C–H Functionalization *Via* Photochemically Generated Peroxides: Method Development and Mechanistic Studies

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Abstract

The goal of the thesis was to explore the feasibility of C–H functionalization *via* photochemically generated hydroperoxides. A practical method for the C–H functionalization of tetrahydrocarbazole derivatives *via* intermediate hydroperoxides with the aid of oxygen, visible light and catalytic amounts of a cheap Brønsted acid and a sensitizer has been developed. The reaction can be run in two steps or in a one-pot fashion, does not require synthetic oxidants, expensive metal catalysts, elevated temperatures or protective groups and can afford the coupling products in high yields within 5–6 hours. The developed methodology has also been applied to the synthesis of some representative pharmaceutically active compounds. The detailed investigations of the reaction mechanism explained the exclusive C–H amination in the 1-position of the tetrahydrocarbazole scaffold and also proved that a hydroperoxide moiety can be used as leaving group under optimized acidic conditions.

Das Ziel der Arbeit war es, die Machbarkeit der C–H Funktionalisierung über photochemisch erzeugte Hydroperoxide zu untersuchen. Eine praktische Methode für die C–H Funktionalisierung von Tetrahydrocarbazolderivaten mittels intermediär gebildeten Hydroperoxiden unter der Verwendung von Sauerstoff, sichtbarem Licht, einem Sensibilisator und katalytischer Mengen an Brønsted-Säure wurde entwickelt. Die Reaktion kann sowohl zweistufig als auch als Eintopfreaktion durchgeführt werden und erfordert weder die Verwendung von synthetischen Oxidationsmitteln, teuren Metallkatalysatoren oder erhöhte Temperaturen, die Produkte werden in hohen Ausbeuten nach 5-6 Stunden erhalten. Die entwickelte Methode konnte weiterhin für die Synthese einiger pharmazeutisch aktiver Verbindungen genutzt werden. Die detaillierte Untersuchung des Reaktionsmechanismus erklärt die exklusive C–H Aminierung in der 1–Position des Tetrahydrocarbazol–Gerüsts und belegt, dass die Hydroperoxid–Gruppe unter optimierten sauren Bedingungen als Abgangsgruppe genutzt werden kann.

List of abbreviations

Ac	Acetyl
acac	Acetylacetonate
BHT	Butylated hydroxy toluene
Boc	*t*-Butyloxycarbonyl
Bz	Benzoyl
Bn	Benzyl
DCA	1,9-Dicyanoanthracene
DMAc	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
$DMSO_2$	Dimethyl sulfone
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
FePc	Iron phthalocyanine
HSAB	Hard and soft acid and base
HCV	Hepatitis-C-Virus
HPV	Human papillomavirus
$LiAH_4$	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LED	Light emitting diode
MA	Maleic Anhydride
MsOH	methanesulfonic acid

MeOH	methanol
Me	Methyl
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium-*p*-toluenesulfonate
Pv	Pivaloyl
Py	Pyridine; Solvent, base, catalyst
PTSA	*p*-toluene sulfonic acid
RT	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBHP	*t*-Butylhydroperoxide
TEA	Triethylamine
Tf	Triflate (Trifluoromethanesulphonate)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TfOH	trifluoromethanesulfonic acid
TPP	meso-Tetraphenylporphyrin
VEGF	Vascular endothelial growth factor

Anerkennung

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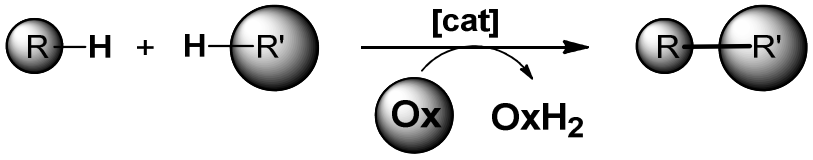
1 Introduction

The development of novel methods for forming new bonds plays a crucial role in the field of organic synthesis. Nucleophilic additions, substitutions, and Friedel-Craft-type reactions are common methods for connecting two different molecular frameworks. These methods usually require the prefunctionalization of the two coupling partners.[1]

Moreover, the efficiency and the scope of organic chemistry reactions was greatly extended by the development of pericylic reactions and transition metal catalyzed coupling reactions.[1] Transition metal catalyzed reactions have attracted much attention in recent years.[1] Richard Heck,[2] Ei-ichi Negishi[3] and Akira Suzuki[4] revolutionized cross coupling reactions and, for this reason, have been awarded the noble prize in chemistry in 2010. These reactions have greatly extended the scope of organic synthesis and have been widely applied in the development of pharmaceuticals, agrochemicals and functional materials.[5] However, these reactions also require prefunctionalized building blocks and generate stoichiometric amounts of waste.[6]

On the other hand, the oxidative coupling strategy does not rely on the prefunctionalization of starting materials (Scheme 1).



Scheme 1: General scheme for oxidative coupling reactions

By using a suitable combination of an oxidant and catalyst, new bonds can be formed starting from two C–H bonds or one C–H and one X–H bond.[5a, 7] The use of unfunctionalized starting materials for coupling reactions is enviromentally benign and an atom economical process. It saves steps, time and material and thus is very attractive for green chemistry.[8] The direct oxidative coupling of desired fragments provides an attractive alternative to the common multistep techniques.[9] Such chemical field has recently grown exponentially and represents a powerful and attractive strategy for forming new bonds.[5a, 7, 10] C–H bonds are generally less reactive and most organic compounds contain more than

one C–H bond. As a consequence of this, the regioselective functionalization of one C–H bond over the other is the main problem associated with this technique. Very often, the requirement of stoichiometric amounts of synthetic oxidants, expensive reagents and harsh conditions diminishes the overall sustainability of the method.[11]

Therefore, many attempts have been made for developing methods that use cheap catalysts, and environmentally benign oxidants.[12] Sustainable oxidative coupling reactions can be achieved by using oxygen or hydrogen peroxide as terminal oxidant which can potantially produce water or H_2O_2 as the waste products.[7a]

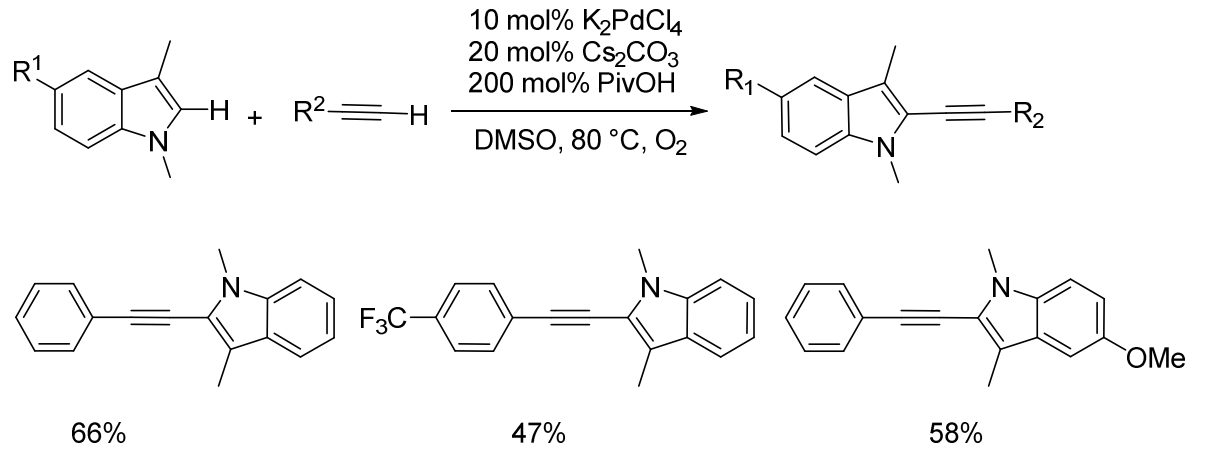
2 Background

2.1 Aerobic oxidative couplings

2.1.1 Oxidative coupling of indole derivatives:

The indole ring key structure is present in optelectronic materials as well as in a large variety of biologically active natural and unnatural compounds.[13] Several methods have been developed for the synthesis of substituted indoles.[14] Synthesis of substituted indoles by oxidative coupling using molecular oxygen as oxidant can represent an appealing alternative, avoiding the need of stoichiometric amounts of synthetic oxidants. A considerable attention has been paid to this strategy in the last few decades.

The research group of Chao-Jun Li has reported a palladium catalyzed direct oxidative Heck-Cassar-Sonogashira type alkynylation of indoles with terminal alkynes by using molecular oxygen as the terminal oxidant. A buffer system composed of 20 mol% Cs_2CO_3 and 200 mol% PivOH was used to aid the deprotonation of terminal alkyne and the reoxidation of Pd^0 to Pd ^{II} (Scheme 2).[15]

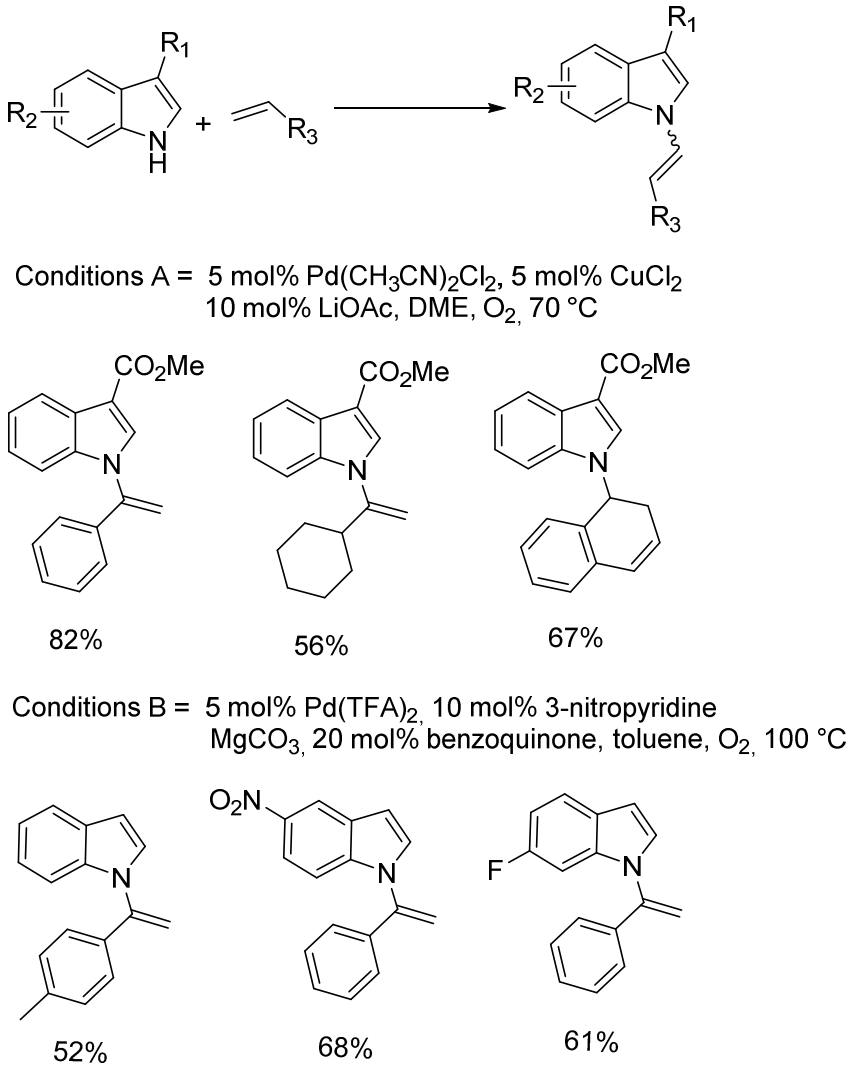


Scheme 2: Alkynylation of indoles with terminal alkynes

Homocoupling of the alkynes was suppressed by its slow addition. However, the reaction is limited to 1,3–dialkyl indoles and good yields were obtained by using electron rich alkynes.

Indoles are known to react through N–H, C–2 and C–3 positions. Therefore, the regioselective alkenylation of free indoles is a long standing goal in organic

chemistry. The research group of Phil S. Baran described the chemoselective *N*-*tert*-prenylation of indoles by using stoichiometric amounts of AgOTf and $Cu(OAc)_2$ as oxidants.[16] Later on, Weiping Su *et al*. have demonstrated that palladium catalyzed regioselective *N*-alkenylation of indoles can be achieved by using molecular oxygen as terminal oxidant. The alkenylation can be achieved with a variety of different alkenes (Scheme 3).



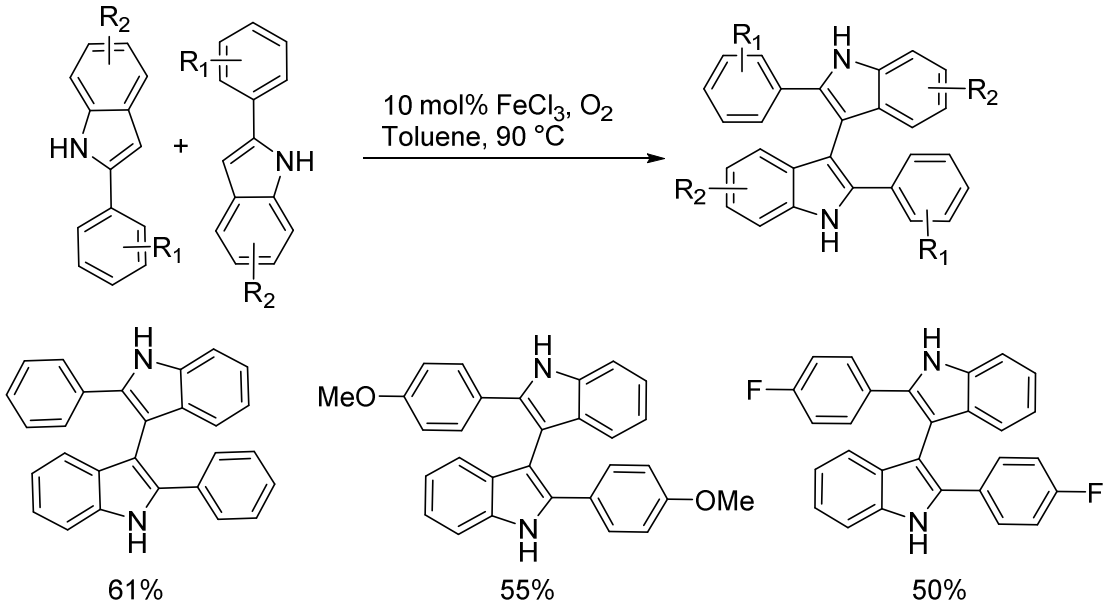
Scheme 3: Regioselective alkenylation of free indoles

Two different sets of protocols have been developed for the direct *N*-alkenylations

of indoles bearing substituents at position-3 (Scheme 3, conditions A) and for indoles lacking substituents at position-3 with different alkenes (Scheme 3, conditions B). [17]

These two protocols complement each other to cover a broad range of substrate scope for both of the coupling partners, and allow this aerobic oxidative cross-coupling to proceed with excellent selectivity in generally good yields.[17]

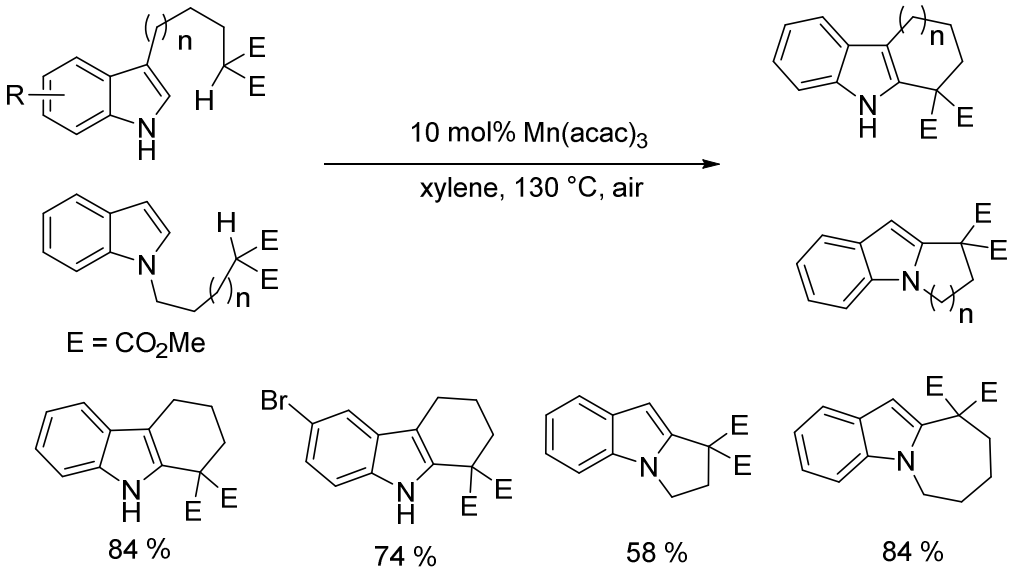
Recently, the research group of Yuhong Zhang has shown that dimerization of indoles can be achieved directly without the need for prefunctionalization by using $FeCl_3$ as catalyst and molecular oxygen as terminal oxidant.[18] The reaction is compatible with different alkyl and halogen groups on the 2-aryl ring of indole. Despite being remarkably effective, the reaction is limited to the presence of aryl group at C-2 position (Scheme 4).[18]



Scheme 4: Dimerization of indoles

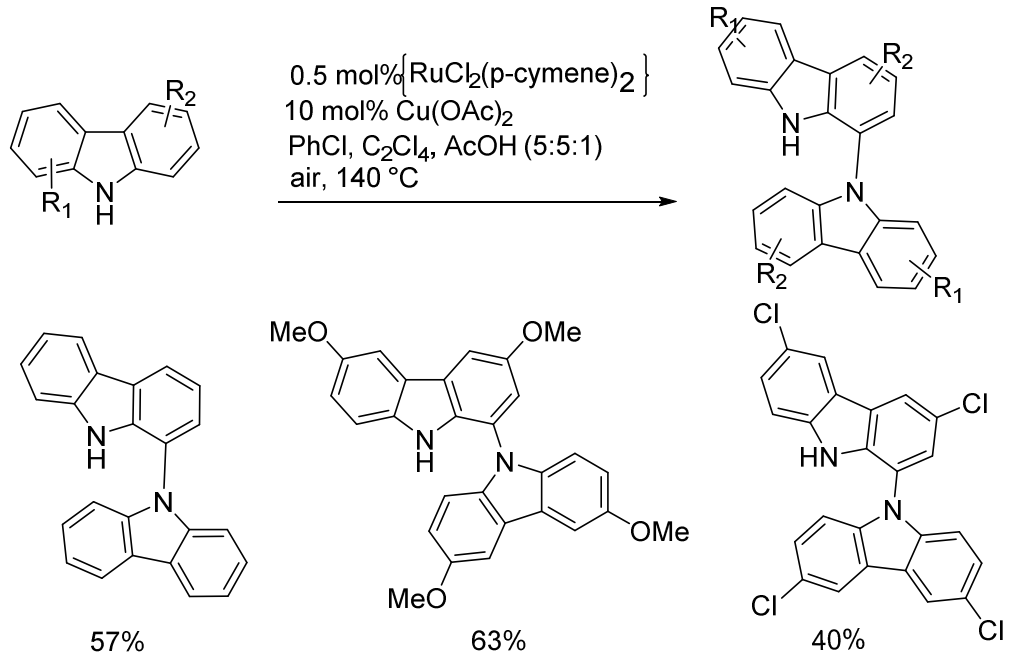
Motomu Kanai *et al*. have utilized molecular oxygen as terminal oxidant for the manganese catalyzed oxidative cyclization between indoles and malonic esters to produce ring fused indole skeletons.[19] Six membered rings are formed in good yields as a result of C-3 to C-2 cyclization. This cyclization leads towards the formation of five and seven membered rings in poor yields.

However, N-1 to C-2 cyclization also yields five membered rings and seven member rings in good yields (Scheme 5).[19]



Scheme 5: Manganese catalyzed dehydrogenative cyclization between indoles and malonic esters; E=CO_2Me

Louillat and Patureau have recently reported a reaction for the homocoupling of carbazoles. The reaction requires the use of oxygen as an oxidant and a mixture of Ru and Cu catalysts (Scheme 6).[20].



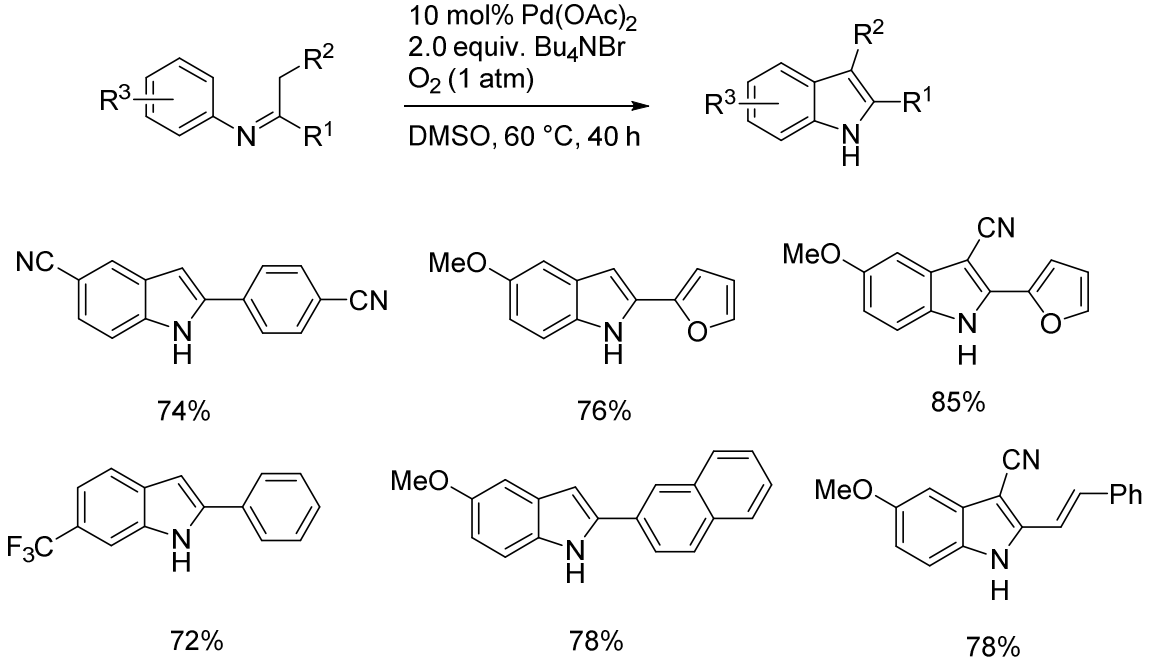
Scheme 6: Regioselective homocoupling of carbazoles

The exact mechanism of the reaction is still not clear. However, the presence of both metals was found to be essential for the bond forming step (Scheme 6).[20] The reaction is limited to homocoupling of carbazoles, requires long reaction time, high temperatues and delivers products in only moderate yields. However, it provides an interesting basis for further developments.

2.1.2 Synthesis of indoles by oxidative coupling reactions

A practical and atom economical synthesis of idoles is highly desired by pharmaceutical and fine chemical industries. The use of anilines as starting material can be very attractive as they are cheap and a vast variety of anilines are commercially available. Well established methods normally require aryl hydrazines (Fischer indole synthesis) and *o*-haloanilines (Larock indole synthesis).[14] In this context a great breakthrough was made by the Glorius group who achieved the synthesis of indoles from anilines and β-dicarbonyl compounds by using palladium as catalyst and $Cu(OAc)_2$ as oxidant.[21]

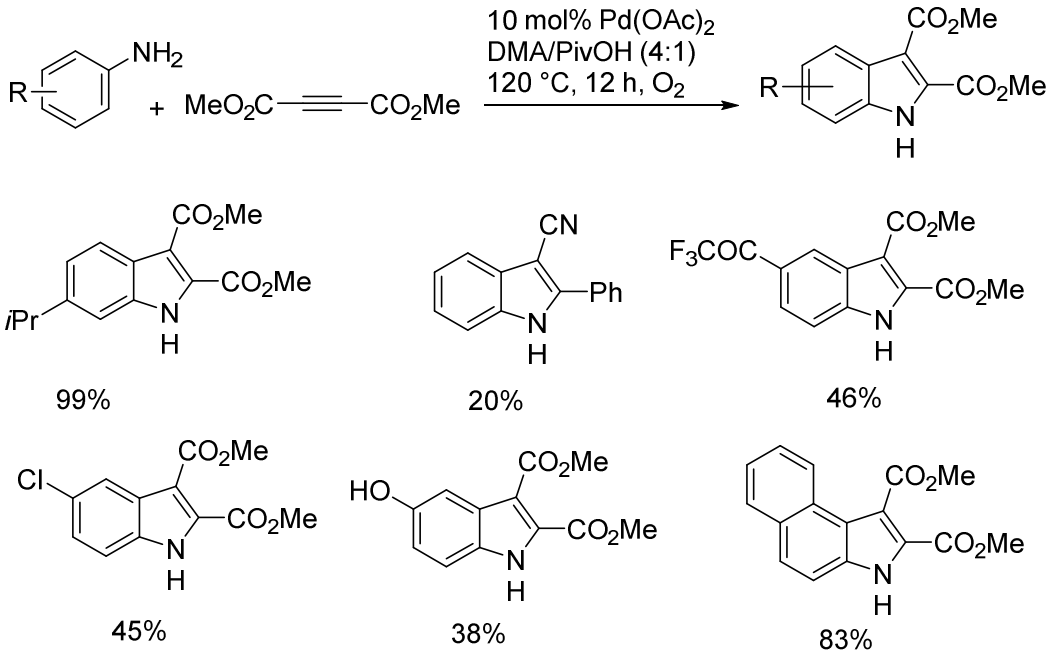
Based upon this pioneering work, Yoshikai *et al.* have developed the aerobic palladium catalyzed synthesis of different indole derivatives through aryl imines by using molecular oxygen as terminal oxidant. The reaction works in two steps starting from readily available anilines and ketones (Scheme 8).



