Organocatalytic Oxidative Couplings: From Mechanistic Studies to New Radical Reactions

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„Dem Anwenden muss das Erkennen vorausgehen”

(„Before you can apply something, you have to understand it“)

Max Planck

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ABSTRACT

The use of peroxides as intermediates in oxidative coupling chemistry is presented in this PhD work. A one pot protocol for a metal-free C-H functionalization of protected tetrahydroisoquinolines, proceeding via acid catalysed substitution of a peroxide moiety was developed. Mechanistic studies on the autoxidative coupling reaction of xanthene and ketones were performed and a novel mode of activation of simple ketones in the presence of a hydroperoxide and a strong acid was identified. Rationalisation of this phenomenon was achieved via the involvement of alkenyl peroxides as crucial intermediates. α-Carbonyl radicals are generated in this process and their synthetic utility was evaluated. In particular, a multicomponent oxidative radical addition of ketones and hydroperoxides to olefins, affording valuable γ-peroxyketones, was developed.

In dieser Arbeit wird die Verwendung von Peroxiden als Intermediate in der oxidativen Kupplungschemie vorgestellt. Ein Eintopfverfahren zur metallfreien C-H Funktionalisierung geschützter Tetrahydroisochinoline, welches über eine säurekatalysierte Substitution einer Peroxidgruppe verläuft, wurde entwickelt. Es wurden mechanistische Untersuchungen an der autooxidativen Kupplung von Xanthen mit Ketonen durchgeführt und es konnte ein neuer Aktivierungsmodus für einfache Ketone in der Gegenwart eines Hydorperoxids und einer starken Säure identifiziert werden. Diese Reaktivität wurde über die Beteiligung von Alkenylperoxiden als Schlüsselintermediate rationalisiert. In diesem Prozess werden α-Carbonylradikale gebildet, deren synthetischer Nutzen untersucht wurde. In diesem Kontext wurde eine oxidative Multikomponenten-Radikaladdition von Ketonen und Hydroperoxiden an Olefine entwickelt, welche wertvolle γ-Peroxyketone ergibt.

LIST OF ABBREVIATIONS

Ac	acetyl
AcO	acetate
AIBN	azobisisobutyronitrile
Alk	alkyl
app.	apparent
aq.	aqueous
Ar	aryl, aromatic
ATRA	atom transfer radical addition
BINOL	1,1'-bi-2-naphthol
BHT	2,6-di-tert-butylphenol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
Calcd	calculated
CAN	cerium ammonium nitrate
cat.	catalyst/catalytic
Cbz	carboxybenzyl
CHP	cumene hydroperoxide
conv.	conversion
Cy	cyclohexyl
d	doublet
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
DTBP	di-tert-butyl peroxide
E	electrophile
EI	electron impact
ee	enantiomeric excess
ent	enantiomer(ic)
equiv	equivalent(s)

er	enantiomeric ratio
Et	ethyl
ESI	electrospray ionization
GC (GC-MS)	gas chromatography (gas chromatography coupled with mass detection)
h	hour(s)
HAT	hydrogen atom transfer
*i*Pr	isopropyl
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
LG	leaving group
Lit.	literature
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet
M	molar (concentration)
M	metal
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mesityl	mesityl (2,4,6-trimethylphenyl)
MS	mass spectrometry, molecular sieves
Ms	methylsulfonyl
MTBE	methyl *tert*-butyl ether
MW	molecular weight
m/*z*	atomic mass units per charge
n	normal
N	normal (concentration)
n.a.	not available
n.d.	not determined
NHC	*N*-heterocyclic carbene
NHPI	*N*-hydrophthalimide
NMR	nuclear magnetic resonance spectroscopy
N.R.	no reaction
Nu-H/Nu	nucleophile
o	*ortho*
OAc	acetyl
P	product
p	*para*
PINO	phthalimide-*N*-oxyl radical

Ph	phenyl
PMP	paramethoxyphenyl
Pr	propyl
PT	proton transfer
pTSA	*para*-toluenesulfonic acid
Py	pyridine
quint	quintet
rac.	racemic
r.t.	room temperature
S	substrate
sept	septet
SET	single electron transfer
sext	sextet
SM	starting material
SOMO	singly occupied molecural orbital
t	*tert, tertiary*
t	triplet
T-HYDRO	70% solution of *tert*-butyl hydroperoxide in water
TBHP	5.5M *tert*-butly hydroperoxide solution in decane
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	tertiary butyl
TCA	trichloroacetic acid
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin layer chromatography
TMS	trimethylsilyl
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
Ts	*para*-toluenesulfonyl
wt	weight

ACKNOWLEDGEMENTS

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I am very grateful to the members of my PhD committee: Prof. Dr. Berkessel for agreeing to take the time to correct this dissertation, Prof. Dr. Klein and Dr. Deska for serving in my committee. I also have to give special thanks to Manuel Van Gemmeren and Dr. Thomas James for proof reading this dissertation and giving me helpful insight and suggestions.

I want to thank the people who were directly involved in the projects I worked on. First of all, Dr. Áron Pintér, Dr. Abhishek Sud and Dr. Devarajulu Sureshkumar, without their previous work on the (aut)oxidative coupling chemistry, none of the projects I worked on would have been possible. Dr. Phillipp Schulze and Stefanie Dehn for their knowledge of analytical techniques and their help in the mechanistic study. Joachim Demaerel and Hauke Engler's help on the oxidative radical addition of ketone and hydroperoxides to olefins has been invaluable and without their contributions, I would probably still be working on this project by the time I write these lines.

For all the good scientific (and also non-scientific) discussions I am indebted to Dr. Kevin Jones, Naeem Gulzar, Dr. Nobuhito Umeida, Manuel Van Gemmeren, Mattia Monaco, Dr. Daniel O'Donovan, Dr. Chandra Kanta De, Prof. Nuno Maulide and many others.

Finally and perhaps most importantly, I want to thank all the people who made my time inside and outside of the lab enjoyable: in no particular order, Kevin, Paola, Manuel, Daniel, Fabio, Mattia and in general all the members of the List, Klußmann and Maulide groups for the good atmosphere.

1 INTRODUCTION

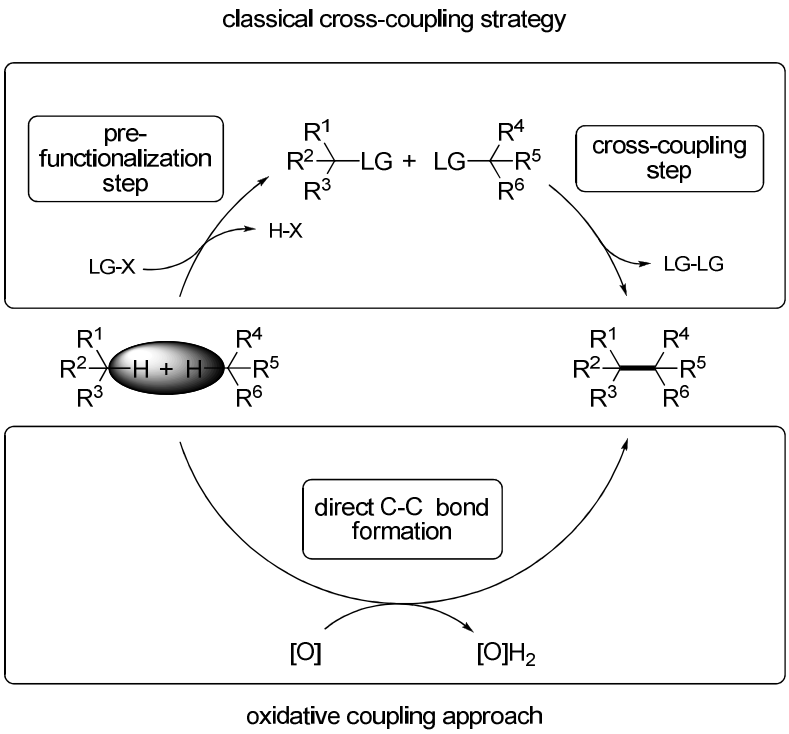
Organic synthesis can be described as the art of building complex molecules from the assembly of smaller and simpler building block molecules. In order to assemble these building blocks, synthetic chemists rely on a large toolbox of chemical reactions allowing the formation of new covalent bonds between different atoms. Among these reactions, the ones allowing the formation of bonds between two carbon atoms are some of the most valuables ones for the assembly of complex molecules and countless methodologies have therefore been developed for this purpose.[1]

The development of cross-coupling chemistry has allowed chemists to construct new C-C bonds in a reliable and predictable manner and has now become an indispensable part of organic synthesis,[2] as recognized by the 2010 Nobel prize in chemistry awarded to Richard Heck, Ei-Ichi Negishi and Akira Suzuki for their work on *"palladium catalyzed cross-couplings in organic synthesis".* [3] The success of this chemistry lies in the chemo- and regioselectivity that these reactions offer. Indeed, the new C-C bond is selectively formed in positions determined by the leaving groups (LG) on both substrates (Scheme 1-1, top part).

However, this strategy inevitably leads to the formation of stoichiometric amounts of side products, resulting from the installation and departure of the leaving groups. Additionaly, the substrates have to be prefunctionalised, increasing the number of synthetic steps required for the overall transformation. This is clearly in contradiction with the first and second principles of green chemistry stating that "it is better to prevent waste formation than to treat or clean up waste after it is formed" and that "synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product".[4]

The oxidative coupling approach on the other hand does not rely on prefunctionalization of the starting materials and can potentially fulfil the requirements of green chemistry (Scheme 1-1, bottom part). In the presence of a suitable combination of oxidant and catalyst, a new C-C bond is formed starting from two C-H bonds. In an ideal case, the only by-product is water, when molecular oxygen is used as the terminal oxidant.

Evidently, such an approach is much more challenging than the use of prefunctionalized starting materials since C-H bonds are ubiquitous in organic materials. Therefore, an issue often associated with C-H functionalization approaches is regioselectivity, the different C-H bonds inside a same molecule having similar dissociation energies. Additionaly, C-H bonds are much stronger than the C-X bonds (where X is a halogen atom) classically relied upon in chemical synthesis and therefore relatively harsh reaction conditions such as high temperatures are often encountered. It can however provide synthetic routes that are much more efficient that the ones designed using "classical" disconnections.



Scheme 1-1: Strategies for the selective formation of new C-C bonds.

The fields of oxidative coupling and C-H activation have attracted the attention of the chemical community and have seen a tremendous growth in the past decades. More importantly, it is beginning to change the way chemists think about the synthetic routes they design, particularly in natural product synthesis,[5] by "gradually infusing a C-H activation mindset".[5b]

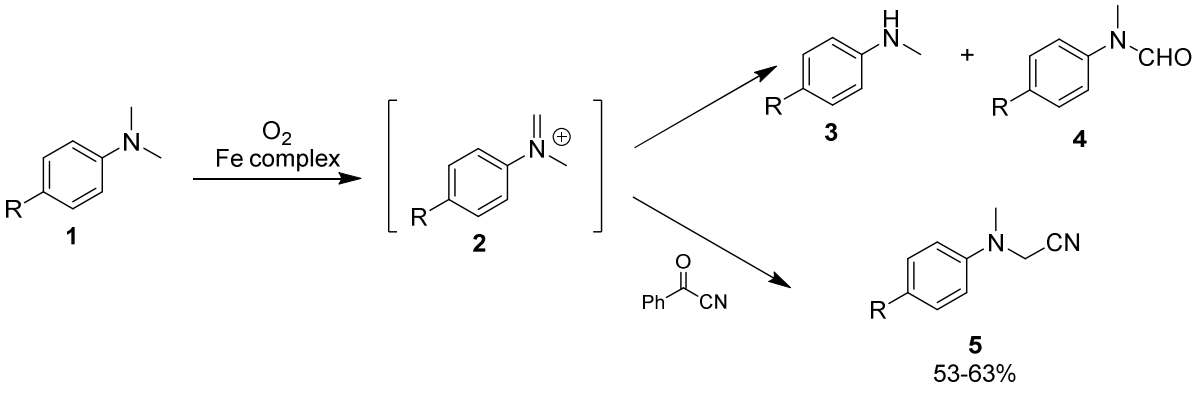
2 BACKGROUND

2.1 C-H Functionalization of Tertiary Amines

The field of C-H activation and oxidative coupling chemistry has attracted a lot of attention since its early stages and tremendous progress has been made.[6] It is therefore not intended to extensively cover such a large area of research in this section but rather to look at historical developments and key reports for the specific topic that was dealt with in this work: the oxidative coupling chemistry of tertiary amines and related compounds. Even in this particular area, it would be impossible to cover all reports of the scientific literature and the interested reader is directed to the excellent reviews that were written on the subject, covering it in depth.[6g, 6k, 6m, 6n]

2.1.1 Historical developments

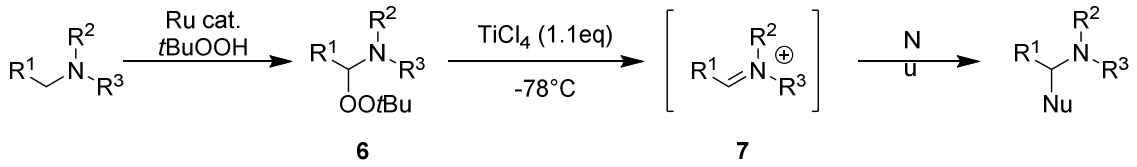
The basis of oxidative coupling of tertiary amines finds its roots in the wish of chemists to study and replicate the activity of biological systems. Cytochrome P-450 is a superfamily of monooxygenase proteins catalyzing the oxidation of organic substances in living organisms. One of the important P-450 specific reactions is the oxidative *N*-dealkylation of amines. P-450 enzymes contain a heme cofactor and therefore, a number of iron porphyrin model systems have been used to simulate their activity and elucidate their mode of action.[7] Of particular interest for the further developments of oxidative coupling of tertiary amines are the reports from Masahiro Miura[8] and Shun-Ichi Murahashi,[9] both studying P-450-type oxidations of tertiary amines.



Scheme 2-1: Aerobic oxidation of substituted *N*-*N* dimethyl anilines and their oxidative cyanation .

In 1989, the group of Miura reported on the aerobic oxidation of tertiary anilines **1** using an iron catalyst, forming demethylated aniline **3** and formanilides **4**.[8a, 8b] The mechanism, used in living organisms for the degradation of nitrogen containing molecules, involves the generation of an intermediate iminium ion **2**. Later in 1993, they reported the oxidative cyanation under similar conditions in the presence of benzoyl cyanide to afford the cyanated products **5** in moderate yields (Scheme 2-1).[8c] Hydrolysis of benzoyl cyanide to benzoic acid liberates a cyanide anion, which is trapped by **2**. This represents, to the best of our knowledge, the first example of a direct one-step oxidative coupling of tertiary amines, in the way it was extensively studied in later years.

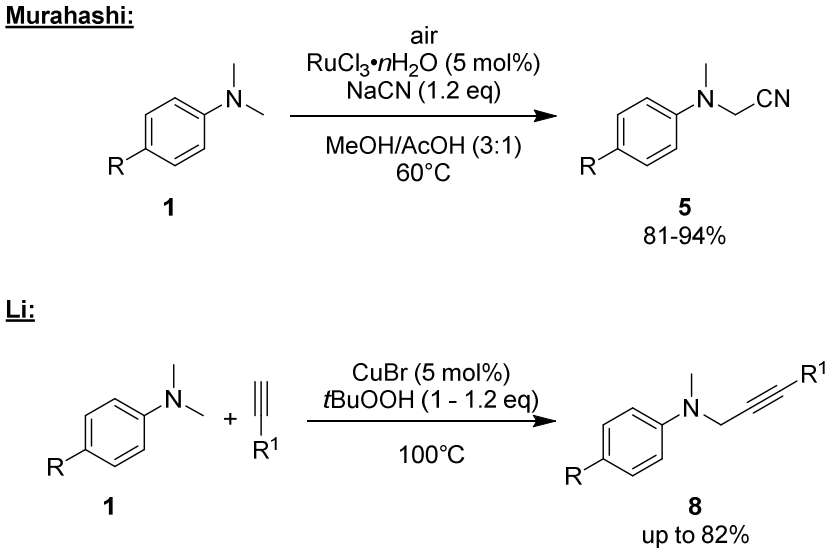
The group of Murahashi used a different approach, also derived from the wish to mimick cytochrome P-450 oxidations (Scheme 2-2).



Scheme 2-2: Ruthenium catalyzed formation of aminoperoxides and further coupling with nucleophiles by Lewis acid treatment .

Between 1988 and 1990, they reported on the conversion of diverse tertiary amines and amides to the corresponding peroxides **6** in the presence of a ruthenium catalyst and *t*-butylhydroperoxide as oxidant.[9a, 9b] Further treatment of these peroxides with stoichiometric amounts of $TiCl_4$ in the presence of a nucleophile afforded the corresponding coupling products, which were postulated to be formed through the generation of iminium ions **7**.[9c]

It is almost 15 years later that the synthetic potential of these reactions was noticed and developed by the chemical community with a series of reports from the groups of Shun-Ichi Murahashi and Chao-Jun Li (Scheme 2-3).



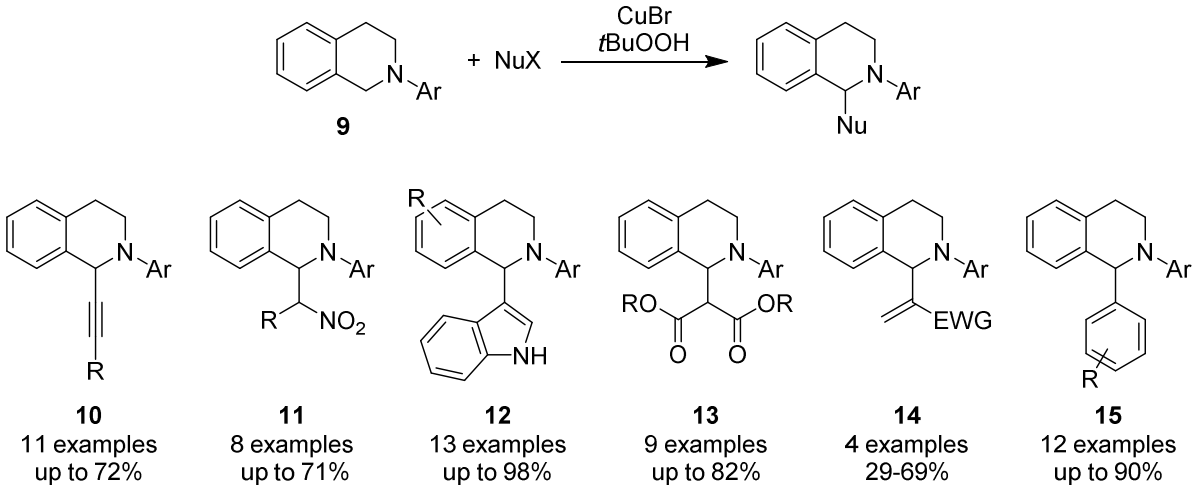
Scheme 2-3: Aerobic ruthenium catalyzed cyanation and copper catalyzed alkynylation of anilines.

In 2003, Murahashi expanded his ruthenium catalyzed system to achieve a highly efficient aerobic cyanation of anilines with sodium cyanide,[10] similar to the iron catalysed reaction reported by Miura.[8c] In 2004, the first of a long series of reports from the group of Li revealed the copper catalyzed alkynylation of anilines using *t*BuOOH as oxidant under neat conditions at high temperatures in good yields.[11]

These reports set the basis of the whole field of oxidative coupling chemistry of tertiary amines and already showed the challenges to be met in this type of transformations, which will be discussed later in this section.

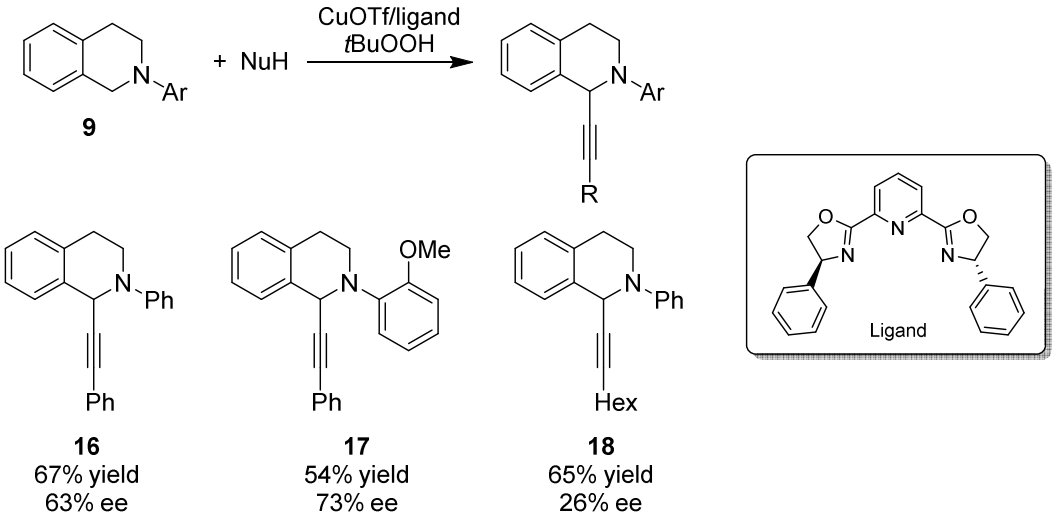
2.1.2 Metal Based Systems for Oxidative Coupling Reactions

As already mentioned, Chao-Jun Li is certainly one of the major pioneers of this field, it is therefore of no surprise that a lot of the initial exploration of conditions and scope was performed within his research group. Having identified an efficient catalytic system (Scheme 2-3, bottom part), it was applied to a wide range of nucleophiles, using *N*-aryl tetrahydroisoquinolines **9** as a standard proelectrophile (Scheme 2-4).



Scheme 2-4: Combination of copper complexes and tBuOOH for the oxidative coupling of **9** to diverse nucleophiles.

As can be seen, a wide variety of nucleophiles can be coupled with **9**. Alkynes,[11-12] nitroalkanes,[13] indoles,[14] and activated methylene compounds[15] give the corresponding coupling products in good yields using the previously developed CuBr/*t*BuOOH system. Further development led to a formal Morita-Baylis-Hilman reaction, or α-vinylation, using DABCO as a co-catalyst.[6b] Using arylboronic acids as nucleophiles, an efficient α-arylation was also achieved.[16] It is to be noted that very early in the development of this chemistry, an asymmetric variant of the alkynylation reaction was reported (Scheme 2-5).[12]

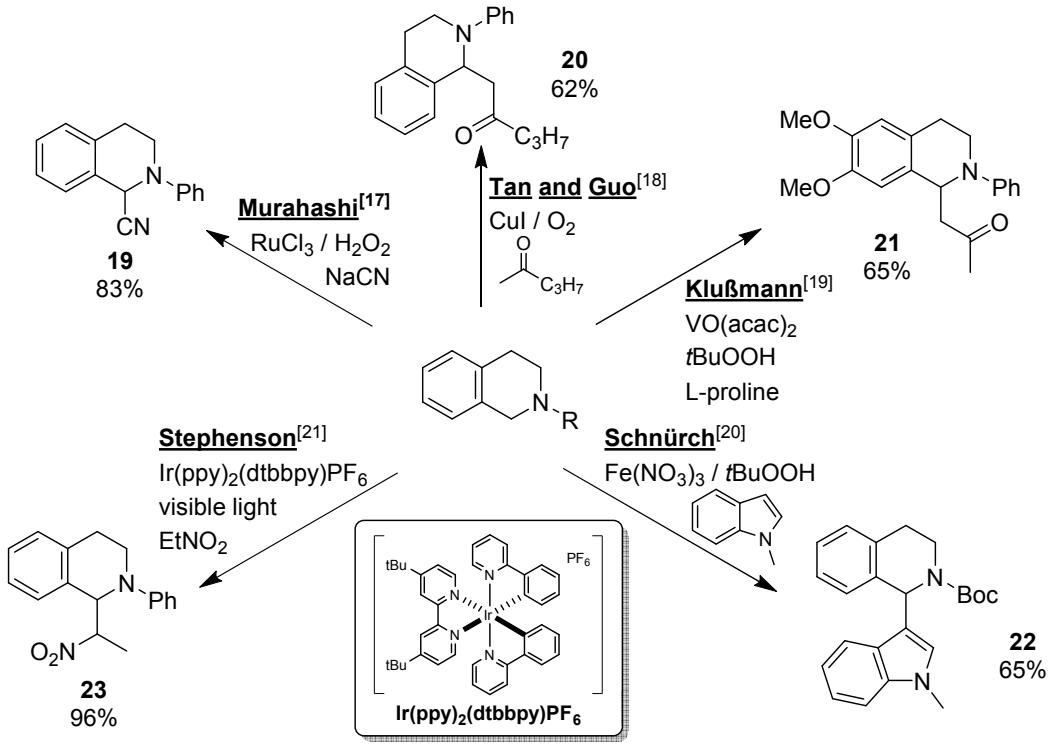


Scheme 2-5: Asymetric oxidative alkynylation of tetrahydroisoquinlines.

The combination of copper triflate and a chiral ligand allowed the synthesis of enantioenriched coupling products. The yields and enantioselectivities reported are modest

as shown by the representative examples in Scheme 2-5. Indeed, yields vary between 48% and 72% and the highest reported enantiomeric excess (ee) is 73% for **17**. Aliphatic alkynes in particular gave very low ee values, as seen for **18**. This represents the first example of such an asymmetric transformation and illustrates the challenge to achieve a highly enantioselective oxidative coupling of tertiary amines which remains until today.

It is already evident from these reports that the nucleophile scope of such transformations is very broad, and not limited to a particular class of compounds. Most efforts have then been dedicated to the identification of new catalytic systems and a large number of conditions have been reported and some examples are shown in Scheme 2-6.

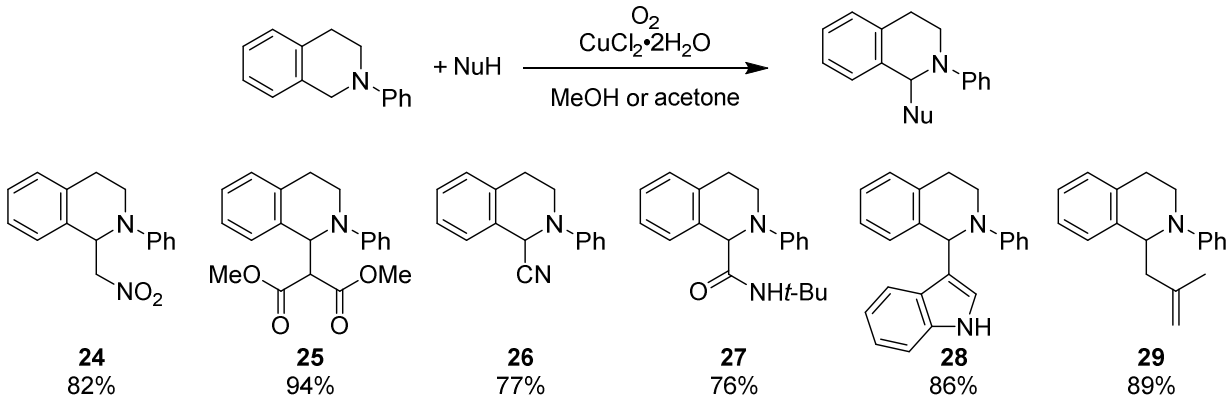


Scheme 2-6: Examples of catalytic systems for the oxidative coupling of tetrahydroisoquinolines.

Murahashi reported the use of $RuCl_3$ together with hydrogen peroxide as oxidant for an oxidative cyanation to products like **19**.[17] Coupling of methyl ketones was achieved by Tan and Guo to afford **20** with CuI as catalyst under an atmosphere of oxygen.[18] The combination of $VO(acac)_2$ and the organocatalyst L-proline together with tBuOOH as oxidant allowed the formation of **21**, in a racemic form, by the group of Klußmann.[19] Schnürch reported on the use of $Fe(NO_3)_3$ and *t*BuOOH for the synthesis of carbamate protected **22**.[20] Finally, the use of photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ was used by Stephenson for a visible

light induced aza-Henry reaction to afford **23**.[21]

However, most of these reports focus on one type of nucleophile and the generality of the catalytic system described is usually not demonstrated. Two exceptions are to be noted: the CuBr/*t*BuOOH system introduced by Chao-Jun Li (see Scheme 2-4),[6b, 11-15, 22] and the $CuCl_2/O_2$ system introduced by Martin Klußmann (Scheme 2-7).[23]



Scheme 2-7: Aerobic copper catalyzed oxidative coupling of tertiary amines.

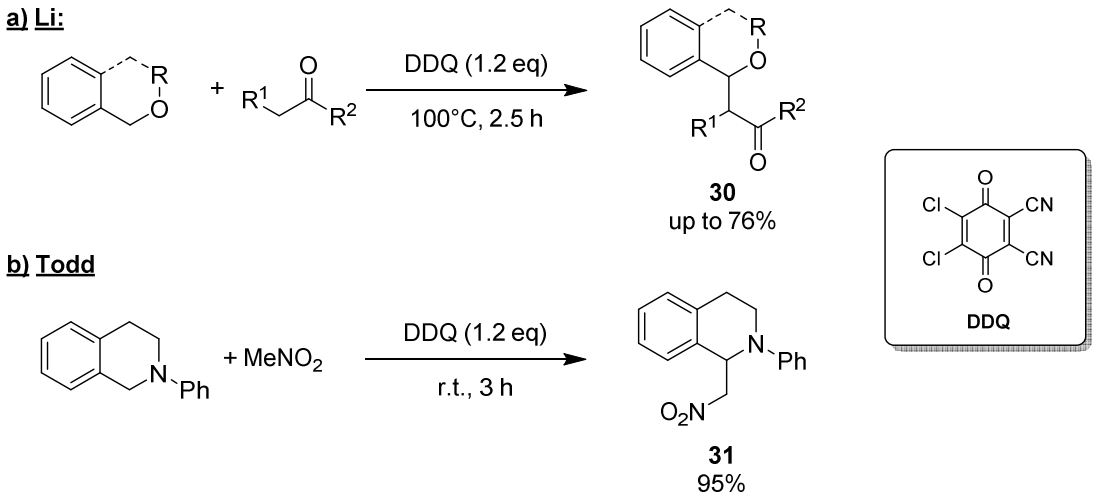
First developed for the use of silyl enol ethers and silyl ketene acetals as nucleophiles,[23a] the use of $CuCl_2 \bullet 2H_2O$ as catalyst and molecular oxygen as the terminal oxidant was found to be very general in terms of nucleophile scope. Free nitroalkanes (**24**), malonates (**25**), cyanides (**26**) or isocyanides (**27**), electron rich aromatics (**28**) and allyl silanes (**29**) have all been shown to be suitable substrates for this catalytic system, making it one of the most general described to date.

2.1.3 Efforts Towards Metal-Free Oxidative Coupling Reactions

Developing reaction conditions avoiding the use of expensive transition metal reagants or catalyst is one of the current hot topics in chemical research. Indeed, metal impurities are often toxic and difficult to completely remove from reaction mixtures. Therefore, the use of metal based catalysts and especially reagants is a major problem for the synthesis of fine chemicals such as pharmaceuticals. It is of no surprise that efforts to develop metal-free conditions for oxidative coupling of tertiary amines have been reported.[6n]

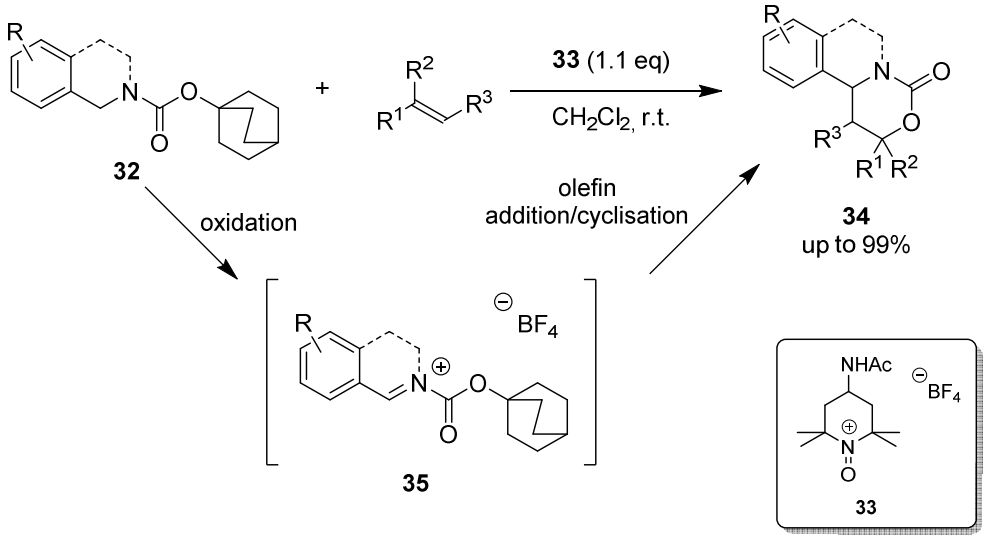
Chao-Jun Li pioneered this area once again by demonstrating in 2006 that DDQ

could be used as an organic oxidant in stoichiometric amounts to allow the oxidative coupling of benzylic ethers and ketones at 100°C (Scheme 2-8, a).[24] Todd later demonstrated that this approach was also applicable to amines under much milder conditions in an aza-Henry reaction of tetrahydroisoquinolines (Scheme 2-8, b).[25]



Scheme 2-8: DDQ mediated oxidative coupling of ethers and tetrahydroisoquinolines.

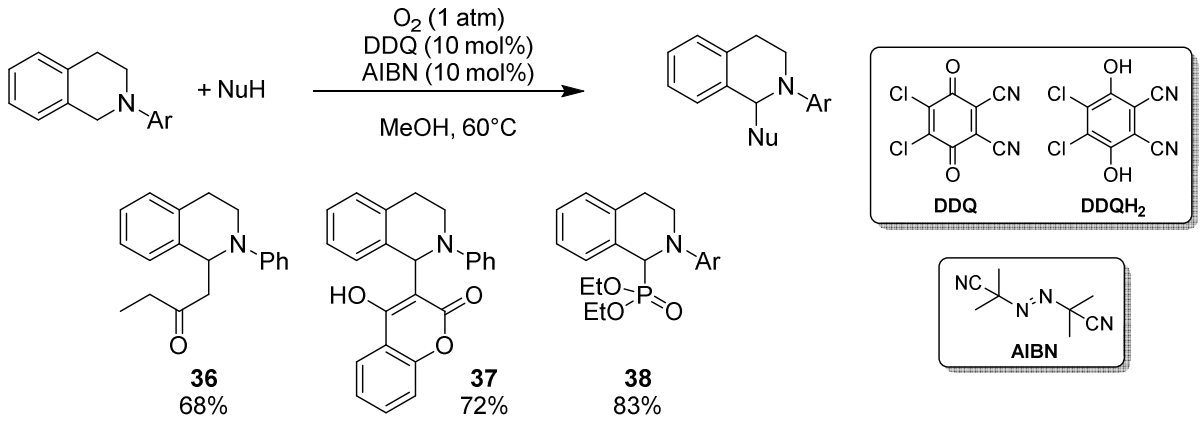
In 2010, the group of Olga García Mancheño introduced the use of TEMPO derived oxoamonium salts analoguous to **33** as mild oxidants for oxidative coupling reactions of benzylic ethers and tetrahydroisoquinolines in combination with an iron catalyst.[26] In 2012, they reported an interesting generation of polycyclic compounds **34** under metal-free conditions using **33** as oxidant and olefins as nucleophiles (Scheme 2-9)**.**[27]



Scheme 2-9: Oxoamonium salts promoted tandem α-alkylation/cyclization of carbamates with simple olefins.

This reaction is believed to involve the intermediate iminium **35** generated from the oxidation of the starting carbamate **32**. Addition of the olefin and nucleophilic attack of one oxygen atom of the carbamate group results in cyclisation to **34** and release of adamantol.

Although the use of non-peroxide oxidants and mild reaction conditions are attractive features of these systems, these three examples use stoichiometric amounts of a high molecular weight oxidant, with all the drawbacks that this implies in terms of waste generation and atom economy. A 2012 report by Prabhu showed a significant step forward and the use of catalytic amounts of DDQ and molecular oxygen as terminal oxidant in the presence of azabisisobutyronitrile (AIBN) as a cocatalyst (Scheme 2-10).[28]



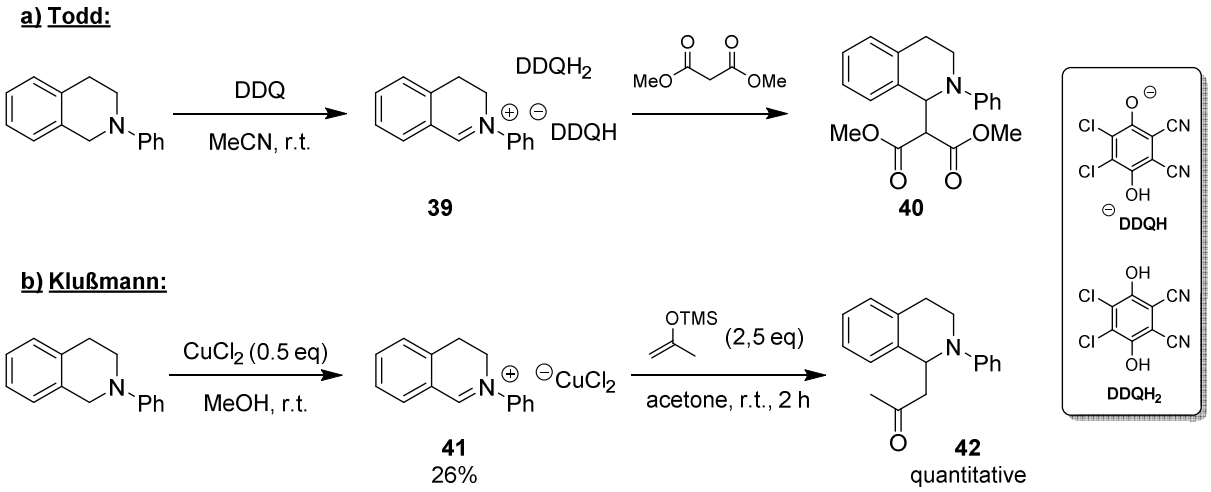
Scheme 2-10: DDQ catalysed oxidative coupling of tetrahydroisoquinolines under an atmosphere of oxygen.

In this case, AIBN is used as a source of radicals, postulated by the authors to serve as a red-ox mediator between $DDQH_2$, the reduced form of DDQ, and molecular oxygen. Indeed, all components of this catalytic system are necessary for the reaction to proceed.

2.1.4 Mechanistic Considerations and Challenges to be Met in Oxidative Coupling Chemistry

As seen from the selected examples of sections 2.1.2 and 2.1.3, a large number of catalyst/oxidant systems can be used in reactions for the oxidative coupling of tertiary amines. Since the reactivity of all these systems is quite similar, it is fair to assume that a common intermediate is present in all these reactions. The obvious choice for this

intermediate is the iminium ion oxidatively generated from the parent tertiary amines. Indeed, such an iminium ion has first been observed and characterised in 2011 by Todd in the DDQ mediated reaction of Scheme 2-8 (Scheme 2-11; a).[29] Interestingly, the iminium was trapped in a solid matrix comprising two molecules of the reduced oxidant: $DDQH_2$ and $DDQH^-$. The solid isolated was fully characterised as complex **39**.



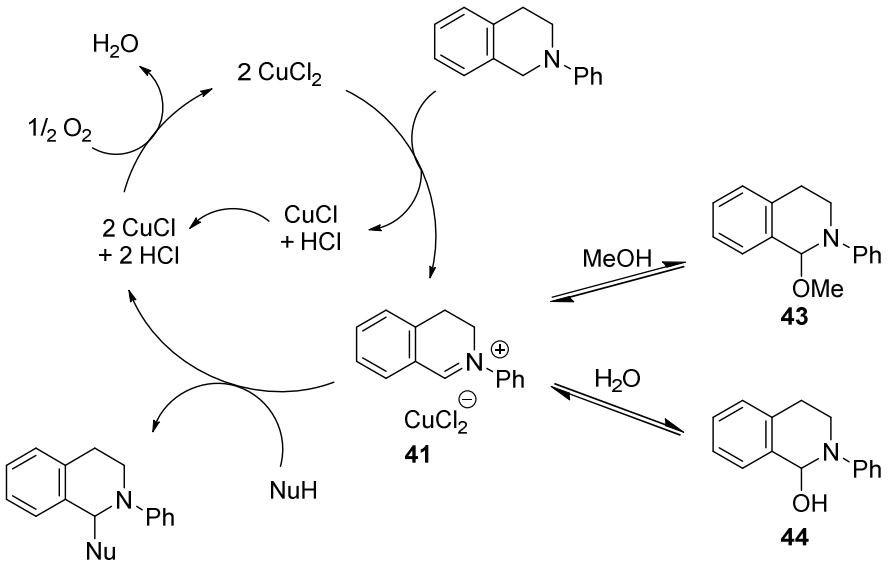
Scheme 2-11: Isolation and reaction of iminium ions in oxidative coupling of *N*-phenyl tetrahydroisoquinoline.

Accordingly, when **39** was isolated and subjected to reaction conditions, substitution products were obtained in good yields, including **40**, resulting from the attack of di-methyl malonate, a nucleophile that was not usable in the one step protocol.

Similarly, an iminium dichlorocuprate was isolated and characterised in 2011 by Klußmann from the reaction of copper salts with *N*-phenyl tetrahydroisoquinoline under aerobic conditions (Scheme 2-11; b).[23b] When **41** was subjected to reaction conditions, quantitative formation of **42** was observed in two hours, consistent with the involvement of **41** as a reaction intermediate.

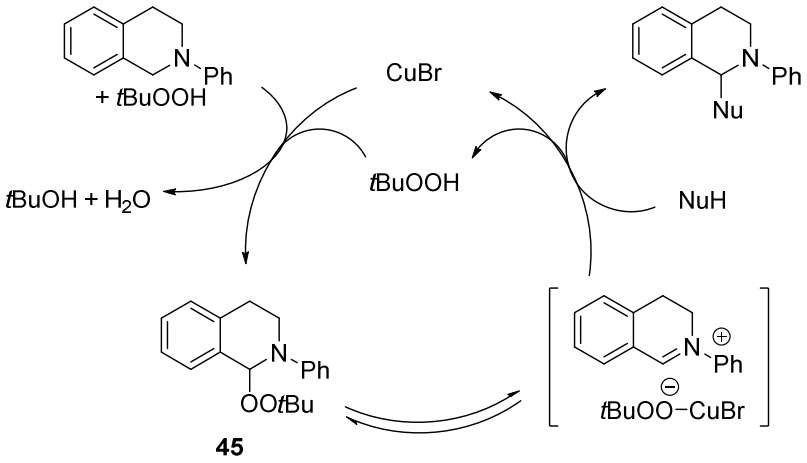
The mechanism of formation of iminium ion intermediates under copper catalysis has been the subject of detailed studies from the Klußmann and Doyle groups. In a 2011 study, Klußmann and coworkers studied the very succesful $CuBr/O_2$ system (see Scheme 2-7)[23a] they introduced previously (Scheme 2-12).[23b, 23c] The formation of **41** requires two equivalents of $CuCl_2$ since two electrons need to be transferred. One of these two equivalents stays as the conterion of **41**, while the other dissociates to CuCl and HCl. After attack of the nucleophile to form the product, the two equivalents of the reduced catalyst

are reoxidised by molecular oxygen to close the catalytic cycle. The strong positive effect of methanol as solvent was found to be due to the formation of **43**, which is in equilibrium with **41** under reaction conditions, acting as a stable reservoir for the highly reactive intermediate iminium ion. Thanks to this effect, the concentration of **41** is always kept low in solution, preventing side reactions and resulting in cleaner reaction mixtures. If another solvent, such as acetone, was used instead of methanol, the same effect is achieved, to a lower extent, through the attack of water on **41** to form **44**.



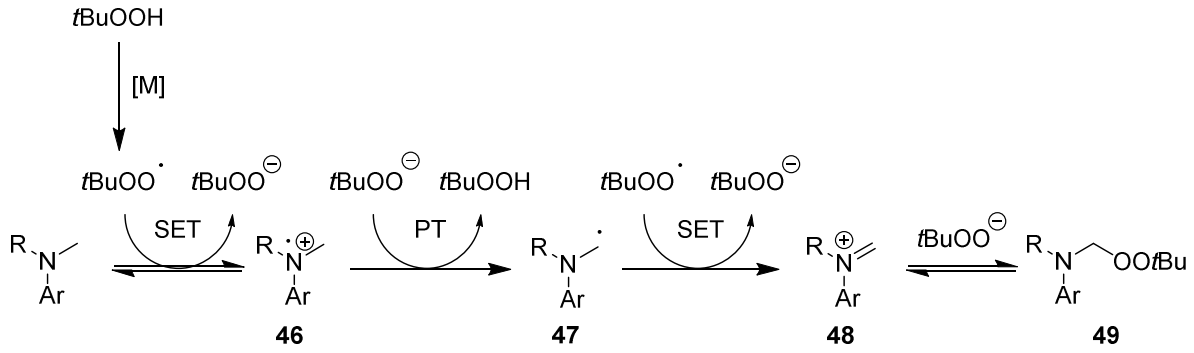
Scheme 2-12: Mechanistic studies on the CuBr catalysed aerobic coupling of *N*-phenyltetrahydroisoquinoline.

Further mechanistic studies in the Klußmann group, dealing with the CuBr/*t*BuOOH system introduced by Li showed a different mechanistic picture than from the copper catalysed aerobic system.[23c] As already suggested by the initial reports of Murahashi,[9] an aminoperoxide **45** was found to be a crucial intermediate, proposed to be formed *via* a Hydrogen Atom Transfer (HAT) mechanism, and part of the catalytic cycle, as a precursor to the iminium ion rather than an off-cycle species (Scheme 2-13).



Scheme 2-13: Klußmann's proposal for the mechanism of the CuBr/*t*BuOOH oxidative coupling of *N*-phenyl tetrahydroisoquinoline.

A later study by the group of Doyle published in 2013 proposed an alternative oxidation pathway and postulated the iminium ion to be the primary oxidation product through a series of single electron transfers (SET) and proton transfer (PT) (Scheme 2-14).[30]



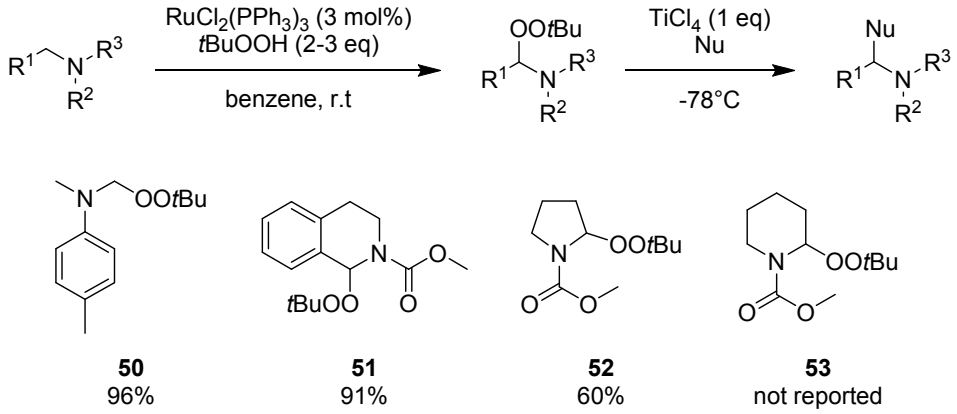
Scheme 2-14: Doyle's proposal for the mechanism of the tBuOOH mediated oxidative coupling of tertiary anilines.

In agreement with the large number of metals amenable to such transformations, it was also demonstrated that the role of the transition metal catalyst is solely to convert *t*BuOOH into *t*BuOO• radicals, then postulated to act as the real oxidizing species. A first SET furnishes the radical cation **46** and *t*BuOO$^-$. A PT to *t*BuOO$^-$ then furnishes the α-carbon centered radical **47** and regenerates *t*BuOOH. A second SET provides the iminium ion **48**, which is then trapped by the released *t*BuOO$^-$ or any suitable nucleophile present in the reaction medium. Similarly to the methanol adduct **43**, the *t*BuOOH adduct **49** acts as a stable reservoir, but contrary to Klußmann's proposal, it is described as an off-cycle species rather than the primary product of oxidation. The definitive elucidation of the elemental

steps of this oxidation process is still a subject of research and future studies should shed more light on this reaction.

Based on these mechanistic studies and the already broad scope of reported nucleophiles, it is fair to say that the challenge in oxidative coupling chemistry lies in the *oxidative* part of the reaction, and not in the *coupling*. As is evident from the examples presented in this chapter, *N*-phenyl tetrahydroisoquinoline is one of the most reactive tertiary amines towards oxidation and therefore by far the most widely used proelectrophile. Accordingly, apart from *N,N*-dimethyl aniline derivatives, only a few different other structures have been reported so far.

Indeed, looking to amide and carbamate substrates, of greater synthetic interest than aromatic substituents for further functionalizations, one realises the lack of a general method for such reactions and the challenge that these substrates pose. Already in the seminal report of Murahashi in 1990, carbamates were used as substrates for the formation of peroxyamides (Scheme 2-15).[9a]



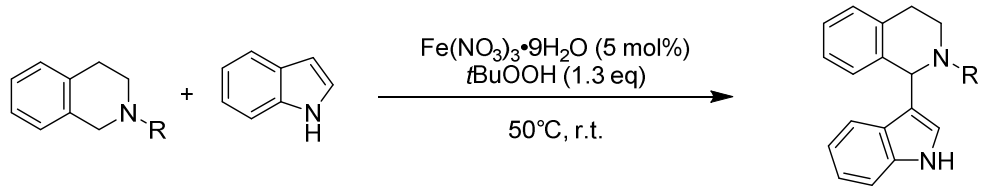
Scheme 2-15: Ruthenium catalyzed formation of aminoperoxides.

The oxidation yield was comparable between aniline **50** (96%) and tetrahydroisoquinoline **51** (91%) but going to pyrrolidine **52**, a major drop in yield was observed (60%).[9a] Althought the substitution step was later reported for piperidine **53**,[9c] no yield was reported for this substrate in the oxidation step, suggesting a very inefficient reaction. These results illustrate several facts: 1) aniline derivatives in general are substrates of choice; 2) the tetrahydroisoquinoline core, with its structural specificity (one of the α

carbons is on a benzylic position) allows to some extent to avoid an aromatic substituent on the nitrogen atom; 3) aliphatic amines/amides are particularly challenging substrates.

This effect of substituents is further illustrated by the reports of Schnürch and coworkers in 2010 and 2011 (Table 2-1).[20, 31] Phenyl substituted tetrahydroisoquinoline was indolated in a good 65% yield (entry 1). As expected, this substrate was the best of the ones studied. An aliphatic substituent such as benzyl was very poorly tolerated and the corresponding product obtained in only 7% (entry 2), while a benzoyl substituent was only marginally better (entry 3, 22%). Carbamate protecting groups were better suited and a Boc substituent was found to give the best yield of non aromatic substituents (entry 5, 54%), followed by its Cbz analogue (41%, entry 4). Interestingly, changing their iron catalyst to a copper salt, unprotected tetrahydroisoquinoline could also be employed, furnishing the coupling product in 48% yield (entry 6).

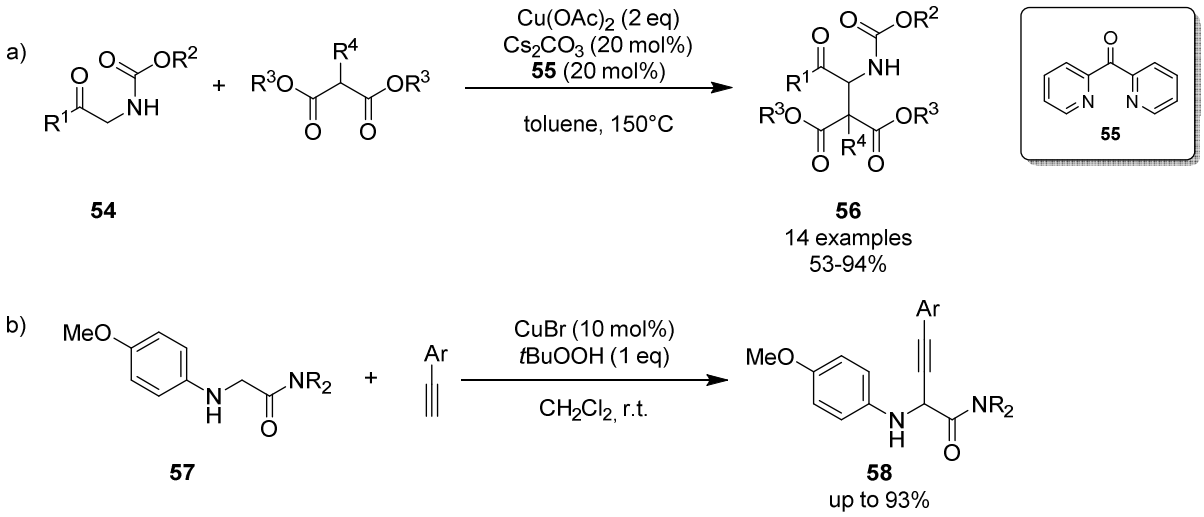
Table 2-1: Effect of the nitrogen substituent on the indolation of tetrahydroisoquinoline:



Entry	R	Yield (%)
1	Ph	65
2	Bn	7
3	Bz	22
4	Cbz	41
5	Boc	54
6[a]	H	48

a) $Cu(NO_3)_3 \bullet 3H_2O$ (5 mol%) used as catalyst

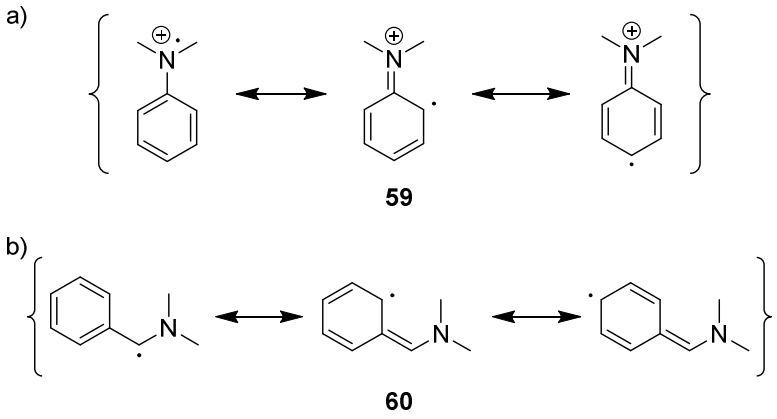
Another representative example for the difficulty to use alternative core structures and substitution patterns is shown in Scheme 2-16.



Scheme 2-16: Oxidative coupling of glycine derivatives with malonates and alkynes.

The group of Chao-Jun Li succeeded in coupling glycine derivatives with malonates and alkynes, showing the first example of the use of a secondary amine or amide in such reactions. However, a striking difference in reactivity is observed in the two cases. When amides **54** were subjected to the classical CuBr/*t*BuOOH system in the presence of a malonate nucleophile, no reaction was observed. Only in the presence of two equivalents of $Cu(OAc)_2$ as a stoichiometric oxidant and ligand **55** could the coupling products **56** be obtained in good yields. When the nitrogen protecting group was changed from an acetate to a para-methoxyphenyl (PMP) group, the CuBr/*t*BuOOH was again effective and the alkynylation proceeded smoothly to afford products **58** in good yields. These examples illustrate once more the fact that the oxidation potential of an amide is much lower than that of an amine, particularly bearing an electron rich arene substituent, explaining the success of *N*-aryl substituted amines compared to amides. It is not suprising that only a very limited number of alternative tertiary amine substrates have been reported to undergo oxidative coupling chemistry.[19, 32]

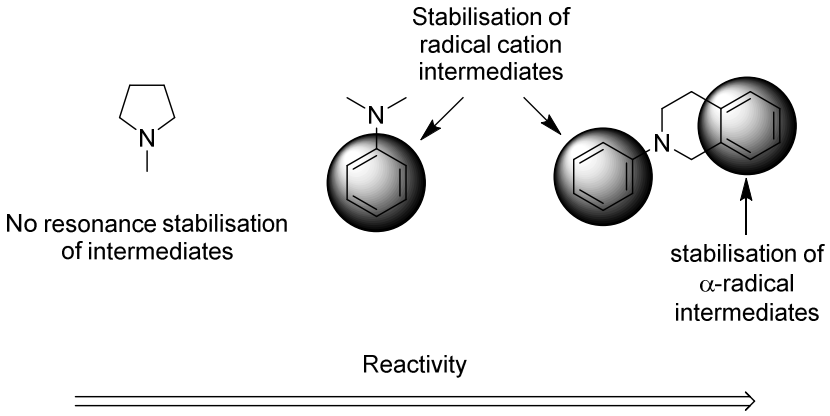
This behaviour can be rationalized by looking at the intermediates involved in the oxidation process (Scheme 2-17).



Scheme 2-17: Resonance stabilisation of intermediates in iminium ion formation.

An aromatic substituent will stabilize a nitrogen centered radical cation such as **59**, involved in SET processes (i.e. in the $CuCl_2 \bullet 2H_2O/O_2$ catalytic system and the Doyle proposal of Scheme 2-14) through resonance (Scheme 2-17, a). The same resonance stabilization will be achieved on benzylic positions for the second oxidation intermediate (i.e. **60**) in the case of Doyle's proposal or after hydrogen atom abstraction in Klußmann's mechanism (Scheme 2-17, b).

Accordingly, the ranking of reactivity of amine substrates can be explained through these resonance stabilizing effects (Scheme 2-18).



Scheme 2-18: Resonance stabilisation of intermediates in iminium ion formation.

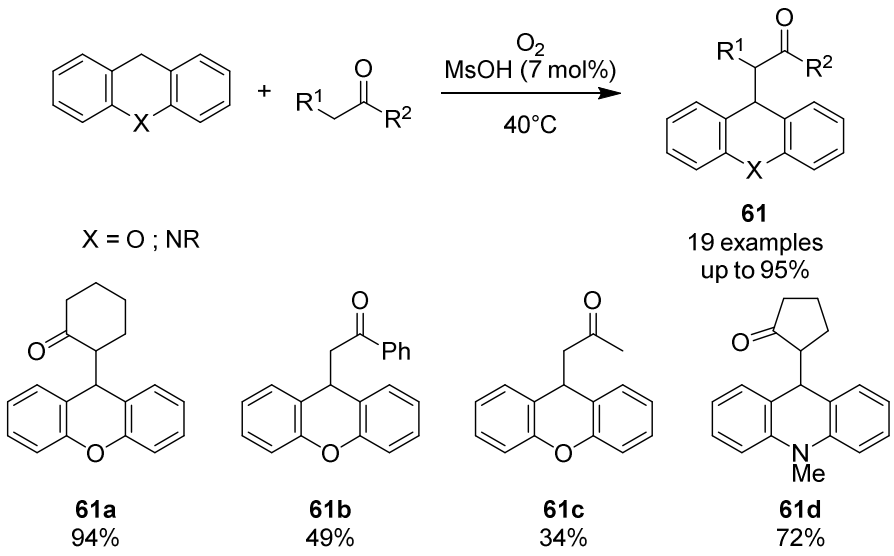
Aliphatic amines such as *N*-methyl pyrrolidine do not have any of these stabilizing groups. Therefore, both radical cation and α-carbon radical intermediates will very unstable and short lived if they can be accessed. The aromatic group of anilines will provide stabilization to radical cation intermediates. *N*-Phenyl tetrahydroisoquinoline combines this

effect of the aromatic substituent on the nitrogen and the benzylic character of the α-carbon, providing stabilisation to α-radical intermediates, to achieve optimal stability of both reactive intermediates, facilitating its oxidation.

2.2 Autoxidative Coupling Reactions

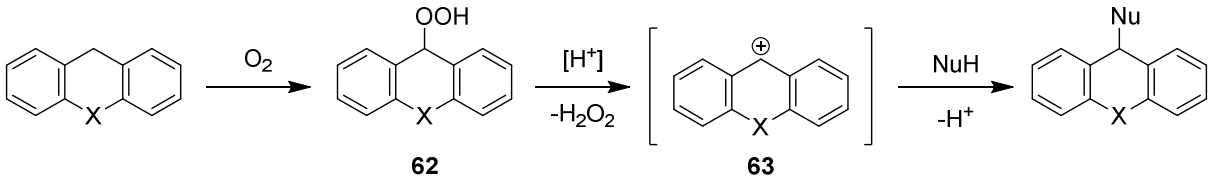
2.2.1 Autoxidative Coupling of Xanthene and Acridanes

In the context of the discussion about oxidative coupling of tertiary amines of the previous chapter, a particularly interesting reaction was developed in the Klußmann group and reported in 2010 (Scheme 2-19).[33]



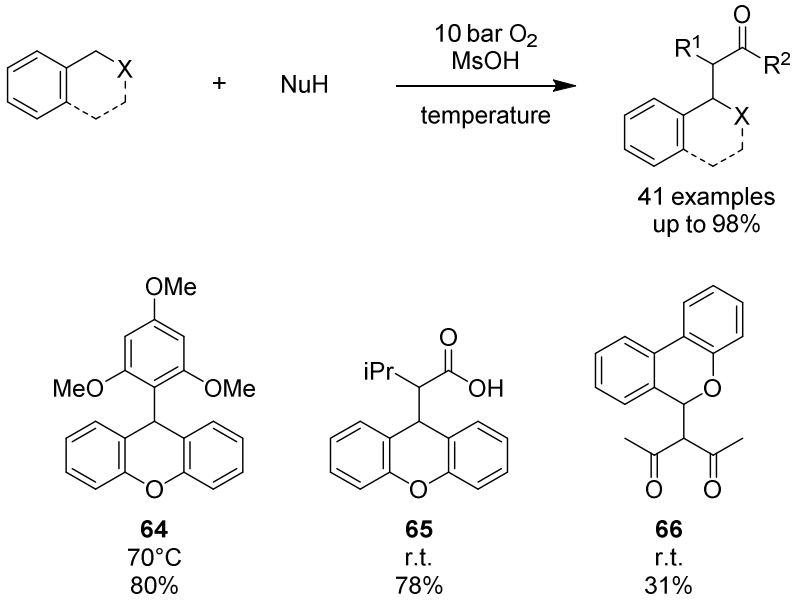
Scheme 2-19: Autoxidative coupling of xanthene and acridanes.

The developed reaction allows the coupling of xanthene (X = O) or acridanes (X = NR) with carbonyl nucleophiles under an atmosphere of oxygen in the presence of methane sulfonic acid (MsOH) in neat conditions at slightly elevated temperature. In light of the chemistry discussed in section 2.1, several features of this reaction are surprising. The most striking one is the absence of a stoichiometric synthetic oxidant, such as DDQ or a peroxide, and of a transition metal salt, which could enter a red-ox cycle using molecular oxygen as terminal oxidant, such as in the copper catalysed aerobic reactions shown in the previous chapter. Instead, a simple Brønsted acid, which cannot enter such red-ox cycles, is used. Based on results which will be further discussed in section 4.2 in detail, it was assumed that the reaction was initiated by an autoxidation mechanism, hence the term autoxidative coupling. The mechanism that was proposed in the original publication is shown in Scheme 2-20.



Scheme 2-20: Proposed mechanism of the autoxidative coupling of xanthene and acridanes.

An autoxidation reaction takes place to afford the hydroperoxide **62**, which in the presence of the acid catalyst releases H_2O_2 and generates a highly stabilised carbocation **63**. Trapping of this cation by a nucleophile then forms the isolated coupling products. The original conditions showed some quite severe limitation of scope. Indeed, nucleophiles other than ketones (also used as solvent) were unreactive and proelectrophiles other than xanthene and acridanes were only poorly tolerated. This led to the use of more forcing conditions to enable more challenging combinations of substrates (Scheme 2-21).[33b]

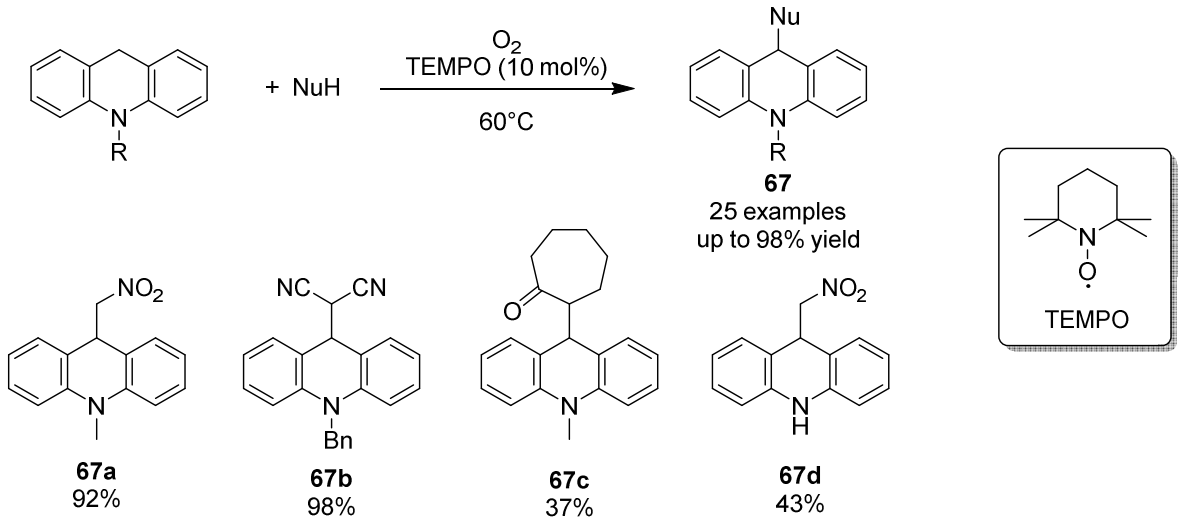


Scheme 2-21: Sulfonic acid catalyzed autoxidative carbon-carbon coupling reaction.

In accordance with the proposed autoxidation step prior to the ionic substitution, increasing the partial pressure of oxygen and/or the temperature led to a more efficient reaction. The addition of 1,3,5-trimethoxybenzene to xanthene to afford **64** was not possible under standard autoxidative coupling conditions but a yield of 80% was achievable using a high pressure of oxygen and elevated temperature. Similarly, aldehydes were suitable partners under elevated pressure and afforded carboxylic acids **65**, after aerobic oxidation of the aldehyde. Finally, benzyl ethers were also suitable substrates under these conditions and

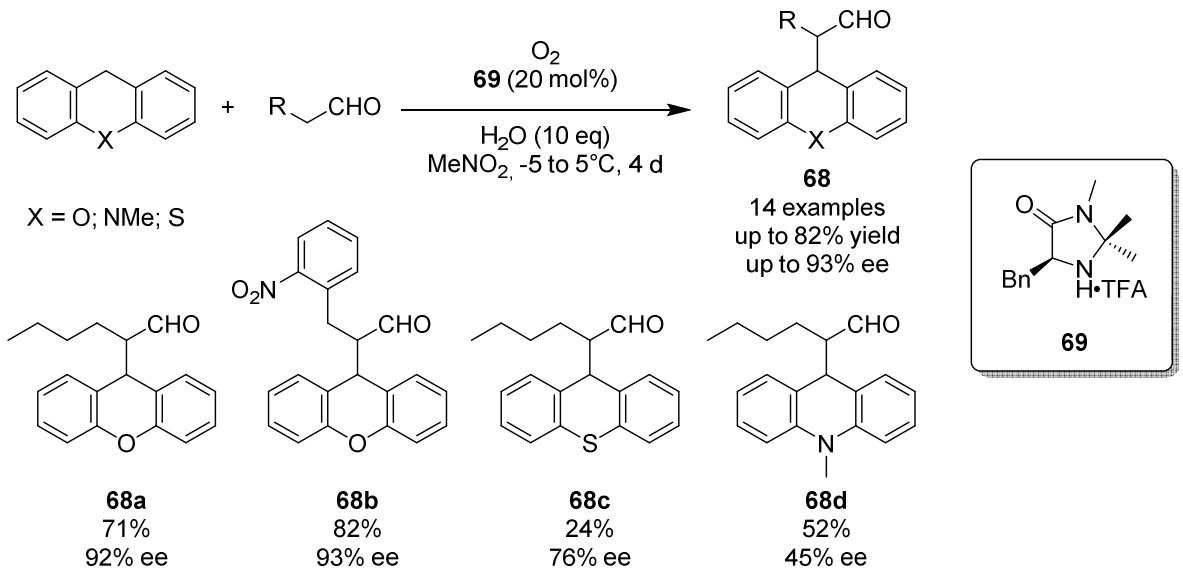
66 could be isolated in moderate yield.

The group of Jiao followed up on this chemistry and reported a TEMPO catalyzed version in 2012 where acridanes could be coupled with nitroalkanes and carbonyl nucleophiles with molecular oxygen as terminal oxidant (Scheme 2-22).[34] Using TEMPO as catalyst, acridanes could be coupled with a range of carbon nucleophiles at 60°C. Under the previously reported conditions in the absence of TEMPO, no reaction was observed, in accordance with the results obtained in the Klußmann group.[33] TEMPO is believed to serve as a radical initiator by abstracting a hydrogen atom on the benzylic position of the substrate, leading to the formation of peroxides, analogous to the mechanism postulated for the reaction of xanthene in Scheme 2-20.



Scheme 2-22: TEMPO catalyzed oxidative coupling of acridanes under oxygen atmosphere.

By using a chiral amine catalyst, Jiao could achieve a enantioselective addition of aldehydes to xanthene derivatives in good yields and enantioselectivities (Scheme 2-23).[35]



Scheme 2-23: Enantioselective addition of aldehydes to xanthene derivatives.

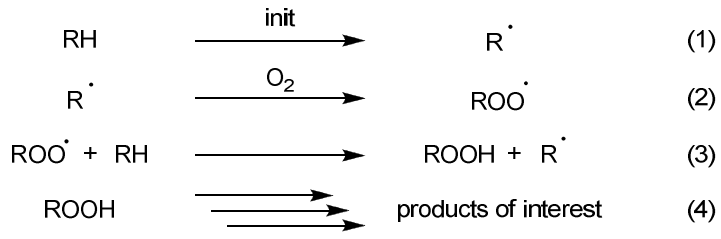
Good yields and enantioselectivities could be achieved using the Mac-Millan type salt **69**. Nitromethane was found to be the solvent of choice since apart from acetonitrile, all other solvents tested gave very low conversions. The catalyst is believed to serve for a dual purpose and enter two different catalytic cycles. The amine part is involved in the classical enamine catalysis cycle, while the conjugated acid of the counterion is thought to act as an acid catalyst to generate the benzylic cation (see Scheme 2-20), which is then trapped by the enamine nucleophile.

It is clear from these reports that the autoxidative reaction of xanthene and derivatives is a very attractive approach to oxidative coupling chemistry. It does not involve a transition metal or stoichiometric amounts of a synthetic oxidant and therefore has the potential to follow the principles of green chemistry.[4] However, the limitations in terms of scope are quite severe. Appart from xanthene and analogues, the electrophile scope is extremely limited and only a few examples of alternative structures have been reported by Klußmann, [33] and by others.[34-35] Additionaly, the mechanism of the reaction is only poorly understood and the proposed mechanism does not account for the limitations observed. Therefore, having a better understanding of the basic chemical steps involved in this process would allow to have a rational approach for the improvement of this chemistry.

2.2.2 General Considerations about Autoxidation Reactions

Autoxidation is defined as the oxidation of chemical compounds by molecular oxygen to form (hydro)peroxides. It can be regarded as a slow flameless combustion, especially in the case of organic compounds. The autoxidation of hydrocarbons is of particular industrial importance, both in productive and destructive ways. Indeed, it is well know that upon standing in air, fats and oils will become rancid, as a result of their oxidation. On the other hand, a large number of oxygenated chemicals can be synthesized from hydrocarbons by controlled autoxidation processes. The most famous, and perhaps most industrially relevant, example of such a process is the conversion of cyclohexane to a mixture of cyclohexanone and cyclohexanol, known as KA oil, under pressurised air at high temperature.[36] This process is conducted on industrial scale of about 10^6 tons per year and is the first step for the production of adipic acid, a precursor to 6,6-nylon. Other industrially relevant autoxidations are the formation of cumyl hydroperoxide, accounting for most of the modern production of phenol,[37] or the oxidation of isobutene to *tert*-butyl hydroperoxide, a widely used oxidant.[38]

Autoxidation reactions are widely accepted to be of a radical nature. Despite their industrial relevance, the details of their mechanism are not fully understood and still to this day a research area of interest.[39] A generally accepted simplified mechanism is represented in Scheme 2-24.



Scheme 2-24: General mechanism of autoxidation.

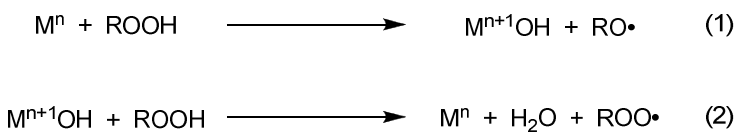
The first and most important step is an initiation to afford free radicals (equation 1). Trapping of these radicals by molecular oxygen generates peroxyl radicals (equation 2), which serve as chain propagating species. Hydrogen atom abstraction of the substrate by these peroxyl radicals forms a hydroperoxide and regenerates one molecule of the starting free radical (equation 3). The hydroperoxide, the primary product of all autoxidation

reactions, can then be converted or decomposed to the oxygenated products of interest, thermally or with the aid of a catalyst (equation 4).

Even though the oxidation of hydrocarbons is a highly exothermic reaction, the kinetics of such reactions are extremely unfavourable. This is illustrated by the fact that hydrocarbons can exist in open air, consisting of 21% of molecular oxygen, without spontaneously combusting. Researchers at the Du Pont company, estimated the half life of the spontaneous aerobic oxidation of cyclohexane at 25°C to be about 2×10^{20} years,[39g] when the age of the universe has been measured to be 13.798×10^{9} years. At a higher temperature of 300°C, the half life of oxidation goes down to "only" 2×10^{9} years. Although the propensity of hydrocarbons to undergo autoxidation processes heavily depends on their structure, these numbers illustrate the fact that most autoxidation reactions need an external activation in order to be of practical interest.

The most straightforward way to initiate autoxidation reactions is to rely on the use of radical initiators. Peroxides are commonly used for this purpose. Indeed, the O-O bond is much weaker than virtually any other bond type in the products consumed or formed during autoxidation reactions. Homolytic cleavage of peroxide bonds therefore generates two equivalents of oxyradicals, which can abstract hydrogen atoms from substrates to initiate chain reactions (see Scheme 2-24). In order to facilitate these initiation reactions, the most obvious way to accelerate the cleavage of the peroxide bond is to use elevated temperatures, above which the peroxide bond spontaneously dissociates.

Another approach relies on the presence of transition metal salts in the reaction mixtures. Mainly cobalt, copper and manganese complexes are used. Their role is to catalyse the decomposition of hydroperoxides through the Haber-Weiss cycle (Scheme 2-25).[40]

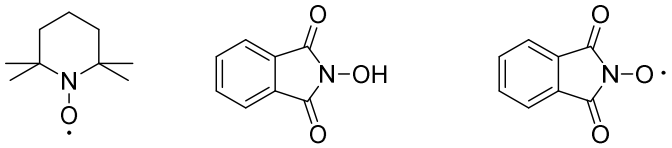


Scheme 2-25: Haber-Weiss mechanism of decomposition of hydroperoxides.

These transition metals in the presence of a hydroperoxide will facilitate the

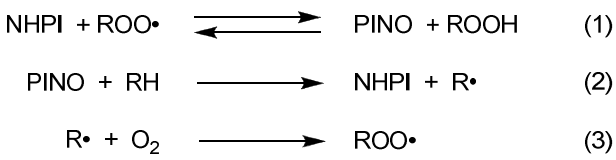
homolytic cleavage of the peroxide bond, generating a hydroxyl-complex of higher oxidation state and an alkoxyl radical. The hydroxyl complex in the presence of another molecule of hydroperoxide then regenerates the metal center in its starting oxidation state, one molecule of water and a peroxyl radical. Because hydroperoxides are primary products of all autoxidation processes, and therefore continuously regenerated in the reaction medium, they both serve as chain propagating species and in situ generated initiators to compensate for termination reactions.

Organocatalytic approaches have also been reported and rely on the unique reactivity of N-O• radicals such as TEMPO or the phthalimide-*N*-oxyl radical (PINO). The most prominentely used catalyst for autoxidation is certainly *N*-hydroxyphthalimide (NHPI) and the corresponding PINO radical (Scheme 2-26).



Scheme 2-26: Structure of TEMPO, N-hydroxyphthalimide (NHPI) and the corresponding phthalimide-N-oxyl radical (PINO).

Ishii reported on the use of NHPI and analogues as catalyst for the oxidation of several substrates in the liquid phase, with or without the presence of metal salts.[41] This catalyst has been reported for a large number of oxidative functionalization of different kinds of substrates.[42] A key characteristic of the PINO radical is its persistent nature, PINO radicals do not recombine to form dimers, unlike most radicals.[43]



Scheme 2-27: General mechanism for the NHPI catalyzed autoxidation reaction.

