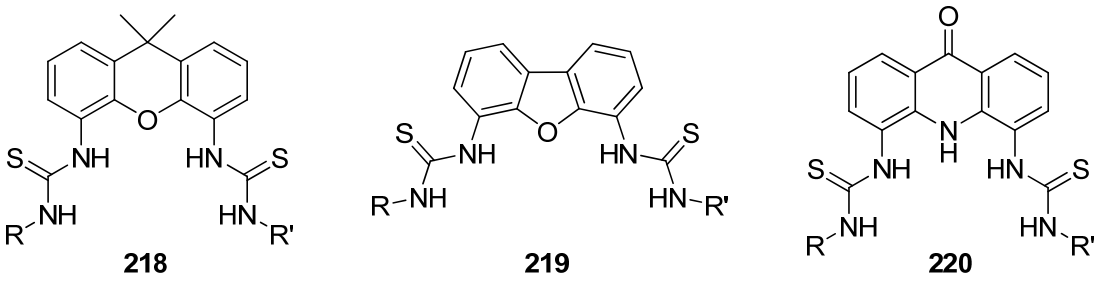
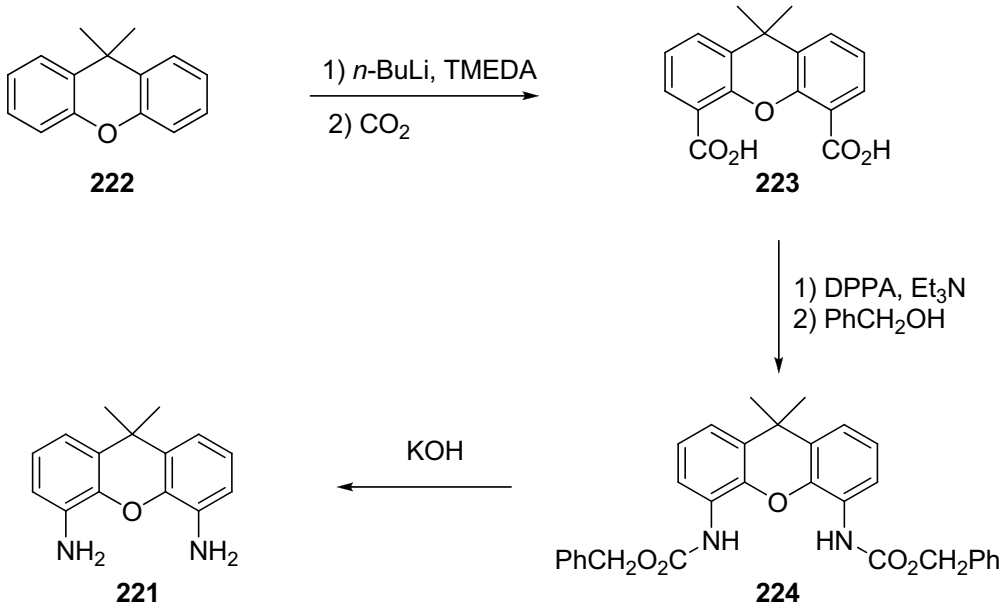


Figure 6.4: New motifs of bisthiourea catalysts.

Catalyst **218** can in principle be easily prepared by reacting diamine **221** with the desired isothiocyanate compounds. The diamine **221** can in turn be generated in four steps by double functionalization of the commercial 9,9-dimethylxanthene **222** according to the methodology reported by *Barloy et al.* (Scheme 6.5).[255] The carboxylation of **222** would afford the dicarboxylic acid **223**, which would then be further converted to the dicarbamate **224** *via* a Curtius rearrangement. Basic hydrolysis of **223** would lead to 9,9-dimethyl-9*H*-xanthene-4,5-diamine (**221**). A similar procedure could be used for the synthesis of dibenzofuran diamine and acridin-9(10*H*)-one diamine, which could be further converted to the bisthiourea catalysts **219** and **220**.



Scheme 6.5: Preparation of the diamine **221** as linker for the bisthiourea catalyst **218**.

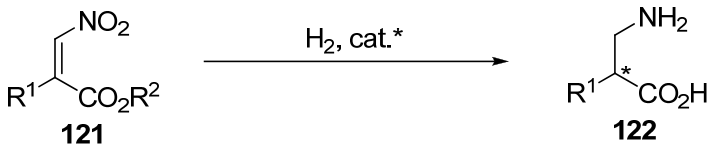
To elucidate the exact mechanism of the transfer hydrogenation of nitroolefins **120** (as well as the *β*-nitroacrylates **121**) further mechanistic studies should be undertaken. For example, it would be interesting to perform the reaction in completely anhydrous conditions (e.g. in the presence of molecular sieves) as well as with different amounts of water (up to 1.0 equivalent with respect to the catalyst amount) to evaluate the influence of water on the catalyst activity.

We observed from our ESI-MS analyses that catalyst **57b** might interact with the Hantzsch ester **90c** during the transfer hydrogenation reaction. It would then be of interest to analyze deuterated toluene solution of **57c** with different amounts of dihydropyridine **90c** by NMR and examine the effect of the Hantzsch ester addition on the chemical shifts of the protons of the catalyst (especially on the protons of the thiourea moiety). Moreover, it would be useful to obtain a crystal structure of the intermediate **F** (see Chapter 4.4.5, Schemes 4.67 and 4.68), formed by the catalyst, nitroolefin and Hantzsch ester. To gain a more detailed insight into the reaction mechanism computational calculations would be needed.

6.3 Transfer Hydrogenation of *β*-Nitroacrylates: a Route to *β*²-Amino Acids

Organocatalysis is an attractive alternative to metal catalysis, especially for the synthesis of pharmaceuticals, for which the removal of potentially toxic metal impurities from the reaction product is crucial but often difficult to achieve. The development of a metal-free, organocatalytic asymmetric transfer hydrogenation of *β*-nitroacrylates **121** to the corresponding *β*-nitroesters **119**, as a key step for the synthesis of *β*²-amino acids **122** is therefore a very useful and interesting strategy. However, the use of metal for the hydrogenation of nitroesters **119** to *β*²-amino acids **122** diminishes the benefits of the previous organocatalytic steps. It would then be of interest to develop a metal-free and environmentally friendlier hydrogenation of nitroesters **119** to *β*²-amino acids **122**.

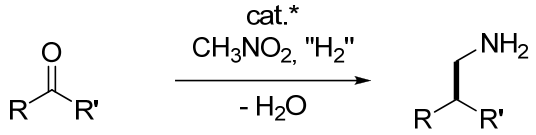
In theory, it would be also possible to directly convert the *β*-nitroacrylates **121** to the corresponding enantiopure *β*²-amino acids **122** in a one-pot process, for example in the presence of molecular hydrogen and an appropriate catalyst (Scheme 6.6). It would be interesting to establish such an elegant and innovative strategy.



121 **122**

Scheme 6.6: Direct catalytic hydrogenation of *β*-nitroacrylates **121** to *β*²-amino acids **122**.

Even more challenging would be the development of a methodology for the catalytic reductive aminomethylation of ketones or α-ketoacids in the presence of nitromethane and a hydrogen source (Scheme 6.7) in analogy to Nature's enzymatic reductive amination of α-ketoacids with ammonia (see Chapter 3.3, Scheme 3.11)



Scheme 6.7: Catalytic reductive aminomethylation.

7 Experimental Part

7.1 General Experimental Conditions

7.1.1 General mode of operation

All reactions were carried out under an atmosphere of argon in dried solvents and oven dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. The solvents and reagents were added to the reaction mixtures using dried syringes or cannulae. Unless otherwise stipulated, the aqueous solutions of sodium chloride, sodium bicarbonate, sodium hydroxide, and ammonium chloride were used as saturated solutions. The organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Solvents

Dried dibutyl ether, 1,4-dioxane, *tert*-butanol, and DMSO were purchased from Sigma-Aldrich and used without further purification. All other solvents were obtained by distillation over appropriate drying agent (see below) and then kept under an atmosphere of argon: acetone (calcium hydride), acetonitrile (calcium hydride), benzene (calcium hydride), chloroform (calcium hydride), dichloromethane (calcium hydride), diethyl ether (sodium/potassium-alloy), diisopropylamine (calcium hydride), ethanol (magnesium), hexane (sodium/potassium-alloy), methanol (magnesium), pentane (sodium/potassium-alloy), tetrahydrofuran (sodium/potassium-alloy), toluene (sodium/potassium-alloy) and triethylamine (calcium hydride).

Chromatographic methods

The reactions were monitored by thin-layer chromatography (TLC) using silica gel precoated glass plates (20 cm x 20 cm, 0.25 mm thickness, silica gel 60F-254, E. Merck) or silica gel precoated aluminium foil plates (40 mm x 80 mm, 0.20 mm thickness, Polygram SIL G/UV254, Macherey-Nagel) and mixtures of ethyl acetate/hexanes, diethyl ether/pentane or methanol/dichloromethane as eluent. The chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining with ninhydrin, vanillin, anisaldehyde, phosphomolybdic acid or potassium permanganate stains.

Flash column chromatography was performed using silica gel 60 (type 9385, 230-400 mesh, particle size 0.040–0.063 mm, pore diameter 60 Å, Merk). Pure solvent (hexanes or pentane) or solvent mixtures (ethyl acetate/hexanes, diethyl ether/pentane or methanol/dichloromethane) were used as eluent.

7.1.2 Analytical Methods

NMR-Spectroscopy

The ^{1}H-, ^{13}C-NMR spectra were recorded at room temperature in $CDCl_3$ (unless otherwise noted) on Bruker DPX-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), AV-400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) or AV-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers. The chemical shifts for the protons and the carbons are reported in parts per million (δ ppm) and are relative to tetramethylsilane (TMS) with the resonance of the deuterated solvent as the internal standard (e.g. with $CDCl_3$: δ 7.26 ppm for ^{1}H-NMR and δ 77.0 ppm for ^{13}C-NMR). The ^{1}H-NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, qt = quintet, m = multiplet; br = broad), coupling constants (*J*) in Hertz (Hz) and assignment (Ar = aromatic, Cq = quaternary carbon, cycl. = cyclic, pyr. = pyrrolyl).

Gas Chromatography (GC)

Analytical gas chromatography (GC) was performed on Hewlett-Packard 6890 and 5890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors. The enantiomeric ratios of chiral molecules were measured using chiral columns containing the following chiral stationary phases:

- *BGB 176*: 6-*tert*-butyl-dimethylsilyl-*β*-cyclodextrin (chiral component) and *SE 52* or *BGB-15* (achiral component), 30 m × 0.25 mm × 0.25 µm.
- *BGB 178*: 6-*tert*-butyl-dimethylsilyl-*β*-cyclodextrin (chiral component) and *OV 1701* (achiral component), 30 m × 0.25 mm × 0.25 µm.
- *G-TA*: *γ*-cyclodextrin trifluoracetyl (only chiral), 30 m × 0.25 mm × 0.25 µm.
- *Ivadex-1*: dimethylpentyl-*β*-cyclodextrin (chiral component) and *PS086* (achiral component), 25 m × 0.25 mm × 0.25 µm.
- *Ivadex-7*: diethyl-*tert*-butyl-dimethyl-*β*-cyclodextrin (only chiral), 25 m × 0.25 mm × 0.25 µm.

- *Lipodex-A*: hexakis-2,3,6-tri-*O*-pentyl-*α*-cyclodextrin (only chiral), 25 m × 0.25 mm × 0.25 µm.
- *Lipodex G*: octakis-2,3-*O*-dipentyl-6-*O*-methyl-*γ*-cyclodextrin (only chiral), 25 m × 0.25 mm × 0.25 µm.
- *Hydrodex β-TBDAC*: heptakis-(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethyl-silyl)-*β*-cyclodextrin (only chiral), 25 m × 0.25 mm × 0.25 µm.

High performance liquid chromatography (HPLC)

For some products, the separation of the (*R*)- and (*S*)-enantiomers and the determination of the enantiomeric ratios were done by analytical HPLC. The measurements were performed on a Shimadzu LC-20AD HPLC-system equipped with a spectrophotometric detector (monitoring at 220 nm or 254 nm) using Daicel chiral columns containing the following chiral stationary phases:

- *Chiralpak AS-H*: 1-phenylethylcarbamate of amylase, 25 cm × 0.46 cm.
- *Chiralcel OD-H*: 3,5-dimethylphenylcarbamate of cellulose, 25 cm × 0.46 cm.
- *Chirobiotic T2*: teicoplanin, 25 cm × 0.21 cm.

The separation of the (*E*)- and (*Z*)-isomers of the compound **120m** was performed by preparative HPLC on a Shimadzu LC-8A HPLC-system equipped with a FRC-10A fraction collector and a BIAX column (125 mm x 20 mm) and pentane as the mobile phase.

Mass Spectrometry (MS)

The mass spectra were measured on Finnigan MAT 8200 (70 eV) or MAT 8400 (70 eV) by electron ionization, chemical ionization, of fast atom/ion bombardment techniques. Accurate mass determinations were obtained on a Bruker APEX III FT-MS (7 T magnet).

The mechanism of the transfer hydrogenations of enone **107b** and nitroalkene **120a** was investigated by ESI-MS with a Finnigan Ultra Mass TSQ 7000.

Gas Chromatography with Mass Spectrometric Detector (GC/MS)

The GC/MS spectra were measured on Agilent Technolgy GC 6890 Series and MSD 5973 (using helium as carrier gas) with HP6890 Series Injector. For these measurements a *Hewlett Packard HP-5* column (crosslinked silicone gum capillary column: 30 m × 0.32 mm × 0.25 µm) was used.

Melting point (m.p.)

The melting points were measured on a Büchi 540 melting point apparatus in an open glass capillary and are uncorrected.

Specific Rotation ([α])

The optical rotations (α) were measured on a Perkin-Elmer polarimeter model 343 at a wavelength of 589 nm (sodium D line, D) and at 20 °C using a 1 mL cell with a 1 dm path length (l). The measurements were carried out in different solvents, which are specified for each specific rotation. The sample concentrations (c) are given in g/100 mL. The specific rotations ($[\alpha]_D^{20}$, in 10^{-1} deg cm^2 g^{-1}) are calculated using the following equation (eq. 1):

$$[\alpha]_D^{20} = \frac{\alpha_D^{20} \bullet 100}{c\ [\text{g}/100\ \text{mL}] \bullet l\ (\text{dm})} \qquad \text{(eq.1)}$$

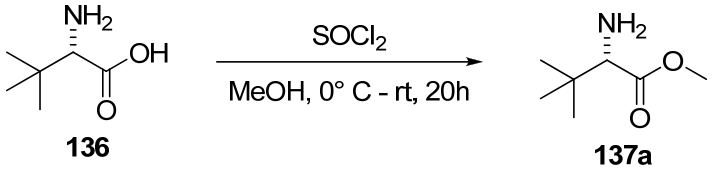
7.2 Synthesis of Organocatalysts for the Transfer Hydrogenation of Enones

Only the syntheses that were undertaken by the author of this Ph.D. thesis as well as the preparation of (*R*)-TRIP ((*R*)-**126a**), which was partially carried out with *S. Marcus*, are reported in this chapter. The syntheses of compounds (e.g. BINOL derived counteranions **126b-g**) that were performed by colleagues, and syntheses that *M. Hannappel* carried out following the procedures provided by the author of this Ph.D. work are not reported in this chapter.

7.2.1 Synthesis of Amino Esters

All amino esters reported in this section are known compounds. The obtained physical data were identical in all respects to those previously reported in the literature, in the case such data were provided.

7.2.1.1 Synthesis of L-*tert*-Leucine Methyl Ester (137a)[206]

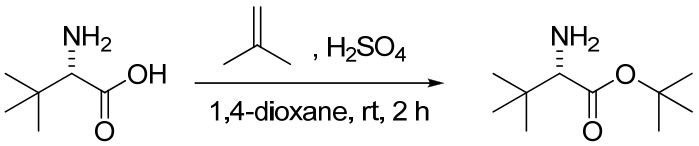


136 **137a**

A suspension of L-*tert*-leucine (**136**, 5.00 g, 38.12 mmol, 1.0 equiv) in dried methanol (80 mL) was stirred at 0 °C for 5 minutes. Thionyl chloride (8.3 mL, 114.36 mmol) was then slowly added to the suspension, leading to the homogenization of the solution. The reaction mixture was stirred at room temperature for 20 hours. After the addition of a saturated solution of sodium bicarbonate (40 mL) and ethyl acetate (40 mL), the organic and aqueous phases were separated. The aqueous layer was then extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10-30% of ethyl acetate in hexanes) to provide L-*tert*-leucine methyl ester (**137a**, 1.69 g, 11.64 mmol, 31% yield) as a pale yellow oil.

137a: $C_7H_{15}NO_2$ (145.20 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.67 (s, 3H, OC***H***$_3$), 3.13 (s, 1H, C***H***NH_2), 1.57 (br s, 2H, N***H***$_2$), 0.93 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.4 (***C***=O), 63.4 (***C***HNH_2), 51.3 (O***C***H_3), 34.3 (***C***$(CH_3)_3$), 26.5 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 146 (0.09), 115 (10), 89 (100), 57 (51), 41 (50), 28 (20).

7.2.1.2 Synthesis of L-*tert*-Leucine *tert*-Butyl Ester (137b)[208]

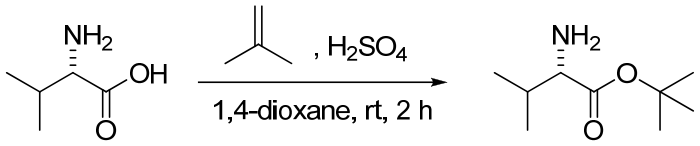


136 **137b**

Concentrated sulfuric acid (5.0 mL; 1 mL/g of amino acid) was slowly added to a suspension of L-*tert*-leucine (**136**, 5.00 g, 38.12 mmol, 1.0 equiv) in dioxane (45 mL, 5-10 mL/g amino acid), followed by the addition of an equal volume of condensed 2-methylpropene (45 mL). The reaction mixture was stirred at room temperature, leading to the formation of a highly viscous mixture, which solidified. As a result, after ca. 1.5 hours the mixture could not be further stirred. The reaction was then stopped and carefully quenched with sodium hydroxide (2 N, 60 mL), which dissolved the solid. The organic and aqueous phases were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (12% of ethyl acetate in hexanes) to provide the title compound (**137b**, 1.71 g, 9.13 mmol, 24% yield) as a pale yellow oil.

137b: $C_{10}H_{21}NO_2$ (187.28 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.99 (s, 1H, C***H***NH_2), 1.52 (brs, 2H, N***H***$_2$), 1.44 (s, 9H, C(C***H***$_3)_3$), 0.94 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.1 (***C***=O), 83.6 (O***C***$(CH_3)_3$), 63.9 (***C***HNH_2), 34.3 (***C***$(CH_3)_3$), 28.1 (OC(***C***$H_3)_3$), 26.6 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 188 (8), 158 (41), 132 (52). The physical data were identical in all respects to those previously reported.[256]

7.2.1.3 Synthesis of L-Valine *tert*-Butyl Ester (139a)[208]



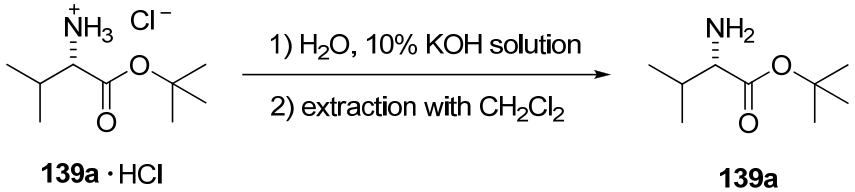
140 **139a**

According to the procedure reported in Chapter 7.2.1.2, 2-methylpropene (70 mL, condensed at -78 °C) was carefully added to a suspension of L-valine (**140**, 7.00 g, 59.75 mmol, 1.0 equiv) in dioxane (70 mL) and concentrated sulfuric acid (7.0 mL). The reaction mixture was stirred at room temperature for two hours and then quenched with sodium hydroxide (2 N, 100 mL), leading to the formation of a precipitate which was dissolved by adding diethyl ether. The two phases were separated and the aqueous layer extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude amino ester was purified by flash chromatography (1% of methanol in dichloromethane) to provide L-valine *tert*-butyl ester (**139a**, 3.71 g, 21.41 mmol, 36% yield) as a pale yellow oil.

139a: $C_9H_{19}NO_2$ (173.25 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.16 (d, *J* = 4.8 Hz, 1H, C***H***NH_2), 2.00-1.96 (m, 1H, C***H***$(CH_3)_2$), 1.54 (brs, 2H, N***H***$_2$), 1.46 (s, 9H, C(C***H***$_3)_3$), 0.96 (d, *J* = 6.9 Hz, 3H, CH(C**H**$_3)_2$), 0.89 (d, *J* = 6.9 Hz, 3H, CH(C***H***$_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.7 (***C***=O), 80.8 (O***C***$(CH_3)_3$), 60.3 (***C***HNH_2), 32.1 (***C***$H(CH_3)_2$), 28.1 (C(***C***$H_3)_3$), 19.3 (CH(***C***$H_3)_2$), 17.0 (CH(***C***$H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 174 (0.01), 130 (0.3), 116 (0.3), 102 (1). 72 (100), 55 (27), 41 (17), 29 (9); **HRMS** (EIpos) calcd for ($[C_9H_{19}NO_2+Na]^+$): 196.1308, found: 196.1308. The physical data were identical in all respects to those previously reported.[257]

7.2.1.4 Preparation of Free Amino Esters from their Corresponding Hydrochloride Salts (139a)

Preparation of L-valine tert-butyl ester (139a)



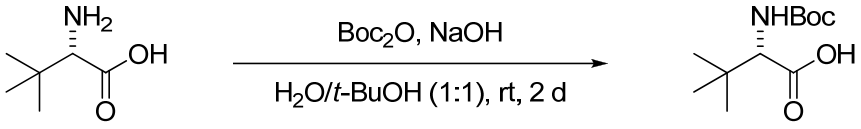
139a · HCl **139a**

L-Valine *tert*-butyl ester hydrochloride ([**139a**·HCl], 1.00 g, 4.77 mmol, 1.0 equiv) was dissolved under stirring in water (13 mL). An aqueous solution of potassium hydroxide (2 N, 3.0 mL) was added to the solution until a basic pH was reached. The aqueous and organic layers were then separated and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried over magnesium sulfate and filtered. The filtrate was then concentrated *in vacuo* to give the free amine **139a** (0.82 g, 4.76 mmol, >99%) as a pale yellow oil. The physical data were identical in all respects to those previously reported in Chapter 7.2.1.3.

Following the procedure reported for the preparation of the free L-valine *tert*-butyl ester (**139a**) from [**139a**·HCl], alanine, valine, phenylalanine and phenylglycine derived salts (**141a-b**, **139b**, **142** and **143**, respectively) were converted to the free amino esters. They were then treated *in situ* with TFA or TRIP (1.0 equiv) to generated their corresponding trifluoroacetate salts and test their activity for the transfer hydrogenations of 3-methylcyclohexenone (**107b**, see Chapter 7.4.3).

7.2.2 Synthesis of the Amino Amides 144a and 147

7.2.2.1 Synthesis of L-*tert*-leucine-*N*,*N*-dimethylamide (144a)[209,210]

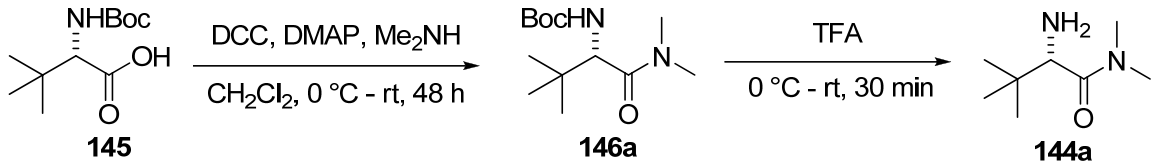


136 **145**

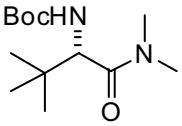
Preparation of N-Boc-L-tert-leucine (**145**):[209] Boc_2O (23.96 g, 109.78 mmol, 1.2 equiv) was added to a solution of L-*tert*-leucine (**136**, 12.00 g, 91.48 mmol, 1.0 equiv) and sodium hydroxide (4.39 g, 109.78 mmol, 1.2 equiv) in a mixture of water and *tert*-butanol (120 mL of each). The reaction mixture was stirred at room temperature for two days. The organic and aqueous phases were then separated and the aqueous layer extracted with ethyl acetate (3 x 200 mL). The combined organic layers were extracted with a saturated solution of sodium bicarbonate (3 × 100 mL). The combined aqueous layers were acidified with hydrochloric acid (2N) until pH of 1.5-2.0 was reached and extracted with ethyl acetate (4 × 100 mL).

Finally, the combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude Boc-protected amino acid was purified by flash chromatography (50% of ethyl acetate in hexanes) to provide *N*-Boc-L-*tert*-leucine (**145**, 20.51 g, 88.68 mmol, 97% yield) as a colorless solid.

145: $C_{11}H_{21}NO_4$ (231.29 g/mol); **m.p.**: 119-124 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.55 (brs, 1H, CO_2***H***), 5.11 (br d, *J* = 9.5 Hz, 1H, N***H***Boc), 4.11 (d, *J* = 9.5 Hz, 1H, C***H***NHBoc), 1.44 (s, 9H, OC(C***H***$_3$)$_3$), 1.27 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.8 (***C***=O), 155.6 (***C***=O), 80.0 (O***C***(CH$_3$)$_3$), 61.6 (***C***HNHBoc), 34.5 (C***C***(CH$_3$)$_3$), 28.3 (C(***C***H$_3$)$_3$), 26.5 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 231 (0.3), 186 (1), 175 (22), 160 (4), 130 (16), 119 (97), 101 (37), 86 (9), 75 (12), 57 (100), 41 (18), 29 (9); **HRMS** (EIpos) calcd for ([$C_{11}H_{21}NO_4$+Na]$^+$): 254.1363, found: 254.1364.



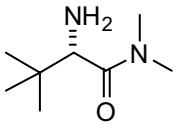
145 **146a** **144a**



Preparation of N-Boc-L-tert-leucine dimethylamide (**146a**): L-*tert*-Leucine dimethylamide (**144a**) was synthesized in analogy to the reported procedure.[210] DCC (2.14 g, 10.38 mmol, 1.2 equiv) was added to a solution of *N*-Boc-L-*tert*-leucine (**145**, 2.00 g, 8.65 mmol, 1.0 equiv) in dichloromethane (12 mL) at 0 °C, followed by the addition of a catalytic amount of DMAP (11 mg, 0.09 mmol, 0.01 equiv). After a few minutes a dichloromethane (4 mL) solution of dimethylamine (1.1 mL, 21.62 mmol, 2.5 equiv) was added. The mixture was stirred for 48 hours at room temperature and then filtered through celite. The solid residue was washed with ethyl acetate and the resulting filtrate concentrated under reduced pressure. The crude product was purified by flash column chromatography (15% of ethyl acetate in hexanes) yielding *N*-Boc-L-*tert*-leucine dimethylamide (**146a**, 1.80 g, 6.97 mmol, 81%) as a colorless solid.

146a: $C_{13}H_{26}N_2O3$ (258.36 g/mol); **m.p.**: 35-40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.33 (brd, *J* = 9.7 Hz, 1H, N***H***Boc), 4.51 (d, *J* = 6.1 Hz, 1H, C***H***NHBoc), 3.12 (s, 3H, NC***H***$_3$), 2.95 (s, 3H, NC***H***$_3$), 1.41 (s, 9H, OC(C***H***$_3$)$_3$), 0.96 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.9 (***C***=O), 156.0 (***C***=O), 79.2 (O***C***(CH$_3$)$_3$), 55.8 (***C***HNHBoc), 38.3 (N***C***H$_3$), 35.7

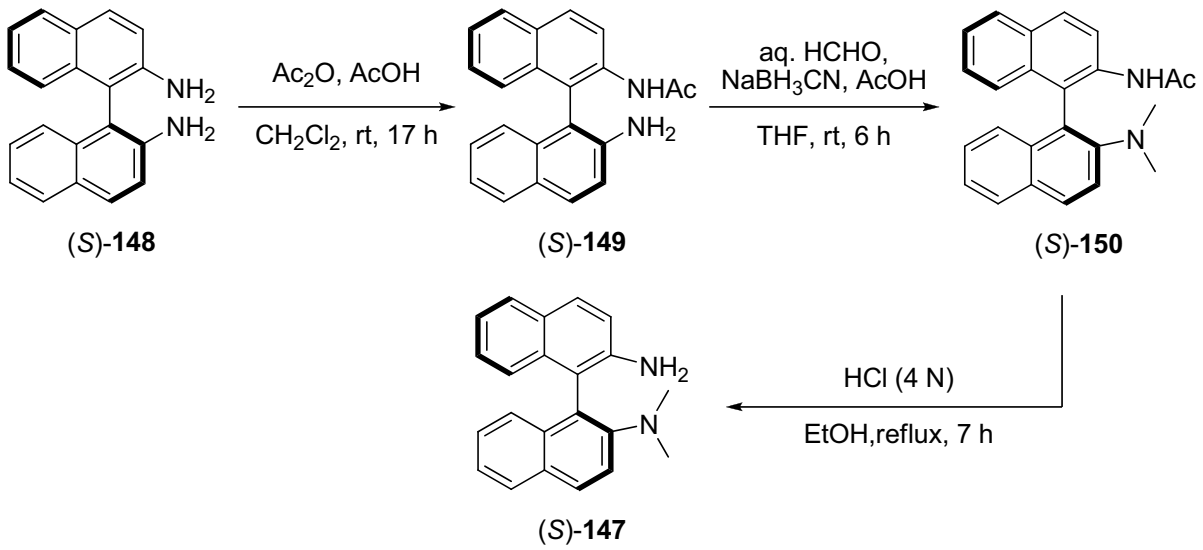
(C***C***$(CH_3)_3$), 35.5 (N***C***H_3), 28.3 (C(***C***$H_3)_3$), 26.5 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 258 (3), 186 (45), 146 (33), 130 (71), 112 (4), 101 (10), 86 (100), 72 (32), 57 (87), 41 (16), 29 (10); **HRMS** (EIpos) calcd for ([$C_{13}H_{26}N_2O_3$+Na]$^+$) 281.1836, found: 281.1834.



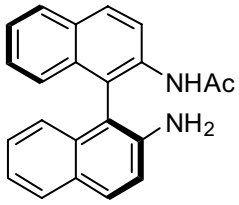
Preparation of L*-tert-leucine dimethylamide* (**144a**): Boc-L-*tert*-leucine dimethylamide (**146a**, 1.70g, 6.58 mmol) was then deprotected in neat TFA. For this purpose a slow addition of TFA (10.0 mL, 101.17 mmol, 15.0 equiv) was performed at 0°C. The reaction was stirred at room temperature for 30 minutes. The volatile compounds were removed *in vacuo* and the residue was dissolved in water and treated with an aqueous solution of potassium hydroxide (10%) at 0 °C to reach a basic pH. Dichloromethane (30 mL) was added to the solution and the two resulting layers were separated. The aqueous phase was then extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried over magnesium sulfate, filtrated and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% of methanol in dichloromethane) giving L-*tert*-leucine dimethylamide (**144a**, 1.00g, 6.32 mmol, 96%) as colorless oil.

144a: $C_8H_{18}N_2O$ (258.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.54 (s, 1H, C***H***NH_2), 3.06 (s, 3H, NC***H***$_3$), 2.94 (s, 3H, NC***H***$_3$), 1.91 (br s, 2H, N***H***$_2$), 0.95 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.3 (***C***=O), 57.5 (***C***HNH_2), 38.0 (N***C***H_3), 35.5 (***C***$(CH_3)_3$), 35.2 (N***C***H_3), 26.2 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 158 (1), 101 (25), 86 (100), 69 (15), 57 (6), 46 (27), 41 (11), 30 (6); **HRMS** (EIpos) calcd for ([$C_8H_{18}N_2O$+Na]$^+$): 181.1311, found: 181.1313. The physical data were identical in all respects to those previously reported.[98]

7.2.2.2 Synthesis of (*S*)-N^2,N^2-dimethyl-1,1'-binaphthyl-2,2'-diamine ((*S*)-147)[106]

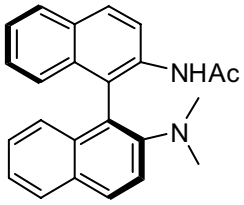


(*S*)-**148** (*S*)-**149** (*S*)-**150** (*S*)-**147**



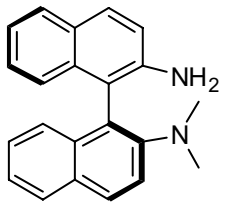
Preparation of (S)-N-(2'-amino-1,1'-binaphthyl-2-yl)acetamide ((*S*)-**149**):[106] To a solution of (*S*)-1,1'-binaphthyl-2,2'-diamine ((S)-**148,** 0.50 g, 1.76 mmol, 1.0 equiv) and acetic acid (1.0 mL, 17.58 mmol, 10.0 equiv) in dichloromethane (20 mL) was added acetic anhydride (166 µL, 1.76 mmol, 1.0 equiv) at 0 °C. The resulting solution was stirred at room temperature for twelve hours. A solution of sodium hydroxide (2 N) was then added to adjust the pH of the solution to 7. The two resulting layers were then separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. After the solvent was removed *in vacuo*, the crude product was purified by flash chromatography (30-50% of ethyl acetate in hexanes) to afford the amino acetamide (*S*)-**149** (0.46 g, 1.41 mmol, 80%) as a colorless oil.

(*S*)-**149**: $C_{22}H_{18}N_2O$ (326.39 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 8.9 Hz, 1H, C***H***$_{Ar}$), 8.00-7.80 (m, 4H, C***H***$_{Ar}$), 7.40-6.91 (m, 7H, C***H***$_{Ar}$), 7.01 (br s, 1H, N***H***Ac), 3.60 (brs, 2H, N***H***$_2$), 1.83 (s, 3H, CC***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.8 (***C***=O), 142.4 (***C***q$_{Ar}$), 135.1 (***C***q$_{Ar}$), 133.6 (***C***q$_{Ar}$), 132.4 (***C***q$_{Ar}$), 131.3 (***C***$_{Ar}$), 130.4 (***C***$_{Ar}$), 129.3 (***C***$_{Ar}$), 128.4 (***C***$_{Ar}$), 128.2 (***C***$_{Ar}$), 128.2 (***C***$_{Ar}$), 127.3 (***C***$_{Ar}$), 126.8 (***C***$_{Ar}$), 125.4 (***C***$_{Ar}$), 125.1 (***C***$_{Ar}$), 123.7 (***C***H$_{Ar}$), 122.9 (***C***H$_{Ar}$), 121.0 (***C***H$_{Ar}$), 120.6 (***C***H$_{Ar}$), 118.2 (***C***H$_{Ar}$), 111.0 (***C***H$_{Ar}$), 24.6 (***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 326 (53), 284 (28), 267 (100), 239 (4).



Preparation of (S)-N-(2'-(dimethylamino)-1,1'-binaphthyl-2-yl)acetamide ((S)-**150**):[106] Amino acetamide (*S*)-**149 (**0.45 g, 1.38 mmol, 1.0 equiv) and aqueous formaldehyde (37%, 1.20 mL, 15.90 mmol, 11.5 equiv) were combined in THF (10 mL) and stirred for 15 minutes. Sodium cyanoborohydride (0.60 g, 9.51 mmol, 6.9 equiv) was added. The solution was stirred for 15 minutes and acetic acid (1.8 mL) was added. The resulting solution was stirred for four hours at room temperature. A solution of sodium hydroxide (2 N) was then added to adjust the pH of the solution to 7. The two resulting layers were then separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. After the solvent was removed *in vacuo*, the crude product was purified by flash chromatography (5-20% of ethyl acetate in hexanes) to afford the dimethylamino acetamide (*S*)-**150** (0.41 g, 1.14 mmol, 83%) as a brown solid.

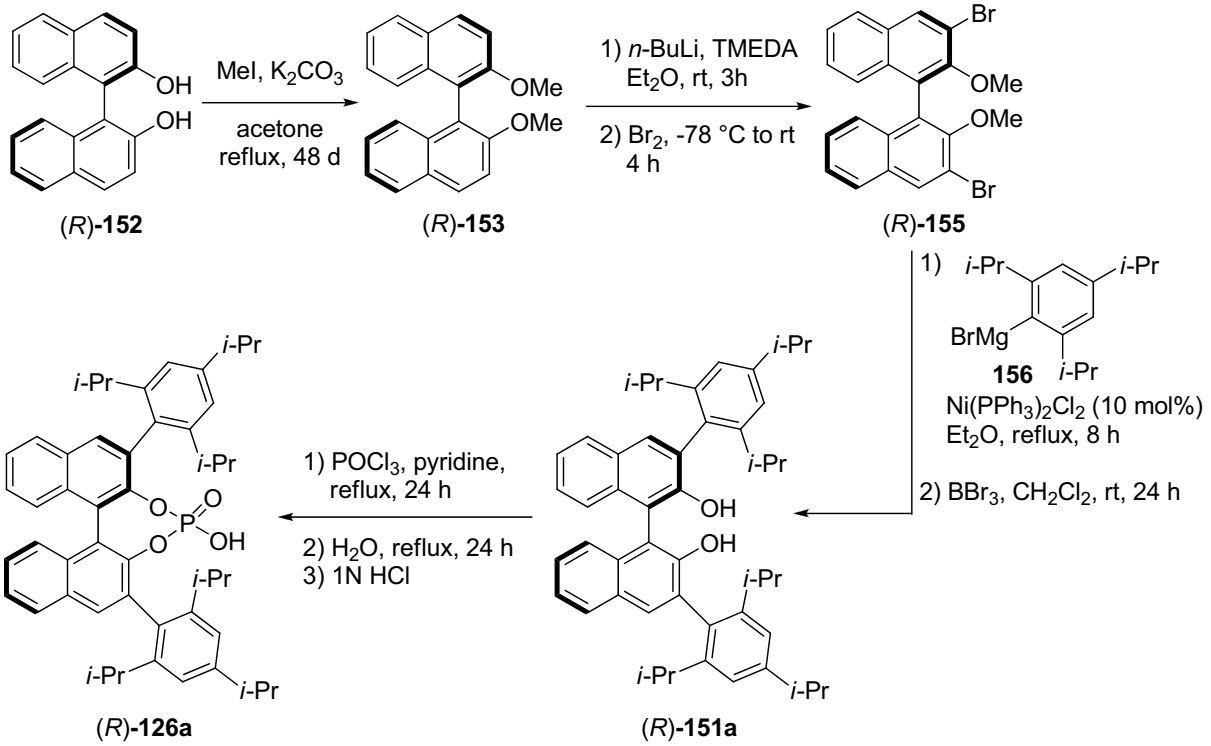
(*S*)-**150**: $C_{24}H_{22}N_2O$ (354.44 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.9 Hz, 1H, C***H***$_{Ar}$), 7.95-7.85 (m, 4H, C***H***$_{Ar}$), 7.48 (br s, 1H, N***H***Ac), 7.49-7.11 (m, 6H, C***H***$_{Ar}$), 6.92 (d, *J* = 8.6 Hz, 1H, C***H***$_{Ar}$), 2.56 (s, 6H, N(C***H***$_3$)$_2$), 1.75 (s, 3H, CC***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3 (***C***=O), 149.0 (***C***q$_{Ar}$), 133.7 (***C***q$_{Ar}$), 133.4 (***C***q$_{Ar}$), 131.2 (***C***q$_{Ar}$), 130.2 (***C***$_{Ar}$), 129.2 (***C***$_{Ar}$), 128.6 (***C***$_{Ar}$), 128.3 (***C***$_{Ar}$), 127.9 (***C***$_{Ar}$), 127.1 (***C***$_{Ar}$), 126.8 (***C***$_{Ar}$), 126.4 (***C***$_{Ar}$), 125.3 (***C***$_{Ar}$), 124.8 (***C***$_{Ar}$), 124.0 (***C***H$_{Ar}$), 122.8 (***C***H$_{Ar}$), 122.1 (***C***H$_{Ar}$), 121.6 (***C***H$_{Ar}$), 118.8 (***C***H$_{Ar}$), 113.2 (***C***H$_{Ar}$), 43.4 (N***C***H$_3$), 24.6 (C***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 354 (79), 340 (7), 311 (20), 294 (21), 281 (24), 267 (27), 198 (25), 157 (100).

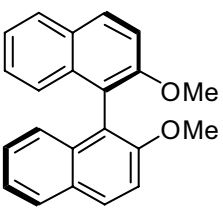


Preparation of (S)-N,N-dimethyl-1,1'-binaphthyl-2,2'-diamine ((*S*)-**147**):[106] To a solution of acetamide (*S*)-**150** (0.40 mg, 1.13 mmol) in ethanol (35 mL) was added a solution of hydrochloric acid (4 N, 13 mL). The resulting solution was stirred under reflux for seven hours. A solution of sodium hydroxide (2 N) was then added to adjust the pH of the solution to 7. The two resulting layers were then separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine and dried over magnesium sulfate. After the solvent was removed *in vacuo*, the crude product was purified by flash chromatography (10% of ethyl acetate in hexanes) to afford the free dimethylamino amine (*S*)-**147** (0.35 g, 1.12 mmol, quant.) as a colorless oil.

(S)-**147**: $C_{22}H_{20}N_2$ (312.40 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.9 Hz, 1H, C***H***$_{Ar}$), 7.81-7.75 (m, 3H, C***H***$_{Ar}$), 7.50 (br d, *J* = 8.9 Hz, 1H, C***H***$_{Ar}$), 7.20-7.08 (m, 6H, C***H***$_{Ar}$), 6.97 (d, *J* = 8.2 Hz, 1H, C***H***$_{Ar}$), 3.60 (brs, 2H, N***H***$_2$), 2.57 (s, 6H, N(C***H***$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.6 (***C***q$_{Ar}$), 142.0 (***C***q$_{Ar}$), 134.3 (***C***q$_{Ar}$), 133.6 (***C***q$_{Ar}$), 129.4 (***C***$_{Ar}$), 129.0 (***C***$_{Ar}$), 128.2 (***C***$_{Ar}$), 128.0 (***C***$_{Ar}$), 128.0 (***C***$_{Ar}$), 127.8 (***C***$_{Ar}$), 126.6 (***C***$_{Ar}$), 126.3 (***C***$_{Ar}$), 124.9 (***C***$_{Ar}$), 124.7 (***C***H$_{Ar}$), 123.9 (***C***H$_{Ar}$), 122.1 (***C***H$_{Ar}$), 119.7 (***C***H$_{Ar}$), 118.3 (***C***H$_{Ar}$), 116.9 (***C***H$_{Ar}$), 43.1 (N***C***H$_3$); **MS** (EI, 70 eV):: *m*/*z* (%) = 312 (100), 294 (8), 280 (22), 268 (27), 239 (5), 157 (61), 140 (8), 127 (6); **HRMS** (EIpos) calcd for ([$C_{22}H_{20}N_2$+H]$^+$): 313.1699, found: 313.1698. The physical data were identical in all respects to those previously reported.[106]

7.2.3 Synthesis BINOL Derived (*R*)-TRIP ((*R*)-126a)

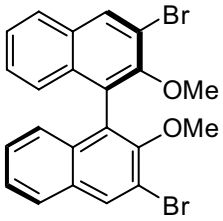




Preparation of (R)-2,2'-dimethoxy-1,1'-binaphthyl ((*R*)-**153**): A suspension of (*R*)-BINOL ((*R*)-**152**, 5.10 g, 17.81 mmol, 1.0 equiv) was heated at reflux in acetone (40 mL) to give a homogeneous solution. To this solution were added potassium carbonate (8.30 g, 60.00 mmol, 3.4 equiv) and methyl iodide (9.94 g, 70.00 mmol, 3.9 equiv), and the mixture was refluxed for 24 hours.

Additional methyl iodide (4.26 g, 30.00 mmol, 1.7 equiv) was added, and heating was continued for 12 hours. The solvent was evaporated to leave a volume of 30 mL, which was cooled to 25 °C and treated with water (160 mL). The mixture was stirred for eight hours, and the resulting solid was washed with water and dried under reduced pressure to afford the protected BINOL (*R*)-**153** (5.47 g, 17.40 mmol, 98%) as a white solid.

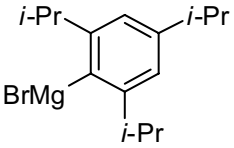
(*R*)-**153**: $C_{22}H_{18}O_2$ (314.38 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 7.78 (d, *J* = 8.1 Hz, 2H, C***H***$_{Ar}$), 7.37 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 7.23 (t, *J* = 7.3 Hz, 2H, C***H***$_{Ar}$), 7.12 (t, *J* = 7.4 Hz, 2H, C***H***$_{Ar}$), 7.02 (d, *J* = 8.5 Hz, 2H, C***H***$_{Ar}$), 3.68 (s, 6H, O***C***H$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.6 (***C***q$_{Ar}$), 133.7 (***C***q$_{Ar}$), 129.0 (***C***H$_{Ar}$), 128.9 (***C***q$_{Ar}$), 127.6 (***C***H$_{Ar}$), 125.9 (***C***H$_{Ar}$), 124.9 (***C***H$_{Ar}$), 123.1 (***C***H$_{Ar}$), 119.3 (***C***q$_{Ar}$), 113.9 (***C***H$_{Ar}$), 56.6 (O***C***H$_3$).



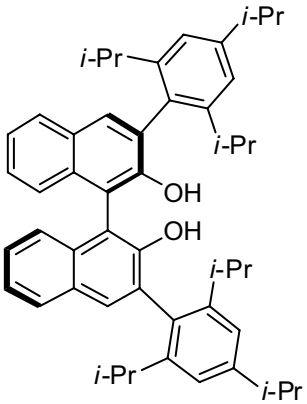
Preparation of (R)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl ((*R*)-**155**): To a solution of TMEDA (1.92 mL, 12.74 mmol, 2.2 equiv) in diethyl ether (100 mL) was added *n*-butyl lithium (1.6 M in hexane, 10.9 mL, 17.37 mmol, 3.0 equiv) at room temperature. After the solution was stirred for 15 minutes, solid (*R*)-**153**, 1.82 g, 5.79 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was stirred for three hours at room temperature. The resulting light brown suspension was cooled to −78 °C, and bromine (3.6 mL, 70.00 mmol, 12.0 equiv) was added over a period of ten minutes. The mixture was allowed to warm to room temperature, and after four hours, a saturated aqueous solution of sodium sulfate (60 mL) was added cautiously. The reaction mixture was stirred for an additional four hours, and diluted with diethyl ether and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography (8% of ethyl acetate in hexanes) providing the dibromo BINOL derivative (*R*)-**155** (1.94 g, 4.11 mmol, 71%) of as a pale yellow solid.

(*R*)-**155**: $C_{22}H_{16}Br_2O_2$ (472.17 g/mol); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.20 (s, 2H, C***H***$_{Ar}$), 7.74 (d, *J* = 8.5 Hz, 2H, C***H***$_{Ar}$), 7.34 (t, *J* = 7.5 Hz, 2H, C***H***$_{Ar}$), 7.19 (t, *J* = 7.5 Hz, 2H, C***H***$_{Ar}$), 7.00 (d, *J* = 8.0 Hz, 2H, C***H***$_{Ar}$), 3.43 (s, 6H, OC***H***$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.5 (***C***q$_{Ar}$), 133.1 (***C***q$_{Ar}$), 133.0 (***C***H$_{Ar}$), 131.4 (***C***q$_{Ar}$), 127.1 (***C***H$_{Ar}$), 126.9 (***C***H$_{Ar}$), 126.5 (***C***q$_{Ar}$), 125.9 (***C***H$_{Ar}$), 125.8 (***C***H$_{Ar}$), 117.5 (***C***q$_{Ar}$), 61.1 (O***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 474 (51),

472 (100), 470 (51), 426 (19), 376 (8), 361 (11), 239 (14), 156 (18), 125 (5), 120 (11), 113 (13); **HRMS** (EIpos) calcd for ($[C_{22}H_{16}Br_2O_2+Na]^+$): 492.9410, found: 492.9412.



Preparation of (2,4,6-triisopropylphenyl)magnesium bromide (**156**)**:** A three-neck round-bottom flask containing activated magnesium turnings (3.00 g, 125.00 mmol, 1.8 equiv) was equipped with a condenser and an addition funnel. A solution of 2,4,6-triisopropylphenyl bromide (1.4 M, 20.00 g in 50 mL of diethyl ether, 70.60 mmol, 1.0 equiv) was prepared, and 10 mL of this solution were added to the reaction mixture *via* the addition funnel. After five minutes, a catalytic amount of 1,2-dibromoethane (0.20 mL, 0.002 mmol) was added to the mixture. Once the solution began to reflux, the remaining 2,4,6-triisopropylphenyl bromide solution (40 mL) was slowly added over one hour. After the addition was complete, the reaction was allowed to reflux for 12 hours and then cooled to room temperature.

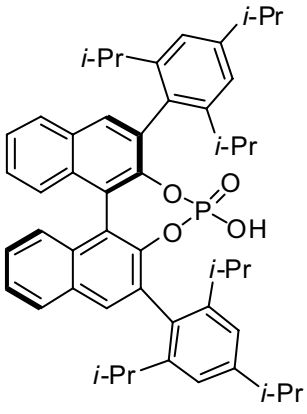


Preparation of (R)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol ((*R*)-**151a**)**:** (*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl ((*R*)-**155a**, 4.00 g, 8.50 mmol, 1.0 equiv) and bis(triphenylphosphine) nickel(II) dichloride (0.60 g, 0.90 mmol, 0.1 equiv) were suspended in diethyl ether (100 mL). To this suspension was added (2,4,6-triisopropylphenyl)magnesium bromide (**156**, 0.8 M in diethyl ether, 31.7 mL, 25.40 mmol, 3.0 equiv) slowly at room temperature. The mixture was stirred at room temperature for ten minutes and the resulting dark green solution was then refluxed for eight hours. The reaction was chilled to 0 °C and quenched slowly by the addition of a solution of hydrochloric acid (1.0 M, 50 mL). The resulting aqueous layer was separated from the organic phase and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to afford, after recrystallization from dichloromethane and hexanes, (*R*)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl (4.70 g, 6.64 mmol, 77%) as a colorless solid. This compound was then deprotected to yield (*R*)-**151a**.

