New Catalytic Routes to α-Amino Acids and Their Derivatives

Inaugural-Dissertation

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Dedicated to

My parents and
the memory of my grandmother

Acknowledgements

The entire work embodied in this thesis is the result of investigations carried out by me from September 2005 to March 2008 at the Department of Homogeneous Catalysis of the Max-Planck-Institut für Kohlenforschung under the supervision of Prof. Dr. Benjamin List.

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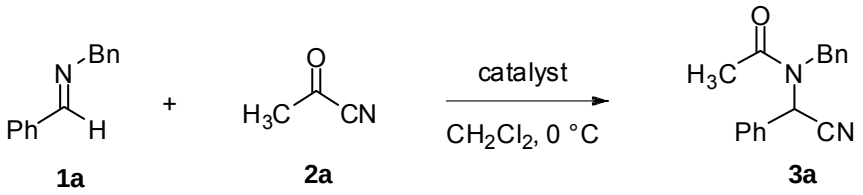
1 Summary

This thesis concerns the development of two new catalytic reactions for the synthesis of α-amino acids and their derivatives. The first reaction discussed is the acylcyanation of imines, which is a new variant of the Strecker reaction and acylcyanides are used for the first time in a catalytic asymmetric Strecker process. The second variation is a catalytic three-component Ugi reaction involving aldehydes, primary amines and isocyanides, which is a new variant of the Ugi reaction and could potentially be conducted in an asymmetric fashion.

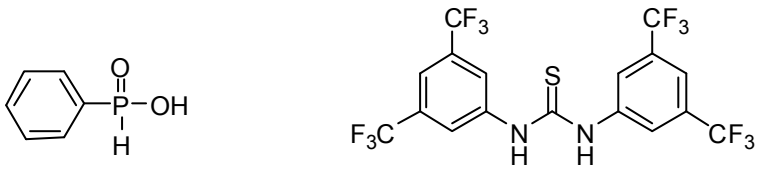
The atom-economic reaction between *N*-benzyl aldimine **1a** and acetylcyanide **2a** was initially studied (Scheme 1.1), and *N*-acetylated α-amino nirile product **3a** could be further converted to the corresponding racemic α-amino acid.



1a **2a** **3a**

Scheme 1.1 Catalytic acetylcyanation of imine **1a**.

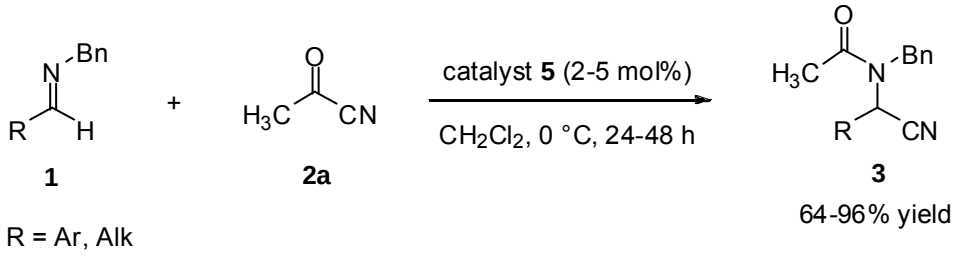
The reaction was catalyzed in a facile manner by both specific and hydrogen-bonding type general Brønsted acids **4** and **5** giving 90% and 99% conversions respectively after 24 hours (Scheme 1.2). Product **3a** was isolated in 88% yield from the reaction with Schreiner thiourea catalyst **5**.



4 **5**

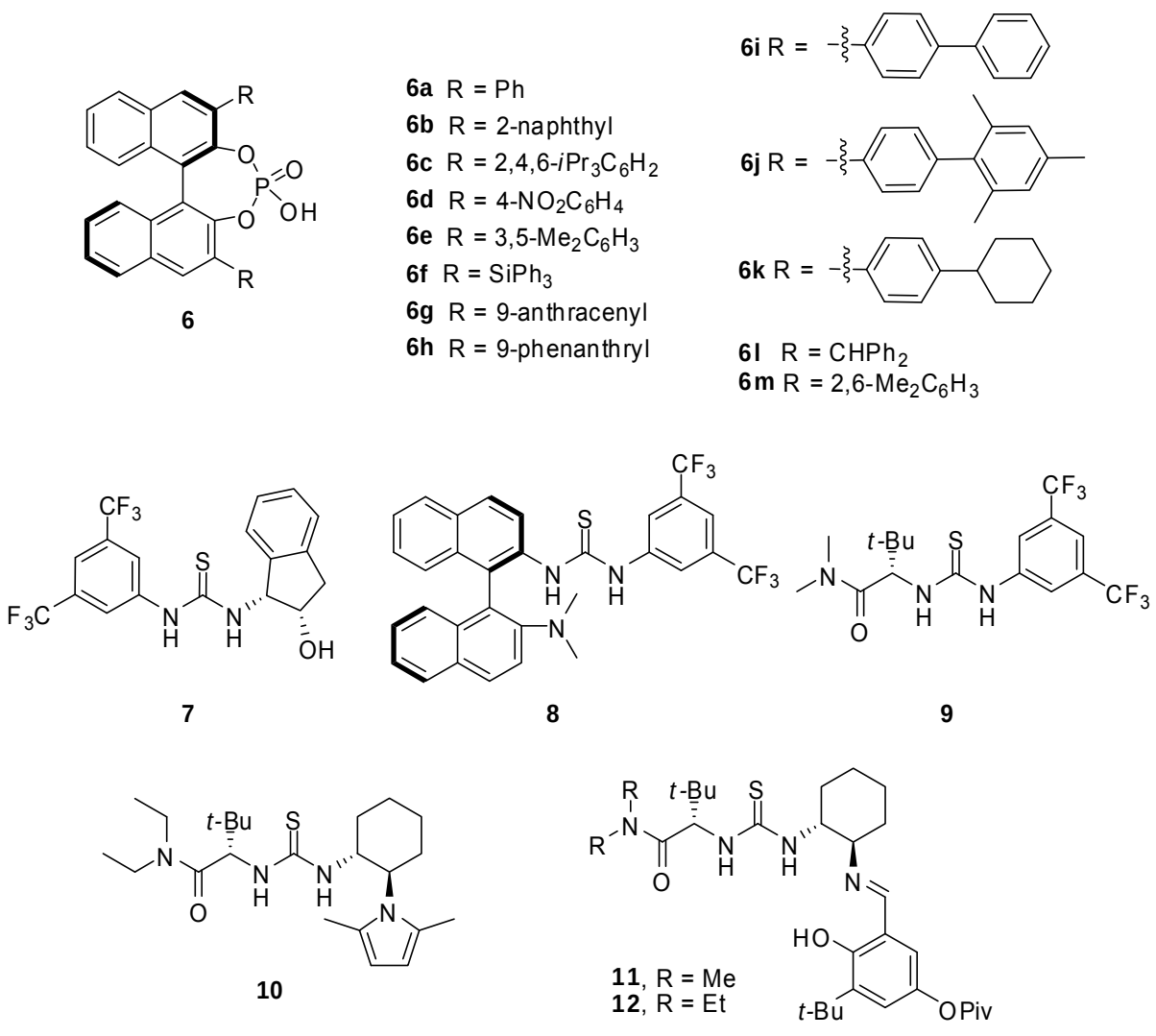
Scheme 1.2 Brønsted acid catalysts investigated for acetylcyanation of imine **1a**.

Catalyst **5** was then applied to the acetylcyanation of different aromatic and aliphatic aldehyde derived benzyl imines **1**. With 2-5 mol% of catalyst **5,** *N*-acetylated α-amino nirile products **3** were obtained in 64-96% yields (Scheme 1.3).



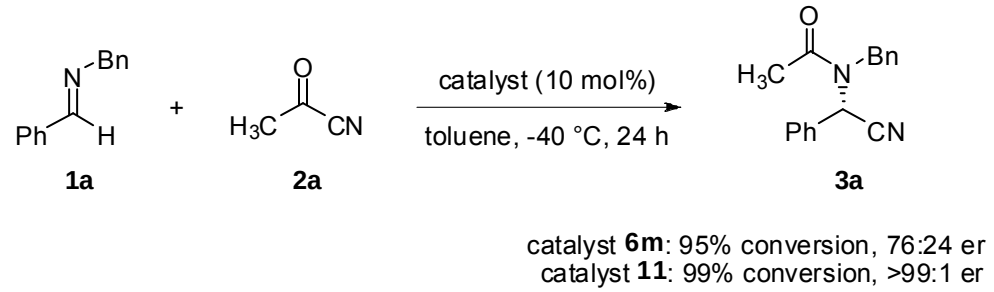
Scheme 1.3 Catalytic acetylcyanation of different imines.

Several chiral BINOL-derived phosphoric acid catalysts **6a-m** were initially tested for the development of an asymmetric version of this useful transformation (Scheme 1.4). These catalysts were found to catalyze the reaction efficiently and the highest enantioselectivity (76:24 er) was obtained with catalyst **6m** (Scheme 1.5).



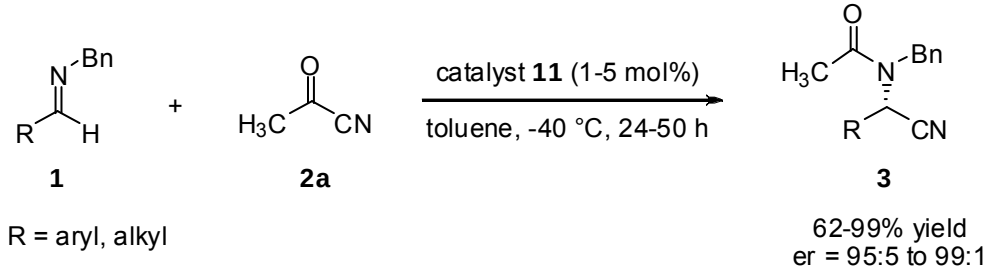
Scheme 1.4 Chiral phosphoric acid and thiourea catalysts.

Subsequently a range of chiral thiourea catalysts **7**-**12** was prepared (Scheme 1.4). Catalysts **11** and **12** were found to be the best catalysts giving product **3a** in essentially enantiomerically pure form (Scheme 1.5). Even 1 mol% of catalyst **11** was sufficient to give product **3a** in high conversion (94%) and with excellent enantioselectivity (98:2 er).



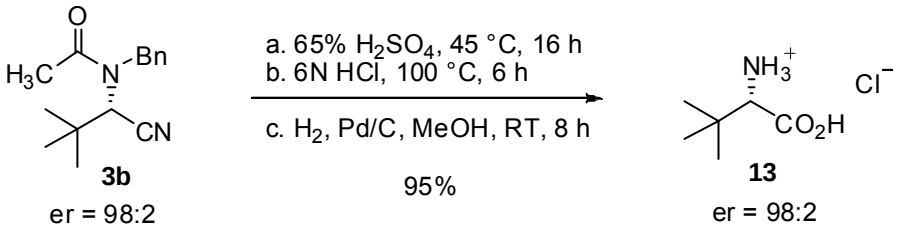
Scheme 1.5 Catalytic asymmetric acetylcyanation of imine **1a**.

Catalyst **11** was investigated with a number of different imines and very high enantioselectivities were obtained with a variety of aromatic, heteroaromatic, aliphatic and unsaturated aldimines (Scheme 1.6).



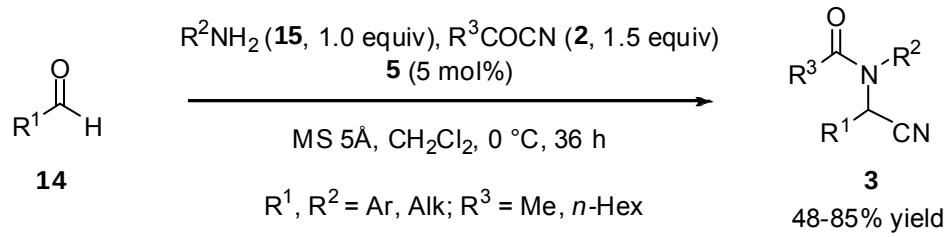
Scheme 1.6 Catalytic asymmetric acetylcyanation of different imines.

Afterwards, *N*-acetylated α-amino nitrile **3b** was converted into the HCl salt of *tert*-leucine (**13**) via acid-mediated hydrolysis and hydrogenolysis in high yield and without racemization (Scheme 1.7).



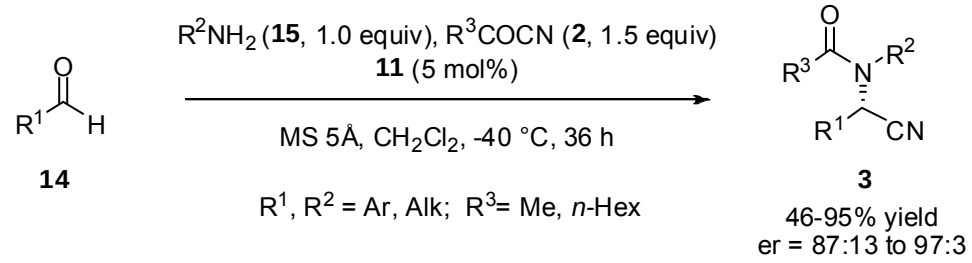
Scheme 1.7 Conversion of **3b** to *tert*-leucine salt **13**.

Following these studies, a one-pot variant of the acylcyanation reaction was developed. The best result (99% conversion) was obtained when the mixture of aldehyde, amine, 5Å molecular sieves (MS), and catalyst **5** were stirred together at room temperature for 2 hours before the addition of acetylcyanide at 0 °C. A wide range of aldehydes **14** (aromatic and aliphatic), amines **15** (benzyl and alkyl) and acylcyanides **2** gave products **3** in moderate to high yields under these reaction conditions (Scheme 1.8).



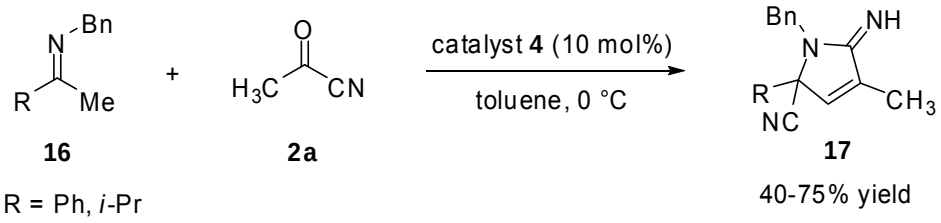
Scheme 1.8 Catalytic three-component acyl-Strecker reaction.

For the development of an asymmetric one-pot acyl-Strecker variant, the reaction was studied with catalyst **11**. The most promising result was obtained if the aldehyde was first mixed with the amine and MS 5Å for 2 hours at room temperature before catalyst **11** and acetylcyanide **2a** were subsequently added at –40 °C. Under the optimized conditions, various aldehydes **14**, amines **15** and acylcyanides **2** were investigated and good results (87:13 to 97:3 er) were obtained (Scheme 1.9).



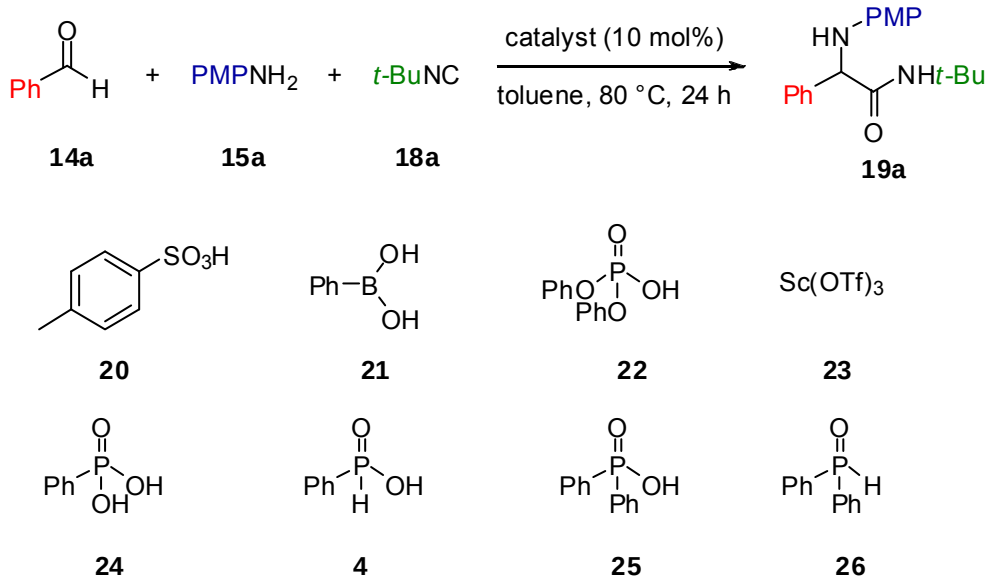
Scheme 1.9 Catalytic asymmetric three-component acyl-Strecker reaction.

When the substrate scope of the acetylcyanation reaction was extended to ketimines, the desired addition product was not observed. Instead, novel five membered amidine derivatives **17** were isolated from the reaction of ketimines **16** with acetylcyanide **2a** in the presence of catalyst **4** (Scheme 1.10), and moderate to high yields (40-75%) were achieved.



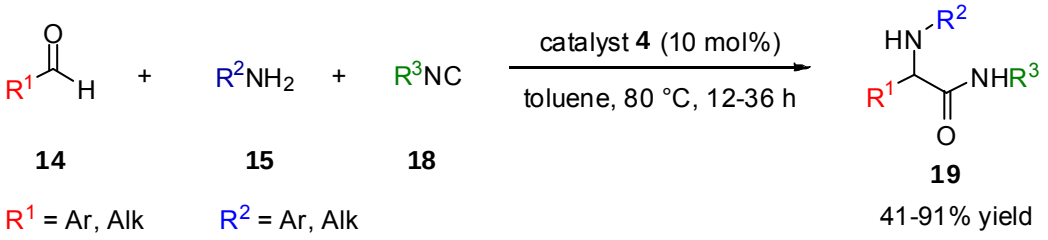
Scheme 1.10 Formation of amidines **17** from the reaction of ketimines **16** with acetylcyanide **2a**.

A model reaction between benzaldehyde (**14a**), *para*-anisidine (**15a**) and *tert*-butyl isocyanide (**18a**) was designed for the development of a catalytic atom-economic three-component Ugi reaction (Scheme 1.11). After screening a number of Brønsted and Lewis acid catalysts (**4**, **20**-**26**), **4** was found to be the optimum catalyst and gave the desired α-amino amide product **19a** in 91% yield (Scheme 1.11).



Scheme 1.11 Three-component Ugi reaction and different Brønsted acid catalysts.

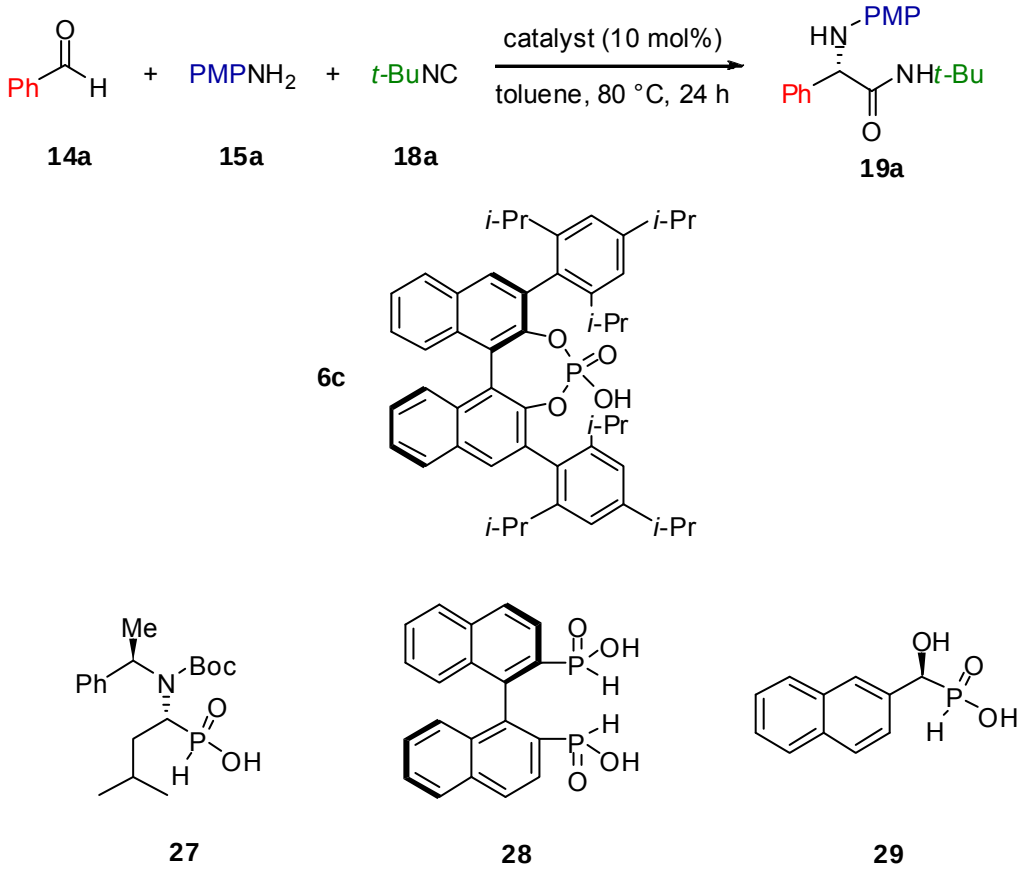
Different aldehydes **14** (aromatic and aliphatic), amines **15** (aryl and alkyl) and isocyanides **18** were screened with catalyst **4** and a library of compounds of type **19** was synthesized in



Scheme 1.12 Three-component Ugi reaction with different aldehydes, amines and isocyanides.

moderate to high yields (41-91%) (Scheme 1.12).

A remarkable aspect is the development of a catalytic asymmetric variant of this reaction. The best phosphoric acid catalyst identified for this reaction was **6c** (TRIP) and provided product **19a** in 15% yield with 59:41 er (Scheme 1.13). From the information in the non-asymmetric variant, further studies were carried out with various novel chiral phosphinic acid catalysts **27**-**29**. In the presence of these catalysts, product **19a** was formed in high yields (80-95%); however low enantioselectivities (<55:45 er) were obtained (Scheme 1.13). Nevertheless, high enantioselectivities could potentially be realized by other chiral phosphinic acid catalysts in future investigations.

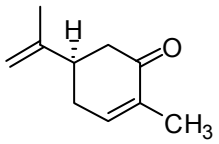


Scheme 1.13 Catalytic asymmetric three-component Ugi reaction and different chiral catalysts.

In summary, two new catalytic atom-economic approaches for the synthesis of α-amino carbonyl frameworks have been developed. Brønsted acid catalysts have been found to catalyze the reactions in high efficiencies. These two methodologies will not only be useful for the synthesis of α-amino acids and their derivatives, but also for diversity-oriented synthesis and medicinal chemistry.

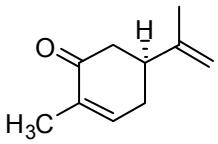
2 Introduction

Most naturally occurring compounds are chiral: they are not superimposable on their mirror images. Nature has chosen to make most of its living structures from chiral molecules (amino acids, sugars), and has selected a single enantiomer form of each. In addition to natural products, there are different synthetic compounds whose properties vary with the spatial orientation of the atoms and groups within the molecule.[1] Although, many chemical and physical properties of enantiomers are identical, they differ in their interactions with chiral reagents and environments. Biological systems commonly distinguish between enantiomers and two enantiomers may have completely different biological properties. Enzymes in living systems are chiral, and thus they are capable of distinguishing between enantiomers. Even a human's nose is capable of differentiating between enantiomers. This is because the receptor sites for the sense of smell are chiral. For example, the natural (*R*)-(–)-carvone **30** has the fragrance associated with spearmint oil, whereas (*S*)-(+)-carvone *ent*-**30** has the tangy odor of caraway seed (Scheme 2.1). Thus, for a fragrance and perfume manufacturer, the distinction between enantiomers of the same molecule is of great importance.



(*R*)-(-)-Carvone

30

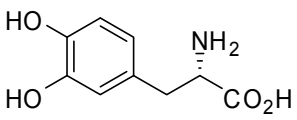


(*S*)-(+)-Carvone

ent-**30**

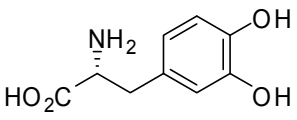
Scheme 2.1 The enantiomers of the natural compound carvone.

For the case of drug molecules, making the right enantiomer can be a matter of life and death. Parkinson's disease sufferers are treated with the non-proteinogenic α-amino acid Dopa (3-



(*S*)-Dopa

31



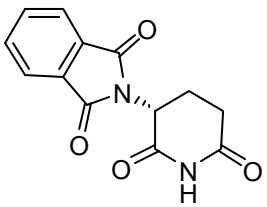
(*R*)-Dopa

ent-**31**

Scheme 2.2 The enantiomers of Dopa.

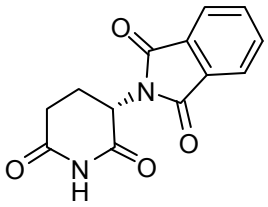
(3,4-dihydroxyphenyl)alanine) **31**. Dopa is chiral, and only (*S*)-Dopa **31** is effective in restoring nerve function (Scheme 2.2).[2] (*R*)-Dopa *ent*-**31** is not only ineffective, it is, in fact quite toxic. So, the drug must be administered as a single enantiomer.

This kind of difference is also shown by the drug thalidomide **32** which was administered to pregnant women for the prevention of morning sickness. (*R*)-thalidomide **32** has desirable sedative properties, but its (*S*)-enantiomer *ent*-**32** is teratogenic (Scheme 2.3).[3] Moreover, the *in vivo* racemization of the (*R*)-enantiomer[4] caused a high incidence of fatal deaths and congenital malformations.



(*R*)-(+)-Thalidomide

32



(*S*)-(-)-Thalidomide

ent-**32**

Scheme 2.3 The enantiomers of the drug thalidomide.

These examples are among numerous cases where biological systems respond in a different way to the enantiomeric forms of a certain molecule. The continually increasing challenges associated with the treatment of new and existing diseases necessitates that potential therapeutics contain higher levels of molecular complexity with one or more asymmetric centres to achieve potency, selectivity and desirable physical properties. It is thus required to prepare molecules in enantiomerically pure forms to have the desired physical, chemical and biological properties. Nature has provided a variety of enantiomerically pure compounds referred to as the 'chiral pool'.[5] Besides this, there are two general methods for obtaining enantiopure compounds: the mechanical or chemical resolution of racemic mixtures and the asymmetric synthesis.

The method of resolution was initiated in 1848 by Louis Pasteur when he mechanically separated the crystals of the two optical isomers of sodium ammonium tartrate by slow evaporation of an aqueous solution. Pasteur later developed the method of selective crystallization of one enantiomer by diastereomeric salt formation with another chiral compound; and it is still used for the preparation of enantiomerically pure acids and amines. Other methods of resolution are the covalent bond formation between racemic substrate and

an enantiomerically pure compound. In most cases, the diastereomeric products are separated by column chromatography and the appropriate diastereomer could be converted to the desired enantiomer by chemical methods. Preparative chiral chromatographic techniques are also now employed for the large scale separation of enantiomers. However, the theoretical yield of this strategy is limited to only 50%.

In asymmetric synthesis, the use of chiral auxiliaries was originally found to be a powerful tool for the preparation of one enantiomer. A diastereoselective reaction is carried out, which, because of the fixed spatial orientation of the chiral auxiliary, gives only one diastereomer of the product. Although the chiral auxiliaries can be recycled, one drawback of this method is the requirement of stoichiometric quantity of the chiral auxiliary.

Asymmetric catalysis, in which each molecule of chiral catalyst, by virtue of being continually regenerated, can yield many molecules of chiral product, has significant potential advantages over the previously described procedures. Indeed, enantiomerically pure compounds are produced in nature by such chirality transfer from enzyme catalysts. Until the last decade, there were two classses of asymmetric catalysts: enzymes and synthetic metal complexes.[6] A major breakthrough in transition metal catalysis occurred in the early 1970s, when William R. Knowles and his colleagues at Monsanto demonstrated that rhodium complexes containing chiral phosphine ligands are able to carry out the catalytic asymmetric hydrogenation of olefins.[7] In recognition of his achievement, Knowles shared the 2001 Nobel Prize in chemistry with Ryoji Noyori, also for work on the asymmetric catalytic hydrogenation,[4] and with K. Barry Sharpless for his work on the asymmetric catalytic oxidation.[8] Although many metal-catalyzed transformations are invaluable to the pharmaceutical industry, especially in chemical development and process research, many of these reactions require specific expertise and equipment that is not always available.

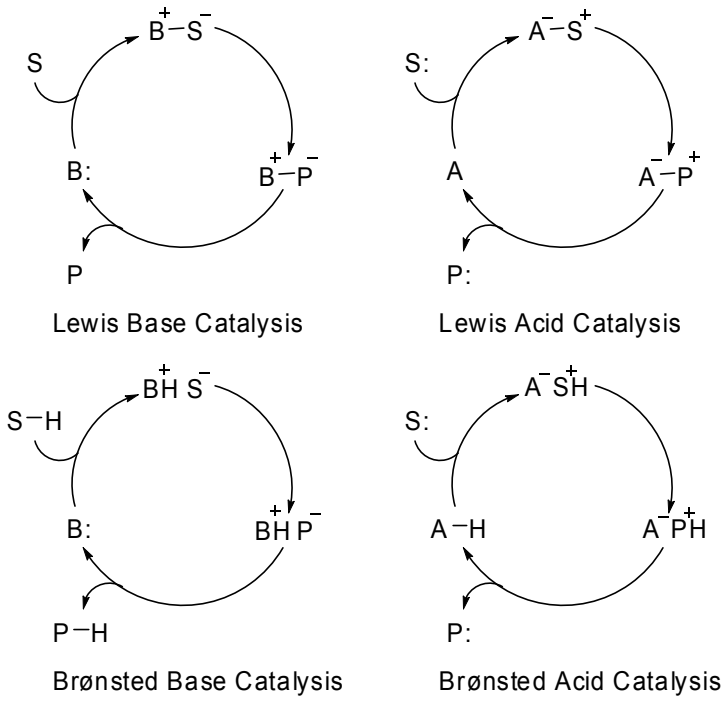
Over the past seven years, purely organic catalysts as a third class of asymmetric catalysts, namely organocatalysis has had a significant impact in chemical synthesis.[9–15] The historic roots of organocatalysis go back to the works of Bredig, Langenback and Pracejus.[16] Further breakthroughs were achieved by Hajos et al. and Wiechert et al. in 1970s when they used proline as an asymmetric catalyst for the Robinson annulation.[17] Although this field is in its infancy, the breadth of different reactions that can be catalyzed make it a complementary discipline to conventional metal catalysis. Most importantly, it offers a mild, practical and generally simple method for making small, functionalized molecules with high enantiopurity. ‘Asymmetric organocatalysis’ has become a highly interested topic as proved by the escalating number of publications appearing day after day as well as two published books[11,14] and several reviews.[9,12,15]

3 Background

3.1 Asymmetric Organocatalysis

Organocatalysis is the process where a purely organic small molecule is used to catalyze a chemical reaction. This type of catalysis is complementary with transition metal catalysis and biocatalysis. It often has some notable advantages like small organic molecule catalysts are generally stable and fairly easy to design and synthesize. They are often based on nontoxic compounds, such as sugars, peptides, or even amino acids, and can easily be linked to a solid support, making them useful for industrial applications.

Organocatalysts are broadly classified as Lewis bases, Lewis acids, Brønsted bases and Brønsted acids.[12] The corresponding simplified catalytic cycles are shown in Scheme 3.1. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) and releases the product and catalyst in a similar manner. Brønsted base (B:) catalytic cycles are initiated by partial or full deprotonation. Similarly Brønsted acid (A-H) catalytic cycles commence via a partial or full protonation of an electron rich substrate.

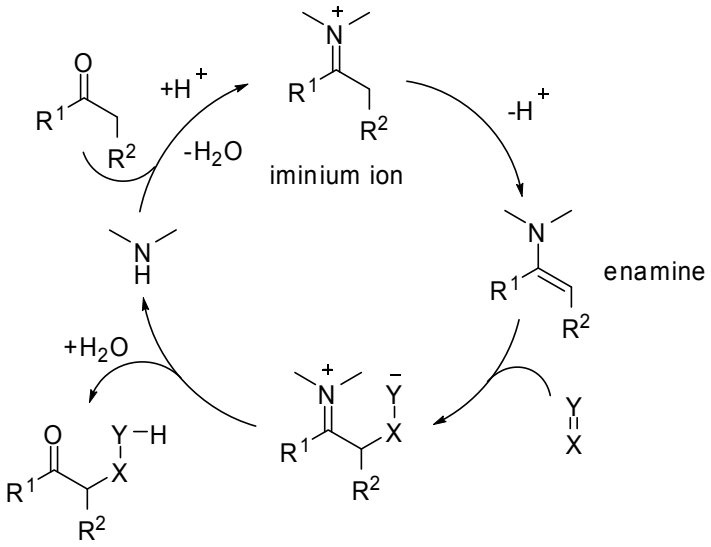


Scheme 3.1 Different organocatalytic cycles.

Lewis Base Catalysis

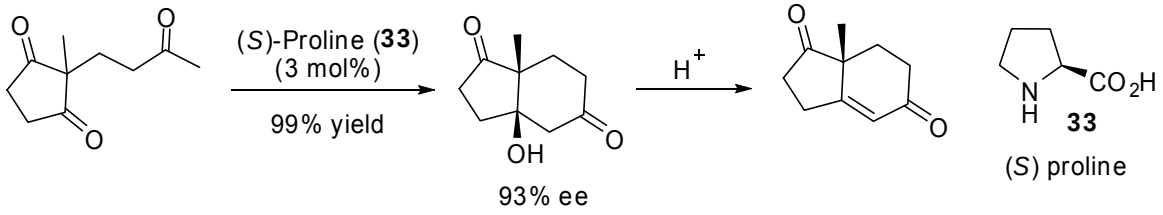
Lewis base catalysis is the process by which an electron pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species.[18] The majority of organocatalysts are N-, C-, O-, P-, and S-based Lewis bases that operate through diverse mechanisms. Typical reactive intermediates for N-based catalysts are iminium ions, enamines etc.

Enamine catalysis involves a catalytically generated enamine intermediate that is formed via deprotonation of an iminium ion and reacts with various electrophiles or undergoes pericyclic reactions (Scheme 3.2).[19] Thus, the basis of enamine catalysis is the reversible generation of enamines from a catalytic amount of an amine and a carbonyl compound (Scheme 3.2).

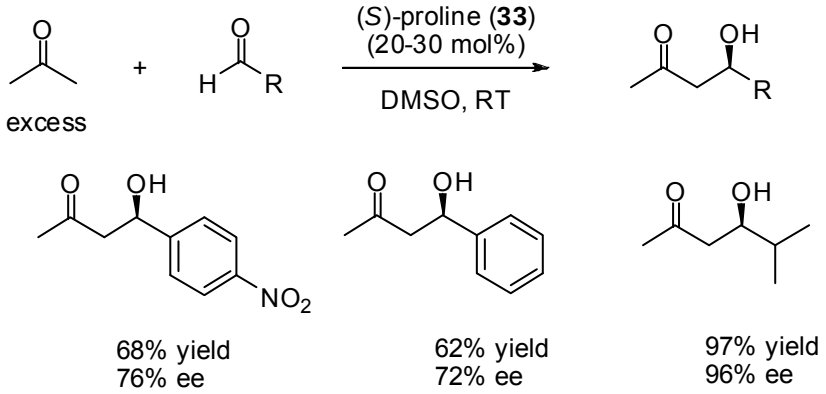


Scheme 3.2 Enamine catalysis (arrows may be considered equilibria).

The first example of asymmetric enamine catalysis is the Hajos-Parrish-Eder-Sauer-Wiechert reaction[17], an intramolecular aldol reaction catalyzed by proline (**33**) (Scheme 3.3). About thirty years later a revival of this chemistry was initiated by List et al. with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction (Scheme 3.4).[20] Although L-proline (**33**) was originally used for this type of catalysis, several proline derivatives and other chiral secondary amines were developed; and this catalysis strategy has been found to be a powerful tool for an impressive amount of highly enantioselective transformations.[19]

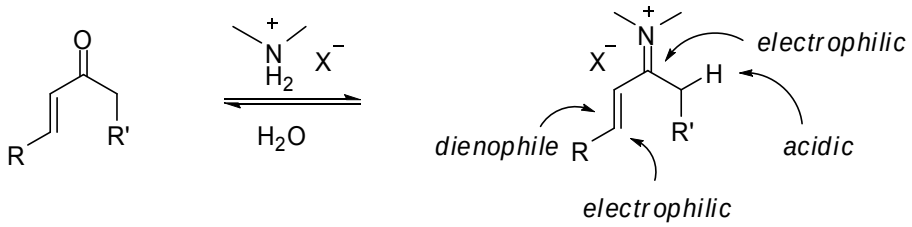


Scheme 3.3 The Hajos-Parrish-Eder-Sauer-Wiechert reaction**.**



Scheme 3.4 Proline catalyzed intermolecular aldol reaction with acetone.

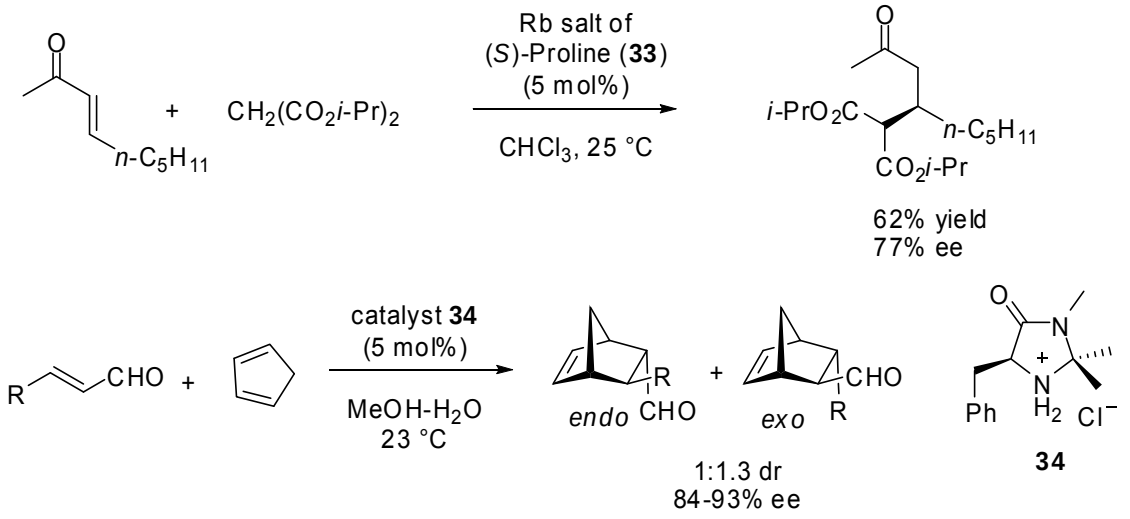
In iminium catalysis, the active species is an iminium ion formed by the reversible reaction of a primary or secondary amine catalyst with a carbonyl substrate (Scheme 3.5). The *in situ* generation of an iminium ion from a carbonyl compound lowers the LUMO energy of the system and nucleophilic additions including conjugate additions as well as pericyclic reactions are facilitated.[21]



Scheme 3.5 Iminium catalysis.

In 1993, Yamaguchi and co-workers developed the first asymmetric iminium catalytic conjugate addition reaction using a rubidium salt of proline (**33**) and good enantioselectivities were achieved (Scheme 3.6).[22a] In 2000, MacMillan and co-workers reported the first highly

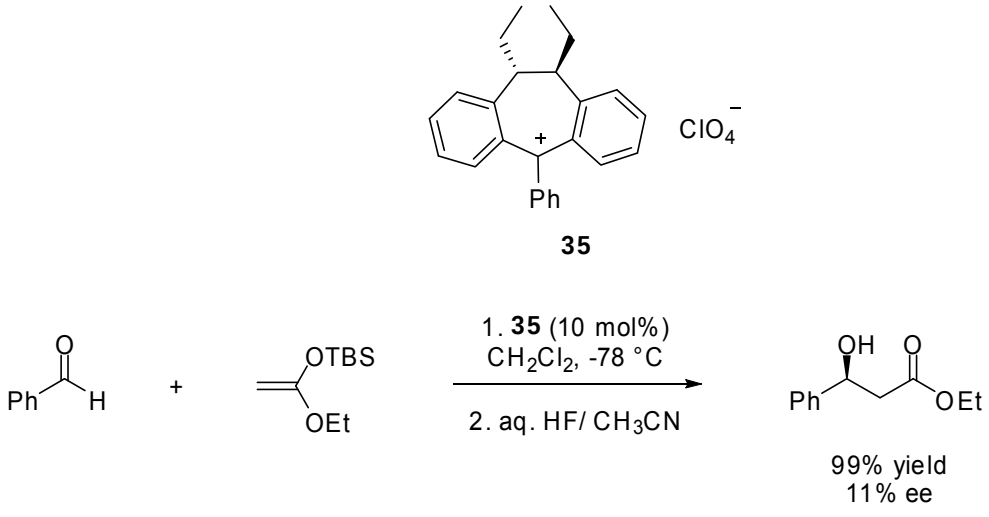
enantioselective example of the iminium catalysis strategy in the asymmetric Diels-Alder reaction (Scheme 3.6).[23] Since then 1,3-dipolar cycloadditions and nucleophilic 1,4-conjugate addition reactions using chiral secondary amines as catalysts were developed.[21] The combination of these two catalysis principles (i.e. enamine and iminium catalysis) in tandem sequences has also recently been developed.[24]



Scheme 3.6 Iminium catalytic asymmetric reactions.

Lewis Acid Catalysis

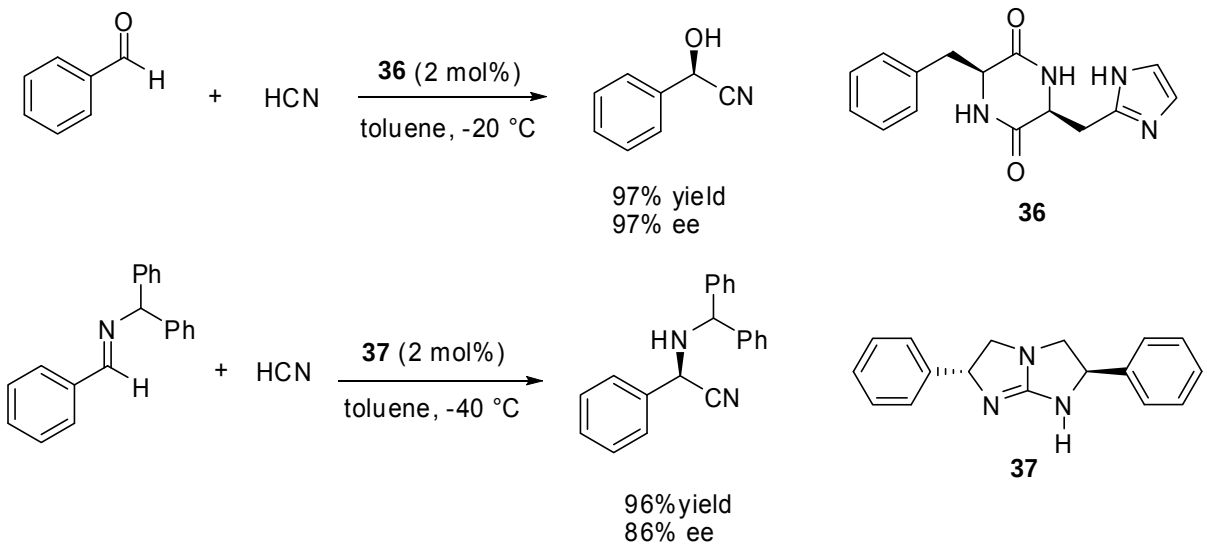
Triarylcarbenium ions are an interesting class of Lewis acid organic catalysts.[25] Chen and co-workers reported the first chiral triarylcarbenium catalyst **35** and applied it for an asymmetric Mukaiyama aldol reaction (Scheme 3.7).[25c]



Scheme 3.7 Chiral triarylcarbenium-ion-catalyzed Mukaiyama aldol reaction.

Brønsted Base Catalysis

Typical initial examples of organic Brønsted base catalysis in asymmetric synthesis are hydrocyanation reactions e.g. cyanohydrin synthesis and Strecker reaction. Inoue and co-workers applied cyclopeptide **36** as a catalyst for the addition of HCN to various aldehydes achieving high asymmetric inductions (Scheme 3.8).[26] Corey and Grogan reported the Strecker reaction using a synthetic chiral C_2-symmetric guanidine catalyst **37** (Scheme 3.8).[27] Though cinchona alkaloid catalysts were also previously used as chiral base catalysts, only recently they have been found to be versatile Brønsted base catalysts for different asymmetric transformations.[11]



Scheme 3.8 Brønsted base catalyzed hydrocyanation reactions.

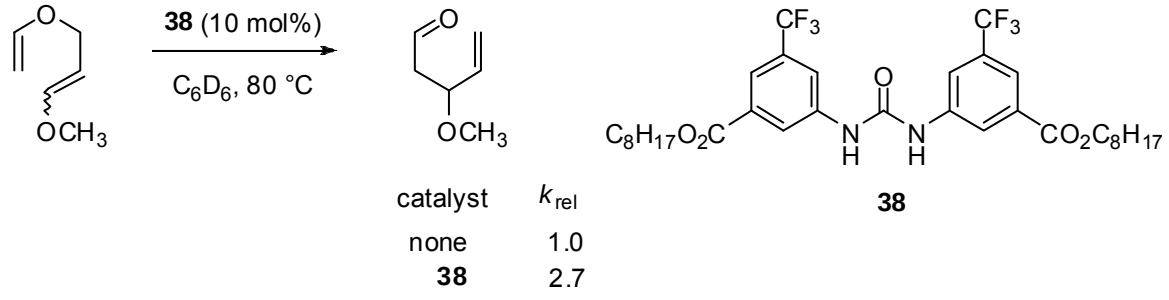
Brønsted Acid Catalysis

Chiral Brønsted acid catalysis is classified into two categories: General Brønsted acid catalysis (catalysts that partially protonate the transition state of the reaction) and Specific Brønsted acid catalysis (catalysts that are strong enough to protonate the substrate).

General Brønsted Acid Catalysis

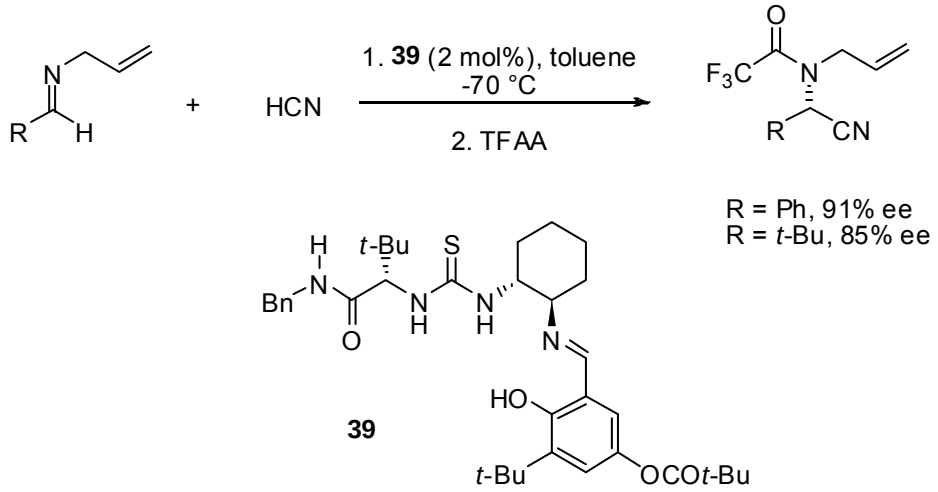
Catalysis through hydrogen bonding[28] has been considered a powerful methodology for asymmetric catalysis. This catalysis is described as general acid catalysis, as it is somewhat related to the enzymatic catalysis where H-bonding to a transition state occurs. In pioneering studies, Hine and co-workers identified *meta*- and *para*-substituted phenols and biphenylene diols as catalysts for addition of diethylamine to phenyl glycidyl ether.[29] Etter and co-

workers recognized the ability of electron-deficient diaryl ureas to form co-crystals with Lewis bases such as nitroaromatic compounds, ethers, ketones, and sulfoxides.[30] These studies provided the basis for the development of achiral thiourea-based H-bond donor catalysts. In 1994, Curran and Kuo demonstrated for the first time that urea derivatives are competent organic catalysts in the context of the allylation of cyclic sulfinyl radicals with allyltributylstannane and in the Claisen rearrangement of allyl vinyl ethers (Scheme 3.9).[31] Recently, Schreiner reported a similar thiourea catalyst **5** which could promote different chemical transformations.[32]



Scheme 3.9 Claisen rearrangement catalyzed by achiral urea.

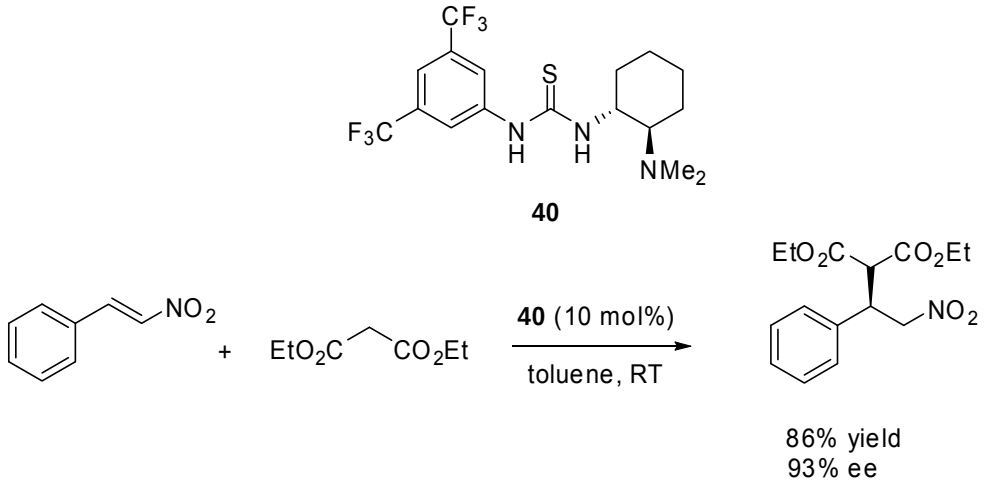
In 1998, Sigman and Jacobsen serendipitiously discovered that urea and thiourea derivatives could catalyze enantioselective hydrocyanation reactions of imines derived from both aromatic and aliphatic aldehydes (Scheme 3.10).[33] The Jacobsen group subsequently developed enantioselective Mannich,[34] hydrophosphonylation,[35] and acyl-Pictet-Spengler[36] reactions using urea and thiourea catalyst-motifs. These catalysts seem to activate the imine



Scheme 3.10 Thiourea catalyzed asymmetric Strecker reaction.

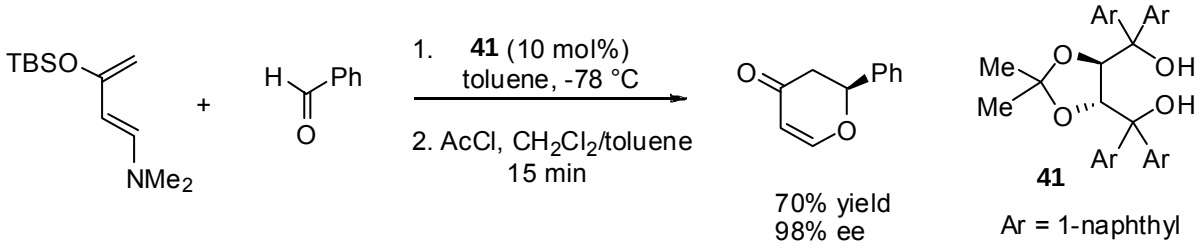
substrate by forming hydrogen bonds from the urea hydrogens to the imine nitrogen in a bridging mode.

Takemoto and co-workers demonstrated that chiral thiourea derivatives with neighbouring tertiary amino groups function as bifunctional organic catalysts activating imines and nitro compounds for enantioselective aza-Henry[37] and Michael[38] reactions. The thiourea moiety is assumed to interact with the nitro group or the imine via hydrogen-bonding activation and the neighbouring tertiary amino group activates the nucleophile. For example, nitroolefins react with malonates in the presence of catalyst **40** forming the corresponding Michael adducts with up to 93% ee (Scheme 3.11).



Scheme 3.11 Bifunctional thiourea catalyzed Michael reaction.

Rawal and co-workers[39] discovered that chiral alcohols could catalyze enantioselective hetero-Diels-Alder reaction of aldehydes with dienes. For instance, in the presence of chiral alcohol *(R,R)*-1-naphthyl TADDOL (**41**), the hetero Diels-Alder cycloadduct was formed as a single diastereomer, which was converted to dihydropyrone on treatment with acetyl chloride (Scheme 3.12). It is proposed that the OH groups of the catalyst activate the carbonyl group via hydrogen bonding.

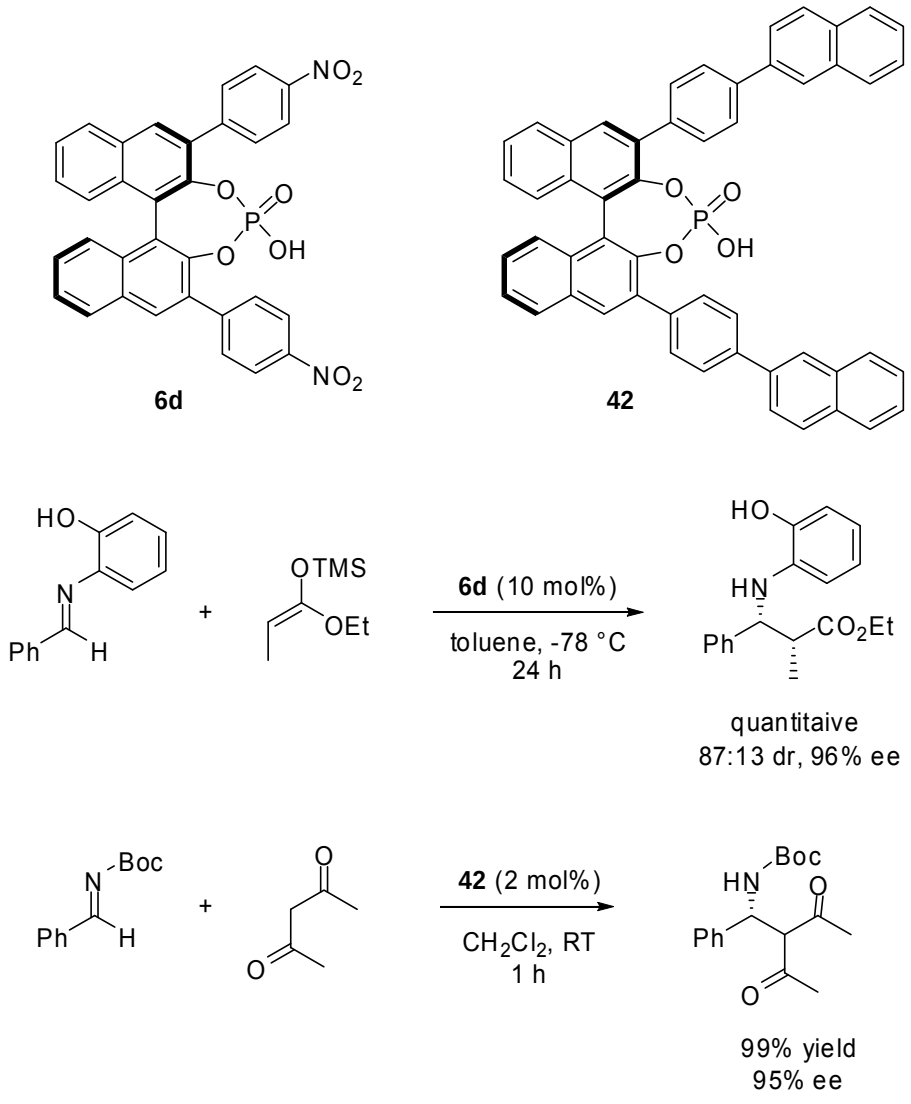


Scheme 3.12 Asymmetric hetero-Diels-Alder reaction by Rawal et al.

Specific Brønsted Acid Catalysis

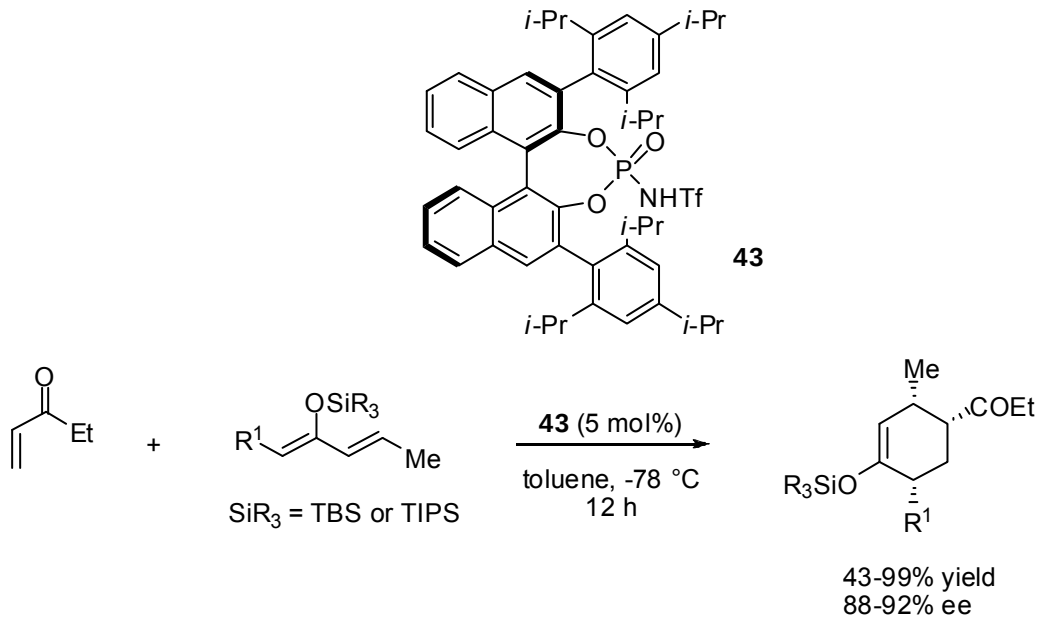
In specific Brønsted acid catalysis, stronger acids are used and function by the protonation of the substrate. The potential of using relatively strong chiral organic Brønsted acids as catalysts has been essentially ignored over the last decades. In 2004, Akiyama et al.[40] and Terada et al.[41] demonstrated in pioneering studies that relatively strong chiral binaphthol derived phosphoric acids are efficient and highly enantioselective catalysts for the Mannich reactions of aldimines (Scheme 3.13).

These chiral phosphoric acids have recently widely been utilized as efficient enantioselective catalysts for different organic transformations including the Friedel-Crafts alkylation of furan, the Diels-Alder reaction, the Pictet-Spengler reaction, the Strecker reaction and the transfer hydrogenation of imines.[42]



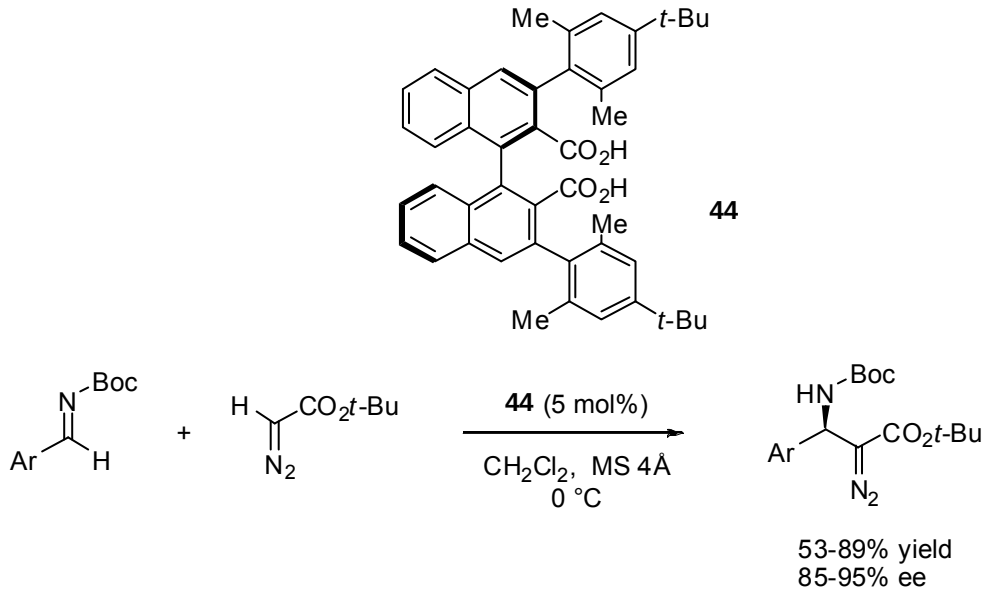
Scheme 3.13 Chiral phosphoric acids pioneered by Akiyama and Terada.

Yamamoto and co-workers designed a stronger chiral Brønsted acid in an effort to expand the substrate scope for the chiral Brønsted acid-catalyzed reactions. BINOL derived *N*-triflyl phosphoramide **43** catalyzed the Diels-Alder reaction of α,β-unsaturated ketones with electron-rich dienes to give cyclohexene derivatives with high enantioselectivities (Scheme 3.14).[43]



Scheme 3.14 Chiral *N*-triflyl phosphoramide catalyzed Diels-Alder reaction.

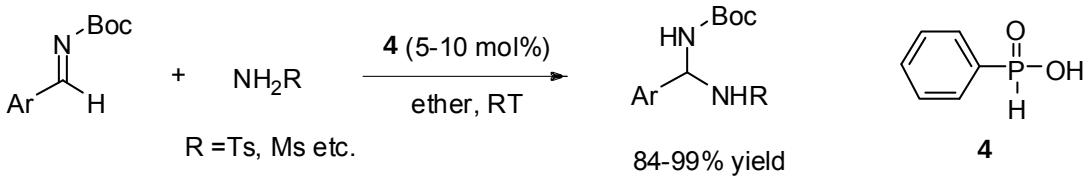
Maruoka and co-workers prepared chiral dicarboxylic acid catalyst **44**, which contains two carboxylic acids and an axially chiral binaphthyl moiety, and applied them to highly enantioselective Mannich reaction of *N*-Boc imines and diazo compounds (Scheme 3.15).[44]



Scheme 3.15 Chiral dicarboxylic acid catalyzed Mannich reaction.

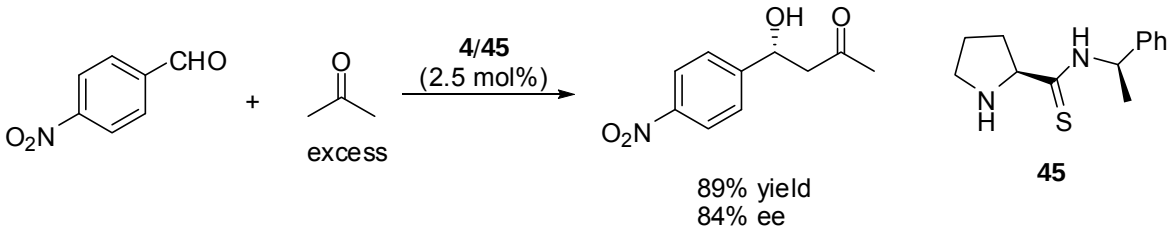
3.2 Phosphinic Acids

Hypophosphorous acid is a phosphorous oxoacid and a powerful reducing agent with the molecular formula H_3PO_2. Inorganic chemists refer to the free acid by this name (abbreviated as "HPA") although its IUPAC name is phosphinic acid. Though different types of phosphinic acids have been prepared, their use in catalysis is very rare. Recently, Antilla and co-workers used phenyl phosphinic acid **4** as a Brønsted acid catalyst for the amidation of *N*-Boc imines. With 5-10 mol% of catalyst **4**, good to excellent yields (84-99%) were obtained for different *N*-Boc imines (Scheme 3.16).[45]



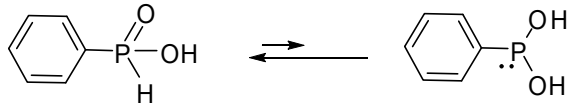
Scheme 3.16 Imine amidation developed by Antilla et al.

Very recently Gryko and co-workers used phenyl phosphinic acid **4** as an additive in the aldol reactions catalyzed by L-proline-derived thioamide **45**. With 2.5 mol% of the salt formed from **4** and **45**, the aldol product was obtained in high yield and with high enantioselectivity (Scheme 3.17).[46]



Scheme 3.17 Aldol reaction developed by Gryko et al.

Phenyl phosphinic acid **4** has been shown to have 'keto' form **4a** on the basis of NMR and infrared spectroscopy; however based on chemical evidence, Frank has suggested that this compound is a mixture of tautomers, form **4a** being the most predominant species (Scheme 3.18).[47] Reuben and co-workers found that phenyl phosphinic acid **4** undergoes exchange with deuterium solvent in both acidified ethanol-water mixtures and in aqueous alkaline solution.[48]



4a **4b**

Scheme 3.18 Tautomerization of phosphinic acid **4**.

3.3 Multicomponent Reactions

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously.[49] Such processes are of great interest, not only because of their atom-economy but also for their application in diversity-oriented synthesis, especially to generate compound sortiments for screening purposes. They are as well important because of the formation of lower level of by-products, simpler procedures, lower costs, time, and energy, as well as for the more environmentally friendly criteria.[50a]

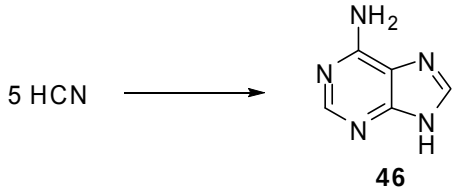
In spite of the significant useful attributes of MCRs for modern organic chemistry and their suitability for building up large compound libraries, these reactions were of limited interest in the past fifty years. However, in the last decade, with the introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focussed especially on the design and development of multi-component procedures for the generation of libraries of different compounds.

Most of the fundamental multicomponent reactions are based on deoxo-bisubstitution reactions of carbonyl compounds in which an oxo-group is displaced by two new σ-bonds. In the majority of cases, one σ-bond is connected to a nitrogen atom and another to a carbon atom. When the both new σ-bonds are C–C bonds then the process has been termed carba-acetalization.[50b]

3.3.1 History of Multicomponent Chemistry

Examples of MCRs are also abundant in nature, especially in the context of evolution. It seems that adenine **46**, one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN which is a plentiful component of the

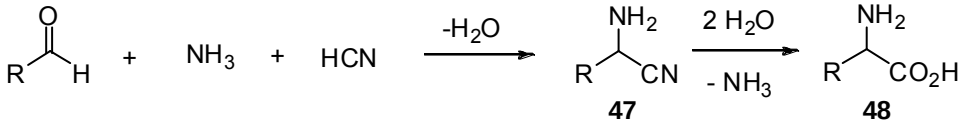
prebiotic atmosphere (Scheme 3.19).[51] The other nucleic bases have been generated in similar reactions involving HCN and H_2O.



46

Scheme 3.19 Prebiotic synthesis of adenine.

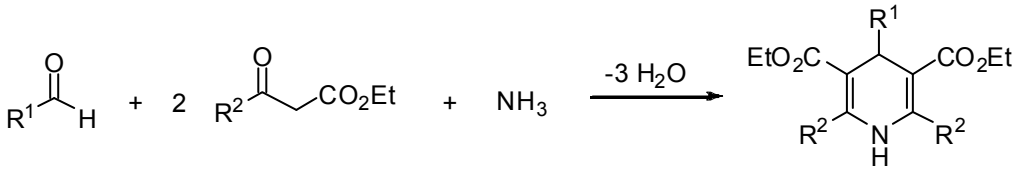
In 1850, a pioneering contribution to the development of multicomponent chemistry was made by A. Strecker.[52] The key step in the well-known Strecker synthesis of α-amino acids is the one-pot formation of α-amino nitriles **47** from aldehydes, HCN and NH_3; and this is an example of deoxo-bisubstitution reaction of aldehydes. Subsequent hydrolysis of α-amino nitriles results in α-amino acids **48** (Scheme 3.20).



47 **48**

Scheme 3.20 Strecker synthesis of α-amino acids.

Further achievement of multicomponent chemistry can be attributed to the work of Hantzsch in 1881.[53] He synthesized symmetrically substituted dihydropyridines **49** from NH_3, aldehydes and two equivalents of β-ketoesters (Scheme 3.21). This is an example of carba-acetalization reaction of aldehydes.

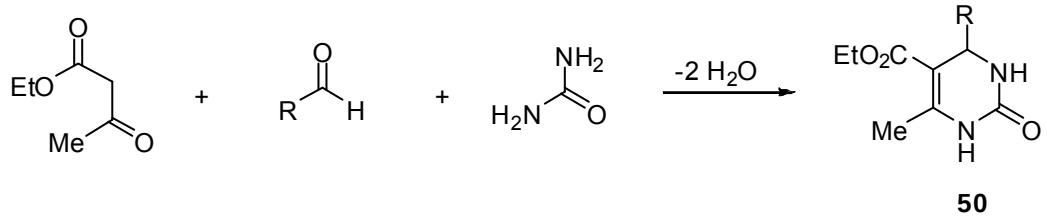


49

Scheme 3.21 Hantzsch multicomponent synthesis of dihydropyridines.

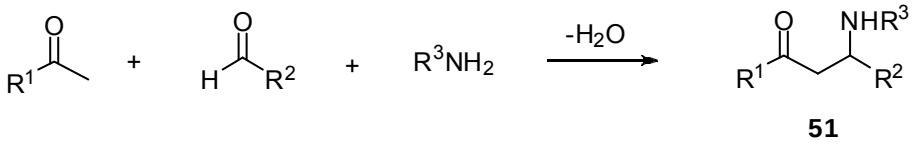
The Biginelli reaction first described in 1893, represents a multicomponent synthesis of substituted dihydropyrimidines **50** by acid-catalyzed cyclocondensation of β-ketoesters, aldehydes and urea (Scheme 3.22).[54] Like the Strecker reaction, this is a deoxo-bisubstitution

reaction of aldehydes where the C=O bond of aldehyde is displaced by a C–C σ-bond and a C–N σ-bond.