Scheme 7: Synthesis of different indole derivatives through aryl imines

The reaction works well under mild aerobic conditions and is tolerant to the presence of different electron withdrawing, electron donating, and halogenated functional groups. However, the reaction requires stoichiometric amounts of Bu_4NBr and does not give access to *N*-1 and C-2 unsubstituted indoles. (Scheme 8).[13, 22]

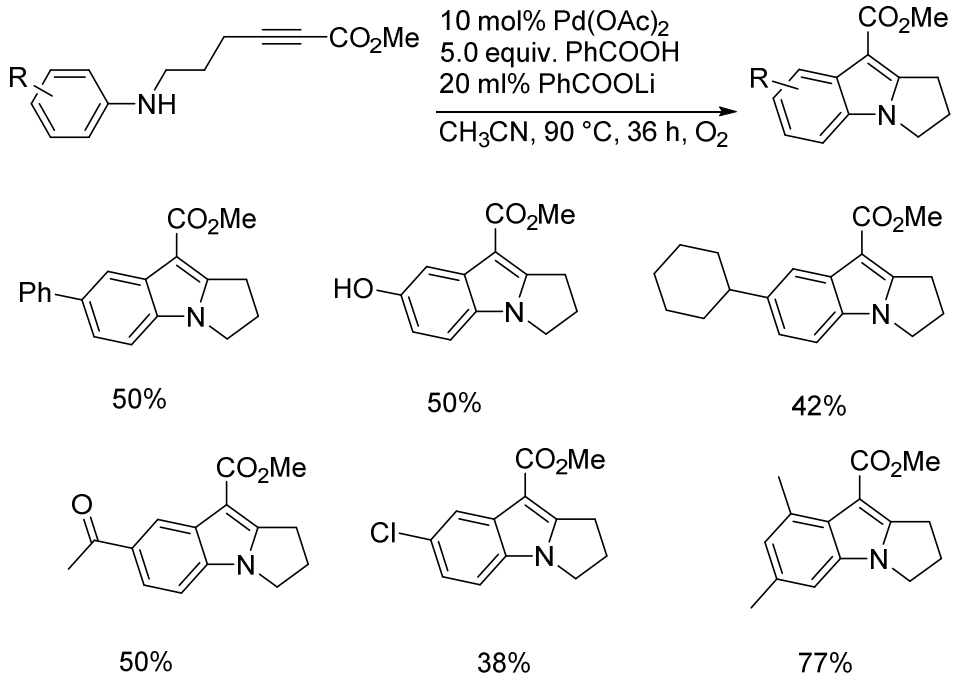
Later on, the research group of N. Jiao has reported the palladium catalyzed one pot synthesis of indoles from simple anilines and disubstituted alkynes (Scheme 8). [23] Additionaly, the reaction requires a combination of dimethylacetamide/pivalic acid (4:1) as solvent and molecular oxygen as sole oxidant. The reaction is compatible with a large variety of anilines and works in good to excellent yields in the presence of different electron donating and electron withdrawing groups. However, the reaction requires disubstituted alkynes having electron withdrawing ester goups (Scheme 8). Poor yields of the coupling product was achieved when ester group on the alkyne was replaced by cyano group.[23]



Scheme 8: Synthesis of indoles from alkynes and aniline

Following this work, N. Jiao *et al*. have demonstrated the aerobic palladium catalyzed synthesis of 1,2,3-trisubstituted indoles through intramolecular hydroamination and C–H functionalization of *N*-alkynyl anilines (Scheme 9). The reaction works in moderate yields with different electron withdrawing and electron donating groups on the benzene ring of aniline. The reaction was tolerant to the

presence of different substituents on benzene ring of aniline. However, the reaction is limited to the below shown substituents at *N*-1, C-2 and C-3 position of indole.[24]

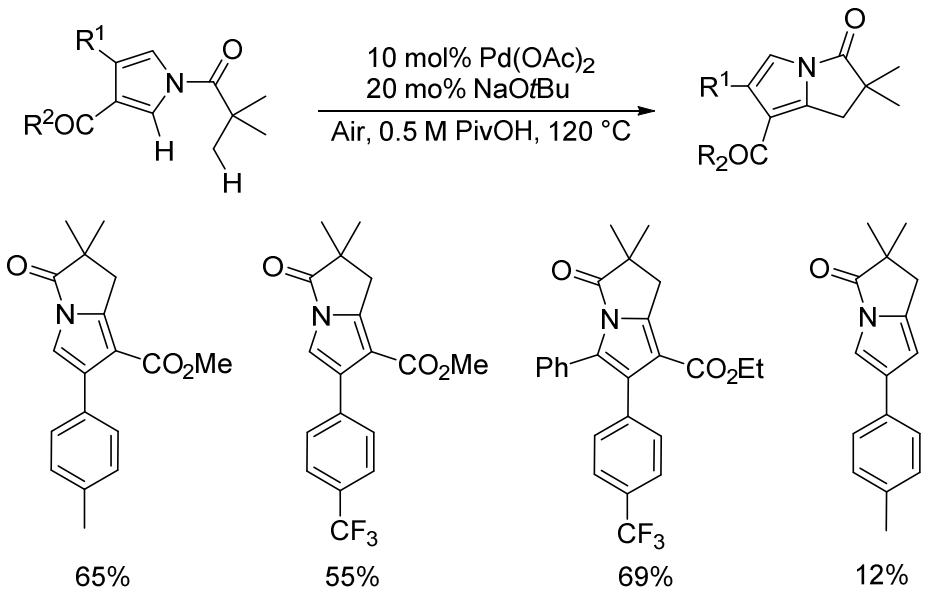


Scheme 9: Synthesis of 1,2,3-trisubstituted indoles

2.1.3 Oxidative coupling with azoles:

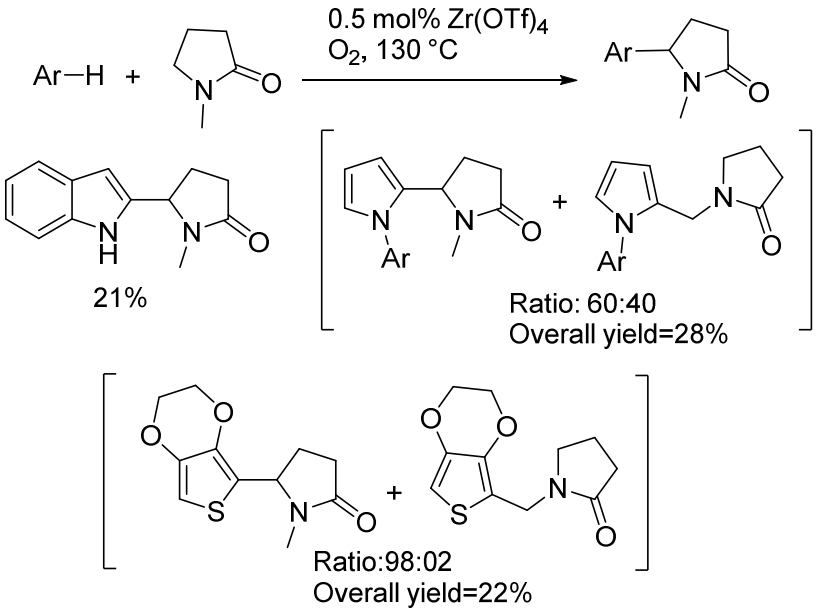
Azole heterocyclic scaffolds are abundant in different biologically active compounds. In recent years, the use of molecular oxygen as terminal oxidant has enabled the oxidative coupling of these aromatic heterocyclic compounds with different coupling partners.

Keith Fagnou *et al*. have described the palladium catalyzed coupling of substituted pyrroles with an unactivated methyl group. The use of air as oxidant at ambient pressure was found to be even more effective than other oxidants such as copper(II) acetate and silver(I) acetate. However, this method is limited to the combined presence of phenyl group and an electron withdrawing group on pyrrole ring. The removal of either of these groups results in the lowering of the yield (Scheme 10).[25]



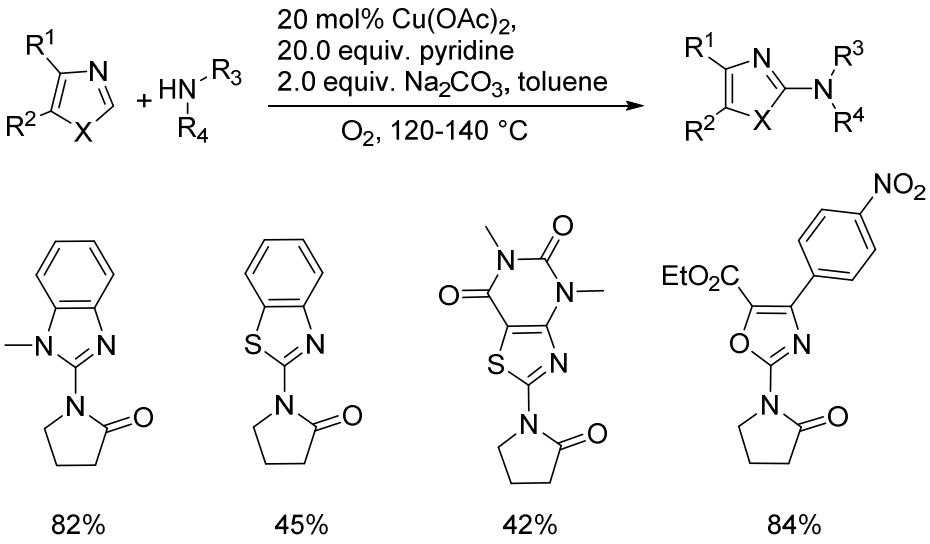
Scheme 10: Coupling of substituted pyrroles with an unactivated methyl group

Yusuke Kawakami *et. al*. have reported the only single example of Lewis acid catalyzed oxidative coupling reactions of heterocyclic compounds with lactams using oxygen as terminal oxidant.[26] *N*-methyl pyrrolidinone could be coupled with electron rich aromatic nucleophiles in moderate yields under an atmosphere of oxygen at 130°C. The reaction works with poor yields but low loading of the catalyst was used in comparison to most of the other examples presented here (Scheme 11).[26]



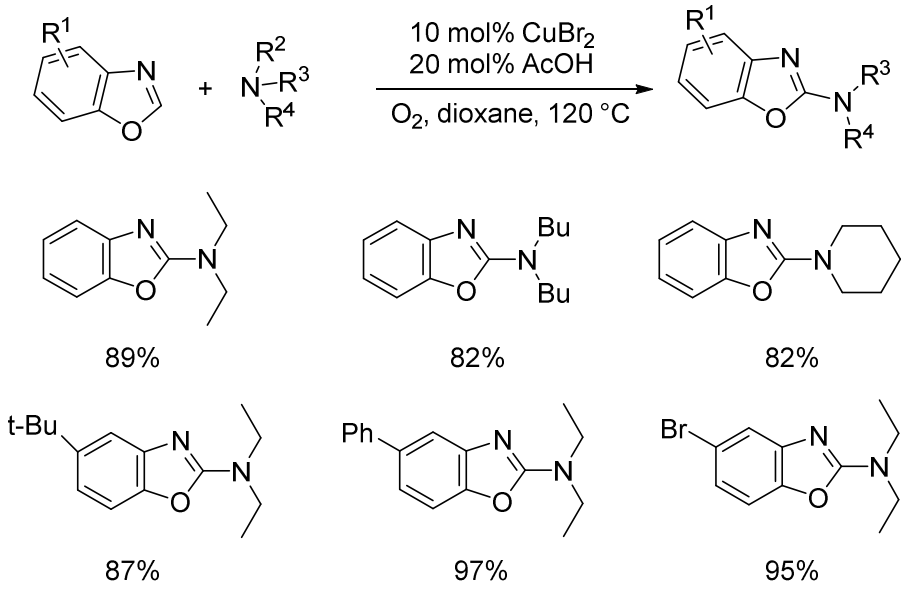
Scheme 11: Oxidative coupling of heterocyclic compounds with lactams

In 2011, the research group of Atsunori Mori described the aerobic copper catalyzed oxidative amination of azoles with different cyclic and acyclic secondary amines.[27] After this pioneering work by Mori, the aerobic copper catalyzed coupling of 2-benzimidazoles and caffeine with cyclic amides, urea, carbamates and sulfonamides has been achieved by Stuart L. Schreiber et al (Scheme 11).[28]



Scheme 12: Oxidative amination of azoles with different amides

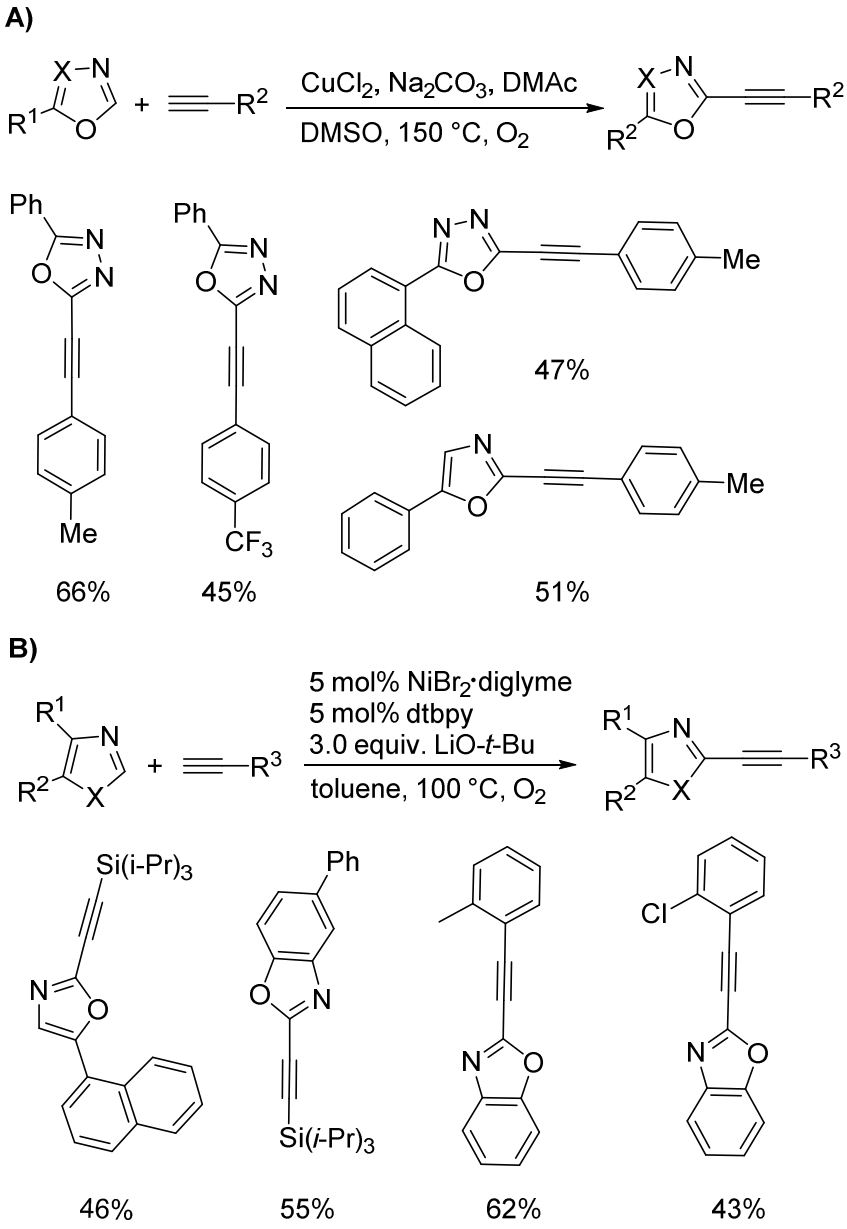
Hanmin Huang *et al*. have recently furnished the oxidative amination of azoles by using tertiary amines as nitrogen source (Scheme 13).[29] The reaction proceeds under aerobic conditions by using catalytic amounts of $CuBr_2$ and acetic acid *via* the cleavage of C–H and C-N bonds. The products are delivered in good yields with almost all the tertiary amines bearing α-H adjacent to the nitrogen atom. The yield of the reaction is not affected by the presence of different halogens, aryl and alkyl groups on benzoxazole. However, poor yield was obtained by the presence of strongly electron withdrawing nitro group on the benzene ring of benzoxazole (Scheme 13).[29]



Scheme 13: Oxidative amination of azoles by using tertiary amines as nitrogen source

The combination of Cu/O_2 was also found to be attractive for other transformations like cross coupling of azoles with terminal alkynes. The research group of Mashahiro Miura has described the aerobic copper mediated oxidative cross coupling of 1,3,4-oxadiazole and oxazole with terminal alkynes.[30] The reaction works smoothly with terminal alkynes bearing electron donating group. However, lower yields were obtained by the introduction of electron withdrawing group on the alkyne. The yield of the reaction is not strongly affected by the presence of electron withdrawing, electron donating and sterically more demanding groups on azole ring (Scheme 14A).[30] The reaction failed to give the desired products under N_2 atmosphere showing that the presence of O_2 is necessary and it might work as terminal oxidant.

Although, the reaction provides a straightforward access to arylacetylenes, yet the use of stoichiometric amounts of copper diminishes the overall sustainability of the reaction. Later on, Miura *et al*. found that use of stoichiometric amounts of copper can be avoided by using 5 mol% of $NiBr_2$ as catalyst (Scheme 14B).[31]

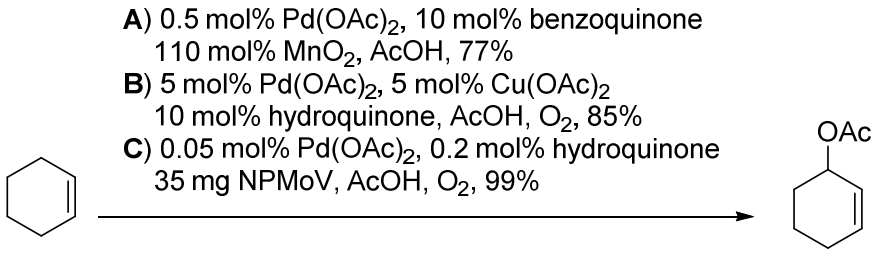


Scheme 14: Oxidative cross coupling of azoles with terminal alkynes

Followed by the pioneering work of Miura, the research group of Sukbok Chang has accomplished the oxidative alkynylation of azole heterocycles by using catalytic amounts of palladium in combination with oxygen as terminal oxidant.[32]

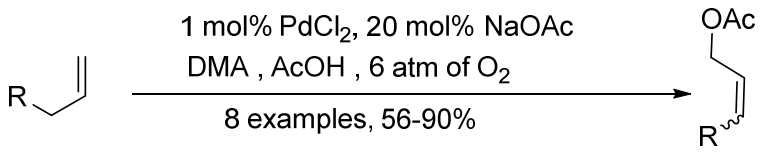
2.1.4 Allylic activation:

In 1973, Barry M. Trost showed that allylic alkylation of non-functionalized alkenes can be achieved by using stoichiometric amounts of palladium.[33] This important discovery was of little practical use as non-catalytic use of expensive metal is not cost effective. The catalytic version requires conditions under which the reduced form of catalyst can be re-oxidized again for further participation in the reaction. Björn Åkermark showed in 1989 that allylic activation of non-activated olefins can be achieved by using catalytic amounts of palladium, but this required stoichiometric amounts of MnO_2 as oxidant (Scheme 23A).[34] Although, it was an important breakthrough yet the excess use of oxidant does not fulfil the demands of sustainable chemistry. Later on, in 1990, the same research group developed an alternative predure for the reoxidation of palladium which was accomplished by a combination of molecular oxygen, benzoquinone and copper acetate. Benzoquinone is suspected to act as reoxidant and ligand to palladium and copper catalyst act as oxidant for hydroquinone (Scheme 23B).[35] The research group of Yasutaka Ishii furnished the same reaction using combination of O_2, ammonium containing molybdovanadophosphate (NPMoV), and hydroquinone for reoxidation of Pd(0) (Scheme 23C).[36]



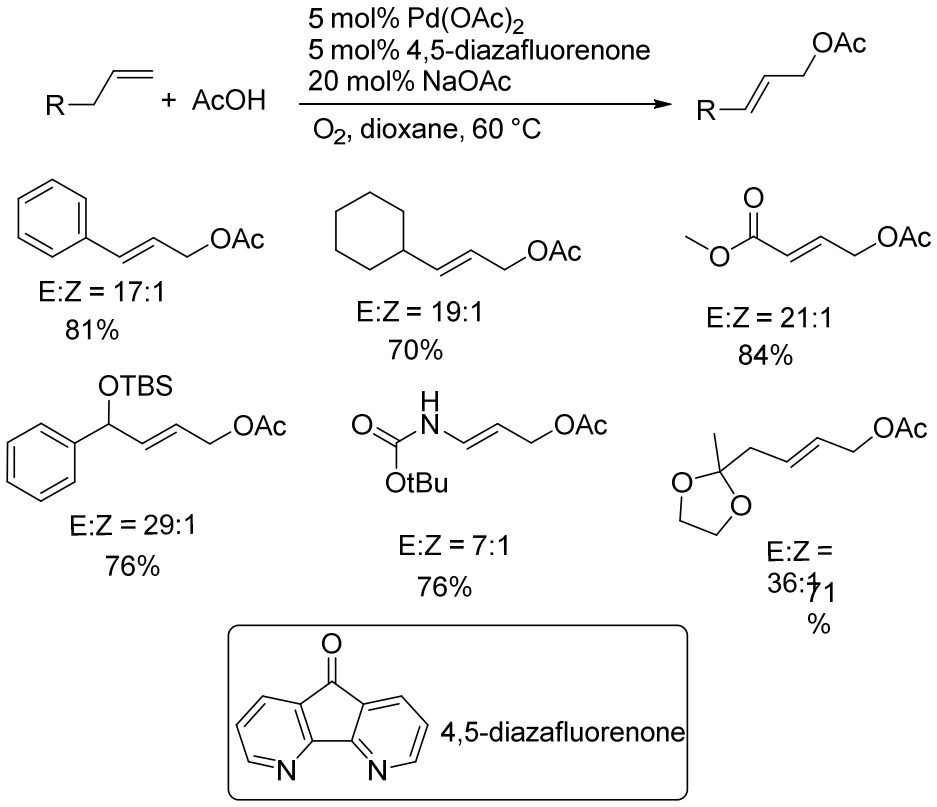
Scheme 15: Allylic C–H acetoxylation

Kiyotomi Kaneda *et al*. have achieved the palladium catalyzed regioselective allylic acetoxylation of terminal olefins to linear allylic acetates without the use of cocatalysts using $PdCl_2$ in DMA under elevated pressure (6 atm) of oxygen. The reaction requires the use of 20 mol% NaOAc in combination with molecular oxygen for reoxidation of palladium (Scheme 16).[37]



Scheme 16: Allylic C–H acetoxylation

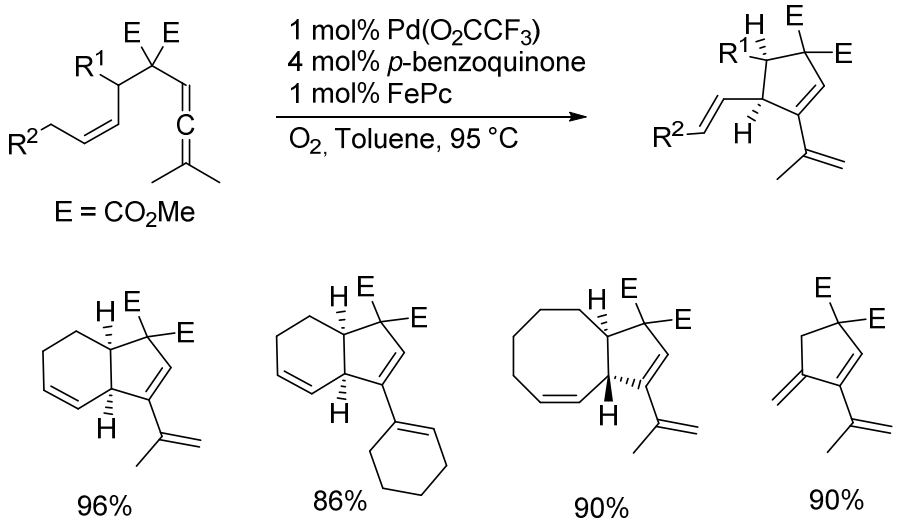
In 2010 Shannon S. Stahl reported that Pd catalyzed allylic C–H acetoxylation can be achieved by using 4,5-diazafluorenone (Scheme 17) as ligand. By this combination of ligand and molecular oxygen, they could successfully avoid the use of benzoquinone, copper acetate and elevated pressure of oxygen which were previously necessary for reoxidation of catalyst. This ligand plays a key role in this transformation. Among different ligands screened for this transformation, only 4,5-diazafluorenone was found to be effective. The reaction is selective for terminal olefins. Nearly all the tested terminal olefins gave linear acetoxylation product in good yields. Silyl ethers, esters, acetals, amides and carbamates were stable against the reaction conditions (Scheme 17).[38]



Scheme 17: Allylic C–H acetoxylation of terminal olefins

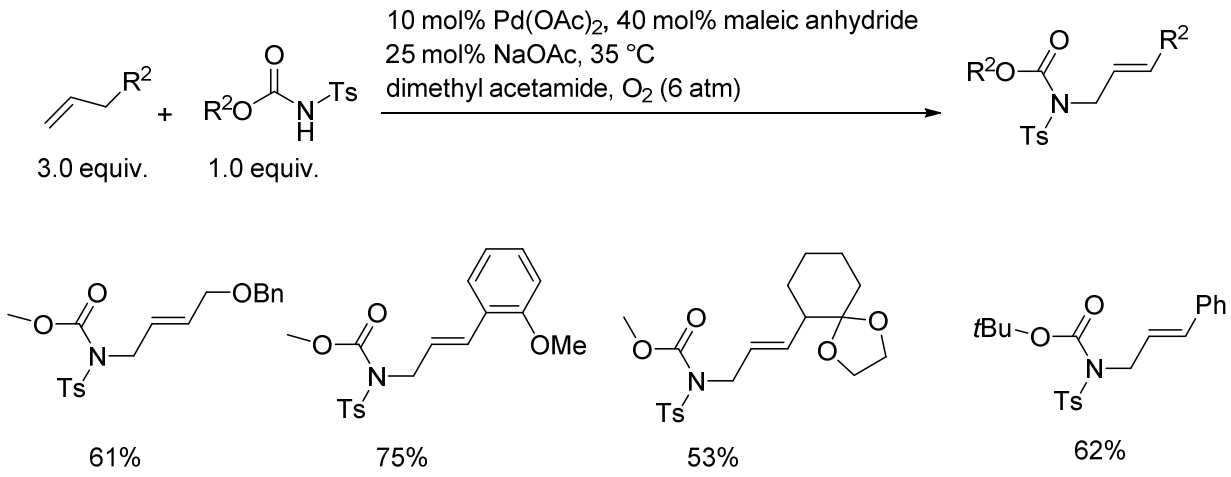
At present there is a lack of efficient C-C bond formation reactions by the aerobic allylic activation of alkenes. Jan-E. Bäckwell *et al*. have reported a palladium catalyzed aerobic oxidative carbocyclization reaction (Scheme 18).[39]

A triple coupled oxidant system consisting of a combination of O_2, iron phthalocyanine (FePc) and benzoquinone was used for the reoxidation of palladium. The reaction leads towards the carbocyclization of allene substituted olefins yielding mono- and bicyclic triene systems. (Scheme 18).[39]



Scheme 18: Carbocyclization of allene substituted olefins

Very few aerobic allylic intermoleculer C–H amination reactions are known. In 2007, the research group of Guosheng Liu described the aerobic palldium catalyzed allylic amination of olefins (Scheme 19).[40] The reaction proceeds in good to excellent yields with a variety of terminal olefins featuring benzyl ether, methyl aryl ether, phthalimidyl, and ketal functional groups. However, the reaction is limited to the presence of olefin in excess (3.0 equivalent) and 25 mol% sodium acetate as cocatalyst. The scope of the reaction is also limited to *N*-tosyl protected cabamates used as amination substrates. Poor yields were obtained by using *N*-tosyl protected amides as coupling partners.[40b]

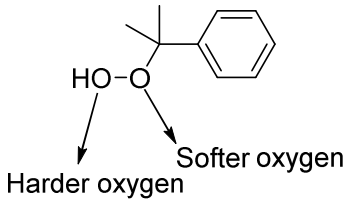


Scheme 19: Areobic allylic amination of olefins

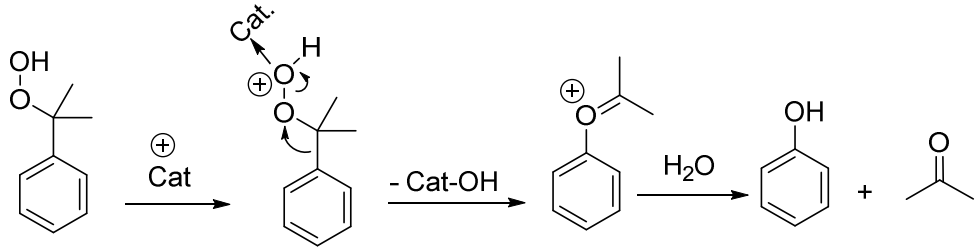
2.1.5 Selected examples of acid catalyzed coupling of peroxides

Hydroperoxides are often formed by the autoxidation of organic molecules.[41] However, hydroperoxides have rarely been used as electrophiles for coupling with different nucleophiles.[42] The research group of Minisci *et al*.[44] showed that cumene hydroperoxide (**1**) could be coupled with other nucleophiles under acidic conditions. They rationalized the selective activation of the oxygens contained in cumene hydroperoxide (**1**) based on hard soft acid base principle.[43] They proposed that the oxygen bound to proton is harder than the oxygen bound to carbon (Scheme 20a).

a) Harder and softer oxygens of cumene hydroperoxide as proposed by Minisci *et al*.



b) Suggested mechanism for Hock rearrangement using Brønsted acids



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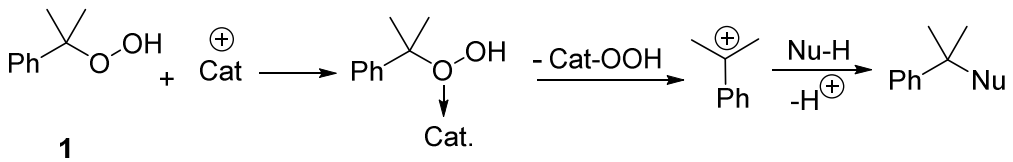
c) Suggested mechanism for substitution reaction using Lewis acids



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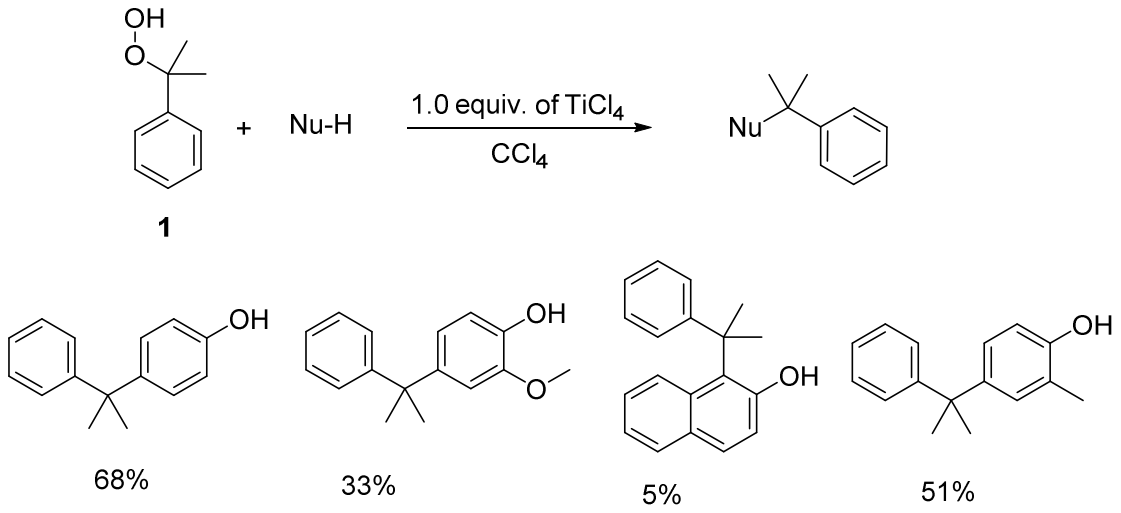
Scheme 20: Suggested mechanism for Hock rearrangement and for substitution reaction based upon HSAB principle.