For this purpose, a solution of (*R*)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl (4.00 g, 5.60 mmol, 1.0 equiv) in dichloromethane (150 mL) was slowly charged with a dichloromethane solution of boron tribromide (1.0 M, 39.0 mL, 38.90 mmol,

6.9 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 24 hours. The mixture was then cooled to 0 °C, and quenched by the slow addition of water (50 mL). After the two resulting phases were separated, the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and the solvent evaporated *in vacuo* to yield an colorless solid, which was washed with hexanes, filtered, and dried *in vacuo* to afford the diol (*R*)-**151a** (3.76 g, 5.44 mmol, 97% yield, i.e. 75% overall yield over two steps) as a white solid .

(*R*)-**151a**: $C_{50}H_{58}O_2$ (690.99 g/mol); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.1 Hz, 2H, C***H***$_{Ar}$), 7.69 (s, 2H, C***H***$_{Ar}$), 7.30 (t, *J* = 6.7 Hz, 2H, C***H***$_{Ar}$), 7.26-7.20 (m, 4H, C***H***$_{Ar}$), 7.05 (d, *J* = 8.3 Hz, 4H, C***H***$_{Ar}$), 4.85 (s, 2H, O***H***), 2.91-2.86 (m, 2H, C***H***$(CH_3)_2$), 2.80-2.75 (m, 2H, C***H***$(CH_3)_2$), 2.64-2.59 (m, 2H, C***H***$(CH_3)_2$), 1.24 (d, *J* = 6.9 Hz, 12H, CH(C***H***$_3)_2$), 1.12 (d, *J* = 6.8 Hz, 6H, CH(C***H***$_3)_2$), 1.04-1.00 (m, 12H, CH(C***H***$_3)_2$), 0.95 (d, *J* = 6.9 Hz, 6H, CH(C***H***$_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 150.6 (***C***q$_{Ar}$), 149.1 (***C***q$_{Ar}$), 147.8 (***C***q$_{Ar}$), 147.7 (***C***q$_{Ar}$), 133.4 (***C***q$_{Ar}$), 130.7 (***C***H$_{Ar}$), 130.4 (***C***q$_{Ar}$), 129.1 (***C***q$_{Ar}$), 129.0 (***C***q$_{Ar}$), 128.2 (***C***H$_{Ar}$), 126.6 (***C***H$_{Ar}$), 124.5 (***C***H$_{Ar}$), 123.8 (***C***q$_{Ar}$), 121.2 (***C***H$_{Ar}$), 121.2 (***C***H$_{Ar}$), 34.3 (***C***H), 30.9 (***C***H), 30.8 (***C***H), 24.3 (***C***H$_3$), 24.3 (***C***H$_3$), 24.1 (***C***H$_3$), 24.0 (***C***H$_3$), 23.9 (***C***H$_3$), 23.7 (***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 692 (14), 691 (53), 690 (100), 647 (2), 605 (2), 563 (2), 521 (2), 329 (4), 287 (5), 219 (3); **HRMS** (EIpos) calcd for ($[C_{50}H_{58}O_2+Na]^+$): 713.4329, found: 713.4332.



Preparation of (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((*R*)-**TRIP**, (*R*)-**126a**)**:** The diol (*R*)- **151a** (1.67 g, 2.42 mmol. 1.0 equiv) was suspended in pyridine (7.0 mL) in a two-necked flask. Phosphorous oxychloride (0.74 g, 0.46 mL, 4.84 mmol, 2.0 equiv) was added dropwise at room temperature with rapid stirring and the resulting suspension was refluxed for 24 hours until all of the starting material was consumed. The reaction mixture was then cooled to room temperature and water (2 mL) added very slowly. The resulting mixture was heated to 100 °C and stirred at this temperature for an additional 24 hours. The reaction mixture was diluted with dichloromethane and the pyridine was removed through washing by hydrochloric acid (1 N). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash column chromatography (2-10% of

isopropanol in dichloromethane) yielding (*R*)-**TRIP** ((*R*)-**126a**, 1.73 g, 2.30 mmol, 95%) as a colorless solid.

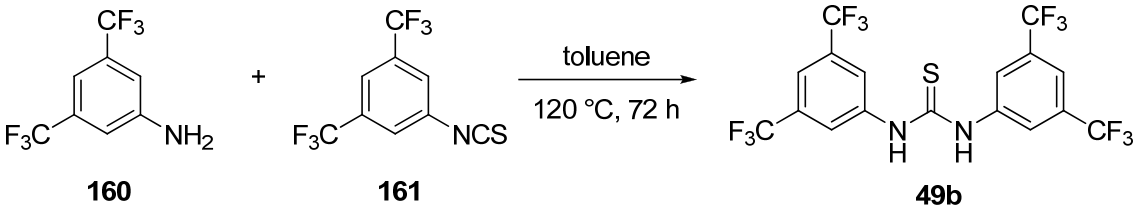
(*R*)-**126a**: $C_{50}H_{57}O_4P$ (752.96 g/mol); **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.00 (d, *J* = 8.1 Hz, 2H, C***H***$_{Ar}$), 7.93 (s, 2H, C***H***$_{Ar}$), 7.43 (t, *J* = 7.2 Hz, 2H, C***H***$_{Ar}$), 7.29 (t, *J* = 7.3 Hz, 2H, ***H***$_{Ar}$), 7.06 (d, *J* = 1.5 Hz, 2H, C***H***$_{Ar}$), 7.00 (s, 1H, C***H***$_{Ar}$), 6.98 (s, 3H, C***H***$_{Ar}$), 2.87-2.82 (m, 2H, C***H***$(CH_3)_2$), 2.65-2.60 (m, 2H, C***H***$(CH_3)_2$), 2.48-2.43 (m, 2H, C***H***$(CH_3)_2$), 1.18 (dd, *J* = 1.6, 6.9 Hz, 12H, CH(C***H***$_3)_2$), 1.09 (d, *J* = 6.9 Hz, 6H, CH(C***H***$_3)_2$), 1.05 (d, *J* = 6.7 Hz, 6H, CH(C***H***$_3)_2$), 1.00 (d, *J* = 6.9 Hz, 6H, CH(C***H***$_3)_2$), 0.83 (d, *J* = 6.8 Hz, 6H, CH(C***H***$_3)_2$); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 147.8 (***C***q$_{Ar}$), 147.3 (***C***q$_{Ar}$), 146.5 (***C***q$_{Ar}$), 145.9 (***C***q$_{Ar}$), 145.8 (***C***q$_{Ar}$), 132.3 (***C***H$_{Ar}$), 131.7 (***C***q$_{Ar}$), 131.6 (***C***q$_{Ar}$), 130.4 (***C***q$_{Ar}$), 128.5 (***C***H$_{Ar}$), 126.7 (***C***H$_{Ar}$), 125.7 (***C***H$_{Ar}$), 125.6 (***C***H$_{Ar}$), 121.2 (***C***q$_{Ar}$), 120.8 (***C***H$_{Ar}$), 119.9 (***C***H$_{Ar}$), 33.6 (***C***H), 30.7 (***C***H), 30.3 (***C***H), 26.2 (***C***H$_3$), 24.6 (***C***H$_3$), 24.1 (***C***H$_3$), 24.0 (***C***H$_3$), 23.2 (***C***H$_3$), 22.8 (***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 754 (15), 753 (50), 752 (91), 709 (100), 667 (36), 625 (36), 583 (27), 541 (29), 313 (13); **HRMS** (EIneg) calcd for ($[C_{50}H_{56}O_4P]^-$): 751.3922, found: 751.3926. The enantiomers were analyzed by HPLC using a Chiralpak OD-H column (mobile phase: heptane/methanol/TFA = 10:90:0.1, 0.5 mL/min); (*S*)-**126a**: t_R = 20.6 min, (*R*)-**126a**: t_R = 24.8 min.

7.3 Synthesis of Hydrogen Bonding (Thio)ureas

All the (thio)urea catalysts reported in this chapter were synthesized by the author of this Ph.D. thesis. The missing catalysts (i.e. **50**, **67a**, **164b**) were prepared by colleagues and kindly shared.

7.3.1 Synthesis of Mono(thio)ureas

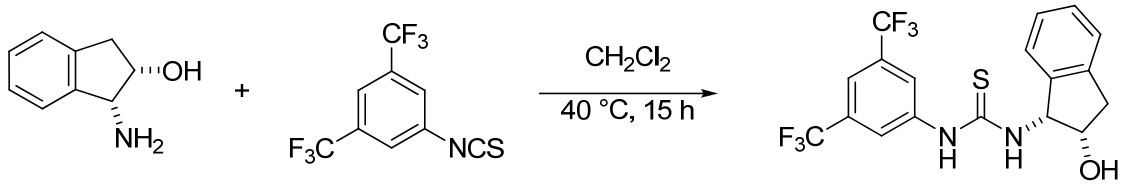
7.3.1.1 Synthesis of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (49b)[218]



3,5-Bis(trifluoromethyl)aniline (**160**, 0.73 mL, 4.61 mmol, 1.2 equiv) was added to a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**, 0.72 mL, 3.84 mmol, 1.0 equiv) in toluene (10 mL). The resulting mixture was refluxed at 120 °C for 72 hours. After evaporation of the solvent *in vacuo*, the crude product was purified by recrystallization from chloroform once, and the resulting slightly yellow solid, was dissolved in a minimum amount of diethyl ether to be re-precipitated by addition of hexanes. The pure thiourea **49b** (1.54 g, 3.08 mmol, 80%) was obtained as a colorless solid.

49b: $C_{17}H_8F_{12}N_2S$ (500.30 g/mol); **m.p.**: 169-174 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 8.23 (s, 4H, C***H***$_{Ar}$), 7.70 (s, 2H, C***H***$_{Ar}$), 4.59 (br s, 2H, N***H***); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 182.9 (***C***=S), 143.0 (***C***q$_{Ar}$), 133.4 (***C***H$_{Ar}$), 126.4 (***C***q$_{Ar}$), 125.2 (C***C***F$_3$), 123.7 (***C***H$_{Ar}$), 119.4 (***C***H$_{Ar}$); **MS** (EI, 70 eV): *m*/*z* (%) = 500 (34), 481 (12), 271 (25), 252 (10), 229 (100), 213 (21), 182 (6); **HRMS** (EI) calcd for [$C_{17}H_8F_{12}N_2S$]: 500.0217, found: 500.0215. The physical data were identical in all respects to those previously reported.[218]

7.3.1.2 Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)thiourea (162)[219]

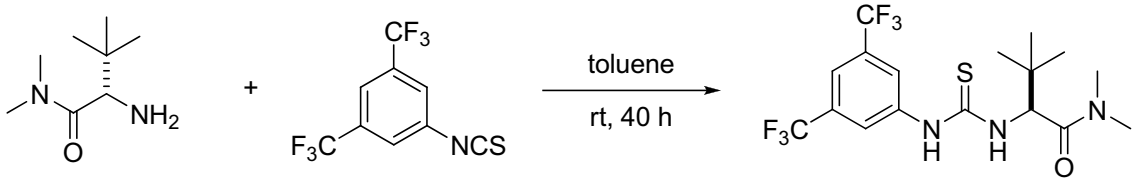


163 **161** **162**

To a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**, 0.51 mL, 2.79 mmol, 1.0 equiv) in dichloromethane (7 mL) was added (1*R*,2*S*)-*cis*-1-amino-2-indanol (**163**, 0.50 g, 3.35 mmol, 1.2 equiv) in one portion. The resulting solution was heated at 40 °C for 15 hours. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (1% of methanol in dichloromethane), providing the thiourea **162** (1.17 g, 2.78 mmol, >99%) as a colorless solid.

162: $C_{18}H_{14}F_6N_2OS$ (420.37 g/mol); **m.p.**: 78-83°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.70 (br s, 1H, N***H***), 7.81 (s, 2H, C***H***$_{Ar}$), 7.61 (s, 1H, C***H***$_{Ar}$), 7.32-7.06 (m, 5H: C***H***$_{Ar}$ (4H), C***H*** (1H)), 5.83 (brs, 1H, O***H***), 4.63-4.60 (m, 1H, C***H***), 3.10 (dd, *J* = 16.8, 5.2 Hz, 1H, C***H***$_2$), 2.79 (d, *J* = 16.9 Hz, 1H, C***H***$_2$), 2.33 (br s, 1H, N***H***); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 180.7 (***C***=S), 139.5 (***C***q$_{Ar}$), 139.2 (***C***q$_{Ar}$), 138.9 (***C***q$_{Ar}$), 132.5 (***C***$_{Ar}$CF$_3$), 128.7 (***C***H$_{Ar}$), 127.3 (***C***H$_{Ar}$), 125.4 (***C***H$_{Ar}$), 124.6 (***C***H$_{Ar}$), 124.1 (C***C***F$_3$), 123.5 (***C***H$_{Ar}$), 121.4 (***C***H$_{Ar}$), 119.1 (***C***H$_{Ar}$), 73.7 (***C***H), 62.8 (***C***H), 39.7 (***C***H$_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 421 (0.01), 402 (100), 386 (13), 343 (6), 271 (17), 252 (7), 213 (9), 174 (14), 148 (21), 131 (65), 115 (21), 91 (5), 77 (8); **HRMS** (EIpos) calcd for ([$C_{18}H_{14}F_6N_2OS$+Na]$^+$): 443.0623, found: 443.0626. The physical data were identical in all respects to those previously reported.[219]

7.3.1.3 Synthesis of (*S*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-*N*,*N*,3,3-tetramethylbutanamide (164a)



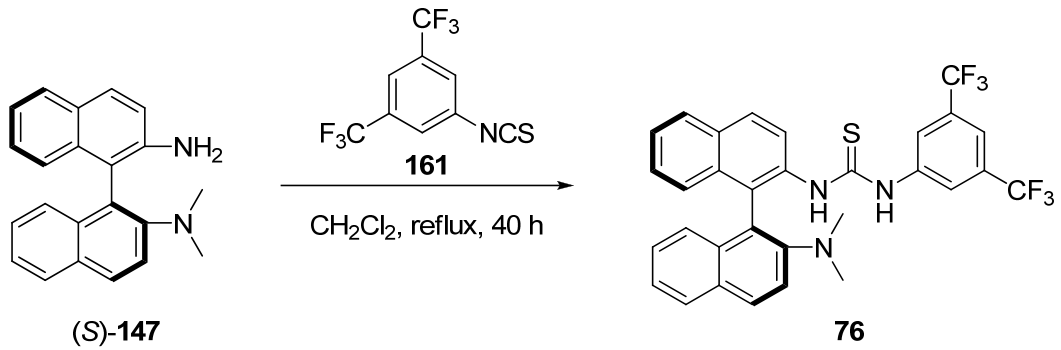
144a **161** **164a**

To a solution of L-*tert*-leucine dimethylamide (**144a**, 0.35 g, 2.21 mmol, 1.0 equiv) in toluene (5 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**, 0.5 mL, 2.74 mmol,

1.2 equiv). The reaction mixture was stirred for 41 hours at room temperature and then concentrated *in vacuo*. The crude product was purified by flash chromatography (25% of ethyl acetate in hexanes) to yield thiourea **164a** (0.86g, 1.99 mmol, 90%) as a colorless solid.

164a: $C_{17}H_{21}F_6N_3OS$ (429.42 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.33 (br s, 1H, $C_{Ar}N\boldsymbol{H}$), 7.96 (s, 2H, $C\boldsymbol{H}_{Ar}$), 7.89 (d, *J* = 9.0 Hz, 1H, CHN***H***), 7.55 (br s, 1H, $C\boldsymbol{H}_{Ar}$), 5.64 (d, *J* = 9.1 Hz, 1H, $C\boldsymbol{H}C(CH_3)_3$), 3.35 (s, 3H, $NC\boldsymbol{H}_3$), 2.97 (s, 3H, $NC\boldsymbol{H}_3$), 1.12 (s, 9H, $C(C\mathbf{H}_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 181.7 (***C***=S), 173.7 (***C***=O), 140.3 ($\boldsymbol{C}q_{Ar}$), 131.7 ($\boldsymbol{C}q_{Ar}CF_3$), 131.3 ($\boldsymbol{C}q_{Ar}CF_3$), 124.9 ($\boldsymbol{C}H_{Ar}$), 123.4 ($C\boldsymbol{C}F_3$), 121.3 ($\boldsymbol{C}H_{Ar}$), 117.9 ($\boldsymbol{C}H_{Ar}$), 117.8 ($\boldsymbol{C}H_{Ar}$), 60.7 ($\boldsymbol{C}HC(CH_3)_3$), 38.9 ($N\boldsymbol{C}H_3$), 36.1 ($\boldsymbol{C}(CH_3)_3$), 35.8 ($N\boldsymbol{C}H_3$), 27.1 ($C(\boldsymbol{C}H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 429 (5), 410 (2), 384 (44), 369 (46), 328 (5), 300 (2), 272 (13), 252 (6), 213 (6), 194 (2), 163 (2), 145 (3), 101 (11), 86 (77), 72 (29), 46 (100); **HRMS** (EIpos) calcd for $[(C_{17}H_{21}F_6N_3OS+Na]^+]$: 452.1202, found: 452.1202.

7.3.1.4 (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(2'-(dimethylamino)-1,1'-binaphthyl-2-yl)thiourea (76)

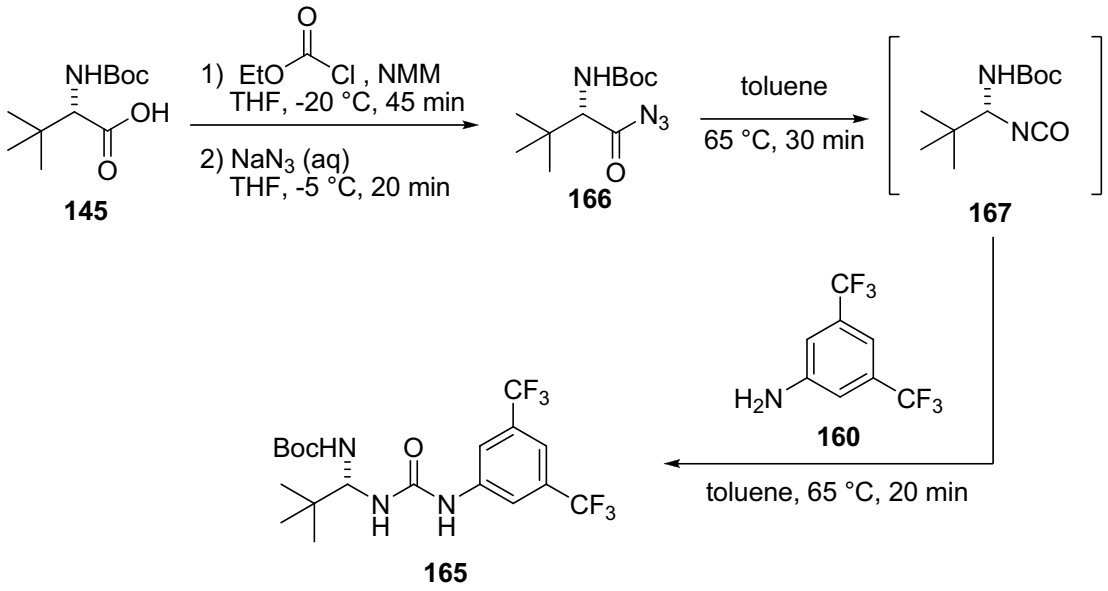


For the synthesis of (*S*)-*N*,*N*-dimethyl-1,1'-binaphthyl-2,2'-diamine ((*S*)-**147**) see Chapter 7.2.2.2.

To a solution of diamine (*S*)-**147** (87 mg, 0.28 mmol, 1.0 equiv) in dichloromethane (1 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**, 67 µL, 0.36 mmol, 1.3 equiv). The reaction mixture was stirred for 40 hours at reflux and then concentrated *in vacuo*. The crude product was purified by flash chromatography (10-20% of ethyl acetate in hexanes) to yield thiourea **76** (155 mg, 2.65 mmol, 95%) as a pale yellow solid.

76: $C_{31}H_{23}F_6N_3S$ (583.59 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.30 (s, 1H, N***H***), 8.02 (d, *J* = 8.7 Hz, 1H, C***H***$_{Ar}$), 7.94 (d, *J* = 8.2 Hz, 2H, C***H***$_{Ar}$), 7.82-7.76 (m, 2H, C***H***$_{Ar}$), 7.62 (m, 2H (1H, C***H***$_{Ar}$, 1H, N***H***)), 7.50-7.46 (m, 3H, C***H***$_{Ar}$), 7.31-7.26 (m, 4H, C***H***$_{Ar}$), 7.11 (t, *J* = 7.5 Hz, 1H, C***H***$_{Ar}$), 6.89 (d, *J* = 8.4 Hz, 1H, C***H***$_{Ar}$), 2.55 (s, 6H, N(C***H***$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 179.7 (C=S), 149.9 (***C***q$_{Ar}$), 139.6 (***C***q$_{Ar}$), 134.0 (***C***q$_{Ar}$), 133.3 (***C***q$_{Ar}$), 133.2 (***C***q$_{Ar}$), 132.9 (***C***q$_{Ar}$), 132.0 (***C***q$_{Ar}$), 131.8 (***C***H$_{Ar}$), 131.6 (***C***q$_{Ar}$), 130.5 (***C***q$_{Ar}$CF$_3$), 130.0 (***C***H$_{Ar}$), 129.9 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 128.4 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 127.2 (***C***H$_{Ar}$), 126.8 (***C***H$_{Ar}$), 125.0 (***C***H$_{Ar}$), 124.6 (***C***H$_{Ar}$), 124.2 (***C***H$_{Ar}$), 123.9 (C***C***F$_3$), 122.9 (***C***H$_{Ar}$), 121.8 (***C***H$_{Ar}$), 118.9 (***C***H$_{Ar}$), 44.0 (N(***C***H$_3$)$_2$); ; **MS** (EI, 70 eV): *m*/*z* (%) = 583 (5), 354 (5), 312 (100), 294 (10), 271 (90), 252 (17), 213 (21), 157 (64), 69 (5); **HRMS** (EIpos) calcd for [($C_{31}H_{23}F_6N_3S$+Na]$^+$]: 606.1409, found: 606.1405. The physical data were identical in all respects to those previously reported.[106]

7.3.1.5 (*S*)-tert-Butyl 1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2,2-dimethyl-propylcarbamate (165)



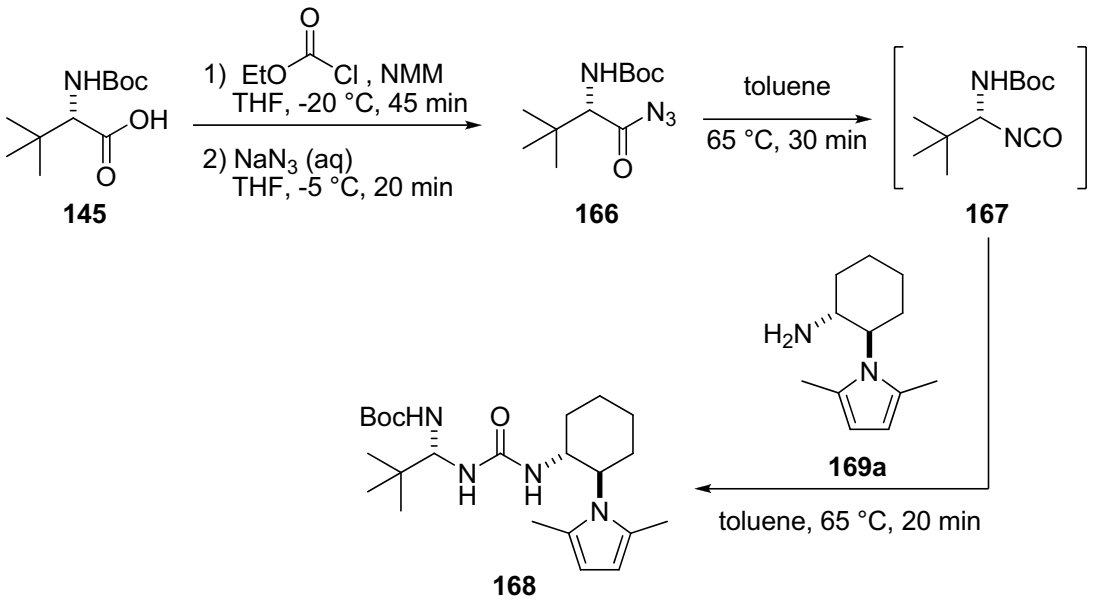
N-Boc-L-tert-leucine (**145**, 1.00 g, 4.32 mmol, 1.0 equiv) was dissolved in THF (13 mL) and cooled to -20 °C. After addition of ethylchloroformate (0.45 mL, 4.76 mmol, 1.1 equiv) and *N*-methylmorpholine (0.52 mL, 4.76 mmol, 1.1 equiv), the mixture was stirred at -20 °C for 45 minutes. The resulting white suspension was allowed to warm to -5 °C and was treated with a solution of sodium azide (0.70 g, 10.81 mmol, 2.5 equiv) in water (2 mL). The mixture was stirred for 20 minutes, diluted with ethyl acetate, washed with brine, dried over

magnesium sulfate, filtered and concentrated under reduced pressure to give the acyl azide **166** which was used without further purification.

Toluene was added to the compound **166** and the resulting solution heated to 65 °C under stirring. After the gas evolution had stopped (after ca. 30 minutes), the amine **160** (0.67 mL, 4.32 mmol, 1.0 equiv) was added. The mixture was stirred at 65 °C for 20 minutes, leading to the formation of a solid. This solid solid was filtered and washed with cold pentane, yielding pure urea **165** (0.55 g, 1.20 mmol, 28%) as a colorless solid.

165: $C_{19}H_{25}F_6N_3O_3$ (457.41 g/mol); **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.41 (br s, 1H, N***H***), 8.05 (s, 2H, C$\boldsymbol{H}_{Ar}$), 7.60 (br s, 1H, C$\boldsymbol{H}_{Ar}$), 7.17 (br s, 1H, N***H***), 6.45 (br s, 1H, N***H***), 5.17 (br s, 1H, C***H***C(CH$_3$)$_3$), 1.42 (br s, 9H, OC(C***H***$_3$)$_3$), 0.91 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 154.8 (***C***=O), 153.8 (***C***=O), 149.9 (NH***C***q$_{Ar}$), 142.3 (***C***CF$_3$), 130.7 (d, *J* = 32.5 Hz, (Cq$_{Ar}$***C***F$_3$), 117.1 (***C***H$_{Ar}$), 113.7 (***C***H$_{Ar}$), 77.9 (O***C***(CH$_3$)$_3$, 64.1 (***C***HNHBoc), 37.0 (C***C***(CH$_3$)$_3$), 28.2 (OC(***C***H$_3$)$_3$), 25.3 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 457 (3), 400 (12), 344 (79), 300 (14), 229 (23), 130 (35), 89 (39), 86 (61), 70 (26), 57 (100), 41 (18); **HRMS** (EIpos) calcd for [(C$_{19}$H$_{25}$F$_6$N$_3$O$_3$+Na]$^+$]: 480.1692, found: 480.1692.

7.3.1.6 tert-Butyl-(*S*)-1-(3-((1*R*,2*R*)-2-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl)-ureido)-2,2-dimethylpropylcarbamate (168)



N-Boc-L-tert-leucine (**145**, 1.00 g, 4.32 mmol, 1.0 equiv) was dissolved in THF (13 mL) and cooled to -20 °C. After addition of ethylchloroformate (0.45 mL, 4.76 mmol, 1.1 equiv) and *N*-methylmorpholine (0.52 mL, 4.76 mmol, 1.1 equiv), the mixture was stirred at -20 °C for

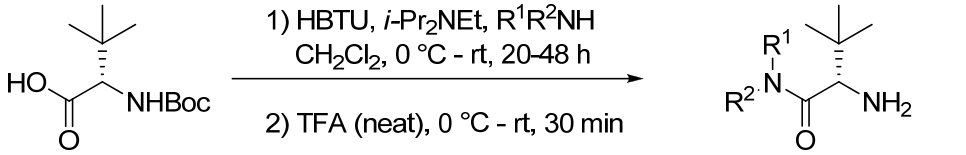
45 minutes. The resulting white suspension was allowed to warm to -5 °C and was treated with a solution of sodium azide (0.70 g, 10.81 mmol, 2.5 equiv) in water (2 mL). The mixture was stirred for 20 minutes, diluted with ethyl acetate, washed with brine, dried over over magnesium sulfate, filtered and concentrated under reduced pressure to give the acyl azide **166** which was used without further purification.

Toluene was added to the compound **166** and the resulting solution heated to 65 °C under stirring. After the gas evolution stopped (after ca. 30 minutes), the amine **169a** (0.83 g, 4.32 mmol, 1.0 equiv) was added. The mixture was stirred at 65 °C for 20 minutes, leading to the formation of a solid. After the solid was filtered and washed with cold pentane, pure thiourea **168** (1.70 g, 4.04 mmol, 93%) was obtained as a pale red solid.

168: $C_{23}H_{40}N_4O_3$ (420.59 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.37 (br s, 1H, N***H***), 5.68 (br s, 1H, N***H***), 5.65 (s, 2H, C***H***$_{Ar}$), 4.87 (d, *J* = 9.0 Hz, 1H, CHN***H***Boc), 4.70 (d, *J* = 8.9 Hz, 1H, C***H***NHBoc), 4.28-4.23 (m, 1H, NHC***H*** cycl.), 3.80-3.74 (m, 1H, NC***H*** cycl.), 2.37-2.30 (br s, 6H, C_{Ar}C***H***$_3$), 2.03-1.70 (m, 6H, C***H***$_2$ cycl.), 1.42 (s, 9H, OC(C***H***$_3$)$_3$), 0.97 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 183.9 (***C***=O), 157.4 (***C***=O), 129.3 (***C***q$_{Ar}$), 126.8 (***C***q$_{Ar}$), 108.7 (***C***H$_{Ar}$), 106.2 (***C***H$_{Ar}$), 80.4 (O***C***(CH$_3$)$_3$, 66.5 (N***C***H cycl.), 60.4 (***C***HNHBoc), 51.3 (N***C***H cycl.), 34.7 (***C***H$_2$ cycl.), 34.3 (C***C***(CH$_3$)$_3$), 32.0 (***C***H$_2$ cyclic), 28.2 (OC(***C***H$_3$)$_3$), 26.1 (C(***C***H$_3$)$_3$), 25.9 (***C***H$_2$ cycl.), 25.4 (***C***H$_{3\ pyrrolyl}$), 25.3 (***C***H$_2$ cycl.), 25.0 (***C***H$_{3\ pyrrolyl}$), 25.4 (***C***H$_{3\ pyrrolyl}$); **MS** (EI, 70 eV): *m*/*z* (%) = 420 (28), 364 (8), 303 (21), 218 (27), 175 (6), 130 (15), 86 (27), 57 (100); **HRMS** (EIpos) calcd for [($C_{23}H_{40}N_4O_3$+Na)$^+$]: 443.2992, found: 443.2990.

7.3.2 Synthesis of *Jacobsen*-Type Monothioureas

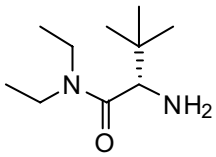
7.3.2.1 Synthesis of L-*tert*-Leucine Derived Amides (144a-d)



145

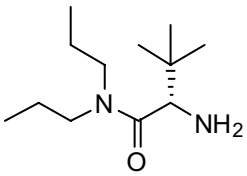
144b: $R^1 = R^2 = Et$
144c: $R^1 = R^2 = Bn$
144d: $R^1 = R^2 = n\text{-Pr}$
144e: $R^1 = Bn$, $R^2 = Me$
144f: $R^1 = Bn$, $R^2 = H$

Amino amide **144c** and **144f** were prepared by *M. Hannappel* according to the protocol I gave her. For these reason, the preparation and characteristics of these compounds is not described here.



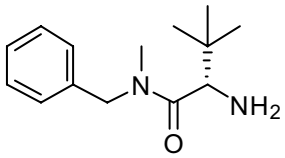
Preparation of (S)-2-amino-N,N-diethyl-3,3-dimethylbutanamide (**144b**): To a solution of *N*-Boc-L-*tert*-leucine (**145**, 4.00 g, 17.29 mmol, 1.0 equiv) in dichloromethane (150 mL) was added HTBU (7.21 g, 19.02 mmol, 1.1 equiv). The white suspension was stirred for five minutes, followed by the addition of diisopropylethylamine (3.5 mL, 20.75 mmol, 1.2 equiv) and diethylamine (2.0 mL, 19.02 mmol, 1.1 equiv). The reaction mixture was then stirred for 48 hours at room temperature. The mixture was combined with dichloromethane and water and the organic layer was separated, washed with hydrochloric acid (1N, 3 × 50 mL), and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield the crude Boc-protected amide as a colorless oil. The oil was dissolved in TFA (20 mL) at 0 °C. The reaction mixture was then stirred for one hour at room temperature. All volatile compounds were removed *in vacuo* and the residue was dissolved in water and treated with potassium hydroxide (10% aqueous solution) at 0 °C. The resulting mixture was extracted with dichloromethane and the combined organic layers were dried over magnesium sulfate. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography (5-10% of ethyl acetate in hexanes) yielding L-*tert*-leucine diethylamide (**144b**, 2.90 g, 15.57 mmol, 90%) as a colorless oil.

144b: $C_{10}H_{22}N_2O$ (186.29 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.73-3.67 (m, 1H, C***H***$_2$CH$_3$), 3.60-3.54 (m, 1H, C***H***$_2$CH$_3$), 3.38 (s, 1H, C***H***NH$_2$), 3.21-3.15 (m, 1H, C***H***$_2$CH$_3$), 3.09-3.03 (m, 1H, C***H***$_2$CH$_3$), 1.64 (br s, 2H, N***H***$_2$), 1.74 (t, *J* = 7.2 Hz, 3H, CH$_2$C***H***$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, CH$_2$C***H***$_3$), 0.97 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.8 (***C***=O), 57.7 (***C***HNH$_2$), 42.4 (***C***H$_2$CH$_3$), 40.3 (***C***H$_2$CH$_3$), 35.1 (***C***(CH$_3$)$_3$), 26.4 (C(***C***H$_3$)$_3$), 14.7 (CH$_2$***C***H$_3$), 13.0 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 186 (3), 129 (20), 100 (4), 86 (100), 72 (11), 58 (4), 44 (6), 29 (7); **HRMS** (EI-FE) calcd for [$C_{10}H_{22}N_2O$]: 186.1732, found: 186.1732.



Preparation of (S)-2-amino-3,3-dimethyl-N,N-dipropylbutanamide (**144d**): Following the procedure described for amino amide **144b**, amino amide **144d** was synthesized starting from *N*-Boc-L-*tert*-leucine (**145**, 5.00 g, 17.29 mmol, 1.0 equiv) and dipropylamine (2.6 mL, 19.02 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 48 hours. After work-up, the crude product was purified by flash chromatography (2-5% of methanol in dichloromethane) to yield amino amide **144d** (3.30 g, 15.40 mmol, 89%) as a pale orange oil.

144d: $C_{12}H_{26}N_2O$ (214.35 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.72-3.65 (m, 1H, NC***H***$_2$CH$_2$), 3.44-3.52 (m, 1H, NC***H***$_2$CH$_2$), 3.38 (s, 1H, C***H***NH$_2$), 3.11-3.01 (m, 1H, NC***H***$_2$CH$_2$), 2.91-2.85 (m, 1H, NC***H***$_2$CH$_2$), 1.60-1.52 (br m, 6H: N***H***$_2$ (2H), CH$_2$C***H***$_2$CH$_3$ (4H)), 0.97 (s, 9H, C(C***H***$_3$)$_3$), 0.91-0.87 (m, 6H, CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.4 (***C***=O), 57.8 (***C***HNH$_2$), 50.2 (N***C***H$_2$), 48.1 (N***C***H$_2$), 35.1 (***C***(CH$_3$)$_3$), 26.7 (C(***C***H$_3$)$_3$), 22.7 (***C***H$_2$CH$_3$), 21.0 (***C***H$_2$CH$_3$), 11.5 (CH$_2$***C***H$_3$), 11.2 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 214 (3), 157 (17), 128 (2), 100 (8), 86 (100), 69 (5), 41 (6); **HRMS** (EI-FE) calcd for [$C_{12}H_{26}N_2O$]: 214.2045, found: 214.2044.

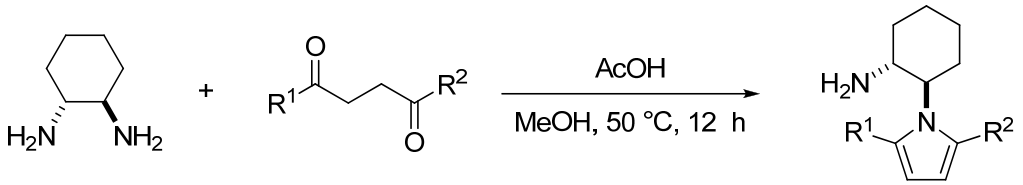


Preparation of (S)-2-amino-N-benzyl-N,3,3-trimethylbutanamide (**144e**): Following the procedure described for amino amide **144b**, amino amide **144e** was synthesized starting from *N*-Boc-L-*tert*-leucine (**145**, 5.00 g, 17.29 mmol, 1.0 equiv) and methylbenzylamine (2.5 mL, 19.02 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 20 hours. After work-up, the crude product was purified by flash chromatography (3-8% of methanol in

dichloromethane) to yield amino amide **144e** (3.70 g, 15.79 mmol, 91%) as a yellow-orange oil.

144e: $C_{14}H_{22}N_2O$ (234.34 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$; the compound is obtained as a ~4:2 mixture of rotamers: the major rotamer is denoted by "*"): δ 7.36-7.19 (m, 5H, C***H***$_{Ar}$), 4.95 (d, *J* = 15.3 Hz, 1H, PhC***H***$_2$), 4.73 (d, *J* = 14.5 Hz, 1H, PhC***H***$_2$*), 4.48 (d, *J* = 15.2 Hz, 1H, PhC***H***$_2^*$), 4.31 (d, *J* = 15.6 Hz, 1H, PhC***H***$_2$), 3.54 (s, 1H, C***H***NH_2^*), 3.49 (s, 1H, C***H***NH_2), 2.97 (m, 1H, NC***H***$_3^*$), 2.94 (m, 1H, NC***H***$_3$), 1.62 (br s, 2H, N***H***$_2$), 0.99 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$; compound exists as a ~4:2 mixture of rotamers: the major rotamer is denoted by "*"): δ 175.5 (***C***=O), 174.8 (***C***=O*), 137.3 (***C***q_{Ar}*), 136.7 (***C***q_{Ar}), 128.9 (***C***H_{Ar}*), 128.5 (***C***H_{Ar}), 128.6 (***C***H_{Ar}*), 128.3 (***C***H_{Ar}), 128.2 (***C***H_{Ar}*), 127.7 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 127.4 (***C***H_{Ar}*), 126.4 (***C***H_{Ar}*), 58.0 (***C***HNH_2), 57.9 (***C***HNH_2*), 53.1 (N***C***H_2), 51.1 (N***C***H_2*), 35.5 (***C***$(CH_3)_3$), 35.5 (***C***$(CH_3)_3$*), 35.5 (N***C***H_3), 34.1 (N***C***H_3*), 26.3 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m/z* (%) = 234 (1), 177 (8), 148 (1), 120 (6), 91 (39), 86 (100), 69 (7), 57 (2), 41 (5); **HRMS** (EIpos) calcd for [($C_{14}H_{22}N_2O$+Na)$^+$]: 257.1624, found: 257.1626.

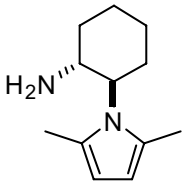
7.3.2.2 Synthesis of Pyrrolylcyclohexanamine Derivatives (169a-d)[90]



171

175a: $R^1 = R^2$ = Me
175b: $R^1 = R^2$ = Et
175c: R^1 = Me, R^2 = Ph
175d: $R^1 = R^2$ = Ph

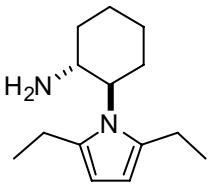
169a: $R^1 = R^2$ = Me
169b: $R^1 = R^2$ = Et
169c: R^1 = Me, R^2 = Ph
169d: $R^1 = R^2$ = Ph



Preparation of (1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)cyclohexylamine:[90] To a solution of (*R*,*R*)-1,2-diaminocyclohexane (**171**, 1.50 g, 13.14 mmol, 1.0 equiv) in methanol (75 mL) were added sequentially acetic acid (750 µL, 13.14 mmol, 1.0 equiv) and 2,5-hexanedione (**175a**, 1.55 mL, 13.14 mmol, 1.0 equiv). The mixture was heated at 50 °C and stirred for twelve hours, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between dichloromethane (250 mL) and an aqueous solution of sodium hydroxide (4 N, 250 mL). The two phases were separated, and the aqueous layer extracted with dichloromethane (3 × 40 mL). The combined

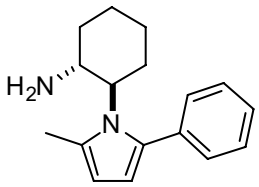
organic phases were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (5% of methanol in dichloromethane), yielding the amine **169a** (2.20 g, 11.44 mmol, 87%) as a yellow-orange oil.

169a: $C_{12}H_{20}N_2$ (192.30 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.77 (br s, 1H, C***H***$_{Ar}$), 5.75 (br s, 1H, C***H***$_{Ar}$), 3.61-3.57 (m, 1H, NH_2C***H*** cycl.), 3.29-3.22 (m, 1H, NC***H*** cycl.), 2.36 (br s, 3H, C***H***$_3$), 2.23 (br s, 3H, C***H***$_3$), 2.03-2.07 (m, 1H, C***H*** cycl.), 1.91-1.78 (m, 4H, CH_2C***H***$_2$ cycl.), 1.40-1.34 (m, 2H, C***H*** cycl.), 1.27-1.23 (m, 1H, C***H*** cycl.), 1.21 (br s, 2H, N**H**$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 129.8 (***C***q$_{Ar}$), 126.8 (***C***q$_{Ar}$), 107.9 (***C***H$_{Ar}$), 105.3 (***C***H$_{Ar}$), 63.6 (N***C***H cycl.), 52.9 (NH_2***C***H cycl.), 35.4 (***C***H_2 cycl.), 31.3 (***C***H_2 cycl.), 26.2 (***C***H_2 cycl.), 25.1 (***C***H_2 cycl.), 12.2 (***C***H_3), 13.7 (***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 192 (100), 174 (5), 162 (4), 148 (6), 134 (11), 122 (24), 110 (26), 96 (83), 81 (16), 69 (16), 56 (19), 42 (14), 30 (23), 27 (7); **HRMS** (EI-DE) calcd for [$C_{12}H_{20}N_2$]: 192.1626, found: 192.1629. The physical data were identical in all respects to those previously reported.[90]



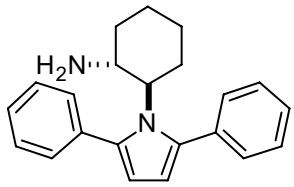
Preparation of (1R,2R)-2-(2,5-diethyl-pyrrol-1-yl)cyclohexylamine (**169b**): Following the procedure described for amine **169a**,[90] amine **169b** was prepared starting from (*R*,*R*)-1,2-diaminocyclohexane (**171**, 1.00 g, 8.76 mmol) and 3,6-octanedione (**175b**, 1.25 g, 8.76 mmol), yielding the desired product (**169b**, 1.84 g, 8.35 mmol, 95%) as a yellow oil.

169b: $C_{14}H_{24}N_2$ (220.35 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.90 (d, *J* = 3.2 Hz, 1H, C***H***$_{Ar}$), 5.83 (d, *J* = 3.2 Hz, 1H, C***H***$_{Ar}$), 3.67-3.60 (m, 1H, NH_2C***H*** cycl.), 3.31-3.24 (m, 1H, NC***H*** cycl.), 2.81-2.66 (m, 2H, C***H***$_2$$CH_3$), 2.66-2.50 (m, 2H, C***H***$_2$$CH_3$), 2.06 (d, *J* = 12.6 Hz, 1H, C***H***$_2$ cycl.), 2.00-1.79 (br m, 4H, C***H***$_2$ cycl.), 1.44-1.33 (br m, 2H, C***H***$_2$ cycl.), 1.30-1.21 (br m, 9H: C***H***$_2$ cycl. (1H), N***H***$_2$ (2H), C***H***$_3$(6H)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.9 (***C***q$_{Ar}$), 133.9 (***C***q$_{Ar}$), 105.1 (***C***H$_{Ar}$), 103.4 (***C***H$_{Ar}$), 63.4 (N***C***H cycl.), 52.9 (NH_2***C***H cycl.), 35.5 (***C***H_2 cycl.), 31.5 (***C***H_2 cycl.), 26.3 (***C***H_2 cycl.), 25.1 (***C***H_2 cycl.), 21.7 (***C***$H_2$$CH_3$), 20.9 (***C***$H_2$$CH_3$), 13.3 ($CH_2$***C***$H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 220 (66), 205 (7), 188 (16), 174 (12), 162 (5), 148 (12), 134 (9), 124 (100), 108 (46), 97 (43), 81 (11), 69 (11), 56 (14), 41 (9), 30 (16); **HRMS** (EIpos) calcd for [($C_{14}H_{24}N_2$+Na)$^+$]: 243.1832, found: 243.1829.



Preparation of (1R,2R)-2-(2-methyl-5-phenyl-pyrrol-1-yl)cyclohexanamine (**169c**): Following the procedure described for amine **169a**,[90] amine **169c** was prepared starting from (*R*,*R*)-1,2-diaminocyclohexane (**171**, 1.00 g, 8.76 mmol) and 1-phenylpentane-1,4-dione (**175c**,1.54 g, 8.76 mmol), yielding the desired product (**169c**, 2.04 g, 8.02 mmol, 92%) as an orange oil.

169c: $C_{17}H_{22}N_2$ (254.37 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H, C***H***$_{Ar}$), 6.05 (br s, 1H, C***H***$_{Ar,pyr.}$), 5.98 (br s 1H, C***H***$_{Ar,pyr.}$), 3.81-3.75 (m, 1H, NH_2C***H*** cycl.), 3.24-3.19 (m, 1H, NC***H*** cycl.), 2.46 (br s, 3H, C***H***$_3$), 2.04-1.96 (br m, 2H, C***H***$_2$ cycl.), 1.70-1.63 (br m, 2H, C***H***$_2$ cycl.), 1.35-1.20 (br m, 2H, C***H***$_2$ cycl.), 1.16 (br s, 2H, N***H***$_2$), 1.02-0.90 (br m, 2H, C***H***$_2$ cycl.); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.1 (***C***q$_{Ar}$), 134.6 (***C***H$_{Ar}$), 129.5 (***C***H$_{Ar}$), 129.0 (***C***q$_{Ar,pyr.}$), 128.3 (***C***q$_{Ar,pyr.}$), 126.7 (***C***H$_{Ar}$), 109.6 (***C***H$_{Ar,pyr.}$), 107.8 (***C***H$_{Ar,pyr.}$), 64.4 (N***C***H cycl.), 53.2 (NH_2***C***H cycl.), 35.2 (***C***H_2 cycl.), 31.8 (***C***H_2 cycl.), 26.0 (***C***H_2 cycl.), 25.1 (***C***H_2 cycl.), 15.3 (***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 254 (100), 198 (5), 172 (20), 157 (99), 141 (4), 128 (7), 115 (9), 97 (20), 81 (9), 69 (7), 56 (15), 43 (8), 30 (16); **HRMS** (EIpos) calcd for [($C_{17}H_{22}N_2$+H)$^+$]: 255.1856, found: 255.1854. The physical data were identical in all respects to those previously reported.[90]

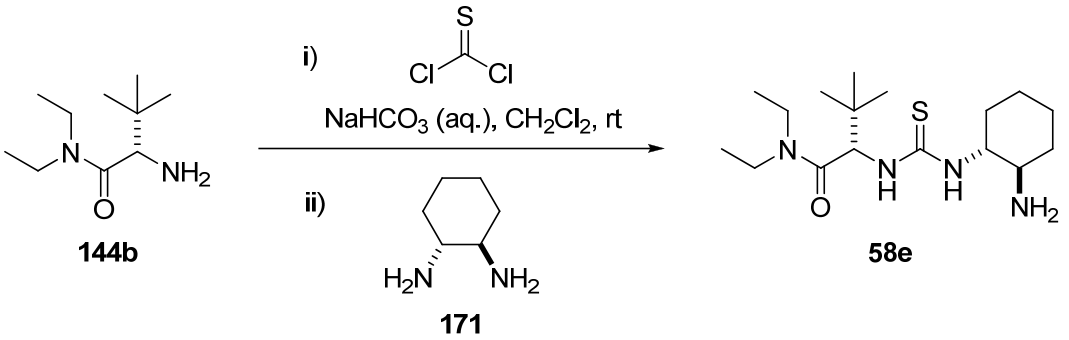


Preparation of (1R,2R)-2-(2,5-diphenyl-pyrrol-1-yl)cyclohexylamine (**169d**): Following the procedure described for amine **169a**[90], amine **169d** was prepared starting from (*R*,*R*)-1,2-diaminocyclohexane (**171**, 1.00 g, 8.76 mmol) and 1,4-diphenylbutane-1,4-dione (**175d**, 2.09 g, 8.76 mmol), yielding the desired product (**169d**, 2.10 g, 6.64 mmol, 76%) as a yellow solid.