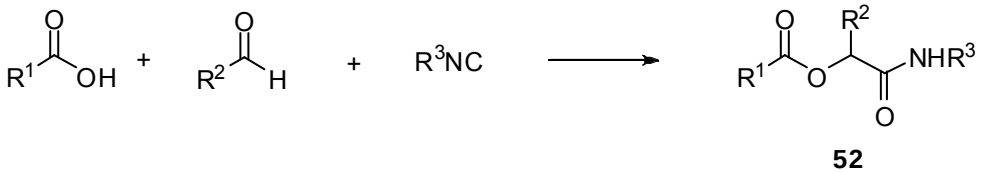
Scheme 3.22 Biginelli multicomponent synthesis of dihydropyrimidine.

In 1912, C. Mannich developed a three-component reaction between an enolizable CH-acidic carbonyl compound, an amine, and an aldehyde to produce β-amino carbonyl compounds **51** (Scheme 3.23).[55]



Scheme 3.23 Three-component Mannich reaction.

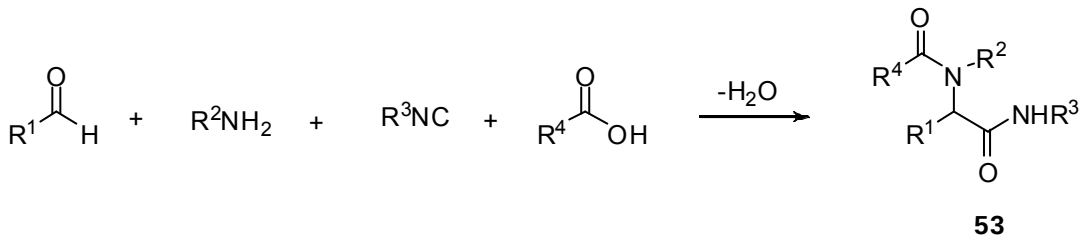
The first MCR involving isocyanides was discovered in 1921 by Passerini. Carboxylic acids, carbonyl compounds and isocyanides afforded α-acyloxy carboxamides **52** in a one-pot procedure (Scheme 3.24).[56] This is a monoaddition reaction to aldehydes where a new C–C σ-bond is formed and the C=O π-bond of aldehyde is converted to a C–O σ-bond.



Scheme 3.24 Passerini three-component reaction.

One of the most utilized multicomponent reactions was discovered in 1959 by I. Ugi.[57] Synthesis of α-acylamino amides **53** was achieved in a four-component reaction of aldehydes,

primary amines, carboxylic acids and isocyanides (Scheme 3.25). This is yet another example of a deoxo-bisubstitution reaction of aldehydes.

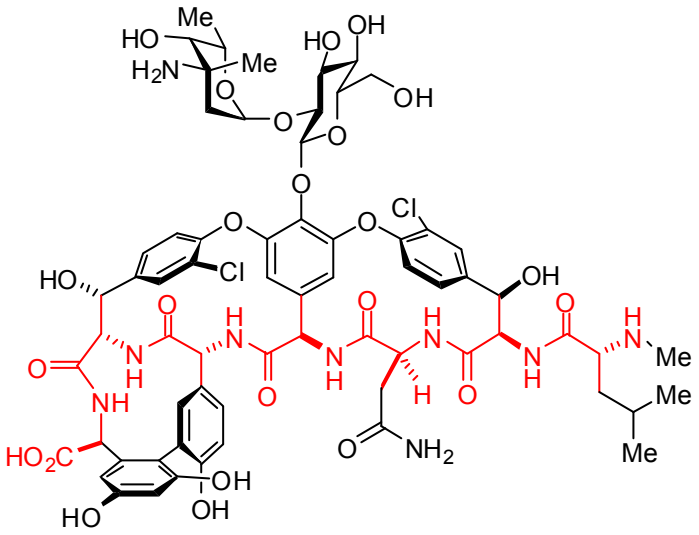


53

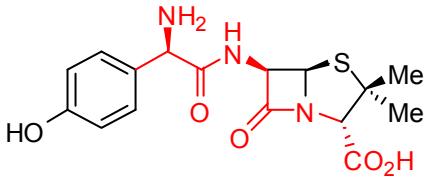
Scheme 3.25 Ugi four-component reaction.

3.4 Routes to Optically Pure α-Amino Acids

α-Amino acids are one of the five most important families of natural products[58] and are essential molecules in many scientific areas. They are continuously employed in the elaboration of peptides and proteins as chiral catalysts and as a chiral pool in the ligand design and total synthesis.[59] Amino acids are divided into two groups: proteinogenic acids and non-proteinogenic acids. Proteinogenic acids are found in proteins and the non-proteinogenic acids are not found in proteins. There are twenty common proteinogenic α-amino acids which are coded in the standard genetic code. α-Amino acids are important components in many natural and nonnatural drugs.[60] The extremely potent natural antibiotic vancomycin (**54**) and nonnatural antibiotic amoxicillin (**55**) have a vast array of nonnatural α-amino acids (Scheme 3.26).



Vancomycin **54**



Amoxicillin **55**

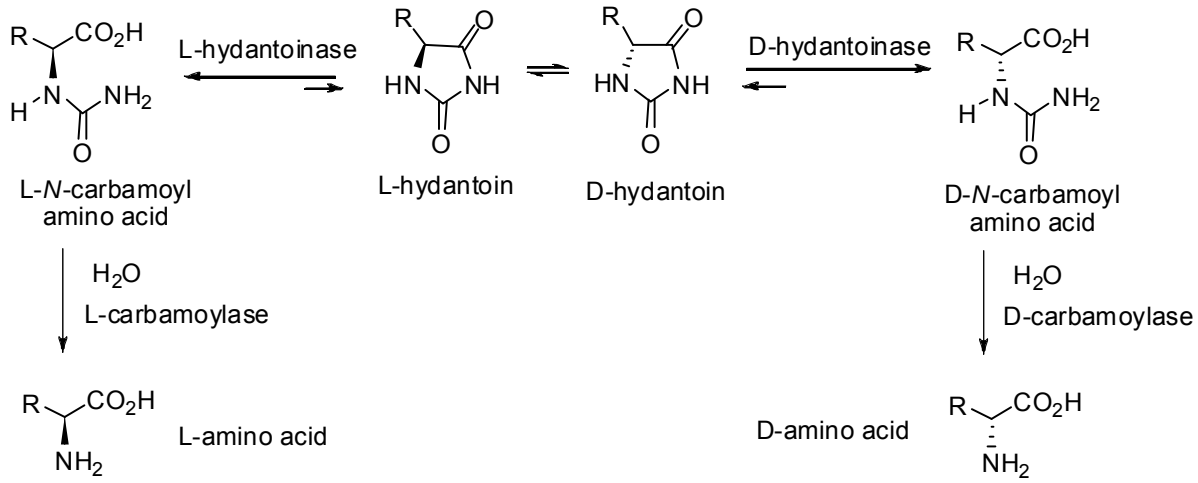
Scheme 3.26 α-Amino acid containing natural and nonnatural drugs.

Besides non-natural L-amino acids, there is also significant interest in natural or non-natural D-amino acids. Many antibiotics, pharmaceuticals and pesticides have components which consist of D-amino acids and they are found to be more active and stable compared to their L-containing analogs. Most importantly, α-amino acids are frequently used as chiral auxiliaries, organocatalysts and also as ligands for transition-metal catalysis in organic synthesis.[61,62]

The increasing demand of these optically active compounds prompted synthetic organic chemists to develop new methodologies. Basically, α-amino acids are obtained through the so-called classical methods i.e. chemical and enzymatic resolutions, isolation of α-amino acids from natural sources; and employing asymmetric synthesis. Catalytic asymmetric methods constitute the most versatile and powerful way to achieve all sorts of optically enriched α-amino acids.[63]

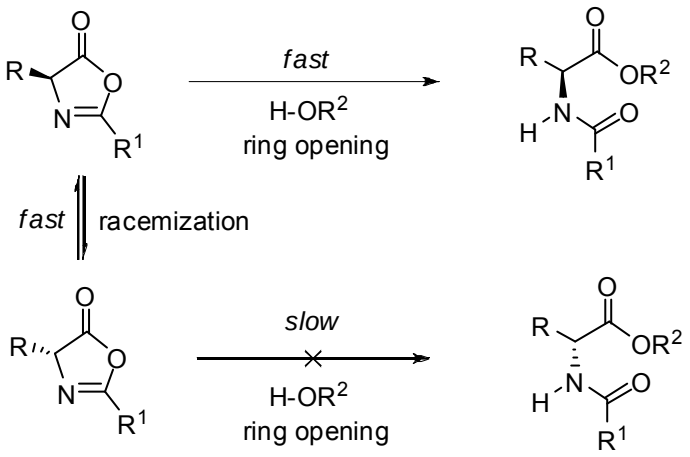
3.4.1 Resolution of Racemic α-Amino Acids

Chiral α-amino acids can be prepared from racemic α-amino acids either by dynamic kinetic resolution (DKR) or kinetic resolution (KR) of suitable intermediates. 5-monosubstituted hydantoins, cyclic ureides of α-amino acids, racemize through keto enol tautomerism, and hence were used as substrates for dynamic kinetic resolution (Scheme 3.27). Various enzymes, namely hydantoinases, facilitate the hydrolysis of hydantoins and convert them to either D- or L-*N*-carbamoyl α-amino acids (or hydantoic acid). Another enzyme known as *N*-carbamoylase catalyzes the further hydrolysis of hydantoic acid to free amino acid (Scheme 3.27).[64]



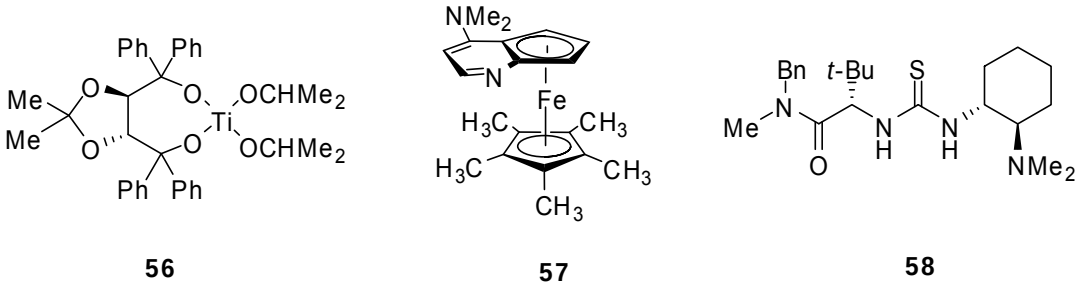
Scheme 3.27 Dynamic kinetic resolution of hydantoins.

Oxazol-5(4H)-ones, commonly known as azlactones, are useful intermediates for the synthesis of α-amino acids via DKR as they racemize through keto enol tautomerism (Scheme 3.28).



Scheme 3.28 Dynamic kinetic resolution of azlactones.

Proteases[65] and lipases[66] have been used for efficient enzymatic DKR of azlactones. In 1997, Seebach et al. showed that arylalanine-derived azlactones (R = CH_2Ar) could be resolved using titanium-taddolates **56** in combination with Al(O*i*-Pr)$_3$ in good yields and moderate enantioselectivities (up to 72% ee) (Scheme 3.29).[67] In the next year, Fu et al. found that planar-chiral DMAP derivative **57** catalyzes the DKR of azlactones (Scheme 3.29).[68] With 5 mol% of catalyst **57** and methanol as the nucleophile, enantiomeric excesses of 44-61% ee were obtained for different azlactones (R^1 = Ph, R = Alk). Berkessel and co-workers recently applied bifunctional thiourea catalyst **58** for an efficient DKR of a variety of azlactones (R^1 = Ph, R = Ar, Alk) (Scheme 3.28).[69] With 5 mol% of catalyst **58** and allyl alcohol as the nucleophile, moderate to high yields (29-94%) and high enantioselectivities (61-95% ee) were achieved.



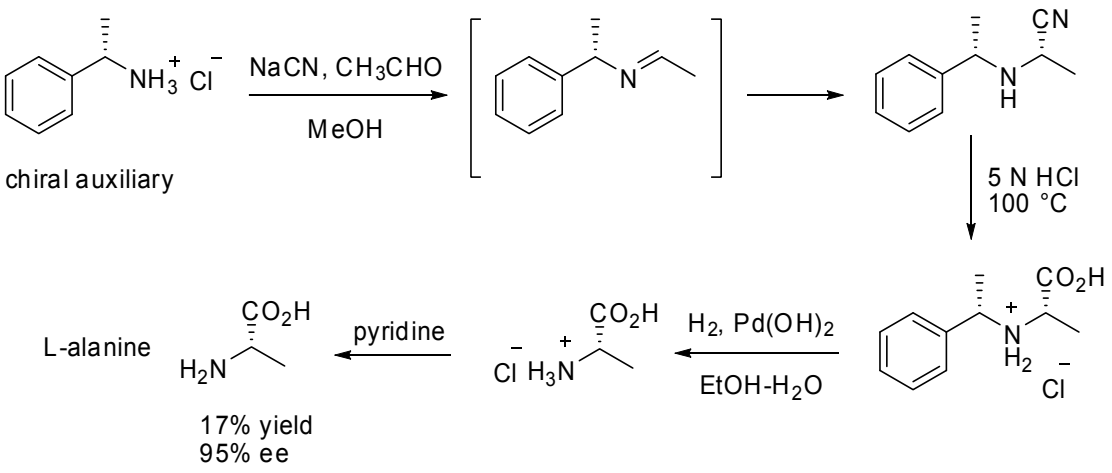
56 **57** **58**

Scheme 3.29 Chiral catalysts for the dynamic kinetic resolution of azlactones.

3.4.2 Stereoselective Synthesis of α-Amino Acids with Chiral Auxiliaries

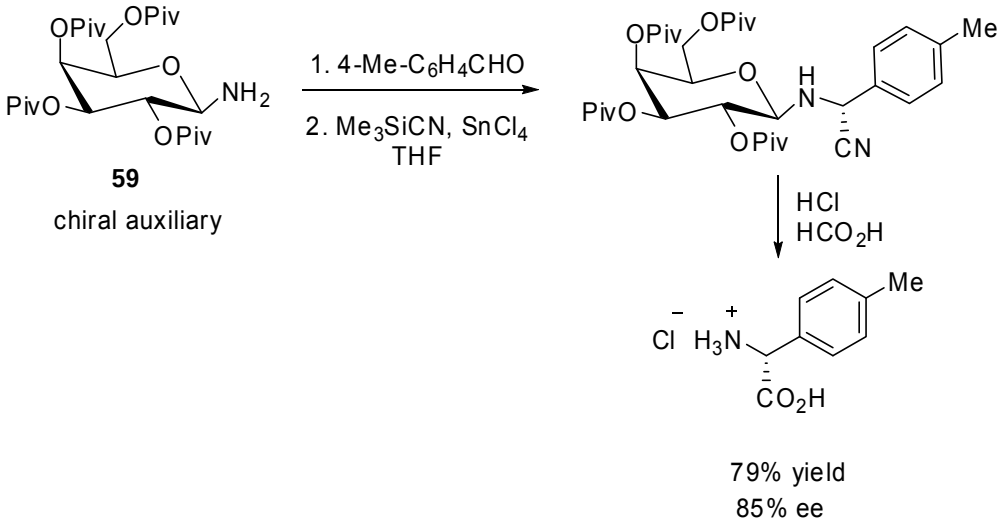
3.4.2.1 Diastereoselective Strecker Reaction

The Strecker reaction of preformed or *in situ* generated imines and hydrogen cyanide is one of the most direct and viable strategies for the synthesis of α-amino acids and their derivatives.[52] Significant progress has been made in the development of stereoselective versions of this reaction using chiral imines, derived from the reaction of aldehydes with chiral amines. In pioneering studies, Harada et al. developed the first diastereoselective Strecker reaction in the synthesis of L-alanine (95% ee) using (–)-α-methylbenzylamine as the chiral auxiliary (Scheme 3.30).[70]



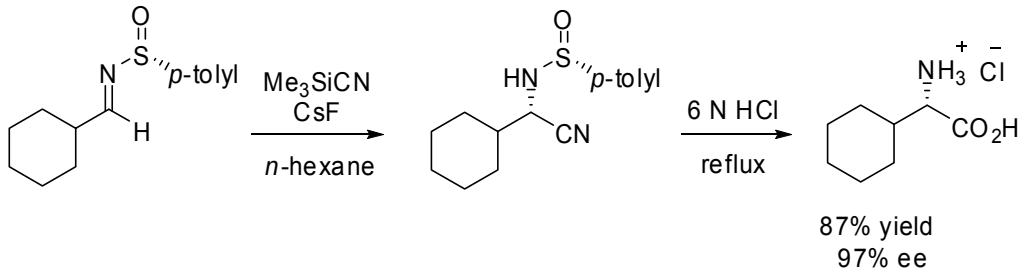
Scheme 3.30 Harada's diastereoselective synthesis of L-alanine.

Using the concept that the chirality of carbohydrates can be exploited for diastereoselective reactions, Kunz and co-workers developed a Strecker synthesis with glycosyl amines as chiral auxiliaries. In particular, 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine **59** proved to be especially effective, giving the target α-amino acids in high enantioselectivities (74-86% ee) (Scheme 3.31).[71]



Scheme 3.31 Kunz's diastereoselective synthesis of α-amino acids.

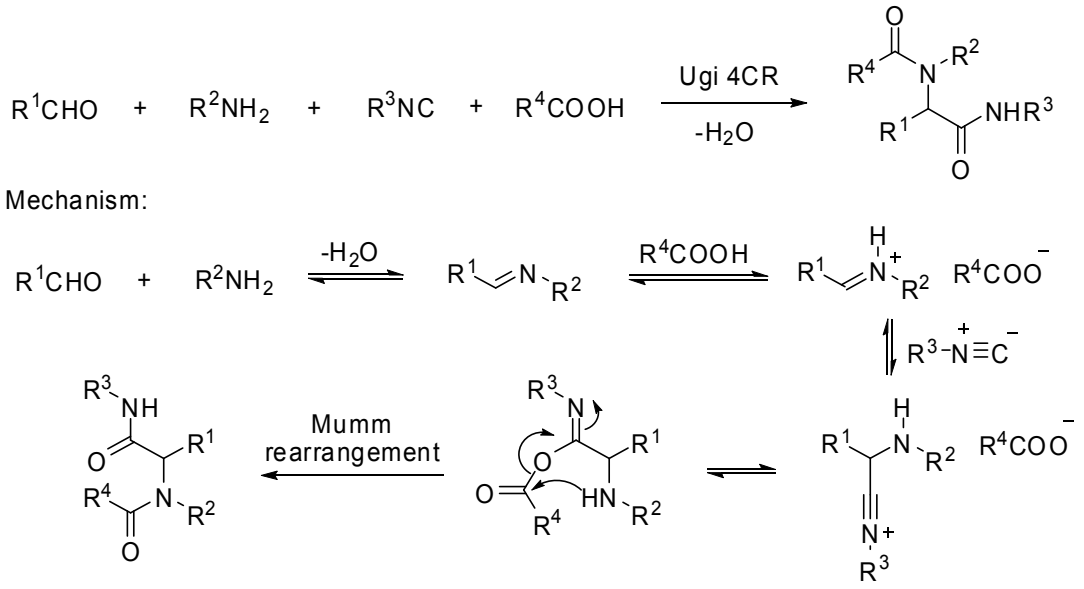
Recently Li and co-workers achieved high enantioselectivities for the asymmetric Strecker reaction using sulfinimines as the chiral imines (Scheme 3.32).[72]



Scheme 3.32 Li's diastereoselective synthesis of α-amino acids.

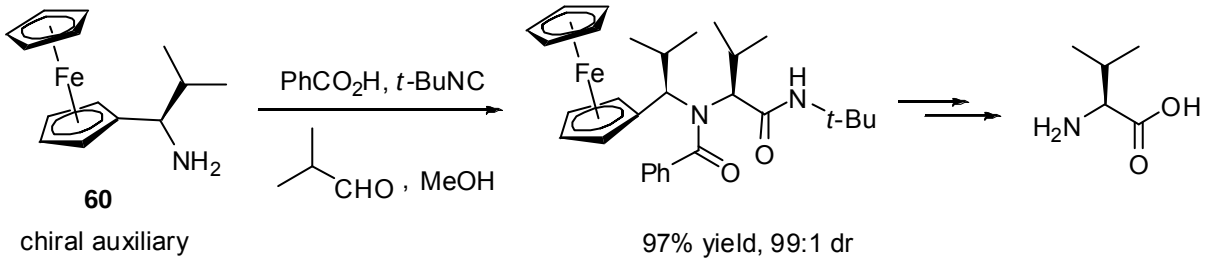
3.4.2.2 Diastereoselective Ugi Reaction

The classical Ugi reaction (Ugi 4CR) involves the interaction of an aldehyde, an amine, an isonitrile and a carboxylic acid to obtain α-acylamino amide (Scheme 3.33). The first step is the condensation of the aldehyde with the amine to give an imine which is protonated by the carboxylic acid. The isonitrile then adds to the iminium ion and a nitrilium ion is generated. Nucleophilic addition of the carboxylate ion followed by Mumm-rearrangement leads to the final product (Scheme 3.33).[57,73]



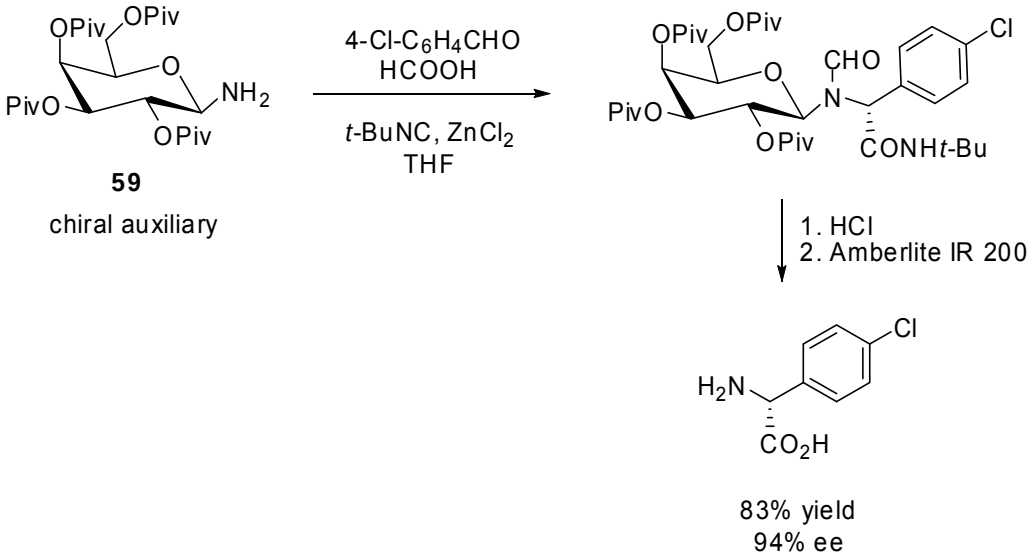
Scheme 3.33 Ugi multicomponent reaction.

To date most efforts have been carried out with chiral amines to develop a stereoselective version of this reaction. At the beginning of the 1970s Ugi et al. reported the use of (+)-α-ferrocenylbutyl amine **60** in the condensation of *iso*-butyraldehyde, benzoic acid and *tert*-butyl isocyanide and high diastereoselectivity has been achieved (Scheme 3.34).[74] However this method has a drawback that the removal of chiral auxiliary requires an acid treatment which is not always compatible with other parts of the molecule.



Scheme 3.34 Use of ferrocenylamine **60** for Ugi reaction.

Kunz et al. used chiral auxiliary **59** for the Ugi reaction and high diastereoselectivities have been obtained. In this method the chiral auxiliary could be easily removed, and aryl and heteroaryl glycine derivatives, even such ones containing sulphur or strongly acidifying moieties could be synthesized (Scheme 3.35).[75]



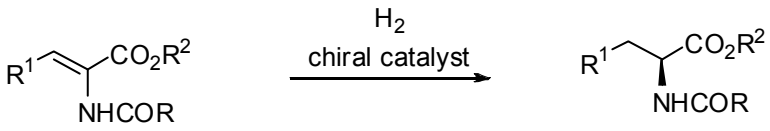
Scheme 3.35 Use of galactopyranosylamine **59** by Kunz for Ugi reaction.

Although auxiliary-based methods provide high enantioselectivities, they are not suitable for a large scale synthesis of α-amino acid because of the high cost of the auxiliary that is needed in stoichiometric quantity.

3.4.3 Catalytic Asymmetric Synthesis of α-Amino Acids

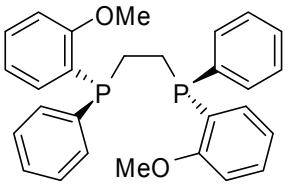
3.4.3.1 Asymmetric Hydrogenation of α,β-Didehydroamino Acid Derivatives

Asymmetric hydrogenation of α,β-didehydroamino acid derivatives was found as one of the most efficient and cost effective routes to a diverse array of natural and unnatural α-amino acids (Scheme 3.36).[76]

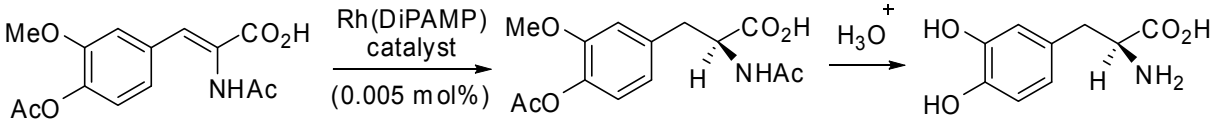


Scheme 3.36 Asymmetric hydrogenation of α,β-didehydroamino acid derivatives.

The pioneering work of enantioselective hydrogenation was done by Knowles in 1968 for the synthesis of L-Dopa using DiPAMP-Rh complex (Scheme 3.37).[77] Since then, many efforts to develop suitable chiral ligands for the general enantioselective hydrogenation have been



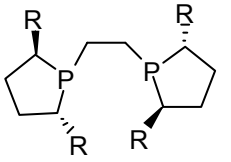
DiPAMP **61**



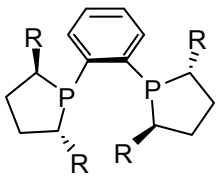
100% yield, 98% ee L-Dopa

Scheme 3.37 L-Dopa synthesis by Knowles.

made. Among others, the work of Horner[78] using P-stereogenic ligands and Kagan[79] employing C_2-symmetric chiral phosphines are notable. Cationic rhodium complexes of the type $[(diene)Rh(diphosphine)]^+X^-$ (diene = 1,5-cyclooctadiene or norboradiene, diphosphine = chiral diphosphine, X = non-coordinating anions like BF_4, SbF_4) have been found to be the most efficient and highly enantioselective catalyst precursors for α-enamide hydrogenation. An important fact about this reaction is that high enantioselectivities have been primarily obtained for *Z*-α-enamide substrates. The *E*-α-enamide isomer in general gives poor enantioselectivity. Although DiPAMP (**61)** appeared to be the most commonly used ligand, more recent studies showed that BPE (**62**) and particularly DuPHOS (**63**) are better than other ligands for rhodium catalyzed asymmetric hydrogenation of enamides (Scheme 3.38).[80]



BPE **62**



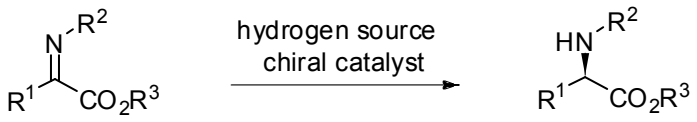
DuPHOS **63**

Scheme 3.38 Chiral bis(phosphines) ligands for Rh-catalyzed asymmetric hydrogenation.

Rhodium catalysts derived from the Me-DuPHOS (**63**, R = Me) and Et-DuPHOS (**63**, R = Et) ligands have also been shown to be highly efficient for providing excellent enantioselectivities in the hydrogenation of a wide variety of β,β-disubstituted α-enamides[81] and substrate to catalyst ratios as high as 50000:1 have been observed.

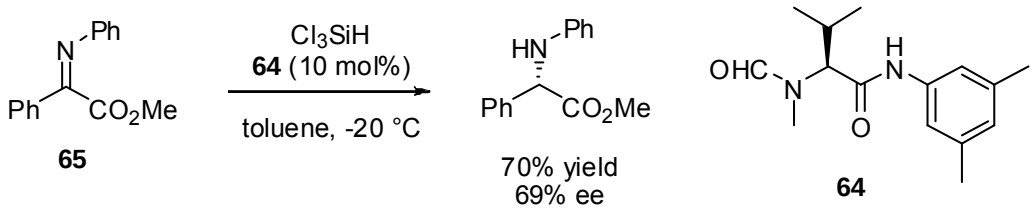
3.4.3.2 Asymmetric Reduction of C=N Bond onto α-Imino Esters

The asymmetric reduction of C=N double bond present in a ketimine is one of the most useful transformations for the prepapartion of chiral secondary amines. In particular, reduction of α-imino esters is an attractive route for the synthesis of α-amino acids (Scheme 3.39).



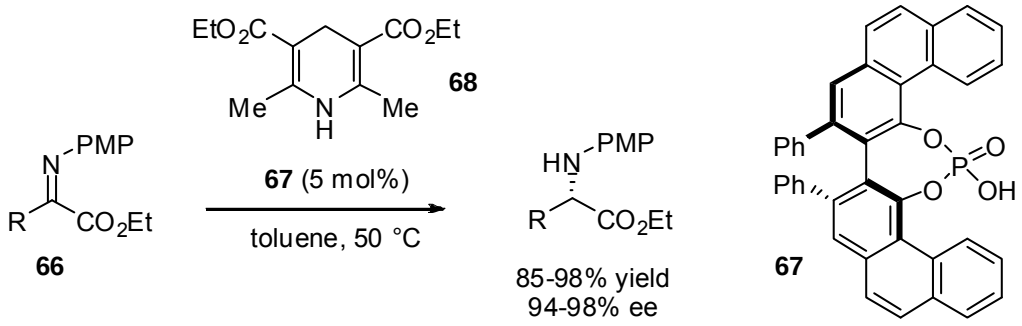
Scheme 3.39 Asymmetric reduction of α-imino esters.

In recent years, organometallic and organocatalytic reduction of α-imino esters have been reported.[82-84] The reduction of α-imino ester derivatives have been published using chiral transition metal complexes of Rh, Ir, Pd and Ru with chiral diphosphines, giving good enantioselectivities.[82] A metal-free hydrosilylation protocol has also been recently applied to the synthesis of α-amino acids. Valine derived catalyst **64** was found to be a moderately enantioselective catalyst in the hydrosilylation of α-imino ester **65** (Scheme 3.40).[83]



Scheme 3.40 Asymmetric hydrosilylation of imines.

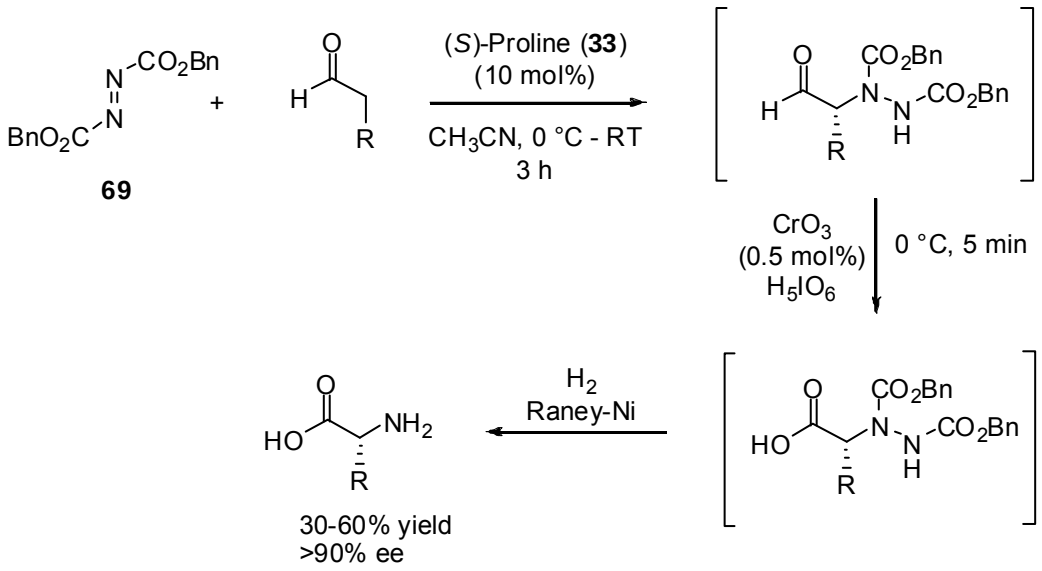
Antilla and co-workers recently reported an organocatalytic asymmetric transfer hydrogenation of α-imino ester **66** using VAPOL-derived chiral phosphoric acid catalyst **67** and commercially available Hantzsch ester **68**. Using 5 mol% of catalyst **67**, good to excellent yields (85-98%) and excellent enantioselectivities (94-98% ee) have been obtained for different aryl and alkyl substituted α-imino esters (Scheme 3.41).[84]



Scheme 3.41 Biaryl phosphoric acid catalyzed reduction of α-imino esters.

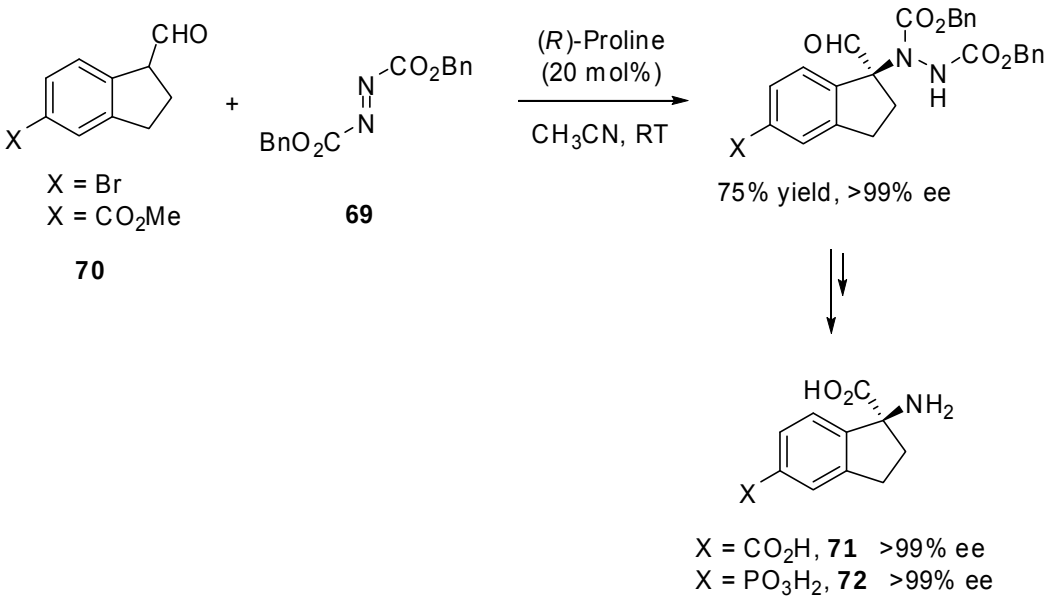
3.4.3.3 Electrophilic Amination

One of the most direct and simple approaches to α-amino acids is the amination of enolates with nitrogen containing electrophilic reagents like diazodicarboxylate.[85] Through enamine mechanism, proline was found to be a powerful organocatalyst for the electrophilic amination of aldehydes and ketones. In 2002, List[86] and Jørgensen et al.[87] independently developed the first organocatalytic enantioselective amination of aldehydes using proline (**33**) as the catalyst. In the method of List, dibenzyl diazodicarboxylate (**69**) was used as the electrophile and the resulting α-hydrazino aldehyde products could be easily oxidized to the carboxylic acid (Scheme 3.42). Reductive N-N bond cleavage and simultaneous protecting-group removal provided free α-amino acids in moderate yields and with high enantioselectivities (>90% ee).[86b]



Scheme 3.42 Direct catalytic asymmetric α-amination in the synthesis of α-amino acids.

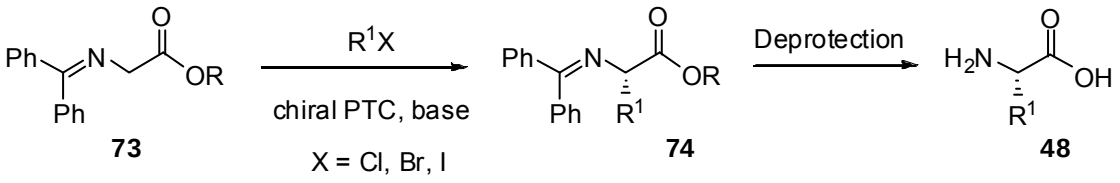
The substrate scope of the proline-catalyzed direct α-amination reaction was extended to racemic α,α-disubstituted aldehydes.[88a] Barbas and co-workers synthesized the metabotropic glutamate receptor ligands (*S*)-AIDA **71** and (*S*)-APICA **72** via the proline catalyzed reaction of diazodicarboxylate **69** with functionalized indanecarboxaldehyde **70** (Scheme 3.43).[88b]



Scheme 3.43 Synthesis of (*S*)-AIDA **71** and (*S*)-APICA **72** by Barbas et al.

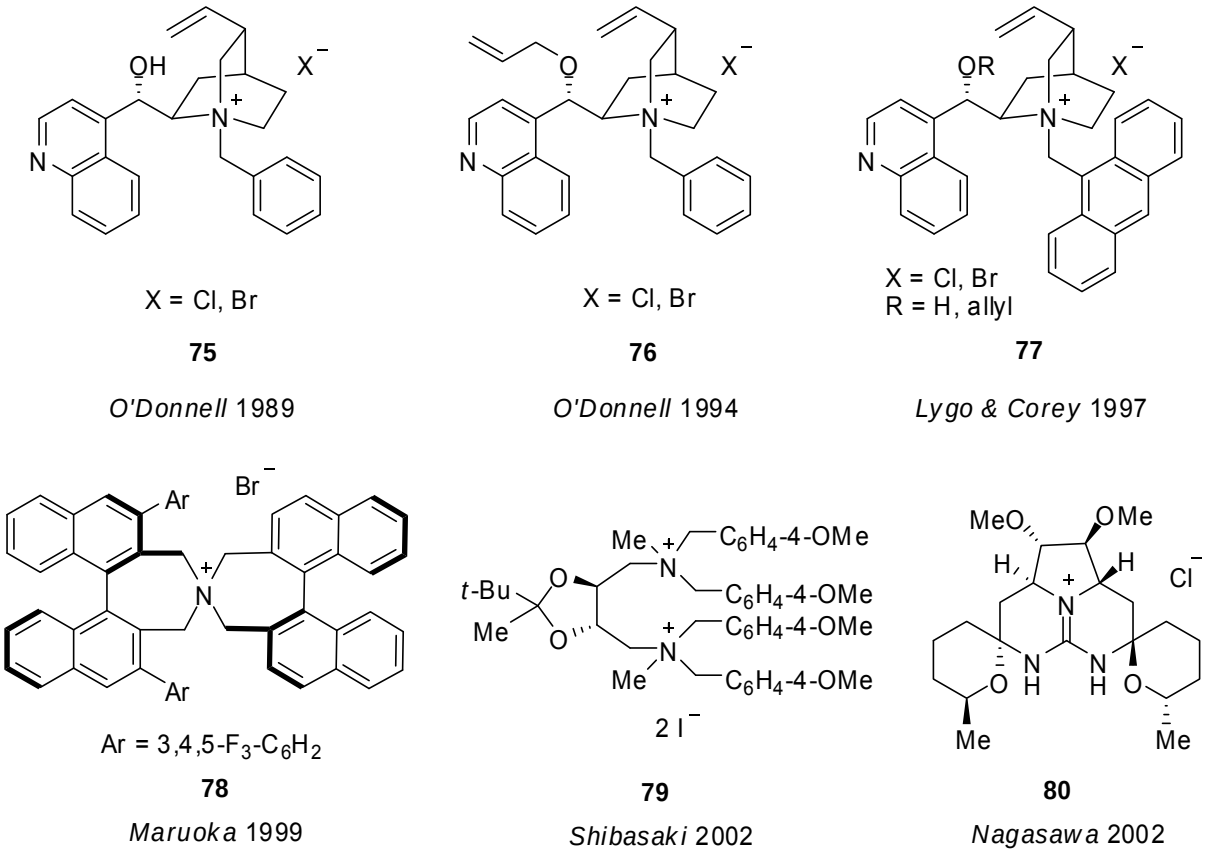
3.4.3.4 Electrophilic Alkylation of Glycine Derivatives

The electrophilic alkylation of imino glycinates is another excellent method for the preparation of chiral α-amino acid derivatives. Chiral phase-transfer (PTC) catalysts are suitable for the generation of an ion-pair with imino ester **73** facilitating the transfer of a molecule or ion from one reaction phase to another and product **74** is formed (Scheme 3.44).[89]



Scheme 3.44 Alkylation of glycine derivative **73** for the preparation of α-amino acids.

The most efficient and commonly used chiral phase transfer reagents are enantiomerically pure quaternary ammonium salts (Scheme 3.45). In 1989, O'Donnell first reported an asymmetric alkylation of glycine imine *tert*-butyl ester **73** (R = *t*-Bu in Scheme 3.44) using 10



Scheme 3.45 Selected PTC catalysts for the asymmetric alkylation of glycine derivatives.

mol% of cinchona-alkaloid derived PTC catalyst **75**; and moderate enantioselectivities (maximum 66% ee) were obtained (Scheme 3.45).[90] Few years later, the same group applied a new *O*-allylated PTC **76** for the improvement of enantioselectivities up to 81% ee.[91]

In 1997, an impressive enhancement of enantioselectivity was independently achieved by the groups of Corey[92] and Lygo[93]. They replaced the *N*-benzyl group of the O'Donnell catalyst with a 9-anthracenylmethyl group. The resulting PTCs (**77**) with either free or allylated OH were found to have the potential to give enantioselectivities >99% ee with both activated and non-activated alkyl halides as alkylating agents.

In 1999, Maruoka and co-workers developed a completely new type of structurally rigid, C_2-symmetric spiro ammonium salts **78** consisting of two chiral binaphthyl moieties, and applied them for the asymmetric alkylation of glycine imine *tert*-butyl ester **73**. In the presence of 0.2-1.0 mol% of PTC **78**, high yields (up to 98%) and excellent enantioselectivities (often 99% ee) were obtained for a wide variety of electrophiles.[94] Although these catalysts are

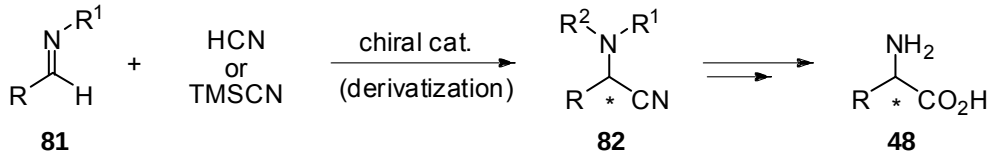
competitive to the cinchona-alkaloid derived catalysts in terms of enantioselectivities, they have drawbacks for large scale applications due to their long synthetic route and quite expensive starting materials.

In 2002, Shibasaki and co-workers reported a tartarate-derived two-centered C_2-symmetric PTC catalyst **79** for the alkylation of **73** (R = *t*-Bu in Scheme 3.44) with active halides.[95] Using 10 mol% of catalyst **79**, high yields (up to 92%) and enantioselectivities (up to 93% ee) were obtained for a wide range of substrates.

In the same year, Nagasawa and co-workers introduced a chiral C_2-symmetric pentacyclic guanidinium cation **80** for the asymmetric alkylation of **73** (R = *t*-Bu in Scheme 3.44) and with 30 mol% of **80**, different alkylated products were obtained with moderate to good yields (61-85%) and good enantioselectivities (76-90%).[96]

3.4.3.5 Catalytic Asymmetric Hydrocyanation of Imines

Catalytic asymmetric hydrocyanation of imines (Strecker reaction) is arguably the most important method for the synthesis of α-amino acids. In recent years considerable efforts have been devoted for the asymmetric versions of this reaction.[97] Most of the catalytic asymmetric methods by this route are based on the use of preformed imines **81** and subsequent addition of HCN or TMSCN in the presence of a chiral catalyst to generate **82** (Scheme 3.46). The enantioselective catalysts for the imine cyanation can be broadly divided into two major classes: chiral metal complexes and organocatalysts.



81 **82** **48**

Scheme 3.46 Catalytic enantioselective cyanation of imines.

3.4.3.5.1 Strecker Reactions Using Chiral Metal Complexes

A number of chiral Lewis acid catalysts containing different metals (e.g. aluminium, titanium, zirconium, lanthanoid etc.) have emerged as powerful catalysts for the Strecker reaction

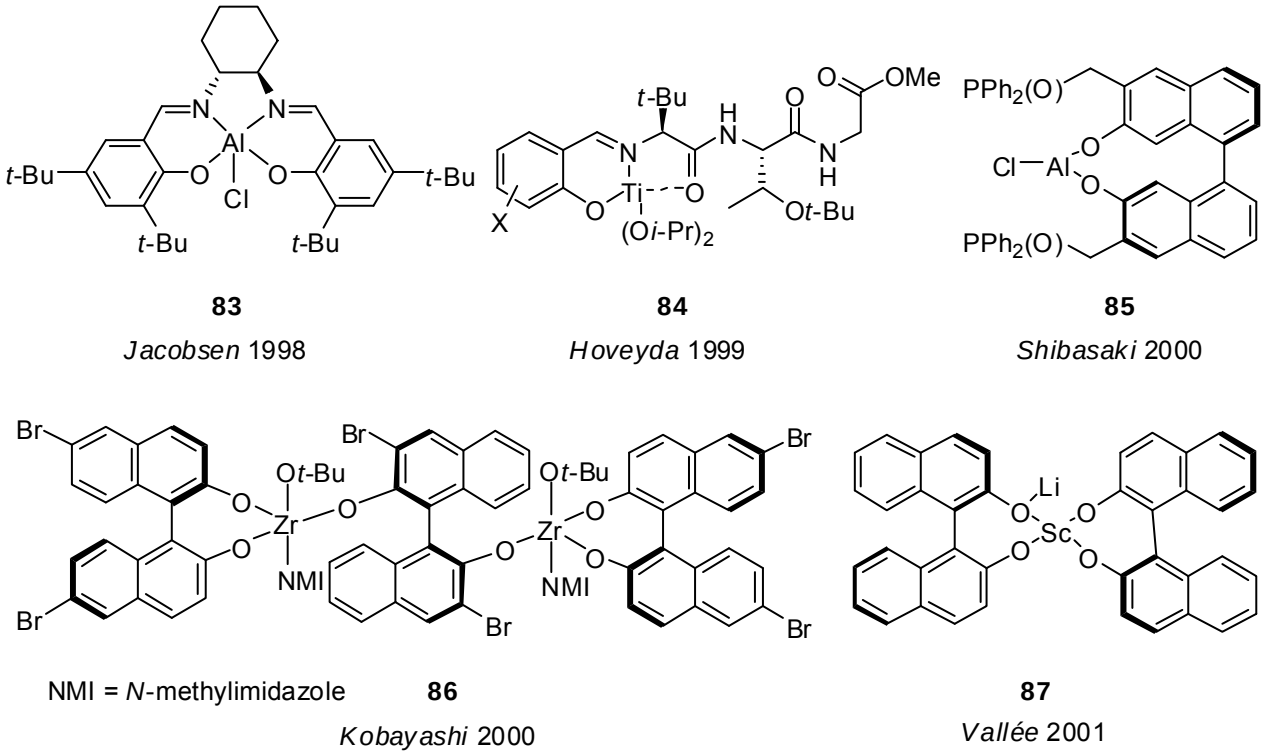
during the last few years (Scheme 3.47).[97a] In 1998, Jacobsen et al. reported the first example of a catalytic enantioselective addition of hydrogen cyanide to *N*-allyl imines **81** (R^1 = allyl) using a chiral Al(III)-salen complex **83**.[98] With 5 mol% of catalyst **83** and at −70 °C, trifluoroacetamide products **82** ($R^2 = CF_3CO$; Scheme 3.46) were isolated in good yields (69-99%) and in moderate to excellent enantioselectivities (37-95% ee). Substituted arylimines **81** (R = Ar, Scheme 3.46) are the best substrates (79-95% ee), while alkyl substituted imines gave lower enantioselectivities (37-57% ee).[98]

A year later, Snapper, Hoveyda and co-workers used Ti-complex **84** (Scheme 3.47) of a modular Schiff base ligand for the enantioselective Strecker reaction of aromatic *N*-benzhydryl imines **81** ($R^1 = CHPh_2$, Scheme 3.46) to give addition product **82** ($R^1 = CHPh_2$, R^2 =H; Scheme 3.46).[99] Using TMSCN as the cyanide source and *i*-PrOH as the additive, good to excellent enantioselectivities (85 to >99% ee) have been achieved with 5-10 mol% of **84** at 4 °C temperature. α-Amino nitriles **82** ($R^1 = CHPh_2$, R^2 =H; Scheme 3.46) are stable and can be readily converted to the corresponding amino acids with 6 N HCl by concomitant cyanide hydrolysis and amine deprotection.[99a]

Shibasaki and co-workers applied the bifunctional Lewis acid-Lewis base catalyst **85** (Scheme 3.47) for a general asymmetric Strecker reaction with a variety of aromatic, aliphatic, heterocyclic, and α,β-unsaturated *N*-fluorenyl imines.[100] With 9 mol% of catalyst **85** at −40 °C and TMSCN as the cyanide source, α-amino nitrile products **82** were obtained in good to excellent yields (80-97%) and enantioselectivities (72-95% ee). The origin of high enantioselectivity is supposed to be attributed to the simultaneous activation of imines and TMSCN by the Lewis acidic Al(III) and the Lewis basic oxygen atom of the phosphane oxide, respectively.[100]

Kobayashi et al. developed chiral zirconium binuclear catalyst **86** (Scheme 3.47) for the asymmetric synthesis of α-aminonitriles from aldimines with tributyltin cyanide (Bu_3SnCN).[101] An *ortho*-hydroxyphenyl group as an *N*-substituent of the imine **81** was found to be beneficial for high asymmetric induction. Different aromatic, aliphatic, and heterocyclic aldimines were employed and high levels of enantioselectivities (up to 91% ee) were observed. The Kobayashi group later described a direct three-component asymmetric Strecker reaction starting from aldehydes, amines and hydrogen cyanide using the same catalyst **86**.[102]

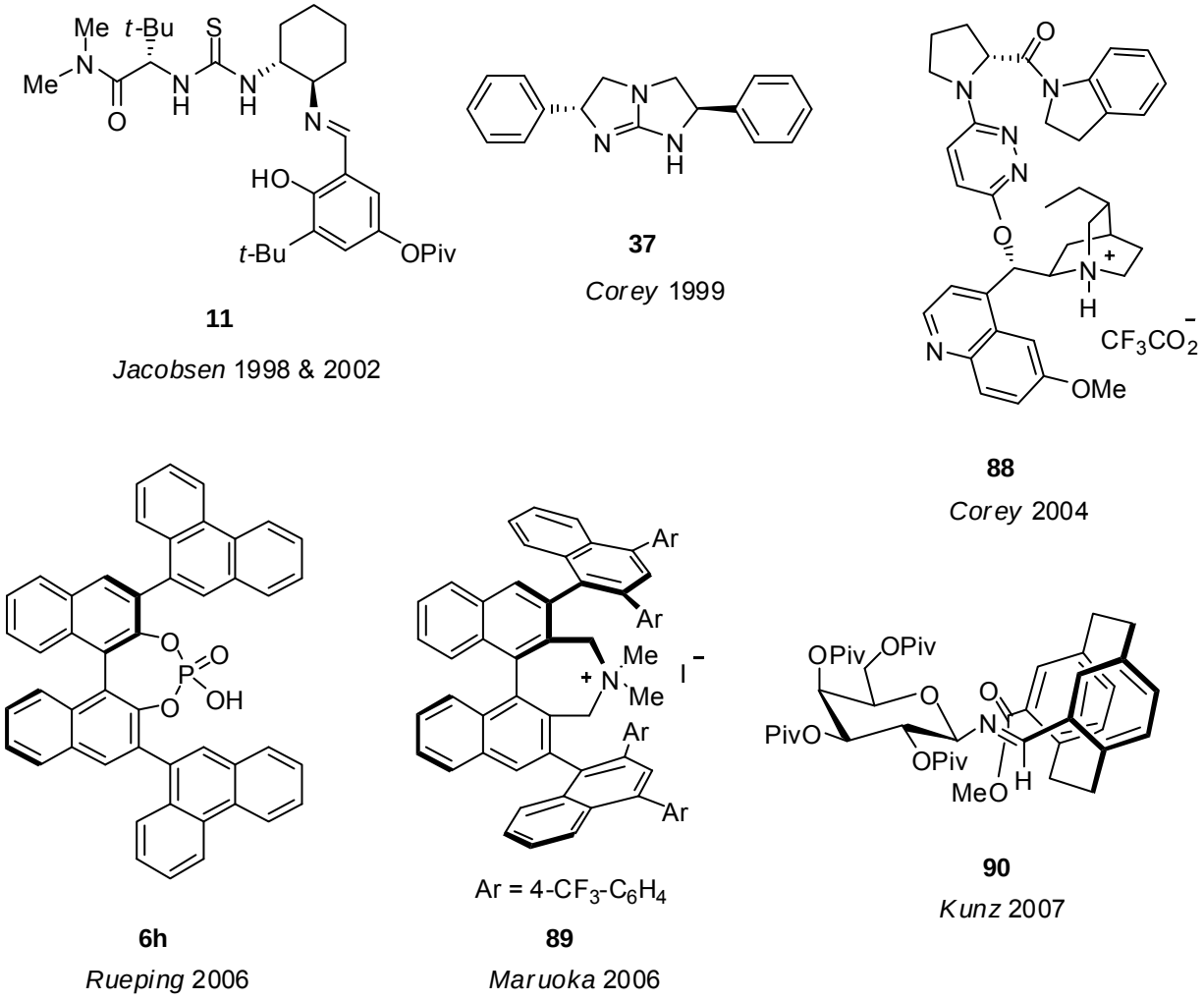
Vallée and co-workers reported the catalytic asymmetric trimethylsilylcyanation of different *N*-benzyl aldimines **81** ($R^1 = PhCH_2$, R = alkyl/aryl; Scheme 3.46) using heterobimetallic scandium complex **87** (Scheme 3.47).[103] In the presence of 10 mol% of **87**, high yield (80%) and enantioselectivity (91% ee) were obtained for *N*-benzyl benzaldimine (R = Ph; Scheme 3.46).



Scheme 3.47 Chiral metal catalysts for the asymmetric hydrocyanation of imines.

3.4.3.5.2 Strecker Reactions Using Chiral Organocatalysts

Organocatalytic enantioselective Strecker reactions are the most successful and prolific methods to obtain α-amino acid derivatives.[97a] In 1998, Jacobsen and co-workers identified a new type of organocatalyst via high throughput screening (HTS) of resin-bound derivatives.[33] This highly modular Schiff base-(thio)urea organocatalyst **11** (Scheme 3.48) was optimized through iterative structural modification of various components. When using aliphatic as well as aromatic *N*-benzyl (also *N*-allyl) aldimines in the presence of 1 mol % of optimized catalyst **11**, excellent yields (up to 99%) and enantioselectivities in the range of 96-99% ee were obtained for trifluoroacetyl derivatized α-amino nitrile products **82** (R^2 = $COCF_3$, Scheme 3.46).[33,104] An interesting process development study was carried out by the Jacobsen group for the synthesis of the aliphatic α-amino nitrile (R = *t*-Bu, Scheme 3.46), and demonstrated that the recycling of a resin-bound version of catalyst **11** can be successfully done. They have also reported a very detailed structural and mechanistic study for the hydrocyanation reaction. It is believed that the imine was activated by the reversible binding of its *Z*-isomer to the catalyst through bifurcated hydrogen bonding from



Scheme 3.48 Chiral organocatalysts for the asymmetric Strecker reaction.

the thiourea NHs and the addition of HCN takes place over the diaminocyclohexane portion of the catalyst.[104b]

In 1999, Corey and Grogan reported a C_2-symmetric bicyclic guanidine as an efficient catalyst for the addition of hydrogen cyanide to *N*-benzhydryl imines **81** (R^1 = $CHPh_2$, Scheme 3.46).[27] In the presence of 10 mol% of **37**, different aromatic and aliphatic *N*-benzhydryl imines underwent hydrocyanation reaction to afford products in high yields (88-99%) and high enantioselectivities (up to 86% ee). In contrast to the high enantioselectivities achieved with imines bearing *N*-benzhydryl substituent, remarkably lower asymmetric induction (0-25% ee) was observed for the other types of *N*-substituents like *N*-benzyl or *N*-(9-fluorenyl). The hydrogen atom (attached to the nitrogen atom of the guanidine) is essential for the catalytic activity as it was found that the *N*-methylated catalyst is inactive. In the mechanism, it was proposed that the hydrogen atom of the guanidine binds the nitrogen of the imine bond in the transition state.[27] Guanidine catalyst **37** can be easily recovered from the crude reaction mixture by extraction with oxalic acid (80-90% yield).

In 2004, the Corey group reported another type of catalyst, namely a chiral ammonium salt **88**, formed by a dihydroquinidine fragment and a segment derived from L-proline, for the hydrocyanation reaction of different *N*-allyl aromatic aldimines (R^1 = allyl, Scheme 3.46).[105] With 10 mol% of **88** and at −70 °C, the corresponding trifluoroacetyl derivatized (*S*)-α-amino nitrile products ($R^2 = COCF_3$, Scheme 3.46) were isolated in high yields (86-98%) and with good to excellent enantioselectivities (79 to >99% ee). The choice of the *N*-substituent is also important here as the *N*-benzyl or *N*-benzhydryl aldimines provided products with lower enantioselectivities.[105] A polar ionic hydrogen-bonding activation of the imine by the protonated quinuclidine core is proposed such that the aryl imine is held within the pocket formed by the dihydroindole and quinoline rings of the catalyst. Dichloromethane was the favoured solvent over toluene, presumably due to the ability of toluene to compete with the aldimine substrate for the U-shaped binding pocket.

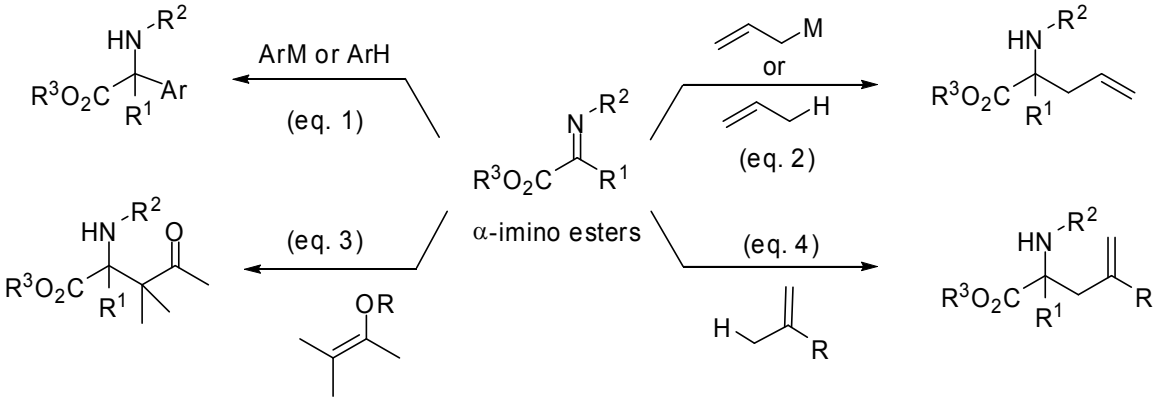
In 2006, Rueping and co-workers reported the Strecker reaction of different *N*-benzyl aldimines with chiral phosphoric acid catalyst **6h** (Scheme 3.48).[106] In the presence of 10-mol% of the catalyst, hydrocyanation occurred with a series of *N*-benzyl aromatic aldimines and the α-amino nitrile products were isolated as their trifluoroacetyl derivatives ($R^2 = COCF_3$, Scheme 3.46) in moderate to high yields (50-97%) and with good to excellent enantioselectivities (85 to 99% ee). A significant difference in enantioselectivity has been observed by the subtle changes of the 3,3'-substituents of the catalyst.[106]

In the same year, Maruoka and co-workers developed an alternative approach by using nonvolatile potassium cyanide in a highly enantioselective phase-transfer-catalytic asymmetric Strecker reaction of *N*-sulfonylated aldimines ($R^1 = SO_2Mes$, Scheme 3.46).[107] In the presence of 10 mol% of **89**, high yields of 81-98% and enantioselectivities of 88-98% ee were obtained for different aliphatic *N*-sulfonylated aldimines after only 2-8 hours reaction time.

Recently, Kunz and co-workers developed a new type of Brønsted base organocatalyst **90** for the enantioselective Strecker reaction which consists of glycosyl amines and planar-chiral [2.2] paracyclophane derivatives (Scheme 3.48).[108] Using 10 mol% of catalyst **90**, imines derived from aliphatic aldehydes afforded products in good yields (up to 89%) with high enantioselectivities (up to 99% ee). On the contrary, the reaction with aromatic aldimines gave slightly lower enantioselectivity (maximum 82% ee). The authors have explained the mechanism of the reaction where the first step is the trapping of the proton of HCN by a Brønsted basic centre cooperatively formed by the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group present in the catalyst.[108] The aldimine could then be activated by the protonated catalyst and asymmetric cyanation takes place.

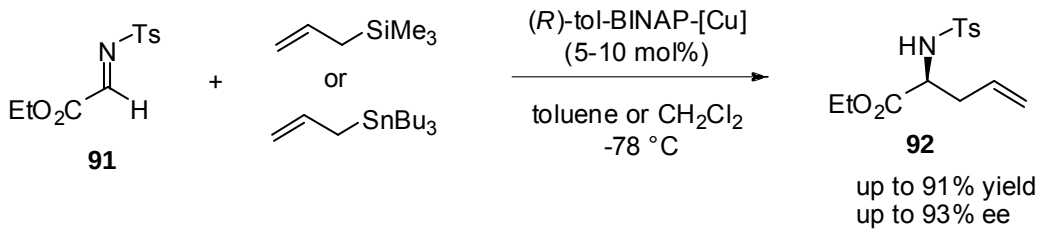
3.4.3.6 Miscellaneous Examples of α-Amino Acid Synthesis

The α-imino esters could act as versatile electrophiles providing a vast array of α-amino acid derivatives according to the general addition reactions (Scheme 3.49). Chiral organocatalysts and chiral metal complexes are found to be effective in the enantioselective addition reactions and a large amount of processes dealing with these types of asymmetric transformations are developed.[11,109]



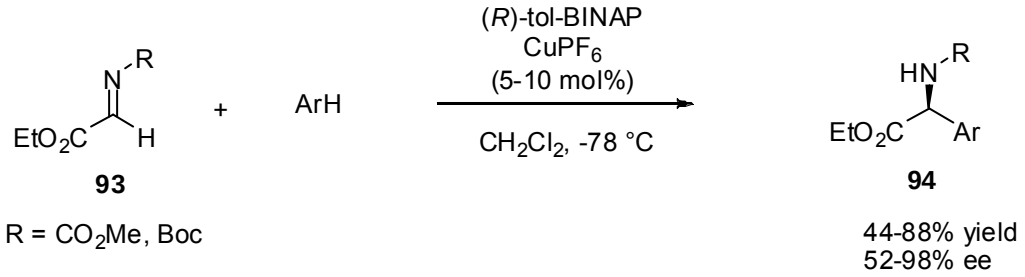
Scheme 3.49 Reaction of α-imino esters with different nucleophiles.

Allylic amino acid derivatives can be obtained by the reaction of α-imino esters with allylsilanes or stannanes. The allylation of glyoxylic *N*-tosylimines **91** was independently developed by the groups of Lectka[110] and Jørgensen[111] and with similar (*R*)-tol-BINAP-[Cu] complexes (Scheme 3.50). Lectka et al. used allylsilanes as the allylating agents whereas Jørgensen and co-workers used allylstannanes; and in both cases resulting products **92** were obtained in very high yields (up to 91% yield) and with high enantioselectivities (up to 93% ee).



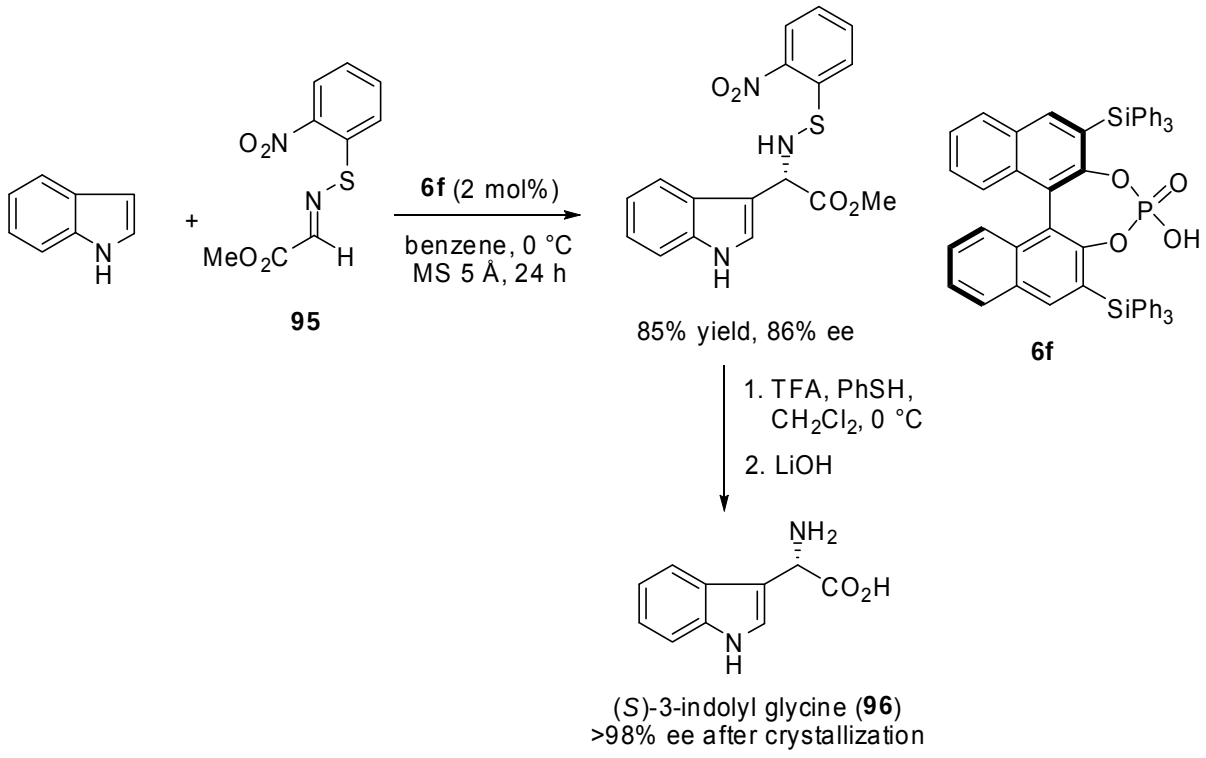
Scheme 3.50 Catalytic asymmetric allylation of glyoxylic *N*-tosylimines.

Johannsen[112] and Jørgensen[113] group independently reported a combination of $CuPF_6$ and (*R*)-tol-BINAP in the addition reactions of electron-rich aromatic compounds to α-imino esters **93** (Scheme 3.51). The reaction led to protected α-aryl α-amino acid esters **94** in good to high yields and high enantioselectivities (up to 98% ee).



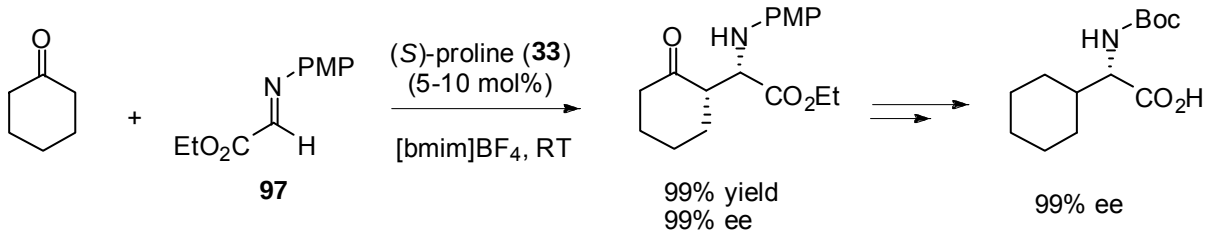
Scheme 3.51 Catalytic asymmetric arylation of α-imino esters.

Recently, Hiemstra and co-workers reported a synthesis of enantiopure (*S*)-indolylglycine (**96**) by organocatalyzed Friedel–Crafts alkylation of indole with *N*-sulfenyl imine **95** (Scheme 3.52).[114] Using 2 mol% of chiral phosphoric acid catalyst **6f**, high yield of 85% and enantioselectivity of 86% ee have been obtained.



Scheme 3.52 Organocatalytic synthesis of (*S*)-3-indolylglycine (**96**).

Organocatalytic Mannich reactions of *N*-PMP-α-imino ester **97** and aldehydes and ketones have recently been reported by different groups.[11] One of the examples developed by Barbas and co-workers employing proline (**33**) and ionic solvent [bmim]BF_4 is shown in Scheme 3.53.[115]

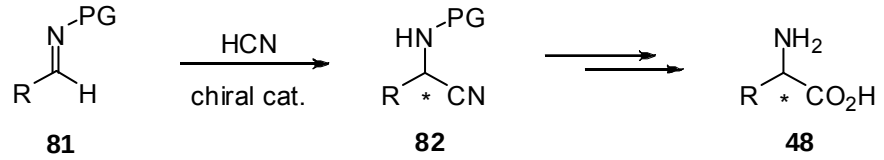


Scheme 3.53 Organocatalytic Mannich reaction of α-imino esters.

4 Concept

4.1 Use of Acyl Cyanides as Cyanide Source in the Strecker Reaction: Development of a Catalytic as well as an Asymmetric Catalytic Variant

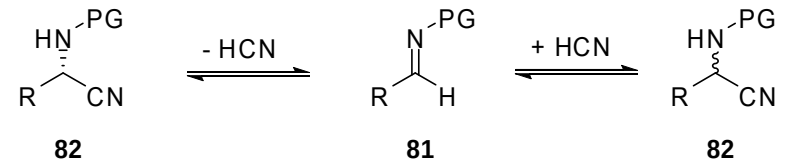
The aim of this thesis was to develop new methods for the synthesis of α-amino acids. The hydrocyanation of preformed or *in situ* generated imines **81** has been identified as one of the most efficient methods for the preparation of α-amino nitriles **82**, which are useful intermediates in the synthesis of α-amino acids **48** (Scheme 4.1).[97]



81 **82** **48**

Scheme 4.1 Asymmetric hydrocyanation of imines, PG = protecting group.