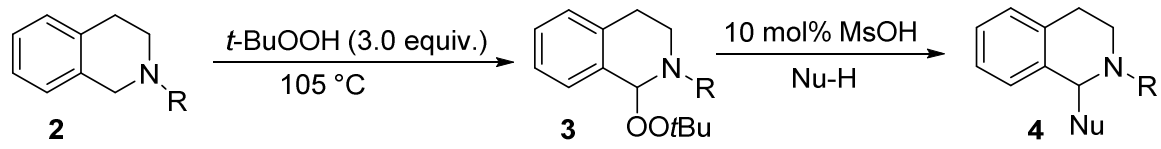
The coordination of hard acid, such as Brønsted acids, with oxygen bound to proton leads to the formation of phenol (Scheme 20b) while preferred coordination of soft acids, such as Lewis acids, with the oxygen directly bound to carbon result mainly in the formation of substitution products (Scheme 20c).[44]

However, the reaction required stoichiometric amounts of metal salts for the substitution of peroxide moiety of cumene hydroperoxide (Scheme 21).[44] Additionally, poor to moderate yields of the coupling products were obtained using this method.



Scheme 21: Substitution of the peroxide moiety of cumene hydroperoxide (1) by using stoichiometric amounts of $TiCl_4$ as catalyst

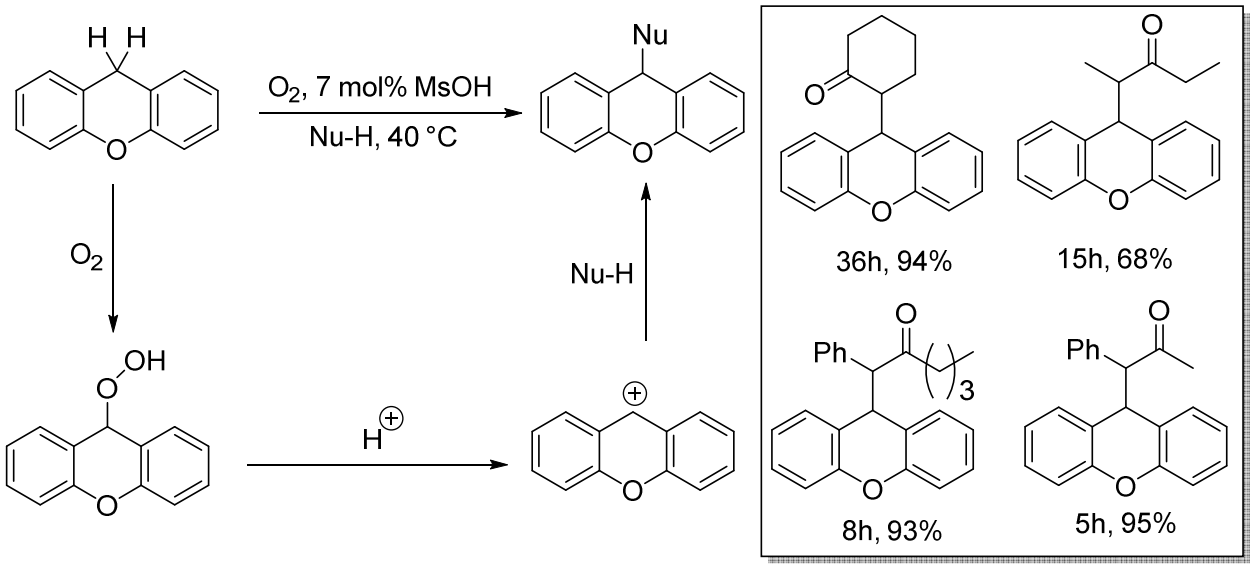
The Klussmann group described the coupling of tetrahydroisoquinoline peroxide **3** with different carbon based nucleophiles in which good to excellent yields of the coupling products could be achieved (Scheme 22).[45] The reaction worked in two separate steps *i.e*. i) the synthesis of peroxide ii) The substitution of peroxide **3** with a wide range of nucleophiles under acidic conditions. However, the reaction was limited to tetrahydroisoquinolines and required stoichiometric amounts of *t*-BuOOH as oxidant. Prior to this work, Murahashi *et al*. also described a similar transformation using stoichiometric amounts of *t*-BuOOH as oxidant and $TiCl_4$ as Lewis acid.[42c, 46]



Scheme 22: General scheme for the introduction of peroxide group followed by the substitution in a separate step

Recently, the Klussmann group discovered an oxidative coupling reaction of xanthene with enolizable ketones. The coupling products were formed by simply

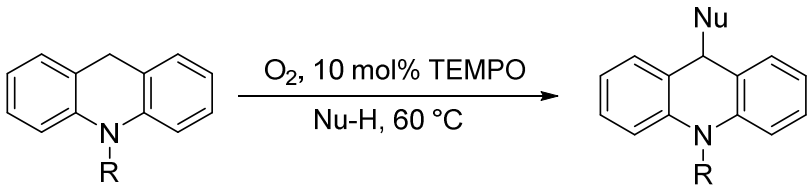
stirring the two coupling partners under air or oxygen in the presence of catalytic amounts of methanesulfonic acid. The reaction was believed to proceed *via* the formation of an intermediate peroxide (Scheme 23).[42b, 47] The reaction proceeds at room temperature and does not require any redox active catalyst



Scheme 23: Aerobic oxidative coupling of xanthene through intermediate hydroperoxide

However the reaction was limited the coupling of xanthene with different ketones and the products have so far not found applications.

The research group of Jiao accomplished the coupling of acridanes with nitroalknes and carbonyl compounds using molecular oxygen as terminal oxidant.[48] The reaction might proceed through the formation of intermediate peroxides. However, the mechanism of the reactions has not been suggested by the authors.



Scheme 24: Aerobic oxidative coupling of acridanes

2.2 Singlet oxygen

2.2.1 Formation of singlet oxygen

Molecular oxygen has two low lying singlet excited states ($^1\Delta_g$, $^1\Sigma_g^+$) above the triplet ground state ($^1\Sigma_g^-$). Singlet oxygen is commonly used for low lying excited state ($^1\Delta_g$) of molecular oxygen (Figure 1). There are several ways of generating singlet oxygen.[49] Photosensitized generation of singlet oxygen is a simple and controllable method[50] as it requires only oxygen, light of suitable wavelength and senstizer capable of absorbing light energy and transferring it to oxygen at ground state.

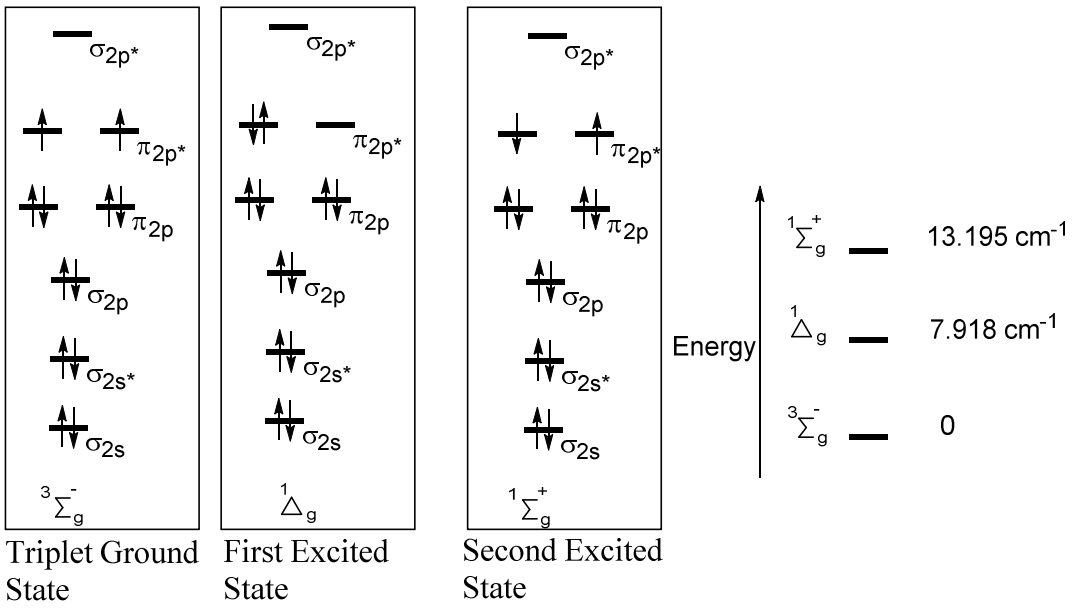


Figure 1: MO diagram of three states of oxygen

Excitation of sensitizer from singlet ground state (S_0) to lowest excited singlet state (S_1) is achieved *via* photon transition. Absorption of two photons can even lead to higher excited state (S_m). Relaxation of higher excited state by internal conversion gives lower excited state (S_0). Then the triplet state (T_1) is generated by intersystem crossing. The longer life time of T_1 as compared to S_1 allows the energy transfer *via* collision of sensitizer with triplet oxygen. Formation of singlet oxygen ($^1\Delta_g$) involves the transfer of energy from excited state of sensitizer to the ground state of oxygen ($^1\Sigma_g^-$). This transfer of energy may also result in the formation of second excited singlet state of oxygen. However, this state is short lived and rapidly decays to first excited state (Figure 2).

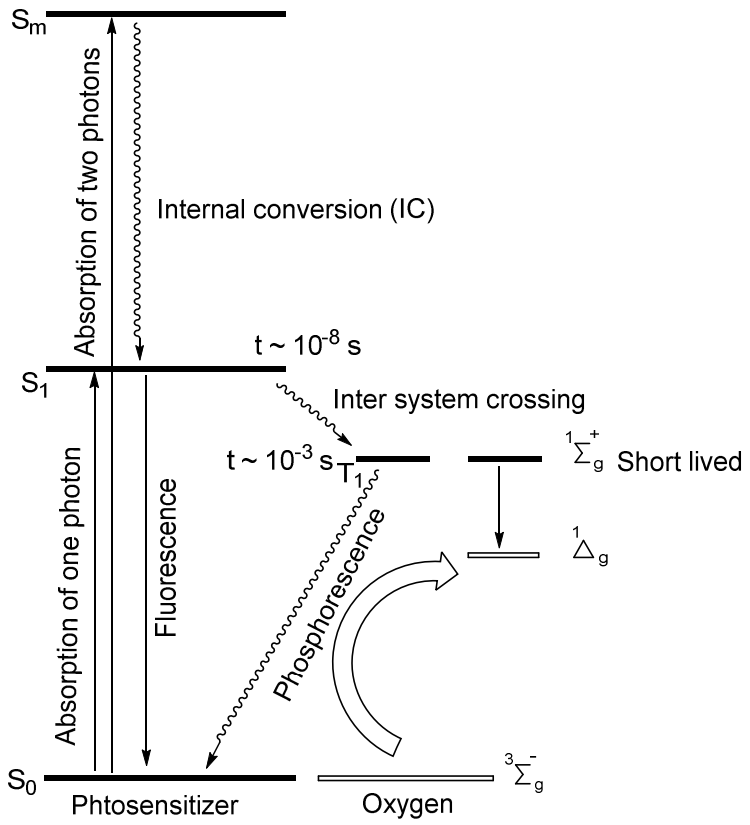
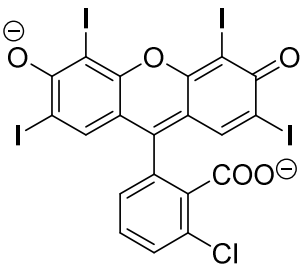
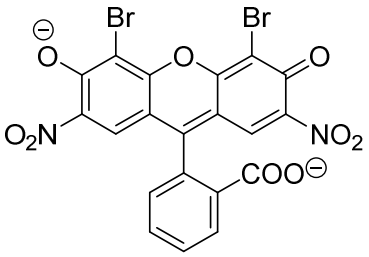


Figure 2: Photosensitized production of $^1O_2$

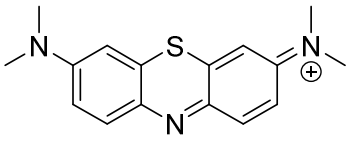
Different dyes as rose bengal, eosin blue and methylene blue, 9,10-dicyanoanthracene, porphyrins, and phthalocyanines, possess triplet states of appropriate energies and are generally used for sensitization of oxygen (Scheme 25).[50]



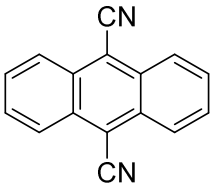
Rose bengal



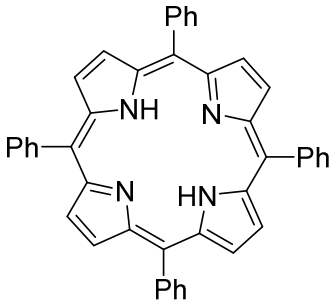
Eosin blue



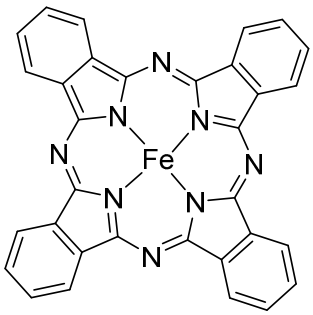
Methylene blue



9,10-dicyanoanthracene



Tetraphenylporphyrin



Iron phthalocyanine

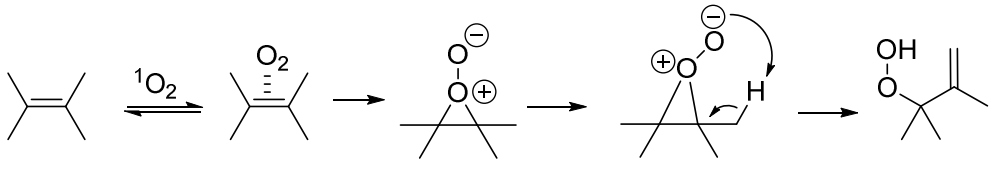
Scheme 25: Commonly used sensitizers

2.2.2 Fundamental reaction types with singlet oxygen

Singlet oxygen can react with different classes of molecules with different mechanisms to give structurally diverse products.[51] Some of the well-known reactions of singlet oxygen are described below.

2.2.2.1 Ene reaction

Alkenes having allylic hydrogens are known to react by ene reaction with singlet oxygen[51a, 51b] and give allylic hydroperoxides by the mechanism shown below (Scheme 26).

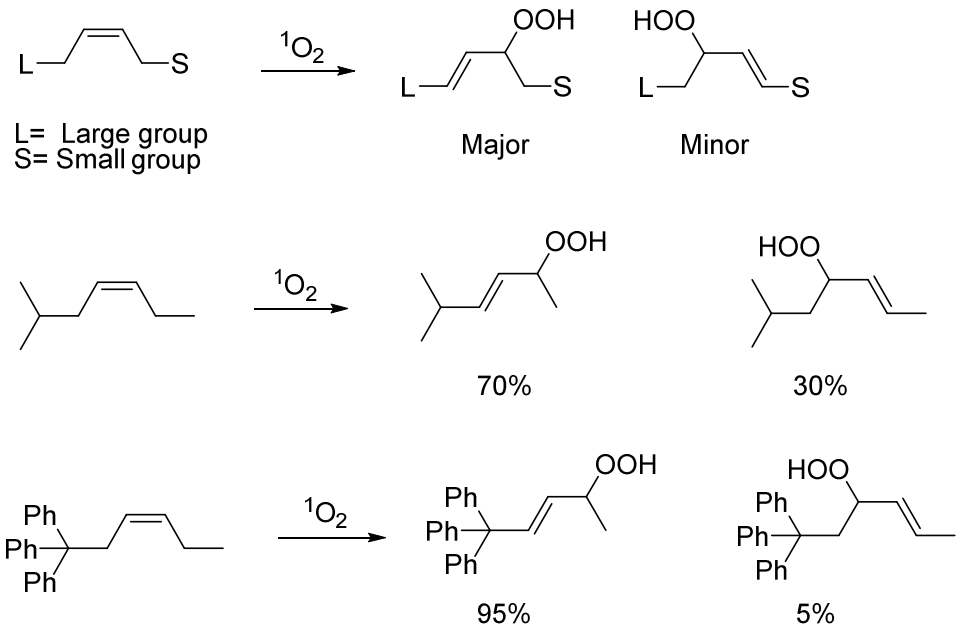


Exciplex

Perepoxide

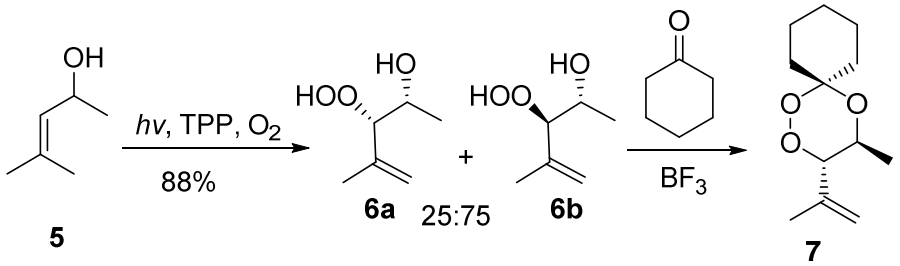
Scheme 26: Mechanism of reaction of $^1O_2$ with alkenes

In case of non-symmetrical *cis* disubstituted alkenes the double bond is preferentially formed next to bulkier group. The repulsive 1,3-non-bonded interactions between large group and oxygen in the intermediate perepoxide were found to be responsible for this regioselectivity (Scheme 27).[51b]



Scheme 27: Regioselectivity with *cis*-disubstituted alkenes

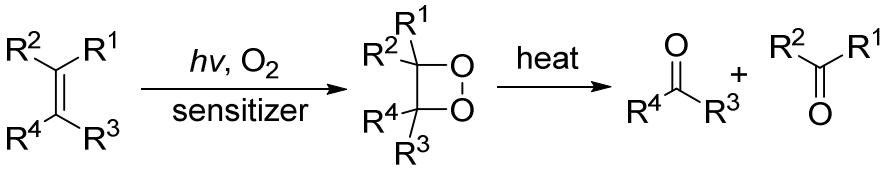
Recently, the ene reaction has been applied to the synthesis of compound **7** (Scheme 28) which possess a high antimalarial activity. Photooxidation of allylic alcohol **5** gave a mixture of diastereomeric hydroperoxides (**6a**, **6b**).[52] The diastereoselectivity was rationalized by the interaction of hydroxyl group with singlet oxygen. The acetalization of peroxide **6b** with cyclohexanone afforded the desired product **7** (Scheme 28).[53] Similarly, singlet oxygen ene reaction has been used as key step for the synthesis of antimalarial peroxide dyads.[54]



Scheme 28: Use of ene reaction in the synthesis of antimalarial compound

2.2.2.2 [2+2] Cycloadditions

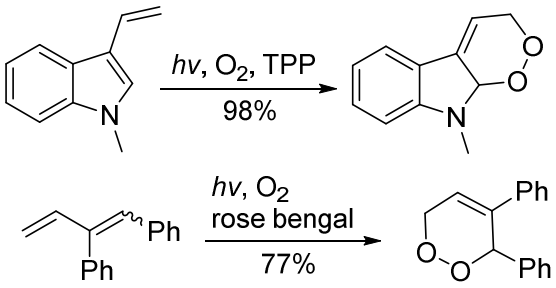
Electron rich alkenes and alkenes containing geometrically inaccessible hydrogens give [2+2] cycloadditions with singlet oxygen.[51c, 55] The formed dioxetanes are thermally sensitive and decompose to give dicarbonyl compounds (Scheme 29). This transformation will be briefly discussed in section 2.3.



Scheme 29: Thermal cleavage of dioxetane

2.2.2.3 [4+2] Cycloadditions

Endoperoxides are formed as a result of [4+2] Cycloadditions of singlet oxygen with conjugated dienes (Scheme 30).[56]



Scheme 30: [4+2] Cycloadditions

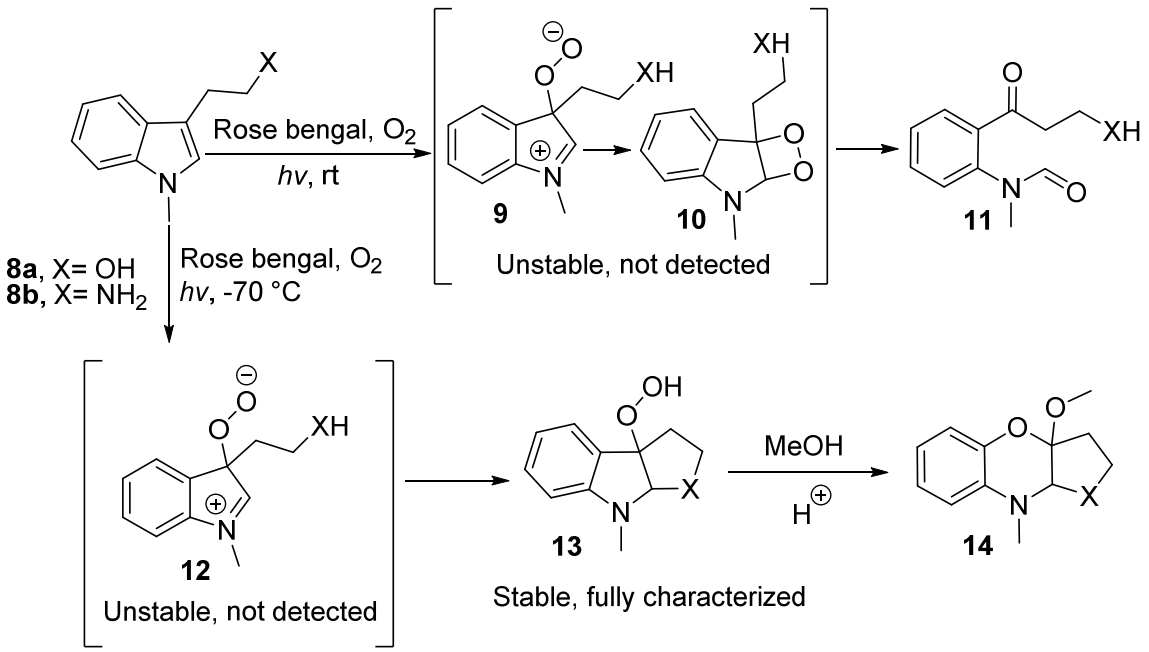
2.2.2.4 Zwitterion reactions

Indoles are known to react through zwitterion mechanism. [51d, 51e, 57] Reactions of indoles are discussed below.

2.3 Photooxidation of indole derivatives

The dye–sensitized photooxygenation of indole dervivatives has been extensively studied.[51d, 51e, 57] The reaction of singlet oxygen with indole derivatives gives rise to different products and these transformations are attributed to different pathways that are available for the decomposition after the primary photooxygenation of indole substrates. These decomposition reactions are highly dependent on substituents, temperature and solvent.