169d: $C_{22}H_{24}N_2$ (316.44 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.34 (m, 10H, C***H***$_{Ar}$), 6.20 (br s, 2H, C***H***$_{Ar,pyr.}$), 3.73-3.67 (m, 1H, NH_2C***H*** cycl.), 2.58-2.52 (m, 1H, NC***H*** cycl.), 2.17-2.12 (br m, 1H, C***H***$_2$ cycl.), 1.88-1.77 (m, 1H, C***H***$_2$ cycl.), 1.72-1.63 (br m, 2H, C***H***$_2$ cycl.), 1.51-1.47 (br m, 1H, C***H***$_2$ cycl.), 1.14-1.03 (br m, 3H: C***H***$_2$ cycl. (1H), N***H***$_2$ (2H)), 0.93-0.76 (m, 2H, C***H***$_2$ cycl.); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 133.0-128.1 (br m, 14C: ***C***q$_{Ar,pyr.}$ (2C), ***C***q$_{Ar}$ (2C), ***C***H$_{Ar}$ (10C)), 113.9 (***C***H$_{Ar,pyr.}$), 108.2 (***C***H$_{Ar,pyr.}$), 66.0 (N***C***H cycl.), 53.7 (NH_2***C***H cycl.), 35.1 (***C***H_2 cycl.), 33.9 (***C***H_2 cycl.), 26.0 (***C***H_2 cycl.), 24.9 (***C***H_2 cycl.); **MS** (EI, 70 eV): *m*/*z* (%) = 316 (54), 260 (1), 219 (100), 202 (2), 158 (3), 141 (1), 115 (10),

97 (4), 81 (4), 56 (6), 43 (3); **HRMS** (EIpos) calcd for [($C_{22}H_{24}N_2$+H)$^+$]: 317.2012, found: 317.2012. The physical data were identical in all respects to those previously reported.[90]

7.3.2.3 Synthesis of (*S*)-2-(3-((1*R*,2*R*)-2-Aminocyclohexyl)thioureido)-*N*,*N*-diethyl-3,3-dimethylbutanamide (58e)[95]

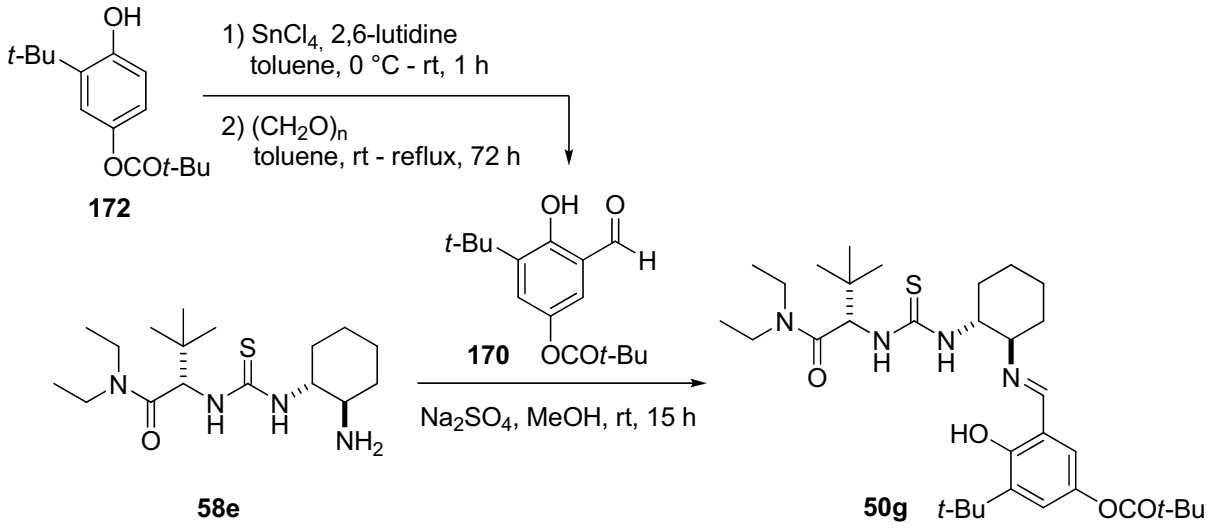


An aqueous solution of sodium bicarbonate (5 mL) was added to a solution of L-*tert*-leucine dimethylamide (0.25 g, 1.57 mmol, 1.0 equiv) in dichloromethane (7 mL) at 0 °C. The mixture was stirred for 30 minutes, then stirring was stopped and thiophosgene (110 µL, 1.48 mmol, 1.1 equiv) was added to the organic phase *via* syringe. The resulting orange mixture was stirred at 0 °C for one hour. Dichloromethane (15 mL) was added, and the organic phase separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated, yielding (*S*)-2-isothiocyanato-*N*,*N*,3,3-tetramethylbutanamide as a solid, which was used without further purification. The crude product was dissolved in dichloromethane (5 mL) and (*R*,*R*)-1,2-diaminocyclohexane (**171**, 0.17 g, 1.48 mmol, 1.1 equiv) was added in one portion. The reaction mixture was allowed to stir for four hours at room temperature. The volatile compounds were then removed *in vacuo* and the crude product purified by flash column chromatography (2 M solution of ammonia in a solution of 10% methanol in dichloromethane) yielding the desired product (**58e**, 0.29 g, 0.85 mmol, 63%) as a colorless solid.

58e: $C_{17}H_{34}N_2OS$ (342.54 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.91(br s, 1H, N***H***), 6.61 (br s, 1H, N***H***), 5.49 (d, *J* = 9.1 Hz, 1H, C***H***C(CH_3)), 3.77-3.69 (m, 3H: C***H***$_2$$CH_3$ (2H), NC***H*** cycl. (1H)), 3.42-3.37 (m, 1H, C***H***$_2$$CH_3$), 3.03-2.96 (m, 1H, C***H***$_2$$CH_3$), 2.60-2.30 (br m, 3H: NC***H*** cycl. (1H), C***H***$_2$ cycl. (2H)), 2.04 (br s, 1H, C***H***$_2$ cycl.), 1.92 (br s, 1H, C***H***$_2$ cycl.), 1.69 (d, *J* = 7.2 Hz, 2H, C***H***$_2$ cycl.), 1.30 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$), 1.28-1.21 (br m, 4 H: C***H***$_2$

cycl. (2H), N***H***$_2$ (2H)), 1.11 (t, *J* = 7.1 Hz, 3H, CH$_2$C***H***$_3$), 1.04 (s, 9H, C(C***H***$_3$)); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 182.5 (***C***=S), 170.9 (***C***=O), 60.9 (N***C***H cycl.), 60.7 (***C***HC(CH$_3$)$_3$), 55.7 (N***C***H cycl.), 42.9 (***C***H$_2$CH$_3$), 39.9 (***C***H$_2$CH$_3$), 36.2 (***C***(CH$_3$)$_3$), 34.6 (CH***C***H$_2$ cycl.), 32.2 (CH***C***H$_2$ cyclic), 27.0 (C(***C***H$_3$)$_3$), 24.8 (CH$_2$***C***H$_2$ cycl.), 24.7 (CH$_2$***C***H$_2$ cycl.), 14.5 (CH$_2$***C***H$_3$), 12.8 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 342 (6), 325 (3), 269 (4), 173 (27), 145 (8), 129 (3), 97 (100), 86 (36), 81 (9), 74 (63), 56 (10), 41 (7); **HRMS** (EIpos) calcd for [($C_{17}H_{34}N_2OS$+H)$^+$]: 343.2526, found: 343.2526. The physical data were identical in all respects to those previously reported.[95]

7.3.2.4 Synthesis of *Jacobsen*(-Type) Thiourea 50g[95]



3-*tert*-Butyl-4-hydroxyphenyl pivalate (**172**) was prepared by *R. Rios*. For the synthesis of thiourea **58e** see Chapter 7.3.2.3.

Preparation of 3-tert-butyl-5-formyl-4-hydroxyphenyl pivalate (**170**):[95] 3-*tert*-Butyl-4-hydroxyphenyl pivalate (**172**, 3.00 g, 11.98 mmol, 1.0 equiv) was dissolved in toluene (30 mL), followed by the addition of tin chloride (0.56 mL, 4.79 mmol, 0.4 equiv) and 2,6-lutidine (2.23 mL, 19.13 mmol, 1.6 equiv). The reaction mixture was stirred at 0 °C for one hour and then at room temperature for additional 30 minutes. Paraformaldehyde (2.20 g, 73.10 mmol, 6.1 equiv) was added at room temperature and the reaction mixture was refluxed for 72 hours. Water (100 mL) was added to the reaction mixture, followed by acidification with hydrochloric acid (2 N) until a pH of 2 was reached. The organic phase was separated, filtered, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was

purified by flash column chromatography (10% of ethyl acetate in hexanes) to yield compound **170** (1.69 g, 6.07 mmol, 51%) as a yellow solid.

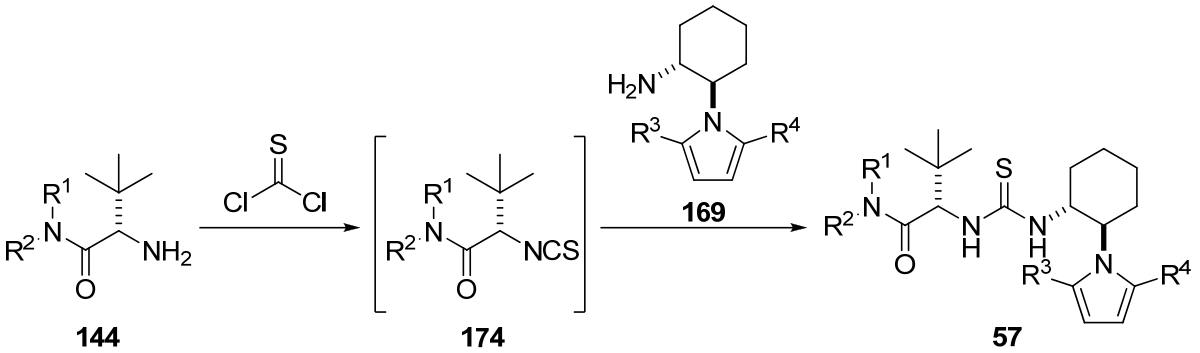
170: $C_{16}H_{22}O_4$ (278.34 g/mol); **m.p.** = 79-81°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.69 (s, 1H, C***H***O), 9.82 (s, 1H, O***H***) 7.17-7.14 (m, 2H, C***H***$_{Ar}$), 1.41 (s, 9H, C(C***H***$_3$)$_3$), 1.37 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.4 (C(***C***O)H), 177.3 (O(***C***O)C), 158.8 (***C***q$_{Ar}$OH), 142.8 (***C***q$_{Ar}$O(CO)C), 140.0 (***C***q$_{Ar}$C(CH$_3$)$_3$), 127.9 (***C***q$_{Ar}$(CO)H), 123.1 (***C***H$_{Ar}$), 120.0 (***C***H$_{Ar}$), 39.0 ((CO)***C***(CH$_3$)$_3$), 35.0 (Cq$_{Ar}$***C***(CH$_3$)$_3$), 29.0 (C(***C***H$_3$)$_3$), 27.1 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 278 (15), 194 (43), 179 (43), 151 (5), 85 (13), 57 (100), 41 (14), 29 (9); **HRMS** (EI-DE) calcd for [$C_{16}H_{22}O_4$]: 278.1518, found: 278.1521. The physical data were identical in all respects to those previously reported.[98]

Formation of 3-tert-Butyl-5-((E)-((1R,2R)-2-(3-((S)-1-(diethylamino)-3,3-dimethyl-1-oxo-butan-2-yl)thioureido)cyclohexylimino)methyl)-4-hydroxyphenyl pivalate **50g**:[95] Amine **58e** (200mg, 0.58 mmol, 1.0 equiv) was dissolved in methanol (2 mL) with stirring. Once the solution became homogeneous, sodium sulfate (300 mg, 2.04 mmol, 3.5 equiv) was added. In a separate flask 3-*tert*-butyl-5-formyl-4-hydroxyphenyl pivalate (**170**, 160 mg, 0.58 mmol, 1.0 equiv) was dissolved in methanol (2 mL), and then transferred to the reaction mixture. Additional methanol (2 mL) was used to ensurequantitative transfer of the aldehyde into the reaction mixture. The reaction was stirred at room temperature for 15 hours, and then concentrated *in vacuo* with sodium sulfate still present. The resulting mixture was combined with hexanes (25 ml) and filtered, and then the solids were rinsed with hexanes. The filtrate was concentrated under reduced pressure to yield thiourea **50g** (346 mg, 0.57 mmol, 98%) as a yellow solid.

50g: $C_{33}H_{54}N_4O_4S$ (602.87 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.60 (s, 1H, O***H***), 8.30 (s, 1H, N=C***H***), 6.91 (d, *J* = 2.7 Hz, 1H, C***H***$_{Ar}$), 6.82 (d, *J* = 2.8 Hz, 1H, C***H***$_{Ar}$), 6.65 (br s, 1H, N***H***), 6.30 (br s, 1H, N***H***), 5.51 (d, *J* = 9.2 Hz, 1H, C***H***C(CH$_3$)$_3$), 3.95 (br s, 1H, NC***H*** cycl.), 3.70-3.62 (m, 2H: C***H***$_2$CH$_3$), 3.31-3.27 (m, 1H, C***H***$_2$CH$_3$), 3.12 (br s, 1H, NC***H*** cycl.), 2.98-2.91 (m, 1H, C***H***$_2$CH$_3$), 2.15 (br s, 1H, C***H***$_2$ cycl.), 1.91 (br s, 1H, C***H***$_2$ cycl.), 1.85-1.66 (br m, 3H, C***H***$_2$ cycl.), 1.48-1.30 (br m, 3H, C***H***$_2$ cycl), 1.38 (s, 9 H, C$_{Ar}$C(C***H***$_3$)$_3$), 1.33 (s, 9 H, OC(C***H***$_3$)$_3$), 1.18 (t, *J* = 7.1 Hz, 3H, CH$_2$C***H***$_3$), 1.07 (t, *J* = 7.0 Hz, 3H, CH$_2$C***H***$_3$), 0.92 (s, 9H, CHC(C***H***$_3$)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.3 (***C***=S), 177.9 (O(***C***O)C), 170.8

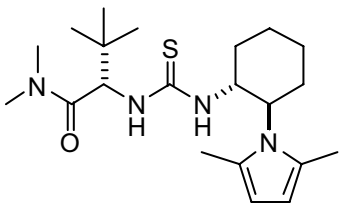
(***C***=O), 164.9 (***C***H=N), 158.6 (***C***q_{Ar}OH), 141.8 (***C***q_{Ar}O(CO)C), 138.6 (***C***$q_{Ar}C(CH_3)_3$), 122.9 (***C***q_{Ar}CH=N), 121.5 (***C***H_{Ar}), 118.2 (***C***H_{Ar}), 71.5 (***C***$HC(CH_3)_3$), 60.7 (***C***H cycl.), 56.5 (N***C***H cycl.), 42.9 (***C***H_2CH_3), 40.0 (***C***H_2CH_3), 39.0 ((CO)***C***$(CH_3)_3$), 36.3 (***C***$(CH_3)_3$), 35.0 (***C***$(CH_3)_3$), 33.0 (CH***C***H_2 cycl.), 29.2 (CH***C***H_2 cyclic), 29.0 (C(***C***$H_3)_3$), 27.2 (C(***C***$H_3)_3$), 26.8 (C(***C***$H_3)_3$), 24.1 (CH_2***C***H_2 cycl.), 23.5 (CH_2***C***H_2 cycl.), 14.5 (CH_2***C***H_3), 12.8 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 602 (23), 568 (33), 529 (16), 468 (22), 416 (91), 357 (100), 325 (38), 272 (31), 252 (12), 224 (7), 193 (3), 154 (23), 81 (17), 57 (40); **HRMS** (EIpos) calcd for [($C_{33}H_{54}N_4O_4S$+Na)$^+$]: 625.3758, found: 625.3755.

7.3.2.5 Synthesis of *Jacobsen*(-Type) Thioureas 57a-l[96]



The preparations of the amino amides **144** and amines **169** are reported in Chapters 7.2.2.1 (for **144a**) and 7.3.2.1 (for **144b,d,e**) and 7.3.2.2 (for **169 a-d**).

***(S)-2-(3-((1R,2R)-2-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl)thio-ureido)-N,N,3,3-tetra-methylbutanamide* (57a):**[90]



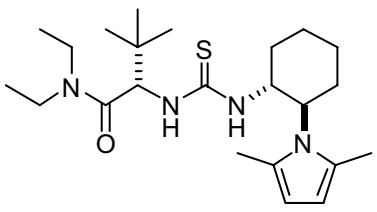
Saturated aqueous sodium bicarbonate (5 mL) was added to a solution of L-*tert*-leucine dimethylamide (**144a**, 0.20 g, 1.26 mmol) in dichloromethane (9 mL) at 0 °C. The mixture was stirred for 30 minutes, then stirring was stopped and thiophosgene (110 µL, 1.39 mmol, 1.1 equiv) was added to the organic phase by syringe. The resulting orange mixture was stirred at 0 °C for one hour. Dichloromethane (15 mL) was added, and the organic phase separated. The aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over magnesium sulfate

and concentrated, yielding crude (*S*)-2-isothiocyanato-*N*,*N*,3,3-tetramethylbutanamide, which was used without further purification.

The crude isothiocyanate was dissolved in dichloromethane (12 mL) and (1*R*,2*R*)-2-(2,5-dimethyl-pyrrol-1-yl)cyclohexylamine (**169a**, 0.29 g, 1.52 mmol, 1.2 equiv) was added in several portions over 15 minutes. The reaction mixture was allowed to stir at room temperature for 14 hours. All volatile compounds were removed *in vacuo* and the crude product purified by flash column chromatography (10-20% of ethyl acetate in hexanes) yielding thiourea **57a** (0.43 g, 1.10 mmol, 87%) as a colorless solid.

57a: $C_{21}H_{36}N_4OS$ (392.60 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.36 (br d, *J* = 8.5 Hz, 1H, N***H***), 5.97 (br d, *J* = 6.0 Hz, 1H, N***H***), 5.72 (s, 2H, C***H***$_{Ar}$), 5.47 (d, *J* = 9.3 Hz, 1H, C***H***C$(CH_3)_3$), 4.35-4.32 (m, 1H, C***H*** cycl.), 3.86-3.80 (m, 1H, C***H*** cycl.), 3.19 (s, 3H, NC***H***$_3$), 2.92 (s, 3H, NC***H***$_3$), 2.37-2.22 (br m, 6H, C_{Ar}C***H***$_3$), 1.95-1.80 (m, 4H, C***H***$_2$ cycl.), 1.43-1.20 (m, 4H, C***H***$_2$ cycl.), 0.94 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.2 (***C***=S), 172.0 (***C***=O), 127.5 (***C***q$_{Ar}$), 127.5 (***C***q$_{Ar}$), 108.8 (***C***H$_{Ar}$), 106.4 (***C***H$_{Ar}$), 60.1 (N***C***H cycl.), 59.4 (***C***HC$(CH_3)_3$), 55.8 (N***C***H cycl.), 38.5 (N***C***H$_3$), 36.0 (***C***$(CH_3)_3$), 35.6 (N***C***H$_3$), 34.0 (***C***H$_2$ cycl.), 32.4 (***C***H$_2$ cycl.), 26.6 (C(***C***H$_3$)$_3$), 25.8 (***C***H$_2$ cycl.), 24.6 (***C***H$_2$ cycl.), 21.0 (C_{Ar}***C***H$_3$), 14.2 (C_{Ar}***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 392 (86), 347 (22), 332 (10), 286 (15), 272 (5), 253 (10), 234 (76), 224 (11), 203 (12), 175 (100), 155 (61), 128 (5), 108 (7), 96 (37), 86 (32), 72 (24), 41 (12); **HRMS** (EIpos) calcd for [($C_{21}H_{36}N_4OS$+Na)$^+$]: 415.2502, found: 415.2498. The physical data were identical in all respects to those previously reported.[90]

(S)-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)cyclohexyl)thio-ureido)-N,N-diethyl-3,3-dimethylbutanamide **(57b):**

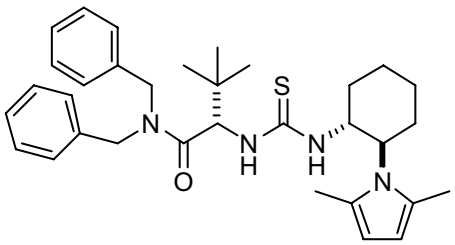


Thiourea **57b** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine diethylamide (**144b**, 0.30 g, 1.61 mmol), yielding the desired product (**57b**, 0.60 g, 1.43 mmol, 89%) as a pale red solid.

57b: $C_{23}H_{40}N_4OS$ (420.65 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.28 (br d, *J* = 9.2 Hz, 1H, N***H***), 5.71-5.68 (s and d, 3H: C***H***$_{Ar}$ (2H), N***H*** (1H)), 5.40 (d, *J* = 7,3 Hz, 1H, C***H***C$(CH_3)_3$), 4.42-4.34 (m, 1H, C***H*** cycl.), 3.86-3.79 (m, 1H, C***H*** cycl.), 3.71-3.60 (m, 2H, NC***H***$_2$CH$_3$), 3.33 (q, *J* = 7.3 Hz, 1H, NC***H***$_2$CH$_3$), 3.07 (q, *J* = 6.8 Hz, 1H, C***H***$_2$CH$_3$), 2.50 (br d, *J* = 13.2 Hz, 1H, C***H***$_2$ cycl.), 2.43-2.16 (br m, 6H, C_{Ar}C***H***$_3$), 1.96-1.79 (m, 4H, C***H***$_2$ cycl.), 1.50-1.18

(m, 3H, C***H***$_2$ cycl.), 1.25 (t, *J* = 7.1 Hz, 3H, NC***H***$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, NC***H***$_3$), 0.96 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.1 (***C***=S), 170.7 (***C***=O), 127.9 (***C***q$_{Ar}$), 127.7 (***C***q$_{Ar}$), 108.7 (***C***H$_{Ar}$), 106.3 (***C***H$_{Ar}$), 60.0 (N***C***H cycl.), 59.4 (***C***HC(CH$_3$)$_3$), 55.8 (N***C***H cycl.), 42.9 (N***C***H$_2$CH$_3$), 40.1 (N***C***H$_2$CH$_3$), 36.2 (***C***(CH$_3$)$_3$), 34.0 (***C***H$_2$ cycl.), 32.4 (***C***H$_2$ cycl.), 26.8 (C(***C***H$_3$)$_3$), 25.8 (***C***H$_2$ cycl.), 24.7 (***C***H$_2$ cycl.), 15.2 (C$_{Ar}$***C***H$_3$), 14.6 (NCH$_2$***C***H$_3$), 13.3 (C$_{Ar}$***C***H$_3$), 12.8 (NCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 420 (100), 387 (4), 324 (10), 286 (10), 234 (69), 203 (8), 175 (89), 155 (60), 129 (5), 96 (38), 86 (45), 74 (17), 41 (13); **HRMS** (EIpos) calcd for [(C$_{23}$H$_{40}$N$_4$OS+Na)$^+$]: 443.2815, found: 443.2815.

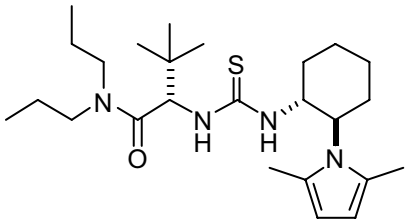
(S)-N,N-dibenzyl-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)cyclo-hexyl)thioureido)-3,3-dimethylbutanamide **(57c):**



Thiourea **57c** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine dibenzylamide (**144c**, 0.30 g, 0.97 mmol), yielding the desired product (**57c**, 0.46 g, 0.84 mmol, 87%) as a colorless solid.

57c: C$_{33}$H$_{44}$N$_4$OS (544.79 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.23 (m, 8H, C***H***$_{Ar}$), 7.17 (d, *J* = 7.7 Hz, 2H, C***H***$_{Ar}$), 6.48 (br d, *J* = 9.0 Hz, 1H, N***H***), 5.75 (br s, 1H, N***H*** or C***H***C(CH$_3$)$_3$), 5.74 (s, 2H, C***H***$_{Ar,pyr.}$), 5.08 (d, *J* = 14.4 Hz, 1H, PhC***H***$_2$), 4.92 (d, *J* = 15.8 Hz, 1H, PhC***H***$_2$), 4.54-4.46 (m, 1H, C***H*** cycl.), 4.31 (d, *J* = 15.9 Hz, 1H, PhC***H***$_2$), 3.90 (d, *J* = 14.6 Hz, 1H, PhC***H***$_2$), 3.85-3.80 (m, 1H, C***H*** cycl.), 2.53 (br d, *J* = 13.2 Hz, 1H, C***H***$_2$ cycl.), 2.42-2.21 (br m, 6H, C$_{Ar}$C***H***$_3$), 1.99-1.79 (m, 5H, C***H***$_2$ cycl.), 1.51-1.20 (m, 2H, C***H***$_2$ cycl.), 0.95 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.8 (***C***=S), 172.1 (***C***=O), 136.8 (***C***q$_{Ar}$), 135.8 (***C***q$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.6 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 128.2 (***C***q$_{Ar,pyr.}$), 127.9 (***C***q$_{Ar,pyr.}$), 127.5 (***C***H$_{Ar}$), 108.5 (***C***H$_{Ar,pyr.}$), 106.3 (***C***H$_{Ar,pyr.}$), 60.0 (N***C***H cycl.), 59.3 (***C***HC(CH$_3$)$_3$), 55.9 (N***C***H cycl.), 50.8 (N***C***H$_2$), 47.4 (N***C***H$_2$), 39.9 (***C***(CH$_3$)$_3$), 33.9 (***C***H$_2$ cycl.), 32.4 (***C***H$_2$ cycl.), 26.8 (C(***C***H$_3$)$_3$), 25.8 (***C***H$_2$ cycl.), 24.7 (***C***H$_2$ cycl.), 15.1 (C$_{Ar}$***C***H$_3$), 14.2 (C$_{Ar}$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 544 (93), 511 (6), 448 (7), 347 (38), 314 (8), 286 (19), 253 (7), 234 (45), 175 (57), 155 (33), 91 (100), 69 (11), 41 (9); **HRMS** (EIpos) calcd for [(C$_{33}$H$_{44}$N$_4$OS+Na)$^+$]: 567.3128, found: 567.3129.

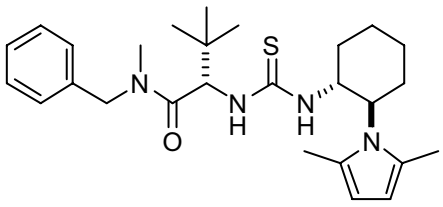
***(S)-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)cyclohexyl)-thioureido)-3,3-dimethyl-N,N-dipropylbutanamide* (57d):**



Thiourea **57d** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine dipropylamide (**144d**, 0.30 g, 1.40 mmol), yielding the desired product (**57d**, 0.51 g, 1.14 mmol, 81%) as a pale red solid.

57d: $C_{25}H_{44}N_4OS$ (448.71 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.29 (br d, *J* = 9.2 Hz, 1H, N***H***), 5.70 (br s, 2H, C***H***$_{Ar}$), 5.66 (br d, *J* = 7.4 Hz, 1H, N***H***), 5.45 (br s, 1H, C***H***C$(CH_3)_3$), 4.43-4.32 (m, 1H, C***H*** cycl.), 3.85-3.78 (m, 1H, C***H*** cycl.), 3.66-3.51 (m, 2H, NC***H***$_2$CH$_2$), 3.18-3.10 (m, 1H, NC***H***$_2$CH$_2$), 2.92-2.85 (m, 1H, NC***H***$_2$CH$_2$CH$_3$), 2.49 (br d, *J* = 13.0 Hz, 1H, C***H***$_2$ cycl.), 2.37-2.21 (br m, 6H, C$_{Ar}$C***H***$_3$), 1.98-1.79 (m, 4H, C***H***$_2$ cycl.), 1.76-1.67 (m, 1H, CH$_2$C***H***$_2$CH$_3$), 1.65-1.58 (m, 1H, CH$_2$C***H***$_2$CH$_3$), 1.54 (q, *J* = 7.6 Hz, 2H, CH$_2$C***H***$_2$CH$_3$), 1.47-1.34 (m, 2H, C***H***$_2$ cycl.), 1.26-1.20 (m, 1H, C***H***$_2$ cycl.), 0.95 (s, 9H, C(C***H***$_3$)$_3$), 0.90 (q, *J* = 7.4 Hz, 6H, CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.0 (***C***=S), 171.2 (***C***=O), 127.9 (***C***q$_{Ar}$), 127.7 (***C***q$_{Ar}$), 108.5 (***C***H$_{Ar}$), 106.2 (***C***H$_{Ar}$), 60.0 (***C***H cycl.), 59.4 (***C***HC$(CH_3)_3$), 55.8 (N***C***H cycl.), 50.5 (N***C***H$_2$), 47.6 (N***C***H$_2$), 36.4 (***C***$(CH_3)_3$), 34.0 (***C***H$_2$ cycl.), 32.4 (***C***H$_2$ cycl.), 26.8 (C(***C***H$_3$)$_3$), 25.9 (***C***H$_2$ cycl.), 24.7 (***C***H$_2$ cycl.), 22.5 (***C***H$_2$CH$_3$), 20.9 (***C***H$_2$CH$_3$), 14.8 (C$_{Ar}$***C***H$_3$), 11.5 (CH$_2$***C***H$_3$), 11.1 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 448 (100), 415 (5), 347 (38), 319 (8), 287 (16), 234 (83), 203 (7), 175 (85), 155 (60), 128 (4), 86 (35), 69 (8), 43 (11); **HRMS** (EIpos) calcd for [$(C_{25}H_{44}N_4OS+Na)^+$]: 471.3128, found: 471.3132.

***(S)-N-benzyl-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)-cyclohexyl)-thioureido)-N,3,3-trimethylbutanamide* (57e):**

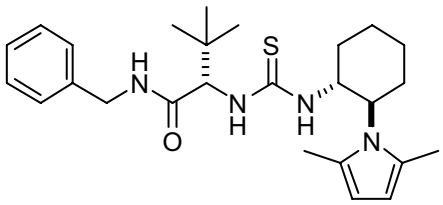


Thiourea **57e** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine benzylmethylamide (**144e**, 0.30 g, 1.28 mmol), yielding the desired product (**57e**, 0.46 g, 0.98 mmol, 77%) as a colorless solid.

57b: $C_{27}H_{40}N_4OS$ (468.70 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$; compound is obtained as a ~4:1 mixture of rotamers: the major rotamer is denoted by *): δ 7.34-7.20 (m, 10H, C***H***$_{Ar}$, C***H***$_{Ar}$*), 6.40 (d, *J* = 9.2 Hz, 2H, N***H***, N***H****), 5.86 (d, *J* = 7.2 Hz, 2H, N***H***, N***H****), 5.74 (s, 4H,

C***H***$_{Ar,pyr.}$, C***H***$_{Ar,pyr.}$*), 5.50 (d, *J* = 9.3 Hz, 2H, C***H***C(CH$_3$)$_3$, C***H***C(CH$_3$)$_3$*), 5.00 (d, *J* = 15.3 Hz, 1H, PhC***H***$_2$), 4.67 (d, *J* = 14.6 Hz, 1H, PhC***H***$_2$*), 4.50-4.40 (m, 2H, C***H*** cycl., C***H*** cycl.*), 4.48 (d, *J* = 14.6 Hz, 1H, PhC***H***$_2$*), 4.42 (d, *J* = 15.6 Hz, 1H, PhC***H***$_2$), 3.89-3.82 (m, 2H, C***H*** cycl., C***H*** cycl.*), 3.12 (s, 3H, NC***H***$_3$*), 2.81 (s, 3H, NC***H***$_3$), 2.57-2.54 (br d, *J* = 13.4 Hz, 2H, C***H***$_2$ cycl., C***H***$_2$ cycl.*), 2.40-2.20 (br m, 12H, C$_{Ar}$C***H***$_3$, C$_{Ar}$C***H***$_3$*), 2.03-1.80 (m, 8H, C***H***$_2$ cycl., C***H***$_2$ cycl.*), 1.52-1.32 (m, 4H, C***H***$_2$ cycl., C***H***$_2$ cycl.*), 1.28-1.16 (m, 2H, C***H***$_2$ cycl., C***H***$_2$ cycl.*), 0.98 (s, 9H, C(C***H***$_3$)$_3$*), 0.96 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$; compound is obtained as a mixture of rotamers: only the major rotamers are reported): δ 182.4 (***C***=S), 172.3 (***C***=O), 136.7 (***C***q$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.6 (***C***H$_{Ar}$), 128.1 (***C***H$_{Ar}$), 127.9 (***C***q$_{Ar,pyr.}$), 127.8 (***C***q$_{Ar,pyr.}$), 127.4 (***C***H$_{Ar}$), 108.4 (***C***H$_{Ar,pyr.}$), 106.2 (***C***H$_{Ar,pyr.}$), 60.3 (N***C***H cycl.), 59.4 (***C***HC(CH$_3$)$_3$), 56.0 (N***C***H cycl.), 51.3 (N***C***H$_2$Ph), 36.1 (N***C***H$_3$), 36.0 (***C***(CH$_3$)$_3$), 34.0 (***C***H$_2$ cycl.), 32.5 (***C***H$_2$ cycl.), 26.8 (C(***C***H$_3$)$_3$), 25.7 (***C***H$_2$ cycl.), 24.7 (***C***H$_2$ cycl.), 21.6 (C$_{Ar}$***C***H$_3$), 14.2 (C$_{Ar}$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 468 (100), 435 (5), 372 (10), 347 (31), 332 (7), 287 (13), 234 (60), 203 (7), 175 (80), 155 (53), 122 (14), 91 (59), 69 (10), 41 (8); **HRMS** (EIpos) calcd for [(C$_{27}$H$_{40}$N$_4$OS+Na)$^+$]: 491.2815, found: 491.2819.

((S)-N-benzyl-2-(3-((1R,2R)-2-(2,5-dimethyl-pyrrol-1-yl)-cyclohexyl)-thioureido)-3,3-dimethylbutanamide **(57f):**

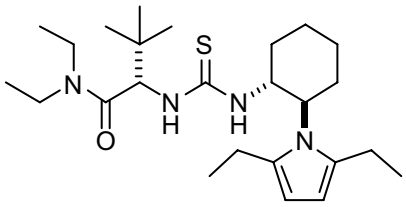


Thiourea **57f** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine benzylamide (**144f**, 0.30 g, 1.36 mmol), yielding the desired product (**57f**, 0.53 g, 1.17 mmol, 86%) as a light red solid.

57f: C$_{26}$H$_{38}$N$_4$OS (454.67 g/mol); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.33-7.24 (m, 3H, C***H***$_{Ar}$), 7.22-7.20 (m, 2H, C***H***$_{Ar}$), 6.38 (br s, 2H: N***H*** (2H) or N***H*** (1H), C***H***C(CH$_3$)$_3$ (1H)), 5.70 (s, 2H, C***H***$_{Ar,pyrrol}$), 4.61-4.52 (m, 1H, C***H*** cycl.), 4.38 (dd, *J* = 14.8 Hz, 6.0 Hz, 1H, PhC***H***$_2$), 4.27 (dd, *J* = 14.8 Hz, 5.4 Hz, 1H, PhC***H***$_2$), 3.88-3.81 (m, 1H, C***H*** cycl.), 2.52 (br d, *J* = 12.6 Hz, 1H, C***H***$_2$ cycl.), 2.42-2.15 (br m, 6H, C$_{Ar}$***C***H$_3$), 2.05-1.77 (m, 5H, C***H***$_2$ cycl.), 1.57-1.32 (m, 2H, C***H***$_2$ cycl.), 1.22-1.10 (m, 1H, C***H***$_2$ cycl.), 0.94 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 182.5 (***C***=S), 170.7 (***C***=O), 137.7 (***C***q$_{Ar}$), 128.7 (***C***H$_{Ar}$), 127.9 (***C***H$_{Ar}$), 127.8 (***C***H$_{Ar}$), 127.6 (***C***q$_{Ar,pyr.}$), 127.5 (***C***q$_{Ar,pyr.}$), 108.4 (***C***H$_{Ar,pyr.}$), 106.4 (***C***H$_{Ar,pyr.}$), 60.4 (N***C***H cycl.), 59.3 (***C***HC(CH$_3$)$_3$), 56.7 (N***C***H cycl.), 43.5 (N***C***H$_2$Ph), 34.6 (***C***(CH$_3$)$_3$), 33.8 (***C***H$_2$

cycl.), 32.3 (***C***H_2 cycl.), 26.8 (C(***C***$H_3)_3$), 25.9 (***C***H_2 cycl.), 24.7 (***C***H_2 cycl.), 22.0 (C_{Ar}***C***H_3), 14.2 (C_{Ar}***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 454 (100), 421 (11), 358 (15), 287 (6), 234 (77), 203 (7), 175 (89), 155 (63), 91 (57), 69 (12), 41 (9); **HRMS** (EIpos) calcd for [($C_{26}H_{38}N_4OS$+Na)$^+$]: 477.2659, found: 477.2655.

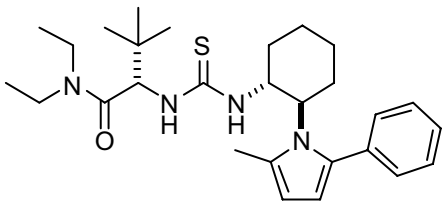
***(S)-2-(3-((1R,2R)-2-(2,5-diethyl-pyrrol-1-yl)cyclohexyl)-thioureido)-N,N-diethyl-3,3- dimethyl butanamide* (57g):**



Thiourea **57g** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine diethylamide (**144b**, 0.20 g, 1.07 mmol) and (1*R*,2*R*)-2-(2,5-diethyl-pyrrol-1-yl)cyclohexylamine (**169b**, 0.28 mg, 1.29 mmol), yielding the desired product (**57g**, 0.30 g, 0.67 mmol, 62%) as a white solid.

57g: $C_{25}H_{44}N_4OS$ (448.71 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.25 (br d, *J* = 8.9 Hz, 1H, N***H***), 5.81 (br s, 2H, C***H***$_{Ar}$), 5.56 (br d, *J* = 6.4 Hz, 1H, N***H***), 5.42 (br s, 1H, C***H***C$(CH_3)_3$), 4.43-4.40 (m, 1H, C***H*** cycl.), 3.89-3.82 (m, 1H, C***H*** cycl.), 3.71-3.62 (m, 2H, NC***H***$_2CH_3$), 3.30 (q, *J* = 7.3 Hz, 1H, NC***H***$_2CH_3$), 3.04 (q, *J* = 6.8 Hz, 1H, NC***H***$_2CH_3$), 2.79-2.67 (br m, 2H, C***H***$_2$ cycl.), 2.64-2.46 (br m, 3H, C***H***$_2$ cycl.), 2.03-1.80 (br m, 4H, C_{Ar}C***H***$_2CH_3$), 1.50-1.35 (br m, 2H, C***H***$_2$ cycl.), 1.29-1.21 (m, 10H: C***H***$_2$ cycl. (1H), $C_{Ar}CH_2$C***H***$_3$ (6H), NCH_2C***H***$_3$ (3H)), 1.11 (t, *J* = 7.1 Hz, 3H, NCH_2C***H***$_3$), 0.96 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.9 (***C***=S), 170.5 (***C***=O), 134.7 (***C***q_{Ar}), 134.4 (***C***q_{Ar}), 105.6 (***C***H_{Ar}), 104.4 (***C***H_{Ar}), 59.8 (***C***H cycl.), 59.1 (***C***HC$(CH_3)_3$), 55.8 (***C***H cycl.), 42.9 (N***C***H_2CH_3), 40.1 (N***C***H_2CH_3), 36.3 (***C***$(CH_3)_3$), 34.1 (***C***H_2 cycl.), 32.5 (***C***H_2 cycl.), 26.7 (C(***C***$H_3)_3$), 25.9 (***C***H_2 cycl.), 24.7 (***C***H_2 cycl.), 21.5 (C_{Ar}***C***H_2CH_3), 20.8 (C_{Ar}***C***H_2CH_3), 14.6 (NCH_2***C***H_3), 13.4 ($C_{Ar}CH_2$***C***H_3), 12.9 (NCH_2***C***H_3), 12.7 ($C_{Ar}CH_2$***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 448 (100), 415 (4), 375 (56), 314 (18), 262 (65), 224 (17), 203 (48), 188 (17), 174 (5), 155 (52), 124 (42), 108 (12), 86 (34); **HRMS** (EIpos) calcd for [($C_{25}H_{44}N_4OS$+Na)$^+$]: 471.3128, found: 471.3129.

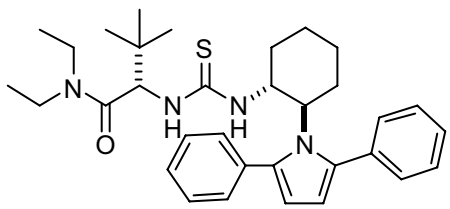
***(S)-N,N-diethyl-3,3-dimethyl-2-(3-((1R,2R)-2-(2-methyl-5-phenyl-1-pyrrol-1-yl)cyclohexyl)-thioureido)butanamide* (57h):**



Thiourea **57h** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine diethylamide (**144b**, 0.20 g, 1.07 mmol) and (1*R*,2*R*)-2-(methyl-5-phenyl-pyrrol-1-yl)cyclohexylamine (**169c**, 0.33 g, 1.29 mmol), yielding the desired product (**57h**, 0.34 g, 0.70 mmol, 66%) as a pale yellow solid.

57h: $C_{28}H_{42}N_4OS$ (482.74 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, C***H***$_{Ar}$), 6.00 (br s, 2 H: C***H***$_{Ar,pyrrol}$ (1H), N***H***(1H)), 5.85 (br s, 1H, C***H***$_{Ar,pyrrol}$), 5.40 (br s, 1H, N***H***), 5.06 (br s, 1H, C***H***C$(CH_3)_3$), 4.44 (br s, 1H, C***H*** cycl.), 4.02-3.95 (m, 1H, C***H*** cycl.), 3.74-3.63 (m, 2H, NC***H***$_2$CH$_3$), 3.30 (q, *J* = 7.4 Hz, 1H, NC***H***$_2$CH$_3$), 3.08 (q, *J* = 6.8 Hz, 1H, NC***H***$_2$CH$_3$), 2.48 (br s, 3H, C$_{Ar}$C***H***$_3$), 2.26-2.19 (br m, 3H, C***H***$_2$ cycl.), 1.88-1.84 (br m, 2H, C***H***$_2$ cycl.), 1.74-1.71 (br m, 1H, C***H***$_2$ cycl.), 1.41-1.36 (br m, 1H, C***H***$_2$ cycl.), 1.27-1.23 (m, 4H: C***H***$_2$ cycl. (1H), NCH$_2$C***H***$_3$ (3H)), 1.14 (t, *J* = 7.1 Hz, 3H, NCH$_2$C***H***$_3$), 0.96 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.8 (***C***=S), 170.6 (***C***=O), 136.0 (***C***q$_{Ar}$), 129.7 (***C***H$_{Ar}$), 129.5 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.6 (***C***q$_{Ar,pyr.}$), 127.0 (***C***q$_{Ar,pyr.}$), 110.1 (***C***H$_{Ar,pyr.}$), 108.7 (***C***H$_{Ar,pyr.}$), 60.0 (***C***H cycl.), 59.6 (***C***HC$(CH_3)_3$), 55.9 (***C***H cycl.), 42.9 (N***C***H$_2$CH$_3$), 40.2 (N***C***H$_2$CH$_3$), 36.3 (***C***$(CH_3)_3$), 33.7 (***C***H$_2$ cycl.), 32.2 (***C***H$_2$ cycl.), 26.7 (C(***C***H$_3$)$_3$), 25.7 (***C***H$_2$ cycl.), 24.6 (***C***H$_2$ cycl.), 15.4 (***C***H$_3$), 14.7 (***C***H$_3$), 12.9 (***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 482 (84), 449 (5), 409 (33), 394 (8), 324 (12), 296 (36), 253 (8), 237 (100), 170 (6), 155 (33), 129 (4), 86 (33); **HRMS** (EIpos) calcd for [($C_{28}H_{42}N_4OS$+Na)$^+$]: 505.2971, found: 505.2973.

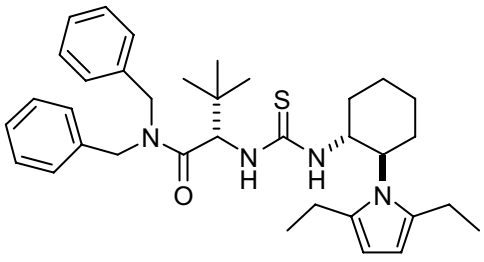
***(S)-2-(3-((1R,2R)-2-(2,5-diphenyl-pyrrol-1-yl)cyclohexyl)thioureido)-N,Ndiethyl-3,3-dimethylbutanamide* (57i):**



Thiourea **57i** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine diethylamide (**144b**, 0.20 g, 1.07 mmol) and (1*R*,2*R*)-2-(2,5-diphenyl-pyrrol-1-yl)cyclohexylamine (**169d**, 0.41 g, 1.29 mmol), yielding the desired product as a white foam (**57i**, 0.45 g, 0.83 mmol, 77%).

57i: $C_{33}H_{44}N_4OS$ (544.79 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49-7.36 (m, 10H, C***H***$_{Ar}$), 6.18 (br s, 2 H, C***H***$_{Ar,pyr.}$), 5.92 (d, *J* = 9.2 Hz, 1H, N***H***), 5.46 (d, *J* = 9.12 Hz, 1H, N***H***), 5.21 (br s, 1H, C***H***C(CH$_3$)$_3$), 4.04-3.97 (m, 1H, C***H*** cycl.), 3.74-3.61 (m, 2H, NC***H***$_2$CH$_3$), 3.57 (br s, 1H, C***H*** cycl.), 3.31 (q, *J* = 7.3 Hz, 1H, NC***H***$_2$CH$_3$), 3.05 (q, *J* = 6.9 Hz, 1H, NC***H***$_2$CH$_3$), 2.21 (d, *J* = 12.4 Hz, 1H, C***H***$_2$ cycl.), 2.14 (d, *J* = 12.8 Hz, 1H, C***H***$_2$ cycl.), 1.95-1.77 (br m, 2H, C***H***$_2$ cycl.), 1.68 (d, *J* = 13.2 Hz, 1H, C***H***$_2$ cycl.), 1.51 (d, *J* = 12.8 Hz, 1H, C***H***$_2$ cycl.), 1.27 (t, *J* = 6.6 Hz, 3H, NCH$_2$C***H***$_3$), 1.10 (t, *J* = 7.1 Hz, 3H, NCH$_2$C***H***$_3$), 1.03 (s, 9H, C(C***H***$_3$)$_3$), 0.96-0.88 (br m, 1H, C***H***$_2$ cycl.), 0.83-0.73 (br m, 1H, C***H***$_2$ cycl.); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.4 (***C***=S), 170.5 (***C***=O), 131.3 (***C***q$_{Ar}$), 131.2 (***C***q$_{Ar}$), 129.5 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 127.8 (***C***q$_{Ar,pyr.}$), 127.5 (***C***q$_{Ar,pyr.}$), 112.5 (***C***H$_{Ar,pyr.}$), 109.4 (***C***H$_{Ar,pyr.}$), 60.8 (***C***H cycl.), 60.2 (***C***HC(CH$_3$)$_3$), 56.5 (***C***H cycl.), 42.9 (N***C***H$_2$CH$_3$), 40.1 (N***C***H$_2$CH$_3$), 36.1 (***C***(CH$_3$)$_3$), 33.8 (***C***H$_2$ cycl.), 33.1 (***C***H$_2$ cycl.), 26.8 (C(***C***H$_3$)$_3$), 26.5 (***C***H$_2$ cycl.), 25.8 (***C***H$_2$ cycl.), 14.7 (NCH$_2$***C***H$_3$), 12.9 (NCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 544 (66), 511 (5), 471 (31), 456 (7), 410 (1), 359 (17), 324 (12), 299 (100), 253 (9), 219 (40), 191 (2), 155 (17), 86 (28), 41 (3); **HRMS** (EIpos) calcd for [(C$_{33}$H$_{44}$N$_4$OS+Na)$^+$]: 567.3128, found: 567.3126.

(S)-N,N-dibenzyl-2-(3-((1R,2R)-2-(2,5-diethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-3,3-dimethylbutanamide **(57j):**

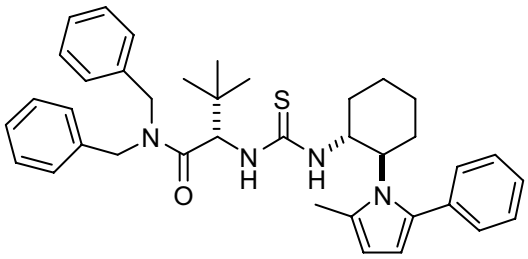


Thiourea **57j** was prepared according to the procedure used to synthesize catalyst **57a**, starting from L-*tert*-leucine dibenzylamide (**144c**, 0.27 g, 0.87 mmol) and (1*R*,2*R*)-2-(2,5-diethyl-pyrrol-1-yl)cyclohexyl-amine (**169b**, 0.23 mg, 1.04 mmol), yielding the desired product (**57j**, 0.37 g, 0.64 mmol, 74%) as a pale yellow solid.