However, it has drawbacks such as HCN is very toxic and volatile. As an alternative, trimethylsilyl cyanide (TMSCN) is also used. However, due to its high toxicity and price, access to alternative cyanation reagents is desirable. Another problem with the Strecker reaction is the isolation of enantiomerically pure α-amino nitriles **82**. Due to the good leaving group ability of cyanide ion, products **82** can racemize (depending on the protecting group) via its imine precursor **81** (Scheme 4.2).



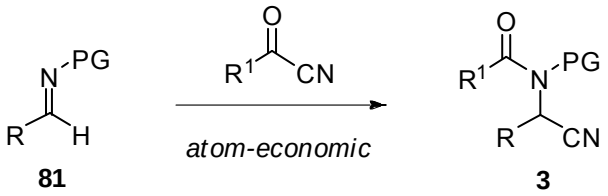
82 **81** **82**

enantiopure *racemic*

Scheme 4.2 Racemization of α-amino nitriles **82**.

Thus derivatization with trifluoroacetic anhydride (TFAA) is often required as shown by Jacobsen and co-workers.[33,104] We decided to investigate the addition reaction of

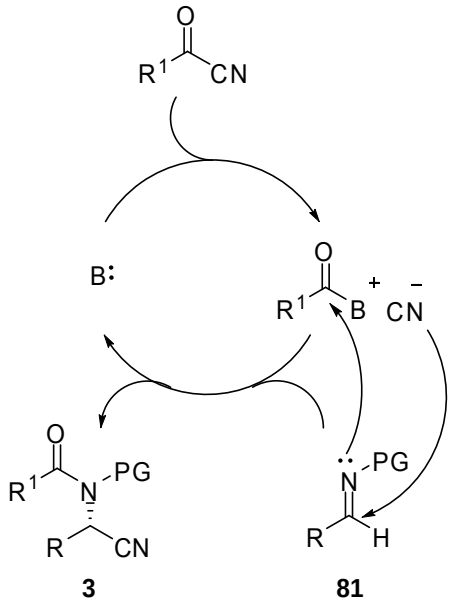
acylcyanides (R^1COCN) to imines. Acyl cyanides are useful source of cyanide ions as they are commercially available and less toxic than HCN or TMSCN. More importantly, on reaction with imines, acylcyanides would provide the stable *N*-acylamino nitriles **3** in an atom-economic fashion (Scheme 4.3).



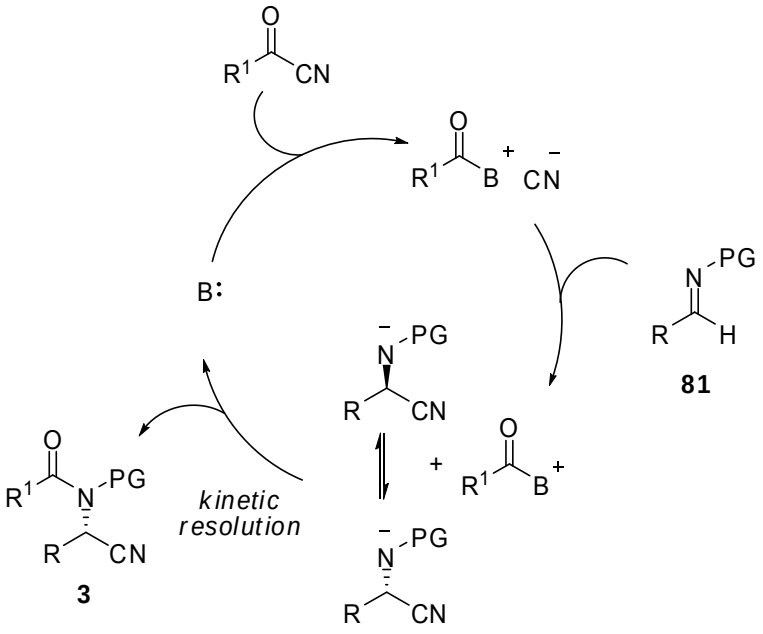
Scheme 4.3 Acylcyanation of imines.

Though acetylcyanide (R^1 = Me; Scheme 4.3) and other α-oxonitriles (R^1 = Et, Ph, OMe, OEt etc.; when R^1 = OMe, OEt then they are called cyanoformate esters) have previously been used for the acylcyanation of carbonyl compounds,[116] their reactions with imines have significantly been less studied. In 1958, Dornow and Lüpfert showed that α-oxonitriles readily react with imines to give the corresponding *N*-acylamino nitriles **3** both in the absence of a catalyst and in the presence of a catalytic amount of triethylamine.[117] A survey of the literature revealed that there are no other catalytic versions of this reaction.[118] We realized the potential of the stable *N*-acylamino nitrile products in the synthesis of α-amino acids and their derivatives. Thus the the goal of this work was to develop a catalytic as well as an asymmetric version of this rarely used reaction.

We speculated that the Lewis base catalytic acylcyanation reaction could occur in two pathways: a) the concerted acyl transfer and cyanide addition to imines **81** (Scheme 4.4); b) reversible cyanide addition to imines **81** followed by enantioselective acyl transfer by kinetic resolution (Scheme 4.5).

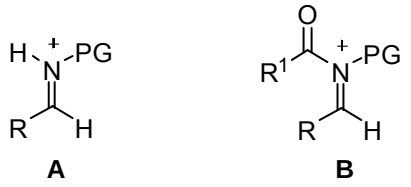


Scheme 4.4 Lewis base catalytic acylcyanation, path a.



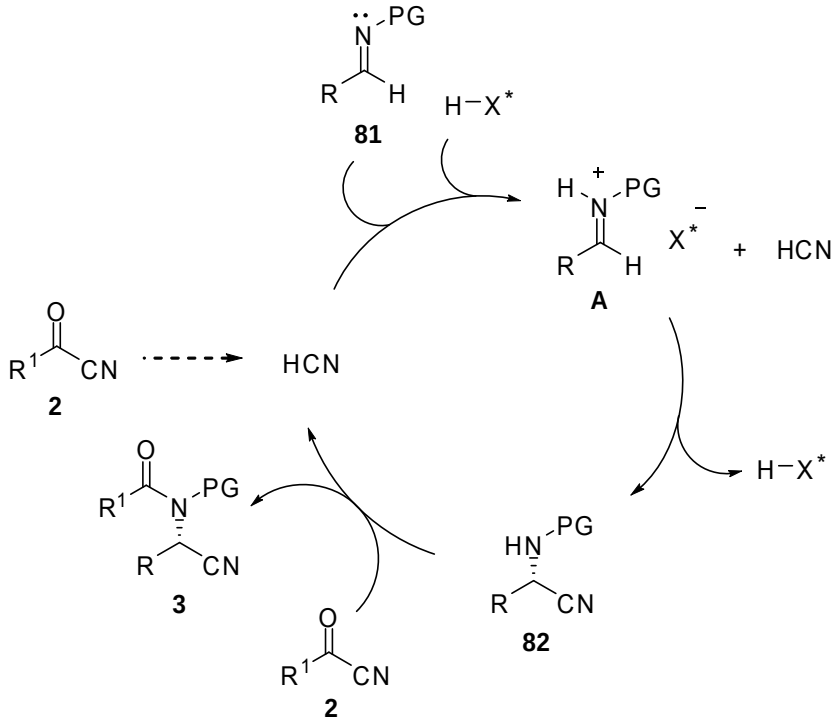
Scheme 4.5 Lewis base catalytic acylcyanation, path b.

We reasoned that in addition to base catalysis, an acid-catalyzed pathway should be possible as well. The reaction could proceed either via iminium ion intermediate **A** (if small amount of HCN is generated from acylcyanide) or *N*-acyl-iminium ion intermediate **B** resulting from the direct substitution reaction of imine **81** with acylcyanide (Scheme 4.6).



Scheme 4.6 Iminium and *N*-acyl iminium ion.

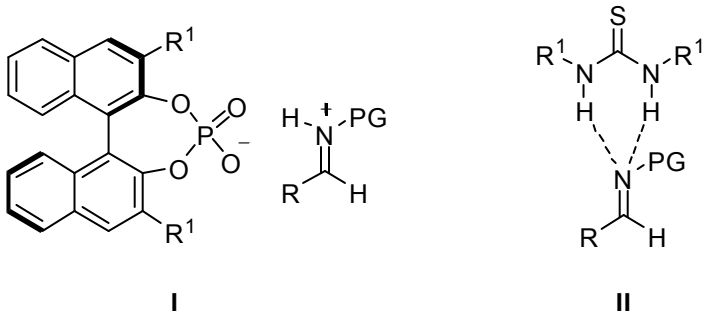
We speculated that (if HCN is present in the reaction medium) chiral Brønsted acids could react with imines **81** to generate a chiral iminium ion pair **A** which would react with HCN to provide the enantiopure α-amino nitrile **82**. α-Amino nitrile **82** then undergoes acyltransfer reaction with acylcyanide **2** to provide **3** and HCN is regenerated (Scheme 4.7).



Scheme 4.7 Acid catalytic acylcyanation mechanism, path a.

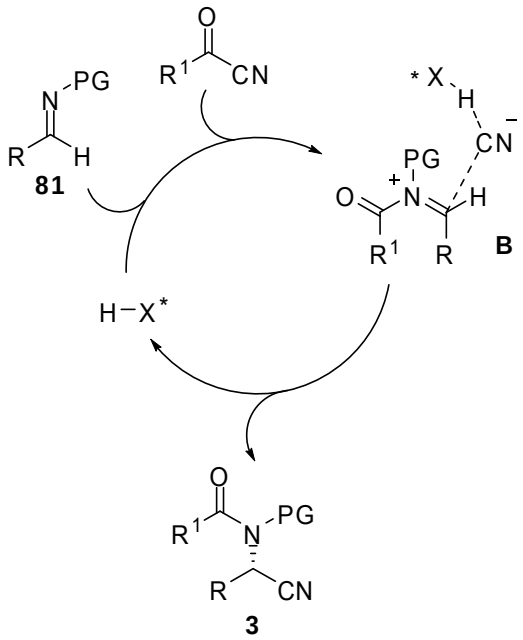
From the pioneering works of Akiyama and Terada, it was known that addition reactions to imines which proceed through iminium ion intermediate **A** could be conducted in a highly enantioselective fashion using chiral binaphthol-based phosphoric acids **6**, **42** as catalysts, because of the generation of chiral iminium-phosphate ion pair **I** (Scheme 4.8).[40-42] Similarly, the activation of imines by general Brønsted acids like urea and thiourea has been demonstrated by the group of Jacobsen.[28] Here the imines are activated by the bifurcated

hydrogen bondings from both NHs of the thiourea moiety and the nucleophilic attack to imines gets facilitated (**II** in Scheme 4.8).



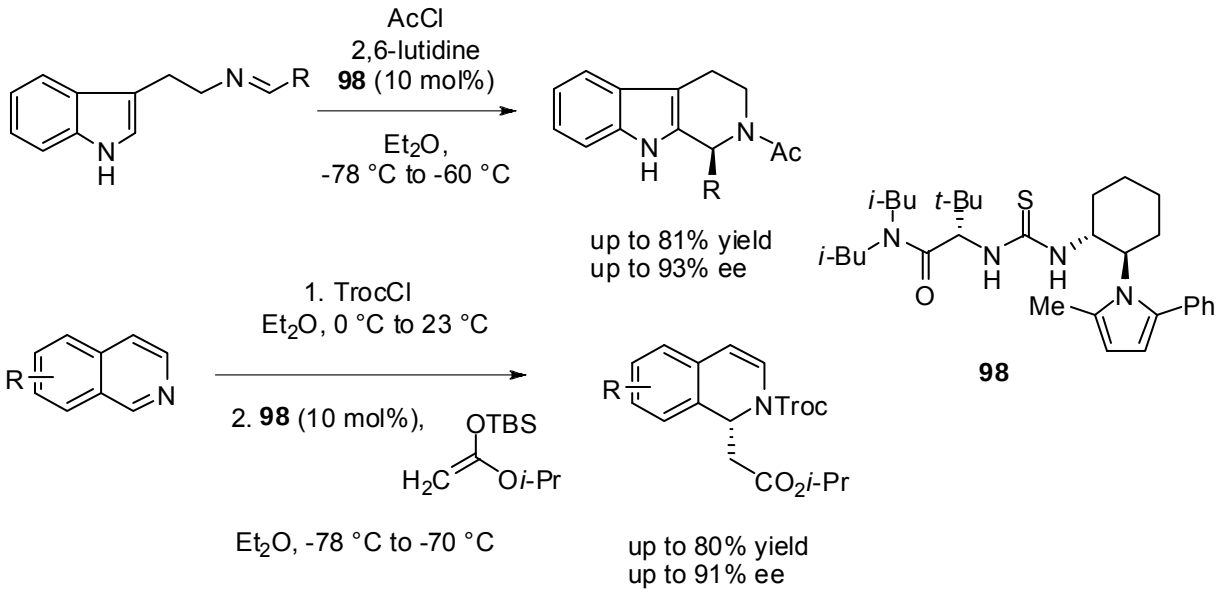
Scheme 4.8 Imine activation.

Alternatively, the reaction could work with the *N*-acyl-iminium ion intermediate **B**. In this case the role of the acid catalyst might be to generate a chiral cyanide nucleophile which could react enantioselectively with the *N*-acyl-iminium ion intermediate **B** and product **3** is formed (Scheme 4.9).



Scheme 4.9 Acid catalytic acylcyanation mechanism, path b.

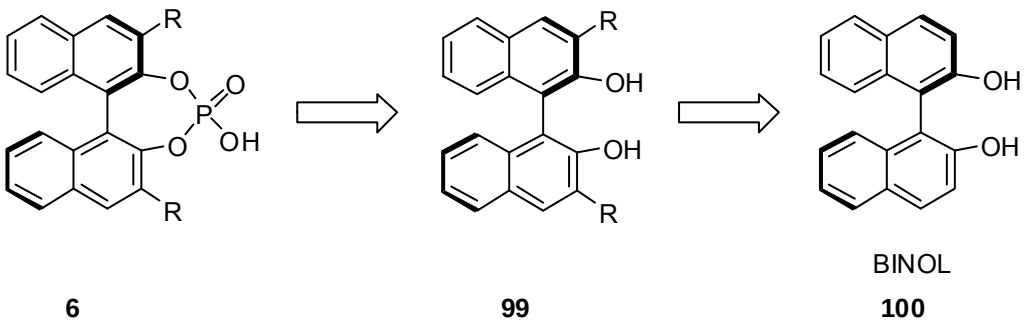
The Jacobsen group has also shown that chiral thiourea catalyst **98** could promote highly enantioselective Pictet-Spengler[36] and Mannich-type[119] reactions through initial acylation of imines and isoquinolines, respectively (Scheme 4.10).



Scheme 4.10 Enantioselective acyl-Pictet-Spengler and acyl-Mannich reaction; Troc = 2,2,2-trichloroethyl formate.

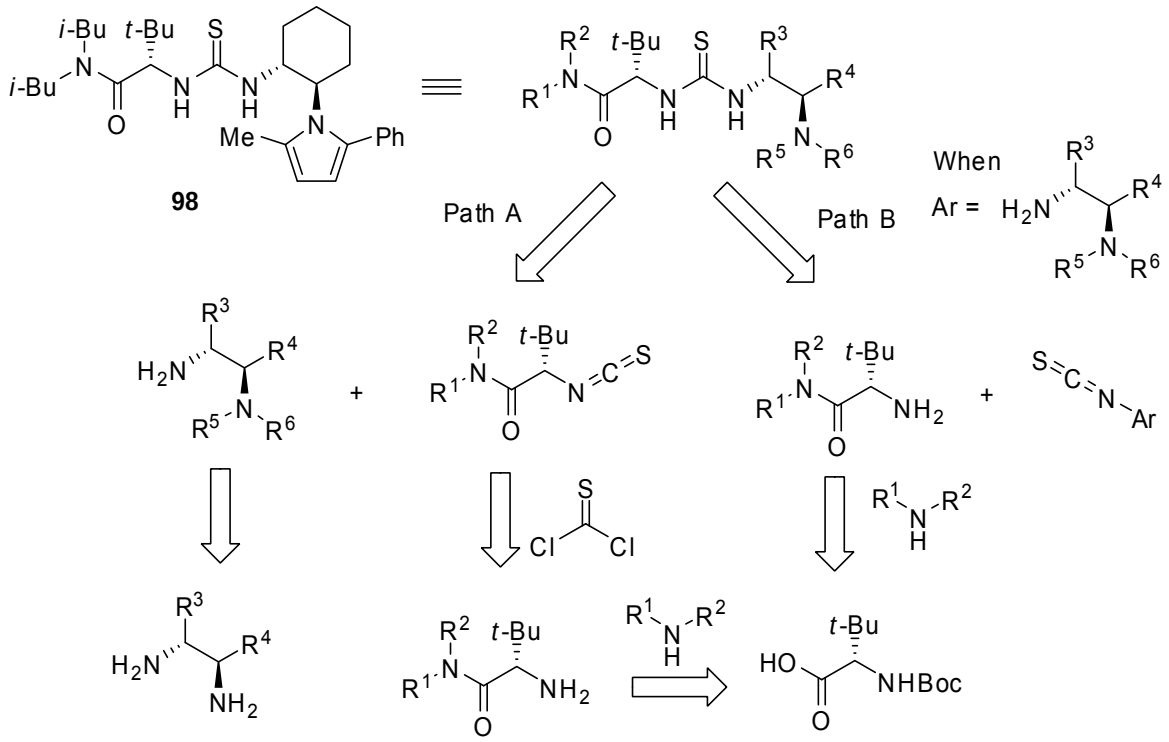
The process by which the resulting *N*-acyliminium ions **B** are induced to undergo enantioselective additions with a simple hydrogen-bond donor catalyst such as thiourea is intriguing. The role of the urea catalyst here might not be to activate the electrophile but rather to bind the nucleophile (cyanide ion in our case), thus effectively creating a chiral counteranion nucleophile,[120] which could react enantioselectively with the *N*-acyl iminium ion **B**.[121] This mechanism could be a consequence of the well-known anion-binding properties of thioureas.[122] The possibility of high levels of enantioinduction obtained through chiral counteranion interactions has recently been demonstrated in the context of asymmetric counteranion-directed catalysis by List and co-workers.[123]

A major advantage of using chiral phosphoric acids and thiourea catalysts is their modular structure. Structures of binaphthol based chiral phosphoric acids **6** can be easily modified by changing their 3,3´-substituents. Thus a structural optimization can be carried out to find the best catalyst. They are prepared from 3,3´-substituted BINOL **99** by phosphorylation in one step. 3,3´-Substituted BINOL **99** can in turn be synthesized from commercially available (*R*)- or (*S*)-BINOL (**100**) in three to four steps (Scheme 4.11).[40-42]



Scheme 4.11 Retrosynthetic analysis of chiral phosphoric acid **6**.

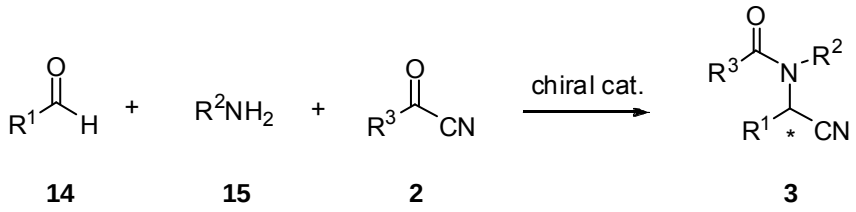
The structures of the chiral thiourea catalysts can also be easily modulated. A representative example of the chiral thiourea catalyst is Jacobsen catalyst **98**. This catalyst is a combination of a chiral thiourea unit and a chiral *trans*-1,2-diaminocyclohexane moiety (Scheme 4.12).[36] They can be combined together in one step by the reaction of the diamino moiety with isothiocyanate (Path A). Isothiocyanate can in turn be prepared from *tert*-leucine amide by the reaction with thiophosgene. Different *tert*-leucine amides can easily be synthesized from the commercially available *N*-Boc *tert*-leucine. Similarly, different diamino moieties could be easily generated from the commercially available chiral cyclohexyl *trans*-1,2-diamine. When 1,2-diaminocyclohexane moiety is replaced by an aryl group then path B is followed (Scheme



Scheme 4.12 Possible mode of variation and retrosynthesis of thiourea catalyst **98**.

4.12). Here the preparation of catalyst is much shorter; *tert*-leucine amide directly reacts with aryl isothiocyanates. Since different aryl isothiocyanates are commercially available, the structure can be easily modulated.

Another aim of this work was to develop a three-component acyl-Strecker reaction. It was understood that a useful extension of the catalytic imine acylcyanation (if it worked) would be avoiding the isolation of the preformed imine intermediate entirely and to develop a one-pot three-component acylcyanation. Only Kobayashi and co-workers reported a direct catalytic asymmetric three-component Strecker reaction of aldehydes, aromatic amines, and HCN by using a chiral zirconium catalyst.[102] It was thus highly desirable to replace the highly toxic and volatile HCN in such catalytic asymmetric Strecker reactions with a more convenient cyanide source such as acylcyanide and to expand the scope of the amine component in the reaction. Accordingly, an attractive one-pot three-component catalytic asymmetric acyl-Strecker reaction could be possible (Scheme 4.13).

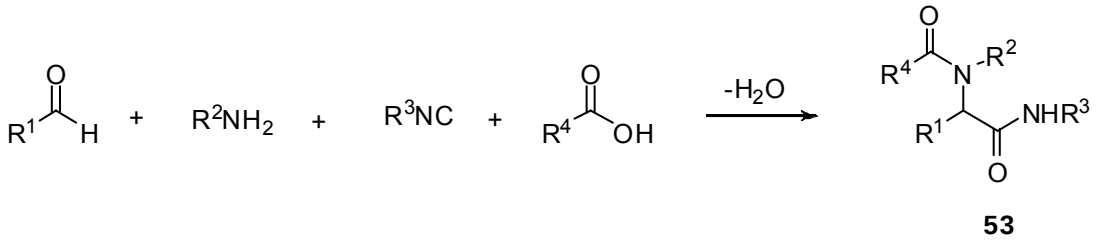


Scheme 4.13 Catalytic asymmetric three-component acyl-Strecker reaction.

Such a process would constitute the first organocatalytic asymmetric three component Strecker-type reaction. Moreover, this reaction would not only simplify the approach towards α-amino acid derivatives but also provide a potentially useful entry towards molecular diversity if assortments of reagents were used. We decided to investigate similar achiral and chiral catalysts like in the two-component variant, as analogous modes of actions were expected. An irreversible reaction of acylcyanide and amine to an amide could be a barrier of the concept but this side reaction could be avoided by sequencing the addition of reagents in a suitable order.

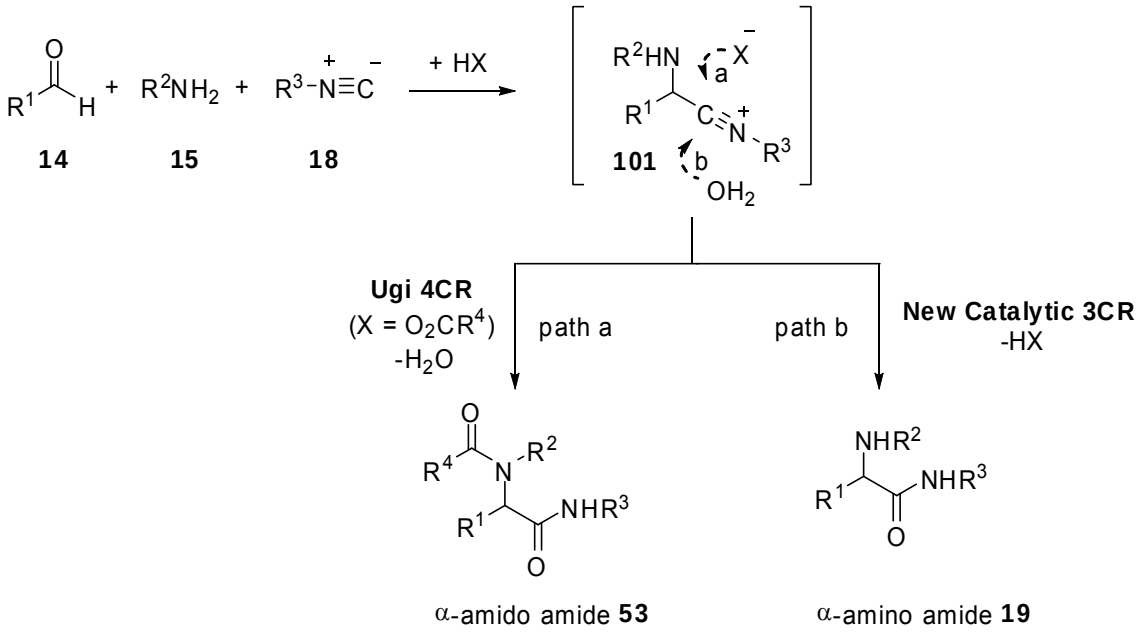
4.2 Catalytic Three-Component Ugi Reaction

The second goal of this dissertation was to develop a new variant of the Ugi reaction which should be catalytic in acid and potentially be conducted asymmetrically using chiral catalysts. The Ugi four-component reaction (Ugi 4CR) is one of the milestone multicomponent reactions and great efforts have been devoted to the exploration of the potential of this transformation.[73] A primary amine, a carbonyl compound, a carboxylic acid and an isocyanide react together to give α-amido amides **53** in this remarkable reaction (Scheme 4.14, see also Scheme 3.33). A truly catalytic as well as a catalytic asymmetric variant of the Ugi reaction is unknown.



Scheme 4.14 Four component Ugi reaction.

Mechanistically, the Ugi reaction is believed to proceed via a nitrilium ion intermediate (**101**) resulting from the addition of isocyanide **18** to an *in situ* generated iminium ion (Scheme 4.15). Nucleophilic addition of the carboxylate ion (HX = R^4CO_2H) to nitrilium ion **101**

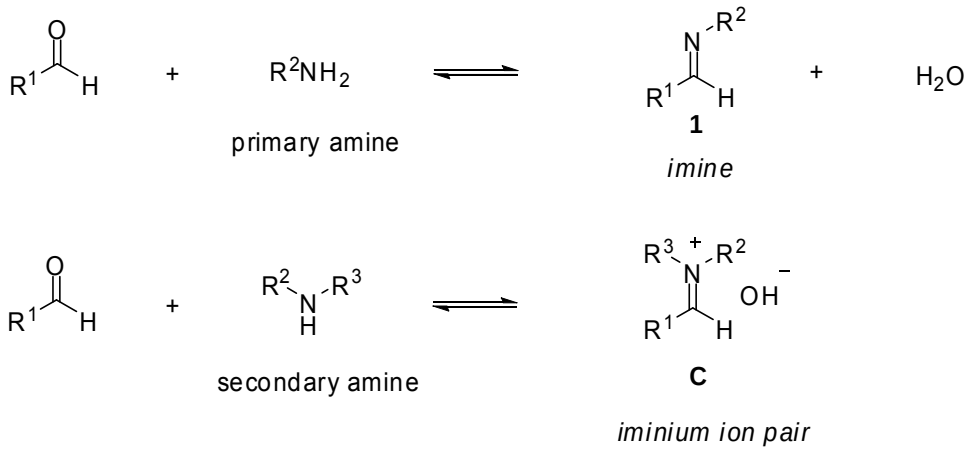


Scheme 4.15 Ugi 4CR and new three-component reaction.

followed by Mumm-rearrangement leads to the final product and water as the only by-product (Scheme 4.15, path a).

We reasoned that it should be possible to intercept nitrilium ion **101** not with the carboxylate ion but rather with the *in situ* generated water molecule. This would require using acids (HX) other than carboxylic acids and potentially render the process catalytic in acid (Scheme 4.15, path b).

Such a *three*-component Ugi reaction between an aldehyde, a primary amine and an isocyanide to generate an α-amino amide is unknown. Previously only, secondary amines were used in a non-catalytic three-component Ugi reaction.[124] We realized that secondary amines on reaction with non-enolizable aldehydes provide an iminium ion pair **C** (Scheme 4.16). Thus, there is a possiblity of a background addition reaction of iminium ion **C** with neutral isocyanide **18** without further activation. On the contrary, imine **1** is likely to be activated by a Brønsted or Lewis acid for an effective addition of isocyanide **18** (Scheme 4.16).



Scheme 4.16 Imine **1** and iminium ion pair **C**.

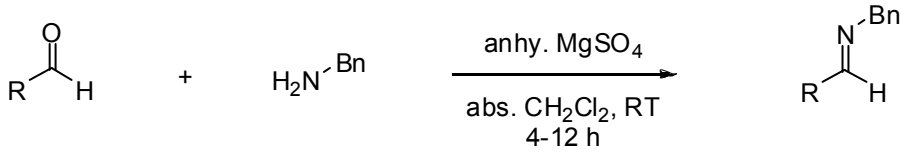
Thus the goal of this work was to develop a new catalytic Ugi reaction with primary amines. The resulting α-amino products will be useful for the synthesis of α-amino acids and their derivatives. As the reaction proceeds through imine intermediate **1**, we thought to investigate different achiral and chiral Brønsted and Lewis acid catalysts to promote this reaction. Moreover, this approach may lead to the development of a catalytic asymmetric variant of the Ugi reaction for the first time.

5 Results and Discussion

5.1 Catalytic Acylcyanation of Imines with Acetylcyanide

5.1.1 Preparation of Imines

Imines were prepared from aldehydes **14** and benzyl amine (**15b**) following a modified literature procedure reported by Yamamoto et al (Scheme 5.1).[125] In all of the cases, the products were obtained in essentially quantitative yields.



14a, R = Ph
14c, R = 4-$MeOC_6H_4$
14d, R = 4-ClC_6H_4
14e, R = 2-ClC_6H_4
14f, R = 2-furyl
14g, R = 3-pyridyl
14h, R = *i*-Pr
14b, R = *t*-Bu
14i, R = 1-cyclohexenyl
14j, R = *t*-$BuCH_2$
14k, R = 2-naphthyl
14l, R = 1-cinnamyl
14m, R = cyclohexyl

15b

1a, R = Ph, 99%
1c, R = 4-$MeOC_6H_4$, 99%
1d, R = 4-ClC_6H_4, 99%
1e, R = 2-ClC_6H_4, 99%
1f, R = 2-furyl, 99%
1g, R = 3-pyridyl, 99%
1h, R = *i*-Pr, 99%
1b, R = *t*-Bu, 99%
1i, R = 1-cyclohexenyl, 99%
1j, R = *t*-$BuCH_2$, 99%
1k, R = 2-naphthyl, 99%
1l, R = 1-cinnamyl, 99%
1m, R = cyclohexyl, 99%

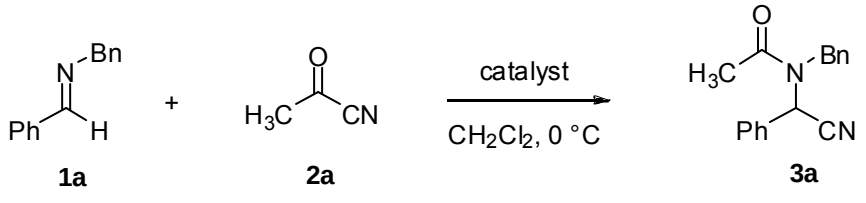
Scheme 5.1 Preparation of imines.

5.1.2 Catalyst Screening and Optimization of the Reaction Conditions

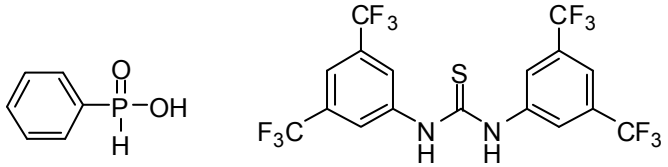
Initially the background reaction of benzaldehyde-derived imine **1a** with acetylcyanide (**2a**) at 0 °C without any catalyst was studied. After 72 hours, 40% conversion to desired *N*-acetylated α-amino nitrile product **3a** was obtained in dichloromethane as the solvent (entry 1,

Table 5.1). The formation of **3a** was confirmed by its ^{1}H and ^{13}C NMR spectral data. The ^{1}H NMR spectrum showed the presence of methyl proton resonance at δ 2.14 while a 12-line ^{13}C NMR spectrum exhibited the characteristic amide carbonyl resonance at δ 171.3 and the cyanide carbon resonance at δ 116.1. Then, according to the observations of Dornow and Lüpfert,[117] triethylamine was explored as catalyst for this reaction; surprisingly however, only 4% conversion into product **3a** was obtained after 72 hours (entry 2, Table 5.1). In addition to bases, different Brønsted acid catalysts were investigated for this reaction. While highly acidic TFA (pK_a 0.53) did not give any conversion (entry 3, Table 5.1), moderately acidic phenyl phosphinic acid (**4**, pK_a 1.65) gave 90% conversion in 24 hours (entry 4, Table 5.1). Then it was found that the reaction can be catalyzed not only by stronger, specific acid catalysts[42] but also by hydrogen-bonding type, general acid catalysts.[28]

Table 5.1 Catalytic acetylcyanation of imine **1a**.



1a **2a** **3a**



4 **5**

Entry[a]	Catalyst	Loading (mol%)	Time (h)	Conversion[b] (%)
1	none	-	72	40
2	Et_3N	20	72	4
3	TFA	20	72	0
4	**4**	20	24	90
5	**5**	10	24	99
6	**5**	2	24	98
7	**5**	1	24	93

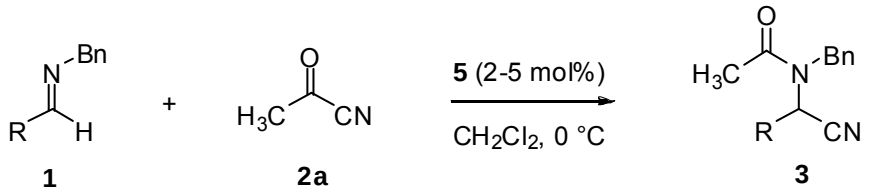
[a] All reactions were performed using 0.1 mmol of imine **1a** with 0.15 mmol of acetylcyanide (**2a**). [b] Determined by GC.

In particular, Schreiner thiourea catalyst **5**[32] was found to be quite efficient in promoting the reaction and gave almost quantitative conversion to product **3a** (entry 5, Table 5.1). A decrease in catalyst loading from 10 mol% to 2 mol% essentially preserved the conversion (entry 6, Table 5.1), but a decrease to only 1 mol% of the catalyst lowered the conversion to 93% (entry 7, Table 5.1). Consequently, 2-5 mol% of catalyst **5** was used in subsequent experiments.

5.1.3 Substrate Scope

Using dichloromethane as the solvent and thiourea **5** as the catalyst (2–5 mol%), we explored the scope of this reaction (Table 5.2). The substrate scope was studied in collaboration with

Table 5.2 Catalytic acetylcyanation of different imines.



Entry[a]	R	Time (h)	Product	Yield[b]
1	Ph	24	**3a**	88
2	4-MeOC_6H_4	24	**3c**	84
3	4-ClC_6H_4	24	**3d**	79
4	2-ClC_6H_4	24	**3e**	83
5	2-Furyl	24	**3f**	67
6	3-Pyridyl	24	**3g**	96
7[c]	*i*-Pr	48	**3h**	76
8[c]	*t*-Bu	48	**3b**	64
9[c]	1-Cyclohexenyl	48	**3i**	82
10[c]	*t*-BuCH_2	48	**3j**	81

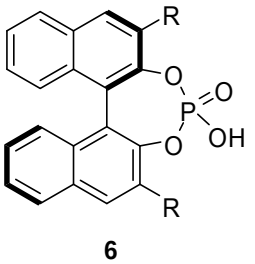
[a] All reactions were performed using 2 mol% of the catalyst unless otherwise stated. [b] Yields of pure product after silica gel column chromatography. [c] 5 mol% of the catalyst.

Dr. J. Zhou. It turned out that the selected reaction conditions are broadly useful for a variety of different substrates. Both aromatic aldimines (entries 1–4) with electron-donating and electron-withdrawing substituents, as well as heteroaromatic aldimines (entries 5 and 6) were used with similar efficiencies; and in the presence of 2 mol% of catalyst **5**, high yields (67-96%) have been obtained. Furthermore, aliphatic branched, unbranched, and unsaturated aldimines can also be employed to give moderate to good yields (64-82%) of **3** with 5 mol% of catalyst **5** (entries 7–10).[126] With 2 mol% of catalyst **5**, the yields were lower for the aliphatic substrates.

5.2 Catalytic Asymmetric Acylcyanation of Imines

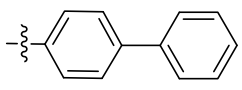
5.2.1 Catalyst Screening and Optimization of the Reaction Conditions

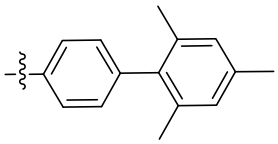
In contrast to the reports of Dornow and Lüpfert, bases were found to be less effective as catalysts in the acetylcyanation reaction, while acidic catalysts proved to be quite active. In particular, phenyl phosphinic acid (**4**) and Schreiner thiourea catalyst (**5**) were found to

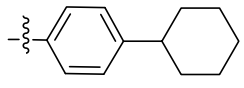


6

6a R = Ph
6b R = 2-naphthyl
6c R = 2,4,6-*i*Pr$_3$C$_6$H$_2$
6d R = 4-NO$_2$C$_6$H$_4$
6e R = 3,5-Me$_2$C$_6$H$_3$
6f R = SiPh$_3$
6g R = 9-anthracenyl
6h R = 9-phenanthryl

6i R = 

6j R = 

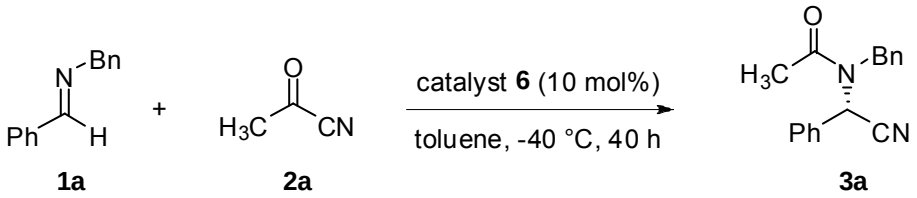
6k R = 

6l R = CHPh$_2$
6m R = 2,6-Me$_2$C$_6$H$_3$

Scheme 5.2 Binaphthol-based different phosphoric acid catalysts.

catalyze the acetylcyanation reaction efficiently. We decided to investigate possible asymmetric catalytic versions using chiral binol phosphates or thiourea catalysts. Initially, the reaction of benzaldehyde derived imine **1a** with acetylcyanide (**2a**) at –40 °C was investigated and toluene was found to be the optimal solvent. Several chiral BINOL-derived phosphoric acid catalysts **6a**-**m** were tested for this reaction (Scheme 5.2). During the optimization study, Rueping et al. demonstrated that chiral phosphoric acids also catalyze the Strecker reaction with hydrogen cyanide in high enantioselectivities.[106]

Table 5.3 Catalytic asymmetric acetylcyanation of imine **1a** with phosphoric acids **6**.

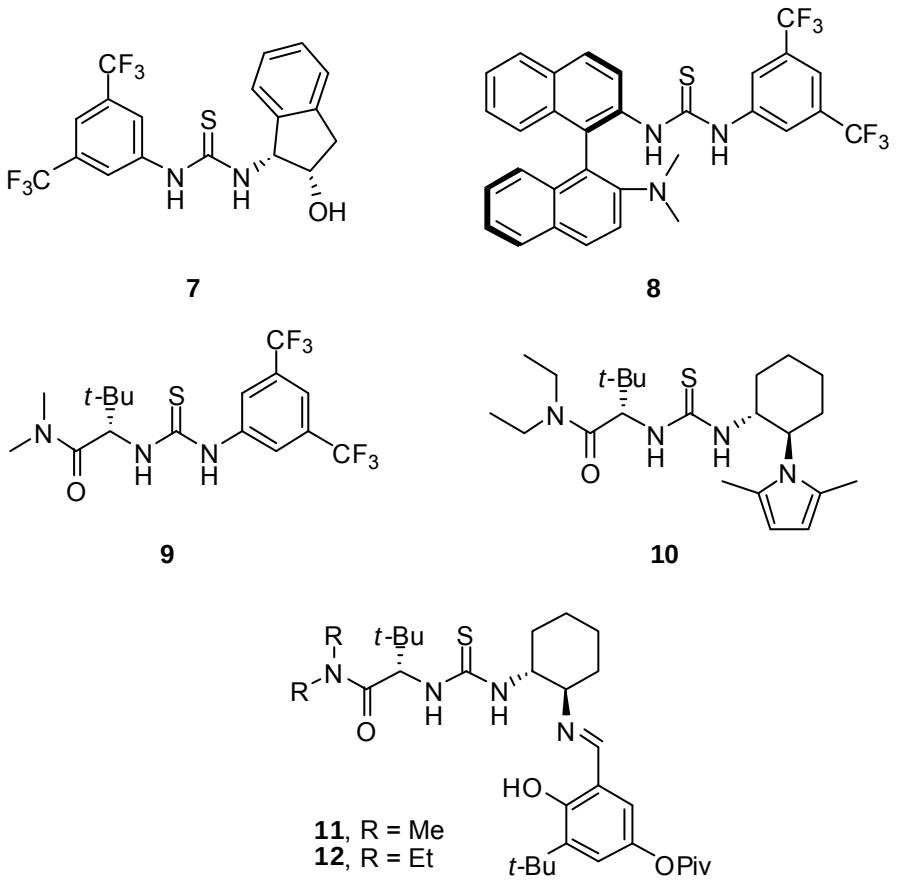


1a **2a** **3a**

Entry[a]	Catalyst	Conversion (%)[b]	er[c]
1	**6a**	95	60:40
2	**6b**	95	57:43
3	**6c**	95	58:42
4	**6d**	92	55:45
5	**6e**	95	58:42
6	**6f**	90	52:48
7	**6g**	70	62:38
8	**6h**	70	67:33
9	**6i**	95	60:40
10	**6j**	95	65:35
11	**6k**	90	61:39
12	**6l**	90	70:30
13	**6m**	95	76:24

[a] Reaction conditions: Aldimine **1a** (0.1 mmol), acetylcyanide **2a** (0.15 mmol) and catalyst **6** (0.01 mmol) were stirred together at –40 °C in dry toluene (0.5 ml). [b] Determined by GC. [c] Determined by chiral HPLC.

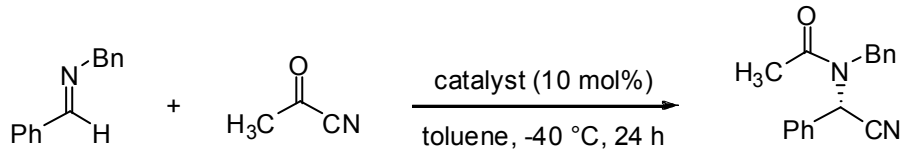
Initial experiments showed that in the presence of 10 mol% of phosphoric acid catalyst **6a**, imine **1a** underwent facile acetylcyanation at –40 °C to produce *N*-acetylated α-amino nitrile product **3a** and after 40 hours, 95% conversion was obtained with an enantioselectivity of 60:40 er (Table 5.3, entry 1). Then, it was decided to increase the steric bulk at the 3,3′-positions of the phosphoric acid catalyst. However, with bulky catalysts **6b** and **6c**, no improvement in enantioselectivity was observed (entries 2 and 3). Catalyst **6d** and **6e** having electronically different phenyl groups in the 3,3′-positions could also not alter the enantioselectivity (entries 4 and 5). Subsequently different sterically congested catalysts **6f-6k** were prepared. However, while it was found that these catalysts provided *N*-acetylated α-amino nitrile product **3a** in high yields, enantioselectivities were only moderate (maximum 67:33 er) (entries 6-11). Catalyst **6l** having a new benzhydryl substituent could improve the enantioselectivity slightly (70:30 er) (entry 12). Finally, the best result (79:21 er) was obtained with catalyst **6m** (entry 13). Because of the lack of excellent enantioselectivities with chiral phosphoric acids we next dediced to focuss our attention on chiral thiourea catalysts. Thus, a range of chiral thiourea catalysts **7-12** (Scheme 5.3) were prepared, some of which were similar or identical to those introduced by Jacobsen and co-workers.



Scheme 5.3 Structures of different thiourea catalysts.

Initial experiments have proven these thiourea catalysts to be quite active catalysts for the acylcyanation of imines; in the presence of 10 mol% of thiourea catalyst **7** (derived from *cis*-1-amino-2-indanol),[127] imine **1a** was completely consumed within 24 hours at –40 °C. However, the product **3a** was obtained in racemic form (Table 5.4, entry 1). Bifunctional thiourea catalyst **8**[128] could also promote the reaction but a racemic product was obtained (entry 2). Catalyst **9** having a chiral α-amino acid moiety provided product **3a** in moderate enantioselectivity (60:40 er) (entry 3). The best results were obtained with Jacobsen catalysts **10**-**12**. An escalating enantioselectivity (97:3 er) was achieved with catalyst **10** having a chiral *trans*-1,2-diaminocyclohexane moitety and a symmetrical pyrrole moiety (entry 4). Remarkably, catalysts **11** and **12** containing an imine component derived from 2-hydroxy-5-pivaloyloxy-3-*tert*butyl benzaldehyde provided product **3a** in essentially enantiomerically pure form (>99:1 er) (entries 5 and 6, Table 5.4).

Table 5.4 Catalytic asymmetric acetylcyanation of imine **1a** with thiourea catalysts.



1a **2a** **3a**

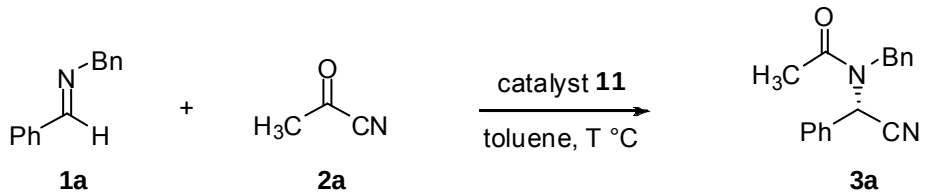
Entry[a]	Catalyst	Conversion (%)[b]	er[c]
1	**7**	99	51:49
2	**8**	99	51:49
3	**9**	99	60:40
4	**10**	98	97:3
5	**11**	99	>99:1
6	**12**	99	>99:1

[a] Aldimine **1a** (0.1 mmol), acetylcyanide **2a** (0.15 mmol) and catalyst **6** (0.01 mmol) were stirred together at –40 °C in dry toluene (0.5 ml). [b] Determined by GC. [c] Determined by HPLC.

In the further optimization, the catalyst loading was lowered and it was found that the yield and enantioselectivity (98:2 er) were not much altered with 5 mol% of catalyst **11** (entry 2, Table 5.5). Even 1 mol% of catalyst **11** was sufficient to give product **3a** in high yield as well as with excellent enantioselectivity of 98:2 er (entry 3, Table 5.5). The reaction became faster

after increasing the reaction temperature to 0 °C; however a little decrease in enantioselectivity (97:3 er) was observed (entry 4, Table 5.5). Interestingly, the reaction also worked at room temperature and the reaction time became shorter (4 hours). However, the yield and enantioselectivity obtained in this case were 93% and 94:6 er respectively (entry 5). Thus it was decided to study further reactions at –40 °C with 1-5 mol% of the catalyst loading.

Table 5.5 Catalytic asymmetric acetylcyanation of imine **1a** with catalyst **11**: Effect of catalyst loading and temperature.



1a **2a** **3a**

Entry[a]	Loading (mol%)	Temp (T °C)	Time (h)	Conversion (%)	er
1	10	–40	24	99	>99:1
2	5	–40	24	99	98:2
3	1	–40	24	99	98:2
4	1	0	10	99	97:3
5	1	RT	4	93	94:6

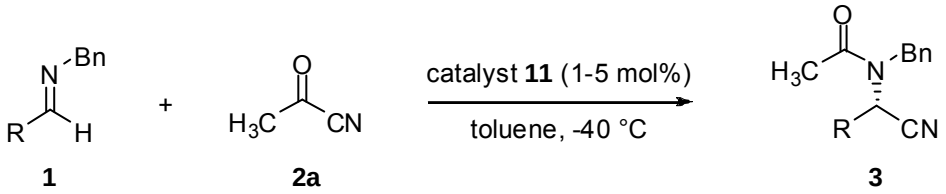
[a] Analogous reaction conditions as described in Table 5.4 were used. RT = room temperature.

5.2.2 Substrate Scope

Under the standard reaction condition, catalyst **11** was investigated with a number of different imines and the results are summarized in Table 5.6.[129] It was found that the reaction gave products in good yields and in very high enantioselectivities with different aromatic and heteroaromatic imines (entries 1-6). The highest enantioselectivity (99:1 er) was obtained when 4-chlorobenzaldehyde and 2-chlorobenzaldehyde were employed (entries 3-4). Furan-2-carbaldehyde derived imine **1f** provided product **3f** in 94% yield and with a slight lower enantioselectivity (95:5 er) (entry 6). Remarkably, good yields and high enantioselectivities were obtained with different aliphatic branched, unbranched and unsaturated imines (entries

7-13). α,β-Unsaturated imines afforded the products in high enantioselectivities (97:3 to 99:1 er) (entries 7-8). With 1 mol% of catalyst **11**, cyclohexanecarbaldehyde derived imine **1m** provided product **3m** in 99% yield with 96:4 er; and the enantioselectivity was not improved with 5 mol% of the catalyst loading. Pivalaldehyde derived imine **1b** gave product **3b** with an enantioselectivity of 98:2 er, however the yield was moderate (62%) (entry 11). Prolonging the reaction time to 72 hours could not improve the yield of product **3b** (63%).

Table 5.6 Catalytic asymmetric acetylcyanation of different imines.



Entry[a]	R	Time (h)	Product	Yield	er
1	Ph	20	**3a**	94	98:2
2	4-$MeOC_6H_4$	20	**3c**	95	98:2
3	4-ClC_6H_4	20	**3d**	87	99:1
4[b]	2-ClC_6H_4	36	**3e**	86	99:1
5	2-Naphthyl	20	**3k**	92	98:2
6[b]	2-Furyl	20	**3f**	94	95:5
7	1-Cinnamyl	20	**3l**	83	97:3
8[b]	1-Cyclohexenyl	36	**3i**	82	99:1
9[b]	*i*-Pr	20	**3h**	87	97:3
10	Cyclohexyl	20	**3m**	99	96:4
11[b]	*t*-Bu	50	**3b**	62	98:2
12[b]	*n*-Bu	20	**3n**	76	97:3
13[b]	*t*-$BuCH_2$	20	**3j**	87	98:2

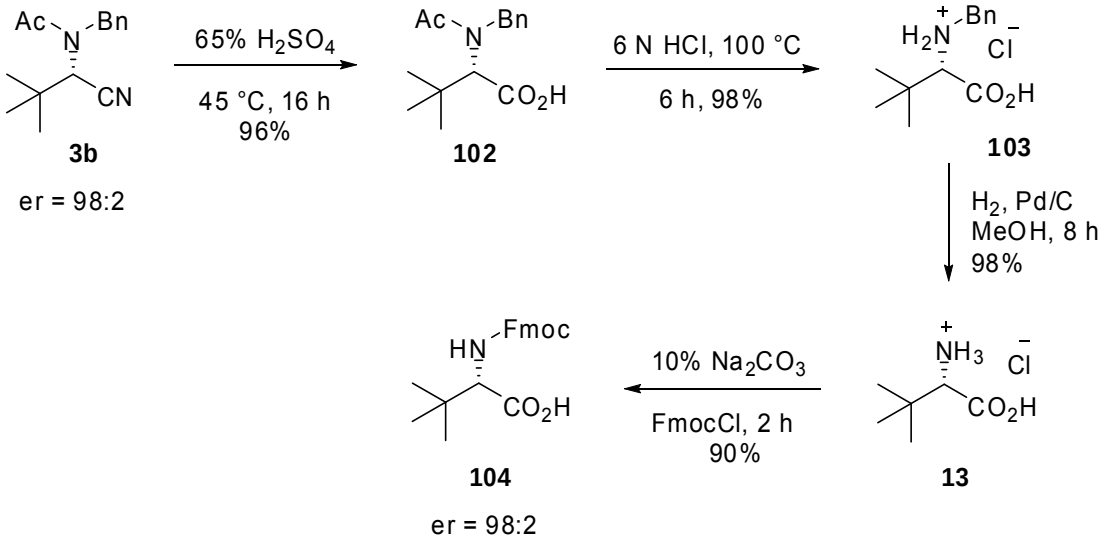
[a] All reactions were run with 1 mol% of the catalyst, unless otherwise stated. [b] 5 mol% of the catalyst **11**.

Nevertheless, this could enable a facile synthesis of enantiomerically enriched *tert*-leucine, which is an important chiral building block and not accessible by the asymmetric alkylation of glycine derivatives. Also surprisingly, α-unbranched alkyl imines which are challenging substrates for the previously developed Strecker variants, provided products **3n** and **3j** with high enantioselectivities (97:3 to 98:2 er) and in high yields (76-87%) (entries 12-13).

Interestingly, for some substrates the enantioselectivity varies with the catalyst loading. For example, if the reaction of *iso*-butyraldehyde derived imine **1h** was run in the presence of 1 mol% of catalyst **11**, desired product **3h** was obtained with an er value of only 78:22. However, with 2 mol% of catalyst **11**, the er value was 96:4 and reached 97:3 with 5 mol% of the catalyst (Table 5.6, entry 9). Additional increases in the catalyst loading did not improve the er value any further. Most probably, uncatalyzed or substrate-catalyzed background reactions play a role at lower catalyst loadings.

5.3 Conversion to α-Amino Acid and Determination of the Absolute Configuration

N-Acylated α-amino nitrile **3b** was converted into *tert*-leucine salt **13** via acid mediated hydrolysis and hydrogenolysis (Scheme 5.4).[129] In compound **3b,** cyano group was first hydrolyzed to the carboxylic group using 65% H_2SO_4 and compound **102** was obtained in 96% yield. Then the *N*-acetyl group in **102** was removed with 6 N HCl to obtain carboxylic acid **103** in high yield (98%).



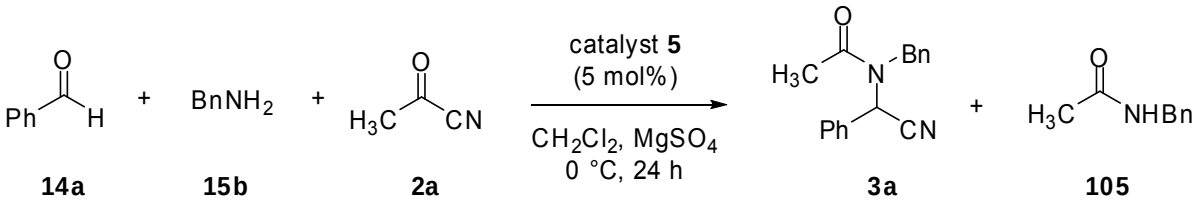
Scheme 5.4 Conversion of the α-amino nitrile **3b** to the α-amino acid salt **13** and determination of the absolute configuration.

Pd/C hydrogenation was next chosen for the removal of the benzyl group in compound **103**. The product α-amino acid salt **13** was obtained in 98% yield and it was then converted to *N*-Fmoc amino acid **104** under basic condition. The enantioselectivity of compound **104** was determined to be 98:2 er. An authentic sample of this compound was independently prepared from L-*tert*-leucine and the absolute configuration of product **3b** was determined to be *S* by comparing the retention times in chiral HPLC. The stereochemistry of the reaction products was found to be the same as in the case of Jacobsen's Strecker reaction (using the same enantiomer of catalyst **11**).[104] Other α-amino nitrile products could potentially be converted to the desired α-amino acids in similar ways without losing enantiopurity.

5.4 Catalytic One-Pot, Three-Component Acyl-Strecker Reaction

5.4.1 Optimization of the Reaction Conditions

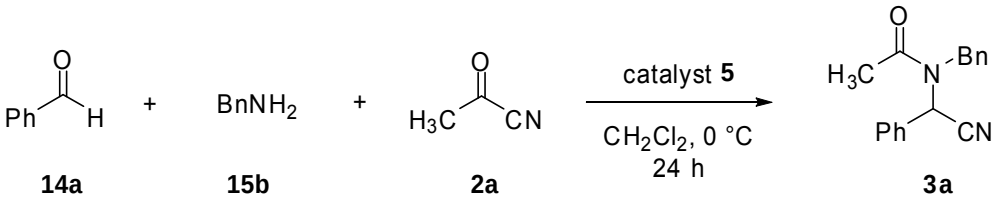
In an attempt to circumvent imine preformation and develop an *in situ* three-component variant; benzaldehyde (**14a**), benzyl amine (**15b**), $MgSO_4$, thiourea catalyst **5**, and acetylcyanide (**2a**) were stirred at 0 °C for 24 hours in dichloromethane. However, a poor conversion (40%) to the desired product **3a** was obtained and a considerable amount of side product was formed (Scheme 5.5). It was not surprising to find that *N*-benzyl acetamide (**105**) was the side product (confirmed by ^{1}H and ^{13}C spectra) resulting from the direct reaction of benzyl amine with acetylcyanide.



Scheme 5.5 Direct three-component reaction.

It was envisioned that in order to suppress this side reaction, the order of reagent mixing may be crucial. Thus, aldehyde **14a**, amine **15b**, drying reagent and catalyst **5** were stirred together at 0 °C for 2 hours before acetylcyanide **2a** (1.5 equiv.) was added. Significant conversion of 86% was obtained at the initial attempt using $MgSO_4$ as the drying agent (entry 1, Table 5.7). Interestingly, the use of MS 5Å as the drying reagent further improved the conversion to 92% (entry 2). The best result (99% conversion) was obtained when the mixture of aldehyde, amine, MS 5Å, and catalyst **5** were stirred together at room temperature for 2 hours before the addition of acetylcyanide at 0 °C (entry 3). Lowering the catalyst loading to 1 mol% resulted in lower conversion (70%) to product **3a** and a considerable side-product formation (entry 4). In the next experiments it was decided to use 5 mol% of catalyst **5** and the mixture of aldehyde, amine, MS 5Å, and catalyst were stirred together at room temperature for 2 hours before the addition of acetylcyanide at 0 °C.

Table 5.7 Optimization of the reaction conditions for the one-pot, three-component acylcyanation.



14a **15b** **2a** **3a**

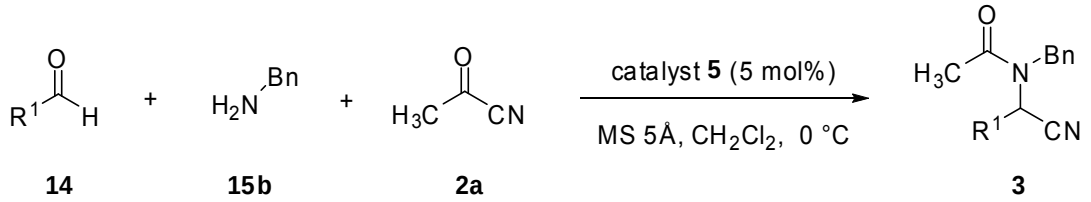
Entry[a]	Catalyst **5** (mol%)	Drying Reagent	Conversion (%)[b]
1	5	$MgSO_4$	86
2	5	MS 5Å	92
3[c]	5	MS 5Å	99
4[c]	1	MS 5Å	70

[a] Reaction condition: aldehyde **14a**, amine **15b**, drying reagent, and catalyst **5** were stirred together at 0 °C for 2 hours before acetylcyanide **2a** (1.5 equiv.) was added. [b] Determined by GC. [c] Aldehyde **14a**, amine **15b**, drying reagent, and catalyst **5** were stirred together at RT for 2 hours before acetylcyanide **2a** (1.5 equiv.) was added at 0 °C.

5.4.2 Substrate Scope

After establishing suitable reaction condition, we decided to explore the scope of this new three-component reaction. First, a variety of different aldehydes **14a–j** was examined with benzyl amine **15b** as the amine component and acetylcyanide **2a** as the cyanide source (Table 5.8, entries 1–10). Like the two-component variant, here also both aromatic aldehydes (entries 1–4) with electron-donating and -withdrawing substituents, as well as heteroaromatic aldehydes (entries 5 and 6) can be used. The products were obtained in high yields (73-84%) after 36-48 hours. High yield of 84% was obtained with 3-pyridyl carbaldehyde (entry 6). Additionally, moderate to good yields (48-85%) were obtained when aliphatic branched, unbranched, and unsaturated aldehydes were employed (entries 7–10). Isobutyraldehyde provided product **3h** in 78% yield (entry 7). Pivalaldehyde showed a lower reactivity for this reaction and a moderate yield of 48% was obtained after 48 hours (entry 8). Additional reaction time could not improve the yield of product **3b**. An α,β-unsaturated aldehyde like cinnamaldehyde provided product **3l** in good yield (85%) (entry 9). Notably, good yield of 82% was also obtained with an α-unbranched aldehyde like *n*-pentanal (entry 10).[130]

Table 5.8 Three-component acylcyanation with different aldehydes.



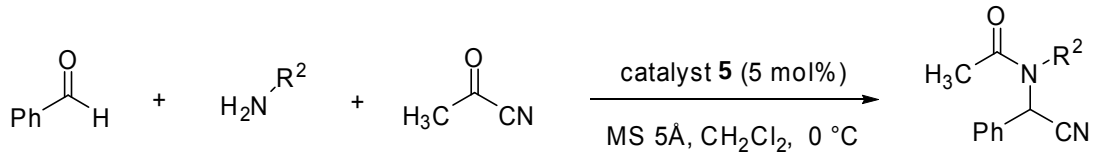
14 **15b** **2a** **3**

Entry[a]	R^1	Time (h)	Product	Yield
1	Ph	36	**3a**	80
2	4-$MeOC_6H_4$	36	**3c**	82
3	4-ClC_6H_4	48	**3d**	73
4	2-Naphthyl	36	**3k**	83
5	2-Furyl	36	**3f**	76
6	3-Pyridyl	36	**3g**	84
7	*i*-Pr	36	**3h**	78
8	*t*-Bu	48	**3b**	48
9	1-Cinnamyl	36	**3l**	85
10	*n*-Bu	36	**3n**	82

[a] Aldehyde **14**, amine **15b**, MS 5Å, and catalyst **5** were stirred together at RT for 2 hours before acetylcyanide **2a** (1.5 equiv.) was added at 0 °C.

A variety of amines was studied next with benzaldehyde (**14a**) as the aldehyde component and acetylcyanide (**2a**) as the cyanide source (Table 5.9, entries 1-6). The three component acylcyanation processes could work well with several amines. Benzyl amines with electron-withdrawing or -donating groups were used with similar efficiencies (entries 2 and 3). 4-Chlorobenzyl amine afforded product **3p** in 81% yield. Comparable yield of 78% was obtained with 4-methoxybenzyl amine (entry 3). Furfuryl amine having a heteroaromatic moiety (entry 4) can also be employed and good yield was obtained (76%). Noteworthy, the reaction also afforded products with allyl or even simple alkyl amines (entries 5-6). Allyl amine provided product **3s** in 68% yield (entry 5). The reaction became faster with *n*-pentyl amine and a good yield of 75% for **3t** was obtained after 36 hours (entry 6).[130]

Table 5.9 Three-component acylcyanation with different amines.



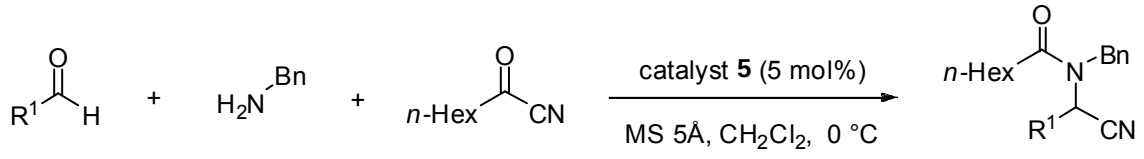
14a **15** **2a** **3**

Entry[a]	R^2	Time (h)	Product	Yield
1	1-NaphCH_2	36	**3o**	77
2	4-$ClC_6H_4CH_2$	36	**3p**	81
3	4-$MeOC_6H_4CH_2$	36	**3q**	78
4	Furfuryl	48	**3r**	76
5	Allyl	48	**3s**	68
6	*n*-Pent	36	**3t**	75

[a] Aldehyde **14a**, amine **15**, MS 5Å, and catalyst **5** were stirred together at RT for 2 hours before acetylcyanide **2a** (1.5 equiv.) was added at 0 °C.

The third component of this reaction could also be varied. Heptanoylcyanide (**2b**) as another commercially available acylcyanide has been used and the results are summarized in Table 5.10. Benzaldehyde reacted with benzyl amine (**15b**) and heptanoylcyanide (**2b**) to provide product **3u** in 72% yield (entry 1).

Table 5.10 Three-component acylcyanation with heptanoyl cyanide.



17 **15b** **2b** **3**

Entry[a]	R^1	Time (h)	Product	Yield
1	Ph	36	**3u**	72
2	2-Naphthyl	36	**3v**	77

[a] Analogous reaction conditions as described in Table 5.9 were used.

Similarly, 2-naphthaldehyde provided product **3v** in 77% yield (entry 2). However, cyanoformate esters did not provide the desired product in this reaction.

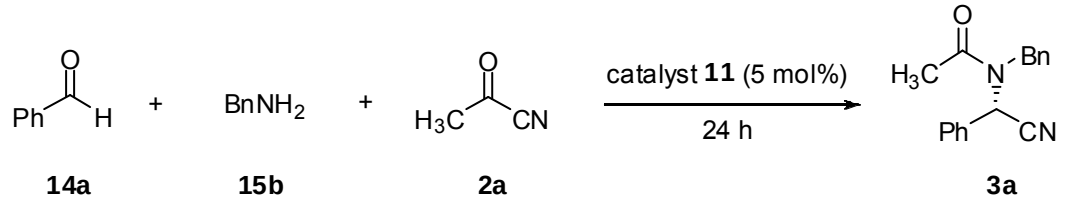
While the reaction may not be strictly considered a three-component reaction but rather an *in situ* sequence, it improved the original two step protocol significantly in terms of practicality. Whereas in the two-component variant only benzyl imine (**1a**) was used, here different amines were applied and in addition to acetylcyanide (**2a**), heptanoylcyanide (**2b**) was also used. Thus the broad scope, operational simplicity, and mild reaction conditions render it an attractive approach for the generation of diverse sortiments of racemic α-amido nitriles.

5.5 Catalytic Asymmetric Three-Component Acyl-Strecker Reaction

5.5.1 Optimization of the Reaction Conditions

After the success in developing a one-pot variant of the acylcyanation reaction, it was decided to study a one-pot asymmetric variant using Jacobsen thiourea catalyst **11** which gave high enantioselectivities in the analogous preformed imine variant.[129] According to the findings in the non-asymmetric three-component version, acetylcyanide (**2a**) was added at last to realize efficient conversion to the desired product. However, the product was formed with poor enantioselectivity (57:43 er) when aldehyde, amine, $MgSO_4$ and catalyst **11** were stirred for 2 hours at 0 °C before acetylcyanide (**2a**) was added at 0 °C (entry 1, Table 5.11). Switching the drying reagent to 5Å molecular sieves and the solvent to dichloromethane significantly improved the enantioselectivity (up to 87:13 er) (entries 2-5). Even higher enantioselectivity (94:6 er) was observed when acetylcyanide (**2a**) was added at –40 °C and the reaction was run at this temperature (entry 6). Finally, the best result (98% conversion, 97:3 er) was obtained when the aldehyde was first mixed with the amine and MS 5Å for 2 hours at room temperature before the catalyst and acetylcyanide were added subsequently at –40 °C (entry 7).

Table 5.11 Optimization of the reaction conditions for the asymmetric three-component acylcyanation



14a **15b** **2a** **3a**

Entry[a]	Solvent	Drying Reagent	Temp (°C)	Conversion	er
1	Toluene	$MgSO_4$	0	84	57:43
2	Toluene	MS 5Å	0	10	80:20
3	CH_2Cl_2	none	0	63	74:26
4	CH_2Cl_2	$MgSO_4$	0	68	78:22
5	CH_2Cl_2	MS 5Å	0	66	87:13
6[b]	CH_2Cl_2	MS 5Å	–40	83	94:6
7[c]	CH_2Cl_2	MS 5Å	–40	98	97:3

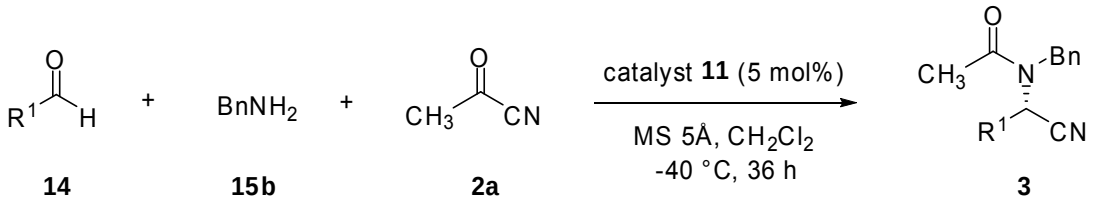
[a] Aldehyde, amine, drying reagent, and catalyst **11** were stirred for 2 hours at 0 °C before acetylcyanide (**2a**) was added. [b] Aldehyde, amine, and MS 5Å were stirred for 2 hours at 0 °C before the catalyst **11** and acetylcyanide **2a** (at -40 °C) were added. [c] Aldehyde, amine, and MS 5Å were stirred for 2 hours at RT before the catalyst **11** and acetylcyanide **2a** (at -40 °C) were added.

5.5.2 Substrate Scope

With the optimal reaction condition, the scope of this new catalytic asymmetric three-component reaction was explored. First, the reaction of a variety of different aldehydes **14** with benzyl amine (**15b**) as the amine component and acetylcyanide (**2a**) was examined (Table 5.12). Interestingly, the reactions took place efficiently in good to excellent yields (46-97%) with high levels of enantioselectivities (94:6 to 97:3 er) for all studied aldehydes. In particular, high enantioselectivities (96:4 to 97:3 er) were observed with various aromatic aldehydes (entries 1-4). High enantioselectivity (97:3 er) was also achieved with an α,β-unsaturated aldehyde (entry 5). But even an aliphatic branched- and an α-trisubstituted aldehyde gave excellent enantioselectivities (entries 6-7). For example, pivalaldehyde provided product **3b** in moderate yield (46%) but with high enantioselectivity (97:3 er) (entry 7). Additional reaction time could not improve the yield of this reaction. In the case of the α-unbranched aldehydes, slightly lower er values were obtained, but the products were formed

in high yields (75-97%) (entries 8-9). In the case of 3,3-dimethylbutanal, the er of **3j** could be significantly increased to 96:4 er (94:6 er with 5 mol% of the catalyst) using 10 mol% of catalyst **11**.[131]

Table 5.12 Catalytic asymmetric acylcyanation of different aldehydes with acetylcyanide (**2a**) and benzyl amine (**15b**).