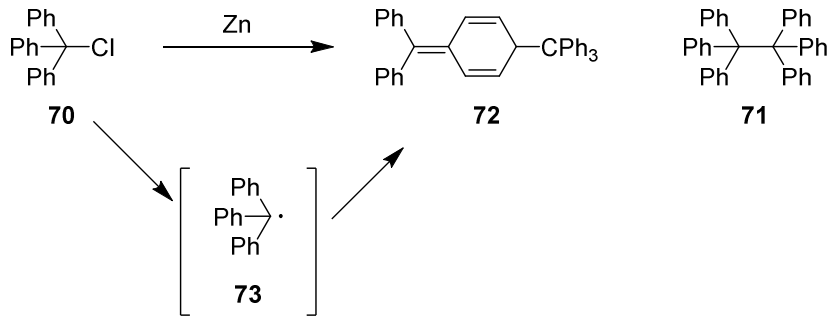
The catalytic behaviour of NHPI is explained by its in situ conversion to PINO by ROO• radicals in an equilibrium (Scheme 2-27, 1). PINO radicals are very efficient hydrogen atom abstracting species, which regenerate NHPI (Scheme 2-27, 2) along with ROO• radicals

and therefore propagate the radical chain (Scheme 2-27, 3).

2.3 Radical Reactions of Carbonyl Compounds

2.3.1 General Remarks on Radicals

The field of free radical chemistry was started by Moses Gombert by his report of "An Instance of Trivalent Carbon: Triphenylmethyl" in 1900.[44] He isolated a hydrocarbon from his attempts of synthesizing hexaphenylethane **71** from triphenylchlormethane **70**, which by a series of structure elucidation experiments, he attributed to the tetraphenylmethane radical **73** (Scheme 2-28).



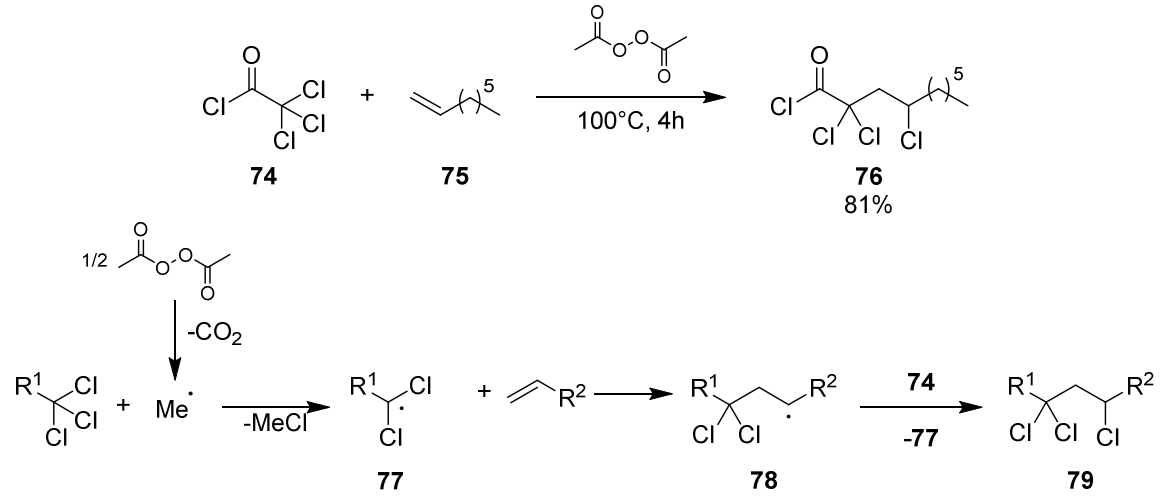
Scheme 2-28: Gombert's attemps to synthesize **71** and isolation of **72**.

This claim of a stable and isolable trivalent carbon sparked interest of many chemists at this time, despite his repeated "wish to reserve the field for [him]self". Particular controversy arised from the exact structure of the hydrocarbon isolated by Gombert,[45] which was proven after almost 70 years of controversy to be the dimer **72**, rather than the free radical **73**, made through the recombination of **73**, a behaviour of free radicals now familiar to present time chemists.

Free radicals are chemical entities with at least one unpaired electron, therefore violating the octet rule. This peculiar nature confers to free radicals exceptional reactivities, in pathways that are often inaccessible to ionic chemistry. Free radical chemistry has therefore been the subject of countless studies, reviews and books and will therefore not be covered in detail in this section. Only selected examples of a very particular area of this huge field will be presented: the generation of free radicals in the α-position of carbonyl compounds.

2.3.2 Generation of Radicals from Radical Precursors

The formation of carbon centered free radicals often relies on the homolytic cleavage of a carbon-halogen bond in the presence of a radical initiator. A prime example related to the chemistry studied in this dissertation is certainly the Atom Transfer Radical Addition (ATRA), also know as the Kharasch reaction.[46] Along with the original publication on the addition of carbon tetrachloride to olefins,[46a] Kharasch reported in 1945 on the addition of trichloroacetylchloride **74** to 1-octene, which yielded the addition product **76** by heating in the presence of a peroxide initiator (Scheme 2-29).[46b]

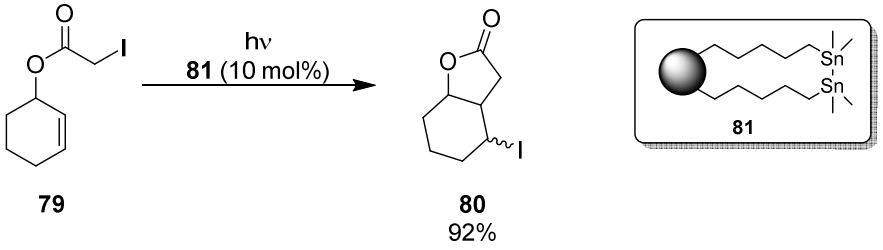


Scheme 2-29: Kharasch addition of trichloroacetylchloride to 1-octene.

The mechanism starts with the thermal decomposition of diacetyl peroxide to afford carbon dioxide and methyl radicals. By reacting with the substrate, radical **77** is formed along with chloromethane. **77** adds to the olefin, affording a second alkyl radical **78** which, after abstracting a chlorine atom from the starting material, regenerates **77** and propagates the chain, yielding the final product **76**.

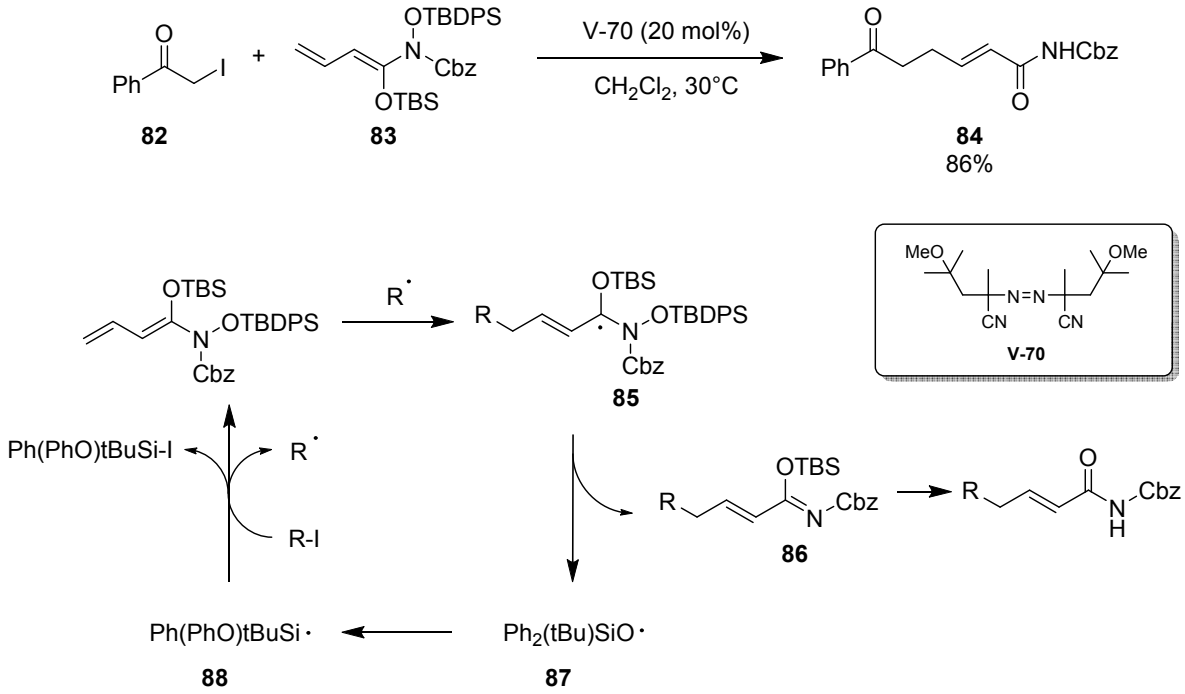
Most radical chain reactions are carried out in the presence of tin hydride reagants, the most widely used one being tributyltin hydride.[47] However, trialkyl tin hydrides are notoriously toxic compounds and the tin byproducts generated are difficult to completely remove from reaction mixtures, preventing the use of such reagents in an industrial context. It is therefore not surprising that many efforts have been dedicated to the development of clean or tin-free radical chemistry.[48] One of such examples is illustrated in

Scheme 2-30. In 2004, Kilburn reported on the use of a polymer bound ditin reagent **81** to efficiently perform the ATRA cyclisation of **79** to **80** in excellent yield, comparable to soluble reagants.[49] The use of an immobilized reagent allows its removal by simple filtration to afford a product containing very low residual levels of tin.



Scheme 2-30: ATRA cyclisation using a polymer bound tin reagant.

These ATRA reactions incorporate the halogen atoms used as radical precursors due to the nature of the radical chain mechanism and the propagating species. This is not always the case, and reductive cyclisations are possible, as shown in a 2004 report from Kim, where a silicon centered radical takes this role for an interesting γ-alkylation of amide equivalents (Scheme 2-31).[50]



Scheme 2-31: Radical γ-alkylation of amide equivalents.

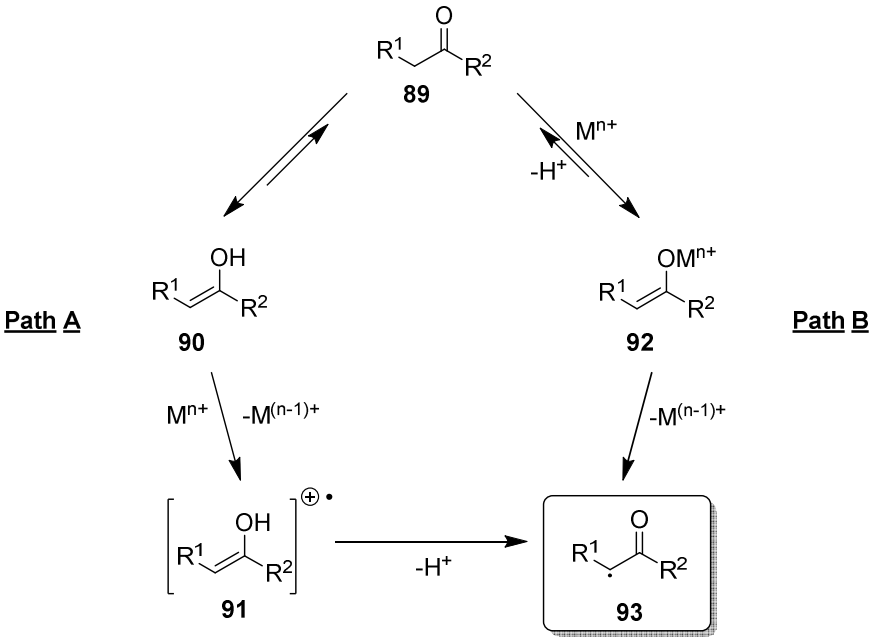
In the presence of the radical initiator V-70, iodoacetophenone **82** adds to **83** to

afford a γ-aklylated unsaturated amide **84** in excellent yield under mild conditions. In this case, the propagating species is the silicon centered radical **88**, formed from the decomposition of the intermediate radical **85**. This fragmentation affords the oxygen centered radical **87**, which rearranges to **88** and the desired product after aqueous work up.

2.3.3 Oxidative Generation of Free Radicals of Enolizable Compounds

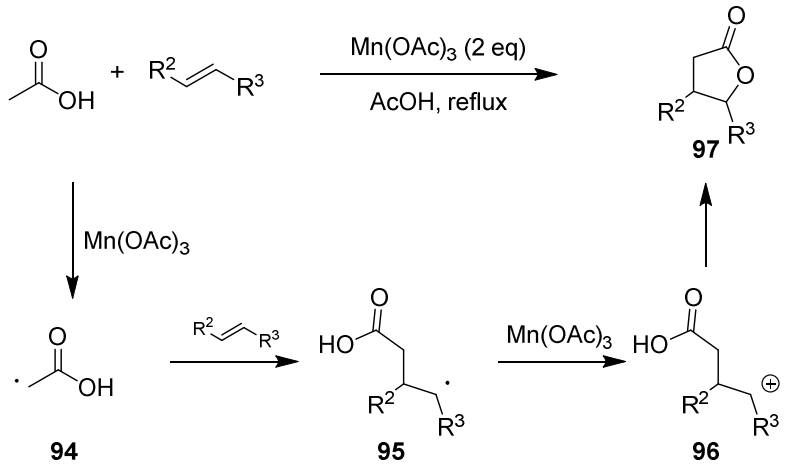
The use of radical precursors, such as halogen atoms, has some inherent advantadges, in particular, the predictability of the position of the future radical. However, this approach has the same drawbacks already mentioned in section 2.1. The use of a leaving group leads to the formation of stoichiometric amounts of side products and the starting material needs to be synthesized, a task that can be step, time and resource consuming. Therefore the use of non functionalized starting materials is of great advantage in this regard.

Metallic oxidants have been widely used to generate radicals next to an enolisable carbonyl group. In particular $Mn(OAc)_3$ in acetic acid and cerium(IV) ammonium nitrate (CAN) are the most active systems.[51] [52] These two oxidants have similar oxidation potentials (+1.54 V vs. NHE for $Mn(OAc)_3$ and +1.61 V vs. NHE for CAN), therefore comparable reactivity patterns are to be expected from the two systems. One advantadge of CAN over manganese(III) oxidants is the possibility to use solvents other than acetic acid, such as acetonitrile or methanol, at lower temperatures. The general mechanism for the oxidation of enolisable carbonyl compounds is shown in Scheme 2-32. Two pathways are imaginable starting from **89**. Path A starts with the enolization to **90** and subsequent single electron transfer to afford the radical cation **91**, which after loss of a proton generates **93**. Path B starts with the formation of the metal enolate **92** and direct oxidation within the metal ligand sphere to **93**. Distinction is not easy and is still in debate. It is however clear from studies of Fristad that the rate of radical generation is directly correlated with the C-H acidity of the substrate.[53]



Scheme 2-32: Possible mechanisms for the metal mediated generation of radicals from enolisable carbonyls.

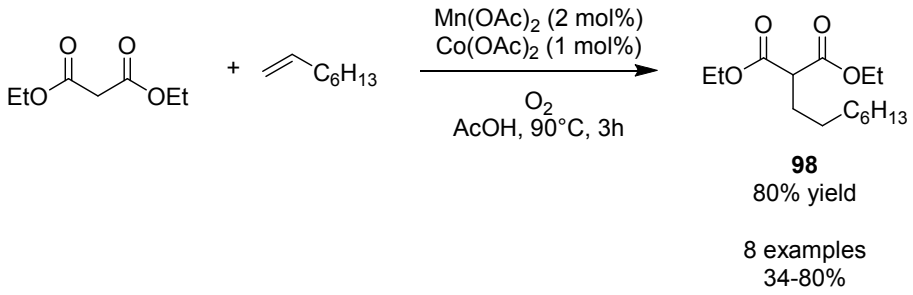
A typical use of manganese(III) oxidants and carbonyl compounds is the lactonisation reaction simultaneously and independantly reported by Bush and Finkbeiner,[54] and by Heiba in 1968.[55] In this reaction, acetic acid – used as solvent – adds to an olefin after being oxidised to the corresponding radical **94**. further oxidation of the resulting radical **95** and intramolecular trapping of the cation **96** yields the lactone **97** (Scheme 2-33).



Scheme 2-33: Lactone formation from acetic acid and an olefin.

This methodology can be used for other substrates than acetic acid but – as is the

case for this chemistry in general – carbonyl compounds that are more easily enolised than the acetic acid solvent have to be used to provide efficient reactions. Therefore an additional electronwithdrawing substituent is usually needed on the α-position to avoid side reactions resulting from the competing oxidation of acetic acid used as solvent. Another drawback is the use of stoichiometric quantities of the metal oxidant, often used in excess. An appealing solution to this problem was reported by Ishii in 2002 with the use of a combination of $Mn(OAc)_2$ and $Co(OAc)_2$ as catalsyts (Scheme 2-34).[56]

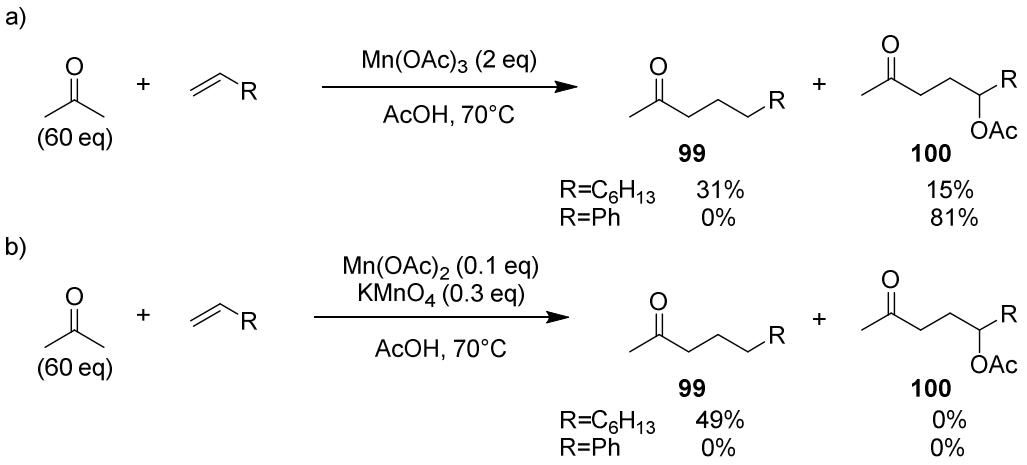


Scheme 2-34: Addition of carbonyl compounds catalyzed by a combination of manganese and cobalt salts.

This combination of catalysts is particularly attractive because it uses molecular oxygen as the final oxidant. If any of the two metal was ommited, hardly any reaction was observed. The authors therefore propose that manganese(II) is continuously reoxidised by a cobalt(III) species generated from the cobalt(II) salt used and molecular oxygen. This system does not however address the issue of high temperature or the large excess of carbonyl compound needed (15 to ~45 equivalents) compared to the radical acceptor.

Examples of the use of ketones, instead of 1,3-dicarbonyls or equivalents, are much more limited, due to their lower acidity.[53] In this context, Linker reported on the addition of acetone to olefins (Scheme 2-35).[57] By using the classical conditions, an excess of manganese(III) acetate in acetic acid and solvent quantities of acetone, a mixture of products was obtained (Scheme 2-35, a). The saturated product **99** was the main product when aliphatic alkenes such as 1-octene were used, along with small amounts of the corresponding acetate **100**. If styrene was used, **100** was the only product isolated in good yield. They developed the use of the combination of $KMnO_4$ and $Mn(OAc)_2$ to selectively afford **99** (Scheme 2-35, b). This is achieved by the slow addition of $KMnO_4$, which slowly converts manganese(II) to manganese(III), keeping the concentration of the active

manganese(III) oxidant low, therefore preventing overoxidation of the radical product of addition to the corresponding cation and trapping by acetic acid. The selectivity to the saturated product **99** was complete if 1-octene was used, even though the yield is still a relatively low 49%, but if styrene was used, no product of addition was obtained, only polymeric adducts.



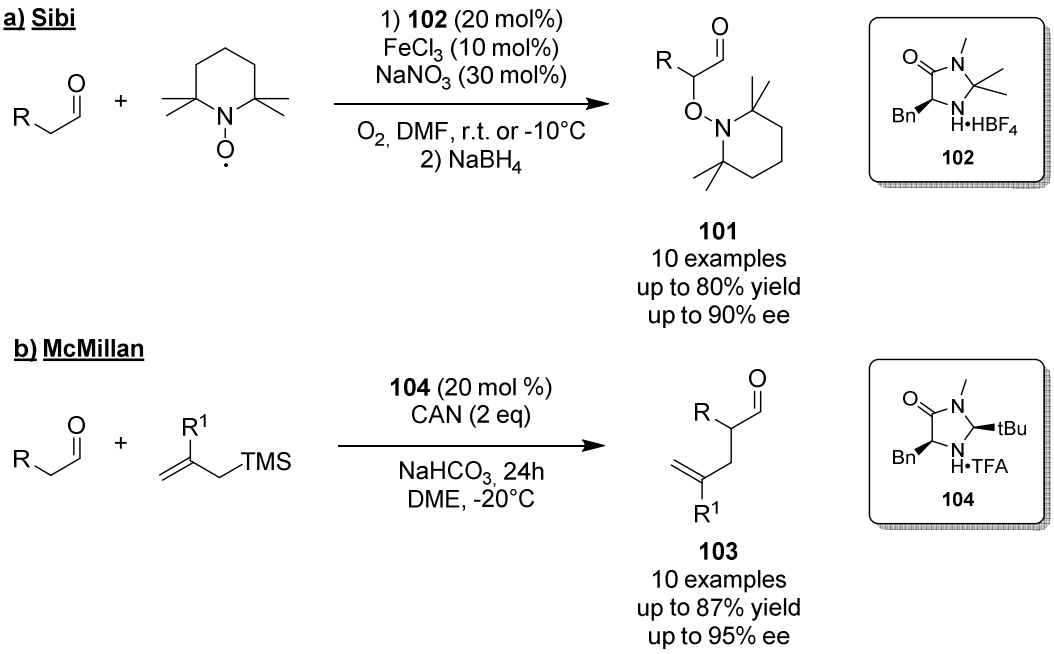
Scheme 2-35: Radical addition of acetone to olefins.

These examples perfectly illustrate the challenges associated with the use of simple ketones with manganese(III) oxidants. In general, high temperatures are used in acetic acid as solvent and even though the ketone partner is used in large excess – often in solvent quantities – the yields of addition product are rather low, a result of the competing oxidation of acetic acid, leading to undesired side products.

2.3.4 SOMO Catalysis

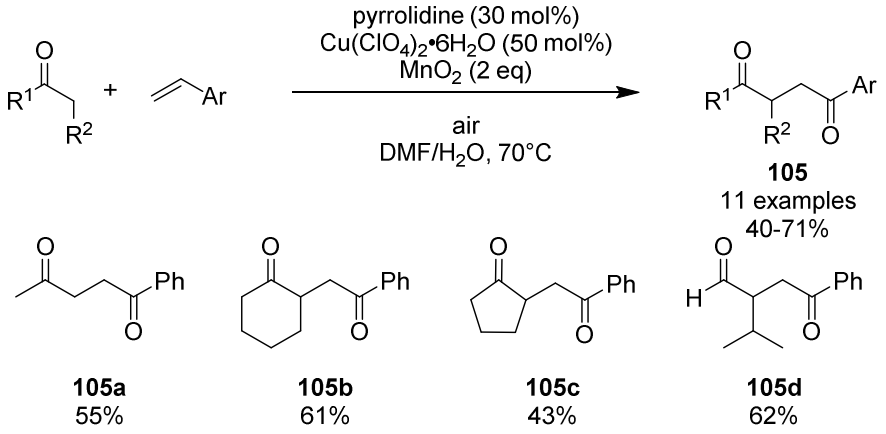
In 2007, Sibi and MacMillan reported on the activation of aldehydes by secondary amine catalysts in the presence of single electron oxidants to afford oxygenated and allylated aldehydes, respectively (Scheme 2-36).[58] Both approaches rely on the use of a chiral imidazolidinone salt to activate the aldehyde substrate to afford the corresponding enamine, which is then oxidised by the single electron transfer reagent to the corresponding radical cation. In the approach of Sibi, the radical is then trapped by TEMPO to afford the α-oxygenated aldehydes **101** in good yields and enantioselectivities.[58a] It is to be noted that in this case, the single electron transfert reagent, $FeCl_3$, is used in catalytic amounts and that molecular oxygen is the terminal oxidant, using sodium nitrate as mediator. MacMillan used

cerium ammonium nitrate (CAN) and an allyl silane reagant to construct a new C-C bond and generate the allylated aldehydes **103** in excellent yields and enantioselectivities.[58b]

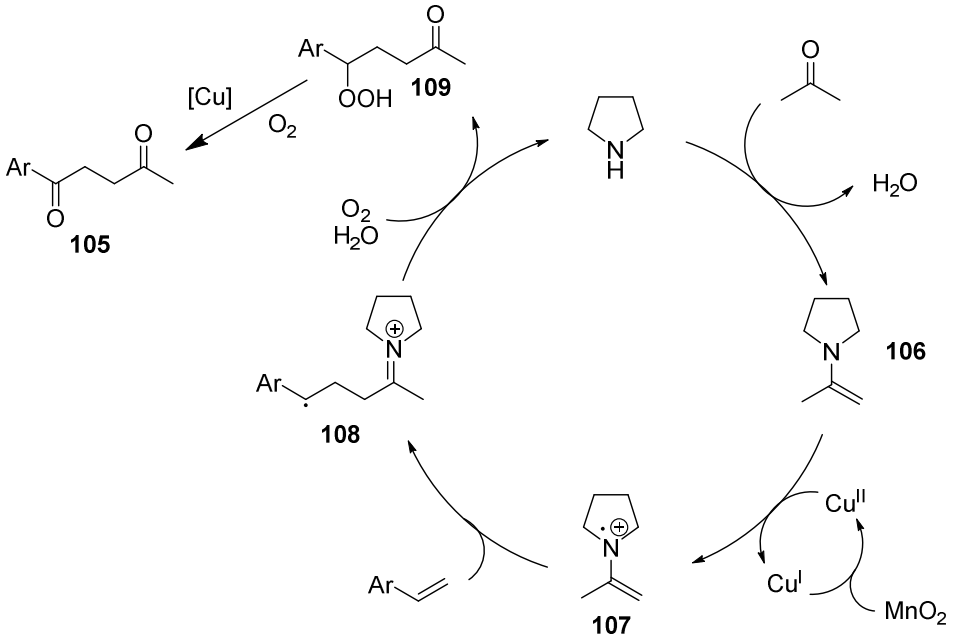


Scheme 2-36: First examples of SOMO activation of aldehydes.

This new mode of activation, complementary to the now classical iminium and enamine activation of carbonyls, was designated as SOMO catalysis.[58b] MacMillan later developed this chemistry to achieve a large number of enantioselective transformations of aldehydes.[59] Compared with aldehydes, only one example of use of a ketone was reported by MacMillan, presumably due to unsatisfactory levels of enantioinduction.[60] One report from Huang suggests that apart from this problem of enantioselectivity, reactivity of ketones using this mode of activation is satisfactory (Scheme 2-37).[61] Using a combination of pyrrolidine, $Cu(ClO_4)_2 \bullet 6H_2O$ as SET reagent and MnO_2 as terminal oxidant under an air atmosphere, a range of 1,4-dicarbonyls could be synthesised in moderate to good yields. In particular, simple ketones such as acetone could be used, in a much smaller excess (6 equivalents) than in previous methods, resulting in moderate product yields (see Scheme 2-35). The suggested mechanism of SOMO activation applied to this transformation is shown in Scheme 2-38.



Scheme 2-37: Synthesis of 1,4-dicarbonyls through SOMO catalysis.



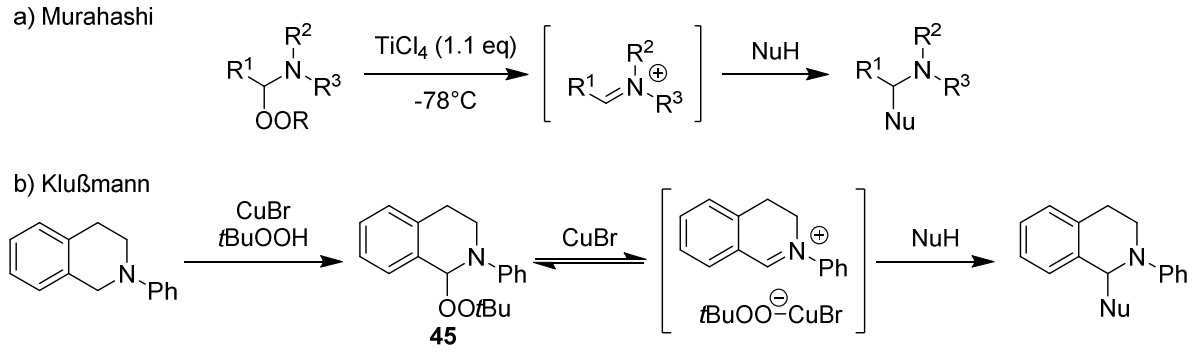
Scheme 2-38: Mechanism of synthesis of 1,4-dicarbonyls by SOMO activation of ketones.

The catalytic cycle starts with the formation of enamine **106** from the ketone substrate and the amine catalyst. Single electron oxidation of **106** provides the radical cation **107**, which after attack of styrene gives the benzylic radical **108**. Hydrolysis of the iminium and trapping of the radical by molecular oxygen affords hydroperoxide **109** and regenerates the amine catalyst. **109** then undergoes a metal mediated decomposition to give the final 1,4-dicarbonyl **105**.

3 OBJECTIVES OF THIS Ph.D. WORK

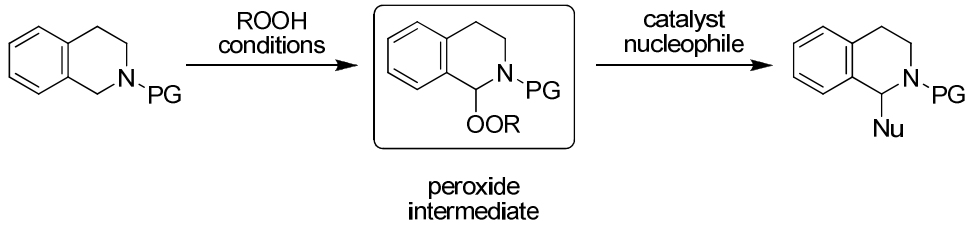
3.1 Validation of the CHIPs Concept: C-H Functionalization of Tertiary Amines

The first project of this dissertation is based on the seminal reports from Murahashi and the mechanistic studies conducted previously in the Klußmann group.[9, 23b, 23c] It was demonstrated in the early studies of Murahashi that under Lewis acid catalysis, peroxide intermediates such as **45** were precursors to iminium ions (Scheme 3-1, a).[9] These peroxides were also found to be intermediates in the tBuOOH mediated oxidative coupling reactions of tertiary amines from mechanistic studies previously performed in the Klußmann group (Scheme 3-1, b).[23b, 23c]



Scheme 3-1: Peroxides as precursors to iminium ions.

The first objective of this PhD work was to test the generality of this behaviour of peroxidic compounds and apply it to oxidative coupling chemistry: the C-H functionalisation *via* Intermediate Peroxides (CHIPs) concept. In order to confirm the generality of this concept, tetrahydroisoquinolines (THIQs) appeared as ideal test substrates, given the plethora of reports using this core structure for oxidative coupling chemistry (Scheme 3-2).

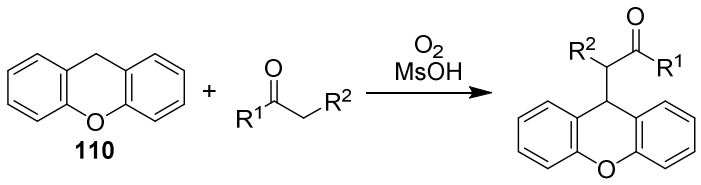


Scheme 3-2: Envisioned C-H functionnalisation *via* Intermediate Peroxides (CHIPs) of *N*-protected tetrahydroisoquinolines.

Besides the validation of this CHIPs concept, particular emphasis was put on the substitution pattern of the tertiary amine used. Most methods rely on an aromatic substituent on the nitrogen atom, but an easily removable protecting group would be much more synthetically useful. Efforts were therefore directed towards the use of *N*-protected THIQs as substrates in the attempt of overcoming current limitations in amine scope for this type of reaction.

3.2 Mechanistic Elucidation of the Autoxidative Coupling of Xanthene and Ketones

The second part of this work is dealing with a reaction developed earlier in the Klußmann group and discussed in section 2.2.1.[33] In this reaction, a benzylic compound, such as xanthene **110,** is coupled with carbon nucleophiles in an oxidative manner under Brønsted acid catalysis (Scheme 3-3).



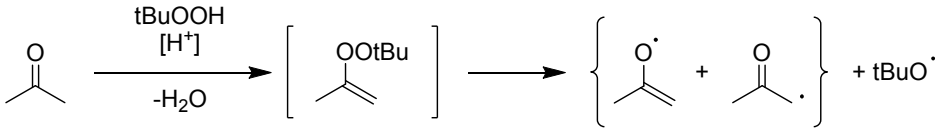
Scheme 3-3: General autoxidative coupling of benzylic compounds.

This reaction possesses several unique and attractive features for the future developpement of oxidative coupling chemistry. The most striking one is the complete absence of a red-ox active catalyst or of a synthetic oxidant and the use of a combination of a simple Brønsted acid and molecular oxygen instead. Because it was postulated to involve an autoxidation step, it was termed autoxidative coupling. However, the limitations in terms of scope were quite severe: mainly one type of pro-electrophile core structure was tolerated and nucleophiles other than ketones were difficult to use.

The second goal of this work was to perform detailed mechanistic studies of this reaction in order to understand its elementary steps and potentially overcome its current limitations.

3.3 Oxidative Generation of α-Carbonyl Radicals from Unactivated Ketones

During the mechanistic study of section 4.2, an intriguing mode of activation of ketones *via* the formation of alkenyl-peroxides and their decomposition to α-carbonyl radicals was discovered and rationalised (Scheme 3-4).



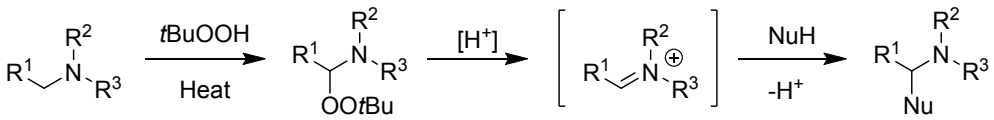
Scheme 3-4: Oxidative generation of α-carbonyl radical *via* alkenyl peroxide intermediates.

The final goal of this PhD work was to explore the synthetic utility of this new mode of activation and potentially develop novel reactions to synthetically valuable products.

4 RESULTS AND DISCUSSION

4.1 Metal-free C-H Functionalisation *via* Intermediate Peroxides of Tertiary Amines and Amides

Our investigations began with the study of the generality of the substitution of peroxide groups under acid catalysis (Scheme 4-1). We hypothesised that forming peroxides of type **111** without the involvement of a metal catalyst or reactant could be performed under thermal conditions. Homolytic cleavage of the hydroperoxide introduced would trigger a radical reaction leading to our desired target peroxide. Under acidic conditions, an iminium ion would be generated and trapped by a suitable nucleophile



111

Scheme 4-1: Desired metal-free C-H functionnalisation of tertiary amines *via* intermediate peroxides.

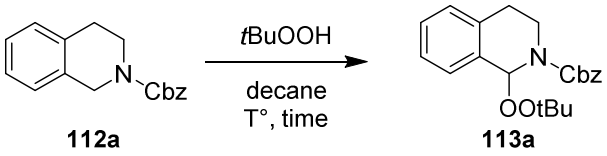
4.1.1 Investigations on the Thermal Formation of Tetrahydroisoquinoline Peroxides

We selected tetrahydroisoquinolines as model substrates based on the large number of literature reports using this core as substrate. However, as discussed in Section 2, most of the methods heavily rely on *N*-aryl substitution patterns to achieve reactivity. The synthetic utility of such substituents is low, and although subsequently reported,[62] at the time this work was conducted, no succesfull attemps to remove them had been reported. We decided to study a wider range of substituents, especially aiming at readily removable protecting groups. Therefore, *N*-Cbz tetrahydroisoquinoline **112a** was selected as starting point for our investigations (Table 4-1).

Pleasingly, compound **113a** was indeed formed when **112a** was allowed to react with three equivalents of tBuOOH at 80°C for 48 hours in a 66% isolated yield (entry 1). Increasing the temperature gradually to 105°C showed an increase of yield from 66% to 73% (entries 1 to 4) and a parallel reduction of reaction times from 48 hours to 4 hours was observed. Further increase of the reaction temperature was detrimental to the isolated yield

as shown by the result at 120°C where full conversion was observed in 2 hours 15 minutes but the yield dropped to 67%. Optimal temperature being identified, the amount of hydroperoxide was varied next. When two equivalents of tBuOOH were used instead of three, a sharp reduction of yield was observed (37%, entry 7), while increasing it to four equivalents had no effect (entry 8). Finally the reaction could be performed without any additional decane as solvent without any detrimental effect on the yield and only a reduced reaction time (entry 9). It is to be noted that this reaction could be performed on a gram scale without any difference in yield or reaction time.

Table 4-1: Optimisation of thermal formation of peroxide **113a**[a]

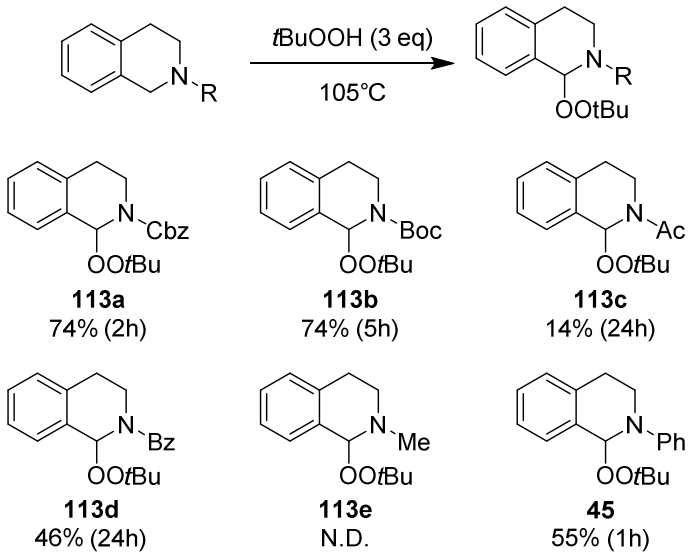


112a **113a**

Entry	T (°C)	Time (h)	*t*BuOOH (equiv)	Yield (%)
1	80	48	3	66
2	90	28	3	65
3	100	8	3	72
4	105	4	3	73
5	110	4	3	70
6	120	2:15	3	67
7	105	4	2	37
8	105	4	4	73
9[b]	105	2	3	74[c] ; 73[d]

[a] Standard conditions: 1a (1 mmol), *t*BuOOH (5.5 M in decane), decane (0.92 M concentration). [b] no additional decane. [c] average of 5 experiments. [d] performed on a 1.068 g scale.

The scope of formation of peroxides was then explored using these optimised conditions (Scheme 4-2). Carbamate substituted peroxides **113a** and **113b** were formed in identical yields of 74%, however the Boc analoge **113b** required a longer reaction time of 5 hours. An acetyl substituent gave poor results and only 14% of **113c** were isolated after 24 hours, while a benzoyl group afforded an acceptable 46% of **113d** after 24 hours. *N*-methyl tetrahydroisoquinoline was not tolerated under these conditions and peroxide **113e** was not observed, only overoxidation products. Finally, peroxide **45** was very quicky formed with full consumption of the parent amine observed after one hour but only isolated in a moderate 55% yield.



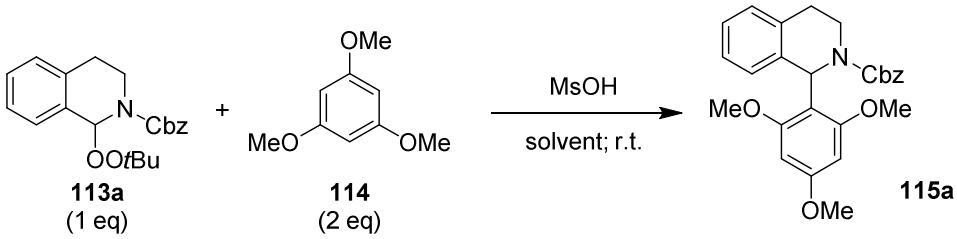
Scheme 4-2: Scope for the formation of *N*-substituted tetrahydroisoquinoline peroxides.

If compounds **113a** and **113b** proved to be surprisingly stable to isolation by column chromatography and storage, it was not the case for others, particularly **45**, which spontaneously decomposed over time. Additionaly, the carbamate substituted amines gave clean and fast reactions while other substrates generally led to several byproducts and longer reaction times.

4.1.2 Optimisation of the Peroxide Substitution Step

Having synthesised a range of tetrahydroisoquinoline peroxides, we explored the substitution of the peroxide unit by a suitable nucleophile with methane sulfonic acid as catalyst. For this purpose, 1,3,5-trimethoxybenzene **114** was selected as model nucleophile and Cbz substituted peroxide **113a** as model electrophile (Table 4-2). Pleasingly, substitution product **115a** was obtained both in toluene and dichloromethane as solvents, albeit in modest yields (entries 1 and 2, 43% and 37%, respectively). Surprisingly, even after prolonged reaction times, full conversion of the starting peroxide was never observed and a similar 46% yield was obtained (entry 3), suggesting a potential deactivation of the acid catalyst. Increasing the amount of acid was benefitial to conversion and yield (entries 4 and 5, 48% and 69%, respectively) but a stoichiometric amount of acid was required to achieve full conversion (entry 6, 57%) at the expense of the yield of product. Based on the assumption of a deactivation of the acid catalyst, it was added in two portions. This resulted in a better 57% yield than when the same amount of acid was added in a single portion (entry 7 compared to entry 4).

Table 4-2: Optimisation of the substitution step:



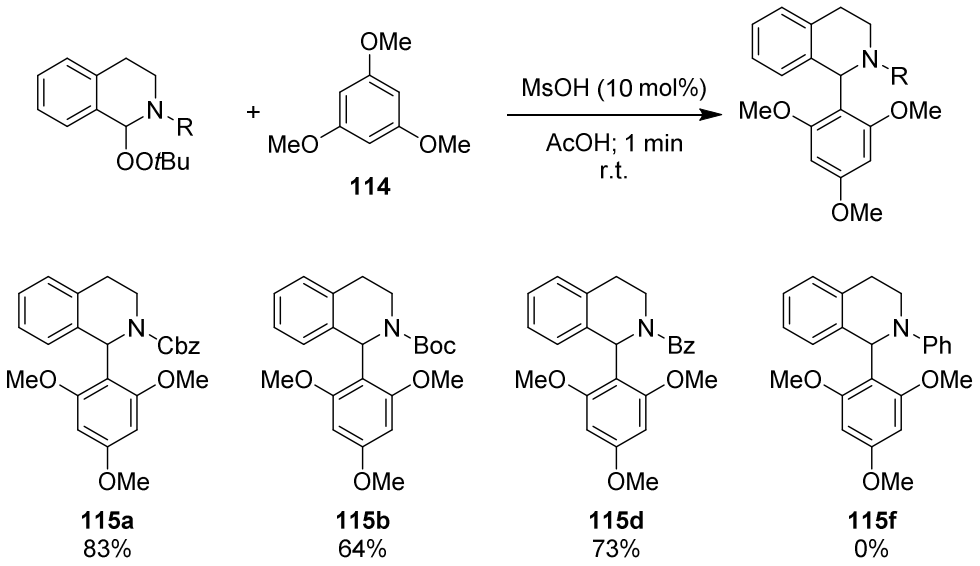
113a (1 eq) + **114** (2 eq) → **115a**

Entry	Solvent	MsOH (mol%)	Time	Yield (%)
1	toluene	10	3h	43
2	DCM	10	1h	37
3	toluene	5	48h	46
4	toluene	20	48h	48
5	toluene	50	48h	69
6	toluene	100	1h	57
7	toluene	20[a]	5h	57
8	toluene	10	18h[b]	41
9	toluene	10	18h[c]	41
10	toluene	10	1h30[d]	57
11	AcOH	10	~1min	83
12	AcOH	-	18h	46
13	AcOH	10	~1min	83[e]

[a] MsOH was added in 2 portions, 3 hours apart [b] 10% of MnO_2 was added [c] 1eq of TBHP was added [d] 5eq of AcOH were added [e] 1 eq of **114** used

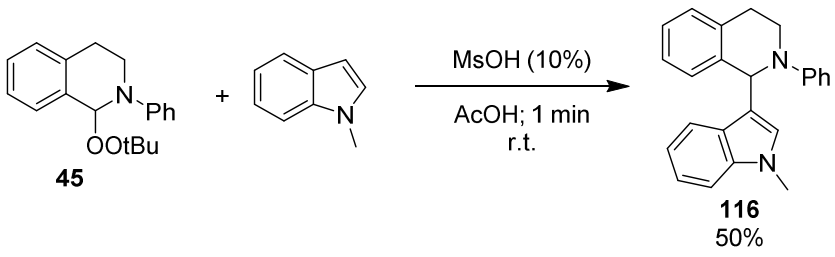
The effect of the *t*BuOOH released during the substitution was then studied. Adding MnO_2 to decompose any hydroperoxide formed did not have any effect on the yield (entry 8, 41%) as well as adding a full equivalent of *t*BuOOH at the beginning of the reaction (entry 9, 41%). This suggested that *t*BuOOH released in the reaction mixture had no detrimental effect on the reaction outcome. Acetic acid was then used as an additive on the assumption of acid deactivation over time. Indeed, the yield was improved when 5 equivalents of acetic acid were added (entry 10, 57%). A dramatic change was observed when the reaction solvent was changed to acetic acid (entry 11). Full conversion was achieved upon addition of methane sulfonic acid and the coupling product was isolated in 83% yield. In the absence of methane sulfonic acid, acetic acid could still promote the substitution but at a significantly reduced rate, affording only a 46% yield after 18 hours (entry 12). Finally, one equivalent of nucleophile could be used without any detrimental effect (entry 13, 83%).

The generality of the reaction and the influence of the substitution on the nitrogen atom was then studied with the previously synthesised peroxides (Scheme 4-3).



Scheme 4-3: Scope of the formation of *N*-substituted tetrahydroisoquinoline peroxides.

As seen in Table 4-2, product **115a** was formed in good 83% yield, while its Boc analogue **115b** showed a reduced 64% yield. *N*-Bz substituted product **115d** was obtained in a satisfactory 73% yield while product **115f**, bearing a phenyl substituent was not obtained even after 24 hours. To confirm that this absence of reactivity is due to a lack of electrophilicity of the resulting iminium ion, *N*-methyl indole was employed as a nucleophile (Scheme 4-4)



Scheme 4-4: Coupling of **45** with *N*-methyl indole.

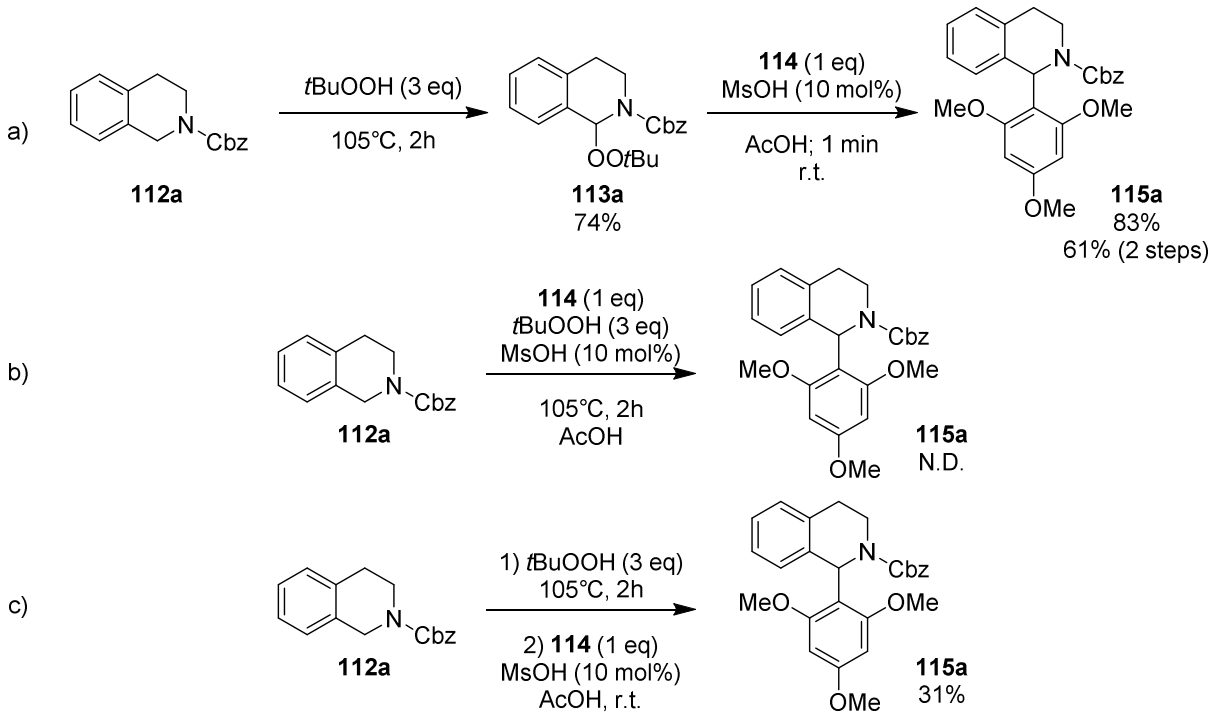
As can be seen, the coupling product **116** could be obtained in 50% isolated yield under the previously optimised conditions. This corroborates the generality of the peroxide substitution process and is in agreement with a lower electrophilicity of the corresponding iminium ion, which was estimated before.[23c]

As discussed earlier, carbamates are especially interesting because of their ease of removal. Additionaly, their corresponding peroxides are easily formed under our

optimised conditions and give higher yields in the substitution step than their amide or alkyl analogues. Therefore the Cbz group was selected for further studies on this transformation.

4.1.3 Attempts for Alternative Procedures

In terms of praticality, a two step protocol is far from ideal, therefore we tried to combine these conditions to start from the non activated tetrahydroisoquinolines **112a** (Scheme 4-5).



Scheme 4-5: Comparison of alternative procedures for metal-free C-H functionnalisation of tetrahydroisoquinolines.

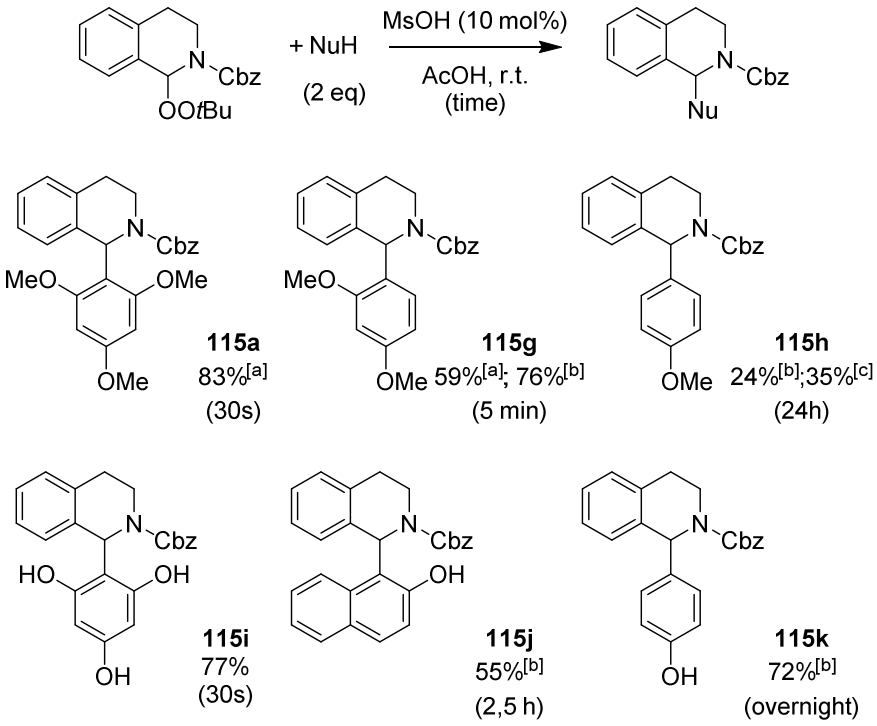
As can be seen, the two step procedure affords the desired coupling product in 61% overall yield (Scheme 4-5, a). When it was attempted to directly combine the developed conditions for the separate steps, only a trace of the desired product could be detected (Scheme 4-5, b). This might be attributed to undesirable oxidation of the nucleophile under these relatively harsh reaction conditions. Finally, when the reaction was performed in a one-pot, two-step fashion, a lower overall yield of 31% was obtained and a more difficult isolation of the coupling product resulted (Scheme 4-5, c).

Even though the two step procedure has some inherent disadvantages such as an additional purification step required, it was superior to the alternatives tested in terms of

overall yields. Therefore it was selected to study the nucleophile scope of this reaction.

4.1.4 Exploration of the Nucleophile Scope of the Reaction

In order to investigate the nucleophile scope, a series of diverse nucleophiles were selected. Initial screening of electron rich arene nucleophiles was performed, as shown in Scheme 4-6.

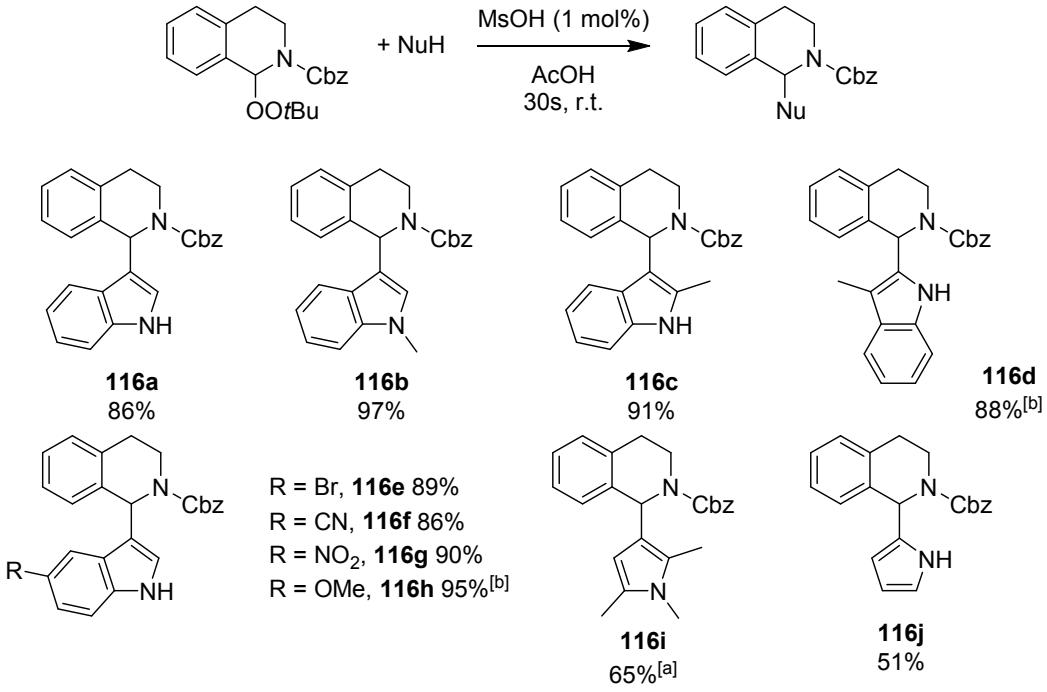


Scheme 4-6: Arenes as nucleophiles, [a] 1 equivalent of nucleophile, [b] 50°C, [c] yield based on recovered starting material.

While trimethoxybenzene reacted smoothly under the previously optimised conditions, weaker nucleophiles required heating and two equivalents to afford moderate to good yields. Coupling product **115g** was obtained in a moderate 59% yield under the optimised conditions. When the same reaction was performed with two equivalents of nucleophile and at 50°C, 76% of **115g** was obtained. Even anisole was a suitable nucleophile and gave 24% of **115h**. Althought this yield is quite low, it is still remarkable, as comparable coupling reactions with anisole have not been reported previously at such a low temperature.[31, 63] It should also be noted that full conversion was not achieved in this case and that the unreacted peroxide could be reisolated from the reaction mixture. A 35% yield based on the recovered starting material was then obtained. This result can be attributed to

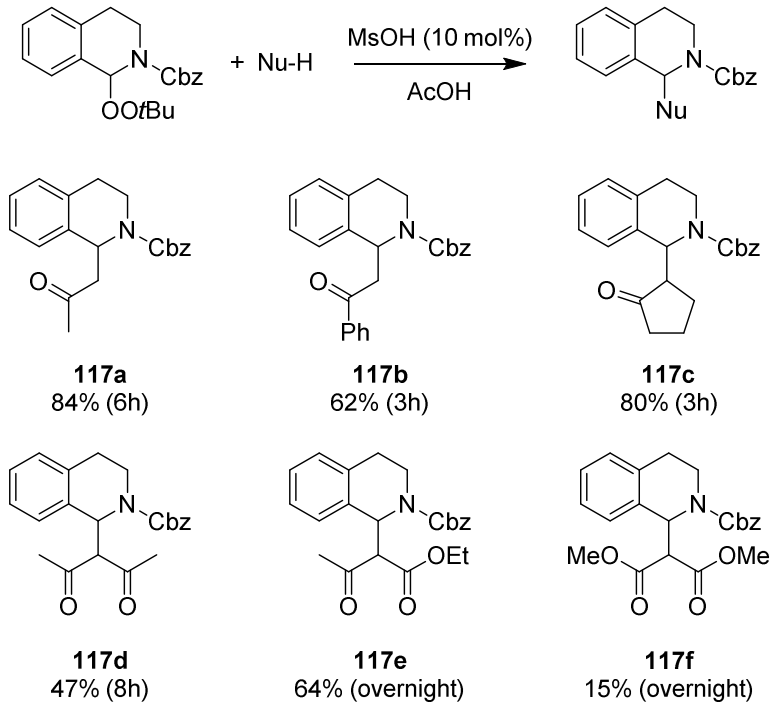
the weaker nucleophilicity of anisole as compared to the equivalent of *t*BuOOH released, which can continuously regenerate peroxide **113a** from the iminium intermediate under the reaction conditions, thus preventing full conversion. Phenol derivatives were more reactive than their methoxy analogues. Phloroglucinol gave product **115i** in a satisfaying 77% yield at room temperature. 2-Naphthol and phenol needed 50°C to give products **115j** and **115k** in 55% and 72%, respectively. In the case of phenol, a regioisomer resulting from addition on the *ortho*-position was also observed in small amounts (8% yield).

Pleasingly, with indoles and pyrroles as nucleophiles, the acid loading could be reduced to 1 mol% (Scheme 4-7). In almost all cases, the reaction was complete upon addition of the catalyst and gave excellent yields. Unsbstituted indoles as well as indoles bearing methyl substituents in different positions gave products **116a** to **116d** in yields from 86% to near quantitative yield. Substitution on the 5-position of the indoles showed no significant effect on the outcome of the reaction. Electron poor indoles (**116e** to **116g**) gave yields of 86% to 90% while electron rich 5-methoxyindole gave **116h** in an excellent 95% yield. Surprisingly, **116d** and **116h** both needed 30 minutes to achiveve full conversion of starting materials but still gave excellent results. Trisubstituted pyrrole gave a satisfaying 65% yield of **116i** while unsubstituted pyrrole gave **116j** in 51% yield.



Scheme 4-7: Heteroarenes as nucleophiles; [a] 15 minutes reaction time, [b] 30 minutes reaction time.

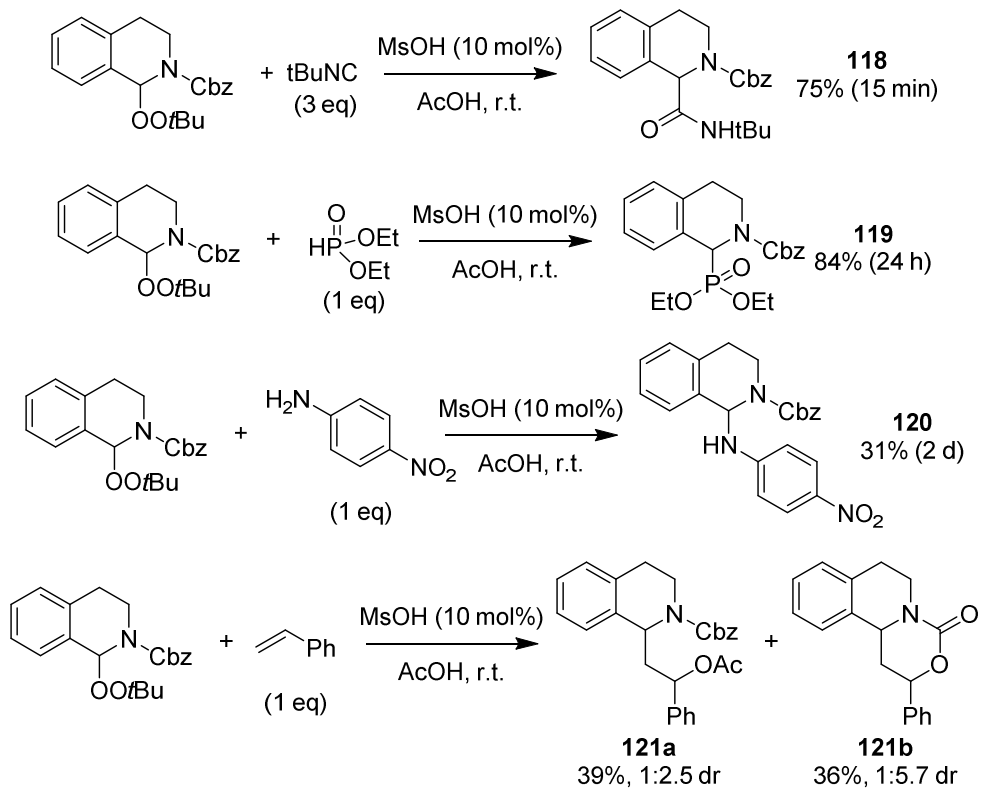
With a good understanding of the addition of arene addition to **113a**, alternative nucleophiles were screened. Carbonyl nucleophiles were then evaluated under optimised conditions (Scheme 4-8). In general, 5 equivalents of nucleophile had to be used in order to prevent double substitution products to be formed in significant amounts. Simple ketones such as acetone (**117a**, 84%), acetophenone (**117b** , 62%) and cyclopentanone (**117c**, 80%) gave good yields of the corresponding coupling products. 1,3-Dicarbonyl compounds were also found to be competent nucleophiles for this transformation as exemplified by acetyl acetone (**117d**, 47%) and ethyl acetoacetate (**117e**, 64%). Disappointingly, dimethyl malonate only gave a poor 15% yield of product **117f**.



Scheme 4-8: Carbonyl containing compounds as nucleophiles.

The reactivity of **113a** was also tested towards less common nucleophiles (Scheme 4-9). An isocyanide nucleophile allowed the formation of the amincoacid derivative **118** in a good 75% yield after a short time. Carbon-heteroatom bonds could also be formed under these conditions. Diethyl phosphite was a good nucleophile and gave product **119** in 84% yield after 24 hours of reaction. *Para*-nitro aniline afforded the corresponding hemiaminal **120** in a modest 31% yield after two days. The reaction with styrene proved to be more sluggish than under the conditions reported by the group of Mancheño.[27] Indeed, the desired tricyclic compound **121b** was obtained in 36% yield but at the same time, the

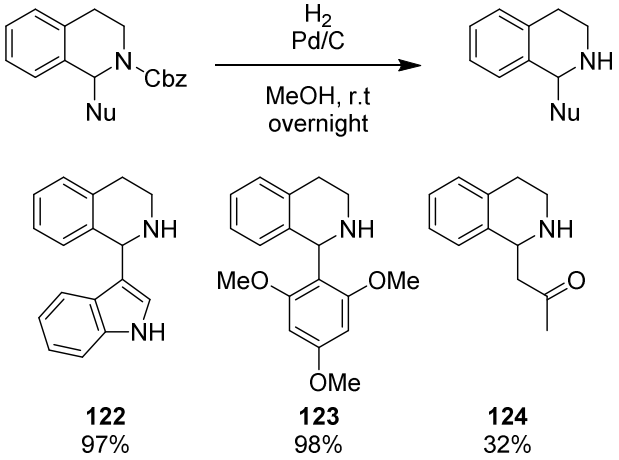
acetate **121a** was isolated from the mixture in a 39% yield.



Scheme 4-9: Miscalaneous nucleophiles.

4.1.5 Deprotection of Coupling Products

The deprotection of selected coupling products was performed to check the possiblity of further modification of our products and the synthetic utility of our method (Scheme 4-10).

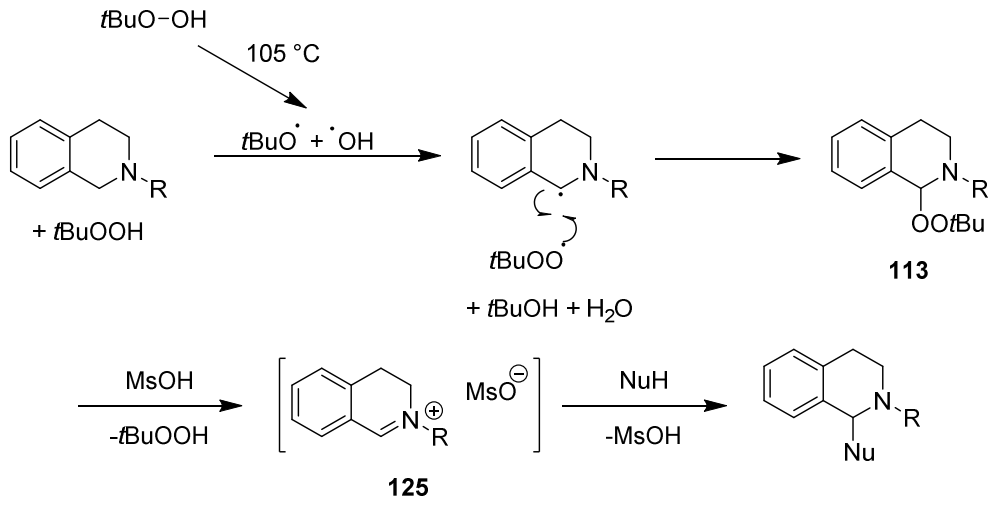


Scheme 4-10: Deprotection of selected coupling products.

As could be expected from the hydrogenation of a Cbz group, nearly quantitative and clean deprotection was achieved for products **115a** and **116a**, affording products **122** and **123** in 97% and 98% yield, respectively. By contrast, and perhaps not surprisingly, product **124** was found to be unstable and could only be obtained in 32% yield, presumably through retro-Michael reactions and further degradation under hydrogenation conditions.

4.1.6 Mechanistic Considerations

The reactivity of **113a** under our developed reaction conditions is very similar to previous reports using substrates bearing a similar substitution pattern[20, 27, 64] therefore it is fair to assume that a common intermediate is involved in all these reactions. The most suitable candidate for this is the classically postulated iminium ion **125**. In previous mechanistic studies conducted in the Klußmann group on *N*-phenyl tetrahydroisoquinoline **112f**, the lowest nucleophilicity parameter *(N*) of nucleophiles reacting with the corresponding iminium ion was found to be 3.8,[23c] in terms of Mayr's nucleophilicity scale.[65] In the case of the Cbz substituted tetrahydroisoquinoline, the lowest value was found to be -1.2 for anisole.[66] This implies that the electrophilicity of the corresponding iminium ion is approximately 5 orders of magnitude higher than its *N*-phenyl analogue.



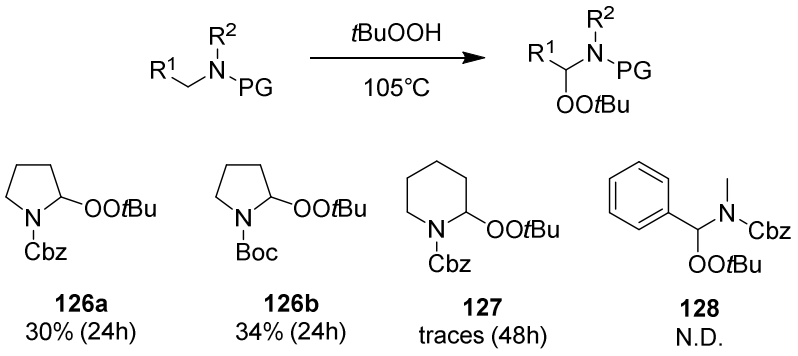
Scheme 4-11: Proposed reaction mechanism.

The postulated reaction mechanism is shown in Scheme 4-11. Homolytic cleavage of the peroxide bond in *t*BuOOH under thermal conditions leads to the formation of *t*BuO• and HO• radicals. By abstracting a hydrogen atom from the starting material and another equivalent of *t*BuOOH, *t*BuOO• radicals and a carbon centered radical are formed. Upon

recombination, these two radicals afford the peroxide **113**. The high selectivity to the peroxide, and the absence of the corresponding ether, has been reported before for related radical reactions, and can be rationalised by the persistent radical effect.[67] The *t*BuOO• radical is persistent,[67d] meaning it has a relatively long lifetime under reaction conditions. The carbon centered radical on the other hand is very reactive and therefore transient: its lifetime is significantly shorter than that of *t*BuOO•. Therefore, during the course of the reaction, an excess of *t*BuOO• radicals is present in solution and a selective recombination of the transient radical with the persistent radical is achieved. As an alternative to this hydrogen atom transfer mechanism, a mechanism involving single electron transfers and proton transfer, as described by Doyle and discussed in section 2.1.4 (see Scheme 2-14),[30] cannot be ruled out. In the second step, activation of the peroxide moiety by methane sulfonic acid generates iminium ion **125** and release one molecule of *t*BuOOH. The reactive iminium ion is then trapped by a suitable nucleophile to afford the desired coupling products.

4.1.7 Extension of Substrate Scope Beyond Tetrahydroisoquinolines

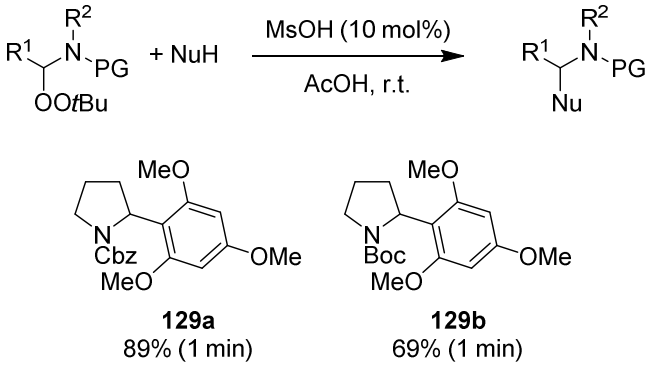
While C1 substituted tetrahydroisoquinolines are often found in natural products and pharmaceuticals,[68] extending the field of oxidative coupling of tertiary amines to other types of structures is still a challenge and examples remain very scarce.[5a, 6c, 6f, 6g, 6k, 69] For this purpose, we explored the possibility of using less common starting materials for the formation of peroxides under our optimised conditions (Scheme 4-12)



Scheme 4-12: Formation of more challenging peroxides.

As can be seen, the substrates tested were generally less reactive than *N*-Cbz tetrahydroisoquinoline and the corresponding peroxides obtained in much lower yields, if at all. Carbamate protected pyrrollidines afforded peroxides **126a** and **126b** in similar yields of

30% and 34% respectively. *N*-Cbz piperidine was however not suitable and the corresponding peroxide **127** was only detected in trace amounts. Similarly, acyclic peroxide **128** was not detected in the reaction mixture. Nevertheless, the substitution step was investigated for peroxides **126a** and **126b** (Scheme 4-13).



Scheme 4-13: Substitution of pyrrolidine derived peroxides.

Very similar results were obtained to that of tetrahydroisoquinolines. In both cases, the substitution occurred very quickly and cleanly to afford the coupling products **129a** and **129b** in 89% and 69% yield, respectively. The same trend as before was observed with the superiority of the Cbz protecting group in terms of yield of substitution. A conclusion from these reactions can be that the oxidation step is the crucial problem in this type of oxidative coupling chemistry and the real challenge to be met. Once the iminium ion or one of its precursors is formed, the nucleophilic addition is not a problem and will occur with a wide range of suitable nucleophiles.

4.1.8 Concluding Remarks

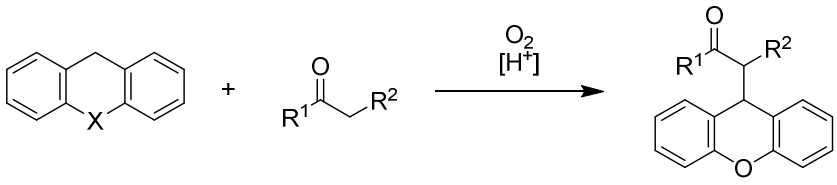
As discussed in this chapter, the concept of utilizing a peroxide group as a leaving group has been further demonstrated and could pave the way to hitherto unexplored reactivity.[I] This approach is especially attractive if the formation of the peroxide intermediate and its substitution can be achieved under the same conditions, with the same catalytic system. The reaction presented here has the advantadges of not involving any metal based catalyst in the whole process and being able to convert usefully protected amines, a feature lacking to many of the reported methods.

[I] PhD dissertation of Naeem Gulzar at Köln university, expected for 2014.

It is however far from being ideal. The main drawback is obviously the step-wise nature of the process and the need to isolate an intermediate peroxide. This results in the handling of potentially explosive materials in pure form, preventing its use on large scale. More challenging, but perhaps more synthetically valuable, amines such as pyrrolidines are only poorly tolerated in the oxidation step. This is however a common trait of the all the reported methods and explains the extensive use of the tetrahydroisoquinoline and isochromane structures as model substrates in studies of this type of reaction. Even though the overall yields are still relatively low, to the best of our knowledge this represents the first example of oxidative coupling of protected amines using Brønsted acids and shows a promising starting point for the further development of oxidative coupling of amines. This holds particular potential in light of the information gathered in the next chapters and the preliminary results which will be discussed in section 4.2.9.

4.2 Mechanism Elucidation of the Autoxidative Coupling of Xanthene

As discussed in section 2.2.1, our group recently reported an unusual oxidative coupling reaction of benzylic compounds and carbonyl nucleophiles in the presence of catalytic amounts of a strong Brønsted acid and using only molecular oxygen as oxidant (Scheme 4-14).[33]



Scheme 4-14: Autoxidative coupling of xanthene with ketone nucleophiles.

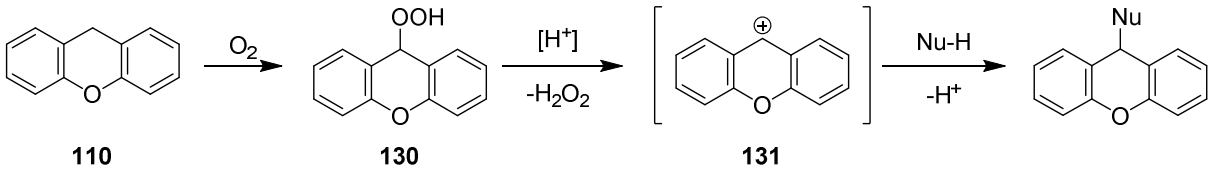
Although unique in terms of reactivity and catalytic system used, the limitation in terms of scope were quite severe. Mainly xanthene (X = O) and acridanes (X = NR) were tolerated as the electrophilic component while originally only ketones were found to be suitable nucleophiles. The goal of this project was to elucidate the mechanism of the autoxidative coupling reactions in the hope that understanding its elementary steps could provide an explanation for these limitations and a handle to overcome them.

The results summarized section 4.2.1 as well as some preliminary kinetic studies were originally obtained by Dr. Áaron Pintér, Dr. Abishek Sud and Dr. Devarajulu Sureshkumar. Most of these results were later repeated and confirmed during the course of this PhD work. The data obtained during this PhD work are presented in this dissertation.

4.2.1 Preliminary Mechanistic Considerations and Previous Results

This reaction possesses several interesting and unusual features in the field of oxidative coupling chemistry, the most striking one being the absence of a red-ox active catalyst. The involvement of trace metal impurities was investigated and found to be very unlikely.[33a] Indeed, performing the reaction in a glass apparatus without any contact with metal surfaces such as needles, the reaction still proceeded in the same manner. When subjected to trace element analysis, this reaction mixture showed no trace of transition metals above the detection limit of 0.5 ppm. In fact, it was found that metal salts,

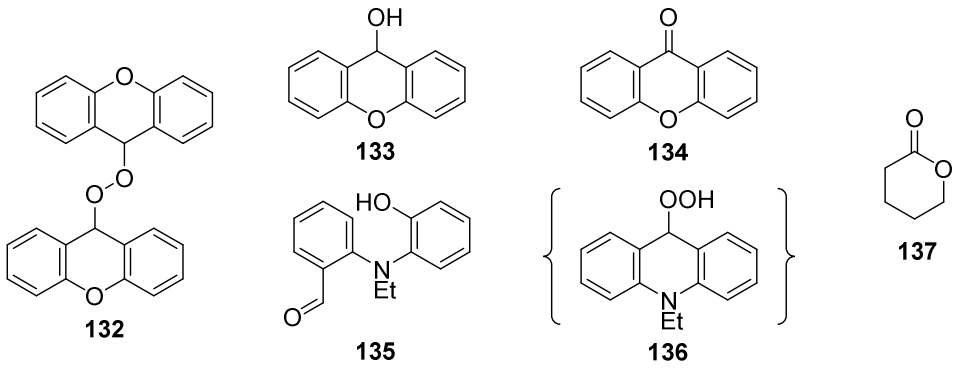
particularly iron and copper - the use of which was initially intended - inhibited the reaction as compared to the use of only a Brønsted acid, such as methane sulfonic acid, suggesting that a metal is most likely not involved in the mechanism. The initial mechanistic proposal reported in the seminal publication is as follows (Scheme 4-15).[33a]



Scheme 4-15: Postulated mechanism of the autoxidative coupling of xanthene.