57j: $C_{35}H_{48}N_4OS$ (572.85 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 8H, C***H***$_{Ar}$), 7.20-7.17 (m, 2H, C***H***$_{Ar}$), 6.46 (br s, 1H, N***H***), 5.83 (d, *J* = 10.2 Hz, 2H, C***H***$_{Ar,pyr.}$), 5.56 (br s, 1H, N***H*** or C***H***C(CH$_3$)$_3$), 5.13 (d, *J* = 14.3 Hz, 1H, PhC***H***$_2$), 4.91 (d, *J* = 15.6 Hz, 1H, PhC***H***$_2$), 4.54-4.47 (m, 1H, C***H*** cycl.), 4.27 (d, *J* = 15.8 Hz, 1H, PhC***H***$_2$), 3.86-3.82 (m, 2H: PhC***H***$_2$ (d, *J* = 14.7 Hz, 1H,), C***H*** cycl. (br s, 1H)), 2.80-2.71 (br m, 2H, C***H***$_2$ cycl.), 2.62-2.48 (br m, 2H, C***H***$_2$ cycl.), 1.97-1.80 (br m, 4H, C$_{Ar}$C***H***$_2$CH$_3$), 1.52-1.34 (br m, 2H, C***H***$_2$ cycl.), 1.28-1.22 (br m, 7H: C$_{Ar}$CH$_2$C***H***$_3$ (6H), C***H***$_2$ cycl.(1H)), 0.94 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.7 (***C***=S), 164.9 (***C***=O), 136.8 (***C***q$_{Ar}$), 135.7 (***C***q$_{Ar}$), 134.5 (***C***H$_{Ar}$),

128.8 (***C***H_{Ar}), 128.6 (***C***H_{Ar}), 128.0 (***C***$q_{Ar,pyr.}$), 127.5 (***C***$q_{Ar,pyr.}$), 105.6 (***C***$H_{Ar,pyr.}$), 104.5 (***C***$H_{Ar,pyr.}$), 59.9 (***C***H cycl.), 59.0 (***C***$HC(CH_3)_3$), 56.0 (***C***H cycl.), 50.7 (N***C***H_2Ph), 47.4 (N***C***H_2Ph), 37.0 (***C***$(CH_3)_3$), 34.0 (***C***H_2 cycl.), 32.6 (***C***H_2 cycl.), 26.7 ($C(\boldsymbol{C}H_3)_3$), 26.0 (***C***H_2 cycl.), 24.6 (***C***H_2 cycl.), 21.4 ($C_{Ar}\boldsymbol{C}H_2CH_3$), 20.8 ($C_{Ar}\boldsymbol{C}H_2CH_3$), 13.4 ($C_{Ar}CH_2\boldsymbol{C}H_3$), 12.9 ($C_{Ar}CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 572 (100), 448 (9), 375 (58), 347 (6), 314 (10), 262 (42), 224 (10), 203 (41), 188 (14), 155 (40), 124 (30), 108 (11), 91 (66), 69 (8), 41 (5); **HRMS** (EIpos) calcd for [$(C_{35}H_{48}N_4OS+Na)^+$]: 595.3441, found: 595.3437.

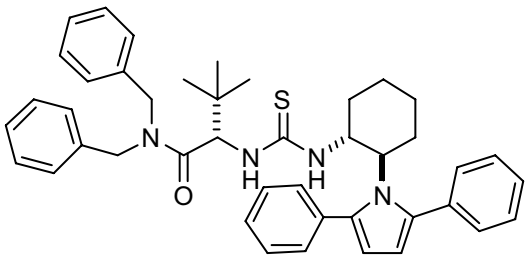
***(S)-N,N-dibenzyl-3,3-dimethyl-2-(3-((1R,2R)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)butanamide* (57k):**



Thiourea **57k** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine dibenzylamide (**144c**, 0.27 g, 0.87 mmol) and (1*R*,2*R*)-2-(methyl-5-phenyl-pyrrol-1-yl)cyclohexylamine (**169c**, 0.26 g, 1.03 mmol), yielding the desired product (**57k**, 0.45 g, 0.74 mmol, 86%) as a pale yellow solid.

57k: $C_{38}H_{46}N_4OS$ (606.86 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.39 (m, 4H, C***H***$_{Ar}$), 7.33-7.26 (m, 9H, C***H***$_{Ar}$), 7.20 (d, *J* = 7.7 Hz, 2H, C***H***$_{Ar}$), 6.17 (br s, 1H, N***H***), 6.03 (br s, 1H, C***H***$_{Ar,pyrrol}$), 5.90 (d, *J* = 5.7 Hz, 1H, C***H***$_{Ar,pyrrol}$), 5.71 (br s, 1H, C***H***$C(CH_3)_3$ or N***H***), 5.19 (d, *J* = 14.3 Hz, 1H, NC***H***$_2$Ph), 5.11 (br s, 1H, C***H***$(CH_3)_3$ or N***H***), 4.94 (d, *J* = 15.6 Hz, 1H, NC***H***$_2$Ph), 4.51 (br s, 1H, C***H*** cycl.), 4.22 (d, *J* = 15.8 Hz, 1H, NC***H***$_2$Ph), 4.01 (br s, 1H, C***H*** cycl.), 3.84 (d, *J* = 14.6 Hz, 1H, NC***H***$_2$Ph), 2.56 (br s, 3H, $C_{Ar}C\boldsymbol{H}_3$), 2.29-2.22 (br m, 3H, C***H***$_2$ cycl.), 1.89 (d, *J* = 10.8 Hz, 1H, C***H***$_2$ cycl.), 1.76-1.72 (br m, 2H, C***H***$_2$ cycl.), 1.45-1.38 (br m, 1H, C***H***$_2$ cycl.), 1.28-1.23 (br m, 1H, C***H***$_2$ cycl.), 0.97 (s, 9H, $C(C\boldsymbol{H}_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.6 (***C***=S), 172.6 (***C***=O), 136.9 (***C***q_{Ar}), 135.7 (***C***q_{Ar}), 134.3 (***C***q_{Ar}), 129.5 (***C***H_{Ar}), 128.8 (***C***H_{Ar}), 128.7 (***C***H_{Ar}), 128.6 (***C***H_{Ar}), 128.6 (***C***$q_{Ar,pyr.}$), 128.3 (***C***H_{Ar}), 127.9 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 127.0 (***C***$q_{Ar,pyr.}$), 110.2 (***C***$H_{Ar,pyr.}$), 108.9 (***C***$H_{Ar,pyr.}$), 60.4 (***C***H cycl.), 59.9 (***C***$HC(CH_3)_3$), 56.0 (***C***H cycl.), 50.8 (N***C***H_2Ph), 47.3 (N***C***H_2Ph), 37.0 (***C***$(CH_3)_3$), 33.6 (***C***H_2 cycl.), 32.3 (***C***H_2 cycl.), 26.8 ($C(\boldsymbol{C}H_3)_3$), 25.7 (***C***H_2 cycl.), 24.6 (***C***H_2 cycl.), 15.5 ($C_{Ar}\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 606 (100), 448 (9), 410 (47), 394 (5), 348 (4), 297 (34), 253 (10), 237 (98), 198 (17), 155 (28), 106 (5), 91 (54); **HRMS** (EIpos) calcd for [$(C_{38}H_{46}N_4OS+Na)^+$]: 629.3285, found: 629.3286.

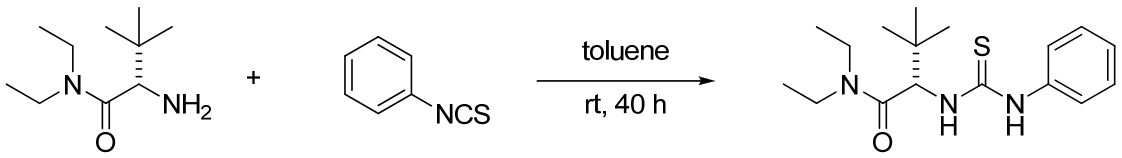
***(S)-N,N-dibenzyl-2-(3-((1R,2R)-2-(2,5-diphenyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-3,3-dimethylbutanamide* (57l):**



Thiourea **57-l** was prepared following the procedure described for catalyst **57a**, starting from L-*tert*-leucine dibenzylamide (**144c**, 0.27 g, 0.87 mmol) and (1*R*,2*R*)-2-(2,5-diphenyl-pyrrol-1-yl)cyclohexylamine (**169d**, 0.33 g, 1.03 mmol), yielding the desired product (**57-l**, 0.49 g, 0.73 mmol, 84%) as a colorless solid.

57-l: $C_{43}H_{48}N_4OS$ (668.93 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54-7.24 (m, 18H, C***H***$_{Ar}$), 7.18 (d, *J* = 5.3 Hz, 2H, C***H***$_{Ar}$), 6.10-6.25 (m, 2H, C***H***$_{Ar,pyr.}$), 6.04 (d, *J* = 9.1 Hz, 1H, N***H***), 5.78 (br s, 1H, N***H***), 5.14 (br s, 1H, C***H***C$(CH_3)_3$), 5.09 (d, *J* = 14.5 Hz, 1H, NC***H***$_2$Ph), 4.96 (d, *J* = 15.6 Hz, 1H, NC***H***$_2$Ph), 4.28 (d, *J* = 15.6 Hz, 1H, NC***H***$_2$Ph), 4.11-4.04 (br m, 1H, C***H*** cycl.), 3.90 (d, *J* = 14.5 Hz, 1H, NC***H***$_2$Ph), 3.78 (br s, 1H, C***H*** cycl.), 2.24 (d, *J* = 12.8 Hz, 1H, C***H***$_2$ cycl.), 2.17 (d, *J* = 12.6 Hz, 1H, C***H***$_2$ cycl.), 1.91-1.86 (br m, 1H, C***H***$_2$ cycl.), 1.72-1.68 (br m, 1H, C***H***$_2$ cycl.), 1.52 (d, *J* = 15.3 Hz, 1H, C***H***$_2$ cycl.), 1.18-1.12 (br m, 1H, C***H***$_2$ cycl.), 1.02 (s, 9H, C(C***H***$_3$)$_3$), 0.96-0.94 (br m, 1H, C***H***$_2$ cycl.), 0.87-0.85 (br m, 1H, C***H***$_2$ cycl.); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.4 (***C***=S), 172.0 (***C***=O), 136.9 (***C***q$_{Ar}$), 135.7 (***C***q$_{Ar}$), 132.0 (***C***q$_{Ar}$), 129.7 (***C***q$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.5 (***C***$_{Ar}$), 128.3 (***C***$_{Ar}$), 127.9 (***C***$_{Ar}$), 127.5 (***C***$_{Ar}$), 112.9 (***C***H$_{Ar,pyr.}$), 109.8 (***C***H$_{Ar,pyr.}$), 60.9 (***C***H cycl.), 60.3 (***C***HC$(CH_3)_3$), 56.8 (***C***H cycl.), 50.9 (N***C***H$_2$Ph), 47.2 (N***C***H$_2$Ph), 36.8 (***C***$(CH_3)_3$), 33.7 (***C***H$_2$ cycl.), 33.1 (***C***H$_2$ cycl.), 26.9 (C(***C***H$_3$)$_3$), 25.9 (***C***H$_2$ cycl.), 24.1 (***C***H$_2$ cycl.); **MS** (EI, 70 eV): *m*/*z* (%) = 668 (71), 472 (47), 448 (8), 359 (21), 299 (100), 253 (9), 219 (40), 198 (14), 155 (15), 91 (45); **HRMS** (EIpos) calcd for [$(C_{43}H_{48}N_4OS+Na)^+$]: 691.3441, found: 691.3443.

7.3.2.6 Synthesis of (*S*)-*N*,*N*-Diethyl-3,3-dimethyl-2-(3-phenylthioureido)butanamide (176)



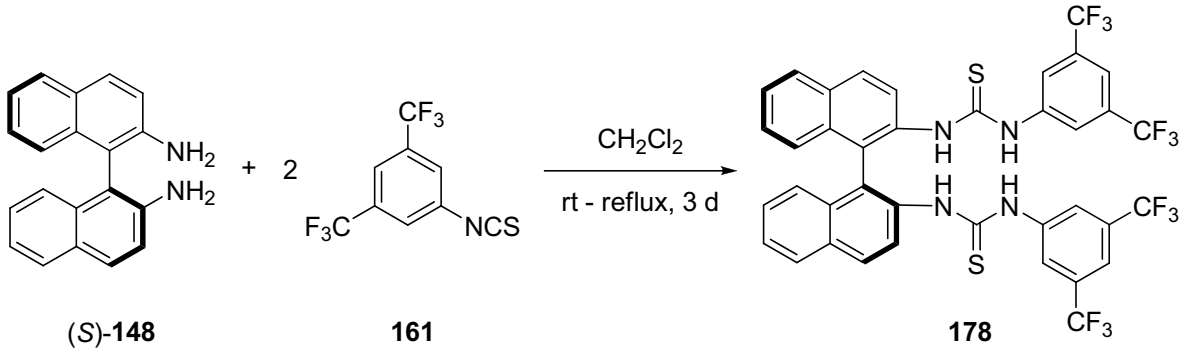
144b **177** **176**

To a solution of L-*tert*-leucine diethylamide (**144b**, 0.25 mg, 1.34 mmol, 1.0 equiv) in toluene (3 mL) was added isothiocyanatobenzene (**177**, 0.2 ml, 1.75 mmol, 1.3 equiv). The reaction mixture was stirred at 40 °C for five hours and then concentrated *in vacuo*. The crude product was purified by flash chromatography (15-20% of ethylacetate in hexanes) to yield thiourea **176** (0.42 g, 1.31 mmol, 97%) as a colorless solid.

176: $C_{17}H_{27}N_3OS$ (321.48 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 (br s, 1H, $C_{Ar}N\boldsymbol{H}$), 7.44-7.39 (s, 2H, $C\boldsymbol{H}_{Ar}$), 7.28-7.23 (s, 3H, $C\boldsymbol{H}_{Ar}$), 7.04 (br d, *J* = 9.1 Hz, 1H, N***H***CH), 5.58 (d, *J* = 9.5 Hz, 1H, C***H***C$(CH_3)_3$), 3.74-3.68 (m, 2H, $C\boldsymbol{H}_2CH_3$), 3.39-3.34 (q, *J* = 7.1 Hz, 1H, $C\boldsymbol{H}_2CH_3$), 3.02-2.95 (q, *J* = 6.8 Hz, 1H, $C\boldsymbol{H}_2CH_3$), 1.32 (t, *J* = 7.1 Hz, 3H, $CH_2C\boldsymbol{H}_3$), 1.08 (t, *J* = 7.1 Hz, 3H, $CH_2C\boldsymbol{H}_3$), 0.98 (s, 9H, $C(C\boldsymbol{H}_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 180.3 (***C***=S), 170.0 (***C***=O), 136.2 ($\boldsymbol{C}q_{Ar}$), 130.0 ($\boldsymbol{C}H_{Ar}$), 127.0 ($\boldsymbol{C}H_{Ar}$), 124.8 ($\boldsymbol{C}H_{Ar}$), 60.4 ($\boldsymbol{C}HC(CH_3)_3$), 42.9 ($N\boldsymbol{C}H_2CH_3$), 40.1 ($N\boldsymbol{C}H_2CH_3$), 36.5 ($\boldsymbol{C}(CH_3)_3$), 26.8 ($C(\boldsymbol{C}H_3)_3$), 14.6 ($CH_2\boldsymbol{C}H_3$), 12.7 ($CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 321 (10), 248 (69), 233 (44), 221 (11), 192 (6), 163 (2), 136 (17), 93 (17), 86 (100), 74 (63), 57 (5), 41 (10); **HRMS** (EIpos) calcd for $[(C_{17}H_{27}N_4OS+Na)^+]$: 344.1767, found: 344.1769.

7.3.3 Synthesis Bisthioureas

7.3.3.1 (*S*)-1,1'-(1,1'-binaphthyl-2,2'-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)-thiourea) (178)

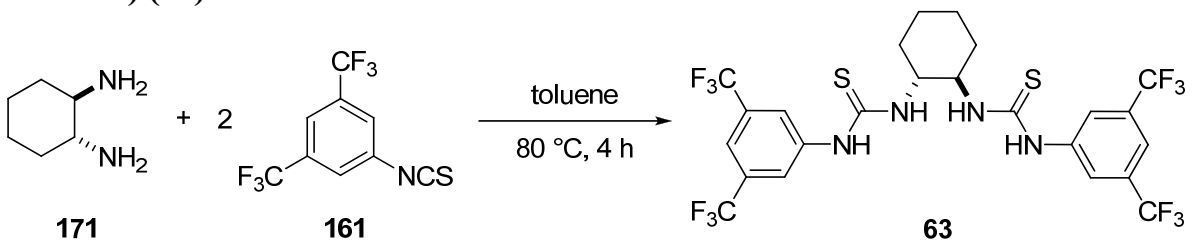


(*S*)-**148** **161** **178**

To a solution of BINAM (*S*)-**148** (0.30 g, 1.06 mmol, 1.0 equiv) in dichloromethane (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**, 0.5 mL, 2.61 mmol, 2.5 equiv). The reaction mixture was stirred for 20 hours at room temperature and refluxed for two additional days. The solution was then concentrated *in vacuo* and the crude product purified by flash chromatography (10-20% of ethyl acetate in hexanes) to yield bisthiourea **178** (0.49 g, 0.59 mmol, 95%) as a pale yellow solid.

178: $C_{38}H_{22}F_{12}N_4S_2$ (826.72 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.17 (br s, 2H, N***H***), 8.08 (d, *J* = 8.8 Hz, 2H, C***H***$_{Ar}$), 7.77 (d, *J* = 8.2 Hz, 2H, C***H***$_{Ar}$), 7.84 (br s, 2H, C***H***$_{Ar}$), 7.74 (s, 4H, C***H***$_{Ar}$), 7.68 (s, 2H, C***H***$_{Ar}$), 7.56 (br s, 2H, N***H***), 7.48 (t, *J* = 7.2 Hz, 2H, C***H***$_{Ar}$), 7.27 (t, *J* = 7.2 Hz, 2H, C***H***$_{Ar}$), 7.12 (d, *J* = 8.4 Hz, 2H, C***H***$_{Ar}$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 180.0 (C=S), 138.8 (***C***q$_{Ar}$), 133.5 (***C***q$_{Ar}$), 132.8 (***C***q$_{Ar}$), 132.4 (***C***q$_{Ar}$), 132.0 (***C***H$_{Ar}$), 131.8 (***C***q$_{Ar}$CF$_3$), 128.8 (***C***H$_{Ar}$), 128.0 (***C***H$_{Ar}$), 127.6 (***C***H$_{Ar}$), 127.0 (***C***H$_{Ar}$), 125.4 (***C***H$_{Ar}$), 124.6 (***C***H$_{Ar}$), 124.0 (C***C***F$_3$), 121.4 (***C***H$_{Ar}$), 119.5 (***C***H$_{Ar}$); **MS** (EI, 70 eV): *m*/*z* (%) = 826 (1), 521 (33), 326 (100), 268 (35), 133 (8); **HRMS** (EIpos) calcd for [($C_{38}H_{22}F_{12}N_4S_2$+H)$^+$]: 827.1094, found: 827.1182. The physical data were identical in all respects to those previously reported.[258]

7.3.3.2 1,1'-((1*R*,2R)-Cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)-thiourea) (63)[98]

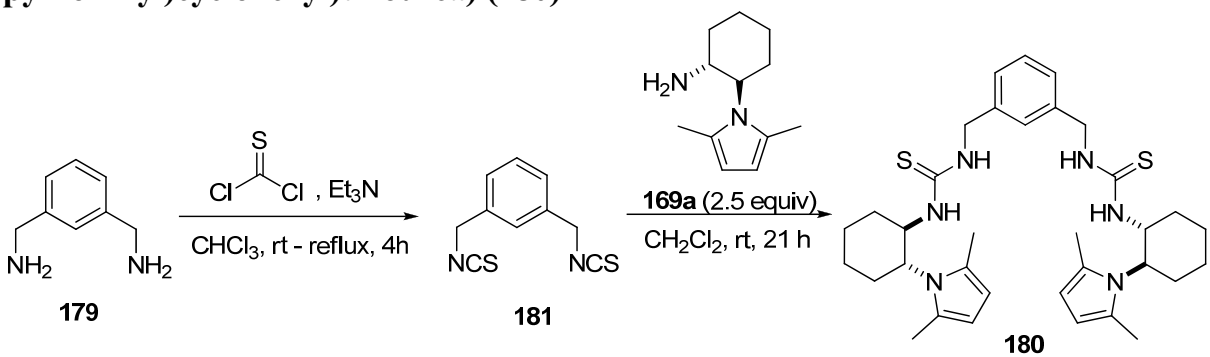


171 **161** **63**

To a solution of (1*R*,2*R*)-(–)-1,2-diaminocyclohexane (**171**, 0.30 g, 2.60 mmol, 1.0 equiv) in toluene (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**161**,1.18 mL, 5.98 mmol, 2.3 equiv). The reaction mixture was stirred for four hours at 90°C and then concentrated *in vacuo*. The crude product was purified by flash chromatography (4% of methanol in dichloromethane) to yield the bisthiourea **63** (1.65g, 2.51 mmol, 96%) as a colorless solid.

63: $C_{24}H_{20}F_{12}N_4S_2$ (656.55 g/mol); **m.p**. = 129-135°C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.19 (br s, 2H, $C_{Ar}N\boldsymbol{H}$), 7.81 (s, 4H, $C\boldsymbol{H}_{Ar}$), 7.68 (s, 2H, $C\boldsymbol{H}_{Ar}$), 7.13 (br s, 2H, CHN***H***), 4.37 (br s, 2H, $CH_2C\boldsymbol{H}CH$ cycl.), 2.18 (br s, 2H, $CH_2C\boldsymbol{H}_2CH$ cycl.), 1.80 (br s, 2H, $CH_2C\boldsymbol{H}_2CH$ cycl.), 1.35 (br s, 4H, $CH_2C\boldsymbol{H}_2CH_2$ cycl.); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 180.5 (*C*=S), 138.6 ($\boldsymbol{C}q_{Ar}$), 133.0 ($\boldsymbol{C}q_{Ar}$), 132.5 ($\boldsymbol{C}q_{Ar}CF_3$), 124.5 ($\boldsymbol{C}H_{Ar}$), 124.1 ($C\boldsymbol{C}F_3$), 120.9 ($\boldsymbol{C}H_{Ar}$), 119.7 ($\boldsymbol{C}H_{Ar}$), 59.4 (***C***H cyclic), 31.7 ($CH_2C\boldsymbol{H}_2CH$ cycl.), 24.4 ($CH_2C\boldsymbol{H}_2CH_2$ cycl.); **MS** (EI, 70 eV): *m*/*z* (%) = 657 (15), 637 (11), 368 (100), 339 (48), 326 (25), 289 (26), 271 (94), 213 (36), 140 (15), 97 (81), 81 (34), 69 (19); **HRMS** (EIpos) calcd for [($C_{24}H_{20}F_{12}N_4S_2$+H)$^+$]: 657.1011, found 657.1017. The physical data were identical in all respects to those previously reported.[98]

7.3.3.3 1,1'-(1,3-Phenylenebis(methylene))bis(3-((1*R*,2*R*)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea) (180)



179 **181** **180**

Preparation of 1,3-bis(isothiocyanatomethyl)benzene (**181**):[225] To a solution of 1,3-phenylenedimethanamine (4.8 mL, 36.71 mmol, 1.0 equiv) and triethylamine (19.3 mL,

139.50 mmol, 3.8 equiv) in chloroform (200 mL, previously filtered through aluminium oxide) was added thiophosgene (6.2 mL, 80.76 mmol, 2.2 equiv) in chloroform (120 mL, previously filtered through aluminium oxide) dropwise at 0 °C under stirring over a period of 30 minutes. After two hours at room temperature, the mixture was refluxed for two hours. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography (10-20% of ethyl acetate in hexanes). Pure bisisothiocyanate **181** (3.70 g, 16.79 mmol, 46%) was obtained as a yellow-orange oil.

181: $C_{10}H_8N_2S_2$ (220.31 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42 (t, *J* = 7.9 Hz, 1H, $CH_{Ar}C\boldsymbol{H}_{Ar}CH_{Ar}$), 7.30 (d, *J* = 8.1 Hz, 2H, $CC\boldsymbol{H}_{Ar}CH_{Ar}$), 7.25 (s, 1H, $CC\boldsymbol{H}_{Ar}C$), 4.74 (s, 4H CCH_2); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 135.2 ($\boldsymbol{C}q_{Ar}$), 133.0 (N$\boldsymbol{C}$S), 129.7 ($\boldsymbol{C}H_{Ar}$), 126.8 ($\boldsymbol{C}H_{Ar}$), 125.2 ($\boldsymbol{C}H_{Ar}$), 48.4 ($C\boldsymbol{H}_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 220 (83), 162 (100), 134 (17), 116 (20), 104 (75), 89 (6), 78 (18), 63 (9), 51 (14), 39 (10); **HRMS** (EI-ED) calcd for [$C_{10}H_8N_2S_2$]: 220.0129, found: 220.0129.

Preparation of 1,1'-(1,3-phenylenebis(methylene))bis(3-((1R,2R)-2-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl)thiorea (**180**): To a solution of 1,3-bis(isothiocyanato-methyl)benzene (**181**, 0.40 g, 1.82 mmol, 1.0 equiv) in dichloromethane (7 mL) was added amine **169a** (0.87 g, 4.54 mmol, 2.5 equiv). The reaction mixture was stirred for 21 hours at room temperature and then concentrated *in vacuo*. The crude product was purified by flash chromatography (20-40% of ethyl acetate in hexanes) to afford the bisthiourea **180** (1.01g, 1.67 mmol, 92%) as a yellow-orange solid.

180: $C_{34}H_{48}N_6S_2$ (604.92 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 7.6 Hz, 1H, $CH_{Ar}C\boldsymbol{H}_{Ar}CH_{Ar}$), 7.02 (d, *J* = 7.5 Hz, 2H, $CC\boldsymbol{H}_{Ar}CH_{Ar}$), 6.78 (s, 1H, $CC\boldsymbol{H}_{Ar}C$), 6.01 (br s, 2H, N***H***), 5.88 (br s, 2 H, N***H***), 5.67 (br d, *J* = 13.4 Hz, 4H, $C\boldsymbol{H}_{Ar}$), 4.40 (br s, 2H, NHC***H*** cycl.), 4.20 (br s, 4H, $C\boldsymbol{H}_2$), 3.82-3.75 (m, 2H, NC***H*** cycl.), 2.36-2.16 (br ss, 12H, $C\boldsymbol{H}_3$), 2.00-1.74 (m, 10H, $C\boldsymbol{H}_2$ cycl.), 1.43-1.13 (m, 4H, $C\boldsymbol{H}_2$ cycl.), 1.10-1.08 (m, 2H, $C\boldsymbol{H}_2$ cycl.); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 181.8 (*C*=S), 137.4 ($\boldsymbol{C}q_{Ar}$), 129.3 ($\boldsymbol{C}q_{Ar,pyr.}$), 128.8 ($\boldsymbol{C}H_{Ar}$), 127.0 ($\boldsymbol{C}H_{Ar}$), 126.8 ($\boldsymbol{C}q_{Ar,pyr.}$), 126.4 ($\boldsymbol{C}H_{Ar}$), 108.7 ($\boldsymbol{C}H_{Ar,pyr.}$), 106.2 ($\boldsymbol{C}H_{Ar,pyr.}$), 59.6 ($\boldsymbol{C}$H cycl.), 56.5 ($\boldsymbol{C}$H cycl.), 48.2 ($C_{Ar}\boldsymbol{C}H_2NH$), 33.8 ($\boldsymbol{C}H_2$ cycl.), 31.9 ($\boldsymbol{C}H_2$ cyclic), 25.7 ($\boldsymbol{C}H_2$ cycl.), 25.6 ($\boldsymbol{C}H_2$ cycl.), 14.2 ($\boldsymbol{C}H_3$), 13.7 ($\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 604 (0.5), 426 (23), 370 (9), 234 (82), 175 (47), 96 (100), 81 (65); **HRMS** (EIpos) calcd for [$(C_{34}H_{48}N_6S_2+H)^+$]: 605.3455, found: 605.3456.

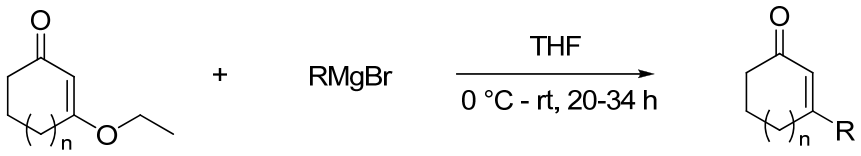
7.4 Enantioselective Transfer Hydrogenation of α,β-Unsaturated Ketones

7.4.1 Synthesis of the Starting Materials

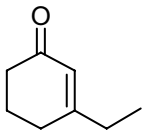
7.4.1.1 Synthesis of the α,β-Unsaturated Cyclic Ketones 107

General Procedure for the Synthesis of β-Substituted Cyclic Enones

3-Methylcyclohexenone **107b** and 3-methylcyclopentenone **107c** were purchased from Sigma-Aldrich. 3-Benzylcyclohexenone **107a** was prepared by *J. Zhou*. The other cyclic enones were synthesized according to the following procedure.[163]

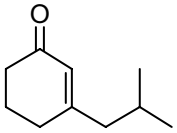


184a-b **107a-i**



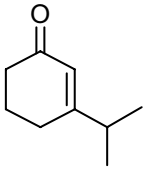
3-Ethylcyclohexenone (107d): A flame-dried flask was charged with ethylmagnesium bromide (14.3 mL, 42.8 mmol, 3.0 M in diethyl ether, 2.0 equiv) and cooled to 0 °C. 3-Ethoxycyclohexenone (**184a**, 3.00 g, 21.40 mmol) in THF (15 mL) was added to the Grignard reagent dropwise. Once the addition was complete the reaction mixture was left at room temperature until complete disappearance of the starting material. After 20 hours the reaction was slowly quenched with a solution of hydrochloric acid (1 N, 100 mL). The aqueous phase was separated and extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed successively with a saturated aqueous solution of sodium dicarbonate, brine and water. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10-20% of diethyl ether in pentane) to provide the title compound (**107d**, 1.40 g, 11.27 mmol, 53% yield, reduced yield due to high volatility) as a yellow oil.

107d: $C_8H_{12}O$ (124.18 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.86 (dd, *J* = 2.1 Hz, 1.2 Hz, 1H, C(O)C***H***=C), 2.34 (dt, *J* = 7.2 Hz, 1.4 Hz, 2H, C(O)C***H***$_2$), 2.27 (t, *J* = 5.8 Hz, 2H, CC***H***$_2$ cycl.), 2.22 (q, *J* = 7.5 Hz, 2H, CC***H***$_2$CH$_3$), 1.97 (qt, *J* = 6.5 Hz, 2H, C***H***$_2$ cycl.), 1.08 (q, *J* = 7.5 Hz, 2H, CCH$_2$C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 200.0 (***C***=O), 167.9 (***C***=CH), 124.5 (C=***C***H), 37.3 (C(O)***C***H$_2$ cycl.), 30.8 (C***C***H$_2$CH$_2$ cycl.), 29.7 (C***C***H$_2$CH$_3$), 22.7 (CH$_2$***C***H$_2$CH$_2$ cycl.), 11.2 (CCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 124 (52), 96 (100), 81 (24), 67 (24), 53 (14), 39 (20), 27 (11); **HRMS** (EI-FE) calcd for [$C_8H_{12}O$]: 124.0888, found: 124.0889. The physical data were identical in all respects to those previously reported.[259]



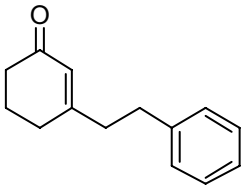
3-Isobutylcyclohexenone (**107e**)**:** Enone **107e** was prepared following the procedure described for **107d**, starting from 3-ethoxycyclohexenone (**184a**, 3.00 g, 21.40 mmol) and isobutylmagnesium bromide (14.3 mL, 42.8 mmol, 3.0 M in diethyl ether). After purification by flash chromatography (15% of diethyl ether in pentane), the title compound (**107e**, 2.51 g, 16.49 mmol, 77% yield) was obtained as a yellow oil.

107e: $C_{10}H_{16}O$ (152.23 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.83 (s, 1H, C(O)C***H***=C), 2.34 (t, *J* = 6.7 Hz, 2H, C(O)C***H***$_2$), 2.25 (t, *J* = 6.1 Hz, 2H, CC***H***$_2$ cycl.), 2.07 (d, *J* = 7.2 Hz, 2H, C***H***$_2$CH(CH$_3$)$_2$), 1.97 (qt, *J* = 6.3 Hz, 2H, C***H***$_2$ cycl.), 1.96-1.86 (m, 1H, CH$_2$C***H***(CH$_3$)$_2$), 1.07 (d, *J* = 7.2 Hz, 6H, CH$_2$CH(C***H***$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.9 (***C***=O), 165.6 (***C***=CH), 126.9 (C=***C***H), 47.6 (***C***H$_2$CH(CH$_3$)$_2$), 37.3 (C(O)***C***H$_2$ cycl.), 29.6 (C***C***H$_2$CH$_2$ cycl.), 26.3 (CH$_2$***C***H(CH$_3$)$_2$), 22.7 (CH$_2$***C***H$_2$CH$_2$ cycl.), 22.5 (CH$_2$CH(***C***H$_3$)$_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 152 (35), 137 (21), 124 (7), 110 (22), 82 (100), 67 (6), 53 (8), 41 (16), 27 (10); **HRMS** (EI-FE) calcd for [$C_{10}H_{16}O$]: 152.1201, found: 152.1202. The physical data were identical in all respects to those previously reported.[260]



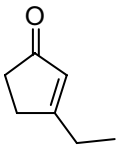
3-Isopropylcyclohexenone (**107f**)**:** Enone **107f** was prepared following the procedure described for **107d**, starting from 3-ethoxycyclohexenone (**184a**, 3.00 g, 21.40 mmol) and isopropylmagnesium bromide (21.4 mL, 42.8 mmol, 2.0 M in diethyl ether). After purification by flash chromatography (10-20% of diethyl ether in pentane), the title compound (**107f**, 2.02 g, 14.62 mmol, 68% yield) was obtained as a yellow oil.

107f: $C_9H_{14}O$ (138.21 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.87 (s, 1H, C(O)C***H***=C), 2.43-2.28 (m, 5H: C(O)C***H***$_2$ (2H), CC***H***$_2$ cycl. (2H), C***H***$(CH_3)_2$ (1H)), 1.98 (qt, *J* = 6.4 Hz, 2H, C***H***$_2$ cycl.), 1.07 (d, *J* = 7.2 Hz, 6H, CH(C***H***$_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 200.3 (***C***=O), 171.8 (***C***=CH), 123.6 (C=***C***H), 37.6 (C(O)***C***H_2 cycl.), 35.7 (***C***$H(CH_3)_2$), 27.7 (C***C***H_2CH_2 cycl.), 22.9 (CH_2***C***H_2CH_2 cycl.), 20.6 (CH(***C***$H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 138 (39), 123 (7), 110 (73), 95 (100), 82 (20), 67 (52), 55 (12), 41 (25), 27 (9); **HRMS** (EI-FE) calcd for [$C_9H_{14}O$]: 138.1045, found: 138.1047. The physical data were identical in all respects to those previously reported.[261]



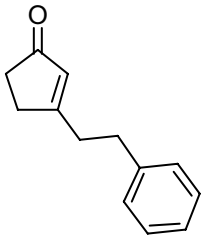
3-Phenethylcyclohexenone (**107g):** Magnesium turnings (1.24 g, 51.00 mmol) and THF (25 mL) were placed into a dry flask. 2-Phenylethylbromide (**195**, 7.0 mL, 51.00 mmol) was placed into a separate dry flask, dissolved in THF (25 mL) and then added via syringe to the magnesium solution. The resulting mixture was then heated at 60 °C and after 15 hours cooled to 40 °C (at room temperature the Grignard solidifies). The solution of Grignard reagent was then separated from remaining magnesium solid by transferring the solution via syringe to another dry flask. Enone **107g** was prepared following the procedure described for **107d**, starting from 3-ethoxycyclohexenone (**184a**, 3.00 g, 21.40 mmol). After purification by flash chromatography (20-30% of ethyl acetate in hexanes), the title compound (**107g**, 3.90 g, 19.47 mmol, 91% yield) was obtained as a yellow oil.

107g: $C_{14}H_{16}O$ (200.28 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H, C***H***$_{Ar}$), 5.90 (s, 1H, C(O)C***H***=C), 2.87-2.80 (m, 2H, C(O)C***H***$_2$), 2.55-2.50 (m, 2H, CH_2C***H***$_2$Ph), 2.38-2.29 (m, 4H: C***H***$_2CH_2$Ph (2H), CC***H***$_2$ cycl. (2H)), 2.04-1.94 (m, 2H, C***H***$_2$ cycl.); **^{13}C NMR** (75 MHz, CDCl3): δ 199.8 (***C***=O), 165.0 (***C***=CH), 140.7 (***C***q_{Ar}), 129.0 (***C***H_{Ar}), 128.5 (***C***H_{Ar}), 128.2 (***C***H_{Ar}), 126.4 (***C***H_{Ar}), 126.2 (***C***H_{Ar}), 123.6 (C=***C***H), 39.6 (C(O)***C***H_2 cycl.), 39.2 (C***C***H_2), 37.3 (C***C***H_2), 29.8 (CH_2***C***H_2Ph), 22.6 (CH_2***C***H_2CH_2 cycl.); **MS** (EI, 70 eV): *m*/*z* (%) = 200 (16), 182 (6), 129 (10), 91 (100), 65 (9), 39 (6); **HRMS** (EI-DE) calcd for [$C_{14}H_{16}O$]: 200.1201, found: 200.1203. The physical data were identical in all respects to those previously reported.[262]



3-Ethylcyclopentenone (**107h):** Enone **107h** was prepared following the procedure described for **107d**, starting from 3-ethoxycyclopentenone (**184b**, 2.00 g, 15.85 mmol) and isopropylmagnesium bromide (8.0 mL, 23.78 mmol, 3.0 M in diethyl ether). After purification by flash chromatography (50% of diethyl ether in pentane), the title compound (**107h**, 0.60 g, 5.45 mmol, 34% yield, reduced yield due to high volatility) was obtained as a yellow oil.

107h: $C_7H_{10}O$ (110.15 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.92 (s, 1H, C(O)C***H***=C), 2.58-2.56 (m, 2H: C(O)C***H***$_2$), 2.43-2.37 (m, 4H: ***C***H_2CH_3 (q, *J* = 7.3 Hz, 2H), CC***H***$_2$ cycl. (2H)), 1.17 (t, *J* = 7.4 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (100 MHz, CDCl3): δ 210.1 (***C***=O), 184.4 (***C***=CH), 128.6 (C=***C***H), 35.3 (C(O)***C***H_2 cycl.), 31.3 (***C***H_2CH_3), 26.6 (C***C***H_2 cycl.), 11.4 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 110 (95), 95 (18), 81 (100), 67 (61), 53 (59), 51 (13), 41 (23), 39 (37), 27 (31); **HRMS** (EI-FE) calcd for [$C_7H_{10}O$]: 110.0731, found: 110.0732. The physical data were identical in all respects to those previously reported.[263]

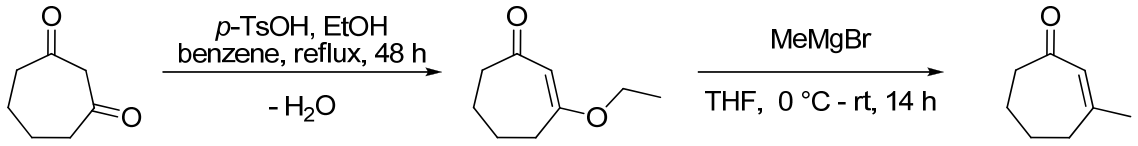


3-Phenethylcyclopentenone (**107i):** Magnesium turnings (0.72 g, 40.00 mmol) and THF (20 mL) were placed into a dry flask. 2-Phenylethylbromide (**195**, 5.5 mL, 40.0 mmol) was placed into a separated dry flask, dissolved in THF (20 mL) and then added via syringe to the magnesium solution. The resulting mixture was then heated at 60 °C and after 15 hours cooled to 40 °C. The solution of Grignard reagent was then separated from remaining solid magnesium by transferring the solution via syringe to another dry flask. Enone **107i** was prepared following the procedure described for **107d**, starting from 3-ethoxycyclopentenone (**184b**, 2.00 g, 15.85 mmol). After purification by flash chromatography (20-30% of ethyl acetate in hexanes), the title compound (**107i**, 2.61 g, 14.01 mmol, 88% yield) was obtained as an orange oil.

107i: $C_{13}H_{14}O$ (186.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.19 (m, 5H, C***H***$_{Ar}$), 5.98 (s, 1H, C(O)C***H***=C), 2.94-2.89 (m, 2H, C(O)C***H***$_2$), 2.76-2.74 (m, 2H, CH_2C***H***$_2$Ph), 2.60-2.57 (m, 2H, C***H***$_2CH_2$Ph), 2.41-2.38 (m, 2H, CC***H***$_2$ cycl.); **^{13}C NMR** (100 MHz, CDCl3): δ 209.9 (***C***=O), 181.7 (***C***=CH), 140.5 (***C***q$_{Ar}$), 129.8 (***C***H$_{Ar}$), 129.0 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 128.1 (***C***H$_{Ar}$), 126.3 (C=***C***H), 35.2 (C(O)***C***H_2 cycl.), 35.0 (CH_2***C***H_2Ph), 33.2 (CH_2***C***H_2Ph), 31.7 (C***C***H_2CH_2 cycl.); **MS** (EI, 70 eV): *m*/*z* (%) = 186 (23), 143 (1), 129 (3), 115 (1), 104 (1), 91

(100), 77 (2), 65 (9), 51 (3), 39 (5), 27 (2); **HRMS** (EI-DE) calcd for [$C_{13}H_{14}O$]: 186.1045, found: 186.1043. The physical data were identical in all respects to those previously reported.[264]

Preparation of 3-Methylcycloheptenone **(107j)**



187 **184c** **107j**

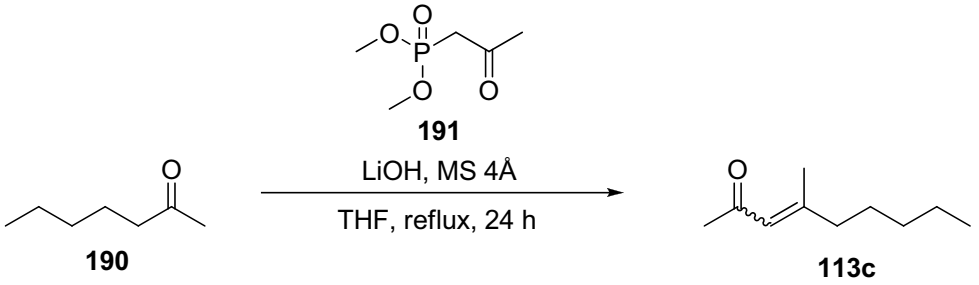
3-Ethoxycycloheptenone was prepared according to the procedure of de Meijere *et al*.[228] In a flame-dried flask equipped with a condenser and a Dean-stark apparatus a mixture of cycloheptane-1,3-dione (**187**, 1.57 g, 12.20 mmol), ethanol (3 mL), and a catalytic amount of *para*-toluene sulfonic acid (31 mg, 0.16 mmol) in benzene (80 mL) was refluxed. After two days the reaction was stopped (despite incomplete conversion) and the solvent was evaporated *in vacuo*. By flash chromatography (20% of diethyl ether in pentane) cycloheptane-1,3-dione (**187**) and 3-ethoxycycloheptenone (**184c**) could not be separated. The resulting mixture of both compounds (1.5g, cycloheptane-1,3-dione (**187**) / 3-ethoxycycloheptenone (**184c**) about 2:1 according to NMR) was used without further purification for the synthesis of 3-methylcycloheptenone (**107j**).

Enone **107j** was then prepared according to the procedure used to synthesize **107d**, starting from this mixture of cycloheptane-1,3-dione (**187**) and 3-ethoxycycloheptenone (**184c**) in THF (8 mL) and methylmagnesium bromide (5.2 mL, 15.60 mmol, 3.0 M in diethyl ether). After purification by flash chromatography (20-25% of diethyl ether in pentane), the title compound (**107j**, 0.70 g, 5.64 mmol, 46% overall yield) was obtained as a pale yellow oil.

107j: $C_8H_{12}O$ (124.18 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.93 (s, 1H, C(O)C***H***=C), 2.58 (t, *J* = 3.9 Hz, 2H, C(O)C***H***$_2$), 2.42 (t, *J* = 3.5 Hz, 2H, CC***H***$_2$ cycl.), 1.96 (s, 3H, CC***H***$_3$),1.74-1.85 (m, 4H, $CH_2C\boldsymbol{H}_2CH_2$ (2H), $CH_2C\boldsymbol{H}_2CH_2$ (2H)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.7 (***C***=O), 158.4 (***C***=CH), 129.9 (C=***C***H), 42.5 (C(O)***C***H$_2$ cycl.), 34.6 (C***C***H$_2$CH$_2$ cycl.), 27.6 ($CH_2\boldsymbol{C}H_2CH_2$), 25.2 (C***C***H$_3$), 21.5 ($CH_2\boldsymbol{C}H_2CH_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 124 (66), 109 (24), 95 (100), 82 (82), 67 (50), 53 (20), 39 (36), 27 (18); **HRMS** (EI-DE) calcd for [$C_8H_{12}O$]: 124.0888, found: 124.0887.

7.4.1.2 Synthesis of the α,β-Unsaturated Acyclic Ketones 113c

Preparation of 4-methylnon-3-en-2-one (113c) through Horner-Wadsworth-Emmons olefination [231]

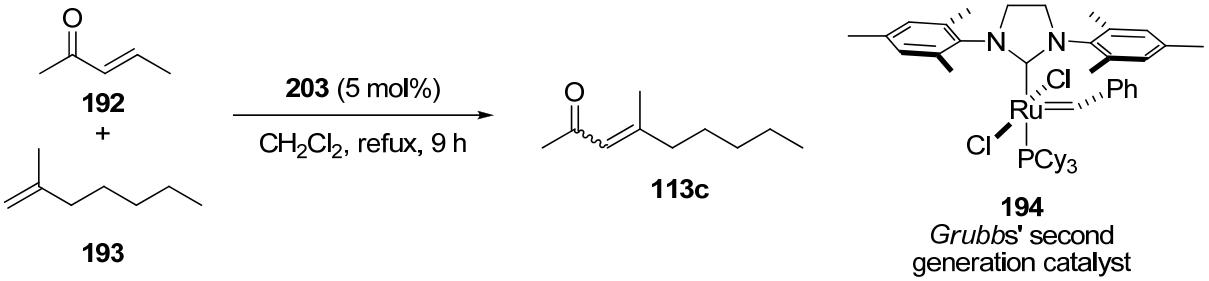


A suspension of heptan-2-one (**190**, 3.7 mL, 26.27 mmol, 1.0 equiv), dimethyl-2-oxopropylphosphonate (**191**, 2.8 mL, 28.90 mmol, 1.1 equiv) and activated 4 Å molecular sieves (40 g) in THF (250 mL) was stirred at reflux. Lithium hydroxide monohydrate (0.69 g, 28.90 mmol, 1.1 equiv; previously dried in oven at 180 °C for two hours) was added in three portions, during the reaction course. The reaction mixture was stirred under at reflux during 48 hours and then cooled to room temperature. The molecular sieve was filtered off and a saturated aqueous solution of ammonium chloride (100 mL) and diethyl ether (100 mL) were added to the filtrate. The two remaining layers were then separated and the aqueous phase extracted with diethyl ether (3 × 75 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (3% of diethyl ether in pentane) to provide the title compound **113c** (enriched (*E*)- and enriched (*Z*)-isomers) as a pale yellow oil.

Enriched (*Z*)-**113c**: *Z*/*E* = 9:1, 0.04 g, 0.26 mmol, 1% yield. $C_{10}H_{18}O$ (154.24 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.05 (s, 1H, C(O)C***H***=C), 2.56 (t, *J* = 7.8 Hz, 2H, C=CC***H***$_2$CH$_2$) 2.14 (s, 3H, C(O)C***H***$_3$), 1.86 (s, 3H, C=CC***H***$_3$), 1.45-1.41 (br m, 2 H, CH$_2$***C***H$_2$CH$_2$), 1.35-1.25 (br m, 4H: CH$_2$***C***H$_2$CH$_2$ (2H), CH$_2$***C***H$_2$CH$_3$ (2H)), 0.93-0.85 (br m, 2H, CH$_2$***C***H$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.0 (***C***=O), 159.4 (***C***=CH), 123.7 (C=***C***H), 36.4 (C=C***C***H$_2$CH$_2$), 33.2 (C(O)***C***H$_3$), 31.6 (CH$_2$***C***H$_2$CH$_2$), 27.5 (CH$_2$***C***H$_2$CH$_2$), 25.1 (CH$_2$***C***H$_2$CH$_2$), 22.2 (C=C***C***H$_3$), 13.7 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 154 (2), 139 (20), 111 (26), 98 (64), 83 (73), 69 (45), 55 (48), 43 (100), 41 (32), 29 (17); **HRMS** (EI-FE) calcd for [$C_{10}H_{18}O$]: 154.1358, found: 154.1359. The physical data were identical in all respects to those previously reported (^{1}H NMR).[265]

Enriched (*E*)-**113c**: *E*/*Z* = 2.3:1, 0.13 g, 0.84 mmol, 3% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.06 (s, 1H, C(O)C***H***=C), 2.17 (s, 3H, C(O)C***H***$_3$), 2.14-2.08 (m, 5H: C=CC***H***$_2$CH$_2$ (2H), C=CC***H***$_3$ (3H)), 1.48-1.44 (br m, 2 H, CH$_2$***C***H$_2$CH$_2$), 1.32-1.25 (br m, 4H: CH$_2$***C***H$_2$CH$_2$ (2H), CH$_2$***C***H$_2$CH$_3$ (2H)), 0.89 (t, *J* = 7.1 Hz, 3H, CH$_2$***C***H$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.6 (***C***=O), 158.7 (***C***=CH), 123.1 (C=***C***H), 40.9 (C=C***C***H$_2$CH$_2$), 31.4 (C(O)***C***H$_3$), 31.1 (CH$_2$***C***H$_2$CH$_2$), 26.8 (CH$_2$***C***H$_2$CH$_2$), 22.1 (CH$_2$***C***H$_2$CH$_2$), 18.9 (C=C***C***H$_3$), 13.6 (CH$_2$***C***H$_3$).