14 **15b** **2a** **3**

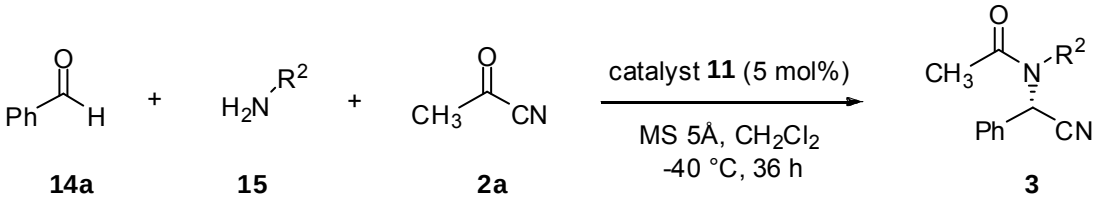
Entry[a]	R^1	Product	Yield	er
1	Ph	**3a**	94	97:3
2	4-$MeOC_6H_4$	**3c**	88	97:3
3	4-ClC_6H_4	**3d**	78	96:4
4	2-Naphthyl	**3k**	92	97:3
5	1-Cinnamyl	**3l**	82	97:3
6	*i*-Pr	**3h**	92	96:4
7	*t*-Bu	**3b**	46	97:3
8	*n*-Bu	**3n**	75	94:6
9[b]	*t*-$BuCH_2$	**3j**	97	96:4

[a] Aldehyde **14** (0.5 mmol), benzyl amine (**15b**, 0.5 mmol), and MS 5Å (150 mg) were stirred at RT for 2 hours in CH_2Cl_2 (2 mL). Catalyst **11** (0.025 mmol) and after cooling to –40 °C acetylcyanide (**2a**, 0.75 mmol) were added. [b] Using 10 mol% of catalyst **11**.

A variety of amines was investigated next using benzaldehyde (**14a**) as the aldehyde component under the same reaction conditions as described for Table 5.12. It turned out that three different benzyl amines can be used to give the products in high yields and with excellent enantioselectivities (97:3 er) (Table 5.13, entries 1-3). The electron properties of the aromatic system of the amine component do not seem to influence the yield and enantioselectivity of the reaction. Furfuryl amine having a heteroaromatic moiety can also be employed and high enantioselectivity (90:10 er) of **3r** was obtained (entry 4). Allyl amine has

also been used and still gave desired product **3s** in a good result of 94:6 er (entry 5). Moreover, the reaction also afforded the product with a simple alkyl amine although in slightly lower enantioselectivity (87:13 er) (entry 6).[131] From the best of our knowledge, simple alkyl amines were not previously used for asymmetric Strecker type reactions.

Table 5.13 Catalytic asymmetric acylcyanation of benzaldehyde (**17a**) with different amines and acetylcyanide.



14a **15** **2a** **3**

Entry[a]	R^2	Product	Yield	er
1	4-$MeOC_6H_4CH_2$	**3q**	95	97:3
2	4-$ClC_6H_4CH_2$	**3p**	93	97:3
3	1-NaphthylCH_2	**3o**	92	97:3
4	2-FurylCH_2	**3r**	83	90:10
5	Allyl	**3s**	88	94:6
6	*n*-Pent	**3t**	76	87:13

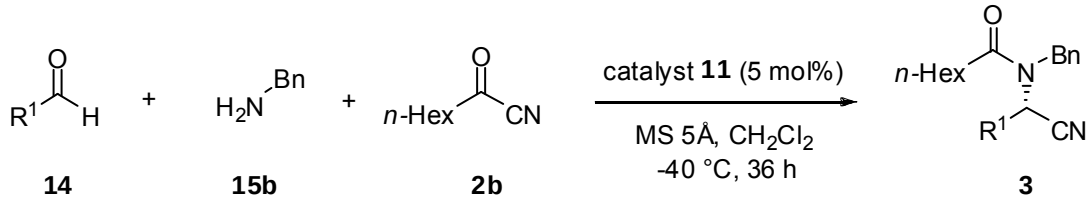
[a] Analogous reaction conditions as described in Table 5.12 were used.

The third component of this reaction was also varied like in the non-asymmetric variant, and the results are summarized in Table 5.14. Heptanoylcyanide (**2b**) reacted with benzaldehyde and benzyl amine (**15b**) and product **3u** was formed in 84% yield and with 94:6 er (Table 5.14, entry 1). Similarly, high yield (87%) and enantioselectivity (90:10 er) were obtained for the product **3v** from the reaction of 2-naphthaldehyde, benzyl amine (**15b**) and heptanoyl cyanide (**2b**) (entry 2).[131]

Thus, the first organocatalytic asymmetric variant of the classical three-component Strecker reaction was developed using acylcyanides as the cyanide source. The operational simplicity, practicability, and mild reaction condition make it a useful approach for the preparation of different α-amido nitriles. Despite its obvious use for the synthesis of α-amino acids and their

derivatives, this reaction may find use in diversity-oriented synthesis and medicinal chemistry.

Table 5.14 Catalytic asymmetric acylcyanation with heptanoyl cyanide (**2b**).



14 **15b** **2b** **3**

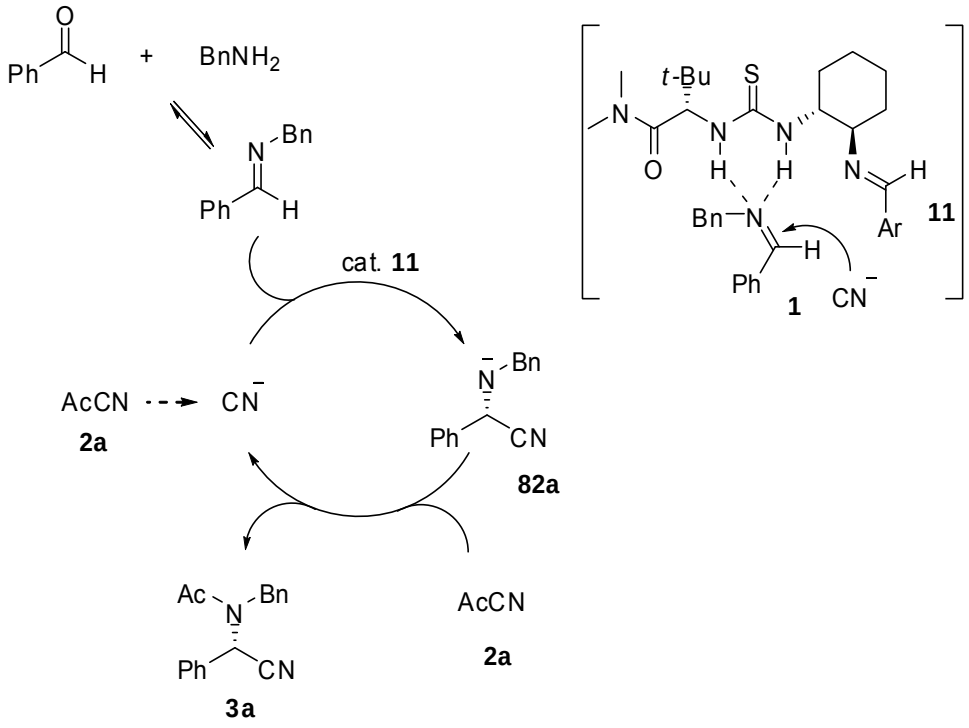
Entry	R^1	Time (h)	Product	Yield	er
1	Ph	36	**3u**	84	94:6
2	2-Naphthyl	36	**3v**	87	90:10

[a] Analogous reaction conditions as described in Table 5.12 were used.

5.6 Mechanism for the Acylcyanation of Imines

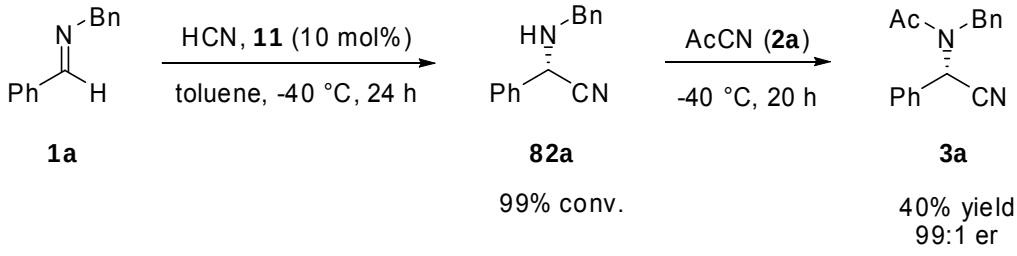
Two probable mechanisms for the acylcyanation reaction were considered. First, the imine (generated *in situ*) may react with a small amount of cyanide ion. However, the ^{1}H NMR and ^{13}C NMR spectra of the commercially available acetylcyanide (**2a**) did not show the presence of HCN. The proton of HCN shows a signal at δ 4.10 in the ^{1}H NMR spectrum. However, no peak at δ 4.10 was observed. Also, a 3-line ^{13}C NMR spectrum of acetyl cyanide (**2a**) exhibited only one cyanide signal at δ 113.5. However, traces of cyanide ion (CN^-) may be formed in the reaction mixture from acetylcyanide. The resulting α-amino nitrile product (**82a**) would react with acetylcyanide (**2a**) to give observed product **3a** and cyanide ion will be regenerated (Scheme 5.6). Accordingly, the mechanism of the key Strecker step would be identical to that of the Jacobsen variant,[33,104] in which the urea is proposed to activate the imine through general acid catalysis (bifurcated H-bonding from two NHs which have pK_as ~ 12.60). The Jacobsen group had found that Schiff base catalyst **11** has a well-defined secondary structure in solution. This result has been confirmed by NOE NMR spectroscopic data. The hydrocyanation reaction proceeds according to a Michaelis-Menten kinetic model, with a first-order dependence on **11** and HCN, and saturation kinetics with respect to the imine substrate. Therefore, a reversible formation of a complex between **11** and the imine through a hydrogen bond is expected. In addition, it was found that the Strecker reactions

involve binding of the imine as the *Z*-isomer. A detailed 3D structure of the substrate-catalyst complex supported by molecular modeling revealed that the large group of the imine is directed away from the catalyst. This explains why **11** catalyzed hydrocyanation of most aldimines with high enantioselectivities, regardless of the steric and electronic properties of the substrate.



Scheme 5.6 Possible Strecker mechanism.

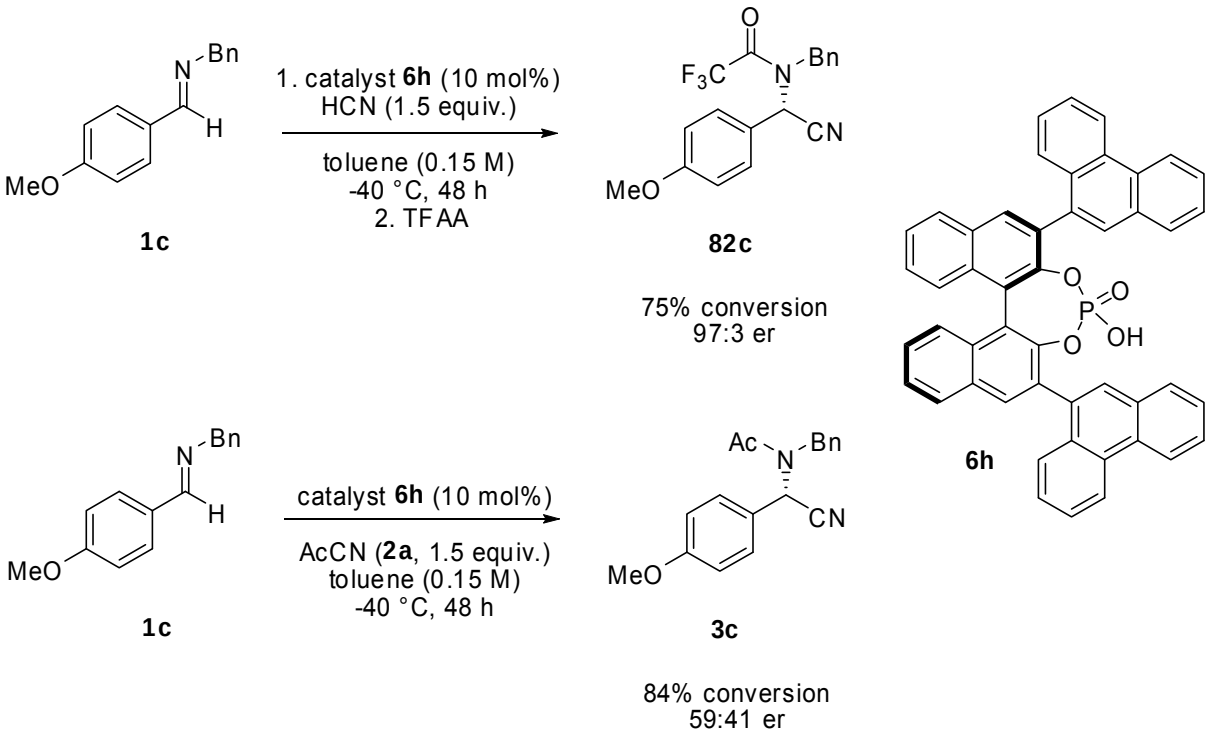
To prove or disprove this hydrocyanation mechanism in our reaction, an experiment was carried out. The hydrocyanation of imine **1a** (0.5 mmol) with catalyst **11** (0.05 mmol) and HCN (0.75 mmol) at –40 °C was first conducted (Scheme 5.7). Subsequently acetylcyanide (**2a**, 0.75 mmol) was added. However, after 20 hours, product **3a** was obtained in only 40% yield (99:1 er). Under our original conditions, product **3a** was obtained in 96% yield.



Scheme 5.7 Hydrocyanation followed by derivatization.

Therefore, the intermediacy of Strecker product **82a** is questionable, and the above mechanism is less likely.

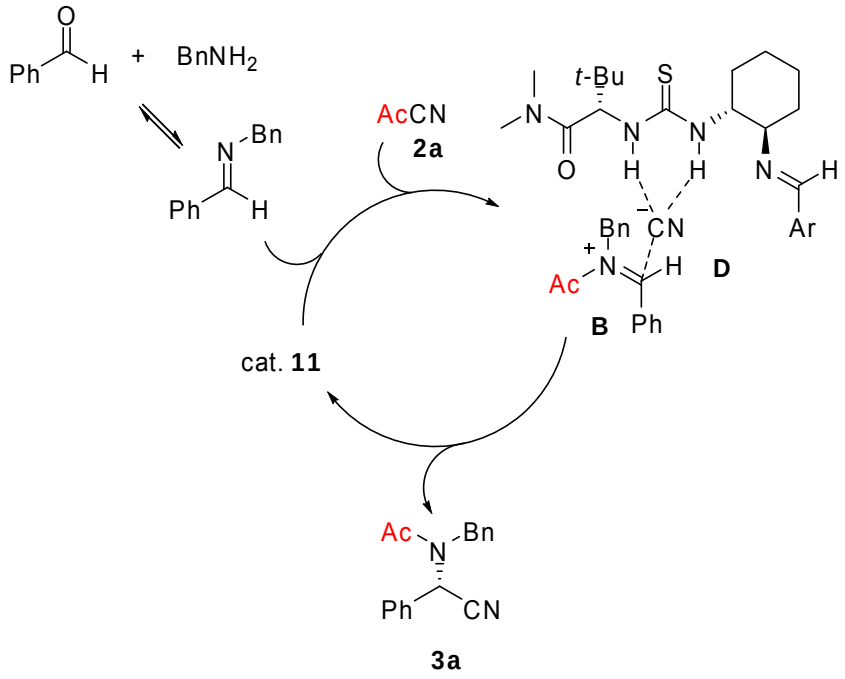
The non-occurrence of the Strecker mechanism was also fortified by performing another experiment (Scheme 5.8). Rueping et al. demonstrated catalyst **6h** as a highly enantioselective catalyst for the hydrocyanation of aldimines.[106] For example, hydrocyanation of imine **1c** at –40 °C for 48 hours followed by derivatization with trifluoroacetic anhydride (TFAA) provided product **82c** in 75% conversion with 97:3 er (Scheme 5.8). Under the same reaction condition, acetylcyanation of imine **1c** was carried out. However, product **3c** was obtained in 84% conversion with 59:41 er (Scheme 5.8). Thus, there is a significant difference in enantioselectivity (65%) in these two reactions. This is additional evidence that our reaction does not follow the hydrocyanation pathway.



Scheme 5.8 Hydrocyanation versus acetylcyanation using phosphoric acid catalyst.

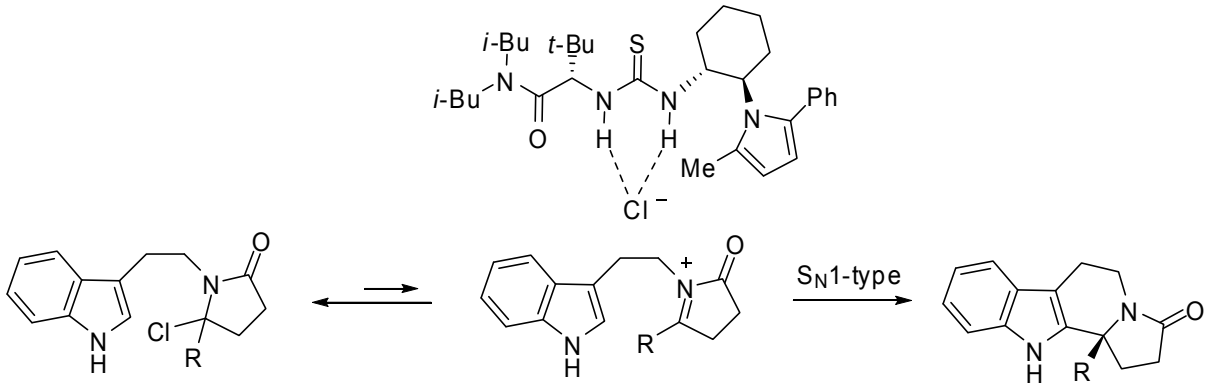
In an interesting alternative mechanism, the reaction could proceed via *N*-acyl iminium ion intermediate **B**. This species may be formed by the substitution reaction of the imine with acetylcyanide (**2a**) (Scheme 5.9).[132] We speculated that in the *N*-acyl iminium ion **B**, there is no feasible Lewis basic site for a productive catalyst binding. Jacobsen and co-workers have found that DFT calculations of fully ionized *N*-acyliminium ions interacting with thiourea derivatives failed to converge on any ground state bound structure.[36b] However, in the

transition state of the reaction, the positive charge of the *N*-acyl iminium ion **B** gets minimized revealing the character of an amide which in principle could be activated by the thiourea catalyst. But, we realized that the role of the thiourea catalyst in this case would presumably be to bind cyanide due to its negative charge. This binding effectively creates a chiral anion nucleophile, which could react enantioselectively with *N*-acyl iminium ion **B**; and possibly a chiral *N*-acyl iminium-cyanide-thiourea complex **D** is formed (Scheme 5.9). This kind of interaction might be the outcome of the well-known anion-binding properties of the thioureas.[122]



Scheme 5.9 Thiourea catalyzed mechanism involving *N*-acyl iminium ion.

This mechanism is supported by the recent studies of an acyl-Pictet–Spengler reaction from the Jacobsen group,[36b] which also proceeds via an *N*-acyl iminium ion and is catalyzed by a thiourea catalyst (Scheme 5.10). Jacobsen et al. suggested that there is anion binding (Cl^-) by the thiourea protons of the catalyst in their reaction (Scheme 5.10).

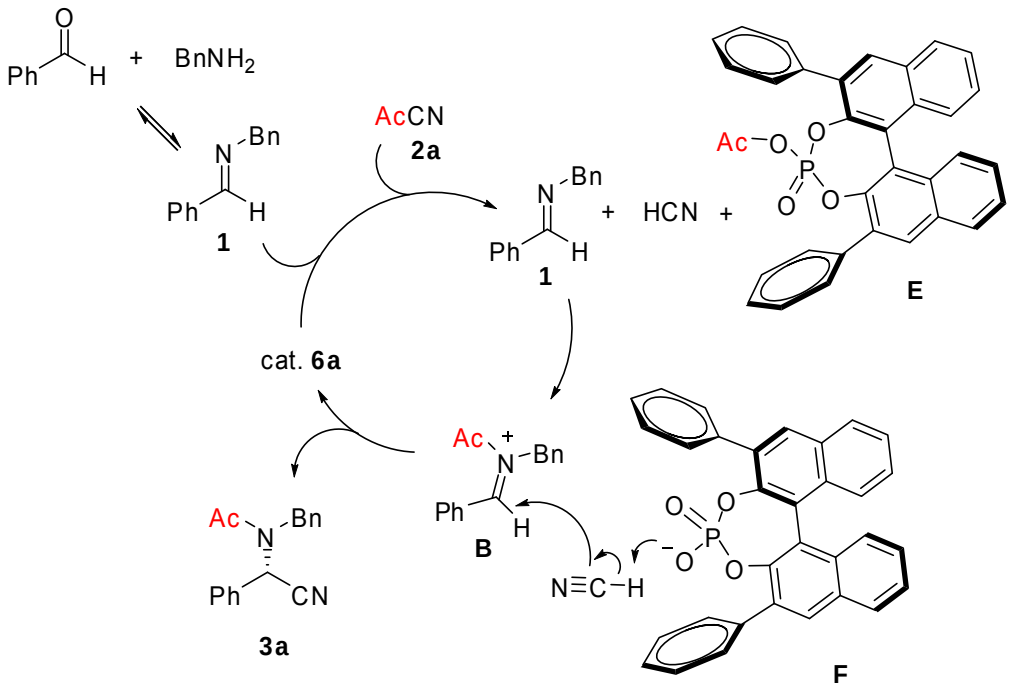


Scheme 5.10 Proposed mechanism for the acyl-Pictet-Spengler reaction.

The Jacobsen group did a model experiment with tetrabutylammonium chloride (TBAC) and found that the addition of 1 equivalent of tetrabutylammonium chloride (TBAC) to thiourea catalyst in $CDCl_3$ resulted in a pronounced downfield shift of both thiourea proton resonances. They observed a downfield shift of 0.56 ppm which is in consonance with a direct interaction between the thiourea protons and chloride ion.

The possibility of high levels of enantioinduction induced through counterion interactions is well-precedented in chiral phase-transfer catalysis[89] (see chapter 3.4.3.4 for details) and has recently been established in the context of asymmetric counteranion-directed catalysis.[123] We expect that asymmetric catalysis via anion-binding mechanisms may be applicable to a wide variety of valuable transformations involving highly reactive cationic intermediates.

Chiral phosphoric acid catalysts could catalyze the acylcyanation reaction in a different way (Scheme 5.11). Due to the nucleophilic nature and high acidity of phosphoric acids (pK_a ~ 1.30), we speculated that they can react with acetylcyanide (**2a**) to generate HCN and acylphosphate **E** (Scheme 5.11). Imine **1** then undergoes an acyl transfer reaction with acylphosphate **E** to afford *N*-acyl iminium ion **B**. The resulting phosphate anion **F** then deprotonates HCN for the addition of cyanide ion to *N*-acyl iminium ion **B** and provides the desired product **3a,** and catalyst **6a** is regenerated (Scheme 5.11). It is proposed that 3,3'-diaryls, which are not coplanar with the naphthyl groups would effectively shield the phosphate moiety, leading to efficient asymmetric induction for the transfer of cyanide ion (Scheme 5.11).

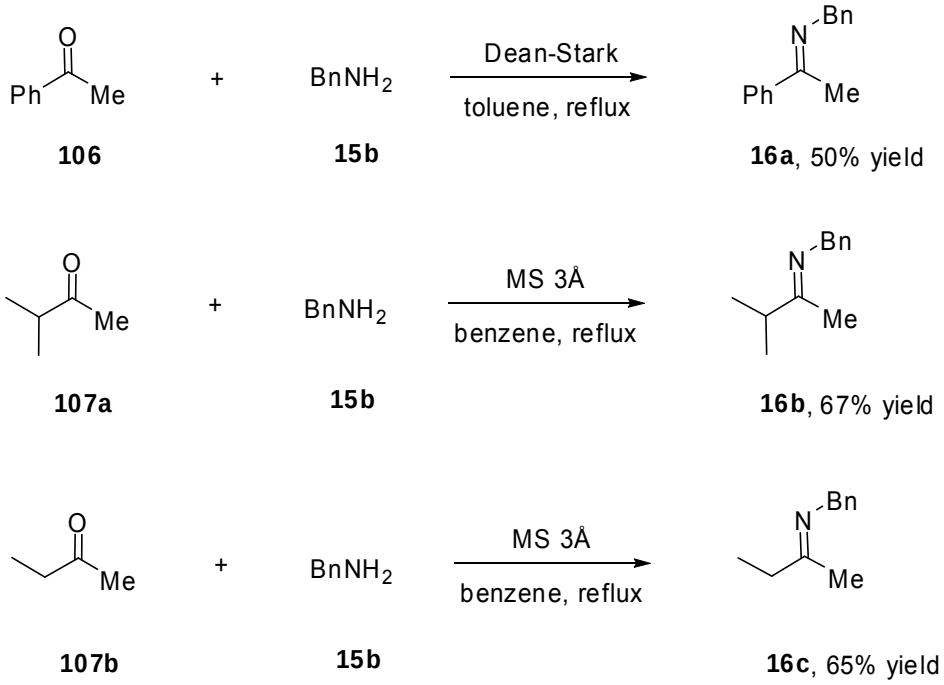


Scheme 5.11 Phosphoric acid catalyzed mechanism involving acylphosphate **E**.

5.7 Amidine Formation from the Reaction of Acetylcyanide with Ketimines

5.7.1 Preparation of Ketimines

Ketimines **16a-c** were prepared from ketones and benzyl amine (**15b**) following the procedure reported by Buchwald et al. (Scheme 5.12).[133] The imines were obtained in 50-67% yields.



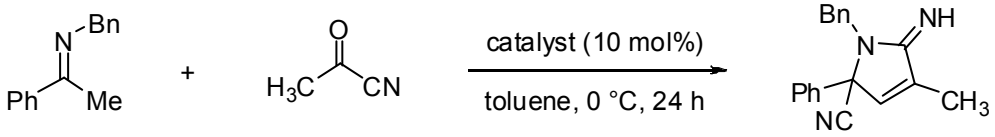
Scheme 5.12 Preparation of ketimines.

5.7.2 Catalyst Screening and Optimization of the Reaction Conditions

We decided to extend our acylcyanation chemistry to ketimines. According to the findings in the catalytic acylcyanation of aldimines, **4** and **5** were used as the catalysts. Remarkably however, when acetophenone derived benzyl imine **16a** was used as the substrate for the reaction with acetylcyanide **2a** (1.5 equiv.) and catalyst **5,** the desired addition product was not observed. Instead, a novel five membered amidine derivative **17a** was obtained in 50%

conversion (Table 5.15, entry 1). Its structure was unambiguously assigned from ^{1}H-NMR, ^{13}C-NMR, HMQC, and HRMS. ^{1}H-NMR spectrum showed the appearence of two doublets one of a vinyl proton at δ 6.30 (1H) and another of allyl methyl group at δ 2.01 (3H). A 14 line ^{13}C-NMR spectrum exhibited the presence of characterisitic amidine carbon resonance at δ 166.9. The conversion to product **17a** was slightly higher (60%) with catalyst **4** (entry 2). As the stoichiometry of the reaction required two equivalents of acetylcyanide, its amount was increased even further. High conversion (95%) was obtained when three equivalents of acetylcyanide (**2a**) was used (entry 3). From the literature survey we found that there were no previous reports describing the synthesis of amidines of type **17a**.

Table 5.15 Optimization of the reaction conditions for the formation of amidine **17a**.



16a **2a** **17a**

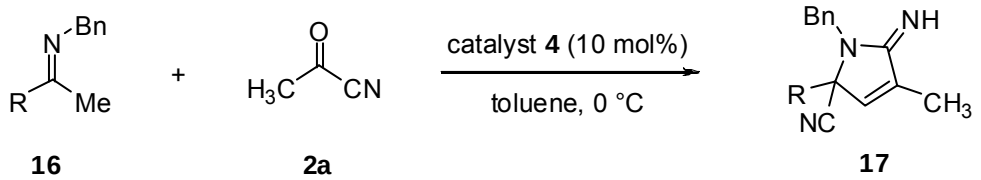
Entry	Catalyst	Equivalents of **2a**	Conversion (%)[a]
1	**5**	1.5	50
2	**4**	1.5	60
3	**4**	3.0	95

[a] Determined by GC.

5.7.3 Substrate Scope

After establishing suitable reaction conditions for the conversion of imine **16a**, two other imines were also studied. Product **17a** was isolated in 75% yield after silica gel column chromatography (Table 5.16, entry 1). Aliphatic ketone derived ketimines **16b** and **16c** could also be used in this novel reaction and provided products **17b** and **17c** in 40% and 38% isolated yields respectively (entry 2 and entry 3).[132] Amidines **17** are rather stable and are not hydrolyzed even after treatment with 6 N HCl at room temperature for 24 hours. Use of different chiral thiourea and phosphoric acid catalysts gave only poor enantioselectivity (<52:48 er) of amidine **17a**.

Table 5.16 Formation of different amidines **17**.



16 **2a** **17**

Entry	R	Time (h)	Product	Yield[a]
1	Ph	24	**17a**	75
2	*i*-Pr	48	**17b**	40
3	Et	48	**17c**	38

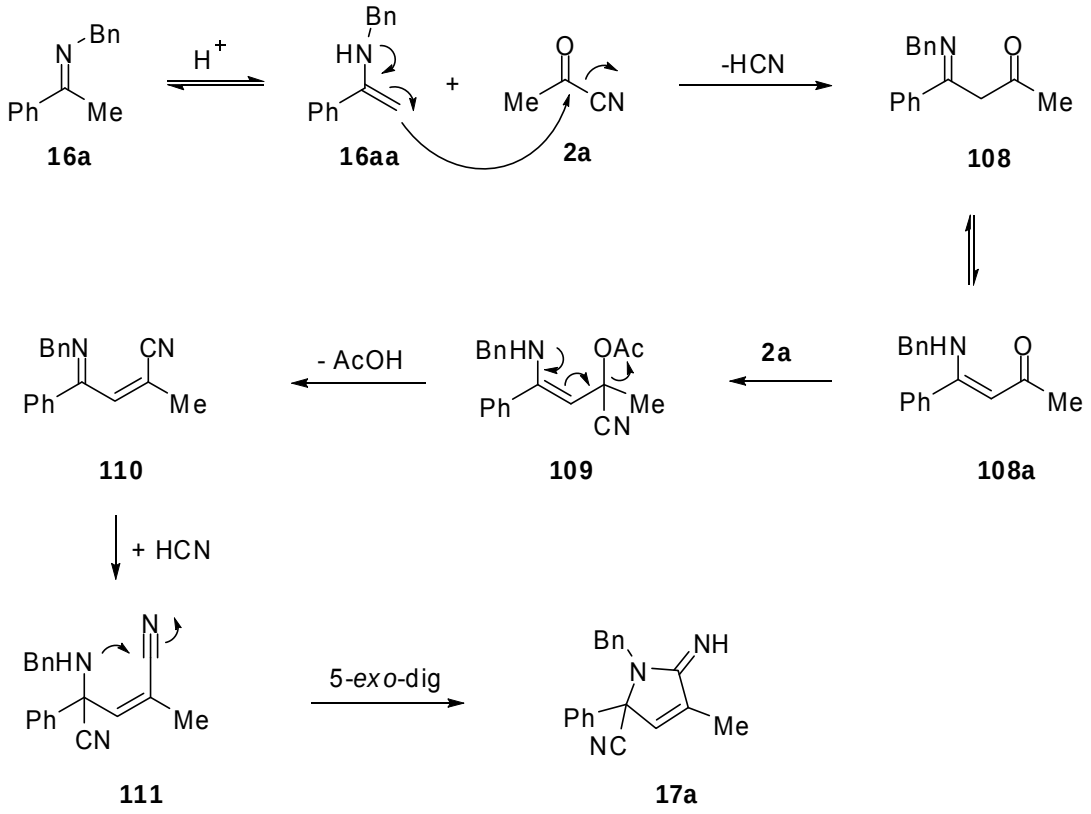
[a] Yield of the isolated product after silica gel column chromatography.

5.7.4 Mechanism of Amidine Formation

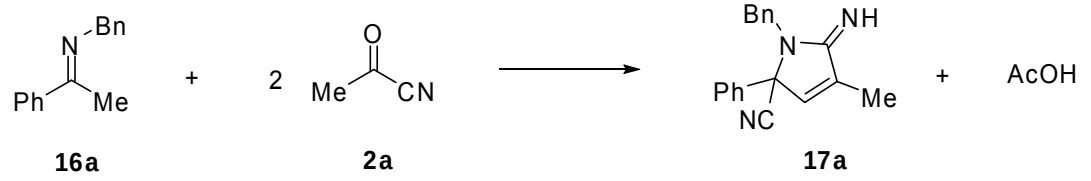
A plausible mechanism of the formation of **17a** may involve an initial *C*-acylation of imine **16a** via its enamine tautomer **16aa** to furnish imine **108** (Scheme 5.13). We speculated that the tautomerization of **16a** could be acid catalyzed. Imine **108** would isomerize to its more stable enaminone tautomer **108a** (Scheme 5.13). The carbonyl group in enaminone **108a** further reacts with acetylcyanide (**2a**) and provides intermediate **109**. Imine **110** is then generated from **109** upon elimination of AcOH (Scheme 5.13). Hydrogen cyanide, which is liberated during the formation of **108**, then adds to imine **110** to provide the cyano nitrile **111**. In this step a chiral centre is generated. The N atom in **111** is nucleophilic enough to undergo cyclization reaction with the nitrile group and amidine **17a** is formed (Scheme 5.13).[132] This is a favourable cyclization process (5-*exo*-dig) according to Baldwin's rules.

We observed from the stoichiometry of the reaction that one molecule of acetic acid is produced in the reaction (Scheme 5.14). It is noticeable from the reaction mechanism that acetic acid is generated before the formation of the chiral centre. Thus acetic acid could catalyze the hydrocyanation of imine **110**. This might be a cause for the poor enantioselectivities observed in the reaction with chiral thiourea or phosphoric acid catalysts. However, amidine **17a** was not formed without the phosphinic acid catalyst. Thus this catalyst could be involved in the tautomerization of **16a**. A ^{1}H NMR spectrum of **16a** did not show the presence of tautomer **16aa**. However, when 1 equivalent of **16a** and one equivalent of catalyst

4 were stirred in $CDCl_3$ solvent for 2 hours at room temperature, a 1:2:0.5 mixture of the protonated **16a, 16a** and **16aa** was obtained. The presence of **16aa** was confirmed by the ^1H NMR spectrum of the mixture which showed the appearance of characteristic methylene protons of the olefin bond at δ 3.82 and by ninhydrin staining (purple color) in thin layer chromatography (TLC).



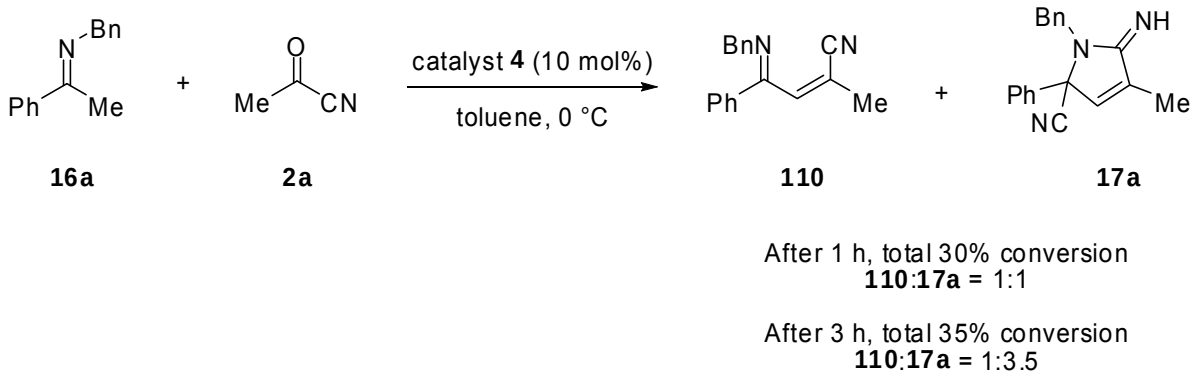
Scheme 5.13 Plausible mechanism of the formation of amidine **17a**.



Scheme 5.14 The stoichiometry of amidine formation reaction.

To support our proposed mechanism, another control experiment was performed using 1 equivalent of acetyl cyanide (**2a**) (Scheme 5.15) and we were able to detect one of the reaction intermediate **110** (m/z: 66, 105, 155, 245, 260) in GCMS. After 1 hour, the reaction

mixture showed a 30% conversion to a 1:1 mixture of intermediate **110** and product **17a** (Scheme 5.15). However, after 3 hours, the ratio of intermediate **110** and product **17a** changed to 1:3.5 with a total conversion of 35% (Scheme 5.15). This indicates that intermediate **110** is slowly converted to product **17a** by the reaction with HCN.



Scheme 5.15 Control experiment with 1 equivalent of acetylcyanide (**2a**).

5.8 Catalytic Three-Component Ugi Reaction

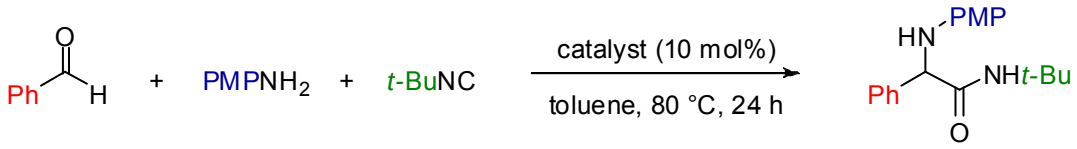
5.8.1 Catalyst Screening and Optimization of the Reaction Conditions

Though different Ugi reaction variants have been reported in the litearture there is no catalytic version of this useful reaction for the generation of an α-amino carbonyl framework.[73] Initially we investigated the background reaction by mixing benzaldehyde (**14a**), *para*-anisidine (**15a**), and *tert*-butyl isocyanide (**18a**) without any catalyst. Stirring at room temperature for 3 days in toluene (1 M concentration) resulted in no detectable quantities of desired product **19a** (Table 5.17). Even heating the reaction mixture at 80 °C for 24 hours did not result in the formation of product **19a**. At this point, we started to investigate different Brønsted acid catalysts for this reaction (Table 5.17). *Para*-toluenesulfonic acid (**20**) gave no conversion to the product either at room temperature or at 80 °C (Table 5.17, entry 1). Little conversion (determined by GC) to product **19a** could be realized when phenyl boronic acid (**21**) or diphenyl phosphate (**22**) were used as catalysts (entries 2-3). $Sc(OTf)_3$ (**23**) could also promote this reaction but with only 30% conversion (entry 4). Phenyl phosphonic acid (**24**) gave a moderate conversion of 35% (entry 5). Remarkably, phenyl phosphinic acid (**4**) was found to be a highly active catalyst for the reaction giving desired product **19a** in 95% conversion (entry 6). The structure of **19a** was supported by its ^{1}H and ^{13}C NMR spectral data and by HRMS. The ^{1}H NMR spectrum of **19a** showed the presence of two singlets at δ 4.44 (1H) and 1.23 (9H) which are the characteristic peaks of the proton of the α-amino carbonyl functionality and the *tert*-butyl group respectively. Further, a 13-line ^{13}C NMR spectrum (with a characteristic amide carbonyl peak at δ 170.1) confirmed the formation of product **19a**. Diphenyl phosphinic acid (**25**) and diphenyl phosphine oxide (**26**) were also investigated as catalysts for this novel transformation. However, both are not active catalysts for this new reaction and only gave 0-8% conversions (entries 7-8). Decreasing the catalyst loading of phenyl phosphinic acid (**4**) to 5 mol% resulted in considerably lower conversion (83%) (entry 9). When the reaction was carried out in 0.5 M solvent concentration, also a lower conversion (65%) was obtained (entry 10).

Table 5.17 Identification of an efficient catalyst for the three-component Ugi reaction.

20 **21** **22** **23**

24 **4** **25** **26**



14a **15a** **18a** **19a**

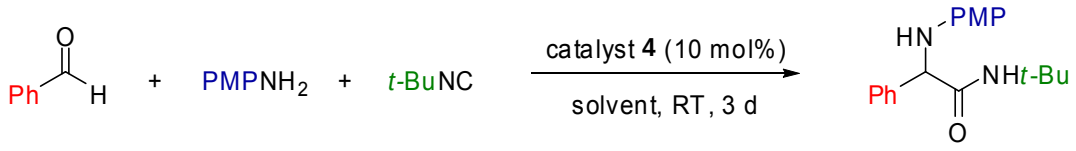
Entry[a]	Catalyst	Conversion (%)[b]
1	**20**	0
2	**21**	8
3	**22**	15
4	**23**	30
5	**24**	35
6	**4**	95
7	**25**	8
8	**26**	0
9[c]	**4**	83
10[d]	**4**	65

[a] Reaction condition: Aldehyde **14a** (0.5 mmol), amine **15a** (0.5 mmol), isocyanide **18a** (0.5 mmol) and catalyst (10 mol%) were stirred in 0.5 mL of dry toluene. [b] Determined by GC. [c] 5 mol% of the catalyst. [d] Reaction was carried out in 0.25 mL of toluene.

Further examinations concentrated on the solvent (Table 5.18) and for comparison, the reactions were run at room temperature for 3 days. While the three-component Ugi reaction

could be performed in all the solvents tested, the best conversions were achieved in nonpolar aromatic solvents (Table 5.18, entry 1-2), followed by polar aprotic solvents (entries 3-8). It was intriguing for us that the polar protic solvents such as methanol and trifluoroethanol, which are the best solvents for the four component Ugi reactions, gave poor conversions for this new three-component reaction (entries 9 and 10, Table 5.18).

Table 5.18 Screening of different solvents for the three-component Ugi reaction.



14a **15a** **18a** **19a**

Entry	Solvent	Conversion (%)[a]
1	Toluene	96
2	Benzene	94
3	CH_2Cl_2	95
4	$CHCl_3$	92
5	CH_3CN	85
6	1,4-Dioxane	89
7	DMF	89
8	DMSO	93
9	MeOH	30
10	CF_3CH_2OH	52

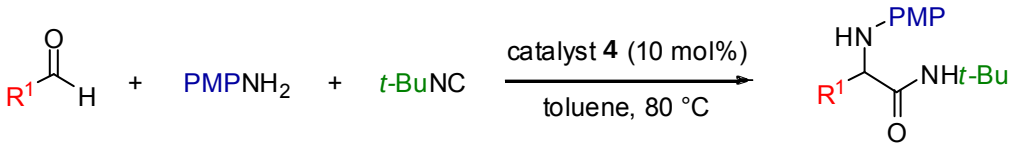
[a] Determined by GC.

5.8.2 Substrate Scope

Using phenyl phosphinic acid (**4**) as the catalyst and toluene as the solvent, we next studied the scope of this new three-component reaction. First, the reaction of a variety of different aldehydes **14** with *para*-anisidine (**15a**) as the amine component and *tert*-butyl isocyanide (**18a**) was examined (Table 5.19). Noteworthy, the reactions took place efficiently in good yields for all studied aldehydes. Particularly high yields (78-91%) were observed with

aromatic aldehydes (entries 1-5) and an α,β-unsaturated aldehyde (entry 6). Heteroaromatic 3-pyridyl carbaldehyde can also be employed and moderate yield (51%) of **19g** was obtained (entry 7). Even aliphatic α-branched aldehydes and an α-unbranched aldehyde gave good yields (entries 8-11). For example, *iso*-butyraldehyde provided product **19h** in 74% yield (entry 8) and 52% yield was obtained with pivalaldehyde (entry 10).[134]

Table 5.19 Catalytic three-component Ugi reaction of different aldehydes with *t*-butyl isocyanide and *p*-anisidine.



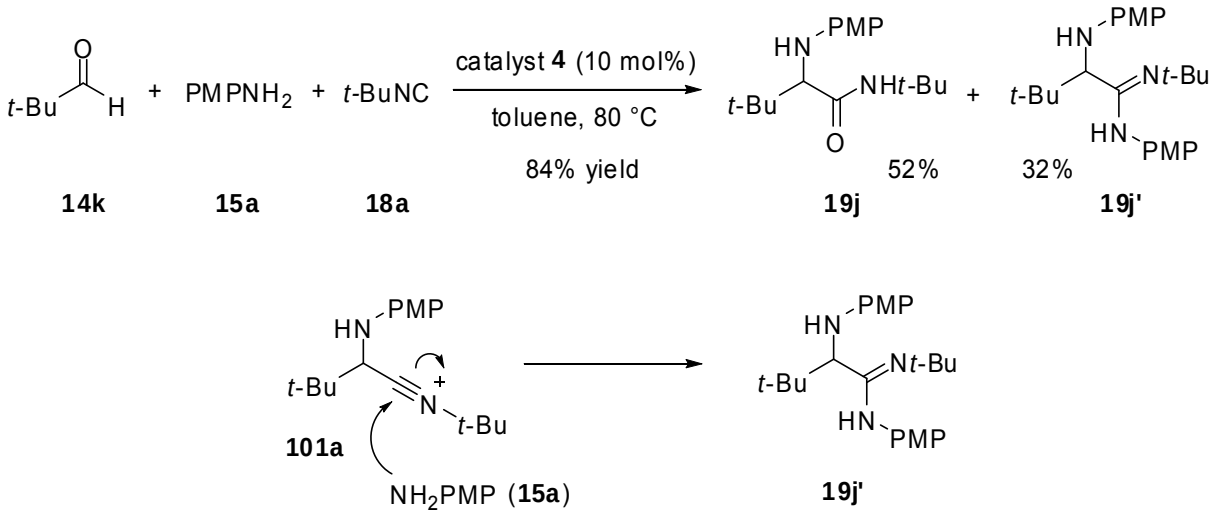
14 **15a** **18a** **19**

Entry[a]	R^1	Product	Time (h)	Yield (%)
1	Ph	**19a**	12	91
2	4-$MeOC_6H_4$	**19b**	12	88
3	4-ClC_6H_4	**19c**	20	78
4	2-ClC_6H_4	**19d**	20	82
5	2-Naphthyl	**19e**	20	87
6[b]	1-Cinnamyl	**19f**	20	83
7	3-Pyridyl	**19g**	20	51
8	*i*-Pr	**19h**	20	74
9	*c*-Hex	**19i**	20	81
10	*t*-Bu	**19j**	20	52
11	*n*-Bu	**19k**	20	61

[a] Reaction conditions as described in Table 5.17, entry 6 were used. [b] Using 20 mol% of catalyst **4**.

For pivalaldehyde, a side product α-amino amidine **19j'** was obtained in 32% yield where two molecules of *para*-anisidine were consumed (Scheme 5.16). Its structure was confirmed by its ^1H NMR and ^{13}C NMR spectral data. In the ^1H NMR spectrum, two singlet methyl proton resonances were observed at δ 3.71 and δ 3.67, suggesting the presence of two *para*-

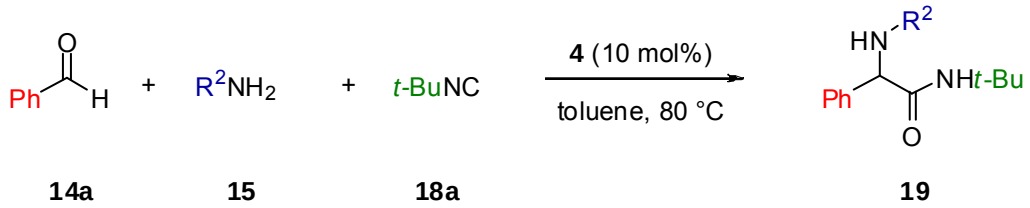
methoxyphenyl (PMP) groups. The presence of amidine carbon was confirmed by the appearence of a characteristic peak at δ 154.1 in the ^{13}C NMR spectrum. One molecule of *para*-anisidine (**15a**) was utilized for the imine formation and another molecule was used for the generation of amidine functionality that was formed from the addition reaction of *para*-anisidine (**15a**) to nitrilium ion **101a** (Scheme 5.16).



Scheme 5.16 The three-component reaction with pivalaldehyde (**14k**).

A variety of amines was investigated using benzaldehyde (**14a**) as the aldehyde component and *tert*-butyl isocyanide (**18a**) as the other component (Table 5.20). It turned out that different aromatic amines could be used to provide products in high yields (74-88%) (entries 1-4, Table 5.20). The electronic properties of the aromatic system of the amine component do not seem to influence the outcome of the reaction. Pyridyl amine having a heteroaromatic moiety has been used and gave desired product **19p** in good yield of 81% (entry 5). The reaction also worked with benzyl amine and benzhydryl amine albeit with slightly lower yields (36-42%) (entries 6-7, Table 5.20). In these cases, the corresponding imines were formed in full conversions but were less reactive. A non-aromatic (allyl) amine has also been employed and moderate yield (40%) was observed (entry 8). Finally a secondary amine (diphenyl amine) was probed and provided product **19t** in 41% yield (entry 9).[134]

Table 5.20 Catalytic three-component Ugi reaction of benzaldehyde with different amines and *t*-butyl isocyanide.



14a **15** **18a** **19**

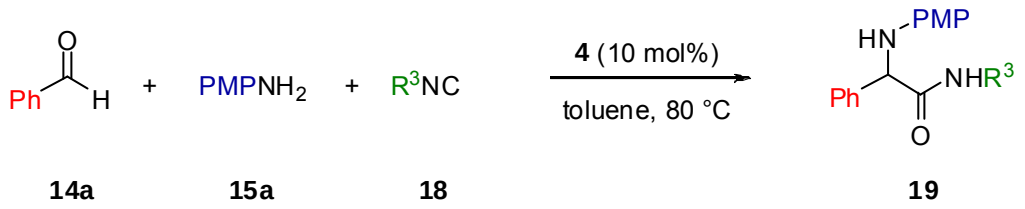
Entry[a]	R^2	Product	Time (h)	Yield (%)
1	2-Naphthyl	**19l**	20	83
2	4-$CF_3C_6H_4$	**19m**	20	81
3	4-$CO_2EtC_6H_4$	**19n**	20	88
4	3-ClC_6H_4	**19o**	20	74
5	3-Pyridyl	**19p**	20	81
6	$PhCH_2$	**19q**	20	42
7[b]	$(Ph)_2CH$	**19r**	36	36
8	Allyl	**19s**	20	40
9	$R^2{}_2NH = (Ph)_2NH$	**19t**	36	41

[a] Reaction conditions as described in Table 5.17, entry 6 were used. [b] Using 20 mol% of catalyst **4**.

The isocyanide component of our reaction can equally be varied (Table 5.21). Cyclohexyl isocyanide and benzyl isocyanide gave corresponding products **19u** and **19v** in 78% and 64% yields respectively (entries 1-2). Good result (62%) was also obtained with a longer chain isocyanide (entry 3). Even functionalized isocyanides provided products **19x** and **19y** in high yields (68-83%) (entries 4-5).[134]

The broad scope, operational simplicity, practicability, and mild reaction conditions of this process render it an attractive approach for the preparation of different α-amino amides which are buiding blocks in many natural products and obviously in peptides. The reaction will be useful not only for the synthesis of α-amino acid derivatives, but also for the diversity oriented synthesis[149] and for the design of pharmaceutical and agrochemical substance sortiments.

Table 5.21 Catalytic three-component Ugi reaction of benzaldehyde with *p*-anisidine and different isocyanides.



14a **15a** **18** **19**

Entry[a]	R^3	Product	Time (h)	Yield (%)
1	*c*-Hex	**19u**	20	78
2	$PhCH_2$	**19v**	36	64
3	*t*-$BuCH_2C(Me_2)$	**19w**	20	62
4	EtO_2CCH_2	**19x**	20	83
5	*p*-$TsCH_2$	**19y**	20	68

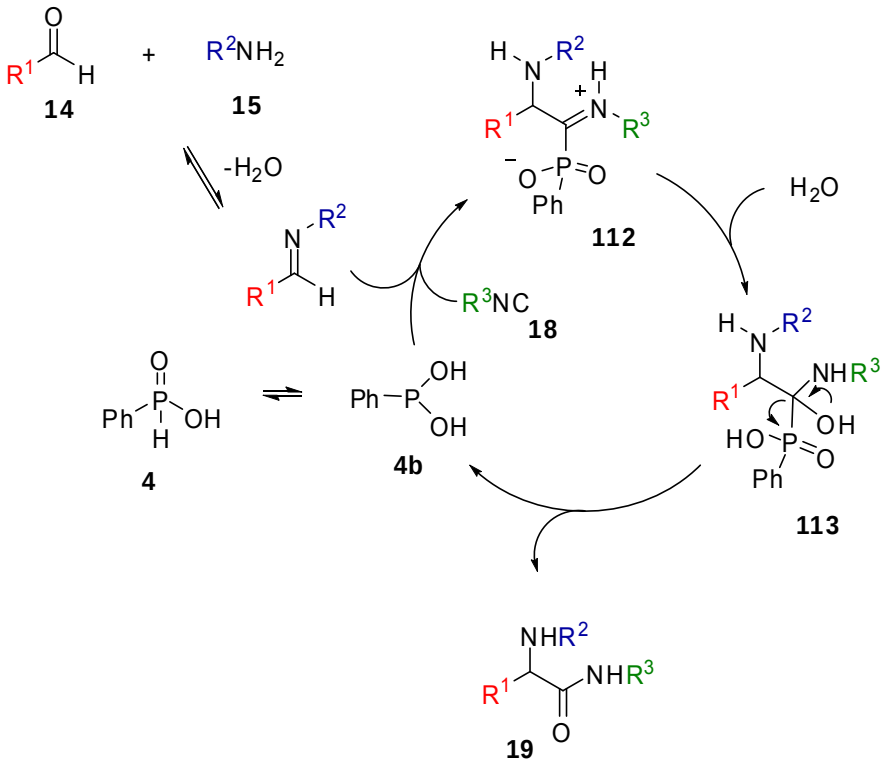
[a] Reaction conditions as described in Table 5.17, entry 6 were used.

5.8.3 Mechanism of the Three-Component Ugi Reaction

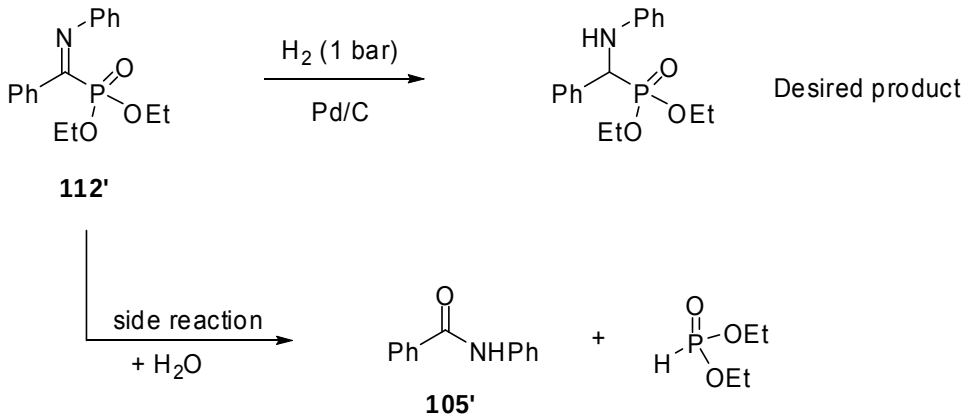
A catalytic cycle for the three-component Ugi reaction leading to α-amino amide product **19** was envisaged and shown in Scheme 5.17. Phenyl phosphinic acid (**4**) can be considered a Brønsted acid and, in the form of its phenyl phosphonous acid tautomer (**4b)**, a Lewis base. It is speculated that both properties are required for effective catalysis. Thus, the catalytic cycle may be initiated via protonation of the *in situ* generated imine from aldehyde **14** and amine **15** (Scheme 5.17). Subsequently, the nitrilium ion that is formed after the addition of isocyanide **18** could be trapped by the nucleophilic phosphinate anion giving intermediate **112**. It was interesting to notice that the both protons of catalyst **4** are transferred to the two nitrogen atoms in **112** (Scheme 5.17). H_2O, which is liberated during the imine formation, reacts with the activated imino group in intermediate **112** and geminal amino alcohol **113** is formed. Amino alcohol **113** could then fragment to α-amino amide **19** and catalyst **4** (Scheme 5.17).[134] This might be a consequence of the good leaving group ability of the phosphinate group.

Goulioukina et al. reported an interesting synthetic study on α-iminophosphonates **112'** that provides a support for this mechanistic hypothesis (Scheme 5.18).[135] The authors have

observed the hydrolysis of α-iminophosphonate **112'** to the corresponding amide (**105'**) as an unwanted side reaction in their hydrogenation reaction (Scheme 5.18). In our reaction mechanism, α-iminophosphinate **112** is an intermediate. Thus, it is possible that it could also react with water in similar way generating amino alcohol **113** which fragments to amide **19** and catalyst **4**.

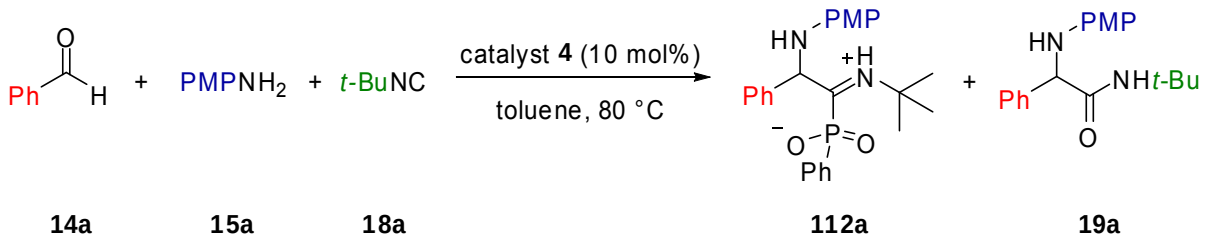


Scheme 5.17 Proposed mechanism for the catalytic three-component Ugi reaction.



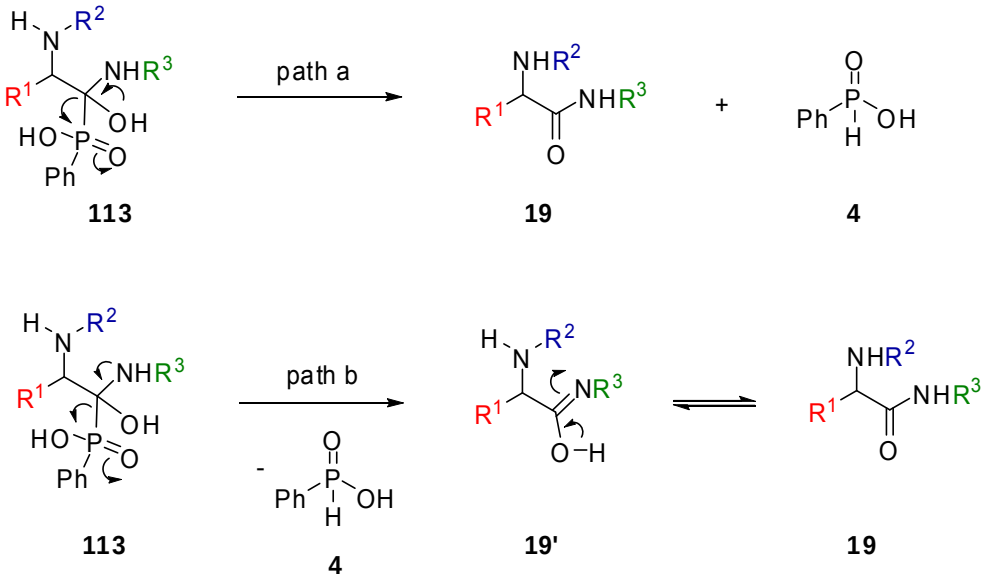
Scheme 5.18 Hydrogenation reaction of α-iminophosphonate **112'** by Goulioukina et al.

To confirm the reaction mechanism, we carried out ESI (electrospray ionisation) mass spectrometry study of the reaction between benzaldehyde (**14a**), *para*-anisidine (**15a**) and *tert*-butyl isocyanide (**18a**) in toluene at 80 °C. We could clearly detect intermediate **112a** (exact molecular mass 436.1916, found 436.1920) in this study (Scheme 5.19). The amount of both **112a** and product **19a** slowly increased over the time from 1 hour to 6 hour. Thus, the *in situ* generated imine gradually reacted with isocyanide **18a** to form intermediate **112a** which became converted to product **19a**. However, we could not find the corresponding water addition intermediate **113a** (R^1 = Ph, R^2 = PMP, R^3 = *t*-Bu in Scheme 5.17) by this study. This might be due to very temporary stability of **113a**.



Scheme 5.19 ESI-MS study of the reaction between benzaldehyde (**14a**), *para*-anisidine (**15a**) and *tert*-butyl isocyanide (**18a**).

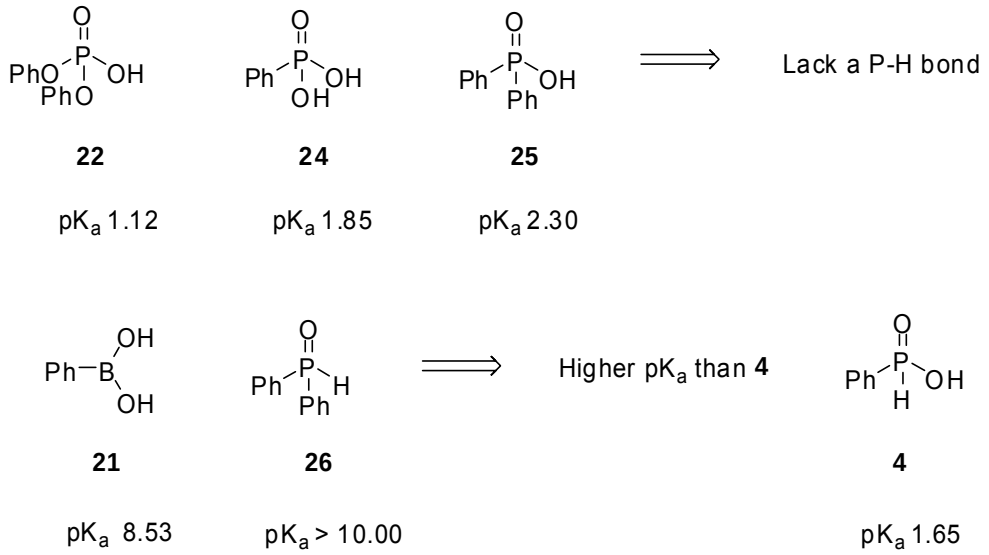
We considered that amino alcohol **113** could fragment to α-amino amide **19** in two pathways (Scheme 5.20). Either alcohol or the amino group could participate in the elimination process



Scheme 5.20 Fragmentation of the amino alcohol **113**.

(path a and path b). When the alcohol group participates, then α-amino amide **19** is formed directly (path a). However, when the amino group takes part, then imino alcohol **19'** is first formed which tautomerizes to amide **19** (Scheme 5.20). As the amines are more nucleophilic than the alcohols, path b could be more probable.

That the other catalysts are not active might be due to the fact that they do not have either appropriate pK_a or they lack the bifunctional character of a Lewis base and a Brønsted acid. For example, catalysts **22**, **24** and **25** could not act as the Lewis base through phosphorous atom as they don't have a P-H bond and hence could not tautomerize to phosphonous acid isomer (Scheme 5.21). *Para*-toluene sulfonic acid (**20,** pK_a -0.43), phenyl boronic acid (**21**, pK_a 8.53) and $Sc(OTf)_3$ (**23**) also lack the properties of Lewis base. On the contrary, catalyst **26** could act as Lewis base but it is a very weak Brønsted acid as its pK_a value (> 10.00) is much higher than that of catalyst **4** (pK_a 1.65) (Scheme 5.21). Thus, this catalyst is not strong enough to activate the imine for the addition of isocyanide **18** and no product **19a** was formed.



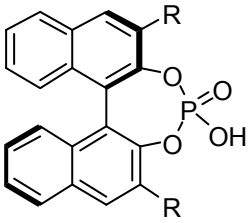
Scheme 5.21 Inactive catalysts **21**, **22**, **24**, **25**, **26** and their pK_as in water.

5.9 Catalytic Asymmetric Three-Component Ugi Reaction

5.9.1 Catalyst Screening

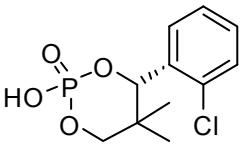
To develop an asymmetric version, the reaction of benzaldehyde (**14a**), *para*-anisidine (**15a**) and *tert*-butyl isocyanide (**18a**) in toluene was investigated. Chiral BINOL-derived phosphoric acid catalysts **6b**, **6c**, **6f**, **6g** were first screened followed by two other

commercially available chiral phosphoric acid catalysts **114** and **115** (Scheme 5.22). BINOL-derived phosphoric acid catalysts provided product **19a** in low yields and with poor enantioselectivities (Table 5.22, entries 1-4). The highest enantioselectivity (59:41 er) was obtained with catalyst **6c** (TRIP) (entry 2). Catalyst **114** and **115** could promote the reaction with better conversion (67-68%); however a racemic product was obtained (entries 5-6).

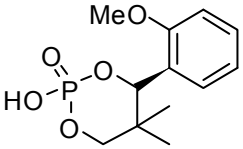


6

6b (R = 2-naphthyl)
6c (R = 2,4,6-*i*-$Pr_3C_6H_2$)
6f (R = $SiPh_3$)
6g (R = 9-anthracenyl)



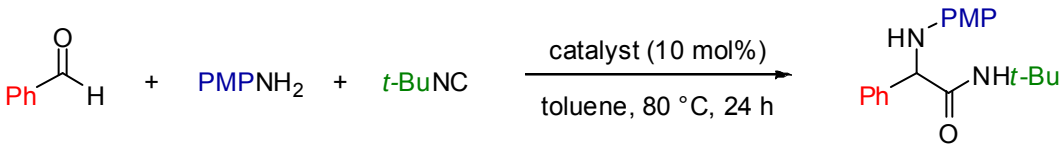
114



115

Scheme 5.22 Structures of different chiral phosphoric acid catalysts.

Table 5.22 Catalytic asymmetric three-component Ugi reaction using chiral phosphoric acids as catalysts.



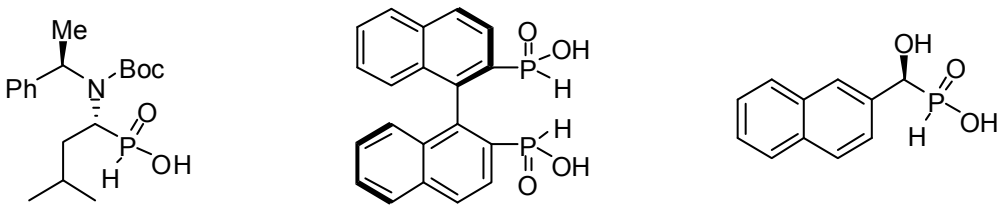
14a **15a** **18a** **19a**

Entry[a]	Catalyst	Conversion (%)	er
1	**6b**	14	51:49
2	**6c**	15	59:41
3	**6f**	12	51:49
4	**6g**	14	56:44
5	**114**	68	50:50
6	**115**	67	50:50

[a] Reaction conditions: Aldehyde **14a** (0.2 mmol), amine **15a** (0.2 mmol), isocyanide **18a** (0.2 mmol) and catalyst (10 mol%) were stirred in 0.2 mL of dry toluene.

Changing the reaction temperature and the solvent could not improve the enantioselectivity of this reaction.

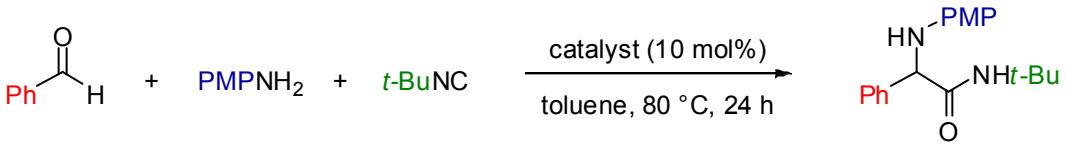
Then different chiral phosphinic acid catalysts **27**-**29** were prepared (Scheme 5.23). Chiral phosphinic acids were not previously used in asymmetric catalysis. *N*-Boc protected α-amino phosphinic acid **27** provided product **19a** in 45% conversion with 51:49 er (Table 5.23, entry 1). Then binaphthyl moiety containing bisphosphinic acid **28** was prepared. Though this catalyst significantly improved the conversion (90%) of product **19a**, enantioselectivity was unchanged (52:48 er) (Table 5.23, entry 2). Finally, a chiral α-hydroxy phosphinic acid **29** was tested for this reaction. Though, this catalyst was also found to catalyze the reaction efficiently, only low enantioselectivity (53:47 er) was obtained (Table 5.23, entry 3). Nevertheless, with some other chiral phosphinic acid catalysts, the enantioselectivity could be improved.



27 **28** **29**

Scheme 5.23 Structures of different chiral phosphinic acid catalysts.

Table 5.23 Catalytic asymmetric three-component Ugi reaction using chiral phosphinic acids as catalysts.



14a **15a** **18a** **19a**

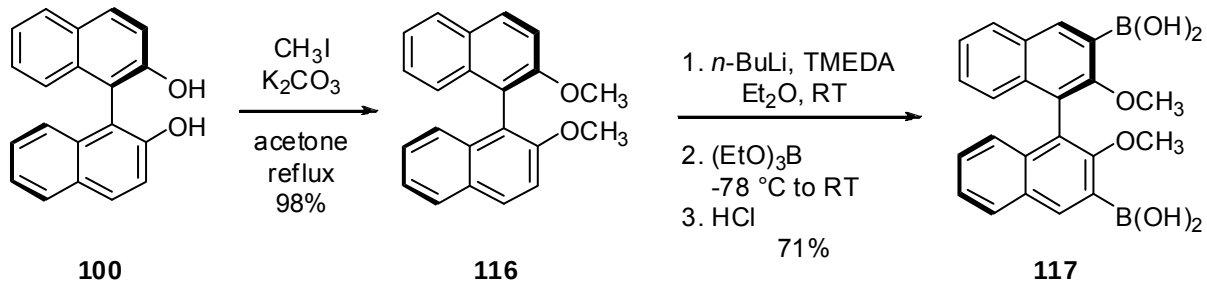
Entry[a]	Catalyst	Conversion (%)	er
1	**27**	45	51:49
2	**28**	90	52:48
3	**29**	82	53:47

[a] Reaction conditions as described in Table 5.22 were used.