The first step involves the activation of xanthene **110** through an autoxidation process (see section 2.2) to afford xanthene hydroperoxide **130**. Under acidic conditions, formation of the highly stabilised carbocation **131** is triggered by the loss of H_2O_2. This cation is then trapped by a suitable nucleophile, in most cases the enol form of a ketone used as solvent to afford the desired coupling product.

Several experimental facts pointed at the mechanism described in Scheme 4-15, such as the byproducts isolated from some reaction mixtures (Scheme 4-16).



Scheme 4-16: Isolated side products suggesting the presence of hydroperoxides

Indeed, even though hydroperoxide **130** itself was never isolated or even detected in reaction mixtures, peroxide **132** was isolated in small amounts from a reaction performed with trifluoroacetic acid as catalyst and is most likely a secondary product of combination of **130** and the cation **131**. Similarly, xanthone **134** was seen in almost all experiments and is most likely a secondary product originating from the decomposition of

130 as is commonly observed in autoxidation reactions.

When *N*-ethyl acridane was oxidatively coupled to cyclopentanone using triflic acid as catalyst, **135** could be isolated from the reaction mixture along with the desired coupling product. This product indirectly proves the presence of hydroperoxide **136**, which underwent a Hock rearrangement under acidic conditions.[70]

Another strong indication for the presence of hydroperoxides in our reaction mixtures was the observation that cyclopentanone was converted to valerolactone **137** under the reaction conditions through a Bayer-Villiger oxidation.

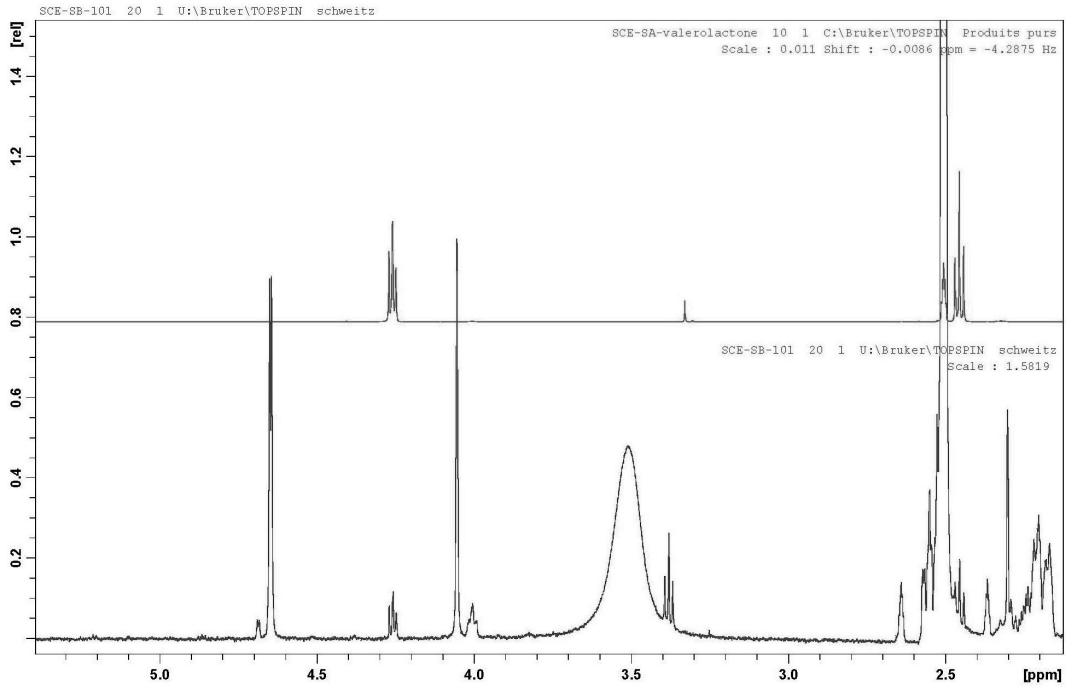


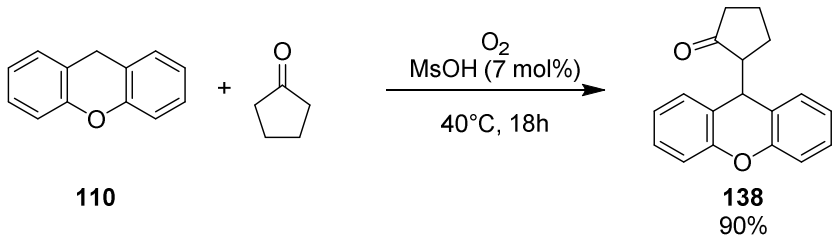
Figure 4-1: ^{1}H NMR spectrum of a crude reaction mixture (bottom) and valerolactone (top) in d6-DMSO

Close examination of the ^{1}H NMR spectrum of a crude reaction mixture (Figure 4-1) showed the presence of valerolactone **137** in approximately 25% yield (based on **110**) resulting from a Bayer-Villiger oxidation of cyclopentanone. Both triplets of **137** at 4.26 ppm and 2.47 ppm are clearly visible in the spectrum.

4.2.2 Investigation of the Separate Postulated Steps

For further studies of this reaction in the course of this PhD work, the reaction of xanthene **110** and cyclopentanone was selected as a model system. Indeed, the reaction is highly reproducible and gives high yield of coupling product **138** in a reasonable time (Scheme 4-17). Furthermore, yields are conveniently determined utilising ^{1}H NMR

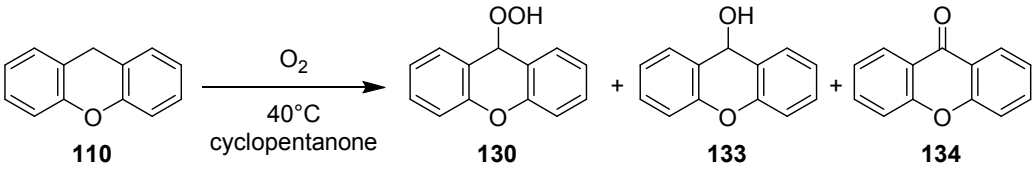
spectroscopy (see experimental part 7.3.1 for details).



110 **138** 90%

Scheme 4-17: Standard autoxidative coupling of xanthene and cyclopentanone.

When **110** was subjected to reaction conditions in the absence of an acid catalyst, rapid full conversion to oxygenated products was observed in about 24 hours. Hydroperoxide **130** was the major product and decomposed over time to secondary products xanthydrol **133** and xanthone **134** (Figure 4-2).



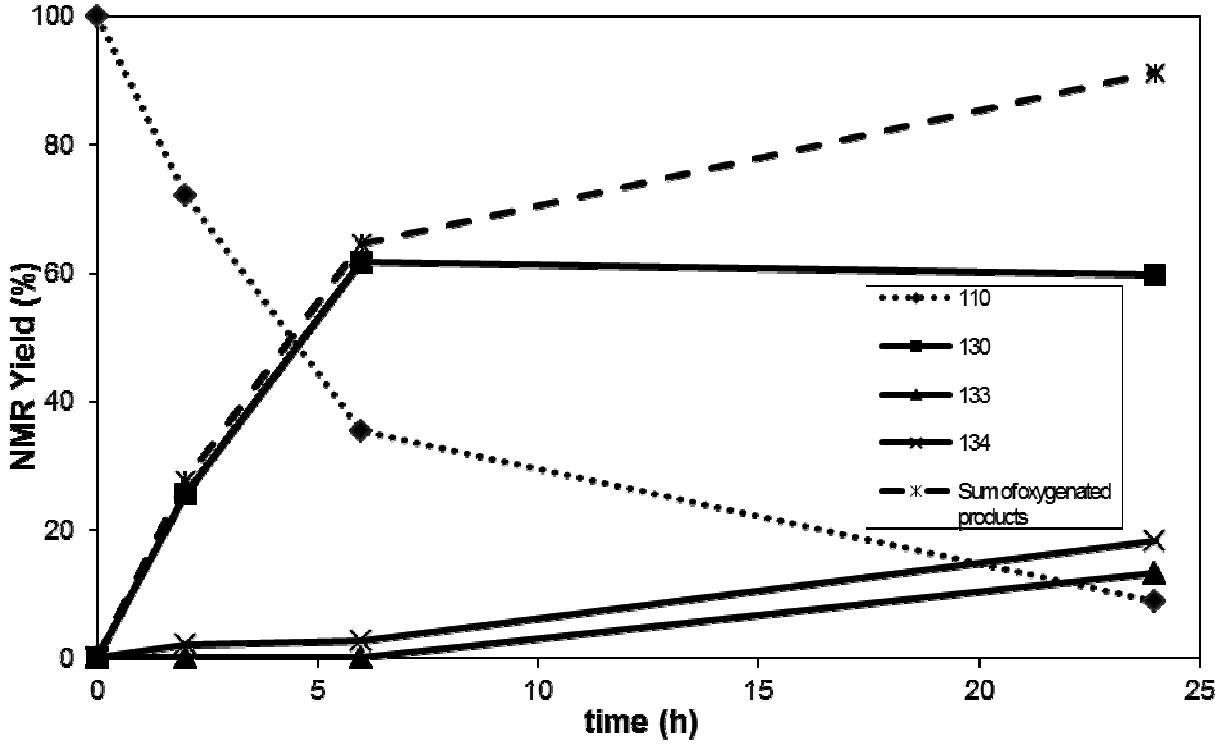
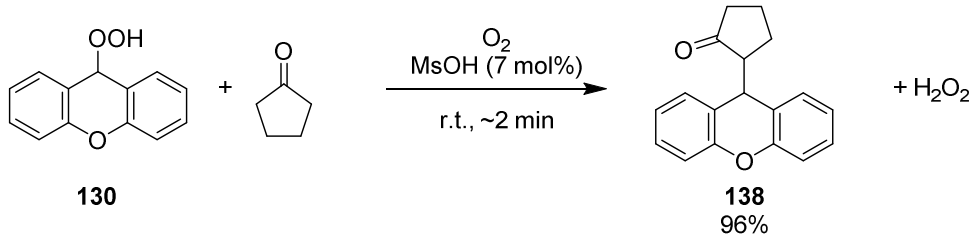


Figure 4-2: Representative example of oxygenated products of xanthene under autoxidation conditions, yields determined by NMR spectroscopy as described in section 7.3.1.

The selectivity for hydroperoxide **130** remained very high even at rather high

conversion (60% conversion, 95% selectivity) but secondary products started to appear upon longer reaction times. Kinetic data clearly show that **133** and **134** are products arising from the decomposition of **130** under reaction conditions and not formed through an alternative oxidation pathway. It was therefore fair to assume that such an autoxidation would also occur in the presence of an acid catalyst and **130**, the postulated precursor to **131** was also subjected to reaction conditions (Scheme 4-18).



130 **138** 96%

Scheme 4-18: Conversion of **130** to **138** under Brønsted acidic conditions, yield determined by NMR spectroscopy as described in section 7.3.1.

In less than two minutes, hydroperoxide **130** was converted to the coupling product **138** in essentially quantitative yield at room temperature, releasing one equivalent of H_2O_2. In collaboration with Dr. Philipp Schulze, hydrogen peroxide could be detected from the reaction of Scheme 4-18 via UV-Vis spectroscopy after reaction with K_2CrO_4 (see section 7.3.3 for experimental details).

At this stage of our mechanistic study, all results supported the mechanism shown in Scheme 4-15 and as a final confirmation, we decided to check the kinetics of the reaction. Indeed, our postulated mechanism involved two distinct steps, a slow rate determining autoxidation and a fast ionic substitution of the intermediate hydroperoxide. The obtained results were very different from those expected (Figure 4-3).

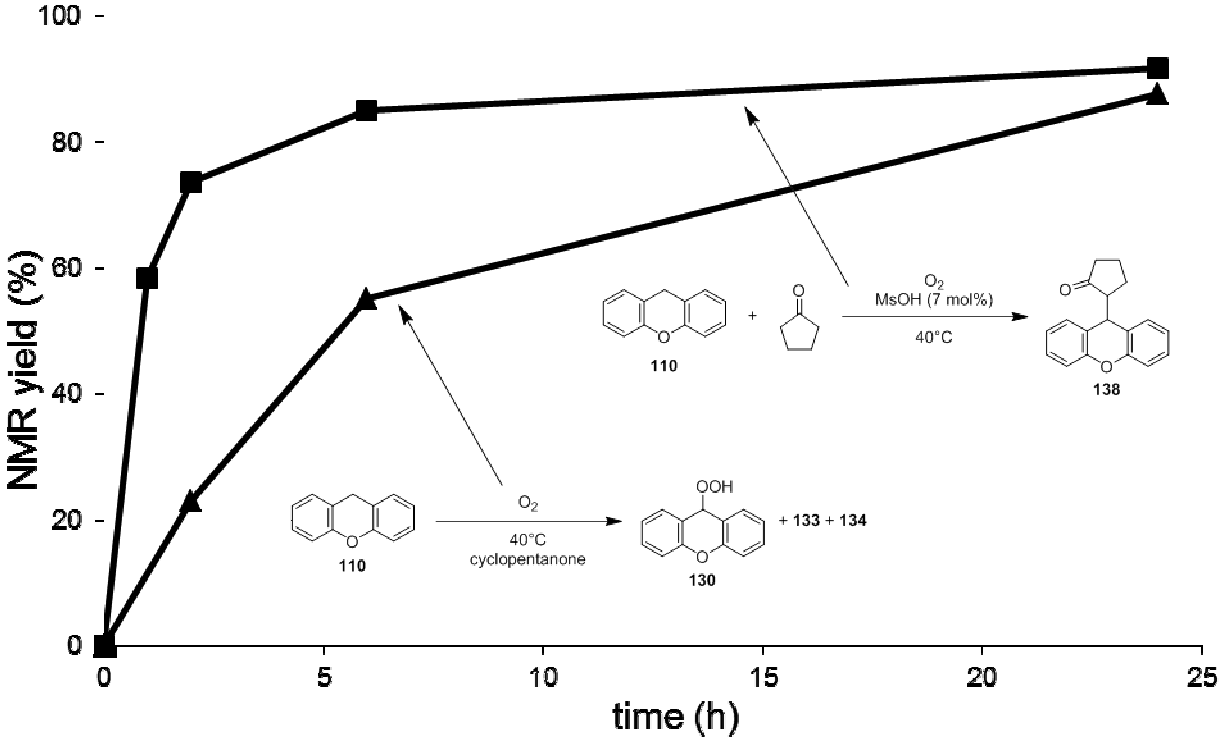


Figure 4-3: Comparison of reaction rates: autoxidative coupling (squares) and autoxidation (triangles), yields determined by NMR spectroscopy as described in section 7.3.1.

Surprisingly, when the autoxidation rate was compared to the rate of the overall reaction of Scheme 4-17, it was found that it was significantly *slower*. This result suggests that another factor is influencing the kinetics of the autoxidation process, that we overlooked a secondary pathway or that a completely different reaction mechanism is taking place. Additionaly, contrary to what would be expected, hydrogen peroxide was not present in detectable amounts during or after completion of the reaction. Therefore we decided to study the autoxidation process into more detail.

4.2.3 Solvent Effects on the Autoxidation of Xanthene

We initially studied the autoxidation of **110** separately and realised its very strong solvent dependence (Figure 4-4).

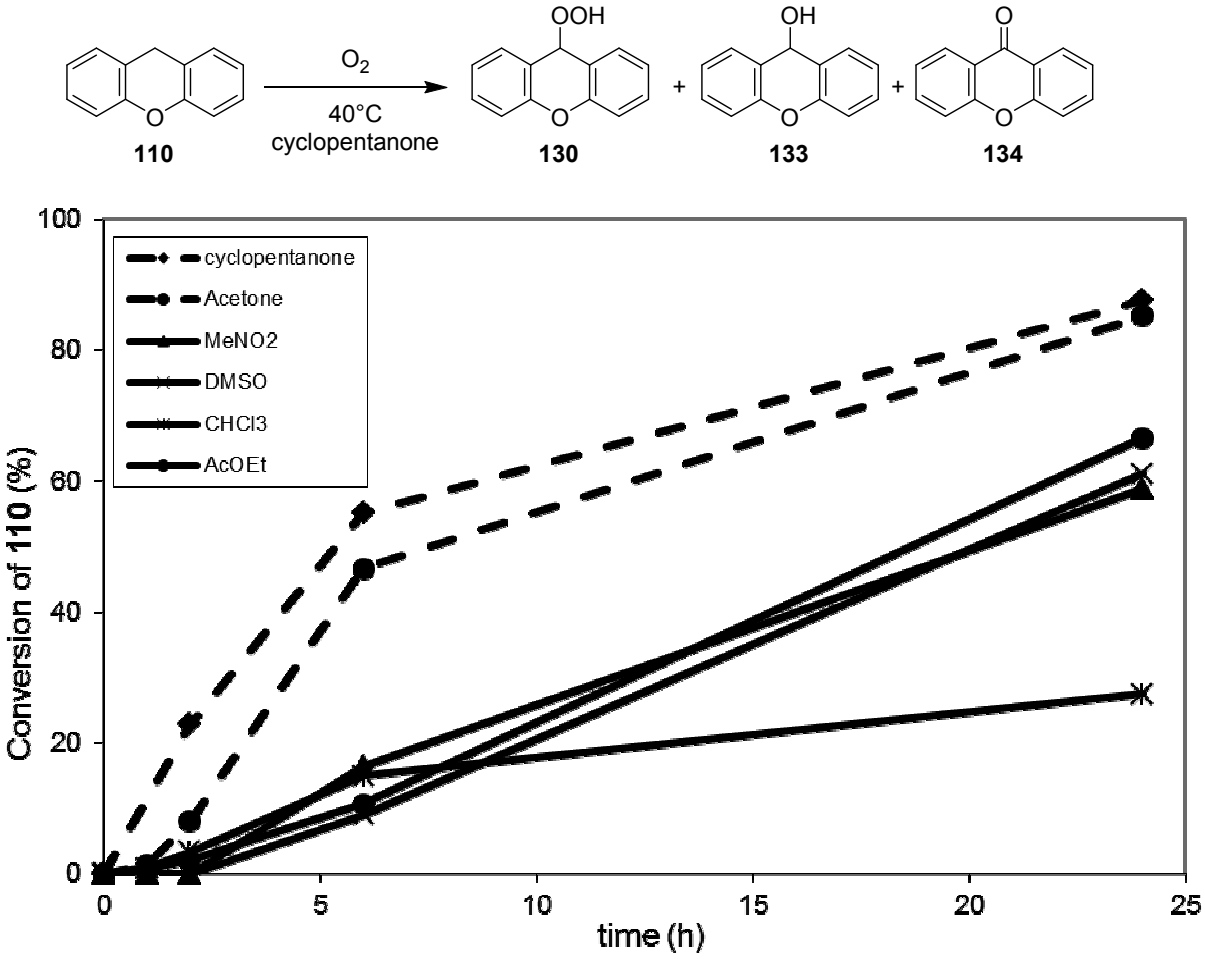


Figure 4-4: Solvent effects on the autoxidation of **110**, yields determined by NMR spectroscopy as described in section 7.3.1.

Of all solvents tested, ketones were generally much better and gave the highest reaction rates (acetone and cyclopentanone, dashed lines, discs and diamonds, respectively). Moderate conversions and rates were obtained when using nitromethane, DMSO and ethyl acetate (solid lines, triangles, crosses and discs, respectively). Choloroform proved to be much less efficient (solid line, stars) and DCM and hexane were found to be even worse, with hardly any conversion taking place (data not shown). Interestingly, a strong induction period was detected in most solvents, in accordance with the generally accepted autoxidation mechanism involving radical chains. These results explain the difficulties encountered to achieve high yields with nucleophiles other than ketones[33] and solvent effects observed in a related reaction.[35] If an autoxidative mechanism is indeed taking place, solvents barely able to promote it will not be suitable for the overall process.

Autoxidation processes have been known for a very long time[39f, 71] but the study

of their mechanism has received relatively little attention as compared to their industrial importance. However, it has been reported that ketones accelerate the autoxidation of cyclohexane at 145°C through internal H atom transfer[39c] but the rate at wich xanthene is fully converted in cyclopentanone at only barely elevated temperature is still remarkable.

4.2.4 Acid Effects on the Autoxidation of Xanthene

We then turned to investigate if the Brønsted acid catalyst employed could influence the autoxidation of Figure 4-2. An obvious challenge is the deconvolution of the autoxidation and coupling steps when strong acids such as methane sulfonic acid were used (see Scheme 4-18). In order to evaluate potential problems, we studied first the rate of the coupling step with different acids (Figure 4-5).

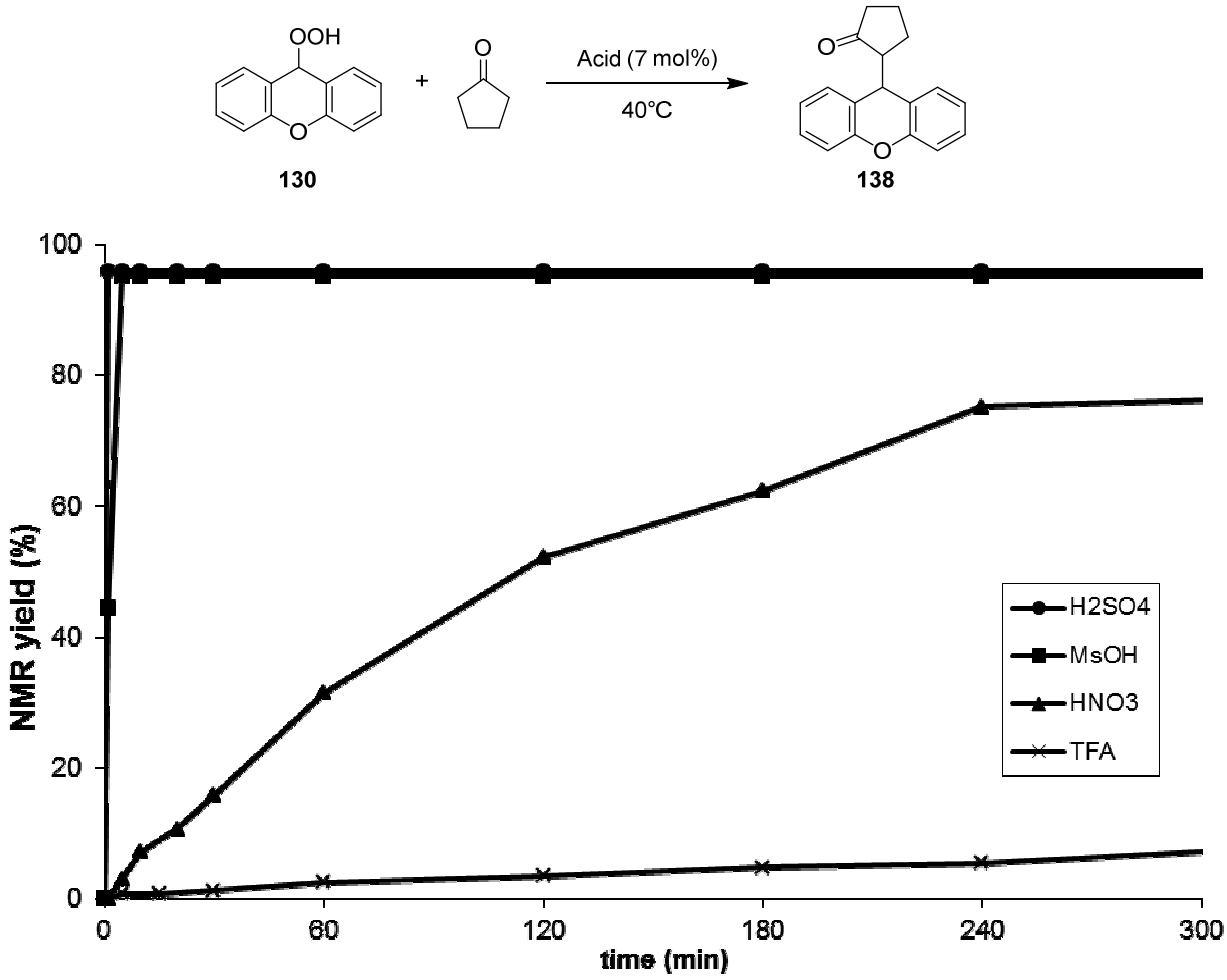


Figure 4-5: Acid effect on the substitution of **130** with cyclopentanone, yields determined by NMR spectroscopy as described in section 7.3.1.

Strong acids such as sulfuric acid (discs) and methane sulfonic acid (squares) were equally efficient, full conversion to **138** being observed in 1-5 minutes. Nitric acid (triangles)

gives a reasonable conversion of 75% in 4 hours but a limit is observed when going to trifluoroacetic acid (crosses) where only 5% conversion could be achieved after 4 hours. Even prolonged reaction time (22 hours) did not lead to full conversion (37%, not shown on Figure 4-5). In accordance to what was observed before,[33a] significant amounts of the mixed peroxide **132** were observed in the reaction mixture.

From these data, it can be concluded that acids weaker than trifluoroacetic acid will most likely not promote the coupling step under autoxidative reaction conditions to a significant extent. Stronger acids, however, will always convert the primary product of autoxidation **130** to **138** with high rates, making it impossible to deconvolute the two separate steps in these cases.

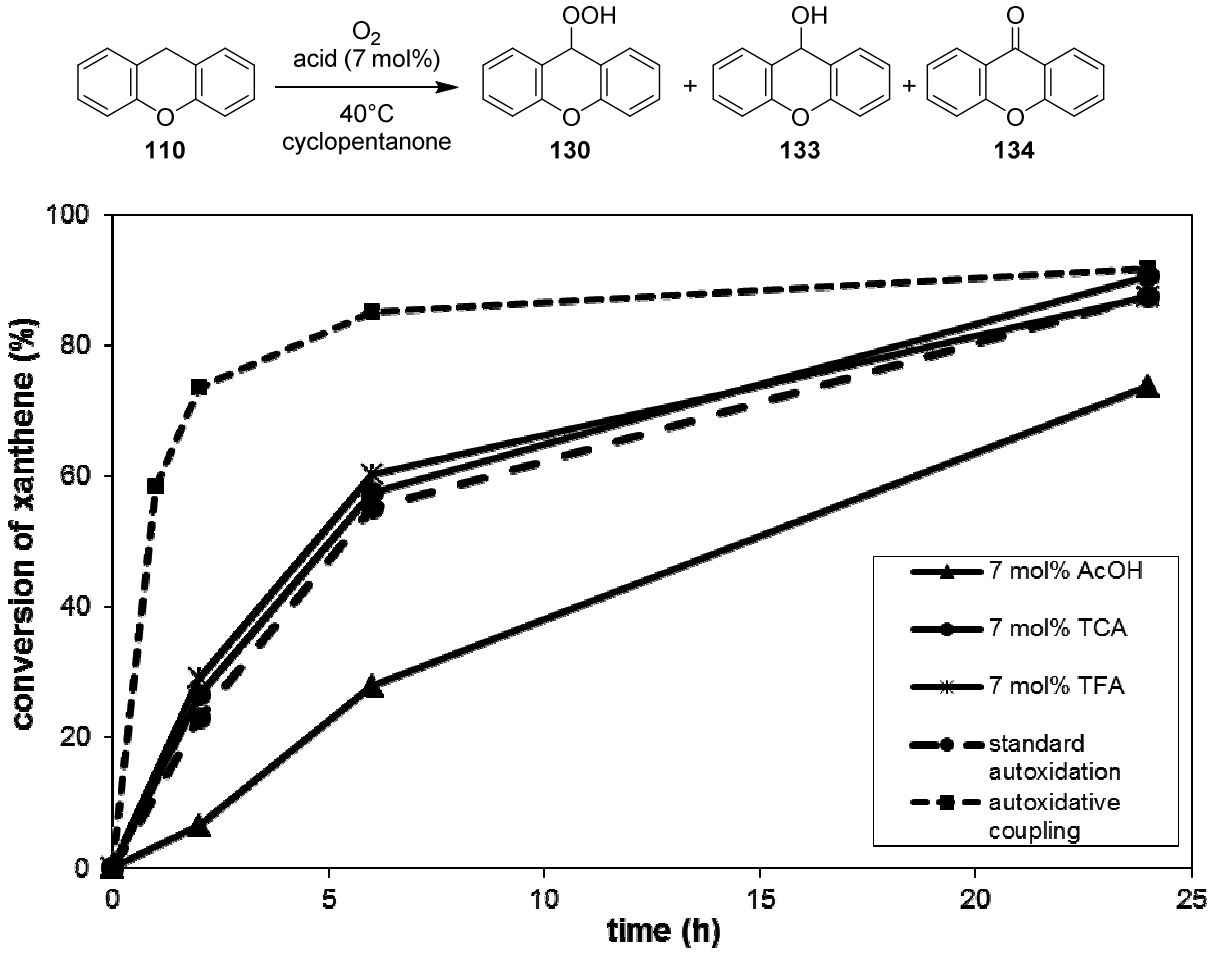
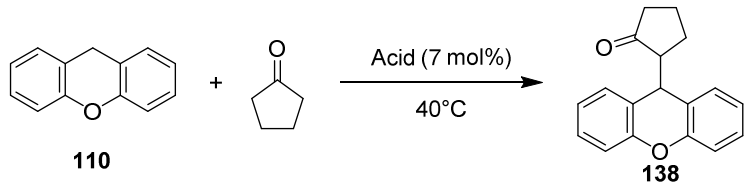


Figure 4-6: Effect of weaker acids on the autoxidation of **110,** yields determined by NMR spectroscopy as described in section 7.3.1.

The effect of weaker acids on the formation of **130** was first investigated (Figure 4-6). As can be seen, catalytic amounts of acetic acid slow the autoxidation (solid line, triangles compared to dashed line, discs). Stronger trichloroacetic acid (TCA, solid line, discs)

and trifluoroacetic acid (TFA, solid line, stars) showed identical rates of conversion than in the absence of an acid catalyst (dashed line, circles). It is to be noted that in the case of TCA and TFA, coupling product **138** started to appear overtime. Xanthene hydroperoxide was still the major product but up to 20% of **138** were detected in these reaction mixtures after 24 hours.

Strong acids were then evaluated by looking at the formation of **138** and comparing it to the standard autoxidation (Figure 4-7). Methane sulfonic acid (dashed line, squares), sulfuric acid (solid line, triangles) and nitric acid (solid line, crosses) all showed accelerated rates as compared to standard autoxidation (dashed line, discs). It seems from these results that there is an optimal pK_a value for the autoxidative coupling reaction. Indeed, acids weaker than trifluoroacetic acid showed no acceleration whatsoever (Figure 4-6), nitric acid (pK_a= -1.3) showed a lower increase in rate than methane sulfonic acid (pK_a= -2.6) while sulfuric acid (pK_a= -3) gave similar rates to nitric acid.



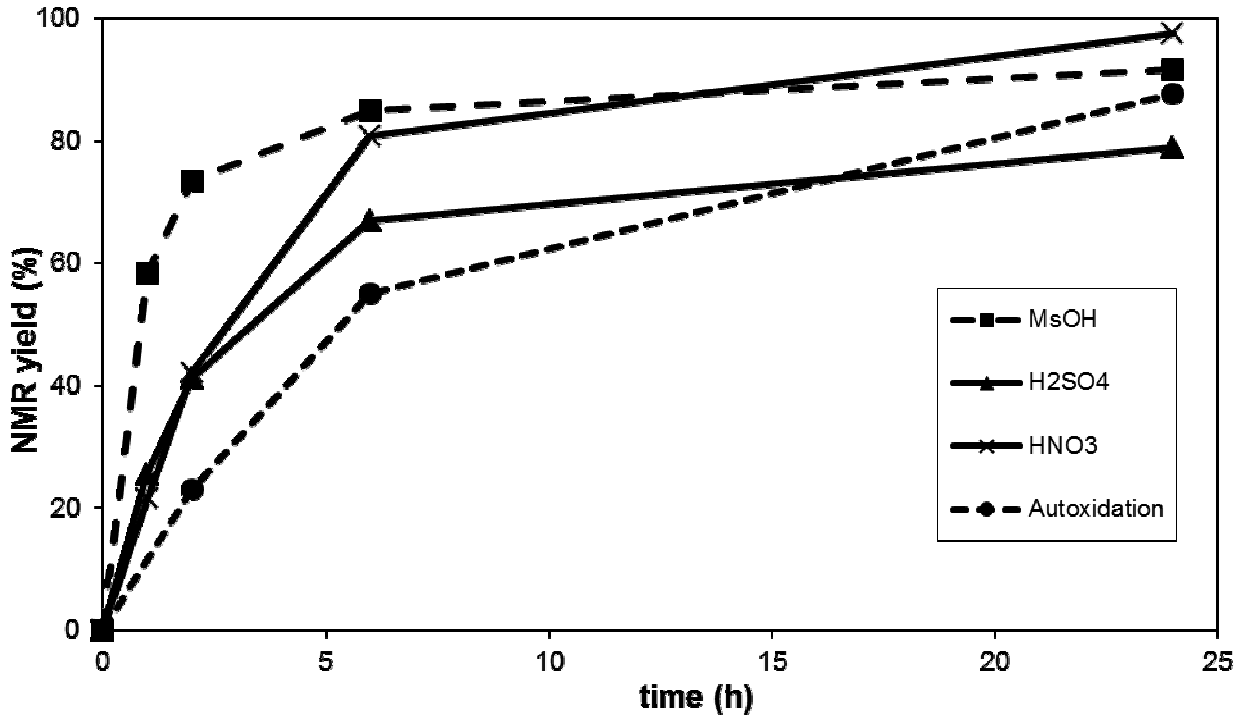
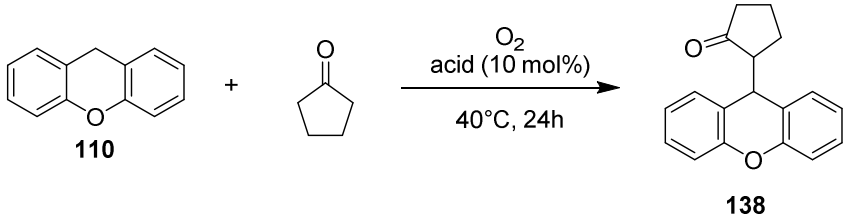


Figure 4-7: Effect of strong acids on the autoxidative coupling rates of **110**, yields determined by NMR spectroscopy as described in section 7.3.1.

Another factor that remains unexplained by an acid effect is the absence of detectable amounts of H_2O_2 in the reaction mixtures. Since it could be envisioned that peracids would be formed in the presence of H_2O_2 then acting as an additional oxidant, we decided to vary the nature of the acid catalyst to structures unable to form such secondary oxidants (Table 4-3).

Table 4-3: Effect of the nature of the acid catalyst on the autoxidative coupling of **110**.



110 **138**

Entry	Acid	pKa	Yield (%)[a]
1	MsOH	-2.6	88-92
2	HNO_3	-1.3	84-98
3	H_2SO_4	-3	60-79
4	HCl	-8	21
5	TFA	-0.25	13-29
6	TCA	0.65	13-21
7	AcOH	4.76	0

[a] Yields determined by NMR spectroscopy as described in section 7.3.1.

As long as the acid was strong enough, different natures of acid could be used. Methane sulfonic acid and nitric acid gave very similar yields (entries 1 and 2, 88 and 84%) while sulfuric acid (entry 3, 60%) was less effective. An ether solution of HCl showed dramatically reduced activity but still significant conversion (entry 4, 21%). Trichloroacetic acid and trifluoroacetic acid gave even lower yields (entries 5 and 6). Acetic acid did not give any **138** (entry 7), while still allowing the autoxidation to proceed (Figure 4-6). From the yields and comparing them with the pKa values of the different acids, it can be concluded that the nature of the acid probably does not have a strong influence on the outcome of the reaction. The acidity is more likely to be crucial in this transformation as can be seen from the optimal value of -1.3 to -2.6. Stronger acids most likely lead to more degradation pathways and diminished yields while weaker acids are just not strong enough to allow an efficient conversion of the intermediate **130** to the coupling product. Furthermore, the fact that an inorganic acid such as HCl still promotes the reaction, although with a lower efficiency than MsOH, is in disagreement with the involvement on peracidic structures acting as oxidant under these conditions.

In order to detect a possible induction period, a reaction was performed on a larger scale (four times greater than standard conditions) to allow for more data points (Figure 4-8).

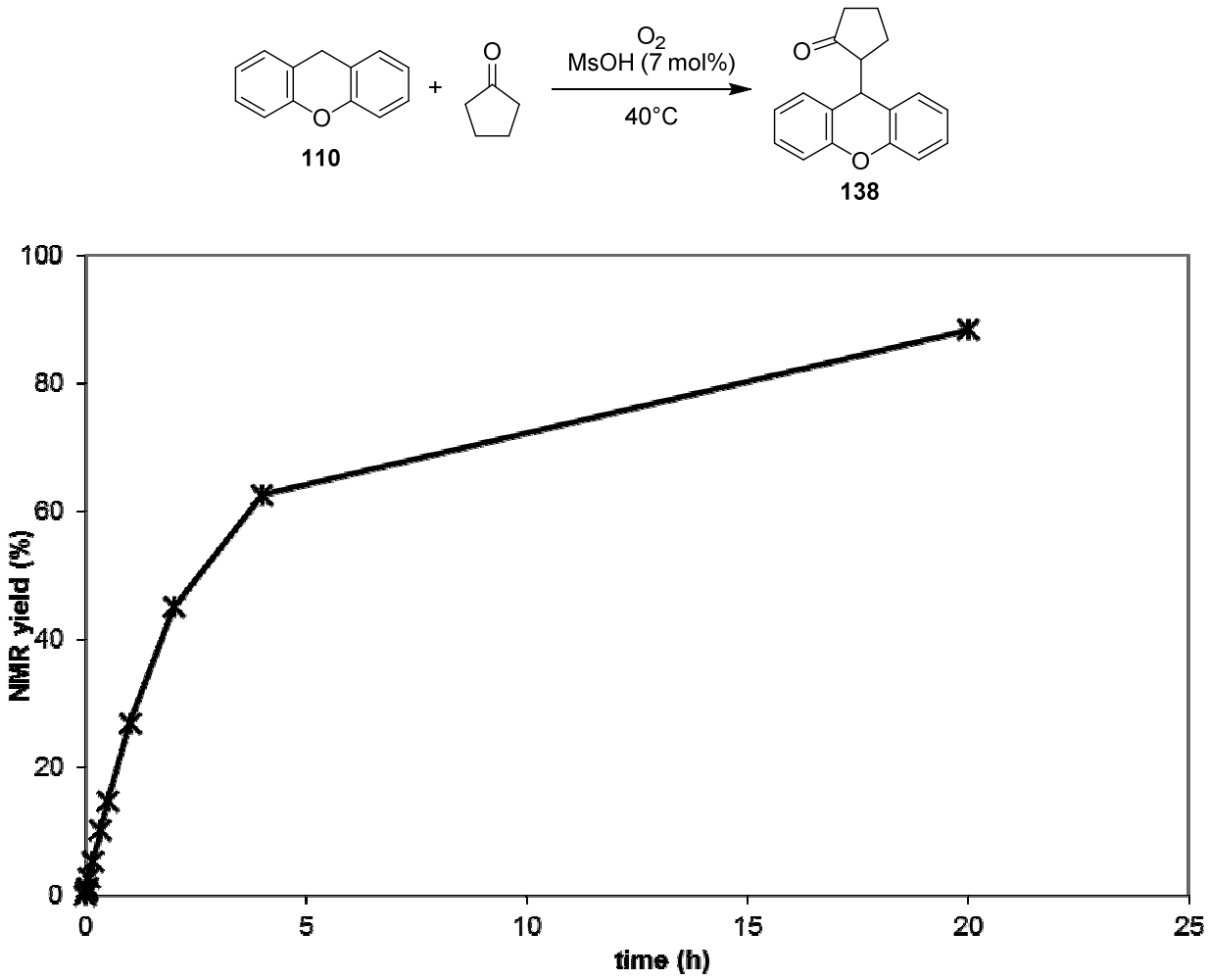
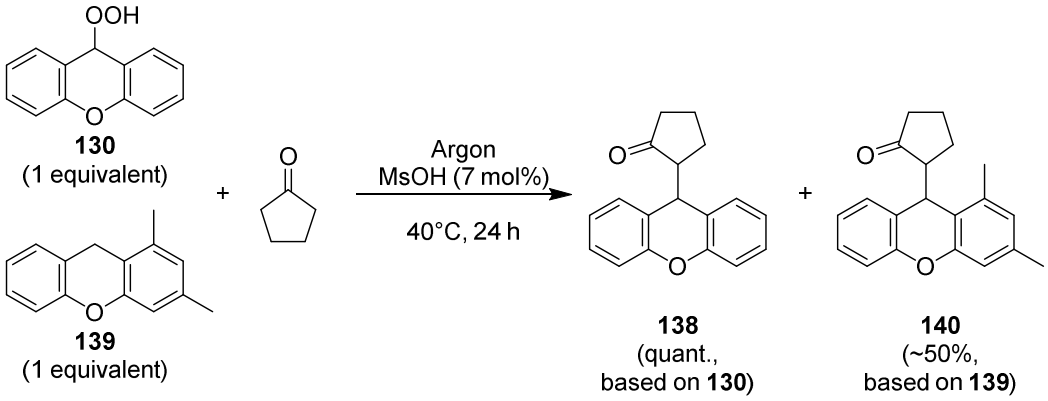


Figure 4-8: Attempt to detect an induction period for the autoxidative coupling of **110** to **138**, yields determined by NMR spectroscopy as described in section 7.3.1.

As can be seen, the reaction rate is slightly lower than the one previously found under standard conditions (see Figure 4-3) but is still larger than for the autoxidation of xanthene. This difference is attributed to the different exchange surface area in this large scale experiment compared to standard conditions since it is well known that biphasic systems are greatly influenced by such parameters. However, no induction period could be detected, in contrast to the normal autoxidation (see Figure 4-4). This suggested that another activation factor is at play from the very early stages of the reaction and suppresses the classically observed induction period of most autoxidation processes.

4.2.5 Studies on the Role of Released Hydrogen Peroxide

Although hydrogen peroxide usually needs transition metal catalysts to be activated in oxidative coupling reactions,[17, 72] we wondered if it could enter another reaction pathway, explaining its absence from our reaction mixtures. Furthermore it has been shown that the oxidative power of hydrogen peroxide is enhanced under acidic conditions,[73] suggesting the possibility of hydrogen peroxide serving as an alternative oxidant. To test this hypothesis, we first used aqueous or anhydrous hydrogen peroxide but the results were not exploitable due to solubility and reproducibility problems. Therefore, to stay as close to the reaction conditions as possible, we designed the experiment shown in Scheme 4-19.



Scheme 4-19: Oxidative coupling of **139** by hydrogen peroxide generated in situ as a byproduct in the reaction of **130** with cyclopentanone, yields determined by NMR spectroscopy as described in section 7.3.1.

Xanthene hydroperoxide **130** and dimethyl xanthene **139**[74] were dissolved in cyclopentanone. After carefull exclusion of oxygen to suppress any autoxidation pathway, methane sulfonic acid was introduced. As expected, complete conversion of **130** to **138** was observed and interestingly, roughly 50% of **139** was also converted to its corresponding coupling product **140**.

In a separate experiment, a representative conversion profile was obtained by monitoring the reaction over time (Figure 4-9).

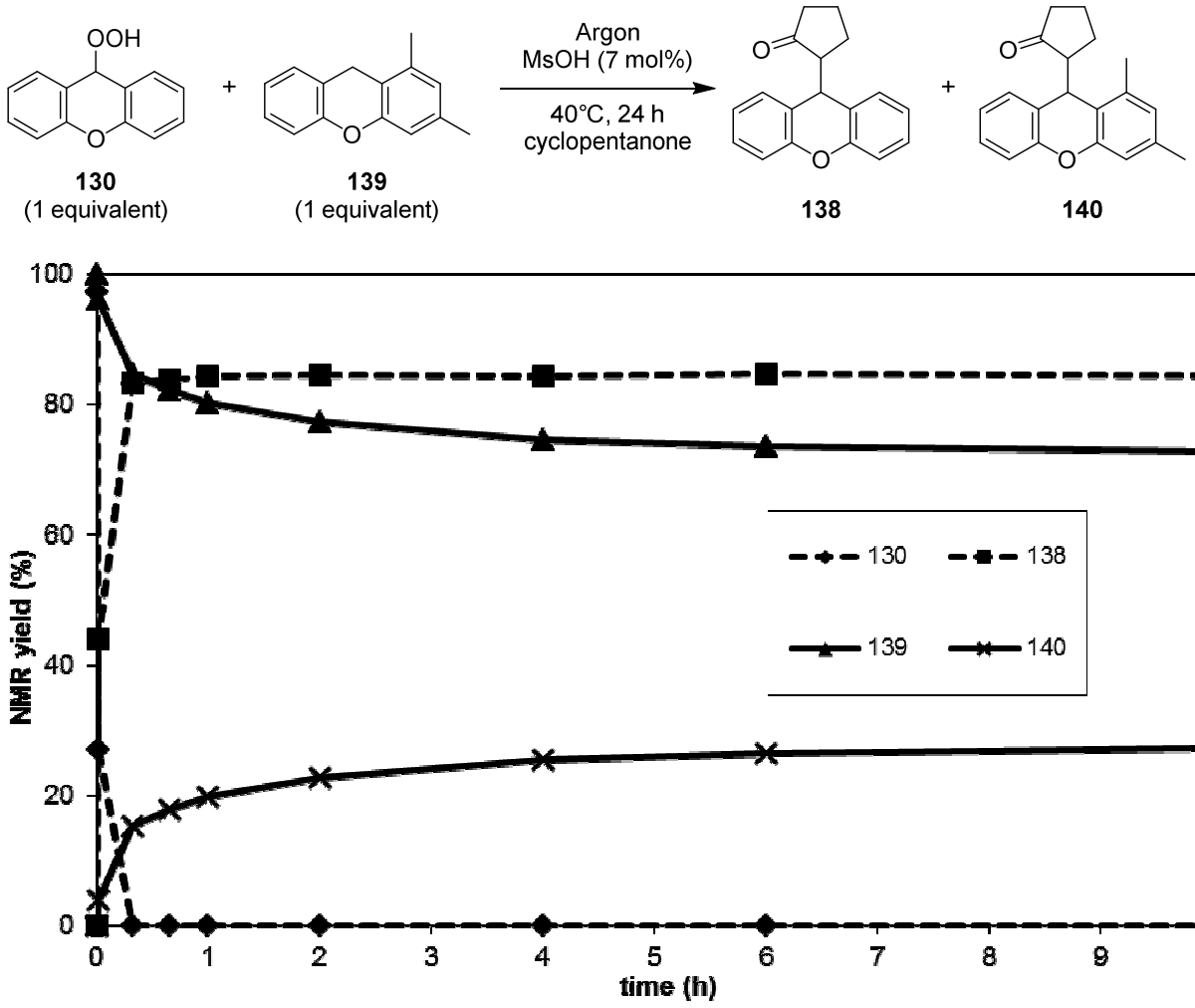
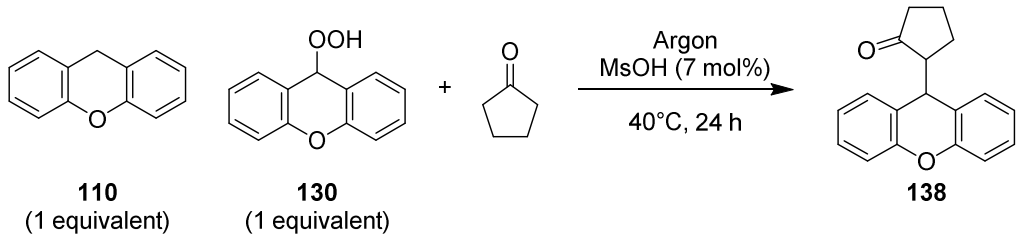


Figure 4-9: Conversion profile for the conversion of **139** to **140** using in situ generated hydrogen peroxide, yields determined by NMR spectroscopy as described in section 7.3.1.

As expected, conversion of **130** to **138** (dashed lines) is very fast and complete within a few minutes while the conversion of **139** to **140** (solid lines) is much slower, excluding the involvement of **130** itself as an oxidant. However, as can already be seen from these two experiments, reproducibility of yields was an issue, our first experiment giving around 50% yield of **140** while the second afforded **140** in 35% yield.

Similar experiments were conducted using a 1:1 mixture of **110** and **130** and similar results were obtained. While the general outcome of the reaction was reproducible, the yields of **138** varied between 15% and 46% after 3 to 5 hours, depending on the experiments, as shown by representative conversion profiles of several repetition of experiments in Figure 4-10.



110 (1 equivalent) **130** (1 equivalent) **138**

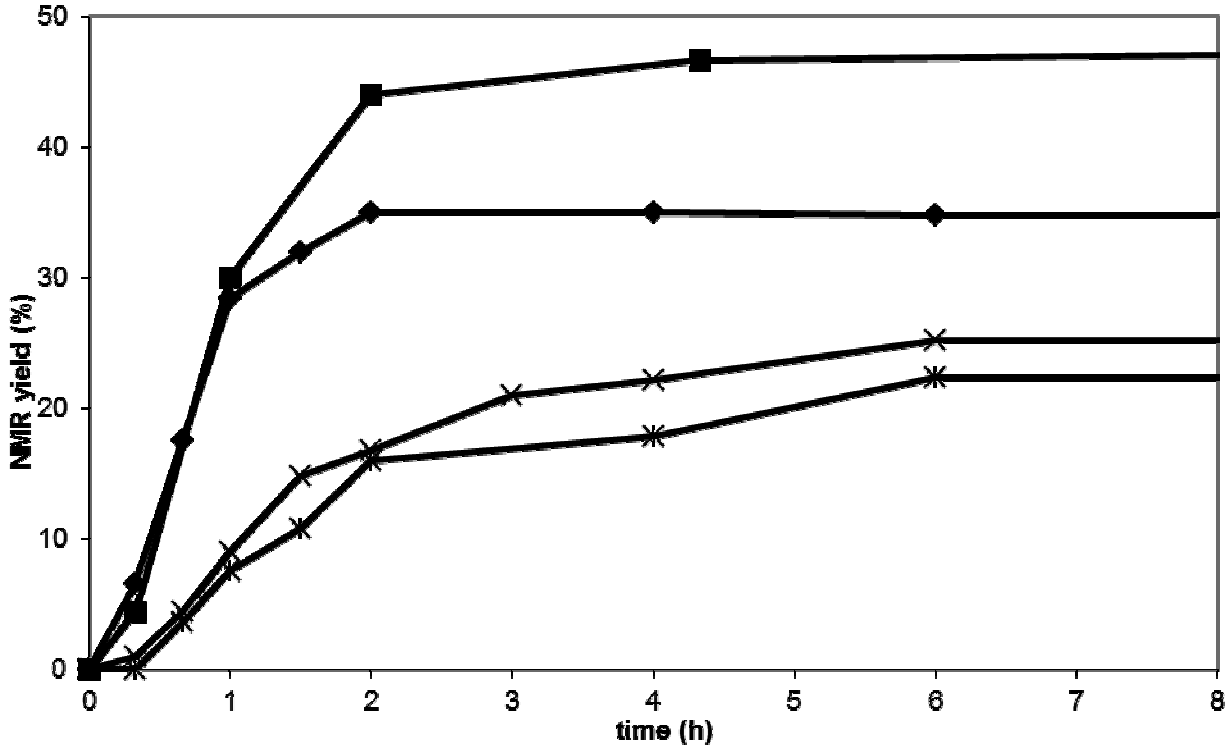
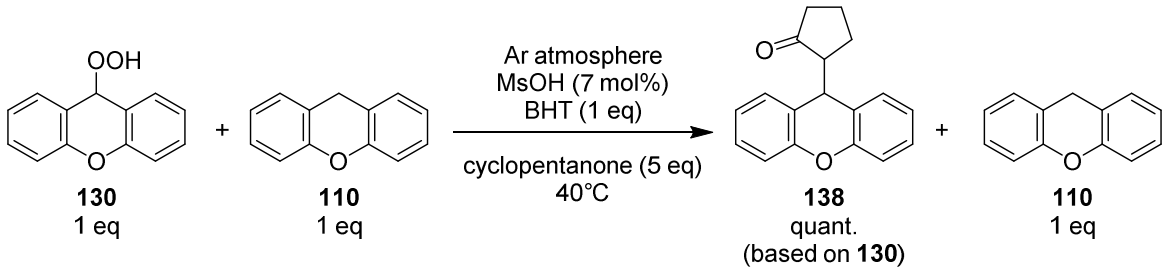


Figure 4-10: Representative experiments of conversion of **110** to **138** using in situ generated hydrogen peroxide, yields determined by NMR spectroscopy as described in section 7.3.1.

The kinetic profiles obtained show that this process occurs on the same timescale as the overall coupling reaction of Scheme 4-17, supporting the hypothesis that the equivalent of hydrogen peroxide released in the reaction mixture is used in a secondary pathway, resulting in an overall enhancement of the rate of reaction compared to the autoxidation alone.

Finally, when this experiment was performed in the presence of one equivalent of 2,6-di-tert-butylphenol (BHT) as a radical inhibitor, conversion of **130** to **138** occurred as expected but **110** was left unreacted (Scheme 4-20).

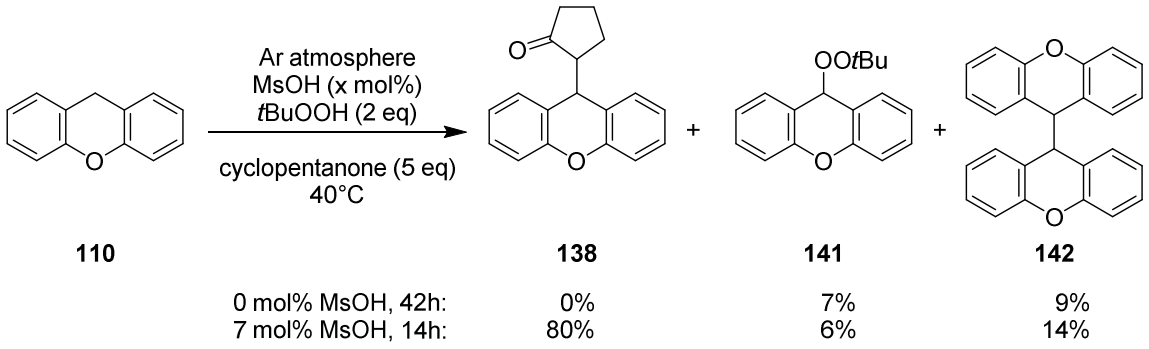


Scheme 4-20: Oxidative coupling of **110** by hydrogen peroxide generated in situ as a byproduct of the reaction of **130** with cyclopentanone in presence of a radical inhibitor, yields determined by NMR spectroscopy as described in section 7.3.1.

This experiment clearly shows the duality of the mechanisms involved. The substitution of the hydroperoxide unit (i.e. conversion of **130** to **138**) is clearly ionic, as previously postulated in Scheme 4-15 and in studies of decomposition of hydroperoxides in acidic media.[73b] The activation of the unactivated xanthene **110** however involves radical species and thus differs from the previously suggested mechanisms for the activation of hydrogen peroxide in acidic media, which were all ionic.[73]

4.2.6 Modeling the Role of Hydrogen Peroxide: tBuOOH

As mentioned in section 4.2.5, the use of aqueous or anhydrous hydrogen peroxide was very unpractical and led to unexploitable results. Even though the system described in Scheme 4-19 is by far the closest to our reaction conditions, the preparation of large amounts of **130** and **139** is not ideal from a practical point of view and a more reproducable system was sought after. We chose *tert*-butylhydroperoxide (as an anhydrous solution in decane) as a cheap, safe and easily accessible model hydroperoxide oxidant and tested it under anaerobic conditions (Scheme 4-21).



Scheme 4-21: Anaerobic oxidative coupling of **110** in the presence of *t*BuOOH as oxidant, yields determined by NMR spectroscopy as described in section 7.3.1.

Stirring xanthene in cyclopentanone under argon in the presence of two equivalents of *t*BuOOH only gave a very low conversion after 42 hours of reaction time. The products identified from this reaction were the mixed peroxide **141** and the dimer **142** in low amounts (7% and 9%, respectively). In the presence of 7 mol% of methane sulfonic acid, the coupling product **138** was obtained in 80% yield along with dimer **142** (14%) and xanthone **134** (6%).The presence of **142** is again a very strong support for the involvement of free radicals, in particular of xanthenyl radicals, in this process. Interstingly, when the reaction was monitored over time, **141** was detected as an intermediate by ^{1}HNMR spectroscopy (Figure 4-11).

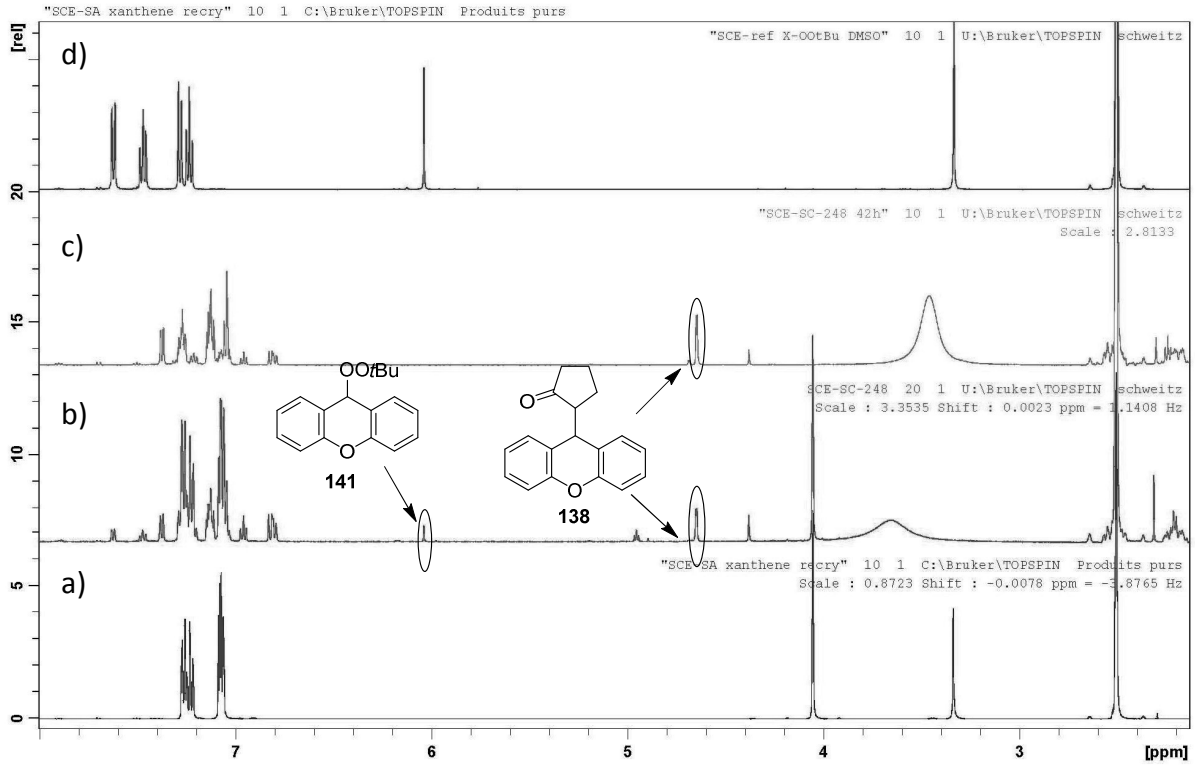


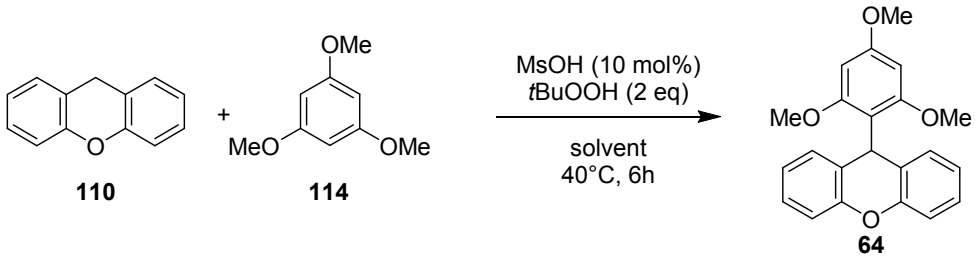
Figure 4-11: ^{1}H NMR monitoring of the reaction from Scheme 4-21 : from bottom to top: a) reference spectrum of xanthene **110**; b) reaction mixture after 2 hours; c) reaction mixture after 42 hours; d) reference spectrum of **142**.

After 2 hours, the coupling product **138** (doublet at 4.6 ppm) and the intermediate peroxide **141** (singlet at 6 ppm) are clearly visible. After prolonged reaction time, **110** and **141** have completely disappeared and only **138**, **134** and traces of dimer **142** are detectable. This is in clear contrast with all our attempts and failures to detect hydroperoxide **130** under the aerobic conditions and can be rationalised by a reduced reactivity of **141** as compared to **130** towards acid activation. It is to be noted that two

equivalents of *t*BuOOH are needed to achieve full conversion of xanthene. If only one equivalent was used, the reaction reached 50% conversion and stopped until a second equivalent was added. Only then did the reaction reach completion, giving identical results to Scheme 4-21.

Solvent effects were investigated but in all cases, low conversion to unidentified products was observed. As the solvent used is also the nucleophile, we needed to separate these two factors. For this purpose, 1,3,5-trimethoxybenzene **114** was chosen as a nucleophilic partner (Table 4-4). For comparison, aerobic formation of **64** needed more forcing conditions: 70°C, 10 bars partial pressure of oxygen and 24 hours of reaction to obtain a 80% yield while no coupling product was observed at 40°C and ambient pressure of oxygen.[33b]

Table 4-4: Solvent effects on the anaerobic oxidative coupling of **110** and **114**.



Entry	Solvent	110 (%)[b]	64 (%)[b]	142 (%)[b]
1	acetone	7	92	<1
2	cyclopentanone	52	48	<1
3	CH_3CN	73	27	<1
4	MeOH	78	21	1
5	AcOEt	79	17	1
6	$CHCl_3$	81	18	1
7	CH_3NO_2	84	15	1
8	DMSO	90	7	0
9	toluene	90	8	1
10	MTBE	93	5	1

[a] **110** (0.25 mmol), **114** (0.25 mmol) solvent (0.25 ml), *t*BuOOH (0.5 mmol, in decane), MsOH (0.025 mmol), in closed vials (without exclusion of oxygen) for 6 hours, [b] determined by ^{1}H-NMR analysis of the crude reaction mixture.

The reaction of xanthene, **114** and two equivalents of *t*BuOOH in acetone afforded nearly full conversion and almost perfect selectivity for **64**. Only traces of dimer **142** could be detected as side product (entry 1). When cyclopentanone was used as solvent, reactivity was decreased compared to acetone but still a reasonable yield of 48% was obtained (entry 2). Interestingly, no trace of coupling with cyclopentanone (i.e. product **138**) could be detected. In all the other solvents tested, conversions were much lower (5-27%,

entries 3 to 10). Conversion was achieved in all solvents but the superiority of acetone and cyclopentanone is striking. Indeed, no rationalisation on solvent polarity could be made, since both DMSO and toluene both gave very low conversions (entries 8 and 9). The ketonic nature of the solvent seemed to be the decisive factor.

4.2.7 The Combination of an Acid, a Ketone and a Hydroperoxide as Radical Precursors

The results of Scheme 4-19, Scheme 4-20 and Table 4-4 strongly suggest that a radical mechanism is responsible for the oxidative coupling of **110** under oxygen free conditions and in the presence of hydro(gen) peroxide under acidic conditions. Furthermore a ketone seems to be needed for this mechanism to occur. Although catalytic formation of radical species without the involvement of a metal species is extremely rare, it has been suggested by Solyanikov that under such conditions, radicals can be formed through the involvement of peroxyacetals of the type of compounds **143 – 147**[75].

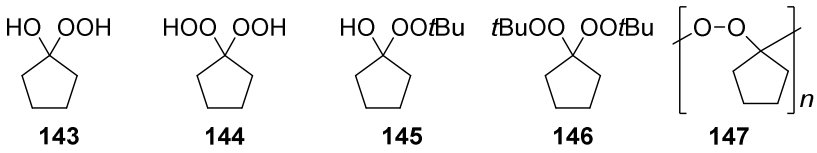
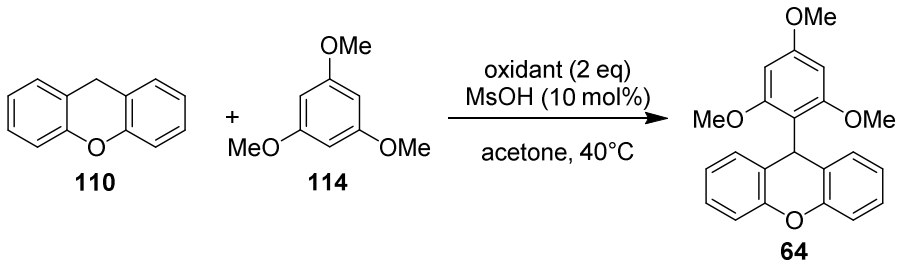


Figure 4-12: Potential radical precursors formed *in situ*.

These type of compound can obviously be formed by Brønsted acid catalysis under our reaction conditions in the presence of hydrogen peroxide or *t*BuOOH and could then undergo homolytic cleavage of the peroxidic O-O bond to afford free radicals. In order to test this phenomenon and eliminate the possibility of an acid catalysed decomposition of *t*BuOOH, several oxidants were tested under anaerobic conditions (Table 4-5).

Table 4-5: Effect of the nature of the oxidant in the oxidative coupling of **110** and **114**.



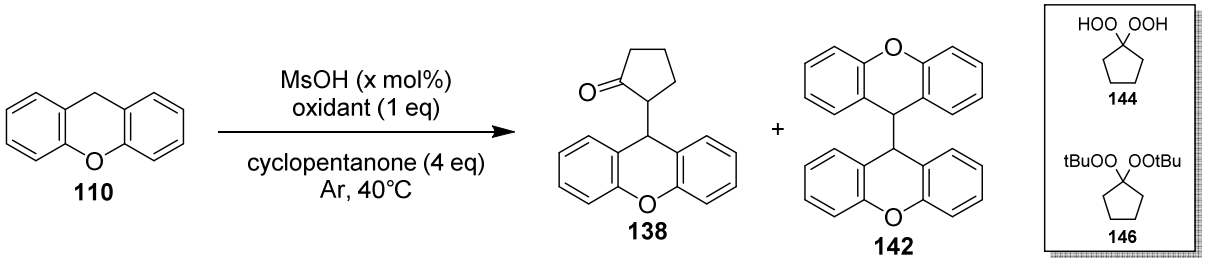
110 **114** **64**

Entry	Time	Oxidant	Conversion	Yield
1	48h	O_2	0%	0%
2	18h	TBHP	Full	96%[a]
3	48h	T-HYDRO	74%[a]	68%[a]
4	18h	CHP	21%[b]	20%[b]
5	18h	DTBP	trace	trace[b]

TBHP: 5.5 M solution of *t*BuOOH in decane; T-HYDRO: 70% aqueous solution of *t*BuOOH; CHP: 80% solution of cumene hydroperoxide; DTP: di-*tert*-butyl peroxide; a) determined by isolation b) determined by ^{1}H NMR analysis of the crude mixture.

As previously reported, molecular oxygen at ambient pressure and temperature is not effective in promoting the coupling reaction between **110** and **114** (entry 1), elevated temperature and partial pressure of oxygen are required for this reaction.[33b] On the other hand, after 18 hours, full conversion and an excellent 96% yield of **64** is obtained if an anhydrous solution of tBuOOH is used (entry 2, see also Table 4-4). An aqueous solution of *t*BuOOH (T-HYDRO) was also competent, but gave lower yield and conversion after 48 hours of reaction (entry 3, 68%). Cumene hydroperoxide (CHP), even though giving a low 21% conversion and 20% yield, is still a suitable oxidant (entry 4). On the other hand, di-*tert*butyl peroxide (DTBP), unable to form peroxyacetals, only gave traces of **64**. To further confirm this assumption, **144** and **146** were synthesised from cyclopentanone by acid catalysis[76] and evaluated as oxidants in their pure form (Table 4-6).

Table 4-6: Evaluation of **144** and **146** as oxidants.

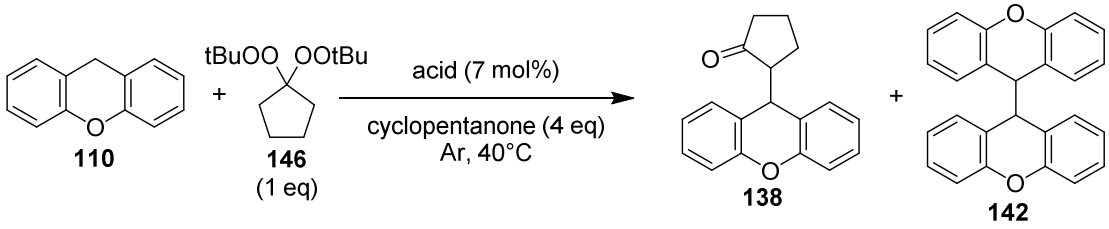


Entry	MsOH loading	Time (h)	Oxidant	138 (%)	142 (%)
1	0	12	**144**	0	0
2	0	12	**146**	0	0
3	7	1	**144**	4	5
4	7	1	**146**	25	35

Yields determined by NMR spectroscopy as described in section 7.3.1.

In the absence of acid, no reaction was observed by using both **144** and **146** (entries 1-2). However, when methane sulfonic was present, conversion was observed in both cases giving coupling product **138** and dimer **142** after one hour of reaction. **144** gives quite low conversion and yields of **138** and **142** of 4% and 5%, respectively (entry 3) but **146** is much more effective, giving 25% and 35% of **138** and **142** (entry 4). The acid effect was then investigated using **146** as oxidant (Table 4-7).

Table 4-7: Acid effect on the oxidative coupling of **110** using **146** as oxidant.



Entry	Acid	138 (%)	142 (%)
1	H_2SO_4	18	38
2	MsOH	25	35
3	HNO_3	0	0
4	TFA	0	0

Yields determined by NMR spectroscopy as described in section 7.3.1.

Both sulfuric and methane sulfonic acid promoted the decomposition of **146** and the formation of **138** and **142** in significant amounts (Table 4-7, entries 1-2). Weaker acids such as nitric and trifluoroacetic acid where however completely ineffective and no conversion was observed (Table 4-7, entries 3-4). In the case of methane sulfonic acid, a

conversion profile was obtained (Figure 4-13).

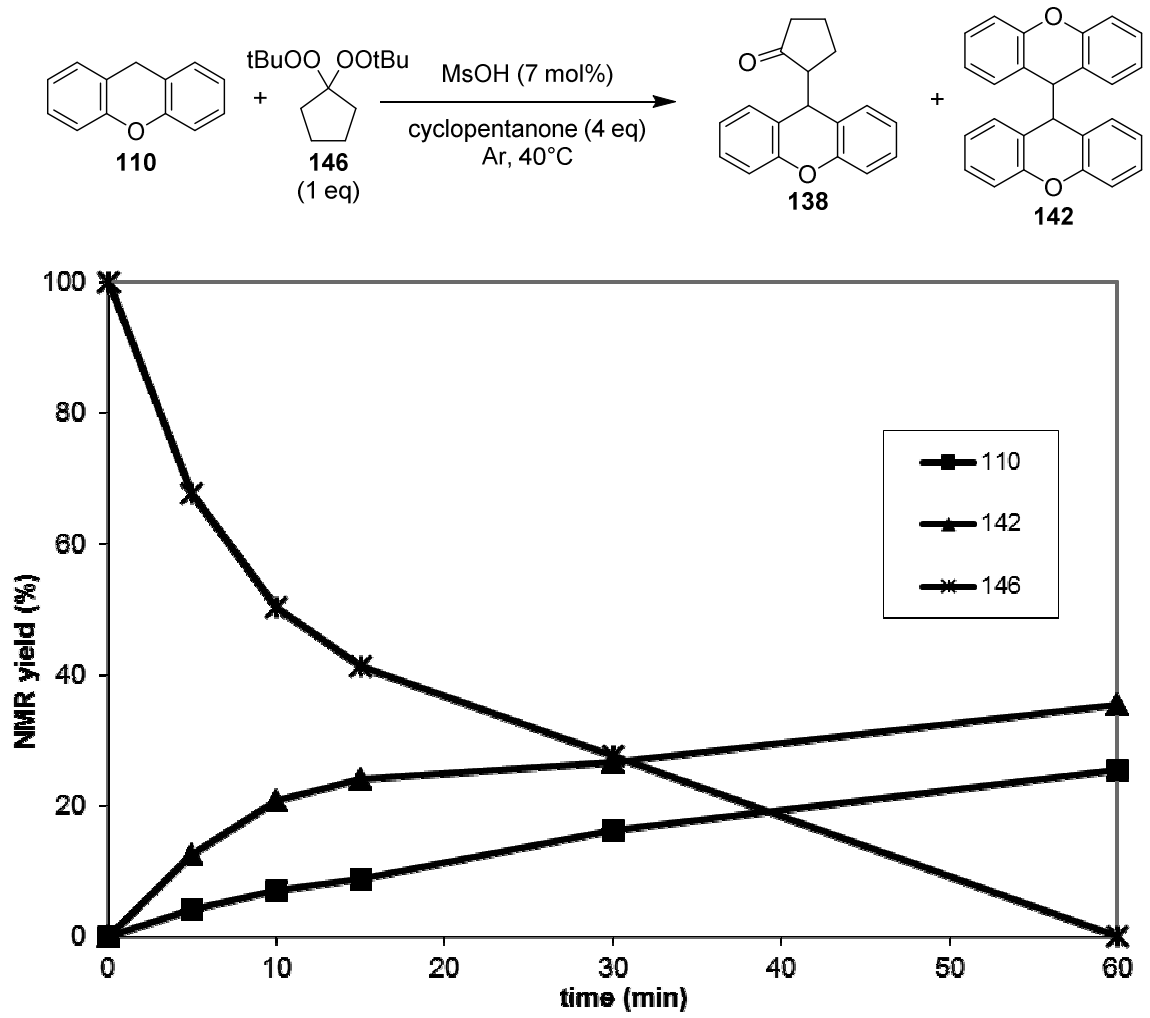


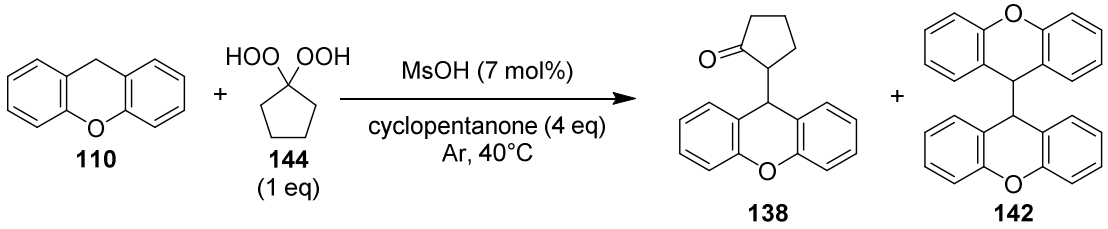
Figure 4-13: Reaction profile of the reaction of Table 4-7 entry 2, yields determined by NMR spectroscopy as described in section 7.3.1.

It can be seen that all of **146** (stars) is completely decomposed after one hour while **138** (squares) and **142** (triangles) were formed during this time. Upon full conversion of **146**, no further product formation was observed (data not shown). A similar reaction profile was obtained with sulfuric acid, showing in this case full consumption of **146** in less than 30 minutes.

The high yields of dimer **142** point to a purely radical mechanism for the activation of xanthene by this mechanism. Additionaly, there seems to be a threshold in pK_a for the acid to be competent in activating **146**.

The anaerobic coupling reaction could also be triggered by the use of **144** in the presence of strong acids (Table 4-8). Low but clearly detectable amounts of **138** and **142** were formed using methane sulfonic acid (entry 1) while trifluoroacetic acid was again completely ineffective (entry 3). Contrary to **146**, **144** could be decomposed by nitric acid (entry 2) but the yields were again very low.

Table 4-8: Acid effect on the oxidative coupling of **110** using **144** as oxidant.