Preparation of 4-methylnon-3-en-2-one (113c) through ruthenium-catalyzed olefin cross-metathesis [232]

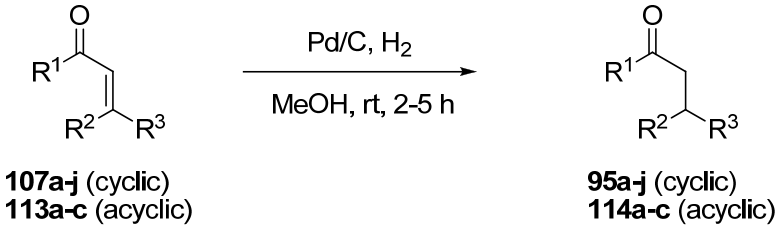


To a flask equipped with a condenser was added *Grubbs*' second generation ruthenium catalyst (**194**, 1.82 g, 2.14 mmol, 0.05 equiv) in dichloromethane (17 mL). To this mixture were successively added (*E*)-pent-3-en-2-one (**192**, 3.9 mL, 42.79 mmol, 1.0 equiv) and 2-methylhept-1-ene (**193**, 26.9 mL, 171.16 mmol, 4.0 equiv) under stirring at room temperature. The reaction mixture was stirred under reflux for nine hours and then allowed to cool to room temperature. The volatile compounds were removed under reduced pressure and the crude product was purified by flash column chromatography (3% of diethyl ether in pentane) to provide the title compound **113c** (enriched (*E*)- and enriched (*Z*)-isomers) as a pale yellow oil. Enriched (*E*)-**113c**: *E*/*Z*: 14:1, 80 mg, 0.52 mmol, 1%); enriched (*Z*)-**113c**: *Z*/*E* = 14:1, 40 mg, 0.26 mmol, 1% yield).

7.4.2 General Procedure for the Synthesis of the Racemic Products

3-Methylcyclohexanone (**95b**) and 3-methylcyclopentanone (**95c**) were purchased from Sigma-Aldrich. The other racemic ketones (**95a,d-j** and **114a-c**) were prepared through palladium-catalyzed conjugate reduction of the enones **107a,d-j** and **113a-c** with molecular hydrogen.[233]

General procedure:

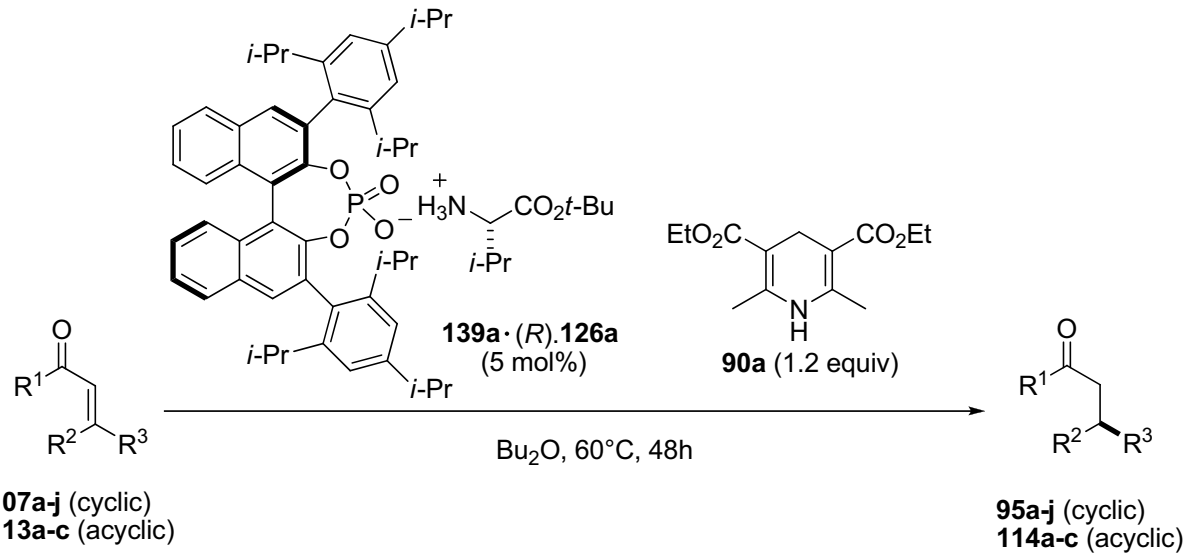


107a-j (cyclic)
113a-c (acyclic)

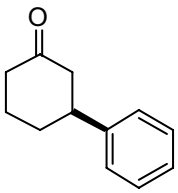
95a-j (cyclic)
114a-c (acyclic)

In a flask (dried and under an atmosphere of argon) charged with palladium on charcoal (8.5 mg, 0.08 mmol, 0.1 equiv) in methanol (5 mL) was added enone (**107** or **113**, 0.80 mmol). The flask was then carefully evacuated and filled with molecular hydrogen. The reaction mixture was stirred at room temperature for two to five hours. The solution was then filtered through celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluents: diethyl ether/pentane) to provide the desired saturated ketone (**95** or **114**).

7.4.3 Asymmetric Transfer Hydrogenation of *α,β*-Unsaturated Ketones

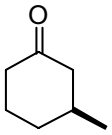


To *β*-substituted-*α,β*-unsaturated ketone (**107** or **113**, 0.100 mmol) in dibutyl ether (0.3 mL, 0.3 M), catalyst [**139a**·(*R*)-**126a**] (4.6 mg, 0.005 mmol, 0.05 equiv) and Hantzsch ester **90a** (30.4 mg, 0.12 mmol, 1.2 equiv) were added. The reaction mixture was stirred at 60 °C under an atmosphere of argon for 48 hours and then treated with an aqueous solution of sodium hydroxide (2 N, 2 mL) and diethyl ether (2 mL). The two layers were separated and the aqueous phase extracted with diethyl ether (3 × 2 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluents: diethyl ether/pentane) to afford the desired saturated ketone (**107** or **113**).

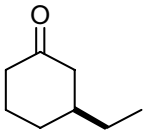


(*S*)-3-Phenylcyclohexanone (95a): The enantiomers were analyzed by GC using a chiral BGB 176 column (100 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 41.20 min, minor enantiomer: t_R = 41.76 min. **95a** (17.2 mg, 0.099 mmol, 99%; 92:8 *er*): $C_{12}H_{14}O$ (174.24 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H, C***H***$_{Ar}$), 7.25-7.21 (m, 3H, C***H***$_{Ar}$), 3.05-2.98 (m, 1H, C(O)CH$_2$C***H***Ph), 3.60-3.35 (m, 4H: C(O)C***H***$_2$CH (2H), C(O)C***H***$_2$CH$_2$ (2H)), 2.18-2.07 (m, 1H, CH$_2$C***H***$_2$CH), 2.08-2.01 (m, 2H: (1H), , 1.99-1.90 (m, 2H, CH$_2$C***H***$_2$CH), 1.98-1.75 (m, 2H, CH$_2$C***H***$_2$CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.0 (***C***=O), 144.3 (***C***q$_{Ar}$), 128.7 (***C***H$_{Ar}$), 126.7 (***C***H$_{Ar}$), 126.5 (***C***H$_{Ar}$), 48.9 (C(O)***C***H$_2$CH), 44.7 (***C***HPh), 41.2 (C(O)***C***H$_2$CH$_2$), 32.8 (CH$_2$***C***H$_2$CH$_2$), 25.5 (CH$_2$***C***H$_2$CH); **HRMS** (EI-FE) calcd

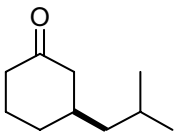
for [$C_{12}H_{14}O$]: 174.1045, found: 174.1043. The physical data were identical in all respects to those previously reported.[135]



(*S*)-3-Methylcyclohexanone (95b): The enantiomers were analyzed by GC using a chiral BGB-178 column (2 min at 50 °C, 5 °C/min until 100 °C, 1 min at 100 °C, 20 °C/min until 150 °C, 2 min at 150 °C); major enantiomer: t_R = 12.38 min, minor enantiomer: t_R = 12.19 min. **95b** (11.1 mg, 0.099 mmol, 99%; 97:3 *er*): $C_7H_{12}O$ (112.17 g/mol); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.39-2.30 (m, 2H, C(O)C***H***$_2$), 2.25-2.19 (m, 1H, C(O)C***H***$_2$), 2.04-1.96 (m, 2H: C(O)C***H***$_2$ (1H), CH_2C***H***CH_3 (1H)), 1.91-1.82 (m, 2H, CH_2C***H***$_2CH_2$), 1.69-1.61 (m, 1H, CH_2C***H***$_2CH$), 1.36-1.28 (m, 1H, CH_2C***H***$_2CH$), 1.01 (d, *J* = 6.5 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 212.0 (***C***=O), 50.0 (C(O)***C***H_2CH), 41.1 (C(O)***C***H_2CH_2), 34.2 (***C***HCH_3), 33.3 (CH_2***C***H_2CH), 25.3 (CH_2***C***H_2CH_2), 22.0 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) =112 (39), 97 (13), 69 (100), 56 (44), 41 (43), 39 (22), 27 (14); **GC-MS** (GC-EI): 112. The physical data were identical in all respects to those of the commercially available **95b** (Sigma-Aldrich).

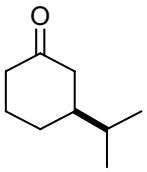


(*S*)-3-Ethylcyclohexanone (95d): The enantiomers were analyzed by GC using a chiral Lipodex-A column (5 min at 50 °C, 0.5 °C/min until 70 °C, 18 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 30.53 min, minor enantiomer: t_R = 30.03 min. **95d** (12.4 mg, 0.098 mmol, 98%; 98:2 *er*): $C_8H_{14}O$ (126.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.44-2.19 (m, 3H: C(O)C***H***$_2CH_2$ (2H), C(O)C***H***$_2$CH (1H)), 2.07-1.86 (m, 3H: C(O)C***H***$_2$CH (1H), $C(O)CH_2C$***H*** (1H), CH_2C***H***$_2$CH (1H)), 1.71-1.58 (m, 2H, CH_2C***H***$_2CH_2$), 1.41-1.24 (m, 3H: CH_2C***H***$_2$CH (1H), CHC***H***$_2CH_3$ (2H)), 0.89 (t, *J* = 7.4 Hz, 3H, $CHCH_2C$***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.2 (***C***=O), 53.4 (C(O)***C***H_2CH), 47.8 (C(O)***C***H_2CH_2), 41.5 (***C***HCH_2CH_3), 41.8 (CH_2***C***H_2CH), 30.9 (CH***C***H_2CH_3), 25.3 (CH_2***C***H_2CH_2), 11.1 ($CHCH_2$***C***H_3); **GC-MS** (GC-EI): 126. The physical data were identical in all respects to those previously reported.[135]

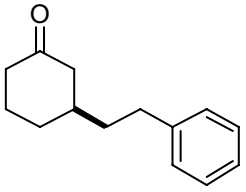


(*S*)-3-Isobutylcyclohexanone (95e): The enantiomers were analyzed by GC using a chiral Lipodex-A column (50 °C, 1 °C/min until 120 °C, 18 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 32.58 min, minor enantiomer: t_R = 31.97 min. **95e** (13.7 mg, 0.089 mmol, 89%; 98:2 *er*): $C_{10}H_{18}O$ (154.24 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.41-2.37 (m, 3H: C(O)C***H***$_2CH_2$ (2H), C(O)C***H***$_2$CH (1H)), 2.05-1.84 (m, 3H: C(O)C***H***$_2$CH (1H), $C(O)CH_2C$***H*** (1H), CH_2C***H***$_2$CH (1H)), 1.66-1.62

(m, 2H, $CH_2C\boldsymbol{H}_2CH_2$), 1.45-1.22 (m, 4H: $CH_2C\boldsymbol{H}_2CH$ (1H), $CH_2C\boldsymbol{H}(CH_3)_2$ (1H), $C\boldsymbol{H}_2CH(CH_3)_2$ (2H)), 0.86 (d, J = 7.3 Hz, 6H, $CH_2CH(C\boldsymbol{H}_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.1 (***C***=O), 48.3 (C(O)***C***H_2CH), 46.1 (C(O)***C***H_2CH_2), 41.5 (CH***C***$H_2CH(CH_3)_2$), 36.7 (***C***$HCH_2CH(CH_3)_2$), 31.5 ($CH_2\boldsymbol{C}H_2CH$), 25.3 ($CHCH_2\boldsymbol{C}H(CH_3)_2$), 24.7 ($CH_2\boldsymbol{C}H_2CH_2$), 22.7 ($CHCH_2CH(\boldsymbol{C}H_3)_2$), 22.6 ($CHCH_2CH(\boldsymbol{C}H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 154 (16), 139 (7), 111 (27), 97 (100), 83 (9), 69 (15), 55 (40), 41 (27), 27 (6); **HRMS** (EI-DE) calcd for [$C_{10}H_{18}O$]: 154.1358, found: 154.1358. The physical data were identical in all respects to those previously reported.[135]

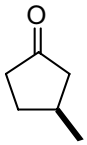


(*S*)-3-Isopropylcyclohexanone (95f): The enantiomers were analyzed by GC using a chiral Lipodex-A column (10 min at 50 °C, 1.2 °C/min until 120 °C, 18 °C/min until 180 °C, 5 min at 180 °C); major enantiomer: t_R = 24.69 min, minor enantiomer: t_R = 24.29 min. **95f** (13.2 mg, 0.094 mmol, 94%; 99:1 *er*): $C_9H_{16}O$ (140.22 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.38-2.12 (m, 3H: C(O)C$\boldsymbol{H}_2CH_2$ (2H), C(O)C$\boldsymbol{H}_2$CH (1H)), 2.10-2.00 (m, 2H: C(O)C$\boldsymbol{H}_2$CH (1H), C(O)$CH_2C\boldsymbol{H}$ (1H)), 1.88-1.81 (m, 1 H, $CH_2C\boldsymbol{H}_2CH$), 1.60-1.49 (3H: $CH_2C\boldsymbol{H}_2CH_2$ (2H), C***H***$(CH_3)_2$ (1H)), 1.36-1.30 (m, 1H, $CH_2C\boldsymbol{H}_2CH$), 0.89 (dd, J = 6.5 Hz, 2.2 Hz, 6H, $CH(C\boldsymbol{H}_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.5 (***C***=O), 45.4 (C(O)***C***H_2CH), 45.3 (***C***$HCH(CH_3)_2$), 41.4 (C(O)***C***H_2CH_2), 32.4 (CH***C***$H(CH_3)_2$), 28.3 ($CH_2\boldsymbol{C}H_2CH$), 25.4 ($CH_2\boldsymbol{C}H_2CH_2$), 19.3 ($CH(\boldsymbol{C}H_3)_2$), 19.0 ($CH(\boldsymbol{C}H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 140 (27), 97 (100), 82 (25), 69 (45), 55 (62), 41 (54), 27 (11); **HRMS** (EI-DE) calcd for [$C_9H_{16}O$]: 140.1201, found: 140.1203. The physical data were identical in all respects to those previously reported.[266]

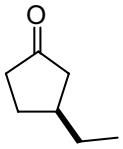


(*S*)-3-Phenethylcyclohexanone (95g): Purification by flash chromatography (5-10% of diethyl ether in pentane) afforded the pure product (**95g**, 20.0 mg, 0.099 mmol, 99%; 98:2 *er*) as a colorless oil. The enantiomers were analyzed by HPLC using a chiral Chiralpak AS-H column (n-heptane/2-propanole = 90:10, flow rate = 0.5 mL/min, wavelength = 220 nm). Major enantiomer: t_R = 16.55 min, minor enantiomer: t_R = 14.98 min. **95g**: $C_{14}H_{18}O$ (202.29 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H, C$\boldsymbol{H}_{Ar}$), 7.19-7.15 (m, 3H, C$\boldsymbol{H}_{Ar}$), 2.62 (t, J = 8.0 Hz, 2H, $CH_2C\boldsymbol{H}_2$Ph), 2.49-2.46 (m, 1H, C(O)C$\boldsymbol{H}_2$CH), 2.38-2.30 (m, 1H, C(O)C$\boldsymbol{H}_2CH_2$), 2.16-2.10 (m, 1H, C(O)C$\boldsymbol{H}_2CH_2$), 2.08-2.01 (m, 2H: C(O)C$\boldsymbol{H}_2$CH (1H), C(O)$CH_2C\boldsymbol{H}$ (1H)), 1.99-1.90 (m, 1H, $CH_2C\boldsymbol{H}_2CH_2$), 1.85-1.70 (m, 1H, $CH_2C\boldsymbol{H}_2CH_2$), 1.69-1.60 (m, 3H: C$\boldsymbol{H}_2CH_2$Ph (2H), $CH_2C\boldsymbol{H}_2$CH (1H)), 1.43-1.36 (m, 1H,

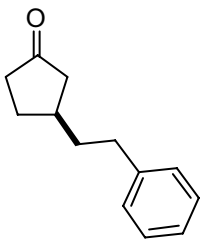
$CH_2C\boldsymbol{H}_2CH$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.6 (***C***=O), 141.8 (***C***q_{Ar}), 128.4 (***C***H_{Ar}), 128.2 (***C***H_{Ar}), 125.8 (***C***H_{Ar}), 48.0 (C(O)***C***H_2CH), 41.4 (C(O)***C***H_2CH_2), 38.5 (***C***H_2CH_2Ph), 38.3 ($CH_2\boldsymbol{C}H_2Ph$), 32.9 (***C***HCH_2CH_2Ph), 31.2 ($CH_2\boldsymbol{C}H_2CH$), 25.1 ($CH_2\boldsymbol{C}H_2CH_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 202 (26), 111 (3), 105 (4), 97 (100), 91 (45), 77 (4), 65 (7), 55 (11), 41 (10); **HRMS** (EI-FE) calcd for [$C_{14}H_{18}O$]: 202.1358, found: 202.1360. The physical data were identical in all respects to those previously reported.[135]



(*S*)-3-Methylcyclopentanone (95c): The enantiomers were analyzed by GC using a chiral BGB-178 column (2 min at 50 °C, 5 °C/min until 100 °C, 1 min at 100 °C, 20 °C/min until 150 °C, 2 min at 150 °C); major enantiomer: t_R = 10.25 min, minor enantiomer: t_R = 10.08 min. **95c** (7.7 mg, 0.078 mmol, 78%; 99:1 *er*): $C_6H_{10}O$ (98.14 g/mol); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.38-2.10 (m, 5H, C(O)C***H***$_2$CH (1H), C(O)C***H***$_2CH_2$ (2H), $CH_2C\boldsymbol{H}_2CH$ (1H), $CH_2C\boldsymbol{H}CH_3$ (1H)), 1.77 (dd, *J* = 18.0 Hz, 9.5 Hz, 1H, C(O)C***H***$_2$CH), 1.54-1.45 (m, 1H, $CH_2C\boldsymbol{H}_2CH$), 1.1 (d, *J* = 6.9 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 220.3 (***C***=O), 46.8 (C(O)***C***H_2CH), 38.5 (C(O)***C***H_2CH_2), 31.7 (***C***HCH_3), 31.3 ($CH_2\boldsymbol{C}H_2CH$), 20.2 (CH***C***H_3); **GC-MS** (GC-EI): 98. The physical data were identical in all respects to those of commercially available material **95c** (Sigma-Aldrich).

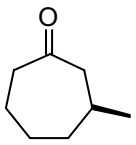


(*S*)-3-Ethylcyclopentanone (95h): The enantiomers were analyzed by GC using a chiral BGB 178 / OV-1701 column (10 min at 50 °C, 2 °C/min until 130 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 35.95 min, minor enantiomer: t_R = 35.55 min. **95h** (8.0 mg, 0.071 mmol, 71%; 98:2 *er*): $C_7H_{12}O$ (112.17 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.40-2.21 (m, 2H: C(O)C***H***$_2CH_2$ (1H), C(O)C***H***$_2$CH (1H)), 2.20-2.06 (m, 3H: C(O)C***H***$_2CH_2$ (1H), C(O)C***H***$_2$CH (1H), C(O)$CH_2C\boldsymbol{H}$ (1H)), 1.82-1.75 (m, 1H, $CH_2C\boldsymbol{H}_2CH$), 1.49-1.41 (m, 3H: $CH_2C\boldsymbol{H}_2CH$ (1H), CHC***H***$_2CH_3$ (2H)); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 220.0 (***C***=O), 45.0 (C(O)***C***H_2CH), 38.9 (C(O)***C***H_2CH_2), 38.5 (C(O)$CH_2\boldsymbol{C}H$), 29.1 ($CH_2\boldsymbol{C}H_2CH$), 28.4 (CH***C***H_2CH_3), 12.2 ($CHCH_2\boldsymbol{C}H_3$); **GC-MS** (GC-EI): 112. The physical data were identical in all respects to those previously reported.[135]

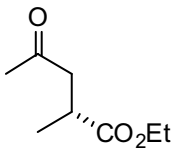


(*S*)-3-Phenethylcyclopentanone (95i): Purification by flash chromatography (5-10% of diethyl ether in pentane) afforded the pure product (**95g**, 13 mg, 0.07 mmol, 68%) as a colorless oil. The enantiomers were analyzed by HPLC using a chiral Chiralcel OD-H column (n-heptane/2-propanol = 90:10, flow rate = 0.5 mL/min, wavelength =

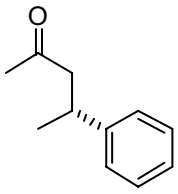
220 nm). Major enantiomer: t_R = 19.40 min, minor enantiomer: t_R = 16.74 min. **95i** (12.8 mg, 0.068 mmol, 68%; 98:2 *er*): $C_{13}H_{16}O$ (188.27 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H, C***H***$_{Ar}$), 7.20-7.16 (m, 3H, C***H***$_{Ar}$), 2.66 (t, *J* = 7.8 Hz, 2H, $CH_2C\boldsymbol{H}_2Ph$), 2.43-2.33 (m, 1H, C(O)C***H***$_2$CH), 2.31-2.24 (m, 1H, C(O)C***H***$_2CH_2$), 2.19-2.13 (m, 3H: C(O)C***H***$_2CH_2$ (1H), C(O)C***H***$_2$CH (1H), $C(O)CH_2C\boldsymbol{H}$ (1H)), 1.86-1.75 (m, 3H: C***H***$_2CH_2Ph$ (2H), $CH_2C\boldsymbol{H}_2CH$ (1H)), 1.55-1.46 (m, 1H, $CH_2C\boldsymbol{H}_2CH$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 219.5 (***C***=O), 141.9 (***C***q$_{Ar}$), 128.5 (***C***H$_{Ar}$), 128.2 (***C***H$_{Ar}$), 125.9 (***C***H$_{Ar}$), 45.0 (C(O)***C***H$_2$CH), 38.5 (***C***H_2CH_2Ph), 37.9 (C(O)***C***H_2CH_2), 36.6 ($CH_2\boldsymbol{C}H_2Ph$), 34.1 ($CH_2\boldsymbol{C}H_2CH_2$), 29.5 ($C(O)CH_2\boldsymbol{C}H$). The physical data were identical in all respects to those previously reported.[267]



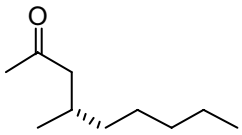
(*S*)-3-Methylcycloheptanone (95j): The enantiomers were analyzed by GC using a chiral Ivadex-7 column (80 °C, 1.2 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 11.09 min, minor enantiomer: t_R = 12.86 min. **95j** (12.6 mg, 0.099 mmol, >99%; 98:2 *er*): $C_8H_{14}O$ (126.20 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.45-2.44 (m, 4H, C(O)C***H***$_2CH_2$ (2H), C(O)C***H***$_2$CH (2H)), 1.80-1.94 (m, 4H, $CH_2C\boldsymbol{H}_2C\boldsymbol{H}_2CH_2$), 1.56-1.67 (m, 1H, $C(O)CH_2C\boldsymbol{H}$), 1.36-1.47 (m, 1H, $CH_2C\boldsymbol{H}_2CH$), 1.19-1.34 (m, 1H, $CH_2C\boldsymbol{H}_2CH$), 1.00 (d, *J* = 4.2 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 214.4 (***C***=O), 51.8 (C(O)***C***H_2CH), 44.1 (C(O)***C***H_2CH_2, 39.2 ($CH_2\boldsymbol{C}H_2CH$), 31.3 (***C***HCH_3), 28.6 ($CH_2\boldsymbol{C}H_2CH_2$), 24.2 ($CH_2\boldsymbol{C}H_2CH_2$), 23.6 (CH***C***H$_3$); **GC-MS** (GC-EI): 126.



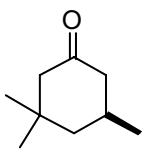
(*R*)-Ethyl 2-methyl-4-oxopentanoate (114a): The enantiomers were analyzed by GC using a chiral BGB 176 / SE 52 column (10 min at 60 °C, 0.8 °C/min until 90 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 31.11 min, minor enantiomer: t_R = 29.50 min. **114a** (12.8 mg, 0.081 mmol, 81%; 85:15 *er*): $C_8H_{14}O_3$ (158.19 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.11 (q, *J* = 7.1 Hz, $OC\boldsymbol{H}_2CH_3$), 2.94-2.85 (m, 2H, C(O)C***H***$_2$CH), 2.50-2.40 (m, 1H, $CH_2C\boldsymbol{H}CH_3$), 2.14 (s, 3H, C(O)C***H***$_3$), 1.23 (t, *J* = 7.1 Hz, $OCH_2C\boldsymbol{H}_3$), 1.16 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.6 (***C***=O), 175.8 (***C***=O), 60.5 (O***C***H_2CH_3), 46.5 (C(O)***C***H_2CH), 34.7 ($C(O)CH_2\boldsymbol{C}H$), 30.0 (C(O)***C***H_3), 17.0 (CH***C***H$_3$), 14.1 ($OCH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 158 (7), 113 (30), 101 (14), 88 (10), 73 (13), 43 (100), 29 (15); **HRMS** (ESIpos) calcd for [($C_{14}H_{18}O$+Na^+)]: 181.0835, found: 181.0834. The physical data were identical in all respects to those previously reported.[268]



(*R*)-4-Phenylpentan-2-one (114b): The enantiomers were analyzed by GC using a chiral BGB 176 / SE 52 column (10 min at 60 °C, 0.8 °C/min until 90 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 43.52 min, minor enantiomer: t_R = 43.07 min. **114b** (16.1 mg, 0.099 mmol, >99%; 92:8 *er*): $C_{11}H_{14}O$ (162.23 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.31 (m, 2H, C***H***$_{Ar}$), 7.27-7.23 (m, 3H, C***H***$_{Ar}$), 3.36 (m, *J* = 7.1 Hz, 1H, $CH_2C\boldsymbol{H}CH_3$), 2.81 (dd, *J* = 16.3 Hz, 6.5 Hz, 1H, C(O)C***H***$_2$CH), 2.71 (dd, *J* = 16.3 Hz, 7.9 Hz, 1H, C(O)C***H***$_2$CH), 2.12 (s, 3H, C(O)C***H***$_3$), 1.32 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.5 (***C***=O), 145.8 (***C***q_{Ar}), 128.2 (***C***H_{Ar}), 126.4 (***C***H_{Ar}), 126.0 (***C***H_{Ar}), 51.7 (C(O)***C***H_2CH), 35.1 (C(O)CH_2***C***H), 30.2 (C(O)***C***H_3), 21.7 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 162 (71), 147 (71), 129 (8), 119 (21), 105 (100), 91 (37), 77 (19), 51 (9), 43 (65); **HRMS** (EI-FE) calcd for [$C_{11}H_{14}O$]: 162.1045, found: 162.1047. The physical data were identical in all respects to those previously reported.[269]

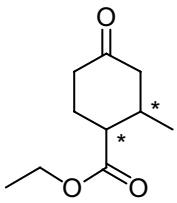


(*R*)-4-Phenylpentan-2-one (114c): The enantiomers were analyzed by GC using a chiral BGB 176 / SE 52 column (10 min at 60 °C, 0.8 °C/min until 90 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 43.52 min, minor enantiomer: t_R = 43.07 min. **114c** (10.2 mg, 0.065 mmol, 65%; 84:16 *er*): $C_{10}H_{20}O$ (156.27 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.40 (dd, *J* = 15.7 Hz, 5.8 Hz, 1H, C(O)C***H***$_2$CH), 2.20 (dd, *J* = 15.7 Hz, 8.0 Hz, 1H, C(O)C***H***$_2$CH), 2.11 (s, 3H, C(O)C***H***$_3$), 2.02-1.96 (br m, 1H, $CH_2C\boldsymbol{H}(CH_3)CH_2$), 1.32-1.14 (br m, 8H, $CH_2C\boldsymbol{H}_2CH_2$), 0.89-0.85 (m, 6H: $CH_2C\boldsymbol{H}_3$ (3H), CHC***H***$_3$ (3H)); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 209.2 (***C***=O), 51.3 (C(O)***C***H_2CH), 36.9 (CH***C***H_2CH_2), 31.9 ($CH_2\boldsymbol{C}H_2CH_2$), 30.3 (C(O)***C***$H_3$), 29.3 (***C***$HCH_2CH_2$), 26.6 ($CHCH_2\boldsymbol{C}H_2$), 22.6 ($CH_2\boldsymbol{C}H_2CH_2$), 19.8 (CH***C***$H_3$), 14.0 ($CH_2\boldsymbol{C}H_3$); **GC-MS** (GC-EI): 156. The physical data were identical in all respects to those previously reported.[270]



(*S*)-3,3,5-trimethylcyclohexanone (106a): The enantiomers were analyzed by GC using a chiral BGB-176 column (1.2 °C/min until 110 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 12.06 min, minor enantiomer: t_R = 13.72 min. **106a** (5.9 mg, 0.042 mmol, 42%; 94:6 *er*): $C_9H_{16}O$ (140.23 g/mol); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.34-2.29 (m, 1H, C(O)C***H***$_2$CH), 2.17-1.87 (m, 4H: C(O)C***H***$_2$CH (1H), C(O)C***H***$_2CH_2$ (2H), $CH_2C\boldsymbol{H}CH_3$ (1H)), 1.60-1.55 (m, 1H, CC***H***$_2$CH), 1.33-1.22 (m, 1H, CC***H***$_2$CH), 1.05 (s, 3H, CC***H***$_3$), 0.95 (d, *J* = 6.2 Hz, 3H, CHC***H***$_3$), 0.88 (s, 3H, CC***H***$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 212.0 (***C***=O), 54.2

(C(O)***C***H_2CH_2), 49.3 (C(O)***C***H_2CH), 47.3 (***C***H_2CH), 35.4 (***C***$(CH_3)_2$), 32.1 (***C***HCH_3), 29.6 (CH***C***H_3), 25.8 (***C***H_3), 22.5 (***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 140 (22), 125 (10), 97 (7), 83 (100), 69 (51), 55 (45), 41 (26), 39 (11), 29 (10); **HRMS** (EI-FE) calcd for [$C_9H_{16}O$]: 140.1201, found: 140.1203. The physical data were identical in all respects to those of commercially available material (**106a**, Sigma-Aldrich).

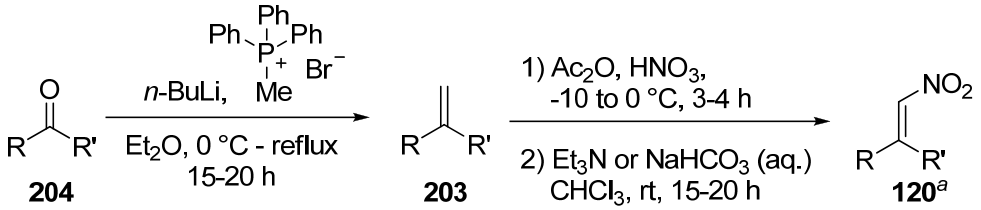


Ethyl 2-methyl-4-oxocyclohexanecarboxylate (199): The enantiomers were analyzed by GC using a chiral BGB-176/SE column (1.2 °C/min until 220 °C, 10 min at 220 °C); *major product*: major enantiomer: t_R = 40.66 min, minor enantiomer: t_R = 41.42 min; *minor product*: major enantiomer: t_R = 39.56 min, minor enantiomer: t_R = 38.37 min. **199** (6.6 mg, 0.036 mmol, 36%; diast. 1: 75:25 *er*, diast. 2: 72:28 *er*): $C_{10}H_{16}O_3$ (184.23 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$, major product): δ 4.16 (dq, *J* = 7.2 Hz, 1.9 Hz, 2H, OC***H***$_2CH_3$), 2.85-2.81 (m, 1H, C***H***CO_2), 2.54-2.04 (m, 7H: C***H***CH_3 (1H), C(O)C***H***$_2$CH (2H), C(O)C***H***$_2CH_2$ (2H), CH_2C***H***$_2$CH (2H)), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2C***H***$_3$), 0.96 (d, *J* = 6.7 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, CDCl3, *major product*): δ 212.6 (***C***=O), 173.4 (O***C***=O), 60.4 (O***C***H_2CH_3), 46.9 (C(O)***C***H_2CH), 44.2 (***C***HCO_2), 38.8 (C(O)***C***H_2CH_2), 33.9 (***C***HCH_3), 24.8 (CH_2***C***H_2CH), 16.6 (CH***C***H_3), 14.2 (OCH_2***C***H_3); **^{13}C NMR** (75 MHz, $CDCl_3$, *minor product*): δ 209.5 (***C***=O), 174.4 (O***C***=O), 60.6 (O***C***H_2CH_3), 49.0 (***C***HCO_2), 48.0 (C(O)***C***H_2CH), 39.7 (C(O)***C***H_2CH_2), 35.3 (***C***HCH_3), 27.9 (CH_2***C***H_2CH), 20.4 (CH***C***H_3), 15.2 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 184 (34), 155 (11), 139 (27), 128 (44), 114 (53), 110 (89), 95 (12), 84 (30), 69 (65), 55 (100), 41 (59), 29 (56); **HRMS** (EI-FE) calcd for [$C_{10}H_{16}O_3$]: 184.1099, found: 184.1101.

7.5 Enantioselective Transfer Hydrogenation of *β*,*β*-Disubstituted Nitroalkenes

7.5.1 Synthesis of the Starting Materials

7.5.1.1 Synthesis of the Nitroolefins 120a-m

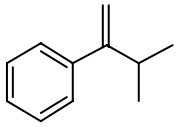


2-Phenyl-1-propene (**203a**), 2-(4-methyl)-1-propene (**203f**), 2-(4-fluorophenyl)-1-propene (**203h**), 2-(4-chlorophenyl)-1-propene (**203i**), 2,3,3-trimethylbut-1-ene (**203l**) and 2-methylbut-1-ene (**203n**) were commercially available. The other alkenes were prepared by Wittig olefination of the corresponding ketones **204** according to the procedure described below.[241]

***General procedure for the preparation of the alkenes* (203):**

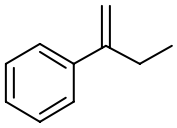
In a two-necked round-bottomed flask under argon, a solution of methyltriphenylphosphinium bromide (16.25 g, 45.50 mmol, 0.9 equiv) and *n*-butyl lithium (2.5 M in diethylether: 18.2 mL, 45.50 mmol, 0.9 equiv) in diethyl ether (130 mL) was prepared. After stirring the reaction mixture for four hours at 0 ºC, a solution of ketone **204** (50.00 mmol, 1.0 equiv) in diethyl ether (20 mL) was added. The reaction mixture was stirred at reflux for 15-20 hours and filtered. The resulting solution was poured into water and extracted with diethyl ether (3 × 80 mL). The combined organic phases were dried over magnesium sulfate, concentrated *in vacuo* and the crude material was purified by flash chromatography (eluent: hexanes or pentane) to afford the pure alkene **203**.

2-Phenyl-1-pentene (**203d**) and 4-(prop-1-en-2-yl)benzonitrile (**203g**) were prepared by *L. Ozores*.



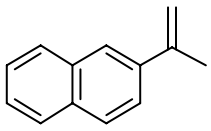
3-Methyl-2-phenyl-1-butene (203b): Alkene **203b** was prepared according to the general procedure starting from 2-methyl-1-phenylpropan-1-one (**204b**, 7.41 g, 50.00 mmol). After purification by flash chromatography (eluent: pentane), the title compound (**203b**, 5.44 g, 37.20 mmol, 74% yield) was obtained as a colorless oil.

203b: $C_{11}H_{14}$ (146.23 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H, C***H***$_{Ar}$), 5.14 (t, *J* = 0.5 Hz, 1H, C=C***H***$_2$, *H*^{1}), 5.03 (t, *J* = 1.3 Hz, 1H, C=C***H***$_2$, *H*^{2}), 2.85-2.81 (m, 1H, CC***H***$(CH_3)_2$), 1.10 (d, *J* = 6.8 Hz, 6H, CH(C**H**$_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.8 (***C***=CH_2), 142.9 (***C***q_{Ar}), 128.1 (***C***H_{Ar}), 127.0 (***C***H_{Ar}), 126.6 (***C***H_{Ar}), 109.9 (C=***C***H_2), 32.3 (C***C***H$(CH_3)_2$), 22.0 (CCH(***C***$H_3)_2$); **HRMS** (EI-FE) calcd for [$C_{11}H_{14}$]: 146.1096, found: 146.1098. The physical data were identical in all respects to those previously reported.[270]



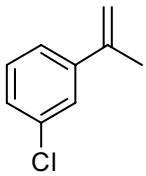
2-Phenyl-1-butene (203c): Alkene **203c** was prepared according to the general procedure starting from propiophenone (**204c**, 6.71 g, 50.00 mmol). After purification by flash chromatography (eluent: pentane), the title compound (**203c**, 4.92 g, 37.22 mmol, 74% yield) was obtained as a colorless oil.

203c: $C_{10}H_{12}$ (132.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.24 (m, 5H, C***H***$_{Ar}$), 5.27 (t, *J* = 1.5 Hz, 1H, C=C***H***$_2$, *H*^{1}), 5.06 (qt, *J* = 1.5 Hz, 1H, C=C***H***$_2$, *H*^{2}), 2.56-2.48 (m, 2H, CC***H***$_2CH_3$), 1.10 (t, *J* = 7.4 Hz, 3H, CCH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.0 (***C***=CH_2), 141.5 (***C***q_{Ar}), 128.1 (***C***H_{Ar}), 127.2 (***C***H_{Ar}), 126.3 (***C***H_{Ar}), 110.9 (C=***C***H_2), 28.0 (C***C***H_2CH_3), 12.9 (CCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 132 (72), 117 (100), 103 (46), 91 (26), 77 (26), 65 (10), 51 (17), 39 (11), 28 (5). The physical data were identical in all respects to those previously reported.[271]



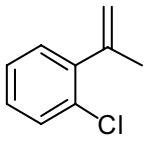
2-Naphthyl-1-propene (203e): Alkene **203e** was prepared according to the general procedure starting from 1-(naphthalen-2-yl)ethanone (**204b**, 8.51 g, 50.00 mmol). After purification by flash chromatography (eluent: hexanes), the title compound (**203e**, 5.14 g, 30.55 mmol, 61% yield) was obtained as a colorless solid.

203e: $C_{11}H_{12}$ (168.23 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.87-7.80 (m, 4H, C$\boldsymbol{H}_{Ar}$), 7.69 (dd, *J* = 8.6 Hz, 1.9 Hz, 1H, C$\boldsymbol{H}_{Ar}$), 7.50-7.43 (m, 2H, C$\boldsymbol{H}_{Ar}$), 5.56 (d, *J* = 0.4 Hz, 1H, C=C$\boldsymbol{H}_2$, H^1), 5.56 (q, *J* = 1.4 Hz, 1H, C=C$\boldsymbol{H}_2$, H^2), 2.30 (s, 3H, CC$\mathbf{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 143.0 (***C***=CH_2), 138.3 (***C***q_{Ar}C=CH_2), 133.4 (***C***q_{Ar}), 132.8 (***C***q_{Ar}), 128.2 (***C***H_{Ar}), 127.7 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 126.1 (***C***H_{Ar}), 125.8 (***C***H_{Ar}), 124.2 (***C***H_{Ar}), 123.9 (***C***H_{Ar}), 113.0 (C=***C***H_2), 21.9 (C***C***H_3); **HRMS** (EI-FE) calcd for [$C_{11}H_{12}$]: 168.0939, found: 168.0937. The physical data were identical in all respects to those previously reported.[272]



2-(3-Chlorophenyl)-1-propene (203j): Alkene **203j** was prepared according to the general procedure starting from 1-(3-chlorophenyl)ethanone (**204j**, 7.73 g, 50.00 mmol). After purification by flash chromatography (eluent: pentane), the title compound (**203j**, 3.53 g, 23.13 mmol, 46% yield) was obtained as a colorless oil.

203j: C_9H_9Cl (152.62 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45-7.43 (m, 1H, C$\boldsymbol{H}_{Ar}$), 7.36-7.32 (m, 1H, C$\boldsymbol{H}_{Ar}$), 7.26-7.24 (m, 2H, C$\boldsymbol{H}_{Ar}$), 5.38 (m, 1H, C=C$\boldsymbol{H}_2$, H^1), 5.13 (qt, *J* = 1.4 Hz, 1H, C=C$\boldsymbol{H}_2$, H^2), 2.14 (m, *J* = 0.7 Hz, 3H, CC$\boldsymbol{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.1 (***C***=CH_2), 142.1 (***C***q_{Ar}C=CH_2), 134.2 (***C***q_{Ar}Cl), 129.4 (***C***H_{Ar}), 127.3 (***C***H_{Ar}), 125.8 (***C***H_{Ar}), 123.6 (***C***H_{Ar}), 113.6 (C=***C***H_2), 21.7 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 152 (100), 137 (16), 117 (77), 102 (19), 91 (10), 75 (13), 63 (7), 58 (8), 51 (10), 38 (9); **HRMS** (EI-FE) calcd for [C_9H_9Cl]: 152.0393, found: 1152.0391.



2-(2-Chlorophenyl)-1-propene (203k): Alkene **203k** was prepared according to the general procedure starting from 1-(2-chlorophenyl)ethanone (**204k**, 7.73 g, 50.00 mmol). After purification by flash chromatography (eluent: pentane), the title compound (**203k**, 4.99 g, 32.70 mmol, 65% yield) was obtained as a colorless oil.

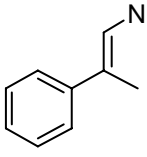
203k: C_9H_9Cl (152.62 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.33 (m, 1H, C$\boldsymbol{H}_{Ar}$), 7.22-7.17 (m, 3H, C$\boldsymbol{H}_{Ar}$), 5.24 (qt, *J* = 1.6 Hz, 1H, C=C$\boldsymbol{H}_2$, H^1), 4.97 (q, *J* = 0.9 Hz, 1H, C=C$\boldsymbol{H}_2$, H^2), 2.11 (t, *J* = 1.2 Hz, 3H, CC$\boldsymbol{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.4 (***C***=CH_2), 142.8 (***C***q_{Ar}C=CH_2), 131.8 (***C***q_{Ar}Cl), 129.8 (***C***H_{Ar}), 129.6 (***C***H_{Ar}), 128.2 (***C***H_{Ar}), 126.6 (***C***H_{Ar}), 116.2

(C=***C***H_2), 23.3 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 152 (84), 137 (19), 117 (100), 101 (22), 91 (12), 75 (18), 63 (11), 58 (31), 51 (16), 39 (12); **HRMS** (EI-FE) calcd for [C_9H_9Cl]: 152.0393, found: 1152.0393.

General procedure for the preparation of the nitroolefins **(120):**

In a two-necked round-bottomed flask, acetic anhydride (70 mL) was cooled to -10°C and 53% nitric acid (12.5 mL) was slowly added at this temperature under vigorous stirring. The reaction mixture was allowed to warm to 0 ºC. The mixture was stirred for ten minutes at 0 ºC before adding the alkene **203** (41.00 mmol). The reaction mixture was stirred at this temperature for three hours and quenched at 0 °C with ice-water (300 mL). The resulting mixture was stirred for one hour. The two phases were separated and the aqueous phase extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with an aqueous solution of sodium bicarbonate and water, and dried over magnesium sulfate. The volatile compounds were removed *in vacuo* and the crude product was used in the next step without further purification.

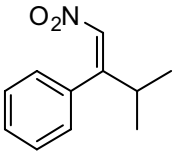
To a solution of the resulting crude product (nitro acetate) in chloroform (50 mL) was added triethylamine (25 mL, ca 180 mmol). After stirring at room temperature for 15-20 hours the reaction mixture was extracted with dichloromethane (3 × 50 mL) and the resulting organic layer was washed with hydrochloric acid (10%) and brine. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (0-5% of diethyl ether in hexanes) to afford the pure nitroalkene **120**.



(*E*)-2-Phenyl-1-nitro-1-propene (120a): Nitroolefin **120b** was prepared according to the general procedure starting from 2-phenyl-1-propene (**203a**, 4.85 g, 41.00 mmol). After purification by flash chromatography (eluent: 1-4% of ethyl acetate in hexanes), the title compound (**120a**, 2.48 g, 15.20 mmol, 37% yield) was obtained as a yellow oil.

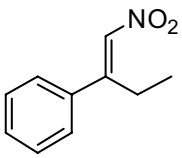
120a: $C_9H_9NO_2$ (163.17 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.43 (m, 5H, C***H***$_{Ar}$), 7.31 (d, *J* = 1.4 Hz, 1H, C***H***NO_2), 2.65 (d, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.9 (Cq$_{Ar}$***C***=CH), 138.3 (***C***q$_{Ar}$C=CH), 136.3 (C=***C***HNO_2), 130.3 (***C***H$_{Ar}$), 129.0 (***C***H$_{Ar}$), 126.8 (***C***H$_{Ar}$), 18.5 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 163 (26), 146 (14), 131 (8), 115 (100), 105

(23), 91 (79), 77 (35), 65 (22), 51 (30), 39 (24), 27 (7); **HRMS** (EI-FE) calcd for [$C_9H_9NO_2$]: 163.0633, found 163.0632. The physical data were identical in all respects to those previously reported.[173b]



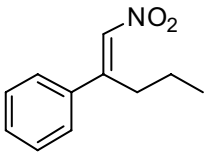
(*Z*)-3-Methyl-2-phenyl-1-nitro-1-butene (120b): Nitroolefin **120b** was prepared according to the general procedure starting from 3-methyl-2-phenyl-1-butene (**203b**, 6.00 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120b**, 1.05 g, 5.49 mmol, 13% yield) was obtained as a yellow oil.

120c: $C_{11}H_{13}NO_2$ (191.23 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.41 (m, 3H, C***H***$_{Ar}$), 7.09-7.12 (m, 2H, C***H***$_{Ar}$), 7.00 (d, *J* = 1.0 Hz, 1H, C***H***NO_2), 2.69-2.74 (m, 1H, C***H***$(CH_3)_2$), 1.12 (d, *J* = 6.8 Hz, 6H, CH(C***H***$_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.6 (Cq_{Ar}***C***=CH), 136.0 (***C***q_{Ar}C=CH), 134.5 (C=***C***HNO_2), 128.3 (***C***H_{Ar}), 128.3 (***C***H_{Ar}), 126.7 (***C***H_{Ar}), 35.7 (***C***$H(CH_3)_2$), 20.7 (CH(***C***$H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 191 (35), 176 (44), 159 (32), 147 (56), 128 (49), 115 (54), 103 (56), 91 (100), 77 (66), 65 (24), 51 (33), 43 (86), 27 (30); **HRMS** (EI-FE) calcd for [$C_{11}H_{13}NO_2$]: 191.0946, found 191.0944. The physical data were identical in all respect to those previously reported.[266]



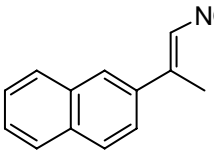
(*E*)-2-Phenyl-1-nitro-1-butene (120c): Nitroolefin **120c** was prepared according to the general procedure starting from 2-phenyl-1-butene (**203c**, 5.42 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120c**, 1.31 g, 7.39 mmol, 18% yield) was obtained as a yellow oil.

120c: $C_{10}H_{11}NO_2$ (177.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.41 (m, 5H, C***H***$_{Ar}$), 7.19 (br s, 1H, C***H***NO_2), 3.09 (q, *J* = 7.5 Hz, 2H, C***H***$_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.7 (Cq_{Ar}***C***=CH), 137.1 (***C***q_{Ar}C=CH), 135.8 (C=***C***HNO_2), 130.3 (***C***H_{Ar}), 129.1 (***C***H_{Ar}), 127.2 (***C***H_{Ar}), 24.8 (***C***H_2CH_3), 12.8 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 177 (24), 160 (9), 145 (10), 133 (30), 115 (52), 105 (35), 91 (100), 77 (46), 65 (17), 51 (26), 43 (17), 27 (12); **HRMS** (EI-FE) calcd for [$C_{10}H_{11}NO_2$]: 177.0790, found 177.0788. The physical data were identical in all respects to those previously reported.[170]



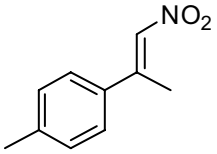
(*E*)-2-Phenyl-1-nitro-1-pentene (120d): Nitroolefin **120d** was prepared according to the general procedure starting from 2-phenyl-1-pentene (**203d**, 6.00 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120d**, 1.36 g, 7.11 mmol, 18% yield) was obtained as a yellow oil.