5.10 Synthesis of Catalysts

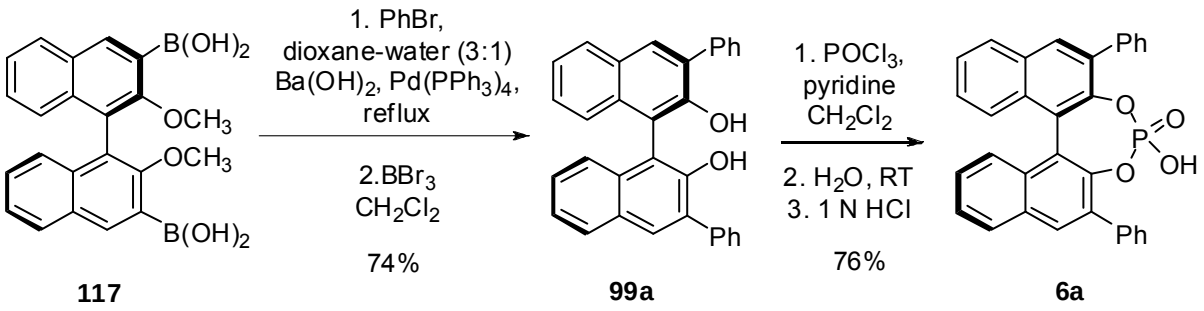
5.10.1 Preparation of Chiral BINOL-Derived Phosphoric Acid Catalysts

Chiral phosphate **6a** was synthesized starting from chiral BINOL **100**. Methylation of BINOL **100** with methyl iodide provided dimethoxybinaphthyl **116** in 98% yield (Scheme 5.24). Compound **116** was converted to diol **99a** according to the literature procedure by Wipf et al. (Scheme 5.24).[136] First, **116** was treated with *n*-BuLi and *N,N,N′,N′*-tetramethylenediamine (TMEDA) in ether at room temperature to generate the *ortho*-dilithiated compound, which was reacted with triethylborate at −78 °C. During acidic workup, the borate was hydrolyzed to give boronic acid **117** in 71% yield (Scheme 5.24).



Scheme 5.24 Preparation of bis(boronic acid) **117** from BINOL **100**.

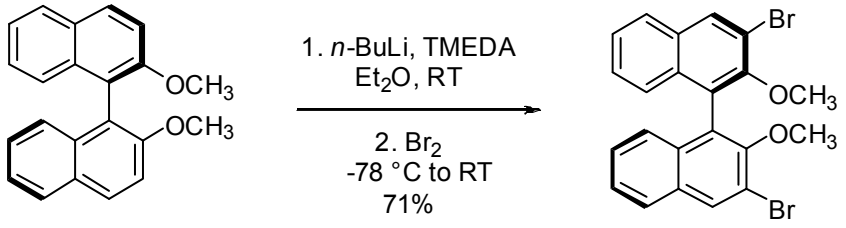
Suzuki cross-couplings of boronic acid **117** with bromobenzene was performed using $Pd(PPh_3)_4$ as catalyst in combination with barium hydroxide base (Scheme 5.25).[136] The crude product was demethylated using BBr_3 to afford diol **99a** in 74% yield. Then phosphorylation of diol **99a** was accomplished with phosphoryl trichloride in pyridine at room temperature (Scheme 5.25). Finally, hydrolysis of the phosphoryl chloride with water and acidic workup provided chiral phosphoric acid **6a** in 76% yield (Scheme 5.25). Catalysts **6b**, **6d**, **6e**, **6g**, **6h**, **6i**, **6j**, **6k**, **6m** were prepared by other group members according to the similar methodology.



117 **99a** **6a**

Scheme 5.25 Preparation of BINOL phosphate **6a** from bis(boronic acid) **117**.

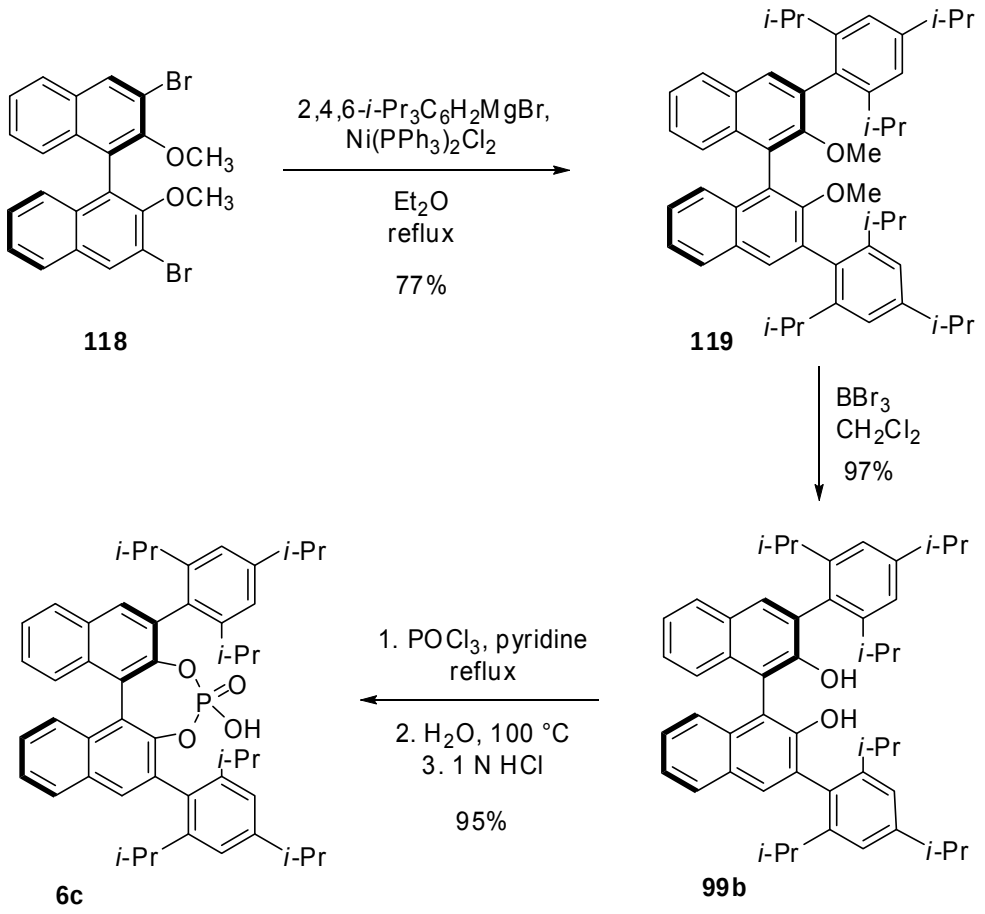
For the preparation of catalyst **6c**,[137] dibromide **118** was chosen as the starting point and the procedure of Schrock et al. for the preparation of diol **99b** was followed (Scheme 5.26 and 5.27).[138] Dibromide **118** was prepared from **116** by *ortho*-lithiation with *n*-BuLi and TMEDA followed by quenching with bromine (Scheme 5.26).



116 **118**

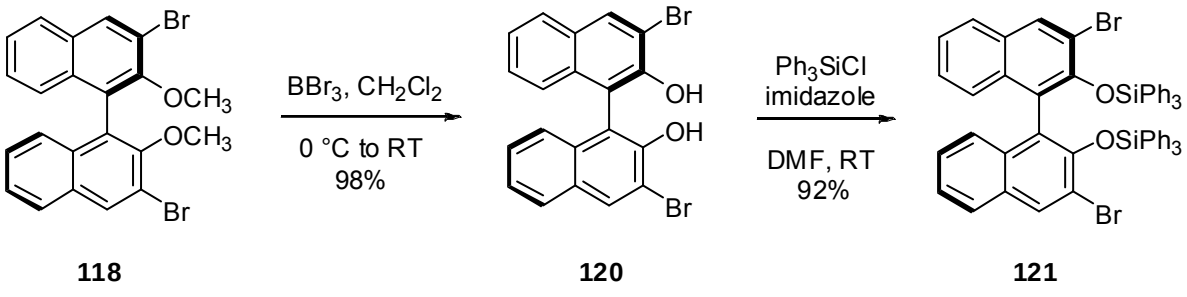
Scheme 5.26 Preparation of dibromide **118** from **116**.

Then Kumada coupling of dibromide **118** was carried out with (2,4,6-triisopropylphenyl) magnesium bromide in the presence of $Ni(PPh_3)_2Cl_2$ to provide 3,3′-diaryl methylether **119** in 77% yield (Scheme 5.27). Deprotection of the methyl groups was accomplished using BBr_3 in dichloromethane and diol **99b** was obtained in 97% yield (Scheme 5.27). Then phosphorylation of **99b** was achieved using phosphoryl trichloride in pyridine under reflux condition (Scheme 5.27). Finally, hydrolysis with water at reflux temperature followed by treating with 1 N HCl afforded phosphoric acid catalyst **6c** in high yield (95%) (Scheme 5.27).



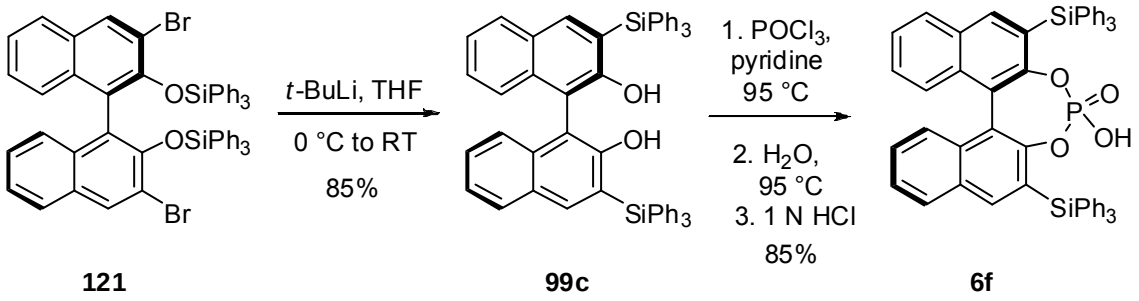
Scheme 5.27 Preparation of BINOL phosphate **6c** from dibromide **118**.

For catalyst **6f**,[139] the requisite diol **99c** was prepared according to the literature procedure by Yamamoto et al.[140] Bis(silyl) ether **121** was readily obtained from **118** in two steps. Thus, the demethylation of **118** with BBr_3 (5.5 equiv.) in CH_2Cl_2 at room temperature for 3 hours afforded diol **120** in almost quantitative yield (Scheme 5.28). Diol **120** was then treated with triphenylsilyl chloride and imidazole in DMF at room temperature for several hours, producing bis(triphenylsilyl)ether **121** in 92% yield (Scheme 5.28).



Scheme 5.28 Preparation of bis(triphenylsilyl)ether **121** from **118**.

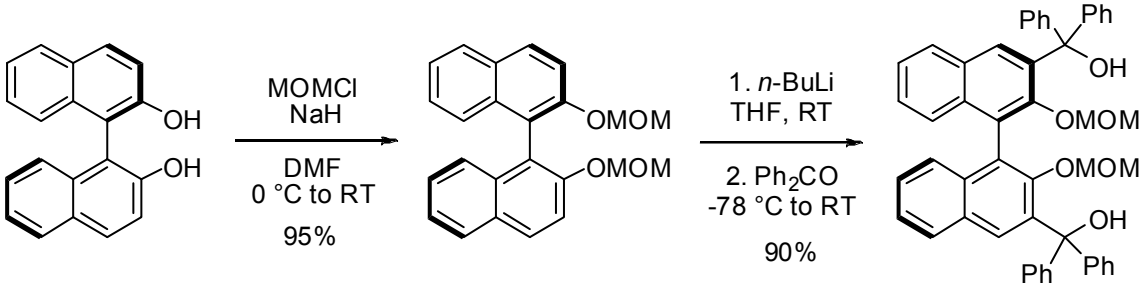
Treatment of **121** with *t*-BuLi (3.0 equiv.) in THF generated the lithiated carbanions which underwent facile 1,3-silyl transfer and furnished the corresponding 3,3′-bis(triphenylsilyl)-BINOL **99c** in 85% yield (Scheme 5.29). Then phosphorylation of **99c** was accomplished using phosphoryl trichloride in pyridine at 95 °C.[139] Finally, hydrolysis with water at the same temperature followed by workup with 1 N HCl afforded phosphoric acid catalyst **6f** in 85% yield (Scheme 5.29).



121 **99c** **6f**

Scheme 5.29 Preparation of phosphoric acid catalyst **6f** from **121**.

For the preparation of catalyst **6l**, requisite diol **99d** was prepared according to the procedure reported by Fan et al. (Scheme 5.31) [141] At first MOM-protected BINOL **122** was prepared in 95% yield from (*R*)-BINOL **100** using MOMCl and sodium hydride (Scheme 5.30).[142] Then compound **122** was lithiated with *n*-BuLi followed by reaction with benzophenone to provide diol **123** in 90% yield (Scheme 5.30).[141]

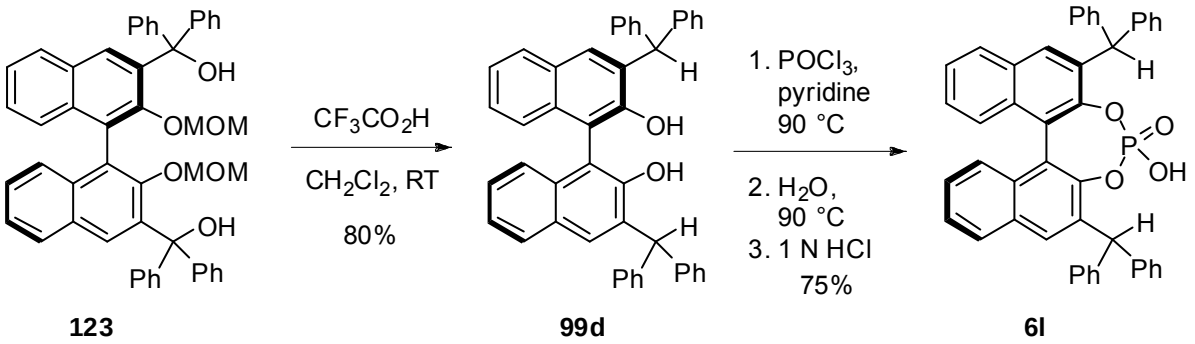


100 **122** **123**

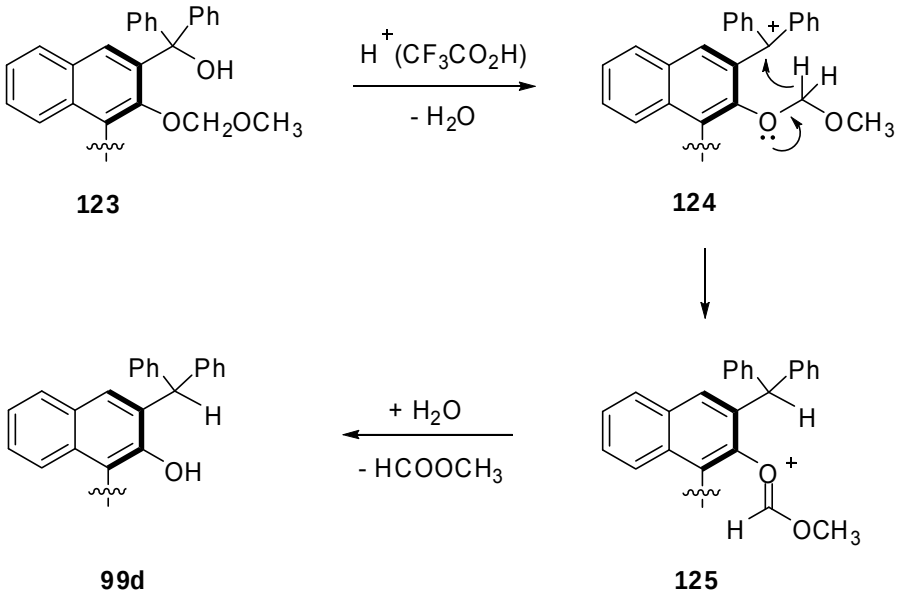
Scheme 5.30 Preparation of intermediate **123** from BINOL **100**.

3,3′-Dibenzhydryl BINOL **99d** was synthesized in high yield by treatment of **123** with trifluoroacetic acid (3.5 equiv.) in dichloromethane at room temperature (Scheme 5.31). A pathway including hydride transfer as the key step for this reaction is proposed (Scheme 5.32). First, triarylmethylium cation **124** was obtained by treatment of **123** with trifluoroacetic acid. A dark-red mixture was immediately observed after addition of trifluoroacetic acid. This

indicated the formation of cations. Then, an oxonium ion **125** was formed through a hydride-transfer step (Scheme 5.32). Reaction of **125** with water provided **99d** and methyl formate (Scheme 5.32). Phosphorylation of **99d** using phosphoryl trichloride in pyridine at 90 °C followed by hydrolysis with water at the same temperature and workup with 1 N HCl provided desired new phosphoric acid catalyst **6l** in 75% yield (Scheme 5.31).



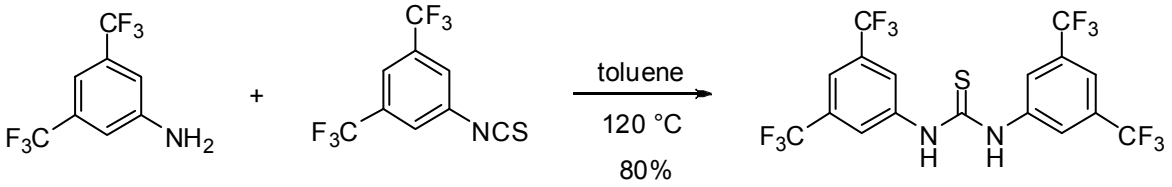
Scheme 5.31 Preparation of phosphoric acid catalyst **6l** from **123**.



Scheme 5.32 Proposed mechanism for the reaction of **123** with trifluoroacetic acid.

5.10.2 Preparation of Thiourea Catalysts

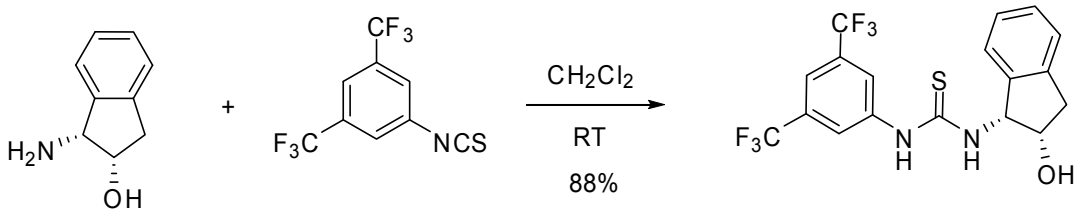
Schreiner thiourea catalyst **5** was prepared according to a modified procedure reported by Schreiner et al.[143] After stirring 3,5-bis(trifluoromethyl)aniline (**126**) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**127**) in toluene at 120 °C, catalyst **5** was isolated in 80% yield (Scheme 5.33).



126 **127** **5**

Scheme 5.33 Preparation of thiourea catalyst **5**.

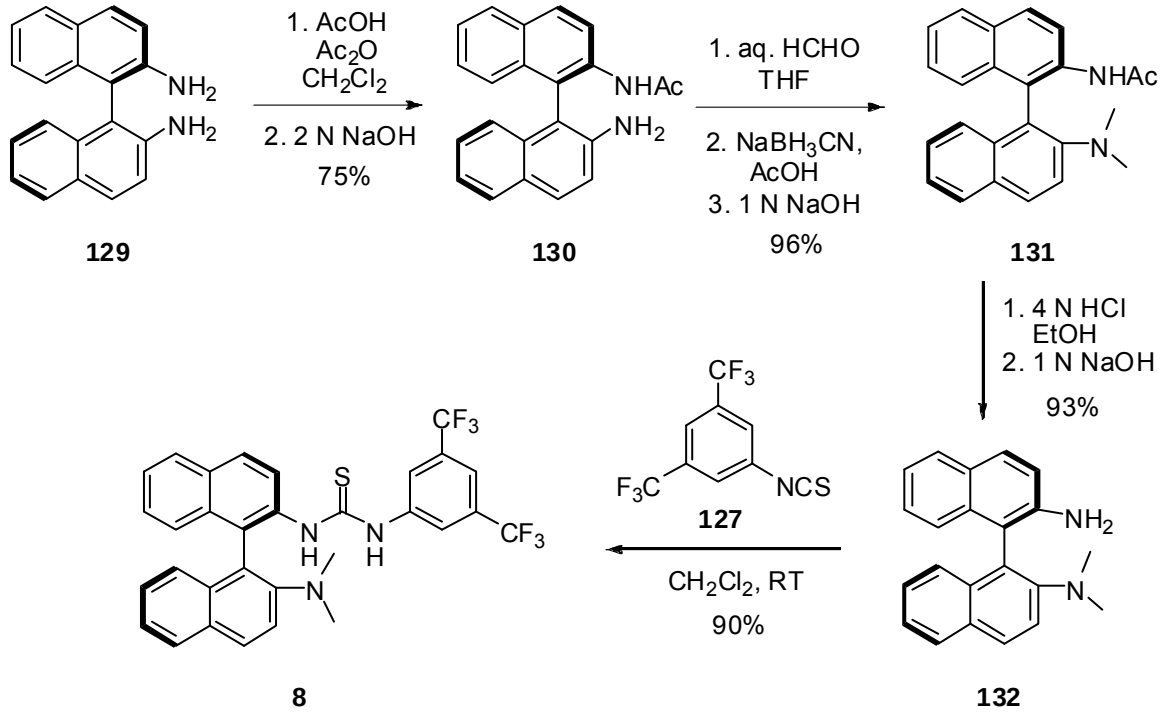
Thiourea catalyst **7** was prepared according to the procedure by Ricci et al. (Scheme 5.34).[127] After stirring (1*R*,2*S*)-*cis*-1-amino-2-indanol (**128**) with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**127**) in dichloromethane at room temperature, compound **7** was obtained as white solid in 88% yield (Scheme 5.34).



128 **127** **7**

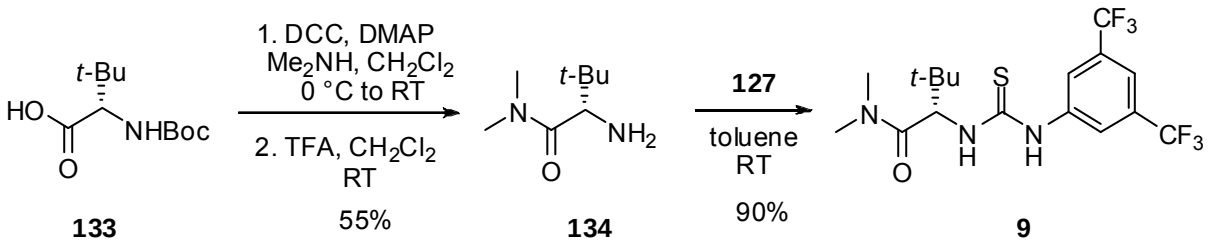
Scheme 5.34 Preparation of thiourea catalyst **7**.

For the preparation of catalyst **8**, the literature procedure of Wang et al.[128] was followed. (*R*)-1,1′-Binaphthyl-2,2′-diamine (**129**) was first converted to monoacetamide **130** using acetic anhydride in the presence of acetic acid (Scheme 5.35). Tertiary amine **131** was obtained in high yield after treatment of compound **130** with aqueous formaldehyde followed by reduction with sodium cyanoborohydride (Scheme 5.35). The acetamide group in **131** was hydrolyzed with HCl to get free amine **132** which was converted to thiourea catalyst **8** after stirring with isothiocyanate **127** (Scheme 5.35).



Scheme 5.35 Preparation of thiourea catalyst **8**.

Catalyst **9** was prepared starting from *N*-Boc-L-*tert*-leucine (**133**) (Scheme 5.36). **133** was first converted to *N*-Boc-L-*tert*-leucine dimethylamide using dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)-pyridine (DMAP) and dimethylamine. The *N*-Boc group was then deprotected using trifluoroacetic acid to get free amine **134** in overall 55% yield.[104b] Finally, catalyst **9** was obtained after stirring **134** and **127** in toluene at room temperature (Scheme 5.36).

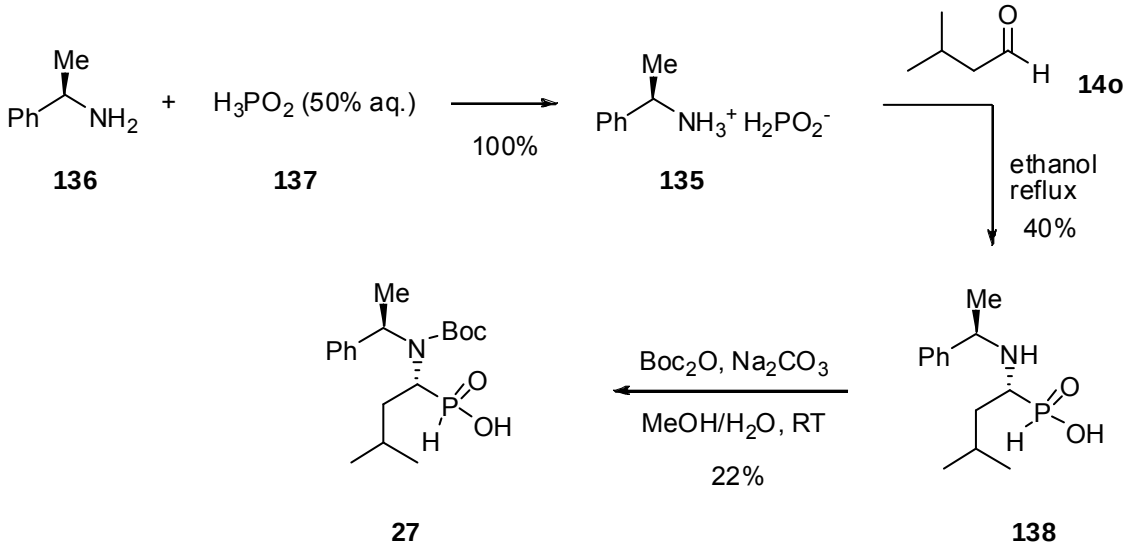


Scheme 5.36 Preparation of thiourea catalyst **9**.

Catalysts **10**, **11** and **12** were prepared by Dr. J. Zhou and other group members according to the procedure of Jacobsen et al.[36,104b]

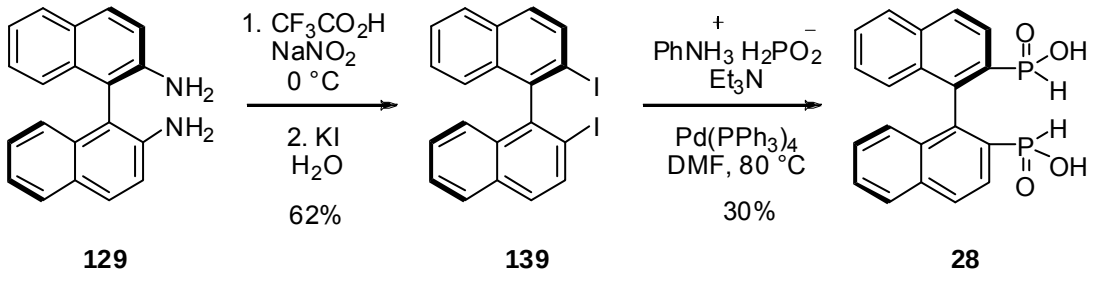
5.10.3 Preparation of Chiral Phosphinic Acids

Catalyst **27** was prepared according to the procedure reported by Hamilton et al.[144] At first, chiral hypophosphorus acid salt **135** was prepared by mixing (*R*)-*N*-α-methylbenzylamine **136** with aqueous hypophosphorus acid **137** (Scheme 5.37). Then salt **135** was reacted with a small excess of aldehyde **14o** in refluxing ethanol to give a precipitate of α-amino phosphinic acid **138** in 40% yield (Scheme 5.37). In this case the imine formation and the hypophosphite addition to imine took place in one pot. Finally, *N*-Boc protection of **138** provided *N*-protected α-amino phosphinic acid **27** in moderate yield (Scheme 5.37).



Scheme 5.37 Preparation of chiral phosphinic acid catalyst **27**.

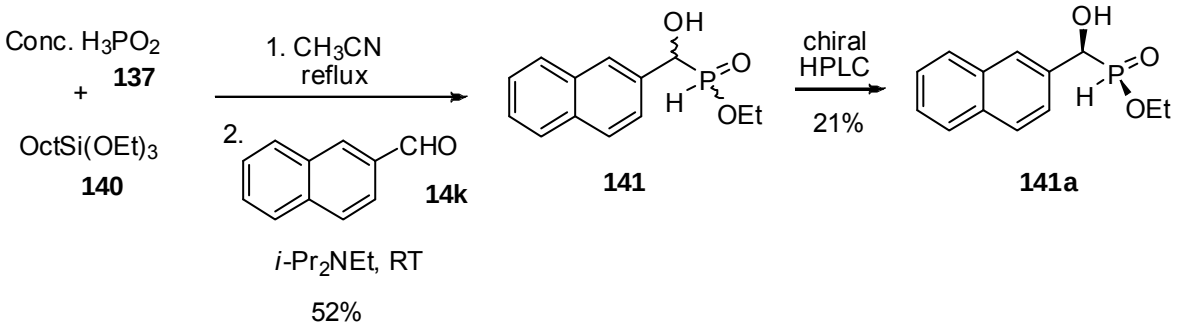
Catalyst **28** was prepared according to the procedure by Montchamp et al.[145] At first, diiodide **139** was prepared from 2,2'-diamino-1,l'-binaphthyl (**129**) by Sandmeyer reaction conditions ($CF_3CO_2H/NaNO_2$ followed by quenching with KI) and good yield (62%) was obtained after



Scheme 5.38 Preparation of chiral phosphinic acid catalyst **28**.

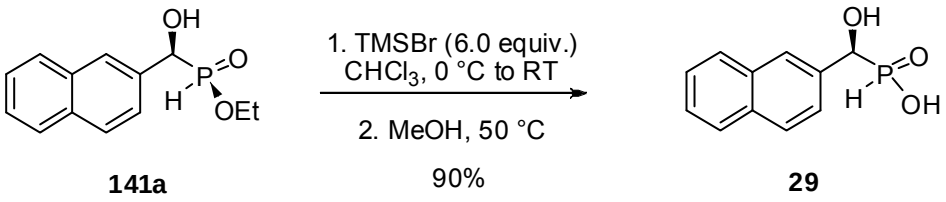
sublimation of the crude product (Scheme 5.38).[146] Then the crucial cross-coupling of **139** with anilinium hypophosphite was carried out in the presence of tetrakis(triphenylphosphine) palladium catalyst and triethylamine base to get new phosphinic acid catalyst **28** in moderate yield (Scheme 5.38).[145]

For the preparation of catalyst **29**, the procedure by Montchamp et al.[147] was followed. Concentrated hypophosphorous acid **137** and octyltriethoxysilane **140** were refluxed in acetonitrile for 2 hours to get a hypophosphite ester which then reacted with naphthaldehyde **14k** in the presence of anhydrous *i*-Pr_2NEt to provide α-hydroxy phosphite **141** in moderate yield (Scheme 5.39). Preparative chiral HPLC separation afforded one enantiomer **141a** (the absolute and relative stereochemistry of **141a** was not determined) out of four stereoisomers in good yield (Scheme 5.39).



Scheme 5.39 Preparation of enantiopure hypophosphite ester **141a**.

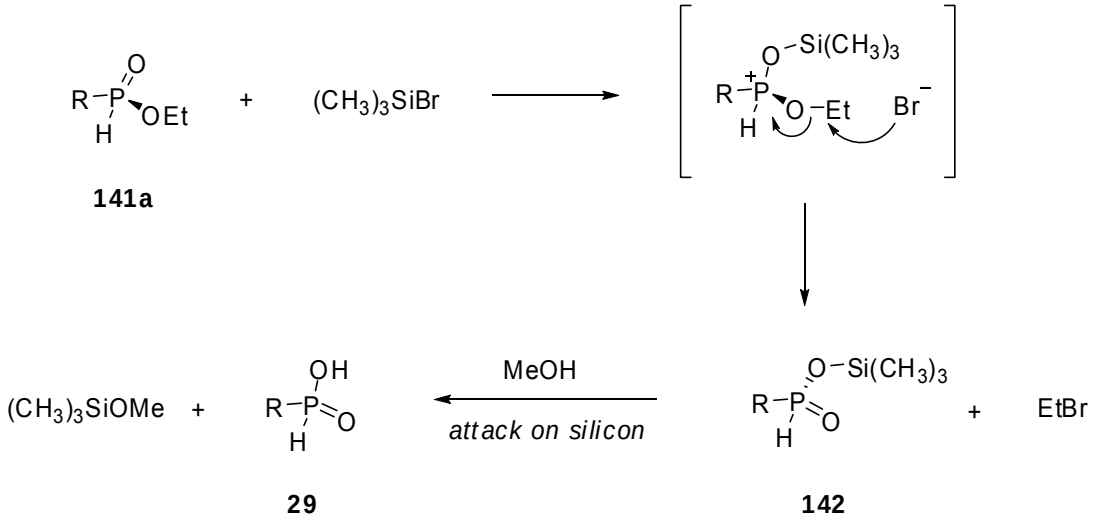
Conversion of 1**41a** to new α-hydroxy phosphinic acid **29** was achieved using trimethylsilyl bromide (TMSBr) and methanol[148] (Scheme 5.40).



Scheme 5.40 Preparation of enantiopure phosphinic acid **29**.

A proposed mechanism for the reaction between **141a** and TMSBr invokes analogy with the Arbuzov reaction: attack on silicon by the phosphoryl oxygen of **141a** is followed by substitution of the displaced bromide ion on the phosphinate ester alkyl group of the same

molecule to generate trimethylsilyl ester **142** of phosphinic acid (Scheme 5.41). Attack of methanol on silicon carbon in **142** provides phosphinic acid **29** (Scheme 5.41).

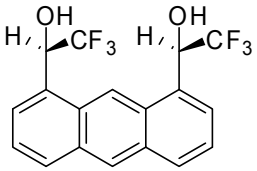


Scheme 5.41 Proposed mechanism for the formation of **29**.

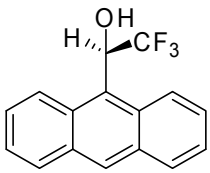
6 Outlook

6.1 Acylcyanation of Imines

The catalytic asymmetric acylcyanation of imines described herein is a versatile method that is applicable for the preparation of a variety of *N*-acetylated α-amino nitriles with excellent enantioselectivities and in high yields. This method would not only be useful for the synthesis of α-amino acids and their derivatives but also may find use in diversity oriented synthesis[149] and medicinal chemistry. Jacobsen thiourea catalyst **11** (see sections 5.2.2 and 5.5.2) was found to be an excellent and highly enantioselective catalyst for this rarely used reaction. Though this catalyst is highly active and at the same time highly enantioselective one drawback is its high molecular weight. As this reaction is general Brønsted acid-catalyzed, there is a possibility that chiral alcohols could also be suitable catalysts for the reaction and high enantioselectivities might be obtained. Several arylalkyl-carbinols are effective as chiral solvating reagents and carbinols **143** and **144** (Scheme 6.1) were used as chiral auxiliaries in the Diels-Alder reactions.[150] However, they were not utilized as catalysts in asymmetric reactions. It will be interesting to apply them as catalysts in our reaction and high enantioselectivities could be achieved.



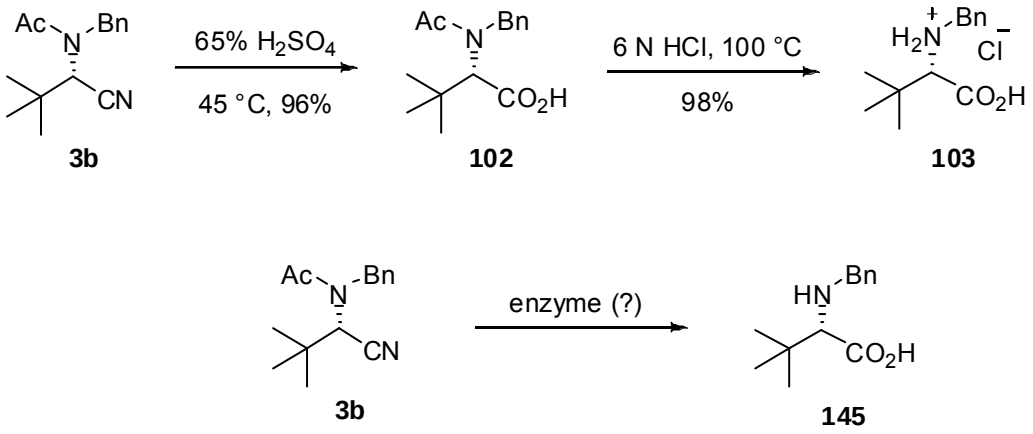
143



144

Scheme 6.1 α,α'-Bis(trifluoromethyl)-1,8-anthracenedimethanol **143** and 2,2,2-trifluoro-1-(9-anthryl)ethanol **144**.

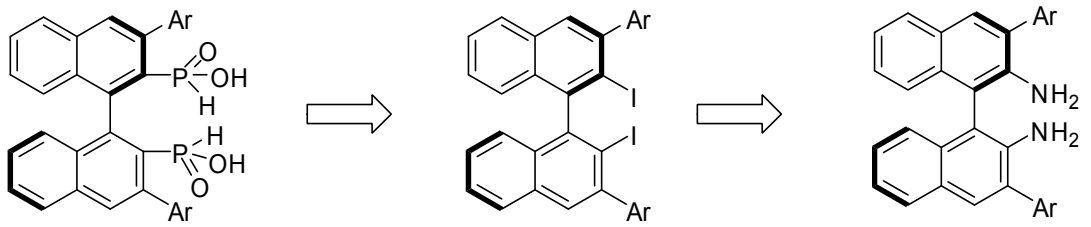
It will be also attractive to find a shorter route for the preparation of α-amino acids from the *N*-acetylated α-amino nitrile products. In the reported method, two steps were required for the conversion of **3b** to **103**. Some enzymes might be active for the transformation of **3b** to **145** and could hydrolyze both *N*-acetyl and cyano group in a single step without losing optical purity (Scheme 6.2).



Scheme 6.2 Chemical and enzymatic conversion of **3b** to *N*-benzylated α-amino acid.

6.2 Three-Component Ugi Reaction

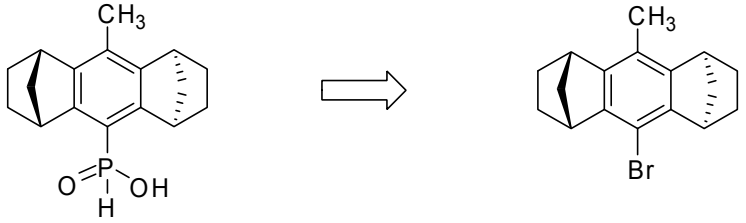
The catalytic three-component Ugi reaction presented herein is an efficient and potentially useful new reaction for the generation of different α-amino amides. The desired products are formed in good yields upon mixing readily available substrates with phenyl phosphinic acid catalyst. The broad scope, operational simplicity, practicability, and mild reaction conditions are attractive points of this reaction. However, the development of an asymmetric catalytic version would certainly be desirable. Since chiral BINOL phosphates are not active catalysts, the development of new chiral phosphinic acids is required. Chiral phosphinic acid **28** gave an enantioselectivity of only 52:48 er. 3,3'-Substituted phosphinic acids **146** might give higher enantioselectivities. Such catalysts can be synthesized from 3,3'-substituted 2,2'-iodo-1,1'-binaphthyls **147** which in turn can be prepared from 3,3'-substituted 2,2'-amino-1,1'-binaphthyls **148** (Scheme 6.3).



146 **147** **148**

Scheme 6.3 A bulky phosphinic acid catalyst **146** and its precursors **147** and **148**.

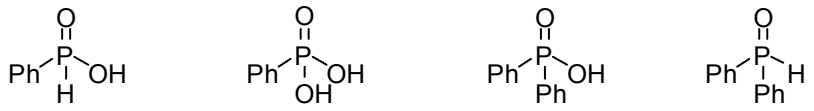
Another attractive chiral phosphinic acid catalyst would be C_2-symmetric **149** which could be prepared from **150** in one step (Scheme 6.4). Compound **150** is readily acccessible and the synthesis of similar compounds was already reported by Berkessel et al.[151]



149 **150**

Scheme 6.4 A C_2-symmetric phosphinic acid catalyst **149** and its precursor **150**.

Another point will be to better understand the role of phenyl phosphinic acid catalyst **4**. It was quite exciting for us that other phosphorous acids **24**, **25** and **26** were not active catalysts for this reaction (Scheme 6.5). Additional use of the bifunctionality of phosphinic acids in asymmetric catalysis appears attractive.

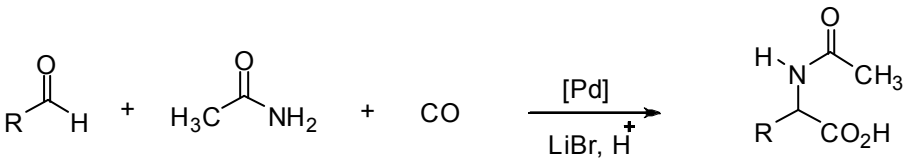


4 **24** **25** **26**

Scheme 6.5 Phenyl phosphinic acid **4** and related phosphorus acids.

6.3 Designing New Reactions

The previous reactions are perfectly atom-economic routes for the preparation of α-amino carbonyl frameworks where two sp-hybridized nucloeophiles (cyanide and isocyanide) were utilized. Another sp-hybridized nucloeophile is carbon monoxide (CO) and could potentially be used for the synthesis of α-amino acids. An atom-economic example of an efficient three-component reaction for the synthesis of *N*-acyl-α-amino acids **151** from aldehydes, amides and carbon monoxide was described by Wakamatsu in 1971 using cobalt carbonyls.[152] Recently, Beller and co-workers have re-investigated this three-component amidocarbonylation reaction using palladium catalysts (Scheme 6.6).[153]



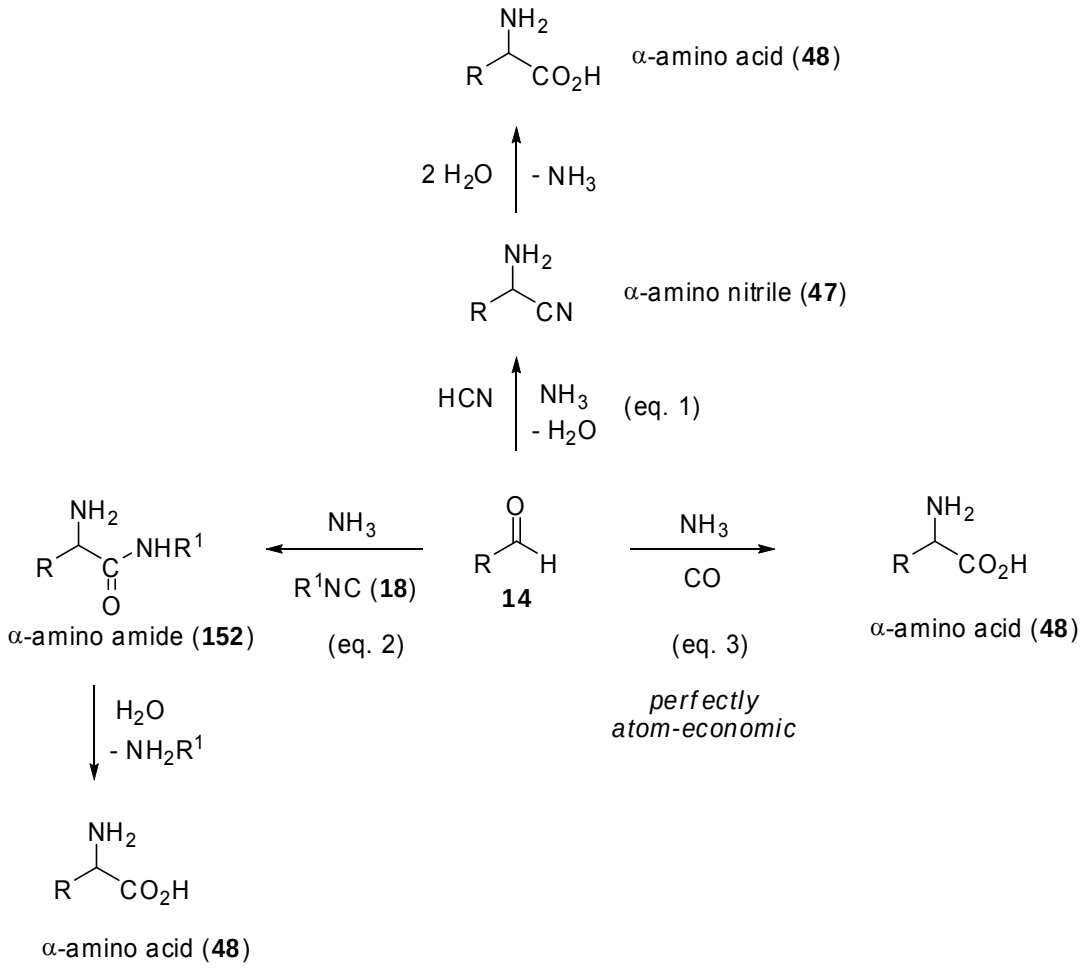
151

Scheme 6.6 Palladium catalyzed amidocarbonylation by Beller et al.

In the Strecker synthesis of α-amino acids, the first step is the preparation of α-amino nitrile **47** where one molecule of H_2O is generated (Scheme 6.7, eq. 1). α-Amino nitrile **47** could be converted to desired α-amino acid **48** using two water (H_2O) molecules; and one molecule of ammonia (NH_3) is liberated in this process.

If aldehyde **14** reacts with one molecule of ammonia and one molecule of isocyanide **18**, then corresponding α-amino amide **152** would be formed in a completely atom-economic fashion like in our Ugi three-component reaction (Scheme 6.7, eq. 2). Furthermore, the hydrolysis of α-amino amide **152** to α-amino acid **48** will require only one molecule of water rather than two molecules of water in the Strecker synthesis.

However, the perfect atom-economic reaction for the preparation of α-amino acids will be a reaction between an aldehyde, ammonia and carbon monoxide (Scheme 6.7, eq. 3). In this method, the *in situ* generated water molecule is utilized for the hydrolysis of carbon monoxide adduct to the carboxylic acid. Moreover, if this reaction be made enantioselectively it would be the most direct and shortest synthesis of chiral α-amino acids **48**.



Scheme 6.7 Strecker synthesis of α-amino acid and two new reactions.

7 Experimental Part

7.1 General Experimental Conditions

Solvents and Reagents

All solvents were purified by distillation before use following standard procedures.[154] Absolute diethyl ether, tetrahydrofuran and toluene were obtained by distilling over sodium, using benzophenone as indicator. Absolute acetonitrile, chloroform and dichloromethane were obtained by distillation over calcium hydride. Absolute *tert*-butanol was obtained by distilling over calcium oxide. Ethanol, *iso*-propanol and methanol were dried by distilling over magnesium. Dimethylformamide was refluxed over calcium hydride and distilled under an inert atmosphere with reduced pressure (15 mbar, 75 °C). Commercial reagents were obtained from various commercial sources and used as received.

Inert Gas Atmosphere

Air and moisture-sensitive reactions were conducted under an argon atmosphere. Argon was obtained from the company *L'Air Liquide* with purity higher than 99.5%.

Thin Layer Chromatography (TLC)

Materials: *Macherey-Nagel* MN POLYGRAM Sil G/UV254 plates (0.20 mm thick)
The spots were visualized in UV-light (λ = 254 nm) and/or by staining with iodine, ninhydrin, vanilline or phosphomolybdic acid.

Flash Column Chromatography

Materials: Silicagel 60 (*Merck* 60 Å, 230-400 mesh 0.040-0.063 mm).

Gas chromatography (GC)

Apparatus: *Agilent Technolgy* GC 6890 N (Carrier gas: Helium) with HP 6890 Series Injector
Materials: *Hewlett Packard* HP-5 (30 m, 0.25 mm ID, 0.25 μm film thickness)
MN Optima 5 (30 m, 0.25 mm ID, 0.25 μm film thickness)

Gas Chromatography with Mass Spectrometric Detector (GC/MS)

Apparatus: *Agilent Technolgy* GC 6890 Series and MSD 5973 (Carrier gas: Helium) with HP6890 Series Injector

Materials: *Hewlett Packard* HP-5: Crosslinked Silicone Gum capillary column (Film thickness: 30 m × 0.32 mm × 0.25 μm)

Analytical High Performance Liquid Chromatography (HPLC)

Apparatus: *Shimadzu* LC-2010C HPLC-system equipped with a spectrophotometric detector.

Materials: *Daicel* Chiralpak AS-H column (0.46 cm × 25 cm)
Daicel Chiralpak OJ-H column (0.46 cm × 25 cm)
Daicel Chiralcel OD-H column (0.46 cm × 25 cm)
Daicel Chiralpak AD-H column (0.46 cm × 25 cm)
Daicel Chiralpak OD-H column (0.46 cm × 25 cm)

Nuclear magnetic resonance spectroscopy (NMR)

Apparatus: *Bruker* DPX 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz)
Bruker AV 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz)
Bruker AV 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz)

Spectra were recorded at room temperature (298 K) unless otherwise stated. Chemical shifts for protons and carbons were reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and were referenced to residual proton in the NMR solvents (e.g. $CHCl_3$: δ 7.26 in ^{1}H) and carbon resonances of the solvents (e.g. $CDCl_3$: δ 77.0) respectively. The coupling constants (*J*) were reported in Hertz (Hz). For the fine structure interpretation the abbreviations of the signals are the following: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The signal multiplicities for the ^{13}C-spectra were determined by DEPT experiments and the interpretations of the abbreviations are Cq = quaternary carbon, C_{ar} = aromatic carbon, Cq_{ar} = quaternary aromatic carbon.

Mass Spectrometry (MS)

Apparatus: *Finnigan* MAT 8200 (70 eV)
Finnigan MAT 8400 (70 eV)
Bruker ESQ 3000
Bruker APEX III FT-MS (7 T magnet)

Mass spectra were measured on a Finnigan MAT 8200 (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).

Melting Point (MP)

Apparatus: *Büchi* 540 Melting Point

All the melting points were measured in open glass capillary and the values are uncorrected.

Specific Rotation ([α])

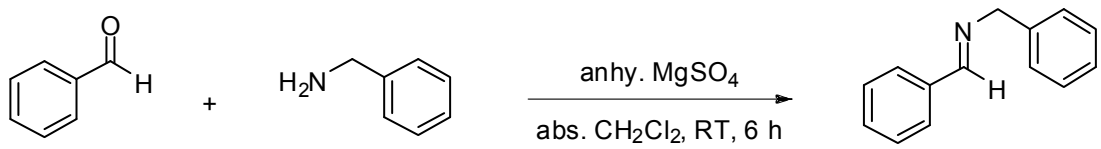
Apparatus: *Perkin Elmer* 343

Optical rotations were measured using a 1 mL cell with a 1 dm path length. Measurements were carried out in different wavelengths using sample solution in chloroform at 20 °C. The sample concentrations are given in g/100 mL unit.

7.2 Catalytic Acylcyanation of Imines

7.2.1 Preparation of Aldimines

7.2.1.1 Preparation of *N*-benzylidene-1-phenyl-methanamine 1a

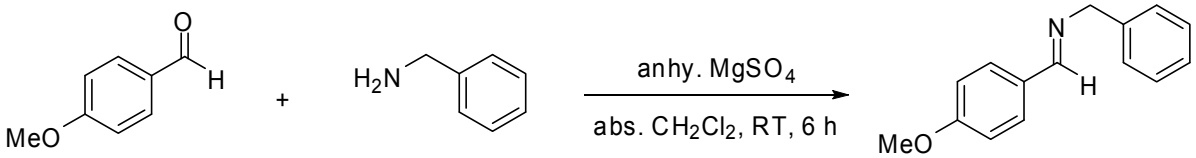


14a **15b** **1a**

In a 50 mL oven-dried round bottom flask charged with magnetic stirring bar and anhy. $MgSO_4$ (3.0 g, 24.90 mmol, 1.26 equiv.) 10 mL of abs. CH_2Cl_2 was added. To this suspension benzaldehyde **14a** (2.00 mL, 19.70 mmol, 1.00 equiv.) was added followed by benzyl amine **15b** (2.15 mL, 19.70 mmol, 1.00 equiv.). The resulting mixture was then stirred at room temperature under argon atmosphere for 6 hours. $MgSO_4$ was filtered off and the solvent was removed *in vacuo* to obtain highly viscous oil (3.83 g, 99 %).

1a	$C_{14}H_{13}N$ (195.26 g/mol)
Yield	3.83 g (19.60 mmol, 99%)
^{1}H-NMR	(400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.70-7.68 (m, 2H), 7.34-7.13 (m, 8H), 4.73 (s, 2H).
^{13}C-NMR	(100 MHz, $CDCl_3$): δ 161.7 (N=CH), 138.9 (C_{ar}), 135.8 (C_{ar}), 130.5 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 127.9 (C_{ar}), 127.7 (C_{ar}), 126.7 (C_{ar}), 64.7 (CH_2).

7.2.1.2 Preparation of *N*-(4-methoxybenzylidene)-1-phenyl-methanamine 1c



14c **15b** **1c**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a white solid (1.57 g, 99%).

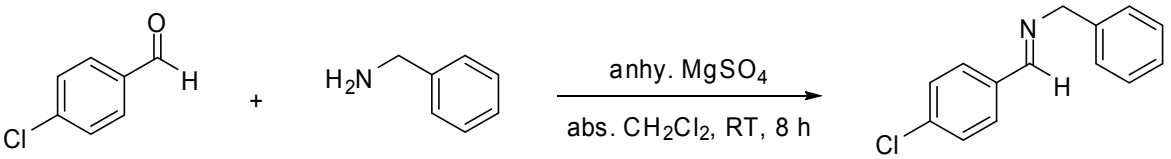
1c $C_{15}H_{15}NO$ (225.29 g/mol)

Yield 1.57 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.26-7.16 (m, 5H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.71 (s, 2H), 3.75 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.4 (N=CH), 161.0 (Cq_{ar}), 139.2 (C_{ar}), 129.5 (C_{ar}), 128.8 (C_{ar}), 128.1 (C_{ar}), 127.6 (C_{ar}), 126.5 (C_{ar}), 113.6 (C_{ar}), 64.6 (CH_2), 55.0 (OCH_3).

7.2.1.3 Preparation of *N*-(4-chlorobenzylidene)-1-phenyl-methanamine 1d



14d **15b** **1d**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a white solid (1.60 g, 99%).

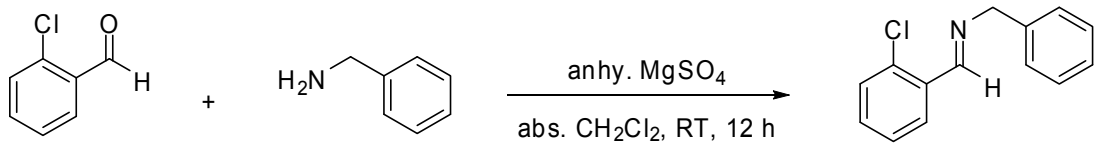
1d $C_{14}H_{12}ClN$ (229.70 g/mol)

Yield 1.60 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.44-7.28 (m, 7H), 4.86 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.2 (N=CH), 138.7 (C_{ar}), 136.4 (C_{ar}), 134.3 (C_{ar}), 129.1 (C_{ar}), 128.5 (C_{ar}), 128.2 (C_{ar}), 127.6 (C_{ar}), 126.7 (C_{ar}), 64.6 (CH_2).

7.2.1.4 Preparation of *N*-(2-chlorobenzylidene)-1-phenyl-methanamine 1e



14e **15b** **1e**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a white solid (1.60 g, 99%).

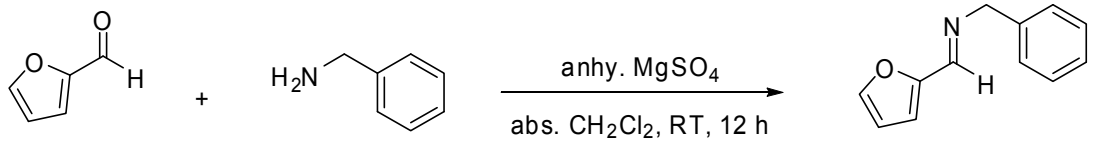
1e $C_{14}H_{12}ClN$ (229.70 g/mol)

Yield 1.60 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), 7.44-7.30 (m, 8H), 4.92 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.3 (N=CH), 138.8 (C_{ar}), 134.9 (C_{ar}), 132.9 (C_{ar}), 131.3 (C_{ar}), 129.4 (C_{ar}), 128.2 (C_{ar}), 127.7 (C_{ar}), 126.8 (C_{ar}), 126.7 (C_{ar}), 65.0 (CH_2).

7.2.1.5 Preparation of *N*-(furan-2-ylmethylene)-1-phenyl-methanamine 1f



14f **15b** **1f**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain an oil which became yellowish white solid on standing in the refrigerator (1.29 g, 99%).

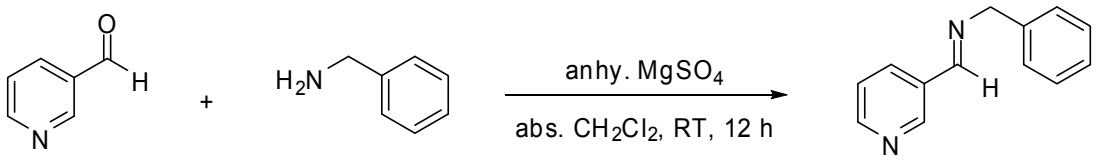
1f $C_{12}H_{11}NO$ (185.22 g/mol)

Yield 1.29 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.54 (s, 1H), 7.40-7.28 (m, 5H), 6.80 (d, *J* = 4.5 Hz, 1H), 6.50-6.48 (m, 1H), 4.81 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.0 (N=CH), 150.8 (Cq_{ar}), 145.2 (C_{ar}), 139.2 (C_{ar}), 128.9 (C_{ar}), 128.6 (C_{ar}), 127.5 (C_{ar}), 114.6 (C_{ar}), 112.0 (C_{ar}), 65.5 (CH_2).

7.2.1.6 Preparation of 1-phenyl-*N*-(pyridin-3-ylmethylene)-methanamine 1g



14g **15b** **1g**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a yellow solid (1.37 g, 99%).

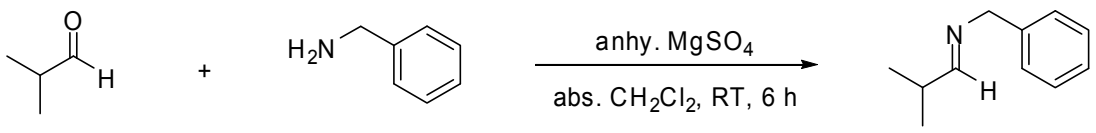
1g $C_{13}H_{12}N_2$ (196.25 g/mol)

Yield 1.37 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.91 (d, *J* = 1.6 Hz, 1H), 8.67 (dd, *J* = 1.7, 4.8 Hz, 1H), 8.44 (s, 1H), 8.18 (td, *J* = 1.9, 7.9 Hz, 1H), 7.40-7.28 (m, 6H), 4.86 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.6 (N=CH), 151.3 (Cq_{ar}), 150.0 (C_{ar}), 138.4 (C_{ar}), 134.2 (C_{ar}), 131.3 (C_{ar}), 128.2 (C_{ar}), 127.7 (C_{ar}), 126.9 (C_{ar}), 123.3 (C_{ar}), 64.9 (CH_2).

7.2.1.7 Preparation of *N*-(2-methylpropylidene)-1-phenyl-methanamine 1h



14h **15b** **1h**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a clear oil (1.12 g, 99%).

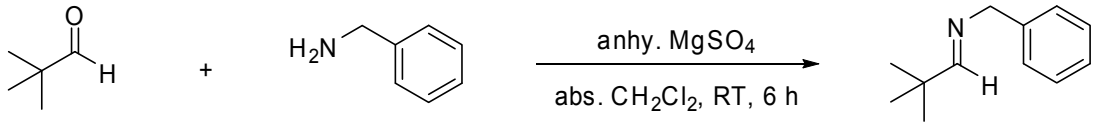
1h $C_{11}H_{15}N$ (161.24 g/mol)

Yield 1.12 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (td, *J* = 1.2, 4.9 Hz, 1H), 7.39-7.26 (m, 5H), 4.60 (s, 2H), 2.57-2.53 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6 (N=CH), 139.1 (Cq_{ar}), 128.1 (C_{ar}), 127.4 (C_{ar}), 126.5 (C_{ar}), 64.5 (CH_2), 33.8 (CH), 19.0 (CH_3).

7.2.1.8 Preparation of *N*-(2,2-dimethylpropylidene)-1-phenyl-methanamine 1b



14b **15b** **1b**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a clear oil (1.22 g, 99%).

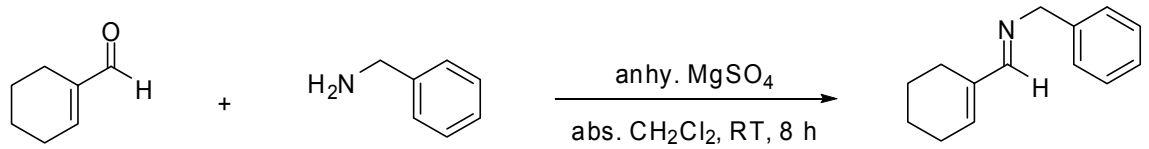
1b $C_{12}H_{17}N$ (175.27 g/mol)

Yield 1.22 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.56 (t, *J* = 1.3 Hz, 1H), 7.24-7.14 (m, 5H), 4.49 (s, 2H), 1.03 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0 (N=CH), 139.4 (Cq_{ar}), 128.0 (C_{ar}), 127.3 (C_{ar}), 126.4 (C_{ar}), 64.2 (CH_2), 35.5 (Cq), 26.7 (CH_3).

7.2.1.9 Preparation of *N*-(cyclohexenylmethylene)-1-phenyl-methanamine 1i



14i **15b** **1i**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a highly viscous oil (1.39 g, 99%).

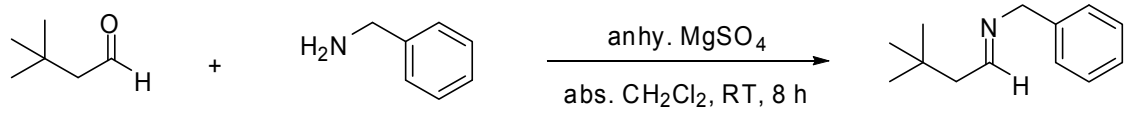
1i $C_{14}H_{17}N$ (199.29 g/mol)

Yield 1.39 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.25-7.12 (m, 5H), 6.10-6.08 (m, 1H), 4.57 (s, 2H), 2.27-2.25 (m, 2H), 2.15-2.12 (m, 2H), 1.61-1.53 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.2 (N=CH), 139.5 (Cq_{ar}), 138.8 (C=C), 137.8 (C=C), 128.0 (C_{ar}), 127.5 (C_{ar}), 126.4 (C_{ar}), 64.4 (CH_2), 25.8 (CH_2), 23.4 (CH_2), 22.1 (CH_2), 21.7 (CH_2).

7.2.1.10 Preparation of *N*-(3,3-dimethylbutylidene)-1-phenyl-methanamine 1j



14j **15b** **1j**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a clear oil (1.32 g, 99%).

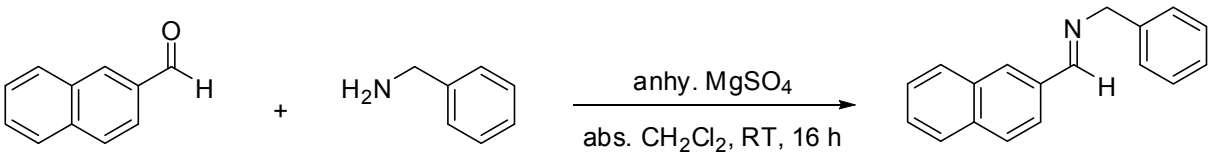
1j $C_{13}H_{19}N$ (189.30 g/mol)

Yield 1.32 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (t, *J* = 5.7 Hz, 1H), 7.26-7.16 (m, 5H), 4.52 (s, 2H), 2.14 (d, *J* = 5.6 Hz, 2H), 0.92 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.8 (N=CH), 138.9 (Cq_{ar}), 128.1 (C_{ar}), 127.6 (C_{ar}), 126.5 (C_{ar}), 64.9 (CH_2), 49.0 (CH_2), 30.7 (Cq), 29.3 (CH_3).

7.2.1.11 Preparation of *N*-(naphthalene-2-ylmethylene)-1-phenyl-methanamine 1k



14k **15b** **1k**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a pale yellow solid (1.71 g, 99%).

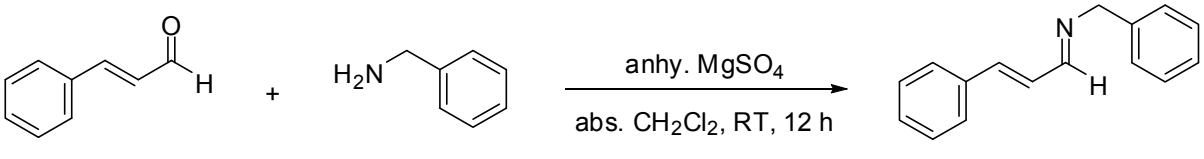
1k $C_{18}H_{15}N$ (245.32 g/mol)

Yield 1.71 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.11-8.08 (m, 2H), 7.94-7.87 (m, 3H), 7.59-7.52 (m, 2H), 7.44-7.28 (m, 5H), 4.92 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 162.5 (N=CH), 139.7 (Cq_{ar}), 135.2 (C_{ar}), 134.2 (C_{ar}), 133.5 (C_{ar}), 130.5 (C_{ar}), 129.0 (C_{ar}), 128.9 (C_{ar}), 128.8 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 127.6 (C_{ar}), 127.4 (C_{ar}), 126.9 (C_{ar}), 124.3 (C_{ar}), 65.5 (CH_2).

7.2.1.12 Preparation of *N*-(3-phenylallylidene)-1-phenyl-methanamine 1l



14l **15b** **1l**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a pale yellow solid (1.54 g, 99%).

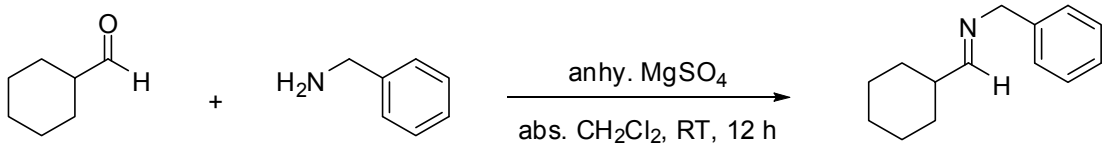
1l $C_{16}H_{15}N$ (221.29 g/mol)

Yield 1.54 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20-8.17 (m, 1H), 7.53-7.50 (m, 2H), 7.42-7.28 (m, 8H), 7.02-7.01 (m, 2H), 4.76 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.1 (N=CH), 141.7 (Cq_{ar}), 138.8 (Cq_{ar}), 135.4 (C=C), 128.9 (C_{ar}), 128.5 (C_{ar}), 128.3 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 126.9 (C_{ar}), 126.7 (C=C), 64.9 (CH_2).

7.2.1.13 Preparation of *N*-(cyclohexylmethylene)-1-phenyl-methanamine 1m



14m **15b** **1m**

The same procedure as before (see section 7.2.1.1) was followed on a 7.00 mmol scale to obtain a highly viscous liquid (1.40 g, 99%).

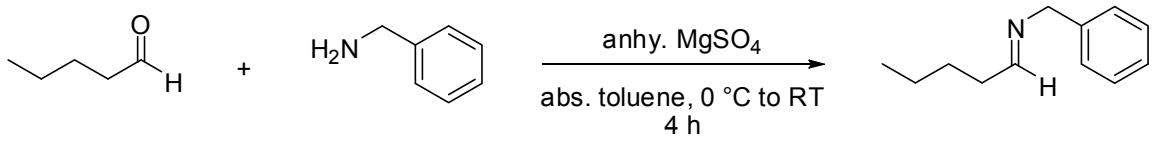
1m $C_{14}H_{19}N$ (201.30 g/mol)

Yield 1.40 g (7.00 mmol, 99%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 (td, J = 1.1, 5.1 Hz, 1H), 7.37-7.24 (m, 5H), 4.59 (s, 2H), 2.30-2.27 (m, 1H), 1.90-1.69 (m, 5H), 1.40-1.22 (m, 5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.9 (N=CH), 139.2 (Cq_{ar}), 128.1 (C_{ar}), 127.4 (C_{ar}), 126.5 (C_{ar}), 64.6 (CH_2), 43.2 (CH), 29.4 (CH_2), 25.7 (CH_2), 25.1 (CH_2).

7.2.1.14 Preparation of *N*-(pentylidene)-1-phenyl-methanamine 1n



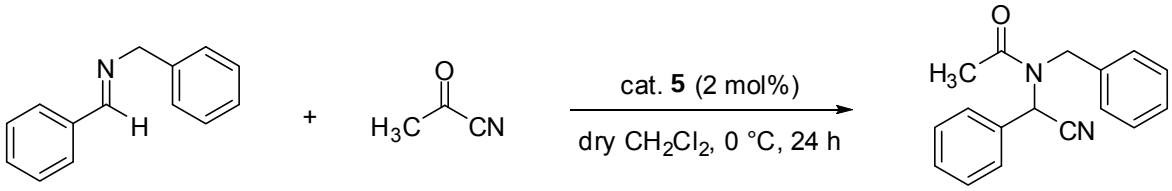
14n **15b** **1n**

In a 5 mL oven-dried round bottom flask charged with magnetic stirring bar and anhy. $MgSO_4$ (80 mg, 0.63 mmol, 1.26 equiv.) 1.2 ml of abs. toluene was added. To this suspension pentanal **14n** (53 µL, 0.50 mmol, 1.00 equiv.) was added at 0 °C followed by benzyl amine **15b** (54 µL, 0.50 mmol, 1.00 equiv.). The resulting mixture was then warmed to room temperature under argon atmosphere over 4 hours. $MgSO_4$ was filtered off and the solution was directly used for the further experiment.