Entry	Acid	138 (%)	142 (%)
1	MsOH	4	5
2	HNO_3	2	1
3	TFA	0	0

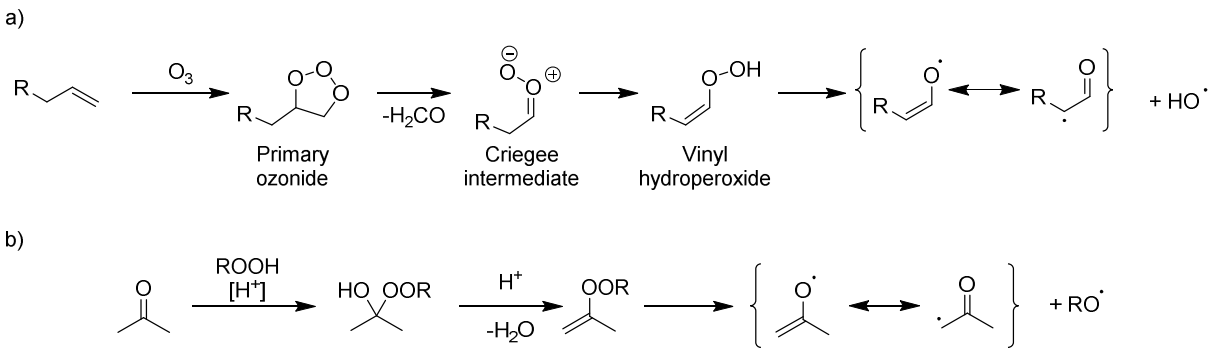
Yields determined by NMR spectroscopy as described in section 7.3.1.

These experiments do not unequivocally determine if **144** or **146** are true intermediates in the reactions studied but they provide support to the involvement of such a type of compounds as radical precursors.

4.2.8 Mechanism of the Autoxidative Coupling Reaction

All the experiments described in this chapter provide support to a more complex mechanism than was initially assumed, a mechanism which now involves generation of free radicals from the combination of a ketone, a hydroperoxide and a strong acid. While the catalytic generation of free radicals without the involvement of metal based oxidants or halides is a rare phenomenon, it is not unknown. Indeed, studies on atmospheric chemistry have postulated that vinyl hydroperoxides, generated from ozonolysis of olefins are the major source of OH radicals in the upper atmosphere at night, when photochemical processes are no longer possible (Scheme 4-22).[77]

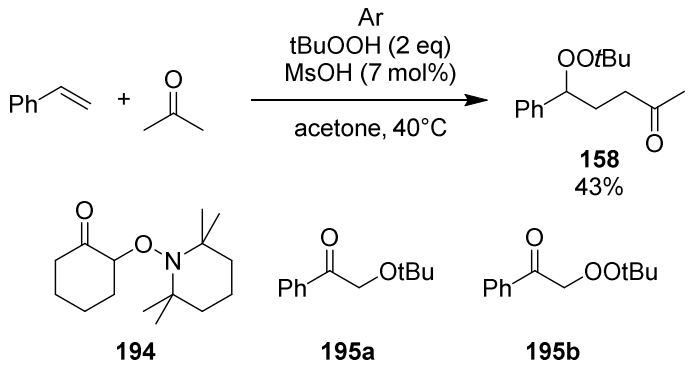
After formation of the primary ozonide, a rearrangement affords the Criegee intermediate, which can form a vinyl hydroperoxide via proton transfer from its α-carbon if in the right *cis* geometry. Facile homolytic cleavage of the peroxidic bond then afford OH• radicals and a vinyloxy radical, which is best described as its resonance structure where the unpaired electron is residing on the carbon atom (Scheme 4-22, a).



Scheme 4-22: Formation and decomposition of vinyl (hydro)peroxides.

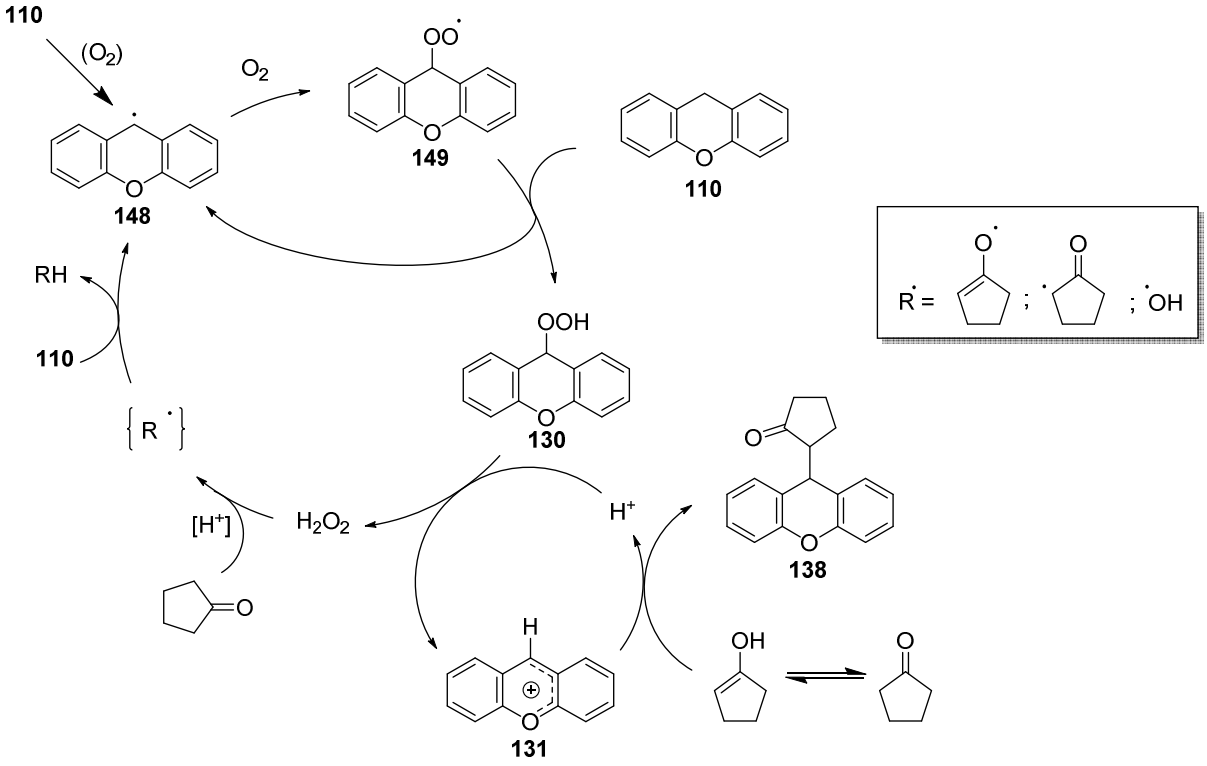
It has been postulated that the decomposition of vinyl hydroperoxides is a barrier-free process (meaning that no activation energy is needed and no identifiable transition state is present in the O-O bond dissociation) but recent studies seem to contradict this assumption.[77d] By analogy, the involvement of vinyl peroxides under our reaction conditions seems reasonable (Scheme 4-22,b). Under acidic conditions and in the presence of a hydroperoxide, a vinyl peroxide can be envisioned to be formed through a peroxy hemi acetal and further dehydration. This vinyl peroxide would then undergo facile thermal homolytic cleavage to afford two free radicals in a similar manner as described for vinyl hydroperoxides.

Experimental evidence for the formation of α-carbonyl radicals under similar reaction conditions has later been obtained through trapping experiments and products such as **158**, **194**, **195a** and **195b** could be formed (Scheme 4-23). The involvement of such radicals supports this mechanistic proposal involving alkenylperoxides and these reactions are discussed in detail in sections 4.3.



Scheme 4-23: Experimental evidence for the involvement of α-carbonyl radicals.

With all these results, a detailed reaction mechanism is proposed in Scheme 4-24. In the presence of oxygen, the autoxidation of **110** is initiated to give hydroperoxide **130** via radicals **148** and **149**. In the presence of a strong Brønsted acid, **130** generates a highly stabilised carbocation **131** and one equivalent of hydrogen peroxide. The enol form of cyclopentanone, used as both solvent and reactant then traps **131** to afford the observed coupling product **138**. A second pathway is opened through the release of the primary waste product H_2O_2. In the presence of a ketone and a strong Brønsted acid, free radicals are formed (see Scheme 4-22, noted as R• radicals in Scheme 4-24), which in turn generate xanthenyl radicals **148**, then quickly trapped by molecular oxygen to enter the autoxidation channel, as in the purely aerobic autoxidation.



Scheme 4-24: Reaction mechanism of the autoxidative coupling of xanthene **110** with cyclopentanone to **130**.

This second mode of generation of radicals **148** adequately explains the acceleration of rates observed when comparing the autoxidative coupling of **110** to its simple autoxidation to **130**, as well as our failure to detect the presence of hydrogen peroxide under the reaction conditions. An added positive points to the "green" nature of this reaction is that hydrogen peroxide is no longer the stoichiometric waste product generated, as we believed in our initial mechanistic proposal, but water is the ultimate waste

product. It further increases the atom economy of the reaction, since the reduced form of molecular oxygen, H_2O_2, is also used as an oxidant in the overall reaction.

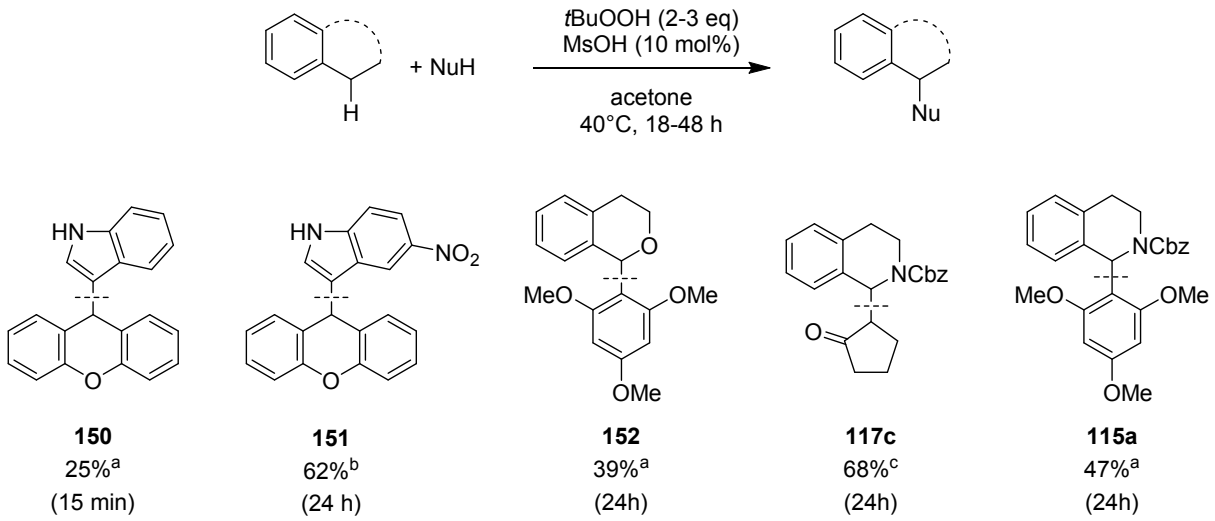
At this stage, several comments should be made on the choice of the acid catalyst. As described in this chapter, an optimal pK_a value has to be used to achieve maximum efficiency. The acid has to be strong enough to efficiently promote the substitution of **130** (see Figure 4-5) and liberate hydrogen peroxide, but it should also be sufficiently powerfull to enable the formation of free radicals to promote the second pathway described in this section.

Good examples for this behaviour are trifluoroacetic acid and nitric acid. In the case of nitric acid, being close to the threshold in pKa for an efficient conversion of **130** to **138** (see Figure 4-5) and also to the threshold for the generation of radicals (see Table 4-6 and Table 4-7), only a minor increase of rate is observed (see Figure 4-7) but good yields are achieved eventually. If an acid stronger than methane sulfonic acid is used, such as sulfuric acid, the reaction is obviously less efficient, presumably due to additional side reactions or decomposition of intermediates and products. By contrast, if weak acids, such as trifluoroacetic acid, are used, the conversion of **130** to **138** is very inefficient (see Figure 4-5), only liberating hydrogen peroxide in small amounts. Furthermore, they are not able to promote the formation of free radicals (see Table 4-6 and Table 4-7). Therefore, the conversion of xanthene follows the one observed in the absence of acid (see Figure 4-6).

4.2.9 Extension of Reactivity Exploiting the Brønsted Acid Catalysed Formation of Radicals

Inspired by the results obtained, we wondered if this radical generation mechanism could be exploited to expand the synthetic utility of oxidative coupling chemistry (Scheme 4-25). In addition to product **64**, several products could be obtained using these new conditions. The oxidative coupling of xanthene and indole could be achieved, giving a low 25% yield of **150**. This low yield was due to competing oxidation and dimerisation of the indole since after 15 minutes, all indole had been consumed but large amounts of xanthene were still present. Accordingly, using two equivalents of 5-nitro indole, which is much less sensitive to acidic and oxidative conditions, as nucleophile, an acceptable 62% of product

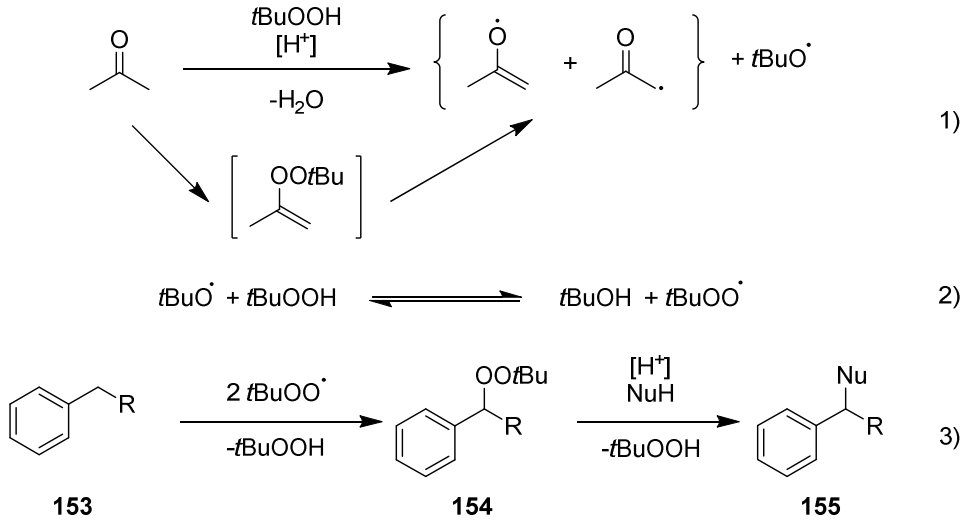
151 could be obtained. Isochromane was another suitable pro-electrophile and gave product **152** in a modest 39%. These products had previously been synthesised using oxidative coupling strategies but relying on transition metal catalysis[31] or high temperature and quinone oxidants.[78] We then revisited selected products made using our previously discussed two step method (see section 4.1). Pleasingly, **117c** and **115a** were formed in 68% and 47% yield, respectively. This system already shows comparable yields for cyclopentanone as nucleophile – full conversion was not achieved and based on the recovered starting material, the yield of **117c** was 85% - without the need for a purification of the intermediate peroxide. In the case of product **115a**, a slightly lower yield was obtained under these conditions, as compared to the two step method. This is due to the presence of side products, the identification of which steered our interest towards radical C-C bond forming reactions using the knowledge developed in this mechanistic study and discussed in details in section 4.3.



Scheme 4-25: Application of the Brønsted acid catalysed radical formation. New bonds are indicated by a dashed line. a) 1 equivalent of nucleophile; b) 2 equivalents of nucleophile; c) 5 equivalents of cyclopentanone used as solvent and nucleophile.

A plausible reaction mechanism for these organocatalytic oxidative coupling reactions is shown in Scheme 4-26. As discussed previously, acetone - used as solvent - (or cyclopentanone in the case of product **117c**) activates *t*BuOOH through the formation of alkenyl peroxide, generating tBuO• radicals (equation 1). In the presence of excess *t*BuOOH, *t*BuOO• radicals are formed though a fast equilibrium favouring *t*BuOO• radicals (equation 2).[79] The substrate **153** is then oxidised to **154**, either through a hydrogen atom abstraction

and radical recombination mechanism or through the single electron and proton transfer mechanism described by Doyle in the case of amide substrates (see section 2.1.4 for a discussion on these mechanisms).[30] Finally, Brønsted acid promoted substitution of the peroxide moiety of **154** affords the desired coupling product **155** along with *t*BuOOH.

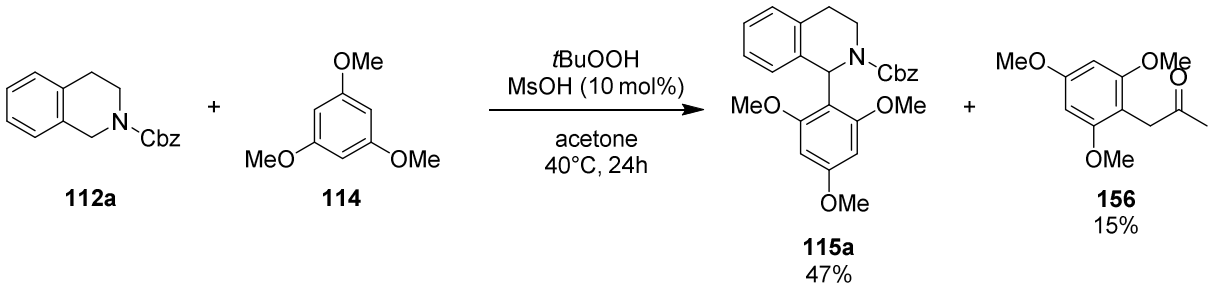


Scheme 4-26: Plausible mechanism for Brønsted acid catalysed oxidative coupling reactions.

4.3 Oxidative Functionalization of Olefins Under Acid Catalysis

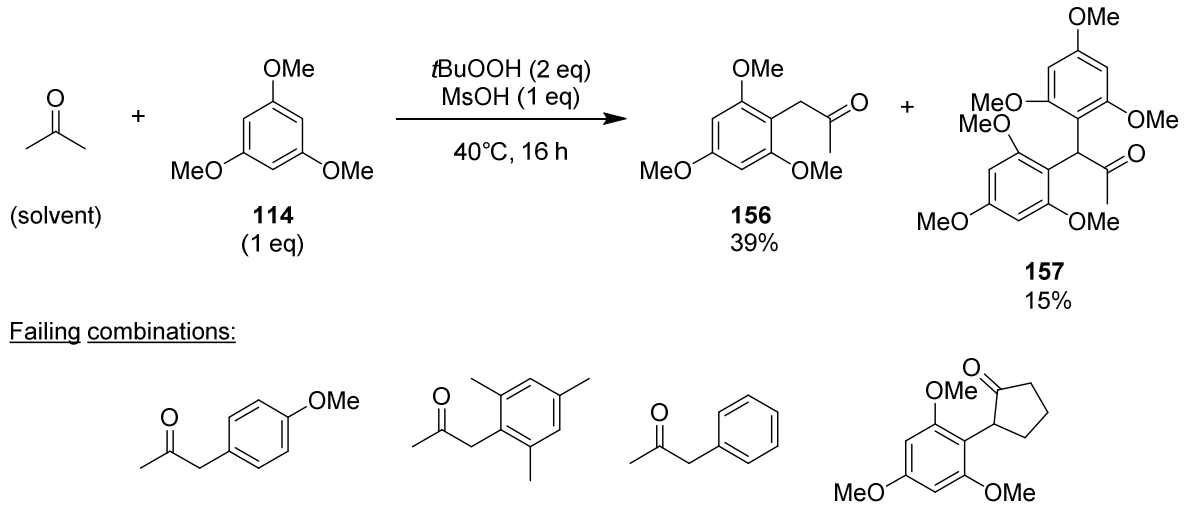
4.3.1 Identification of Side Products

As mentioned in the previous section, when we tried to expand the scope of oxidative coupling chemistry using our newly discovered free radicals forming process, a side products was formed and identified as product **156** (Scheme 4-27).



Scheme 4-27: Identification of the side products of the oxidative coupling of **112a** and **114**.

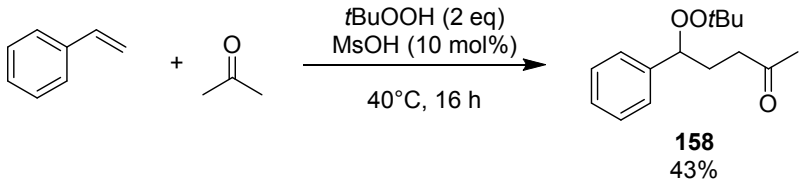
The acetone used as solvent had performed a radical C-C bond forming reaction, resembling the Minisci reaction,[80] with the electron rich arene **114** and product **156** was obtained in 15% yield along the desired **115a**. This result confirmed the involvement and the structure of radicals discussed in the previous chapter (see Scheme 4-22).



Scheme 4-28: Optimised conditions for the coupling of acetone and **114**.

After a quick optimisation, it was found that higher acid loadings improved yields

(Scheme 4-28, upper part). Indeed, when one equivalent of methane sulfonic acid and two equivalents of tBuOOH were used, **156** was obtained in 39% yield but **157**, resulting from overreaction of **156,** was also obtained in 15% yield. However, when other substrates were investigated under these "optimised" conditions, no other combination was found to give arylation of ketones (Scheme 4-28, bottom part). Since aromatic compounds were clearly not the ideal reaction partner, another free radical acceptor was sought for and styrene was used instead (Scheme 4-29).



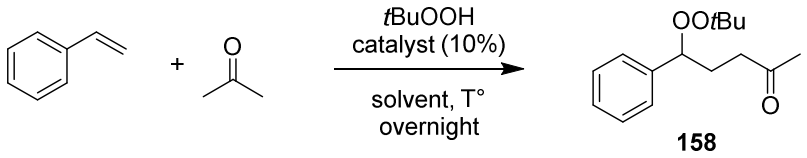
Scheme 4-29: Initial experiment using styrene as a radical acceptor.

Interestingly, product **158** was obtained in 43% isolated yield after one night of reaction. This product presented an interesting 1,4 oxygenation pattern that would normally require *Umpolung* reactivity to be accessed by classical ionic reactivities. It also resulted from a double oxidative functionalization of a simple olefin, a subject of great interest.[81]

4.3.2 Optimisation of Reaction Conditions

The reaction conditions for the formation of **158** were then optimised (Table 4-9). Since it was found that **158** was stable under reaction conditions, all reactions were performed overnight to ensure full conversion of *t*BuOOH and for convenience purposes. As compared to Scheme 4-29, increasing the temperature to 60°C and using 4 equivalents of *t*BuOOH improved the yield to 55% (entry 1). Other catalysts were investigated and red-ox active copper and iron salts only gave complicated reaction mixtures with no trace of **158** detected (entries 2-5). On the other hand, Brønsted acids seemed very suitable. As expected from the results of the previous chapters, strong acids had to be used. Sulfuric, nitric and sulfonic acids all gave similar yields of 53% to 57% (entries 1, 6,7 and 9), with para-toluene sulfonic acid (pTSA) giving the highest yield (entry 9). If TFA was used, only 9% of **158** was obtained (entry 8).

Table 4-9: Optimisation of the reaction conditions for the formation of **158**.



158

Entry	Solvent	T° (°C)	Catalyst	n° eq *t*BuOOH	Yield (%)[a]
1	acetone	60	MsOH	4	55
2	acetone	60	CuBr	4	0
3	acetone	60	$CuCl_2$	4	0
4	acetone	60	$FeCl_2$	4	0
5	acetone	60	$Fe(OTf)_3$	4	0
6	acetone	60	H_2SO_4	4	55
7	acetone	60	HNO_3	4	53
8	acetone	60	TFA	4	9
9	acetone	60	pTSA	4	57
10	MeCN	60	pTSA	4	58
11	MeCN	60	pTSA	4	31[b]
12	MeCN	60	pTSA	4	49[c]
13	MeCN	60	pTSA	3	48
14	MeCN	60	pTSA	5	58
15	MeCN	50	pTSA	4	62
16	**MeCN**	**50**	**pTSA**	**4**	**74 (74)[d]**
17	MeCN	50	$Zn(OTf)_2$	4	0
18	MeCN	50	$TiBr_4$	4	0
19	MeCN	50	$AlCl_3$	4	46
20	MeCN	50	$Sc(OTf)_3$	4	65

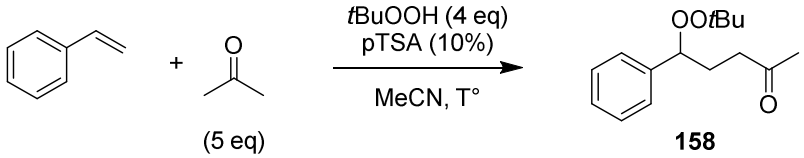
Reaction conditions: styrene (0.5 mmol), acetone (2.5 mmol), *t*BuOOH (5.5 M solution in decane) and acid (0.05 mmol) mixed in solvent (2 mL) and let to react overnight (~16h) a: NMR yields using mesitylene as an internal standard, isolated yield in parentheses. b) 1 equivalent of acetone c) 3 equivalents of acetone d) degassed mixture

After screening solvents, it was found that acetonitrile was as effective as acetone itself using pTSA as catalyst (entry 10 compared to entry 9). However, an excess of acetone had to be used in order to keep the same efficiency, with 5 equivalents being an optimal amount (entries 11 and 12 compared to entry 10). Similarly, reducing the amount of *t*BuOOH to three equivalents reduced the yield to 48% (entry 13), while increasing it to five equivalents had no effect (entry 14, 58%). Reducing the temperature to 50°C proved to be beneficial (entry 15, 62%) as well as performing the reaction with strict exclusion of oxygen (entry 16, 74%).

Under these optimised conditons, selected Lewis acids were reinvestigated but none showed any improvement of yields as compared to pTSA. Zinc triflate and titanium tetrabromide gave no conversion (entries 17 and 18), while aluminum trichloride and

scandium triflate gave moderate to good yields of **158** (entries 19 and 20, 46% and 65%, respectively). The fact that some Lewis acids are potent catalysts for this reaction supports the fact that this reaction is truly an acid catalysed process and does not involve redox chemistry. However, even though Lewis acids are also suitable catalysts, for obvious cost reasons and ease of handling, pTSA was preferred for the rest of this study.

Table 4-10: Effect of temperature on the formation of **158**.



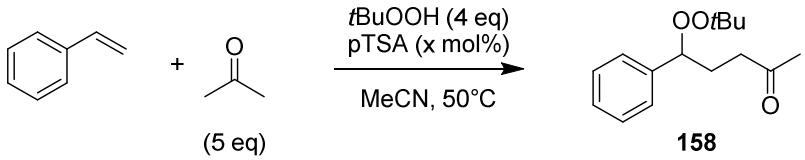
Entry	Temperature	Time (h)	Yield (%)
1	50	4	74
2	40	21	72
3	35	16	68
4	30	16	59
5	r.t.	72	0

The effect of temperature was then investigated (Table 4-10). Lowering the temperature from 50°C (entry 1, 74%) to 40°C (entry 2) led to a similar 72% yield of **158** but needed a longer reaction time (more than 6 hours compared to 4 hours). Lowering the temperature further to 35°C and 30°C and stopping reactions after 16 hours showed a similar trend to give 68% and 59%, respectively (entries 3 and 4). If the reaction was run at room temperature, no conversion was observed after three days (entry 5). Since the reactions were equally clean than for the optimised conditions, we assume that letting the reactions run longer would lead to similar yields and that the reaction rate is the only factor influenced by reaction temperature.

Similarly to temperature, the acid loading only seemed to influence the reaction rates (Table 4-11). Under the previously optimised conditions, full conversion is achieved in 4 hours to afford 74% of **158** (entry 1). Using 5 mol% of pTSA, a longer reaction time was needed (more than 6 hours, left to react overnight) but a slightly improved yield of 76% was obtained (entry 2). Similarly, when 2 mol% was used, full conversion was achieved overnight and and identical 76% yield obtained (entry 3). By reducing the acid loading further to 1 mol%, however, full conversion was not observed in 24 hours and a slightly reduced 71% yield obtained (entry 4). The limit of reactivity was attained when 0.1 mol% of pTSA were

used. In this case, after 3 days of reaction, only traces of **158** were detected (entry 5, 3%).

Table 4-11: Effect of acid loading on the formation of **158**.



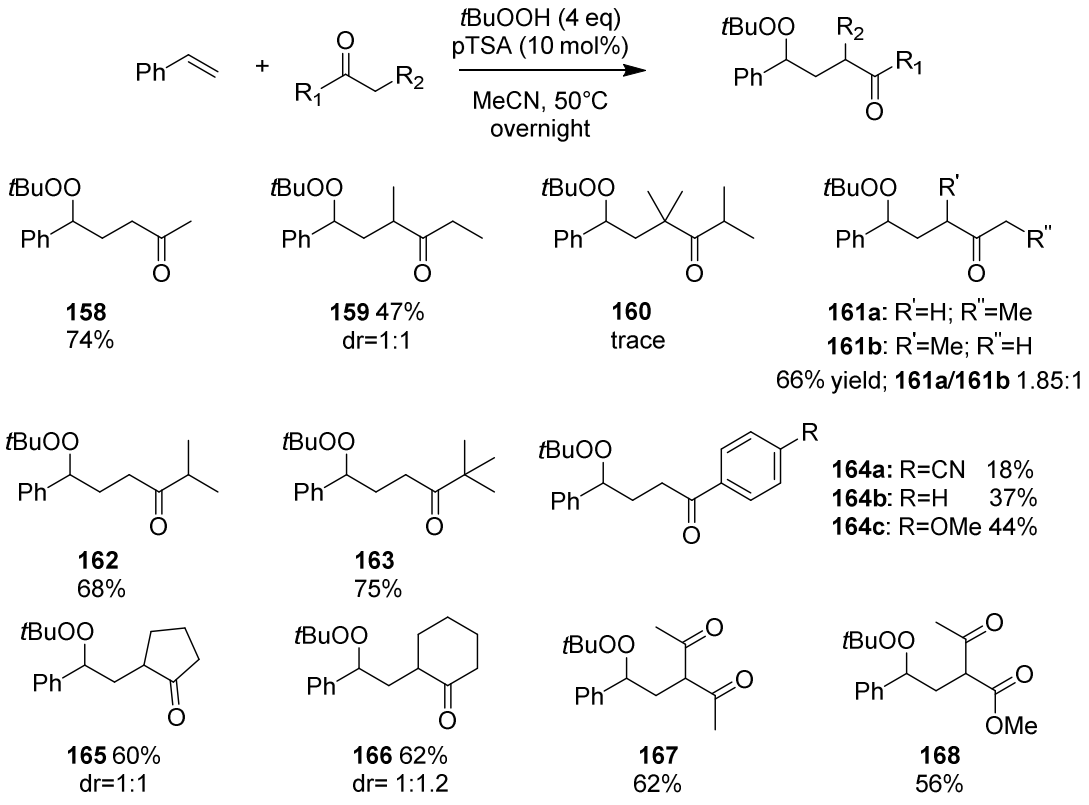
Entry	Loading (%)	Time (h)	Yield (%)
1	10	4	74
2	5	16	76
3	2	16	76
4	1	24	71
5	0.1	72	3

4.3.3 Substrate Scope of the Peroxydation-alkylation of Styrene Derivatives

The substrate scope of this transformation was then explored. To study the ketone partner, we chose the conditions reported in Table 4-9 entry 16 – i.e. 5 equivalents of ketone, 4 equivalents of *t*BuOOH and 10 mol% of pTSA let to react overnight at 50°C (Scheme 4-30). Indeed, lowering the acid loading from 10 mol% to 2 mol% was possible with acetone without any impact on the yield of product (see Table 4-11) but this behaviour was not general for all ketones, therefore the original optimised conditions were chosen instead.

If acetone gave product **158** in a high 74% yield, a major drop in reactivity was observed when moving from ketones with primary α-carbons to secondary and tertiary α-carbons. Indeed, using diethyl ketone afforded product **159** in 47% yield and diisopropyl ketone only gives traces of **160**. This lack of reactivity could be attributed to the increasing steric hindrance of the attacking radical. Alternatively, the relative increased stability of this radical could favour termination processes and prevent addition to styrene. Interestingly, selectivity towards primary carbon was observed when two regioisomers could be formed. In the case of butanone, where a primary and a secondary carbon can react, a mixture of linear (**161a**) and branched (**161b**) product was formed in a 1:1.85 ratio in favour of **161a** in an overall yield of 66%. When a primary and a tertiary carbon were present in the α-position, such as in 3-methyl-2-butanone, the product resulting from the attack of the primary carbon was the exclusive product observed to give **162** in a good 68% yield. Pinacolone was a

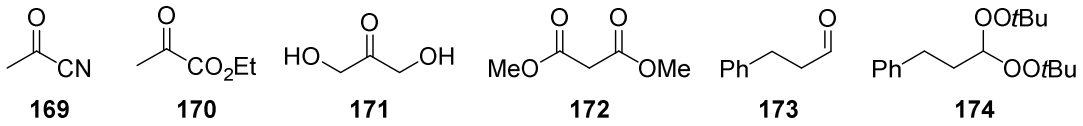
similarly good partner as acetone and gave product **163** in 75% yield. In order to probe the effect of the electronic properties of the ketone, substituted acetophenones were used. An electron-withdrawing cyano group gave a reduced yield (**164a**, 18%) as compared to unsubstituted acetophenone (**164b**, 37%). An electron donating methoxy substituent further improved the yield of **164c** to a moderate 44%. Cyclic ketones were well tolerated and cyclopentanone and cyclohexanone gave good yields of products **165** and **166** (60% and 62%, respectively). It is to be noted that these yields were higher than when their acyclic counterpart was used. Indeed, product **159** was obtained in only 47% while both cyclic ketones investigated gave products **165** and **166** in yields above 60%. 1,3-Dicarbonyl compounds were also suitable for this transformation. Acetyl acetone gave **167** as a single regioisomer in 62% yield while methyl acetoacetate afforded **168** in 56% yield.



Scheme 4-30: Scope of the ketone partner of the peroxidation-alkylation of styrene.

Some ketones failed to give keto-peroxides (Scheme 4-31). As could already be envisioned from the results of electron deficient acetophenones, electron poor ketones were not reactive under these conditions. Acetyl cyanide **169** and ethyl pyruvate **170**, bearing strongly electron withdrawing substituents directly adjacent to the carbonyl group gave no conversion. Dihydroxy acetone **171** similarly led to no formation of the

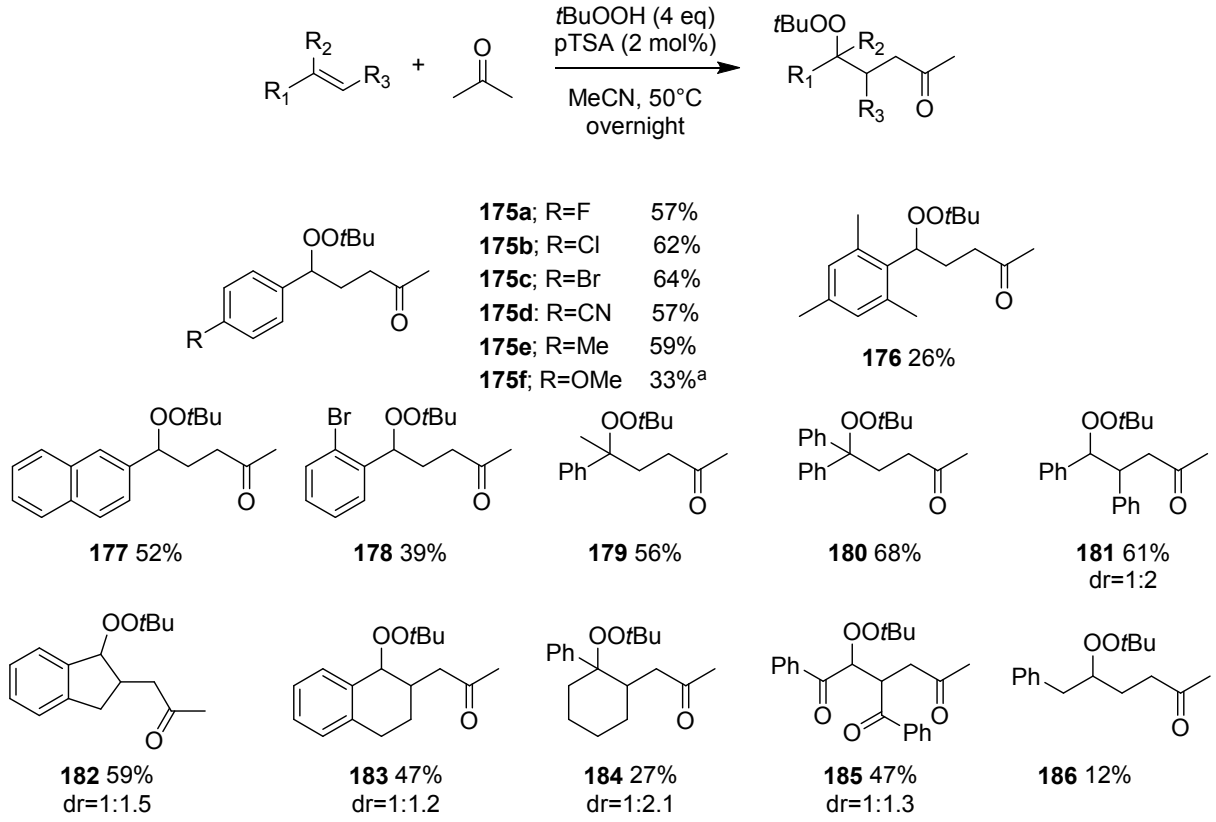
corresponding peroxide, suggesting that free hydroxyl groups are not tolerated in this transformation. Dimethyl malonate **172** proved to be unreactive under these conditions and no conversion was observed. When hydrocinnamaldehyde **173** was used, the only isolated product was the bis peroxide adduct **174**.



169 **170** **171** **172** **173** **174**

Scheme 4-31: Carbonyl substrates failing to give desired peroxides under optimised conditions.

The olefin partner of the reaction was then explored using slightly different conditions (Scheme 4-32). Since it was found in Table 4-11 that a lower acid loading only resulted in lower reaction rates but a slightly increased yield, we chose these conditions to study the olefin scope using acetone as a standard ketone. Therefore, the conditions used were as follows: 5 equivalents of acetone in acetonitrile, 4 equivalents of *t*BuOOH and 2% of pTSA let to react overnight at 50°C.



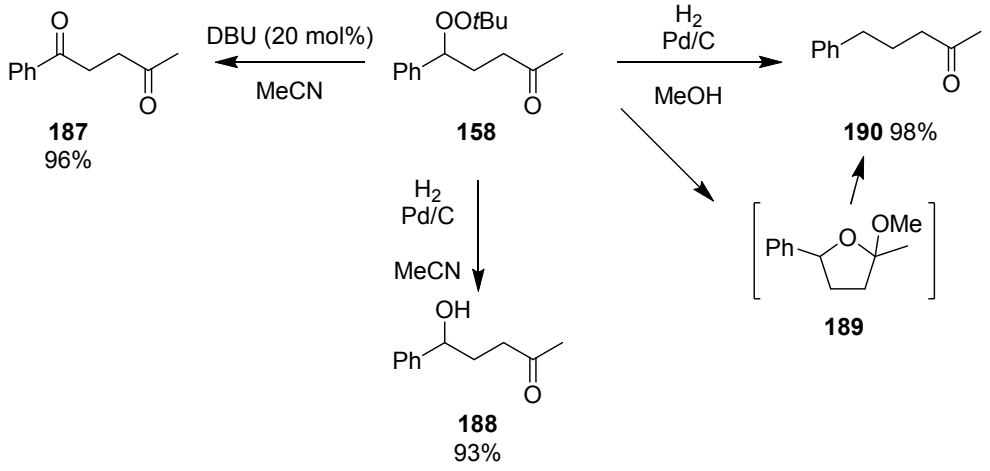
Scheme 4-32: Scope of the olefin partner of the peroxidation-alkylation of styrene. a) acetone as solvent, 10 mol% pTSA and 40°C.

The effect of the electronic properties of styrenes were first evaluated. Halogen substituents were generally well tolerated and gave high yields of products **175a**-**175c** in 57% to 64%. A strongly electron withdrawing cyano substituent had no significant effect on the yield of **175d** (57%). Similarly, a mildly electron donating methyl substituent gave **175e** in 59% yield. By contrast, a strongly electron donating methoxy group led to a sharp reduction in yield and only traces of **175f** were observed under these conditions. This is however attributed to thermal instability of **175f** under our reaction conditions as degradation products could be observed by TLC analysis of the reaction mixture, the estimated amount of **175f** remaining more or less constant with increasing conversion. If the reaction was run in acetone as solvent at 40°C using 10 mol% of pTSA, **175f** could be isolated in 33% yield. 2,4,6-Trimethyl styrene, combining electron donating groups and steric hindrance gave **176** in a low 26% yield. The influence of steric hindrance was then studied and vinyl naphthalene gave a reduced yield of 52% of **177** as compared to styrene. 2-Bromostyrene, having a very bulky substituent in close proximity of the reactive site similarly gave a moderate 39% yield of **178**. Substitution on the α-carbon of the styrene partner resulted in moderate to good yields of products as shown by the reaction of α-methyl styrene (**179**, 56%) and diphenyl ethylene (**180**, 68%). Substitution on the β-carbon was similarly well tolerated. *trans*-Stilbene gave 61% of **181** in a 1:2 dr. *cis*-Stilbene gave an identical ratio of diastereoisomers but in a much lower 21% yield, as previously reported for the reactivity of stilbenes towards free radicals.[82] Cyclic styrene derivatives could also be used. Indene gave **182** in 59% yield and dihydronaphthalene gave **183** in 47% yield. Using phenyl-cyclohexene, in which both α and β carbons are substituted, only 27% of **184** could be obtained. Vinyl pyridines did not give any conversion, due to their inherent basicity, showing once more the importance of the acid catalyst in this transformation.

Dibenzoylethene, a non styrenic olefin having an electron withdrawing substituent was a suitable substrate and gave **185** in a moderate 47% yield. On the other hand, allyl benzene, bearing no resonance stabilising group adjacent to the double bond, was a poor substrate and afforded **186** in only 12% yield, along with relatively large amounts of its saturated analogue. This strongly suggests that a resonance stabilising group adjacent to the peroxide group being introduced is essential to achieve good reactivity under these reaction conditions.

4.3.4 Further Transformations of γ-keto-peroxides

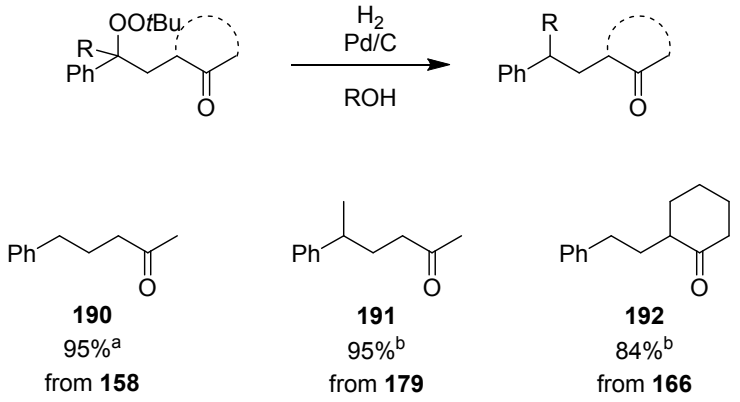
Using **158** as a model substrate, transformations of our peroxides to more synthetically useful products were then investigated (Scheme 4-33).



Scheme 4-33: Further transformations of **158** to valuable compounds.

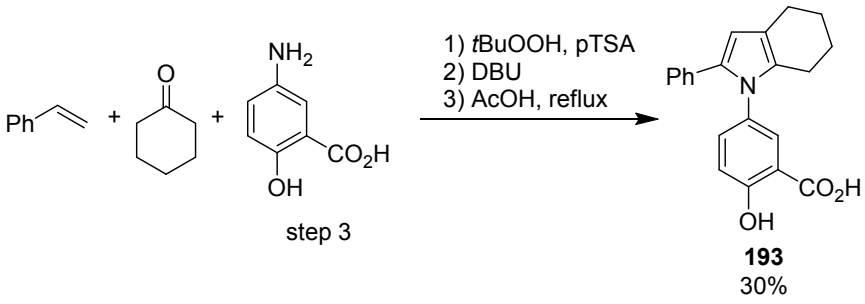
In the presence of catalytic amounts of base, a Kornblum-DelaMare elimination was achieved,[83] affording the 1,4-diketone **187** in an excellent 96% yield. This type of dicarbonyl compounds is an important class of intermediates in the synthesis of heterocycles such as furans[84] and pyrroles or thiophenes.[85] When subjected to hydrogenation conditions in acetonitrile, the homo aldol product **188** was obtained in 93% yield. If the hydrogenation was performed in methanol as solvent, complete and quantitative reduction of the benzylic position was observed through the formation and further reduction of the cyclic acetal **189**, which could be isolated if the reaction was not run to completion. The ketone **190** was then obtained in 98% yield, resulting from a formal two step hydroalkylation of styrene.

In order to confirm that this reduction behaviour is a general characteristic of this type of compounds, different substrates were tested under these conditions (Scheme 4-34). If the reduction of **158** was performed in isopropanol instead of methanol, **190** was still isolated in excellent yield. When **179** and **166** were subjected to the same conditions, the corresponding alkanes **191** and **192** were isolated in 95% and 84% respectively. These results strongly support the generality of this transformation.



Scheme 4-34: Reduction of selected keto-peroxides; a) reaction performed in isopropanol; b) reaction performed in methanol.

Even though we never experienced any problem with working or handling the keto-peroxides described in this chapter, the isolation and handling of peroxides is generally assumed to be hazardous. Therefore we explored the possibility of using them as intermediates without the need for isolation, in a one-pot fashion (Scheme 4-35).

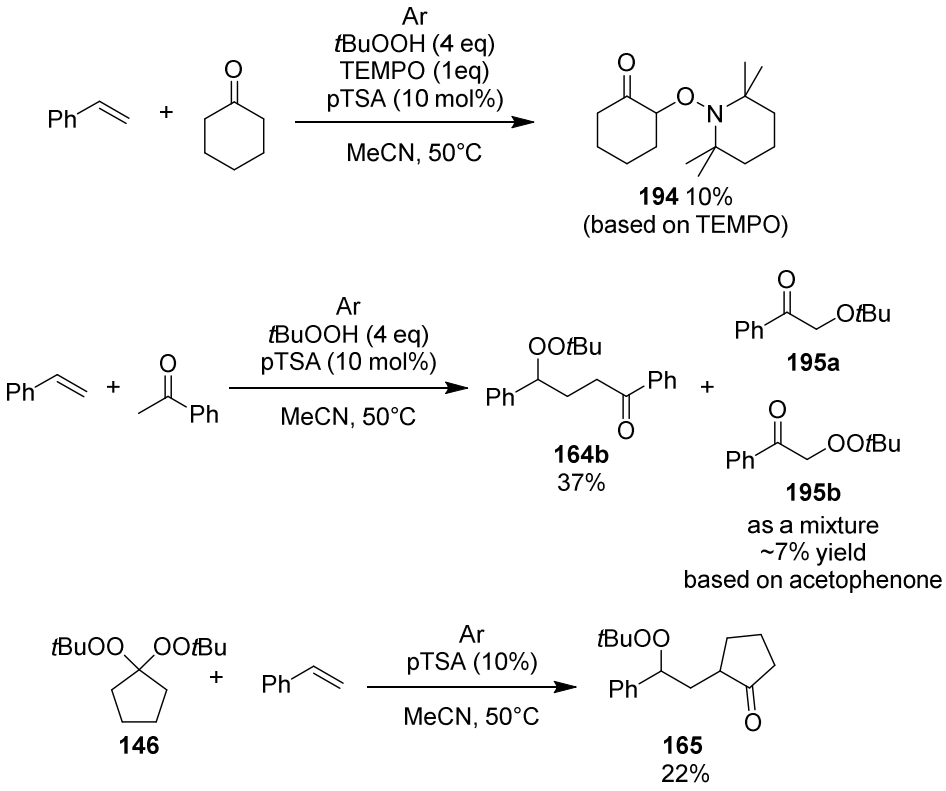


Scheme 4-35: One-pot synthesis of a biologically relevant pyrrole.

Pleasingly, we could combine the formation of **166** (see Scheme 4-30) with the formation of the corresponding 1,4-diketone (see Scheme 4-33) and literature reports for a pyrrole ring formation. We could obtain **193**, a non steroidal anti-inflammatory agent,[86] in a moderate 30% yield over three steps performed in the same flask and after a single purification. If all the steps were performed separately and the corresponding intermediates isolated, an only marginally better overall 42% yield over three steps was achieved, showing the competitiveness of these one-pot conditions.

4.3.5 Mechanistic Considerations

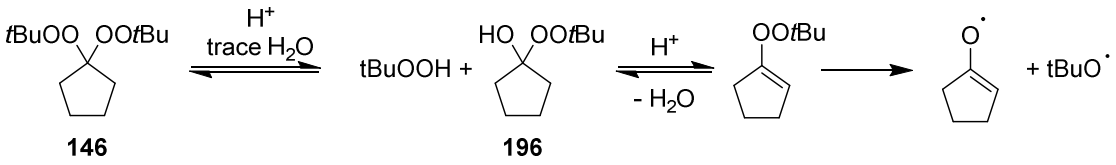
In order to better understand and confirm some assumptions of section 4.2.7, the following experiments were performed (Scheme 4-36).



Scheme 4-36: Mechanistic experiments on the oxidative functionalization of olefin under Brønsted acid catalysis.

When the reaction of styrene and cyclohexanone was performed in the presence of one equivalent of TEMPO, a radical trapping reagent, the formation of **166** was completely suppressed and 10% (based on TEMPO) of the adduct **194** could be detected in the reaction mixture. During the isolation of product **164b**, small amounts (5-10% yield, based on acetophenone) of side products **195a** and **195b** were also isolated. These two experiments unequivocally confirm the radical nature of the bond forming processes and the involvent of an α-carbonyl free radical, as well as that of *t*BuO• and *t*BuOO• radicals. Finally and by analogy with the discussion in section 4.2.8, **146** was used as a radical precursor. **165** was indeed obtained in 22% yield, supporting the role of peroxy acetals in the reaction mechanism. The direct involvement of **146** for the formation of radicals is however unlikely

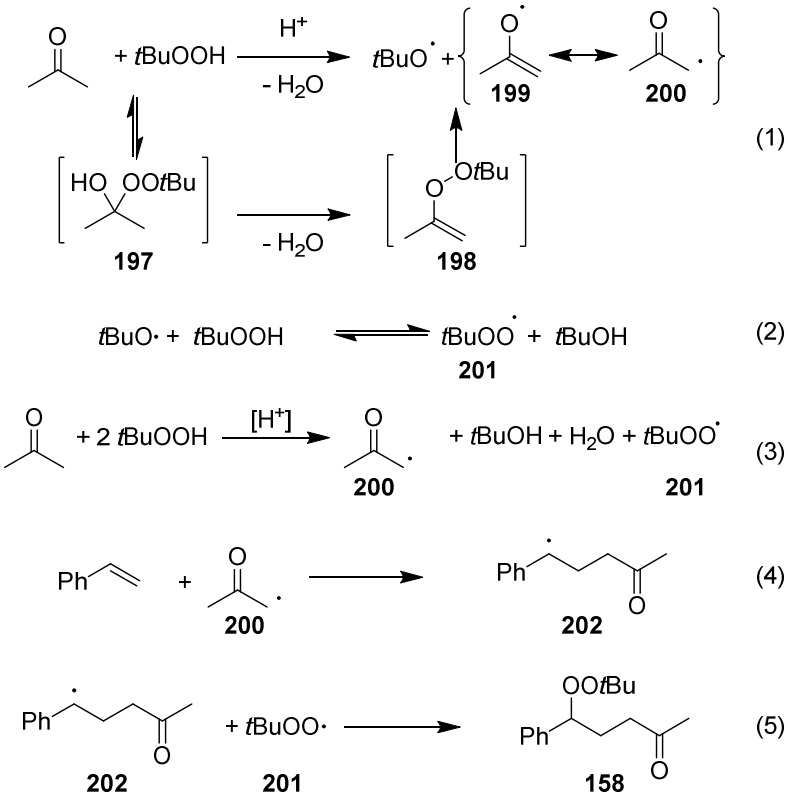
and presumably proceeds as shown in Scheme 4-37.



Scheme 4-37: Plausible mechanism of radical formation from **146**.

In the presence of traces of water, **146** collapses to the hemiacetal **196** and *t*BuOOH. As discussed in section 4.2.8, **196** affords a vinyl peroxide, which decomposes to two free radicals.

Based on this information, a plausible mechanism is shown (Scheme 4-38).



Scheme 4-38: Plausible mechanism of the peroxidation-alkylation of styrene.

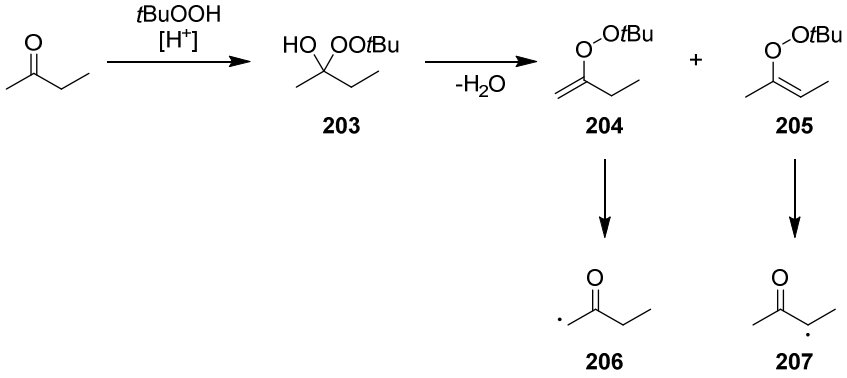
By analogy with the mechanism described in section 4.2.8 (Scheme 4-22), the carbon centered radical **200** is formed via a multistep process. In the presence of a strong acid and a hydroperoxide, acetone forms intermediate **197**, which upon dehydration gives the vinyl peroxide **198**. Very facile homolytic cleavage of the peroxide bond affords **199**,

which is best described as its resonance structure **200**, and a *t*BuO• radical (equation 1). This radical then abstracts a hydrogen atom from excess *t*BuOOH to give the radical **201** and *tert*-butanol in a fast equilibrium (equation 2).[79] By combining these separate steps, a balanced equation is shown (equation 3). Under acidic conditions, one equivalent of acetone reacts with two equivalents of *t*BuOOH to generate radicals **200** and **201**, one equivalent of *t*BuOH and one equivalent of water. **200** adds to the double bond of styrene to afford the stabilised radical **202** (equation 4), which recombines with **201** to afford the γ-ketoperoxide **158** (equation 5). Obviously, all these intermediate radicals can be subject to termination processes such as dimerisation, concurrent radical-radical coupling and polymerisations, explaining the need for a relatively large excess of reactants. The selectivity – which can again be attributed to the persistent radical effect[67] - and yields of the reaction are still quite remarkable, given the complex interplay of radical species involved.

The results of Table 4-10 and Table 4-11 seem to imply that temperature and acid loading are only affecting the reaction rate and not the yield of product. This would be consistent with a rate determining step involving the acid catalyst. Based on the results discussed in section 4.2, the generation of free radicals from the ketone seems a good candidate for this rate determining step (equation 1 of Scheme 4-38). Radical reactions are generaly known to be governed by very high reaction rates.[87] Indeed, it is generally assumed that ionic reactions are several orders of magnitude slower than their radical counterparts, as shown by typical rates of 1 to 10^{-6} $M^{-1}s^{-1}$ while radical reactions involve rates of 10^{2} to 10^{8} $M^{-1}s^{-1}$. The radical addition/combination steps can then reasonably assumed to be considerably faster than the steps preceeding their formation. Furthermore, the decomposition of alkenylperoxides such as **198** via homolytic bond cleavage of the O-O bond has been shown to be an extremely facile process.[77] One can then expect the lifetime of **198** under the reaction conditions to be very short. Therefore, the formation of **197** or its dehydration to **198** are most likely the decisive steps for the kinetics of the reaction.

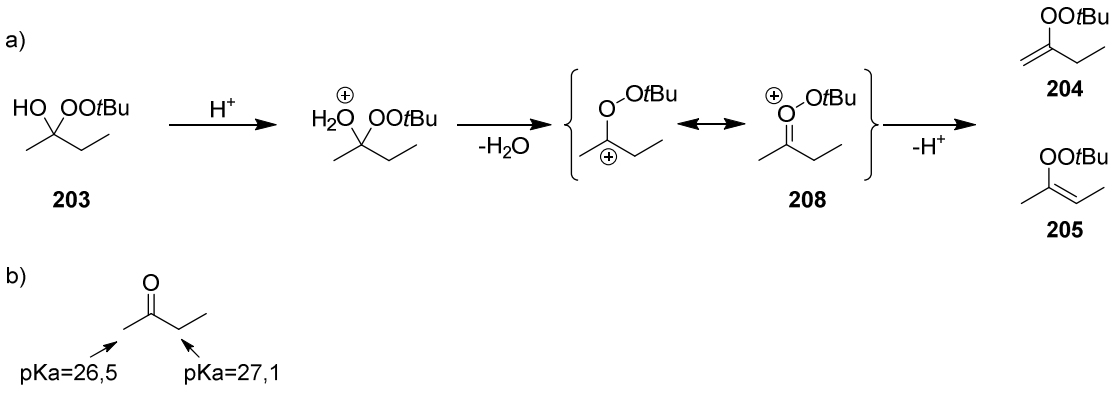
Another puzzling aspect of this reaction is the regioselectivity observed in the case of unsymmetrical ketone substrates. When butanone was used (see Scheme 4-30, product **161a** and **161b**), the product showed a modest preference (1:1.85 ratio) for the least substituted position of the ketone partner. This is in apparent contradiction with the

expected stability of the corresponding vinyl peroxide intermediate. Indeed, the final position of the unpaired electron on either one of the two carbon centers is most likely governed by the position of the unsaturation in the vinyl peroxide intermediate. Therefore, the elimination pathway to access the vinyl peroxide intermediate is crucial in controlling the regioselectivity of the radical formation. Following the mechanism of Scheme 4-38, one could expect that the formation of a tri-substituted internal alkene (**205**) from the tetrahedral intermediate **203** would be thermodynamically preferred compared to the formation of a di-substituted terminal alkene (**204**). Therefore, it would be reasonable to assume **207** to be preferred as compared to **206** (Scheme 4-39).



Scheme 4-39: Formation of unsymmetrical vinyl peroxides.

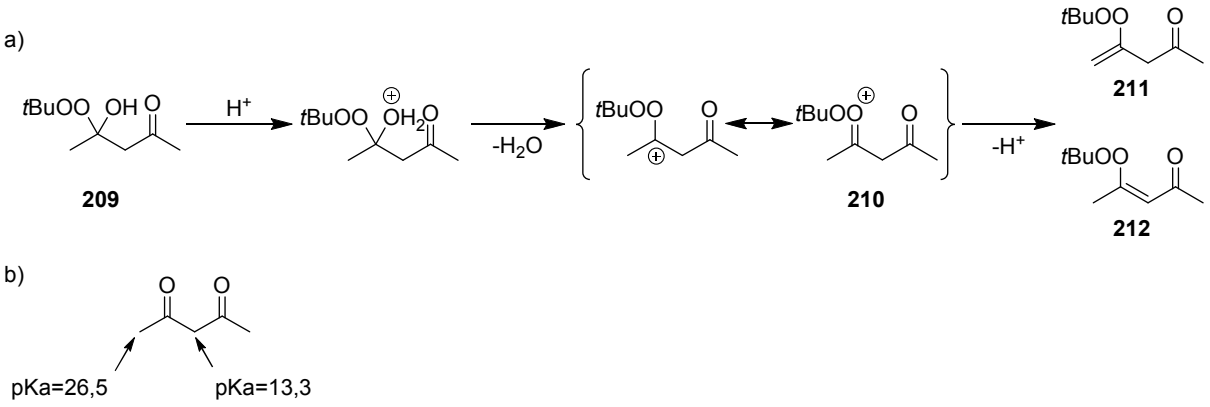
Under acidic conditions, the elimination must procede through the cation intermediate **208** *via* protonation of the OH group in **203** and loss of a water molecule. Further loss of a proton then generates the vinyl peroxide intermediates **204** and **205** (Scheme 4-40, a).



Scheme 4-40: Elimination mechanism towards vinyl peroxides and pKa values of butanone in DMSO.

Although **205** is certainly thermodynamically preferred as compared to **204**, steric factors are in its disfavour. **204**, on the other hand, is the easiest to form and therefore the kinetic product. Additionally, the homolytic decompositions of vinyl hydroperoxides are reported to be extremely facile and fast processes.[77c, 77d] Therefore, it is to be expected for the ratio of **206** and **207** to closely follow that of **204** and **205** formed under the reaction conditions, showing that the reaction is under kinetic rather than thermodynamic control.

In the case of a 1,3-dicarbonyl substrate, such as acetylacetone, the observed selectivity is the opposite: the more sterically hindered **167** is the only product detected (see Scheme 4-30). In this case, the acidities of the C-H bonds involved are very different and this difference is most likely the reason for the observed selectivity (Scheme 4-41).



Scheme 4-41: Elimination pathway to **211** and **212** and pKa values of acetylacetone in DMSO.

Unlike butanone, the pKa values of the two possible sites of elimination are extremely different, with a difference of 13 units of pKa. The same sterics and thermodynamic arguments can be raised for the intermediate **210** than for **208** but the acidity difference for the two positions is so large that it can be expected to completely dominate steric factors in this case. Therefore, the exclusive site of elimination will be the central carbon, leading to **212**, as shown by the product isolated and the absence of detectable amounts of the other regioisomer derived from **211**.

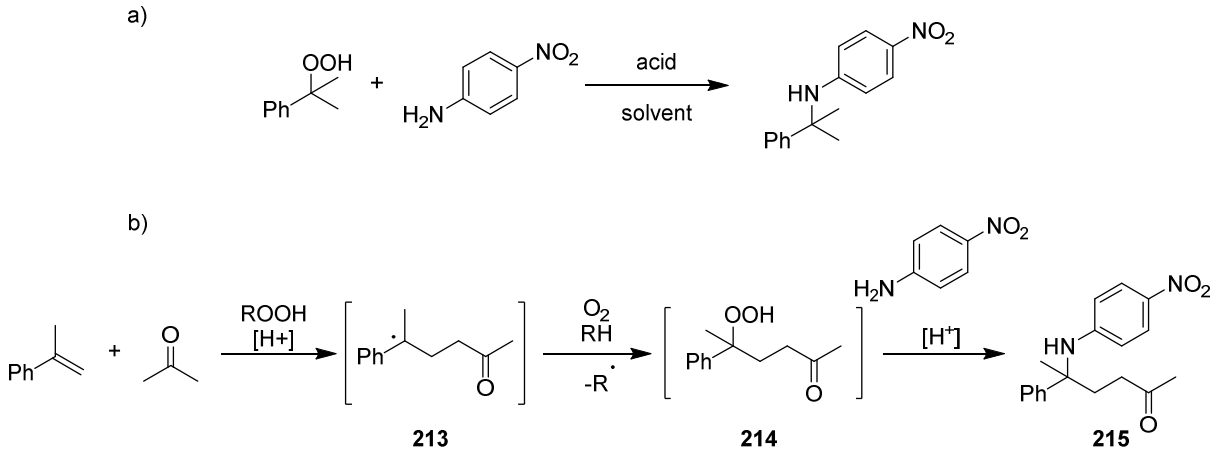
4.3.6 Concluding remarks

The reaction described in this chapter takes advantadge of the observation that radicals are formed from ketones and hydroperoxides in the presence of a strong acid catalyst that was made during the mechanistic study of the autoxidative coupling of xanthene described in section 4.2. This phenomenon had been observed before,[75] and exploited as a mild method of initiation of radical polymerisations.[88] It was however not understood in detail in terms of mechanism and the nature of radicals generated. To the best of our knowledge, the work presented in this dissertation represents the first rationalization of this phenomenon and its exploitation for an unprecedented and synthetically useful transformation. Because this chemistry relies on the reactivity of free radicals, it can access products which would be unaccessible through classical ionic pathways. In particular, the 1,4 arrangement of the oxygenated moieties obtained in the transformation described in this chapter is a challenge for ionic chemistry and requires *Umpolung* reactivity of one the components. Additionaly, the developed conditions are experimentally simple, water tolerant and use cheap and simple starting materials and catalysts.

4.4 Synthesis of Tetrahydroquinolines and Oxidative Cleavage of Styrene Derivatives

4.4.1 Initial Design and Experiment.

In an attempt to unify the concepts developed in the previous chapters and some studies that were conducted in our lab by Naeem Gulzar on the substitution of benzylic hydroperoxides (Scheme 4-42, a),[II] the following reaction was designed (Scheme 4-42, b).



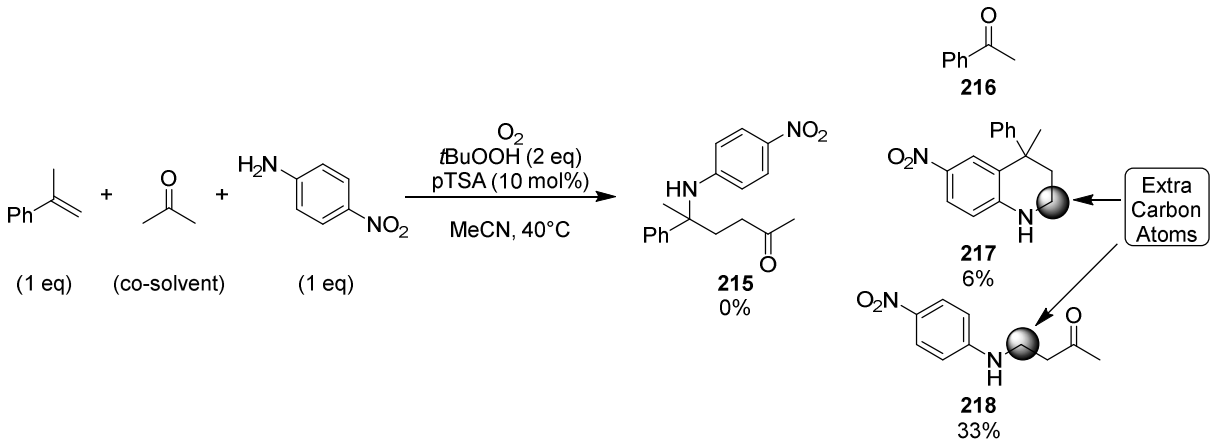
Scheme 4-42: Designed multicomponent alkylation-amination of styrene.

Following the same principle as in section 4.3, a radical attack of acetone onto α–methyl styrene would lead to radical **213**. If the reaction was performed under an oxygen atmosphere, the benzylic hydroperoxide **214** was expected to be formed. Based on the results of section 4.2.6, the hydroperoxide analogue of **179** was expected to be more reactive towards substitution than its *t*Bu analogue, to afford product **215**.

Accordingly, the experiment was performed but the results were quite different from expected (Scheme 4-43). Indeed, when acetone was allowed to react with α-methyl styrene and *para*-nitro aniline in the presence of *t*BuOOH and pTSA under an atmosphere of oxygen, **215** was not detected from the reaction mixture but other products were isolated instead. Acetophenone **216** was qualitatively identified as a reaction product. **217** and **218**, incorporating one additional carbon atom from what would be expected from the starting

[II] PhD dissertation of Naeem Gulzar in Köln university, expected for 2014.

material used, were isolated from the reaction mixture in 6% and 33% yields, respectively. While the mechanism of formation of these products was mysterious at this stage, we decided to optimise the formation of **217**.

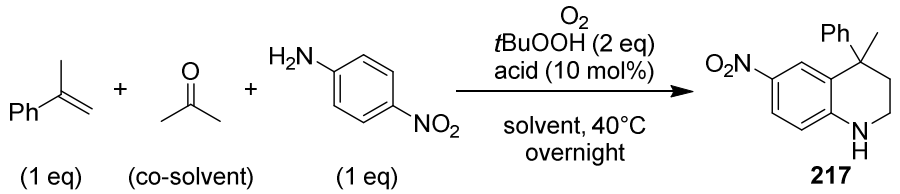


Scheme 4-43: Initial experiment.

4.4.2 Optimisation of the Reaction Conditions and Preliminary Scope.

A first screening of simple reaction conditions was performed to identify a starting point (Table 4-12).

Table 4-12: Solvent and acid screening.



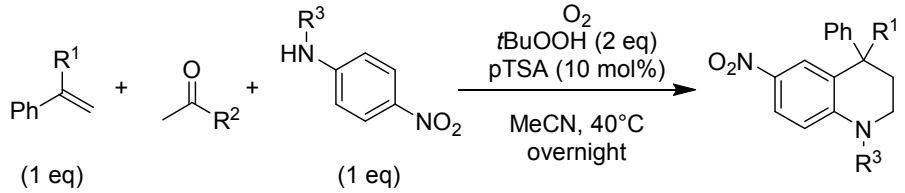
Entry	Solvent	Acid	Yield[a]
1	acetone	pTSA	trace
2	MeCN	pTSA	5%
3	toluene	pTSA	trace
4	AcOEt	pTSA	3%
5	DMSO	pTSA	-
6	MeCN	MsOH	2%
7	MeCN	TfOH	4%
8	MeCN	TFA	-
9[b]	MeCN	pTSA	-
10[c]	MeCN	pTSA	-

Reactions performed on a 0.5 mmol scale, 2 mL total volume using 0.5 mL of acetone; a) NMR yield using mesytilene as an internal standard, b) no *t*BuOOH, c) Argon atmoshpere

Screening of solvents showed that acetonitrile and ethyl acetate are compatible

with the formation of **217**, albeit in very low yields of 5% and 3%, respectively (entries 2 and 4). Acetone, toluene and DMSO gave traces of product at best (entries 1, 3 and 5). As expected from the previous chapters, a strong acid was needed, pTSA being slightly better than methane sulfonic acid (2%, entry 6), triflic acid (4%, entry 7) and trifluoroacetic acid, which was unable to give any conversion (entry 8). In the absence of *t*BuOOH, no reaction was observed (entry 9) and under an argon atmosphere, product **179**, resulting from the alkylation peroxidation of styrene, was exclusively formed (see section 4.3) showing that molecular oxygen is crucial for the formation of **217**. Variation of substrates was then performed (Table 4-13).

Table 4-13: Variation of substrates.

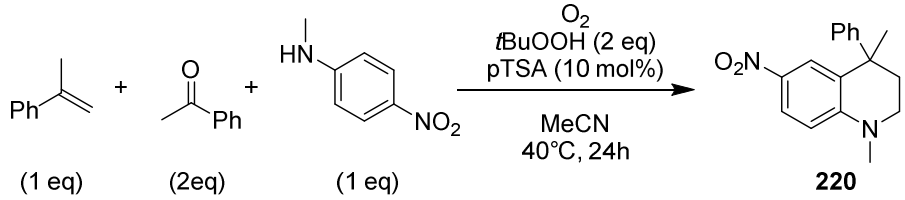


Entry	R^1	R^2	R^3	Product	Yield[a]
1	H	Me	H	**219**	-
2[b]	Me	Ph	H	**217**	5%
3[c]	Me	Me	H	**217**	3%
4	Me	Me	Me	**220**	15%
5[b]	Me	Ph	Me	**220**	15%

Reactions performed on a 0.5 mmol scale using 0.5 mL of acetone, 2mL total volume; a) NMR yield using mesitylene an internal standard, b) 2 equivalents of acetophenone instead of acetone, c) hydrogen peroxide instead of *t*BuOOH.

When simple styrene was used, the corresponding product **219** was not detected in the reaction mixture (entry 1). If 2 equivalents of acetophenone were used instead of acetone in large excess, an identical 5% of **217** was obtained (entry 2). If hydrogen peroxide was used instead of *t*BuOOH, conversion was still achieved but gave a lower 3% yield (entry 3). Because all the reaction described until now were hetereogeneous, due to the low solubility of the aniline starting material, a methyl substituted analogue was evaluated. If acetone was used as co-solvent, the reaction was homogeneous and 15% of **220** were obtained (entry 4). If acetophenone was used instead of acetone, an identical yield was achieved (entry 5). These conditions were selected for further optimisation (Table 4-14).

Table 4-14: Effect of additives, temperature and concentration.



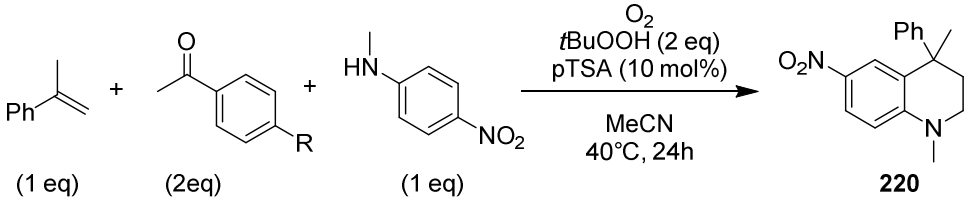
Entry	Additive	Solvent (mL)	Temperature (°C)	Yield[a] (%)
1	AcOH (5 eq)	1,25	40	19
2	benzoic acid (1 eq)	1,25	40	15
3	mCPBA (1 eq)	1,25	40	17
4	pTSA (0.9 eq)	1,25	40	19
5	AcOH (10 eq)	1,25	40	20
6	AcOH (1:1 with solvent)	1,25	40	24
7	AcOH (1:1 with solvent)	0,625	40	20
8	AcOH (1:1 with solvent)	2,5	40	18
9	AcOH (1:1 with solvent)	1,25	50	28
10	AcOH (1:1 with solvent)	1,25	60	24
11	AcOH (1:1 with solvent)	1,25	70	20
12[b]	AcOH (1:1 with solvent)	1,25	50	29

Reactions performed on a 0.5 mmol scale; a) NMR yield using mesytilene as an internal standard, b) 48 hours reaction time

Acid additives were first investigated. Adding five equivalents of acetic acid improved the yield of **220** to 19% (entry 1). One equivalent of benzoic or meta-chloroperbenzoic acid, being an acid and an oxidant, had no significant effect and gave **220** in 15% and 17%, respectively (entries 2 and 3). Using a stoichiometric amount of pTSA gave an identical 19% as compared to five equivalents of acetic acid (entry 4). The amount of acetic acid was then increased up to a 1:1 mixture of acetonitrile and acetic acid. The yields improved with increasing the amount of acid (entries 5 and 6) to afford 24% of **220**. Concentration was then varied but concentrating or diluting the mixture both led to diminished yields (entries 7 and 8). Increasing the temperature to 50°C was beneficial (entry 9, 28%) but further increase in temperature led to lower yields (entries 10 and 11). Performing the reaction for 48 hours instead of 24h had no significant effect on the yield (entry 12).

Since it was observed that the same product **220** was formed no matter if acetone or acetophenone was employed, the ketone partner was then varied to assess any difference in behaviour (Table 4-15).

Table 4-15: Effect of the nature of the ketone on the reaction outcome.

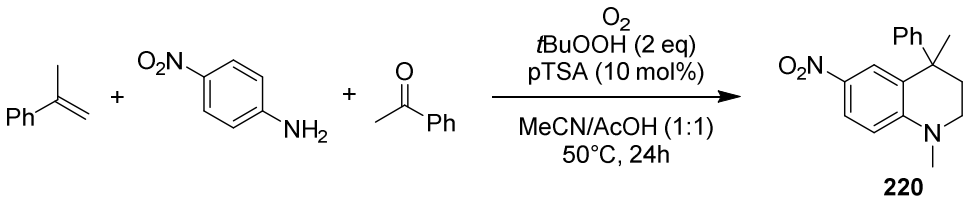


Entry	R	Yield[a] (%)
1	NO_2	21
2	CN	20
3	H	29
4	Me	30
5	OMe	28

Reactions performed on a 0.5 mmol scale; a) NMR yield using mesytilene as an internal standard.

In all cases, **220** was formed but the electronic nature of the ketone had an effect on the yield. As could be expected from the results of section 4.3, electron poor ketones were less efficient than electron neutral or rich ones. Nitro and cyano substituted acetophenones afforded **220** in 21% and 20% yield, respectively (entries 1 and 2). Methyl and methoxy substituted acetophenones gave almost identical yields to acetophenone (entries 3-5, 28% to 30%). For the purpose of convenience, acetophenone was then chosen as the standard ketone for the rest of this study. The stoechiometry of the reactants was then investigated (Table 4-16).

Table 4-16: Varying the stoechiometry of reactants.