120d: $C_{11}H_{13}NO_2$ (191.23 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.46 (m, 5H, C***H***$_{Ar}$), 7.20 (br s, 1H, C***H***NO_2), 3.08-3.03 (m, 2H, CC***H***$_2CH_2CH_3$), 1.60-1.47 (m, 2H, CH_2C***H***$_2CH_3$), 0.97 (t, *J* = 7.3 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.4 (Cq$_{Ar}$***C***=CH), 137.4 (***C***q$_{Ar}$C=CH), 136.2 (C=***C***HNO_2), 130.2 (***C***H$_{Ar}$), 129.0 (***C***H$_{Ar}$), 127.1 (***C***H$_{Ar}$), 33.0 (CH_2***C***H_2CH_3), 21.8 (***C***H_2CH_3), 14.1 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 191 (21), 174 (11), 162 (19), 147 (14), 128 (26), 115 (51), 103 (26), 91 (100), 77 (39), 65 (18), 51 (15), 51 (20), 41 (24), 29 (16); **HRMS** (EI-FE) calcd for [$C_{11}H_{13}NO_2$]: 191.0946, found 191.0944. The physical data were identical in all respects to those previously reported. [173b]



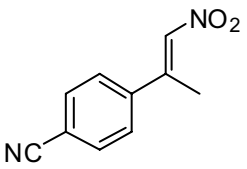
(*E*)-2-(2'-Naphthyl)-1-nitro-1-propene (120e): Nitroolefin **120e** was prepared according to the general procedure starting from 2-naphthyl-1-propene (**203e**, 6.90 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120e**, 1.24 g, 5.82 mmol, 14% yield) was obtained as a yellow solid.

120e: $C_{13}H_{11}NO_2$ (213.23 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 1.6 Hz, 1H, C***H***$_{Ar}$), 7.91-7.86 (m, 3H, C***H***$_{Ar}$), 7.58-7.51 (m, 3H, C***H***$_{Ar}$), 7.46-7.47 (q, *J* = 1.4 Hz, 1H, C***H***NO_2), 2.75 (d, *J* = 1.4 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.8 (Cq$_{Ar}$***C***=CH), 136.6 (***C***q$_{Ar}$C=CH),, 135.4 (C=***C***HNO_2), 134.0 (***C***q$_{Ar}$), 133.0 (***C***q$_{Ar}$), 128.9 (***C***H$_{Ar}$), 128.6 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 127.02 (***C***H$_{Ar}$), 127.01 (***C***H$_{Ar}$), 123.7 (***C***H$_{Ar}$), 18.5 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 213 (100), 196 (33), 182 (19), 165 (89), 152 (76), 141 (27), 128 (22), 115 (30), 102 (6), 82 (13), 63 (8), 51 (6), 39 (4); **HRMS** (EI-FE) calcd for [$C_{13}H_{11}NO_2$]: 213.0790, found 213.0788. The physical data were identical in all respects to those previously reported. [268]



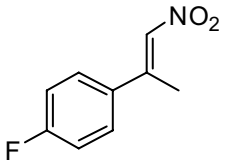
(*E*)-2-(4-Methylphenyl)-1-nitro-1-propene (120f): Nitroolefin **120f** was prepared according to the general procedure starting from 2-(4-methyl)-1-propene (**203f**, 5.42 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120f**, 1.63 g, 9.20 mmol, 22% yield) was obtained as a yellow oil.

120f: $C_{10}H_{11}NO_2$ (177.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.2 Hz, 2H, C***H***$_{Ar}$), 7.32 (d, *J* = 1.3 Hz, 1H, C***H***NO_2), 7.24 (d, *J* = 8.2 Hz, 2H, C***H***$_{Ar}$), 2.63 (d, *J* = 1.3 Hz, 3H, CC***H***$_3$), 1.12 (s, 3H, $Cq_{Ar}C$***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.0 (Cq_{Ar}***C***=CH), 140.9 (***C***q_{Ar}C=CH), 135.8 (***C***$q_{Ar}CH_3$), 135.3 (C=***C***HNO_2), 129.8 (***C***H_{Ar}), 126.8, (***C***H_{Ar}) 21.3 (C***C***H_3), 18.4 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 177 (43), 160 (20), 145 (9), 128 (27), 115 (100), 105 (29), 91 (86), 77 (31), 65 (27), 51 (21), 39 (23), 27 (8); **HRMS** (EI-FE) calcd for [$C_{10}H_{11}NO_2$]: 177.0790, found 177.0787.



(*E*)-2-(4-Cyanophenyl)-1-nitro-1-propene (120g): Nitroolefin **120g** was prepared according to the general procedure starting from 4-(prop-1-en-2-yl)benzonitrile (**203g**, 5.87 g, 41.00 mmol). After purification by flash chromatography (5% of ethyl acetate in hexanes), the title compound (**120g**, 1.49 g, 7.92 mmol, 19% yield) was obtained as a slightly yellow oil.

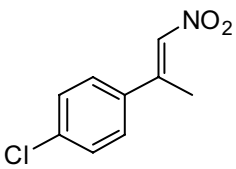
120g: $C_{10}H_8N_2O_2$ (163.17 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.5 Hz, 2H, C***H***$_{Ar}$), 7.61 (d, *J* = 8.5 Hz, 2H, C***H***$_{Ar}$), 7.32 (d, *J* = 1.4 Hz, 1H, C***H***NO_2), 2.65 (d, *J* = 1.4 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.3 (Cq_{Ar}***C***=CH), 142.5 (***C***q_{Ar}C=CH), 137.4 (C=***C***HNO_2), 132.6 (***C***H_{Ar}), 127.4 (***C***H_{Ar}), 117.8(Cq_{Ar}***C***N), 113.6 (***C***q_{Ar}CN), 18.1 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 188 (36), 171 (14), 159 (8), 140 (60), 130 (25), 116 (100), 103 (27), 89 (31), 75 (16), 63 (22), 51 (18), 43 (4), 39 (42), 27 (9); **HRMS** (EI-FE) calcd for [$C_{10}H_8N_2O_2$]: 188.0586, found 188.0587.



(*E*)-2-(4-Fluorophenyl)-1-nitro-1-propene (120h): Nitroolefin **120h** was prepared according to the general procedure starting from 2-(4-fluorophenyl)-1-propene (**203h**, 5.58 g, 41.00 mmol). After purification by

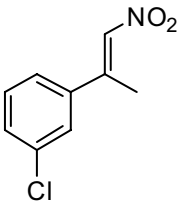
flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120h**, 1.72 g, 9.49 mmol, 23% yield) was obtained as a yellow oil.

120h: $C_9H_8FNO_2$ (181.16 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48-7.42 (m, 2H, C***H***$_{Ar}$), 7.28 (q, *J* = 1.3 Hz, 1H, C***H***NO_2), 7.16-7.10 (m, 2H, C***H***$_{Ar}$), 2.62 (q, *J* = 1.3 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.2 (***C***F), 162.7 (Cq$_{Ar}$***C***=CH), 148.6 (***C***q$_{Ar}$C=CH), 136.2 (C=***C***HNO_2), 134.3 (***C***H_{Ar}), 128.9 (***C***H_{Ar}), 116.3 (***C***H_{Ar}), 116.1 (***C***H_{Ar}), 18.5 (***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 181 (69), 164 (11), 150 (11), 133 (98), 120 (21), 115 (51), 109 (100), 103 (22), 97 (16), 83 (24), 75 (20), 63 (12), 57 (12), 51 (9), 39 (23); **HRMS** (EI-FE) calcd for [$C_9H_8FNO_2$]: 181.0539, found 181.0537.



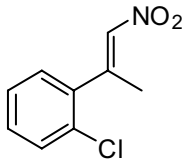
(*E*)-2-(4-Chlorophenyl)-1-nitro-1-propene (120i): Nitroolefin **120i** was prepared according to the general procedure starting from 2-(4-chlorophenyl)-1-propene (**203i**, 6.26 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120i**, 0.67 g, 3.40 mmol, 8% yield) was obtained as a yellow oil.

120i: $C_9H_8ClNO_2$ (197.62 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.38 (m, 4H, C***H***$_{Ar}$), 7.28 (q, *J* = 1.4 Hz, 1H, C***H***NO_2), 2.62 (q, *J* = 1.4 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.4 (Cq$_{Ar}$***C***=CH), 136.6 (***C***q$_{Ar}$C=CH), 136.5 (C=***C***HNO_2), 131.7 (***C***Cl), 129.3 (***C***H_{Ar}), 128.1 (***C***H_{Ar}), 18.4 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 197 (32), 162 (15), 149 (8), 139 (13), 125 (21), 115 (100), 103 (23), 89 (19), 75 (21), 63 (15), 51 (14), 39 (15); **HRMS** (EI-FE) calcd for [$C_9H_8ClNO_2$]: 197.0244, found 197.0246.The physical data were identical in all respects to those previously reported.[266]



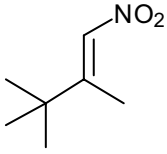
(*E*)-2-(3-Chlorophenyl)-1-nitro-1-propene (120j): Nitroolefin **120j** was prepared according to the general procedure starting from 2-(3-chlorophenyl)-1-propene (**203j**, 6.00 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120j**, 0.51 g, 2.58 mmol, 6% yield) was obtained as a yellow oil.

120j: $C_9H_8ClNO_2$ (197.62 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44-7.31 (m, 4H, C***H***$_{Ar}$), 7.27-7.26 (q, *J* = 1.5 Hz, 1H, C***H***NO_2), 2.61 (q, *J* = 1.5 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.1 (Cq$_{Ar}$***C***=CH) 140.1 (***C***q$_{Ar}$C=CH), 136.9 (C=***C***HNO_2), 135.1 (***C***Cl), 130.3 (***C***H$_{Ar}$), 127.0 (***C***H$_{Ar}$), 124.9 (***C***H$_{Ar}$), 18.4 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 197 (36), 162 (20), 152 (8), 134 (11), 125 (22), 115 (100), 103 (25), 89 (23), 75 (22), 63 (16), 51 (14), 39 (15); **HRMS** (EI-FE) calcd for [$C_9H_8ClNO_2$]: 197.0244, found 197.0242.



(*E*)-2-(2-Chlorophenyl)-1-nitro-1-propene (120k): Nitroolefin **120k** was prepared according to the general procedure starting from 2-(2-chlorophenyl)-1-propene (**203k**, 6.26 g, 41.00 mmol). After purification by flash chromatography (1% of ethyl acetate in hexanes), the title compound (**120k**, 0.34 g, 1.72 mmol, 4% yield) was obtained as a yellow oil.

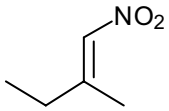
120k: $C_9H_8ClNO_2$ (197.62 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 1H, C***H***$_{Ar}$), 7.34-7.29 (m, 2H, C***H***$_{Ar}$), 7.17-7.15 (q, *J* = 1.5 Hz, 1H, C***H***NO_2), 7.10-7.07 (m, 1H, C***H***$_{Ar}$), 2.19 (q, *J* = 1.5 Hz, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 146.6 (Cq$_{Ar}$***C***=CH), 140.1 (***C***q$_{Ar}$C=CH), 136.6 (C=***C***HNO_2), 129.7 (***C***Cl), 129.5 (***C***H$_{Ar}$), 127.0 (***C***H$_{Ar}$), 23.0 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 197 (0.3), 162 (100), 145 (7), 132 (52), 125 (6), 115 (41), 103 (8), 89 (15), 77 (18), 63 (13), 51 (10), 39 (11), 27 (2); **HRMS** (EI-FE) calcd for [$C_9H_8ClNO_2$]: 197.0244, found 197.0246.



(*E*)-2,3,3-Trimethyl-1-nitro-1-butene (120l): Nitroolefin **120l** was prepared according to the general procedure starting from 2,3,3-trimethylbut-1-ene (**203l**, 4.03 g, 41.00 mmol). After purification by flash chromatography (0-1% of diethyl ether in pentane), the title compound (**120l**, 1.66 g, 11.59 mmol, 28% yield) was obtained as a slightly yellow oil.

120l: $C_7H_{13}NO_2$ (143.18 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.00 (d, *J* = 1.1 Hz, 1H, C***H***NO_2), 2.20 (d, *J* = 1.1 Hz, 3H, CC***H***$_3$), 1.17 (s, 9H, C(C***H***$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.5 (C***C***=CH), 134.5 (C=***C***HNO_2), 37.1 (***C***$(CH_3)_2$), 28.0 (C(***C***H_3)$_2$), 15.0 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 144 (0.2), 128 (13), 97 (36), 94 (12), 81 (10), 69 (40), 57 (85), 55

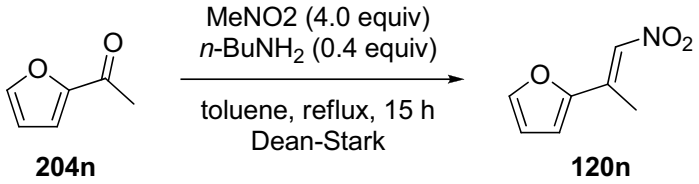
(100), 53 (18), 43 (48), 41 (95), 39 (44), 29 (46); **HRMS** (EIpos) calcd for [($C_7H_{13}NO_2$+H)$^+$]: 144.1025, found 144.1024.



(*E*)-2-methyl-1-nitrobutene (120m): Nitroolefin **120m** was prepared according to the general procedure starting from 2-methylbut-1-ene (**203m**, 2.87 g, 41.00 mmol). After purification by flash chromatography (0-1% of diethyl ether in pentane), the title compound (**120m**, 0.48 g, 4.17 mmol, 10% yield) was obtained as a slightly yellow oil.

120m: $C_9H_9NO_2$ (163.17 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.95 (br s, 1H, C***H***NO_2), 2.27-2.19 (m, 5H: C***H***$_2CH_3$ (2H) and CC***H***$_3$ (3H)), 1.13 (t, *J* = 7.4 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.8 (C***C***=CH), 134.7 (C=***C***HNO_2), 31.2 (***C***H_2CH_3), 18.6 (CH_2***C***H_3), 11.7 (C***C***H_3); **GC/MS** *m*/*z* (%) = 115. The physical data were identical in all respects to those previously reported.[266]

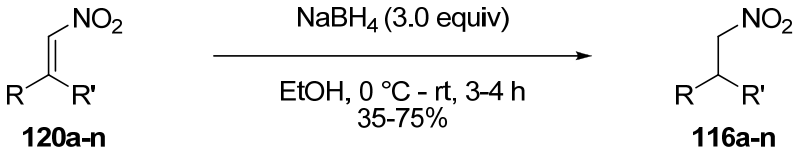
7.5.1.2 Synthesis of (*E*)-2-(Furan-2-yl)-1-nitro-1-propene (120n)



In a 100 mL flask under argon a solution of 1-(furan-2-yl)ethanone (**204n**, 5.51 g, 50.00 mmol, 1.0 equiv), nitromethane (10.7 mL, 200.00 mmol, 4.0 equiv) and *n*-butylamine (2.0 mL, 20.00 mmol, 0.4 equiv) in toluene (32 mL) was prepared. The resulting mixture was stirred under reflux for 15 hours with a Dean-Stark apparatus. It was then cooled to room temperature, diluted with ethyl acetate and quenched by addition of an aqueous solution of ammonium chloride. The organic phase was separated, dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (1% of diethyl ether in hexanes) to afford pure nitroolefin **120n** (0.93 g, 6.08 mmol, 12%) as a brown oil.

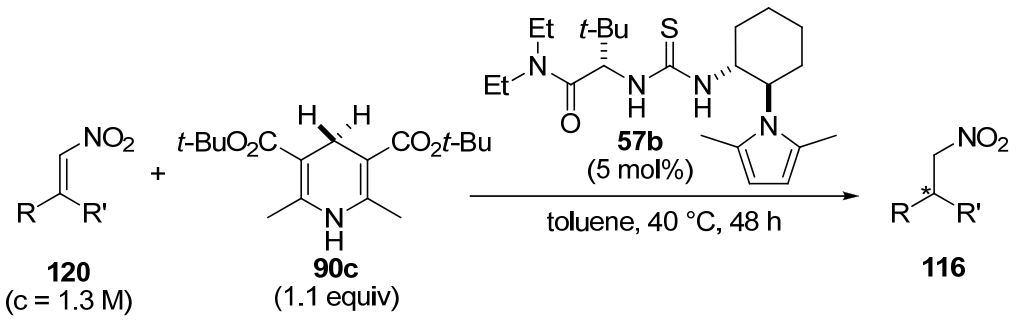
120n: $C_7H_7NO_3$ (153.04 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66 (br s, 1H, C***H***$_{Ar}$), 7.54 (d, *J* = 1.7 Hz, 1H, C***H***NO_2), 6.90 (d, *J* = 3.5 Hz, 1H, C***H***$_{Ar}$), 6.55 (dd, *J* = 3.5 Hz, 1.7 Hz, 1H, C***H***$_{Ar}$), 2.55 (br s, 3H, CC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.7 (O***C***q_{Ar}C=CH), 145.7 (OCq_{Ar}***C***=CH), 136.7 (***C***HNO_2), 133.1 (O***C***$H_{Ar}CH_{Ar}$), 115.9 (***C***H_{Ar}), 112.9 (***C***H_{Ar}), 14.9 (C***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 153 (88), 136 (23), 110 (49), 92 (10), 83 (100), 77 (73), 63 (20), 55 (54), 53 (40), 39 (55), 29 (13), 27 (38); **HRMS** (EI-FE) calcd for [$C_7H_7NO_3$]: 153.0426, found: 153.0427. The physical data were identical in all respects to those previously reported.[268]

7.5.2 General Procedures for the Synthesis of the Racemic Products

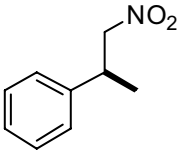


To a solution of nitroolefin **120** (0.26 mmol, 1.0 equiv) in ethanol (0.6 mL) at 0 °C, sodium borohydride (30 mg, 0.78 mmol, 3.0 equiv) was added in several portions over 15 minutes. The reaction mixture was stirred at 0 °C for one hour and then quenched at 0 °C with a saturated solution of ammonium chloride. The two phases were separated and the aqueous layer extracted with diethyl ether (3 × 1 mL). The combined organic phases were dried over magnesium sulfate. The volatile compounds were removed *in vacuo* and the crude product was purified by flash chromatography (1-5% of diethyl ether in pentane) to afford the pure *β*,*β*-disubstituted nitroalkane **116**.

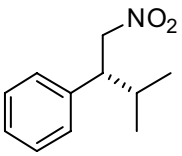
7.5.3 Asymmetric Transfer Hydrogenation of *β,β*-Disubstituted Nitroalkenes



To a solution of *β,β*-disubstituted nitroalkene **120** (0.390 mmol) in toluene (0.3 mL, 1.3 M), thiourea catalyst **57b** (8.2 mg, 0.02 mmol, 0.05 equiv) and Hantzsch ester **90c** (133 mg, 0.43 mmol, 1.1 equiv) were added. The reaction mixture was stirred at 40 °C for 48 hours under argon atmosphere. The solvent was then removed *in vacuo* and the resulting mixture purified by flash column chromatography (eluents: diethyl ether / pentane).

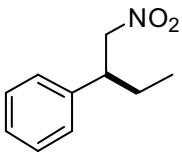


(*S*)-2-Phenyl-1-nitropropane (116a): The enantiomers were analyzed by GC using a chiral Ivadex 1 / PS086 column (5 min at 60 °C, 0.7 °C/min until 125 °C, 20 °C/min until 300 °C, 10 min at 300 °C); major enantiomer: t_R = 80.13 min, minor enantiomer: t_R = 82.07 min. **116a** (62.4 mg, 0.378 mmol, 97%; 97:3 *er*): slightly yellow oil, $C_9H_{11}NO_2$ (165.19 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H, C***H***$_{Ar}$), 7.30-7.22 (m, 3H, C***H***$_{Ar}$), 4.56 (dd, *J* = 12.0 Hz, 7.2 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.49 (dd, *J* = 12.0 Hz, 8.1 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 3.68-3.60 (m, 1H, C***H***CH_3), 1.39 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.9 (***C***$q_{Ar}CH$), 128.9 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 126.9 (***C***H_{Ar}), 81.8 (***C***H_2NO_2), 38.6 (***C***HCH_3), 18.7 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 165 (3), 118 (100), 103 (13), 91 (89), 77 (17), 51 (13), 41 (24); **HRMS** (EI-FE) calcd for [$C_9H_{11}NO_2$]: 165.0790, found 165.0790. The physical data were identical in all respects to those previously reported.[173b]

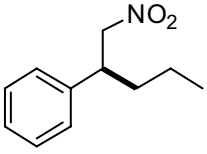


(*R*)-3-Methyl-2-phenyl-1-nitrobutane (116b): The enantiomers were analyzed by GC using a chiral Ivadex 1/PS086 column (5 min at 80 °C, 0.7 °C/min until 180 °C, 20 °C/min until 300 °C, 10 min at 300 °C); major enantiomer: t_R = 67.26 min, minor enantiomer: t_R = 66.71 min. **116b** (69.4 mg, 0.359 mmol, 92%; 92:8 *er*): slightly yellow oil, $C_{11}H_{15}NO_2$ (193.24 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ

7.34-7.25 (m, 3H, C***H***$_{Ar}$), 7.16-7.13 (m, 2H, C***H***$_{Ar}$), 4.76 (dd, *J* = 12.3 Hz, 5.7 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.64 (dd, *J* = 12.3 Hz, 9.8 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 3.27-3.19 (m, 1H, C***H***CH$_2$NO$_2$), 2.01-1.90 (m, 1H, CHC***H***(CH$_3$)$_2$), 1.01 (d, *J* = 6.7 Hz, 3H, CH(C***H***$_3$)$_2$, *CH*$_3^1$), 0.81 (d, *J* = 6.7 Hz, 3H, CH(C***H***$_3$)$_2$, *CH*$_3^2$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 138.6 (***C***q$_{Ar}$CH), 128.6 (***C***H$_{Ar}$), 128.1 (***C***H$_{Ar}$), 127.4, (***C***H$_{Ar}$) 79.1 (***C***H$_2$NO$_2$), 51.0 (***C***HCH$_3$), 31.3 (***C***H(CH$_3$)$_2$), 20.6 (CH(***C***H$_3$)$_2$), 20.2 (CH(***C***H$_3$)$_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 193 (4), 146 (51), 131 (25), 115 (5), 104 (100), 91 (48), 77 (11), 65 (5), 43 (35), 27 (7); **HRMS** (EI-FE) calcd for [C$_{11}$H$_{15}$NO$_2$]: 193.1103, found 193.1102. The physical data were identical in all respect to those previously reported.[266]

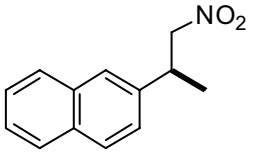


(*S*)-2-Phenyl-1-nitrobutane (116c): The enantiomers were analyzed by GC using a chiral Ivadex 1/PS086 column (80 °C, 1.2 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 40.37 min, minor enantiomer: t_R = 40.98 min. **116c** (65.8 mg, 0.367 mmol, 94%; 97:3 *er*): slightly yellow oil, C$_{10}$H$_{13}$NO$_2$ (179.22 g/mol); **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.36-7.32 (m, 2H, C***H***$_{Ar}$), 7.30-7.26 (m, 1H, C***H***$_{Ar}$), 7.20-7.17 (m, 2H, C***H***$_{Ar}$), 4.63-4.51 (m, 2H, C***H***$_2$NO$_2$), 3.40-3.33 (m, 1H, C***H***CH$_2$NO$_2$), 1.80-1.66 (m, 2H, CHC***H***$_2$CH$_3$), 0.85 (t, *J* = 7.4 Hz, 3H, CH$_2$C***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 139.3 (***C***q$_{Ar}$CH), 128.8 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 80.7 (***C***H$_2$NO$_2$), 46.0 (***C***HCH$_2$CH$_3$), 26.1 (CH***C***H$_2$CH$_3$), 11.5 (CHCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 179 (4), 132 (79), 117 (29), 104 (27), 91 (100), 77 (12), 65 (8); **HRMS** (EI-FE) calcd for [C$_{10}$H$_{13}$NO$_2$]: 179.0946, found 179.0946. The physical data were identical in all respects to those previously reported.[170]

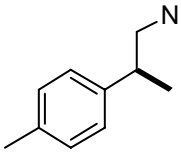


(*S*)-2-Phenyl-1-nitropentane (116d): The enantiomers were analyzed by GC using a chiral Ivadex 1/PS086 column (5 min at 60 °C, 0.7 °C/min until 140 °C, 20 °C/min until 300 °C, 10 min at 300 °C); major enantiomer: t_R = 96.94 min, minor enantiomer: t_R = 97.58 min. **116d** (75.0 mg, 0.388 mmol, >99%; 98:2 *er*): slightly yellow oil, C$_{11}$H$_{15}$NO$_2$ (193.24 g/mol); $[\alpha]_D^{26}$ = -33.8° (*c* = 1.20, CHCl$_3$);[273] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.36-7.26 (m, 3H, C***H***$_{Ar}$), 7.20-7.18 (m, 2H, C***H***$_{Ar}$), 4.56-4.52 (m, 2H, C***H***$_2$NO$_2$), 3.51-3.41 (m, 1H, C***H***CH$_2$NO$_2$), 1.71-1.63 (m, 2H, CHC***H***$_2$CH$_2$), 1.28-1.16 (m, 2H, CH$_2$C***H***$_2$CH$_3$), 0.88 (t, *J* = 7.3 Hz, 3H, CH$_2$C***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 139.5 (***C***q$_{Ar}$CH), 128.9 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 127.5 (***C***H$_{Ar}$), 81.0 (***C***H$_2$NO$_2$), 44.1 (***C***HCH$_2$CH$_2$), 37.1 (CH***C***H$_2$CH$_2$), 20.1 (CH$_2$***C***H$_2$CH$_3$), 13.7 (CH$_2$CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 193 (4), 146 (39), 131 (24), 118 (87), 104 (32), 91 (100), 77 (11), 65 (6), 51 (6), 41 (12); **HRMS**

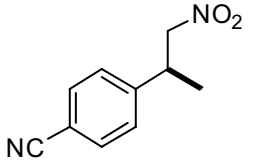
(EI-FE) calcd for [$C_{11}H_{15}NO_2$]: 193.1103, found 193.1101. The physical data were identical in all respects to those previously reported.[173b]



(*S*)-2-(2'-naphthyl)-1-nitropropane (116e): The enantiomers were analyzed by HPLC using a chiral Chiralcel AS-H column (*i*PrOH/Heptane = 90:10, flow rate = 0.3 mL/min, wavelength = 220 nm). Major enantiomer: t_R = 30.97 min, minor enantiomer: t_R = 33.39 min. **116e** (83.6 mg, 0.388 mmol, >99%; 96:4 *er*): colorless solid, $C_{13}H_{13}NO_2$ (215.25 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.86-7.80 (m, 3H, C***H***$_{Ar}$), 7.68 (d, *J* = 1.4 Hz, 1H, C***H***$_{Ar}$), 7.53-7.45 (m, 2H, C***H***$_{Ar}$), 7.38-7.34 (m, 1H, C***H***$_{Ar}$), 4.70-4.54 (m, 2H, C***H***$_2$NO$_2$), 3.85-3.78 (m, 1H, C***H***CH$_3$), 1.48 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.2 (***C***q$_{Ar}$CH), 133.5 (***C***q$_{Ar}$), 132.7 (***C***q$_{Ar}$), 128.8 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 127.7 (***C***H$_{Ar}$), 126.4 (***C***H$_{Ar}$), 126.0 (***C***H$_{Ar}$), 125.7 (***C***H$_{Ar}$), 124.8 (***C***H$_{Ar}$), 81.8 (***C***H$_2$NO$_2$), 38.8(***C***HCH$_3$), 18.7 (CH***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 215 (55), 168 (100), 153 (26), 141 (56), 128 (24), 115 (12), 101 (2), 76 (8), 63 (4), 51 (2), 41 (8); **HRMS** (EI-FE) calcd for [$C_{13}H_{13}NO_2$]: 215.0946, found 215.0947.

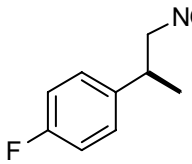


(*S*)-2-(4-Methylphenyl)-1-nitropropane (116f): The enantiomers were analyzed by GC using a chiral Ivadex 1/PS086 column (80 °C, 1 °C/min until 150 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 51.87 min, minor enantiomer: t_R = 52.69 min. **116f** (69.2 mg, 0.386 mmol, 99%; 97:3 *er*): slightly yellow oil, $C_{10}H_{13}NO_2$ (179.22 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.14-7.11 (m, 4H, C***H***$_{Ar}$), 4.54 (dd, *J* = 11.9 Hz, 7.2 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.46 (dd, *J* = 12.0 Hz, 8.3 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 3.64-3.56 (m, 1H, C***H***CH$_3$), 2.33 (s, 3H, C$_{Ar}$C***H***$_3$), 1.37 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.8 (***C***q$_{Ar}$CH), 137.2 (***C***q$_{Ar}$CH$_3$), 129.6 (***C***H$_{Ar}$), 126.7 (***C***H$_{Ar}$), 82.0 (***C***H$_2$NO$_2$), 38.3 (***C***HCH$_3$), 21.0 (Cq$_{Ar}$***C***H$_3$), 18.8 (CH***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 179 (1), 147 (20), 132 (91), 117 (46), 105 (100), 91 (46), 77 (25), 65 (18), 51 (11), 41 (30), 30 (29); **HRMS** (EI-FE) calcd for [$C_{10}H_{13}NO_2$]: 179.0946, found 179.0947.

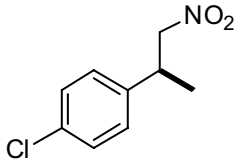


(*S*)-2-(4-Cyanophenyl)-1-nitropropane (116g): The enantiomers were analyzed by GC using a chiral G-TA column (80 °C, 1 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 89.26 min, minor enantiomer: t_R = 90.26 min. **116g** (73.4 mg, 0.386 mmol, 99%; 95:5 *er*): yellow oil, $C_{10}H_{10}N_2O_2$ (190.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66-7.62 (m, 2H, C***H***$_{Ar}$), 7.37-7.34 (m, 2H, C***H***$_{Ar}$), 4.60-4.49 (m, 2H, C***H***$_2$NO$_2$), 3.74-3.67 (m, 1H, C***H***CH$_3$), 1.40 (d, *J* = 7.0

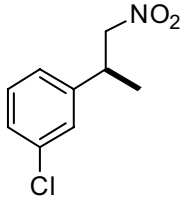
Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 146.2 (***C***q_{Ar}CH), 132.8 (***C***H_{Ar}), 127.8 (***C***H_{Ar}), 118.4 (Cq_{Ar}***C***N), 111.7 (***C***q_{Ar}CN), 80.8 (***C***H_2NO_2), 38.6 (***C***HCH_3), 18.5 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 190 (1), 143 (100), 128 (8), 116 (84), 103 (7), 89 (10), 77 (7), 63 (4), 51 (6), 41 (12), 27 (3); **HRMS** (EIpos) calcd for [($C_{10}H_{10}N_2O_2$+H)$^+$]: 191.0815, found 191.0813.



(*S*)-2-(4-Fluorophenyl)-1-nitropropane (116h): The enantiomers were analyzed by GC using a chiral BGB 176/SE column (80 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 50.66 min, minor enantiomer: t_R = 51.49 min. **116h** (69.2 mg, 0.378 mmol, 97%; 95:5 *er*): slightly yellow oil, $C_9H_{10}NO_2$ (183.18 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.22-7.17 (m, 2H, C***H***$_{Ar}$), 7.07-7.00 (m, 2H, C***H***$_{Ar}$), 4.55-4.43 (m, 2H, C***H***$_2NO_2$), 3.67-3.59 (m, 1H, C***H***CH_3), 1.37 (d, *J* = 7.1 Hz, 3H, CHC***H***$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, 244.6 Hz, ***C***q_{Ar}F), 136.6 (d, 3.2 Hz, ***C***q_{Ar}CH), 128.4 (d, 8.2 Hz, ***C***H_{Ar}), 115.9 (d, 21.6 Hz, ***C***H_{Ar}), 81.8 (***C***H_2NO_2), 37.9 (***C***HCH_3), 18.8 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 183 (6), 136 (100), 122 (14), 109 (85), 101 (10), 96 (8), 83 (6), 75 (6), 41 (17); **HRMS** (EI-FE) calcd for [$C_9H_{10}FNO_2$]: 183.0696, found 183.0695.

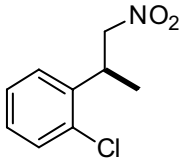


(*S*)-2-(4-Chlorophenyl)-1-nitropropane (116i): The enantiomers were analyzed by GC using a chiral G-TA column (80 °C, 1 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 58.10 min, minor enantiomer: t_R = 60.13 min. **116i** (77.1 mg, 0.386 mmol, 99%; 97:3 *er*): slightly yellow oil, $C_9H_{10}ClNO_2$ (199.63 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34-7.29 (m, 2H, C***H***$_{Ar}$), 7.19-7.14 (m, 2H, C***H***$_{Ar}$), 4.56-4.43 (m, 2H, C***H***$_2NO_2$), 3.66-3.58 (m, 1H, C***H***CH_3), 1.36 (d, *J* = 7.0 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.3 (***C***q_{Ar}CH), 133.4 (***C***q_{Ar}Cl), 129.1 (***C***H_{Ar}), 128.3 (***C***H_{Ar}), 81.5 (***C***H_2NO_2), 38.1 (***C***HCH_3), 18.7 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 199 (8), 152 (100), 139 (12), 125 (81), 117 (19), 103 (23), 89 (8), 77 (19), 63 (7), 51 (13), 41 (35), 27 (4); **HRMS** (EI-FE) calcd for [$C_9H_{10}ClNO_2$]: 199.0400, found 199.0398.The physical data were identical in all respects to those previously reported.[266]

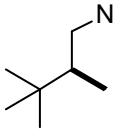


(*S*)-2-(3-Chlorophenyl)-1-nitropropane (116j): The enantiomers were analyzed by GC using a chiral G-TA column (80 °C, 1 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 58.28 min, minor enantiomer: t_R = 58.89 min. **116j** (75.5 mg, 0.378 mmol, 97%; 95:5 *er*): slightly yellow oil, $C_9H_{10}ClNO_2$ (199.63 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H, C***H***$_{Ar}$), 7.24-

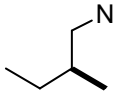
7.22 (m, 1H, C***H***$_{Ar}$), 7.13-7.10 (m, 1H, C***H***$_{Ar}$), 4.57-4.44 (m, 2H, C***H***$_2$NO$_2$), 3.66-3.58 (m, 1H, C***H***CH$_3$), 1.37 (d, *J* = 7.1 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 142.9 (***C***q$_{Ar}$CH), 134.8 (***C***q$_{Ar}$Cl), 130.2 (***C***H$_{Ar}$), 127.8 (***C***H$_{Ar}$), 127.1 (***C***H$_{Ar}$), 125.2 (***C***H$_{Ar}$), 81.4 (***C***H$_2$NO$_2$), 38.3 (***C***HCH$_3$), 18.6 (CH***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 199 (10), 152 (100), 138 (7), 125 (83), 117 (22), 103 (19), 91 (8), 77 (16), 63 (6), 51 (11), 41 (28), 27 (3); **HRMS** (EI-FE) calcd for [C$_9$H$_{10}$ClNO$_2$]: 199.0400, found 199.0402.



(*S*)-2-(2-Chlorophenyl)-1-nitropropane (116k): The enantiomers were analyzed by GC using a chiral BGB 176/SE column (80 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 49.87 min, minor enantiomer: t_R = 49.08 min. **116k** (65.5 mg, 0.328 mmol, 84%; 83:17 *er*): slightly yellow oil, C$_9$H$_{10}$ClNO$_2$ (199.63 g/mol); **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.41-7.39 (m, 1H, C***H***$_{Ar}$), 7.29-7.20 (m, 3H, C***H***$_{Ar}$), 4.67 (dd, *J* = 12.2 Hz, 6.1 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.57 (dd, *J* = 12.2 Hz, 8.6 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.20-4.13 (m, 1H, C***H***CH$_3$), 1.41 (d, *J* = 6.9 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 138.0 (***C***q$_{Ar}$CH), 133.7 (***C***q$_{Ar}$Cl), 130.2 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 127.4 (***C***H$_{Ar}$), 127.3 (***C***H$_{Ar}$), 80.0 (***C***H$_2$NO$_2$), 34.8 (***C***HCH$_3$), 17.4 (CH***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 199 (11), 152 (63), 139 (8), 125 (100), 115 (24), 103 (18), 91 (14), 77 (15), 63 (6), 51 (11), 41 (13), 27 (2); **HRMS** (EI-FE) calcd for [C$_9$H$_{10}$ClNO$_2$]: 199.0400, found 199.0398.

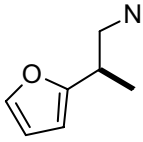


(*S*)-2,3,3-Trimethyl-1-nitrobutane (116l): The enantiomers were analyzed by GC using a chiral BGB 176/SE column (60 °C, 1.2 °C/min until 120 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 23.48 min, minor enantiomer: t_R = 24.47 min. **116l** (46.5 mg, 0.320 mmol, 82%; 96:4 *er*): slightly yellow oil, C$_7$H$_{15}$NO$_2$ (145.20 g/mol); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 4.53 (dd, *J* = 11.5 Hz, 7.7 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.12-4.06 (m, 1H, C***H***$_2$NO$_2$, *H*^{2}), 2.17 (m, 1H, C***H***CH$_3$), 0.97 (d, *J* = 6.8 Hz, 3H, CHC***H***$_3$), 0.93 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 79.6 (***C***H$_2$NO$_2$), 42.3 (***C***HCH$_3$), 32.4 (***C***(CH$_3$)$_3$), 27.1 (C(***C***H$_3$)$_3$), 12.9 (CH***C***H$_3$); **GC/MS** *m*/*z* (%) = 145.



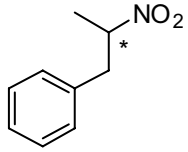
(*S*)-2-methyl-1-nitrobutane (116m): The enantiomers were analyzed by GC using a chiral BGB 176/SE column (60 °C, 1.0 °C/min until 85 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 14.99 min, minor enantiomer: t_R = 15.42 min. **116m** (42.3 mg, 0.378 mmol, 97%; 82:18 *er*): slightly yellow oil, C$_5$H$_{11}$NO$_2$ (117.15 g/mol); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 4.33 (dd, *J* = 11.6 Hz, 6.4 Hz, 1H, C***H***$_2$NO$_2$,

H^1), 4.19 (dd, *J* = 11.6 Hz, 8.0 Hz, 1H, C***H***$_2$NO$_2$, H^2), 2.28-2.23 (m, 1H, C***H***CH$_3$), 1.44-1.25 (m, 2H, C***H***$_2$CH$_3$), 1.01 (d, *J* = 6.7 Hz, 3H, CHC***H***$_3$), 0.95 (t, 7.4 Hz, 3H, CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 81.4 (***C***H$_2$NO$_2$), 34.1 (***C***HCH$_3$), 26.5 (***C***H$_2$CH$_3$), 16.7 (CH***C***H$_3$), 10.9 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 118 (0.02), 71 (26), 55 (45), 43 (100), 41 (48), 39 (18), 29 (44), 27 (20); **GC/MS** *m*/*z* (%) = 117.



(*R*)-2-(Furan-2-yl)-1-nitropropane (116n): The enantiomers were analyzed by GC using a chiral BGB 176/SE column (80 °C, 1.2 °C/min until 140 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 22.55 min, minor enantiomer: t_R = 24.31 min. **116n** (50.9 mg, 0.328 mmol, 84%; 96:4 *er*): orange oil, C$_7$H$_9$NO$_3$ (155.15 g/mol); **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.35 (dd, *J* = 1.8 Hz, 0.6 Hz, 1H, C***H***$_{Ar}$), 6.31 (dd, *J* = 3.2 Hz, 1.9 Hz, 1H, C***H***$_{Ar}$), 6.13-6.12 (m, 1H, C***H***$_{Ar}$), 4.67 (dd, *J* = 12.2 Hz, 6.5 Hz, 1H, C***H***$_2$NO$_2$, H^1), 4.43 (dd, *J* = 12.2 Hz, 8.0 Hz, 1H, C***H***$_2$NO$_2$, H^2), 3.77-3.70 (m, 1H, C***H***CH$_3$), 1.37 (d, *J* = 7.1 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 153.8 (***C***q$_{Ar}$CH), 142.1 (O***C***H$_{Ar}$), 110.3 (***C***H$_{Ar}$), 105.9 (***C***H$_{Ar}$), 79.5 (***C***H$_2$NO$_2$), 32.4 (***C***HCH$_3$), 16.1 (CH***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 155 (11), 108 (100), 94 (22), 81 (24), 65 (13), 53 (20), 43 (7), 41 (28), 27 (14); **HRMS** (EI-FE) calcd for [C$_7$H$_9$NO$_3$]: 155.0582, found 155.0584. The physical data were identical in all respects to those previously reported.[266]

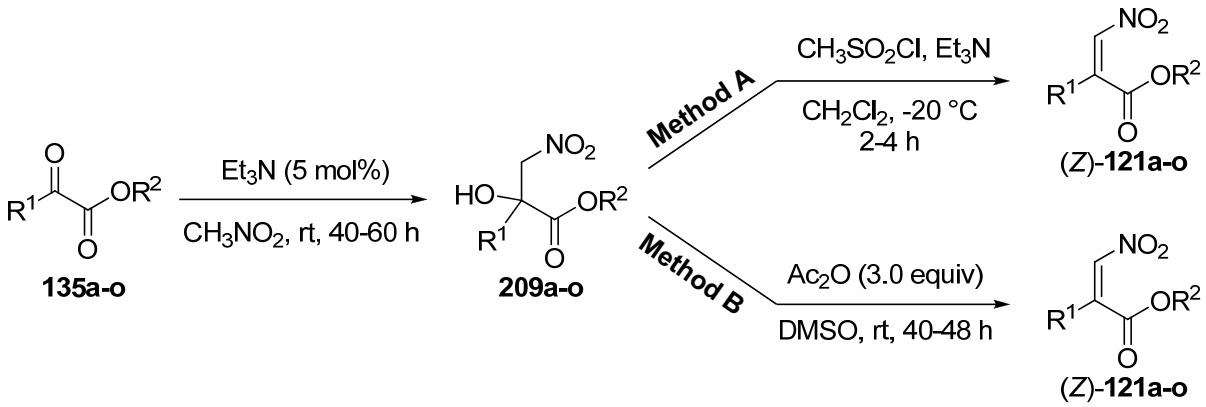
***Asymmetric Transfer Hydrogenation of (E)-1-phenyl-2-nitropropene* (207):**



1-Nitro-2-phenylpropane (**208**) was obtained almost racemic form from the asymmetric transfer hydrogenation of commercially available (*E*)-1-phenyl-2-nitropropene (**207**, Sigma-Aldrich). The enantiomers were analyzed by GC using a chiral BGB-176/SE column (1.2 °C/min until 170 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 39.39 min, minor enantiomer: t_R = 38.74 min. **208** (64.1 mg, 0.388 mmol, >99%; 52:48 *er*): slightly yellow oil, C$_9$H$_{11}$NO$_2$ (165.19 g/mol); **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.35-7.25 (m, 3H, C***H***$_{Ar}$), 7.18-7.15 (m, 2H, C***H***$_{Ar}$), 4.78 (m, *J* = 6.8 Hz, 1H, C***H***CH$_3$), 3.33 (dd, *J* = 14.0 Hz, 7.4 Hz, 1H, C***H***$_2$CHNO$_2$, H^1), 3.01 (dd, *J* = 14.0 Hz, 6.9 Hz, 1H, C***H***$_2$CHNO$_2$, H^2), 1.55 (d, *J* = 6.7 Hz, 3H, CHC***H***$_3$); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 135.5 (***C***q$_{Ar}$CH$_2$), 129.9 (***C***H$_{Ar}$), 129.0 (***C***H$_{Ar}$), 128.8 (***C***H$_{Ar}$), 127.4 (***C***H$_{Ar}$), 84.4 (***C***HNO$_2$), 41.2 (***C***H$_2$CHNO$_2$), 14.1 (CH***C***H$_3$); **HRMS** (EI-FE) calcd for [C$_9$H$_{11}$NO$_2$]: 165.0790, found 165.0790. The physical data were identical in all respects to those previously reported.[173b]

7.6 Enantioselective Transfer Hydrogenation of *β*-Nitroacrylates: a Route to *β*²-Amino Acids

7.6.1 Synthesis of the Starting Materials

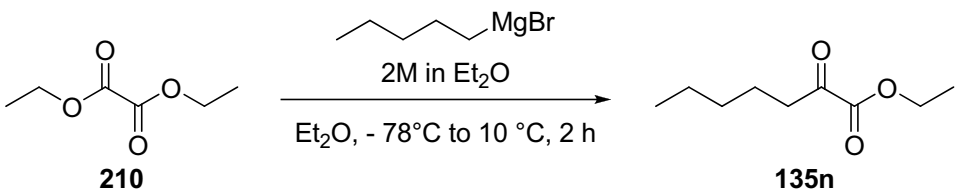


7.6.1.1 Synthesis of the *α*-Ketoesters 135

Ethyl 2-oxopropanoate (**135a**), methyl 2-oxo-2-phenylacetate (**135c**), ethyl 2-oxo-2-phenylacetate (**135d**), ethyl 2-(4-methylphenyl)-2-oxoacetate (**135g**), ethyl 2-(4-methoxyphenyl)-2-oxoacetate (**135h**), ethyl 2-(4-fluorophenyl)-2-oxoacetate (**135i**), ethyl 2-(4-chlorophenyl)-2-oxoacetate (**135j**), ethyl 2-oxo-2-(thiophen-2-yl)acetate (**135m**) and ethyl 3-methyl-2-oxobutanoate (**135o**) were commercially available.

Isopropyl, *tert*-butyl and benzyl 2-oxo-2-phenylacetate (**135b**, **135e** and **135f**, respectively) as well as *tert*-butyl 2-(4-methoxyphenyl)-2-oxoacetate (**135k**) and *tert*-butyl 2-(4-fluorophenyl)-2-oxoacetate (**135l**) were prepared by *X. Cheng* according to the procedures reported in Chapter 4.5.1.1 (Schemes 4.69-4.70).

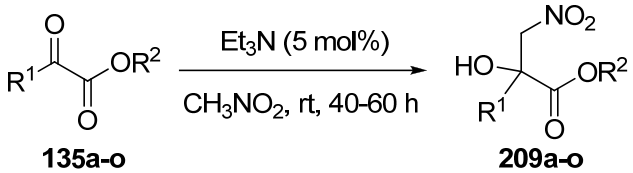
Preparation of ethyl 2-oxoheptanoate **(135n)**[245]



Pentylmagnesium bromide (2 M in diethyl ether, 33.0 mL, 66.00 mmol, 1.1 equiv) was added over one hour using a syringe pump to a solution of diethyloxalate (9.10 g, 62.27 mmol, 1.0 equiv) in diethyl ether (90 mL) at -78 °C. After one hour at -78 °C, the mixture was warmed to 10 °C and quenched with a solution of hydrochloric acid (3 N, 40 mL) and water (40 mL). The two resulting phases were separated and the aqueous layer extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with brine and dried over magnesium sulfate. The volatile compounds were removed *in vacuo* and the crude product was purified by flash chromatography (5-10% of diethyl ether in pentane) to afford the pure ethyl 2-oxoheptanoate (**135n**, 7.70 g, 44.71 mmol, 72%) as a yellow oil.

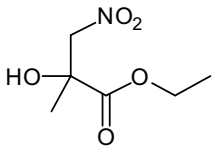
135n: $C_9H_{16}O_3$ (172.22 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.31 (q, *J* = 7.1 Hz, 2H, C***H***$_2$CH$_3$), 2.81 (t, *J* = 7.3 Hz, 2H, C***H***$_2$CO), 1.65-1.61 (m, 2H, CH$_2$C***H***$_2$CH$_2$), 1.38-1.28 (m, 7H: t, *J* = 7.1 Hz, OCH$_2$C***H***$_3$ (3H), CH$_2$C***H***$_2$CH$_2$ (2H), CH$_2$C***H***$_2$CH$_3$ (2H)), 0.91-0.87 (m, 3H, CH$_2$CH$_2$C**H**$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 194.8 (***C***=O), 161.3 (O***C***=O), 62.3 (O***C***H$_2$CH$_3$), 39.2 (C(O)***C***H$_2$CH$_2$), 31.1 (CH$_2$***C***H$_2$CH$_2$), 22.6 (CH$_2$***C***H$_2$CH$_2$), 22.3 (CH$_2$***C***H$_2$CH$_3$), 14.0 (CH$_2$CH$_2$***C***H$_3$), 13.8 (OCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 172 (5), 99 (100), 71 (50), 55 (11), 43 (87), 29 (27); **HRMS** (EI-FE) calcd for [$C_9H_{16}O_3$]: 172.1099, found 172.1098. The physical data were identical in all respects to those previously reported.[274]

7.6.1.2 Synthesis of the *β*-nitro-*α*-hydroxyester 209



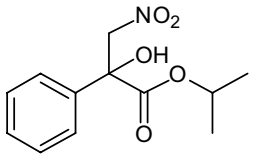
135a-o **209a-o**

In a dried two-necked round-bottomed flask, the α-ketoester **135** (20.00 mmol) was added to nitromethane (80 mL) followed by dried triethylamine (0.55 mL, 3.97 mmol). The mixture was then stirred at room temperature until complete conversion of the starting material (TLC monitoring). Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to give the pure *β*-nitro-*α*-hydroxyesters **209**.