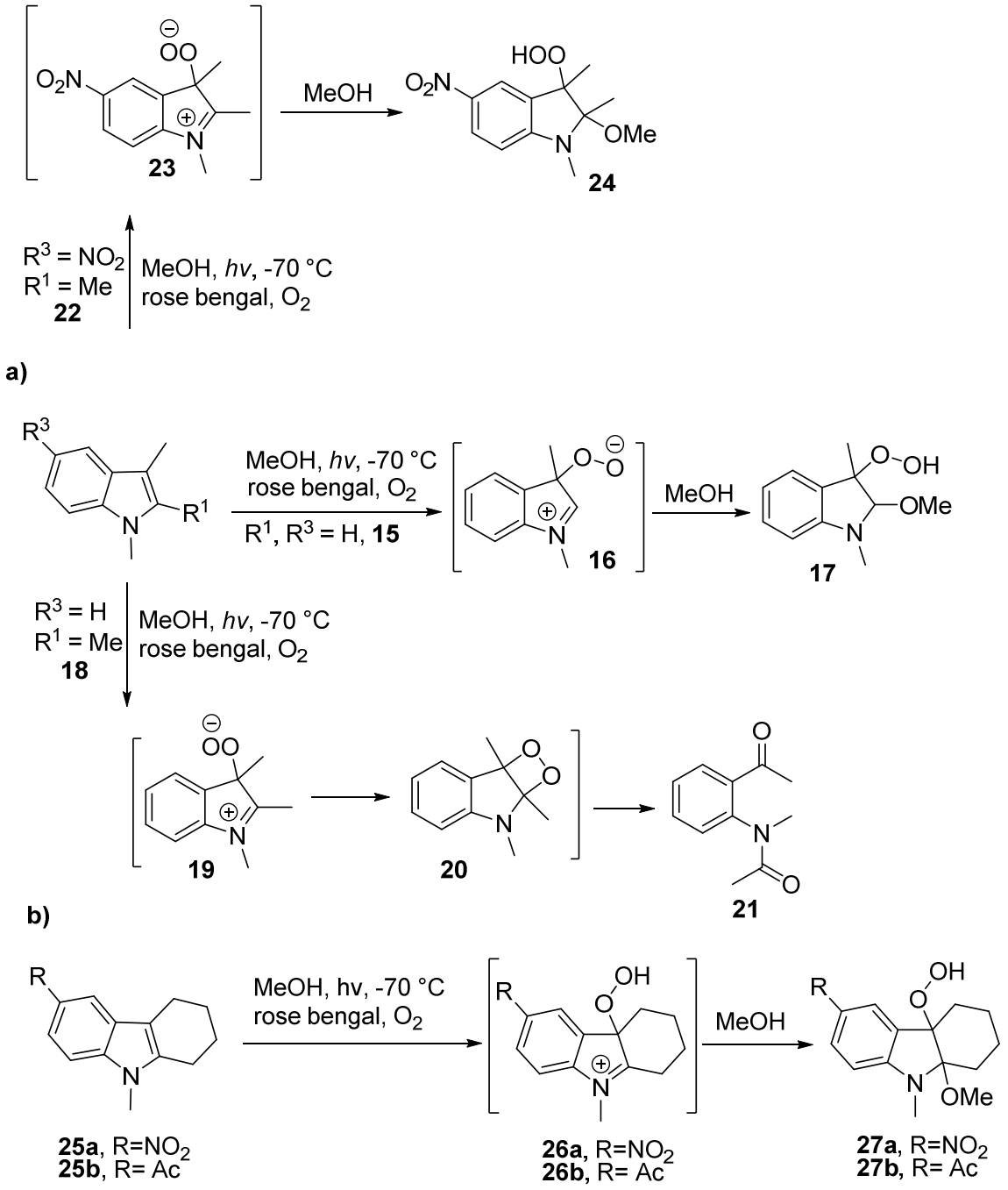
The research group of Saito *et al*. in 1975 observed that rose bengal sensitized phtooxygenation of *N*-methyl tryptophol (**8a**) and *N*-methyl tryptamine (**8b**) led to the formation of C2–C3 bond cleaved product **11** (Scheme 31). It was supposed to be formed through dioxetane intermediate **10**. However, 3-hydroperoxyindoline **13** was formed in quantitative yields when the same reaction was performed at –70 °C. Treatment of this hydroperoxide **13** with acid yielded a new product **14** which arises after Hock rearrangement (Scheme 31). The photo oxygenation of *N*-methylindole-3-propionic acid in the presence of acid also gave the similar product arising from hydroperoxide intermediate.[58]



Scheme 31: Photooxidation of tryptophol (X=O) and tryptamine (X=N)

In order to observe the effect of substituents on the path of the reaction, the

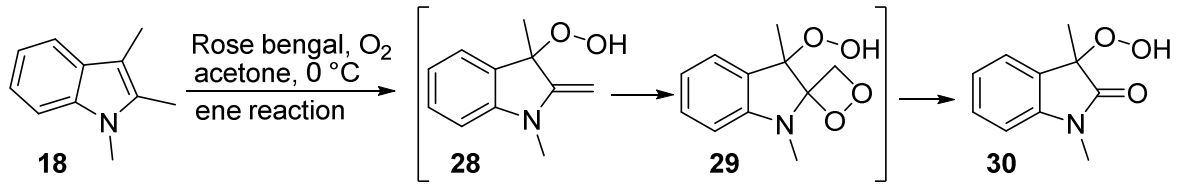
reaction was then performed at –70°C by using 1,3-dimethyl indole (**15**) as starting material. The intermolculer interception of intermediate zwitterion **16** by methanol, used as solvent, led to the exclusive formation of product **17** (Scheme 32a).[59] The substituents played an important role in determining the course of this phtooxidation reaction. The path of the reaction was completely changed when methyl group was introduced at C-2 position of indole (**18**). The photooxidation of indole **18** under exactly same conditions gave the ring cleaved product **21** as the only product (Scheme 32a). The course of the reaction was again changed when nitro group was introduced on the benzene ring of indole **22**. The trapping product **24** was formed as the only product when photooxidation reaction was performed by using nitroindole **22** as starting material. Similar trapping products (**27a**, **27b**) were observed during the photooxidation of carbazole **25a** and carbazole (**25b**) (Scheme 32b). Therefore, it was concluded that introduction of an electron withdrawing group in the benzene ring favors the trapping of intermediate products (**27**, **24**) by solvent molecule over the oxidative cleavage of C2–C3 bond.



Scheme 32: Effect of substituents on the course of reaction; all the reactions were performed at –70°C using molecular O_2 as oxidant, rose bengal as sensitizer and methanol as solvent.

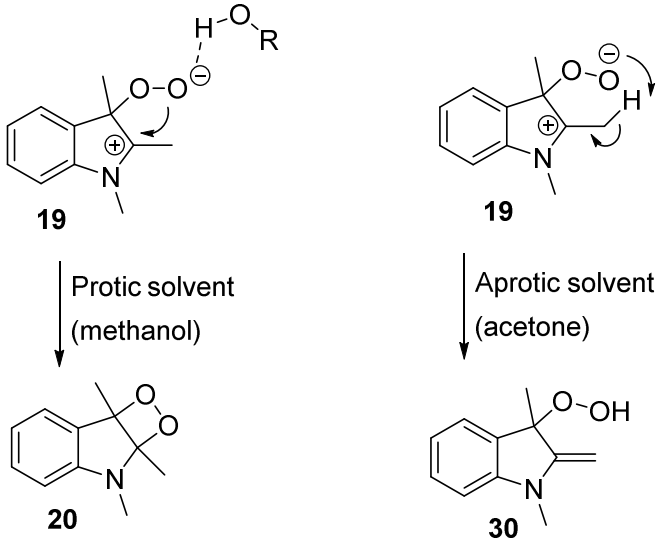
However, when the photooxidation of 1,2,3–trimethyl indole (**18**) was performed in aprotic solvent at 0 °C, 2.0 equiv. of O_2 were absorbed, 3-hydroperoxy–2–indolinone (**30**) was formed as major product and formaldehyde was liberated during the reaction (Scheme 33). The formation of product **30** was explained by the presence of enamine **28** as intermediate which further reacted with singlet

oxygen to give dioxetane **29**. The dioxetane **29** was then decomposed to the observed product **30**.



Scheme 33: Effect of acetone as solvent on the course of reaction

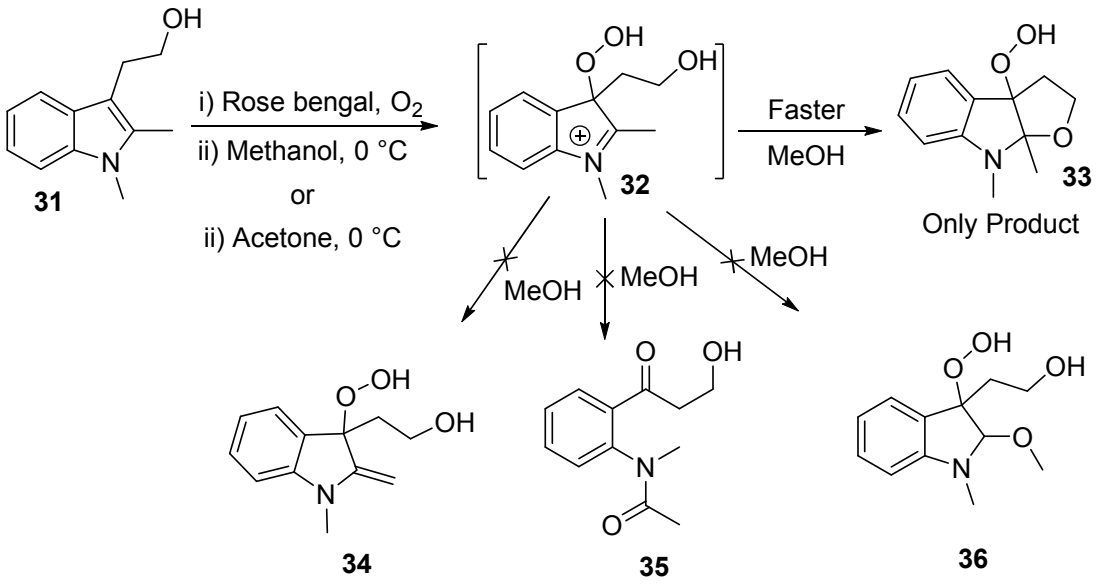
It was postulated that protic solvents coordinate with the negatively charged oxygen of zwitterion **19** thus reducing its ability to abstract the allylic proton to give the ene reaction. On the other hand, the coordination of solvent with negatively charged oxygen is not possible in aprotic solvents. Therefore, the ene product was observed when the reaction was performed in acetone as solvent (Scheme 34).[60]



Scheme 34: Trapping products versus ene product

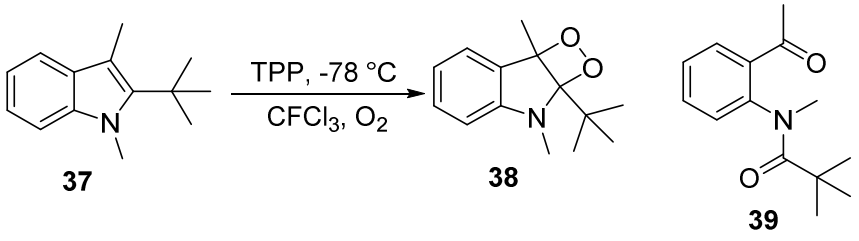
In contrast to indole **18**, the photooxidation of indole **31** is independent of the nature of solvent. The product **33** formed as result of intramolecular trapping was obtained when the photooxidation of 1,2-dimethyl tryptophol (**31**) was performed in acetone or methanol as solvent (Scheme 35). This result showed that there was a intermediate (zwitterion **32**) which was trapped intramolecularly by alcohol group present in the side chain before this could give ene product **34** by the abstraction of allylic proton, trapping product **36** formed by the interception with methanol or

could result in the oxidative cleavage of C2-C3 bond through dioxetane intermediate to afford product **35** (Scheme 35). This result showed that the intramolecular trapping of zwitterion **32** to afford product **33** is faster than other three possible reactions which could yield products **34**, **35** and **36**.



Scheme 35: Intramolecular trapping versus intermolecular trapping and ene reaction

The different dioxetanes discussed so far are highly unstable and decompose rapidly to dicarbonyl fragments. Therefore there is no analytical evidence for the presence of these dioxetanes in solution. However, the dioxetane **38** could be observed and characterized in solution by the introduction of *tert*-butyl group at C-2 position of indole **38** and performing the photooxidation in $CFCl_3$ as solvent (Scheme 36).[61]

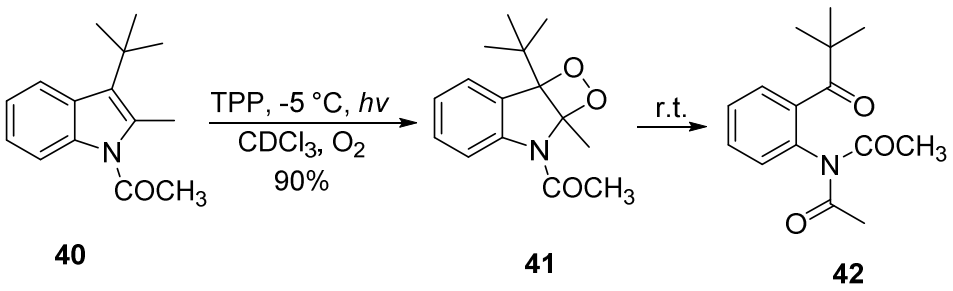


Scheme 36: Observation of dioxetane

The stability of this dioxetane is highly temperature and solvent dependent. It was decomposed rapidly to product **39**, formed as result of C2-C3 bond cleavage, by increasing the temperature to 0°C. Similarly, the product **39** was observed as the

only product when the reaction was performed in methanol at -78°C (Scheme 36).

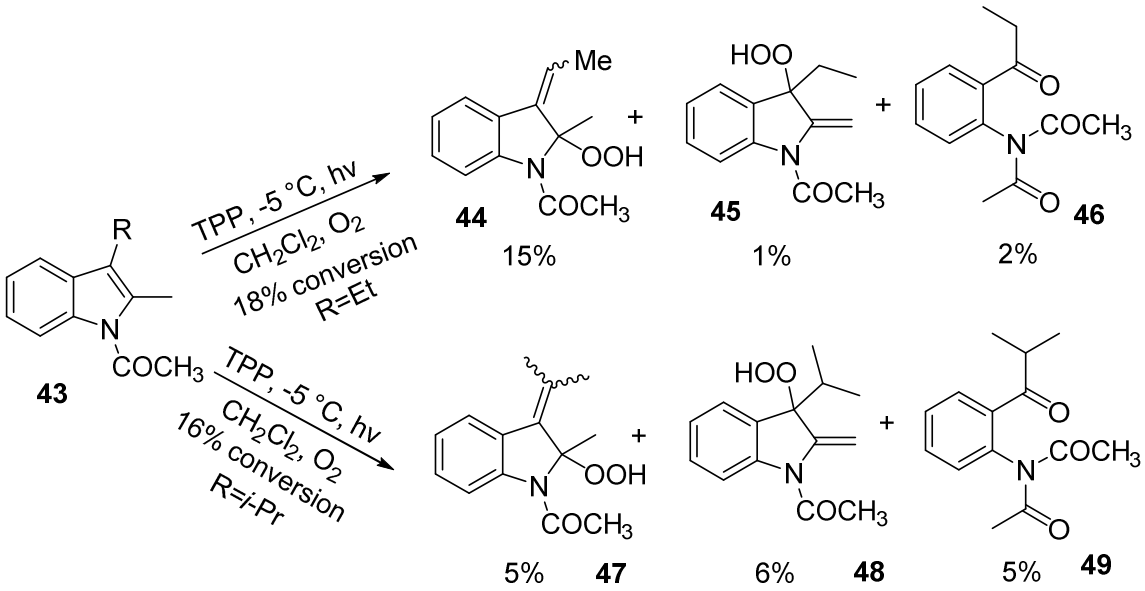
Additionally, later on, Zhang *et al*. also observed the formation of stable dioxetane **41** by introducing electron withdrawing moiety at nitrogen of indole **40** (Scheme 37).[62]



40 **41** **42**

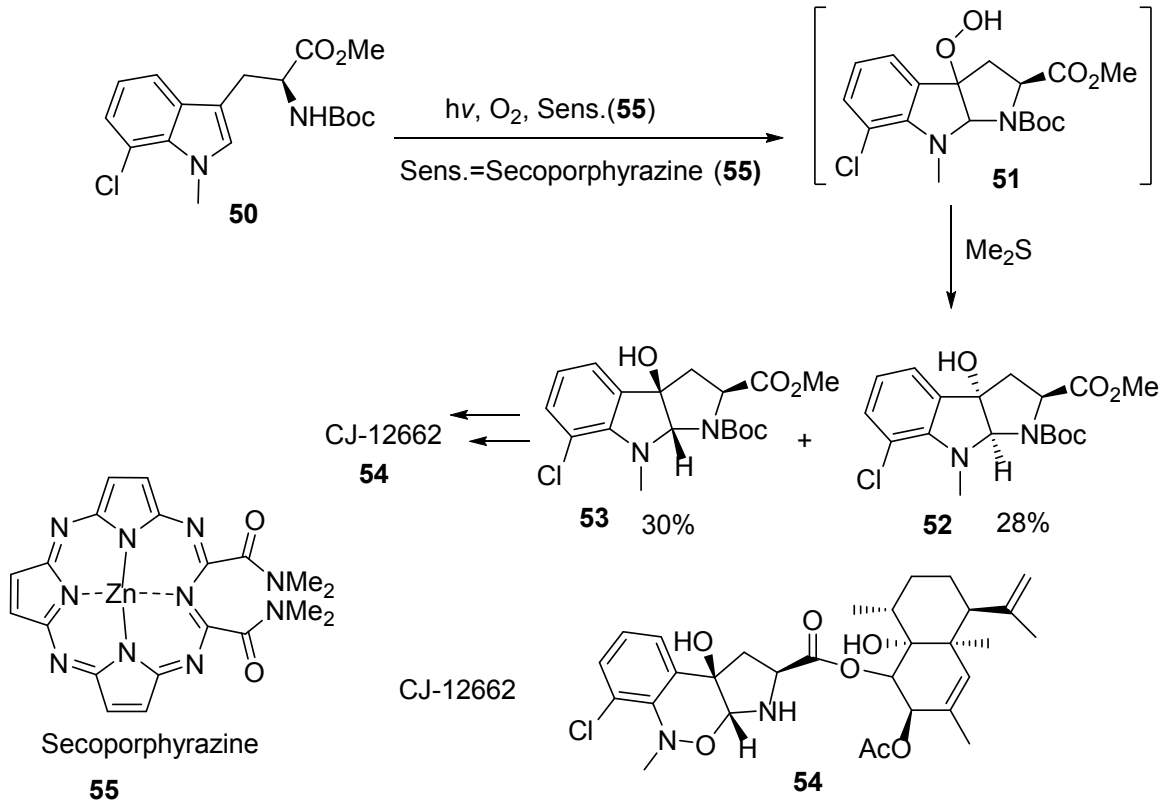
Scheme 37: Effect of EWG on nitrogen on the stability of dioxetane

The presence of *tert*-butyl was important for the formation of dioxetane **41**. A mixture of different products was obtained when *tert*-butyl group was replaced with ethyl and isopropyl groups (Scheme 38). These indoles undergo different singlet oxygen ene reactions. The formation of 2-hydroperoxyindoline **44** was favored over the formation of 3-hydroperoxyindoline **45** using ethyl group at C-3 position of indole. When the abstraction of the proton from the substituent at C-3 was made difficult by the introduction of sterically more hindered *iso*-propyl group then there was competition between the formation of two regioisomers of peroxides (**47** and **48**) and C2-C3 ring cleavage product **49** was also observed in significant ratio (Scheme 38).



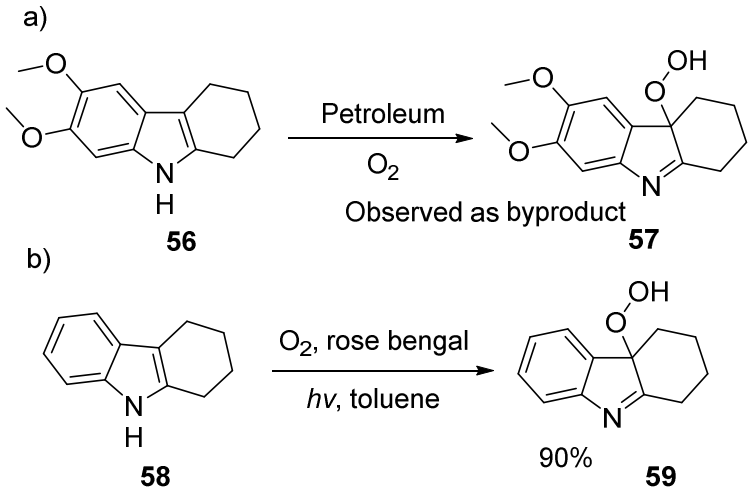
Scheme 38: Effect of substituents on the ene reaction

Nevertheless, photooxidation of indoles has also been used as key step in the synthesis of natural products.[51e, 53] Photooxidation of a tryptophan **50** was used as a key step in the synthesis of pyrrolobenzoxazine CJ-12662 (**54**) natural product (Scheme 39).[63] The oxidation of **50** gave the intermediate hydroperoxide which was cleanly reduced to the corresponding alcohols **52** and **53** by dimethyl sulfide. The diastereomer **53** was further used to complete the synthesis of natural product.



Scheme 39: Photooxiodation as key step in the synthesis of CJ-12662 (55)

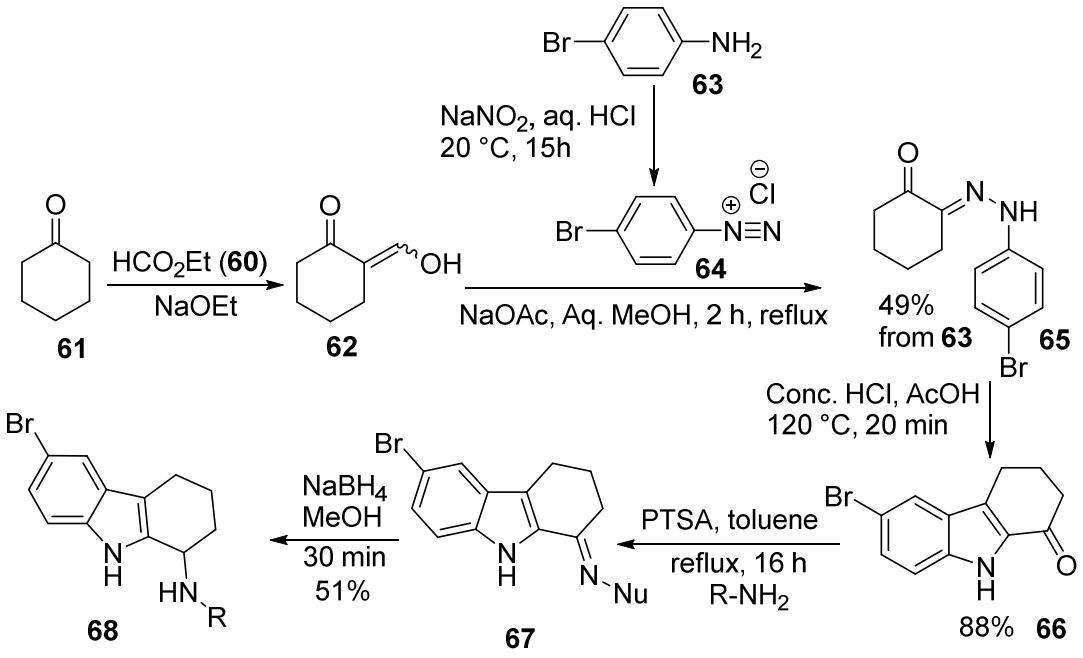
During the purification of 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (**56**), A. B. Woodier *et al*. isolated a new compound **57** instead of the expected carbazole **56**. It was assigned to be hydroperoxide **57** (Scheme 40a). They found that 6,7-carbazole **57** and 1,2,3,4-tetrahydrocarbazole (**58**) readily combines with oxygen to form corresponding hydroperoxides **57** and **59**.[64] Later on, the research group of F. H. Cano demonstrated that rose bengal-sensitized photooxygenation of carbazole **58** in toluene leads towards the peroxide **59** in excellent yields (Scheme 40b).[65]



Scheme 40: Synthesis of peroxides 57 and 59

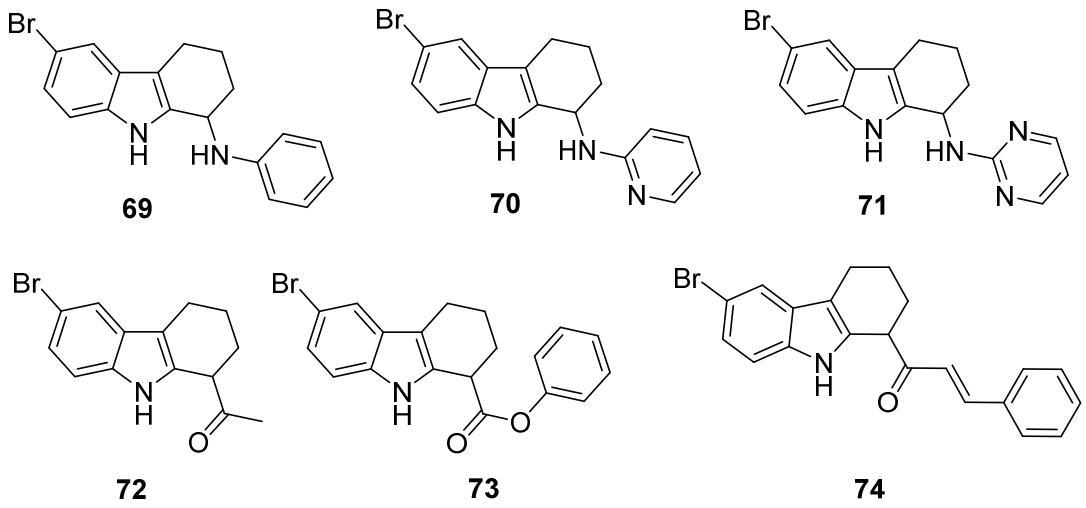
2.4 Selected examples for the synthesis of different tetrahydrocarbazole derivatives

The research group of K. S. Gudmundsson has demonstrated the synthesis of tetrahydrocarbazole derivatives with potent activity against human papillomaviruses. The synthetic approach consists of the initial synthesis of hydrazone **65** by Japp–Klingemann reaction. The acid-catalyzed cyclization gives ketone **66**. The amination followed by reduction delivers the desired product **68** (Scheme 41).[66]



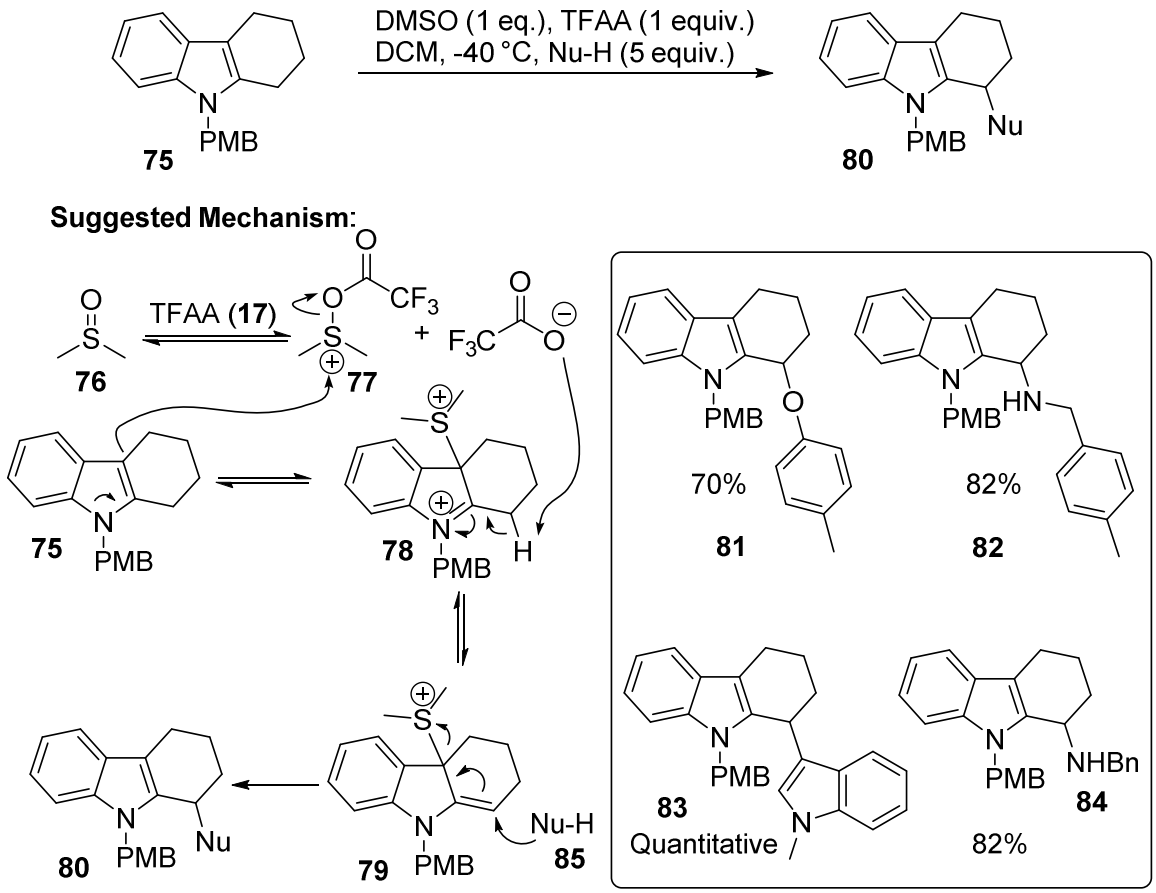
Scheme 41: Multistep functionalization of 1-position of tetrahydrocarbazole

The compounds **69**-**74** are active against Human papillomavirus (HPV) (Scheme 42). However, **69** was found to be the most effective. It was also found to be effective against Hepatitus C Virus (HCV) and Vascular Endothelial Growth Factor (VEGF).[66-67] The requirement for multiple synthetic steps and expensive chemicals as well as low yields usually obtained after the reactions, is the main problem associated with this approach.[66]