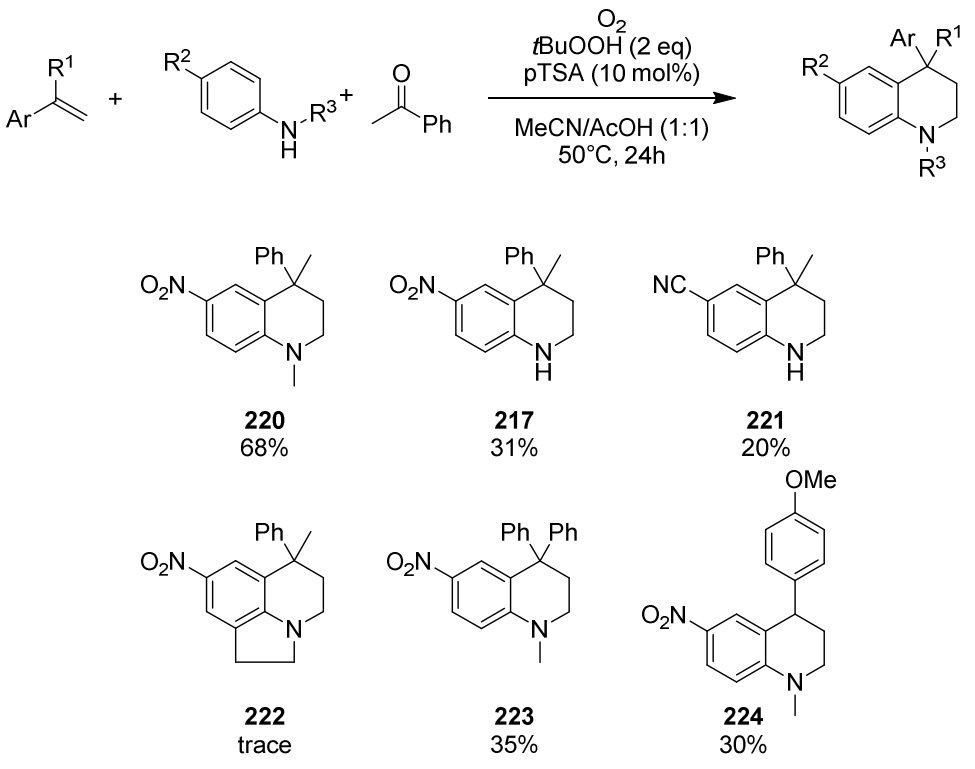


Entry	Styrene (eq)	Aniline (eq)	Acetophenone (eq)	Yield[a] (%)
1	1	1	2	29
2[b]	1	1	2	21
3	1	1	1	26
4	1	4	4	30
5	2	1	2	52
6	3	1	3	56
7	4	1	4	68
8	5	1	5	72
9	4	1	1	62
10	4	1	2	62

Reactions performed on a 0.5 mmol scale; a) NMR yield using mesytilene as an internal standard, b) 4 equivalents of *t*BuOOH

When the amount of tBuOOH was increased from two equivalents (entry 1, 29%) to four equivalents, a drop in yield was observed (entry 2, 21%). Decreasing the amount of acetophenone to one equivalent only had a marginal effect and **220** was obtained in 26% yield (entry 3). To determine which component is the crucial reagent to achieve good yields, a large excess of both aniline and acetophenone were used (entry 4) but no improvement in yield was observed. If para-nitro aniline was used as the limiting reagent and the styrene and acetophenone used in two equivalents, the yield went from 29% to 52% (entry 5) suggesting that styrene is the crucial reagent of this reaction. Further increasing the excess of styrene and ketone led to a steady improvement of yield (entries 6 to 8) up to 72% when five equivalents of both reagants were used (entry 8). It seems, however, that a large excess of ketone is not required since using only one equivalent of both aniline and ketone and four equivalents of styrene only had a minor effect on the yield (entry 7, 68% versus entry 9 and 10, 62%).

With these optimised conditions in hand, we looked at a preliminary scope of this transformation (Scheme 4-44).

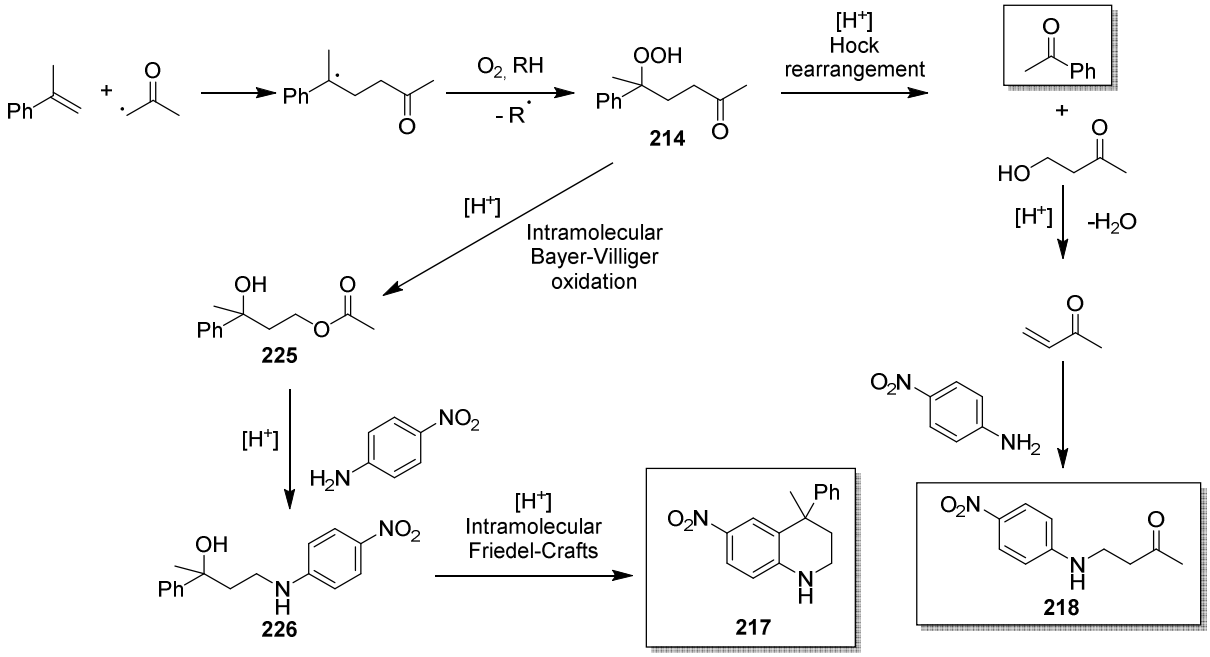


Scheme 4-44: Preliminary substrate scope for the synthesis of tetrahydroquinolines.

Under optimised conditions **220** was isolated in 68% yield. Using unsubstituted anilines generally gave much lower yields as exemplified by product **217**, isolated in 31% yield. A nitro substituent on the aniline was not required since cyano substituted product **221** was obtained, albeit in a low 20% yield. Plain aniline was however found to be unreactive under these conditions, suggesting that an electron withdrawing substituent is necessary. *Para*-nitro indolenine, however, only gave traces of **222**. Varying the styrene partner was also possible. Diphenyl ethylene and *para*-nitro aniline afforded **223** in a modest yield of 35%, while *para*-methoxy styrene gave **224** in 30% yield. This quick evaluation of potential reaction partners was rather disappointing since apart from the optimised combination of α-methyl styrene, *para*-nitro aniline and acetophenone, all other combinations tried proved to give much lower yields. However, at this stage, the main question remaining unanswered was the mechanism of this reaction.

4.4.3 Mechanistic Considerations

Based on the information we gathered and discussed in the previous chapters, a tentitative mechanism was proposed (Scheme 4-45).



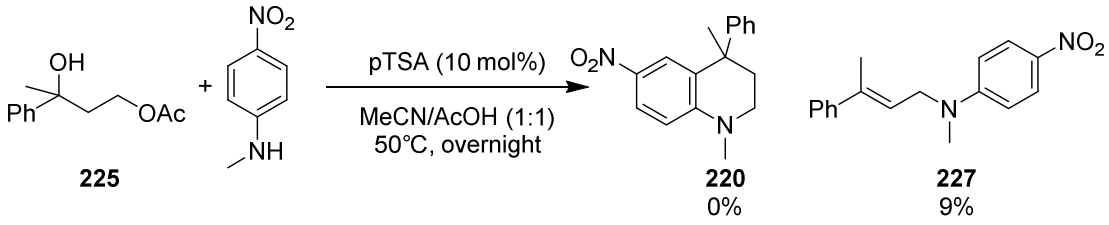
Scheme 4-45: Tentitative mechanism for the formation of **217**.

As discussed in the introduction of this chapter, the reaction was assumed to involve hydroperoxide **214** as a central intermediate, formed according to Scheme 4-42.

Since the most surprising feature of this reaction is the incorporation of an extra carbon in **217** as compared to the starting styrene and aniline, it was assumed that this extra carbon was previously part of the ketone through loss of an acyl fragment. Therefore it was envisioned that an intramolecular Bayer-Villiger oxidation of **214** would afford **225**, bearing a benzylic alcohol where the hydroperoxide fragment was and an acetate in place of the ketone. Subsitution of the acetate moiety by the aniline nucleophile would result in **226,** which could undergo an intramolecular Friedel-Crafts alkylation under acidic conditions to afford **217**. Although most of these individual steps seemed reasonable and explained the extra carbon incorporated in **217**, the Bayer-Villiger oxidation of a linear ketone had no real precedent.[89]

In order to explain the side products observed in the initial experiment (see Scheme 4-43), the following sequence was assumed. Starting from the hydroperoxide **214**, an acid catalysed Hock rearrangement would afford acetophenone and a β-hydroxyketone, which under acidic conditions would dehydrate to methyl vinyl ketone. This Michael acceptor would then be trapped by para-nitro aniline to afford **218**. Once more, the Hock rearrangement would be unusual in terms of products obtained, since phenyl migration is normally favored over migration of alkyl chains.

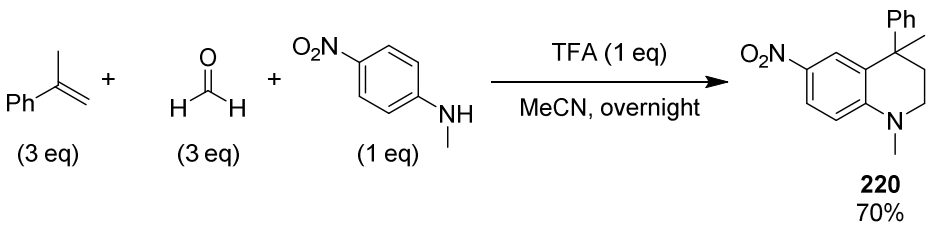
Well aware of the problems associated with this proposed mechanism, we decided to investigate its feasibilty nonetheless (Scheme 4-46).



Scheme 4-46: Evaluation of **225** as reaction intermediate.

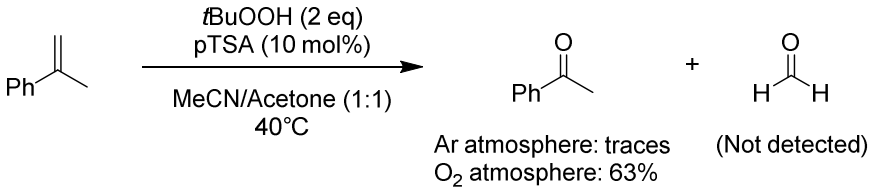
225 was synthesised according to a literature report by Thompson et al.[90] and subjected to our reaction conditions. However, and perhaps not surprisingly, **220** was not detected and only small amounts of **227** (9% yield) could be isolated. Substitution of the acetate had occurred but rather than substitution of the benzylic alcohol, only elimination

occurred. This result discounted **225** as a reaction intermediate and already disproved our proposed mechanism, therefore we searched for an alternative. By looking at literature reports on the synthesis of analogues of **220**, the use of formaldehyde as a carbon source and otherwise very similar acidic conditions caught our attention (Scheme 4-47).[91]



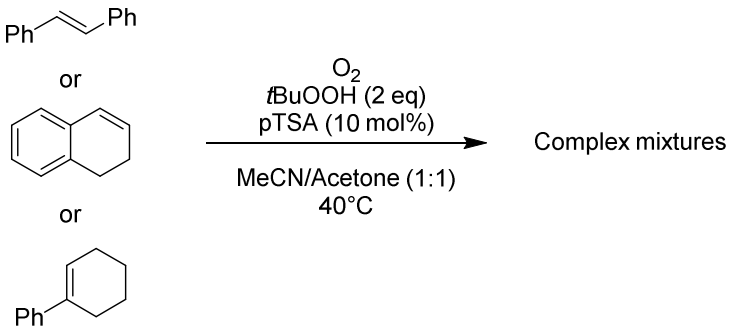
Scheme 4-47: Synthesis of **220** using formaldehyde.

Using the conditions described, we could also obtain **220** in 70% yield with formaldehyde as an extra carbon atom source and looking back at Scheme 4-43, where acetophenone was observed as a side product, the involvement of formaldehyde through oxidative cleavage of the styrene double bond was hypothesised and evaluated.



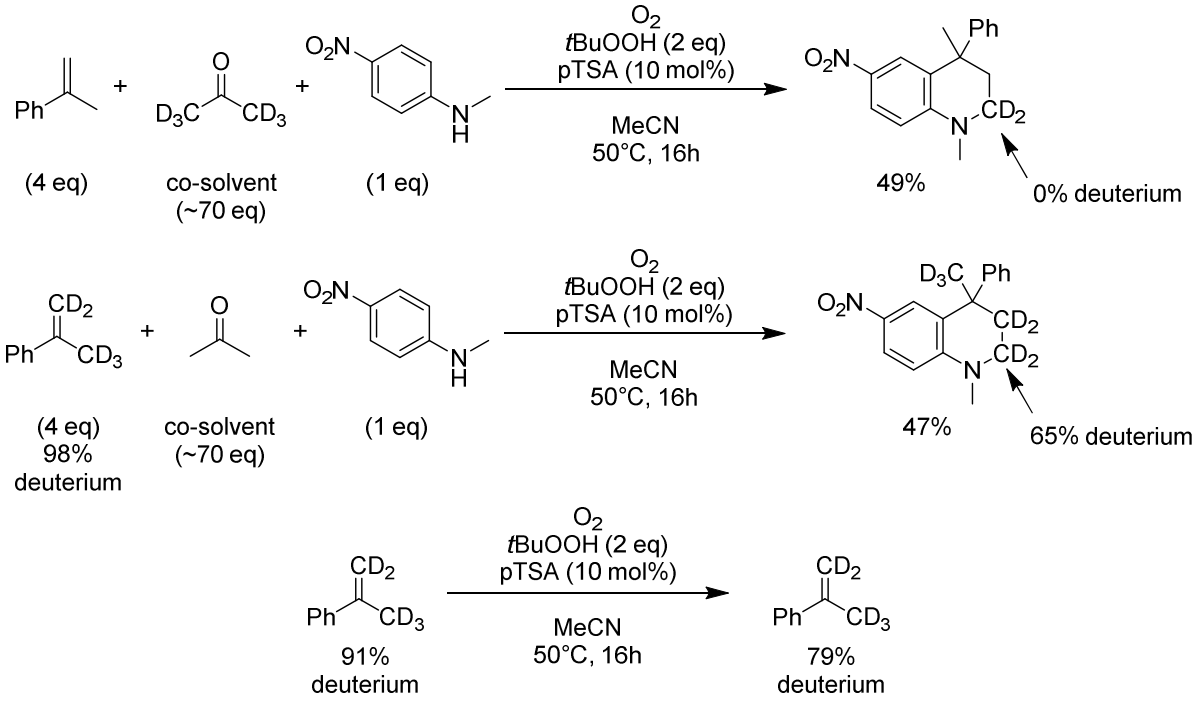
Scheme 4-48: Oxidative cleavage of α–methyl styrene.

By subjecting α-methyl styrene to the reaction conditions in the absence of nucleophile, the oxidative cleavage of the double bond was indeed observed (Scheme 4-48). Interestingly, an oxygen atmosphere proved to be crucial for this reaction to proceed. If the reaction was performed under inert atmosphere, only traces of acetophenone were obtained whereas if the atmosphere was pure oxygen, acetophenone was isolated in a 63% yield. We could not however detect any aldehyde product from these reaction mixtures. We then looked at substituted styrene derivatives with the hope of detecting aldehyde products more easily (Scheme 4-49).



Scheme 4-49: Attemps to detect aldehyde products in the oxidative cleavage of styrene derivatives.

Disappointigly, when stilbene, dihydronaphthalene or phenyl cyclohexene were subjected to our reaction conditions, only complex mixtures were obtained. However, when the reactions were performed in deuterated solvents and the reaction mixture directly analysed, traces of aldehyde products could be detected. Since these experiments do not unequivocally prove or disprove the involvement of formaldehyde in this reaction, labelling experiments were then performed (Scheme 4-50).

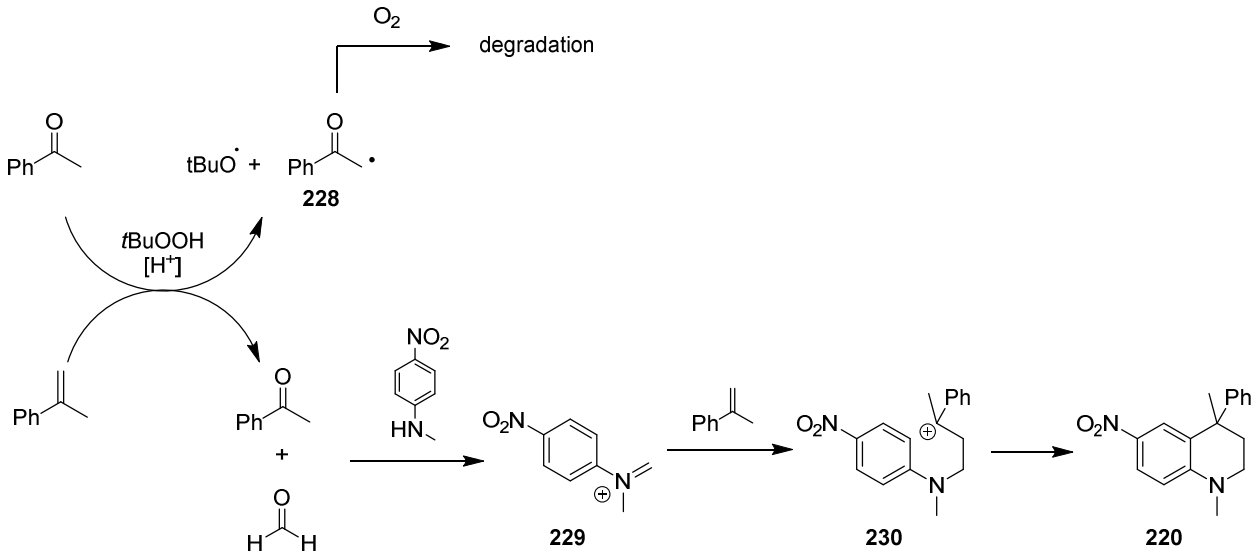


Scheme 4-50: Deuterium labelling experiments.

Deuterated acetone was first used but no deuterium incorporation was observed even though it was used in solvent quantities. If deuterated α-methyl styrene was used, a 65% deuterium incorporation was observed on the extra carbon in addition to the expected

other two fully deuterated carbons. If deuterated α-methyl styrene was subjected to reaction conditions alone, a decrease of the deuterium content was observed, explaining the relatively low 65% deuterium incorporation observed.

All these results clearly pointed to the generation of formaldehyde from an oxidative cleavage of the styrene starting material and its involvement in the formation of the tetrahydroquinoline product isolated, as shown in the postulated mechanism of Scheme 4-51.

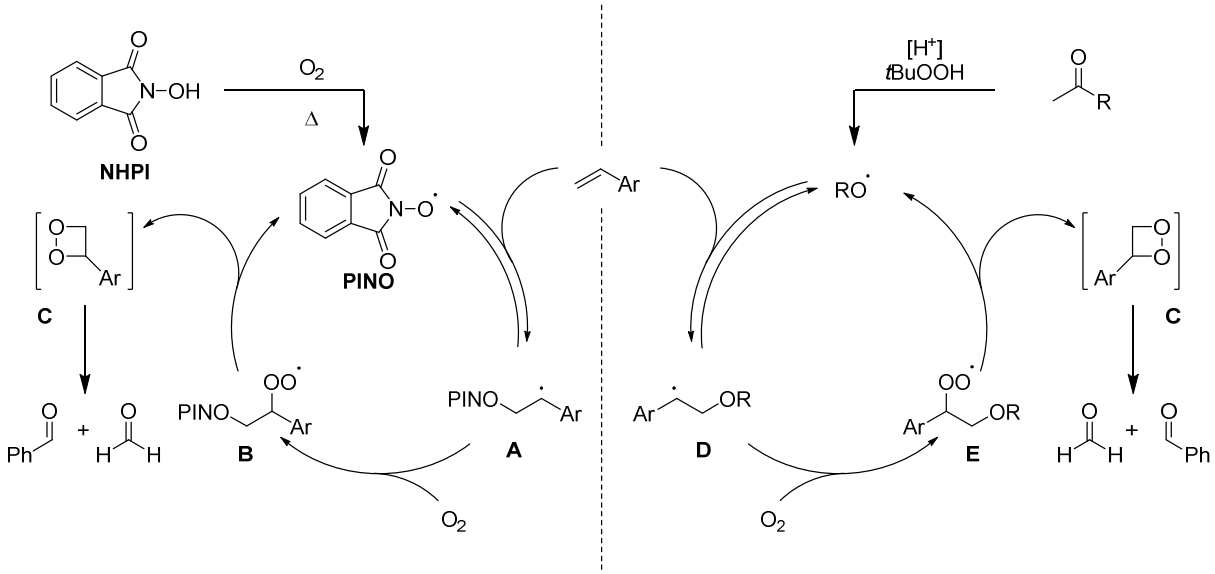


Scheme 4-51: Mechanism of formation of tetrahydroquinoline product **220**.

Under acidic conditions and in the presence of *t*BuOOH, α-methyl styrene is cleaved to acetophenone and formaldehyde, generating one equivalent of *t*BuO• radical and one equivalent of **228**. This α-carbonyl radical is trapped by molecular oxygen to enter degradation pathways, preventing it from adding to the olefin substrate. Under acidic conditions, the aniline substrate condenses with formaldehyde to form the iminium intermediate **229**, which can be attacked by the nucleophilic alkene to form **230** and ultimately **220**.

A still open question was however, what the mechanism of the oxidative cleavage of the double bond is. Clearly, radicals and molecular oxygen are involved in this transformation. A recent report from Jiao and co-workers shed some light on a potential

mechanism.[92] They report on the *N*-hydroxy phthalimide (NHPI) catalysed oxidative cleavage of styrenes under an oxygen atmosphere to afford ketones and aldehydes, similarly to what we observed during this study. Their proposed mechanism is shown in the left part of Scheme 4-52. The catalytic cycle starts with the generation of the stable PINO radical from NHPI. This stable radical adds to the olefin to generate radical **A**, which is then trapped by molecular oxygen to afford radical **B**. Cyclisation of **B** to exclude PINO closes the catalytic cycle and forms a highly unstable dioxetane **C**. Thermal decomposition of **C** then leads to the formation of the carbonyl compounds.



Scheme 4-52: Mechanism of the NHPI catalysed oxidative cleavage of styrene (left) and proposed mechanism for the aerobic acid catalysed cleavage of styrene (right).

We postulate that a similar chain of events is responsible for the observed reactivity (right part of Scheme 4-52). As discussed in sections 4.2 and 4.3, the combination of a ketone, a hydroperoxide and a strong acid, oxygen centered radicals are generated. Addition of these radicals to the olefin similarly generates **D,** then **E** upon trapping by molecular oxygen and finally affords the same dioxetane **C** than in the presence of NHPI.

The only discrepancy between this proposed mechanism and our previous studies is the fact that we never observed any side product derived from **D** under an inert atmosphere. A plausible explanation for this could come from the reversibility of addition of the oxygen centered radical to the olefin. By contrast, addition of a carbon centered radical generates a C-C bond, which is much more difficult to break once formed. Additionaly, the

increased stability – and therefore decreased reactivity towards addition – of oxygen centered radicals as compared to carbon centered radicals favors the C-C bond formation process in the absence of molecular oxygen. Finally, under aerobic conditions, the carbon centered radical derived from the ketone would be trapped by molecular oxygen in a diffusion controlled manner, rendering its addition to the olefin impossible. Therefore, we believe that such a mechanism adequately explains the reactivity described in this chapter.

4.4.4 Concluding remarks

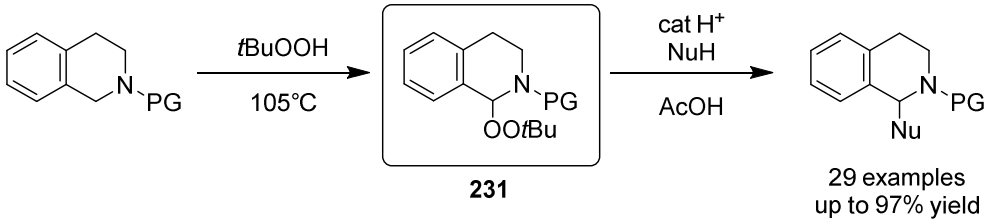
In this chapter, an unexpected formation of tetrahydroquinoline products was observed and optimized. The synthetic utility of this reaction was however shown to be poor, with reported methods achieving identical products under simpler reaction conditions.[91] Once the reaction was optimized, the reaction mechanism could be studied and was found to involve an intriguing oxidative cleavage of olefins under aerobic conditions. Rationalization of this transformation was done by analogy with a reported reaction and is postulated to involve *t*BuO• and/or *t*BuOO• radicals generated under our discovered radical generating conditions involving ketones, hydroperoxides and an acid catalyst.

The duality of the reactions of section 4.3 and this chapter from very similar reaction conditions highlight the high potential for the discovery of new reactivity of our developed catalytic system.

5 SUMMARY

Given the importance and attractiveness of oxidative coupling chemistry in terms of atom efficiency and potential for greener chemistry, a lot of attention is currently dedicated to the improvement of the mechanistic knowledge of this type of transformation. The work described in this dissertation is mainly dedicated to this task. The information gathered in this endeavour was also applied to develop new reactions and methodologies.

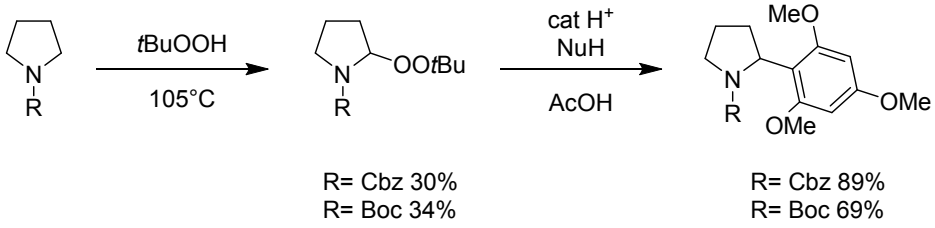
Based on previous mechanistic studies conducted in our group, a novel metal-free system was developed for the functionnalisation of tertiary amines *via* intermediate peroxides. The separate optimisation of the two postulated steps in oxidative coupling chemistry – oxidation and further coupling - allowed for the developpement of a metal-free two step protocol to achieve good yields of desired coupling products, validating our CHIPs concept of C-H functionnalisation *via* Intermediate Peroxides (Scheme 5-1).



Scheme 5-1: Two step protocol for the C-H functionnalisation *via* Intermediate Peroxides (CHIPs) of tertiary amines.

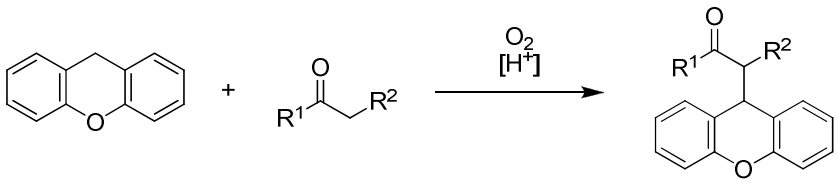
Under thermal conditions, a range of protected peroxides **231** could be accessed and easily purified. Using a cheap Brønsted acid, a wide variety of nucleophiles, such as indoles and phenol derivatives, non activated carbonyl nucleophiles, isocyanides or olefins, could then be introduced by substitution in this transformation. Most of these products had not been synthesised before or only using transition metal catalysis. This broad nucleophile scope showed that the main challenge to be solved in oxidative coupling chemistry of tertiary amines and amides is not the coupling step but the oxidation to an iminium ion or a precursor, such as **231**. Once this oxidation is better understood, more challenging substrates could be used in contrast to the widely used tetrahydroisoquinoline core present in most reports to date. A first step towards this goal has been accomplished with carbamate

protected pyrrolidine, a rare example of use of this type of protected amines for oxidative coupling reactions (Scheme 5-2). The yields of the separate steps illustrate the challenging oxidation and the facile substitution step. Therefore, we believe that the separate study of the oxidation step will allow for the extension of the scope of this type of chemistry. Further rationalisation of the oxidation step and its possible combination with separately developed substitution conditions is expected to lead to a wide expansion of the accessible substrates.



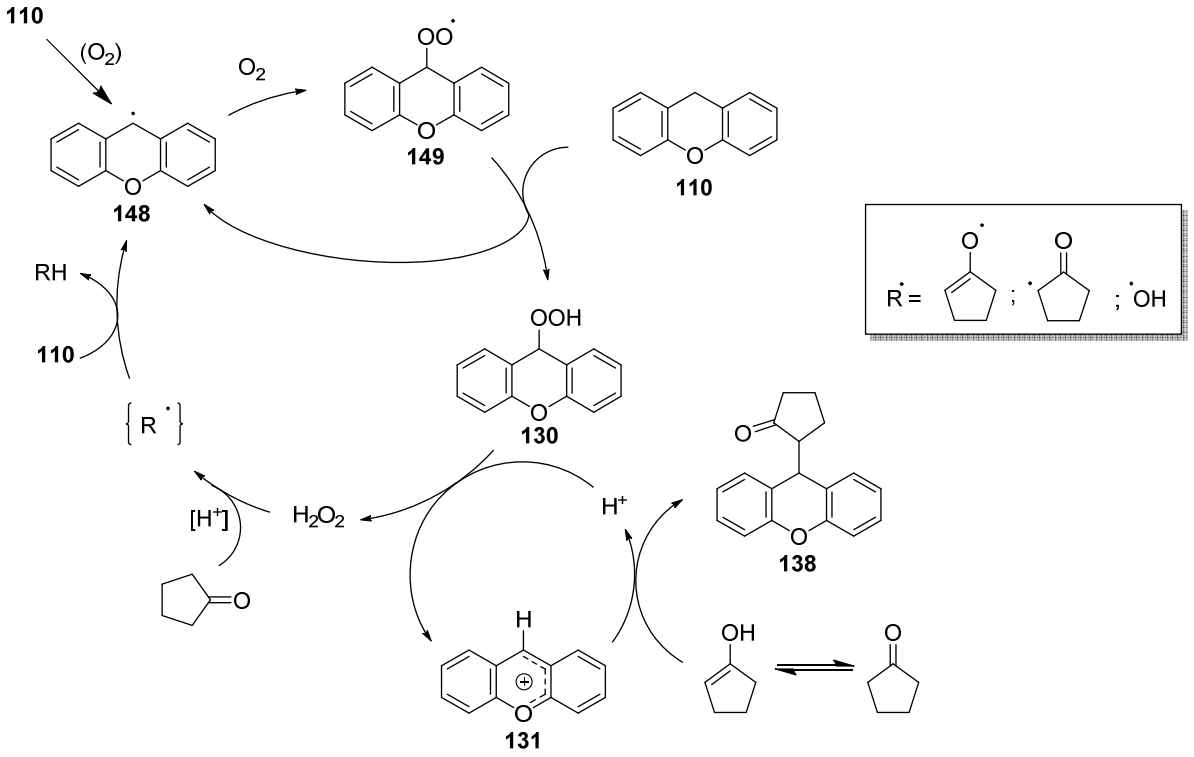
Scheme 5-2: Preliminary results towards the use of carbamate protected pyrrolidines in Brønsted acid catalysed oxidative coupling of tertiary amides.

Another aspect of the work described in this dissertation is about the autoxidative coupling of xanthene and unactivated ketones under Brønsted acid catalysis and molecular oxygen (Scheme 5-3).



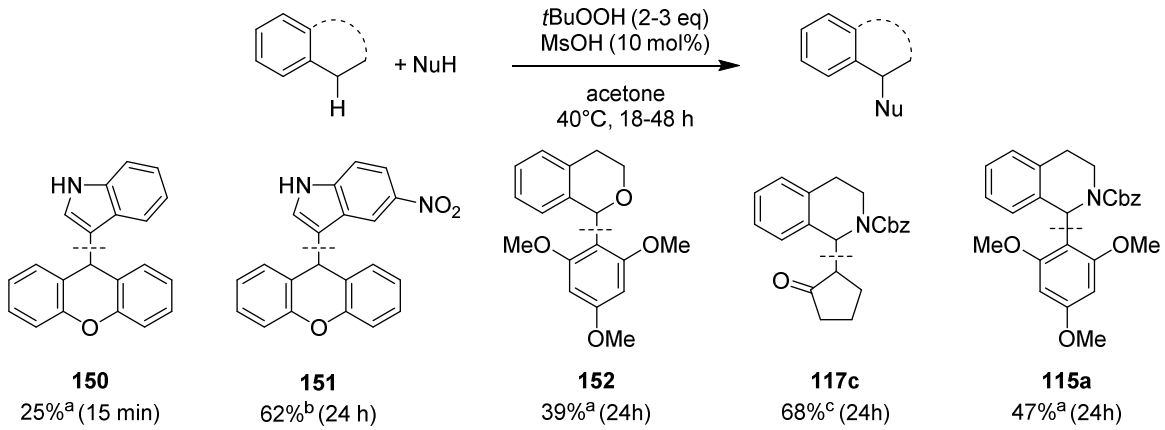
Scheme 5-3: Initially developed autoxidative coupling of xanthene and unactivated ketones.

This particularly attractive approach to oxidative coupling chemistry – not involving any transition metal or stoichiometric synthetic oxidants – was poorly understood from a mechanistic point of view and the synthetic challenges associated with it could therefore not be approached rationally. Detailled mechanistic investigations led to the confirmation of the original assumption that this transformation was initiated by an autoxidation process followed by an ionic substitution of the hydroperoxide group, in line with our CHIPs concept. Kinetic analysis revealed a second pathway involving the generation of free radicals from a combination of a ketone, a hydroperoxide (or hydrogen peroxide) and a strong acid catalyst, resulting in an autoinductive effect of hydrogen peroxide on the formation of the desired coupling product (Scheme 5-4).



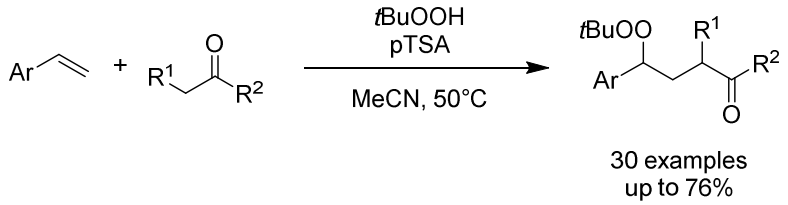
Scheme 5-4: Mechanism of the autoxidative coupling of xanthene and cyclopentanone, showing the autoinductive effect of the waste product, hydrogen peroxide.

Direct use of the information gathered in this mechanistic study allowed for the identification of a novel metal-free catalytic system consisting of a ketone and a strong Brønsted acid for oxidative coupling reactions using hydroperoxide oxidants. Preliminary experiments on a small range of test substrates showed the viability of this approach as compared to previously reported methods (Scheme 5-5).



Scheme 5-5: Application of the Brønsted acid catalysed radical formation. New bonds are indicated by a dashed line. a) 1 equivalent of nucleophile; b) 2 equivalents of nucleophile; c) 5 equivalents of cyclopentanone used as solvent and nucleophile

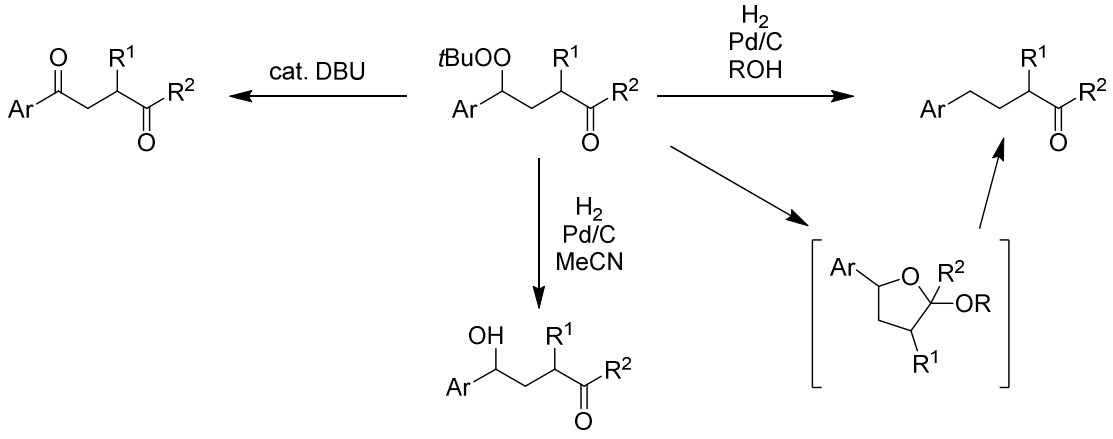
Based on this study and the analysis of side products, a new oxidative double functionalization of olefins has been developed (Scheme 5-6).



Scheme 5-6: Oxidative functionalisation of olefins by a ketone and a hydroperoxide under Brønsted acid catalysis.

A range of peroxides was synthesised *via* a three-component reaction involving an olefin, a ketone and hydroperoxide under strong Brønsted acid catalysis. This reaction is characterised once again by the absence of any transition metal catalyst or oxidants used for this type of chemistry. It is particularly attractive in that it is very suitable for simple non activated ketones as radical precursors, most reported methods being limited to activated methylene compounds such as 1,3-dicarbonyls.[93]

The synthetic utility of the synthesised peroxides was demonstrated by their easy and high yielding conversion to products with three different oxidation states from the same precursor (Scheme 5-7).

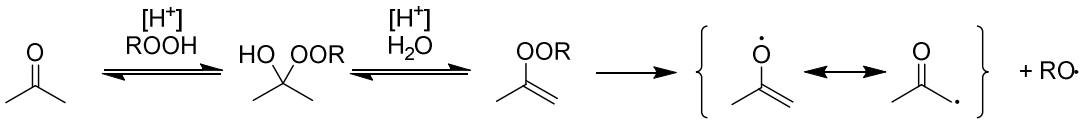


Scheme 5-7: Conversion of peroxides to ketones, alcohols and alkanes under suitable conditions.

A catalytic amount of base cleanly afforded the corresponding 1,4-diketone via a Kornblum-Delamare elimination.[83] The corresponding homo-aldol product was obtained through hydrogenation on palladium in acetonitrile, while the fully reduced alkane was

obtained under the same conditions in an alcohol solvent. The synthesis of these products would require *Umpolung* reactivity to be achieved by classical ionic mechanisms in one step.

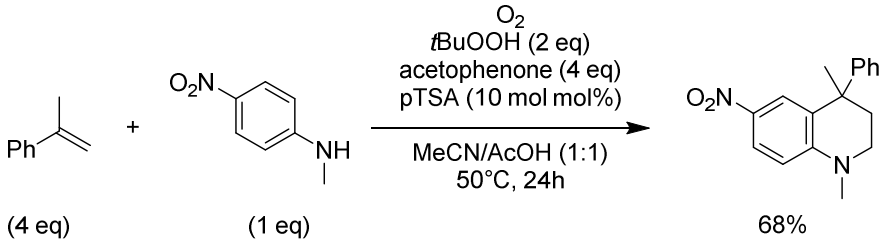
This reaction is enabled by the formation of α-carbonyl radicals from ketones via a previously unknown mechanism. In the presence of a strong acid catalyst, addition of a hydroperoxide to the ketone and further dehydration delivers an alkenyl peroxide. Facile homolytic bond cleavage of the peroxide then delivers the desired carbon centered radical (Scheme 5-8).



Scheme 5-8: Mechanism of formation of radicals from ketones and hydroperoxides under acid catalysis.

This phenomenon of radical generation had already been described in the literature, in particular in the context of polymer chemistry.[75, 88] It was however poorly understood from a mechanistic point of view, and this PhD work provides a plausible mechanism, supported by experimental as well as theoretical evidences.[94]

Finally, when trying to combine the knowledge developed during this work and studies made simultaneously in our group by Naeem Gulzar,[III] an unexpected formation of tetrahydroquinoline products was observed (Scheme 5-9).

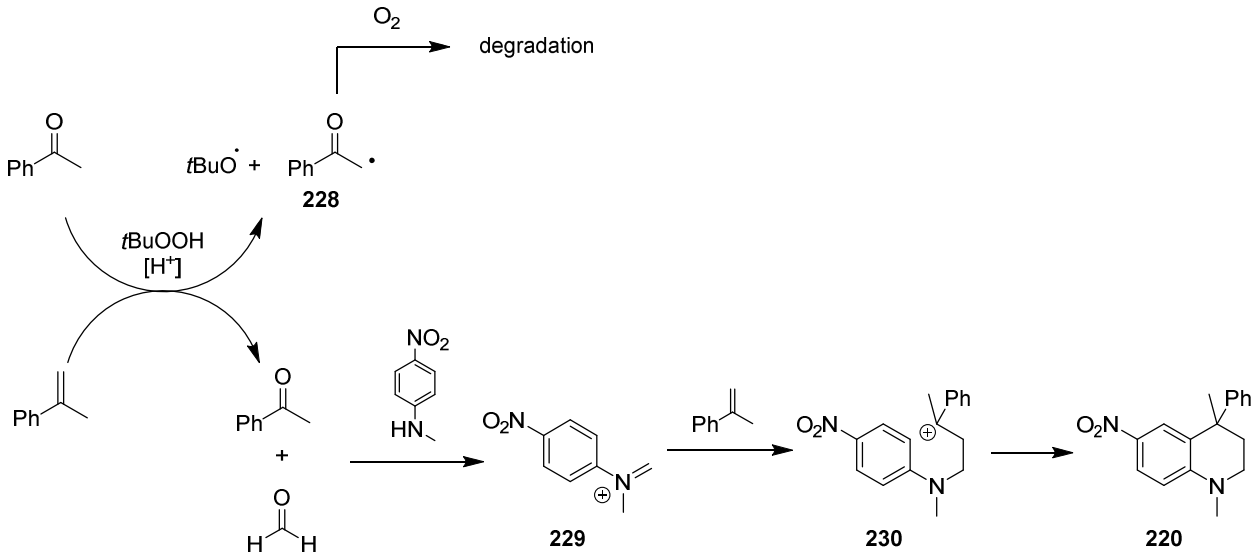


Scheme 5-9: Unexpected formation of tetrahydroquinoline.

This reaction was optimised and studied to find that the transformation involved the oxidative cleavage of styrenes under the previously developed conditions in presence of

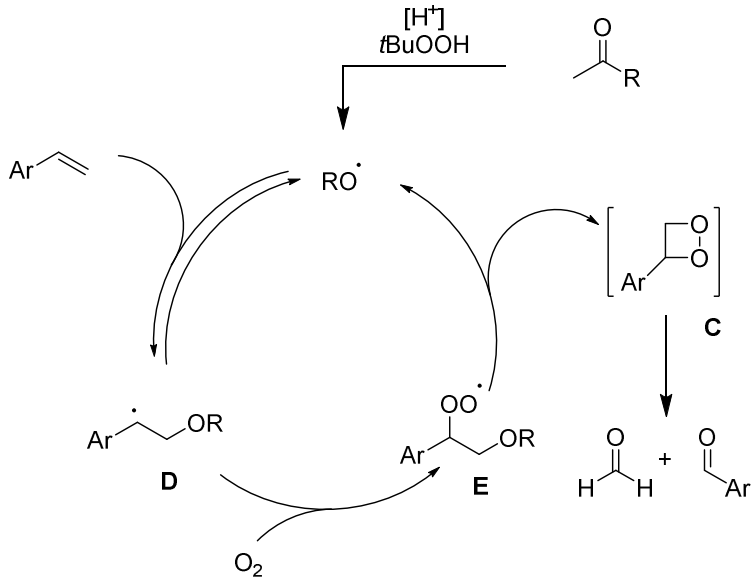
[III] PhD dissertation of Naeem Gulzar in Köln university, expected for 2014.

molecular oxygen to afford formaldehyde as a crucial step (Scheme 5-10).



Scheme 5-10: Mechanism of formation of tetrahydroquinoline product **220**.

This oxidative cleavage reaction was rationalised by analogy with a reported similar reaction (Scheme 5-11).[92]



Scheme 5-11: Radical triggered oxidative cleavage of styrenes in the presence of molecular oxygen.

Under the previously discovered reaction conditions, oxygen centered radicals are generated, which add reversibly to the olefin. In the presence of molecular oxygen, a very unstable dioxetane **C** is generated, precursor to the carbonyl compounds ultimately

generated. Although this transformation is not yet synthetically usefull, it bears potential to afford an organocatalytic alternative to ozonolysis for the oxidative cleavage of olefins.

The reactions described in section 4.3 and 4.4 show that similar reaction conditions can lead to very different reactivity and highlight the potential of our newly developed catalytic system for the development of new reactivities.

Part of the work described in this dissertation has been published in the following peer-reviewed publications:

[95] Brønsted Acid Catalyzed C–H Functionalization of *N*-Protected Tetrahydroisoquinolines via Intermediate Peroxides: B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666-671.

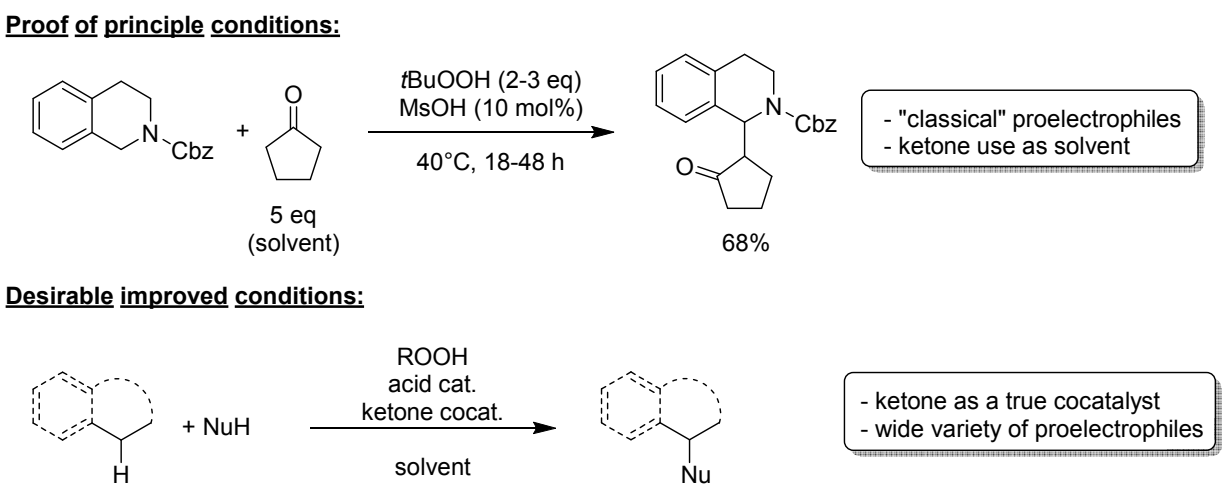
[96] Synergistic Effect of Ketone and Hydroperoxide in Brønsted Acid Catalyzed Oxidative Coupling Reactions: B. Schweitzer-Chaput, A. Sud, Á. Pintér, S. Dehn, P. Schulze, M. Klussmann*, Angew. Chem., Int. Ed.* **2013***, 52, 13228-13232; Angew. Chem.* ***2013****, 125, 13470-13474.*

[97] Acid Catalysed Oxidative Radical Addition of Ketones to Olefins: B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem., Int. Ed.* **2014***, accepted manuscript (*DOI: 10.1002/anie.201401062); *Angew. Chem.* ***2014****, accepted manuscript* (DOI: 10.1002/ange.201401062.

6 OUTLOOK

6.1 Oxidative Coupling Chemistry

Continuation of the search for mild oxidation condition to apply to the oxidative coupling chemistry is expected to provide a wide expansion of the substrate scope accessible to this type of transformation. Since we demonstrated that the generation of the iminium intermediate is the real bottleneck for further developpement of oxidative coupling of tertiary amines and amides, more efforts should be directed towards this goal. Finding catalytic systems allowing mild oxidation conditions and ideally the use of environmentally friendly oxidants is already a subject of study of many research groups. The findings of this PhD work provide a novel approach towards organocatalytic C-H functionalisation via Intermediate Peroxides (CHIPs concept)

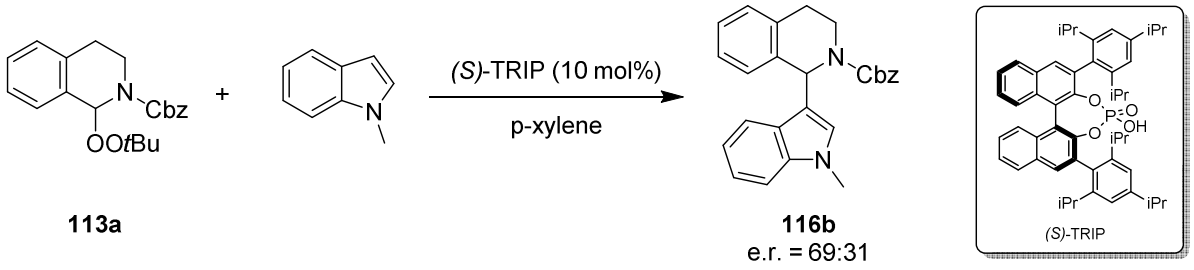


Scheme 6-1: Proof of principle for the direct organocatalyzed C-H functionalization *via* Intermediate Peroxides.

As already demonstrated as a proof of principle, the combination of a strong Brønsted acid, a hydroperoxide oxidant and a ketone is a viable catalytic system for the oxidative coupling of a range of diverse proelectrophiles (Scheme 6-1). A direction for further development of this chemistry is the search for conditions in which the ketone partner can be used in sub-stoichiometric amounts - as a true co-catalyst, therefore eliminating potential chemoselectivity problems - in combination with an acid catalyst. Another challenging task is the extension of reactivity away from the tetrahydroisoquinoline

moiety used nearly exclusively in most literature reports so far. As has already been demonstrated in section 4.2.9, the use of more diverse and challenging proelectrophiles is in principle possible and more efforts dedicated towards this goal are expected to give valuable methods for the chemical community.

One particularly attractive feature of the conditions discussed in this work is the use of a Brønsted acid as catalyst. In light of the wide interest in asymmetric Brønsted and Lewis acid catalysis, preliminary experiments conducted showed the viability of this approach to access enantioenriched coupling products using the chiral phosphoric acid *(S)*-TRIP (Scheme 6-2).[98]



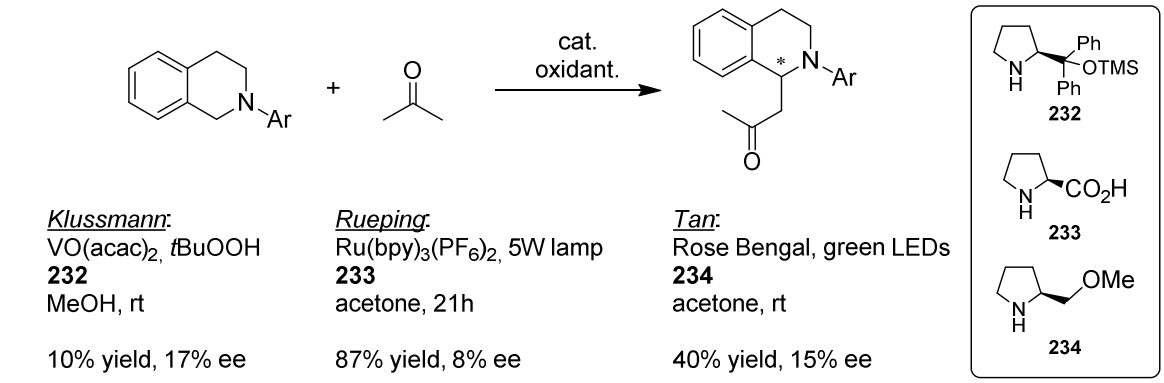
113a

116b
e.r. = 69:31

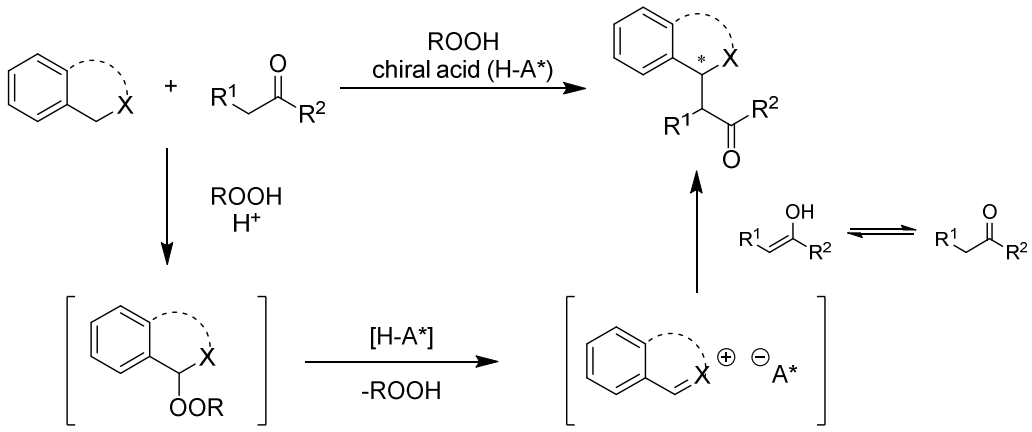
Scheme 6-2: Chiral phosphoric acid catalysed reaction of **113a** to an enantioenriched coupling product **116b**.

Combination of this proof of principle with the reaction conditions developed in section 4.2.9 is expected to provide an organocatalytic approach towards the challenging asymmetric induction in oxidative coupling chemistry, especially using simple ketones as nucleophiles. Indeed, only moderate success has been achieved so far by our group[19] and others[99] (Scheme 6-3).[100] The reported asymmetric variants of the reaction between a tetrahydroisoquinoline and acetone all show very low levels of enantioselectivity - less than 20% ee - using a secondary amine catalysis approach. On the other hand, chiral Brønsted acid catalysis is expected to provide a good handle to address this issue,[101] as shown by recent reports from the group of Wang, in which a simple BINOL derived phosphoric acid gave some enantioinduction for an intramolecular version of the reaction shown in Scheme 6-3.[102] Additionaly, the Toste group later reported on the use of chiral phosphoric acids in an intramolecular oxidative C-N bond forming reaction affording high levels of enantioselectivity.[103]

Secondary amine catalysis approach:



Chiral Bronsted acid catalysis approach:

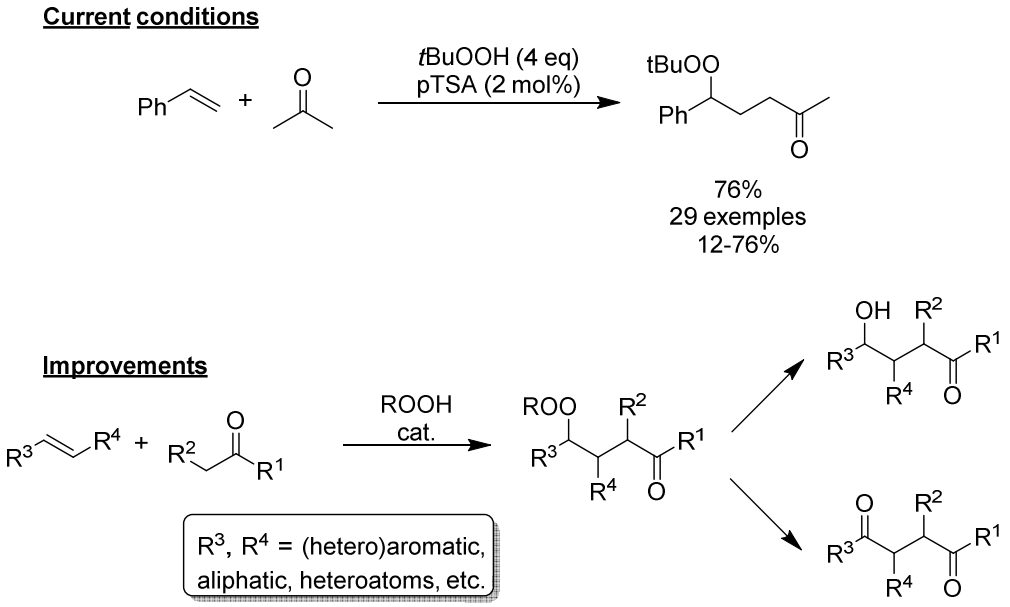


Scheme 6-3: Reported secondary amine catalysis approaches and proposed chiral acid catalysis approach for asymmetric oxidative coupling reactions.

6.2 Organocatalytic Radical Bond Forming Reactions

Free radical chemistry has seen a renewed interest with the development of tin-free conditions.[48b, 48c] Much efforts have already been dedicated to the development of clean and environementaly friendly conditions to exploit the power of free radicals to generate complex products from simple materials by bond forming processes which are difficult or impossible to mimick using ionic chemistry. Therefore, the discovery of new free radical forming mechanisms is always desirable and the results described in this work are expected to be amenable to many of the already described reactivities of free radicals.

Based on the results of sections 4.3 and 4.4, a first obvious continuation of this work is the extension of the substrate scope beyond styrene derivatives, a clear limitation of the current protocol (Scheme 6-4).

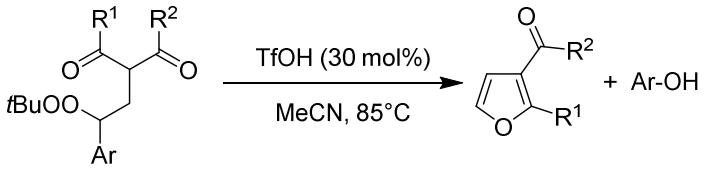


Scheme 6-4: Current limitations of the reaction developed in section 4.3 and desirable improvements.

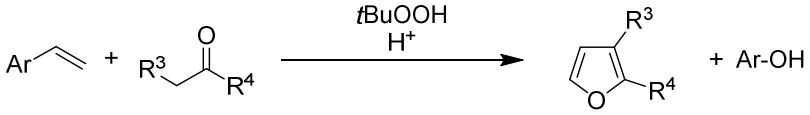
In particular, finding conditions for the efficient trapping of the radical resulting from the attack of a non conjugated olefin would greatly expand the synthetic utility of this reaction to allow the generation of valuable functionalised products, such as 1,4-diketones or homoaldol products, from cheap and simple starting materials. Ideally, the reaction would tolerate a wide range a diversely substituted olefins, both terminal and internal, to afford the corresponding oxygenated products in a highly efficient manner. Further conversion to synthetically useful products would be done following the reactions already described in this work, ideally in a one-pot fashion.

In light of a recent report by the group of Zhiping Li on the rearrangement of similar γ-keto-peroxides to furans,[93] a direct one step reaction from a ketone and an olefin to a furan can be envisioned (Scheme 6-5).

Li's rearrangement of ketoperoxides



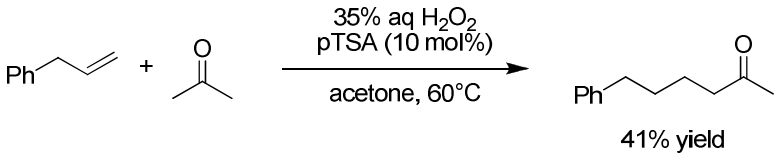
Direct synthesis of furans from ketones and olefins



Scheme 6-5: One step synthesis of furans from ketones and olefins based on Li's report.[93]

It would further have the advantadge of the possibility to use simple ketones and not necessarily a 1,3-dicarbonyl partner for the reaction, a limitation of the cobalt catalysed approach used by Li for the synthesis of the γ-keto-peroxides.

Preliminary results show that hydroalkylation of olefins is possible if the oxidant used is hydrogen peroxide instead of a hydroperoxide (Scheme 6-6).[98]



Scheme 6-6: Preliminary results for the Brønsted acid catalysed hydroalkylation of olefins.

Because it does not generate a relatively stable peroxy radical in the process, hydrogen atom abstraction becomes the favored mode of termination, resulting in the net hydroalkylation of an olefin. This reaction could become a complementary organocatalytic approach to the traditional metal catalysed hydroacylation reaction.[104]

7 EXPERIMENTAL PART

7.1 General Experimental Conditions

Solvents and reagents

All solvents were purified by distillation before use following standard procedures. Absolute solvents were obtained by distillation over appropriate drying agent and then kept under an atmosphere of argon: diethyl ether, tetrahydrofuran, dichloromethane, triethylamine (calcium hydride), acetonitrile. Other commercial reagents were obtained from various sources and used without further purification.

Inert gas atmosphere

Air and moisture-sensitive reactions were conducted under an atmosphere of argon (*Air Liquide*, >99.5% purity).

Chromatographic methods

Whenever possible, reactions were monitored by thin layer chromatography (TLC) using silica gel pre-coated plastic sheets (0.2 mm, Machery-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and/or potassium permanganate (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH, 200 mL H_2O) or *p*-anisaldehyde (0.7 mL *p*-anisaldehyde, 250 mL EtOH, 9.5 mL conc. H_2SO_4, 2.7 mL glacial AcOH) stains. Flash column chromatography was performed using Merck silica gel (60, particle size 0.040-0.063 mm) using a specified solvent mixture and elevated pressure.

High pressure liquid chromatography (HPLC) was performed on a Shimadzu LC-2010C system equipped with a spectrophotometer or a diode array. Commercial HPLC-grade solvents were used, and measurements were conducted at 25 °C.

Nuclear magnetic resonance spectroscopy (NMR)

Proton and carbon NMR spectra were recorded on Bruker AV-600 or Bruker AV-

500 or Bruker AV-400 or Bruker AV-300 spectrometers in deuterated solvents. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (C_6D_6, δ 7.16 ppm; $CDCl_3$ δ 7.26; THF-d_8, δ 1.85 (OCH_2CH_2) ppm; CD_3OD, δ 3.31 ppm; $(CD_3)_2CO$, δ 2.05 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constants (Hz) and integration. ^{13}C Chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (C_6D_6, δ 128.06 ppm; $CDCl_3$, δ 77.0; THF-d_8, δ 25.6 (OCH_2CH_2) ppm; $(CD_3)_2CO$, δ 29.84 ppm).

Mass spectrometry (MS)

Mass spectra were measured on a Finnigan MAT 8200 (70 eV) or an Agilent 5973 (70 eV) spectrometer by electron ionization, chemical ionization, or fast atom/ion bombardment techniques. High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). All masses are given in atomic units/elementary charge (*m/z*) and reported in percentage relative to the basic peak.

7.2 Metal-free C-H Functionalisation of Tertiary Amines via Intermediate Peroxides

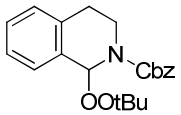
7.2.1 Synthesis of Amino-peroxides

Copies of NMR spectra can be found in the supporting information of the following publication: Brønsted Acid Catalyzed C–H Functionalization of *N*-Protected Tetrahydroisoquinolines via Intermediate Peroxides: B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666-671.[95]

General procedure for the synthesis of tBu-peroxides from tertiary amines:

A 4mL screw cap vial was charged with the corresponding tertiary amine (1mmol) and a 5,5M solution of TBHP in decane (540µl ; 3mmol) was added. The mixture was stirred at 105°C using an aluminium hotplate for the indicated time (see Scheme 4-2 and Scheme 4-12). After cooling, the resulting mixture was directly subjected to flash chromatography on silica gel to afford the corresponding peroxide aminoperoxide.

Benzyl 1-(*tert*-butylperoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (113a)[95]



Following the general procedure, the reaction of **112a** (267 mg, 1 mmol) with TBHP afforded peroxide **113a** (266 mg, 74%) after flash chromatography (elution with pentane/AcOEt 95/5) as a colorless oil which upon standing at room temperature or cooling gives a white solid

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz: 2 rotamers in 1:0,55 ratio) 7.46-7.22 (m, 8H); 7.20-7.14 (m, 1H); 6.77 (s, 1H, minor); 6.67 (s, 1H, major); 5.35-5.12 (m, 2H); 4.30 (ddd, 1H, J=2.0, 5.8, 13 Hz, major); 4.19-4.1 (m, 1H, minor); 3.65-3.55 (m, 1H, minor); 3.52 (app td, 1H, J=4.2, 12.4 Hz, major); 3.0-2.86 (m, 1H); 2.85-2.77 (m, 1H); 1.3 (s, 9H, minor); 1.23 (s, 9H, major)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz: 2 rotamers) 155.5 (q, major); 155.3 (q, minor); 136.6 (q, major); 136.5 (q, minor); 136.3 (q, major); 136.0 (q, minor); 130.5 (ArH); 130.1 (ArH); 129.4 (ArH); 129.0 (ArH); 128.9 (ArH); 128.8 (ArH); 128.6 (ArH); 128.5 (ArH); 128.4 (ArH); 128.3

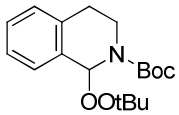
(ArH); 128.0 (ArH, 2C); 127.9 (ArH); 126.3 (ArH, minor); 126.2 (ArH, major); 84.8 (CH, minor); 84.4 (CH, major); 80.8 (q, minor); 80.5 (q, major); 67.3(CH_2, major); 67.1 (CH_2, minor); 37.8 (CH_2, minor); 37.0 (CH_2, major); 28.3 (CH_2, minor); 28.2 (CH_2, major); 26.5 (CH_3, minor); 26.4 (CH_3, major)

To confirm that the two sets of signals are rotamers, high temperature NMR analysis were performed in d6-DMSO. At room temperature, two sets of broad signals are visible which coalesce at 80 °C.

^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.43-7.17 (m, 9H); 6.59 (s, 1H); 5.25-5.10 (m, 2H); 4.12-3.98 (m, 1H); 3.54-3.36 (m, 1H); 2.88-2.77 (m, 2H); 1.16 (s, 9H)
^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.26 (q); 136.31 (Ar q); 135.54 (Ar q); 129.81 (Ar q); 128.59 (ArH); 128.52 (ArH); 128.12 (ArH); 127.82 (ArH); 127.33 (ArH); 127.11 (ArH); 125.72 (ArH); 83.97 (CH); 79.54 (q); 66.17 (CH_2); 27.08 (CH_2); 25.80 (CH_3)

MS (EI): 355(0.03); 266(30); 222(41); 91(100)
HRMS (ESI): calculated for $[C_{21}H_{25}NO_4Na]^+$ (M+Na^+): 378,167791; found: 378,167577

***tert*-Butyl 1-(*tert*-butylperoxy)-3,4-dihydroisoquinoline-2(1H)-carboxylate (113b)[95]**



Following the general procedure, the reaction of **112b** (233 mg, 1 mmol) with TBHP afforded peroxide **113b** (238 mg, 74%) after flash chromatography (elution with pentane/AcOEt 98/2) as a colorless oil which upon standing at room temperature or cooling gives a white solid.

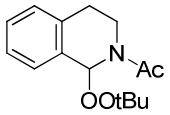
^{1}H NMR: (r.t. $CDCl_3$; 500MHz: 2 rotamers in 1:0,41 ratio) 7.46-7.41 (m, 1H); 7.33-7.22 (m, 3H); 7.21-7.13 (m, 1H); 6.73 (s, 1H, minor); 6.59 (s, 1H, major); 4.31-4.22 (m, 1H, major); 4.1-4.0 (m, 1H, minor); 3.55 (m, 1H, minor); 3.43 (m, 1H, major); 3.0-2.83(m, 1H); 2.83-2.75 (m, 1H); 1.53 (s, 9H); 1.31 (s, 9H)
^{13}C NMR: (r.t. $CDCl_3$; 125 MHz: 2 rotamers) 154.5 (q, minor); 154.4 (q, major); 136.5 (Ar q, major); 136.2 (Ar q, minor); 130.8 (Ar q, minor); 130.5 (Ar q, major); 129.4 (ArH), 128.9 (ArH); 128.88 (ArH); 128.83 (ArH); 128. (ArH); 126.2(ArH, minor); 126.1 (ArH, major); 84.79 (CH,

major); 84.2 (CH, minor); 80.5 (q, minor); 80.3 (q, major); 80.1 (q, major); 79.9 (q, minor); 37.9 (CH_2); 36.0 (CH_2); 28.4 (CH_3, 3C); 26.6 (CH_3, 3C)

MS (EI): 321 (0.07); 232 (17); 176 (100); 132 (42); 57 (63)

HRMS (ESI): calculated for $[C_{18}H_{27}NO_4Na]^+$ ($M+Na^+$) : 344,183163; found: 344,183224

1-(1-(*tert*-Butylperoxy)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (113c)[95]



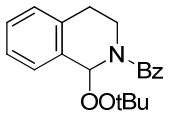
Following the general procedure, the reaction of **112c** (175 mg, 1 mmol) with TBHP afforded peroxide **113c** (44 mg) after flash chromatography (elution with pentane/AcOEt 8/2) as a colorless oil. The product was isolated along with the overoxidation product in a 1:0.07 ratio. Yield after correction based on this ratio is 14%.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 7.42 (d, 1H, J=7.3 Hz); 7.34-7.24 (m, 2H); 7.19 (d, 1H, J=7.3 Hz); 6.33 (s, 1H); 4.64 (dddd, 1H, J=1, 2.8, 5.8, 13 Hz); 3.27 (app td, 1H, J=3.2, 12 Hz); 2.93-2.83 (m, 1H); 2.82-2.75 (m, 1H); 2.34 (s, 3H); 1.27 (s, 9H)

MS (EI): 264 (0,1); 174(100); 132(97); 43(25)

HRMS (ESI): calculated for $[C_{15}H_{21}NO_3Na]^+$ ($M+Na^+$): 286.141436; found: 286.141360

(1-(*tert*-Butylperoxy)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (113d)[95]



Following the general procedure, the reaction of **112d** (237 mg, 1 mmol) with TBHP afforded peroxide **113d** (151 mg, 46%) after flash chromatography on silica gel (elution with pentane/AcOEt 95/5) as a white solid.

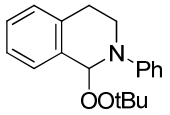
^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 7.48-7.42 (m, 3H); 7.42-7.37 (m, 2H); 7.37-7.32 (m, 1H); 6.30 (s, 1H); 4.73 (dd, 1H, J=5:7, 12 Hz); 3.56 (td, 1H, J=4.3, 12 Hz); 3.16-3.06 (m, 1H); 2.96-2.88 (m, 1H); 1.16 (s, 9H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 172.2 (q); 136.6 (Ar q); 136.1 (Ar q); 129.8 (ArH); 129.5 (ArH); 129.3 (ArH); 129.1 (ArH); 128.2 (ArH); 128.0 (ArH); 126.3 (ArH); 87.7 (CH); 80.9 (q); 35.0 (CH_2); 28.2 (CH_2); 26.3 (CH_3)

MS (EI): 236 (100; M^+-OOtBu); 105 (96); 77 (24)

HRMS (ESI): Calculated for $[C_{20}H_{23}NO_3Na]^+$: 348.157012; found: 348.157020

1-(*tert*-Butylperoxy)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (45)[95]



Following the general procedure, the reaction of **112f** (209 mg, 1 mmol) with TBHP afforded peroxide **45** (164 mg; 55%) after flash chromatography (elution with pentane/AcOEt 98/2) as a colorless oil which upon standing at room temperature or cooling gives a white solid.

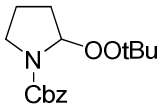
Note: peroxide **45** decomposes on silica TLC plates so the progress of the reaction had to be checked using ^{1}H NMR. The progress of elution during flash chromatography had to be checked using Alumina TLC plates and concentrated spots to get a reliable detection.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz):7.41-7.37 (m, 1H): 7.30-7.20 (m, 5H); 7.18-7.13 (m, 2H); 6.86 (t, 1H, J=7.2 Hz); 6.21 (s, 1H); 3.79-3.73 8m, 1H); 3.62-3.55 (m, 1H); 3.15-3.07 (m, 1H); 3.05-2.97 (m, 1H); 1.15 (s, 9H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 148.9 (Ar q); 136.6 (Arq); 133.0 (Ar q); 129.1 (ArH); 129.0 (ArH); 128.6 (ArH); 127.7 (ArH); 126.0 (ArH); 118.9 (ArH); 114.9 (ArH); 90.7 (CH); 80.1 (q); 42.6 (CH_2); 28.2 (CH_2); 26.6 (CH_3)

HRMS (ESI): calculated for $[C_{19}H_{23}NO_2]^+$ (M^+) : 297.172881; found 297.172790

benzyl 2-(tert-butylperoxy)pyrrolidine-1-carboxylate (126a)



Following the general procedure, the reaction of *N*-Cbz pyrrolidine (171 mg, 1 mmol) with TBHP afforded peroxide **126a** (88 mg, 30%) after flash chromatography on silica gel (elution with pentane/AcOEt 98/2) as a clear oil.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, 2 rotamers): 7.46-7.28 (m, 5H); 5.73 (br d, J=3.3 Hz, 1H, minor); 5.66 (br d, J=3 Hz, 1H, major); 5.27-5.11 (m, 2H); 3.58 (app t, J=10 Hz, 1H); 3.50-3.34 (m, 1H); 2.55-1.98 (m, 2H); 1.94-1.74 (m, 2H); 1.26 (s, 9H, minor); 1.16 (s, 9H, major)

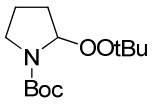
^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, 2 rotamers): 154.92 (C, minor); 154.70 (C, major); 136.64 (Ar

q, minro); 136.51 (Ar q, major); 128.40 (Ar CH); 128.14 (Ar CH); 127.99 (Ar CH); 90.74 (CH, minor); 89.83 (CH, major); 80.60 (C, minor); 80.31 (C, major); 67.08 (CH_2, major); 66.80 (CH_2, minor); 46.32 (CH_2, major); 46.22 (CH_2, minor); 30.64 (CH_2, major); 29.94 (CH_2, minor); 26.31 (3x CH_3); 22.53 (CH_2, minor); 21.67 (CH_2, major)

MS (EI): 204 (18); 160 (28); 91 (100); 57 (24)

HRMS (ESI): calculated for $[C_{16}H_{23}NO_4Na]^+$ ($M+Na^+$): 316.151927; found: 316.151622

tert-butyl 2-(tert-butylperoxy)pyrrolidine-1-carboxylate (126b)



Following the general procedure, the reaction of *N*-Boc pyrrolidine (205 mg, 1 mmol) with TBHP afforded peroxide **126b** (88 mg, 34%) after flash chromatography on silica gel (elution with pentane/AcOEt 98/2) as a clear oil.

^{1}H NMR: (r.t. $CDCl_3$; 300 MHz, 2 rotamers): 5.72-5.34 (br m, 1H); 3.51-3.04 (br m, 2H); 2.15-1.85 (m, 2H); 1.84-1.64 (m, 2H); 1.40 (s, 9H); 1.16 (s, 9H)

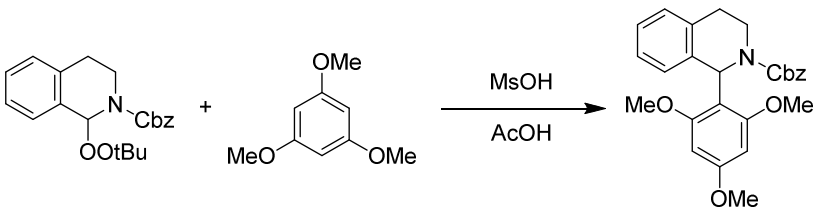
^{13}C NMR: (r.t. $CDCl_3$; 75 MHz, 2 rotamers): 154.04 (C); 91.03 (CH); 89.98 (br, CH); 80.02 (C); 79.82 (br, C); 46.16 (br, CH_2, minor); 45.76 (br, CH_2, major); 30.46 (br, CH_2, ,minor); 29.99 (br, CH_2, major); 28.36 (3x CH_3); 26.38 (3x CH_3); 22.53 (br, CH_2, minor); 21.60 (br, CH_2, major)

MS (EI): 170 (20); 114 (75); 70 (89); 57 (100)

HRMS (ESI): calculated for $[C_{13}H_{25}NO_4Na]^+$ ($M+Na^+$): 282.167576; found: 282.167294

7.2.2 Substitution Products

Benzyl 1-(2,4,6-trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115a)[95]

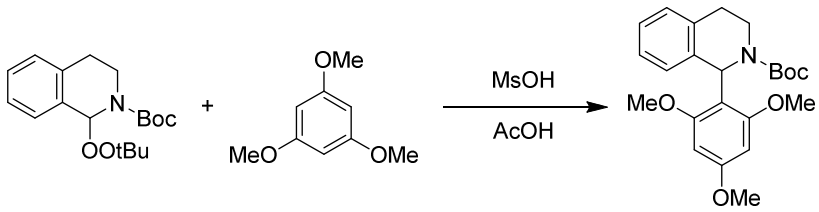


In a 4mL screw cap vial, peroxide **113a** (88.7mg; 0.25mmol) was dissolved in 1 mL of AcoH. 1.3.5-trimethoxybenzene (42mg, 0.25mmol) was then added followed by MsOH (1.77µL;

0.025mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 85/15) on silica gel to afford coupling product **115a** (89mg, 83%) as a clear oil which upon standing at room temperature or cooling often gives a white solid.