7.2.2 General Procedure for the Catalytic Acylcyanation of Aldimines

The imine **1** (2.00 mmol) and catalyst **5** (2-5 mol%) were placed in a dry Schlenk flask. Then, dry CH_2Cl_2 (4 mL) was added to the mixture. The flask was cooled to 0 °C and stirred for 10 min. Acetylcyanide (**2a**) (0.2 mL, 1.5 equiv.) was added, and the mixture was stirred for 24-36 hours at 0 °C. The mixture was directly subjected to silica gel column chromatography to give the pure product **3**.

7.2.2.1 *N*-benzyl-*N*-(cyano(phenyl)methyl)acetamide 3a



1a **2a** **3a**

Compound **3a** was isolated in 88% yield as a colorless liquid after silica gel flash column chromatography (30% EtOAc in hexane).

3a $C_{17}H_{16}N_2O$ (264.32 g/mol)

Yield 465 mg (1.76 mmol, 88%)

TLC R_f = 0.42 (ethylacetate/hexane 30:70)

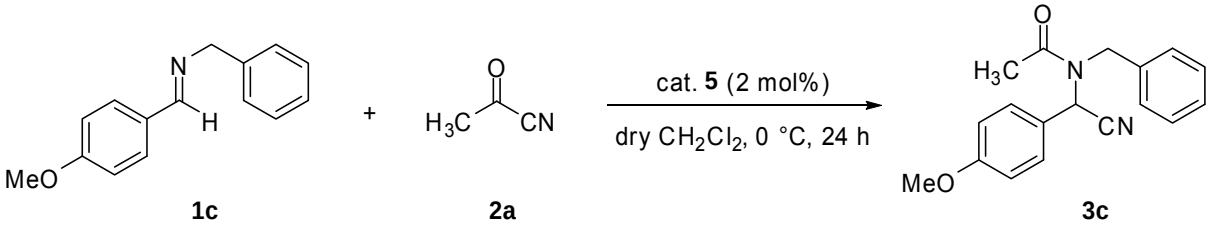
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.38 (m, 5H), 7.31-7.24 (m, 3H), 7.14-7.07 (m, 3H), 4.58 (d, *J* = 17.6 Hz, 1H), 4.49 (d, *J* = 12.9 Hz, 1H), 2.14 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3 (C=O), 135.3 (Cq_{ar}), 131.9 (Cq_{ar}), 129.1 (C_{ar}), 128.8 (C_{ar}), 128.4 (C_{ar}), 127.4 (C_{ar}), 125.9 (C_{ar}), 116.1 (C≡N), 49.2 (CH_2), 48.3 (CH), 21.7 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{17}H_{16}N_2O$] ([M]$^+$): 264.1260
Found: 264.1262

HPLC τR = 23.3 min [(*S*)-**3a**], 37.2 min [(*R*)-**3a**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 0.7 mL/min, 220 nm).

7.2.2.2 *N*-benzyl-*N*-(cyano(4-methoxyphenyl)methyl)acetamide 3c



Compound **3c** was isolated in 84% yield as a yellowish white liquid after silica gel flash column chromatography (30% EtOAc in hexane). It got crystallized on standing at room temperature.

3c $C_{18}H_{18}N_2O_2$ (294.35 g/mol)

Yield 494 mg (1.68 mmol, 84%)

TLC R_f = 0.38 (ethylacetate/hexane 30:70)

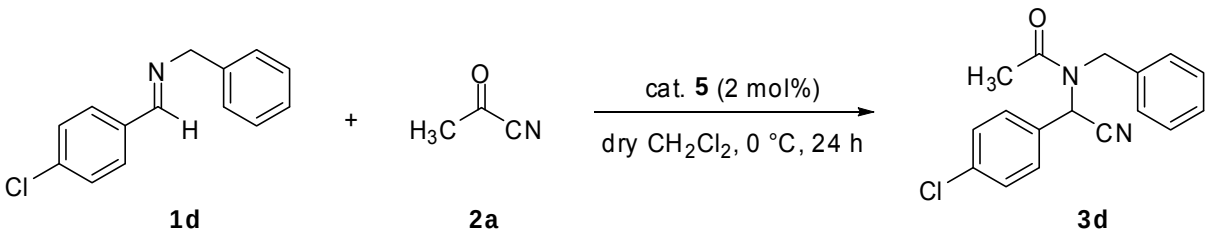
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.13 (m, 5H), 6.97 (d, *J* = 7.3 Hz, 3H), 6.80-6.76 (m, 1H), 4.45 (d, *J* = 17.6 Hz, 1H), 4.36 (d, *J* = 17.4 Hz, 2H), 3.71 (s, 3H), 2.01 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 160.0 (Cq_{ar}), 135.4 (Cq_{ar}), 128.9 (C_{ar}), 128.4 (C_{ar}), 127.3 (C_{ar}), 125.9 (C_{ar}), 123.8 (C_{ar}), 116.4 (C≡N), 124.2 (C_{ar}), 55.0 (O-CH_3), 49.0 (CH_2), 47.7 (CH), 21.7 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{18}H_{18}N_2O_2$] ([M]$^+$): 294.1370
Found: 294.1368

HPLC τR = 24.4 min [(*S*)-**3c**], 35.6 min [(*R*)-**3c**] (Chiralpak AS-H, heptane/*i*-PrOH 70:30, 0.7 mL/min, 220 nm).

7.2.2.3 *N*-benzyl-*N*-(cyano(4-chlorophenyl)methyl)acetamide 3d



1d **2a** **3d**

Compound **3d** was isolated in 79% yield as a white solid after silica gel flash column chromatography (25% EtOAc in hexane).

3d $C_{17}H_{15}ClN_2O$ (298.77 g/mol)

Yield 472 mg (1.58 mmol, 79%)

TLC R_f = 0.45 (ethylacetate/hexane 30:70)

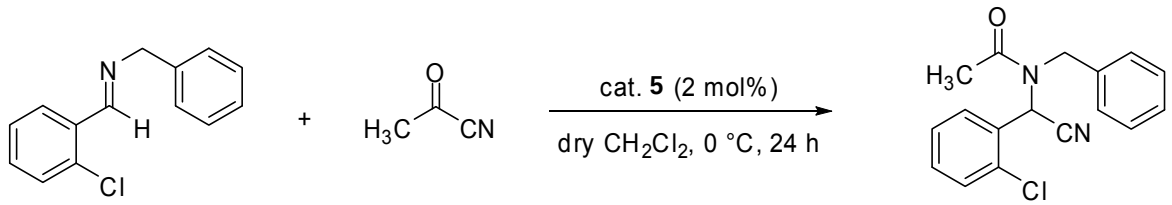
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.14 (m, 2H), 7.00-6.95 (m, 3H), 7.20-7.11 (m, 4H), 7.03 (d, *J* = 4.1 Hz, 1H), 4.47 (d, *J* = 17.5 Hz, 1H), 4.40 (d, *J* = 17.3 Hz, 1H), 2.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 135.1 (Cq_{ar}), 134.9 (Cq_{ar}), 130.6 (Cq_{ar}), 128.9 (C_{ar}), 128.7 (C_{ar}), 128.5 (C_{ar}), 127.5 (C_{ar}), 125.9 (C_{ar}), 115.7 (C≡N), 49.4 (CH_2), 47.8 (CH), 21.6 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{17}H_{15}ClN_2O$] ([M]$^+$): 298.0873
Found: 298.0873

HPLC τR = 24.9 min [(*R*)-**3d**], 28.8 min [(*S*)-**3d**] (Chiralpak OJ-H, heptane/*i*-PrOH 80:20, 1.0 mL/min, 220 nm).

7.2.2.4 *N*-benzyl-*N*-(cyano(2-chlorophenyl)methyl)acetamide 3e



1e **2a** **3e**

Compound **3e** was isolated in 83% yield as a yellowish white solid after silica gel flash column chromatography (25% EtOAc in hexane).

3e $C_{17}H_{15}ClN_2O$ (298.77 g/mol)

Yield 496 mg (1.66 mmol, 83%)

TLC R_f = 0.45 (ethylacetate/hexane 30:70)

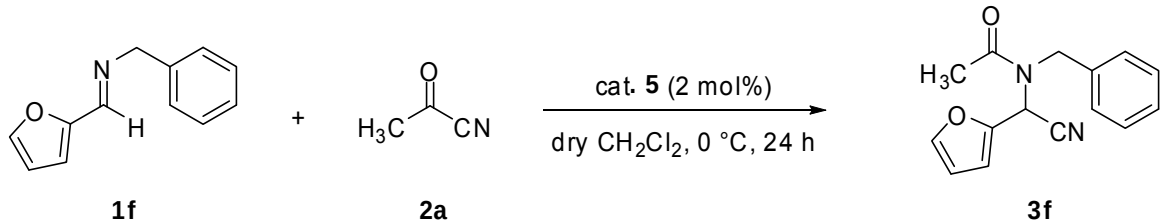
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.59-7.56 (m, 1H), 7.35-7.02 (m, 6H), 6.94 (br s, 3H), 4.44 (d, *J* = 17.4 Hz, 1H), 4.28 (d, *J* = 17.5 Hz, 1H), 2.10 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.8 (C=O), 135.0 (Cq_{ar}), 133.6 (Cq_{ar}), 130.8 (C_{ar}), 130.7 (C_{ar}), 128.8 (Cq_{ar}), 128.4 (C_{ar}), 127.4 (C_{ar}), 126.9 (C_{ar}), 125.8 (C_{ar}), 116.0 (C≡N), 49.2 (CH_2), 47.1 (CH), 21.6 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{17}H_{15}ClN_2ONa$] ([MNa]$^+$): 321.0764
Found: 321.0764

HPLC τR = 33.3 min [(*R*)-**3e**], 38.1 min [(*S*)-**3e**] (Chiralpak OJ-H, heptane/*i*-PrOH 92:8, 1.0 mL/min, 220 nm).

7.2.2.5 *N*-benzyl-*N*-(cyano(furan-2-yl)methyl)acetamide 3f



1f **2a** **3f**

Compound **3f** was isolated in 67% yield as a yellow liquid after silica gel flash column chromatography (30% EtOAc in hexane).

3f $C_{15}H_{14}N_2O_2$ (254.28 g/mol)

Yield 340 mg (1.34 mmol, 67%)

TLC R_f = 0.34 (ethylacetate/hexane 30:70)

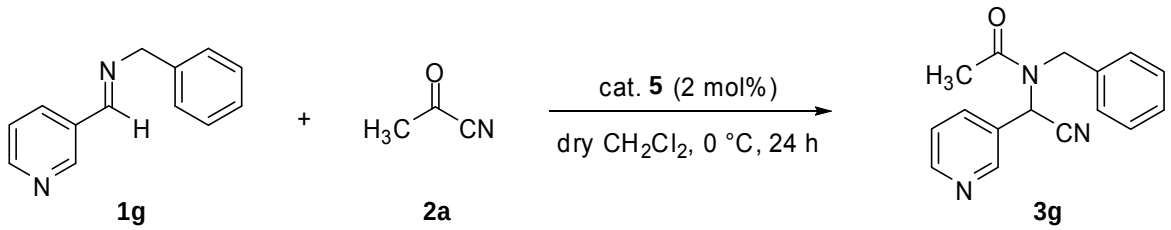
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.12 (m, 4H), 6.96-6.94 (m, 3H), 6.44 (d, *J* = 3.3 Hz, 1H), 6.20 (dd, *J* = 1.9, 3.3 Hz, 1H), 4.57 (d, *J* = 17.6 Hz, 1H), 4.51 (d, *J* = 17.5 Hz, 1H), 2.00 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0 (C=O), 144.5 (Cq_{ar}), 143.7 (C_{ar}), 135.4 (Cq_{ar}), 128.8 (Cq_{ar}), 128.4 (C_{ar}), 127.3 (C_{ar}), 125.5 (C_{ar}), 125.8 (C_{ar}), 114.8 (C≡N), 111.2 (C_{ar}), 110.5 (C_{ar}), 49.3 (CH_2), 42.5 (CH), 21.4 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{17}H_{15}N_2ONa]$ ($[MNa]^+$): 277.0949
Found: 277.0947

HPLC τR = 14.9 min [(*R*)-**3f**], 19.2 min [(*S*)-**3f**] (Chiralpak OJ-H, heptane/*i*-PrOH 70:30, 1.0 mL/min, 220 nm).

7.2.2.6 *N*-benzyl-*N*-(cyano(pyridin-3-yl)methyl)acetamide 3g



Compound **3g** was isolated in 96% yield as a white solid after silica gel flash column chromatography (70% EtOAc in hexane).

3g $C_{16}H_{15}N_3O$ (265.31 g/mol)

Yield 509 mg (1.92 mmol, 96%)

TLC R_f = 0.28 (ethylacetate/hexane 70:30)

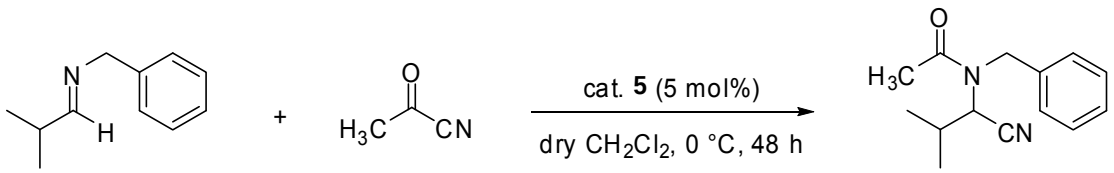
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.53 (d, *J* = 4.1 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.31-7.20 (m, 4H), 7.05-7.03 (m, 2H), 6.96 (s, 1H), 4.58 (s, 2H), 2.16 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0 (C=O), 150.1 (C_{ar}), 148.4 (C_{ar}), 138.0 (Cq_{ar}), 134.9 (C_{ar}), 128.5 (C_{ar}), 127.7 (C_{ar}), 127.0 (C_{ar}), 126.0 (C_{ar}), 123.2 (C_{ar}), 115.1 (C≡N), 49.8 (CH_2), 46.6 (CH), 21.5 (CH_3).

HR-EI-MS Exact molecular mass for $[C_{16}H_{15}N_3O]$ ($[M]^+$): 265.1217
Found: 265.1215

HPLC τR = 27.9 min [(*R*)-**3g**], 32.9 min [(*S*)-**3g**] (Chiralpak OJ-H, heptane/*i*-PrOH 70:30, 1.0 mL/min, 220 nm).

7.2.2.7 *N*-benzyl-*N*-(1-cyano-2-methylpropyl)acetamide 3h



1h **2a** **3h**

Compound **3h** was isolated in 76% yield as a yellow liquid after silica gel flash column chromatography (50% EtOAc in hexane).

3h $C_{14}H_{18}N_2O$ (230.31 g/mol)

Yield 350 mg (1.52 mmol, 76%)

TLC R_f = 0.62 (ethylacetate/hexane 50:50)

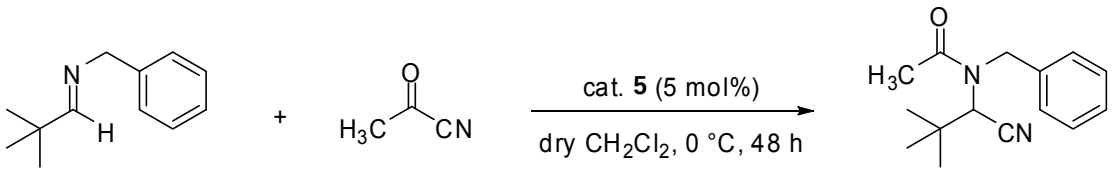
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.09 (d, *J* = 9.7 Hz, 1H), 4.65 (d, *J* = 17.4 Hz, 1H), 4.50 (d, *J* = 17.4 Hz, 1H), 2.16-2.05 (m, 1H), 2.00 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 135.6 (Cq_{ar}), 128.7 (C_{ar}), 127.6 (C_{ar}), 125.9 (C_{ar}), 117.0 (C≡N), 52.6 (CH), 50.6 (CH_2), 30.4 (CH), 21.8 (CH_3), 18.9 (CH_3), 18.5 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{14}H_{18}N_2ONa]$ ($[MNa]^+$): 253.1309
Found: 253.1311

HPLC τR = 36.5 min [(*R*)-**3h**], 38.8 min [(*S*)-**3h**] (Chiralpak OJ-H, heptane/*i*-PrOH 97:3, 1.0 mL/min, 220 nm).

7.2.2.8 *N*-benzyl-*N*-(1-cyano-2,2-dimethylpropyl)acetamide 3b



1b **2a** **3b**

Compound **3b** was isolated in 64% yield as a colorless liquid after silica gel flash column chromatography (25% EtOAc in hexane).

3b $C_{15}H_{20}N_2O$ (244.33 g/mol)

Yield 312 mg (1.28 mmol, 76%)

TLC R_f = 0.44 (ethylacetate/hexane 20:80)

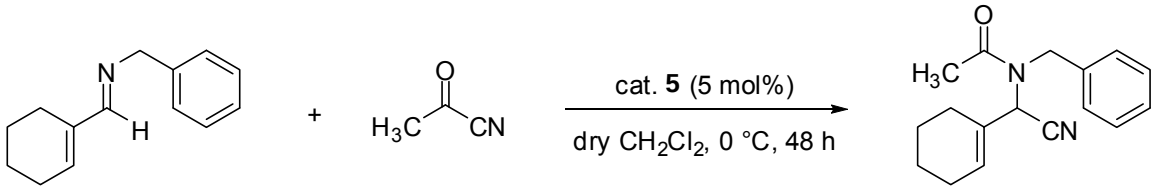
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.14 (m, 5H), 5.68 (br s, 1H), 4.77 (d, *J* = 17.7 Hz, 1H), 4.59 (d, *J* = 17.7 Hz, 1H), 1.89 (s, 3H), 1.05 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.2 (C=O), 136.3 (Cq_{ar}), 128.7 (C_{ar}), 127.3 (C_{ar}), 125.3 (C_{ar}), 116.7 (C≡N), 55.0 (CH), 51.5 (CH_2), 37.4 (Cq), 26.5 (CH_3), 22.1 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{15}H_{20}N_2ONa$] ([MNa]$^+$): 267.1466
Found: 267.1469

HPLC τR = 13.1 min [(*S*)-**3b**], 16.0 min [(*R*)-**3b**] (Chiralpak OJ-H, heptane/*i*-PrOH 95:5, 1.0 mL/min, 220 nm).

7.2.2.9 *N*-benzyl-*N*-(cyano(cyclohexenyl)methylacetamide 3i



1i **2a** **3i**

Compound **3i** was isolated in 82% yield as a colorless liquid after silica gel flash column chromatography (25% EtOAc in hexane).

3i $C_{17}H_{20}N_2O$ (268.35 g/mol)

Yield 440 mg (1.64 mmol, 76%)

TLC R_f = 0.46 (ethylacetate/hexane 30:70)

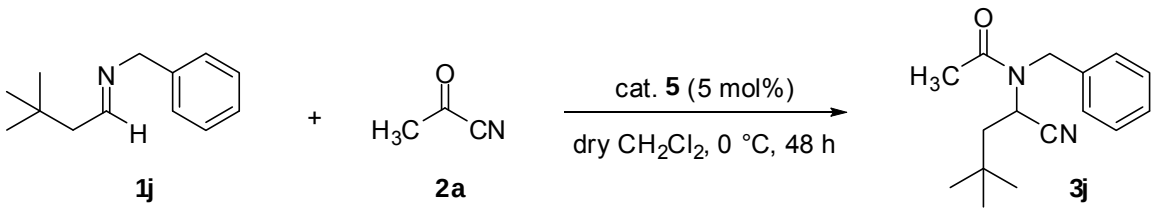
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.21 (m, 5H), 6.30 (s, 1H), 6.11 (s, 1H), 4.58 (d, *J* = 17.4 Hz, 1H), 4.48 (d, *J* = 17.4 Hz, 1H), 2.13 (s, 3H), 2.28-1.78 (m, 4H), 1.60-1.25 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4 (C=O), 135.9 (Cq_{ar}), 129.4 (C_{ar}), 129.0 (C=C), 128.4, 127.3, 126.1, 115.9 (C≡N), 49.9 (CH), 48.6 (CH_2), 25.6 (CH_2), 24.7 (CH_2), 21.7 (CH_3), 21.5 (CH_2), 21.1 (CH_2).

HR-ESI-MS Exact molecular mass for [$C_{17}H_{20}N_2ONa$] ([MNa]$^+$): 291.1466
Found: 291.1468

HPLC τR = 13.3 min [(*S*)-**3i**], 16.3 min [(*R*)-**3i**] (Chiralpak OJ-H, heptane/*i*-PrOH 80:20, 0.7 mL/min, 220 nm).

7.2.2.10 *N*-benzyl-*N*-(1-cyano-3,3-dimethylbutyl)acetamide 3j



Compound **3j** was isolated in 81% yield as a white solid after silica gel flash column chromatography (30% EtOAc in hexane).

3j $C_{16}H_{22}N_2O$ (258.36 g/mol)

Yield 418 mg (1.62 mmol, 76%)

TLC R_f = 0.48 (ethylacetate/hexane 30:70)

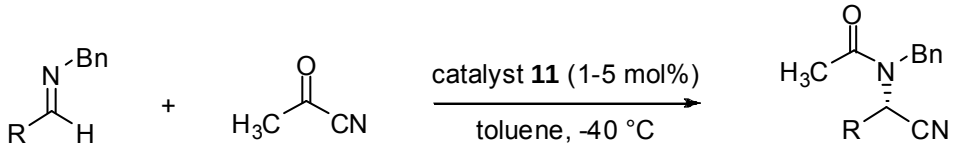
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 5.35 (d, *J* = 5.8 Hz, 1H), 4.64 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 17.4 Hz, 1H), 2.00 (s, 3H), 1.83 (dd, *J* = 9.6, 13.9 Hz, 1H), 1.43 (dd, *J* = 4.0, 14.0 Hz, 1H), 0.89 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6 (C=O), 135.7 (Cq_{ar}), 128.7 (C_{ar}), 127.6 (C_{ar}), 126.1 (C_{ar}), 118.8 (C≡N), 50.2 (CH_2), 45.5 (CH_2), 42.8 (CH), 29.9 (Cq), 28.8 (CH_3), 21.7 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{16}H_{22}N_2O$] ([M]$^+$): 258.1734
Found: 258.1732

HPLC τR = 14.0 min [(*S*)-**3j**], 16.7 min [(*R*)-**3j**] (Chiralpak OJ-H, heptane/*i*-PrOH 95:5, 1.0 mL/min, 220 nm).

7.2.3 General Procedure for the Catalytic Asymmetric Acylcyanation of Aldimines

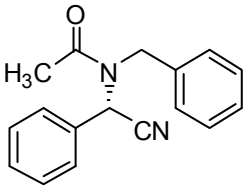


1 **2a** **3**

Imine **1** (0.5 mmol) and catalyst **11** (1-5 mol%) were placed into a dry Schlenk flask. Then 1 mL of dry toluene was added to the mixture. The flask was cooled to –40 °C and stirred for 10 min. Then 50 µL of acetylcyanide (**2a**) (1.5 equiv.) was added to the mixture and stirred for 20-50 hours at –40 °C. The mixture was directly subjected to silica gel column chromatography to get pure product **3**.

7.2.3.1 (*S*)-*N*-benzyl-*N*-(cyano(phenyl)methyl)acetamide 3a

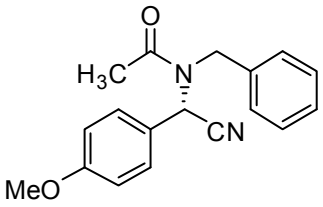
Compound **3a** was isolated in 94% yield (20 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3a** have been described in section 7.2.2.1. The enantiomeric ratio was determined to be 98:2 by chiral HPLC, τR (major 23.3 min), τR (minor 37.2 min).



3a

7.2.3.2 (*S*)-*N*-benzyl-*N*-(cyano(4-methoxyphenyl)methyl)-acetamide 3c

Compound **3c** was isolated in 95% yield (20 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3c** have been described in section 7.2.2.2. The enantiomeric ratio was determined to be 98:2 by

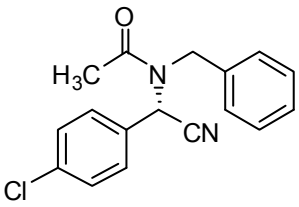


3c

chiral HPLC, τR (major 24.4 min), τR (minor 35.6 min).

7.2.3.3 (*S*)-*N*-benzyl-*N*-(cyano(4-chlorophenyl)methyl)acetamide 3d

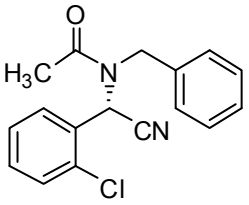
Compound **3d** was isolated in 87% yield (20 h reaction time) after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3d** have been described in section 7.2.2.3. The enantiomeric ratio was determined to be 99:1 by chiral HPLC, τR (minor 24.9 min), τR (major 28.8 min).



3d

7.2.3.4 (*S*)-*N*-benzyl-*N*-(cyano(2-chlorophenyl)methyl)acetamide 3e

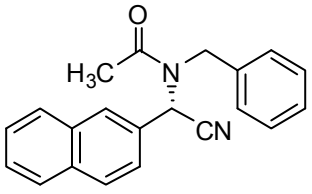
Compound **3e** was isolated in 86% yield (36 h reaction time) after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3e** have been described in section 7.2.2.4. The enantiomeric ratio was determined to be 99:1 by chiral HPLC, τR (minor 33.3 min), τR (major 38.1 min).



3e

7.2.3.5 (*S*)-*N*-benzyl-*N*-(cyano(naphthalene-2-yl)methyl) acetamide 3k

Compound **3k** was isolated in 92% yield (20 h reaction time) as a white liquid after silica gel flash column chromatography (20% EtOAc in hexane). It crystallized on standing at room temperature.



3k

3k $C_{21}H_{18}N_2O$ (314.38 g/mol)

Yield 144 mg (0.46 mmol, 92%)

TLC R_f = 0.54 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.75-7.73 (m, 3H), 7.45-7.43 (m, 2H), 7.32 (s, 1H), 7.19-7.10 (m, 4H), 6.98 (d, *J* = 7.1 Hz, 2H), 4.46 (d, *J* = 17.6 Hz, 1H), 4.36 (d, *J* = 17.4 Hz, 1H), 2.05 (s, 3H).

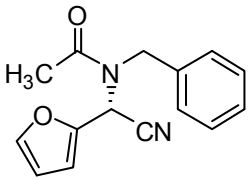
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4 (C=O), 135.3 (Cq_{ar}), 133.0 (C_{ar}), 132.5 (C_{ar}), 129.2 (C_{ar}), 127.1 (C_{ar}), 126.7 (C_{ar}), 125.9 (C_{ar}), 124.2 (C_{ar}), 116.2 (C≡N), 49.2 (CH_2), 48.4 (CH), 21.7 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{21}H_{18}N_2O$] ([M]$^+$): 314.1420
Found: 314.1419

HPLC τR = 29.7 min [minor, (*R*)-**3k**], 35.4 min [major, (*S*)-**3k**] (Chiralpak OJ-H, heptane/*i*-PrOH 70:30, 1.0 mL/min, 220 nm), enantiomeric ratio 98:2.

7.2.3.6 (*S*)-*N*-benzyl-*N*-(cyano(furan-2-yl)methyl)acetamide 3f

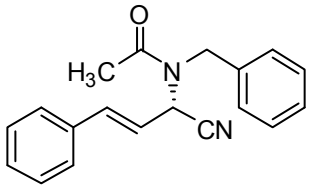
Compound **3f** was isolated in 94% yield (20 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3f** have been described in section 7.2.2.5. The enantiomeric ratio was determined to be 95:5 by chiral HPLC, τR (minor 14.9 min), τR (major 19.2 min).



3f

7.2.3.7 (*S*)-*N*-benzyl-*N*-(1-cyano-3-phenylallyl)acetamide 3l

Compound **3l** was isolated in 83% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (35% EtOAc in hexane).



3l

3l $C_{19}H_{18}N_2O$ (290.36 g/mol)

Yield 120 mg (0.41 mmol, 83%)

TLC R_f = 0.34 (ethylacetate/hexane 30:70)

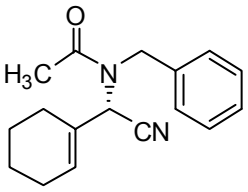
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.11 (m, 10H), 6.77 (dd, *J* = 1.5, 15.9 Hz, 1H), 6.37 (d, *J* = 4.6 Hz, 1H), 5.84 (dd, *J* = 5.4, 15.9 Hz, 1H), 4.62 (d, *J* = 17.4 Hz, 1H), 4.49 (d, *J* = 17.5 Hz, 1H) 2.05 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9 (C=O), 135.8 (Cq_{ar}), 135.6 (C=C), 134.5 (C_{ar}), 128.7 (C_{ar}), 128.5 (C_{ar}), 127.9 (C_{ar}), 127.5 (C_{ar}), 126.0 (C_{ar}), 119.4 (C=C), 115.7 (C≡N), 49.2 (CH_2), 47.1 (CH), 21.5 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{19}H_{18}N_2O$] ([M]$^+$): 290.1419
Found: 290.1420

HPLC τR = 26.3 min [minor, (*R*)-**3l**], 34.2 min [major, (*S*)-**3l**] (Chiralpak OJ-H, heptane/*i*-PrOH 70:30, 1.0 mL/min, 220 nm), enantiomeric ration 97:3.

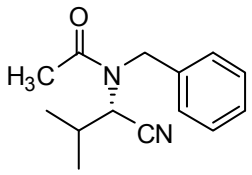
7.2.3.8 (*S*)-*N*-benzyl-*N*-(cyano(cyclohexenyl)methylacetamide 3i



3i

Compound **3i** was isolated in 83% yield (36 h reaction time) after silica gel column chromatography (35% EtOAc in hexane). The spectral and analytical data of compound **3i** have been described in section 7.2.2.9. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (minor 26.3 min), τR (major 34.2 min).

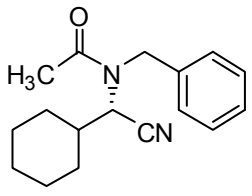
7.2.3.9 (*S*)-*N*-benzyl-*N*-(1-cyano-2-methylpropyl)acetamide 3h



3h

Compound **3h** was isolated in 87% yield (20 h reaction time) after silica gel column chromatography (50% EtOAc in hexane). The spectral and analytical data of compound **3h** have been described in section 7.2.2.7. The enantiomeric ratio was determined to be 98:2 by chiral HPLC, τR (minor 36.5 min), τR (major 38.8 min).

7.2.3.10 (*S*)-*N*-benzyl-*N*-(cyano(cyclohexyl)methylpropyl) acetamide 3m



3m

Compound **3m** was isolated in 88% yield (20 h reaction time) as a white solid after silica gel flash column chromatography (28% EtOAc in hexane).

3m $C_{17}H_{22}N_2O$ (270.37 g/mol)

Yield 118 mg (0.44 mmol, 88%)

TLC R_f = 0.52 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.12 (d, *J* = 9.9 Hz, 1H), 4.65 (d, *J* = 17.3 Hz, 1H), 4.47 (d, *J* = 17.3 Hz, 1H), 2.00 (s, 3H), 2.06-1.57 (m, 6H), 1.16-0.87 (m, 5H).

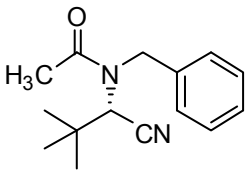
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 135.6 (Cq_{ar}), 128.7 (C_{ar}), 127.6 (C_{ar}), 126.0 (C_{ar}), 116.9 (C≡N), 51.7 (CH), 50.7 (CH_2), 38.9 (CH), 29.4 (CH_2), 28.9 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 21.7 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{17}H_{22}N_2O]$ ($[MNa]^+$): 293.1621
Found: 293.1624

HPLC τR = 15.8 min [major, (*S*)-**3m**], 17.9 min [minor, (*R*)-**3m**] (Chiralpak OJ-H, heptane/*i*-PrOH 92:8, 1.0 mL/min, 220 nm), enantiomeric ratio 96:4.

7.2.3.11 (*S*)-*N*-benzyl-*N*-(1-cyano-2,2-dimethylpropyl)acetamide 3b

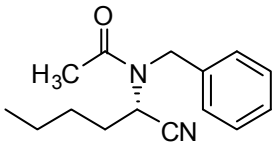
Compound **3b** was isolated in 62% yield (50 h reaction time) after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3b** have been described in section 7.2.2.8. The enantiomeric ratio was determined to be 98:2 by chiral HPLC, τR (major 13.1 min), τR (minor 16.0 min).



3b

7.2.3.12 (*S*)-*N*-benzyl-*N*-(1-cyanopentyl)acetamide 3n

Compound **3n** was isolated in 76% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (30% EtOAc in hexane).



3n

3n $C_{15}H_{20}N_2O$ (244.33 g/mol)

Yield 92 mg (0.38 mmol, 76%)

TLC R_f = 0.44 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.33-7.17 (m, 5H), 5.42 (t, *J* = 7.0 Hz, 1H), 4.67 (d, *J* = 17.5 Hz, 1H), 4.52 (d, *J* = 17.5 Hz, 1H), 2.03 (s, 3H), 1.71-1.56 (m, 2H), 1.36-1.19 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 3H).

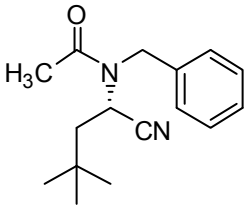
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9 (C=O), 135.8 (Cq_{ar}), 128.7 (C_{ar}), 127.6 (C_{ar}), 125.8 (C_{ar}), 117.6 (C≡N), 49.8 (CH_2), 46.1 (CH), 31.2 (CH_2), 27.5 (CH_2), 21.6 (CH_3), 21.5 (CH_2), 13.3 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{15}H_{20}N_2O]$ ($[MNa]^+$): 267.1465
Found: 267.1467

HPLC τR = 42.7 min [minor, (*R*)-**3n**], 45.5 min [major, (*S*)-**3n**] (Chiralpak OJ-H, heptane/*i*-PrOH 97:3, 0.7 mL/min, 220 nm), enantiomeric ratio 97:3.

7.2.3.13 *N*-benzyl-*N*-(1-cyano-3,3-dimethylbutyl)acetamide 3j

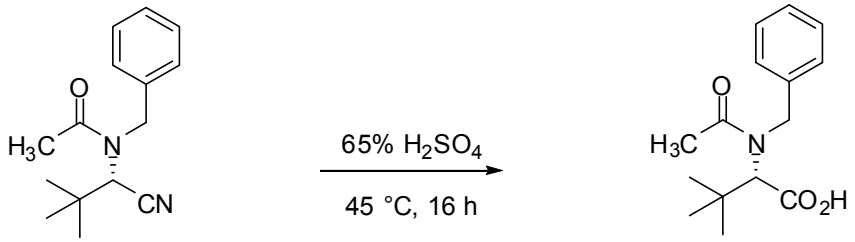
Compound **3j** was isolated in 96% yield (20 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3j** have been described in section 7.2.2.10. The enantiomeric ratio was determined to be 98:2 by chiral HPLC, τR (major 14.0 min), τR (minor 16.7 min).



3j

7.2.4 Conversion to α-Amino Acid and Determination of Absolute Configuration

7.2.4.1 (*S*)-2-(*N*-benzylacetamido)-3,3-dimethylbutanoic acid 102



3b **102**

In a 50 mL round bottom flask, 110 mg (0.45 mmol) of compound **3b** was suspended in 14mL of sulphuric acid (65% w/w). The reaction mixture was allowed to stir at 45 °C for 16 hours. Then the mixture was poured into 40 mL of ice cold water and extracted with ethyl acetate (3 x 40 mL). The organic extracts were washed with water, brine and then dried over $MgSO_4$. The solvent were removed *in vacuo* yielding 114 mg (0.43 mmol, 96%) of compound **102** as yellow solid.

102 $C_{15}H_{21}NO_3$ (263.33 g/mol)

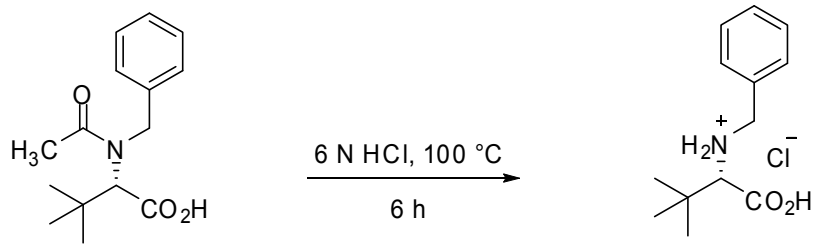
Yield 114 mg (0.43 mmol, 96%)

^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 7.25-6.89 (m, 5H), 4.75 (d, *J* = 17.8 Hz, 1H), 4.49 (d, *J* = 17.8 Hz, 1H), 4.12 (s, 1H), 1.63 (s, 3H), 0.81 (s, 9H).

^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ 172.1 (C=O), 171.3 (C=O), 139.4 (Cq_{ar}), 128.8 (C_{ar}), 128.1 (C_{ar}), 127.0 (C_{ar}), 126.1 (C_{ar}), 65.0 (CH), 51.5 (CH_2), 36.3 (Cq), 27.7 (CH_3), 22.7 (CH_3).

HR-EI-MS Exact molecular mass for $[C_{15}H_{21}NO_3]$ ($[M]^+$): 263.1521
Found: 263.1520

7.2.4.2 (*S*)-*N*-benzyl-1-carboxy-2,2-dimethylpropan-1-aminium chloride 103



102 **103**

In a 50 mL round bottom flask, 100 mg (0.38 mmol) of compound **102** was suspended in 12 mL 6 N HCl. Reaction mixture was allowed to stir at 100 °C for 6 hours, solvent was removed *in-vacuo* to yield 95 mg (0.37 mmol, 97%) of compound **103** as white crystalline solid.

103 $C_{13}H_{20}ClNO_2$ (257.76 g/mol)

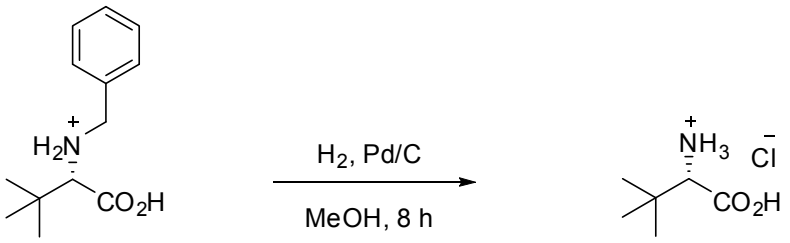
Yield 95 mg (0.37 mmol, 97%)

^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 7.50-7.40 (m, 2H), 7.34-7.15 (m, 3H), 4.20 (d, *J* = 13.4 Hz, 1H), 3.95 (d, *J* = 16.8 Hz, 1H), 3.18 (s, 1H), 0.94 (s, 9H).

^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ 169.3 (C=O), 131.1 (C_{ar}), 130.9 (C_{ar}), 129.6 (C_{ar}), 129.0 (C_{ar}), 67.2 (CH), 50.7 (CH_2), 33.5 (Cq), 26.9 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{13}H_{20}NO_2]$ ($[MH]^+$): 222.1489
Found: 222.1488

7.2.4.3 (*S*)-1-carboxy-2,2-dimethylpropan-1-aminium chloride 13



103 **13**

In a 25 mL double neck round bottom flask 50 mg (0.19 mmol) of **103** was dissolved in 3 ml of dry methanol; and under argon atmosphere 20 mg (0.02 mmol, 0.1 equiv.) of 10% (w/w) palladium on carbon was added. Then argon in the flask was carefully removed by pump and the reaction mixture was allowed to react at room temperature under atmospheric pressure of H_2 for 8 hours. The catalyst was removed by filtration through Celite. The solvents were removed *in vacuo* to yield 30 mg (0.18 mmol, 98%) of *tert*-leucine amine salt **13** as white solid.

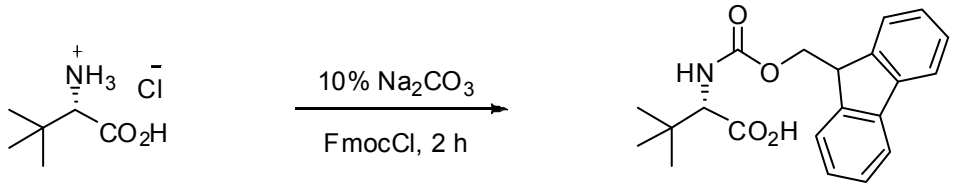
13 $C_6H_{14}ClNO_2$ (167.63 g/mol)

Yield 30 mg (0.18 mmol, 98%)

^{1}H-NMR (400 MHz, (CD_3OD): δ 3.73 (s, 1H), 1.14 (s, 9H).

^{13}C-NMR (100 MHz, (CD_3OD): δ 171.3 (C=O), 63.4 (CH), 34.3 (Cq), 27.3 (CH_3).

7.2.4.4 (*S*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-3,3-dimethylbutanoic acid 104



13 **104**

To a 38 mg (0.23 mmol) of compound **13** in 25 mL round bottom flask was added 1.2 mL of 10% Na_2CO_3 and the flask was cooled to 0 °C. Then a solution of FmocCl (70 mg, 0.27 mmol, 1.2 equiv.) in 0.4 mL of dioxane was slowly added to the reaction mixture. After

stirring for 2 hours at room temperature, the reaction mixture was poured into 10 mL of water, and extracted twice with ether to remove the impurities. The aqueous layer was acidified with concentrated HCl and the pH was adjusted to 1. Then it was extracted with EtOAc and the organic phase was washed with water, brine and dried over $MgSO_4$. Finally evaporation *in vacuo* yielded 70 mg (0.20 mmol, 90%) of compound **104** as white solid.

104 $C_{21}H_{23}NO_4$ (353.41 g/mol)

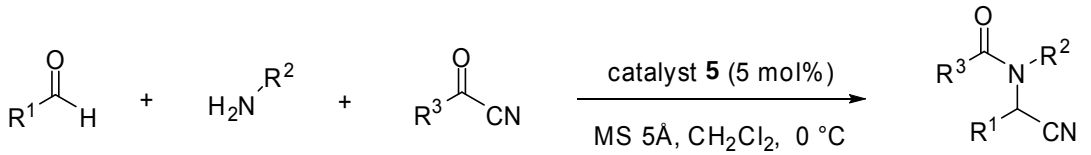
Yield 70 mg (0.20 mmol, 90%)

^{1}H-NMR (400 MHz, (CD_3OD): δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 6.7 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (dt, *J* = 7.5, 1.0 Hz, 2H), 4.39-4.33 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.05 (brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

^{13}C-NMR (100 MHz, (CD_3OD): δ 175.0 (C=O), 159.1 (C=O), 145.7 (Cq_{ar}), 145.6 (Cq_{ar}), 143.0 (Cq_{ar}), 129.2 (C_{ar}), 128.6 (C_{ar}), 128.5 (C_{ar}), 126.7 (C_{ar}), 121.3 (C_{ar}), 68.5 (CH_2), 64.5 (CH), 48.8 (CH), 35.3 (Cq), 27.6 (CH_3).

HPLC τR = 14.3 min [major, (*S*)-**104**], 18.1 min [minor, (*R*)-**104**] (Chiralcel OD-H, heptane/*i*-PrOH/TFA 80:20:0.1, 0.5 mL/min, 220 nm), enantiomeric ratio 98:2.

7.2.5 General Procedure for the Catalytic One-Pot, Three-Component Acyl-Strecker Reaction

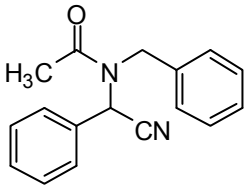


14 **15** **2** **3**

The aldehyde **14** (0.5 mmol), amine **15** (0.5 mmol), 5 Å MS (150 mg) and catalyst **5** (5 mol%) were taken in a dry Schlenk flask. Then 2 mL dry CH_2Cl_2 was added to the mixture and stirred at room temperature for 2 hours. The flask was cooled to 0 °C and stirred for 10 min. Then acyl cyanide **2** (0.75 mmol) was added to the mixture and stirred for 36-48 hours at 0 °C. The mixture was directly subjected to silica gel column chromatography to give the pure corresponding product.

7.2.5.1 *N*-benzyl-*N*-(cyano(phenyl)methyl)acetamide 3a

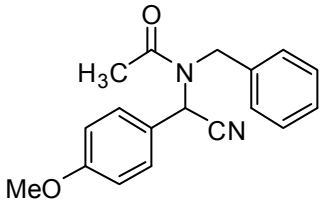
Compound **3a** was isolated in 80% yield (36 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3a** have been described in section 7.2.2.1.



3a

7.2.5.2 *N*-benzyl-*N*-(cyano(4-methoxyphenyl)methyl)acetamide 3c

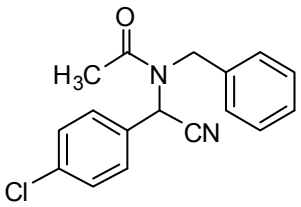
Compound **3c** was isolated in 82% yield (36 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3c** have been described in section 7.2.2.2.



3c

7.2.5.3 *N*-benzyl-*N*-(cyano(4-chlorophenyl)methyl)acetamide 3d

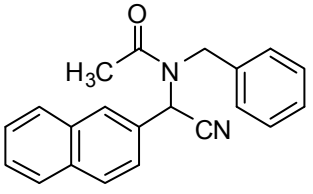
Compound **3d** was isolated in 73% yield (48 h reaction time)after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3d** have been described in section 7.2.2.3.



3d

7.2.5.4 *N*-benzyl-*N*-(cyano(naphthalene-2-yl)methyl)acetamide 3k

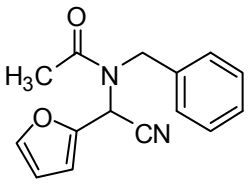
Compound **3k** was isolated in 83% yield (36 h reaction time) after silica gel column chromatography (20% EtOAc in hexane). The spectral and analytical data of compound **3k** have been described in section 7.2.3.5.



3k

7.2.5.5 *N*-benzyl-*N*-(cyano(furan-2-yl)methyl)acetamide 3f

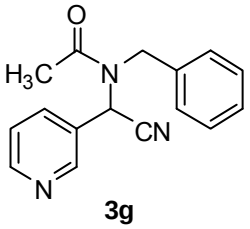
Compound **3f** was isolated in 76% yield (36 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3f** have been described in section 7.2.2.5.



3f

7.2.5.6 *N*-benzyl-*N*-(cyano(pyridin-3-yl)methyl)acetamide 3g

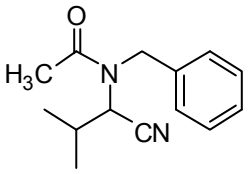
Compound **3g** was isolated in 84% yield (36 h reaction time) after silica gel column chromatography (70% EtOAc in hexane). The spectral and analytical data of compound **3g** have been described in section 7.2.2.6.



3g

7.2.5.7 *N*-benzyl-*N*-(1-cyano-2-methylpropyl)acetamide 3h

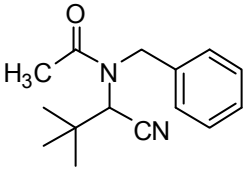
Compound **3h** was isolated in 78% yield (36 h reaction time) after silica gel column chromatography (50% EtOAc in hexane). The spectral and analytical data of compound **3h** have been described in section 7.2.2.7.



3h

7.2.5.8 *N*-benzyl-*N*-(1-cyano-2,2-dimethylpropyl)acetamide 3b

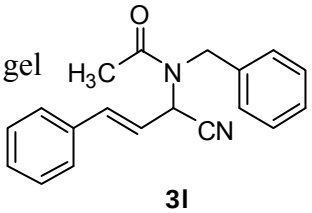
Compound **3b** was isolated in 48% yield (48 h reaction time) after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3b** have been described in section 7.2.2.8.



3b

7.2.5.9 *N*-benzyl-*N*-(1-cyano-3-phenylallyl)acetamide 3l

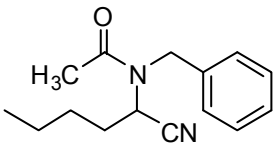
Compound **3l** was isolated in 85% yield (36 h reaction time) after silica gel column chromatography (35% EtOAc in hexane). The spectral and analytical data of compound **3l** have been described in section 7.2.3.7.



3l

7.2.5.10 *N*-benzyl-*N*-(1-cyanopentyl)acetamide 3n

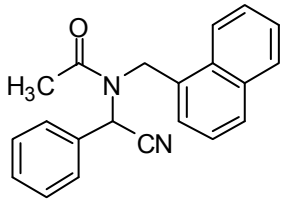
Compound **3n** was isolated in 82% yield (36 h reaction time) after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3n** have been described in section 7.2.3.12.



3n

7.2.5.11 *N*-(cyano(phenyl)methyl)-*N*-(naphthalene-1-ylmethyl) acetamide 3o

Compound **3o** was isolated in 77% yield (36 h reaction time) as a colorless liquid after silica gel flash column chromatography (30% EtOAc in hexane).



3o

3o $C_{21}H_{18}N_2O$ (314.38 g/mol)

Yield 121 mg (0.38 mmol, 77%)

TLC R_f = 0.46 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.90-7.87 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.56-7.51 (m, 2H), 7.47 (br s, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.36-7.34 (m, 3H), 7.28-7.23 (m, 2H), 5.10 (d, *J* = 18.2 Hz, 1H), 4.98 (d, *J* = 18.0 Hz, 1H), 2.16 (s, 3H).

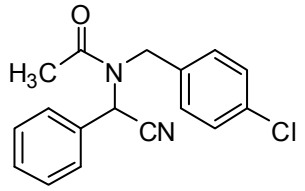
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.6 (C=O), 133.3 (Cq_{ar}), 131.9 (Cq_{ar}), 129.8 (Cq_{ar}), 129.0 (C_{ar}), 128.8 (C_{ar}), 128.7 (C_{ar}), 128.0 (C_{ar}), 127.3 (C_{ar}), 126.2 (C_{ar}), 125.7 (C_{ar}), 124.9 (C_{ar}), 122.8 (C_{ar}), 121.4 (C_{ar}), 116.0 (C≡N), 48.4 (CH_2), 46.9 (CH), 21.2 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{21}H_{18}N_2ONa$] ([MNa]$^+$): 337.1311
Found: 337.1311

HPLC τR = 35.5 min [(*S*)-**3o**], 42.9 min [(*R*)-**3o**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 0.7 mL/min, 220 nm).

7.2.5.12 *N*-(4-chlorobenzyl)-*N*-(cyano(phenyl)methyl)acetamide 3p

Compound **3p** was isolated in 81% yield (36 h reaction time) as a white liquid after silica gel flash column chromatography (35% EtOAc in hexane).



3p

3p $C_{17}H_{15}ClN_2O$ (298.77 g/mol)

Yield 121 mg (0.40 mmol, 81%)

TLC R_f = 0.42 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (s, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 4.55 (d, *J* = 17.6 Hz, 1H), 4.45 (d, *J* = 17.4 Hz, 1H), 2.12 (s, 3H).

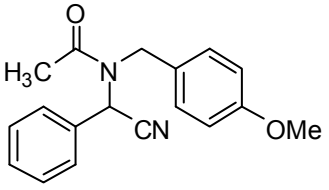
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0 (C=O), 133.8 (Cq_{ar}), 133.2 (Cq_{ar}), 131.7 (Cq_{ar}), 129.2 (C_{ar}), 129.0 (C_{ar}), 128.6 (C_{ar}), 127.3 (C_{ar}), 116.0 (C≡N), 48.6 (CH_2), 48.2 (CH), 21.6 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{17}H_{15}ClN_2ONa$] ([MNa]$^+$): 321.0763
Found: 321.0765

HPLC τR = 23.3 min [(*S*)-**3p**], 39.3 min [(*R*)-**3p**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 0.7 mL/min, 220 nm).

7.2.5.13 *N*-(cyano(phenyl)methyl)-*N*-(4-methoxybenzyl) acetamide 3q

Compound **3q** was isolated in 78% yield (36 h reaction time) as a yellowish white liquid after silica gel flash column chromatography (30% EtOAc in hexane).



3q

3q $C_{18}H_{18}N_2O_2$ (294.35 g/mol)

Yield 114 mg (0.39 mmol, 78%)

TLC R_f = 0.46 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 5H), 6.99 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.73-6.69 (m, 2H), 4.42 (d, *J* = 17.2 Hz, 1H), 4.31 (d, *J* = 17.0 Hz, 1H), 3.68 (s, 3H), 2.04 (s, 3H).

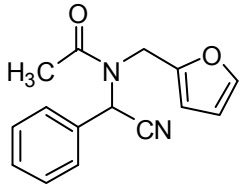
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2 (C=O), 158.8 (Cq_{ar}), 132.0 (Cq_{ar}), 129.0 (C_{ar}), 128.8 (C_{ar}), 128.5 (C_{ar}), 127.3 (C_{ar}), 127.1 (C_{ar}), 116.2 (C≡N), 113.8 (C_{ar}), 54.9 (CH_3), 48.8 (CH_2), 48.2 (CH), 21.7 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{18}H_{18}N_2O_2Na]$ ($[MNa]^+$): 317.1258
Found: 317.1260

HPLC τR = 24.6 min [(*S*)-**3q**], 44.9 min [(*R*)-**3q**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 1.0 mL/min, 220 nm).

7.2.5.14 *N*-(cyano(phenyl)methyl)-*N*-(furan-2-ylmethyl) acetamide 3r

Compound **3r** was isolated in 76% yield (48 h reaction time) as a yellow liquid after silica gel flash column chromatography (40% EtOAc in hexane).



3r

3r $C_{15}H_{14}N_2O_2$ (254.28 g/mol)

Yield 96 mg (0.38 mmol, 76%)

TLC R_f = 0.32 (ethylacetate/hexane 40:60)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.27 (m, 5H), 7.21 (t, *J* = 0.7 Hz, 1H), 6.93 (s, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 5.87 (s, 1H), 4.40 (d, *J* = 17.2 Hz, 1H), 4.22 (d, *J* = 17.1 Hz, 1H), 2.26 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9 (C=O), 148.3 (Cq_{ar}), 142.2 (C_{ar}), 131.5 (Cq_{ar}), 128.9 (C_{ar}), 127.9 (C_{ar}), 127.1 (C_{ar}), 115.6 (C≡N), 110.2 (C_{ar}), 108.8 (C_{ar}), 47.5 (CH), 42.1 (CH_2), 21.3 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{15}H_{14}N_2O_2Na]$ ($[MNa]^+$): 277.0953
Found: 277.0953

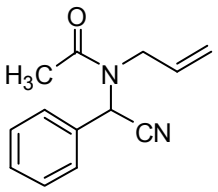
HPLC τR = 16.4 min [(*S*)-**3r**], 31.0 min [(*R*)-**3r**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 1.0 mL/min, 220 nm).

7.2.5.15 *N*-allyl-*N*-(cyano(phenyl)methyl)acetamide 3s

Compound **3s** was isolated in 68% yield (48 h reaction time) as a colorless liquid after silica gel flash column chromatography (30% EtOAc in hexane).

3s $C_{13}H_{14}N_2O$ (214.26 g/mol)

Yield 42 mg (0.34 mmol, 68%)



3s

TLC R_f = 0.46 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 5H), 6.98 (s, 1H), 5.57-7.47 (m, 1H), 5.05 (dd, *J* = 11.4 Hz, 13.3 Hz, 2H), 3.87-3.73 (m, 2H), 2.11 (s, 3H).

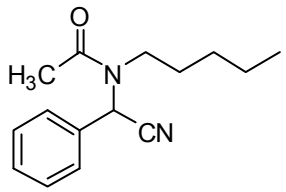
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.8 (C=O), 132.0 (Cq_{ar}), 131.9 (CH), 129.0 (C_{ar}), 128.8 (C_{ar}), 127.2 (C_{ar}), 117.7 (CH_2), 116.3 (C≡N), 48.0 (CH), 47.6 (CH_2), 21.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{13}H_{14}N_2ONa]$ ($[MNa]^+$): 237.0998
Found: 237.0998

HPLC τR = 11.3 min [(*S*)-**3s**], 22.9 min [(*R*)-**3s**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 1.0 mL/min, 220 nm).

7.2.5.16 *N*-(cyano(phenyl)methyl)-*N*-pentylacetamide 3t

Compound **3t** was isolated in 75% yield (36 h reaction time) as a colorless liquid after silica gel flash column chromatography (25% EtOAc in hexane).



3t

3t $C_{15}H_{20}N_2O$ (244.33 g/mol)

Yield 90 mg (0.37 mmol, 75%)

TLC R_f = 0.40 (ethylacetate/hexane 30:70)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.32 (m, 5H), 6.95 (s, 1H), 3.22-3.14 (m, 1H), 3.11-3.03 (m, 1H), 2.15 (s, 3H), 1.58-1.54 (m, 1H), 1.18-1.03 (m, 5H), 0.74 (t, *J* = 7.0 Hz, 3H).

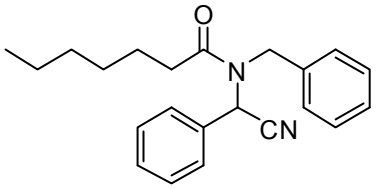
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.3 (C=O), 132.3 (Cq_{ar}), 128.9 (C_{ar}), 128.7 (C_{ar}), 127.0 (C_{ar}), 116.6 (C≡N), 47.3 (CH), 46.0 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 21.6 (CH_2), 20.8 (CH_3), 13.4 (CH_3).

HR-EI-MS Exact molecular mass for $[C_{15}H_{20}N_2O]$ ($[M]^+$): 244.1575
Found: 244.1575

HPLC τR = 8.3 min [(*S*)-**3t**], 15.3 min [(*R*)-**3t**] (Chiralpak AS-H, heptane/*i*-PrOH 80:20, 1.0 mL/min, 220 nm).

7.2.5.17 *N*-benzyl-*N*-(cyano(phenyl)methyl)heptanamide 3u

Compound **3u** was isolated in 72% yield (36 h reaction time) as a white liquid after silica gel flash column chromatography (10% EtOAc in hexane).



3u

3u $C_{22}H_{26}N_2O$ (334.45 g/mol)

Yield 120 mg (0.36 mmol, 72%)

TLC R_f = 0.45 (ethylacetate/hexane 10:90)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H), 7.29-7.26 (m, 3H), 7.21-7.13 (m, 3H), 7.06 (brs, 1H), 6.97 (d, *J* = 6.9 Hz, 2H), 4.49 (d, *J* = 17.4 Hz, 1H), 4.38 (d, *J* = 17.4 Hz, 1H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.58-1.53 (m, 2H), 1.21-1.11 (m, 6H), 0.78 (t, *J* = 6.8 Hz, 3H).

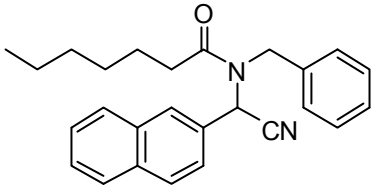
^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.8 (C=O), 135.5 (Cq_{ar}), 132.1 (Cq_{ar}), 128.9 (C_{ar}), 128.8 (C_{ar}), 128.4 (C_{ar}), 127.3 (C_{ar}), 125.9 (C_{ar}), 116.2 (C≡N), 48.6 (CH_2), 48.4 (CH), 33.2 (CH_2), 31.1 (CH_2), 28.5 (CH_2), 24.6 (CH_2), 22.0 (CH_2), 13.6 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{22}H_{26}N_2ONa]$ ($[MNa]^+$): 357.1936
Found: 357.1937

HPLC τR = 14.1 min [(*S*)-**3u**], 20.1 min [(*R*)-**3u**] (Chiralpak AS-H, heptane/*i*-PrOH 90:10, 0.7 mL/min, 220 nm).

7.2.5.18 *N*-benzyl-*N*-(cyano(naphthalen-2-yl)methyl)heptanamide 3v

Compound **3v** was isolated in 77% yield (36 h reaction time) as a colorless liquid after silica gel flash column chromatography (10% EtOAc in hexane).



3v

3v $C_{26}H_{28}N_2O$ (384.51 g/mol)

Yield 148 mg (0.38 mmol, 72%)

TLC R_f = 0.45 (ethylacetate/hexane 10:90)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.76-7.73 (m, 3H), 7.47-7.42 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.22 (br s, 1H), 7.17-7.09 (m, 3H), 6.99 (d, J = 6.9 Hz, 2H),

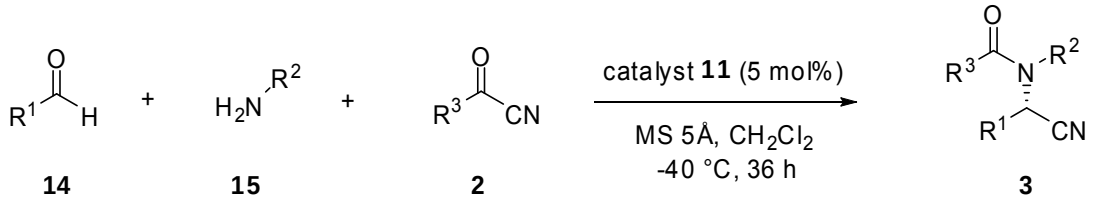
4.48 (d, *J* = 17.5 Hz, 1H), 4.37 (d, *J* = 17.3 Hz, 1H), 2.25 (t, *J* = 6.7 Hz, 2H), 1.62-1.54 (m, 2H), 1.23-1.09 (m, 6H), 0.78 (t, *J* = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.0 (C=O), 135.5 (Cq_{ar}), 132.9 (Cq_{ar}), 132.5 (Cq_{ar}), 129.4 (Cq_{ar}), 128.9 (C_{ar}), 127.8 (C_{ar}), 126.9 (C_{ar}), 126.8 (C_{ar}), 126.6 (C_{ar}), 125.9 (C_{ar}), 124.1 (C_{ar}), 116.2 (C≡N), 48.5 (CH_2), 48.4 (CH), 33.3 (CH_2), 31.1 (CH_2), 28.5 (CH_2), 24.7 (CH_2), 22.1 (CH_2), 13.6 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{26}H_{28}N_2ONa$] ([MNa]$^+$): 407.2090
Found: 407.2094

HPLC τR = 17.7 min [(*S*)-**3v**], 21.2 min [(*R*)-**3v**] (Chiralpak AS-H, heptane/*i*-PrOH 90:10, 0.7 mL/min, 220 nm).

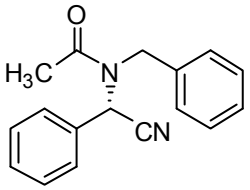
7.2.6 General Procedure for the Catalytic Asymmetric Three-Component Acyl-Strecker Reaction



14 **15** **2** **3**

Aldehyde **14** (0.5 mmol), amine **15** (0.5 mmol), and MS 5Å (150 mg) were placed into a dry Schlenk flask. Dry dichloromethane (2 mL) was added and the mixture was stirred for 2 hours at room temperature. Then catalyst **11** (5 mol%) was added and the flask was cooled to –40 ^{o}C and the mixture was stirred for 10 min. Acylcyanide **2** (0.75 mmol, 1.5 equiv.) was added and the mixture was stirred for 36 hours at –40 °C. The mixture was directly subjected to silica gel column chromatography to get pure product **3**.

7.2.6.1 (*S*)-*N*-benzyl-*N*-(cyano(phenyl)methyl)acetamide 3a

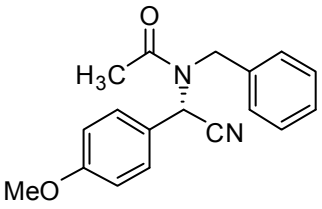


3a

Compound **3a** was isolated in 94% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3a** have been described in 7.2.2.1. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 23.3 min), τR (minor 37.2 min).

7.2.6.2 (*S*)-*N*-benzyl-*N*-(cyano(4-methoxyphenyl)methyl)-acetamide 3c

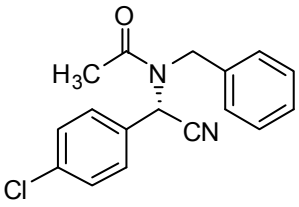
Compound **3c** was isolated in 88% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3c** have been described in section 7.2.2.2. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 24.4 min), τR (minor 35.6 min).



3c

7.2.6.3 (*S*)-*N*-benzyl-*N*-(cyano(4-chlorophenyl)methyl)acetamide 3d

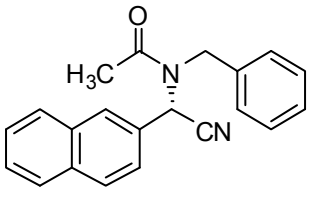
Compound **3d** was isolated in 78% yield after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3d** have been described in section 7.2.2.3. The enantiomeric ratio was determined to be 96:4 by chiral HPLC, τR (minor 24.9 min), τR (major 28.8 min).



3d

7.2.6.4 (*S*)-*N*-benzyl-*N*-(cyano(naphthalene-2-yl)methyl) acetamide 3k

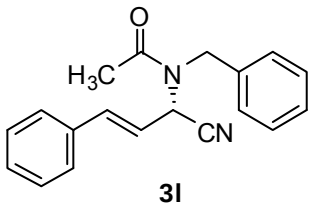
Compound **3k** was isolated in 92% yield after silica gel column chromatography (20% EtOAc in hexane). The spectral and analytical data of compound **3k** have been described in section 7.2.3.5. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (minor 29.7 min), τR (major 35.4 min).



3k

7.2.6.5 (*S*)-*N*-benzyl-*N*-(1-cyano-3-phenylallyl)acetamide 3l

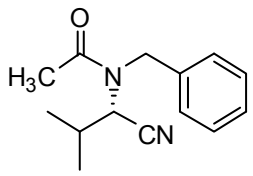
Compound **3l** was isolated in 82% yield after silica gel column chromatography (35% EtOAc in hexane). The spectral and analytical data of compound **3l** have been described in section 7.2.3.7. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (minor 26.3 min), τR (major 34.2 min).



3l

7.2.6.6 (*S*)-*N*-benzyl-*N*-(1-cyano-2-methylpropyl)acetamide 3h

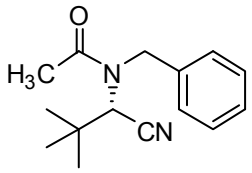
Compound **3h** was isolated in 92% yield after silica gel column chromatography (50% EtOAc in hexane). The spectral and analytical data of compound **3h** have been described in section 7.2.2.7. The enantiomeric ratio was determined to be 96:4 by chiral HPLC, τR (minor 36.5 min), τR (major 38.8 min).



3h

7.2.6.7 (*S*)-*N*-benzyl-*N*-(1-cyano-2,2-dimethylpropyl)acetamide 3b

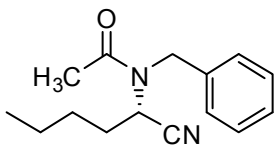
Compound **3b** was isolated in 46% yield after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3b** have been described in section 7.2.2.8. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 13.1 min), τR (minor 16.0 min).



3b

7.2.6.8 (*S*)-*N*-benzyl-*N*-(1-cyanopentyl)acetamide 3n

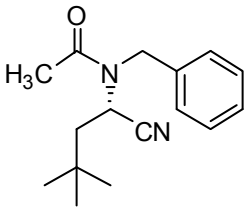
Compound **3n** was isolated in 75% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3n** have been described in section 7.2.3.12. The enantiomeric ratio was determined to be 94:6 by chiral HPLC, τR (minor 42.7 min), τR (major 45.5 min).



3n

7.2.6.9 (*S*)-*N*-benzyl-*N*-(1-cyano-3,3-dimethylbutyl)acetamide 3j

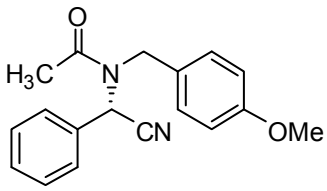
Compound **3j** was isolated in 97% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3j** have been described in section 7.2.2.10. The enantiomeric ratio was determined to be 96:4 by chiral HPLC, τR (major 14.0 min), τR (minor 16.7 min).



3j

7.2.6.10 (*S*)-*N*-(cyano(phenyl)methyl)-*N*-(4-methoxybenzyl) acetamide 3q

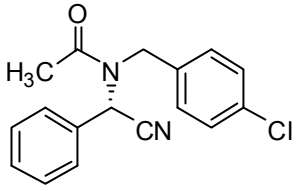
Compound **3q** was isolated in 95% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3q** have been described in section 7.2.5.13. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 24.6 min), τR (minor 44.9 min).



3q

7.2.6.11 (*S*)-*N*-(4-chlorobenzyl)-*N*-(cyano(phenyl)methyl) acetamide 3p

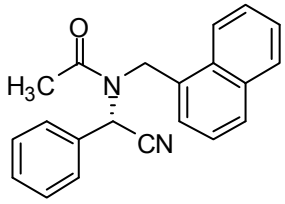
Compound **3p** was isolated in 93% yield after silica gel column chromatography (35% EtOAc in hexane). The spectral and analytical data of compound **3p** have been described in section 7.2.5.12. The enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 23.3 min), τR (minor 39.3 min).



3p

7.2.6.12 (*S*)-*N*-(cyano(phenyl)methyl)-*N*-(naphthalene-1-yl-methyl)acetamide 3o

Compound **3o** was isolated in 92% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3o** have been described in section 7.2.5.11. The

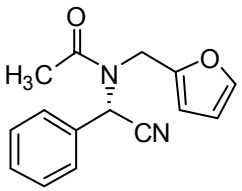


3o

enantiomeric ratio was determined to be 97:3 by chiral HPLC, τR (major 35.5 min), τR (minor 42.9 min).

7.2.6.13 (*S*)-*N*-(cyano(phenyl)methyl)-*N*-(furan-2-ylmethyl) acetamide 3r

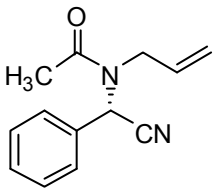
Compound **3r** was isolated in 83% yield after silica gel column chromatography (40% EtOAc in hexane). The spectral and analytical data of compound **3r** have been described in section 7.2.5.14. The enantiomeric ratio was determined to be 90:10 by chiral HPLC, τR (major 16.4 min), τR (minor 31.0 min).



3r

7.2.6.14 (*S*)-*N*-allyl-*N*-(cyano(phenyl)methyl)acetamide 3s

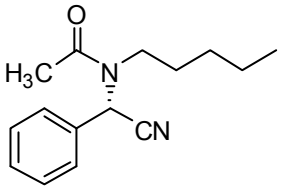
Compound **3s** was isolated in 88% yield after silica gel column chromatography (30% EtOAc in hexane). The spectral and analytical data of compound **3s** have been described in section 7.2.5.15. The enantiomeric ratio was determined to be 94:6 by chiral HPLC, τR (major 11.3 min), τR (minor 22.9 min).