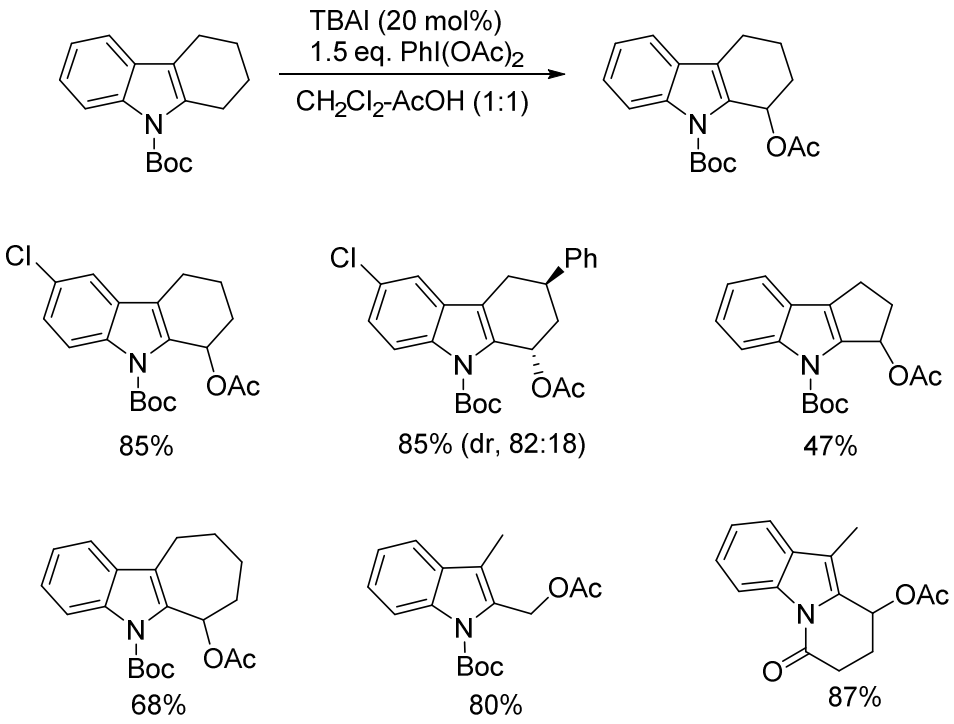
Scheme 42: Scope of the reaction

T. Kawasaki *et al*. have achieved the one pot functionalization at 1-position of tetrahydrocarbazole **75** by using DMSO and trifluroacetic anhydride (TFAA) (Scheme 43).[68] The use of *N*-H tetrahydrocarbazole did not deliver the desired coupling product. Among different protecting groups, *p*-methoxybenzyl was found to be the most suitable for the desired transformation. According to the suggested mechanism, an active thionium species **77** is generated by the combination of DMSO and TFAA. This species then undergoes nucleophilic attack by the tetrahydrocarbazole **75** to give the intermediate **78**. The formation of enamine **79** followed by the attack of the external nucleophile **85** affords the desired coupling product. Good to excellent yields were obtained by using different carbon, oxygen and nitrogen based nucleophiles (compuonds **81**-**84**). However, the use of protecting group, stoichiometric amounts of DMSO and TFAA, and excess of nucleophile (5.0 equivalents) diminishes the overall efficiency of the reaction.[68]



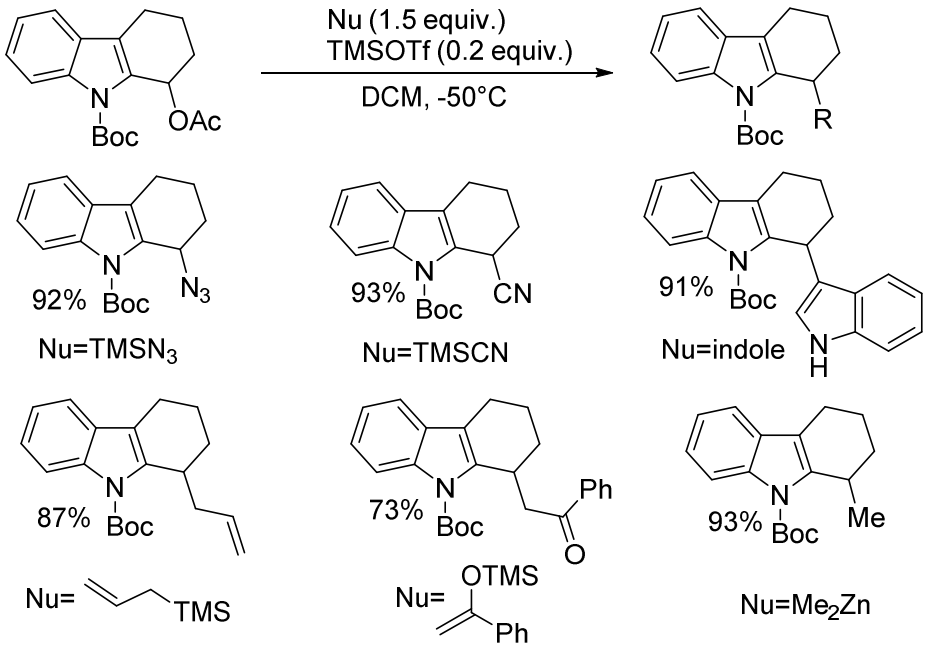
Scheme 43: Functionalization of 1-position of tetrahydrocarbazole through thionium species

Recently, the research group of T. Taniguchi has described the acetoxylation at 1-position of 2,3-disubstituted indoles by using 20 mol% of TBAI and stoichiometric amounts of $PhI(OAc)_2$ (Scheme 44). The reaction works in good yields at 0 °C by using a combination of DCM and AcOH in 1:1 ratio as solvents (Scheme 44).



Scheme 44: Acetoxylation at 1-position of tetrahydrocarbazole

The acetate group thus introduced could be further displaced by other nucleophiles in the second step to get synthetically useful products. This transformation was achieved by using catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and DCM as solvent (Scheme 45).[69]



Scheme 45: Substitution of acetate with other nucleophiles

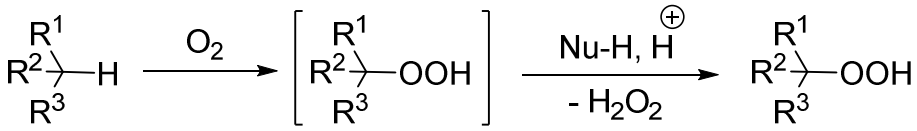
All these methods give excess to an important class of compounds. However, the requirements for stoichiometric amounts of synthetic oxidants, expensive reagents, multiple steps or use of protecting groups the overall sustainability of these methodologies.

4 Objectives of thesis

4.1 C–H functionalization *via* intermediate peroxides

Many organic compounds react slowly with oxygen from air in autoxidation reactions to form hydroperoxides.[41] Very often, the auto oxidation is an unwanted process and leads to decomposition of valuable compounds or materials. Previous studies, in our research group showed that xanthene could be coupled with different ketones under aerobic conditions using catalytic amounts of MsOH (see section 2.1.5 for details).[42b]

As peroxides are formed by autooxidation in air, it was interesting to know if the C–H functionalisation of organic molecules could be achieved by using these intermediate peroxides as leaving groups in the presence of catalytic amounts of an environmentally benign acid. In the ideal case, molecular oxygen would be the only oxidant, therefore this concept of C–H functionalisation *via* intermediate peroxides could be very attractive for green chemistry.[70]



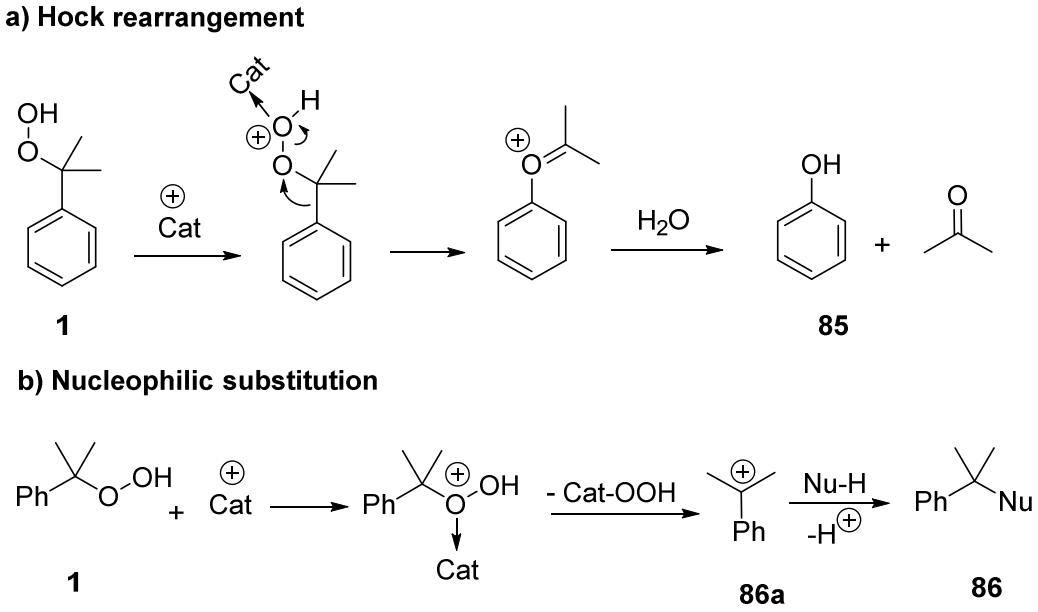
Scheme 46: Concept of C–H functionalization *via* Intermediate Peroxides

In order to explore the feasibility of this concept, two substrate classes were selected for this thesis. Before investigating the concept of C–H functionalisation *via* intermediate peroxides using these two classes, it was decided to gain a deeper insight into the reactivity of hydroperoxides in general by chosing the commercially available and relatively stable cumene hydroperoxide as a test substrate.

4.1 Study on the reactivity of cumene hydroperoxide used as model substrate

The first goal of the thesis was to investigate the possibility of nucleophilic substitution of cumene hydroperoxide (**1**) by using catalytic amounts of environmentally benign catalysts and then to observe the effect of different catalysts and solvents on the possible pathways; Hock rearrangement (Scheme

47a) or nucleophilic substitution (Scheme 47b).



Scheme 47: Suggested mechanism for (a) Hock rearrangement and (b) nucleophilic substitution.

The results of these studies could help in understanding the reactivity of peroxides and might be useful for other projects

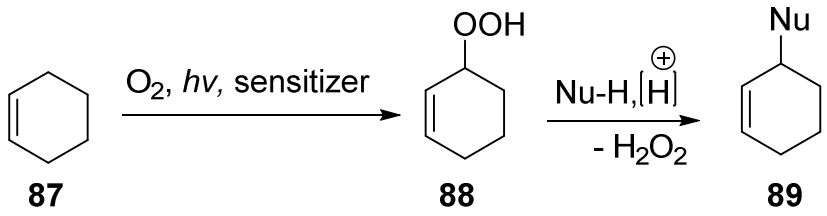
4.2 Allylic C–H functionalization *via* photochemically generated hydroperoxides

Cross coupling reactions with allylic substrates are very useful in the synthesis of complex molecules,[71] but only few aerobic allylic C–H functionalisations are known.[72] The second goal of the thesis was to develop allylic C–H functionalization *via* photochemically generated intermediate hydroperoxide.

For this reason, it was decided to perform the studies with cyclohexene (**87**) as a test substrate (Scheme 48). The choice of cyclohexene (**87**) was driven not only by its commercial availability, but also from the possibility to avoid the complication arising from the regiochemistry of the peroxidation.

The strategy was to synthesize peroxide **88** from cyclohexene (**87**) by a singlet oxygen ene reaction and then to substitute the peroxide with different nucleophiles under acidic conditions (Scheme 48). Cyclohexene (**87**) can be easily oxidized to

the corresponding hydroperoxide **88** by irradiation with visible light in the presence of elemental oxygen and a sensitizer like tetraphenylporphyrin (TPP).[73] However, this method for the formation of peroxide **88** requires the use of base which was not compatible with the expected acidic conditions for substitution. Therefore, it was also necessary to develop a methodology for the oxidation of cyclohexene which was compatible with acidic conditions and did not require the use of special synthetic reagents. The final goal of this project was to perform the reaction in a one pot fashion *i.e. in situ* formation and substitution of peroxide moiety.

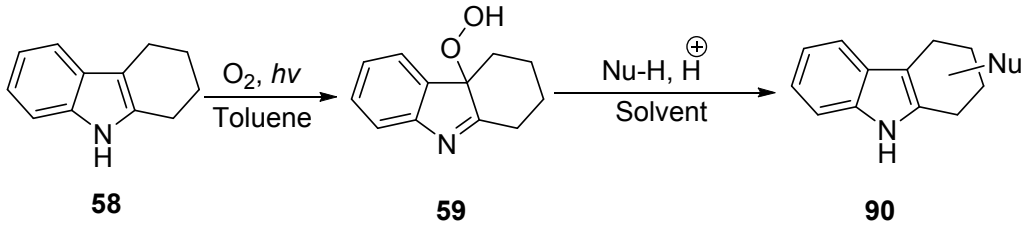


Scheme 48: Allylic C–H functionalization *via* photochemically generated hydroperoxides

4.3 C–H functionalization of tetrahydrocarbazole derivatives *via* photochemically generated hydroperoxides

The third goal of the thesis was to extend the feasibility of the C–H functionalisation concept to the C–H functionalisation of tetrahydrocarbazole derivatives. Tetrahydrocarbazole hydroperoxides can be easily synthesized by reaction with singlet oxygen, which can be generated by photochemical methods, using a sensitizer and visible light. [64] Furthermore, the core of tetrahydrocarbazole is present in a number of biological active compounds.[67, 74]

Following the same strategy as for cyclohexene (**87**), it was planned to introduce the hydroperoxide moiety with the aid of oxygen, a sensitizer and light and then



Scheme 49: Proposed C–H functionalization of tetrahydrocarbazole derivatives *via* photochemically generated hydroperoxides

substitute it with different nucleophiles under acidic conditions (Scheme 49). The next goal of this project was to use the developed method for the synthesis of pharmaceutically active compounds.

4.4 Mechanistic studies on the C–H functionalization of tetrahydrocarbazole *via* photochemically generated hydroperoxides

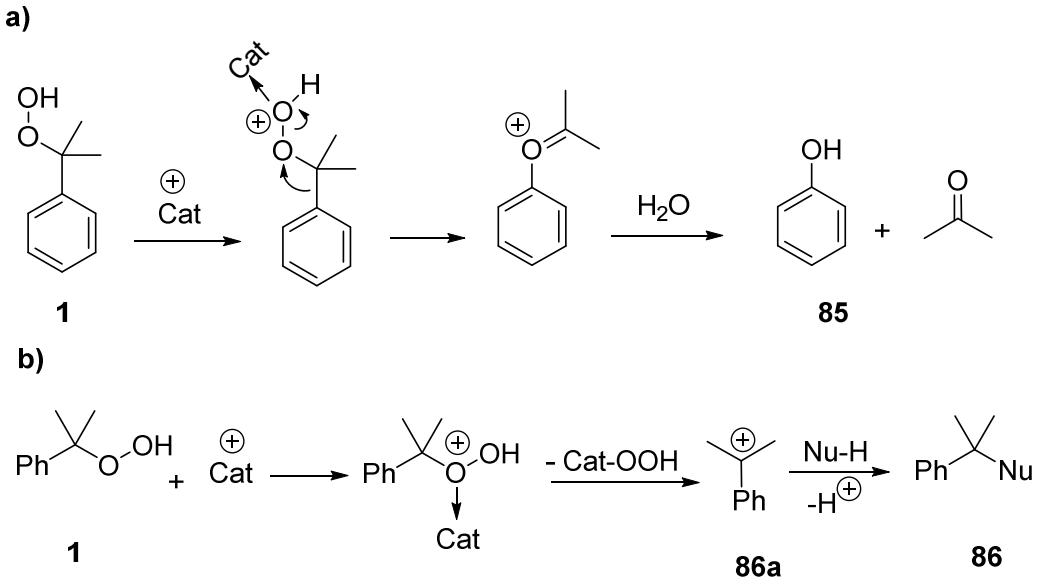
The understading of a reaction mechanism can be helpful in further extending the scope of a concept. Therefore, the final goal of this Ph.D. thesis was to explore the mechanism for the coupling of tetrahydrocarbazole peroxide **59** with nucleophiles under acidic conditions.

5 Results and discussions

5.1 Study on the reactivity of cumene hydroperoxide used as model substrate

5.1.1 Aim of the project

Hydroperoxides are often formed by the autoxidation of organic molecules.[41] In general, hydroperoxides are sensitive compounds and are prone to O-O bond cleavage.[75] They are known to rearrange in the presence of acid. For example phenol (**85**) and acetone are generated by acid catalyzed Hock rearrangement of cumene hydroperoxide (**1**) (Scheme 50a).[76] A similar behaviour is observed for *t*-BuOOH, which gives acetone and methanol.[44]



Scheme 50: Suggested mechanisms for (a) Hock rearrangement and (b) nucleophilic substitution

However, hydroperoxides have rarely been used as electrophiles for coupling reactions with different nucleophiles.[42] Previous studies in our research group with xanthene suggest that hydroperoxide moiety can be substituted with different nucleophiles under specific acidic conditions.[42b] However, it was interesting to generalize this concept and to extend it to other substrates. In order to get deep insight into the reactivity of organic hydroperoxides, cumene hydroperoxide, which is a commercially available and relatively stable hydroperoxide, was selected as

test substrate.

Here I wanted to investigate the possibility of nucleophilic substitution of cumene hydroperoxide, and then the effect of different catalysts and solvents on the outcome of the reaction (Scheme 50b).[44, 77] Moreover, in order to get close to the definition of an ideal green reaction,[70] it was interesting to get required transformation by catalytic amounts of environmentally benign, abundant and inexpensive catalysts.

Minisci *et al*.[44] have discussed the selective activation of oxygens of cumene hydroperoxide based on HSAB principle[43] by using stoichiometric amounts of metal salts.[44] According to their investigations, the coordination of harder acids with oxygen bonded to proton leads to the formation of phenol (**85**) (Scheme 50a) while preferred coordination of Lewis acids softer than proton with the oxygen directly bonded to carbon result mainly in formation of substitution products (Scheme 50b).[44] (see section 2.1.5 for detail)

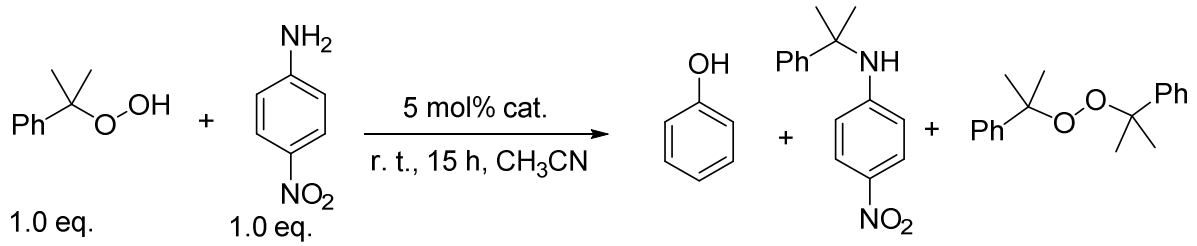
5.1.2 Results and discussions

Based upon the reports by Minisci,[44] a relationship was expected between the hardness of acid catalysts and their behaviour for selective activation of one of the two peroxide oxygens. In order to investigate this hypothesis, a variety of different acid catalysts belonging to different classes, hard acids, soft acids and borderline acids, as described by Pearson in his HSAB concept, were screened (Table 1-3).[43] For these studies *p*-nitroaniline (**91**) was selected as a nucleophile and acetonitrile was selected as solvent. The choice of aniline **91** as nucleophile was driven by its stability under oxidative conditions and by its ability to act as nucleophile without significantly quenching the acid catalyst. Additionally, because of the characteristic yellow color, the products arising from aniline **91** could also be easily identified and isolated. It was found that there was a competition between the formation of phenol (**85**) and the formation of two substitution products (**92**, **93**). Theoretically the carbocation **86a** (as described in Scheme 50b) could be attacked by peroxide **1** and *p*-nitroaniline (**91**) to give substitution products **93** and **92** respectively (Table 1). In order to understand and compare the selectivity of different acid catalyts for rearrangement (Re) to give phenol (**85**) and for nucleophilic substitution products (Sub) to afford products **92**+**93**, a ratio between Re:Sub for all the tested acid catalysts has been calculated and

described in the tables gives below.

During the screening of Brønsted acid, weaker acids like acetic acid and picric acid were not able to promote the reaction (Table 1, entries 1-2). By using TFA, substitution products (**92** and **93**) were observed but the consumption of cumene hydroperoxide (**1**) was low (Table 1, entry 3). By further increasing the strength of Brønsted acid, the consumption of peroxide **1** was increased and phenol (**85)** was found to be the major product of the reaction (Table 1, entries 4, 7- 8).

Table 1: Screening of different Brønsted acid [a]



1 **91** **85** **92** **93**

Entry	Catalyst	Cons. (%)	85 (%)	92+93 (%)	$S^{[b]}_{Re:Sub}$(%)
1	AcOH	0	0	0+0	--
2	Picric Acid	0	0	0+0	--
3	TFA	7	0	4+3	0:100
4	MsOH	90	74	4+12	82:18
5[c]	PTSA	8	1	3+4	12:88
6[c]	Aq. HCl	11	1	4+6	09:91
7	$HClO_4$	83	65	2+16	78:22
8	TfOH	100	86	3+11	86:14

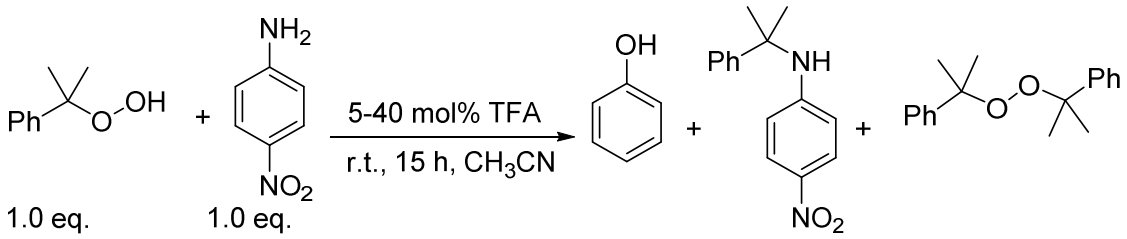
[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of CH_3CN were used. Yields determined by ^1H NMR based upon the overall Consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution [c] A precipitate of anilinium salt was observed

PTSA and HCl did not follow the normal trend presumably due to the deactivation of catalyst by the precipitation of formed anilinium salt (Table 1, entries 5-6). Interestingly less reactivity but higher selectivity for substitution products was observed with these catalysts.

The commercially available solution of peroxide **1** contains approximately 7% cumyl alcohol **94** (composition of solution = 85% peroxide **1**+ 7% cumyl alcohol **94** + unknown compounds). The high selectivity for substitution during low consumptions of peroxide **1** might result from the substitution of alcohol **94** already present in the solution of peroxide **1**. Therefore high selectivities for substitution during low consumptions of peroxide **1**, by using TFA, PTSA and HCl, do not necessarily explain the trend of these catalysts for selective activation of peroxide **1**.

I wanted to further study the effect of catalyst loading and reaction time on the consumption and selectivity. Therefore, I performed the reaction by increasing the loading of the catalyst and checked the progress of the reaction after 15 h (Table 2). The consumption of peroxide **1** was slightly increased by increasing the loading of TFA to 40 mol% (Table 2, entry 5). With this increase in the consumption of peroxide **1**, the selectivity for substitution was decreased (Table 2, entry 1-5). The reaction was then allowed to stir for 5 days by using 10 mol% of TFA but no effect on the consumption of peroxide **1** was observed (Table 2, entry 7). With 20 mol% of TFA, the consumption of peroxide **1** was improved to 54% (Table 2, entry 8) and selectivity for substitution was decreased.

Table 2: Effect of the loading of TFA on the consumption and selectivity of peroxide 1[a]



1 **91** **85** **92** **93**

Entry	TFA (mol%)	Cons. (%)	85 (%)	92+93 (%)	S[b] Re:Sub(%)
1	5	6	0	3+3	0:100
2	10	9	0	4+5	0:100
3	20	12	2	5+5	17:83
4	30	12	2	5+5	17:83
5	40	18	6	5+7	34:66
6[c]	5	6	0	3+3	0:100
7[c]	10	9	0	4+5	0:100
8[c]	20	54	38	4+12	70:30
9[c]	30	82	65	5+12	79:21
10[c]	40	92	76	4+12	82:18

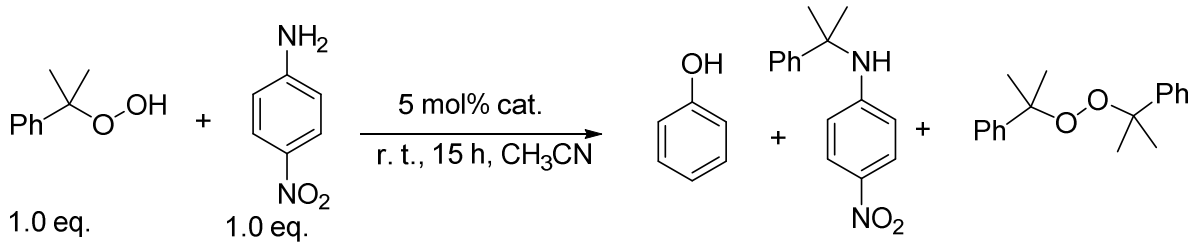
[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity; Rearrangement:Substitution [c] reaction time was 5 days

With the increase in reaction time by using 30 mol% of TFA, a significant effect on the increase in consumption of peroxide **1** and decrease in the selectivity for substitution was observed (Table 2, entry 9-10). These results together with those obtained by using other Brønsted acids (Table 1, entries 4-8) show that they significantly favour the formation of rearrangement products. However, the presence of substitution products in considerable ratios shows that substitution products are also formed from peroxide **1** using these acids.

Different Lewis acids were also screened. For better comparison absolute hardness[78] of catalysts, which were giving comparatively better consumption of peroxide **1**, was also calculated. Based uopn previous assumption,[44] I was expecting that by increasing the hardness of a Lewis acid the selectivity for rearrangement to give phenol should increase and by increasing the softness of an acid the selectivity for substitution should increase.

During the screening of Lewis acids, $Ni(OTf)_2$ and $Zn(OTf)_2$, borderline acids by HSAB principle,[43] were found to be completely unreactive (Table 3, entries 1-2). However $Cu(OTf)_2$, another borderline acid, gave moderate consumption with selectivity for substitution products (Table 3, entry 3). Phenol (**85**) was the major product by using $Sc(OTf)_3$ and $Bi(OTf)_3$ as catalysts (Table 3, entries 4-5). $Bi(OTf)_3$ was found to be the most active Lewis acid for the formation of phenol (**85**). $Fe(OTf)_3$, a harder acid than $Sc(OTf)_3$, afforded exclusively substitution products with full consumption of peroxide **1** (Table 3, entries 6). $Hf(OTf)_4$ having similar hardness as that of $Fe(OTf)_3$ gave a mixture of products and low consumption of peroxide **1** was observed. $In(OTf)_3$, a softer acid than $Fe(OTf)_3$, favoured the formation of phenol (**85**) (Table 3, entry 8). $InBr_3$ was less reactive than $In(OTf)_3$ and low consumption of peroxide **1** was observed. By increasing the loading of $InBr_3$ and allowing the reaction to stir until complete consumption, it was found that it also favored the formation of phenol (**85**) (Table 3, entry 8-9). $SnCl_4$, the hardest among all the screened Lewis acids, favoured the formation of phenol (**85**) with low consumption of peroxide **1** (Table 3, entry 11). In the lanthanide series, $Yb(OTf)_3$ and $La(OTf)_3$ favoured the formation of substitution products (Table 3, entries 13-14).