^{1}H NMR: (80°C; d6-DMSO; 400 MHz): 7.31-7.22 (m, 3H); 7.17-7.10 (m, 3H); 7.06 (tt, 1H, J=2, 7.2Hz); 7.00 (td, 1H, J=2, 7.7Hz); 6.69 (d, 1H, J=7.7Hz); 6.46 (s, 1H); 6.19 (s, 2H); 5.05-4.95 (m, 2H); 4.24 (ddd, 1H, J=3, 5, 12.6Hz); 3.77 (s, 3H); 3.58-3.49 (m, 7H); 2.90-2.75 (m, 2H)
^{13}C NMR: (80°C; d6-DMSO; 100 MHz): 159.89 (Ar q); 158.41 (Ar q); 154.46 (q); 136.79 (Ar q); 136.53 (Ar q); 134.08 (Ar q); 127.67 (ArH); 127.52 (ArH); 126.97 (ArH); 126.80 (ArH); 125.42 (ArH); 125.32 (ArH); 125.05 (ArH); 113.06 (Ar q); 91.62 (ArH); 65.59 (CH^2); 55.33 (CH_3); 54.81 (CH_3); 48.75 (CH); 39.28 (CH_2); 29.19 (CH_2)
MS (EI): 433 (5); 342 (4); 298 (100); 91 (27)
HRMS (ESI): calculated for $[C_{26}H_{27}NO_5Na]^+$ ($M+Na^+$): 456.178527; found: 456.178146

***tert*-Butyl 1-(2,4,6-trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115b)[95]**



In a 4mL screw cap vial, peroxide **113b** (88mg; 0.27mmol) was dissolved in 1.1 mL of AcoH. 1.3.5-trimethoxybenzene (46mg, 0.27mmol) was then added followed by MsOH (1.91µL; 0.027mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **115b** (64mg, 64%) as a clear oil which upon standing at room temperature or cooling gives a white solid.

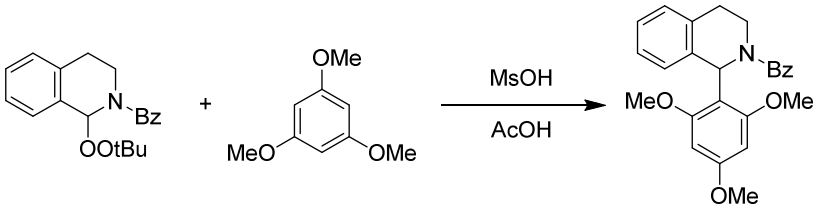
^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 7.05-6.97 (m, 2H); 6.93 (t, 1H, J=14.8Hz); 6.72 (d, 1H, J=7.7Hz); 6.37 (s, 1H); 6.05 (s, 2H); 4.30 (br d, 1H, J=9Hz); 3.73 (s, 3H); 3.61 (s, 6H); 3.41 (td, 1H, J=3, 12Hz); 2.88-2.78 (m, 1H); 2.78-2.70 (m, 1H); 1.20 (s, 9H)
^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 160.15 (Ar q); 158.87 (Ar q); 155.55 (CO); 137.22 (Ar q); 135.25 (Ar q); 128.00 (ArH); 126.41 (ArH); 125.92 (ArH); 125.52 (ArH); 114.02 (Ar q); 90.49

(ArH); 79.20 (C); 55.54 (OMe); 55.28 (OMe); 49.53 (CH); 39.42CH_2); 30.61 (CH_2); 28.35 (CH_3)

MS (EI): 399 (3.4); 343 (10); 298 (100); 57 (54)

HRMS (ESI): Calculated for $[C_{23}H_{29}NO_5Na]^+$: 422.193795; found: 422.193719

Phenyl(1-(2,4,6-trimethoxyphenyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (115d)[95]



In a 4mL screw cap vial, peroxide **113d** (89mg; 0.27mmol) was dissolved in 1.2 mL of AcOH. 1.3.5-trimethoxybenzene (46mg, 0.27mmol) was then added followed by MsOH (1.91µL; 0.027mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 7/3) on silica gel to afford coupling product **115d** (82mg, 73%) as a clear oil.

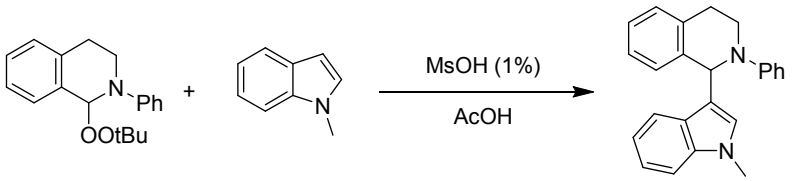
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.41-7.31 (m, 3H); 7.25-7.17 (m, 2H); 7.16-7.12 (m, 1H); 7.08 (br t, 1H, J=7.2 Hz); 7.02 (td, 1H, J=7.5, 1.5 Hz); 6.72 (d, 1H, J=7,5 Hz); 6.65 (br s, 1H); 6.20 (s, 2H); 4.07 (br s, 1H); 3.77 (s, 3H); 3.73-3.55 (m, 1H); 3.60 (s, 6H); 2.92-2.78 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 169.70 (q); 160.38 (Ar q); 158.93 (Ar q); 137.78 (Ar q); 136.95 (Ar q); 134.70 (Ar q); 128.71 (ArH); 127.97 (ArH); 127.84 (ArH); 126.42 (ArH); 125.85 (ArH); 125.83 (ArH); 125.55 (ArH); 112.97 (Ar q); 91.95 (ArH); 49.63 (CH, br); 41.91 (CH_2, br); 29.96 (CH_2, br)

MS (EI): 403 (36); 372 (100); 298 (29); 105 (49); 77 (23)

HRMS (ESI): Calculated for $[C_{25}H_{25}NO_4Na]^+$: 426.167575; found: 426.168033

1-(1-methyl-1H-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (116)[95]



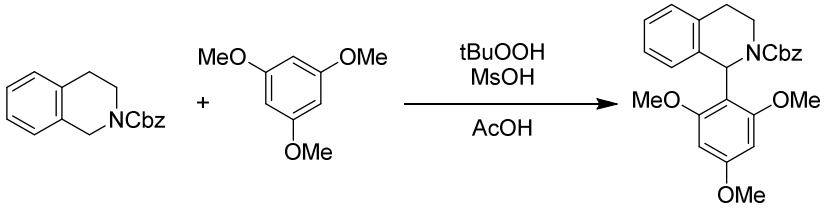
In a 4mL screw cap vial, peroxide **45** (74 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 1-Methyl-indole (32.5 µL, 0.25 mmol) was then added followed by MsOH (0.1 mL of a

0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 24 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 95/5) on silica gel to afford coupling product **116** (42 mg, 50%) as a white solid.

Analytical properties of the isolated product matched those reported in the literature.[14]

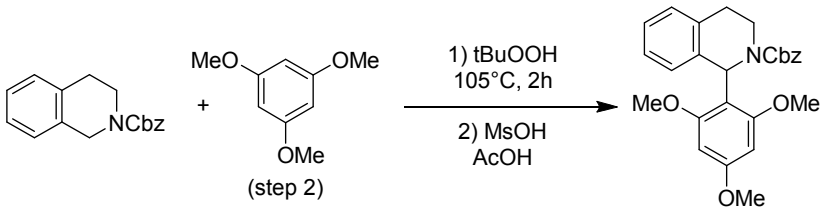
7.2.3 Alternative Procedures

1 step method



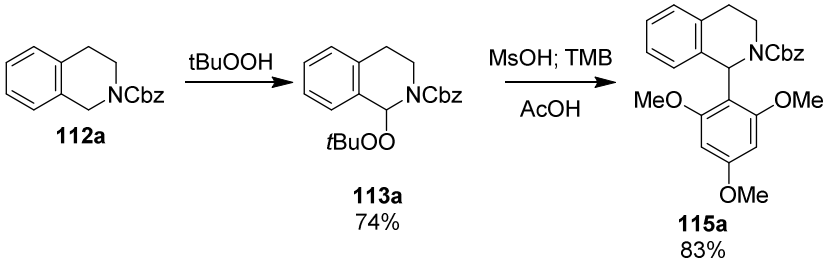
In a 4mL screw-cap vial, **112a** (133.5 mg, 0.5 mmol) was dissolved in AcOH (1.75 mL) then tBuOOH (270 µL of a 5.5M solution in decane, 1.5 mmol), TMB (84 mg, 0.5 mmol) and MsOH (3.54 µL, 0.05 mmol) were added. The reaction mixture was stirred at 105°C for 2 hours. Toluene was then added and solvents evaporated. The resulting brown oil was analyzed by TLC and ^{1}H NMR showing only traces of **115a.**

1 pot method:



In a 4 mL screw-cap vial, **112a** (133.5 mg, 0.5 mmol) was mixed with tBuOOH (270 µL of a 5.5M solution in decane, 1.5 mmol) and stirred at 105°C for 2 hours. After cooling down to room temperature, AcOH (1.75 mL) was added then TMB (84 mg, 0.5 mmol) and MsOH (3.54 µL, 0.05 mmol). The reaction mixture was stirred at room temperature for 30 minutes and subjected directly to flash chromatography (eluant: Pentane/AcOEt 85/15) to afford **115a** (68 mg, 0.159 mmol) in 31% yield. Peroxide **113a** was also isolated form the mixture (56 mg, 0.159 mmol) giving a yield based on recovered **113a** of 46%

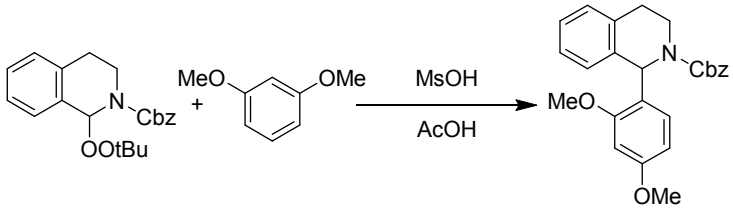
2 step method:



Peroxide **113a** was synthesized according to general procedure (vide supra) in 74% yield then the coupling step was achieved in 83% yield, giving a combined yield of 61% of 115a over the two steps

7.2.4 Substrate Scope

Benzyl 1-(2,4-dimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115g)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. 1.3-dimethoxybenzene (70 µL, 0.5 mmol) was then added followed by MsOH (1.7 µL; 0.025mmol). Mixture was stirred at 50°C for 5 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **115g** (77 mg, 76%) as a clear oil.

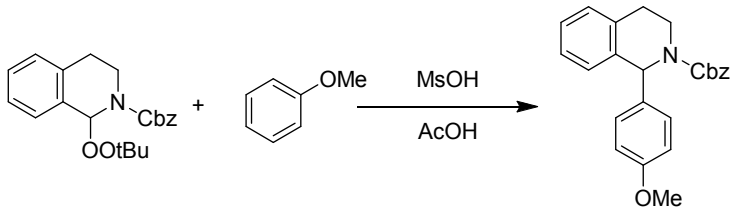
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.36-7.22 (m, 5H); 7.20-7.06 (m, 3H); 6.98 (d, 1H, J=7.4 Hz); 6.81 (d, 1H, J=8.4 Hz); 6.54 (d, 1H, J=2.4 Hz); 6.41 (s, 1H); 6.39 (dd, 1H, J=2.4, 8.4 Hz); 5.10 (d, 1H, J=13 Hz); 5.05 (d, 1H, J=13 Hz); 3.99 (td, 1H; J=5, 13 Hz); 3.73 (s, 3H); 3.67 (s, 3H); 3.49-3.40 (m, 1H); 2.90-2.83 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 159.60 (Ar q); 157.49 (Ar q); 154.19 (q); 136.64 (Ar q); 136.02 (Ar q); 134.12 (Ar q); 129.18 (ArH); 128.05 (ArH); 127.76 (ArH); 127.12 (ArH); 126.99 (ArH); 126.87 (ArH); 125.85 (ArH); 125.49 (ArH); 123.73 (Ar q); 104.52 (ArH); 98.71 (ArH); 65:84 (CH_2); 55.14 (CH_3); 54.83 (CH_3); 52.35 (CH); 38.66 (CH_2); 27.62 (CH_2)

MS (EI): 403 (1.6); 312 (17); 268 (100); 252 (13); 91 (29)

HRMS (ESI): Calculated for $[C_{25}H_{25}NO_4Na]^+$: 426,167625; found: 426.167579

Benzyl 1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115h)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. anisole (54.5 µL, 0.5 mmol) was then added followed by MsOH (1.7 µL; 0.025mmol). Mixture was stirred at 50°C for 24 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 95-5) on a long silica gel column to afford coupling product **115h** (22 mg, 24%) as a clear oil.

Note: Peroxide 113a was not entirely consumed and was recovered after chromatography (27 mg; 30% yield) which gives a yield based on recovered starting material of 35% for **115h**

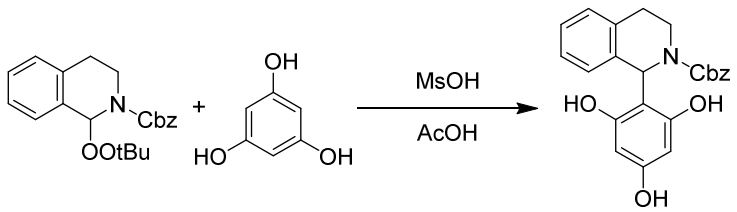
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.37-7.27 (m, 5H); 7.23-7.13 (m, 3H); 7.09-7.03 (m, 3H); 6.85-6.80 (m, 2H); 6.23 (s, 1H); 5.18 (d, 1H, J=12.6 Hz); 5.12 (d, 1H, J=12.6 Hz); 3.97-3.89 (m, 1H); 3.71 (s, 3H); 3.30 (ddd, 1H, J=5, 9.6, 13.3 Hz); 2.93-2.83 (m, 1H); 2.82-2.73 (m, 1H);

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 158.19 (Ar q); 154.28 (q); 136.51 (Ar q); 135.16 (Ar q); 134.35 (Ar q); 134.18 (Ar q); 128.41 (ArH); 128.25 (ArH); 127.89 (ArH); 127.62 (ArH); 127.32 (ArH); 127.08 (ArH); 126.45 (ArH); 125.56 (ArH); 113.40 (ArH); 66.10 (CH_2); 56.63 (CH); 54.76 (CH_3); 37.89 (CH_2); 27.35 (CH_2)

MS (EI): 373 (0.6); 282 (30); 238 (49); 91 (100)

HRMS (ESI): Calculated for $[C_{24}H_{23}NO_3Na]^+$: 396.157009; found: 396.157040

Benzyl 1-(2,4,6-trihydroxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115i)[95]



In a 4mL screw cap vial, peroxide **113a** (177 mg; 0.5 mmol) was dissolved in 2 mL of AcoH. PhloroGlucinol (126 mg, 1 mmol) was then added followed by MsOH (3.54 µL; 0.05mmol). Mixture was stirred at room temperature for 5 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 6/4) on a long silica gel

column to afford coupling product **115i** (150 mg, 77%) as a white solid.

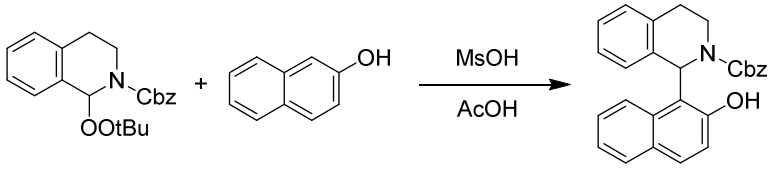
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 8.67 (s, 2H); 8.60 (s, 1H); 7.23-7.12 (m, 5H); 7.02-6.88 (m, 3H); 6.79-6.72 (m, 1H); 6.28 (s, 1H); 5.70 (s, 2H); 5.00 (d, 1H, J=12.9 Hz); 4.94 (d, 1H, J=12.9 Hz); 4.14-4.05 (m, 1H); 3.74-3.63 (m, 1H); 2.78-2.69 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 157.06 (Ar q); 156.58 (Ar q); 154.87 (q); 137.35 (Ar q); 136.85 (Ar q); 133.84 (Ar q); 127.73 (ArH); 127.46 (ArH); 126.96 (ArH); 126.68 (ArH); 125.82 (ArH); 125.13 (ArH); 124.78 (ArH); 108.39 (Ar q); 94.79 (ArH); 94.05 (ArH); 65.68 (CH_2); 49.39 (CH); 39.00 (CH_2); 29.09 (CH_2)

MS (EI): 391 (17); 300 (60); 256 (59); 213 (39); 91 (100)

HRMS (ESI): Calculated for $[C_{23}H_{21}NO_5Na]^+$: 414.131193; found: 414,131437

Benzyl 1-(2-hydroxynaphthalen-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115j)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. 2-Naphtol (72 mg, 0.5 mmol) was then added followed by MsOH (1.77 µL; 0.025mmol). Mixture was stirred at 50°C for 2 and a half hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 95/5) on a long silica gel column to afford coupling product **115j** (57 mg, 55%) as a white solid.

^{1}H NMR: (r.t. d6-DMSO; 400 MHz): 9.65 (br s, 1H); 8.22 (br s, 1H); 7.81 (d, 1H, J=7.8 Hz); 7.75 (d, 1H, J=8.7 Hz); 7.42-7.06 (m, 9H); 6.95 (t, 2H, J=7.4 Hz); 6.85 (s, 1H); 6.56 (d, 1H, J=7.8 Hz); 4.97 (d, 1H, J=12.5 Hz); 4.87 (d, 1H, J=12.5 Hz); 4.35 (d, 1H, J=12.5 Hz); 3.87-3.75 (m, 1H); 3.02-2.87 (m, 2H)

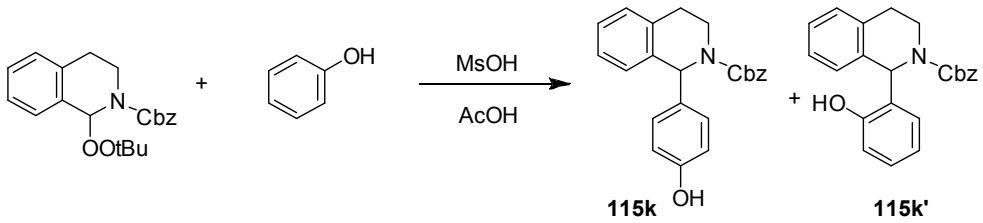
^{13}C NMR: (r.t. d6-DMSO; 100 MHz): 155.01 (CO); 153.22 (Ar q); 137.07 (Ar q); 136.75 (Ar q); 134.81 (Ar q); 133.64 (Ar q); 129.19 (ArH); 128.31 (ArH); 128.15 (ArH); 128.09 (ArH); 128.03 (Ar q); 127.46 (ArH); 127.24 (Ar q); 126.38 (ArH); 125.93 (ArH); 125.75 (ArH); 125.73 (ArH); 122.85 (ArH); 122.18 (ArH); 120.53 (Ar q); 118.85 (ArH); 66.06 (CH_2); 51.34 (CH); 40.01 (CH_2); 29.67 (CH_2)

MS (EI): 409 (30); 318 (75); 274 (95); 231 (75); 91 (100)

HRMS (ESI): Calculated for $[C_{27}H_{23}NO_3Na]^+$: 432.157016; found: 432.157413

Benzyl 1-(4-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115k)[95]

Benzyl 1-(2-hydroxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (115k´)



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Phenol (54.5 mg, 0.5 mmol) was then added followed by MsOH (1.77 µL; 0.025mmol). Mixture was stirred at 50°C overnight and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **115k** (65 mg, 72%) as a white solid.

^{1}H NMR: (80°C d6-DMSO; 400 MHz): 9.06 (br s, 1H); 7.40-7.26 (m, 5H); 7.23-7.12 (m, 3H); 7.06 (d, 1H, H=7.3 Hz); 6.93 (d, 2H, J=8.6 Hz); 6.66 (d, 2H; J=8.6 Hz); 6.19 (s, 1H); 5.17 (d, 1H, J=12 Hz); 5.12 (d, 1H, J=12 Hz); 3.93 (td, 1H, J=5, 13 Hz); 3.34-3.23 (m, 1H); 2.93-2.82 (m, 1H); 2.82-2.72 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 156.24 (Ar q); 154.28 (q); 136.58 (Ar q); 135.38 (Ar q); 134.17 (Ar q); 132.62 (Ar q); 128.43 (ArH); 128.23 (ArH); 127.89 (ArH); 127.64 (ArH); 127.31 (ArH); 127.10 (ArH); 126.36 (ArH); 125.50 (ArH); 114.69 (ArH); 66.09 (CH_2); 56.72 (CH); 37.76 (CH_2); 27.38 (CH_2)

MS (EI): 359 (27); 268 (36); 224 (100); 91 (52)

HRMS (ESI): Calculated for $[C_{23}H_{21}NO_3Na]^+$: 382.141362; found: 382.141721

From the same reaction mixture was also isolated product **115k´** (7 mg; 8%) as a clear oil.

^{1}H NMR: (r.t. ; $CDCl_3$; 500 MHz): 9.4 (br s, 1H); 7.43-7.31 (m, 5H); 7.27-7.15 (m, 4H); 7.03 (d, 1H, J=8 Hz); 6.95 (d, 1H, J=7.6 Hz); 6.73 (t, 1H, J= 7.6 Hz); 6.63 (d, 1H, J= 7.6 Hz); 6.54 (s, 1H); 5.26 (d, 1H, J=12.2 Hz); 5.19 (d, 1H, J=12.2 Hz); 4.16 (dd, 1H, J=5.6, 13 Hz); 3.26 (td, 1H, J=3.2,

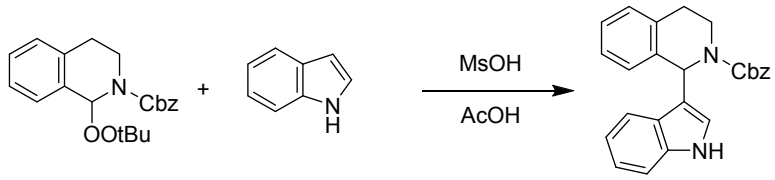
13 Hz); 3.07 (m, 1H); 2.85 (br d, 1H, J=16 Hz)

^{13}C NMR: (r.t. ; $CDCl_3$; 125 MHz): 155.8 (q); 135.8 (Ar q); 134.53 (Ar q); 134.51 (Ar H); 130.3 (ArH); 129.5 (ArH); 128.9 (ArH); 128.8 (ArH); 128.6 (ArH); 128.4 (ArH); 128.2 (arH); 127.9 (Ar q); 127.0 (ArH); 126.4 (ArH); 119.4 (ArH); 117.7 (ArH); 68.3 (CH_2); 52.9 (CH); 37.4 (CH_2); 28.6 (CH_2)

MS (EI): 359 (0.6); 268 (100); 224 (89); 130 (19); 91 (78)

HRMS (ESI): Calculated for $[C_{23}H_{21}NO_3Na]^+$: 382.141361; found: 382.141224

Benzyl 1-(1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116a)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. Indole (30 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling product **116a** (83 mg, 86%) as a white solid.

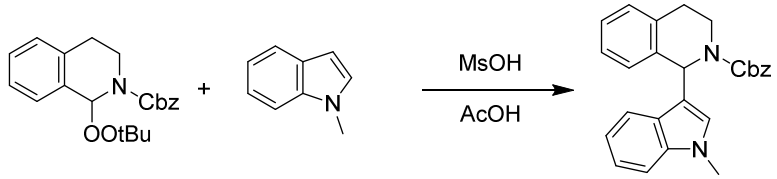
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.77 (br s, 1H); 7.48 (br d, 1H, J=7.9 Hz); 7.43-7.27 (m, 6H); 7.24-7.18 (m, 2H); 7.17-7.12 (2H); 7.10-7.04 (m, 1H); 6.94-6.87 (m, 1H); 6.68 (d, 1H, J=2 Hz); 6.62 (s, 1H); 5.24 (d, 1H, J=12.6 Hz); 5.18 (d, 1H, J= 12.6 Hz); 4.09-3.98 (m, 1H); 3.30-3.19 (m, 1H); 3.01-2.89 (m, 1H); 2.86-2.76 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 153.96 (q); 136.61 (Ar q); 136.17 (Ar q); 135.82 (Ar q); 133.90 (Ar q); 128.43 (ArH); 127.89 (ArH); 127.42 (ArH); 127.33 (ArH); 126.21 (ArH); 125.75 (Ar q); 125.25 (ArH); 124.68 (ArH); 120.81 (ArH); 118.64 (ArH); 118.38 (ArH); 116.38 (Ar q); 111.11 (ArH); 66.07 (CH_2); 51.04 (CH); 37.11 (CH_2); 27.43 (CH_2)

MS (EI): 382 (7); 291 (31); 247 (100); 91 (32)

HRMS (ESI): Calculated for $[C_{25}H_{24}N_2O_2Na]^+$:405.157343; found: 405.157511

Benzyl 1-(1-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116b)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 1-Methyl-indole (32.5 µL, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 95/5) on silica gel to afford coupling product **116b** (96 mg, 97%) as a white solid.

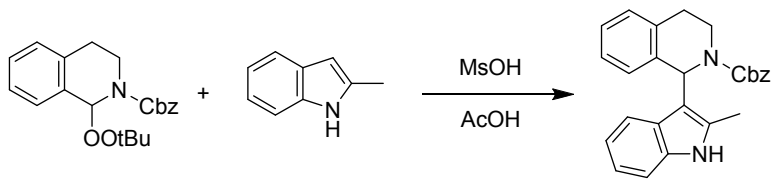
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.44 (d, 1H, J=8.2 Hz); 7.40-7.27 (m, 6H); 7.25-7.20 (m, 2H); 7.17-7.09 (m, 3H); 6.92 (t, 1H, J=7.3 Hz); 6.67 (s, 1H); 6.57 (s, 1H); 5.22 (d, 1H, J=12.6 Hz); 5.16 (d, 1H, J=12.6 Hz); 4.01 (dddd, 1H, J=1, 2.6, 6.2, 13.5 Hz); 3.65 (s, 3H); 3.28-3.19 (m, 1H); 3.0-2.89 (m, 1H); 2.87-2.78 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 153.91 (q); 136.58 (Ar q); 136.57 (Ar q); 135.68 (Ar q); 133.87 (Ar q); 128.88 (ArH); 128.46 (ArH); 127.89 (ArH); 127.43 (ArH); 127.35 (ArH); 127.26 (ArH); 126.26 (ArH); 126.08 (Ar q); 125.34 (ArH); 120.95 (ArH); 118.83 (ArH); 118.49 (ArH); 115.61 (Ar q); 109.17 (ArH); 66.07 (CH_2); 50.84 (CH); 37.10 (CH_2); 31.80 (CH_3); 27.41 (CH_2)

MS (EI): 396 (12); 305 (18); 261 (100); 232 (8); 91 (23)

HRMS (ESI): Calculated for $[C_{26}H_{24}N_2O_2Na]^+$: 419.172993; found: 419.173367

Benzyl 1-(2-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116c)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 2-Methyl-indole (32.7 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product

116c (91 mg, 91%) as a slightly pink solid.

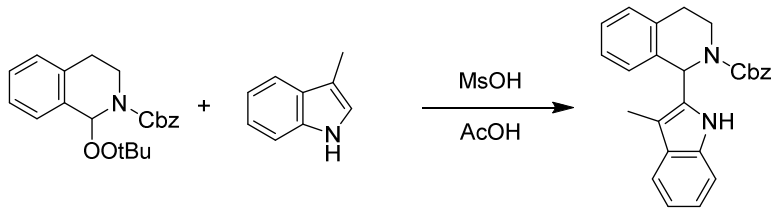
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.67 (br s, 1H); 7.39-7.26 (m, 5H); 7.26-7.15 (m, 3H); 7.07 (t, 1H, J=7.4 Hz); 6.97 (d, 1H, J=7.4 Hz); 6.94-6.87 (m, 2H); 6.75-6.68 (m, 1H); 6.54 (s, 1H); 5.18 (d, 1H, J=12.5 Hz); 5.12 (d, 1H, J=12.5 Hz); 4.19-4.11 (m, 1H); 3.37-3.27 (m, 1H); 3.02-2.95 (m, 1H); 2.92-2.83 (m, 1H); 2.14 (s, 3H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 153.92 (q); 136.59 (Ar q); 136.19 (Ar q); 134.78 (Ar q); 134.04 (Ar q); 133.92 (Ar q); 128.33 (ArH); 127.88 (ArH); 127.39 (Ar q); 127.33 (ArH); 127.24 (ArH); 126.03 (ArH); 125.65 (ArH); 119.55 (ArH); 118.12 (ArH); 111.14 (Ar q); 110.00 (ArH); 66.06 (CH_2); 50.85 (CH); 37.90 (CH_2); 27.73 (CH_2); 11.38 (CH_3)

MS (EI): 396 (7); 305 (6); 261 (100); 232 (2); 91 (227)

HRMS (ESI): Calculated for $[C_{26}H_{24}N_2O_2Na]^+$: 419.172997; found: 419.173363

Benzyl 1-(3-methyl-1H-indol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116d)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 3-Methyl-indole (32.7 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **116d** (86 mg, 88%) as a white solid.

^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.11 (br s, 1H); 7.42 (dd, 1H, J= 0.5, 7.8 Hz); 7.32-7.17 (m, 8H); 7.12 (td, 1H, J=1.2, 7.4 Hz); 7.05-6.99 (m, 1H); 6.99-6.93 (m, 2H); 6.46 (s, 1H); 5,15 (d, 1H, J=12.3 Hz); 5.10 (d, 1H, J=12.3 Hz); 4.17 (td, 1H, J=4.3, 13.2 Hz); 3.64-3.54 (m, 1H); 2.97-2.91 (m, 2H); 2.20 (s, 3H)

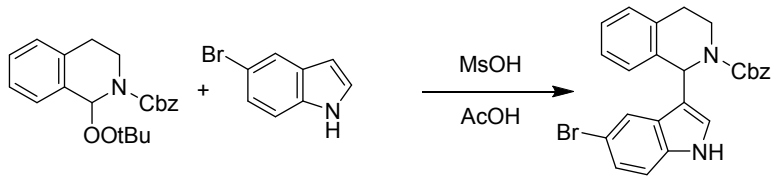
^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.12 (q); 136.39 (Ar q); 135.49 (Ar q); 134.71 (Ar q); 134.26 (Ar q); 134.10 (Ar q); 128.45 (ArH); 127.89 (Ar q); 127.80 (ArH); 127.27 (ArH); 127.22 (ArH); 127.10 (ArH); 126.32 (ArH); 125.76 (ArH); 120.73 (ArH); 117.85 (ArH); 117.72 (ArH);

110.71 (ArH); 107.30 (Ar q); 66.20 (CH_2); 50.52 CH); 38.58 (CH_2); 27.92 (CH_2); 7.87 (CH_3)

MS (EI): 396 (30); 305 (1); 261 (100); 232 (2); 91 (27)

HRMS (ESI): Calculated for $[C_{26}H_{24}N_2O_2Na]^+$: 419.172999; found: 419.173014

Benzyl 1-(5-bromo-2-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116e)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 5-Bromo-indole (49 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **116e** (105 mg, 89%) as a white solid.

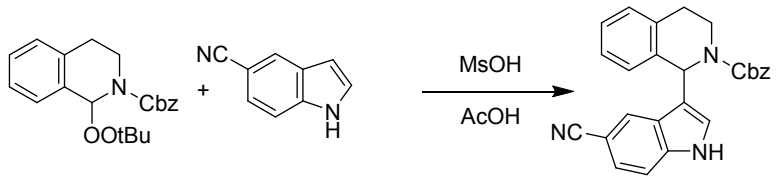
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.99 (br s, 1H); 7.68 (br s, 1H); 7.42-7.25 (m, 6H); 7.23-7.09 (m, 5H); 6.71 (d, 1H, J=2.3 Hz); 6.56 (s, 1H); 5.22 (d, 1H, J=12.5 Hz); 5.17 (d, 1H, J=12.5 Hz); 4.01 (dddd, 1H, J=1, 2.5, 6, 13.3 Hz); 3.23-3.13 (m, 1H, peak behind residual water peak); 2.99-2.87 (m, 1H); 2.85-2.75 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.14 (q); 136.57 (Ar q); 135.42 (Ar q); 134.89 (Ar q); 133.99 (Ar q); 128.57 (ArH); 128.06 (ArH); 127.61 (Ar q); 127.52 (ArH); 127.46 (ArH); 127.25 (ArH); 126.47 (ArH); 126.37 (ArH); 125.46 (ArH); 123.56 (ArH); 121.04 (ArH); 116.36 (Ar q); 113.26 (ArH); 111.39 (Ar q); 66.28 (CH_2); 50.82 (CH); 37.18 (CH_2); 27.43 (CH_2)

MS (EI): 462 (5.6); 460 (5.8); 371 (47); 369 (45); 327 (96); 325 (100); 91 (57)

HRMS (ESI): Calculated for $[C_{25}H_{21}N_2O_2BrNa]^+$: 483.067875; found: 483.068005

Benzyl 1-(5-cyano-2-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116f)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 5-Cyano-indole (35.5 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **116f** (88 mg, 86%) as a white solid.

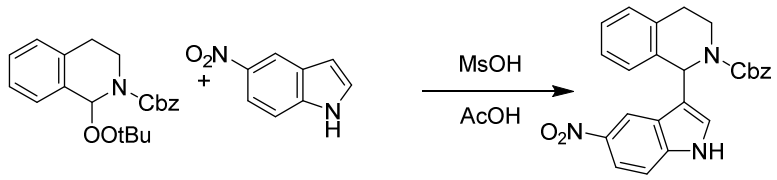
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 11.38 (br s, 1H); 7.91 (s, 1H); 7.52 (dd, 1H, J=0.6, 8.4 Hz); 7.43-7.26 (m, 6H); 7.26-7.22 (m, 2H); 7.18-7.12 (m, 2H); 6.89 (d, 1H, J=2.2 Hz); 6.61 (s, 1H); 5.24-5.16 (m, 2H); 4.02 (dddd, 1H, J=1, 2.6, 6, 13.4 Hz); 3.25-3.15 (m, 1H); 3.01-2.89 (m, 1H); 2.88-2.79 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.06 (Q); 137.81 (Ar q); 136.45 (Ar q); 135.09 (Ar q); 133.96 (Ar q); 128.51 (ArH); 127.96 (ArH); 127.47 (ArH); 127.40 (ArH); 127.28 (ArH); 127.18 (ArH); 126.46 (ArH); 125.51 (Ar q); 125.45 (ArH); 124.09 (ArH); 123.60 (ArH); 120.03 (Ar q); 117.63 (Ar q); 112.59 (ArH); 100.95 (Ar q); 66.25 (CH_2); 50.47 (CH); 37.22 (CH_2); 27.37 (CH_2)

MS (EI): 407 (0.9); 316 (60); 272 (100); 243 (12); 91 (36)

HRMS (ESI): Calculated for $[C_{26}H_{21}N_3O_2Na]^+$: 430.152595; found: 430.153053

Benzyl 1-(5-nitro-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116g)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 5-Nitro-indole (40.5 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 seconds and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product

116g (97 mg, 90%) as a yellow solid.

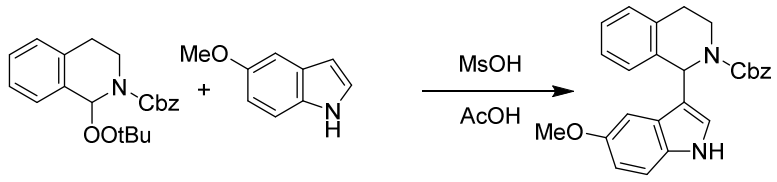
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 11.53 (br s, 1H); 8.56 (d, 1H, J=1.5 Hz); 7.98 (dd, 2H, J=2.4, 9 Hz); 7.53 (d, 1H, J=9 Hz); 7.41-7.13 (m, 9H); 6.93 (s, 1H); 6.68 (s, 1H); 5.25 (d, 1H, J=12.4 Hz); 5.19 (d, 1H, J=12.4 Hz); 4.03 (ddd, 1H, J=2, 6, 13.4 Hz); 3.27-3.14 (m, 1H); 3.03-2.90 (m, 1H); 2.89-2.77 (m, 1H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.08 (q); 140.65 (Ar q); 139.16 (Ar q); 136.42 (Ar q); 134.91 (Ar q); 133.96 (Ar q); 128.53 (ArH); 128.37 (ArH); 127.86 (ArH); 127.47 (ArH); 127.33 (ArH); 127.16 (ArH); 126.52 (ArH); 125.47 (ArH); 124.96 (Ar q); 119.23 (Ar q); 116.26 (ArH); 115.84 (ArH); 111.66 (ArH); 66.26 (CH_2); 50.45 (CH); 37.20 (CH_2); 27.37 (CH_2)

MS (EI): 427 (0.4); 336 (24); 292 (100); 246 (18); 91 (25)

HRMS (ESI): Calculated for $[C_{25}H_{21}N_3O_4Na]^+$: 450.142429; found: 450.142528

Benzyl 1-(5-methoxy-2-methyl-1H-indol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116h)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 5-Methoxy-indole (36.75 mg, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 30 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **116h** (98 mg, 95%) as a slightly pink oil.

^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.59 (br s, 1H); 7.42-7.26 (m, 5H); 7.26-7.19 (m, 3H); 7.18-7.15 (m, 2H); 6.96 (br s, 1H); 6.72 (dd, 1H, J=2.4, 8.7 Hz); 6.61 (d, 1H, J=2.4 Hz); 6.59 (s, 1H); 5.24-5.16 (m, 2H); 4.06-3.97 (m, 1H); 3.59 (s, 3H); 3.27-3.17 (m, 1H); 3.00-2.89 (m, 1H); 2.86-2.77 (m, 1H)

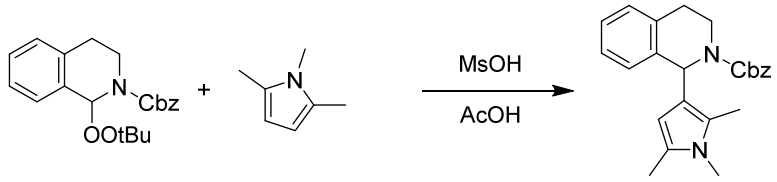
^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.03 (q); 153.06 (Ar q); 136.65 (Ar q); 135.78 (Ar q); 133.95 (Ar q); 131.35 (Ar q); 128.43 (ArH); 127.92 (ArH); 127.47 (ArH); 127.32 (ArH); 127.07 (ArH); 126.25 (ArH); 126.17 (Ar q); 125.32 (ArH); 125.31 (ArH); 116.07 (Ar q); 111.73 (ArH);

111.04 (ArH); 101.15 (ArH); 66.07 (CH_2); 54.97 (CH_3); 51.08 (CH); 37.09 (CH_2); 27.43 CH_2)

MS (EI): 412 (18); 321 (19); 277 (100); 248 (4); 91 (25)

HRMS (ESI): Calculated for $[C_{26}H_{24}N_2O_3Na]^+$: 435.167915; found: 435.168235

Benzyl 1-(1,2,5-trimethyl-1H-pyrrol-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116i)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. 1-2-5 trimethylpyrrole (27.7 µL, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 15 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling product **116i** (61 mg, 65%) as a yellowish foam.

Note: **116i** bearing a pyrrol unit which still has a reactive position, decomposition was observed during high temperature NMR experiments, leading to impurities in the ^{13}C spectra.

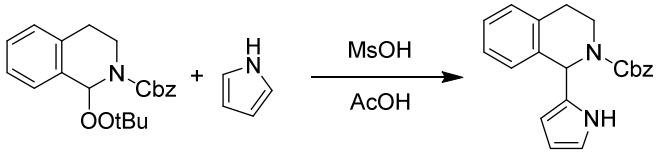
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.40-7.25 (m, 5H); 7.16-7.03 (m, 3H); 6.90 (d, 1H; J= 7.5 Hz); 6.11 (s, 1H); 5.22 (s, 1H); 5.13 (d, 1H, J=12.5 Hz); 5.08 (d, 1H, J=12.5 Hz); 4.03 (dddd, 1H, J=1, 2.5, 6, 13.3 Hz); 3.38-3.28 (m, 1H); 3.29 (s, 3H); 2.92-2.74 (m, 2H); 2.11 (s, 3H); 2.02 (s, 3H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 153.82 (q); 137.20 (Ar q); 136.69 (Ar q); 133.36 (Ar q); 128.12 (ArH); 127.83 (ArH); 127.25 (ArH); 127.12 (ArH); 125.61 (Ar q); 125.56 (ArH); 125.18 (ArH); 124.27 (Ar q); 119.05 (Ar q); 105.15 (ArH); 65.83 (CH_2); 51.04 (CH); 37.19 (CH_2); 29.26 (CH_3); 27.60 (CH_2): 11.42 (CH_3); 9.45 (CH_3)

MS (EI):374 (23); 266 (9); 239 (100); 108 (12); 91 (29)

HRMS (ESI): Calculated for $[C_{24}H_{26}N_2O_2Na]^+$: 397.188645; found: 397.189011

Benzyl 1-(1H-pyrrol-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (116j)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 0.9 mL of AcoH. pyrrole (17.4 µL, 0.25 mmol) was then added followed by MsOH (0.1 mL of a 0,025mM solution of MsOH in AcOH; 0.0025 mmol). Mixture was stirred at room temperature for 2 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 95/5) on silica gel to afford coupling product **116j** (43 mg, 51%) as a clear oil.

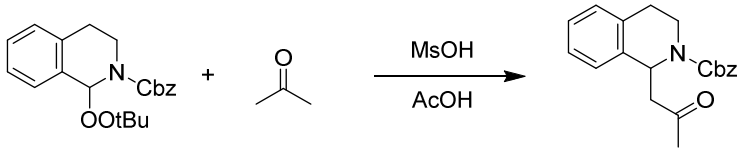
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 10.28 (br s, NH); 7.43-7.24 (m, 5H); 7.22-7.11 (m, 4H); 6.66-6.61 (m, 1H); 6.25 (s, 1H); 5.92-5.88 (m, 1H); 5.64-5.58 (m, 1H); 5.21-5.12 (m, 2H); 4.02-3.93 (m, 1H); 3.40-3.29 (m, 1H); 2.93-2.74 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 154.28 (q); 136.58 (Ar q); 134.75 (Ar q); 133.91 (Ar q); 131.75 (Ar q); 128.24 (ArH); 127.87 (ArH); 127.39 (ArH); 127.26 (ArH); 127.00 (ArH); 126.33 (ArH); 125.33 (ArH); 117.39 (ArH); 106.61 (ArH); 106.51 (ArH); 66.06 (CH_2); 51.98 (CH); 38.00 (CH_2); 27.37 (CH_2)

MS (EI): 332 (14); 241 (37; 197 (100); 91 (62)

HRMS (ESI): Calculated for $[C_{21}H_{20}N_2O_2Na]^+$: 355.141697; found: 355.141399

Benzyl 1-(2-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (117a)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Acetone (91 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 6 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling product **117a** (68 mg, 84%) as a clear oil.

^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.38-7.25 (m, 4H); 7.23-7.10 (m, 4H); 5.57 (t, 1H, J=6.7

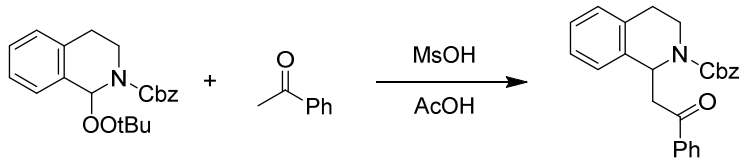
Hz); 5.11 (s, 2H); 3.96 (td, 1H, J=5.1, 13 Hz); 3.45-3.30 (m, 1H); 2.91-2.73 (m, 4H); 2.08 (s, 3H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 205.08 (q); 154.15 (q); 136.454 (Ar q); 136.41 (Ar q); 133.47 (Ar q); 128.37 (ArH); 127.86 (ArH); 127.30 (ArH); 127.04 (ArH); 126.30 (ArH); 126.20 (ArH); 125.68 (ArH); 66.06 (CH_2); 50.66 (CH); 49.96 (CH_2); 37.81 (CH_2); 29.40 (CH_3); 27.20 (CH_2)

MS (EI): 323 (-); 266 (12; 323-57); 232 (26; 323-91); 188 (46; 232-44); 91 (100)

HRMS (ESI): Calculated for $[C_{20}H_{21}NO_3Na]^+$: 346.141360; found: 346.141467

Benzyl 1-(2-oxo-2-phenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (117b)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Acetophenone (145 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 3 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling products **117b** (60 mg, 62%) as a clear oil.

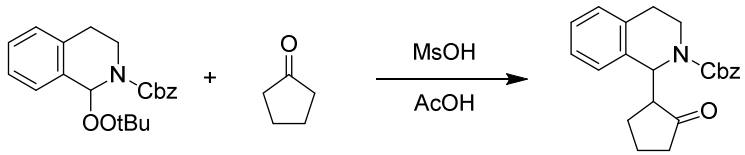
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.96-7.90 (m, 2H); 7.62-7.55 (m, 1H); 7.51-7.43 (m, 2H); 7.34-7.18 (m, 6H); 7.17-7.08 (m, 3H); 5.68 (t, 1H, J=6.6 Hz); 5.07-4.89 (m, 2H); 3.97-3.86 (m, 1H); 3.57-3.40 (m, 3H); 2.90-2.80 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 197.22 (q); 154.17 (q); 136.61 (Ar q); 136.44 (Ar q); 136.40 (Ar q); 133.73 (Ar q); 132.68 (ArH); 128.44 (ArH); 128.25 (ArH); 127.90 (ArH); 127.71 (ArH); 127.30 (ArH); 126.98 (ArH); 126.50 (ArH); 126.36 (ArH); 125.77 (Arh); 66.04 (CH_2); 51.51 (CH); 45.24 (CH_2); 38.20 (CH_2); 27.32 (CH_2)

MS (EI): 385 (0.1); 294 (10); 266 (21); 222 (58); 105 (24); 91 (100)

HRMS (ESI): Calculated for $[C_{25}H_{23}NO_3Na]^+$: 408.157016; found: 408.156970

Benzyl 1-(2-oxocyclopentyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (117c)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Cyclopentanone (110 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 3 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 85/15) on silica gel to afford coupling product **117c** as an unseparable mixture of diastereoisomers in a 1:0.65 ratio (70 mg, 80%) as a clear oil.

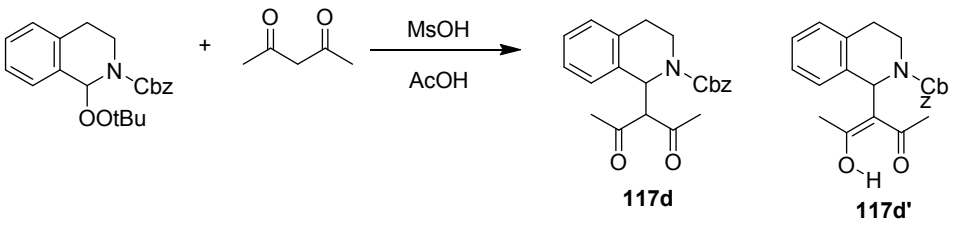
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.41-7.25 (m, 5H); 7.22-7.10 (m, 3H); 7.05-6.94 (m, 1H); 5.45 (d, 1H, J=5.1 Hz, major); 5.26 (d, 1H, J=5.7 Hz, minor); 5.15-5.06 (m, 2H); 4.02-3.74 (m, 1H); 3.59-3.25 (m, 1H); 2.89-2.78 (m, 2H); 2.60-2.43 (m, 1H; overlaps with d6-DMSO signal); 2.22-2.11 (m, 1H); 2.10-1.77 (m, 3H); 1.77-1.43 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 216.56 (q, minor); 216.45 (q, major); 154.47 (q, major); 154.26 (q, minor); 137.22(Ar q); 136.55 (Ar q); 136.45 (Ar q); 134.79 (Ar q); 134.29 (Ar q); 133.41 (Ar q); 128.19 (Ar H); 127.85 (ArH); 127.35 (ArH); 127.24 (ArH); 127.16 (ArH); 126.95 (ArH); 126.69 (ArH); 126.57 (ArH); 126.11 (ArH); 126.02 (ArH); 125.64 (ArH); 66.04 (CH_2, minor)65.96 (CH_2, major); 55.67 (CH); 54.09 (CH); 53.84 (CH); 52.70 (CH); 37.47 (CH_2, major); 36.52 (CH_2, minor); 27.23 (CH_2, major); 27.14 (CH_2, minor); 26.02 (CH_2, major); 25.84 (CH_2, minor); 19.39 (CH_2, major); 19.25 (CH_2, minor)

MS (ESI): m/z=349

HRMS (ESI): Calculated for $[C_{22}H_{23}NO_3Na]^+$: 372.157012; found: 372.156920

Benzyl 1-(2,4-dioxopentan-3-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (117d)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. AcetylAcetone (128 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025

mmol). Mixture was stirred at room temperature for 8 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **117d** (42 mg, 47%) as a slightly yellow oil.

Note: On the NMR timescale, **117d** was observed as 2 rotamers plus its enol form **117d'** in a 1:0.61:0.14 ratio in $CDCl_3$ and in a 1:0.31:0,04 ratio in d6-DMSO

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz; 2 rotamers + **117d'**): 7.42-7.29 (m, 5H); 7.24-6.99 (m, 4H); 6.19 (d, 1H, J=10 Hz; major); 6.08 (d, 1H, J=10 Hz; minor); 5.77 (s, 1H, **117d'**); 5.30-5.03 (m, 2H); 4.52 (ddd; 1H, J=2.7, 4.7, 13.2 Hz; **117d'**); 4.24-4.10 (m, 2H, major); 4.02-3.92 (m, 2H, minor); 3.51-3.40 (m, 1H, major); 3.39-3.28 (m, 1H, minor); 3.23 (dd, 1H, J=3.7, 7.9 Hz; **117d'**); 3.12-2.77 (m, 2H); 2.32-1.95 (m, 6H)

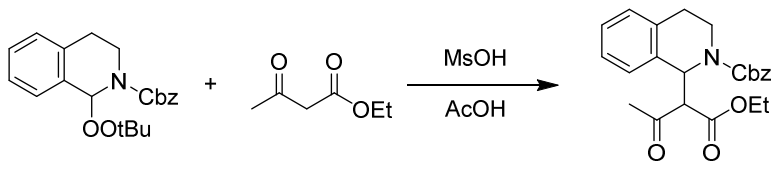
^{1}H NMR: (r.t. d6-DMSO; 500 MHz; 2 rotamers + **117d'**): 7.41-7.27 (m, 5H); 7.25-7.16 (m, 2H); 7.16-7.08 (m, 1H); 7.03-6.89 (m, 1H); 5.90 (d, 1H, J=10 Hz; major); 8.83 (d, 1H, J=9.3 Hz; minor); 5.80 (s, 1H, **117d'**); 5.15-5.01 (m, 2H); 4.58 (d, 1H, J=9.3 Hz, minor); 4.46 (d, 1H, J=10 Hz, major); 4.31 (td, 1H, J=3.8, 13 Hz, **117d'**); 4.00-3.75 (m, 1H); 3.54-3.38 (m, 1H); 2.98-2.81 (m, 2H); 2.12 (s, 3H, major); 2.08 (s, 3H, minor); 2.00 (s, 3H, major); 1.97 (s, 3H, minor)

^{13}C NMR: (r.t. d6-DMSO; 125 MHz; 2 rotamers): 202.90 (q); 200.82 (q); 155.07 (q, major); 154.28 (q, minor); 136.63 (Ar q, major); 126.42 (Ar q, minor); 135.15 (Ar q, major); 134.97 (Ar q, minor); 134.08 (Ar q); 129.34 (ArH); 129.21 (ArH); 128.36 (ArH); 127.87 (ArH); 127.71 (ArH); 127.57 (ArH); 127.45 (ArH); 126.51 (ArH); 126.02 (ArH); 72.46 (CH, major); 72.01 (CH, minor); 66.75 (CH_2, minor); 66.62 (CH_2, major); 53.49 (CH, minor); 53.40 (CH, major); 38.39 (CH_2, major); 38,89 (CH_2, minor); 31.94 (CH_3); 28.90 (CH_3, minor); 28.17 (CH_3, major); 26.74 (CH_2, major); 26.25 (CH_2, minor)

MS (EI): 274 (3); 266 (18); 230 (10); 222 (31); 91 (100);43 (9)

HRMS (ESI): Calculated for $[C_{22}H_{23}NO_4Na]^+$: 388.151924; found: 288.151825

Benzyl 1-(1-ethoxy-1,3-dioxobutan-2-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (117e)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH.

Ethyl acetoacetate (157 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature overnight and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 85/15) on silica gel to afford coupling product **117e** as an unseparable mixture of diastereoisomers in a 1:0.8 ratio (64 mg, 64%) as a clear oil.

Note: the 2 diastereoisomers could be separated on analytical TLC plates but came as a single spot through column chromatography or preparative TLC.

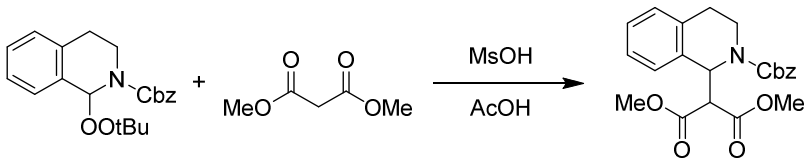
^{1}H NMR: (80°C d6-DMSO; 400 MHz, 2 diastereoisomers): 7.38-7.25 (m, 5H); 7.22-7.04 (m, 4H); 5.90 (d, 1H, J=9 Hz, minor); 5.86 (d, 1H, J=8.3 Hz, major); 5.10 (s, 2H, major); 5.10 (d, 1H, J=12.6 Hz, minor); 5.05 (d, 1H, J=12.6 Hz, minor); 4.19 (d, 1H, J=9 Hz, minor); 4.1-3.93 (m, 1H najor + 2H); 3.93-3.82 (m, 1H); 2.94-2.84 (m, 2H); 2.17 (s, 3H, major); 2.06 (s, 3H, minor); 1.11 (t, 3H, J=7 Hz, minor); 1.02 (t, 3H, J=7 Hz, major)

^{13}C NMR: (80°C d6-DMSO; 100 MHz, 2 diastereoisomers): 200.60 (q, minor); 200.22 (q, major); 167.44 (q, minor); 166.56 (q, major); 154.81 (q, minor); 154.72 (q, major); 136.72 (Ar q, minor); 136.61 (Ar q, major); 135.31 (Ar q, minor); 134.35 (Ar q, minor); 134.34 (Ar q, major); 134.25 (Ar q, major); 128.89 (ArH); 128.27 (ArH, major); 128.22 (ArH, minor); 127.78 (ArH, major); 127.69 (ArH, minor); 127.53 (ArH); 127.46 (ArH); 127.38 (ArH); 126.76 (ArH, minor); 126.64 (ArH, major); 125.91 (ArH, minor); 125.82 (ArH, major); 66.77 (CH_2, major); 66.60 (CH_2, minor); 65.77 (CH, major); 64.54 (CH, minor); 61.09 (CH_2, major); 61.01 (CH_2, minor); 53.51 (CH, minor); 52.80 (CH, major); 39.25(CH_2, major); 38.80 (CH_2, minor); 30.15 (CH_3, major); 28.24 (CH_3, minor); 26.81 (CH_2); 13.54 (CH_3, minor); 13.46 (CH_3, major); [39 signals visible for 42 expected]

MS (EI): 350 (0.1); 304 (6); 266 (23); 260 (15); 222 (46); 91 (100); 43 (4)

HRMS (ESI): Calculated for $[C_{23}H_{25}NO_5Na]^+$: 418.162489; found: 418.162329

Dimethyl 2-(2-(benzyloxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)malonate (117f)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Dimethylmalonate (142 µL, 1.25 mmol) was then added followed by MsOH (1.77 µL; 0.025

mmol). Mixture was stirred at room temperature overnight and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling product **117f** (15 mg, 15%) as a clear oil.

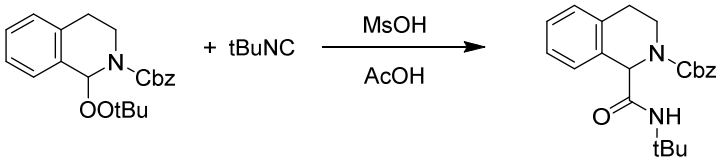
^{1}H NMR: (r.t. $CDCl_3$; 500 MHz; 2 rotamers): 7.37-7.00 (m, 9H); 5.93 (app dd, 1H, J=4.2, 8.5 Hz); 5.11 (app dd, 1H, J=5, 12.6 Hz); 5.04 (app dd, 1H, H=5, 12.6 Hz); 4.04-3.69 (m, 2H); 3.67-3.43 (m, 7H); 2.96-2.76 (m, 2H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz; 2 rotamers): 167.60 (q); 167.48 (q); 167.37 (q); 167.24 (q); 155.60 (q); 155.12 (q); 136.65 (Ar q); 136.37 (Ar q); 134.52 (Ar q); 134.41 (Ar q); 134.32 (Ar q); 129.07 (ArH); 128.57 (ArH); 128.47 (ArH); 128.09 (ArH); 128.03 (ArH); 127.97 (ArH); 127.92 (ArH); 127.59 (ArH); 127.12 (ArH); 126.42 (ArH); 126.27 (ArH); 67.57 (CH_2); 67.35 (CH_2); 58.68 (CH); 58.36 (CH); 54.09 (CH); 53.98 (CH); 52.72 (CH_3); 52.67 (CH_3); 52.52 (CH_3); 52.45 (CH_3); 40.12 (CH_2); 39.22 (CH_2); 27.87 (CH_2); 27.49 (CH_2)

MS (EI): 397 (1.3); 266 (60); 262 (26); 222 (73); 131 (6); 91 (100)

HRMS (ESI): Calculated for $[C_{22}H_{23}NO_6Na]^+$: 420.141760; found: 420.142073

Benzyl 1-(tert-butylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (118)[95]



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Tert-Butyl isonitrile (142 µL, 0.5 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 15 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford coupling product **118** (69 mg, 75%) as a slowly crystallizing oil.

^{1}H NMR: (r.t. d6-DMSO; 500 MHz, 2 rotamers in a 1:1.41 ratio): 7.99-7.96 (2 s, 1H, major+ minor); 7.55-77.50 (2 d, 1H, J=7 Hz, major + minor); 7.46-7.28 (m, 5H); 7.26-7.13 (m, 3H); 5.45-5.42 (2s, 1H, major + minor); 5.25-5.03 (m, 2H); 4.01-3.82 (2 m, 1H, major + minor); 6.79-3.66 (m, 1H); 3.04-2.91 (m, 1H); 2.81-2.69 (m, 1H); 1.22-1.14 (2 s, 9H, major + minor)

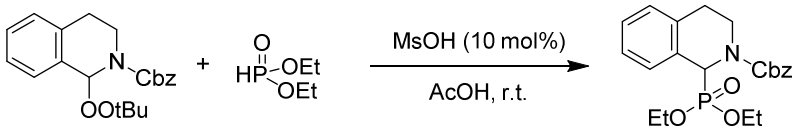
^{13}C NMR: (r.t. d6-DMSO; 125 MHz, 2 rotamers): 170.30 (q, major); 170.25 (q, minor); 154.90 (q, minor); 154.79 (q, major); 136.78 (Ar q, minor); 136.75 (Ar q, major); 135.14 (Ar q,

major); 134.95 (Ar q, minor); 132.76 (Ar q, minor); 132.40 (Ar q, major); 128.36 (ArH); 128.34 (ArH); 128.27 (ArH); 128.19 (ArH); 127.79 (ArH); 127.63 (ArH); 127.50 (ArH); 127.25 (ArH); 126.89 (ArH); 126.70 (ArH); 126.67 (ArH); 126.08 (ArH); 66.35 (CH_2, minor); 66.30 (CH_2, major); 58.14 (CH); 40.49 (CH_2, major); 40.38 (CH_2, minor); 28.38 (CH_3, minor); 28.19 (CH_3, major); 28.13 (CH_2, major); 28.07 (CH_2, minor)

MS (EI): 366 (0.09); 266 (39); 222 (56); 176 (45); 91 (100); 57 (11)

HRMS (ESI): Calculated for $[C_{22}H_{26}N_2O_3Na]^+$: 389.183560; found: 389.183285

benzyl 1-(diethoxyphosphoryl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (119)



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Diethylphosphite (31.7 µL, 0.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature overnight and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 1/1) on silica gel to afford coupling product **119** (84 mg, 84%) as a clear oil.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, 2 rotamers in a 0.55:0.45 ratio): 7.49-7.29 (m, 6H); 7.25-7.10 (m, 3H); 5.73 (d, J=20 Hz, 1H, major); 5.61 (d, J=20 Hz, 1H, minor); 5.28-5.11 (m, 2H); 4.39-4.31 (m, 1H, minor); 4.18-3.86 (m, 4H); 3.84-3.73 (m, 1H); 3.69-3.60 (m, 1H, minor); 3.04-2.83 (m, 2H); 1.27 (t, J=7 Hz, 3H, major); 1.24 (t, J=7 Hz, 3H, minor); 1.15 (t, J=7 Hz, 3H, major); 1.07 (t, J=7 Hz, 3H, minor)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, 2 rotamers): 155.33 (d, J=3.4 Hz, C, major); 154.99 (d, H= 2 Hz, C, major); 136.53 (C, major); 136.22 (C, minor); 134.85 (d, J=6 Hz, C, minor); 134.78 (d, J=6.1 Hz, C, major); 129.38 (d, J=2 Hz, Ar CH, minor); 128.99 (d, J=2 Hz, Ar CH, major); 128.84 (Ar C); 128.51 (Ar CH); 128.31 (ar CH); 128.21 (Ar CH); 128.12 (Ar CH); 128.08 (d, J=4 Hz, Ar CH, major); 127.93 (Ar CH); 127.83 (d, J=4 Hz, Ar CH, minor); 127.57 (d, J=3.2 Hz, Ar CH, minor); 127.45 (d, J=3.2 Hz, Ar CH, major); 126.15 (d, J=3.2 Hz, Ar CH, major); 126.09 (d, J= 3.2 Hz, Ar CH, minor); 67.76 (CH_2, minor); 67.60 (CH_2, major); 63.27 (d, J=7.5 Hz, CH_2, minor); 63.08 (d, J=7.5 Hz, CH_2, major); 62.80 (d, J=7.5 Hz, CH_2, major); 62.56 (d, J=7.5 Hz, CH_2, minor); 53.35

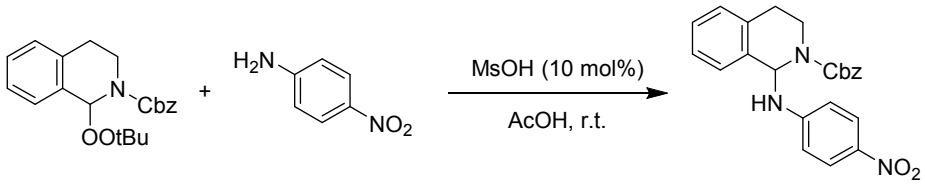
(d, J=150 Hz, CH, minor); 52.87 (d, J= 152 Hz, CH, major); 39.93 (CH_2, major); 39.13 (CH_2, minor); 28.18 (CH_2, major); 27.85 (CH_2, minor); 16.32 (d, J=5.5 Hz, 2x CH_3)

^{31}P NMR: (r.t. $CDCl_3$; 125 MHz, 2 rotamers): 21.46 (major); 21.15 (minor)

MS (EI): 403 (1.22); 266 (67); 222 (74); 91 (100)

HRMS (ESI): Calculated for $[C_{21}H_{26}NO_5PNa]^+$: 426.144085; found: 426.144337

benzyl 1-(4-nitrophenylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate (120)



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. Para-nitroaniline (34.5 mg, 0.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature overnight and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 1/1) on silica gel to afford coupling product **120** (32 mg, 31%) as a yellow solid.

^{1}H NMR: (80°C d6-DMSO; 500 MHz): 7.94 (d, 2H, J=8.5 Hz); 7.70 (d, 1H, J=8 Hz); 7.4-7.2 (m. 7H); 6.96 (d, 2H, J= 8.5 Hz); 6.59 (d, 1H, J=8 Hz); 5.22 (d, 1H, J=12.4 Hz), 5.13 (d, 1H, J=12.4 Hz); 4.1-4.0 (m 1H); 3.48-3.38 (m, 1H); 2.96-2.87 (m, 1H); 2.83-2.76 (m, 1H)

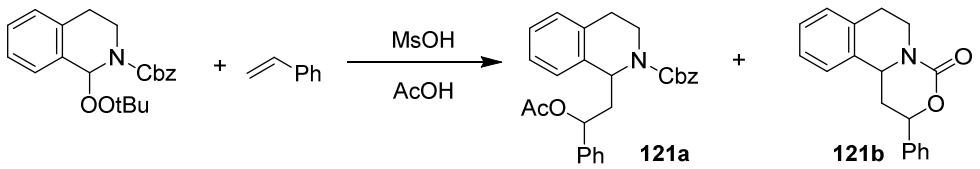
^{13}C NMR: (80°C d6-DMSO; 125 MHz):154.03 (C, br); 152. 02 (Ar q); 137.20 (Ar q); 136.15 (Ar q); 134.35 (Ar q); 133.70 (Ar q); 128.56 (ArH); 127.91 (ArH); 127.80 (ArH); 127.62 (ArH); 127.50 (ArH); 127.42 (ArH, br); 125.87 (ArH); 125.22 (ArH); 111.94 (ArH); 66.42 (CH_2); 61.84 (CH); 36.49 (CH_2); 26.96 (CH_2)

MS (ESI): 829 (2xM+Na^+); 426(M+Na^+)

HRMS (ESI): Calculated for $[C_{23}H_{21}N_3O_4Na]^+$: 426.142425; found: 426.142380

Benzyl 1-(2-acetoxy-2-phenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (121a)[95]

2-Phenyl-1,2,6,7-tetrahydro-[1,3]oxazino[4,3-a]isoquinolin-4(11bH)-one (121b)



In a 4mL screw cap vial, peroxide **113a** (88.7 mg; 0.25 mmol) was dissolved in 1 mL of AcoH.

Styrene (28.7 µL, 0.25 mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at 40°C for 48 hours and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 9/1) on silica gel to afford acetate **121a** as a mixture of diastereoisomers (84 mg, 39%) as a slowly crystallizing oil. dr was determined by ^{1}H NMR analysis of the mixture and was found to be 1:2.5. The diastereoisomers could also be separated by column chromatography for analytical purposes with a reduced yield.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, upper diastereoisomer, major, 2 rotamers in 1:1 ratio): 7.43-7.02 (m, 14H); 5.76 and 5.72 (2 dd, 1H, J= 10.5; 3.5 HZ and J= 10.4; 2.8 Hz); 5.54 and 5.35 (2 dd, 1H, J= 11; 3.7 Hz and J= 10.5; 3 Hz); 5.14 and 5.13 (dd, 2H, J= 171; 12 Hz and J=23; 12 Hz); 4.34-4.08 (2 m, 1H); 3.27-3.13 (m, 1H); 3.07-2.86 (2 m, 1H); 2.75-2.64 (m, 1H); 2.41-2.26 (m, 1H); 2.24-2.14 (m, 1H); 2.12 and 1.71 (s, 3H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, upper diastereoisomer, major): 170.48 and 170.01 (q); 155.62 and 155.53 (Ar q); 140.72 and 140.61 (Ar q); 137.28 and 136.94 (Ar q); 136.79 and 136.51 (Ar q); 134.25 and 133.77 (Ar q); 129.31 (ArH); 129.06 (ArH); 128.53 (ArH); 128.47 (ArH); 128.22 (ArH); 128.06 (ArH); 127.99 (ArH); 127.93 (ArH); 127.90 (ArH); 127.05 (ArH); 126.97 (ArH); 126.85 (ArH); 126.68 (ArH); 126.35 (ArH); 126.29 (ArH); 126.26 (ArH); 126.22 (ArH); 72.92 and 72.52 (CH); 67.66 and 67.32 (CH_2); 51.96 and 51.63 (CH); 43.78 and 42.93 (CH_2); 37.80 and 37.43 (CH_2); 28.39 and 27.92 (CH_2); 21.36 and 20.83 (CH_3)

MS (EI): 369 (0.30); 266 (61); 222 (67); 91 (100)

HRMS (ESI): Calculated for $[C_{27}H_{27}NO_4Na]^+$:452.183231; found: 452.183551

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, lower diastereoisomer, minor, 2 rotamers in a 1:1 ratio): 7.49-7.08 (m, 13 H); 7.02-6.86 (m, 1H); 5.85 (m, 1H); 5.34-5.10 (m, 3H); 4.30-4.01 (2 m, 1H); 3.60-3.44 (m, 1H); 3.09-2.87 (2 m, 1H); 2.86-2.75 (m, 1H); 2.64-2.52 (m, 1H); 2.22-2.09 (m, 1H); 2.06 and 2.01 (2 s, 3H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, lower diastereoisomer, minor, 2 rotamers in a 1:1 ratio): 170.23 (q); 155.51 and 155.34 (q); 140.35 and 140.30 (Ar q); 136.95 and 136.79 Ar q); 136.72 and 136.47 (Ar q); 134.21 and 133.96 (Ar q); 129.19 (ArH) 128.84 (ArH); 128.54 (ArH); 128.45 (ArH); 128.12 (ArH); 128.02 (ArH); 127.86 (ArH); 127.16 (ArH); 126.93 (ArH); 126.71 (ArH); 126.34 (ArH); 126.22 (ArH); 74.12 (CH); 67.57 and 67.23 (CH_2); 52.67 and 52.36 (CH); 43.35

and 43.07 (CH_2); 38.78 and 38.21 (CH_2); 28.37 and 27.98 (CH_2); 21.26 and 21.15 (CH_3)

MS (EI): 369 (0.30); 266 (65); 222 (67); 91 (100)

HRMS (ESI): Calculated for $[C_{27}H_{27}NO_4Na]^+$:452.183231; found: 452.183551

Eluant was then changed to pentane/AcOEt 7/3 and cyclised product **121b** was obtained as a mixture of diastereoisomers (51 mg, 36%) as a white solid. dr was determined by ^{1}H NMR analysis of the mixture and was found to be 1:5.7. The diastereoisomers could also be separated by column chromatography for analytical purposes with a reduced yield.

The assignment of the relative configurations for the diastereomers of **121b** was made based on comparison with literature reported data.[27]

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, upper diastereoisomer, minor): 7.38-7.23 (m, 5H); 7.17-7.06 (m, 3H); 7.03-6.97 (m, 1H); 5.40 (t, 1H, J= 4.4 Hz); 4.55-4.49 (m, 1H); 4.44 (dd, 1H; J=8.9; 5 Hz); 3.07-2.92 (m, 2H); 2.70-2.61 (m, 2H); 2.46-2.38 (m, 1H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, upper diastereoisomer, minor): 152.91 (q); 139.15 (Ar q); 135.54 (Ar q); 135.18 (Ar q); 129.43 (ArH); 128.85 (ArH); 128.10 (ArH); 127.14 (ArH); 126.70 (ArH); 125.00 (ArH); 124.33 (ArH); 75.28 (CH); 51.16 (CH); 42.48 (CH_2); 34.96 (CH_2); 28.75 (CH_2)

MS (EI): 279 (1.8); 234 (27); 175 (100); 104 (84)

HRMS (ESI): Calculated for $[C_{18}H_{17}NONa]^+$:302.115147; found: 302.115269

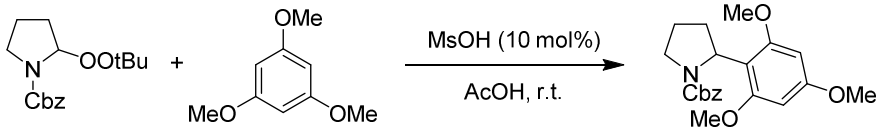
^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, major diastereoisomer): 7.44-7.27 (m, 5H); 7.23-7.09 (m, 4H); 5.38 (dd, 1H, J= 11.7; 1.2 Hz); 4.95 (dd, 1H, J= 11.5; 5.2 Hz); 4.63-4.55 (m, 1H); 3.15-3.04 (m, 2H); 2.84-2.70 (m, 2H); 2.05 (td, 2H, J= 13.5, 13.8 Hz)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, major diastereoisomer): 153.29 (q); 138.78 (Ar q); 135.69 (Ar q); 134.56 (Ar q); 129.33 (ArH); 128.66 (ArH); 126.60 (ArH); 127.12 (ArH); 126.75 (ArH); 125.99 (ArH); 124.97 (ArH); 76.79 (CH); 54.31 (CH); 42.15 (CH_2); 38.30 (CH_2); 28.60 (CH_2)

MS (EI): 279 (1.4); 234 (22); 175 (100); 104 (78)

HRMS (ESI): Calculated for $[C_{18}H_{17}NONa]^+$:302.115147; found: 302.115269

benzyl 2-(2,4,6-trimethoxyphenyl)pyrrolidine-1-carboxylate (129a)



In a 4mL screw cap vial, peroxide **126a** (73.25 mg; 0.25 mmol) was dissolved in 1 mL of AcoH. 1.3.5-trimethoxybenzene (46mg, 0.27mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 1 minute and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **129a** (82 mg, 89%) as a slowly crystallizing oil.

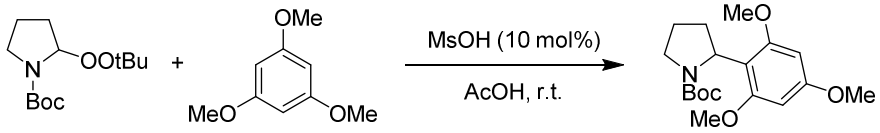
^{1}H NMR: (r.t. $CDCl_3$; 500 MHz, 2 rotamers): 7.37-7.32 (m, 2H); 7.23-7.17 (m, 2H); 6.94-6.88 (m, 1H); 6.15 (s, 2H, minor); 6.07 (s, 2H, major); 5.38 (t, J=7.7 Hz, 1H, minor); 5.31 (t, J=8 Hz, 1H, major); 5.08 (q, J=12.5 Hz, 2H, minor); 5.03 (d, J=12.5 Hz, 1H, major); 4.83 (d, J=12.5 Hz, 1H, major); 3.82 (s, 3H, major); 3.79 (s, 9H, minor); 3.64 (s, 6H, major); 3.80-3.68 (m, 1H); 3.57-3.47 (m, 1H); 2.23-2.14 (m, 1H); 2.11-1.92 (m, 2H); 1.89-1.75 (m, 1H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz, 2 rotamers): 159.81 (C, minor); 158.59 (C, major); 154.72 (Ar C, minor); 153.94 (Ar C; major); 137.64 (Ar C, minor); 137.12 (Ar C, major); 128.32 (Ar CH); 127.97 (Ar CH); 127.61 (Ar CH); 127.22 (Ar CH); 112.19 (Ar C, major); 111.48 (Ar C, minor); 91.26 (CH, minor); 90.96 (CH, major); 66.26 (CH_2, major); 66.01 (CH_2, minor); 55.97 (CH_3) 55.71 (CH_3); 55.27 (CH_3); 55.19 (CH_3); 47.54 (CH_2, major); 47.00 (CH_2, minor); 32.64 (CH_2, major); 31.91 (CH_2, minor); 25.56 (CH_2, minor); 25.16 (CH_2, major)

MS (EI): 371 (11); 236 (64); 91 (100)

HRMS (ESI): Calculated for $[C_{21}H_{25}NO_5Na]^+$:394.162492; found: 394.162324

tert-butyl 2-(2,4,6-trimethoxyphenyl)pyrrolidine-1-carboxylate (X15b)



In a 4mL screw cap vial, peroxide **126b** (67 mg; 0.258 mmol) was dissolved in 1 mL of AcoH. 1.3.5-trimethoxybenzene (43mg, 0.258mmol) was then added followed by MsOH (1.77 µL; 0.025 mmol). Mixture was stirred at room temperature for 2 minutes and the whole reaction mixture was then subjected to flash chromatography (elution with pentane/AcOEt 8/2) on silica gel to afford coupling product **129b** (60 mg, 69%) as a slightly yellow oil.

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 6.13 (s, 2H); 5.19 (app t, J=7.5 Hz, 1H); 3.82 (s, 3H); 3.77 (s, 6H); 3.70-3.61 (m, 1H); 3.50-3.38 (m, 2H); 2.22-2.10 (M, 1H); 2.07-1.88 (m, 2H); 1.84-1.71 (m, 1H); 1.13 (s, 9H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 159.69 (Ar C); 158.62 (2x Ar C); 154.36 (C); 112.79 (Ar C); 90.58 (2x Ar CH); 78.15 (C); 55.72 (2x CH_3); 55.31 (CH_3); 51.91 (CH); 46.81 (CH_2); 32.51 (CH_2); 28.15 (3x CH_3); 25.07 (CH_2)

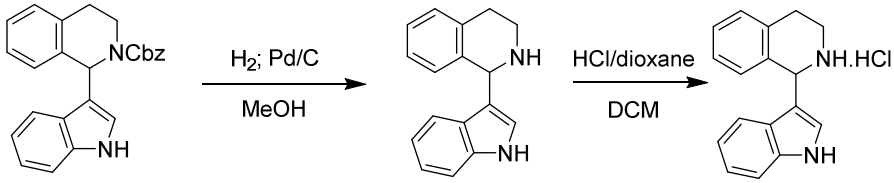
MS (EI): 337 (12); 280 (11); 236 (100); 57 (24)

HRMS (ESI): Calculated for $[C_{18}H_{27}NO_5Na]^+$:360.178139; found: 360.177994

7.2.5 Deprotection of Coupling Products

1-(1H-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (122)[95]

1-(1H-Indol-3-yl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (122')



A 100 mL three necked flask was connected to an argon line and an H_2 Balloon and charged with Pd/C (20 mg) under a stream of argon. The atmosphere was then removed and replaced with argon (3 times) and **116a** (220 mg, 0.57 mmol) was then added as a solution in MeOH (20 mL). The atmosphere was then removed and replaced with H_2 (3 times) and the mixture was left to stir overnight. After the night, reaction mixture was filtered over a pad of Celite and the resulting methanol solution was evaporated to dryness to afford product **122** as an essentially pure white foamy oil (141mg, 0.57mmol, quantitative).