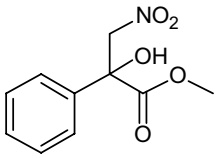
Ethyl 2-hydroxy-2-methyl-3-nitropropanoate (209a): *β*-Nitro-*α*-hydroxyester **209a** was synthesized according to the general procedure starting from ethyl 2-oxopropanoate (**135a**, 5.00 g, 43.06 mmol). After purification by flash chromatography (5-20% of diethyl ether in pentane) ethyl 2-hydroxy-2-methyl-3-nitropropanoate (**209a,** 7.30 g, 41.21 mmol, 96%) was obtained as a colorless oil.

209a: $C_6H_{11}NO_5$ (177.16 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.84 (d, *J* = 13.7 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.55 (d, *J* = 13.8 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.39-4.28 (m, 2H, C***H***$_2$CH$_3$), 3.75 (s, 1H, O***H***), 1.45 (s, 3H, CC***H***$_3$), 1.32 (t, *J* = 7.1 Hz, 3H, CH$_2$C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.4 (***C***=O), 81.0 (***C***H$_2$NO$_2$), 72.4 (***C***CH$_2$NO$_2$), 63.0 (O***C***H$_2$CH$_3$), 23.8(OC***C***H$_3$), 14.0 (C***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 178 (0.03), 134 (1), 117 (1), 104 (61), 85 (2), 73 (1), 58 (32), 43 (100), 29 (63); **HRMS** (EIpos) calcd for [($C_6H_{11}NO_5$+H)$^+$]: 178.0716, found 178.0718. The physical data were identical in all respects to those previously reported.[203]



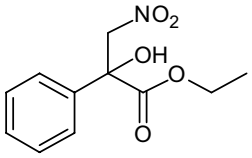
Isopropyl 2-hydroxy-3-nitro-2-phenylpropanoate (209b): *β*-Nitro-*α*-hydroxyester **209b** was synthesized according to the general procedure starting from isopropyl 2-oxo-2-phenylacetate (**135b**, 3.00 g, 15.61 mmol). After purification by flash chromatography (15% of ethyl acetate in hexanes) isopropyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209b,** 3.62 g, 14.29 mmol, 92%) was obtained as a colorless solid.

209b: $C_{12}H_{15}NO_5$ (253.25 g/mol); **m.p.**: 97-100 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.65-7.57 (m, 2H, C***H***$_{Ar}$), 7.44-7.34 (m, 3H, C***H***$_{Ar}$), 5.24 (d, *J* = 14.1 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 5.15-5.23 (m, 1H, C***H***(CH$_3$)$_2$), 4.66 (d, *J* = 14.1 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.22 (s, 1H, O***H***), 1.35 (d, *J* = 6.3 Hz, 3H, CH(C***H***$_3$)$_2$), 1.29 (d, *J* = 6.3 Hz, 3H, CH(C***H***$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.1 (***C***=O), 136.6 (***C***q$_{Ar}$C), 129.1 (***C***H$_{Ar}$), 128.8 (***C***H$_{Ar}$), 125.2 (***C***H$_{Ar}$), 80.8 (***C***H$_2$NO$_2$), 75.9 (***C***CH$_2$NO$_2$), 71.9 (***C***H(CH$_3$)$_2$), 21.5 (CH(***C***H$_3$)$_2$), 21.4 (CH(***C***H$_3$)$_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 253 (0.34), 166 (15), 123 (15), 120 (15), 105 (100), 91 (10), 77 (18), 65 (2), 51 (6), 43 (25); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_5$]: 253.0950, found 253.0950.



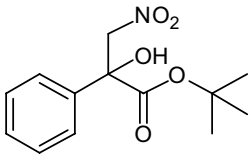
Methyl 2-hydroxy-3-nitro-2-phenylpropanoate (209c): *β*-Nitro-*α*-hydroxyester **209c** was synthesized according to the general procedure starting from methyl 2-oxo-2-phenylacetate (**135c**, 3.00 g, 18.27 mmol). After purification by flash chromatography (10-15% of ethyl acetate in hexanes) methyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209c,** 3.50 g, 15.54 mmol, 41.21 mmol, 85%) was obtained as a colorless oil.

209c: $C_{10}H_{11}NO_5$ (225.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61-7.68 (m, 2H, C***H***$_{Ar}$), 7.44-7.37 (m, 3H, C***H***$_{Ar}$), 5.26 (d, *J* = 14.2 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.68 (d, *J* = 14.2 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.23 (s, 1H, O***H***), 3.91 (s, 3H, OC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (***C***=O), 136.3 (***C***q_{Ar}C), 135.0 (***C***H_{Ar}), 130.1 (***C***H_{Ar}), 129.2 (***C***H_{Ar}), 129.0 (***C***H_{Ar}), 125.2 (***C***H_{Ar}), 80.0 (***C***H_2NO_2), 76.1 (***C***CH_2NO_2), 54.1(O***C***H_3), 14.2; **MS** (EI, 70 eV): *m*/*z* (%) = 225 (6), 166 (37), 123 (24), 105 (100), 91 (21), 77 (21), 65 (4), 51 (6), 39 (2), 30 (1); **HRMS** (EI-FE) calcd for [$C_{10}H_{11}NO_5$]: 225.0637, found 225.0640.



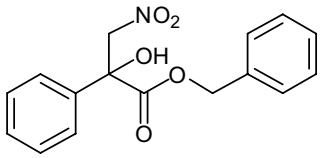
Ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (209d): *β*-Nitro-*α*-hydroxyester **209d** was synthesized according to the general procedure starting from ethyl 2-oxo-2-phenylacetate (**135d**, 5.00 g, 28.06 mmol). After purification by flash chromatography (5-20% of ethyl acetate in hexanes) ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209d,** 6.20 g, 25.92 mmol, 92%) was obtained as a slightly yellow oil.

209d: $C_{11}H_{13}NO_5$ (239.22 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.62-7.58 (m, 2H, C***H***$_{Ar}$), 7.44-7.37 (m, 3H, C***H***$_{Ar}$), 5.26 (d, *J* = 14.2 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.68 (d, *J* = 14.2 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.44-4.31 (m, 2H, C***H***$_2CH_3$), 4.24 (d, *J* = 0.8 Hz, 1H, O***H***), 1.34 (dt, *J* = 7.2 Hz, 1.2 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6 (***C***=O), 136.4 (***C***q_{Ar}C), 129.1 (***C***H_{Ar}), 128.9 (***C***H_{Ar}), 125.2 (***C***H_{Ar}), 80.8 (***C***H_2NO_2), 76.0 (***C***CH_2NO_2), 63.6 (***C***H_2CH_3), 13.9 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 239 (3), 166 (29), 123 (20), 105 (100), 91 (16), 77 (17), 65 (3), 51 (5), 43 (3), 29 (15); **HRMS** (EIpos) calcd for [($C_{11}H_{13}NO_5$+Na)$^+$]: 262.0686, found 262.0688. The physical data were identical in all respects to those previously reported.[203]



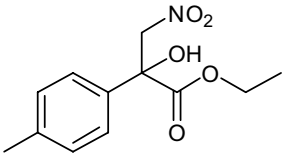
***tert*-Butyl 2-hydroxy-3-nitro-2-phenylpropanoate (209e)**: *β*-Nitro-*α*-hydroxyester **209e** was synthesized according to the general procedure starting from *tert*-butyl 2-oxo-2-phenylacetate (**135e**, 1.30 g, 6.30 mmol). After purification by flash chromatography (5-20% of ethyl acetate in hexanes) *tert*-butyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209e,** 1.30 g, 4.86 mmol, 77%) was obtained as a colorless oil.

209e: $C_{13}H_{17}NO_5$ (267.28 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.59 (m, 2H, C***H***$_{Ar}$), 7.42-7.34 (m, 3H, C***H***$_{Ar}$), 5.19 (d, *J* = 14.0 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.65 (d, *J* = 14.0 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.23 (s, 1H, O***H***), 1.52 (s, 9H, (C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5 (***C***=O), 137.0 (***C***q$_{Ar}$C), 128.9 (***C***H$_{Ar}$), 128.8 (***C***H$_{Ar}$), 125.2 (***C***H$_{Ar}$), 85.0 (***C***(CH$_3$)$_3$), 80.8 (***C***H$_2NO_2$), 75.9 (***C***CH$_2NO_2$), 27.7 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 268 (0.03), 166 (7), 120 (14), 105 (37), 77 (8), 57 (100), 41 (18), 29 (11); **HRMS** (EI-FE) calcd for [($C_{13}H_{17}NO_5$+H)$^+$]: 268.1185, found 268.1185.



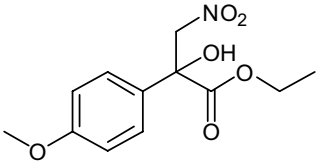
Benzyl 2-hydroxy-3-nitro-2-phenylpropanoate (209f): *β*-Nitro-*α*-hydroxyester **209f** was synthesized according to the general procedure starting from ethyl 2-oxopropanoate (**135f**, 2.00 g, 8.32 mmol). After purification by flash chromatography (20% of ethyl acetate in hexanes) benzyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209f,** 2.11 g, 7.00 mmol, 84%) was obtained as a colorless oil.

209f: $C_{16}H_{15}NO_5$ (301.29 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H, C***H***$_{Ar}$), 7.37-7.26 (m, 8H, C***H***$_{Ar}$), 5.28 (s, 2H, C***H***$_2$Ph), 5.24 (d, *J* = 14.1 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.66 (d, *J* = 14.1 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.26 (s, 1H, O***H***); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6 (***C***=O), 136.2 (***C***q$_{Ar}$C), 134.2 (***C***q$_{Ar}$CH$_2$), 129.1 (***C***H$_{Ar}$), 129.0 (***C***H$_{Ar}$), 128.8 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 125.2 (***C***H$_{Ar}$), 80.6 (***C***H$_2NO_2$), 76.1 (***C***CH$_2NO_2$), 69.2; **MS** (EI, 70 eV): *m*/*z* (%) = 302 (0.03), 166 (29), 123 (16), 105 (80), 91 (100), 77 (20), 65 (15), 51 (9), 39 (7); **HRMS** (EI-FE) calcd for [($C_{16}H_{15}NO_5$+Na)$^+$]: 324.0842, found 324.0841.



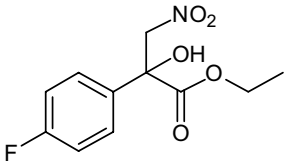
Ethyl 2-hydroxy-3-nitro-2-*p*-tolylpropanoate (209g): *β*-Nitro-*α*-hydroxyester **209g** was synthesized according to the general procedure starting from ethyl 2-oxo-2-*p*-tolylacetate (**135g**, 4.00 g, 20.81 mmol). After purification by flash chromatography (10% of ethyl acetate in hexanes) ethyl 2-hydroxy-3-nitro-2-*p*-tolylpropanoate (**209g,** 4.31 g, 17.02 mmol, 82%) was obtained as a colorless oil.

209g: $C_{12}H_{15}NO_5$ (253.25 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H, C***H***$_{Ar}$), 7.22-7.19 (d, *J* = 8.0 Hz, 2H, C***H***$_{Ar}$), 5.24 (dd, *J* = 14.2 Hz, 0.7 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.66 (d, *J* = 14.1 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.41-4.30 (m, 2H, C***H***$_2CH_3$), 4.19 (s, 1H, O***H***), 2.35 (s, 3H, p-C_{Ar}C***H***$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.8 (***C***=O), 139.1 (***C***$q_{Ar}CH_3$), 133.5 (***C***q_{Ar}C), 129.6 (***C***H_{Ar}), 125.1 (***C***H_{Ar}), 80.8 (***C***H_2NO_2), 75.9 (***C***CH_2NO_2), 63.5 (***C***H_2CH_3), 21.0 (Cq_{Ar}***C***H_3), 13.9 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 253 (5), 180 (17), 137 (8), 119 (100), 105 (3), 91 (21), 65 (6), 29 (3); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_5$]: 253.0950, found 253.0949.



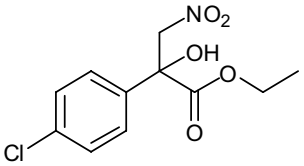
Ethyl 2-hydroxy-3-nitro-2-(4-methoxy-phenyl)propanoate (209h): *β*-Nitro-*α*-hydroxyester **209h** was synthesized according to the general procedure starting from ethyl 2-(4-methoxyphenyl)-2-oxoacetate (**135h**, 4.00 g, 19.21 mmol). After purification by flash chromatography (5-20% of ethyl acetate in hexanes) ethyl 2-hydroxy-3-nitro-2-(4-methoxy-phenyl)propanoate (**209h,** 4.21 g, 15.64 mmol, 81%) was obtained as a slightly yellow oil.

209h: $C_{12}H_{15}NO_6$ (269.25 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 6.91 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 5.22 (d, *J* = 14.1 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.65 (d, *J* = 14.1 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.42-4.30 (m, 2H, C***H***$_2CH_3$), 4.18 (s, 1H, O***H***), 3.81 (s, 3H, OC***H***$_3$), 1.33 (t, *J* = 7.2 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.8 (***C***=O), 160.1 (***C***$q_{Ar}OCH_3$), 128.3 (***C***q_{Ar}C), 126.6 (***C***H_{Ar}), 114.2 (***C***H_{Ar}), 80.8 (***C***H_2NO_2), 75.7 (***C***CH_2NO_2), 63.5 (***C***H_2CH_3), 55.3 (O***C***H_3), 13.9 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 269 (6), 196 (25), 150 (29), 135 (100), 121 (7), 107 (4), 92 (4), 77 (10); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_6$]: 269.0899, found 269.0897. The physical data were identical in all respects to those previously reported.[203]



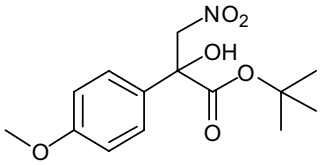
Ethyl 2-(4-fluorophenyl)-2-hydroxy-3-nitropropanoate (209i): *β*-Nitro-*α*-hydroxyester **209i** was synthesized according to the general procedure starting from ethyl 2-(4-fluorophenyl)-2-oxoacetate (**135i**, 4.00 g, 20.39 mmol). After purification by flash chromatography (10% of ethyl acetate in hexanes) ethyl 2-(4-fluorophenyl)-2-hydroxy-3-nitropropanoate (**209i,** 5.10 g, 19.83 mmol, 97%) was obtained as a colorless oil.

209i: $C_{11}H_{12}FNO_5$ (257.22 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.63-7.58 (m, 2H, C***H***$_{Ar}$), 7.12-7.06 (m, 2H, C***H***$_{Ar}$), 5.22 (dd, *J* = 14.0 Hz, 0.5 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.64 (d, *J* = 14.2 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.43-4.32 (m, 2H, C***H***$_2CH_3$), 4.25 (d, *J* = 0.9 Hz, 1H, O***H***), 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2C\boldsymbol{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.4 (***C***=O), 163.1 (d, *J* = 247.4 Hz, ***C***q_{Ar}F), 132.2 (d, *J* = 3.1 Hz, ***C***q_{Ar}C), 127.3 (d, *J* = 8.3 Hz, ***C***H_{Ar}), 115.9 (d, *J* = 21.7 Hz, ***C***H_{Ar}), 80.7 (***C***H_2NO_2), 75.7 (***C***CH_2NO_2), 63.7 (***C***H_2CH_3), 13.9 ($CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 257 (3), 184 (29), 141 (18), 123 (100), 109 (8), 95 (14), 83 (1), 75 (4), 61 (2), 43 (1), 29 (6); **HRMS** (EI-FE) calcd for [$C_{11}H_{12}FNO_5$]: 257.0700, found 257.0699.



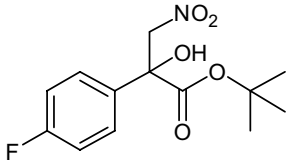
Ethyl2-(4-chlorophenyl)-2-hydroxy-3-nitropropanoate (209j): *β*-Nitro-*α*-hydroxyester **209j** was synthesized according to the general procedure starting from ethyl 2-(4-chlorophenyl)-2-oxoacetate (**135j**, 2.00 g, 9.41 mmol). After purification by flash chromatography (10% of ethyl acetate in hexanes) ethyl 2-(4-chlorophenyl)-2-hydroxy-3-nitropropanoate (**209j,** 2.12 g, 7.75 mmol, 82%) was obtained as a colorless oil.

209j: $C_{11}H_{12}ClNO_5$ (273.67 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H, C***H***$_{Ar}$), 7.40-7.35 (m, 2H, C***H***$_{Ar}$), 5.21 (dd, *J* = 14.0 Hz, 0.6 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.64 (d, *J* = 14.3 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.43-4.31 (m, 2H, C***H***$_2CH_3$), 4.25 (d, *J* = 0.8 Hz, 1H, O***H***), 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2C\boldsymbol{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.3 (***C***=O), 135.3 (***C***q_{Ar}C), 134.9 (***C***q_{Ar}Cl), 129.1 (***C***H_{Ar}), 126.8 (***C***H_{Ar}), 80.6 (***C***H_2NO_2), 75.7 (***C***CH_2NO_2), 63.8 (***C***H_2CH_3), 13.9 ($CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 273 (4), 200 (17), 157 (11), 139 (100), 111 (18), 75 (9), 61 (4), 50 (3); **HRMS** (EI-FE) calcd for [$C_{11}H_{12}ClNO_5$]: 273.0402, found 273.0404. The physical data were identical in all respects to those previously reported.[203]



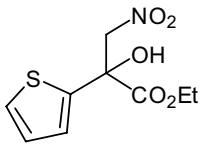
***tert*-Butyl 2-hydroxy-3-nitro-2-(4-methoxyphenyl)-propanoate (209k)**: *β*-Nitro-*α*-hydroxyester **209k** was synthesized according to the general procedure starting from *tert*-butyl 2-(4-methoxyphenyl)-2-oxoacetate (**135k**, 1.50 g, 6.35 mmol). After purification by flash chromatography (20% of ethyl acetate in hexanes) *tert*-butyl 2-hydroxy-3-nitro-2-(4-methoxyphenyl)propanoate (**209k,** 1.30 g, 4.37 mmol, 69%) was obtained as a colorless solid.

209k: $C_{14}H_{19}NO_6$ (297.30 g/mol); **m.p.**: 80-82 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 6.91 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 5.15 (d, *J* = 14.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.62 (d, *J* = 14.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.18 (s, 1H, O***H***), 3.81 (s, 3H, OC***H***$_3$), 1.52 (s, 9H, (C***H***$_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.7 (***C***=O), 160.0 (***C***q$_{Ar}$OCH$_3$), 128.9 (***C***q$_{Ar}$C), 126.5 (***C***H$_{Ar}$), 114.1 (***C***H$_{Ar}$), 84.9 (***C***(CH$_3$)$_3$), 80.9 (***C***H$_2$NO$_2$), 75.6 (***C***CH$_2$NO$_2$), 55.3 (O***C***H$_3$), 27.7 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 297 (7), 196 (43), 150 (39), 135 (100), 121 (4), 92 (4), 77 (8), 57 (65), 41 (11); **HRMS** (EIpos) calcd for [($C_{14}H_{19}NO_6$+Na)$^+$]: 320.1105, found 320.1104.



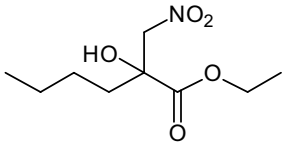
***tert*-Butyl 2-hydroxy-3-nitro-2-(4-fluorophenyl)propanoate (209l):** *β*-Nitro-*α*-hydroxyester **209l** was synthesized according to the general procedure starting from *tert*-butyl 2-(4-fluorophenyl)-2-oxoacetate (**135l**, 1.40 g, 6.24 mmol). After purification by flash chromatography (20% acetone in hexanes) *tert*-butyl 2-hydroxy-3-nitro-2-(4- fluorophenyl)propanoate (**209l,** 1.21 g, 4.24 mmol, 68%) was obtained as a colorless oil.

209l: $C_{13}H_{16}FNO_5$ (285.27 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H, C***H***$_{Ar}$), 7.11-7.06 (m, 2H, C***H***$_{Ar}$), 5.16 (d, *J* = 14.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.62 (d, *J* = 14.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.24 (s, 1H, O***H***), 1.52 (s, 9H, (C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.3 (***C***=O), 163.0 163.1 (d, *J* = 249.4 Hz, ***C***q$_{Ar}$F), 132.7 (***C***q$_{Ar}$C), 127.3 (d, *J* = 32.4 Hz, ***C***H$_{Ar}$), 115.7 (d, *J* = 84.4 Hz, ***C***H$_{Ar}$), 85.3 (***C***(CH$_3$)$_3$), 80.8 (***C***H$_2$NO$_2$), 75.6 (***C***CH$_2$NO$_2$), 27.7 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 286 (0.04), 184 (7), 138 (11), 123 (29), 109 (4), 95 (5), 57 (100), 41 (22); **HRMS** (EIpos) calcd for [($C_{13}H_{16}FNO_5$+Na)$^+$]: 308.0905, found 308.0902.



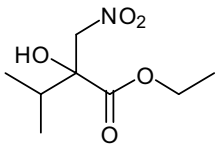
Ethyl 2-hydroxy-3-nitro-2-(thiophen-2-yl)propanoate (209m): *β*-Nitro-*α*-hydroxyester **209m** was synthesized according to the general procedure starting from ethyl 2-oxo-2-(thiophen-2-yl)acetate (**135m**, 7.28 g, 39.50 mmol). After purification by flash chromatography (15% of ethyl acetate in hexanes) ethyl 2-hydroxy-3-nitro-2-(thiophen-2-yl)propanoate (**209m,** 6.29 g, 25.69 mmol, 65%) was obtained as a greenish yellow solid.

209m: $C_9H_{11}NO_5S$ (245.25 g/mol); **m.p.**: 59-62 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H, C***H***$_{Ar}$), 7.15 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H, C***H***$_{Ar}$), 7.02 (dd, *J* = 5.1 Hz, 3.6 Hz, 1H, C***H***$_{Ar}$), 5.18 (d, *J* = 14 Hz, C***H***$_2NO_2$, *H*^{1}), 4.76 (d, *J* =14 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.46-4.35 (m, 3H: O***H*** (1H), C***H***$_2CH_3$ (2H)), 1.37 (t, *J* = 7.2 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.6 (***C***=O), 140.4 (***C***q$_{Ar}$C), 127.5 (***C***H$_{Ar}$), 126.8 (***C***H$_{Ar}$), 125.1 (***C***H$_{Ar}$), 80.6 (***C***H$_2NO_2$), 74.8 (***C***CH$_2NO_2$), 63.9 (***C***H$_2CH_3$), 13.9(CH_2***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 245 (10), 199 (12), 172 (58), 126 (44), 111 (100), 97 (17), 84 (8), 65 (2), 39 (8), 29 (15); **HRMS** (EI-FE) calcd for [$C_9H_{11}NO_5S$]: 245.0358, found 245.0358.



Ethyl 2-hydroxy-2-(nitromethyl)heptanoate (209n): *β*-Nitro-*α*-hydroxyester **209n** was synthesized according to the general procedure starting from ethyl 2-oxoheptanoate (**135n**, 7.60 g, 44.13 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) ethyl 2-hydroxy-2-(nitromethyl)heptanoate (**209n,** 9.70 g, 41.58 mmol, 94%) was obtained as a colorless oil.

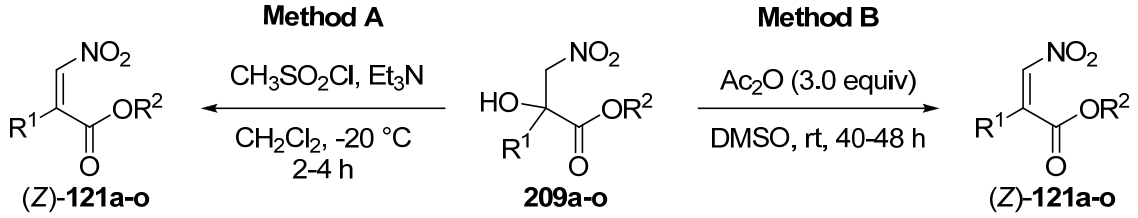
209n: $C_{10}H_{19}NO_5$ (233.26 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.81 (d, *J* = 13.6 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.55 (d, *J* = 13.6 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.40-4.29 (m, 2H, C***H***$_2CH_3$), 3.69 (s, 1H, O***H***), 1.69-1.61 (m, 2H, C***H***$_2$CO), 1.55-1.20 (m, 9H: t, *J* = 7.1 Hz, OCH_2C***H***$_3$ (3H); CH_2C***H***$_2CH_2$ (4H); CH_2C***H***$_2CH_3$ (2H)), 0.87 (t, *J* = 6.8 Hz, 3H, CH_2CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.9 (***C***=O), 80.9 (***C***H$_2NO_2$), 75.3 (***C***CH$_2NO_2$), 63.0 (O***C***H$_2CH_3$), 36.5 (C(O)***C***H$_2CH_2$), 31.5(CH_2***C***H$_2CH_2$), 22.3 (CH_2***C***H$_2CH_2$), 21.9 (CH_2***C***H$_2CH_3$), 14.1 (CH_2CH_2***C***H$_3$), 13.8 (OCH_2***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 234 (0.4), 160 (22), 134 (3), 117 (100), 99 (95), 95 (7), 71 (47), 58 (17), 43 (81), 29 (41); **HRMS** (EIpos) calcd for [($C_{10}H_{19}NO_5$+Na)$^+$]: 256.1155, found 256.1153.



Ethyl 2-hydroxy-3-methyl-2-(nitromethyl)butanoate (209o): *β*-Nitro-*α*-hydroxyester **209o** was synthesized according to the general procedure starting from ethyl 3-methyl-2-oxobutanoate (**135o**, 4.70 g, 32.60 mmol). After purification by flash chromatography (15% of diethyl ether in pentane) ethyl 2-hydroxy-3-methyl-2-(nitromethyl)butanoate (**209o,** 6.51 g, 31.72 mmol, 97%) was obtained as a colorless oil.

209o: $C_8H_{15}NO_5$ (205.21 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.82 (d, *J* = 6.7 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.66 (d, *J* = 6.7 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.40-4.31 (m, 2H, C***H***$_2$CH$_3$), 3.61 (s, 1H, O***H***), 1.98 (qt, *J* = 6.8 Hz, 1H, C***H***(CH$_3$)$_2$), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_2$C***H***$_3$), 0.99 (d, *J* = 6.8 Hz, 3H, CH(C***H***$_3$)$_2$), 0.90 (d, *J* = 6.8 Hz, 3H, CH(C***H***$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.0 (***C***=O), 80.2 (***C***H$_2$NO$_2$), 77.5 (***C***CH$_2$NO$_2$), 62.9 (***C***H$_2$CH$_3$), 34.1 (***C***H(CH$_3$)$_2$), 16.8 (CH(***C***H$_3$)$_2$), 16.2 (CH(***C***H$_3$)$_2$), 14.0 (CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 206 (0.4), 162 (8), 132 (21), 117 (16), 89 (57), 85 (18), 71 (87), 57 (11), 43 (100), 29 (36); **HRMS** (EIpos) calcd for [($C_8H_{16}NO_5$+H)$^+$]: 206.1028, found 206.1027.

7.6.1.3 Synthesis of the *β*-nitroacrylates 121



Method A:

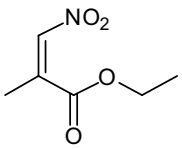
To a stirred solution of *β*-nitro-*α*-hydroxyester **209** (20.00 mmol) in dichloromethane (100 mL) were added methanesulfonyl chloride (4.6 mL, 60.00 mmol) and triethylamine (8.3 mL, 60.0 mmol). After the reaction was complete (TLC monitoring), the mixture was poured into ice-cold water. The two phases were separated and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with a sodium hydroxide solution (15%), water and brine and dried over magnesium sulfate. The volatile

compounds were removed *in vacuo* and the crude product was purified by flash chromatography to afford pure *β*-nitroacrylate **121**.

*Under the conditions of Method A, the dehydring step often leads to a mixture of the desired product **121** and the initial α-ketoester **135** (retro-Henry reaction). Consequently, the yield of the desired nitroacrylates was often low (20-50%). The procedure has been improved by treating the β-nitro-α-hydroxyesters with acetic anhydride (in DMSO) instead of methanesulfonyl chloride (see Method B).*

Method B:

To a stirred solution of *β*-nitro-*α*-hydroxyesters **209** (2.0 mmol) in DMSO (7 mL) was added acetic anhydride (0.57 mL, 6.00 mmol). The reaction was then stirred at room temperature until full conversion of the starting material (TLC monitoring). The mixture was poured into water, the two phases were separated and the aqueous layer extracted with dichloromethane (3 × 3 mL). The combined organic phases were washed with a saturated solution of sodium bicarbonate and dried over magnesium sulfate. The volatile compounds were removed *in vacuo* and the crude product was purified by flash chromatography to afford the pure *β*-nitroacrylates **121**.

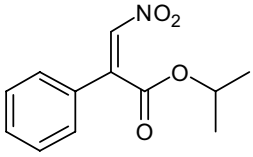


Ethyl 2-methyl-3-nitroacrylate (121a): *β*-Nitroacrylate **121a** was synthesized following Method A starting from ethyl 2-hydroxy-2-methyl-3-nitropropanoate (**209a,** 7.20 g, 40.64 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) (*E*)-ethyl 2-methyl-3-nitroacrylate ((*E*)-**121a,** 0.40 g, 2.51 mmol, 6%) and (*Z*)-ethyl 2-methyl-3-nitroacrylate ((*Z*)-**121a,** 4.40 g, 27.65 mmol, 68%) were obtained as slightly yellow oils.

(E)-**121a**: $C_6H_9NO_4$ (159.14 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (m, 1H, C***H***NO_2), 4.31 (q, *J* = 7.1 Hz, 2H, C***H***$_2CH_3$), 2.32 (d, *J* = 1.7 Hz, 3H, CCC***H***$_3$), 1.35 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2 (***C***=O), 143.9 (***C***HNO_2), 136.8 (***C***$CHNO_2$), 62.6 (O***C***H_2CH_3), 14.0 (C***C***H_3), 13.7 (OCH_2***C***H_3).

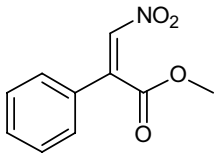
(Z)-**121a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.87 (m, 1H, C***H***NO_2), 4.35 (q, *J* = 7.1 Hz, 2H, C***H***$_2CH_3$), 2.10 (d, *J* = 1.7 Hz, 3H, CCC***H***$_3$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.1 (***C***=O), 140.9 (***C***HNO_2), 135.7 (***C***$CHNO_2$), 62.4 (O***C***H_2CH_3), 17.6 (C***C***H_3), 13.8 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 159 (0.2), 114 (100), 99 (13), 85 (4), 71 (18), 68 (2), 56 (5), 39 (26), 29 (78), 27 (19); **HRMS** (EI-FE) calcd for [$C_6H_9NO_4$]:

159.0532, found 159.0532 The physical data were identical in all respects to those previously reported.[246]



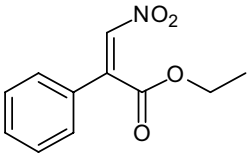
(*Z*)-Isopropyl 3-nitro-2-phenylacrylate (121b): *β*-Nitroacrylate **121b** was synthesized following Method A starting from isopropyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209b,** 3.00 g, 11.85 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) pure (*Z*)-isopropyl 3-nitro-2-phenylacrylate (**121b,** 2.01 g, 8.54 mmol, 72%) was obtained as a yellow solid.

121o: $C_{12}H_{13}NO_4$ (235.24 g/mol); **m.p.:** 49-51 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55-7.44 (m, 5H, C***H***$_{Ar}$), 7.34 (br s, 1H, C***H***NO_2), 5.41-5.35 (m, 1H, C***H***$(CH_3)_2$), 1.39 (d, *J* = 6.3 Hz, 6H, CH(C***H***$_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.2 (***C***=O), 143.4 (***C***$CHNO_2$), 134.3 (***C***HNO_2), 132.0 (***C***H_{Ar}), 129.7 (***C***$q_{Ar}C$), 129.5 (***C***H_{Ar}), 127.4 (***C***H_{Ar}), 70.9 (***C***$H(CH_3)_2$), 21.5 (CH(***C***$H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 235 (9), 193 (15), 175 (76), 165 (12), 147 (11), 132 (8), 120 (14), 102 (100), 91 (12), 76 (17), 63 (7), 51 (6), 43 (99); **HRMS** (EI-FE) calcd for [$C_{12}H_{13}NO_4$]: 235.0845, found 235.0842.



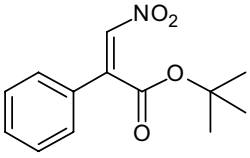
(*Z*)-Methyl 3-nitro-2-phenylacrylate (121c): *β*-Nitroacrylate **121b** was synthesized following Method A starting from methyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209c,** 3.00 g, 13.32 mmol). After purification by flash chromatography (5% ethyl acetate in hexanes) pure (*Z*)-methyl 3-nitro-2-phenylacrylate (**121c,** 1.62 g, 7.82 mmol, 59%) was obtained as a yellow oil.

121c: $C_{10}H_9NO_4$ (207.18 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.54-7.44 (m, 5H, C***H***$_{Ar}$), 7.36 (s, 1H, C***H***NO_2), 4.00 (s, 3H, COC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.3 (***C***=O), 143.1 (***C***$CHNO_2$), 134.6 (***C***HNO_2), 132.2 (***C***H_{Ar}), 129.7 (***C***H_{Ar}), 129.5 (***C***$q_{Ar}C$), 127.5 (***C***H_{Ar}), 53.4 (O***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 207 (41), 190 (7), 175 (45), 158 (22), 145 (24), 131 (6), 120 (27), 102 (100), 91 (28), 76 (32), 63 (16), 59 (52), 51 (18), 39 (11), 30 (6); **HRMS** (EI-FE) calcd for [$C_{10}H_9NO_4$]: 207.0531, found 207.0530.



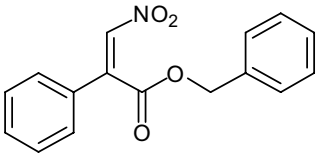
(*Z*)-Ethyl 3-nitro-2-phenylacrylate (121d): *β*-Nitroacrylate **121b** was synthesized following Method A starting from ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209d,** 6.00 g, 25.08 mmol). After purification by flash chromatography (5% ethyl acetate in hexanes) pure (*Z*)-ethyl 3-nitro-2-phenylacrylate (**121d,** 3.51 g, 15.87 mmol, 63%) was obtained as a yellow oil.
Dehydration according to Method B: β-Nitroacrylate **121d** (0.78 g, 3.53 mmol, 88%) was prepared starting from β-nitro-α-hydroxyester **209d** (0.96 g, 4.01 mmol).

121d: $C_{11}H_{11}NO_4$ (221.21 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56-7.44 (m, 5H, C***H***$_{Ar}$), 7.35 (s, 1H, C***H***NO_2), 4.48 (q, *J* = 7.2 Hz, 2H, C***H***$_2CH_3$), 1.40 (t, *J* = 7.2 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.7 (***C***=O), 143.3 (***C***$CHNO_2$), 134.5 (***C***HNO_2), 132.1 (***C***H_{Ar}), 129.5 (***C***H_{Ar}), 128.4 (***C***$q_{Ar}C$), 127.5 (***C***H_{Ar}), 62.5 (O***C***H_2CH_3), 13.8 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 221 (19), 204 (2), 193 (2), 175 (40), 158 (11), 145 (11), 132 (6), 120 (17), 102 (89), 91 (24), 77 (26), 63 (11), 51 (12), 39 (6), 29 (100); **HRMS** (EI-FE) calcd for [$C_{11}H_{11}NO_4$]: 221.0688, found 221.0686. The physical data were identical in all respects to those previously reported.[175a]



(*Z*)-*tert*-Butyl 3-nitro-2-phenylacrylate (121e): *β*-Nitroacrylate **121b** was synthesized following Method A starting from *tert*-butyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209e,** 1.25 g, 4.68 mmol). After purification by flash chromatography (10% ethyl acetate in hexanes) pure (*Z*)-*tert*-butyl 3-nitro-2-phenylacrylate (**121e,** 0.20 g, 0.80 mmol, 17%) was obtained as a yellow solid.
Dehydration according to Procedure B: β-Nitroacrylate **121e** (0.65 g, 2.62 mmol, 88%) was prepared starting from β-nitro-α-hydroxyester **209e** (0.80 g, 2.99 mmol).

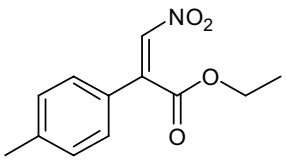
121e: $C_{13}H_{15}NO_4$ (249.26 g/mol); **m.p.**: 82-83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54-7.45 (m, 5H, C***H***$_{Ar}$), 7.30 (br s, 1H, C***H***NO_2), 1.62 (s, 9H, (C***H***$_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.5 (***C***=O), 143.7 (***C***$CHNO_2$), 133.7 (***C***HNO_2), 131.9 (***C***H_{Ar}), 130.0 (***C***$q_{Ar}C$), 129.5 (***C***H_{Ar}), 127.4 (***C***H_{Ar}), 84.8 (***C***$(CH_3)_3$), 27.9 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 249 (2), 193 (15), 176 (22), 158 (6), 102 (30), 57 (100), 41 (17), 29 (11); **HRMS** (EI-FE) calcd for [$C_{13}H_{15}NO_4$]: 249.1001, found 249.0999.



(*Z*)-Benzyl 3-nitro-2-phenylacrylate (121f): *β*-Nitroacrylate **121f** was synthesized following Method A starting from benzyl 2-hydroxy-3-nitro-2-phenylpropanoate (**209f,** 2.00 g, 6.64 mmol). After purification by flash chromatography (15% acetone in hexanes) pure (*Z*)-benzyl 3-nitro-2-phenylacrylate (**121f,** 0.40 g, 1.41 mmol, 21%) was obtained as a yellow oil.

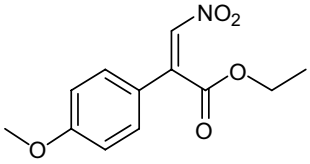
Dehydration according to Procedure B: *β*-Nitroacrylate **121f** (0.22 g, 1.12 mmol, 84%) was prepared starting from β-nitro-α-hydroxyester **209f** (0.40 g, 1.33 mmol).

121f: $C_{16}H_{13}NO_4$ (283.28 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.33 (m, 11H, C***H***$_{Ar}$ and C***H***NO_2), 5.41 (s, 2H, OC***H***$_2$Ph); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.6 (***C***=O), 142.9 (***C***$CHNO_2$), 134.5 (***C***HNO_2), 134.4 (***C***$q_{Ar}CH_2$), 132.1 (***C***H_{Ar}), 129.5 (***C***H_{Ar}), 129.3 (***C***$q_{Ar}C$), 128.9 (***C***H_{Ar}), 128.8 (***C***H_{Ar}), 128.6 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 68.5 (Cq_{Ar}***C***H_2); **MS** (EI, 70 eV): *m*/*z* (%) = 283 (0.1), 177 (10), 159 (3), 133 (11), 102 (16), 91 (100), 77 (11), 65 (14), 51 (7), 39 (6); **HRMS** (EIpos) calcd for [$(C_{16}H_{13}NO_4+Na)^+$]: 306.0737, found 306.0736.



(*Z*)-Ethyl 3-nitro-2-*p*-tolylacrylate (121g): *β*-Nitroacrylate **121g** was synthesized following Method A starting from ethyl 2-hydroxy-3-nitro-2-*p*-tolylpropanoate (**209g,** 4.00 g, 15.79 mmol). After purification by flash chromatography (3% of ethyl acetate in hexanes) pure (*Z*)-ethyl 3-nitro-2-*p*-tolylacrylate (**121g,** 1.94 g, 8.25 mmol, 52%) was obtained as a yellow oil.

121g: $C_{12}H_{13}NO_4$ (235.24 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 736-7.33 (m, 2H, C***H***$_{Ar}$), 7.34 (s, 1H, C***H***NO_2), 7.23-7.20 (m, 2H, C***H***$_{Ar}$), 4.42 (q, *J* = 7.2 Hz, 2H, C***H***$_2CH_3$), 2.34 (s, 3H, C_{Ar}C**H**$_3$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.0 (***C***=O), 143.4 (***C***$CHNO_2$), 143.1 (***C***$q_{Ar}CH_3$), 133.6 (***C***HNO_2), 130.3 (***C***H_{Ar}), 127.5 (***C***H_{Ar}), 126.6 (***C***q_{Ar}C), 62.7 (O***C***H_2CH_3), 21.5 (Cq_{Ar}***C***H_3, 11.9 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 235 (57), 218 (8), 204 (4), 189 (52), 172 (22), 161 (19), 146 (13), 134 (21), 115 (100), 105 (20), 91 (24), 77 (10), 65 (10), 51 (6), 39 (6), 29 (47); **HRMS** (EI-FE) calcd for [$C_{12}H_{13}NO_4$]: 235.0845, found 235.0842.

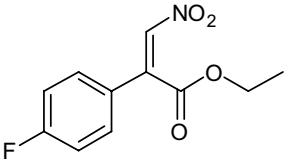


(*Z*)-Ethyl 2-(4-methoxyphenyl)-3-nitroacrylate (121h): *β*-Nitroacrylate **121h** was synthesized following Method A starting from ethyl 2-hydroxy-3-nitro-2-(4-methoxy-phenyl)propanoate (**209h,** 3.20 g, 11.88 mmol). After purification by flash chromatography (20% of acetone in hexanes) pure (*Z*)-ethyl 2-(4-methoxyphenyl)-3-nitroacrylate (**121h,** 1.01 g, 4.02 mmol, 34%) was obtained as a yellow oil.

Dehydration according to Procedure B: β-Nitroacrylate (*Z*)-**121e** (0.28 g, 1.11 mmol, 75%) was prepared starting from β-nitro-α-hydroxyester **209e** (0.40 g, 1.49 mmol).

Note: *β*-Nitroacrylate (*E*)-**121e** (0.04 g, 0.17 mmol) was formed in 11% yield.

121o: $C_{12}H_{13}NO_4$ (251.24 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 7.35 (s, 1H, C***H***NO_2), 6.96 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 4.48 (q, *J* = 7.2 Hz, 2H, C***H***$_2CH_3$), 3.85 (s, 3H, OC***H***$_3$), 1.40 (t, *J* = 7.2 Hz, 3H, CH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.2 (***C***=O), 163.0 (***C***$q_{Ar}OCH_3$), 143.2 (***C***$CHNO_2$), 132.3 (***C***HNO_2), 129.5 (***C***H_{Ar}), 121.5 (***C***$q_{Ar}C$), 115.5 (***C***H_{Ar}), 62.7 (O***C***H_2CH_3), 55.6 (O***C***H_3), 13.9 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 251 (99), 206 (32), 168 (20), 150 (27), 132 (100), 117 (40), 95 (10), 89 (55), 77 (15), 63 (21), 51 (7), 39 (9), 29 (77); **HRMS** (EI-FE) calcd for [$C_{12}H_{13}NO_5$]: 251.0794, found 251.0796.

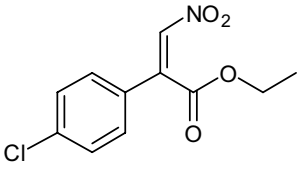


(*Z*)-ethyl 2-(4-fluorophenyl)-3-nitroacrylate (121i): *β*-Nitroacrylate **121i** was synthesized following Method A starting from ethyl 2-(4-fluorophenyl)-2-oxoacetate (**135i**, 5.30 g, 20.60 mmol). After purification by flash chromatography (3% of ethyl acetate in hexanes) pure (*Z*)-ethyl 2-(4-fluorophenyl)-3-nitroacrylate (**121i,** 2.41 g, 10.08 mmol, 49%) was obtained as a yellow oil.

Dehydration according to Procedure B: β-Nitroacrylate **121i** (0.36 g, 1.53 mmol, 87%) was prepared starting from β-nitro-α-hydroxyester **209i** (0.45 g, 1.75 mmol).

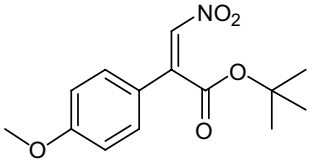
121i: $C_{11}H_{10}FNO_4$ (239.20 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.54-7.49 (m, 2H, C***H***$_{Ar}$), 7.31 (s, 1H, C***H***NO_2), 7.20-7.13 (m, 2H, C***H***$_{Ar}$), 4.47 (q, *J* = 7.2 Hz, 2H, OC***H***$_2CH_3$), 1.39 (t, *J* = 7.2 Hz, 2H, OCH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.6 (***C***=O), 164.0 (d, *J* = 101.1 Hz, ***C***$q_{Ar}F$), 142.2 (***C***$CHNO_2$), 134.6 (***C***HNO_2), 129.8 (d, *J* = 9.0 Hz, ***C***H_{Ar}), 125.7 (d, *J* = 3.4 Hz, ***C***$q_{Ar}C$), 117.0 (d, *J* = 22.1 Hz, ***C***H_{Ar}), 63.0 (O***C***H_2CH_3), 13.8 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 239 (21), 194 (18), 176 (4), 166 (9), 149 (6), 138 (13), 120 (82),

109 (15), 94 (12), 74 (8), 50 (4), 29 (100); **HRMS** (EI-FE) calcd for [$C_{11}H_{10}FNO_4$]: 239.0494, found 239.0592.



(*Z*)-ethyl 2-(4-chlorophenyl)-3-nitroacrylate (121j): *β*-Nitroacrylate **121j** was synthesized following Method A starting from ethyl 2-(4-chlorophenyl)-2-oxoacetate (**135j**, 1.90 g, 6.94 mmol). After purification by flash chromatography (3% of ethyl acetate in hexanes) pure (*Z*)-ethyl 2-(4-chlorophenyl)-3-nitroacrylate (**121j,** 0.95 g, 3.71 mmol, 53%) was obtained as a yellow oil.

121j: $C_{11}H_{10}ClNO_4$ (255.65 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 (s, 4H, C***H***$_{Ar}$), 7.32 (s, 1H, C***H***NO_2), 4.47 (q, *J* = 7.2 Hz, 2H, OC***H***$_2CH_3$), 1.39 (t, *J* = 7.1 Hz, 2H, OCH_2C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.4 (***C***=O), 142.1 (***C***$CHNO_2$), 138.6 (***C***$q_{Ar}Cl$), 134.7 (***C***HNO_2), 129.9 (***C***H_{Ar}), 128.7 (***C***H_{Ar}), 128.0 (***C***$q_{Ar}C$), 63.0 (O***C***H_2CH_3), 13.8 (CH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 255 (38), 210 (29), 192 (10), 174 (100), 154 (11), 136 (80), 125 (13), 101 (33), 89 (6), 75 (19), 63 (4), 51 (8), 29 (62); **HRMS** (EI-FE) calcd for [$C_{11}H_{10}ClNO_4$]: 255.0298, found 255.0297.

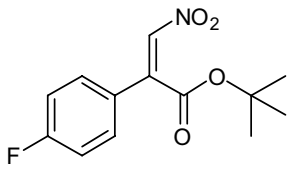


(*Z*)-*tert*-Butyl 2-(4-methoxyphenyl)-3-nitroacrylate (121k): *β*-Nitroacrylate **121k** was synthesized following Method A starting from *tert*-butyl 2-(4-methoxyphenyl)-2-oxoacetate (**135k**, 1.30 g, 4.37 mmol). After purification by flash chromatography (15% of acetone in hexanes) pure (*Z*)-*tert*-butyl 3-nitro-2-(4-methoxyphenyl)acrylate (**121k,** 0.31 g, 1.11 mmol, 25%) was obtained as a yellow solid.

Dehydration according to Procedure B: β-Nitroacrylate **121k** (0.26 g, 0.94 mmol, 88%) was prepared starting from β-nitro-α-hydroxyester **209k** (0.40 g, 1.35 mmol).

121k: $C_{14}H_{17}NO_5$ (279.29 g/mol); **m.p.**: 95-96 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 7.29 (s, 1H, C***H***NO_2), 6.96 (d, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 3.86 (s, 3H, OC***H***$_3$), 1.63 (s, 9H, C(C***H***$_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 163.9 (***C***=O), 162.8 (***C***$q_{Ar}OCH_3$), 143.5 (***C***$CHNO_2$), 131.7 (***C***HNO_2), 129.4 (***C***H_{Ar}), 122.1 (***C***$q_{Ar}C$), 115.0 (***C***H_{Ar}), 84.6 (***C***$(CH_3)_3$), 55.6 (O***C***H_3), 27.9 (C(***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 279 (57), 223 (57),

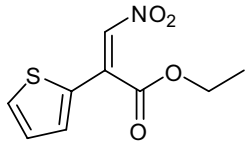
206 (34), 132 (72), 117 (15), 89 (19), 57 (100), 41 (19); **HRMS** (EIpos) calcd for [($C_{14}H_{17}NO_5$+Na)$^+$]: 302.0999, found 302.0998.



(*Z*)-*tert*-Butyl 2-(4-fluorophenyl)-3-nitroacrylate (121l): *β*-Nitroacrylate **121l** was synthesized following Method A starting from *tert*-butyl 2-(4-fluorophenyl)-2-oxoacetate (**135l**, 1.20 g, 4.21 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) pure (*Z*)-*tert*-butyl 3-nitro-2-(4-fluorophenyl)acrylate (**121l,** 0.30 g, 1.12 mmol, 27%) was obtained as a yellow oil.