Table 3: Screening of different Lewis acid [a]



1 **91** **85** **92** **93**

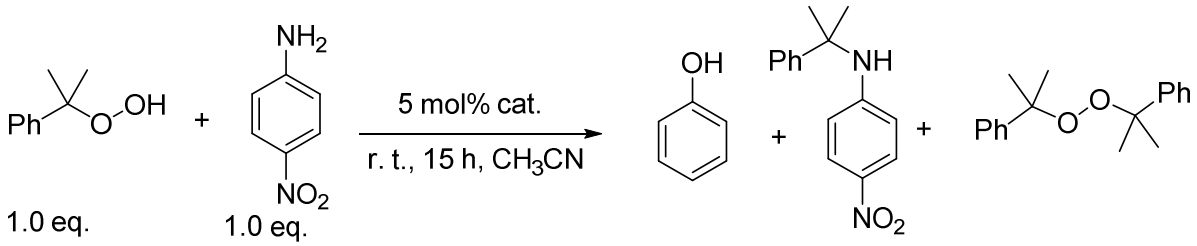
Entry	Catalyst	Cons. (%)	85 (%)	92+93 (%)	Hardness (eV)[e]	$S^{[b]}_{Re:Sub}$(%)
1[c]	$Ni(OTf)_2$	0	0	0+0	N.C	--
2[c]	$Zn(OTf)_2$	0	0	0+0	N.C	--
3[c]	$Cu(OTf)_2$	35	5	9+21	N.C	14:86
4	$Sc(OTf)_3$	51	32	4+15	12.28	63:37
5	$Bi(OTf)_3$	80	64	3+13	12.30	80:20
6	$Fe(OT_f)_3$	100	0	30+70	15.24	00:100
7	$Hf(OTf)_4$	37	16	4+17	16.6	43:57
8	$In(OTf)_3$	72	56	3+13	13.82	78:22
9	$InBr_3$	18	4	4+10	13.82	23:77
10[d]	$InBr_3$	100	81	3+16	13.82	81:19
11	$SnCl_4$	35	21	4+10	19.79	60:40
12[c]	$Y(OTf)_3$	10	1	4+5	N.C	10:90
13[c]	$Yb(OTf)_3$	13	2	5+6	N.C	15:85
14[c]	$La(OTf)_3$	3	0	1+2	N.C	00:100

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of CH_3CN were used. Yields determined by ^1H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution. [c] The absolute hardness was not calculated. N.C stands for not calculated [d] 40 mol% of $InBr_3$ was used and full consumption was obtained after 5 days. [e] The absolute hardness was calculated by using the formula given by Pearson

In general, no real corelation between the hardness of an acid and its selectivity for substitution was observed. The catalyst with similar hardness (Table 3, entries 4-5, and entries 6-7) behaved differently in selectivity for substitution and rearrangement. Additionally they also showed a considerable difference in activating the peroxide **1** and variable consumptions of peroxide **1** were obtained. From these results, it can be easily concluded that the reactivity and the selectivity of peroxide **1** can not be explained on the basis of HSAB principle.

As $Fe(OTf)_3$ was a suitable catalyst fovoring substitution, further iron catalysts were also tested (Table 4). Among different iron catalysts, only $FeCl_2$ resulted in the formation of substitution products with full consumption. $FeCl_3$ and $FeBr_3$, despite being harder than $FeCl_2$, were less reactive (Table 4, entries 2-4). The exceptional behaviour of $FeCl_2$ could also be explained considering that iron(II) can easily be oxidized to iron(III) under oxidative conditions,[79] therefore it is also possible that a different form of iron(III) is the actual reactive catalyst in the mixture. Due to unknown reasons, some other iron(II) catalysts were unable to catalyze the transformation under these conditions (Table 4, entry 5-7).

Table 4: Screening of different iron catalysts [a]



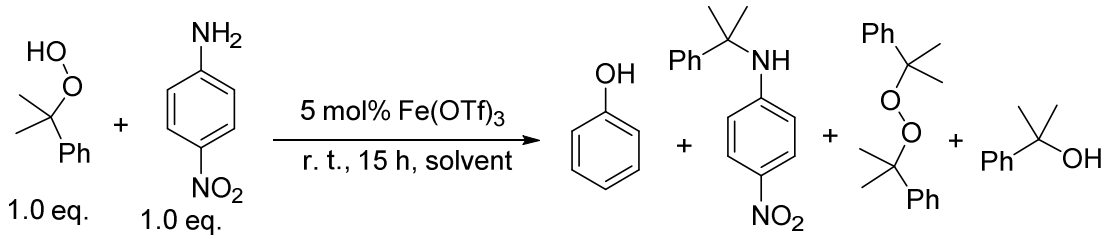
1 **91** **85** **92** **93**

Entry	Catalyst	Cons. (%)	85 (%)	92+93 (%)	$S^{[b]}_{Re:Sub}$(%)
1	$Fe(OTf)_3$	100	0	30+70	00:100
2	$FeCl_2$	100	0	20+80	00:100
3	$FeCl_3$	31	1	11+19	03:97
4	$FeBr_3$	60	0	30+30	00:100
5	FeI_2	0	0	0+0	--
6	$FePO_4$	0	0	0+0	--
7	$Fe(OAc)_2$	2	0	0+2	00:100

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

Next, the behaviour of different solvents for selected catalysts (Table 5) was investigated. Interesting results were found during the screening of different solvents using $Fe(OTf)_3$ as a catalyst.

Table 5: Screening of solvents for the reactions catalyzed by $Fe(OTf)_3$[a]



1 **91** **85** **92** **93** **94**

Entry	Solvent	Cons. (%)	85 (%)	92+93 (%)	94 (%)	$S^{[b]}_{Re:Sub}$ (%)
1	*Iso*-hexane	72	21	0+10	41	68:32
2	Toluene	10	0	0	10	--
3	$CHCl_3$	10	0	0	10	--
4	EtOAc	58	0	5+6	47	0:100
5	AcOH	19	9	3+7	0	47:53
6	DCM	38	26	3+9	0	69:31
7	Acetone	83	60	3+3	17	91:09
8	MeOH	100	0	0	100	--
9	CH_3CN	100	**0**	30+70	0	0:100
10	DMSO	30	0	0	30	--

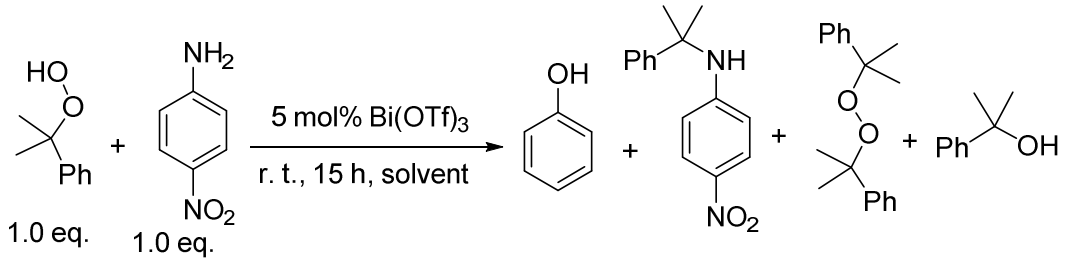
[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

Along with the formation of expected substitution and rearrangement products, the combination of $Fe(OTf)_3$ with different solvents (Table 5) also resulted in the formation of cumyl alcohol **94** in different yields (Table 5, entries 1, 4, 7-8). Mainly starting materials were recovered with toluene and chloroform (Table 5, entry 1, 3). The presence of 10% cumene alcohol **94** suggest that alcohol **94** already present in the solution of peroxide **1** is not reacting under these conditions and peroxide **1** has also slightly decomposed to alcohol **94**. With acetone and DCM, phenol (**85**) was the major product of the reaction (Table 5, entries 1, 6-7) and with CH_3CN, substitution products were formed in excess (Table 5, entries 9).

AcOH afforded both products in similar ratios (Table 5, entry 5). Potentially, the alcohol **94** could be formed through the reduction of peroxide **1** with iron catalyst or by nucleophilic substitution of peroxide[79-80] moiety with residual water in non dry solvents. Combination of $Fe(OTf)_3$ and methanol favored the formation of alcohol **94**. DMSO gave only alcohol **94** in 30% yield.

Then the effect of solvent on the reaction pathway was investigated by screeing different solvents in the presence of $Bi(OTf)_3$ which was most suitable Lewis acid for the formation of phenol (**85**) (Table 6).

Table 6: Screening of solvents for the reactions catalyzed by $Bi(OTf)_3$[a]



1 **91** **85** **92** **93** **94**

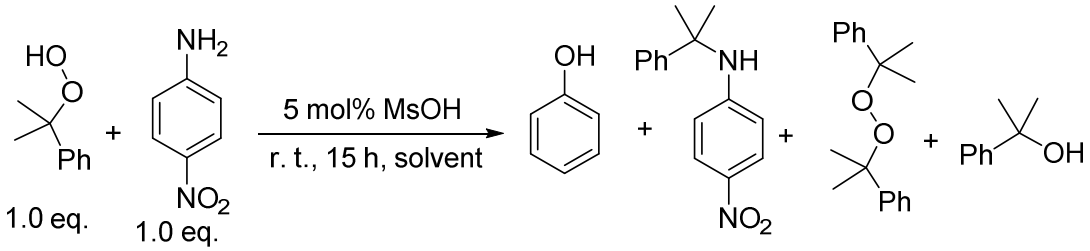
Entry	Solvent	Cons. (%)	85 (%)	92+93 (%)	94 (%)	S[b] Re:Sub (%)
1	*Iso*-hexane	17	11	0+0	6	100:0
2	Toluene	20	8	2+10	0	40:60
3	$CHCl_3$	14	0	5+3	6	0:100
4	EtOAc	6	0	2+4	0	0:100
5	AcOH	59	48	4+7	0	81:19
6	DCM	83	70	4+9	0	84:16
7	Acetone	82	64	3+2	13	93:07
8	MeOH	9	9	0+0	0	100:0
9	CH_3CN	80	64	3+13	0	80:20
10	DMSO	30	0	0+0	30	----

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^1H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

In ethyl acetate, only the substitution products could be observed (Table 6, entry 4). Using toluene as solvent, substitution products were formed prefentially (Table 6, entry 2). Hexane, DCM, Acetone, AcOH, and MeOH led to the higher formation of phenol (**85**) (Table 6, entries 1, 6-8).

MsOH, a suitable Brønsted acid for the formation of phenol (**85**) in acetonitrile as solvent (Table 7, entry 9), was unreactive in most organic solvents (Table 7).

Table 7: Screening of solvents for the reactions catalyzed by MsOH[a]



1 **91** **85** **92** **93** **94**

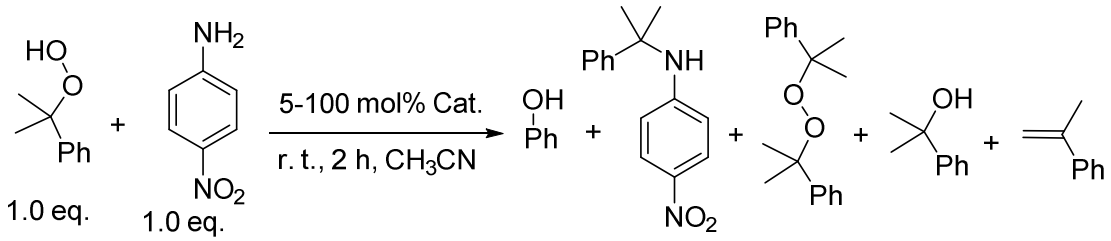
Entry	Solvent	Cons. (%)	85 (%)	92+93 (%)	94 (%)	S[b] Re:Sub (%)
1	*Iso*-hexane	14	4	0+3	7	57:43
2	Toluene	15	8	0+0	7	100:0
3	$CHCl_3$	8	0	0+0	8	--
4	EtOAc	8	0	0+0	8	--
5	AcOH	5	0	0+5	0	--
6	DCM	14	0	3+4	7	
7	Acetone	Complex mixture	0	0+0	0	--
8	MeOH	7	0	0+0	7	--
9	CH_3CN	90	74	4+12	0	82:18
10	DMSO	8	0	0+0	8	--

0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used [a] Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

Slightly better consumption and selectivity for rearrangement was observed using *Iso*-hexane and toluene as solvents (Table 7, entry 1, 2). Low consumption and a complex mixture of products was observed with acetone (Table 7, entry 6). The presence of alcohol **94** was observed in different ratios (always less than 9%) by using $CHCl_3$, EtOAc, AcOH, DCM, MeOH and DMSO as solvents.

Having selected $Bi(OTf)_3$ and $Fe(OTf)_3$ as catalysts, we investigated the effect of catalyst loading on the course of the reaction in acetonitrile as solvent. With 20 mol% and higher catalyst loading, the reaction was completed in only 2h. By increasing the loading of $Bi(OTf)_3$ upto 100 mol%, the selectivity for phenol (**85**) was further increased (Table 8, entries 1-3).

Table 8: Screening of catalyst loading in CH_3CN[a]



Entry	Catalyst	Mol (%)	Cons. (%)	85 (%)	92+93+95 (%)	94 (%)	$S^{[b]}_{Re:Sub}$(%)
1	$Bi(OTf)_3$	5	80	64	3+13+0	0	80:20
2	$Bi(OTf)_3$	20	100	83	2+15+0	0	83:17
3	$Bi(OTf)_3$	40	100	86	3+11+0	0	86:14
4	$Bi(OTf)_3$	100	100	95	0+0+5	0	---
5	$Fe(OTf)_3$	5	100	0	30+70+0	0	0:100
6	$Fe(OTf)_3$	20	100	0	4+67+1	28	0:100
7	$Fe(OTf)_3$	40	100	0	8+33+8	51	0:100
8[c]	$Fe(OTf)_3$	100	100	0	0+27+42	31	0:100

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^1H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution. [c] For entry 1 and 5, the reaction time was 15h

Phenol (**85**) was not observed by using $Fe(OTf)_3$ even up to 100 mol% loading. However alcohol **94** and a new elimination product **95** was observed. The yields of product **94** and product **95** were also increased with higher loading of $Fe(OTf)_3$ (Table 8, entries 5-8).

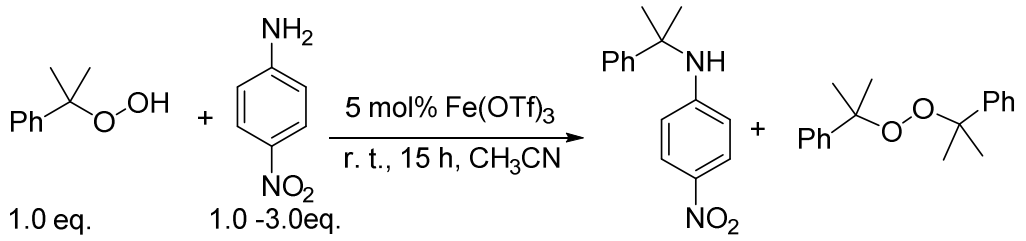
We have already observed that by using $Bi(OTf)_3$ as catalyst rearrangement is preferred over substitution. Therefore by increasing the catalyst loading, the selectivity for rearrangement is further increased. We think that by increasing the catalyst loading, the deactivation of the nucleophile **91** by catalyst is also increased and it is not available for substitution reaction. This unavailability of the nucleophile suppresses the formation of substitution products. Therefore stoichiometric amounts of $Bi(OTf)_3$ also lead towards the formation of elimination product **95** (Table 8, entry 4).

As the combination of $Fe(OTf)_3$ with CH_3CN is not suitable for the formation of phenol (**85**), the deactivation of the nucleophile **91** with $Fe(OTf)_3$ increases the formation of the other byproducts **94** and **95**. These experiments show that selectivity of a catalyst for coordination with oxygens of peroxide **1** is not affected by the loading of catalyst.

From all the above discussed results we see that behavior of catalyst is changed upon changing the solvents. Combination of $Fe(OTf)_3$ with acetonitrile is useful for the selective formation of substitution products while the use of $Fe(OTf)_3$ in acetone gives predominantly phenol (**85**). However, $Bi(OTf)_3$ leads to the exclusive formation of phenol (**85**) in MeCN while substitution products are observed in toluene. Similarly, these catalysts have different reactivity in different solvents.

In order to get better yields of the coupling product (**92**), I performed the reaction by using different molar ratios of *p*-nitroaniline (**91**) with the combination of $Fe(OTf)_3$ in acetonitrile (Table 9). By increasing the molar ratio of **91**, the reaction was slowed down but I got better yields of product **92**. By using 3.0 equivalents of **91**, the reaction was completed in 37 h and 72% coupling product **92** could be isolated (Table 9, entry 5). However with 10 mol% of the $Fe(OTf)_3$, the same reaction was completed in 15 h with slightly improved yield (75% isolated yield).

Table 9: Effect of the excess of Nu-H[a]



1.0 eq. 1.0 -3.0eq.

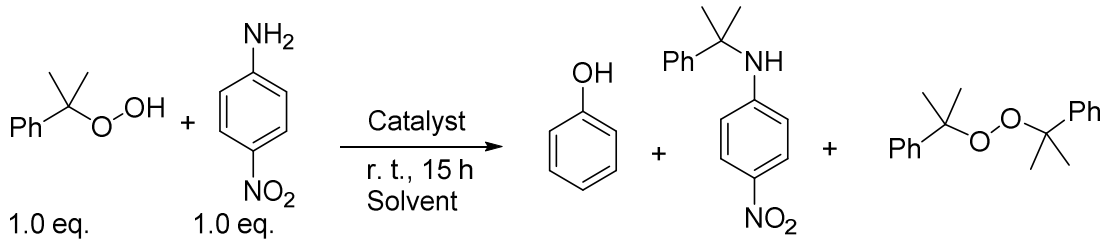
1 **91** **92** **93**

Entry	91 (equiv.)	Cons. (%)	92 (%)	93 (%)
1	1.0	100	30	70
2	1.5	94	41	53
3	2.0	73	40	33
4	3.0	74	57	17
5[b,d]	3.0	100	75 (72)	25
6[c,d]	3.0	100	78 (75)	22

[a] 0.49 mmol of **1** and 0.49-1.47 mmol of **91** were used. 10 mL of solvent were used [a] Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] Reaction time was 37h. [c] 10 mol% of $Fe(OTf)_3$ was used and reaction was completed in 15 h. [d] In brackets are the isolated yields

The reactivity of hydroperoxide **1** was also tested under previously developed conditions for the coupling of tetrahydroisoquinoline *t*-butyl peroxide (10% MsOH in AcOH),[45] and xanthene hydroperoxide (7% MsOH in cyclopentanone as solvent)[42b] (see section 2.1.5 for detail). The unreactivity of peroxide **1** for the first case and formation of phenol (**85**) for the latter one shows that suitable combination of solvent and catalyst is required to activate each hydroperoxide and get the desired selectivity (Table 10, entries 1-3).

Table 10: Test of reaction under our previously developed conditions[a]



1 **91** **85** **92** **93**

Entry	Catalyst (mol%)	Solvent	Product
1	MsOH (10%)	AcOH	-
3[b]	MsOH (7%)	Cylopentanone	Phenol (**85**)

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^{1}H NMR based upon the overall consumption of peroxide **1** and alcohol **94** already present in the solution. [b] The peroxide **1** was quantitatively converted to phenol (**85**).

It is proposed that the substitution might proceed through the coordination of oxygen bonded to carbon, while the activation of oxygen bonded to hydrogen leads to Hock rearrangement. With iron catalysts, a radical mechanism cannot be excluded.[79-80] The reaction might proceed through the reduction of hydroperoxide **1** to alcohol **94** by free radical mechanism with $Fe(OTf)_3$ as catalyst. In order to verify this possibility, a controlled reaction was performed with alcohol **94** as starting material (Figure 3a). It was found that alcohol **94** reacted at much greater rate than peroxide **1** with aniline **91**.

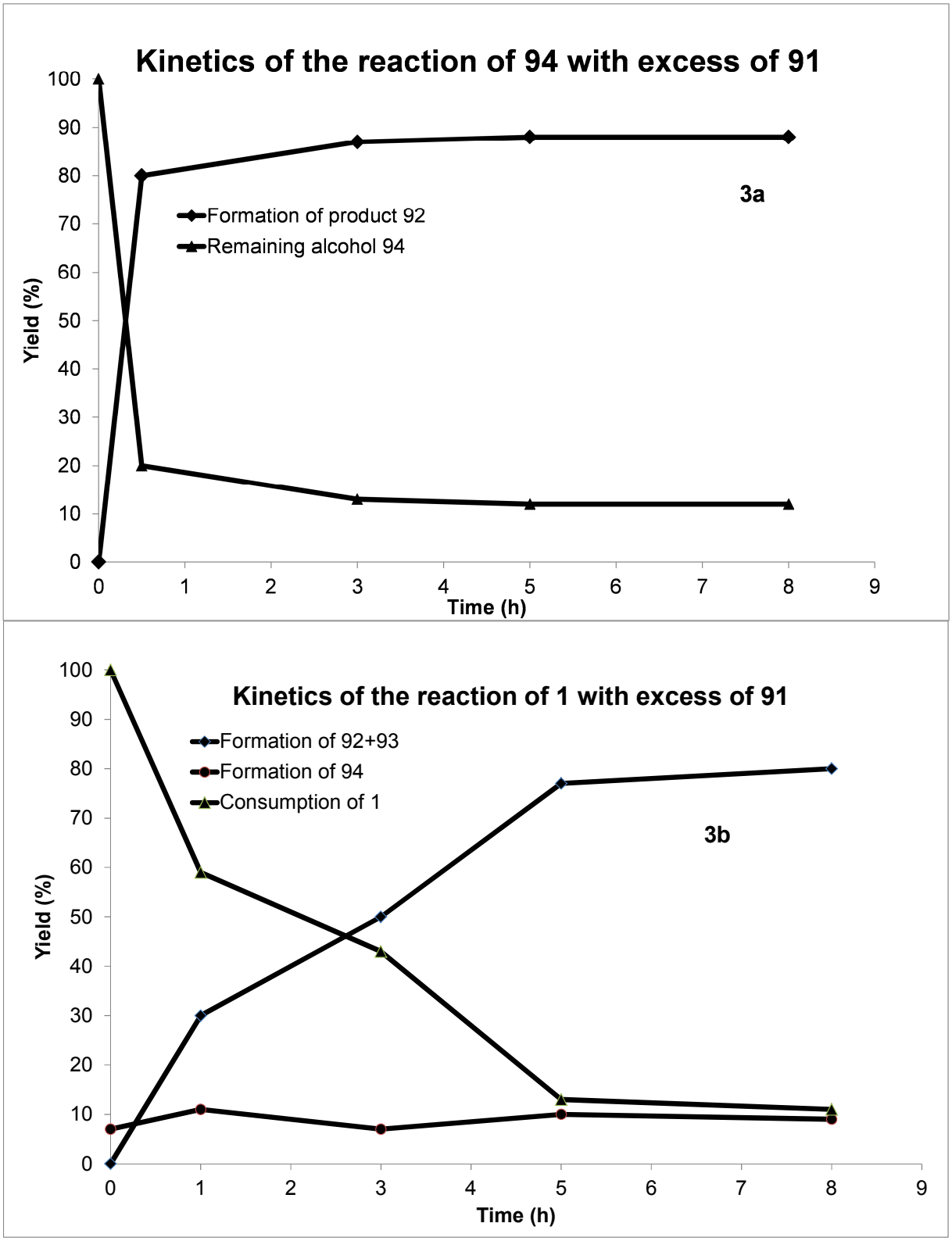


Figure 3: Comparison of rate of reaction of alcohol 94 (Figure 3a) and peroxide 1 (Figure 3b) and; 0.49 mmol of peroxide 1 and 0.49 mmol of alcohol 94, 1.47 mmol of aniline 91, 10 mL of solvent, and 10 mol% of $Fe(OTf)_3$ were used. Yields were determined by ^1H NMR.

After about 80% consumption of alcohol **94** to product **92** an equilibrium was established between coupling product **92** and alcohol **94** and further consumption of alcohol **94** to product **92** could not be achieved (Figure 3a). In comparison to alcohol **94**, the peroxide **1** reacted much slowly and was converted to dimer **93** and product **92** (Figure 3b). The substitution of alcohol **94** with aniline **91** suggested that reduction of peroxide **1** to alcohol **94** might be a rate limiting step followed by the rapid substitution step of alcohol **94** with aniline **91**.

Additionally the control experiment was performed by using comparatively higher molar ratios of alcohol **94** (Figure 4b). After the quantitative consumption of aniline **91** to product **92**, the excess of alcohol **94** did not give any other product (Figure 4b). Based upon this result, I postulated that in case of radical mechanism, after the full conversion of aniline **91** the remaining peroxide **1** should be reduced to alcohol **94**. However, in case of excess of peroxide **1**, it was observed that aniline **91** was not completely consumed and the excess of peroxide **1** was utilized in the formation of dimer **93** (Figure 4a). The formation of dimer **93** by using the excess of peroxide **1** also suggests that reaction does not exclusively proceed through the reduction of peroxide **1**. I further supposed that in case of radical mechanism the absence of nucleophile might result in the formation of alcohol **94** and/or products arising from alcohol **94**. Therefore, a separate reaction was performed without aniline **91** nucleophile (Scheme 51).

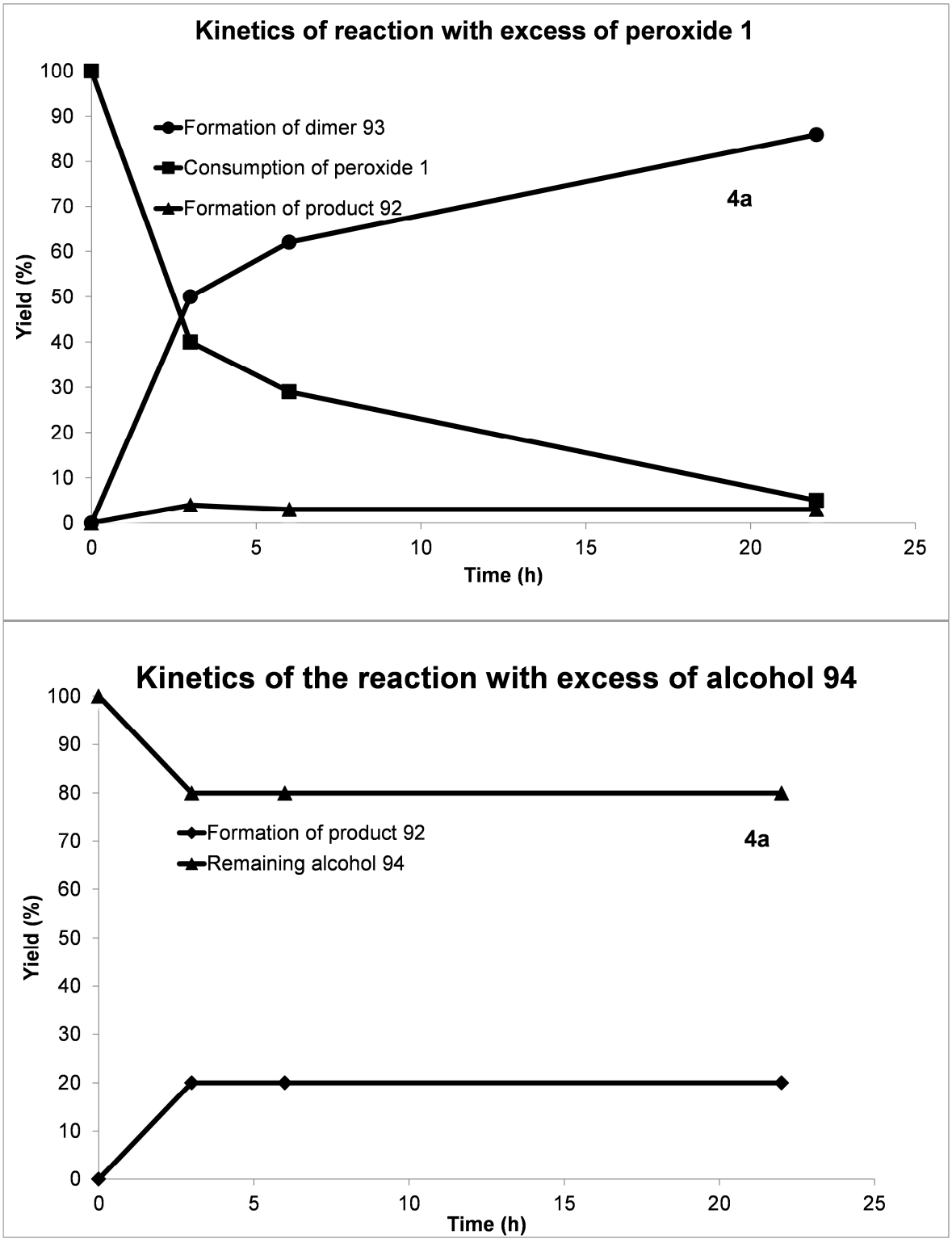
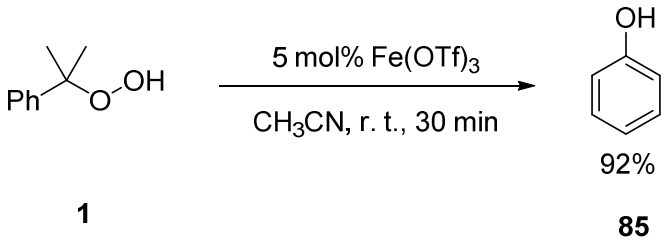


Figure 4: Comparison of reactivity of peroxide 1 (Figure 4a) and alcohol 94 (Figure 4b). For the reaction of alcohol 94 with aniline 91, 2.45 mmol of alcohol 94, and 0.49 mmol of aniline 91 were used. For the reaction of peroxide with aniline 91, 2.45 mmol of peroxide 1, 0.49 mmol of aniline 91, were used. Each reaction was performed at room temperature by using 5 mol% (0.0245 mmol) of catalyst and 10 mL of solvent. Yields were determined by ^{1}H NMR.