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 8.94 (br s, 1H, NH);7.30 (d, 1H, J=8 Hz); 7.05-6.95 (m, 4H); 6.91-6.76 (m, 3H); 6.52 (d, 1H, J=2.2 Hz); 5.33 (s, 1H); 3.16-3.08 (m, 1H); 2.98-2.91 (m, 1H); 2.90-2.82 (m, 1H); 2.79-2.71 (m, 1H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 138.50 (Ar q); 136.72 (Ar q); 135.19 (Ar q); 129.08 (ArH); 128.06 (ArH); 126.43 (Ar q); 126.35 (ArH); 125.84 (arH); 124.32 (arH); 121.97 (ArH); 119.51 (arH); 119.31 (ArH); 118.96 (Ar q); 111.56 (ArH); 53.94 (CH); 41.87 (CH_2); 29.78 (CH_2)

MS (EI): 248 (100); 218 (40)

HRMS (ESI): Calculated for $[C_{17}H_{17}N_2]^+$:249.138622; found: 249.138538

To facilitate analysis and storage, it was then converted to its HCl salt by dissolving it in DCM and adding a solution of HCl in dioxane (0.5 mL, 1mmol). Solvent was then evaporated and the resulting solid washed with DCM to afford product **122'** as a white solid (158mg, 97%).

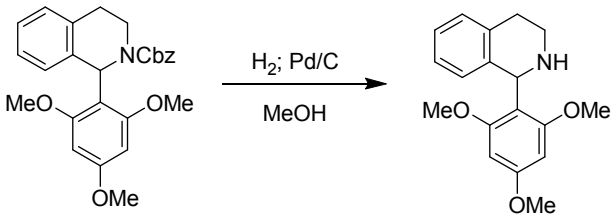
^{1}H NMR: (r.t. d6-DMSO; 500 MHz): 11.56 (s, 1H); 10.16 (br s, 1H); 9.37 (br s, 1H); 7.50-7.41 (m, 2H); 7.34-7.25 (m, 2H); 7.22 (d, 1H, J= 8Hz); 7.13 (t, 2H, J=7.5 Hz); 6.97 (t, 1H, J=7.5 Hz); 6.89 (d, 1H, J=8 Hz); 6.04 (br s, 1H); 3.41 (br s, 2H, overlaps with residual H_2O signal); 3.35-3.25 (m, 1H); 3.18-3.08 (m, 1H)

^{13}C NMR: (r.t. d6-DMSO; 125 MHz): 136.15 (Ar q); 132.90 (Ar q); 132.22 (Ar q); 128.64 (ArH); 127.60 (ArH); 127.51 (ArH); 126.53 (ArH); 125.75 (Ar q); 121.59 (ArH); 119.17 (ArH); 118.94 (ArH); 111.90 (ArH); 110.38 (Ar q); 51.35 (CH); 39.33 (CH_2); 24.92 (CH_2)

MS (EI): 247 (100); 218 (39); 130 (28)

HRMS (ESI): Calculated for $[C_{17}H_{16}N_2Na]^+$: 271.120569; found: 271.120195

1-(2,4,6-Trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (123)[95]



A 100 mL three necked flask was connected to an argon line and an H_2 Balloon and charged with Pd/C (20 mg) under a stream of argon. The atmosphere was then removed and replaced with argon (3 times) and **115a** (207 mg, 0.47 mmol) was then added as a solution in MeOH (20 mL). The atmosphere was then removed and replaced with H_2 (3 times) and the mixture was left to stir overnight. After the night, reaction mixture was filtered over a pad of Celite and the resulting methanol solution was evaporated to dryness to afford product **123** as a white solid (138mg, 98%).

^{1}H NMR: (r.t. $CDCl_3$, 500 MHz): 7.85 (br s, NH); 7.11-7.03 (m, 2H); 6.99 (t, 1H, J= 7.1 Hz); 6.67 (d, 1H, J=7.7 Hz); 6.11 (s, 2H); 5.87 (s, 1H); 3.79 (s, 3H); 3.70 (s, 6H); 3.50 (dd, 1H, J=3.8, 12.2 Hz); 3.36-3.25 (m, 1H); 3.00 (td, 1H, J=3.6, 12.2 Hz); 2.74 (d, 1H, J=16.5 Hz)

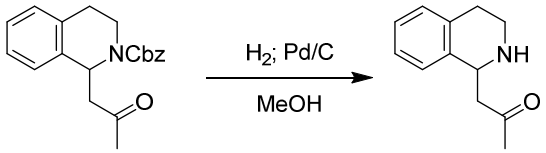
^{13}C NMR: (r.t. $CDCl_3$; 100 MHz): 161.85 (Ar q); 159.22 (Ar q); 135.40 (Ar q); 132.86 (Ar q); 128.28 (ArH); 126.41 (ArH); 126.38 (ArH); 125.62 (ArH); 107.28 (Ar q); 90.97 (Ar q); 56.14

(CH_3); 55.35 (CH_3); 50.79 (CH); 42.79 (CH_2); 26.98 (CH_2)

MS (EI): 299 (100); 268 (58); 168 (18); 132 (48)

HRMS (ESI): Calculated for $[C_{18}H_{21}NO_3Na]^+$: 322.141366; found: 322.141366

1-(1,2,3,4-Tetrahydroisoquinolin-1-yl)propan-2-one (124)[95]



A 100 mL three necked flask was connected to an argon line and an H_2 Balloon and charged with Pd/C (20 mg) under a stream of argon. The atmosphere was then removed and replaced with argon (3 times) and **117a** (212 mg, 0.65 mmol) was then added as a solution in MeOH (20 mL). The atmosphere was then removed and replaced with H_2 (3 times) and the mixture was left to stir overnight. After the night, reaction mixture was filtered over a pad of Celite and the resulting methanol solution was evaporated to dryness. The resulting oil was subjected to flash chromatography (elution with pentane/AcOEt/NEt_3 60/40/1) to give **124** as a slightly yellow oil (39mg, 32%)

^{1}H NMR: (r.t. $CDCl_3$; 500 MHz): 7.10-6.94 (m, 4H); 4.42 (dd, 1H, J=3.2, 9.2 Hz); 3.08 (td, 1H, J=5, 12.2 Hz); 2.95-2.75 (m, 4H); 2.65 (td, 1H, J=5, 16 Hz); 2.22 (br s, NH); 2.13 (s, 3H)

^{13}C NMR: (r.t. $CDCl_3$; 125 MHz): 208.40 (q); 137.81 (Ar q); 135.52 (Ar q); 129.50 (ArH); 126.22 (ArH); 125.90 (ArH); 125.58 (ArH); 51.88 (CH); 50.49 (CH_2); 41.04 (CH_2); 30.72 (CH_3); 29.81 (CH_2)

MS (EI): 189 (9); 132 (100)

HRMS (ESI): Calculated for $[C_{12}H_{15}NO]^+$: 189.115367; found: 189.115252

7.3 Mechanism Elucidation of the Autoxidative Coupling of Xanthene

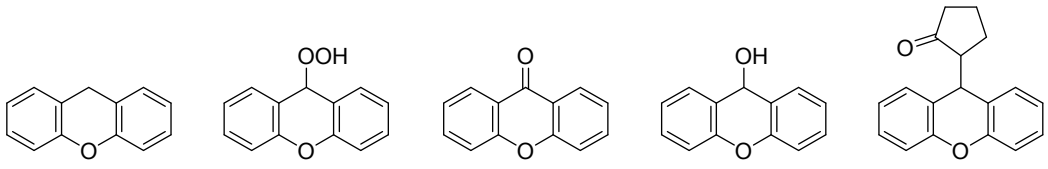
7.3.1 Determination of NMR Yields

Unless otherwise noted, all yields refer to ^{1}H NMR yields. In order to determine these NMR yields, a sample of the reaction mixture (~100µL) was taken and dissolved in d6-DMSO and directly analyzed. All products could be distinguished from the spectrum of a reaction mixture and ratio of products was directly determined by integration of reference peaks (Table 7-1).

In the case of autoxidation reactions, xanthene hydroperoxide **130** decomposes in DMSO to xanthydrol **133** and xanthone **134**. However, if all oxygenated products are considered, the conversion of xanthene remains the same for a given sample and the values are reproducible.

Although the autoxidation of xanthene in DMSO is feasible at 40°C (vide infra), at room temperature and under the dilution of an NMR sample, we never saw any further autoxidation of the samples measured. In order to minimize all these effects, we measured our samples as quickly as possible. If NMR-samples had to be stored for more than a couple hours, they were frozen and kept in a fridge.

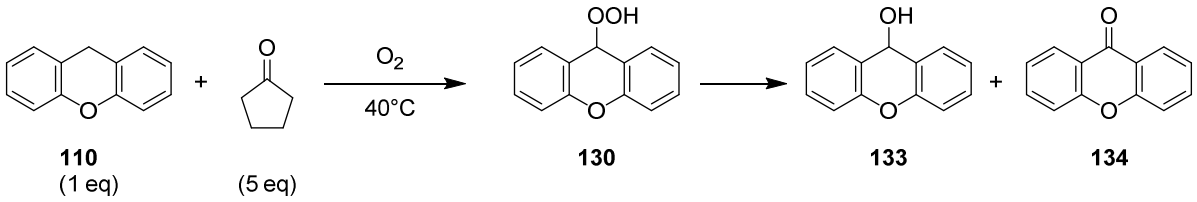
Table 7-1. List of signals considered for the determination of NMR yields in the autoxidative coupling and autoxidation of xanthene



110 **130** **134** **133** **138**

product	signal in d6-DMSO
110	singlet (4ppm; 1H)
138	doublet (4.6ppm; 2H)
130	singlet (5.95ppm; 1H)
134	doublet (8.2ppm; 2H)
133	singlet (5.7ppm; 1H)

7.3.2 General Procedure for the Autoxidation of Xanthene



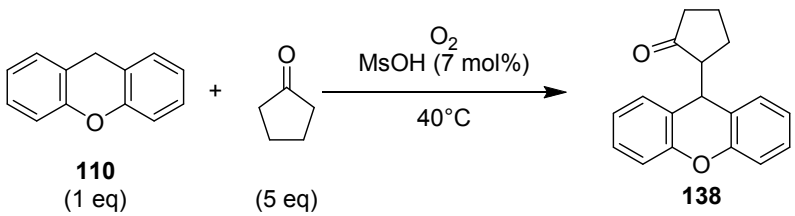
Scheme 7-1: Autoxidation of xanthene in cyclopentanone.

In a 4mL screw cap vial equipped with 2 silicon/Teflon septa, xanthene **110** (91 mg; 0.5 mmol) was dissolved in cyclopentanone (0.22 mL; 2.5 mmol). The reaction vessel was flushed with O_2, closed then connected to an O_2 balloon. The reaction mixture was heated at 40°C in an aluminum heating block and stirred at 400 rpm. If required for reaction progress monitoring, the reaction was performed on a larger scale. The mixture was then directly analyzed by ^{1}H NMR spectroscopy as previously discussed.

7.3.3 Analysis of H_2O_2 in Reaction Mixtures

The experimental work described in this chapter has been performed in collaboration with Dr. Philipp Schulze and Stefanie Dehn.

In this project, the question whether an equimolar amount of H_2O_2 forms, is significant to propose a mechanism for the reaction under study (using ambient temperature in this case, Scheme 7-2).



Scheme 7-2: Conditions used for the analysis of liberated H_2O_2 from the autoxidative coupling of **110**.

The reaction mixture (matrix) contains high amounts of methane sulfonic acid, which acts as a catalyst in the reaction. In addition, oxidative xanthene hydroperoxide species may be formed during the reaction which makes specific H_2O_2 detection

troublesome using redox-based assays such as resorufin derivatives[105] or the oxidative condensation of 4-amino-antipyrin with phenol (Trindler´s reagent).[106]

In classical wet chemical analysis complexation methods to detect H_2O_2 are the method of choice, namely formation of orange-yellow colored TiO_2^{2+}[107] or of blue $CrO(O_2)_2$.[108] Preliminary experiments exhibited that both reactions show negligible cross sensitivities with purified xanthene hydroperoxide. Due to the slightly yellow colour of the dissolved xanthene, the chromium(VI)peroxide formation was chosen to minimize spectral interferences.

7.3.3.1 Protocole:

At ambient temperature of 22.5°C 100 µL of reaction mixture was added to a test tube containing a two phase system of 1 mL $K_2Cr_2O_7$ (0.1 M), 1 mL H_2SO4 (2.5 M) and 5 mL peroxide free diethyl ether. The sample was gently mixed for 20 seconds and then 3 mL of the ether phase were transferred into a closable fused silica cuvette. UV/vis spectra between 200 and 800 nm were recorded using a double beam spectrometer (Varian Cary 5G UV vis NIR). Pure diethyl ether was used as the reference. The absorbance of the chromium(VI)peroxide complex in ether was measured in the blue spectral region at 580 nm.

A positive probe with two different initial H_2O_2 concentrations in cyclopentanone containing methane sulfonic acid is displayed in Figure 7-1 (generated from 35% aqueous H_2O_2 (467 µmol and 46,7 µmol, respectively, corresponding to 1.0 and 0.1 equivalents relative to the initial xanthene concentration as used in the general procedure of the autoxidative coupling reaction) cyclopentanone (0.21 ml) and MsOH (2.1 µl)). The absorbance of the concentrated hydrogen peroxide solution was determined to be 1.92, whereas the 1:10 dilution showed an absorbance of 0.20. A calibration plot (data not shown) exhibited a linear correlation between the H_2O_2 concentration and the absorbance in the range of 467 to 6 µmol, corresponding to 1.0 and ca. 0.015 equivalents, respectively, of H_2O_2 relative to xanthene in the autoxidative coupling reaction.

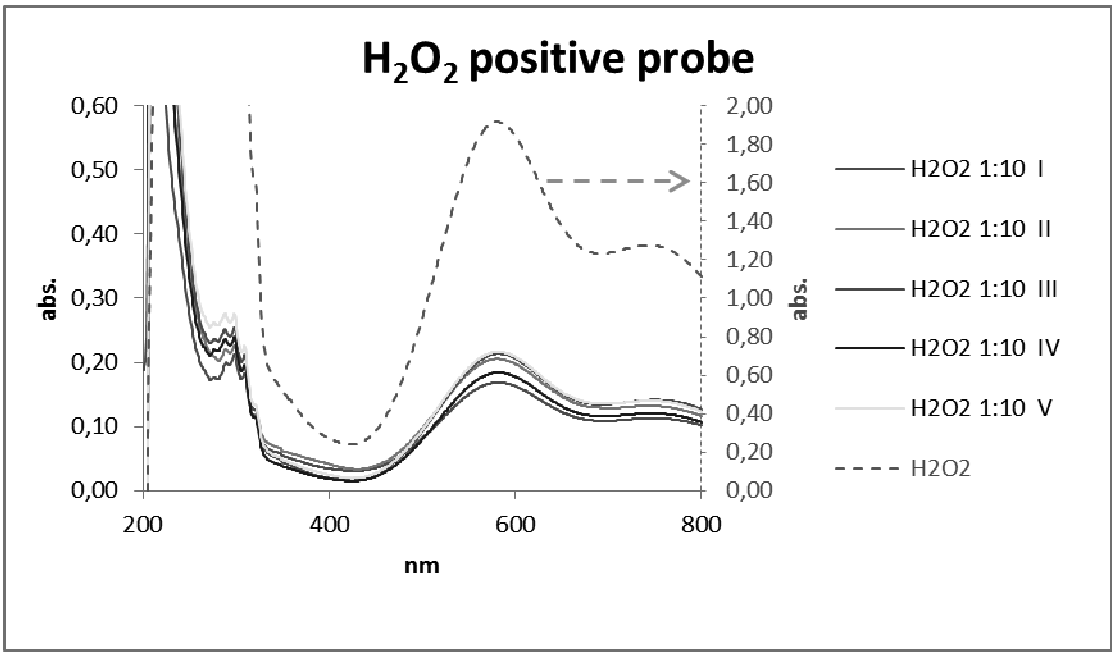


Figure 7-1. Positive test of H_2O_2 samples forming the blue $CrO(O_2)_2$ complex in ether. "H_2O_2" displays a positive probe prepared with 467µmol H_2O_2, which corresponds to the initial concentration of xanthene in the reaction matrix under the general conditions of the autoxidative coupling reaction. "1:10" are repetitive measurements containing an initial concentration of 46.7 µmol H_2O_2.

In Figure 7-2 the same protocol with purified xanthene hydroperoxide instead of hydrogen peroxide was conducted. The undiluted xanthene hydroperoxide solution results in small amounts of $CrO(O_2)_2$ indicating a small concentration of hydrogen peroxide (absorbance 0.21) present. We assume an equilibrium hydrolysis of xanthene hydroperoxide **130** into xanthydrol **133** and H_2O_2 during sample preparation in the presence of H_2SO_4. However, the 1:10 diluted solution of the xanthene hydroperoxide only generates minute amounts of $CrO(O_2)_2$ (absorbance 0.05). In summary, the absorbance of the xanthene hydroperoxide sample is roughly a magnitude lower compared to that of hydrogen peroxide. We conclude that the cross sensitivity of the method is marginal enough to clarify the question whether equimolar amounts of H_2O_2 are formed during the oxidative coupling reaction of xanthene and cyclopentanone in the presence of xanthene hydroperoxide or not.

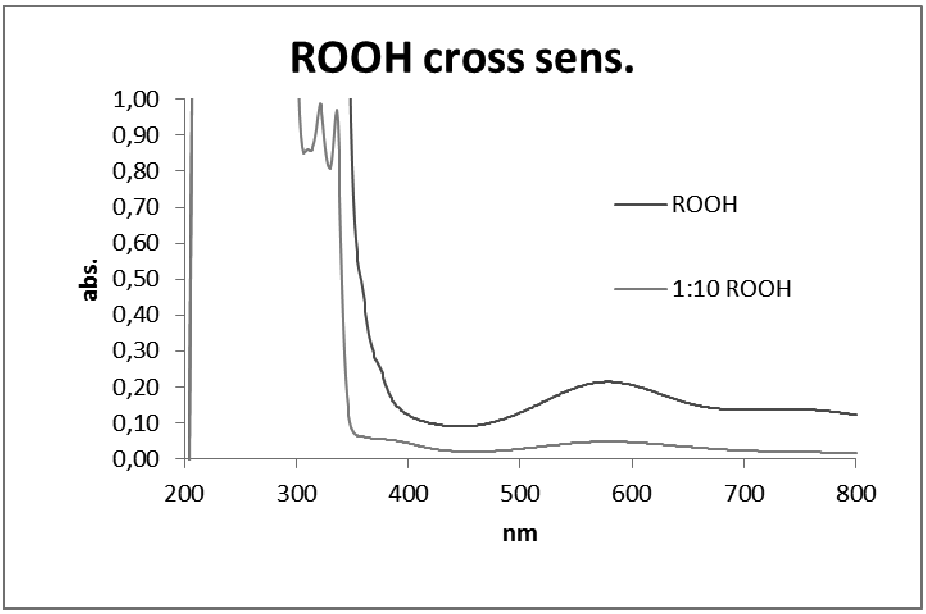
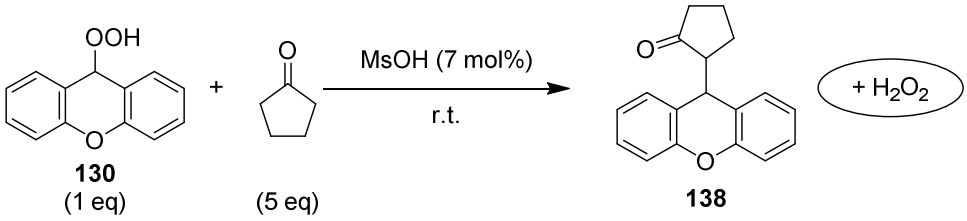


Figure 7-2. UV/Vis spectra of xanthene hydroperoxide 130 in ether, prepared from 467µmol of 130 in 0.21 mL of cyclopentatone, forming small amounts of $CrO(O_2)_2$ out of equilibrium H_2O_2 (abs ~ 0.2). The 1:10 dilution generates only insignificant amounts of H_2O_2 (abs. < 0.05).

7.3.3.2 Liberation of H_2O_2 from xanthenyl hydroperoxide in the presence of acid:

The reaction as shown in Scheme 7-3 was analyzed for the amount of H_2O_2 formed by adding 7 mol% of MsOH to a solution of xanthene hydroperoxide **130** in cyclopentanone at ambient temperature and stirring for 2 minutes. Afterwards, a sample was analysed as described in the protocol above with the exception, that the ether/aqueous two phase system was stirred for exactly 60 seconds at 500 r.p.m.using a stirring bar. About one third equivalent of hydrogen peroxide relative to the xanthenyl hydroperoxide was clearly detected (after subtraction of the blank value, i.e. xanthenyl hydroperoxide in the absence of MsOH). Samples of **130** with MsOH taken after longer reaction times exhibited a slow decline of hydrogen peroxide (e.g. ~ 80 % within 16 hours).



Scheme 7-3: Analysis of hydrogen peroxide liberated by the acid-catalyzed reaction of 130 with cyclopentanone.

7.3.3.3 Analysis of H_2O_2 in the autoxidative coupling reaction (Scheme 7-2):

It is well known that the reaction rate of gaseous/liquid-phase reactions (as in Scheme 7-2) depends on classical parameters (reaction temperature, reaction time etc.) as well as on additional parameters e.g. surface area or stirring intensity. In another set of experiments, a kinetic monitoring regarding a possible H_2O_2 formation was performed over a time period of 50 minutes after initiating the standard reaction as shown in Scheme 7-2 (Figure 7-3). No hydrogen peroxide formation could be observed at room temperature.

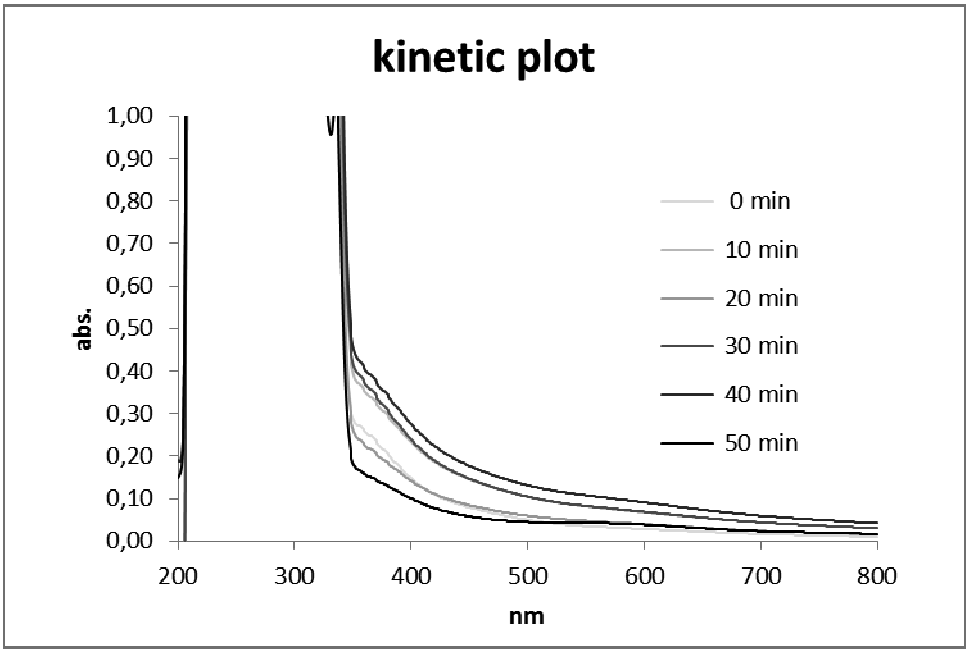


Figure 7-3. Kinetic plot of the reaction mixture falsifies equimolar H2O2 generation within 50 minutes. In case of a positive result, the absorbance at 580 nm would be about 2.0.

A second analytical experiment was conducted in order to analyse H_2O_2 over the entire course of the reaction while verifying that the reaction was actually progressing. To this end, an elongated kinetic study was performed under oxygen atmosphere utilizing ^{1}H NMR spectroscopy to monitor the reaction progress and UV/vis spectroscopy to monitor H_2O_2. Samples from the reaction mixture were taken between 0 and 96 hours. The formation of H_2O_2 in significant amounts can clearly be excluded from the corresponding UV/vis spectra Figure 7-4 and Figure 7-5), while the ^{1}H NMR data shows a steady increase in the concentration of the coupling product (data not shown).

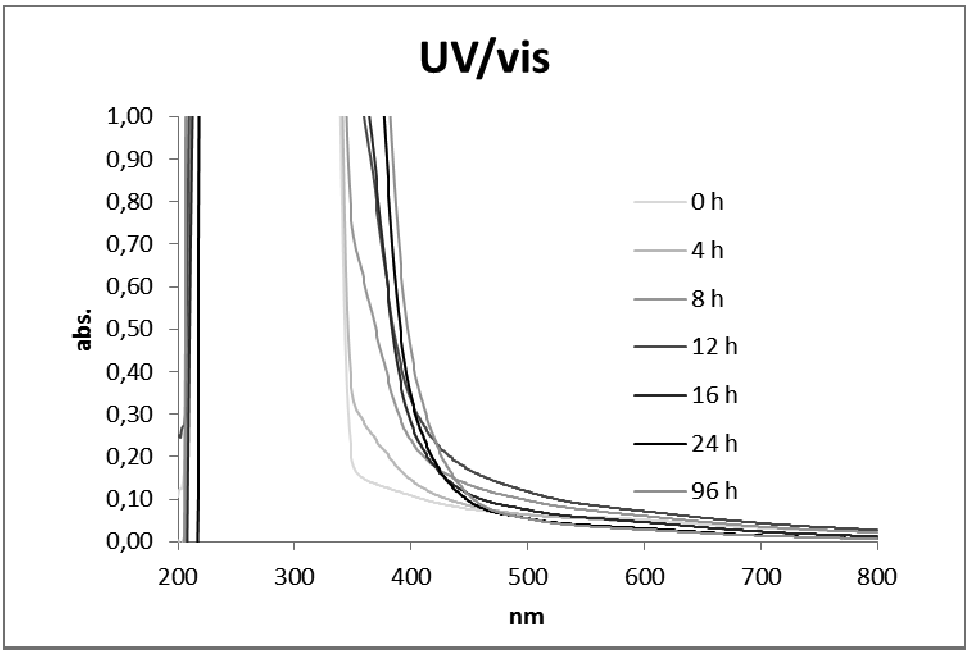


Figure 7-4. Long time kinetic plot conducted with extensive stirring under oxygen atmosphere.

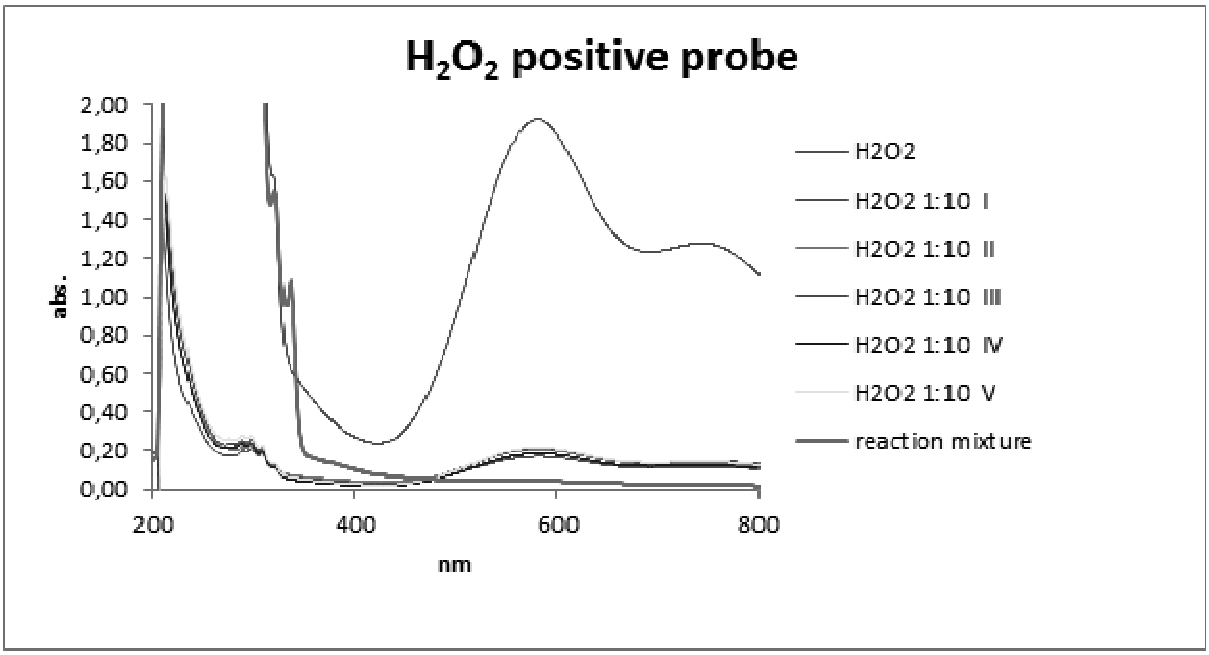


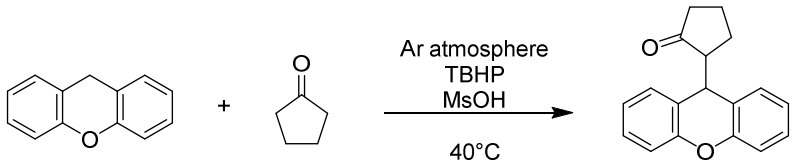
Figure 7-5. Comparison of the UV/Vis measurement of the reaction mixture (taken after 50 minutes reaction time) with reference samples prepared as described above.

In summary, the answer to the inititial question concerning equimolar H_2O_2 formation during the reaction of xanthene and cyclopentanone is negative. H_2O_2 is not formed as a by-product of the reaction in significant concentrations of more than 1.5 mol% relative to the initial amount of xanthene. In contrast, H_2O_2 is formed in the reaction of xanthenyl hydroperoxide **130** with cyclopentanone in the presence of an acid catalyst.

7.3.4 Synthesis of Products

Copies of NMR spectra can be found in the supporting information of the following publication: Synergistic Effect of Ketone and Hydroperoxide in Brønsted Acid Catalyzed Oxidative Coupling Reactions: B. Schweitzer-Chaput, A. Sud, Á. Pintér, S. Dehn, P. Schulze, M. Klussmann, *Angew. Chem., Int. Ed.* **2013**, *52, 13228-13232.*[96]

2-(9H-Xanthen-9-yl)cyclopentanone (138)[96]



In a 4 mL screw cap vial, xanthene (91 mg, 0.5 mmol. 1 eq) was dissolved in cyclopentanone (0.22 ml, 2.5 mmol, 5 eq) then TBHP (182 µL, 1 mmol, solution in decane) and methane sulfonic acid was added (2.3 µL, 7 mol%). The vial was flushed with Argon and connected to an argon balloon. The mixture was let to react at 40°C for 24h then the whole reaction mixture was subjected to column chromatography (toluene) to afford coupling product **138** (122 mg, 93% yield) as a slightly yellow solid.

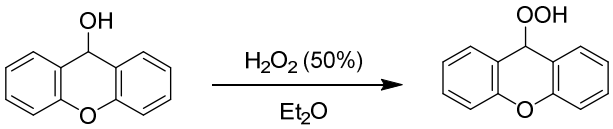
^{1}H NMR: (d6-DMSO; 500 MHz): 7.39-7.34 (m, 1H); 7.30-7.23 (m, 2H); 7.15-7.08 (m, 3H); 7.08-7.01 (m, 2H); 4.64 (d, 1H, *J*=3 Hz); 2.58-2.50 (m, 1H; overlaps with d6-DMSO residual peak); 2.23-2.13 (m, 1H); 1.73-1.46 (m, 4H); 1.29-1.17 (m, 1H)

^{13}C NMR: (d6-DMSO; 125 MHz): 217.72 (C); 152.42 (Ar q); 151.72 (Ar q); 128.90 (Ar CH); 128.63 (Ar CH); 128.36 (Ar CH); 127.90 (Ar CH); 124.12 (Ar q); 123.79 (Ar CH); 123.47 (Ar CH); 121.75 (Ar q); 116.04 (Ar CH); 115.89 (Ar CH); 58.75 (CH); 38.52 (CH_2); 37.07 (CH); 23.72 (CH_2); 19.55 (CH_2)

MS (EI): 264 (1.6); 181 (100)

HRMS (ESI): Calculated for $[C_{18}H_{16}O_2Na]^+$ ($M+Na^+$): 287.104249; found: 287.104020

Xanthene hydroperoxide (130)[96]



Synthesized as a reference compound.

Xanthydrol (3 g, 15.15 mmol) was dissolved in Et_2O (50 mL) then aqueous hydrogen peroxide was added (25 mL). The mixture was allowed to stir overnight at room temperature. Phases were separated and the ethereal phase washed with distilled water (3x 25 mL). Solvent was removed under reduced pressure to afford **130** as a white solid (3.099 g, 14.48 mmol; 95% yield)

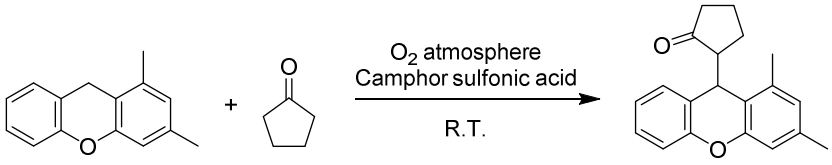
^{1}H NMR: (d6-DMSO; 500 MHz): 11.41 (s; 1H); 7.62 (dd; 2H; *J*=7.6, 1.2 Hz); 7.45 (td; 2H; *J*=7.7, 1.5 Hz); 7.28-7.20 (m; 4H); 5.97 (s, 1H)

^{13}C NMR: (d6-DMSO; 125 MHz): 151.94 (Ar q); 131.19 (AR CH); 130.07 (Ar CH); 123.12 (Ar CH); 119.17 (Ar q); 116.10 (Ar CH); 75.00 (CH)

MS (EI): 214 (2.6); 181 (100)

HRMS (ESI): Calculated for $[C_{13}H_{10}O_3Na]^+$ ($M+Na^+$): 237.052218; found: 237.052294

2-(1,3-Dimethyl-9H-xanthen-9-yl)cyclopentanone (140)[96]



Synthesized as a reference compound.

In a 4mL screw cap vial, dimethyl xanthene[74] **139** (52.5 mg; 0.25 mmol) was dissolved in cyclopentanone (0.11 mL; 1.25 mmol) and camphor sulfonic acid (4 mg; 0.0175 mmol) was added. The vial was flushed with oxygen and connected to an oxygen balloon. The mixture was allowed to react at room temperature for 6 days then the whole mixture was subjected to column chromatography to afford coupling product **140** (46 mg; 63% yield) as a white solid.

^{1}H NMR: (d6-DMSO; 500 MHz): 7.29-7.22 (m; 1H); 7.10 (d, 1H; *J*=7.7 Hz); 7.06-6.96 (m; 2H); 6.82 (s, 1H); 6.79 (s, 1H); 4.69 (d, 1H, *J*=2.1 Hz); 2.5-2.42 (m, 1H, overlaps with residual d6 DMSO peak); 2.33 (s, 3H); 2.25 (s, 3H); 2.21-2.19 (m, 1H); 1.68-1.44 (m, 4H); 1.21-1.11 (m, 1H)

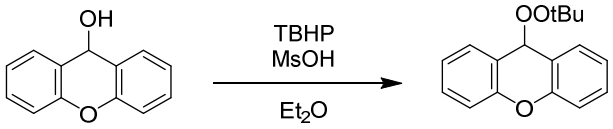
^{13}C NMR: (d6-DMSO; 125 MHz): 218.05 (C); 152.74 (Ar q); 152.15 (Ar q); 136.76 (Ar q); 135.56 (Ar q); 128.71 (Ar CH); 128.23 (Ar CH); 126.29 (Ar CH); 123.29 (Ar CH); 122.59 (Ar q); 119.72 (Ar q); 115.77 (Ar CH); 114.21 (Ar CH); 55.84 (CH); 38.36 (CH_2); 34.35 (CH); 23.73

(CH_2); 20.52 (CH_3); 19.58 (CH_2); 17.75 (CH_3)

MS (EI): 292 (2.7); 209 (100)

HRMS (ESI): calculated for $[C_{20}H_{20}O_2Na]^+$ $(M+Na)^+$: 315.135552; found: 315.135285

9-(tert-Butylperoxy)-9H-xanthene (141)[96]



Synthesized as a reference compound.

Xanthydrol (198 mg, 1 mmol) was dissolved in Et_2O (3 mL) and TBHP (450 µL, 10mmol, solution in decane) added. Methane sulfonic acid (7.11 µL, 0.1 mmol) was added and the mixture allowed to stir for 5 minutes. Distilled water was added and the aqueous phase extracted 3 times with AcOEt. Solvent was removed under reduced pressure to afford peroxide **141** (248 mg, 0.918 mmol, 91% yield) as a clear oil crystallising upon standing at room temperature or cooling.

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.63 (dd; 2H; *J*=7.6, 1 Hz); 7.41 (td; 2H; *J* = 7.8, 1.5 Hz); 7.24 (br d; 2H; *J*=8 Hz); 7.18 (br t; 2H; *J*=7.3 Hz); 5.99 (s, 1H); 1.10 (s, 9H)

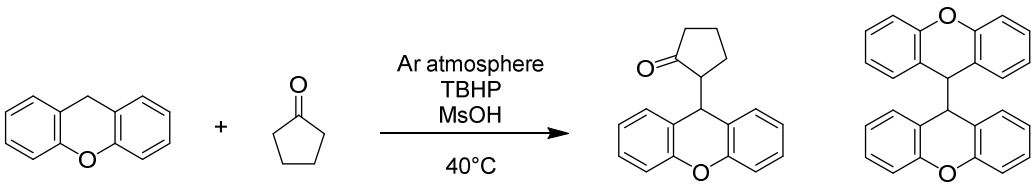
^{1}H NMR: (d6-DMSO; 500 MHz): 7.61 (br d; 2H; *J*=7.5 Hz); 7.46 (br t; 2H; *J*=7.6 Hz); 7.27 (br d; 2H; J=8 Hz); 7.23 (br t; 2H; *J*=7.5 Hz); 6.02 (s; 1H); 0.99 (s; 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 152.65 (Ar q); 131.41 (Ar CH); 130.01 (Ar CH); 122.81 (Ar CH); 119.05 (Ar q); 116.68 (Ar CH); 80.38 (C); 75.44 (CH); 26.35 (CH_3)

MS (ESI): 293(M + Na); 563 (2xM + Na)

HRMS (ESI): Calculated for $[C_{17}H_{18}O_3Na]^+$ $(M+Na^+)$: 293.114811; found: 293.114559

9H,9'H-9,9'-Bixanthene (142)[96]



In a schlenck tube, xanthene (182 mg; 1 mmol) was dissolved in cyclopentanone (0.44 mL; 5 mmol) and TBHP (364 µL; 2 mmol, solution in decane) was added. The mixture was degassed 3 times and then methane sulfonic acid (4.6 µL; 7 mol%) added under a stream of argon. The

tube was closed and the reaction mixture allowed to react at 40°C overnight. After the night, the whole reaction mixture was subjected to column chromatography (toluene). Bixanthene **142** was first isolated (13 mg; 0.0359 mmol; 7% yield) as a white solid and coupling product **138** next.

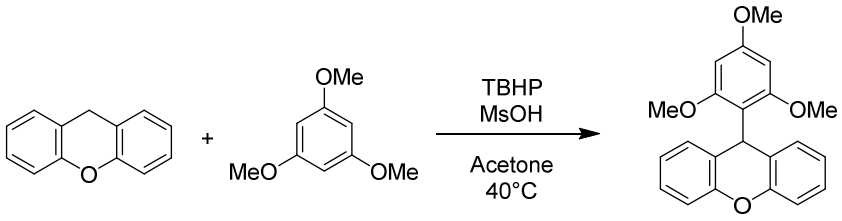
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.12 (m, 4H); 6.85 (td; 4H; *J*=7.45, 1 Hz); 6.79 (dd; 4H; *J*=8.1, 0.8 Hz); 6.58 (dd; 4H; *J*=7.5, 1.5 Hz); 4.12 (s, 2H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 153.05 (Ar q); 129.16 (Ar CH); 128.13 (Ar CH); 122.64 (Ar CH); 121.86 (Ar q); 115.86 (Ar CH); 49.54 (CH)

MS (EI): 181 (100); 152 (7)

HRMS (ESI): Calculated for $[C_{26}H_{18}O_2]^+$ (M^+): 362.1306802; found: 632.130338

9-(2,4,6-Trimethoxyphenyl)-9H-xanthene (64)[96]



In a 4mL screw cap vial, xanthene (91 mg, 0.5 mmol) was dissolved in acetone (0.5 mL) then 1,3,5-trimethoxybenzene (84 mg; 0.5 mmol), TBHP (182µL; 1 mmol, solution in decane) and methane sulfonic acid (2.3 µL; 7 mol%) were added. The reaction mixture was stirred at 40°C for the night in a screw cap vial without exclusion of air. The whole reaction mixture was then subjected to column chromatography (hexanes/DCM 6/4) to afford coupling product **64** (165 mg; 0.4741 mmol; 94%) as a white solid.

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.01 (br t; 2H; *J*=7.5 Hz); 6.91 (br d; 2H; *J*=7.8 Hz); 6.85 (br d; 2H; *J*=7.5 Hz); 6.77 (br t; 2H; *J*=7.3 Hz); 6.00 (br s; 2H); 5.84 (s, 1H); 3.82 (br s; 3H); 3.68 (s; 3H); 3.21 (br s; 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 160.14 (Ar q); 151.57 (Ar q); 128.67 (Ar CH); 126.90 (Ar CH); 124.77 (Ar q); 122.32 (Ar CH); 116.59 (Ar q); 115.45 (Ar CH); 55.27 (CH); 31.76 (CH_3)

MS (EI): 348; 317; 181

HRMS (ESI): Calculated for $[C_2H_{20}O_4Na]^+$ ($M+Na^+$): 371.125378; found: 371.125286

1,1-Dihydroperoxycyclopentane (144) [96]

Synthesized according to a reported method.[76b]

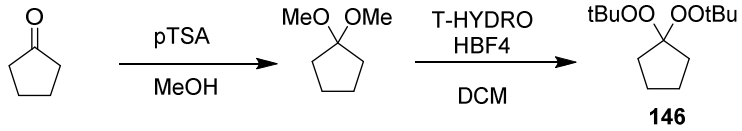
Cyclopentanone (795 µL, 9 mmol) was dissolved in acetonitrile (35 mL), aqueous hydrogen peroxide (35% solution, 27 mL) and strontium chloride (240 mg, 0.9 mmol) were added. The mixture was let to react overnight and then diluted with water (45 mL) and extracted with ether (3x45 mL). Combined organic phases were washed with brine (2x50 mL) and distilled water (50 mL), dried over sodium sulphate and concentrated to afford an essentially pure product **144** (272 mg, 20% yield) as a clear oil. The desired product could be further purified by chromatography on silica (pentane/Et_2O 7:3) to confirm its structure. Spectral data matched literature reports.[76b]

Note: yields were irreproducible and randomly much lower than the one reported here. In all cases, yields reported in the literature were never achieved.

^{1}H NMR: ($CDCl_3$; 300 MHz): 9.5 (br s, 2H); 1.95-1.88 (m, 4H); 1.7-1.65 (m, 4H)

^{13}C NMR: ($CDCl_3$; 75 MHz):122.44 (q); 33.06 (CH_2); 24.51 (CH_2)

1,1-Bis(tert-butylperoxy)cyclopentane (146)[96]



Adapted from a literature reported method.[76a]

Cyclopentanone (883 µL, 10 mmol) was dissolved in methanol (100 mL), para-toluene sulfonic acid (190mg, 1mmol) was added and the mixture let to reat overnight. The mixture was diluted with dichloromethane (100 mL) and washed with distilled water (3x 75 mL). The organic phase was dried over sodium sulphate and concentrated to dryness to afford 567mg of a clear oil. The residue was dissolved in pentane (12 mL), tBuOOH (70% aqueous solution, 1.47mL) and HBF4 (40% aqueous solution, 210 µL) were added. The mixture was let to react for 2 hours, K2CO3 (750 mg) was added and stirring was continued for 10 more minutes. The mixture was diluted with Et2O (20 mL) and washed with distilled water (3x 20 mL). Organic phase was dried, concentrated and subjected to column chromatography (Eluant:

pentane/Et_2O 99/1) to afford product **146** as a clear oil (800 mg, 3,25 mmol).

Analytical data as reported in the literature:[76a]

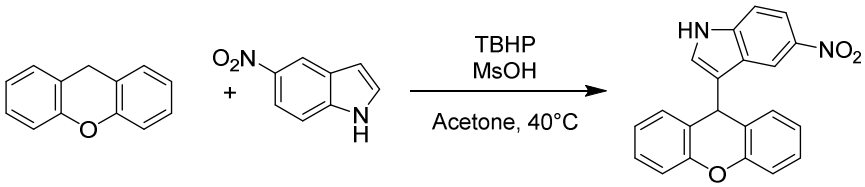
^{1}H NMR: (d6-DMSO; 300 MHz): 1.92-1.80 (m, 4H); 1.66-1.56 (m, 4H); 1.20 (s, 18H)

^{13}C NMR: (d6-DMSO; 75 MHz):117.67 (q); 78.89 (q); 33.25 (CH_2); 26.43 (CH_3); 23.92 (CH_2)

MS (ESI positive): 269 (M+Na); 515 (2xM+Na)

HRMS (ESI): Calculated for $[C_{13}H_{26}O_4Na]^+$ ($M+Na^+$): 269.172331; found: 269.172384

5-Nitro-3-(9H-xanthen-9-yl)-1H-indole (151)[96]



In a 4mL screw cap vial, xanthene (91 mg, 0.5 mmol) was dissolved in acetone (0.5 mL) then 5-nitroindole (162 mg; 1 mmol), TBHP (273 µL; 1.5 mmol, solution in decane) and methane sulfonic acid (3.55 µL; 10 mol%) were added. The reaction mixture was stirred at 40°C for the night, in a closed vial without strict exclusion of air. The whole reaction mixture was then subjected to column chromatography (hexanes/acetone 8/2) to afford coupling product **151** (106 mg; 0.3099 mmol; 62%) as a yellow solid.

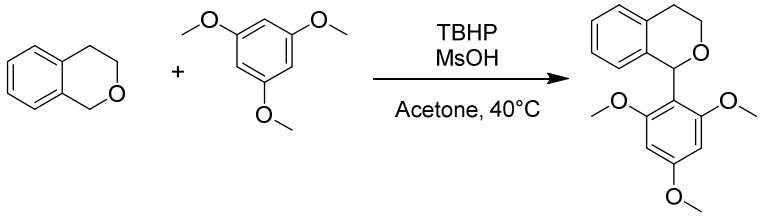
^{1}H NMR: (d6-DMSO; 500 MHz): 11.76 (s, 1H); 8.11 (d, 1H, *J*=2 Hz); 7.90 (dd, 1H, *J*= 9; 2 Hz); 7.63 (d, 1H, *J*=2 Hz); 7.5 (d, 1H, *J*=9 Hz); 7.27-7.20 (m, 4H); 7.16 (br d; 2H); 7.02-6.96 (m, 2H); 5.75 (s, 1H)

^{13}C NMR: (d6-DMSO; 125 MHz): 150.52 (Ar q); 140.20 (Ar q); 139.85 (Ar q); 129.54 (Ar CH); 128.09 (Ar CH); 127.26 (Ar CH); 124.26 (Ar q); 123.83 (Ar q); 123.43 (Ar CH); 122.06 (Ar q); 116.56 (Ar CH); 116.15 (Ar CH); 115.52 (Ar CH); 112.20 (Ar CH); 34.28 (CH)

MS (EI): 342 (100); 295 (37); 265 (19); 181 (48)

HRMS (ESI): Calculated for $[C_{21}H_{14}N_2O_3Na]^+$ ($M+Na^+$): 365.089662; found: 365.090166

1-(2,4,6-Trimethoxyphenyl)isochromane (152)[96]



In a 4mL screw cap vial, isochromane (63.2 µL; 0.5 mmol) was dissolved in acetone (0.5mL) then 1,3,5-trimethoxybenzene (84 mg; 0.5 mmol), TBHP (182 µL; 1 mmol, solution in decane) and methane sulfonic acid (3.55 µL; 10 mol%) were added and the mixture allowed to react overnight, in a closed vial without strict exclusion of air. The whole mixture was then subjected to column chromatography (hexane/AcOEt 9/1) to afford a mixture of coupling product and isochromanone which was then separated by preparative TLC (DCM as eluant) to afford coupling product **152** (59 mg, 0.1966 mmol, 39% yield) as a white solid. Spectroscopic data matches previous report. [31]

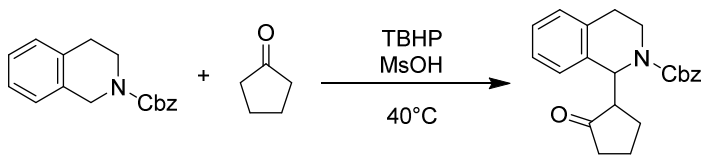
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.14-7.06 (m, 2H); 7.05-6.98 (, 1H); 6.7 (d, 1H, *J*=7.7 Hz); 6.32 (s, 1H); 6.14 (s, 2H); 4.32 (ddd, 1H, *J*=11, 5.5, 2 Hz); 3.95 (dt , 1H, *J*=11, 2.8 Hz); 3.82 (s, 3H); 3.63 (br s, 6H); 3.29-3.19 (m, 1H); 2.69 (br d, 1H, *J*=16 Hz)

^{13}C NMR: ($CDCl_3$; 125 MHz): 161.26 (Ar q); 159.97 (Ar q); 139.76 (Ar q); 133.88 (Ar q); 127.86 (Ar CH); 125.60 (Ar CH); 125.19 (Ar CH); 124.27 (Ar CH); 111.75 (Ar q); 91.44 (broad, Ar q); 70.30 (CH); 65.42 (CH_2); 55.95 (CH_3); 55.29 (CH_3); 29.08 (CH_2)

MS (EI): 300 (100); 269 (45); 239 (54); 195 (39); 168 (40); 132 (24)

HRMS (ESI): Calculated for $[C_{18}H_{20}O_4Na]^+$ ($M+Na^+$): 323.125378; found: 323.125264.

N-Cbz-1-(2-oxocyclopentyl)-3,4-dihydroisoquinoline-2(1H) (117c)[96]



In a 4mL screw cap vial, N-Cbz tetrahydroisoquinoline (67.5 mg; 0.25 mmol) was dissolved in cyclopentanone (0.22 mL; 2.5 mmol). TBHP (136.5 µL; 0.75 mmol, solution in decane) and methane sulfonic acid (1.77 µL; 0.025 mmol) were added and the reaction stirred for 22 hours in a closed vial without strict exclusion of air. The whole mixture was then subjected to column chromatography (hexane/AcOEt 85/15) to afford coupling product **117c** (60 mg;

0.1719 mmol; 68%). From the reaction mixture was also reisolated the starting material (13 mg; 0.0486 mmol; 19%)

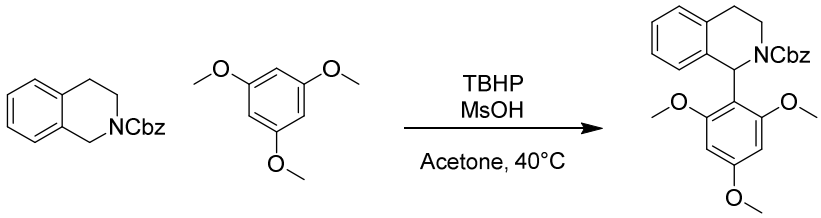
^{1}H NMR: (80°C d6-DMSO; 400 MHz): 7.41-7.25 (m, 5H); 7.22-7.10 (m, 3H); 7.05-6.94 (m, 1H); 5.45 (d, 1H, *J*=5.1 Hz, major); 5.26 (d, 1H, *J*=5.7 Hz, minor); 5.15-5.06 (m, 2H); 4.02-3.74 (m, 1H); 3.59-3.25 (m, 1H); 2.89-2.78 (m, 2H); 2.60-2.43 (m, 1H; overlaps with d6-DMSO signal); 2.22-2.11 (m, 1H); 2.10-1.77 (m, 3H); 1.77-1.43 (m, 2H)

^{13}C NMR: (80°C d6-DMSO; 100 MHz): 216.56 (q, minor); 216.45 (q, major); 154.47 (q, major); 154.26 (q, minor); 137.22(Ar q); 136.55 (Ar q); 136.45 (Ar q); 134.79 (Ar q); 134.29 (Ar q); 133.41 (Ar q); 128.19 (Ar H); 127.85 (ArH); 127.35 (ArH); 127.24 (ArH); 127.16 (ArH); 126.95 (ArH); 126.69 (ArH); 126.57 (ArH); 126.11 (ArH); 126.02 (ArH); 125.64 (ArH); 66.04 (CH_2, minor)65.96 (CH_2, major); 55.67 (CH); 54.09 (CH); 53.84 (CH); 52.70 (CH); 37.47 (CH_2, major); 36.52 (CH_2, minor); 27.23 (CH_2, major); 27.14 (CH_2, minor); 26.02 (CH_2, major); 25.84 (CH_2, minor); 19.39 (CH_2, major); 19.25 (CH_2, minor)

MS (ESI): m/z=349

HRMS (ESI): Calculated for $[C_{22}H_{23}NO_3Na]^+$: 372.157012; found: 372.156920

N-Cbz-1-(2,4,6-trimethoxyphenyl)-3,4-dihydroisoquinoline-2(1H) (115a)[96]



In a 4mL screw cap vial, N-Cbz tetrahydroisoquinoline (133.5 mg; 0.5 mmol) was dissolved in acetone (0.5mL) then trimethoxybenzene (84 mg; 0.5 mmol), TBHP (182 µL; 1mmol, solution in decane) and methane sulfonic acid (2.3 µL; 7 mol%) were added and the mixture allowed to react overnight, in a closed vial without strict exclusion of air. The whole mixture was then subjected to column chromatography (hexane/AcOEt 85/15) to afford coupling product **115a** (108 mg, 0.2494 mmol, 49% yield) as a clear oil which upon standing at room temperature or cooling often gives a white solid.

^{1}H NMR: (80°C; d6-DMSO; 400 MHz): 7.31-7.22 (m, 3H); 7.17-7.10 (m, 3H); 7.06 (tt, 1H, *J*=2, 7.2Hz); 7.00 (td, 1H, *J*=2, 7.7Hz); 6.69 (d, 1H, *J*=7.7Hz); 6.46 (s, 1H); 6.19 (s, 2H); 5.05-4.95 (m,

2H); 4.24 (ddd, 1H, J=3, 5, 12.6Hz); 3.77 (s, 3H); 3.58-3.49 (m, 7H); 2.90-2.75 (m, 2H)

^{13}C NMR: (80°C; d6-DMSO; 100 MHz): 159.89 (Ar q); 158.41 (Ar q); 154.46 (q); 136.79 (Ar q); 136.53 (Ar q); 134.08 (Ar q); 127.67 (ArH); 127.52 (ArH); 126.97 (ArH); 126.80 (ArH); 125.42 (ArH); 125.32 (ArH); 125.05 (ArH); 113.06 (Ar q); 91.62 (ArH); 65.59 (CH^2); 55.33 (CH_3); 54.81 (CH_3); 48.75 (CH); 39.28 (CH_2); 29.19 (CH_2)

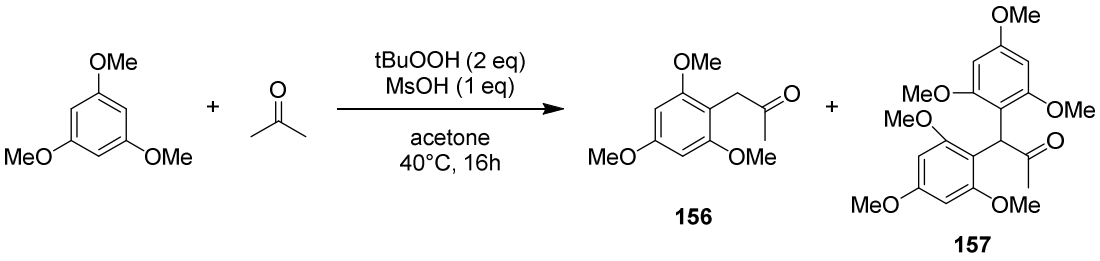
MS (EI): 433 (5); 342 (4); 298 (100); 91 (27)

HRMS (ESI): calculated for $[C_{26}H_{27}NO_5Na]^+$ ($M+Na^+$): 456.178527; found: 456.178146

7.4 Oxidative Functionalization of Olefins Under Acid Catalysis

7.4.1 Synthesis of Products

1-(2,4,6-trimethoxyphenyl)propan-2-one (156) and 1,1-bis(2,4,6-trimethoxyphenyl)propan-2-one (157)



In a Schlenk tube, 1,3,5-trimethxybenzene (84 mg, 0.5 mmol) was dissolved in acetone (0.5 mL) and tBuOOH (5.5M solution in decane, 364µL, 2 mmol) added. The resulting mixture was degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Methane sulfonic acid (35.5 µL, 0.5 mmol) was added under a stream of argon and after closing the flask, the reaction mixture was allowed to react for 16 hours at 40°C. The reaction mixture was then diluted, a small amount of silica was added and solvent removed. The resulting powder was purified by column chromatography on silica gel using a 8:2 mixture of hexane/ethyl acetate as eluant to afford **156** as a clear oil (53 mg, 47%).

1-(2,4,6-trimethoxyphenyl)propan-2-one (156)

^{1}H NMR: (CDCl3; 500 MHz): 6.07 (s, 2H); 3.74 (S, 3H); 3.70 (s, 6H); 3.55 (s, 2H); 2.01 (s, 3H)

^{13}C NMR: (CDCl3; 125 MHz): 208.20 (C); 160.40 (Ar C); 158.83 (Ar C); 104.56 (Ar C); 90.46 (Ar CH); 55.67 (CH_3); 55.34 (CH_3); 38.17 (CH_2); 28.85 (CH_3)

MS (EI): 224 (13); 181 (100); 136 (15); 121 (17)

HRMS (ESI): Calculated for $[C_{12}H_{16}O_4Na]+$ ($M+Na^+$): 247.094077; found: 247.094207

The eluant was then changed to a 6:4 mixture of hexane/ethyl acetate to afford **157** (7 mg, 7%) as a clear oil.

1**,1-bis(2,4,6-trimethoxyphenyl)propan-2-one (157)**

^{1}H NMR: (CDCl3; 500 MHz): 6.10 (s, 4H); 5.47 (s, 1H); 3.78 (s, 6H); 3.66 (s, 12H), 2.11 (s, 3H)

^{13}C NMR: (CDCl3; 125 MHz): 207.51 (C); 159.72 (Ar C); 159.28 (Ar C); 110.15 (Ar C); 91.26 (Ar CH); 55.97 (CH_3); 55.19 (CH_3); 45.97 (CH); 27.93 (CH_3)

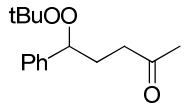
MS (ESI): 390 (0.7); 347 (100); 181 (41); 43 (2)

HRMS (ESI): Calculated for $[C_{21}H_{26}O_7Na]+$ ($M+Na^+$): 413.157073; found: 413.157493

General procedure for the synthesis of γ-ketoperoxides:

In an oven-dried Schlenk flask charged with a magnetic stirring bar, olefin (0.5 mmol, 1 eq), ketone (2.5 mmol, 5 eq) and tBuOOH (5.5M solution in decane, 2 mmol, 4 eq) were dissolved in dry acetonitrile (2 mL). The resulting mixture was then degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Para-toluene sulfonic acid (0.05 mmol, 0.1 eq or 0.01 mmol, 0.02 eq; see article) was then added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 50°C. The reaction mixture was then diluted, a small amount of silica was added and solvent removed. The resulting powder was purified by column chromatography on silica gel using mixtures of hexanes and ethyl acetate to afford the desired γ-ketoperoxide.

5-(tert-butylperoxy)-5-phenylpentan-2-one (158)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 92 mg (74% yield)

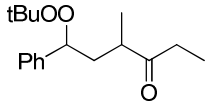
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.39-7.27 (m, 5H); 4.88 (t, J=6.9 Hz; 1H); 2.50 (t, J=7.7 Hz, 2H); 2.2-2.10 (m, 1H); 1.12 (s, 3H); 2.07-1.98 (m, 1H); 1.21 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 208.07 (C); 140.86 (Ar q); 128.25 (AR CH); 127.74 (Ar CH); 126.82 (Ar CH); 84.64 (CH); 80.25 (C); 39.66 (CH_2); 29.96 (CH_3); 28.96 (CH_2); 26.48 (3x CH_3)

MS (EI): 177 (1.87); 161 (88.5); 43 (100)

HRMS (ESI): Calculated for $[C_{15}H_{22}O_3Na]^+$ ($M+Na^+$): 273.146114; found: 273.146160

6-(tert-butylperoxy)-4-methyl-6-phenylhexan-3-one (159)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, mg (47% yield) in a 1:1 dr as determined by NMR analysis.

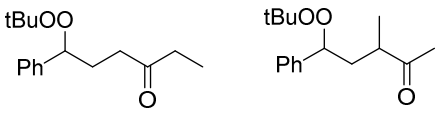
^{1}H NMR: (CDCl3; 500 MHz; 2 diastereosimers): 7.4-7.25 (m, 5H); 4.88-4.80 (m, 1H); 2.79-2.70 (m, 1 H, 1 diastereoisomer); 2.69-2.60 (m, 1 H, 1 diastereoisomer); 2.56-2.29 (m, 3 H); 2.18-2.10 (m, 1 H, 1 diastereoisomer); 1.87-1.79 (m, 1 H, 1 diastereoisomer); 1.65-1.58 (m, 1 H, 1 diastereoisomer); 1.19 (s, 9H, 1 diastereoisomer); 1.18 (s, 9 H, 1 diastereoisomer; 1.12 (app t, 3H, 2 diastereoisomers); 1.04 (t, J=7.3 Hz, 3H)

^{13}C NMR: (CDCl3; 125 MHz, 2 diastereoisomers): 214.38 (C, major); 214.28 (C, minor); 141.30 (Ar q); 128.21 (Ar CH); 127.74 (Ar CH, minor); 127.64 (Ar CH, major); 126.93 (Ar CH, minor); 126.76 (Ar CH, major); 83.86 (CH, minor); 83.71 (CH, major); 80.10 (q, major); 80.09 (q, minor); 42.97 (CH, major); 42.52 (CH, minor); 38.52 (CH_2, minor); 38.20 (CH_2, major); 34.38 (CH_2, major); 34.11 (CH_2, minor); 26.48 (3x CH_3); 17.55 (CH, major); 17.44 (CH, minor); 7.73 (CH_3)

MS (ESI): 301 $[M+Na]^+$

HRMS (ESI): Calculated for $[C_{17}H_{26}O_3Na]+$ $(M+Na^+)$: 301.177416; found: 301.177660

6-(tert-butylperoxy)-6-phenylhexan-3-one (161a)) + 5-(tert-butylperoxy)-3-methyl-5-phenylpentan-2-one (161b)



161a 1.8 : **161b** 1

Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 88mg (67% yield). A clean sample of the linear product was obtained along with mixed fractions by column chromatography but no convenient separation could be achieved. Therefore, total yield was determined by isolating the mixture and performing HPLC analysis to determine the branched/linear product ratio and the dr of the branched product.

The ratio of regioisomers was determined by HPLC and was found to be 1:1.8 in favour of the linear product **161a**. The dr of the branched product **161b** was found to be 1:1.

161a (linear):

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.39-7.23 (m, 5H); 4.86 (dd, J=6.3 and 7.1 Hz, 1H); 2.49-2.42 (m, 2H); 2.38 (q, J=7.4 Hz, 2H); 2.22-1.94 (m, 2H); 1.19 (s, 9H); 1.02 (t, J=7.4 Hz, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 210.63 (C); 140.92 (Ar q); 128.19 (Ar CH); 127.66 (Ar CH); 126.83 (Ar CH); 84.71 (CH); 80.16 (C); 38.28 (CH_2); 35.86 (CH_2); 28.98 (CH_2); 26.46 (3x CH_3); 7.77 (CH_3)

MS (EI): 191 (3); 175 (69); 57 (100)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_3Na]^+$ ($M+Na^+$): 287.161768; found: 287.162050

161b (branched):

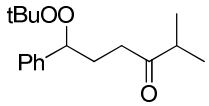
^{1}H NMR: ($CDCl_3$; 300 MHz, 2 diastereoisomers): 7.42-7.19 (m, 5H); 4.92-4.83 (m, 1H); 2.80-2.57 (m, 1H); 2.15-2.14 (2s, 3H); 1.92-1.80 (m, 1H); 1.68-1.56 (m, 1H); 1.19-1.19 (2 s, 9H); 1.16-1.13 (2 d, J=3.5 Hz, 3H)

^{13}C NMR: ($CDCl_3$; 75 MHz, 2 diastereoisomers): 211.57 (C); 211.57 (C); 141.28 (Ar q); 141.24 (Ar q); 128.50 (Ar q); 128.24 (Ar q); 127.71 (Ar q); 126.85 (Ar q); 126.73 (Ar q); 83.75 (CH); 83.62 (CH); 80.09 (C); 80.07 (C); 44.10 (CH); 43.56 (CH); 38.34 (CH_2); 38.23 (CH_2); 28.28 (CH_3); 27.93 (CH_3); 26.44 (3x CH_3); 17.04 (CH_3); 17.02 (CH_3)

MS (EI): 191 (2); 175 (100); 57 (52); 43 (39)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_3Na]^+$ ($M+Na^+$): 287.161762; found: 287.161960

6-(tert-butylperoxy)-2-methyl-6-phenylhexan-3-one (162)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 97/3 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 95 mg (68% yield)

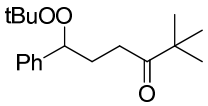
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.29-7.09 (m, 5H); 4.79 (dd, J=7.3 and 6.2 Hz, 1H); 2.53-2.34 (m, 3H); 1.12-1.99 (m, 1H); 1.99-1.85 (m, 1H); 1.11 (s, 9H); 0.98 (d, J=1.5 Hz; 3H); 0.96 (d, J=1.5 Hz, 3H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 213.73 (C); 140.94 (Ar q); 128.13 (Ar CH); 127.59 (Ar CH); 126.80 (Ar CH); 84.66 (CH); 80.06 (C); 40.72 (CH); 36.24 (CH_2); 28.84 (CH_2): 26.43 (3x CH_3); 18.22 (CH_3); 18.17 (CH_3)

MS (EI): 205 (3.5); 189 (100); 71 (89); 43 (50)

HRMS (ESI): Calculated for $[C_{17}H_{26}O_3Na]^+$ ($M+Na^+$): 301.177415; found: 301.177400

6-(tert-butylperoxy)-2,2-dimethyl-6-phenylhexan-3-one (163)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 110 mg (75% yield)

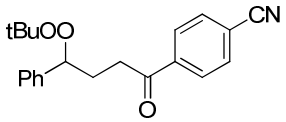
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.28-7.12 (M, 5H); 4.79 (dd, J= 7.5 and 6.2 Hz; 1H); 2.52-2.42 (m, 2H); 2.11-1.97 (m, 1H); 1.97-1.83 (m, 1H); 1.11 (s, 9H); 1.02 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 215,10 (C); 141.11 (Ar q); 128.14 (Ar CH); 127.59 (Ar CH); 126.85 (Ar CH); 84.71 (CH); 80.05 (C); 44.04 (C); 32.56 (CH_2); 29.10 (CH_2); 26.48 (3x CH_3)

MS (EI): 219 (2.6); 203 (100); 117 (74); 57 (63)

HRMS (ESI): Calculated for $[C_{18}H_{28}O_3Na]^+$ ($M+Na^+$): 315.193065; found: 315.193210

4-(4-(tert-butylperoxy)-4-phenylbutanoyl)benzonitrile (164a)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 97/3 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 30 mg (18% yield)

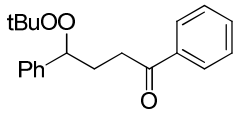
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.95-7.87 (m, 2H); 7.70-7.63 (m, 2H); 7.31-7.16 (m, 5H); 4.90 (dd, J=6 and 7.1 Hz, 1H); 3.09-2.85 (m, 2H); 2.33-2.07 (m, 5H); 1.10 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 198.09 (C); 140.54 (Ar q); 139. 82 (Ar q); 132.42 (Ar CH); 128.38 (Ar CH); 128.29 (Ar CH); 127.83 (Ar CH); 126.78 (Ar CH); 117.88 (C); 116.25 (Ar q); 84.35 (CH); 80.25 (C); 34.80 (CH_2); 29.09 (CH_2); 26.43 (3x CH_3)

MS (EI): 264 (2.1); 248 (100); 130 (87)

HRMS (ESI): Calculated for $[C_{21}H_{23}NO_3Na]^+$ ($M+Na^+$): 360.157011; found: 360.157370

4-(tert-butylperoxy)-1-(4-methoxyphenyl)-4-phenylbutan-1-one (164b)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 58 mg (37% yield) after excess acetophenone was evaporated under high vacuum.

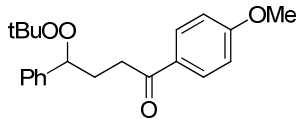
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.96-7.92 (m, 2H); 7.59-7.54 (m, 1H); 7.49-7.44 (m, 2H); 7.42-7.35 (m, 4H); 7.35-7.29 (m, 1H); 5.02 (dd, J=6.3 and 7 Hz); 3.14-3.01 (m, 1H); 2.40-2.31 (m, 1H); 2.28-2.19 (m, 1H); 1.23 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 199.54 (C); 140.99 (Ar q); 136.90 (Ar q); 133.01 (AR CH); 128.57 (Ar CH); 128.29 (Ar CH); 128.02 (Ar CH); 127.76 (Ar CH); 126.89 (Ar CH); 84.75 (CH); 80.26 (C); 34.63 (CH_2); 29.41 (CH_2); 26.52 (3x CH_3)

MS (EI): 239 (4.5); 223 (84); 105 (100); 77 (29)

HRMS (ESI): Calculated for $[C_{20}H_{24}O_3Na]^+$ ($M+Na^+$): 335.161761; found: 335.161753

4-(tert-butylperoxy)-1-(4-methoxyphenyl)-4-phenylbutan-1-one (164c)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 9/1 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 47 mg (33% yield)

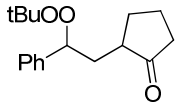
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.93-7.86 (m, 2H); 7.39-7.23 (m, 5H); 6.94-6.88 (m, 2H); 4.98 (dd, J=6.2 and 7.2 Hz, 1H); 3.85 (s, 3H); 3.03-2.94 (m, 2H); 2.38-2.05 (m, 2H); 1.20 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 198.07 (C); 163.37 (Ar q); 141.05 (Ar q); 130.23 (Ar CH); 130.05 (Ar q); 128.20 (Ar CH); 127.65 (Ar CH); 126.86 (Ar CH); 113.65 (Ar CH); 84.79 (CH); 80.16 (C): 55.40 (CH_3); 34.24 (CH_2); 29.59 (CH_2); 26.47 (3x CH_3)

MS (EI): 269 (5.8); 253 (100); 135 (91)

HRMS (ESI): Calculated for $[C_{21}H_{26}O_4Na]^+$ ($M+Na^+$): 365.17327; found: 365.172380

2-(2-(tert-butylperoxy)-2-phenylethyl)cyclopentanone (165)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 83 mg (60% yield) in a 1:1 dr as determined by NMR analysis.

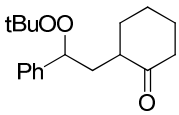
^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereoisomers): 7.30-7.17 (m, 5H); 4.95 (dd, J=5.7 and 8 Hz, 1H, major); 4.86 (t, J=7.3 Hz, 1H, minor); 2.37-1.82 (m, 6H); 1.78-1.38 (m, 3H); 1.11 (s, 9H, major); 1.08 (s, 9H, minor)

^{13}C NMR: ($CDCl_3$; 125 MHz; 2 diastereoisomers): 220.75 (C; major); 220.34 (C, minor); 141.23 (Ar q, minor); 140.66 (Ar q, major); 128.24 (Ar CH, major); 128.19 (Ar CH; minor); 127.89 (Ar CH, major); 127.67 (Ar CH; minor); 127.18 (Ar CH; minor); 126.91 (Ar CH; major); 84.41 (CH, minor); 83.55 (CH, major); 80.10 (C, minor); 80.04 (C, major); 46.44 (CH, major); 46.08 (CH; minor); 37.90 (CH_2, minor); 37.68 (CH_2, major); 35.40 (CH_2, minor); 34.89 (CH_2, major); 30.48 (CH_2, major); 30.25 (CH_2, minor); 26.52 (3x CH_3, major); 26.49 (3x CH_3, minor); 20.71 (CH_2)

MS (EI): 203 (5.5); 187 (100); 169 (58); 91 (84)

HRMS (ESI): Calculated for $[C_{17}H_{24}O_3Na]^+$ ($M+Na^+$): 299.161767; found: 299.161401

2-(2-(tert-butylperoxy)-2-phenylethyl)cyclohexanone (166)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 90 mg (62% yield) in a 1:1.2 dr as determined by HPLC analysis.

^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereoisomers): 7.42-7.22 (m, 5H); 5.02-4.96 (m, 1H); 2.62-2.53 (m, 1H, major); 2.51-2.43 (m, 1H, minor); 2.44-2.38 (m, 1H); 2.38-2.14 (m, 3H); 2.12-2.01 (m, 1H); 1.91-1.81 (m, 1H); 1.74-1.57 (m, 3H); 1.53-1.35 (m, 2H); 1.21 (s, 9H, minor); 1.18 (s, 9H, major)

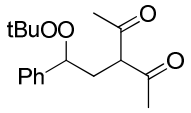
^{13}C NMR: ($CDCl_3$; 125 MHz; 2 diastereoisomers): 212.63 (C); 141.83 (Ar q, major); 141.48 (Ar q, minor); 128.21 (Ar CH, major); 128.17 (Ar CH, minor); 127.63 (Ar CH, minor); 127.53 (Ar CH; major); 126.94 (Ar CH, major); 126.72 (Ar CH; minor); 84.01 (CH, major); 83.05 (CH, minor); 80.08 (C); 47.65 (CH, minor); 47.26 (CH, major); 42.28 (CH_2, major); 42.11 (CH_2,

minor); 35.60 (CH_2, minor); 35.06 (CH_2, major); 34.93 (CH_2, major); 34.41 (CH_2, minor); 28.26 (CH_2, minor); 28.08 (CH_2, major); 26.50 (3x CH_3, major); 26.49 (3x CH_3, minor); 25.33 (CH_2, major); 25.00 (CH_2, minor)

MS (EI): 217 (3.8); 201 (100); 105 (16); 91 (26)

HRMS (ESI): Calculated for $[C_{18}H_{26}O_3Na]^+$ ($M+Na^+$): 313.177418; found: 313.177532

3-(2-(tert-butylperoxy)-2-phenylethyl)pentane-2,4-dione (167)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 90 mg (62% yield)

Note: On the NMR timescale, **167** was observed as a mixture of the two components of a keto-enol equilibrium in a 40:60 ratio in C_6D_6.

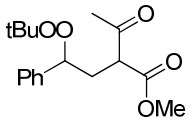
^{1}H NMR: (C_6D_6; 600 MHz): 7.28-7.24 (m, 2H, keto); 7.23-7.19 (m, 2H, enol); 7.14-7.09 (m, 3H, enol); 7.08-7.02 (m, 3H, keto); 4.89 (dd, J=5 and 8.5 Hz; 1H, keto); 4.81 (dd, J=5.8 and 7.7 Hz, 1H, enol); 3.67 (t, J=7 Hz, 1H, keto); 2.57 (dd, J=7.7 and 15.5 Hz, 1H, enol); 2.34 (ddd, J=6.7, 8.6 and 14.5 Hz, 1H, keto); 2.27-2.15 (m, 1H enol + 1H keto); 1.79 (s, 6H, keto); 1.76 (s, 3H, enol); 1.74 (s, 3H, enol); 1.08 (s, 9H, enol); 1.07 (s, 9H, keto)

^{13}C NMR: (C_6D_6; 150 MHz): 202.36 (C, keto); 202.35 (C, enol); 192.05 (C, enol); 141.67 (Ar q, enol); 141.21 (Ar q, keto); 128.54 (Ar CH); 128.53 (Ar CH); 128.29 (Ar CH); 128.09 (Ar CH); 127.93 (Ar CH); 127.08 (Ar CH); 126.70 (Ar CH); 106.61 (C, enol); 86.88 (CH, enol); 83.96 (CH, keto); 80.18 (C, enol); 80.14 (C, keto); 65.69 (CH, keto); 34.33 (CH_2, keto); 34.12 (CH_2, enol); 28.68 (CH_3, keto); 28.21 (CH_3, keto); 26.48 (3x CH_3, keto); 26.41 (3x CH_3, enol); 22.87 (CH_3, enol)

MS (EI): 203 (42); 161 (28); 113 (90); 43 (100)

HRMS (ESI): Calculated for $[C_{17}H_{24}O_4Na]^+$ ($M+Na^+$): 315.156682; found: 315.156354

methyl 2-acetyl-4-(tert-butylperoxy)-4-phenylbutanoate (168)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 86 mg (56% yield)

Note: On the NMR timescale, **168** was observed as a mixture of the two components of a keto-enol equilibrium in a 87:13 ratio in C_6D_6. The dr of the keto form was found to be 1:1.