3s

7.2.6.15 (*S*)-*N*-(cyano(phenyl)methyl)-*N*-pentylacetamide 3t

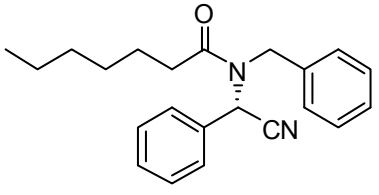
Compound **3t** was isolated in 76% yield after silica gel column chromatography (25% EtOAc in hexane). The spectral and analytical data of compound **3t** have been described in section 7.2.5.16. The enantiomeric ratio was determined to be 87:13 by chiral HPLC, τR (major 8.3 min), τR (minor 15.3 min).



3t

7.2.6.16 (*S*)-*N*-benzyl-*N*-(cyano(phenyl)methyl)heptanamide 3u

Compound **3u** was isolated in 84% yield after silica gel column chromatography (10% EtOAc in hexane). The

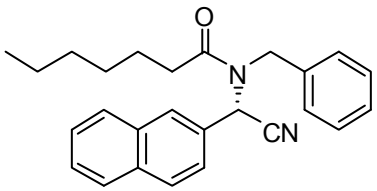


3u

spectral and analytical data of compound **3u** have been described in section 7.2.5.17. The enantiomeric ratio was determined to be 94:6 by chiral HPLC, τR (major 14.1 min), τR (minor 20.1 min).

7.2.6.17 (*S*)-*N*-benzyl-*N*-(cyano(naphthalene-2-yl)methyl)-heptanamide 3v

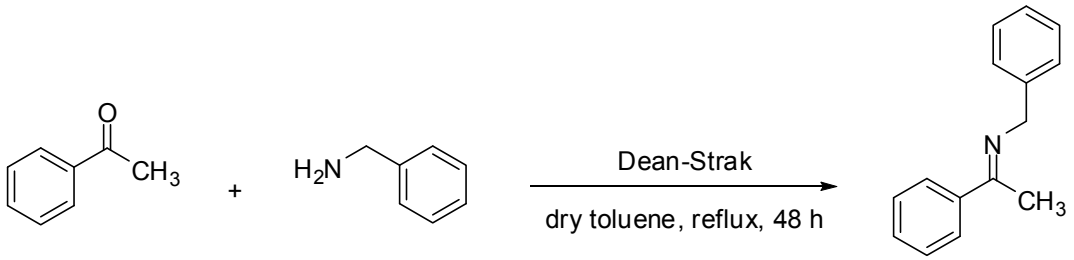
Compound **3v** was isolated in 87% yield after silica gel column chromatography (10% EtOAc in hexane). The spectral and analytical data of compound **3v** have been described in section 7.2.5.18. The enantiomeric ratio was determined to be 90:10 by chiral HPLC, τR (major 17.7 min), τR (minor 21.2 min).



3v

7.2.7 Amidine Formation from the Reaction of Acetylcyanide with Ketimines

7.2.7.1 Preparation of (*E*)-1-phenyl-*N*-(1-phenylethylidene) methanamine 16a[133]



106 **15b** **16a**

In a 100 mL oven-dried round bottom flask, acetophenone **106** (5.58 mL, 50 mmol, 1.00 equiv.) and benzyl amine **15b** (5.45 mL, 50 mmol, 1.00 equiv.) were dissolved in 25 mL of dry toluene. The flask was then connected with a reflux condenser and a Dean-Stark trap and the mixture was heated to reflux for 2 days. Then the solvent was removed *in vacuo*. The

compound was purified by distillation (132 °C**,** 0.08 mmHg) to afford 5.23 g **(**50% yield) of the desired product **16a** which solidified on standing, as a 17:1 mixture of geometric isomers.

16a $C_{15}H_{15}N$ (209.29 g/mol)

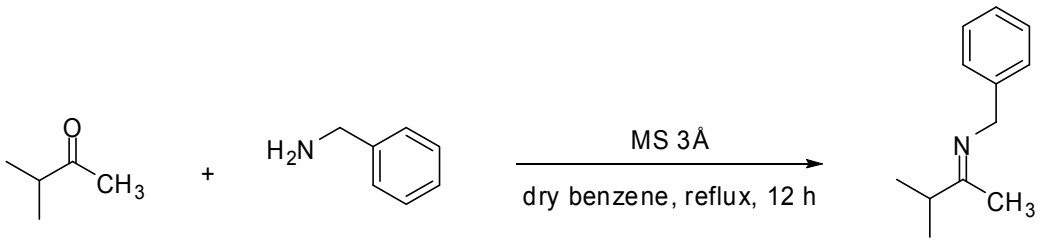
Yield 5.23 g (24.98 mmol, 50%)

M. P. 41-42 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.35-7.07 (m, 8H), 4.64 (s, 2H), 2.22 (s, 3H); minor 4.34 (s, 2H), 2.29 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 165.9 (N=C), 141.1 (Cq_{ar}), 140.6 (Cq_{ar}), 129.6 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 127.7 (C_{ar}), 126.8 (C_{ar}), 126.6 (C_{ar}), 55.7 (CH_2), 15.9 (CH_3).

7.2.7.2 Preparation of (*E*)-*N*-(3-methylbutan-2-ylidene)-1-phenyl methanamine 16b[133]



107a **15b** **16b**

In a 100 mL oven-dried round bottom flask, 3-methyl-2-butanone **107a** (2.10 mL, 20 mmol, 1.00 equiv.) and benzyl amine **15b** (2.18 mL, 20 mmol, 1.00 equiv.) were dissolved in 15 mL of dry benzene and 10 g of 3 Å molecular sieves was added to the mixture under argon atmosphere. The flask was then connected with a reflux condenser and the mixture was heated to reflux for 12 hours. Then the solvent was removed *in vacuo*. The product was purified by distillation (73 °C, 0.26 mmHg) to afford 2.38 g (68% yield) of a clear oil **16b** as a 13:1 mixture of geometric isomers.

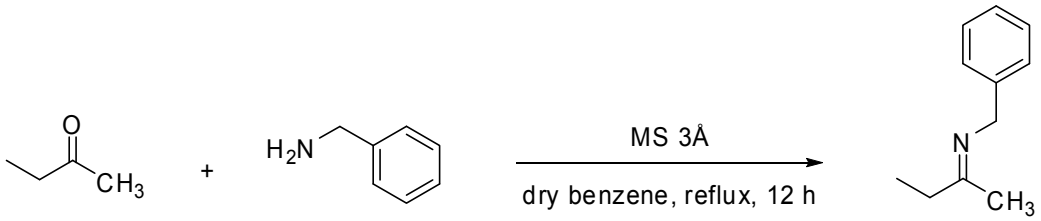
16b $C_{12}H_{17}N$ (175.27 g/mol)

Yield 2.38 g (13.60 mmol, 68%)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34-7.21 (m, 4H), 7.12-7.11 (m, 1H), 4.40 (s, 2H), 2.53-2.45 (m, 1H), 1.80 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 175.3 (N=C), 140.7 (Cq_{ar}), 128.3 (C_{ar}), 127.5 (C_{ar}), 126.4 (C_{ar}), 54.6 (CH_2), 40.2 (CH), 19.5 (CH_3), 15.0 (CH_3).

7.2.7.3 Preparation of (*E*)-*N*-(butan-2-ylidene)-1-phenyl methanamine 16c



107b **15b** **16c**

In a 100 mL oven-dried round bottom flask, 2-butanone **107b** (1.80 mL, 20 mmol, 1.00 equiv.) and benzyl amine **15b** (2.18 mL, 20 mmol, 1.00 equiv.) were dissolved in 15 mL of dry benzene and 10 g of 3 Å molecular sieves was added to the mixture under argon atmosphere. The flask was then connected with a reflux condenser and the mixture was heated to reflux for 12 hours. Then the solvent was removed *in vacuo*. The product was purified by distillation (73 °C, 0.26 mmHg) to afford 2.10 g (65% yield) of a clear oil **16c** as a 5:1 mixture of geometric isomers.

16c $C_{11}H_{15}N$ (161.24 g/mol)

Yield 2.10 g (13.60 mmol, 65%)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22-7.20 (m, 5H), 4.37 (s, 2H), 2.22 (dd, *J* = 7.5, 15.1 Hz, 2H), 1.77 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H).

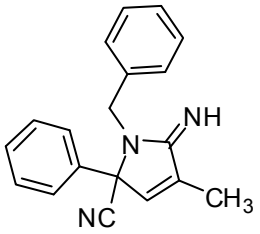
^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.0 (N=C), 140.6 (Cq_{ar}), 128.4 (C_{ar}), 127.7 (C_{ar}), 126.5 (C_{ar}), 55.0 (CH_2), 35.8 (CH_2), 17.4 (CH_3), 10.9 (CH_3).

7.2.7.4 General Procedure for the Catalytic Formation of Amidines

Ketimine **16** (0.5 mmol), acetylcyanide **2a** (0.1 mL, 1.5 mmol) and catalyst **4** (0.05 mmol) were placed into a dry flask. Dry toluene (1.5 mL) was added to the mixture and the mixture was stirred for 24-48 hours at 0 °C. The mixture was directly subjected to silica gel column chromatography (80% EtOAc-hexane) to isolate pure product **17**.

7.2.7.4.1 1-Benzyl-5-imino-4-methyl-2-phenyl-2,5-dihydro-1*H*-pyrrole-2-carbonitrile 17a

Compound **17a** was isolated in 75% yield (24 h reaction time) as a white solid after silica gel flash column chromatography (80% EtOAc in hexane).

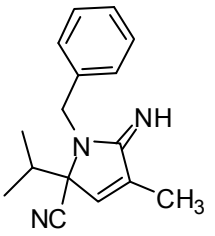


17a

17a	$C_{19}H_{17}N_3$ (287.36 g/mol)
Yield	109 mg (0.38 mmol, 75%)
TLC	R_f = 0.26 (ethylacetate/hexane 80:20)
^{1}H-NMR	(400 MHz, $CDCl_3$): δ 7.29-7.06 (m, 11H), 6.30 (d, *J* = 1.5 Hz, 1H), 4.55 (d, *J* = 15.9 Hz, 1H), 4.17 (d, *J* = 15.9 Hz, 1H), 2.01 (d, *J* = 1.5 Hz, 3H).
^{13}C-NMR	(100 MHz, $CDCl_3$): δ 166.9 (C=NH), 135.8 (Cq_{ar}), 135.3 (Cq), 133.1 (Cq_{ar}), 129.6 (C_{ar}), 129.2 (C_{ar}), 128.4 (C_{ar}), 128.0 (C_{ar}), 127.5 (C_{ar}), 126.2 (CH), 115.8 (C≡N), 68.5 (Cq), 46.0 (CH_2), 11.6 (CH_3).
HR-EI-MS	Exact molecular mass for [$C_{19}H_{17}N_3$] ([M]$^+$): 287.1419 Found: 287.1422
HPLC	τR = 12.6 min and 13.6 min (Chiralpak AD-H, heptane/*i*-PrOH 80:20, 0.7 mL/min, 220 nm).

7.2.7.4.2 1-Benzyl-5-imino-2-isopropyl-4-methyl-2,5-dihydro-1*H*-pyrrole-2-carbonitrile 17b

Compound **17b** was isolated in 40% yield (48 h reaction time) as a yellow liquid after silica gel flash column chromatography (80% EtOAc in hexane).



17b

17b $C_{16}H_{19}N_3$ (253.34 g/mol)

Yield 50 mg (0.20 mmol, 40%)

TLC R_f = 0.22 (ethylacetate/hexane 80:20)

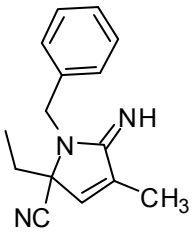
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 6H), 6.20 (d, *J* = 1.4 Hz, 1H), 4.72 (d, *J* = 16.1 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 2.12-2.05 (m, 1H), 1.92 (d, *J* = 1.5 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.49 (d, *J* = 6.7 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.5 (C=NH), 137.9 (Cq_{ar}), 136.5 (CH), 129.5 (C_{ar}), 128.3 (C_{ar}), 127.5 (C_{ar}), 127.2 (C_{ar}), 116.8 (C≡N), 69.5 (Cq), 45.7 (CH_2), 33.3 (CH), 18.0 (CH_3), 14.5 (CH_3), 11.3 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{16}H_{19}N_3$] ([M]$^+$): 253.1575
Found: 253.1578

7.2.7.4.3 1-Benzyl-2-ethyl-5-imino-4-methyl-2,5-dihydro-1*H*-pyrrole-2-carbonitrile 17c

Compound **17c** was isolated in 38% yield (48 h reaction time) as a yellow liquid after silica gel flash column chromatography (80% EtOAc in hexane).



17c

17c $C_{15}H_{14}N_3$ (239.32 g/mol)

Yield 45 mg (0.19 mmol, 38%)

TLC R_f = 0.22 (ethylacetate/hexane 80:20)

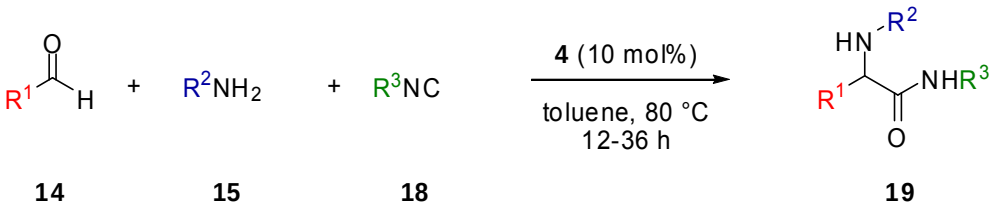
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28-7.18 (m, 6H), 6.25 (d, *J* = 1.5 Hz, 1H), 4.78 (d, *J* = 16.1 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 2.03-2.01 (m, 2H), 1.94 (d, *J* = 1.5 Hz, 3H), 1.08 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.9 (C=NH), 138.1 (Cq_{ar}), 136.3 (CH), 128.7 (C_{ar}), 128.6 (C_{ar}), 127.8 (C_{ar}), 127.6 (C_{ar}), 116.9 (C≡N), 69.8 (Cq), 43.8 (CH_2), 37.8 (CH_2), 17.1 (CH_3), 11.7 (CH_3).

HR-EI-MS Exact molecular mass for $[C_{15}H_{14}N_3]$ ($[M]^+$): 239.1422
Found: 239.1428

7.3 Catalytic Three-Component Ugi Reaction

7.3.1 General Procedure for the Catalytic Three-Component Ugi Reaction

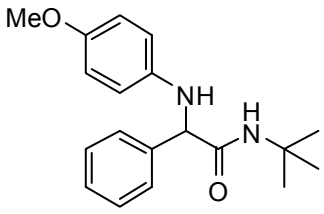


14 **15** **18** **19**

Aldehyde **14** (0.5 mmol), amine **15** (0.5 mmol), isocyanide **18** (0.5 mmol) and catalyst **4** (7.1 mg, 10 mol%) were placed into a dry flask. Dry toluene (0.5 mL) was added to the mixture and it was stirred for 12-36 hours at 80 °C. The mixture was directly subjected to silica gel column chromatography to give pure product **19**.

7.3.1.1 *N-tert*-butyl-2-(4-methoxyphenylamino)-2-phenyl-acetamide 19a

Compound **19a** was isolated in 91% yield (12 h reaction time) as a yellow solid after silica gel flash column chromatography (25% EtOAc in hexane).



19a

19a $C_{19}H_{24}N_2O_2$ (312.41 g/mol)

Yield 142 mg (0.45 mmol, 91%)

TLC R_f = 0.33 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.23 (m, 5H), 6.68 (d, *J* = 10.4 Hz, 2H), 6.50 (d, *J* = 9.6 Hz, 2H),, 4.44 (s, 1H), 4.14 (br s, 1H), 3.64 (s, 3H), 1.23 (s, 9H).

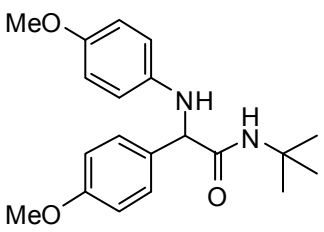
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 152.8 (Cq_{ar}), 140.5 (Cq_{ar}), 139.0 (Cq_{ar}), 128.7 (C_{ar}), 128.0 (C_{ar}), 126.9 (C_{ar}), 114.7 (C_{ar}), 114.5 (C_{ar}), 65.4 (CH), 55.3 (CH_3), 50.7 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{19}H_{24}N_2O_2Na]$ ($[MNa]^+$): 335.1723
Found: 335.1730

HPLC τR = 27.1 min and 32.7 min (Chiralpak AD-H, heptane/*i*-PrOH 90:10, 0.5 mL/min, 220 nm).

7.3.1.2 *N-tert*-butyl-2-(4-methoxyphenyl)-2-(4-methoxyphenyl-amino)acetamide 19b

Compound **19b** was isolated in 88% yield (12 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).



19b

19b $C_{20}H_{26}N_2O_3$ (342.43 g/mol)

Yield 150 mg (0.44 mmol, 88%)

TLC R_f = 0.35 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 9.2 Hz, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 4.39 (s, 1H), 4.06 (br s, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 1.24 (s, 9H).

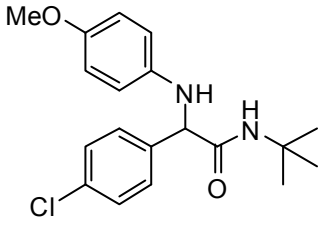
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4 (C=O), 159.2 (Cq_{ar}), 152.7 (Cq_{ar}), 140.6 (Cq_{ar}), 131.2 (Cq_{ar}), 128.1 (C_{ar}), 114.7 (C_{ar}), 114.4 (C_{ar}), 114.1 (C_{ar}), 64.8 (CH), 55.3 (CH_3), 54.9 (CH_3), 50.6 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{20}H_{26}N_2O_3Na]$ ($[MNa]^+$): 365.1837
Found: 365.1836

7.3.1.3 *N-tert*-butyl-2-(4-chlorophenyl)-2-(4-methoxyphenyl-amino)acetamide 19c

Compound **19c** was isolated in 78% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).

19c $C_{19}H_{23}ClN_2O_2$ (346.85 g/mol)



19c

Yield 135 mg (0.39 mmol, 78%)

TLC R_f = 0.34 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.26 (m, 4H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 4.43 (s, 1H), 4.00 (br s, 1H), 3.66 (s, 3H), 1.24 (s, 9H).

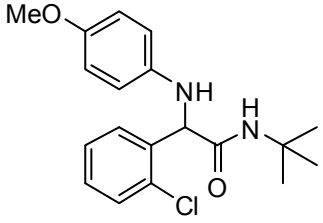
^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.6 (C=O), 152.9 (Cq_{ar}), 140.2 (Cq_{ar}), 137.6 (Cq_{ar}), 133.9 (Cq_{ar}), 128.9 (C_{ar}), 128.3 (C_{ar}), 114.8 (C_{ar}), 114.5 (C_{ar}), 64.6 (CH), 55.3 (CH_3), 50.8 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{19}H_{23}ClN_2O_2Na]$ ($[MNa]^+$): 369.1343

Found: 369.1340

7.3.1.4 *N-tert*-butyl-2-(2-chlorophenyl)-2-(4-methoxyphenyl-amino)acetamide 19d

Compound **19d** was isolated in 82% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (25% EtOAc in hexane).



19d

19d $C_{19}H_{23}ClN_2O_2$ (346.85 g/mol)

Yield 142 mg (0.41 mmol, 82%)

TLC R_f = 0.34 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.18-7.14 (m, 2H), 6.65 (d, *J* = 9.2 Hz, 2H), 6.44 (d, *J* = 8.9 Hz, 2H), 6.36 (br s, 1H), 5.04 (s, 1H), 4.54 (br s, 1H), 3.63 (s, 3H), 1.25 (s, 9H).

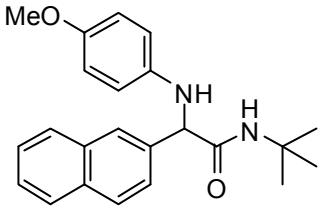
^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.0 (C=O), 152.4 (Cq_{ar}), 140.0 (Cq_{ar}), 136.9 (Cq_{ar}), 133.0 (Cq_{ar}), 129.4 (C_{ar}), 128.9 (C_{ar}), 128.2 (C_{ar}), 127.4 (C_{ar}), 114.5 (C_{ar}), 114.4 (C_{ar}), 60.2 (CH), 55.3 (CH_3), 51.1 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{19}H_{23}ClN_2O_2Na]$ ($[MNa]^+$): 369.1343

Found: 369.1340

7.3.1.5 *N-tert*-butyl-2-(4-methoxyphenylamino)-2-(naphthalene-2-yl)acetamide 19e

Compound **19e** was isolated in 87% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).



19e

19e $C_{23}H_{26}N_2O_2$ (362.46 g/mol)

Yield 156 mg (0.43 mmol, 87%)

TLC R_f = 0.30 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.92-7.84 (m, 4H), 7.56-7.51 (m, 3H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.67-6.64 (m, 3H), 4.74 (s, 1H), 4.43 (br s, 1H), 3.76 (s, 3H), 1.36 (s, 9H).

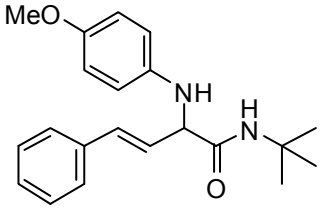
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0 (C=O), 152.8 (Cq_{ar}), 140.6 (Cq_{ar}), 136.5 (Cq_{ar}), 133.1 (Cq_{ar}), 132.9 (Cq_{ar}), 128.8 (C_{ar}), 127.7 (C_{ar}), 127.4 (C_{ar}), 126.3 (C_{ar}), 126.1 (C_{ar}), 125.9 (C_{ar}), 124.4 (C_{ar}), 114.8 (C_{ar}), 114.5 (C_{ar}), 65.3 (CH), 55.3 (CH_3), 50.8 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{23}H_{26}N_2O_2Na$] ([MNa]$^+$): 385.1888

Found: 385.1886

7.3.1.6 *(E)-N-tert*-butyl-2-(4-methoxyphenylamino)-4-phenylbut-3-enamide 19f

Compound **19f** was isolated in 83% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).



19f

19f $C_{21}H_{26}N_2O_2$ (338.44 g/mol)

Yield 140 mg (0.41 mmol, 83%)

TLC R_f = 0.33 (ethylacetate/hexane 25:75)

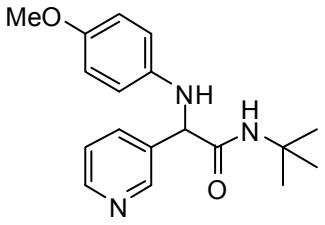
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.17 (m, 5H), 6.72-6.67 (m, 3H), 6.57-6.50 (m, 3H), 6.20 (dd, *J* = 7.2, 16.0 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 4.05 (br s, 1H), 3.67 (s, 3H), 1.26 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.1 (C=O), 152.9 (Cq_{ar}), 140.6 (Cq_{ar}), 135.8 (Cq_{ar}), 133.1 (CH), 128./ (C_{ar}), 128.2 (C_{ar}), 127.7 (C_{ar}), 126.9 (C_{ar}), 126.3 (CH), 114.9 (C_{ar}), 114.5 (C_{ar}), 63.0 (CH), 55.3 (CH_3), 50.7 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{21}H_{26}N_2O_2Na]$ ($[MNa]^+$): 308.1525
Found: 308.1527

7.3.1.7 *N-tert*-butyl-2-(4-methoxyphenylamino)-2-(pyridin-3-yl)acetamide 19g

Compound **19g** was isolated in 51% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (80% EtOAc in hexane).



19g

19g $C_{18}H_{23}N_3O_2$ (313.39 g/mol)

Yield 80 mg (0.26 mmol, 51%)

TLC R_f = 0.24 (ethylacetate/hexane 70:30)

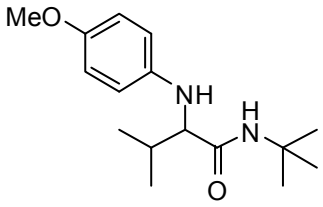
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.58 (d, *J* = 1.8 Hz, 1H), 8.47 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.66-7.63 (m, 1H), 7.22-7.19 (m, 1H), 6.71-6.67 (m, 3H), 6.51 (d, *J* = 6.7 Hz, 2H), 4.50 (s, 1H), 4.17 (br s, 1H), 3.66 (s, 3H), 1.24 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.2 (C=O), 153.1 (Cq_{ar}), 149.3 (C_{ar}), 148.5 (C_{ar}), 139.9 (Cq_{ar}), 134.8 (Cq_{ar}), 134.5 (C_{ar}), 123.5 (C_{ar}), 114.9 (C_{ar}), 114.5 (C_{ar}), 63.0 (CH), 55.4 (CH_3), 50.9 (Cq), 28.1 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{18}H_{23}N_3O_2Na]$ ($[MNa]^+$): 336.1684
Found: 336.1682

7.3.1.8 *N-tert*-butyl-2-(4-methoxyphenylamino)-3-methylbutanamide 19h

Compound **19h** was isolated in 74% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (20% EtOAc in hexane).



19h

19h $C_{16}H_{26}N_2O_2$ (278.39 g/mol)

Yield 103 mg (0.37 mmol, 74%)

TLC R_f = 0.40 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.70 (d, *J* = 9.0 Hz, 2H), 6.60 (br s, 1H), 6.50 (d, *J* = 9.0 Hz, 2H), 3.67 (s, 3H), 3.55 (br s, 1H), 3.24 (d, *J* = 4.2 Hz, 1H), 2.29-2.21 (m, 1H), 1.23 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).

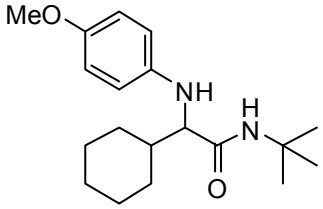
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.6 (C=O), 152.7 (Cq_{ar}), 141.3 (Cq_{ar}), 114.6 (C_{ar}), 114.5 (C_{ar}), 66.2 (CH), 55.3 (CH_3), 50.3 (Cq), 30.7 (CH), 28.2 (CH_3), 19.3 (CH_3), 17.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{16}H_{26}N_2O_2Na]$ ($[MNa]^+$): 301.1883

Found: 301.1886

7.3.1.9 *N-tert*-butyl-2-cyclohexyl-2-(4-methoxyphenylamino)-acetamide 19i

Compound **19i** was isolated in 81% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (25% EtOAc in hexane).



19i

19i $C_{19}H_{30}N_2O_2$ (318.45 g/mol)

Yield 129 mg (0.40 mmol, 81%)

TLC R_f = 0.37 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 (d, *J* = 8.9 Hz, 2H), 6.60 (br s, 1H), 6.49 (d, *J* = 8.9 Hz, 2H), 3.66 (s, 3H), 3.60 (s, 1H), 3.23 (d, *J* = 4.3 Hz, 1H), 1.91-1.84 (m, 1 H), 1.71-1.59 (m, 5H), 1.24 (s, 9H), 1.18-1.05 (m, 5H).

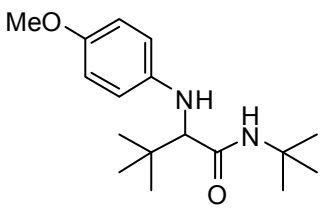
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.6 (C=O), 152.6 (Cq_{ar}), 141.3 (Cq_{ar}), 114.6 (C_{ar}), 114.4 (C_{ar}), 66.1 (CH), 55.3 (CH_3), 50.3 (Cq), 40.8 (CH), 30.0 (CH_2), 28.3 (CH_3), 27.8 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.8 (CH_2).

HR-ESI-MS Exact molecular mass for $[C_{19}H_{30}N_2O_2Na]$ ($[MNa]^+$): 341.2200

Found: 341.2199

7.3.1.10 *N-tert*-butyl-2-(4-methoxyphenylamino)-3,3-dimethylbutanamide 19j

Compound **19j** was isolated in 52% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (20% EtOAc in hexane).



19j

19j $C_{17}H_{28}N_2O_2$ (292.41 g/mol)

Yield 76 mg (0.26 mmol, 52%)

TLC R_f = 0.38 (ethylacetate/hexane 20:80)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.70 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 6.35 (br s, 1H), 3.67 (s, 3H), 3.06 (s, 1H), 1.22 (s, 9H), 1.01 (s, 9H).

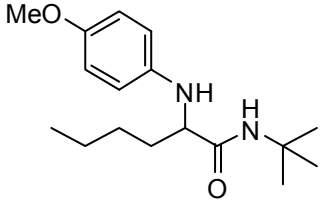
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.2 (C=O), 152.7 (Cq_{ar}), 141.2 (Cq_{ar}), 114.9 (C_{ar}), 114.4 (C_{ar}), 69.9 (CH), 55.3 (CH_3), 50.3 (Cq), 33.5 (Cq), 28.2 (CH_3), 26.9 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{17}H_{28}N_2O_2Na$] ([MNa]$^+$): 315.2042

Found: 315.2043

7.3.1.11 *N-tert*-butyl-2-(4-methoxyphenylamino)-hexanamide 19k

Compound **19k** was isolated in 61% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).



19k

19k $C_{17}H_{28}N_2O_2$ (292.41 g/mol)

Yield 89 mg (0.31 mmol, 61%)

TLC R_f = 0.34 (ethylacetate/hexane 25:75)

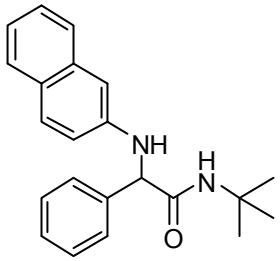
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.70 (d, *J* = 8.9 Hz, 2H), 6.60 (br s, 1H), 6.48 (d, *J* = 8.9 Hz, 2H), 3.67 (s, 3H), 3.35 (dd, *J* = 4.5, 8.2 Hz, 1H), 1.88-1.80 (m, 1H), 1.64-1.50 (m, 1H), 1.41-1.27 (m, 4H), 1.24 (s, 9H), 0.84 (t, *J* = 6.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.6 (C=O), 152.7 (Cq_{ar}), 140.8 (Cq_{ar}), 114.5 (C_{ar}), 114.4 (C_{ar}), 61.0 (CH), 55.3 (CH_3), 50.2 (Cq), 33.0 (CH_2), 28.2 (CH_3), 27.8 (CH_2), 22.1 (CH_2), 13.5 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{17}H_{28}N_2O_2Na]$ ($[MNa]^+$): 315.2042
Found: 315.2043

7.3.1.12 *N-tert*-butyl-2-(naphthalen-2-ylamino)-2-phenylacetamide 19l

Compound **19l** was isolated in 83% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (25% EtOAc in hexane).



19l

19l $C_{22}H_{24}N_2O$ (332.44 g/mol)

Yield 138 mg (0.41 mmol, 83%)

TLC R_f = 0.35 (ethylacetate/hexane 25:75)

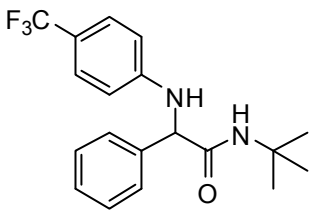
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 8.1, 13.4 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33-7.25 (m, 4H), 7.16-7.13 (m, 1H), 6.84 (dd, *J* = 2.3, 8.8 Hz, 1H), 6.72 (s, 1H), 6.40 (s, 1H), 4.66 (s, 1H), 4.64 (br s, 1H), 1.23 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.7 (C=O), 143.9 (Cq_{ar}), 138.8 (Cq_{ar}), 134.5 (Cq_{ar}), 128.9 (C_{ar}), 128.7 (C_{ar}), 128.2 (C_{ar}), 127.8 (C_{ar}), 127.2 (C_{ar}), 126.1 (C_{ar}), 125.9 (C_{ar}), 122.4 (C_{ar}), 117.7 (C_{ar}), 106.2 (C_{ar}), 64.4 (CH), 50.9 (Cq), 28.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{22}H_{24}N_2ONa]$ ($[MNa]^+$): 355.1784
Found: 355.1781

7.3.1.13 *N-tert*-butyl-2-phenyl-2-(4-(trifluoromethyl)-phenylamino)acetamide 19m

Compound **19m** was isolated in 81% yield (20 h reaction time) as a white solid after silica gel flash column chromatography (20% EtOAc in hexane).



19m

19m $C_{19}H_{21}F_3N_2O$ (350.38 g/mol)

Yield 142 mg (0.41 mmol, 81%)

TLC R_f = 0.42 (ethylacetate/hexane 15:85)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 7H), 6.51 (d, *J*

= 8.4 Hz, 2H), 5.86 (s, 1H), 5.17 (br s, 1H), 4.59 (s, 1H), 1.21 (s, 9H).

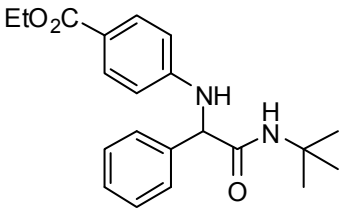
^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.9 (C=O), 148.7 (Cq_{ar}), 138.4 (Cq_{ar}), 129.0 (C_{ar}), 128.3 (C_{ar}), 126.7 (C_{ar}), 126.2 (C_{ar}), 126.1 (C_{ar}), 119.9 (Cq), 119.6 (Cq), 119.3 (Cq), 112.7 (C_{ar}), 62.8 (CH), 51.2 (Cq), 28.1 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{19}H_{21}F_3N_2ONa]$ ($[MNa]^+$): 373.1502

Found: 373.1498

7.3.1.14 Ethyl 4-(2-(*tert*-butylamino)-2-oxo-1-phenylethylamino)-benzoate 19n

Compound **19n** was isolated in 88% yield (20 h reaction time) as a white solid after silica gel flash column chromatography (25% EtOAc in hexane).



19n

19n $C_{21}H_{26}N_2O_3$ (354.44 g/mol)

Yield 156 mg (0.44 mmol, 88%)

TLC R_f = 0.40 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 2.0, 6.9 Hz, 2H), 7.30-7.18 (m, 5H), 6.46 (dd, *J* = 1.9, 8.8 Hz, 2H), 5.95 (s, 1H), 4.64 (s, 1H), 4.20 (dd, *J* = 7.1, 14.2 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.9 (C=O), 166.3 (C=O), 149.8 (Cq_{ar}), 138.4 (Cq_{ar}), 131.0 (C_{ar}), 128.9 (C_{ar}), 128.2 (C_{ar}), 126.7 (C_{ar}), 119.7 (Cq_{ar}), 112.3 (C_{ar}), 62.6 (CH), 59.9 (CH_2), 51.2 (Cq), 28.0 (CH_3), 14.0 (CH_3).

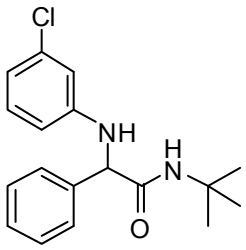
HR-ESI-MS Exact molecular mass for $[C_{21}H_{26}N_2O_3Na]$ ($[MNa]^+$): 377.1840

Found: 377.1836

7.3.1.15 *N*-*tert*-butyl-2-(3-chlorophenylamino)-2-phenylacetamide 19o

Compound **19o** was isolated in 74% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (20% EtOAc in hexane).

19o $C_{18}H_{21}ClN_2O$ (316.83 g/mol)



19o

Yield 117 mg (0.37 mmol, 74%)

TLC R_f = 0.38 (ethylacetate/hexane 15:85)

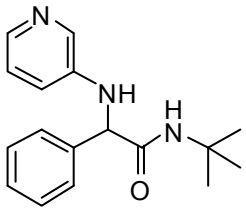
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 5H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.43 (td, *J* = 1.1, 7.6 Hz, 1H), 6.50 (t, *J* = 2.1 Hz, 1H), 6.39 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.07 (br s, 1H), 4.74 (br s, 1H), 4.52 (s, 1H), 1.23 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.0 (C=O), 147.4 (Cq_{ar}), 138.6 (Cq_{ar}), 134.6 (Cq_{ar}), 129.8 (C_{ar}), 128.9 (C_{ar}), 128.2 (C_{ar}), 126.8 (C_{ar}), 118.3 (Cq_{ar}), 113.3 (C_{ar}), 111.6 (C_{ar}), 63.5 (CH), 51.0 (Cq), 28.3 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{18}H_{21}ClN_2ONa$] ([MNa]$^+$): 339.1236
Found: 339.1234

7.3.1.16 *N-tert*-butyl-2-phenyl-2-(pyridin-3-ylamino)acetamide 19p

Compound **19p** was isolated in 81% yield (20 h reaction time) as a white solid after silica gel flash column chromatography (80% EtOAc in hexane).



19p

19p $C_{17}H_{21}N_3O$ (283.37 g/mol)

Yield 115 mg (0.40 mmol, 81%)

TLC R_f = 0.28 (ethylacetate/hexane 80:20)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 2.8 Hz, 1H), 7.90 (dd, *J* = 1.1, 5.8 Hz, 1H), 7.35-7.24 (m, 5H), 6.95 (dd, *J* = 4.7, 8.3 Hz, 1H), 6.77-6.74 (m, 1H), 6.02 (br s, 1H), 4.95 (br s, 1H), 4.55 (d, *J* = 2.8 Hz, 1H), 1.18 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.0 (C=O), 142.3 (Cq_{ar}), 139.5 (C_{ar}), 138.4 (Cq_{ar}), 136.4 (C_{ar}), 128.9 (C_{ar}), 128.2 (C_{ar}), 126.8 (C_{ar}), 123.3 (Cq_{ar}), 119.3 (C_{ar}), 62.9 (CH), 51.1 (Cq), 28.1 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{17}H_{21}N_3ONa$] ([MNa]$^+$): 336.1684
Found: 336.1682

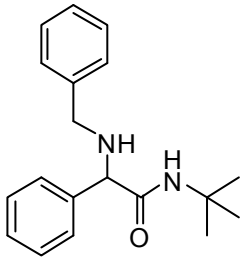
7.3.1.17 2-(benzylamino)-*N-tert*-butyl-2-phenylacetamide 19q

Compound **19q** was isolated in 42% yield (20 h reaction time) as a white solid after silica gel flash column chromatography (25% EtOAc in hexane).

19q $C_{19}H_{24}N_2O$ (296.41 g/mol)

Yield 62 mg (0.21 mmol, 42%)

TLC R_f = 0.36 (ethylacetate/hexane 25:75)



19q

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26-7.17 (m, 10H), 7.02 (br s, 1H), 4.03 (s, 1H), 3.69 (dd, *J* = 13.4, 15.1 Hz, 2H), 1.91 (br s, 1H), 1.26 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6 (C=O), 139.4 (Cq_{ar}), 139.1 (Cq_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 127.8 (C_{ar}), 127.6 (C_{ar}), 127.0 (C_{ar}), 126.9 (C_{ar}), 67.4 (CH), 52.4 (CH_2), 50.3 (Cq), 28.4 (CH_3).

HR-ESI-MS Exact molecular mass for [$C_{19}H_{24}N_2ONa$] ([MNa]$^+$): 319.1783

Found: 319.1781

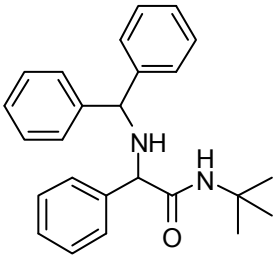
7.3.1.18 2-(benzhydrylamino)-*N*-*tert*-butyl-2-phenylacetamide 19r

Compound **19r** was isolated in 36% yield (36 h reaction time) as a yellow liquid after silica gel flash column chromatography (18% EtOAc in hexane).

19r $C_{25}H_{28}N_2O$ (372.50 g/mol)

Yield 67 mg (0.18 mmol, 36%)

TLC R_f = 0.33 (ethylacetate/hexane 15:85)



19r

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23-7.13 (m, 15H), 6.74 (br s, 1H), 4.69 (s, 1H), 3.98 (s, 1H), 2.39 (br s, 1H), 1.24 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7 (C=O), 142.6 (Cq_{ar}), 139.4 (Cq_{ar}), 128.5 (C_{ar}), 127.6 (C_{ar}), 127.2 (C_{ar}), 127.1 (C_{ar}), 127.1 (C_{ar}), 127.0 (C_{ar}), 126.9 (C_{ar}), 65.2 (CH), 64.7 (CH), 50.5 (Cq), 28.4 (CH_3).

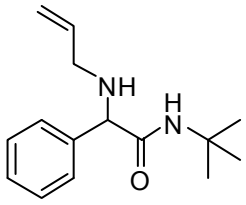
HR-ESI-MS Exact molecular mass for [$C_{25}H_{28}N_2ONa$] ([MNa]$^+$): 395.2097

Found: 395.2094

7.3.1.19 2-(allylamino)-*N*-*tert*-butyl-2-phenylacetamide 19s

Compound **19s** was isolated in 40% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).

19s $C_{15}H_{22}N_2O$ (246.35 g/mol)



19s

Yield 49 mg (0.20 mmol, 40%)

TLC R_f = 0.34 (ethylacetate/hexane 25:75)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.20 (m, 5H), 7.00 (br s, 1H), 5.86-5.76 (m, 1H), 5.13 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.05 (dd, *J* = 1.5, 10.2 Hz, 1H), 4.00 (s, 1H), 3.17-3.15 (m, 2H), 1.67 (br s, 1H), 1.27 (s, 9H).

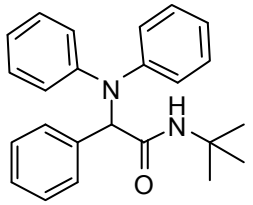
^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7 (C=O), 139.5 (Cq_{ar}), 135.5 (CH), 128.4 (C_{ar}), 127.6 (C_{ar}), 126.9 (C_{ar}), 116.1 (CH_2), 67.1 (CH), 50.6 (CH_2), 50.3 (Cq), 28.3 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{15}H_{22}N_2ONa]$ ($[MNa]^+$): 269.1626

Found: 269.1624

7.3.1.20 *N-tert*-butyl-2-(diphenylamino)-2-phenylacetamide 19t

Compound **19t** was isolated in 41% yield (36 h reaction time) as a white solid after silica gel flash column chromatography (12% EtOAc in hexane).



19t

19t $C_{24}H_{26}N_2O$ (358.47 g/mol)

Yield 73 mg (0.20 mmol, 41%)

TLC R_f = 0.46 (ethylacetate/hexane 20:80)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18-7.16 (m, 2H), 7.12-7.07 (m, 7H), 6.89-6.81 (m, 6H), 6.31 (br s, 1H), 5.37 (s, 1H), 1.21 (s, 9H).

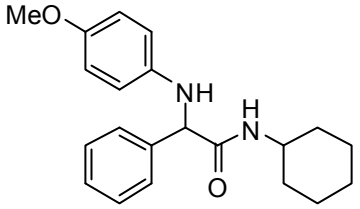
^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.4 (C=O), 146.7 (Cq_{ar}), 135.8 (Cq_{ar}), 129.3 (C_{ar}), 128.7 (C_{ar}), 127.7 (C_{ar}), 127.3 (C_{ar}), 122.7 (C_{ar}), 122.4 (C_{ar}), 70.3 (CH), 50.9 (Cq), 28.1 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{24}H_{26}N_2ONa]$ ($[MNa]^+$): 381.1940

Found: 381.1937

7.3.1.21 *N*-cyclohexyl-2-(4-methoxyphenylamino)-2-phenylacetamide 19u

Compound **19u** was isolated in 78% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (25% EtOAc in hexane).



19u

19u $C_{21}H_{26}N_2O_2$ (338.44 g/mol)

Yield 132 mg (0.39 mmol, 78%)

TLC R_f = 0.38 (ethylacetate/hexane 20:80)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 6.70-6.65 (m, 3H), 6.49 (dd, *J* = 2.2, 6.9 Hz, 2H), 4.54 (s, 1H), 4.14 (br s, 1H), 3.74-3.67 (m, 1H), 3.64 (s, 3H), 1.80-1.69 (m, 2H), 1.59-1.47 (m, 3H), 1.30-0.90 (m, 5H).

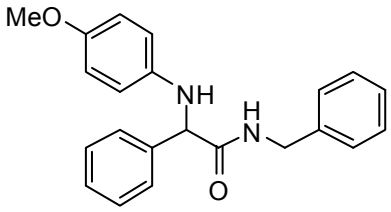
^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.9 (C=O), 152.8 (Cq_{ar}), 140.5 (Cq_{ar}), 138.9 (Cq_{ar}), 128.7 (C_{ar}), 128.0 (C_{ar}), 127.0 (C_{ar}), 114.7 (C_{ar}), 114.5 (C_{ar}), 64.8 (CH), 55.3 (CH_3), 47.6 (CH), 32.6 (CH_2), 32.4 (CH_2), 25.1 (CH_2), 24.4 (CH_2), 24.3 (CH_2).

HR-ESI-MS Exact molecular mass for $[C_{21}H_{26}N_2O_2Na]$ ($[MNa]^+$): 361.1887

Found: 361.1886

7.3.1.22 *N*-benzyl-2-(4-methoxyphenylamino)-2-phenylacetamide 19v

Compound **19v** was isolated in 64% yield (36 h reaction time) as a yellow solid after silica gel flash column chromatography (30% EtOAc in hexane).



19v

19v $C_{22}H_{22}N_2O_2$ (346.42 g/mol)

Yield 111 mg (0.32 mmol, 64%)

TLC R_f = 0.34 (ethylacetate/hexane 30:70)

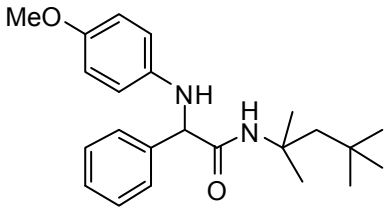
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 1.7, 8.0 Hz, 2H), 7.42-7.36 (m, 3H), 7.31-7.24 (m, 3H), 7.16-7.15 (m, 2H), 6.80 (d, *J* = 6.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 4.77 (s, 1H), 4.52 (dd, *J* = 6.1, 14.9 Hz, 1H), 4.40 (dd, *J* = 5.7, 14.9 Hz, 1H), 3.77 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.1 (C=O), 152.9 (Cq_{ar}), 140.3 (Cq_{ar}), 138.6 (Cq_{ar}), 137.7 (Cq_{ar}), 128.8 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 127.2 (C_{ar}), 127.0 (C_{ar}), 127.0 (C_{ar}), 114.8 (C_{ar}), 114.5 (C_{ar}), 64.7 (CH), 55.5 (CH_3), 43.0 (CH_2).

HR-ESI-MS Exact molecular mass for $[C_{22}H_{22}N_2O_2Na]$ ($[MNa]^+$): 369.1576
Found: 369.1573

7.3.1.23 2-(4-Methoxyphenylamino)-2-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)acetamide 19w

Compound **19w** was isolated IN 62% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (20% EtOAc in hexane).



19w

19w $C_{23}H_{32}N_2O_2$ (368.51 g/mol)

Yield 114 mg (0.31 mmol, 62%)

TLC R_f = 0.44 (ethylacetate/hexane 20:80)

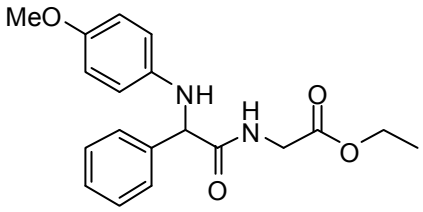
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35-7.21 (m, 5H), 6.68-6.66 (m, 2H), 6.54 (br s, 1H), 6.51-6.49 (m, 2H), 4.45 (s, 1H), 4.28 (br s, 1H), 3.66 (s, 3H), 1.57 (d, *J* = 14.9 Hz, 1H), 1.48 (d, *J* = 14.9 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 0.79 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.6 (C=O), 152.7 (Cq_{ar}), 140.6 (Cq_{ar}), 139.1 (Cq_{ar}), 128.7 (C_{ar}), 127.9 (C_{ar}), 127.0 (C_{ar}), 114.8 (C_{ar}), 114.4 (C_{ar}), 65.2 (CH), 55.3 (CH_3), 54.8 (Cq), 52.8 (CH_2), 31.1 (Cq), 31.0 (CH_3), 28.2 (CH_3), 27.8 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{23}H_{32}N_2O_2Na]$ ($[MNa]^+$): 391.2359
Found: 391.2356

7.3.1.24 Ethyl 2-(2-(4-methoxyphenylamino)-2-phenylacetamido)acetate 19x

Compound **19x** was isolated in 83% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (40% EtOAc in hexane).



19x

19x $C_{19}H_{22}N_2O_4$ (342.39 g/mol)

Yield 142 mg (0.41 mmol, 83%)

TLC R_f = 0.34 (ethylacetate/hexane 40:60)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (m, 2H), 7.30-7.22 (m, 4H), 6.69-6.66 (m, 2H), 6.54-6.50 (m, 2H), 4.64 (s, 1H), 4.18 (br s, 1H), 4.10-4.00 (m, 3H), 3.81 (dd, *J* = 4.9, 18.1 Hz, 1H), 3.64 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5 (C=O), 169.1 (C=O), 152.9 (Cq_{ar}), 140.4 (Cq_{ar}), 138.4 (Cq_{ar}), 128.8 (C_{ar}), 128.2 (C_{ar}), 127.2 (C_{ar}), 114.8 (C_{ar}), 114.5 (C_{ar}), 64.6 (CH), 61.1 (CH_2), 55.3 (CH_3), 40.9 (CH_2), 13.8 (CH_3).

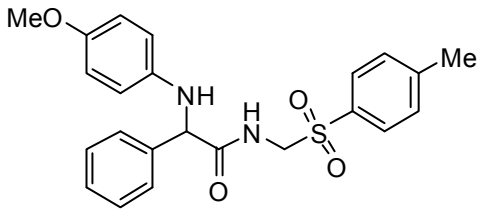
HR-ESI-MS Exact molecular mass for $[C_{19}H_{22}N_2O_4Na]$ ($[MNa]^+$): 365.1470

Found: 365.1471

7.3.1.25 2-(4-Methoxyphenylamino)-2-phenyl-*N*-(tosylmethyl)acetamide 19y

Compound **19y** was isolated in 68% yield (20 h reaction time) as a yellow solid after silica gel flash column chromatography (45% EtOAc in hexane).

19y $C_{23}H_{24}N_2O_4S$ (424.51 g/mol)



19y

Yield 144 mg (0.34 mmol, 68%)

TLC R_f = 0.38 (ethylacetate/hexane 50:50)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (t, *J* = 6.8 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.28-7.23 (m, 5H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 6.45 (d, *J* = 8.9 Hz, 2H), 4.68 (dd, *J* = 7.3, 14.2 Hz, 1H), 4.56 (s, 1H), 4.45 (dd, *J* = 6.4, 14.2 Hz, 1H), 3.65 (s, 3H), 2.29 (s, 3H).

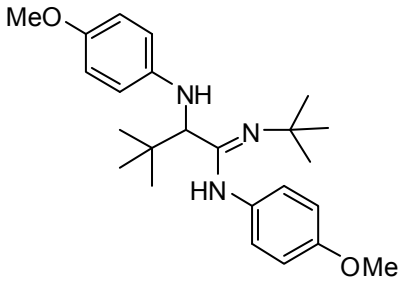
^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.1 (C=O), 153.2 (Cq_{ar}), 144.8 (Cq_{ar}), 139.8 (Cq_{ar}), 137.6 (Cq_{ar}), 133.5 (Cq_{ar}), 129.4 (C_{ar}), 128.8 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 126.9 (C_{ar}), 114.9 (C_{ar}), 114.6 (C_{ar}), 64.3 (CH), 59.7 (CH_2), 55.3 (CH_3), 21.3 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{23}H_{24}N_2O_4SNa]$ ($[MNa]^+$): 447.1353

Found: 447.1349

7.3.1.26 (*N'*)-*tert*-Butyl-*N*-(4-methoxyphenyl)-2-(4-methoxyphenylamino)-3,3-dimethylbutanimidamide 19j'

Compound **19j'** was isolated in 32% yield (20 h reaction time) as a yellow liquid after silica gel flash column chromatography (50% EtOAc in hexane).



19j'

19j' $C_{24}H_{35}N_3O_2$ (397.55 g/mol)

Yield 64 mg (0.16 mmol, 32%)

TLC R_f = 0.40 (ethylacetate/hexane 50:50)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.77-6.73 (m, 4H), 6.65 (d, *J* = 8.9 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 5.25 (br s, 1H), 3.89 (s, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.26 (br s, 1H), 1.34 (s, 9H), 0.84 (s, 9H).

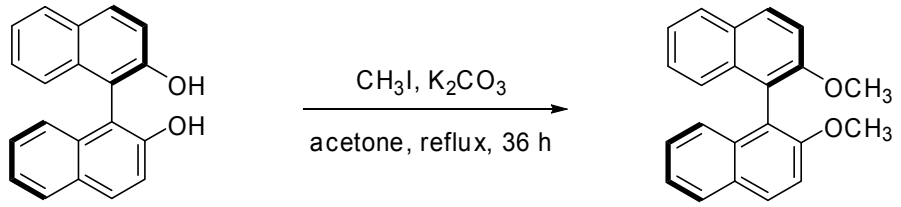
^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.1 (C=N), 153.4 (Cq_{ar}), 153.3 (Cq_{ar}), 144.0 (Cq_{ar}), 141.4 (Cq_{ar}), 123.0 (C_{ar}), 117.1 (C_{ar}), 114.3 (C_{ar}), 113.5 (C_{ar}), 61.9 (CH), 55.3 (CH_3), 55.2 (CH_3), 50.3 (Cq), 34.7 (Cq), 28.2 (CH_3), 27.3 (CH_3),

HR-ESI-MS Exact molecular mass for $[C_{24}H_{35}N_3O_2Na]$ ($[MNa]^+$): 420.2625

Found: 420.2621

7.4 Preparation of Catalysts

7.4.1 Preparation of (*R*)-2,2'-dimethoxy-1,1'-binaphthyl 116[136]



100 **116**

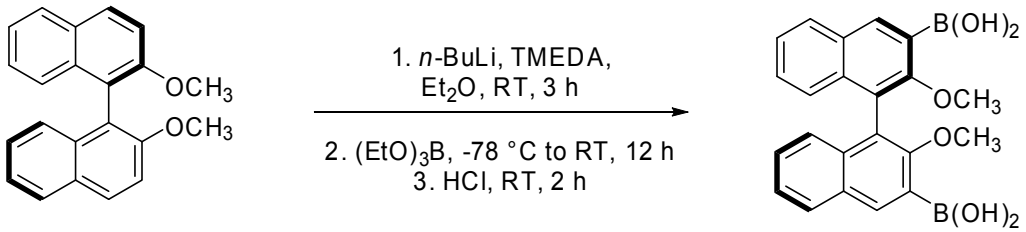
A suspension of (*R*)-1,1'-bi-2-naphthol (**100**, 5.10 g, 17.81 mmol) was heated in acetone (40 mL) to give a homogeneous solution. To this solution were added potassium carbonate (8.3 g, 60.00 mmol) and methyl iodide (9.94 g, 70.00 mmol), and the mixture was heated at reflux temperature for 24 hours after connecting with a reflux condensor. Additional methyl iodide (4.26 g, 30.00 mmol) 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 160 mL of water. The mixture was stirred for 8 hours, and the resulting solid was washed with water and dried to afford 5.47 g (98%) of (*R*)-**116** as a white powder.

116 $C_{22}H_{18}O_2$ (314.38 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 3.68 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 154.6 (Cq_{ar}), 133.7 (Cq_{ar}), 129.0 (C_{ar}), 128.9 (Cq_{ar}), 127.6 (C_{ar}), 125.9 (C_{ar}), 124.9 (C_{ar}), 123.1 (C_{ar}), 119.3 (Cq_{ar}), 113.9 (C_{ar}), 56.6 (CH_3).

7.4.2 Preparation of (*R*)-2,2'-dimethoxy-1,1'-binaphthyl-3,3'-diyldiboronic acid 117[136]



116 **117**

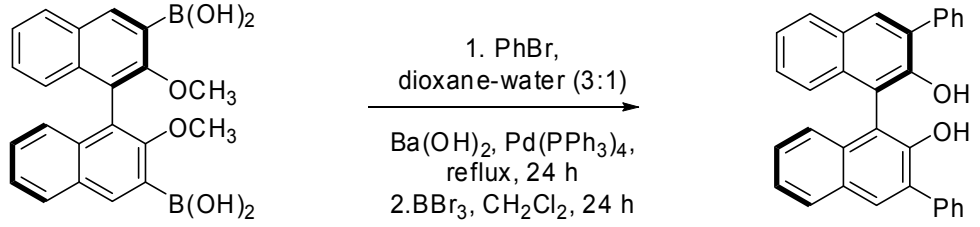
To a solution of TMEDA (5.89 mL, 39 mmol) in ether (200 mL) was added at room temperature 1.6 M *n*-BuLi in hexane (24.4 mL, 39 mmol). The solution was stirred for 30 min, solid (*R*)-2,2'-dimethoxy-1,1'-binaphthyl (**116**, 4.07 g, 13 mmol) was added in one portion, and the reaction mixture was stirred for 3 hours. The resulting light brown suspension was cooled to −78 °C, and ethyl borate (15.48 mL, 91 mmol) was added over a period of 10 min. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C, 1 N HCl solution (100 mL) was added, and the resulting solution was stirred for 2 hours at room temperature. The organic layer was washed with 1 N HCl solution and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting pale yellow solid was recrystallized from toluene to give 3.70 g (71%) of (*R*)-**117** as colorless crystals.

117 $C_{22}H_{20}B_2O_6$ (402.01 g/mol)

^{1}H-NMR (400 MHz, CD_3OCD_3): δ 8.57 (s, 2H), 8.05 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.36-7.32 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.43 (s, 6H), 2.06 (s, 4H).

^{13}C-NMR (100 MHz, CD_3OCD_3): δ 161.6 (Cq_{ar}), 139.4 (C_{ar}), 137.0 (Cq_{ar}), 131.8 (Cq_{ar}), 130.0 (Cq_{ar}), 129.4 (C_{ar}), 128.5 (C_{ar}), 126.5 (C_{ar}), 126.0 (Cq_{ar}), 124.6 (Cq_{ar}), 62.1 (CH_3).

7.4.3 Preparation of (*R*)-3,3'-Diphenyl-1,1'-binaphthyl-2,2'-diol 99a



117 **99a**

To a solution of (*R*)-**117** (402 mg, 1.00 mmol) in degassed dioxane/water (8 mL, 3:1) were added 4-bromophenyl (0.32 mL, 3.00 mmol), $Ba(OH)_2.8H_2O$ (946 mg, 3.00 mmol), and $Pd(PPh_3)_4$ (46.2 mg, 0.04 mmol). The reaction mixture was heated at reflux temperature for 24 hours and cooled to room temperature. Dioxane was removed, and the resulting residue was redissolved in CH_2Cl_2, washed with 1 N HCl solution and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude coupling products. To a solution of these crude products in CH_2Cl_2 (50 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (6.0 mL, 6.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 hours, and quenched with water (1 mL) in an ice bath. The mixture was poured into a stirred mixture of CH_2Cl_2 and water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on SiO_2 (hexanes/EtOAc, 20:1) gave 324 mg (74%) of (*R*)-**99a** as a pale yellow solid.

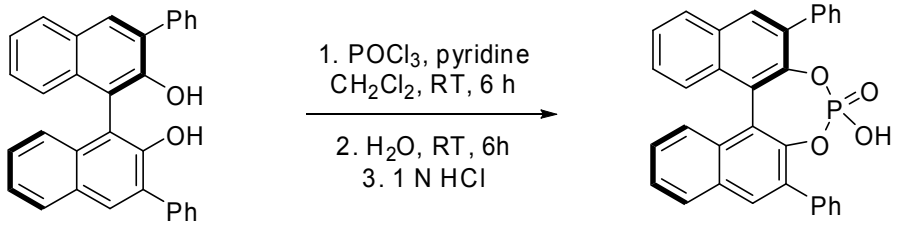
99a $C_{32}H_{22}O_2$ (438.52 g/mol)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 4H), 7.40 (t, *J* = 7.6 Hz, 4H), 7.31 (dd, *J* = 7.8, 16.3 Hz, 4H), 7.23 (t, *J* = 8.2 Hz, 2H), 7.16-7.14 (m, 2H), 5.27 (s, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 150.2 (Cq_{ar}), 137.5 (Cq_{ar}), 133.0 (Cq_{ar}), 131.4 (C_{ar}), 130.7 (Cq_{ar}), 129.6 (C_{ar}), 129.5 (Cq_{ar}), 128.5 (C_{ar}), 128.5 (C_{ar}), 127.8 (C_{ar}), 127.4 (C_{ar}), 124.4 (Cq_{ar}), 124.3 (Cq_{ar}), 112.4 (Cq_{ar}).

HR-ESI-MS Exact molecular mass for $[C_{32}H_{22}O_2Na]$ ($[M]^+$): 461.1508
Found: 461.1512

7.4.4 Preparation of (*R*)-3,3'-Diphenyl-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate 6a



99a **6a**

Diol **99a** (525 mg, 1.20 mmol) was suspended in pyridine (3.0 mL) in a two-necked flask. Phosphorous oxychloride (367 mg, 0.23 mL, 2.40 mmol) was added dropwise at room temperature with rapid stirring and the resulting suspension was stirred for 6 hours at room temperature until all starting material was deemed consumed by TLC. Then, water (1 mL) was added to the reaction mixture. The resulting biphasic suspension was stirred for an additional 6 hours at room temperature. The reaction mixture was diluted with CH_2Cl_2 and the pyridine was removed via washing with 1 N HCl. The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude product as a pale yellow solid. Purification by flash column chromatography (gradient from 2% to 5% *i*-PrOH in CH_2Cl_2) yielded catalyst **13** as a pale yellow solid (456 mg, 76% yield).

6a $C_{32}H_{21}O_4P$ (500.48 g/mol)

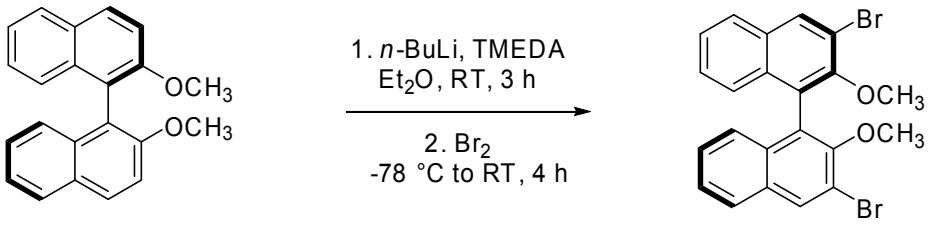
^{1}H-NMR (500 MHz, $(CD_3)_2SO$): δ 8.12 (s, 2H), 8.05 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 7.5 Hz, 4H), 7.46-7.40 (m, 6H), 7.35-7.32 (m, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H).

^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ 145.2 (Cq_{ar}), 137.1 (Cq_{ar}), 133.6 (Cq_{ar}), 131.4 (Cq_{ar}), 131.1 (C_{ar}), 130.7 (Cq_{ar}), 129.8 (C_{ar}), 128.7 (C_{ar}), 128.2 (C_{ar}), 127.5 (C_{ar}), 126.8 (C_{ar}), 126.0 (C_{ar}), 125.7 (C_{ar}), 122.1 (Cq_{ar}).

^{31}P-NMR (202.5 MHz, $(CD_3)_2SO$): δ 1.06

HR-EI-MS Exact molecular mass for $[C_{32}H_{21}O_4P]$ ($[M]^+$): 500.1177
Found: 500.1179

7.4.5 Preparation of (*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl 118[138]



116 **118**

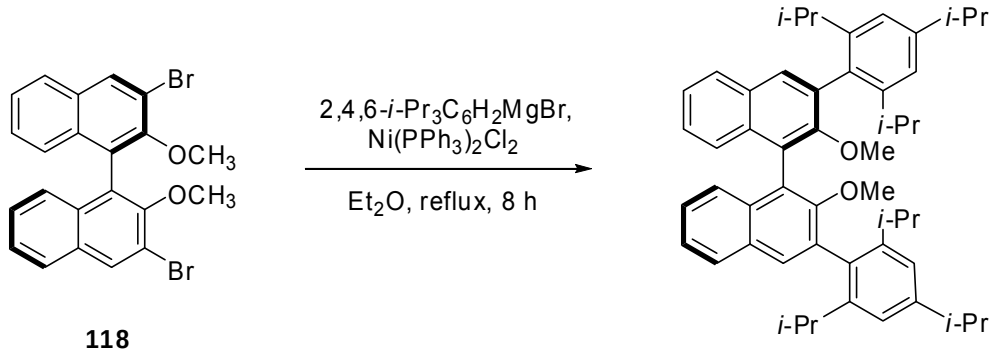
To a solution of TMEDA (1.92 mL, 12.74 mmol) in ether (100 mL) was added at room temperature 1.6 M *n*-BuLi in hexane (10.9 mL, 17.37 mmol). The solution was stirred for 15 min, solid (*R*)-**116** (1.82 g, 5.79 mmol) was added in one portion, and the reaction mixture was stirred for 3 hours at room temperature. The resulting light brown suspension was cooled to −78 °C, and bromine (3.6 mL, 70.00 mmol) was added over a period of 10 min. The mixture was allowed to warm to room temperature, and after 4 hours, a saturated Na_2SO_3 solution (60 mL) was added cautiously. The reaction mixture was stirred for an additional 4 hours, and diluted with ether and water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Silica gel chromatography (hexane/EtOAc, 92:8) provided 1.94 g (71%) of (*R*)-**118** as a pale yellow solid.

118 $C_{22}H_{16}Br_2O_2$ (472.17 g/mol)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 3.43 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 152.5 (Cq_{ar}), 133.1 (Cq_{ar}), 133.0 (C_{ar}), 131.4 (Cq_{ar}), 127.1 (C_{ar}), 126.9 (C_{ar}), 126.5 (Cq_{ar}), 125.9 (C_{ar}), 125.8 (C_{ar}), 117.5 (Cq_{ar}), 61.1 (CH_3).

7.4.6 Preparation of (*R*)-2,2'-Dimethoxy-3,3'-bis(2,4,6-triisopropyl -phenyl)-1,1'-binaphthyl 119



118 **119**

Preparation of (2,4,6-triisopropylphenyl)magnesium bromide: A three-neck round-bottom flask containing Mg (3.00 g, 125.00 mmol) was equipped with a condenser and an addition funnel. A 10.0 mL portion of a 1.4 M solution of 2,4,6-triisopropylphenyl bromide (20.00 g in 50 mL of Et_2O, 70.60 mmol) was added to the flask through the addition funnel. After 5 min, 0.20 mL (0.002 mmol) of 1,2-dibromoethane was added to the mixture. Once the solution began to reflux, the remaining 2,4,6-triisopropylphenyl bromide solution was slowly added over 1 hour. After the addition was complete, the reaction was allowed to reflux for 12 hours and then cooled to room temperature.

Preparation of 119: (*R*)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthyl (**118**, 4.00 g, 8.50 mmol) and $Ni(PPh_3)_2Cl_2$ (0.60 g, 11 mol %, 0.90 mmol) were suspended in 100 mL of Et_2O. To this suspension was added (2,4,6-triisopropylphenyl)magnesium bromide (0.8 M, 31.7 mL, 25.40 mmol) slowly at room temperature. The mixture was allowed to stir at room temperature for 10 min and then the resulting dark green solution was refluxed for 8 hours. The reaction was allowed to chill to 0 °C and quenched slowly by the addition of 50 mL of a 1.0 M solution of HCl. The resulting aqueous layer was separated from the Et_2O layer and washed three times with excess of Et_2O (50 mL). The resulting organic layers were then dried over $MgSO_4$; volatile solvents were removed *in vacuo* to afford the unpurified residue as a white solid that was then recrystallized from CH_2Cl_2/hexanes to afford (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (**119**) as a white solid (4.70 g, 77% yield).

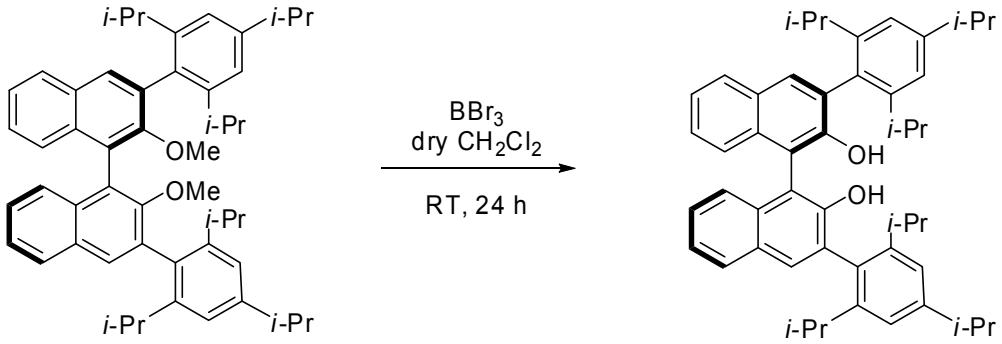
119 $C_{52}H_{62}O_2$ (719.05 g/mol)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.66 (s, 2H), 7.33 (t, *J* = 6.7 Hz, 2H), 7.26-7.19 (m, 4H), 7.00 (d, *J* = 7.3 Hz, 4H), 3.03 (s, 6H), 2.93-2.81 (m, 2H), 2.80-2.67 (m, 4H), 1.24 (d, *J* = 7.0 Hz, 12H), 1.11 (d, *J* = 6.8 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H), 1.04 (d, *J* = 6.9 Hz, 6H), 1.00 (d, *J* = 6.8 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.1 (Cq_{ar}), 148.0 (Cq_{ar}), 147.0 (Cq_{ar}), 146.7 (Cq_{ar}), 134.1 (Cq_{ar}), 133.8 (Cq_{ar}), 133.2 (Cq_{ar}), 130.8 (C_{ar}), 130.2 (Cq_{ar}), 127.8 (C_{ar}), 125.9 (C_{ar}), 125.8 (C_{ar}), 124.7 (Cq_{ar}), 124.5 (C_{ar}), 120.6 (C_{ar}), 59.8 (CH_3), 34.2 (CH), 31.0 (CH), 30.8 (CH), 25.5 (CH_3), 25.2 (CH_3), 24.1 (CH_3), 24.1 (CH_3), 23.4 (CH_3), 23.3 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{52}H_{62}O_2Na]$ ($[M]^+$): 741.4640
Found: 741.4642

7.4.7 Preparation of (*R*)- 3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol 99b[138]



119 **99b**

A solution of 3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (**119**, 4.00 g, 5.60 mmol) in 150 mL of dry CH_2Cl_2 was charged with 39.0 mL of a 1.0 M BBr_3 solution in CH_2Cl_2 (38.90 mmol) slowly at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 24 hours. The mixture was then cooled to 0 °C, and the reaction was quenched by the slow addition of 50 mL water. Aqueous extraction with CH_2Cl_2 (3 x 50 mL), followed by drying of the organic layers over $MgSO_4$ and removal of the solvents *in vacuo* to afford an off-white solid, which was washed with hexanes, filtered, and dried *in vacuo* to afford 3.76 g of a white powder **99b** (5.44 mmol, 97% yield).