The reaction was completed in half an hour and peroxide **1** was quantitatively converted to phenol (**85**) instead of expected products of radical reaction.

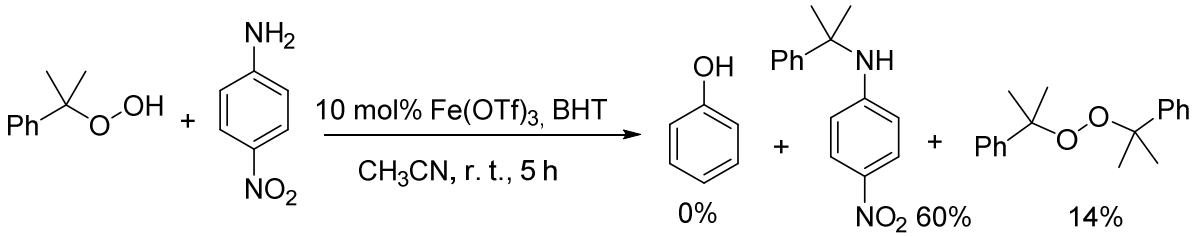


1 **85**

Scheme 51: Control reaction in the absence of aniline 91; 2.45 mmol of 1, 0.025 mmol of $Fe(OTf)_3$ and 10 mL of CH_3CN were used.

The faster reaction in the absence of nucleophile can be explained by the fact that in the presence of aniline **91**, there a is an acid-base reaction between catalyst and aniline **91** which decreses the availability of free cataylst and slows the progress of reaction. In the absence of catalyst there is no such reaction, and used catayst is fully available for the activation of peroxide **1**. Additionally, the change in selectivity can be explained by the assumtion that in the presence of aniline **91**, $Fe(OTf)_3$ might react with aniline **91** to generate another catalyst *in situ* which favors sunstitution reaction. In the absence of aniline **91**, no such reaction is possible and used $Fe(OTf)_3$ is the active catalyst and it favors the formation of phenol (**85**).

In order to get further insight into the reaction mechanism, the reaction was performed using BHT as radical inhibitor (Scheme 52).



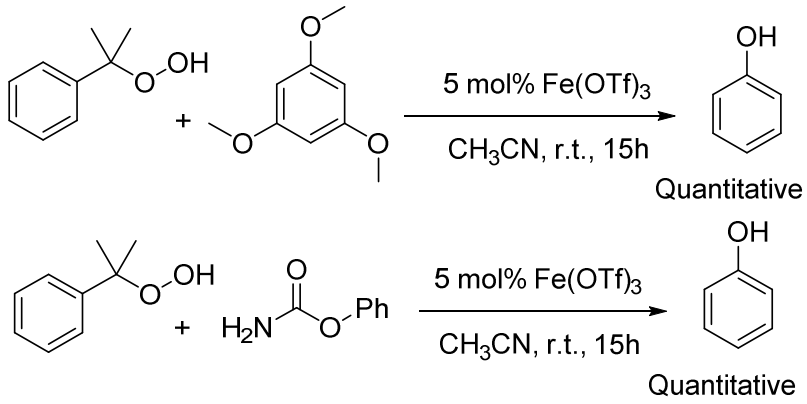
1 **91** **85** **92** **93**

Scheme 52: Control reaction in the presence of radical inhibitor; 0.49 mmol of 1, 1.47 mmol of 91, 0.49 mmol of BHT, 0.049 mmol of $Fe(OTf)_3$ and 10 mL of CH_3CN were used. Yields were determined by ^1H NMR

However, it did not effect the outcome of reaction and similar yields of the substitution products were obtained. This result suggests that reaction does not exclusively proceed through a free radical mechanism.

The formation of substitution products with Brønsted acids also shows that reduction of hydroperoxide **1** is not necessary for the formation of substitution products. Additionally mechanistic studies carried out in our group with xanthene hydroperoxide also suggest that H_2O_2 can serve as leaving group.[12]

I have also tested some other nucleophiles under the best conditions to get substitution products. 1,2,3-trimethoxy benzene and phenyl carbamate were unreactive and phenol (**85**) was formed in quantitative yields (Scheme 53).



Scheme 53: Test of other nucleophiles under standard reaction conditions for substitution

Irreproducible yields were observed by using phenol (**85**) as nucleophile. These results suggest that there is need of further optimization for each new nucleophile.

5.1.3 Summary

In summary, I have found that (i) Different catalysts behaved differently and no corelation was observed between the hardness of an acid and the selectivity for substitution or rearrangement. Therefore, HSAB principle cannot explain the reactivity of cumene hydroperoxide (ii) Solvent plays an important role in the course of acid catalyzed reaction of peroxide **1**. By using the same catalyst in different solvents, the ratio of competing products could be changed. For example, by using $Fe(OTf)_3$ in CH_3CN, substitution products were the only products of the reaction while in acetone, phenol (**85**) was the major product. Similarly, the ratio of

competing products was changed by using $Bi(OTf)_3$ in different solvents. (iii) The selectivity and the reactivity for the catalysts already favoring the rearrangement is further improved by increased catalyst loading. However, elimination product is observed with an increase in catalyst loading of substitution favoring catalyst. Formation of this byproduct suggests that an optimal loading of catalyst is required to yield the desired substitution product. (iv) The course of reaction can be affected by changing the hydroperoxide or by using a different nucleophile.

5.1.4 Consequences for next projects

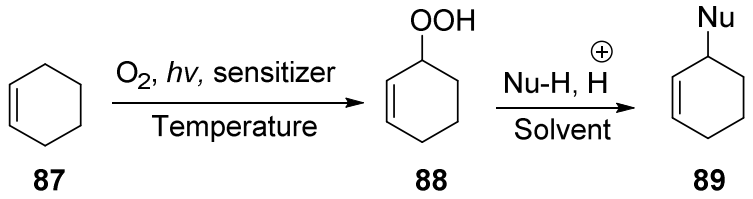
I have found that the course of acid catalysed reaction of hydroperoxide **1** with *p*-nitroaniline (**91**) is affected by the nature of catalyst and solvent. The reactivity and the selectivity is governed by the combination of these factors, the reaction can thus be guided to the one desired direction by using a suitable combination of an acid catalyst and a solvent. The combination of acetonitrile with iron catalysts is suitable to get substitution products while strong Brønsted acids such as MsOH favour the formation of phenol (**85**). Different organic hydroperoxides behave differently and a suitable combination of solvent and catalyst is required to activate each hydroperoxide and get the desired selectivity.

5.2 Allylic C–H functionalization *via* photochemically generated hydroperoxides

5.2.1 Strategy of the project

Cross coupling reactions with allylic substrates are very useful in the synthesis of complex molecules,[71] but only few aerobic allylic C–H functionalizations are known.[72] In order to fulfill the demands of sustainable and green chemistry, I was interested in oxidative C–H functionalization using oxygen as terminal oxidant. For this reason, I started my studies with commonly available cyclohexene (**87**) as a model substrate avoiding any complication from regioselectivity issues.

The strategy of the project was to introduce the hydroperoxide moiety in the cyclohexene (**87**) substrate by singlet oxygen ene reaction with the aid of oxygen, a sensitizer and light and then to substitute it with different nucleophiles under acidic conditions (Scheme 54).



Scheme 54: Project Idea

Cyclohexene **87** can be easily oxidized to the corresponding hydroperoxide **88** by irradiation with visible light in the presence of elemental oxygen and a sensitizer such as tetraphenylporphyrin (TPP).[73] However, this method for the formation of peroxide **88** requires the use of base which is not compatible with my conditions for substitution. There are also few other methods for the formation of peroxide **88** but either they give mixture of products[81] or require special photocatalysts such as $(nBu_4N)_4W_{10}O_{32}$ and $(nBu_4N)_4W_{10}O_{32}$[82].

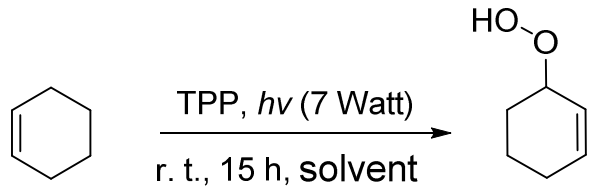
Therefore, I decided to develop a method which could be compatible with acidic conditions and does not require the use of any special synthetic reagents.

5.2.2 Results and discussions

As tetraphenylporphyrin (TPP) has been used before[73] for the transformation of hexene **87** to peroxide **88**, therefore I also initiallly selected tetraphenylporphyrin (TPP) as sensitizer and screened different solvents by using visible light source (7 watt LED) (Table 11).

Among different screened solvents, halogenated solvents (Table 11, entry 5-6) gave comparatively better yields and DCM was selected as solvent for further optimization of this reaction.

Table 11: Screening of solvents[a]



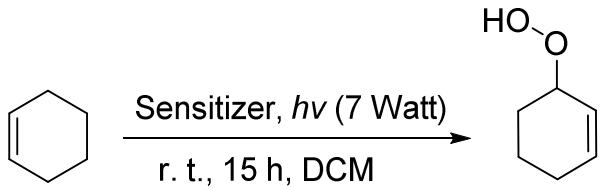
87 **88**

Entry	Solvent	Peroxide 88 (%)
1	CH_3CN	<1
2	MeOH	0
3	EtOAc	5
4	Acetone	5
5	**$CHCl_3$**	**9**
6	**DCM**	**14**
7	Benzene	4
8	Toluene	3
9	Isohexane	0

[a] 0.49 mmol **87**, 10 mL solvent and 1.4 mg (0,0022 mmol, 0.45 mol%) of TPP were used. Yields were determined by ^{1}H NMR based upon the conversion of cyclohexene

Different sensitizers using DCM as solvent were screened (Table 12). Iron phthalocyanine (FePc), rose bengal, 9,10-dicyanoanthracene (DCA) and phthalocyanine were completely inactive under these conditions (Table 12, entry 1-4). Better yields were obtained by using methylene blue and tetraphenylporphyrin (TPP) as sensitizers (Table 12, entry 6-7).

Table 12: Screening of sensitizers[a]



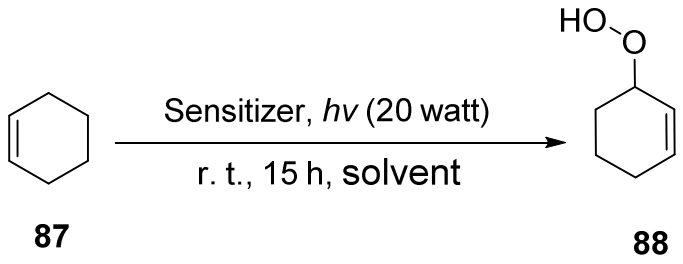
87 **88**

Entry	Sensitizer	Peroxide 88 (%)
1[b]	FePc	0
2	rose bengal	0
3[c]	DCA	0
4	Phthalocyanine	0
5	Tris(bipyridyl) ruthenium chloride	0.2
6	Methylene Blue	13
7	TPP	14

[a]: 0.49 mmol **87**, 1.4 mg sensitizer and 10 mL of solvent were used. Yields were determined by ^{1}H NMR based upon the conversion of cyclohexene. [b] FePC=Iron(II) phthalocyanine. [c] DCA= 9,10-dicyanoanthracene

In order to further optimize the yield of peroxide **88**, I used more intense LED (20 watt) as source of light and tested TPP and Methylene Blue as sensitizers in DCM and $CHCl_3$ (Table 13). A greatly improved yield of 75% was obtained using TPP in $CHCl_3$ (Table 13, entry 3). It showed that intensity of light plays an important role and yield of oxidation step could be improved by using intense source of light.

Table 13: Change of solvents and sensitizers with 20 watt LED[a]



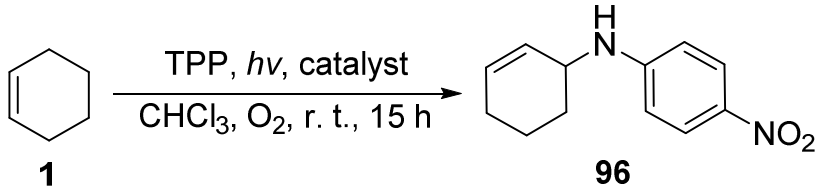
87 **88**

Entry	Solvent	Sensitizer	Peroxide 88 (%)
1	DCM	TPP	43
2	DCM	Methylene blue	0
3	$CHCl_3$	TPP	75
4	$CHCl_3$	Methylene blue	Mixture

[a]: 0.49 mmol **87**, 10 mL solvent and 1.4 mg of sensitizer were used. Yields were determined by ^{1}H NMR based upon the conversion of cyclohexene

Inspired by these results, it was next decided to perform the coupling reaction in one pot using this intense source (20 watt) of visible light (Table 14). The reaction was performed by using $Fe(OTf)_3$ as catalyst. After 15h of reaction time, only starting materials were recovered (Table 14, entry 1). Lewis acids are known to catalyse the ene reaction,[83] therefore in order to facilitate the *in situ* oxidation of hexene **87** to peroxide **88** the reaction was also performed by using other Lewis acids. However, they were also found to be ineffective and oxidation of hexene **87** could not be achieved (Table 14, entry 2-4).

Table 14: Screening of catalyst (One pot)[a]



1 **96**

Entry	Catalyst	Product 96 (%)
1	$Fe(OTf)_3$	0
2	$Fe(OTf)_3$+$AlCl_3$	0
3	$AlCl_3$	0
4	$Fe(OTf)_3$+$ZnCl_2$	0

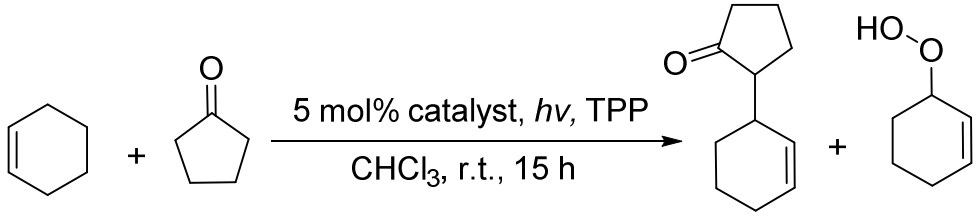
[a]: 0.49 mmol **87**, 10 mL solvent and 1.4 mg (0.0022 mmol, 0.45 mol%) of TPP were used. Light emitting diode of 20 watt was used as source of visible light. Yields were determined by ^{1}H NMR based upon the conversion of cyclohexene

The LED was not fitted with any cooling system and was heated up with time. Therefore, it was difficult to control the temperature of the reaction using this LED and tempeature of the reaction could not be controlled. As the less powerful LED (7 watt) allowed us to maintain the temperature over the course of the reaction this LED was used for further experiments.

The strategy was slightly changed and it was decided to find suitable conditions for the oxidation of cyclohexene **87** to peroxide **88** in the presence of nucleophile. For this purpose, cyclopentanone (**96**) and *para*-nitro aniline (**91**) were used as nucleophiles. Firstly, cyclopentanone (**96**) was employed as nucleophile and the photooxidation reaction was performed using different additives[81] (Table 15, entry 1-3). Among screened additives, $NiCl_2$ gave better results and yield of peroxide **88** was improved to 65% (Table 15, entry 3). There may be two possible explanations for the better outcome of oxidation step by using $NiCl_2$. The first possibility can be the incorporation of Nickel into TPP as a result of ligand exchange and the resulting Ni-TPP sensitizer might be more effective for oxidation of **87** to **88**. The second possibility is that $NiCl_2$ is catalysing the oxidation reaction by working as Lewis acid.[83]

Thus $NiCl_2$ was selected as additive and one pot coupling reactions were performed using different catalysts in the presence of $NiCl_2$. In these reactions catalyst was added together with sensitizer in the beginning of the reaction. Using TFA as catalyst, no coupling product was observed (Table 15, entry 4). The yield of the peroxide **88** was decreased to 33%. However, it was found that formed peroxide **88** is stable under these conditions and does not decompose to other products. PTSA does not significantly effect the formation of peroxide **88**. However, the formed peroxide **88** was also stable under these reaction conditions (Table 15, entry 5). Only starting materials were recovered in the presence of $Fe(OTf)_3$ as catalyst (Table 15, entry 8). Only 8% conversion of hexene **87** to peroxide **88** was observed in the presence of $Sc(OTf)_3$ as catalyst (Table 15, entry 9).

Table 15: Screening of additives and catalysts using cyclopentanone as nucleophile [a]



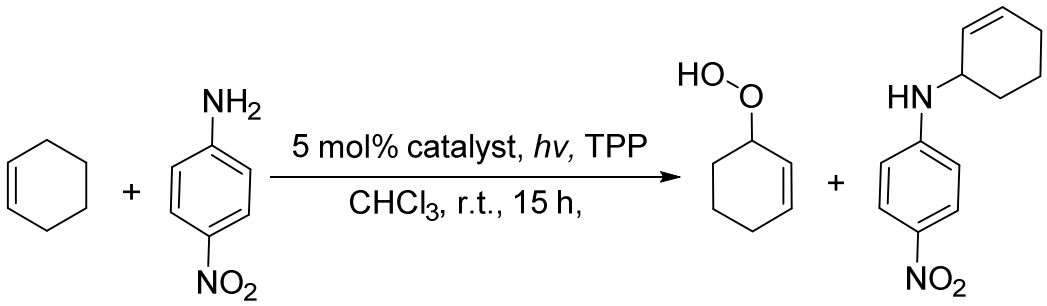
87 **97** **98** **88**

Entry	Additive (5 mol%)	Catalyst	Product 98 (%)	Peroxide 88 (%)
1	$CuCl_2$	-	0	0
2	$MnCl_2$	-	0	24
3	$NiCl_2$	-	0	65
4	$NiCl_2$	TFA	0	33
5	$NiCl_2$	PTSA	0	50
6	$NiCl_2$	$Fe(OTf)_3$	0	0
7	$NiCl_2$	$Sc(OTf)_3$	0	08

[a]: 0.49 mmol **87**, 0.49 mmol of **97**, 10 mL solvent and 1.4 mg (0.0022 mmol, 0.45 mol%) of TPP were used. Yields were determined by ^1H NMR based upon the conversion of cyclohexene

A similar strategy was adopted using *p*-nitroaniline (**91**) as nucleophile (Table 16) and $NiCl_2$ was found to be better additive which gave peroxide **88** in 52% yield (Table 16, entry 3). No oxidation of cyclohexene (**87**) was observed by adding TFA, $Fe(OTf)_3$, and $Sc(OTf)_3$ as catalyst in the beginning of reaction (Table 16, entry 4-6). An improved yield of 59% of peroxide **88** was observed using PTSA as catalyst (Table 16, entry 7). However, the formed peroxide **88** was stable under these conditions and no coupling product could be observed.

Table 16: Screening of additives and catalysts using aniline 91 as nucleophile (One pot method)[a]



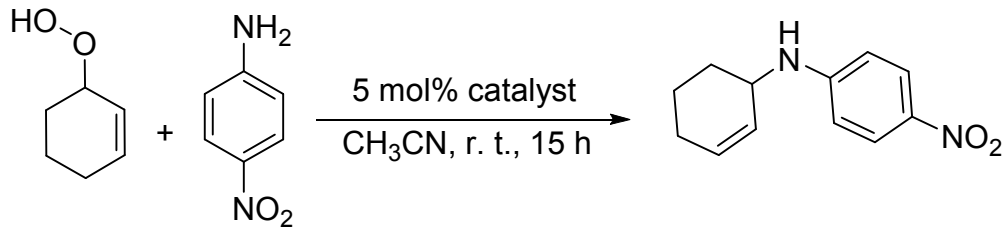
87 **91** **88** **96**

Entry	Additive (5 mol%)	Catalyst	Product 96 (%)	Peroxide 88 (%)
1	$CuCl_2$	-	0	40
2	$MnCl_2$	-	0	0
3	$NiCl_2$	-	0	52
4	$NiCl_2$	TFA	0	0
5	$NiCl_2$	$Fe(OTf)_3$	0	0
6	$NiCl_2$	$Sc(OTf)_3$	0	0
7	$NiCl_2$	PTSA	0	59

[a]: 0.49 mmol **87**, 0.49 mmol of **91**, 10 mL solvent and 1.4 mg (0.0022 mmol, 0.45 mol%) of TPP were used. Yields were determined by ^1H NMR based upon the conversion of cyclohexene

After these experiments, I realized that finding a suitable catalyst for the coupling of peroxide **88** with nucleophile was a significant challenge. For this reason, I screened different Lewis and Brønsted acid catalysts for the coupling of isolated peroxide **88** with aniline **91**. During the studies with cumene hydroperoxide, acetonitrile was found to be a suitable solvent for substitution reaction. Therefore, here also, it was decided to used acetonitrile as solvent for the coupling of coupling of peroxide **88** with aniline **91**. The used Brønsted acids (Table 17, entry 1-3) were completely inactive and only the starting materials were recovered after 15 h. To my delight by using iron triflate peroxide **88** was completely consumed and the desired product was obtained in 11% yield (Table 17, entry 5).

Table 17: Screening of Lewis and Brønsted acid catalysts[a]



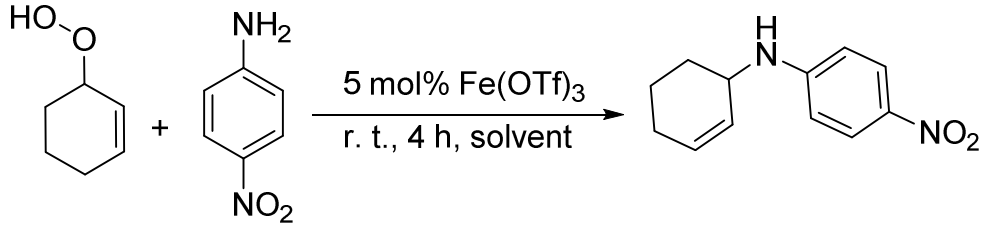
87 **91** **96**

Entry	Catalyst	Product 96 (%)	Peroxide 88 (%)
1	TfOH	0	100
2	MsOH	0	100
3	TFA	0	100
4	$Sc(OTf)_3$	0	100
5	$Fe(OTf)_3$	12	0
6	$(NH_4)_2Fe(SO_4)_2 \cdot 7H_2O$	0	100
7	$FePO_4$	0	100
8	$Fe(NO_3) \cdot 9H_2O$	5-6	0
9	$FeBr_3$	0	0
10	$FeCl_3 \cdot 6H_2O$	0	0
11	$FeCl_2$	0	0
12	$InBr_3$	0	100
13	$Cu(OAc)_2$	0	0
14	$Yb(OTf)_3$	0	100
15	$FeBr_2$	0	0
16	$Bi(OTf)_3$	3	40
17	$Fe(ClO_4)_2 \cdot XH_2O$	4	0
18	$Fe(OTf)_2$	0	0
19	$Fe(OTs)_3 \cdot 6H2O$	0	0
20	$Cu(OTf)_2$	0	0

[a]: 0.49 mmol **87**, 0.49 mmol of **91**, 10 mL solvent and 5 mol% of catalyst were use. Yields were determined by ^1H NMR based upon the conversion of aniline **91**

Because of the volatility of byproducts arising from peroxide **88** and potential danger of explosion during distillation it was difficult to characterize the byproducts of reaction. All the other Lewis acids were either completely inactive or did not promote the formation of the desired product **96** (Table 17, entry 4-20). After this screening of different catalysts, it was decided to investigate the transformation in other solvent systems. For this reason, different solvents using $Fe(OTf)_3$ as catalysts were screened.

Table 18: Screening of solvents[a]



88 **91** **96**

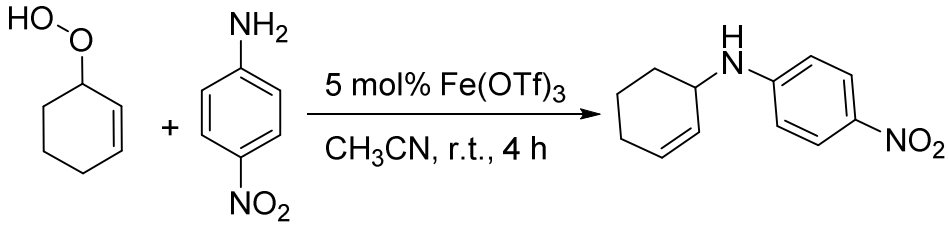
Entry	Solvent	Product 96 (%)	Peroxide 88 (%)
1	Propionitrile	2	0
2	Benzonitril	complex mixture	0
3	Cyanophenol (5.0 equiv)	10	0
4	Toluene	0	0
5	$CHCl_3$	0	0
6	MeOH	0	0
7	DMSO	0	0
8	AcOH	0	0
9	EtOAc	7	0
10	DCM	3	0
11	Acetone	11	0

[a]: 0.49 mmol **88**, 0.49 mmol of **91** and 10 mL of solvent were used. Yields were determined by 1H NMR based upon the conversion of aniline **91**

Few other nitrile group containing solvents were also tried (Table 18, entry 1-3). However, there was no improvement in the yield of desired product. For most of other solvents complete decomposition of peroxide **88** was observed (Table 18, entry 4-8). Among these solvents, comparatively better yield of product **96** was observed by using acetone as solvent (Table 18, entry 11).

The reaction was also performed by varying the molar ratio of nucleophile **91** and it was found that it did not affect the yield of desired product (Table 19, entry 1-3). By decreasing the temperature, the reaction was slowed down and the yield of the product **96** was further decreased (Table 19, entry 4-5).

Table 19: Effect of change of the molar ratio of nucleophile and temperature on the yield of reaction[a]

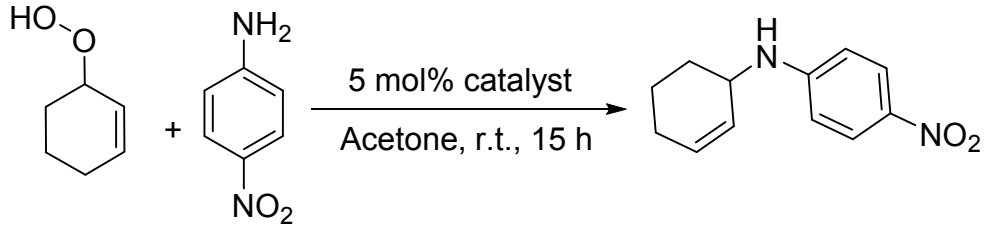


Entry	Equiv. (3)	Temperature (°C)	Product 96 (%)	Peroxide 88 (%)
1	1	r.t.	11	0
2	2	r.t.	11	0
3	3	r.t.	11	0
4	1	0	1	75
5	1	-40	0	90

[a]: 0.49 mmol **88**, 0.49-1.47 mmol of **91** and 10 mL solvent was used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

There was no improvement in yield even after changing different parameters. It was decided to investigate different catalysts in acetone, which was the second suitable solvent so far. Among screened Brønsted acids (Table 20, entry 1-8) MsOH anf TfOH were more effective than others.