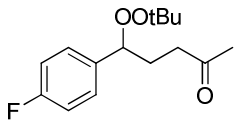
^{1}H NMR: (C_6D_6; 300 MHz): 7.37-7.27 (m, CH2, keto+enol); 7.17-6.99 (m, 3H, keto+enol); 5.01-4.94 (m, 1H, keto+enol); 3.73-3.60 (m, 1H, keto); 3.29 (s, 3H, enol); 3.24(s, 3H, keto, diastereoisomer 1); 3.21 (s, 3H, keto, diastereoisomer 2); 2.66 (dd, J=7.9 and 15 Hz, 1H, enol); 2.59-2.31 (m, 2H keto + 1H enol); 1.87 (s, 3H, keto, diastereoisomer 1); 1.83 (s, 3H, keto, diastereoisomer 2); 1.72 (S, 3H, enol); 1.12 (s, 9H, enol); 1.08 (s, 9H, keto, diastereoisomer 1); 1.08 (s, 9H, keto diastereoisomer 2)

^{13}C NMR: (C_6D_6; 75 MHz; 2 diastereoisomers + enol): 200.90 (C, keto); 200.86 (C, keto); 175.06 (C, enol); 173.68 (C, enol); 169.72 (C, keto); 141.27 (Ar q, enol); 141.20 (Ar q, keto); 128.52 (Ar CH, keto); 128.51 (Ar CH, keto); 128.29 (Ar CH, enol); 128.03 (Ar CH, keto); 127.61 (Ar CH, enol); 127.14 (Ar CH, keto); 127.12 (Ar CH, keto); 126.79 (Ar CH, enol); 96.67 (C, enol); 86.21 (CH, enol); 84.93 (CH, enol); 83.80 (CH, keto); 80.10 (C, keto); 56.72 (CH, keto); 56.25 (CH, keto); 51.81 (CH_3, keto); 51.80 (CH_3, keto); 51.11 (CH_3, enol); 34.26 (CH_2, keto); 34.08 (CH_2, keto); 33.12 (CH_2, enol); 28.81 (CH_3, keto); 28.45 (CH_3, keto); 26.56 (3x CH_3, enol); 26.49 (3x CH_3, keto); 18.82 (CH_3, enol)

MS (EI): 205 (3.5); 189 (100); 71 (89); 43 (50)

HRMS (ESI): Calculated for $[C_{17}H_{24}O_5Na]^+$ ($M+Na^+$): 331.151594; found: 331.151680

5-(tert-butylperoxy)-5-(4-fluorophenyl)pentan-2-one (175a)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 77 mg

(57% yield)

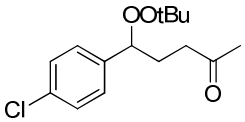
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.32-7.26 (m, 2H); 7.02 (app t, J=8.6 Hz, 2H); 4.84 (dd, J=6.2 and 7.4 Hz, 1H); 2.49 (t, J=7.5 Hz); 2.16-2.02 (m, 1H); 2.12 (s, 3H); 2.02-1.92 (m, 1H); 1.18 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 207.84 (C); 162.30 (d, J=245 Hz, Ar q); 136.78 (d, J=3 Hz, Ar q); 128.44 (d, J=8.3 Hz, Ar CH); 115.08 (d, J=22 Hz, Ar CH); 83.91 (C); 80.27 (C); 39.59 (CH_2); 29.93 (CH_3); 28.93 (CH_2); 26.43 (3x CH_3)

MS (EI): 179 (83); 43 (100)

HRMS (ESI): Calculated for [$C_{15}H_{21}O_3FNa$]+ (M+Na^+): 291.136694; found:291.136770

5-(tert-butylperoxy)-5-(4-chlorophenyl)pentan-2-one (175b)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 88 mg (62% yield)

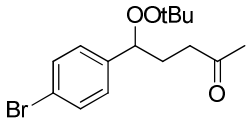
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.34-7.21 (m, 4H); 4.83 (dd, J= 5.9 and 7.6 Hz, 1H); 2.53-2.43 (m, 2H); 2.15-1.83 (m, 2H); 2.11 (s, 3H); 1.18 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 207.61 (C); 139.65 (Ar q); 133.34 (Ar q); 128.38 (Ar CH); 128.11 (Ar CH); 83.81 (CH); 80.27 (C); 39.47 (CH_2); 29.87 (CH_3); 28.92 (CH_2); 26.41 (3x CH_3)

MS (EI): 179 (83); 43 (100)

HRMS (ESI): Calculated for [$C_{15}H_{21}O_3ClNa$]+ (M+Na^+): 307.107142; found:307.107340

5-(4-bromophenyl)-5-(tert-butylperoxy)pentan-2-one (175c)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a white solide, 105 mg (64% yield)

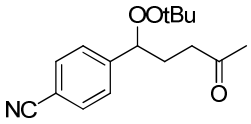
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.49-7.43 (m, 2H); 7.23-7.16 (m, 2H); 4.81 (dd, J=5.9 and 7.6 Hz, 1H); 2.54-2.43 (m, 2H); 2.11 (s, 3H); 2.09-1.89 (m, 2H); 1.18 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 207.54 (C); 140.19 (Ar q); 131.30 (Ar CH); 128.43 (Ar CH); 121.44 (Ar q); 83.81 (CH); 80.26 (C); 39.42 (CH_2); 29.85 (CH_3); 28.87 (CH_2); 26.39 (3x CH_3)

MS (EI): 255 (1); 241 (64); 239 (65); 43 (100)

HRMS (ESI): Calculated for $[C_{15}H_{21}O_3BrNa]+$ $(M+Na^+)$: 351.056638; found:351.056920

4-(1-(tert-butylperoxy)-4-oxopentyl)benzonitrile (175d)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a white solide, 105 mg (64% yield)

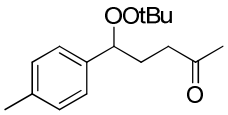
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.59-7.50 (m, 2H); 7.41-7.32 (m, 2H); 4.84 (app t, J=6.7 Hz, 1H); 2.59-2.34 (m, 2H); 2.06 (s, 3H); 1.91 (app q, J=7 Hz, 2H); 1.11 *s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz):

MS (EI): 202 (4.4); 186 (100); 144 (39); 57 (30); 43 (81)

HRMS (ESI): Calculated for $[C_{16}H_{21}NO_3Na]+$ $(M+Na^+)$: 298.141365; found:298.141380

5-(tert-butylperoxy)-5-p-tolylpentan-2-one (175e)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 78 mg (59% yield)

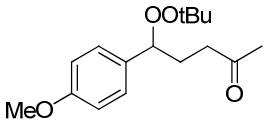
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.23-7.06 (m, 4H); 4.82 (t, J=6.7 Hz, 1H); 2.46 (t, H=7.5 Hz, 2H); 2.34 (s, 3H); 2.22-2.07 (m, 1H); 2.10 (s, 3H); 2.05-1.92 (m, 1H); 1.19 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 207.83 (C); 137.66 (Ar q); 137.28 (Ar q); 128.85 (Ar CH); 126.75 (Ar CH); 84.47 (CH); 80.03 (C); 39.62 (CH_2); 29.77 (CH_3); 28.82 (CH_2); 26.41 (3x CH_3); 21.06 (CH_3)

MS (EI): 191 (2); 175 (100); 157 (23); 43 (80)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_3Na]^+$ $(M+Na^+)$: 287.161760; found: 287.161890

5-(tert-butylperoxy)-5-(4-methoxyphenyl)pentan-2-one (175f)



In an oven-dried Schlenk flask charged with a magnetic stirring bar, 4-methoxystyrene (0.5 mmol, 1 eq) and tBuOOH (5.5M solution in decane, 2 mmol, 4 eq) were dissolved in dry acetone (2 mL). The resulting mixture was then degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Para-toluene sulfonic acid (0.05 mmol, 0.1 eq) was then added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 40°C for 20h. The reaction mixture was then diluted, a small amount of silica was added and solvent removed. The resulting powder was purified by column chromatography on silica gel using a 9:1 mixture of hexanes and ethyl acetate to afford the desired γ-ketoperoxide as a clear oil (47 mg, 33% yield).

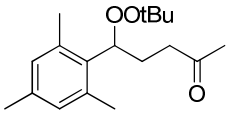
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.15 (d, J=8.6 Hz, 2H); 6.79 (d, J=8.6 Hz, 2H); 4.72 (t, J=6.8 Hz, 1H); 3.72 (s, 3H); 2.37 (t, J=7.6 Hz, 2H); 2.17-1.98 (m, 1H); 2.02 (s, 3H); 1.97-1.83 (m, 1H); 1.10 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 208.02 (C); 159.23 (Ar q); 132.71 (Ar q); 128.18 (Ar CH); 113.63 (Ar CH); 84.80 (CH); 80.08 (C); 55.18 (CH_3); 39.75 (CH_2); 29.84 (CH_3); 28.70 (CH_2); 26.45 (CH_3)

MS (EI): 207 (2); 191 (100); 173 (25); 135 (25); 43 (71)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_4Na]^+$ ($M+Na^+$): 303.156681; found: 303.156780

5-(tert-butylperoxy)-5-mesitylpentan-2-one (176)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 38 mg (26% yield)

^{1}H NMR: ($CDCl_3$; 300 MHz): 6.79 (s, 2H); 5.30 (dd, J=6.1 and 8.7 Hz, 1H); 2.57 (t, J=7.2 Hz, 2H); 2.37 (s, 6H); 2.31-25.17 (m, 1H); 2.24 (s, 3H); 2.12 (s, 3H); 2.08-1.95 (m, 1H); 1.18 (s, 9H)

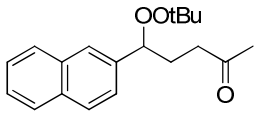
^{13}C NMR: ($CDCl_3$; 75 MHz): 208.14 (C); 136.58 (Ar q); 136.30 (Ar q); 133.88 (Ar q); 129.87 (br, 2x Ar CH); 82.15 (CH); 79.95 (C); 40.32 (CH_2); 29.90 (CH_3); 27.33 (CH_2); 26.52 (3x CH_3); 20.77

(CH_3); 20.65 (CH_3)

MS (EI): 203 (100); 43 (75)

HRMS (ESI): Calculated for $[C_{18}H_{28}O_3Na]^+$ ($M+Na^+$): 315.193060; found: 315.193190

5-(tert-butylperoxy)-5-(naphthalen-2-yl)pentan-2-one (177)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 78 mg (52% yield)

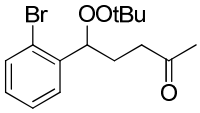
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.90-7.79 (m, 3H); 7.77 (s, 1H); 7.53-7.42 (m, 3H); 5.05 (t, J=6.8 Hz, 1H); 2.52 (t, J=7.5 Hz, 1H); 2.33-2.18 (m, 1H); 2.17-2.03 (m, 1H); 2.10 (s, 3H); 1.23 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 207.77 (C); 138.38 (Ar q); 133.13 (Ar q); 133.11 (Ar q); 128.00 (Ar CH); 127.92 (Ar CH); 127.62 (Ar CH); 125.95 (Ar CH); 125.87 (Ar CH); 125.76 (Ar CH); 124.62 (Ar CH); 84.70 (CH); 80.20 (C); 39.58 (CH_2); 29.82 (CH_3); 28.86 (CH_2); 26.45 (3x CH_3)

MS (EI): 300 (0.8); 227 (5); 211 (100); 193 (38); 43 (79)

HRMS (ESI): Calculated for $[C_{19}H_{24}O_3]^+$ (M^+): 300.172543; found: 300.172261

5-(2-bromophenyl)-5-(tert-butylperoxy)pentan-2-one (178)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 64 mg (39% yield)

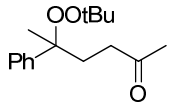
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.49 (td, J=7.8 and 1.3 Hz, 2H); 7.32 (m , 1H); 7.12 (td, J=7.8 and 1.8 Hz, 1H); 5.30 (t, J=6.5 Hz, 1H); 2.60-2.45 (m, 2H); 2.13 (s, 3H); 2.08-1.97 (m, 2H); 1.22 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 207.63 (C), 140.45 (Ar q); 132.53 (Ar CH); 128.85 (Ar CH); 128.02 (Ar CH); 127.43 (Ar CH); 122.50 (Ar q); 83.06 (CH); 80.45 (C); 39.54 (CH_2); 29.78 (CH_3); 28.37 (CH_2); 26.42 (3xCH_3)

MS (EI): 255 (2.4); 241 (43); 239 (45); 43 (100)

HRMS (ESI): Calculated for $[C15H21O3BrNa]^+$ ($M+Na^+$): 351.056640; found: 351.056800

5-(tert-butylperoxy)-5-phenylhexan-2-one (179)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 74 mg (56% yield)

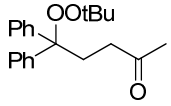
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.39-735 (m, 2H); 7.35-7.29 (m, 2H); 7.25-7.20 (m, 1H);2.53-2.41 (m, 1H); 2.28-2.16 (m, 2H); 2.12-2.02 (m, 1H); 2.06 (s, 3H); 1.58 (s, 3H); 1.25 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 208.92 (C); 144.56 (Ar q); 127.98 (Ar CH); 125.54 (Ar CH); 82.64 (C); 78.97 (C); 38.51 (CH_2); 33.68 (CH_2); 29.95 (CH_3); 26.70 (3x CH_3); 25.31 (CH_3)

MS (EI): 175 (76); 157 (58); 105 (25); 43 (100)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_3Na]^+$ ($M+Na^+$): 287.161764; found: 287.161634

5-(tert-butylperoxy)-5,5-diphenylpentan-2-one (180)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 110 mg (68% yield)

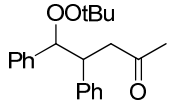
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.27-7.22 (m, 4H); 7.21-7.15 (m, 4H); 7.15-7.09 (m, 2H); 2.70-2.64 (m, 2H); 2.37-2.30 (m, 2H); 1.97 (s, 3H); 1.06 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 209.11 (C); 144.23 (Ar q); 127.71 (Ar CH); 126.95 (Ar CH); 126.88 (Ar CH); 85.65 (C); 79.23 (C); 38.32 (CH_2); 30.09 (CH_3); 29.85 (CH_2); 26.64 (3x CH_3)

MS (EI): 237 (100); 219 (74); 105 (19); 77 (14); 43 (48)

HRMS (ESI): Calculated for $[C_{21}H_{26}O_3Na]^+$ ($M+Na^+$): 349.177413; found: 349.177398

5-(tert-butylperoxy)-4,5-diphenylpentan-2-one (181)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a slowly

solidifying clear oil, 100 mg (61% yield) in a 1:2 dr as determined by NMR analysis

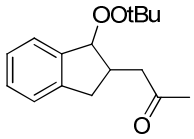
^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereosiomers): 7.32-7.05 (m, 10H); 5.04 (d, J=6.7 Hz, 1H, minor); 4.98 (d, J=8 Hz, 1H, major); 3.71-3.60 (m, 1H); 3.15-2.78 (m, 2H); 2.08 (s, 3H; major); 1.99 (s, 3H, minor); 1.14 (s, 9H, major); 1.10 (S, 9H, minor)

^{13}C NMR: ($CDCl_3$; 125 MHz, 2 diastereoisomers): 207.00 (C, major); 206.88 (C; minor); 140.52 (Ar q, major); 140.25 (Ar q, minor); 139.72 (Ar q, major); 139.59 (Ar q, minor); 128.80 (Ar CH); 128.61 (Ar CH); 128.14 (Ar CH); 127.99 (Ar CH); 127.87 (Ar CH); 127.68 (Ar CH); 127.59 (Ar CH); 127.37 (Ar CH); 127.25 (Ar CH); 126.69 (Ar CH); 88.96 (CH, major); 88.27 (CH, minor); 80.44 (C; minor); 80.43 (C, major); 46.52 (CH, major); 46.00 (CH, major); 45.64 (CH_2, minor); 45.34 (CH_2, major); 30.58 (CH_3, major); 30.50 (CH_3, minor); 26.50 (3x CH_3, major); 26.38 (3x CH_3, minor)

MS (EI): 237 (27); 147 (17); 104 (17); 73 (59); 43 (100)

HRMS (ESI): Calculated for $[C_{21}H_{26}O_3Na]^+$ ($M+Na^+$): 349.177416; found: 349.177561

1-(1-(tert-butylperoxy)-2,3-dihydro-1H-inden-2-yl)propan-2-one (182)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 77 mg (59% yield) in a 1:1.56 dr as determined by NMR analysis

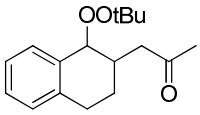
^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereoisomers): 7.40-7.30 (m, 1H); 7.18-7.05 (m, 3H); 5.26 (d, J=5.4 Hz, 1H, minor); 5.06 (d, J=4 Hz, 1H, major);3.33-3.18 (m, 1H, major); 3.10-2.97 (m, 1H, minor); 2.97-2.29 (m, 4H); 1.10 (s, 3H, major); 2.09 (s, 3H, minor); 1.17 (s, 9H, major), 1.09 (s, 9H, minor)

^{13}C NMR: ($CDCl_3$; 125 MHz, 2 diastereoisomers): 208.04 (C, minor); 207.50 (C, major); 143.97 (Ar q, minor); 143.09 (Ar q, major); 140.38 (Ar q, minor); 139.37 (Ar q, major); 128.88 (Ar CH); 128.79 (Ar CH); 126.42 (Ar CH); 126.37 (Ar CH); 126.13 (Ar CH); 126.06 (Ar CH); 124.88 (Ar CH); 124.48 (Ar CH); 91.51 (CH, major); 86.98 (CH, minor); 80.29 (C, minor); 80.22 (C, major); 47.88 (CH_2, major); 42.92 (CH_2, minor); 39.99 (CH, major); 38.89 (CH, minor); 36.57 (CH_2, major); 36.51 (CH_2, minor); 30.12 (CH_3, minor); 29.89 (CH_3, major); 26.36 (3x CH_3, major); 26.30 (3x CH_3, minor)

MS (EI): 189 (4); 173 (100); 43 (95)

HRMS (ESI): Calculated for $[C_{16}H_{22}O_3Na]^+$ ($M+Na^+$): 285.146114; found: 285.146140

1-(1-(tert-butylperoxy)-1,2,3,4-tetrahydronaphthalen-2-yl)propan-2-one (183)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 95/5 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 65 mg (59% yield) in a 1:1.2 dr as determined by NMR analysis

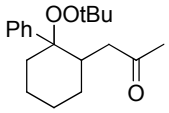
^{1}H NMR: ($CDCl_3$; 300 MHz, 2 diastereoisomers): 7.37-7.28 (m, 1H); 7.19-6.97 (m, 3H); 4.91 (d, J=3 Hz, 1H minor); 6.60 (d, J=4 Hz, 1H, major); 3.05-2.82 (m, H minor + H major); 2.79-2.60 (m, H minor + H major); 2.49-2.14 (m, H minor + H major); 2.14-1.99 (m, H minor+ H major); 2.09 (s, 3H minor); 2.07 (s, 3H, major); 1.89-1.72 (m, 1H major); 1.63-1.46 (m, H); 1.18 (s, 9H, major); 1.11 (s, 9H, minor)

^{13}C NMR: ($CDCl_3$; 75 MHz, 2 diastereoisomers): 208.27 (C, minor); 207.72 (C, major); 137.85 (Ar q, major); 137.30 (Ar q, minor); 134.16 (Ar q, minor); 132.32 (Ar q, major); 131.49 (Ar CH, major); 131.05 (Ar CH; minor); 128.79 (Ar CH, major); 128.73 (Ar CH, minor); 128.19 (Ar CH, major); 127.98 (Ar CH, minor); 125.76 (Ar CH, major); 125.31 (Ar CH, minor); 82.75 (CH, major); 80.56 (CH, minor); 80.12 (C, minor); 79.97 (C, major); 45.34 (CH_2, minor); 44.51 (CH_2, major); 34.05 (CH, minor); 31.21 (CH, major); 30.43 (CH_3, minor); 30.10 (CH_3, major); 26.60 (3x CH_3, major); 26.54 (3x CH_3, minor); 25.37 (CH_2); 23.71 (CH_2, minor); 22.64 (CH_2, major)

MS (EI): 187 (54); 129 (100); 43 (55)

HRMS (ESI): Calculated for $[C_{17}H_{24}O_3Na]^+$ ($M+Na^+$): 299.161767; found: 299.161920

1-(2-(tert-butylperoxy)-2-phenylcyclohexyl)propan-2-one (184)



Synthesized according to the general procedure using 2% of paratoluene sulfonic acid and a 98/2 mixture of hexane and ethyl acetate for chromatography, isolated as a white solid, 41 mg (27% yield) as a mixture of diastereoisomers in a 1:2.1 dr as determined by HPLC analysis.

^{1}H NMR: ($CDCl_3$; 300 MHz, major (lower) diastereoisomer): 7.33-7.22 (m, 2H); 7.22-7.04 (m,

3H); 2.51-2.36 (m, 1H); 2.34-2.17 (m, 2H); 1.97-1.60 (m, 4H); 1.72 (s, 3H); 1.57-1.35 (m, 2H); 1.34-1.61 (m, 2H); 1.01 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz, major (lower) diastereoisomer): 201.54 (C); 144.56 (Ar q); 127.64 (Ar CH); 126.86 (Ar CH); 126.70 (Ar CH); 83.08 (C); 78.36 (C); 43.23 (CH_2); 38.00 (CH); 29.99 (CH_3); 26.82 (CH_2); 26.74 (3x CH_3); 25.93 (CH_2); 21.13 (CH_2); 20.16 (CH_2)

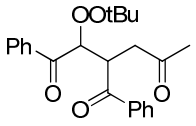
^{1}H NMR: ($CDCl_3$; 300 MHz, minor (upper) diastereoisomer): 7.49-7.40 (m, 2H); 7.34-7.24 (m, 2H); 7.23-7.15 (m, 1H); 2.44-2.21 (m, 4H); 1.89 (s, 3H); 1.83-1.70 (m, 3H); 1.66-1.44 (m, 5H); 1.35 (s, 9H)

^{13}C NMR: ($CDCl_3$; 75 MHz, minor (upper) diastereoisomer): 208.51 (C); 144.82 (Ar q); 127.71 (Ar CH); 126.47 (Ar CH); 126.38 (Ar CH); 84.75 (C); 79.15 (C); 44.73 (CH_2); 44.68 (CH); 34.73 (CH_2); 30.27 (CH_3); 28.44 (CH_2); 26.89 (3x CH_3); 25.90 (CH_2); 21.59 (CH_2)

MS (EI): 215 (63); 157 (100); 43 (27)

HRMS (ESI): Calculated for $[C_{19}H_{28}O_3Na]^+$ ($M+Na^+$):327.193065; found: 327.193210

3-benzoyl-2-(tert-butylperoxy)-1-phenylhexane-1,5-dione (185)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 9/1 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 93 mg (47% yield) as a mixture of diastereoisomers in a 1:1.3 dr as determined by NMR analysis.

^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereoisomers): 8.15-8.06 (m, 2H); 8.02-7.92 (m, 2H); 7.63-7.53 (m, 2H); 7.53-7.41 (m, 4H); 5.60 (s, J=7.2 Hz, 1H, major); 5.28 (d, J=9.7 Hz, 1H, minor);4.71 (td, J=4.1 and 7.5 Hz, 1H, major); 4.62 (td, J=3.3 and 10 Hz, 1H, minor) 3.24-2.54 (m, 2H); 2.17 (s, 3H, major); 2.04 (s, 3H, minor); 1.05 (s, 9H, major); 0.85 (s, 9H, minor)

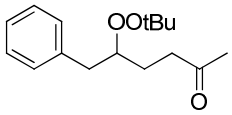
^{13}C NMR: ($CDCl_3$; 125 MHz, 2 diastereoisomers): 205.90 (C; major); 205.39 (C, minor); 201.06 (C, major); 200.26 (C, minor); 196.96 (C, minor); 196.40 (C, major); 137.83 (Ar q, minor); 136.29 (Ar q, major); 135.82 (Ar q, minor); 135.70 (Ar q, major); 133.71 (Ar CH, minor); 133.41 (Ar CH, major); 133.09 (Ar CH, major); 133.05 (Ar CH, minor); 129.10 (Ar CH, minor); 129.04 (Ar CH, major); 128.84 (Ar CH, minor); 128.76 (Ar CH, major); 128.67 (Ar CH, minor); 128.57 (Ar CH; major); 128.42 (ar CH, major); 128.34 (Ar CH, minor); 85.38 (CH, minor); 83.62 (CH, major); 81.40 (C, minor); 80.99 (C, major); 43.08 (CH_2, minor); 42.07 (CH, major); 41.59

(CH_2, major); 41.23 (CH, minor); 30.12 (CH_3, minor); 29.53 (CH_3, major); 26.18 (3x CH_3, major); 25.89 (3x CH_3, minor)

MS (EI): 277 (3); 105 (100)

HRMS (ESI): Calculated for $[C_{23}H_{26}O_5Na]^+$ ($M+Na^+$):405.167245; found: 405.167192

5-(tert-butylperoxy)-6-phenylhexan-2-one (186)



Synthesized according to the general procedure using 10% of paratoluene sulfonic acid and a 99/1 mixture of hexane and ethyl acetate for chromatography, isolated as a clear oil, 16 mg (12% yield)

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.23-7.17 (m, 2H); 7.16-7.09 (m, 3H); 4.07-3.99 (m, 1H); 2.96 (dd, J=5.7 and 13.8 Hz, 1H); 2.62 (dd, J=6.8 and 13.7 Hz, 1H); 2.55-2.41 (m, 2H); 2.04 (s, 3H); 1.83-1.74 (m, 1H); 1.69-1.60 (m, 1H); 1.10 (s, 9H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 208.59 (C); 138.30 (Ar q); 129.56 (Ar CH); 128.25 (Ar CH); 126.20 (Ar CH); 83.47 (CH); 80.12 (C); 39.71 (CH_2); 39.29 (CH_2); 29.89 (CH_3); 26.45 (3x CH_3); 26.44 (CH_2)

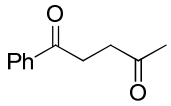
MS (EI): 191 (20); 173 (14); 117 (35); 91 (100); 73 (91); 57 (32); 43 (62)

HRMS (ESI): Calculated for $[C_{16}H_{24}O_3Na]^+$ ($M+Na^+$): 287.161765; found: 287.161490

7.4.2 Further Transformations of γ-keto-peroxides

From preformed 158:

1-phenylpentane-1,4-dione (187)



In a vial, **158** (25mg, 0.1 mmol, 1 eq) was dissolved in acetonitrile (1 mL) and DBU was added (2.9 µL, 0.02 mmol, 0.2 eq) and the reaction mixture allowed to react overnight. Solvent was evaporated and the residue directly purified by column chromatography using an 8/2 mixture of hexanes and ethyl acetate to afford **187** (17 mg, 96% yield) as a clear oil.

^{1}H NMR: ($CDCl_3$; 500 MHz): 8.04-7.97 (m, 2H); 7.62-7.55 (m, 1H); 7.52-7.45 (m, 2H); 3.30 (t,

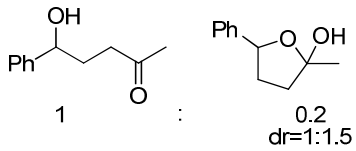
J=6.3 Hz, 2H); 2.92 (t, J=6.3 Hz, 2H); 2.29 (s, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 207.28)C); 198.46 (C); 136.59 (Ar q); 133.13 (Ar CH); 128.56 (Ar CH); 128.01 (Ar CH); 36.99 (CH_2); 32.39 (CH_2); 30.05 (CH_3)

MS (EI): 176 (21); 133 (25); 105 (100); 77 (95) 51 (27); 43 (33)

HRMS (ESI): Calculated for $[C_{11}H_{12}O_2Na]^+$ ($M+Na^+$): 199.072949; found: 199.073020

5-hydroxy-5-phenylpentan-2-one (188)



In a 2 necked-flask, Pd/C (10% dry on carbon, 20 mg) was introduced and the atmosphere replaced with argon, **158** (125mg, 0.5 mmol, 1 eq) was added as a solution in acetonitrile (5 mL). The atmosphere was then replaced with hydrogen and the reaction was let to react at room temperature under vigorous stirring for 1.5 hours. The mixture was filtered on Celite (dichloromethane), the resulting solution concentrated and purified by column chromatography using an 8/2 mixture of hexanes and ethyl acetate to afford **188** (83 mg, 93% yield) as a clear oil.

Analysis of the product showed an open and a closed form in a 1:0.2 ratio. The closed form had a dr value of 1:1.5. All ^{1}H signals were attributed but some aromatic ^{13}C signals of the closed product are missing.

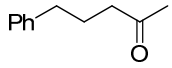
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.44-7.08 (m, 5H); 5.18 (t, J=7 Hz, 1H, closed major); 5.01 (dd, J=6.4 and 10 Hz, 1H, closed minor); 4.67 (t, J=6.3 Hz, 1H, open); 3.14 (br s, 1H, closed minor+major); 3.01 (br s, 1H, open); 5.52 (t, J=7 Hz, 2H, open); 2.34-1.92 (m, 3H, closed minor+major); 2.11 (s, 3H, open); 1.99 (q, J=7 Hz, 2H, open); 1.88-1.79 (m, 1H, closed minor+major); 1.64 (s, 3H, closed major); 1.59 (s, 3H, closed minor);

^{13}C NMR: ($CDCl_3$; 125 MHz): 209.66 (C, open); 144.32 (Ar q, open); 142.95 (Ar q, closed minor); 142.87 (Ar q, major); 128.66 (Ar CH, closed, minor); 128.44 (Ar CH, open); 128.35 (Ar CH, closed major); 127.49 (Ar CH, open); 127.44 (Ar CH, closed minor); 127.31 (Ar CH, closed major); 126.35 (Ar CH, closed); 125.75 (Ar CH, open); 125.67 (Ar CH, closed); 105.70 (C, closed major); 105.33 (C, closed minor); 82.67 (CH, closed minor); 79.95 (CH, closed major); 73.29 (CH, open); 39.81 (CH_2, open); 39.16 (CH_2, closed minor); 37.56 (CH_2, closed major);

34.37 (CH_2, closed minor); 33.96 (CH_2, closed major); 32.67 (CH_2, open); 30.00 (CH_3, open); 27.45 (CH_3, closed major); 27.41 (CH_3, closed minor)

HRMS (ESI): Calculated for [$C_{11}H_{14}O_2$] (M): 178.099377; found: 178.099217

5-phenylpentan-2-one (190)



In a 2 necked-flask, Pd/C (10% dry on carbon, 20 mg) was introduced and the atmosphere replaced with argon, **158** (125mg, 0.5 mmol, 1 eq) was added as a solution in methanol (5 mL). The atmosphere was then replaced with hydrogen and the reaction was let to react at room temperature under vigorous stirring for 4 hours. The mixture was filtered on Celite (methanol), the resulting solution concentrated and purified by column chromatography using a 95/5 mixture of hexanes and ethyl acetate to afford **190** (80 mg, 98% yield) as a clear oil.

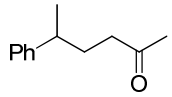
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.33-7.27 (m, 2H); 7.24-7.17 (m, 3H); 2.64 (t, J=;7.6 Hz, 1H); 2.46 (t, J=7.6 Hz, 1H); 2.14 (s, 3H); 1.98-1.89 (m, 2H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 208.78 (C); 141.60 (Ar q); 128.49 (Ar CH); 128.41 (Ar CH); 125.98 (Ar CH); 42.83 (CH_2); 35.03 (CH_2); 29.98 (CH_3); 25.22 (CH_2)

MS (EI): 162 (18); 104 (100); 91 (18); 43 (7)

HRMS (ESI): Calculated for [$C_{11}H_{14}O_2$] (M): 178.099377; found: 178.099217

5-phenylhexan-2-one (191)



In a 2 necked-flask, Pd/C (10% dry on carbon, 20 mg) was introduced and the atmosphere replaced with argon, **179** (132mg, 0.5 mmol, 1 eq) was added as a solution in methanol (5 mL). The atmosphere was then replaced with hydrogen and the reaction was let to react at room temperature under vigorous stirring for 4 hours. The mixture was filtered on Celite (methanol), the resulting solution concentrated and purified by column chromatography using a 95/5 mixture of hexanes and ethyl acetate to afford **191** (84 mg, 95% yield) as a clear oil.

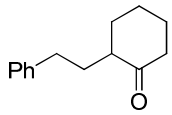
^{1}H NMR: ($CDCl_3$; 300 MHz): 7.32-7.27 (m, 2H); 7.22-7.14 (m, 3H); 2.73-2.64 (m, 1H); 2.37-2.22 (m, 2H); 2.04 (s, 3H); 1.95-1.77 (m, 2H); 1.22 (d, J=7 Hz, 3H)

^{13}C NMR: ($CDCl_3$; 75 MHz): 208.95 (C); 146.46 (Ar C); 128.49 (CH); 127.03 (CH); 126.19 (CH); 41.84 (CH_2; 39.35 (CH); 31.88 (CH_2); 29.96 (CH_3); 22.49 (CH_2)

MS (ESI): 176 (6); 118 (100); 105 (31); 91 (7); 77 (10)

HRMS (ESI): Calculated for [$C_{12}H_{16}O$] (M): 176.120114; found: 176.120038

2-phenethylcyclohexanone (192)



In a 2 necked-flask, Pd/C (10% dry on carbon, 20 mg) was introduced and the atmosphere replaced with argon, **166** (135mg, 0.4655 mmol, 1 eq) was added as a solution in methanol (5 mL). The atmosphere was then replaced with hydrogen and the reaction was let to react at room temperature under vigorous stirring for 4 hours. The mixture was filtered on Celite (methanol), the resulting solution concentrated and purified by column chromatography using a 95/5 mixture of hexanes and ethyl acetate to afford **192** (85 mg, 84% yield) as a clear oil.

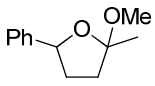
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.33-7.27 (m, 2H); 7.23-7.18 (m, 3H); 2.72-2.60 (m, 2H); 2.46-2.38 (m, 1H); 2.36-2.26 (m, 2H); 2.23-2.12 (m, 2H); 2.11-2.02 (m, 1H); 1.93-1.84 (m, 1H); 1.77-1.61 (m, 2H); 1.59-1.39 (m, 2H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 213.19 (C); 142.25 (Ar C); 128.44 (Ar CH); 128.36 (Ar CH); 125.80 (Ar CH); 49.87 (CH); 42.16 (CH_2); 34.08 (CH_2); 33.26 (CH_2); 31.24 (CH_2); 28.10 (CH_2); 24.97 (CH_2)

MS (ESI): 202 (11); 98 (100); 91 (22)

HRMS (ESI): Calculated for [$C_{14}H_{18}O$] (M): 202.135764; found:202.135558

2-methoxy-2-methyl-5-phenyltetrahydrofuran (189)



In a 2 necked-flask, Pd/C (10% dry on carbon, 20 mg) was introduced and the atmosphere replaced with argon, **158** (125mg, 0.5 mmol, 1 eq) was added as a solution in methanol (5

mL). The atmosphere was then replaced with hydrogen and the reaction was allowed to react at room temperature under vigorous stirring for 1 hour. The mixture was filtered on Celite (methanol), the resulting solution concentrated and purified by column chromatography using a 95/5 mixture of hexanes and ethyl acetate to afford **189** as a clear oil (39 mg, 40% in a 1:1.6 dr) and **190** (20 mg, 25% yield) as a clear oil. **188** was also detected by TLC analysis but not isolated.

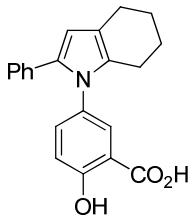
^{1}H NMR: ($CDCl_3$; 500 MHz, 2 diastereoisomers): 7.43-7.34 (m, 4H); 7.32-7.26 (m, 1H); 5.07 (app t, J=7.5 Hz, 1H); 3.37 (s, 3H, minor); 3.34 (s, 3H, major); 2.58-2.44 (m, 1H, major); 2.34-2.09 (m, 3H minor + 1H major); 1.05-1.93 (m, 1H minor + 1 H major); 1.90-1.80 (m, 1H major); 1.60 (s, 3H, major); 1.55 (s, 3H, minor)

^{13}C NMR: ($CDCl_3$; 125 MHz, 2 diastereoisomers): 142.93 (Ar q, major); 142.87 (Ar q, minor); 128.40 (Ar CH, major); 128.34 (Ar CH, minor); 127.43 (Ar CH, minor); 127.36 (Ar CH, major); 126.53 (Ar CH); 125.79 (Ar CH); 108.14 (C, major); 107.86 (C, minor); 82.88 (CH, minor); 80.06 (CH, major); 49.01 (CH_3, minor); 48.72 (CH_3, major); 39.53 (CH_2, minor); 38.11 (CH_2, major); 34.05 (CH_2, minor); 33.80 (CH_2, major); 22.13 (CH_3, minor); 21.57 (CH_3, major)

HRMS (ESI): Calculated for [$C_{12}H_{17}O_2$] (M): 193.122854; found: 193.122663

One-pot synthesis of 193:

2-hydroxy-5-(2-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)benzoic acid (193)



In an oven-dried Schlenk flask charged with a magnetic stirring bar, styrene (57 µL; 0.5 mmol, 1 eq), cyclohexanone (257 µL, 2.5 mmol, 5 eq) and tBuOOH (364 µL; 5.5M solution in decane, 2 mmol, 4 eq) were dissolved in dry acetonitrile (2 mL). The resulting mixture was then degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Para-toluene sulfonic acid (9.5 mg, 0.05 mmol, 0.1 eq) was then added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 50°C. After 16 hours, DBU

(74.5 µL, 0.5 mmol, 1 eq) was added and the mixture let to react for 4 more hours at 50°C. Solvent was then evaporated by freezing the mixture in liquid nitrogen and connecting the flask to a high vacuum pump until acetonitrile evaporated. Acetic acid (1mL) was then added under an argon atmosphere followed by 5-amino-2-hydroxybenzoic acid (153 mg, 1 mmol, 2 eq) and the resulting mixture heated to 130°C for 3 hours. After cooling to room temperature, the crude mixture was directly purified by column chromatography using a 20/1 mixture of hexanes/acetone containing 1% of acetic acid as eluant. Product **193** was obtained as a slightly yellow solid (55 mg, 30% yield)

When isolated after column chromatography, the solid obtained contained 1 equivalent of acetic acid (presumably through carboxylic acid dimer formation) which could be removed by azeotropic distillation with toluene. However, the NMR spectra obtained were very broad and signals were missing when the spectra containing acetic acid were sharp and well defined. Therefore, NMR data reported here include acetic acid.

^{1}H NMR: ($CDCl_3$; 300 MHz): 10.23 (br s, 1H); 9.51 (br s, 1H); 7.67 (d, J=2.6 Hz, 1H); 7.18-6.96 (m, 7H); 6.85 (d, J=8.8 Hz, 1H); 6.16 (s, 1H); 2.58-2.49 (m, 2H); 2.38-2.28 (m, 2H); 1.78-1.67 (m, 4H)

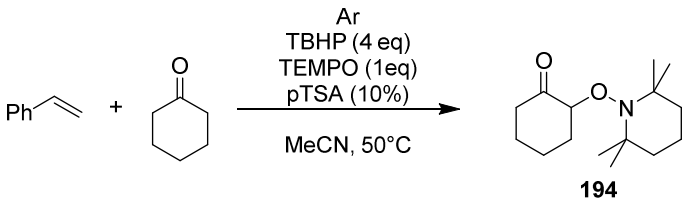
^{13}C NMR: ($CDCl_3$; 75 MHz): 177.67 (C, AcOH); 173.87 (C); 160.82 (Ar q); 136.60 (Ar CH); 133.26 (Ar q); 133.11 (Ar q); 131.05 (Ar q); 129.43 (Ar CH); 128.08 (Ar CH); 127.91 (Ar CH), 125.80 (Ar CH), 118.49 (Ar q); 118.41 (Ar CH); 111.36 (Ar q); 108.72 (Ar CH); 23.55 (CH_2); 23.41 (CH_2); 23.15 (CH_2); 23.02 (CH_2); 1 aromatic quaternary carbon missing presumably due to overlap with other signals

MS (EI): 333 (100); 315 (66); 287 (27); 258 (9); 230 (20)

HRMS (ESI): Calculated for [$C_{21}H_{19}NO_3$] (M): 333.136494; found: 333.136747

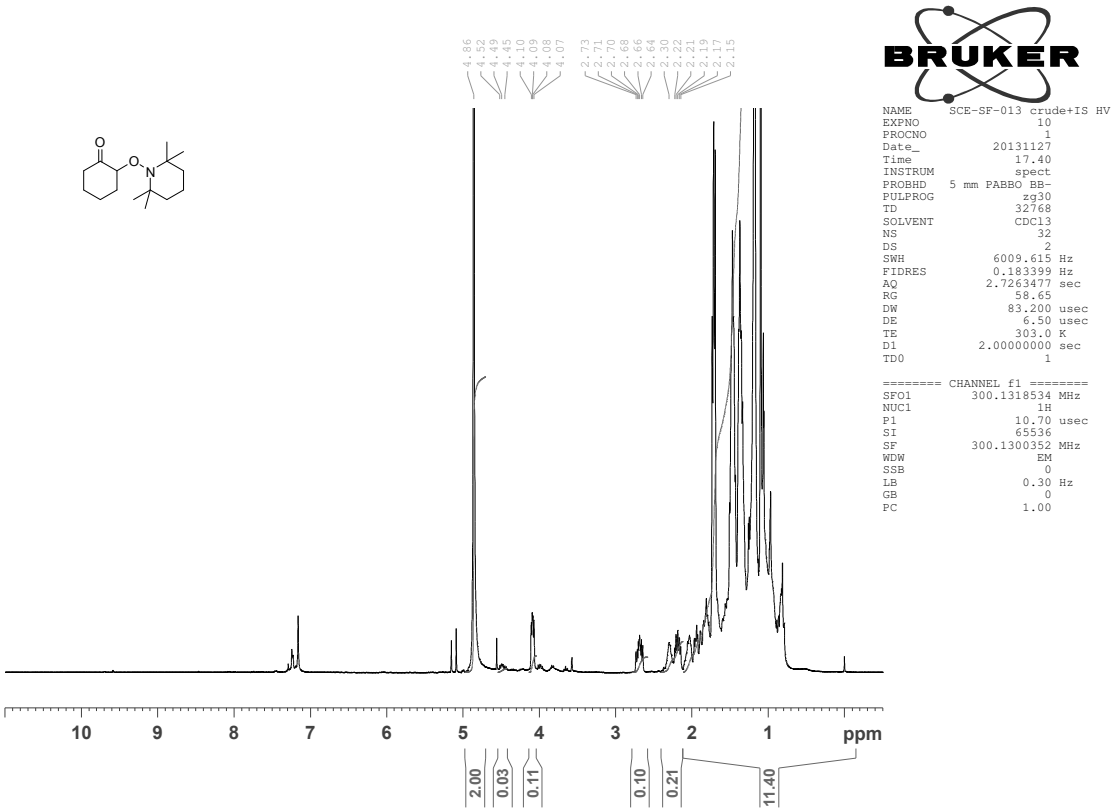
7.4.3 Mechanistic Experiments

TEMPO trapping



194

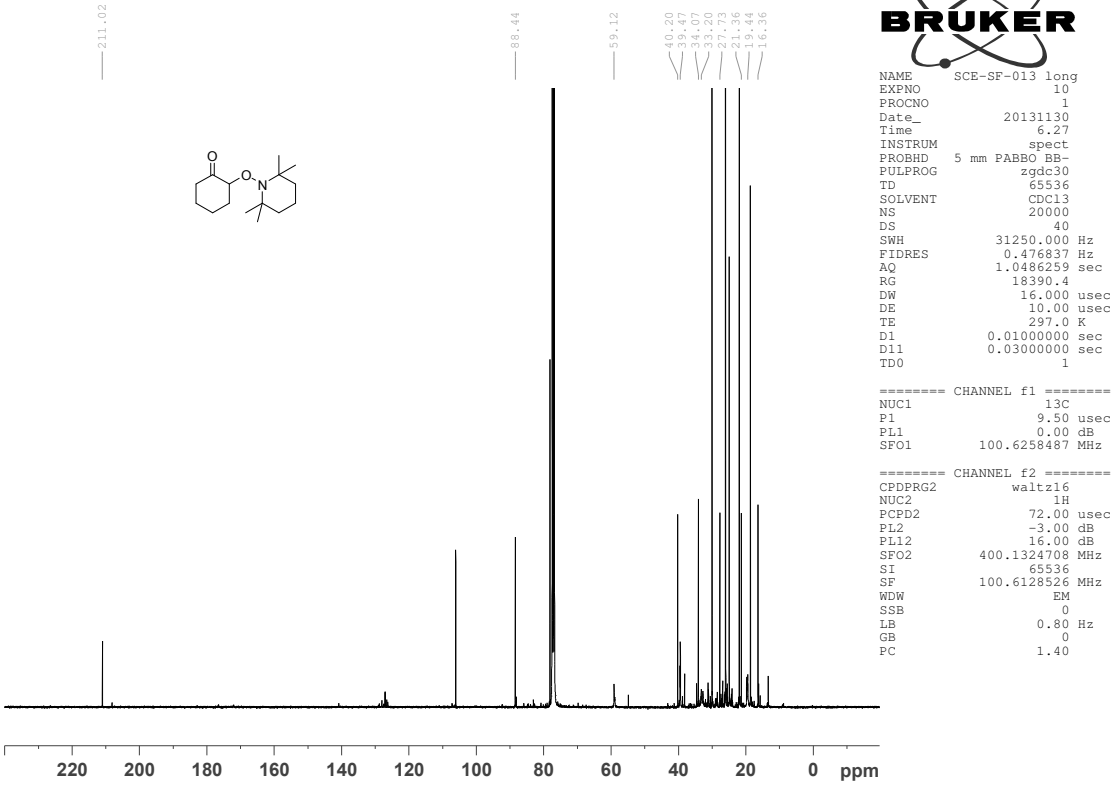
In an oven-dried Schlenk flask charged with a magnetic stirring bar, styrene (57 µL; 0.5 mmol, 1 eq), cyclohexanone (257 µL, 2.5 mmol, 5 eq) and tBuOOH (364 µL; 5.5M solution in decane, 2 mmol, 4 eq) and TEMPO (78 mg, 0,5 mmol, 1 eq) were dissolved in dry acetonitrile (2 mL). The resulting mixture was then degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Para-toluene sulfonic acid (9.5 mg, 0.05 mmol, 0.1 eq) was then added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 50°C. After 16 hours, ethyl acetate (10 mL) was added and the resulting solution was washed with brine (5 mL) and distilled water (5 mL). After drying with Na_2SO_3 and removal of solvent and excess TEMPO under high vacuum, NMR analysis of the crude mixture showed the presence of **194** in a 10% yield, using CH_2Br_2 (39.4µL, 0.5 mmol, 1 eq) as an internal standard and by comparison with reported data[109]



BRUKER

```
NAME          SCE-SF-013 crude+IS HV
EXPNO                             10
PROCNO                             1
Date_                       20131127
Time                           17.40
INSTRUM                        spect
PROBHD    5 mm PABBO BB-
PULPROG                         zg30
TD                             32768
SOLVENT                        CDCl3
NS                                32
DS                                 2
SWH                        6009.615 Hz
FIDRES                    0.183399 Hz
AQ                        2.7263477 sec
RG                             58.65
DW                            83.200 usec
DE                             6.50 usec
TE                             303.0 K
D1                        2.00000000 sec
TD0                                1

======== CHANNEL f1 ========
SFO1                  300.1318534 MHz
NUC1                             1H
P1                            10.70 usec
SI                             65536
SF                    300.1300352 MHz
WDW                              EM
SSB                               0
LB                             0.30 Hz
GB                                0
PC                             1.00
```



BRUKER

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NAME          SCE-SF-013 long
EXPNO                             10
PROCNO                             1
Date_                       20131130
Time                           6.27
INSTRUM                        spect
PROBHD    5 mm PABBO BB-
PULPROG                     zgdc30
TD                             65536
SOLVENT                        CDCl3
NS                             20000
DS                                40
SWH                       31250.000 Hz
FIDRES                    0.476837 Hz
AQ                        1.0486259 sec
RG                           18390.4
DW                            16.000 usec
DE                             10.00 usec
TE                             297.0 K
D1                        0.01000000 sec
D11                       0.03000000 sec
TD0                                1

======== CHANNEL f1 ========
NUC1                             13C
P1                             9.50 usec
PL1                            0.00 dB
SFO1                  100.6258487 MHz

======== CHANNEL f2 ========
CPDPRG2                   waltz16
NUC2                             1H
PCPD2                         72.00 usec
PL2                           -3.00 dB
PL12                          16.00 dB
SFO2                  400.1324708 MHz
SI                             65536
SF                    100.6128526 MHz
WDW                              EM
SSB                               0
LB                             0.80 Hz
GB                                0
PC                             1.40
```

All ^{13}C signals could be found in the mixture as well as some distinctive peaks in the ^{1}H spectrum.

The signals at 4.1-4.0 ppm, 2.77-2.60 ppm and 2.41-2.12 ppm integrating for 1H, 1H and 2H,

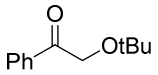
respectively, give a 10% yield of **194** by comparison with the signal of CH_2Br_2 at 4.86 ppm (2H). The presence of a double condensation adduct is also suggested by the signals at 4.55-4.40 ppm, in approximately 1% yield by comparison with the NMR data reported in the literature.[109]

Additionnaly, MS analysis of the crude mixture gave the following data, clearly showing the presence of adduct **194**.

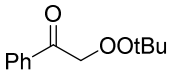
MS (EI): 253 (10); 156 (100)

HRMS (ESI): Calculated for $[C_{15}H_{27}NO_2Na]$ $(M+Na)^+$: 276.193397; found: 276.193510

2-tert-butoxy-1-phenylethanone (195a) and 2-(tert-butylperoxy)-1-phenylethanone (195b)



195a



195b

From the mixture of the reaction of acetophenone and styrene (See product **164b**) was isolated an additional product (34mg, clear oil) which upon NMR and MS analysis showed to be a mixture of ether **195a** and peroxide **195b**. These two products were however undistinguishable by NMR.

^{1}H NMR: ($CDCl_3$; 500 MHz): 8.01-7.94 (m, 2H); 7.60-7.54 (m, 1H); 7.50-7.43 (m, 2H); 4.67 (s, 2H); 1.29 (s, 9H)

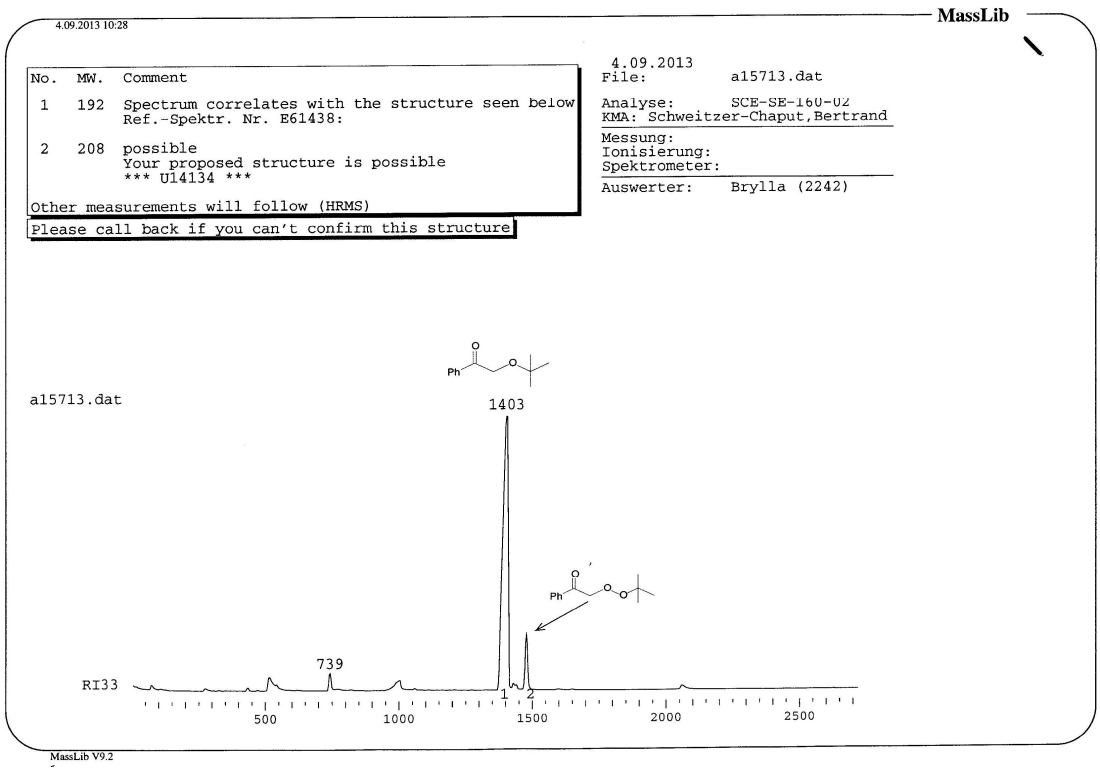
^{13}C NMR: ($CDCl_3$; 125 MHz): 197.18 (C); 135.38 (Ar q); 133.23 (Ar CH); 128.55 (Ar CH); 128.13 (Ar CH); 74.58 (C); 66.28 (CH_2); 27.47 (3x CH_3)

MS (EI; 30a): 192 (1); 135 (3); 119 (10); 105 (100); 91 (13); 77 (19); 57 (33)

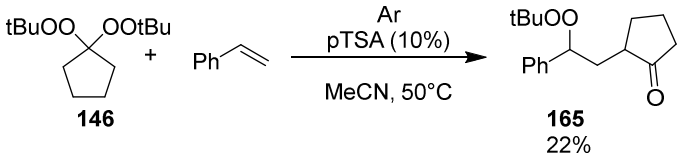
MS (EI; 303): 151 (4); 123 (33); 105 (100); 77 (25); 57 (59)

HRMS (ESI, 30a): Calculated for $[C_{12}H_{16}O_2]$ (M): 192.115027; found: 192.115202

HRMS (ESI, 30b): Calculated for $[C_{12}H_{16}O_3Na]^+$ $(M+Na^+)$: 231.099167; found: 231.099320



Addition of 146 to styrene:



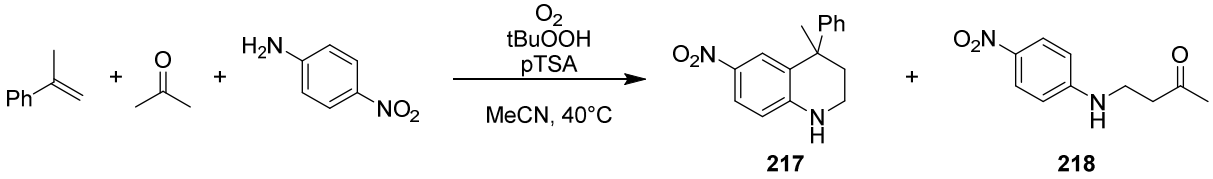
146 **165** 22%

In an oven-dried Schlenk flask charged with a magnetic stirring bar, styrene (57 µL; 0.5 mmol, 1 eq), cyclopentanone (176 µL, 2 mmol, 4 eq) and **146** (123mg, 0.5 mmol, 1eq) were dissolved in dry acetonitrile (2 mL). The resulting mixture was then degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated for a total of three cycles). Para-toluene sulfonic acid (9.5 mg, 0.05 mmol, 0.1 eq) was then added under a stream of argon and after closing the flask, the reaction mixture was allowed to react overnight at 50°C. Purification of the resulting mixture by column chromatography afforded **165** (31mg, 22%) as a clear oil.

7.5 Synthesis of Tetrahydroquinolines and Oxidative Cleavage of Styrene Derivatives

7.5.1 Initial Experiment

4-methyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline (217) and 4-(4-nitrophenylamino)butan-2-one (218)



In a 12ml screw-cap vial, α-methyl styrene (5 µL, 0.5 mmol) and *para*-nitro aniline (70 mg, 0.5 mmol) were dissolved in 5 mL of a 1:1 mixture of acetone and acetonitrile and tBuOOH (5.5M solution in decane, 182 µL, 1 mmol) was added followed by *para*-toluene sulfonic acid (9.5 mg, 0.05 mmol). The vial was flushed with O_2 and connected to an O_2 balloon and let to react at 40°C overnight. The reaction mixture was then diluted, silica added and solvent removed under vacuum. The resulting yellow powder was subjected to column chromatography using a 8:2 mixture of hexane/ethyl acetate as eluant. **217** was first isolated (8 mg, 6%) as a yellow solide followed by **218** (35 mg, 33%) as a yellow oil.

4-methyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline (217)

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.93 (d, J=2.7 Hz, 1H); 7.89(dd, J=2.7 and 8.9 Hz, 1H)7.23-7.17 (m, 2H); 7.15-7.10 (m, 1H); 7.02-6.98 (m, 2H); 6.38 (d, J=8.9 Hz, 1H); 3.31-3.22 (m, 1H); 3.00-2.92 (m, 1H); 2.18-2.09 (m, 1H); 1.93-1.85 (m, 1H); 1.70 (s, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 150.00 (Ar C); 147.84 (Ar C); 137.54 (Ar C); 128.45 (Ar CH); 126.83 (Ar CH); 126.47 (Ar C); 126.41 (Ar CH); 125.39 (Ar CH); 124.59 (Ar CH); 112.71 (Ar CH); 40.71 (C); 38.39 (CH_2); 36.64 (CH_2); 28.82 (CH_3)

MS (ESI): 268 (100); 253 (77); 207 (27); 91 (24)

HRMS (ESI): Calculated for [$C_{16}H_{16}N_2O_2$] (M): 268.121176; found: 268.120963

The spectral properties of **218** matched those reported in the literature.[110]

^{1}H NMR: ($CDCl_3$; 500 MHz): 7.99 (d, J=9.2 Hz, 2H); 6.45 (d, J=9.2 Hz, 2H); 4.93 (br s, 1H); 3.47-3.40 (m 2H); 2.72 (t, J=6 Hz, 2H); 2.13 (s, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 207.26 (C); 152.86 (Ar C); 138.12 (Ar C); 126.43 (Ar CH); 111.04

(Ar CH); 42.07 (CH_2); 37.66 (CH_2); 30.22 (CH_3)

MS (ESI): 208 (26); 151 (100); 108 (48); 105 (49); 55 (40); 43 (62)

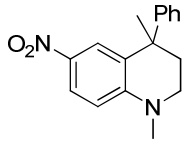
HRMS (ESI): Calculated for [$C_{10}H_{12}N_2O_3Na$] ($M+Na^+$): 231.074011; found: 231.074080

7.5.2 Synthesis of Products:

General procedure for the synthesis of tetrahydroquinolines:

In a 4 mL screw-cap vial, the appropriate styrene (0.8 mmol) and aniline (0.2 mmol) were dissolved in a 1:1 mixture of acetonitrile/acetic acid (2 mL). Acetophenone (93 µL, 0.8 mmol), tBuOOH (5.5M solution in decane, 72 µL, 0.4 mmol) and *para*-toluene sulfonic acid (3.8 mg, 0.02 mmol) were added. The vial was flushed with O_2 and connected to an O_2 balloon. The resulting mixture was let to react at 50°C for 24 hours. The mixture was then diluted, silica was added and the solvents removed under vacuum. The resulting powder was subjected to column chromatography using a mixture of hexane/ethyl acetate as eluant to afford the corresponding tetrahydroquinoline product.

1,4-dimethyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline (220)



Synthesised according to the general procedure and using a 9:1 mixture of hexane/ethyl acetate as eluant for column chromatography. **220** was obtained (39 mg, 68%) as a yellow oil

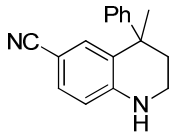
^{1}H NMR: ($CDCl_3$; 500 MHz): 8.07 (dd, J=2.7 and 9.2 Hz, 1H); 7.99 (, J= 2.7 Hz, 1H); 7.29-7.23 (m, 2H); 7.22-7.16 (m, 1H); 7.05-7.00 (m, 2H); 6.55 (d, J=9 Hz, 1H); 3.25 (td, J=4.6 and 12.4 Hz, 1H); 3.09 (ddd J=4.2, 10.8 and 12.4 Hz, 1H); 3.00 (s, 3H); 2.25 (td, J=4.2 and 13.4 Hz, 1H); 1.99 (ddd, J=4.6, 10.8 and 13.4 Hz, 1H); 1.74 (s, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 150.77 (Ar C); 147.65 (Ar C); 136.52 (Ar C); 128.47 (Ar CH); 127.98 (Ar C); 126.74 (Ar CH); 126.40 (Ar CH); 125.01 (Ar CH); 124.31 (Ar CH); 109.14 (Ar CH); 47.72 (CH_2); 40.92 (C); 39.18 (CH_3); 36.60 (CH_2); 29.20 (CH_3)

MS (ESI): 282 (94); 267 (89); 221 (42); 203 (78); 189 (49); 91 (100)

HRMS (ESI): Calculated for [$C_{17}H_{18}N_2O_2$] (M): 282.136828; found: 282.136935

4-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-6-carbonitrile (222)



Synthesised according to the general procedure and using a 85:15 mixture of hexane/ethyl acetate as eluant for column chromatography. **222** was obtained (10 mg, 20%) as a clear oil

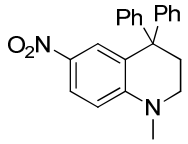
^{1}H NMR: ($CDCl_3$; 500 MHz): 7.23-7.15 (m, 4H); 7.15-7.10 (m, 1H); 7.00 (d, J=7.5 Hz, 2H); 6.40 (d, J=8.3 Hz, 1H); 4.44 (br s, 1H); 3.27-3.18 (m, 1H); 3.00-2.91 (m, 1H); 2.13-2.06 (m, 1H); 1.90-1.81 (m, 1H); 1.63 (s, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 148.34 (Ar C); 147.81 (Ar C); 132.92 (Ar CH); 131.42 (Ar CH); 128.36 (Ar CH); 127.69 (Ar C); 126.93 (Ar CH); 126.30 (Ar CH); 120.93 (Ar C); 113.66 (Ar CH); 97.89 (Ar C); 40.52 (C); 38.20 (CH_2); 37.01 (CH_2); 28.79 (CH_3)

MS (ESI): 248 (84); 233 (100); 169 (26); 155 (39); 91 (30)

HRMS (ESI): Calculated for [$C_{17}H_{16}N_2Na$] (M+Na^+): 271.120565; found: 271.120573

1-methyl-6-nitro-4,4-diphenyl-1,2,3,4-tetrahydroquinoline (223)



Synthesised according to the general procedure and using a 9:1 mixture of hexane/ethyl acetate as eluant for column chromatography. **223** was obtained (39 mg, 68%) as a yellow oil

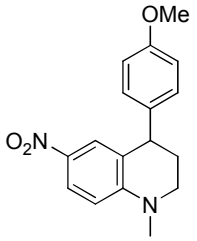
^{1}H NMR: ($CDCl_3$; 500 MHz): 8.09 (dd, J=2.6 and 9.2 Hz, 1H); 7.44 (d, J=2.6 Hz, 1H); 7.36-7.26 (m, 6H); 7.06-6.89 (m, 4H); 6.57 (d, J=9.2 Hz, 1H); 3.20 (t, J=6 Hz, 2H); 3.00 (s, 3H); 2.73 (t, J=6 Hz, 2H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 150.74 (Ar C); 145.55 (Ar C); 136.23 (Ar C); 128.86 (Ar CH); 128.44 (Ar CH); 127.37 (Ar C); 126.95 (Ar CH); 126.78 (Ar CH); 125.29 (Ar CH); 109.08 (Ar CH); 51.29 (C); 47.94 (CH_2); 38.96 (CH_3); 34.15 (CH_2)

MS (ESI): 344 (100); 314 (84); 265 (77); 235 (73); 189 (51); 91 (58)

HRMS (ESI): Calculated for [$C_{22}H_{20}N_2O_2$] (M): 344.152476; found: 344.152682

4-(4-methoxyphenyl)-1-methyl-6-nitro-1,2,3,4-tetrahydroquinoline (224)



Synthesised according to the general procedure and using a 9:1 mixture of hexane/ethyl acetate as eluant for column chromatography. **224** was obtained (18 mg, 30%) as a yellow oil

^{1}H NMR: ($CDCl_3$; 300 MHz): 7.95 (dd, J=2.7 and 9.2 Hz, 1H); 7.61 (dd, J=0.7 and 2.7 Hz, 1H); 6.93-6.85 (m, 2H); 6.81-6.74 (m, 2H); 6.48 (d, J=9.2 Hz, 1H); 3.99 (app t, J=5.5 Hz, 1H); 3.72 (s, 3H); 3.36-3.16 (m, 2H); 3.00 (s, 3H); 2.18-1.93 (m, 2H)

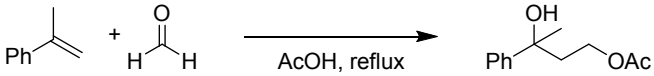
^{13}C NMR: ($CDCl_3$; 75 MHz): 158.43 (Ar C); 151.10 (Ar C); 136.73 (Ar C); 136.11 (Ar C); 129.15 (Ar CH); 125.85 (Ar CH); 124.95 (Ar CH); 123.94 (Ar C); 114.12 (Ar CH); 109.02 (Ar CH); 55.27 (CH_3); 48.29 (CH_2); 42.08 (CH_3); 39.10 (CH); 29.60 (CH_2)

MS (ESI): 298 (100); 189 (98); 121 (22)

HRMS (ESI): Calculated for [$C_{17}H_{18}N_2O_3Na$] ($M+Na^+$): 321.120959; found: 321.120738

7.5.3 Mechanistic experiments

3-hydroxy-3-phenylbutyl acetate (225)

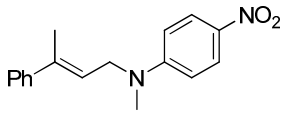


Synthesized according to the report of Thompson.[90]

In a flask, α-methyl styrene (1.95 mL, 15 mmol) and paraformaldehyde (540 mg, 18 mmol) were dissolved in acetic acid. The resulting mixture was heated to reflux for one hour. After cooling, acetic acid was removed under vacuum and the oily residue subjected to column chromatography using a 9:1 mixture of hexane/ethyl acetate as eluant to afford a 1:0.5 mixture of **225** and an elimination product which could not be separated. The mixture was used directly for further reactions.

The identity of **225** was confirmed by comparing with the reported spectroscopic data.

(E)-N-methyl-4-nitro-N-(3-phenylbut-2-enyl)aniline (227)



In a 4 mL screw-cap vial, the mixture of 225 obtained previously (100 mg, 0.5 mmol) was dissolved in acetonitrile (2.5 mL) and *para*-nitro-N-methyl aniline (38 mg, 0.25 mmol) added, followed by para-toluene sulfonic acid (4.75 mg, 0.025 mmol). The reaction mixture was heated to 50°C and let to react overnight. The reaction mixture was then diluted, silica added and solvents evaporated under vacuum. The resulting yellow powder was subjected to column chromatography using a 9:1 mixture of hexane/ethyl acetate as eluant. **227** (6 mg, 9%) was obtained as yellow oil.

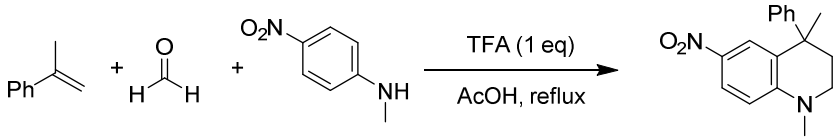
^{1}H NMR: ($CDCl_3$; 500 MHz): 8.05 (d, J=9.4 Hz, 2H); 7.31-7.27 (m, 2H); 7.27-7.21 (m, 2H); 7.21-7.16 (m, 2H); 6.58 (d, J=9.4 Hz, 2H); 5.64 (td, J=1.1 and 6 Hz, 1H); 4.16 (d, J=6 Hz, 2H); 3.06 (s, 3H); 2.09 (d, J=1 Hz, 3H)

^{13}C NMR: ($CDCl_3$; 125 MHz): 153.62 (Ar C); 142.42 (Ar C); 138.79 (Ar C); 137.11 (C); 128.38 (Ar CH); 127.50 (Ar CH); 126.25 (Ar CH); 125.65 (Ar CH); 122.60 (Ar CH); 110.61 (CH); 51.17 (CH_2); 38.57 (CH_3); 16.25 (CH_3)

MS (ESI): 282 (24); 267 (10); 131 (100); 91 (21)

HRMS (ESI): Calculated for [$C_{17}H_{18}N_2O_2Na$] ($M+Na^+$): 305.126046; found: 305.126260

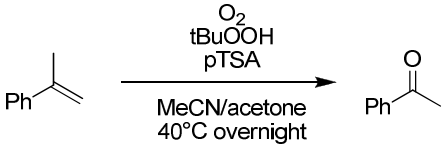
Synthesis of 220 from formaldehyde



In a 4 mL screw-cap vial, *para*-nitro-N-methyl aniline (38 mg, 0.25 mmol) α-methyl styrene (97.2 µL, 0.75 mmol) and paraformaldehyde (37% solution in water, 60 µL, 0.75 mmol) were dissolved in acetonitrile (0.7 mL). The reaction mixture was stirred at room temperature overnight, diluted, silica added and solvents were removed under vacuum. The resulting yellow powder was subjected to column chromatography using a 9:1 mixture of hexane/ethyl acetate as eluant to afford **220** (49 mg, 70%) as a yellow oil.

Analytical data matched with the product obtained *via* the other method.

Cleavage of α-methyl styrene to acetophenone.

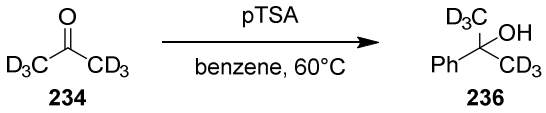


In a 12 mL screw-cap vial, α-methyl styrene (65 µL, 0.5 mmol) was dissolved in a 1:1 mixture of acetonitrile/acetone (5 mL), tBuOOH (5.5M solution in decane, 182 µL, 1 mmol) was added, followed by *para*-toluene sulfonic acid (9.5 mg, 0.05 mmol). The resulting mixture was heated to 40°C and let to react overnight. The reaction mixture was diluted, silica added and solvents were carefully evaporated. The resulting powder was subjected to column chromatography using a 98:2 mixture of pentane/ethyl acetate to afford acetophenone (38 mg, 63%) as a clear oil.

The identity of the isolated compound was confirmed by comparing its spectroscopical data with an authentic sample.

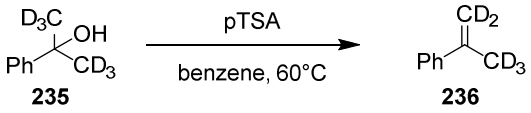
7.5.4 Deuterium Labeling Experiments

d6-2-Phenylpropan-2-ol (235)



In a 2-necked flask equipped with a dropping funnel, d6-acetone (1.5 g, 23.5 mmol) was dissolved in dry Et_2O (40 mL) under argon, phenyl magnesium bromide (2.8M in Et_2O, 9.5 mL, 27 mmol) is slowly added at 0°C over 15 minutes. The resulting mixture was allowed to stir at room temperature for 3.5 hours then a saturated solution of NH4Cl (10 mL) was slowly added at 0°C. Et_2O (100 mL) was added and the resulting mixture washed with brine and water (100 mL each) in an extraction funnel. The resulting ethereal solution was dried over Na2SO4, concentrated and subjected to column chromatography using a 9:1 mixture of pentane/ethyl acetate as eluant to afford **235** as a clear liquid (1.75 g, 52%)

d5-α-methyl styrene (236)

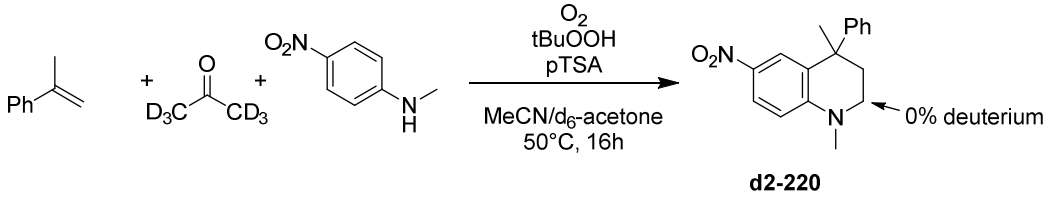


In a 12 mL screw-cap vial, **235** (1g, 7 mmol) was dissolved in benzene (5 mL) and para-toluene sulfonic acid (100 mg, 0.5 mmol) added. The resulting mixture was heated to 60°C

and let to react for one hour. After cooling, the reaction was transferred to an extraction funnel and washed with brine and distilled water (5 mL each). The organic phase was dried over Na_2SO_4 and subjected to column chromatography using pentane as eluant to afford **236** (350 mg, 40%) as a clear liquid.

The deuterium content was found by ^1H NMR spectroscopy to be more than 98% by comparison with an authentic sample of α-methyl styrene.

d2-1,4-dimethyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline (d2-220)

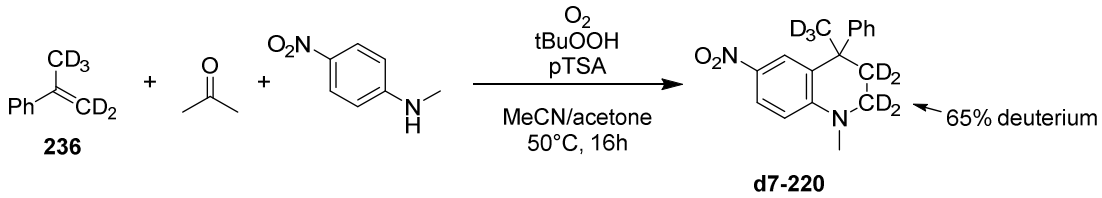


d2-220

In a 12 mL screw-cap vial, α-methyl styrene (260 µL, 2 mmol) and *para*-nitro aniline (76 mg, 0.5 mmol) were dissolved in a 1:1 mixture of acetonitrile/d6-acetone (5 mL). tBuOOH (5.5M solution in decane, 182 µL, 1 mmol) and *para*-toluene sulfonic acid (9.5 mg, 0.05 mmol) were added. The vial was flushed with O_2 and connected to an O_2 balloon. The resulting mixture was let to react at 50°C for 24 hours. The mixture was then diluted, silica was added and the solvents removed under vacuum. The resulting yellow powder was subjected to column chromatography using a 9:1 mixture of hexane/ethyl acetate as eluant to afford **d2-220** (61 mg, 49%) as a yellow oil.

By comparison with a sample of **220**, the deuterium content was determined by ^1H NMR spectroscopy and found as 0% as shown on the reaction scheme.

d7-1,4-dimethyl-6-nitro-4-phenyl-1,2,3,4-tetrahydroquinoline (d7-220)



236 **d7-220**

In a 12 mL screw-cap vial, **236** (246 mg, 2 mmol) and *para*-nitro aniline (76 mg, 0.5 mmol) were dissolved in a 1:1 mixture of acetonitrile/acetone (5 mL). tBuOOH (5.5M solution in decane, 182 µL, 1 mmol) and *para*-toluene sulfonic acid (9.5 mg, 0.05 mmol) were added. The vial was flushed with O_2 and connected to an O_2 balloon. The resulting mixture was let to react at 50°C for 24 hours. The mixture was then diluted, silica was added and the solvents

removed under vacuum. The resulting yellow powder was subjected to column chromatography using a 9:1 mixture of hexane/ethyl acetate as eluant to afford **d7-220** (68 mg, 47%) as a yellow oil.

By comparison with a sample of **220**, the deuterium content was determined by ^{1}H NMR spectroscopy and found as 65% as shown on the reaction scheme.

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9 APPENDIX

9.1 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 – abgesehen von unten angegebenen Teilpublikationen – noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn PD Dr. Martin Klußmann betreut worden.“

Mülheim an der Ruhr, April 2014

Bisher sind folgende Teilpublikationen veröffentlisht worden:

Brønsted Acid Catalyzed C–H Functionalization of *N*-Protected Tetrahydroisoquinolines via Intermediate Peroxides: B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666-671.

Synergistic Effect of Ketone and Hydroperoxide in Brønsted Acid Catalyzed Oxidative Coupling Reactions: B. Schweitzer-Chaput, A. Sud, Á. Pintér, S. Dehn, P. Schulze, M. Klussmann*, Angew. Chem., Int. Ed.* **2013***, 52, 13228-13232; Angew. Chem.* ***2013****, 125, 13470-13474.*

Acid Catalysed Oxidative Radical Addition of Ketones to Olefins: B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem., Int. Ed.* **2014***, accepted manuscript (*DOI: 10.1002/anie.201401062); *Angew. Chem.* ***2014****, accepted manuscript* (DOI: 10.1002/ange.201401062

9.2 Lebenslauf

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