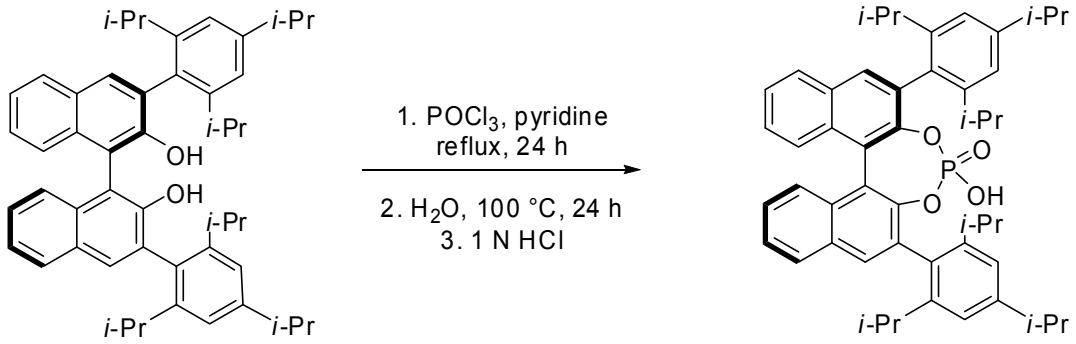
99b $C_{50}H_{58}O_2$ (690.99 g/mol)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.69 (s, 2H), 7.30 (t, *J* = 6.7 Hz, 2H), 7.26-7.20 (m, 4H), 7.05 (d, *J* = 8.3 Hz, 4H), 4.85 (s, 2H), 2.91-2.86 (m, 2H), 2.80-2.75 (m, 2H), 2.64-2.59 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 12H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.04-1.00 (m, 12H), 0.95 (d, *J* = 6.9 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 150.6 (Cq_{ar}), 149.1 (Cq_{ar}), 147.8 (Cq_{ar}), 147.7 (Cq_{ar}), 133.4 (Cq_{ar}), 130.7 (C_{ar}), 130.4 (Cq_{ar}), 129.1 (Cq_{ar}), 129.0 (Cq_{ar}), 128.2 (C_{ar}), 126.6 (C_{ar}), 124.5 (C_{ar}), 123.8 (Cq_{ar}), 121.2 (C_{ar}), 121.2 (C_{ar}), 34.3 (CH), 30.9 (CH), 30.8 (CH), 24.3 (CH_3), 24.3 (CH_3), 24.1 (CH_3), 24.0 (CH_3), 23.9 (CH_3), 23.7 (CH_3).

HR-EI-MS Exact molecular mass for $[C_{50}H_{58}O_2]$ ($[M]^+$): 690.4437
Found: 690.4435

7.4.8 Preparation of (*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate 6c[137]



99b **6c**

Diol **99b** (1.67 g, 2.42 mmol) was suspended in pyridine (7.0 mL) in a two-necked flask. Phosphorous oxychloride (740 mg, 0.46 mL, 4.84 mmol) was added dropwise at room temperature with rapid stirring and the resulting suspension was refluxed for 24 hours until all starting material was deemed consumed by TLC. The reaction mixture was cooled to room temperature and water (2 mL) was added very slowly. The resulting biphasic suspension was heated to 100 °C for an additional 24 hours. The reaction mixture was diluted with CH_2Cl_2 and the pyridine was removed via washing with 1 N HCl. The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude product as a solid. Purification by

flash column chromatography (gradient from 2% to 10% *i*-PrOH in CH_2Cl_2) yielded catalyst **6c** as a white solid (1.73 g, 95% yield).

6c $C_{50}H_{57}O_4P$ (752.96 g/mol)

^{1}H-NMR (500 MHz, $(CD_3)_2SO$): δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.93 (s, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.06 (d, *J* = 1.5 Hz, 2H), 7.00 (s, 1H), 6.98 (s, 3H), 2.87-2.82 (m, 2H), 2.65-2.60 (m, 2H), 2.48-2.43 (m, 2H), 1.18 (dd, *J* = 1.6, 6.9 Hz, 12H), 1.09 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 6.7 Hz, 6H), 1.00 (d, *J* = 6.9 Hz, 6H), 0.83 (d, *J* = 6.8 Hz, 6H).

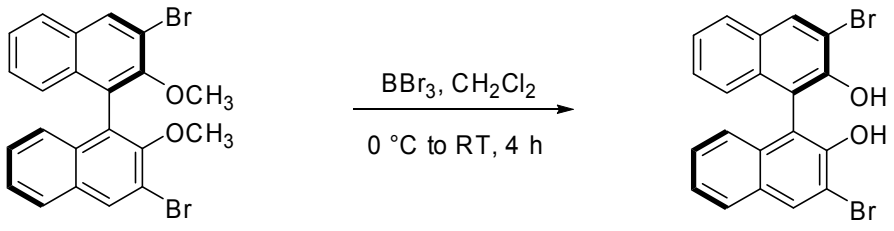
^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ 147.8 (Cq_{ar}), 147.3 (Cq_{ar}), 146.5 (Cq_{ar}), 145.9 (Cq_{ar}), 145.8 (Cq_{ar}), 132.3 (C_{ar}), 131.7 (Cq_{ar}), 131.6 (Cq_{ar}), 130.4 (Cq_{ar}), 128.5 (C_{ar}), 126.7 (C_{ar}), 125.7 (C_{ar}), 125.6 (C_{ar}), 121.2 (Cq_{ar}), 120.8 (C_{ar}), 119.9 (C_{ar}), 33.6 (CH), 30.7 (CH), 30.3 (CH), 26.2 (CH_3), 24.6 (CH_3), 24.1 (CH_3), 24.0 (CH_3), 23.2 (CH_3), 22.8 (CH_3).

^{31}P-NMR (202.5 MHz, $(CD_3)_2SO$): δ 1.41

HPLC τR = 20.6 min [(*S*)-**6c**], 24.8 min [(*R*)-**6c**] (Chiralpak OD-H, heptane/MeOH/TFA 10:90:0.1, 0.5 mL/min, 220 nm).

HR-EI-MS Exact molecular mass for $[C_{50}H_{57}O_4P]$ ($[M]^+$): 752.3994
Found: 752.3996

7.4.9 Preparation of (*R*)-3,3'-Dibromo-1,1'-binaphthyl-2,2'-diol 120[140]



118 **120**

To a solution of (*R*)-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl (**118**) (2.78 g, 5.90 mmol) in CH_2Cl_2 (180 mL) was added BBr_3 (3.13 mL, 33.00 mmol) at 0 °C. The mixture was stirred at room temperature for 4 hours. Then excess BBr_3 was decomposed by adding water

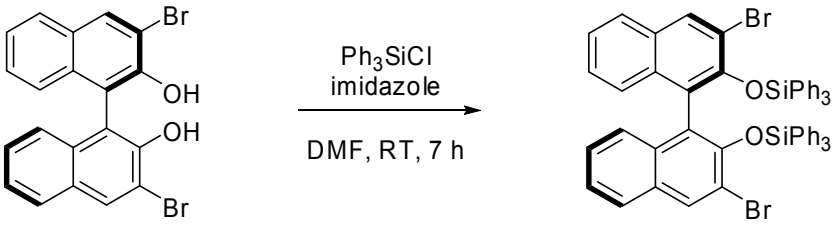
carefully at 0 °C. The mixture was washed with water, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated to provide 2.57 g (98%) of (*R*)-**120** as yellowish white solid.

120 $C_{20}H_{12}Br_2O_2$ (441.12 g/mol)

^{1}H-NMR (500 MHz, CD_3OCD_3): δ 8.45 (brs, 2H), 8.35 (s, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.38 (t, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H).

^{13}C-NMR (125 MHz, CD_3OCD_3): δ 151.3 (Cq_{ar}), 134.4 (Cq_{ar}), 133.8 (C_{ar}), 130.6 (Cq_{ar}), 128.2 (C_{ar}), 127.9 (C_{ar}), 125.2 (C_{ar}), 125.0 (C_{ar}), 116.0 (Cq_{ar}), 114.1 (Cq_{ar}).

7.4.10 Preparation of (*R*)-(3,3'-Dibromo-1,1'-binaphthyl-2,2'-diyl)bis(oxy)bis(triphenylsilane) 121



120 **121**

Compound **120** (2.57 g, 5.83 mmol) was dissolved in 36 mL DMF and then imidazole (1.22 g, 18.00 mmol) followed by triphenylsilyl chloride (4.42 g, 15.00 mmol) was added to it. The mixture was stirred at room temperature for 7 hours, poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic layers were washed again with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated. The crude residue was purified over silica gel column (33:66 CH_2Cl_2/hexane) to furnish bis(triphenyl)silyl ether **121** (5.43 g, 5.65 mmol) in 97% yield.

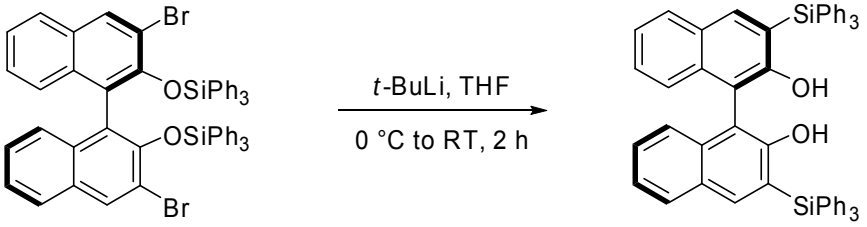
121 $C_{55}H_{40}Br_2O_2Si_2$ (960.89 g/mol)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 2H), 7.38-7.30 (m, 4H), 7.21-6.95 (m, 32H), 6.74 (d, *J* = 8.3 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 147.2 (Cq_{ar}), 134.4 (C_{ar}), 134.2 (Cq_{ar}), 133.6 (C_{ar}), 133.3 (C_{ar}), 132.8 (C_{ar}), 132.2 (C_{ar}), 131.8 (C_{ar}), 128.9 (Cq_{ar}), 128.7 (Cq_{ar}), 128.4 (Cq_{ar}), 128.2 (C_{ar}), 126.9 (Cq_{ar}), 126.7 (Cq_{ar}), 126.2 (C_{ar}), 126.0 (C_{ar}), 125.0 (C_{ar}), 124.9 (C_{ar}), 123.2 (Cq_{ar}), 122.5 (Cq_{ar}), 116.1 (Cq_{ar}).

HR-ESI-MS Exact molecular mass for $[C_{56}H_{44}N_1O_2Si_2Br_2]$ ($[MNH_4]^+$): 976.1267
Found: 976.1272

7.4.11 Preparation of (*R*)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2´-diol 99c[140]



121 **99c**

To a solution of **121** (2.71 g, 2.82 mmol) in dry THF (40 mL) was added dropwise a 1.7 (M) pentane solution of *t*-BuLi (5.0 mL, 8.54 mmol) over a peroid of 10 min at 0 °C. The mixture was stirred at room temperature for 2 hours, poured into saturated NH_4Cl, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated. It was chromatographed on silica gel (55:45 toluene/hexane) to give diol **99c** (1.93 g, 85 % yield) as white solid.

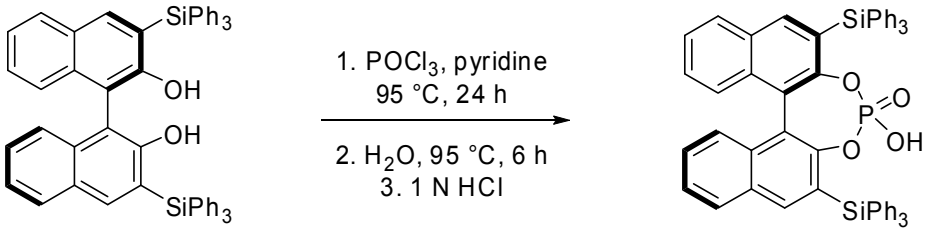
99c $C_{56}H_{42}O_2Si_2$ (803.10 g/mol)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.62-7.56 (m, 8H), 7.35-7.18 (m, 30H), 5.22 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 155.5 (Cq_{ar}), 141.0 (C_{ar}), 135.3 (C_{ar}), 133.7 (Cq_{ar}), 133.3 (Cq_{ar}), 128.5 (C_{ar}), 128.2 (C_{ar}), 128.0 (C_{ar}), 127.2 (C_{ar}), 126.8 (Cq_{ar}), 122.9 (C_{ar}), 122.8 (Cq_{ar}), 122.6 (Cq_{ar}), 109.6 (Cq_{ar}).

HR-ESI-MS Exact molecular mass for $[C_{56}H_{46}N_1O_2Si_2]$ ($[MNH_4]^+$): 820.3068
Found: 820.3061

7.4.12 Preparation of (*R*)-3,3'-Bis-(triphenylsilyl)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate 6f[139]



99c **6f**

Diol **99c** (1.94 g, 2.42 mmol) was suspended in pyridine (7.0 mL) in a two-necked flask. Phosphorous oxychloride (740 mg, 0.46 mL, 4.84 mmol) was added dropwise at room temperature with rapid stirring and the resulting suspension was heated to 95 °C. Upon reaching 95 °C all material had dissolved to provide a pale yellow clear solution. The reaction mixture was stirred for 24 hours at 95 °C until all starting material was deemed consumed by TLC. The reaction mixture was cooled to room temperature and water (2 mL) was added very slowly. The resulting biphasic suspension was heated to 95 °C for an additional 6 hours. The reaction mixture was diluted with CH_2Cl_2 and the pyridine was removed via washing with 1 N HCl. The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude product as a pale yellow solid. Purification by flash column chromatography (gradient from 1% to 5% *i*-PrOH in CH_2Cl_2) yielded catalyst **6f** as a white solid (1.80 g, 85% yield).

6f $C_{56}H_{41}O_4PSi_2$ (865.07 g/mol)

^{1}H-NMR (300 MHz, $(CD_3)_2SO$): δ 7.94 (s, 2H), 7.80 (d, J = 7.5 Hz, 2H), 7.60-7.57 (m, 12H), 7.37-7.28 (m, 22H), 7.06 (d, J = 8.0 Hz, 2H).

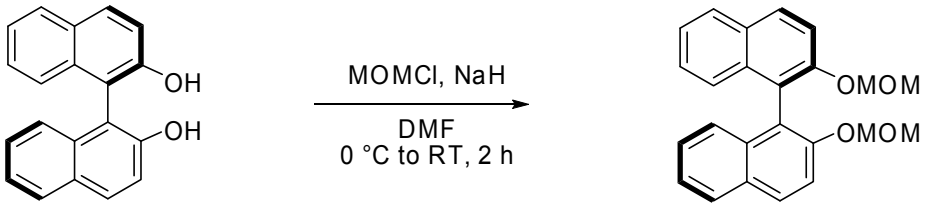
^{13}C-NMR (75 MHz, $(CD_3)_2SO$): δ 152.1 (Cq_{ar}), 152.1 (Cq_{ar}), 141.1 (Cq_{ar}), 136.3 (C_{ar}), 134.0 (Cq_{ar}), 133.5 (Cq_{ar}), 129.8 (C_{ar}), 129.5 (C_{ar}), 128.8 (C_{ar}), 127.7 (Cq_{ar}), 126.2 (Cq_{ar}), 125.8 (C_{ar}), 125.4 (Cq_{ar}), 121.2 (Cq_{ar}).

^{31}P-NMR (121.5 MHz, $(CD_3)_2SO$): δ 2.40

HR-EI-MS Exact molecular mass for $[C_{56}H_{41}O_4PSi_2]$ ($[M]^+$): 864.2281
Found: 864.2296

Sp. Rotation $[\alpha]_D^{23} = -156.0°$ (c = 1.02, $CHCl_3$)

7.4.13 Preparation of (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl 122



100 **122**

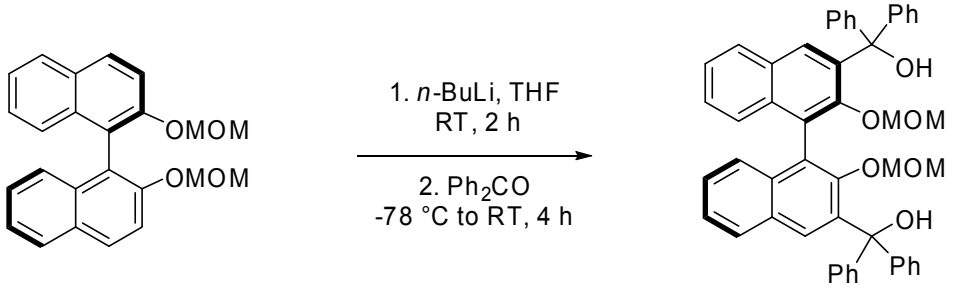
To a suspension of NaH (60% dispersion in mineral oil, 1.15 g, 29.00 mmol) in DMF (30 mL) was added a solution of (*R*)-BINOL **100** (3.62 g, 12.60 mmol) in DMF (30 mL) at 0 °C. The mixture was stirred at room temperature for 20 min, and MOMCl (2.0 mL, 26.30 mmol) was then added. The resulting mixture was gradually allowed to room temperature for 2 hours, and water was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, and after evaporation, compound **122** was obtained as white solid (4.14 g, 12.0 mmol) in 95 % yield.

122 $C_{24}H_{22}O_4$ (374.43 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.0 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H), 7.14-7.06 (m, 4H), 4.97 (d, *J* = 6.8 Hz, 2H), 4.87 (d, *J* = 6.8 Hz, 2H), 3.04 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.3 (Cq_{ar}), 133.7 (Cq_{ar}), 129.6 (Cq_{ar}), 129.1 (C_{ar}), 127.5 (C_{ar}), 126.0 (C_{ar}), 125.2 (C_{ar}), 123.7 (C_{ar}), 121.0 (Cq_{ar}), 117.0 (C_{ar}), 94.9 (CH_2), 55.5 (CH_3).

7.4.14 Preparation of (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl-3,3'-diyl)bis(diphenylmethanol) 123[141]



122 **123**

To a stirred solution of MOM-protected BINOL **122** (2.83 g, 5.30 mmol) in THF (20 mL) was added *n*-BuLi (11.9 mL; 1.60 M in hexane; 19.00 mmol) at room temperature. The mixture was stirred for 2 hours at the same temperature. After cooling to –78 °C, benzophenone (4.08 g, 22.40 mmol) in THF (10 mL) was added slowly. The reaction mixture was stirred for 2 hours at –78 °C and then at room temperature for another 2 hours. After addition of aqueous NH_4Cl (5%; 20 mL), the organic phase was extracted with Et_2O, dried over $MgSO_4$, and concentrated. Column chromatography on silica gel (hexane/EtOAc, 6:1) afforded **123** (3.52 g, 90% yield) as a white solid.

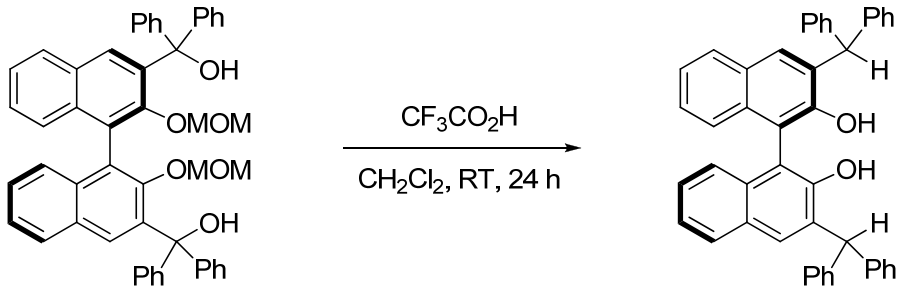
123 $C_{50}H_{42}O_6$ (738.86 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.56-7.10 (m, 28H), 5.73 (s, 2H), 3.74 (d, *J* = 4.8 Hz, 2H), 3.68 (d, *J* = 4.8 Hz, 2H), 2.75 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.6 (Cq_{ar}), 146.4 (Cq_{ar}), 146.0 (Cq_{ar}), 140.0 (Cq_{ar}), 133.4 (Cq_{ar}), 130.1 (Cq_{ar}), 129.2 (C_{ar}), 128.1 (C_{ar}), 127.6 (C_{ar}), 127.6 (C_{ar}), 127.5 (C_{ar}), 127.5(C_{ar}), 127.6 (C_{ar}), 127.4 (C_{ar}), 126.9 (C_{ar}), 126.8 (C_{ar}), 126.2 (C_{ar}), 125.1 (Cq_{ar}), 125.0 (Cq_{ar}), 98.5 (CH_2), 56.7 (CH_3).

HR-EI-MS Exact molecular mass for [$C_{50}H_{42}O_6$] ([M]$^+$): 738.2981
Found: 738.2980

7.4.15 Preparation of (*R*)-3,3'-Dibenzhydryl-1,1'-binaphthyl -2,2'-diol 99d[141]



123 **99d**

To a solution of 1**23** (3.00 g, 4.07 mmol) in CH_2Cl_2 (150 mL) was added CF_3CO_2H (1.07 mL, 14.00 mmol). The reaction mixture was stirred for 24 hours at room temperature. After neutralization with saturated aqueous $NaHCO_3$ (20 mL), the organic layer was separated, dried over $MgSO_4$, and concentrated. Column chromatography on silica gel (hexane/EtOAc, 12:1) provided compound **99d** (2.01 g, 80% yield) as white powder.

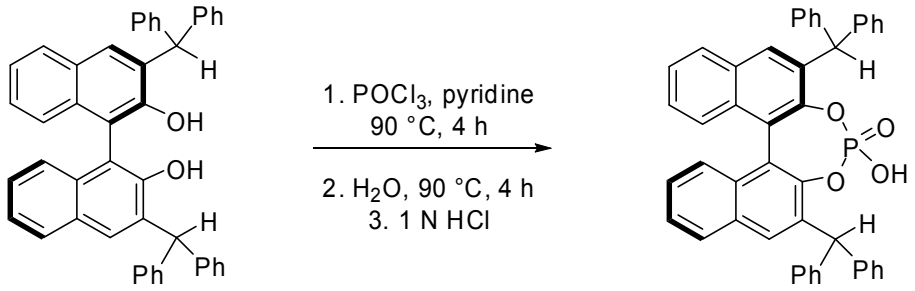
99d $C_{46}H_{34}O_2$ (618.76 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.34 (s, 2H), 7.25-7.10 (m, 24H), 6.99 (d, *J* = 8.2 Hz, 2H), 5.95 (s, 2H), 5.04 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 150.9 (Cq_{ar}), 142.8(Cq_{ar}), 142.5 (Cq_{ar}), 132.6 (Cq_{ar}), 131.9 (Cq_{ar}), 131.0 (Cq_{ar}), 129.2 (C_{ar}), 129.0 (C_{ar}), 128.7 (C_{ar}), 128.1 (C_{ar}), 128.0 (C_{ar}), 128.0(C_{ar}), 126.7 (C_{ar}), 126.2 (C_{ar}), 126.1 (C_{ar}), 123.7 (C_{ar}), 123.5 (C_{ar}), 110.8 (C_{ar}), 50.6 (CH).

HR-EI-MS Exact molecular mass for [$C_{46}H_{34}O_2$] ([M]$^+$): 618.2559
Found: 618.2548

7.4.16 Preparation of (*R*)-3,3'-Dibenzhydryl-1,1'-binaphthalene -2,2'-diyl hydrogen phosphate 6l



99d **6l**

Diol **99d** (1.50 g, 2.42 mmol) was suspended in pyridine (6.0 mL) in a two-necked flask. Phosphorous oxychloride (740 mg, 0.46 mL, 4.84 mmol) was added dropwise at room temperature with rapid stirring and the resulting suspension was heated to 90 °C for 4 hours until all starting material was deemed consumed by TLC. The reaction mixture was cooled to room temperature and water (2 mL) was added very slowly. The resulting biphasic suspension was heated to 90 °C for an additional 4 hours. The reaction mixture was diluted with CH_2Cl_2 and the pyridine was removed via washing with 1 N HCl. The combined organic phase was dried over $MgSO_4$, filtered and concentrated to give crude product as a pale yellow solid. Purification by flash column chromatography (gradient from 1% to 5% *i*-PrOH in CH_2Cl_2) yielded catalyst **6l** as a white solid (1.24 g, 75% yield).

6l $C_{46}H_{33}O_4P$ (680.73 g/mol)

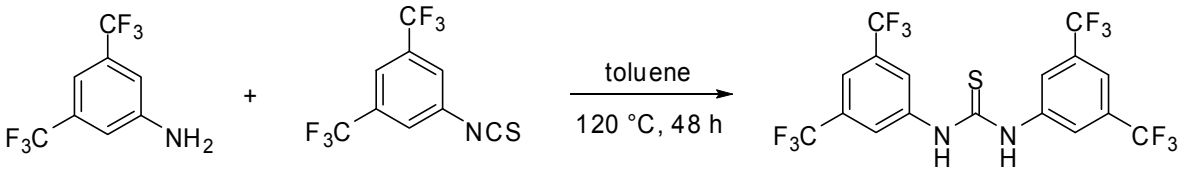
^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.34-7.07 (m, 28H), 6.43 (s, 2H).

^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ 144.5 (Cq_{ar}), 142.9 (Cq_{ar}), 137.3 (Cq_{ar}), 131.2 (Cq_{ar}), 130.3 (C_{ar}), 130.0 (C_{ar}), 129.4 (C_{ar}), 128.7 (C_{ar}), 128.6 (C_{ar}), 126.5 (C_{ar}), 126.2 (C_{ar}), 125.2 (C_{ar}), 122.7 (Cq_{ar}), 49.9 (CH).

^{31}P-NMR (162 MHz, $(CD_3)_2SO$): δ 4.65

HR-EI-MS Exact molecular mass for $[C_{46}H_{33}O_4P]$ ($[M]^+$): 680.2117
Found: 680.2119

7.4.17 Preparation of 1,3-Bis(3,5-bis(trifluoromethyl)phenyl)-thiourea 5[32]

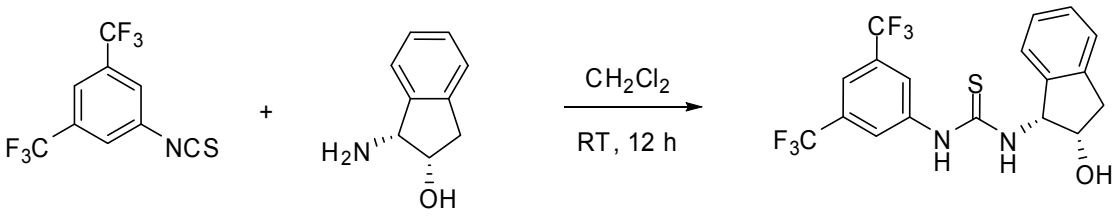


126 **127** **5**

In an oven-dried 100 mL two-necked flask, 12 mL dry toluene was added under argon atmosphere. To this 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**127**, 0.92 mL, 5.00 mmol) and 3,5-bis(trifluoromethyl)aniline (**126**, 0.94 mL, 6.00 mmol) was subsequently added and the resulting mixture was allowed to reflux at 120 °C for 48 hours. After evaporation of the solvent *in vacuo*, the solid 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 *n*-hexane as a colorless solid **5** (2.00 g, 4.00 mmol, 80%).

5	$C_{17}H_8F_{12}N_2S$ (500.30 g/mol)
^{1}H-NMR	(400 MHz, CD_3OD): δ 8.23 (s, 4H), 7.7 (s, 2H), 4.59 (br s, 2H).
^{13}C-NMR	(100 MHz, CD_3OD): δ 182.9 (C=S), 143.0 (Cq_{ar}), 133.4 (q, Cq_{ar}), 126.4 (Cq_{ar}), 125.2 (C_{ar}), 123.7 (Cq_{ar}), 119.4 (C_{ar}).
MP	172-173 °C
HR-EI-MS	Exact molecular mass for $[C_{17}H_8F_{12}N_2S]$ ($[M]^+$): 500.0216 Found: 500.0210

7.4.18 Preparation of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*, 2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)thiourea 7[127]



127 **128** **7**

To a stirred solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**127**, 0.92 mL, 5.00 mmol) in CH_2Cl_2 (10 mL), (1*R*,2*S*)-*cis*-1-amino-2-indanol (**128**, 747 mg, 5.00 mmol) was added in one portion. After stirring the resulting solution at room temperature for 12 hours, the solvent was evaporated under reduced pressure and the white solid purified by crystallisation (*n*-hexane/acetone), affording **7** as a white solid (1.85 g, 4.40 mmol) in 88% yield.

7 $C_{18}H_{14}F_6N_2OS$ (420.37 g/mol)

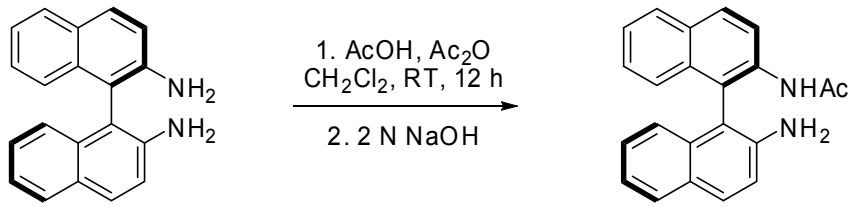
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.70 (br s, 1H), 7.75 (s, 2H), 7.55 (s, 1H), 7.27-7.06 (m, 5H), 5.83 (brs, 1H), 4.63-4.60 (m, 1H), 3.10 (dd, J = 5.2, 16.8 Hz, 1H), 2.79 (d, J = 16.9 Hz, 1H), 2.33 (br s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 180.4 (C=S), 139.2 (Cq_{ar}), 138.9 (Cq_{ar}), 138.5 (Cq_{ar}), 132.2 (q, Cq_{ar}), 128.3 (C_{ar}), 127.0 (C_{ar}), 125.1 (C_{ar}), 124.2 (C_{ar}), 123.8 (C_{ar}), 123.2 (C_{ar}), 121.1 (C_{ar}), 118.7 (C_{ar}), 73.4 (CH), 62.5 (CH), 39.4 (CH_2).

MP 82-84 °C

HR-EI-MS Exact molecular mass for $[C_{18}H_{14}F_6N_2OS]$ ($[M]^+$): 420.0731
Found: 420.0733

7.4.19 Preparation of (*R*)-*N*-(2'-Amino-1,1'-binaphthyl-2-yl)acetamide 130



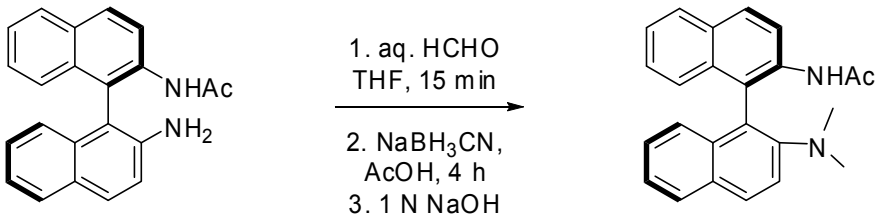
129 **130**

To a solution of (*R*)- 1,1'-binaphthyl-2,2'-diamine **129** (568 mg, 2.00 mmol) and AcOH (1.2 mL, 20.00 mmol) in 20 mL of dried CH_2Cl_2 was added acetic anhydride (208 μL, 2.00 mmol) at 0 °C under argon atmosphere. The resulting solution was stirred for 12 hours at room temperature, and then 2 N NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 2/1) to afford a colorless oil **130** in 75% yield (490 mg, 1.50 mmol).

130 $C_{22}H_{18}N_2O$ (326.39 g/mol)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.9 Hz, 1H), 8.03-7.79 (m, 4H), 7.44-6.85 (m, 7H), 3.60 (br s, 3H), 1.83 (s, 3H).

7.4.20 Preparation of (*R*)-*N*-(2'-(Dimethylamino)-1,1'-binaphthyl-2-yl)acetamide 131



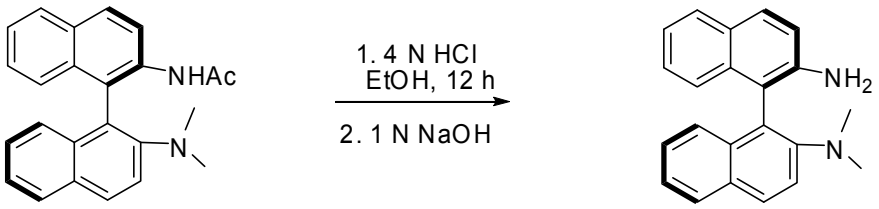
130 **131**

Compound **130** (250 mg, 0.77 mmol) and aqueous formaldehyde (37%, 0.75 mL, 9.0 mmol) were combined in 10 mL of THF and stirred for 15 min. $NaBH_3CN$ (200 mg, 5.3 mmol) was added, followed 15 min later by AcOH (1.0 mL). The resulting solution was stirred for 4 hours at room temperature, and then 1 N NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/5) to afford brown powder **131** in 96% yield (262 mg, 0.74 mmol).

131 $C_{24}H_{22}N_2O$ (354.44 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.9 Hz, 1H), 7.90-7.75 (m, 4H), 7.42 (br s, 1H), 7.32-7.02 (m, 5H), 6.86 (d, *J* = 8.6 Hz, 1H), 2.49 (s, 6H), 1.75 (s, 3H).

7.4.21 Preparation of (*R*)-N^2,N^2-Dimethyl-1,1'-binaphthyl-2,2'-diamine 132



131 **132**

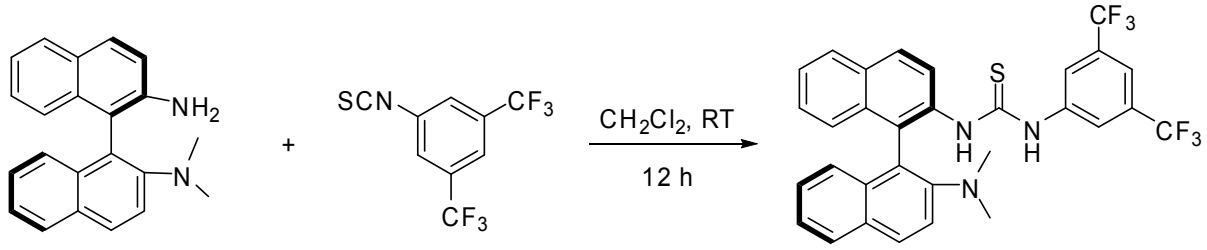
To a solution of acetamide **131** (180 mg, 0.51 mmol) in 15 mL of EtOH was added 4 N HCl (6 mL). The resulting solution was stirred overnight at room temperature, and then 1 N NaOH aqueous solution was added until pH ≈ 7. The reaction mixture was extracted by CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with saturated brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/10) to afford **132** as a colorless oil in 93% yield (148 mg, 0.47 mmol).

132 $C_{22}H_{20}N_2$ (312.40 g/mol)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.9 Hz, 1H), 7.76-7.69 (m, 3H), 7.48 (br s, 1H), 7.14-7.03 (m, 6H), 6.92 (d, *J* = 8.2 Hz, 1H), 2.55 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 141.6 (Cq_{ar}), 133.9 (Cq_{ar}), 133.3 (Cq_{ar}), 129.0 (C_{ar}), 128.7 (C_{ar}), 127.9 (Cq_{ar}), 127.6 (C_{ar}), 127.6 (C_{ar}), 126.3 (C_{ar}), 126.0 (C_{ar}), 124.6 (C_{ar}), 124.4 (C_{ar}), 123.6 (C_{ar}), 121.8 (C_{ar}), 119.4 (C_{ar}), 118.0 (C_{ar}), 43.1 (CH_3).

7.4.22 Preparation of (*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2'-(dimethylamino)-1,1'-binaphthyl-2-yl)thiourea 8[128]



132 **127** **8**

To a solution of amine **132** (108 mg, 0.36 mmol) in 6 mL of dried CH_2Cl_2 was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate **127** (66 mg, 0.40 mmol) at 0 °C under argon atmosphere. The resulting solution was stirred overnight at room temperature. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography (ethyl acetate/hexane = 1/10) to afford a pale yellow solid **8** in 90% yield (190 mg, 0.33 mmol).

8 $C_{31}H_{23}F_6N_3S$ (583.59 g/mol)

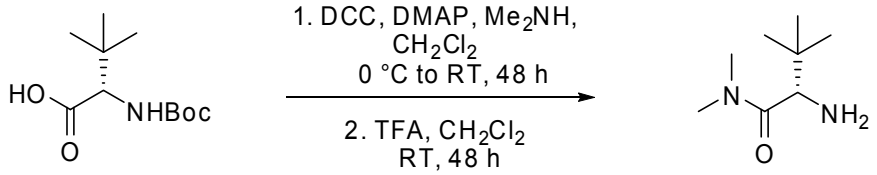
^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.56-7.50 (m, 5H), 7.41 (s, 1H), 7.36 (s, 2H), 7.28-7.23 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 2.59 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.7 (C=S), 149.9 (Cq_{ar}), 139.6 (Cq_{ar}), 134.0 (Cq_{ar}), 133.3 (Cq_{ar}), 133.2 (Cq_{ar}), 132.9 (Cq_{ar}), 132.0 (Cq_{ar}), 131.8 (Cq_{ar}), 131.6 (Cq_{ar}), 130.5 (C_{ar}), 130.0 (C_{ar}), 129.9 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 127.5 (C_{ar}), 127.2 (C_{ar}), 126.8 (C_{ar}), 125.0 (C_{ar}), 124.6 (C_{ar}), 124.2 (C_{ar}), 123.9 (C_{ar}), 122.9 (C_{ar}), 121.8 (C_{ar}), 118.9 (C_{ar}), 44.0 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{31}H_{23}F_6N_3SNa]$ ($[MNa]^+$): 606.1409
Found: 606.1415

Sp. Rotation $[\alpha]_D^{25} = -8.3°$ (c = 0.5, $CHCl_3$)

7.4.23 Preparation of (*S*)-2-Amino-*N*,*N*,3,3-tetramethyl-butanamide 134[104b]



133 **134**

To a solution of *N*-Boc-L-*tert*-leucine (**133**) (2.00g, 8.65 mmol) in CH_2Cl_2 (10 mL) was added dicyclohexylcarbodiimide (DCC, 2.30 g, 11.15 mmol) at 0 °C, followed by 4-(dimethylamino)-pyridine (DMAP, 11.3 mg, 0.09 mmol). After few minutes dimethylamine (1.20 mL, 23.22 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 48 hours at room temperature, filtered through SiO_2 and washed with EtOAc. All volatile compounds were removed *in vacuo* and the residue was purified via flash chromatography (15% EtOAc in hexanes) to yield *N*-Boc-L-*tert*-leucine dimethylamide as a colorless solid (1.80 g, 6.97 mmol, 81%).

The solid (1.70 g, 6.58 mmol) was dissolved in CH_2Cl_2 (30 mL), followed by the addition of trifluoroacetic acid (TFA, 1.12 mL, 15.13 mmol). The reaction was stirred for 48 hours at room temperature. All volatile compounds were removed *in vacuo* and the residue was dissolved in water and treated with KOH (10% aqueous solution) at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$. After filtration and then evaporation of the solvent, the crude product was purified by flash chromatography (5% MeOH in CH_2Cl_2) yielding the *N*-Boc deprotected amide **134** as a colorless oil (0.70 g, 4.42 mmol, 67%).

134 $C_8H_{18}N_2O$ (158.24 g/mol)

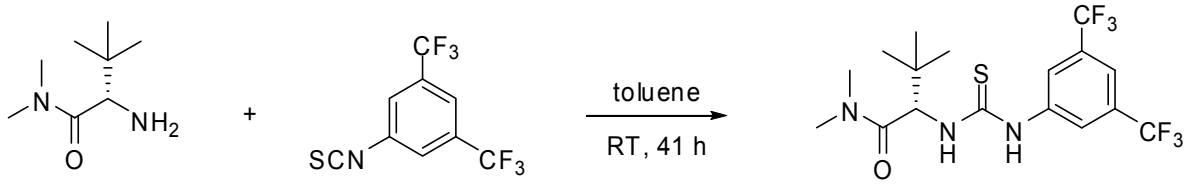
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.54 (s, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 1.91 (br s, 2H), 0.95 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.3 (C=O), 57.5 (CH), 38.0 (Cq), 35.5 (CH_3), 35.2 (CH_3), 26.2 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_8H_{18}N_2ONa]$ ($[MNa]^+$): 181.1311

Found: 181.1313

7.4.24 Preparation of (*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl) thioureido)-*N*,*N*,3,3-tetramethylbutanamide 9



134 **127** **9**

To a solution of L-*tert*-leucine dimethylamide (**134**, 0.35 mg, 2.21 mmol) in toluene (5 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**127**, 0.5 mL, 2.74 mmol). 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% EtOAc in hexanes) to yield **9** (0.85 g, 1.98 mmol, 90%) as a white solid.

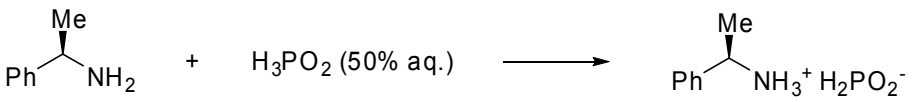
9 $C_{17}H_{21}F_6N_3OS$ (429.42 g/mol)

^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.33 (br s, 1H), 7.96 (s, 2H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.55 (br s, 1H), 5.64 (d, *J* = 9.1 Hz, 1H), 3.35 (s, 2H), 2.97 (s, 2H), 1.12 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 181.7 (C=S), 173.7 (C=O), 140.3 (Cq_{ar}), 131.7 (C_{ar}), 131.3 (Cq_{ar}), 124.9 (C_{ar}), 123.4 (C_{ar}), 121.3 (C_{ar}), 117.9 (C_{ar}), 117.8 (C_{ar}), 60.7 (CH), 38.9 (Cq), 36.1 (CH_3), 35.8 (CH_3), 27.1 (CH_3).

HR-ESI-MS Exact molecular mass for $[C_{17}H_{21}F_6N_3OSNa]$ ($[MNa]^+$): 452.1202
Found: 452.1202

7.4.25 Preparation of (*R*)-1-Phenylethanaminium phosphinate 135[144]



136 **137** **135**

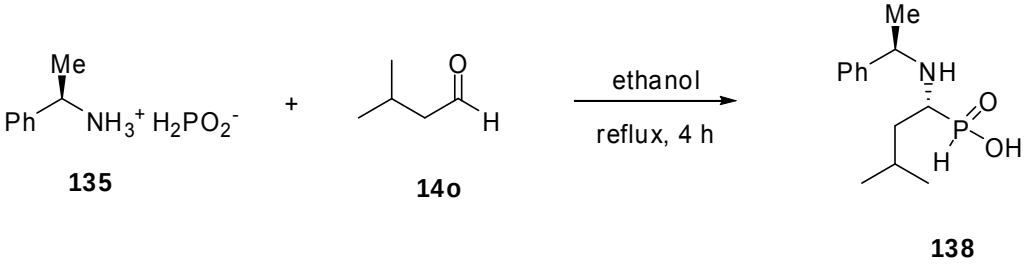
(*R*)-α-methylbenzylamine **136** (6.36 mL, 50.00 mmol) was slowly added to an ice-cold stirred solution of hypophosphorous acid **137** (50% solution in water, 5.50 mL, 50.00 mmol). The

reaction mixture was allowed to warm to room temperature over few minutes. Then the solid was filtered in a Buchner funnel, washed with acetone and ether. Finally it was dried over phosphorous pentoxide *in vacuo* for 24 hours and the white solid **135** (9.35 g, 49.90 mol) was obtained in quantitative yield.

135 $C_8H_{14}NO_2P$ (187.18 g/mol)

^{1}H-NMR (400 MHz, D_2O): δ 7.57 (s, 1H), 7.44-7.35 (m, 5H), 6.27 (s, 1H), 4.45 (q, *J* = 6.9 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H).

7.4.26 Preparation of (*R*)-3-Methyl-1-((*R*)-1-phenylethylamino)-butylphosphinic acid 138[144]



The salt **135** (1.87 g, 10 mmol) was added to a solution of 3-methyl butanal **14o** (1.08 mL, 10.00 mmol) in ethanol (6 mL) and the resulting mixture was refluxed for 4 hours. The product **138** solidified in the flask and it was filtered in a Buchner funnel, washed with dry ethanl and dry ether. Finally it was dried *in vacuo* to provide **138** (1.02 g, 4.00 mmol) in 40% yield.

138 $C_{13}H_{22}NO_2P$ (255.29 g/mol)

^{1}H-NMR (400 MHz, CD_3OD): δ 7.57-7.47 (m, 5H), 7.04 (d, *J* = 528 Hz, 1H), 4.96-4.91 (m, 1H), 2.74-2.68 (m, 1H), 1.73 (d, *J* = 6.9 Hz, 3H), 1.69-1.60 (m, 2H), 1.45-1.37 (m, 1H), 0.79 (d, *J* = 6.2 Hz, 3H), 0.57 (d, *J* = 6.2 Hz, 3H).

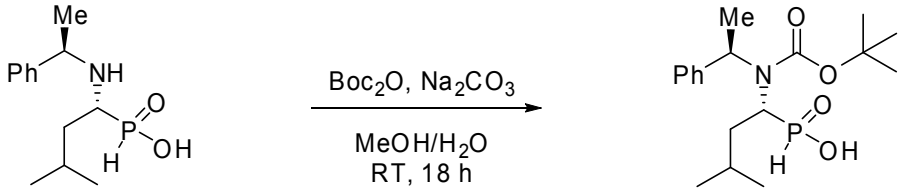
^{13}C-NMR (100 MHz, CD_3OD): δ 139.7 (Cq_{ar}), 133.0 (C_{ar}), 132.8 (C_{ar}), 131.4 (C_{ar}), 62.1 (CH), 57.7 (CH), 56.8 (CH), 39.7 (CH_2), 27.9 (CH), 24.8 (CH_3), 24.0 (CH_3), 22.3 (CH_3).

^{31}P-NMR (162 MHz, CD_3OD): δ 19.41

HR-ESI-MS Exact molecular mass for $[C_{13}H_{21}NO_2P]$ ($[M-H]^-$): 254.1310

Found: 254.1316

7.4.27 Preparation of (*R*)-1-(*tert*-butoxycarbonyl((*R*)-1-phenylethyl)amino)-3-methylbutylphosphinic acid 27



138 **27**

To a solution of compound **138** (600 mg, 2.35 mmol) and Na_2CO_3 (280 mg, 2.58 mmol) in 12 mL MeOH/H_2O (1:1), was added di-*tert*-butyl dicarbonate (570 mg, 2.58 mmol) and the resulting mixture was stirred at room temperature for 18 hours. Methanol was removed completely in rotary evaporator; the aqueous solution was acidified with citric acid solution (pH ≈ 4) and extracted with CH_2Cl_2 (4 x 30 mL) and Et_2O (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to obtain a colorless solid **27** (184 mg, 0.52 mmol, 22%).

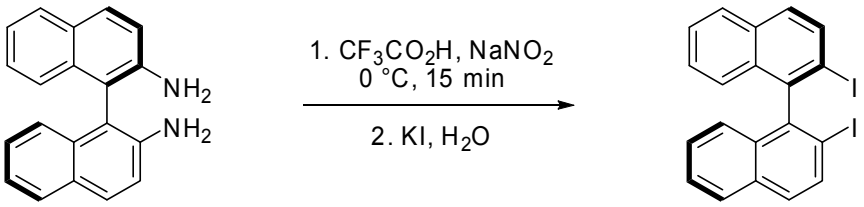
27 $C_{18}H_{30}NO_4P$ (355.41 g/mol)

^{1}H-NMR (400 MHz, CD_3OD): δ 7.45-7.36 (m, 5H), 6.90 (d, *J* = 528 Hz, 1H), 4.84-4.78 (m, 1H), 2.62-2.56 (m, 1H), 1.60 (d, *J* = 6.9 Hz, 3H), 1.55-1.49 (m, 2H), 1.42 (s, 9H), 1.40-1.33 (m, 1H), 0.70 (d, *J* = 6.2 Hz, 3H), 0.51 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR (100 MHz, CD_3OD): δ 157.6 (C=O), 139.8 (Cq_{ar}), 133.1 (C_{ar}), 132.6 (C_{ar}), 131.2 (C_{ar}), 79.8 (Cq), 62.2 (CH), 57.7 (CH), 56.8 (CH), 39.7 (CH_2), 28.8 (CH_3), 27.9 (CH), 24.8 (CH_3), 24.0 (CH_3), 22.3 (CH_3).

^{31}P-NMR (162 MHz, CD_3OD): δ 19.52

7.4.28 Preparation of (*R*)-2,2'-Diiodo-1,1'-binaphthyl 139[146]



129 **139**

A solution of 2,2'-diamino-1,1'-binaphthyl 1**29** (500 mg, 1.76 mmol) in 8.5 mL of CF_3CO_2H was cooled to 0 °C and stirred while $NaNO_2$ **(**420 mg, 6.16 mmol) was added in portions, keeping the temperature below 5 °C. After the addition was complete, the reaction mixture was stirred for an additional 15 min at 0 °C and was then poured into a solution of potassium iodide (833 mg, 5.28 mmol) in 34 mL of water. The solution was extracted with CH_2Cl_2, and the organic phase was washed three times with water, twice with a 10% solution of $NaHCO_3$, then twice with a saturated solution of sodium thiosulfate, and finally with water. The organic extract was dried over $MgSO_4$, and solvent was removed, leaving 800 mg of product. This was chromatographed on a short silica gel column using carbon tetrachloride. Sublimation of the product isolated at 185 °C/0.4 mm gave 550 mg of diiodide **139** (62%) as a light yellow solid.

139 $C_{20}H_{12}I_2$ (506.12 g/mol)

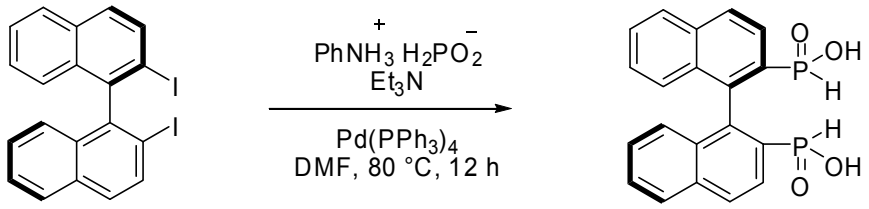
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.42 (dt, *J* = 1.0, 7.8 Hz, 2H), 7.23-7.17 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.4 (Cq_{ar}), 135.3 (C_{ar}), 132.6 (Cq_{ar}), 129.3 (C_{ar}), 127.9 (C_{ar}), 126.9 (C_{ar}), 126.2 (C_{ar}), 126.0 (C_{ar}), 99.4 (Cq_{ar}).

HR-EI-MS Exact molecular mass for [$C_{20}H_{12}O_2$] ([M]$^+$): 505.9029

Found: 505.9028

7.4.29 Preparation of (*R*)-1,1'-Binaphthyl-2,2'-diyldiphosphinic-acid 28



139 **28**

Preparation of anilinium hypophosphite ($PhNH_3H_2PO_2$): Aniline (19.60 g, 0.21 mol) was added over 30 min via an addition funnel, to an ice-cold aqueous solution of H_3PO_2 (50%, 27.80 g, 0.21 mol). The light brown solution rapidly turned into a thick slurry. This was filtered and the off-white crystalline precipitate was washed with cold acetone. The filtrate was concentrated under reduced pressure, and a second crop of crystalline hypophosphite was obtained by adding acetone. The first two crops were combined and washed with ether, then dried *in vacuo* over P_2O_5 for 24 hours. Anilinium hypophosphite (30.40 g, 91%) was obtained as light yellow needles.

Preparation of 28: A solution of diiodide **139** (102 mg, 0.20 mmol), anilinium hypophosphite (96 mg, 0.60 mmol), triethylamine (160 mg, 0.22 mL, 1.60 mmol), and palladium tetrakis(triphenylphosphine) (10 mg, 0.008 mmol) in DMF (2 mL) was heated at 80 °C in a Schlenk flask for 12 hours. The reaction mixture was concentrated under high vacuum, diluted in water, washed with Et_2O, and acidified with aqueous $KHSO_4$ (1 M, saturated with NaCl). The resulting aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the diphosphinic acid **28** (23 mg, 0.06 mmol) in 30 % yield.

28 $C_{20}H_{16}O_4P_2$ (382.29 g/mol)

^{1}H-NMR (400 MHz, CD_3OD): δ 8.10-7.82 (m, 6H), 7.54-7.27 (m, 6H), 7.20-7.11 (m, 2H), 7.00-6.91 (m, 2H).

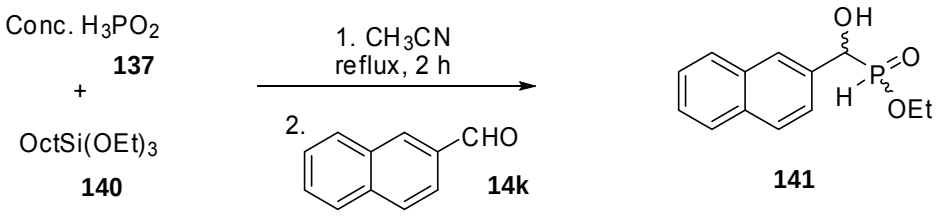
^{13}C-NMR (100 MHz, CD_3OD): δ 140.2 (Cq_{ar}), 136.6 (C_{ar}), 133.5 (Cq_{ar}), 131.5(C_{ar}), 130.4 (C_{ar}), 130.3 (C_{ar}), 129.8 (C_{ar}), 129.7 (C_{ar}), 129.4 (C_{ar}), 129.2 (C_{ar}), 128.3 (C_{ar}), 127.7 (C_{ar}), 127.5 (C_{ar}), 127.3 (C_{ar}), 126.8 (C_{ar}), 123.8 (Cq_{ar}).

^{31}P-NMR (162 MHz, CD_3OD): δ 19.35

HR-ESI-MS Exact molecular mass for $[C_{20}H_{15}O_4P_2]$ ($[M-H]^-$): 381.0442

Found: 381.0451

7.4.30 Preparation of Ethyl hydroxy(naphthalene-2-yl)methyl -phosphinate 141



A mixture of concentrated H_3PO_2 (**137**, initially 50 wt. % aq. solution, 0.57 mL, 5.20 mmol) and octyltriethoxysilane (**140**, 1.62 mL, 5.15 mmol) in CH_3CN (HPLC grade, 10 mL) was refluxed for 2 hours under argon atmosphere and then cooled to room temperature. 2-Naphthaldehyde **14k** (734 mg, 4.70 mmol) and anhydrous *i*-Pr_2NEt (0.90 mL, 5.15 mmol) were added via syringe to the cloudy reaction mixture and the stirring was continued at room temperature for 22 hours. The cloudy biphasic mixture obtained after concentration was then partitioned between EtOAc and aqueous $KHSO_4$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Finally silica gel column chromatography (80:20 EtoAc/hexane) provided product **141 (**675 mg, 2.70 mmol) as a 1.2:1 mixture of diastereomers in 52% yield.

141 $C_{13}H_{15}O_3P$ (250.23 g/mol)

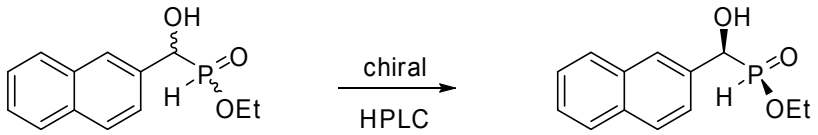
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.79 br s, 2H), 7.73-7.71 (m, 5H), 7.56 (s, 0.5H), 7.45-7.36 (m, 6H), 6.18 (s, 0.5H), 5.09-5.03 (m, 2H), 4.03-3.80 (m, 3H), 1.19-1.09 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 132.9 (Cq_{ar}), 132.8 (Cq_{ar}), 132.3 (Cq_{ar}), 128.0 (C_{ar}), 127.9 (C_{ar}), 127.7 (C_{ar}), 127.4 (C_{ar}), 126.0 (C_{ar}), 125.9 (C_{ar}), 125.7 (C_{ar}), 125.6 (C_{ar}), 125.6 (C_{ar}),125.5 (C_{ar}), 124.2 (C_{ar}), 124.2(C_{ar}), 124.1 (C_{ar}), 71.9 (d, CH), 71.5 (d, CH), 63.3 (d, CH_2), 62.9 (d, CH_2), 15.8 (CH_3), 15.7 (CH_3).

^{31}P-NMR (162 MHz, $CDCl_3$): δ 37.76, 35.24

HR-ESI-MS Exact molecular mass for $[C_{13}H_{15}O_3PNa]$ ($[M+Na]^+$): 273.0652
Found: 273.0651

7.4.31 Preparation of (*S*)-Ethyl ((*S*)-hydroxy(naphthalen-2-yl)-methyl)phosphinate 141a

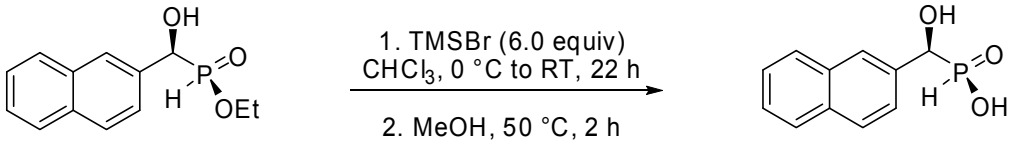


141 **141a**

640 mg (2.56 mmol) of compound **141** was injected in a preparative Chiralcel OD column. The enantiomerically pure **141a** (137 mg, 0.55 mmol) was isolated in 21% yield.

HPLC τR = 32.8 min [mixture], 41.1 min [one enantiomer], 52.8 min [another enantiomer] (Chiralcel OD (250 nm), heptane/*i*-PrOH 95:5, 10.0 mL/min, 220 nm).

7.4.32 Preparation of (*S*)-((*S*)-Hydroxy(naphthalen-2-yl)methyl-phosphinic acid 29



141a **29**

In an oven-dried 25 mL flask, 125 mg (0.50 mmol) of compound **141a** was dissolved in 2.5 mL of $CHCl_3$ under argon atmosphere. Then 0.4 mL (3.00 mmol) of TMSBr was slowly added to the solution at 0 °C and the resulting mixture was stirred at room temperature for 22 hours. The solvents were evaporated *in vacuo* and the solid was dissolved in 8 mL of methanol. It was then stirred at 50 °C for 2 hours. Methanol was removed *in vacuo* and compound **29** was obtained as yellow solid (100 mg, 0.45 mmol, 90%).

29 $C_{11}H_{11}O_3P$ (222.18 g/mol)

^{1}H-NMR (400 MHz, CD_3OD): δ 7.96 (br s, 1H), 7.88-7.84 (m, 3.5H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.50-7.47 (m, 3H), 6.22 (s, 0.5H), 5.07 (d, *J* = 9.0 Hz, 1H).

^{13}C-NMR (100 MHz, CD_3OD): δ 135.5 (Cq_{ar}), 135.1 (Cq_{ar}), 135.1 (Cq_{ar}), 129.4 (C_{ar}), 129.1 (C_{ar}), 127.8 (C_{ar}), 127.7 (C_{ar}), 126.5 (C_{ar}), 126.4 (C_{ar}), 73.8 (d, CH, *J* = 444 Hz).

^{31}P-NMR (162 MHz, CD_3OD): δ 32.5

HR-ESI-MS Exact molecular mass for $[C_{11}H_{10}O_3P]$ ($[M-H]^-$): 221.0367

Found: 221.0373

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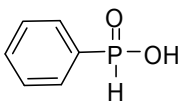
9 Appendix

9.1 Abbreviations

abs.	absolute (distilled and dried)
Ac	Acetyl (CH_3CO)
Alk	Alkyl group
aq.	Aqueous
Ar	Aryl group
Boc	*tert*-butyloxycarbonyl
Bn	Benzyl ($PhCH_2$)
cat.	Catalyst
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane (CH_2Cl_2)
DKR	Dynamic kinetic resolution
DiPAMP	Ethylenebis[(2-methoxyphenyl)phenylphosphine]
DMAP	*N*,*N*-Dimethylamino pyridine
DMF	*N*,*N*-Dimethyl formamide ($HCONMe_2$)
DNA	Deoxyribonucleic acid
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
ent	Enantiomer
equiv.	Equivalent
Et	Ethyl (CH_3CH_2)
GC	Gas chromatography
h	hour
HPLC	High performance liquid chromatography
HR-MS	High resolution mass spectrometry
Hz	Hertz
i-Bu	*iso*-butyl (Me_2CHCH_2)
KR	Kinetic resolution
MCR	Multicomponent reaction
Me	Methyl (CH_3)
min	minute(s)

MS	molecular sieves
NMR	Nuclear magnetic resonance
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
ppm	parts per million
PMP	para-methoxy phenyl
PTC	Phase transfer catalyst
quant	quantitative
R_f	Retention factor
RNA	Ribonucleic acid
RT	Room temperature
sat.	Saturated
t-Bu	tertiary butyl (Me_3C)
TFA	Trifluoroacetic acid (CF_3CO_2H)
TFAA	Trifluoroacetic anhydride [$(CF_3CO)_2O$]
THF	Tetrahydrofuran
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine

9.2 Structure Table



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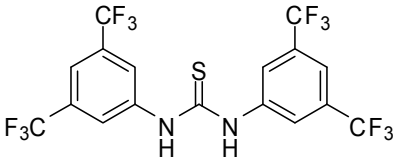

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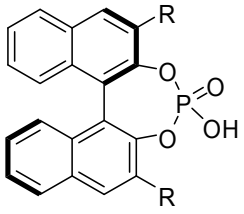
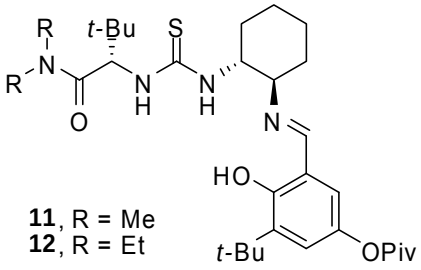
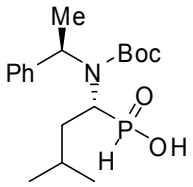


6

6a R = Ph
6b R = 2-naphthyl
6c R = 2,4,6-iPr$_3$C$_6$H$_2$
6d R = 4-NO$_2$C$_6$H$_4$
6e R = 3,5-Me$_2$C$_6$H$_3$
6f R = SiPh$_3$
6g R = 9-anthracenyl
6h R = 9-phenanthryl
6l R = CHPh$_2$
6m R = 2,6-Me$_2$C$_6$H$_3$



11, R = Me
12, R = Et



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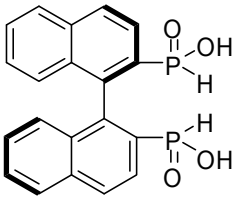

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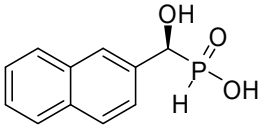

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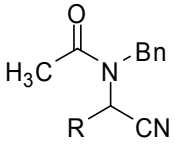
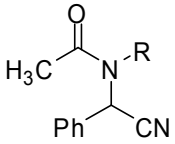


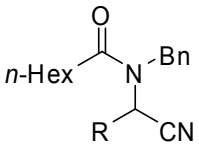
3

3a R = Ph
3c R = 4-MeOC$_6$H$_4$
3d R = 4-ClC$_6$H$_4$
3e R = 2-ClC$_6$H$_4$
3f R = 2-Furyl
3g R = 3-Pyridyl
3h R = i-Pr
3b R = t-Bu
3i R = 1-Cyclohexenyl
3j R = t-BuCH$_2$
3k R = 2-Naphthyl
3l R = 1-Cinnamyl
3m R = Cyclohexyl
3n R = n-Bu



3

3o R = 1-NaphCH$_2$
3p R = 4-ClC$_6$H$_4$CH$_2$
3q R = 4-MeOC$_6$H$_4$CH$_2$
3r R = Furfuryl
3s R = Allyl
3t R = n-Pent



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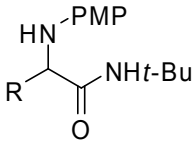
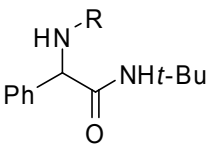
3u R = Ph
3v R = 2-Naphthyl



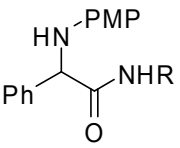
19

19a R = Ph
19b R = 4-MeOC$_6$H$_4$
19c R = 4-ClC$_6$H$_4$
19d R = 2-ClC$_6$H$_4$
19e R = 2-Naphthyl
19f R = 1-Cinnamyl
19g R = 3-Pyridyl
19h R = i-Pr
19i R = c-Hex
19j R = t-Bu
19k R = n-Bu



19

19l R = 2-Naphthyl
19m R = 4-CF$_3$C$_6$H$_4$
19n R = 4-CO$_2$EtC$_6$H$_4$
19o R = 3-ClC$_6$H$_4$
19p R = 3-Pyridyl
19q R = PhCH$_2$
19r R = (Ph)$_2$CH
19s R = Allyl
19t RNH = (Ph)$_2$N



19

19u R = c-Hex
19v R = PhCH$_2$
19w R = t-BuCH$_2$C(Me$_2$)
19x R = EtO$_2$CCH$_2$
19y R = p-TsCH$_2$

9.3 Abstract – Kurzzusammenfassung

In this work, two new atom-economic approaches for the synthesis of α-amino acids and their derivatives have been developed. First, a wide variety of preformed *N*-benzyl aldimines was reacted with acetylcyanide in the presence of Schreiner thiourea catalyst to obtain different *N*-acyl α-amino nitrile products. Then Jacobsen thiourea catalysts were found to be highly enantioselective catalysts for this novel reaction giving the products with excellent enantioselectivities. The substrate scope was broad and one optically active *N*-acyl α-amino nitrile product was converted to the desired α-amino acid without losing enantiopurity. This report was the first catalytic asymmetric acylcyanation of imines.

Then a one-pot three-component variant of the acylcyanation reaction starting from different aldehydes, amines and acylcyanides was developed. Schreiner thiourea and Jacobsen thiourea catalysts were again the best catalysts for the non-asymmetric and asymmetric versions respectively giving a diverse array of products. Thus the first organocatalytic asymmetric three-component Strecker type reaction was developed.

A novel synthesis of cyclic amidines was achieved when ketimines were reacted with acetylcyanide in the presence of phenylphosphinic acid catalyst.

Besides the acylcyanation, a new catalytic three-component Ugi reaction from aldehydes, primary amines and isocyanides was designed and phenyl phosphinic acid (as a new motif for organocatalysis) was found to be the most efficient catalyst for this novel reaction affording a wide variety of α-amino amide products. This reaction could potentially be made asymmetric; however, so far low enantioselectivities were obtained with some new chiral phosphinic acid catalysts. Nevertheless, this is the first approach towards a catalytic asymmetric Ugi reaction.

Im Rahmen der vorliegenden Arbeit wurden zwei neue atomökonomische Zugänge zu α-Aminosäuren und deren Derivaten entwickelt. Die Reaktion von verschiedenen *N*-Benzyl-aldiminen mit Acetylcyanid lieferte unter Einwirkung von *Schreiners* Thioharnstoff-Katalysator die korrespondierenden α-Aminonitrile. Anschließend konnte eine hochgradig enantioselektive Variante dieser Reaktion durch Verwendung chiraler Thioharnstoff-Katalysatoren des *Jacobsen*-Typs realisiert werden. Eine Vielzahl von Substraten und die exemplarische Umwandlung eines Aminonitrils in die entsprechende α-Aminosäure unter Erhalt der Konfiguration zeigen den Stellenwert dieser ersten katalytischen Acylcyanierung von Iminen.

Eine Weiterentwicklung dieser Reaktion konnte durch eine Eintopf-Dreikomponten-Variante der Acylcyanierung unter Verwendung von Aldehyden, Aminen und Acetylcyanid verwirklicht werden. Wiederum lieferten die bereits zuvor verwendeten Katalysatoren die besten Ergebnisse für eine große Anzahl verschiedenster Edukte, sowohl bei asymmetrischer, als auch enantioselektiver Reaktionsführung. Diese Umsetzung stellt damit die erste organokatalytische asymmetrische Dreikomponenten-Strecker-Reaktion dar.

Weiterhin wurde ein neuer synthetischer Zugang zu cyclischen Amidinen durch die Phenylphosphinsäure-katalysierte Reaktion von Ketiminen mit Acetylcyanid entwickelt.

Eine weitere Dreikomponentenreaktion, die neben der Acylcyanierung bearbeitet wurde, ist die katalytische Ugi-Reaktion von Aldehyden, primären Aminen und Isocyaniden. Als bester Katalysator für diese neue Reaktion, und damit zugleich als neue Leitstruktur für Organokatalysatoren, stellte sich Phenylphosphinsäure heraus, deren Verwendung zu einer großen Anzahl von α-Aminoamiden führte. Diese Reaktion zeigte ebenfalls Potenzial für die Entwicklung einer asymmetrischen Variante. Auch wenn erste Versuche, das neue Katalysator-Leitmotiv in Form neuer chiraler Phosphinsäuren auf eine enantioselektive Anwendung zu übertragen nur geringe Selektivitäten lieferten, so ist dies dennoch der erste Bericht einer katalytischen asymmetrischen Ugi-Reaktion.

9.4 Erklärung

"Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit – einschließlich Tabellen, Karten und Abbildungen-, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie noch nicht veröffentlicht worden ist, sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen dieser Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn Professor Dr. Benjamin List betreut worden."

Mülheim an der Ruhr, May 2008

Subhas Chandra Pan

Bisher sind folgende Teilpublikationen veröffentlicht worden:

1. "*Catalytic Acylcyanation of Imines with Acetylcyanide*", S. C. Pan, J. Zhou, B. List, *Synlett* **2006**, 3275-3276
2. "*Catalytic Asymmetric Acylcyanation of Imines*", S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, *119*, 618-620; *Angew. Chem. Int. Ed.* **2007**, *46*, 612-614.
3. "*Catalytic One-Pot, Three-Component Acyl-Strecker Reaction*", S. C. Pan, B. List, *Synlett* **2007**, 318-320.
4. "*Catalytic Asymmetric Three-Component Acyl-Strecker Reaction*", S. C. Pan, B. List, *Org. Lett.* **2007**, *9*, 1149-1151.
5. "*The Catalytic Acylcyanation of Imines*", S. C. Pan, B. List, *Chem. Asian. J.* **2008,** *3*, 430-438.
6. "*Catalytic Three-Component Ugi Reaction*", S. C. Pan, B. List, *Angew. Chem.* **2008**, *120*, 3678-3681; *Angew. Chem. Int. Ed.* **2008**, *47*, 3622-3625.

9.5 Curriculum Vitae

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