Dehydration according to Procedure B: β-Nitroacrylate **121j** (0.96 g, 3.59 mmol, 85%) was prepared starting from β-nitro-α-hydroxyester **209j** (1.20 g, 4.20 mmol).

121l: $C_{13}H_{14}FO_4$ (267.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55-7.51 (m, 2H, C***H***$_{Ar}$), 7.25 (s, 1H, C***H***NO_2), 7.16 (t, *J* = 9.0 Hz, 2H, C***H***$_{Ar}$), 1.62 (s, 9H, C(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.8 (***C***=O), 164.7 (d, *J* = 272.0 Hz, ***C***q_{Ar}F), 142.6 (***C***$CHNO_2$), 133.5 (***C***HNO_2), 129.7 (d, *J* = 8.8 Hz, ***C***H_{Ar}) , 126.2 (d, *J* = 3.0 Hz, ***C***q_{Ar}C), 116.8 (d, *J* = 22.0 Hz, ***C***H_{Ar}), 85.1 (***C***$(CH_3)_3$), 27.9 (C(***C***H_3)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 267 (8), 211 (8), 194 (17), 120 (34), 94 (3), 57 (100), 41 (21); **HRMS** (EIpos) calcd for [($C_{13}H_{14}NO_4F$+Na)$^+$]: 290.0799, found 290.0798.

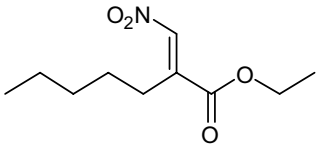


(*E*)-Ethyl 3-nitro-2-(thiophen-2-yl)acrylate (121m): *β*-Nitroacrylate **121m** was synthesized following Method A starting from ethyl 2-hydroxy-3-nitro-2-(thiophen-2-yl)propanoate (**209m,** 6.18 g, 25.20 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) pure (*E*)-ethyl 3-nitro-2-(thiophen-2-yl)acrylate (**121m,** 2.62 g, 11.53 mmol, 46%) was obtained as a yellow solid.

Dehydration according to Procedure B: β-Nitroacrylate **121m** (0.29 g, 1.28 mmol, 78%) was prepared starting from β-nitro-α-hydroxyester **209m** (0.40 g, 1.63 mmol).

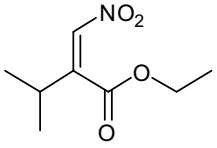
121m: $C_9H_9NO_4S$ (227.24 g/mol); **m.p.**: 55-57 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 5.2, 1.3 Hz, 1H, C***H***$_{Ar}$), 7.38-7.36 (m, 2H: C***H***$_{Ar}$ (1H), C***H***NO_2 (1H)), 7.15 (dd, *J* = 5.1 Hz, 3.8 Hz, 1H, C***H***$_{Ar}$), 4.50 (q, *J* = 7.2 Hz, 2H, C***H***$_2CH_3$), 1.42 (t, *J* = 7.2 Hz, 3H,

$CH_2C\boldsymbol{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.9 ($\boldsymbol{C}$=O), 137.7 ($\boldsymbol{C}HNO_2$), 133.1 ($\boldsymbol{C}H_{Ar}$), 132.6 ($\boldsymbol{C}CHNO_2$), 131.6 ($\boldsymbol{C}H_{Ar}$), 131.6 ($\boldsymbol{C}q_{Ar}C$), 129.0 ($\boldsymbol{C}H_{Ar}$), 63.1 ($O\boldsymbol{C}H_2CH_3$), 13.9 ($CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 227 (28), 182 (28), 154 (25), 138 (31), 112 (73), 108 (100), 97 (15), 83 (43), 69 (30), 58 (20), 45 (39), 39 (10), 29 (82); **HRMS** (EI-FE) calcd for [$C_9H_9NO_4S$]: 227.0252, found 227.0254.



(*E*)-Ethyl 2-(nitromethylene)heptanoate (121n): *β*-Nitroacrylate **121n** was synthesized following Method A starting from ethyl 2-hydroxy-2-(nitromethyl)heptanoate (**209n,** 9.60 g, 41.16 mmol). After purification by flash chromatography (1% of diethyl ether in pentane) pure (*E*)-ethyl 2-(nitromethylene)heptanoate ((*E*)-**121n,** 0.40 g, 1.86 mmol, 5%) and (*Z*)-ethyl 2-(nitromethylene)heptanoate ((*Z*)-**121n**, 5.41 g, 25.13 mmol, 61%) were obtained as yellow oils.

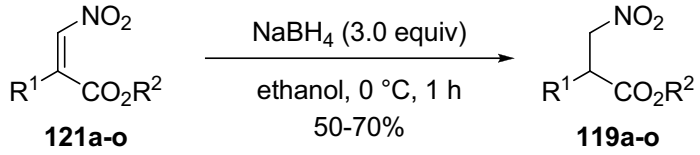
(E)-121n: $C_{10}H_{17}NO_4$ (215.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (s, 1H, $C\boldsymbol{H}NO_2$), 4.31 (q, *J* = 7.1 Hz, 2H, $COC\boldsymbol{H}_2CH_3$), 2.75-2.71 (m, 2H, $CC\boldsymbol{H}_2CH_2$), 1.56-1.51 (m, 2H, $CH_2C\boldsymbol{H}_2CH_2$), 1.38-1.31 (m, 7H: $CH_2C\boldsymbol{H}_2CH_2$ (2H), $CH_2C\boldsymbol{H}_2CH_3$ (2H), $COCH_2C\boldsymbol{H}_3$ (3H)), 0.90 (m, 3H, $CH_2C\boldsymbol{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.1 ($\boldsymbol{C}$=O), 143.3 ($\boldsymbol{C}HNO_2$), 141.2 ($\boldsymbol{C}CHNO_2$), 62.4 ($O\boldsymbol{C}H_2CH_3$), 31.7 ($CH_2\boldsymbol{C}H_2CH_2$), 28.2 ($C(O)\boldsymbol{C}H_2CH_2$), 27.2 ($CH_2\boldsymbol{C}H_2CH_2$), 22.2 ($CH_2\boldsymbol{C}H_2CH_3$), 14.0 ($OCH_2\boldsymbol{C}H_3$), 13.8 ($CH_2CH_2\boldsymbol{C}H_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 216 (0.2), 198 (2), 170 (20), 159 (18), 141 (10), 123 (9), 113 (18), 95 (47), 85 (16), 67 (17), 55 (44), 41 (57), 29 (100); **HRMS** (EIpos) calcd for [($C_{10}H_{17}NO_4$+H)$^+$]: 216.1236, found 216.1238.



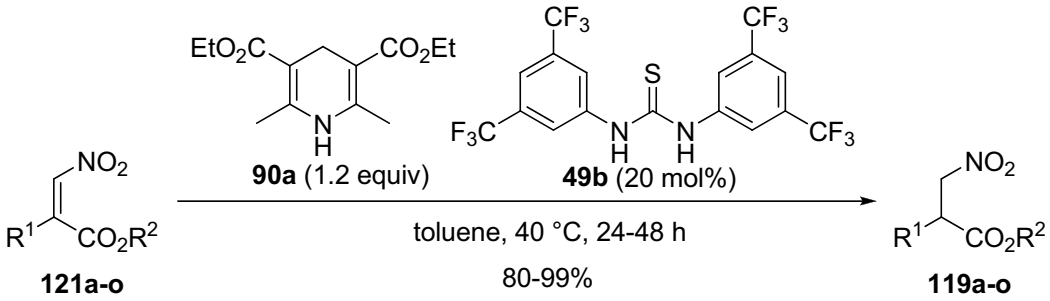
(*Z*)-Ethyl 3-methyl-2-(nitromethylene)butanoate (121o): *β*-Nitroacrylate **121o** was synthesized following Method A starting from ethyl 2-hydroxy-3-methyl-2-(nitromethyl)butanoate (**209o,** 6.50 g, 31.67 mmol). After purification by flash chromatography (10% of diethyl ether in pentane) pure (*Z*)-ethyl 3-methyl-2-(nitromethylene)butanoate (**121o,** 1.80 g, 9.62 mmol, 30%) was obtained as a yellow oil.

121o: $C_8H_{13}NO_4$ (187.19 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.83 (d, *J* = 1.3 Hz, 1H, C***H***NO_2), 4.36 (q, *J* = 7.2 Hz, 2H, C***H***$_2CH_3$), 2.74 (m, 1H, C***H***$(CH_3)_2$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2C***H***$_3$), 1.20 (d, *J* = 6.9 Hz, 6H, $CH(C$***H***$_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.6 (***C***=O), 150.7 (***C***$CHNO_2$), 134.7 (***C***HNO_2), 62.2 (OC***H***$_2CH_3$), 31.4 (***C***$H(CH_3)_2$), 20.3 ($CH($***C***$H_3)_2$), 13.8 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 188 (0.1), 172 (3), 142 (38), 127 (9), 114 (36), 95 (7), 84 (6), 67 (25), 53 (23), 43 (100), 29 (90); **HRMS** (EIpos) calcd for [$(C_8H_{13}NO_4$+H)$^+$]: 188.0923, found 188.0921. The physical data were identical in all respects to those previously reported.[246]

7.6.2 General Procedures for the Synthesis of the Racemic Products



(a)



(b)

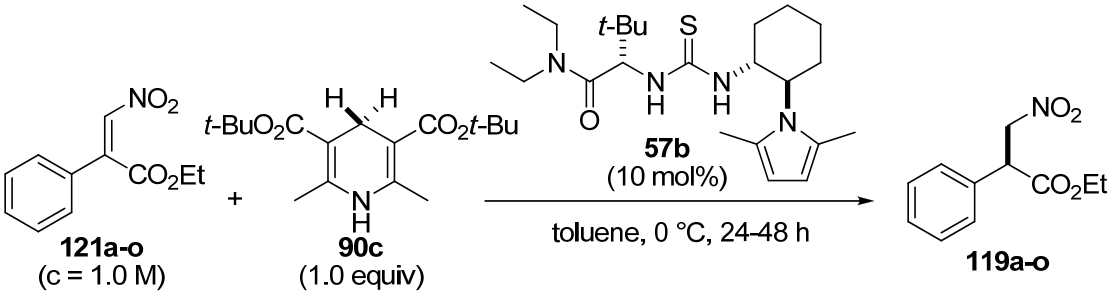
***Preparation of the racemic nitroesters 119 with sodium borohydride (eq. a)*:**

To a solution of *β*-nitroacrylate **121** (0.26 mmol, 1.0 equiv) in ethanol (0.6 mL) at 0 °C, sodium borohydride (30 mg, 0.78 mmol, 3.0 equiv) was added in several portions over 15 minutes. The reaction mixture was stirred at 0 °C during one hour and quenched at 0 °C with a saturated solution of ammonium chloride. The two phases were separated and the aqueous layer extracted with diethyl ether (3 × 1 mL). The combined organic phases were dried over magnesium sulfate. The volatile compounds were removed *in vacuo* and the crude product was purified by flash chromatography (1-5% of diethyl ether in pentane) to afford the pure *β*-nitroester **119**.

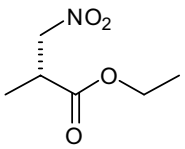
***Preparation of the racemic nitroesters 119 with catalyst 49b (eq. b)*:**

To a solution of *β*-nitroacrylate **121** (0.26 mmol, 1.0 equiv) in toluene (0.2 mL), catalyst **49b** (26 mg, 0.05 mmol, 0.2 equiv) and Hantzsch ester **90c** (79 mg, 0.31 mmol, 1.2 equiv) were added. The reaction mixture was stirred at 40 °C for 24-48 hours until completion of the reaction (TLC control). The solvent was then removed *in vacuo* and the residue purified by flash column chromatography (1-5 % of diethyl ether in pentane).

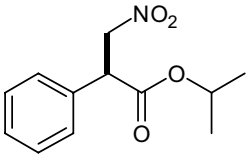
7.6.3 Asymmetric Transfer Hydrogenation of *β,β*-Disubstituted Nitroalkenes



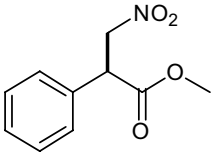
To a solution of *β*-nitroacrylic ester **121** (0.30 mmol) in toluene (0.3 mL, 1.0 M), catalyst **57b** (12.6 mg, 0.03 mmol, 0.1 equiv) and Hantzsch ester **90c** (93 mg, 0.30 mmol, 1.0 equiv) were added. The reaction mixture was stirred at 0 °C for 24-48 hours. The solvent was then removed *in vacuo*[203] and the resulting mixture purified by flash column chromatography (**119a-g,i,j,l-o**: 2% of diethyl ether in pentane; **119h,k**: 1-5% of diethyl ether in pentane).[275]



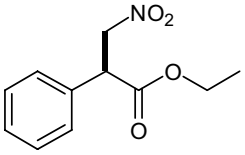
(*R*)-Ethyl 2-methyl-3-nitropropanoate (119a, prepared from (*E*)-121a): The enantiomers were analyzed by GC using a chiral LIPODEX G column (60 °C, 1.2 °C/min until 120 °C, 18 °C/min until 220 °C, 6 min at 220 °C); major enantiomer: t_R = 28.75 min, minor enantiomer: t_R = 29.15 min. **119a** (46.9 mg, 0.291 mmol, 97%; 97:3 *er*): colorless oil, $C_6H_{11}NO_4$ (161.16g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.72 (dd, *J* = 14.0 Hz, 8.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.40 (dd, *J* = 14.0 Hz, 5.6 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.20 (q, *J* = 7.1 Hz, 2H, OC***H***$_2$CH$_3$), 3.28-3.21 (m, 1H, C***H***CH$_2$NO$_2$), 1.30-1.25 (m, 3H, OCH$_2$C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.4 (***C***=O), 76.4 (***C***H$_2$NO$_2$), 61.5 (O***C***H$_2$CH$_3$), 37.6 (***C***HCH$_2$NO$_2$), 14.3 (C***C***H$_3$), 14.0 (OCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 162 (0.2), 116 (23), 88 (24), 73 (16), 69 (46), 59 (14), 41 (52), 29 (100), 27 (18); **HRMS** (EIpos) calcd for [($C_6H_{12}NO_4$+H)$^+$]: 162.0766, found 162.0765.[276,277]



(*S*)-Isopropyl 3-nitro-2-phenylpropanoate (119b): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (100 °C, 1.2 °C/min until 170 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 36.11 min, minor enantiomer: t_R = 35.24 min. **119b** (69.5 mg, 0.293 mmol, 91%; 97:3 *er*): slightly yellow oil, $C_{12}H_{15}NO_4$ (237.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.32 (m, 3H, C***H***$_{Ar}$), 7.27-7.24 (m, 2H, C***H***$_{Ar}$), 5.07 (m, 2H: OC***H***$(CH_3)_2$ (1H), C***H***$_2NO_2$, H^1 (1 H)), 4.53 (dd, J = 14.6 Hz, 5.1 Hz, 1H, C***H***$_2NO_2$, H^2), 4.37 (dd, J = 10.1 Hz, 5.1 Hz, 1H, C***H***CH_2NO_2), 1.26 (d, J = 6.3 Hz, 3H, OCH(C***H***$_3)_2$), 1.12 (d, J = 6.3 Hz, 3H, OCH(C***H***$_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.9 (***C***=O), 133.5 (***C***$q_{Ar}CH$), 129.2 (***C***H_{Ar}), 128.5 (***C***H_{Ar}), 127.8 (***C***H_{Ar}), 75.8 (***C***H_2NO_2), 69.5 (***C***$H(CH_3)_2$), 49.0 (***C***HCH_2NO_2), 21.6 (CH(***C***$H_3)_2$), 21.2 (CH(***C***$H_3)_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 237 (2), 190 (18), 178 (6), 150 (12), 131 (5), 104 (100), 91 (3), 78 (9), 63 (1), 51 (3), 43 (60); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_4$]: 237,1001, found 237.0999.

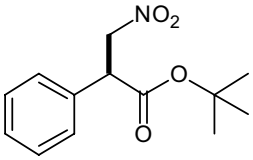


(*S*)-Methyl 3-nitro-2-phenylpropanoate (119c): The enantiomers were analyzed by GC using a chiral G-TA column (100 °C, 1.0 °C/min until 180 °C, 15 min at 180 °C); major enantiomer: t_R = 38.94 min, minor enantiomer: t_R = 41.43 min. **119c** (54.0 mg, 0.258 mmol, 86%; 94:6 *er*): slightly yellow oil, $C_{10}H_{11}NO_4$ (209.20 g/mol); $[\alpha]_D^{26}$ = -126.2° (*c* = 2.8, $CHCl_3$);[278] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.34 (m, 3H, C***H***$_{Ar}$), 7.28-7.25 (m, 2H, C***H***$_{Ar}$), 5.11 (dd, J = 14.4 Hz, 9.9 Hz, 1H, C***H***$_2NO_2$, H^1), 4.55 (dd, J = 14.7 Hz, 5.4 Hz, 1H, C***H***$_2NO_2$, H^2), 4.45 (dd, J = 9.9 Hz, 5.4 Hz, 1H, C***H***CH_2NO_2), 3.73 (s, 3H, OC***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.0 (***C***=O), 133.2 (***C***$q_{Ar}CH$), 129.4 (***C***H_{Ar}), 128.7 (***C***H_{Ar}), 127.9 (***C***H_{Ar}), 75.7 (***C***H_2NO_2), 52.9 (O***C***H_3), 48.6 (***C***HCH_2NO_2); **MS** (EI, 70 eV): *m*/*z* (%) = 209 (5), 178 (3), 162 (100), 150 (6), 131 (20), 121 (25), 104 (79), 91 (14), 77 (25), 63 (5), 59 (22), 51 (13), 39 (6); **HRMS** (EI-FE) calcd for [$C_{10}H_{11}NO_4$]: 209.0688, found 209.0690. The physical data were identical in all respects to those previously reported.[278]

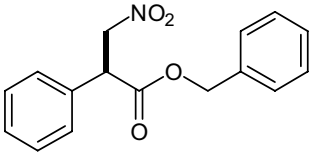


(*S*)-Ethyl 3-nitro-2-phenylpropanoate (119d): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 56.41 min, minor enantiomer: t_R = 55.79 min. **119d** (63.6 mg, 0.285 mmol, 95%; 96:4 *er*): slightly yellow oil, $C_{11}H_{13}NO_4$ (223.23 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 3H, C***H***$_{Ar}$), 7.28-7.26 (m, 2H, C***H***$_{Ar}$), 5.10

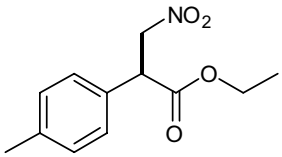
(dd, *J* = 14.6 Hz, 10.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.55 (dd, *J* = 14.6 Hz, 5.2 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.42 (dd, *J* = 10.0 Hz, 5.2 Hz, 1H, C***H***CH$_2$NO$_2$), 4.27-4.13 (m, 2H, OC***H***$_2$CH$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 170.5 (***C***=O), 133.4 (***C***q$_{Ar}$CH), 129.3 (***C***H$_{Ar}$), 128. (***C***H$_{Ar}$)6, 127.9 (***C***H$_{Ar}$), 75.8 (***C***H$_2$NO$_2$), 61.9 (O***C***H$_2$CH$_3$), 48.8 (***C***HCH$_2$NO$_2$), 13.9 (OCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 223 (3), 176 (47), 150 (6), 132 (11), 104 (100), 91 (5), 77 (11), 63 (2), 51 (5), 39 (2), 29 (31); **HRMS** (EI-FE) calcd for [C$_{11}$H$_{13}$NO$_4$]: 223.0845, found 223.0847.



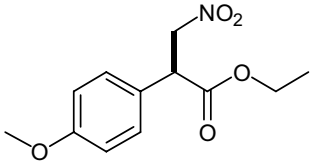
(*S*)-Tert-butyl 3-nitro-2-phenylpropanoate (119e): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 155 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 54.84 min, minor enantiomer: t_R = 54.36 min. **119e** (69.4 mg, 0.276 mmol, 92%; 97:3 *er*): yellow oil, C$_{13}$H$_{17}$NO$_4$ (251.28 g/mol); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.36-7.33 (m, 3H, C***H***$_{Ar}$), 7.27-7.25 (m, 2H, C***H***$_{Ar}$), 5.04 (dd, *J* = 14.6 Hz, 10.1 Hz, 1 H, C***H***$_2$NO$_2$, *H*^{1}), 4.49 (dd, *J* = 14.6 Hz, 5.1 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.32 (dd, *J* = 10.2 Hz, 5.1 Hz, 1H, C***H***CH$_2$NO$_2$), 1.41 (s, 9H, OC(C***H***$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 169.5 (***C***=O), 133.9 (***C***q$_{Ar}$CH), 129.2 (***C***H$_{Ar}$), 128.4 (***C***H$_{Ar}$), 127.8 (***C***H$_{Ar}$), 82.5 (***C***(CH$_3$)$_3$), 76.0 (***C***H$_2$NO$_2$), 49.7 (***C***HCH$_2$NO$_2$), 27.8 (C(***C***H$_3$)$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 251 (0.3), 178 (7), 150 (8), 131 (3), 104 (49), 91 (1), 78 (5), 57 (100), 51 (2), 41 (15), 29 (9); **HRMS** (EIpos) calcd for [(C$_{13}$H$_{17}$NO$_4$+Na)$^+$]: 274.1050, found 274.1049.



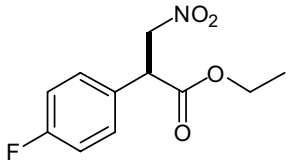
(*S*)-Benzyl 3-nitro-2-phenylpropanoate (119f): The enantiomers were analyzed by HPLC using a chiral Chiralcel AS-H column (*i*PrOH/Heptane = 80:20, flow rate = 0.5 mL/min, wavelength = 254 nm); major enantiomer: t_R = 20.68 min, minor enantiomer: t_R = 25.37 min. **119f** (77.9 mg, 0.273 mmol, 91%; 97:3 *er*): slightly yellow oil, C$_{16}$H$_{15}$NO$_4$ (285.29 g/mol); **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.35-7.20 (m, 10H, C***H***$_{Ar}$), 5.23-5.08 (m, 3H: C***H***$_2$NO$_2$ (1H), *H*^{1}, OC***H***$_2$Ph (2H)), 4.56 (dd, *J* = 14.6 Hz, 5.2 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.48 (dd, *J* = 9.8 Hz, 5.2 Hz, 1H, C***H***CH$_2$NO$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 170.4 (***C***=O), 135.1 (***C***q$_{Ar}$CH$_2$), 133.1 (***C***q$_{Ar}$CH), 129.3 (***C***H$_{Ar}$), 128.7 (***C***H$_{Ar}$), 128.5 (***C***H$_{Ar}$), 128.4 (***C***H$_{Ar}$), 128.0 (***C***H$_{Ar}$), 127.9 (***C***H$_{Ar}$), 75.7 (***C***H$_2$NO$_2$), 67.5 (Cq$_{Ar}$***C***H$_2$), 48.8 (***C***HCH$_2$NO$_2$); **MS** (EI, 70 eV): *m*/*z* (%) = 285 (0.3), 193 (1), 149 (17), 131 (4), 104 (21), 91 (100), 77 (7), 65 (10), 51 (5), 39 (4); **HRMS** (EIpos) calcd for [(C$_{16}$H$_{15}$NO$_4$+Na)$^+$]: 308.0893, found 308.0890.



(*S*)-Ethyl 3-nitro-2-p-tolylpropanoate (119g): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 63.10 min, minor enantiomer: t_R = 62.36 min. **119g** (65.5 mg, 0.276 mmol, 92%; 96:4 *er*): slightly yellow oil, $C_{12}H_{15}NO_4$ (237.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19-7.14 (m, 4H, C***H***$_{Ar}$), 5.08 (dd, *J* = 14.6 Hz, 10.0 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.52 (dd, *J* = 14.6 Hz, 5.2 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.38 (dd, *J* = 10.0 Hz, 5.1 Hz, 1H, C***H***CH_2NO_2), 4.26-4.11 (m, 2H, OC***H***$_2CH_3$), 2.34 (s, 3H, CC***H***$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.7 (***C***=O), 138.5 (***C***$q_{Ar}CH_3$), 130.3 (***C***$q_{Ar}CH$), 130.0 (***C***H_{Ar}), 127.7 (***C***H_{Ar}), 75.9 (***C***H_2NO_2), 61.8 (O***C***H_2CH_3), 48.4 (***C***HCH_2NO_2), 21.1 (Cq_{Ar}***C***H_3), 14.0 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 237 (7), 190 (76), 164 (7), 146 (21), 135 (1), 118 (100), 103 (4), 91 (14), 77 (4), 65 (4), 51 (2), 39 (3), 29 (25); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_4$]: 237.1001, found 237.0999.

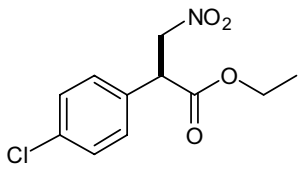


(*S*)-Ethyl 2-(4-methoxyphenyl)-3-nitropropanoate (119h): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 180 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 76.43 min, minor enantiomer: t_R = 75.88 min. **119h** (66.1 mg, 0.261 mmol, 87%; 95:5 *er*): slightly yellow oil, $C_{12}H_{15}NO_5$ (253.25 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20-7.16 (m, 2H, C***H***$_{Ar}$), 6.91-6.87 (m, 2H, C***H***$_{Ar}$), 5.06 (dd, *J* = 14.6 Hz, 10.0 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.51 (dd, *J* = 14.6 Hz, 5.3 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.36 (dd, *J* = 9.9 Hz, 5.3 Hz, 1H, C***H***CH_2NO_2), 4.26-4.11 (m, 2H, OC***H***$_2CH_3$), 3.79 (s, 3H, OC***H***$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8 (***C***=O), 159.7 (***C***$q_{Ar}OCH_3$), 129.0 (***C***H_{Ar}), 125.2 (***C***$q_{Ar}CH$), 114.7 (***C***H_{Ar}), 75.9 (***C***H_2NO_2), 61.8 (O***C***H_2CH_3), 55.3 (O***C***H_3), 48.0 (***C***HCH_2NO_2), 13.9 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 253 (15), 206 (79), 180 (5), 162 (10), 134 (100), 119 (16), 105 (3), 91 (15), 77 (6), 65 (8), 51 (2), 39 (2), 29 (20); **HRMS** (EI-FE) calcd for [$C_{12}H_{15}NO_5$]: 253.0950, found 253.0948.

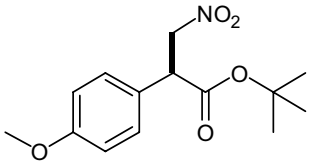


(*S*)-Ethyl 2-(4-fluorophenyl)-3-nitropropanoate (119i): The enantiomers were analyzed by GC using a Hydrodex-TBDAc (100 °C, 1 °C/min until 180 °C, 20 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 59.60 min, minor enantiomer: t_R = 59.19 min. **119i** (70.2 mg, 0.291 mmol, 97%; 94:6 *er*): slightly yellow oil, $C_{11}H_{12}FNO_4$ (241.22 g/mol); **^{1}H NMR** (300

MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H, C***H***$_{Ar}$), 7.09-7.03 (m, 2H, C***H***$_{Ar}$), 5.07 (dd, *J* = 14.4 Hz, 9.6 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.54 (dd, *J* = 14.6 Hz, 5.5 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.40 (dd, *J* = 9.6 Hz, 5.5 Hz, 1H, C***H***CH_2NO_2), 4.27-4.12 (m, 2H, OC***H***$_2CH_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2C***H***$_3$) ; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.3 (***C***=O), 162.8 (d, *J* = 246.5 Hz, ***C***$q_{Ar}F$), 129.6 (d, *J* = 8.4 Hz, ***C***H_{Ar}), 129.2 (d, *J* = 3.5 Hz, ***C***$q_{Ar}CH$), 116.4 (d, *J* = 21.8 Hz, ***C***H_{Ar}), 75.8 (***C***H_2NO_2), 62.0 (O***C***H_2CH_3), 48.0 (***C***HCH_2NO_2), 13.9 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 241 (3), 194 (48), 168 (6), 150 (14), 122 (100), 101 (10), 75 (4), 51 (2), 29 (35); **HRMS** (EIpos) calcd for [($C_{11}H_{12}FNO_4$+Na)$^+$]: 264.0643, found 264.0645.

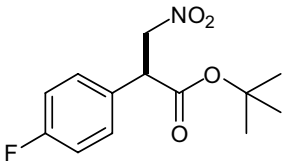


(*S*)-Ethyl 2-(4-chlorophenyl)-3-nitropropanoate (119j): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 170 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 71.54 min, minor enantiomer: t_R = 71.34 min. **119j** (74.2 mg, 0.288 mmol, 96%; 94:6 *er*): slightly yellow oil, $C_{11}H_{12}ClNO_4$ (257.67 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.33 (m, 2H, C***H***$_{Ar}$), 7.24-7.19 (m, 2H, C***H***$_{Ar}$), 5.07 (dd, *J* = 14.5 Hz, 9.5 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.54 (dd, *J* = 14.5 Hz, 5.5 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.40 (dd, *J* = 9.1 Hz, 5.5 Hz, 1H, C***H***CH_2NO_2), 4.24-4.13 (m, 2H, OC***H***$_2CH_3$), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2C***H***$_3$) ; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.1 (***C***=O), 134.8 (***C***$q_{Ar}CH$), 131.9 (***C***H_{Ar}), 129.5 (***C***H_{Ar}), 129.2 (***C***H_{Ar}), 75.6 (***C***H_2NO_2), 62.1 (O***C***H_2CH_3), 48.2 (***C***HCH_2NO_2), 13.9 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 257 (5), 210 (59), 184 (7), 166 (19), 155 (1), 138 (100), 125 (4), 103 (36), 89 (3), 77 (18), 63 (3), 51 (6), 29 (40); **HRMS** (EI-FE) calcd for [$C_{11}H_{12}ClNO_4$]: 257.0455, found 257.0457.

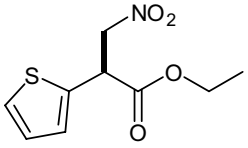


(*S*)-Tert-butyl 2-(4-methoxyphenyl)-3-nitropropanoate (119k): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 77.46 min, minor enantiomer: t_R = 76.74 min. **119k** (51.5 mg, 0.183 mmol, 61%; 96:4 *er*): slightly yellow oil, $C_{14}H_{19}NO_5$ (281.30 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 6.6 Hz, 2.1 Hz, 2H, C***H***$_{Ar}$), 6.88 (dd, *J* = 6.7 Hz, 2.2 Hz, 2H, C***H***$_{Ar}$), 4.99 (dd, *J* = 14.5 Hz, 10.1 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.46 (dd, *J* = 14.5 Hz, 5.3 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.26 (dd, *J* = 10.1 Hz, 5.2 Hz, 1H, C***H***CH_2NO_2), 3.80 (s, 3H, OC***H***$_3$), 1.41 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.8 (***C***=O), 159.6 (***C***$q_{Ar}OCH_3$), 128.9 (***C***H_{Ar}), 125.8 (***C***$q_{Ar}CH$), 114.6 (***C***H_{Ar}), 82.4 (***C***$(CH_3)_3$), 76.1 (***C***H_2NO_2), 55.3 (O***C***H_3), 48.9 (***C***HCH_2NO_2), 27.8 ($C($***C***$H_3)_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 281 (8), 234 (5), 208 (2), 180 (12), 134 (77), 119 (10), 103 (2), 91 (12), 77 (3),

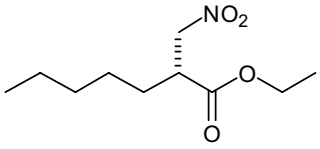
65 (6), 57 (100), 51 (2), 41 (18); **HRMS** (EIpos) calcd for [($C_{14}H_{19}NO_5$+ Na)$^+$]: 304.1155, found 304.1155.



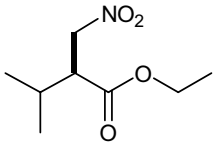
(*S*)-Tert-butyl 2-(4-fluorophenyl)-3-nitropropanoate (119l): The enantiomers were analyzed by GC using a chiral BGB-176 / BGB-15 column (80 °C, 1.2 °C/min until 170 °C, 18 °C/min until 220 °C, 5 min at 220 °C); major enantiomer: t_R = 54.21 min, minor enantiomer: t_R = 53.83 min. **119l** (68.7 mg, 0.255 mmol, 85%; 97:3 *er*): slightly yellow oil, $C_{13}H_{16}FNO_4$ (269.27 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.23 (m, 2H, C***H***$_{Ar}$), 7.08-7.03 (m, 2H, C***H***$_{Ar}$), 5.03-4.97 (dd, *J* = 14.5 Hz, 9.8 Hz, 1H, C***H***$_2NO_2$, *H*^{1}), 4.49 (dd, *J* = 14.5 Hz, 5.4 Hz, 1H, C***H***$_2NO_2$, *H*^{2}), 4.31 (dd, *J* = 9.8 Hz, 5.5 Hz, 1H, C***H***CH_2NO_2), 1.41 (s, 9H, OC(C***H***$_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.4 (***C***=O), 163.7 (d, *J* = 246.4 Hz, ***C***$q_{Ar}F$), 129.8 (d, *J* = 9.0 Hz, ***C***$q_{Ar}CH$), 129.5 (d, *J* = 8.0 Hz, ***C***H_{Ar}), 116.4 (d, *J* = 22.0 Hz, ***C***H_{Ar}), 82.7 (***C***$(CH_3)_3$), 75.9 (***C***H_2NO_2), 48.9 (***C***HCH_2NO_2), 27.9 (d, *J* = 12.3 Hz, C(***C***$H_3)_3$), 27.8; **MS** (EI, 70 eV): *m*/*z* (%) = 269 (1), 196 (6), 168 (10), 122 (40), 101 (4), 75 (2), 57 (100), 41 (21); **HRMS** (EIpos) calcd for [($C_{13}H_{16}FNO_4$+Na)$^+$]: 292.0956, found 292.0956.



(*S*)-Ethyl 3-nitro-2-(thiophen-2-yl)propanoate (119m): The enantiomers were analyzed by GC using a chiral IVADEX 1 / PS086 column (80 °C, 1.2 °C/min until 800 °C, 18 °C/min until 220 °C, 10 min at 220 °C); major enantiomer: t_R = 63.12 min, minor enantiomer: t_R = 63.83 min. **116m** (67.4 mg, 0.294 mmol, 83%; 96:4 *er*): yellow oil, $C_9H_{11}NO_4S$ (229.25 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.28 (t, *J* = 3.2 Hz, 1H, C***H***$_{Ar}$), 7.01-6.98 (m, 2H, C***H***$_{Ar}$), 5.10 (dd, *J* = 14.3 Hz, 9.5 Hz, 1H, C**H**$_2NO_2$, *H*^{1}), 4.70 (dd, *J* = 9.6 Hz, 5.1 Hz, 1H, C**H**CH_2NO_2), 4.63 (dd, *J* = 14.3 Hz, 5.1 Hz, 1H, C**H**$_2NO_2$, *H*^{2}), 4.31-4.16 (m, 2H, OC**H**$_2CH_3$), 1.31-1.22 (m, 3H, OCH_2C**H**$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 169.6 (***C***=O), 134.4 (***C***$q_{Ar}CH$), 127.3 (***C***H_{Ar}), 126.8 (***C***H_{Ar}), 126.1 (***C***H_{Ar}), 75.7 (***C***H_2NO_2), 62.3 (O***C***H_2CH_3), 43.8 (***C***HCH_2NO_2), 13.9 (OCH_2***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 229 (1), 182 (72), 156 (7), 138 (25), 110 (100), 97 (5), 84 (6), 77 (5), 66 (10), 58 (4), 45 (9), 29 (29); **HRMS** (EIpos) calcd for [$C_9H_{11}NO_4S$]: 229.0409, found 229.0411.



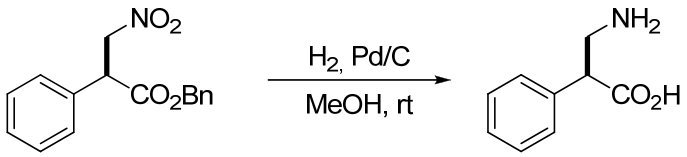
(*R*)-Ethyl 2-(nitromethyl)heptanoate (119n): The enantiomers were analyzed by GC using a chiral G-TA column (100 °C, 1.2 °C/min until 180 °C, 10 min at 180 °C); major enantiomer: t_R = 27.30 min, minor enantiomer: t_R = 26.58 min. **119n** (59.3 mg, 0.273 mmol, 91%; 97:3 *er*): colorless oil, $C_{10}H_{19}NO_4$ (217.26 g/mol); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.73 (dd, *J* = 14.2 Hz, 9.2 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.41 (dd, *J* = 14.2 Hz, 4.8 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.20 (q, *J* = 7.1 Hz, 2H, OC***H***$_2$CH$_3$), 3.20-3.16 (m, 1H, C***H***CH$_2$NO$_2$), 1.70-1.65 (m, 1H, CHC***H***$_2$CH$_2$), 1.58-1.55 (m, 1H, CHC***H***$_2$CH$_2$), 1.35-1.26 (m, 9H: CH$_2$C***H***$_2$CH$_2$ (4H), CH$_2$C***H***$_2$CH$_3$ (2H), *J* = 7.1 Hz, OCH$_2$C***H***$_3$ (3H)), 0.90-0.87 (m, 3H, CH$_2$CH$_2$C***H***$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.3 (***C***=O), 75.2 (***C***H$_2$NO$_2$), 61.3 (O***C***H$_2$CH$_3$), 43.0 (***C***HCH$_2$NO$_2$), 31.4 (CH$_2$***C***H$_2$CH$_2$), 29.2 (C(O)***C***H$_2$CH$_2$), 26.2 (CH$_2$***C***H$_2$CH$_2$), 22.3 (CH$_2$***C***H$_2$CH$_3$), 14.1 (OCH$_2$***C***H$_3$), 13.9 (CH$_2$CH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 216 (0.1), 198 (2), 189 (1), 170 (19), 159 (16), 141 (11), 123 (9), 113 (18), 95 (45), 85 (16), 67 (17), 55 (44), 41 (57), 29 (100); **HRMS** (EIpos) calcd for [$C_{10}H_{20}NO_4$+H)$^+$]: 218.1392, found 218.1394.



(*S*)-Ethyl 3-methyl-2-(nitromethyl)butanoate (119o): The enantiomers were analyzed by GC using a chiral G-TA column (80 °C, 1.0 °C/min until 180 °C, 10 min at 180 °C); major enantiomer: t_R = 32.46 min, minor enantiomer: t_R = 33.57 min. **119o** (52.2 mg, 0.276 mmol, 92%; 97:3 *er*): colorless oil, $C_8H_{15}NO_4$ (189.21 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.79 (dd, *J* = 14.5 Hz, 10.4 Hz, 1H, C***H***$_2$NO$_2$, *H*^{1}), 4.40 (dd, *J* = 15.1 Hz, 4.0 Hz, 1H, C***H***$_2$NO$_2$, *H*^{2}), 4.21 (q, *J* = 7.1 Hz, 2H, OC***H***$_2$CH$_3$), 3.12-3.05 (m, 1H, C***H***CH$_2$NO$_2$), 2.10-2.04 (m, 1H, C***H***(CH$_3$)$_2$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH$_2$C***H***$_3$), 1.00 (d, *J* = 4.1 Hz, 3H, CH(C***H***$_3$)$_2$), 0.98 (d, *J* = 4.1 Hz, 3H, CH(C***H***$_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.7 (***C***=O), 73.7 (***C***H$_2$NO$_2$), 61.2 (O***C***H$_2$CH$_3$), 49.0 (***C***HCH$_2$NO$_2$), 28.8 (***C***H(CH$_3$)$_2$), 19.8 (CH(***C***H$_3$)$_2$), 19.7 (CH(***C***H$_3$)$_2$), 14.1 (OCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 189 (3), 144 (34), 113 (14), 101 (100), 97 (87), 88 (10), 73 (83), 69 (69), 59 (18), 55 (81), 41 (65), 29 (69); **HRMS** (EI-FE) calcd for [$C_8H_{15}NO_4$]: 189.1001, found 189.1003.

7.6.4 Preparation of *β*²-Amino Acids *via* Hydrogenation of *β*-Nitroesters

7.6.4.1 Preparation of *β*²-Amino Acid 122f *via* Hydrogenation



119f
97:3 *er*

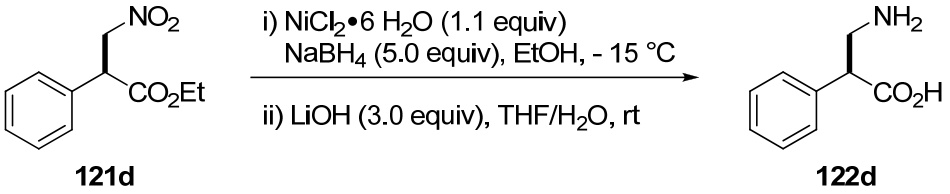
122f
97:3 *er*

A Schlenck tube was charged with palladium on charcoal (7.5 mg, 50% wet, 0.004 mmol) and evacuated for ten minutes. A solution of benzyl 3-amino-2-phenylpropanoate (**121f**, 10 mg, 0.04 mmol) in methanol (1 mL) was added and the reaction mixture was stirred vigorously for six hours. The mixture was filtered through a Celite pad. Methanol was removed under reduced pressure to afford a colorless solid that was redissolved in water (2 mL). The aqueous phase was extracted with ether (1 × 1 mL) and concentrated *in vacuo* to give (*S*)-3-amino-2-phenylpropanoic acid (**122f**, 4.6 mg, 0.03 mmol, 81%; 97:3 *er*) as a colorless solid.

122f: $C_9H_{11}NO_2$ (165.19 g/mol); $[\alpha]_D^{20}$ = -81, (*c* 0.20, H_2O) ; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H, C***H***$_{Ar}$), 3.67 (t, *J* = 7.3 Hz, 1H, C***H***Ph), 3.35 (dd, *J* = 7.3 and 4.6 Hz, 1H, C***H***$_2NH_2$), 3.17 (dd, *J* = 7.3 and 5.3 Hz, 1H, C***H***$_2NH_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.2 (***C***=O), 137.2 (***C***$q_{Ar}CH$), 129.2 (***C***H_{Ar}), 128.1 (***C***H_{Ar}), 127.9 (***C***H_{Ar}), 51.3 (***C***HCH_2NH_2), 42.3 (***C***H_2NH_2); **MS** (EI, 70 eV): *m*/*z* (%) = 165 (1), 136 (5), 118 (11), 104 (4), 91 (10), 77 (5), 63 (3), 51 (3), 30 (100); **HRMS** (EI-FE) calcd for [$C_9H_{11}NO_2$]: 165.0790, found 165.0791. The enantiomers were analyzed by HPLC using a Chirobiotic T2 column (eluent: 50% of methanol in isopropyl, 0.1 mL/min); major enantiomer: t_R = 15.90 min, minor enantiomer: t_R = 23.30 min.

7.6.4.1 Preparation of *β*²-Amino Acids *via* a hydrogenation–hydrolysis sequence

Preparation of (S)-3-Amino-2-phenylpropanoic acid **(122d)**



121d **122d**

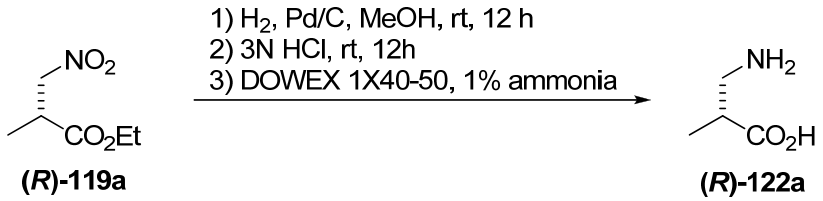
Nickel chloride-hexahydrate (121 mg, 0.51 mmol) was added at -15 °C to a solution of *β*-nitroester **119d** (90 mg, 0.47 mmol) in ethanol (3 mL). After adding sodium borohydride (86 mg, 2.33 mmol) in one portion, a clear green solution was obtained. The reaction mixture was then stirred at 0 °C in an ice-water bath for 15 minutes, followed by the addition of hydrochloric acid (2 N) until the pH of the solution reached a value of 3. A solution of sodium bicarbonate was added until a pH of 9 was obtained. The mixture was concentrated under reduced pressure. Water (10 mL) and ethyl acetate (5 mL) were added to the residue. The biphasic mixture was then filtered to remove precipitates and the aqueous phase extracted with ethyl acetate (2 × 5 mL). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (75% of ethyl acetate in ethanol) to give (*S*)-ethyl 3-amino-2-phenylpropanoate (**225**, 69 mg, 0.36 mmol, 90%).

225: $C_{11}H_{15}NO_2$ (193.24 g/mol); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5H, C***H***$_{Ar}$), 4.19-4.10 (m, 2H, C***H***$_2$CH$_3$), 3.75 (t, *J* = 7.2 Hz, 1H, C***H***Ph), 3.34 (dd, *J* = 4.4 Hz, 8.4 Hz, C***H***$_2$NH$_2$), 3.10 (s, 2H, N***H***$_2$), 3.05 (dd, *J* = 4.4 Hz, 8.4 Hz, 1H, C***H***$_2$NH$_2$), 1.20 (t, *J* = 7.2 Hz, 3H, C***H***$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.8 (***C***=O), 136.7 (***C***q$_{Ar}$CH), 128.8 (***C***H$_{Ar}$), 128.0 (***C***H$_{Ar}$), 127.6 (***C***H$_{Ar}$), 61.0 (O***C***H$_2$CH$_3$), 54.2 (***C***HCH$_2$NH$_2$), 44.8 (***C***H$_2$NH$_2$), 14.0 (OCH$_2$***C***H$_3$); **MS** (EI, 70 eV): *m*/*z* (%) = 193 (31), 103 (11), 118 (55), 136 (39), 148 (3), 164 (100), 176 (2), 193 (1); **HRMS** (EI-FE) calcd for [$C_{11}H_{15}NO_2$]: 193.1103, found 193.1104.

(*S*)-Ethyl 3-amino-2-phenylpropanoate (**225**, 40 mg, 0.21 mmol) was dissolved in THF/water (4:1, v/v, 2 mL) and lithium hydroxide (15 mg, 0.62 mmol) was added to this solution. The reaction mixture was then stirred at room temperature for six hours and concentrated *in vacuo*.

The residue was diluted with water and extracted with diethyl ether (2 × 2 mL). The aqueous phase was concentrated to 1 mL and added to Dowex 50W 8X (H^+ form) with ammonia (1%) as the eluent to afford free amino acid **122d** (25 mg, 0.15 mmol, 73%). **122d**: $C_9H_{11}NO_2$ (165.19 g/mol); $[\alpha]_D^{20}$ = -76, (*c* 0.62, H_2O); **^{1}H NMR** and **^{13}C NMR** see **122f**.

***Preparation of (R)-3-amino-2-methylpropanoic acid* ((*R*)-122a)**



(*R*)-119a **(*R*)-122a**

A schlenk tube was charged with palladium on charcoal (74 mg, 10 %, 50% wet, 0.036 mmol, vaccum dried for one hour before being used) and a solution of *β*-nitroester **121a** (80 mg, 0.359 mmol) in methanol (2 mL) was added at room temperature under an atmosphere of hydrogen gas. The reaction mixture was vigorously stirred at room temperature for twelve hours. The suspension was then filtered through a Celite pad and concentrated under reduced pressure to give a colorless oil, which was dissolved in hydrochloric acid (3N, 2 mL, 6 mmol). The solution was stirred for twelve hours and concentrated to dryness. The residue was filtered through a DOWEX 1X40-50 pad (basic form, 3 cm) with ammonia (1%, 60 mL) as eluent. The collected aqueous phase was concentrated to give (*R*)-3-amino-2-methylpropanoic acid (**122a**, 19 mg, 0.18 mmol, 42%) as a colorless oil that solidified slowly.

122a: $C_4H_9NO_2$ (103.12 g/mol); $[\alpha]_D^{20}$ = **+3.3** (*c* 0.79, H_2O);[277] **^{1}H NMR** (500 MHz, D_2O): δ 3.02-2.90 (m, 2H, C***H***$_2$N), 2.53-2.46 (m, 1H, C***H***CH_3), 1.09 (d, *J* = 7.3 Hz, 3H, C***H***$_3$); **^{13}C NMR** (125 MHz, D_2O): δ 181.7 (***C***=O), 42.3 (***C***HCH_2NO_2), 39.2 (***C***H_2NO_2), 15.1 (CH***C***H_3); **MS** (EI, 70 eV): *m*/*z* (%) = 103 (2), 84 (1), 56 (3), 30 (100); **HRMS** (EI-FE) calcd for [$C_4H_9NO_2$]: 103.0633, found 103.0631. The enantiomers were analyzed by HPLC using a Chirobiotic T2 column (eluent: 20% of water in acetonitrile, 0.3 mL/min); major enantiomer: t_R = 16.40 min, minor enantiomer: t_R = 27.80 min.

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9 Appendix

9.1 Erklärung

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"Organocatalytic Asymmetric Transfer Hydrogenation of Nitroolefins", N. J. A. Martin, L. Ozores, B. List *J. Am. Chem. Soc.* **2007**, *129*, 8976-8977.

"Organocatalytic Asymmetric Transferhydrogenation of β-Nitroacrylates: Accessing β^2-Amino Acids", N. J. A. Martin, X. Cheng, B. List *J. Am. Chem. Soc.* **2008**, *130*, 13862-13863.

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