Table 20: Screening of Brønsted acids with acetone as solvent[a]



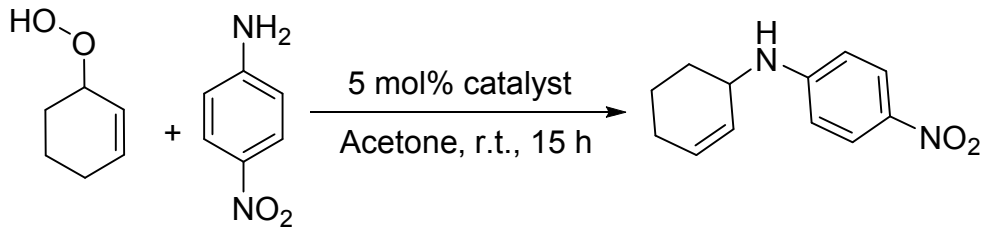
88 **91** **96**

Entry	Catalyst	Product 96 (%)	Peroxide 88 (%)
1	TFA	0	0
2	MsOH	20	0
3	PTSA	13	0
4	TfOH	20	0
5	$HClO_4$	complex	0
6	HCl	0	100
7	HNO_3	2	60
8	H_2SO_4	complex	0

[a]: 0.49 mmol **88**, 0.49 mmol of aniline **91** and 10 mL of solvent were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

Among screened Lewis acids, slightly improved yields were obtained by using $Sc(OTf)_3$, $Fe(OTs)_3 \cdot 6H_2O$, $Yb(OTf)_3$, and $FeCl_3 \cdot 6H_2O$ as catalyst (Table 21, entry 1-4). Either complete decomposition and poor yields were observed by using other Lewis acids (Table 21, entry 5-14).

Table 21: Screening of Lewis acids with acetone as solvent[a]



88 **91** **96**

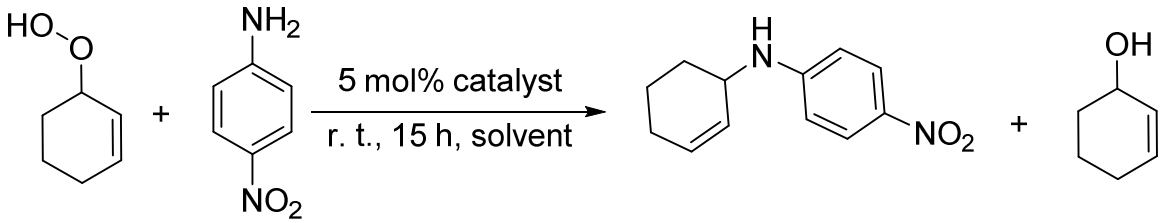
Entry	Catalyst	Product 96 (%)	Peroxide 88 (%)
1	$Sc(OTf)_3$	13	0
2	$Fe(OTs)_3 \cdot 6H_2O$	25	0
3	$Yb(OTf)_3$	22	0
4	$FeCl_3 \cdot 6H_2O$	19	0
5	$FeCl_2$	13	0
6	$Cu(OAc)_2$	0	0
7	$FeBr_3$	10	0
8	$FeBr_2$	3	0
9	$Bi(OTf)_3$	11	0
10	$Fe(ClO_4)_2 \cdot XH_2O$	10	0
11	$Fe(OTf)_2$	10	0
2	$Fe(NO3)_3 \cdot 9H_2O$	2-4	0
13	$Cu(OTf)_2$	7	0
14	$InBr_3$	10	0

[a]: 0.49 mmol 58, 0.49 mmol of aniline **91** and 10 mL of solvent were used. Yields were determined by ^1H NMR based upon the conversion of aniline **91**

In order to further improve the yield I selected promosible catalysts and decided to screen different solvents using these catalysts one by one (Table 22). There was no improvement in the yield of the coupling product **96** using $Fe(OTs)_3 \cdot 6H_2O$ as catalyst in different solvents (Table 22, entry 1-9). A mixture of cyclohexenol,

peroxide **88** and of desired product **96** was observed at the end of reaction using DCM as solvent (Table 22, entry 6). Methane sulfonic acid was found to be completely inactive in most of the used solvents and only starting materials were recovered at the end of reaction. In methanol and EtOAc complete decomposition of peroxide **88** was observed. Only 7% of the desired product **96** was observed using acetonitrile as solvent. Similarly either decomposition or complete unreactivity of peroxide **88** was observed during screening of solvents in the presence of $Sc(OTf)_3$ as catalyst (Table 22, entry 1-9).

Table 22: Screening of solvents with different catalysts[a]



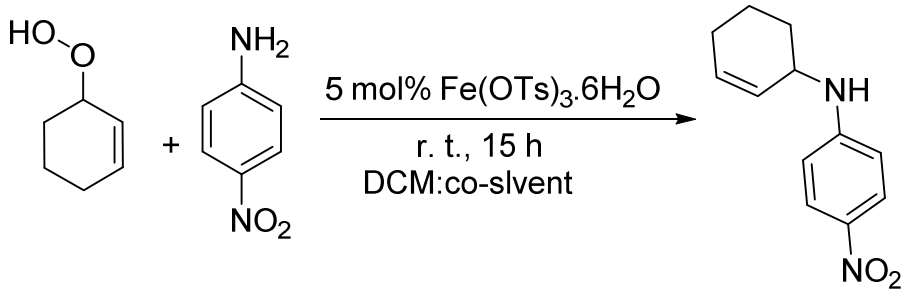
		$Fe(OTs)_3{\cdot}6H_2O$		MsOH		PTSA		$Sc(OTf)_3$	
Entry	**Solvent**	**96(%)**	**88(%)**	**96(%)**	**88(%)**	**96(%)**	**88(%)**	**96(%)**	**88(%)**
1	CH_3CN	4	0	7	5	3	2	7	20
2	MeOH	0	0	0	0	0	0	0	0
3	EtOAc	7	0	0	0	0	0	0	0
4	$CHCl_3$	0	100	0	100	0	100	0	0
5	Benzene	0	100	0	100	0	100	0	100
6	DCM	6	16[b]	0	100	0	100	0	100
7	Toluene	0	70	0	100	0	100	0	100
8	Chlorobenzene	0	100	0	100	0	100	0	100
9	DMF	0	100	0	100	0	100	0	100

[a]: 0.49 mmol **88**, 0.49 mmol of aniline **91** and 10 mL of solvent were used, 5 mol% of each catalyst was used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: 30% cyclohexenol **98** was also observed at the end of reaction

The presence of mixture of alcohol **98** and peroxide **88** at the end of reaction by using $Fe(OTs)_3.6H_2O$ as catalyst in DCM as solvent was interesting to us (Table 22, entry 6).

Potentially, alcohol **98** could be formed through the reduction of peroxide **88** with iron catalyst[79-80] or by nucleophilic substitution of peroxide moiety with residual water already present in non dry solvents. I envisaged that yield of the product **96** could be improved by finding the suitable conditions (e.g. cosolvent and catalyst) which could help in reducing peroxide **88** to alcohol **98** *in situ* and then converting the formed alcohol **98** to product **96** more efficiently. For this purpose I selected DCM as the solvent and screened different co-solvents. The combination of DCM with nitromethane afforded 20% coupling product. The yield was decreased to 10% by using nitroethane as cosolvent and complete decomposition was observed in the presence of nitrobenzene. I then further increased the ratio of nitromethane and it did not show any significant positive effect on the yield of reaction (Table 23, entry 1-6). The yield was decreased to 14% when nitromethane was used as the only solvent. Other chlorinated solvents were also tried in combination with DCM (Table 23, entry 7-12), but no improvement in the yield of the desired product was observed.

Table 23: Screening of co-solvents with DCM as major solvent of reaction[a]



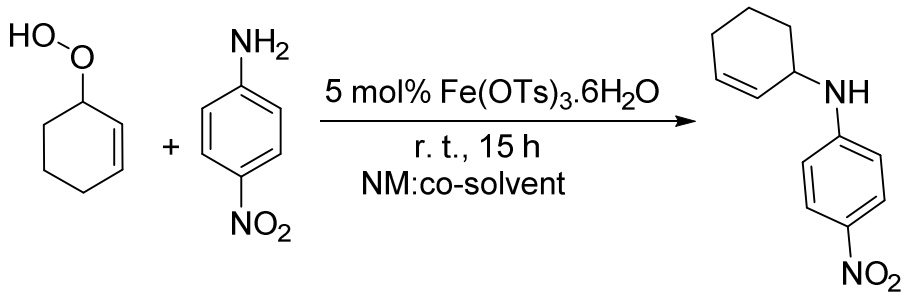
88 **91** **96**

Entry	Ratio; DCM:co-solvent	Product 96 (%)
1	Nitromethane (9:1)	20
2	Nitroethane (9:1)	10
3	Nitrobenzene (9:1)	0
4	Nitromethane (8:2)	20
5	Nitromethane (5:5)	20
6	Nitromethane (0:10)	14
7	Chlorobenzene (9:1)	5
8	CCl_4 (9:1)	0
9	1,1,2-trichloroethane (9:1)	6
10	1,2-dichloropropane (9:1)	0
11	1,2,2,2-tetrachloroethane (9:1)	0
12	$CHCl_3$ (9:1)	7
13	$CHCl_3$ (8:2)	7
14	$CHCl_3$ (5:5)	7

[a]: 0.49 mmol **88**, 0.49 mmol of aniline **91** and 10 mL of solvent were used, a: Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

I selected nitromethane as solvent and screened different co-solvents in the presence of nitromethane as major solvent of reaction. A yield of 20% of product **96** was observed using combination of nitromethane and 1,1,2,2-tetrachloroethane (Table 24, entry 4). And the yield of product was further improved to 25% by using 1:1 ratio of these solvents. The yield of product was decreased when 1,1,2,2-tetrachloroethane was used as the only solvent of reaction (Table 24, entry 8). The use of acetonitrile and chloroform as co-solvents was not helpful in optimizing the yield of product **96**.

Table 24: Screening of co-solvents with nitromethane as major solvent of reaction[a]



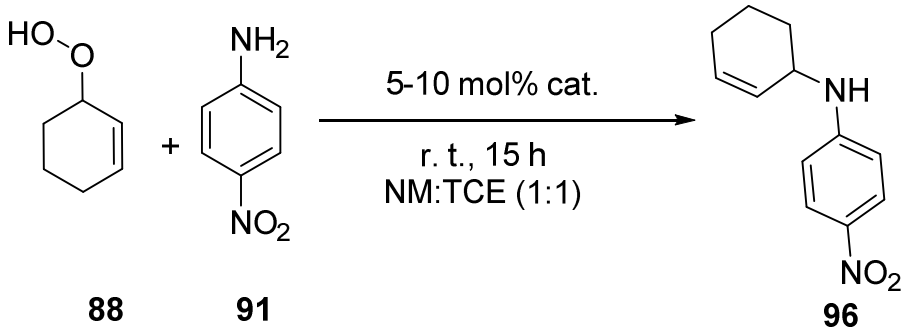
88 **91** **96**

Entry	(Ratio; NM:co-solvent)	Product 96 (%)
1	Ethylene dichloride (9:1)	12
2	1,2-dichloropropane (9:1)	10
3	1,1,2-trichloroethane (9:1)	5
4	1,1,2,2-tetrachloroethane (9:1)	20
5	1,1,2,2-tetrachloroethane (7:3)	25
6	1,1,2,2-tetrachloroethane (5:5)	25
7	1,1,2,2-tetrachloroethane (3:7)	25
8	CH_3CN (9:1)	0
9	$CHCl_3$ (9:1)	11

[a]: 0.49 mmol **88**, 0.49 mmol of aniline **91** and 10 mL of solvent were used, a: Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

As better yields were obtained by using a mixture of nitromethane (NM) and 1,1,2,2-tetrachloroethane (TCE) therefore it was decided decided to screen different catalysts in this solvent mixture. A yield of 23% was obtained using $FeCl_3 \cdot 6H_2O$ as catalyst. The use of 10 mol% of $FeCl_3 \cdot 6H_2O$ was even more beneficial and yield was increased to 30% (Table 25, entry 1-2). Similarly, 10 mol% of $HClO_4$ was more useful than 5 mol% of $HClO_4$ (Table 25, entry 3-4). Therefore, $FeCl_3 \cdot 6H_2O$ and $HClO_4$ were selected as catalysts. By using these catalysts, the molar ratio of aniline **91** was increased to 3.0 equivalents of aniline **91** and yield of product **96** was improved to 45% and 40% with $FeCl_3 \cdot 6H_2O$ and $HClO_4$ respectively (Table 25, entry 5-8). Few other Brønsted acids were also tested but inferior yields of product **96** were obtained (Table 25, entry 9-12).

Table 25: Screening of catalysts using mixture of NM and TCE as solvent[a]



88 **91** **96**

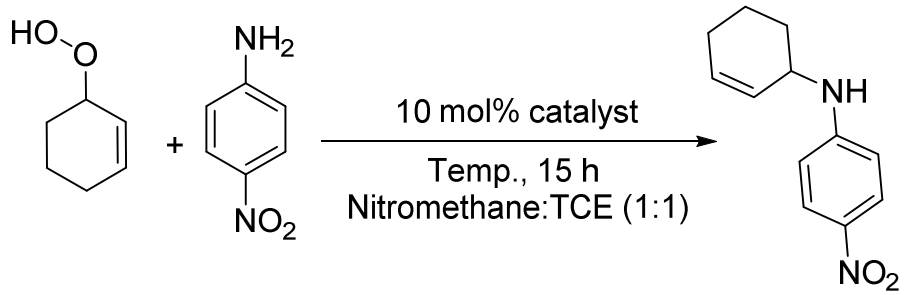
Entry	Catalyst	mol(%)	Aniline 91 (equiv)	Product 96 (%)
1	$FeCl_3 \cdot 6H_2O$	5	1.0	23
2	$FeCl_3 \cdot 6H_2O$	10	1.0	30
3	$HClO_4$	5	1.0	30
4	$HClO_4$	10	1.0	40
5	$FeCl_3 \cdot 6H_2O$	10	3.0	45
6	$FeCl_3 \cdot 6H_2O$	10	5.0	40
7	$HClO_4$	10	3.0	43
8	$HClO_4$	10	5.0	40
9	HCl	10	3.0	10
10	H_2SO_4	10	3.0	15
11	HNO_3	10	3.0	20
12	TfOH	10	3.0	33

Conditions: 0.49 mmol **88**, 0.49-2.45 mmol of aniline **91** and 10 mL of solvent were used, a: Yields were determined by ^1H NMR based upon the conversion of aniline **91**

Before screening other catalysts, I wanted to find an optimal temperature for the reaction. For this reason, the reaction was performed at different temperatures by using the catalysts which afforded comparatively better yields so far. In general, no dramatic effect was observed by varying the temperature between 15-25 °C.

Slightly better yield of 45% was obtained performing the reaction at 25 °C using $FeCl_3 \cdot 6H_2O$ as catalyst (Table 26, entry 12).

Table 26: Screening of temperature using different catalysts[a]



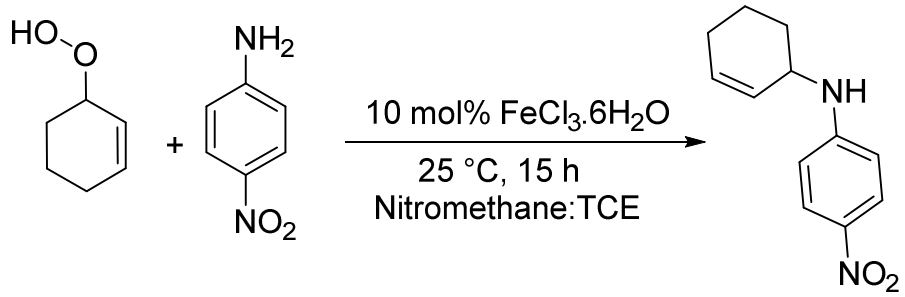
88 **91** **96**

Entry	Catalyst	Temperature (°C)	Product 96 (%)
1	TfOH	15	29
2	TfOH	15	34
3	$FeCl_3 \cdot 6H2O$	15	35
4	$HClO_4$	15	30
5	$Fe(OTS)_3 \cdot 6H_2O$	15	18
6	$Fe(OTS)_3 \cdot 6H_2O$	15	22
7	TfOH	20	35
9	$FeCl_3 \cdot 6H_2O$	20	40
10	$HClO_4$	20	30
11	TfOH	25	28
12	$FeCl_3 \cdot 6H_2O$	25	45
13	$HClO_4$	25	26

[a]: 0.49 mmol **88**, 1.47 mmol of aniline **91** and 10 mL of solvent were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

Subsequently, I investigated the effect of solvent system and the ratio of nitromethane (NM) and 1,1,2,2-tetrachloroethane (TCE) was varied at 25 °C using $FeCl_3 \cdot 6H_2O$ as catalyst. The yield of product **96** was increased by increasing the amount of TCE and the better result was obtained with 1:1 ratio of NM and TCE. The further increase in the ratio of TCE was not useful and a significant drop in the yield of desired product was observed when TCE was used as the only solvent of reaction.

Table 27: Variation in the ratio of nitromethane and TCE[a]



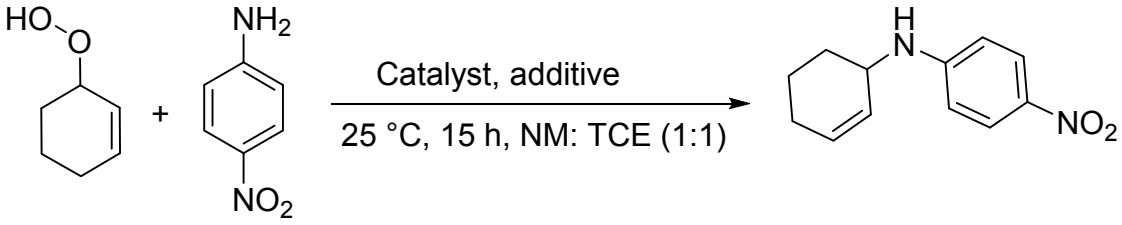
88 **91** **96**

Entry	Ratio (NM:TCE)	Product 96 (%)
1	9:1	41
2	8:2	41
3	7:3	43
4	6:4	43
5	5:5	45
6	4:6	37
7	3:7	37
8	2:8	37
9	1:9	37
10	0:10	27

[a]: 0.49 mmol **88**, 1.47 mmol of aniline **91** and 10 mL of solvent were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

Organic peroxides are known to be reduced to corresponding alcohol with sulfides.[51d, 65, 75, 84] Thus I planned to use an additive which could *in situ* reduce the peroxide **88** to corresponding alcohol **98** which in turn could potentially act as electrophile for the coupling reaction, thus avoiding all the unwanted by products arising from peroxide **88**. For this reason DMSO and dimethyl sulfide (DMS) were tested in combination with $FeCl_3 \cdot 6H_2O$ and $HClO_4$. However this strategy did not prove to be efficient and yield of the product was decreased (Table 28, entry 1-6). The increase and decrease in the loading of the catalyst was also not helpful in the optimization of the yield of product **96** (Table 28, entry 7-9).

Table 28: Effect of DMSO and DMS on the outcome of the reaction[a]



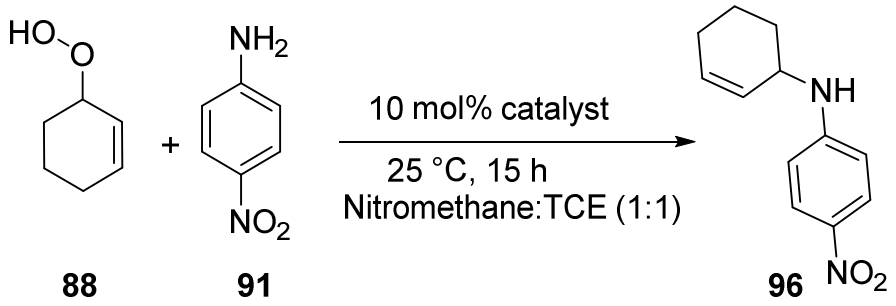
88 **91** **96**

Entry	$FeCl_3.6H_2O$ (mol%)	$HClO_4$ (mol%)	DMSO (Equiv)	DMS (Equiv)	96 (%)
1	10	-	1.0	-	7
2	5	5	1.0		18
3	-	10	1.0		18
4	10	-	-	1.0	12
5	5	5		1.0	12
6	-	10		1.0	20
7	15	-	-	-	32
8	20	-	-	-	32
9	5	-	-	-	11

[a]: 0.49 mmol **88**, 1.47 mmol of **91** and 10 mL solvent was used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**.

Using a combination of nitromethane and tetrachloroethane, I screened different other acid catalysts. Poor yields were obtained by using MsOH and PTSA (Table 29, entry 1-2). Few Lewis acids (Table 29, entry 3-8) were completely inactive for the coupling reaction and resulted in the decomposition of peroxide **88**. However, better yield was obtained by using $Cu(OTf)_2$ (Table 29, entry 3-8) as catalyst. I then tried iron (II) catalysts and an improved yield of 50% was obtained by using $Fe(OTf)_2$ as catalyst (Table 29, entry 10-12). Among iron (III) catalysts, $Fe(ClO4)_2{\cdot}xH_2O$ was most effective and afforded a yield of 50% (Table 29, entry 13-15). Among other Lewis acids, $Bi(OTf)_3$ and $Sc(OTf)_3$ were more effective which also gave a yield of 50% (Table 29, entry 18-20). In general, Lewis acids were more effective than Brønsted acids and better yields were obtained by using Fe $(OTf)_2$, $Bi(OTf)_3$ and $Sc(OTf)_3$ as catalysts. $Hf(OTf)_4$ was also tried and no further improvement was observed (Table 29, entry 21).

Table 29: Screening of acids with a mixture of nitromethane and TCE as solvent[a]



88 **91** **96**

Entry	Catalyst	Product 96 (%)
1	MsOH	15
2	PTSA	18
3	FePc	0
4	$PdCl_2$	0
5	$YbCl_3{\cdot}6H_2O$	0
6	$Fe(OAc)_2$	0
7	$SnCl_4$	0

8	$Cu(OAc)_2$	0
9	$Cu(OTf)_2$	39
10	$FeBr_2$	30
11	$FeCl_2$	42
12[b]	$Fe(OTf)_2$	50 (33)
13	$FeBr_3$	38
14	$Fe\ (NO_3)_3 \cdot 9H_2O$	38
15	$Fe(ClO_4)_2 \cdot xH_2O$	50
16	$La(OTf)_3$	31
17	$Y(OTf)_3$	35
18	$In(OTf)_3$	42
16[b]	$Bi(OTf)_3$	50 (35)
20	$Sc(OTf)_3$	50
21	$Hf(OTf)_4$	48

[a]: 0.49 mmol **87**, 1.47 mmol of aniline **91** were used and 10 mL of solvent. Yields were determined by ^1H NMR based upon the conversion of aniline **91**. [b] Numbers in brackets represent isolated yields

5.2.3 Summary

In summary, It has been shown that the yield of the peroxide **88** could be improved to 75% by using molecular oxygen, visible light, and a sensitizer. Followed by this initial step, the coupling of hydroperoxide **88** with *p*-nitroaniline (**91**) could also be achieved in moderate yields. Because of the volatility of byproducts arising from peroxide **88** and potential danger of explosion during distillation it was difficult to characterize the byproducts of reaction. Therefore, it was not possible to design a strategy for suppressing the formation of these unwanted byproducts and, hence, the yield of the coupling product could not be further improved. However, these results proved that peroxide moiety can be, in general, used as leaving group.

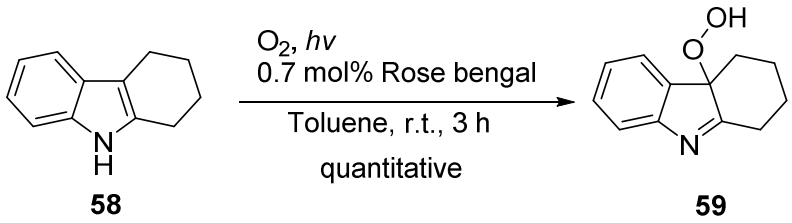
After getting further motivation from this project, I wanted to try other organic hydroperoxides. For this reason, I decided to choose a substrate which could easily be oxidized to corresponding hydroperoxide and was also less volatile. For this reason, tetrahydrocarbazole was selected as substrate for coupling reaction (see next chapter).

5.3 C–H functionalization of tetrahydrocarbazole derivatives *via* photochemically generated hydroperoxides

5.3.1 Strategy of the project

The indolic core is present in a large number of biological active compounds[74a] and indoles are known to form peroxides by autooxidation in air.[64]

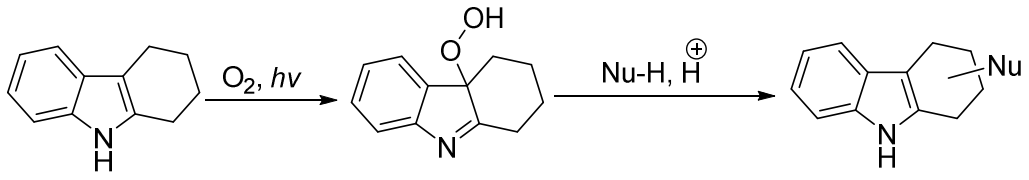
The photooxidation of tetrahydrocarbazole **58** with singlet oxygen[50] using toluene as solvent and rose bengal as sensitizer yields peroxide **59** in quantitative yields.[64-65] The peroxide **59** formed during the reaction can be isolated from the reaction mixture *via* precipitation and can be stored at room temperature for several months without any decomposition. Therefore, I selected 1,2,3,4-tetrahydrocarbazole (**58**) as the standard substrate.



58 **59**

Scheme 55: Photooxidation of carbazole 58 to carbazole hydroperoxide 59

Strategy of the project was to introduce the hydroperoxide moiety in the selected substrate with the aid of oxygen, a sensitizer and light and then substitute it with different nucleophiles under acidic conditions (Scheme 56).



58 **59** **90**

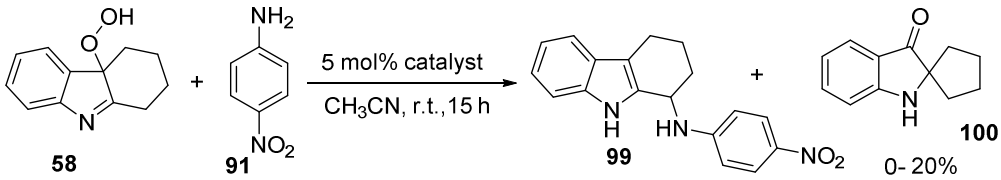
Scheme 56: Project Idea

5.3.2 Results and discussions

5.3.2.1 Development of one pot method

During the studies with cumene hydroperoxide, the use of $Fe(OTf)_3$ as catalyst and acetonitrile as solvent was found to be suitable for substitution reaction. Therefore the reaction was performed by using isolated peroxide **59** as electrophile, *p*-nitroaniline (**91**) as nucleophile and 5 mol% $Fe(OTf)_3$ as catalyst. The reaction mixture was allowed to stir until the full conversion of peroxide **59**. To my delight, 8% of the coupling product could be isolated (10% ^{1}H NMR yield) (Table 30, entry 1). All other iron catalysts gave inferior yields (Table 30, entry 2-14). Among other unidentified byproducts, the spiro product **100** was observed as the major byproduct in different ratios during different reactions. However, due to the overlapping of signals, it was not possible to quantify spiro product **100** in all the reactions. Notably, no product formation was observed in the absence of catalyst.

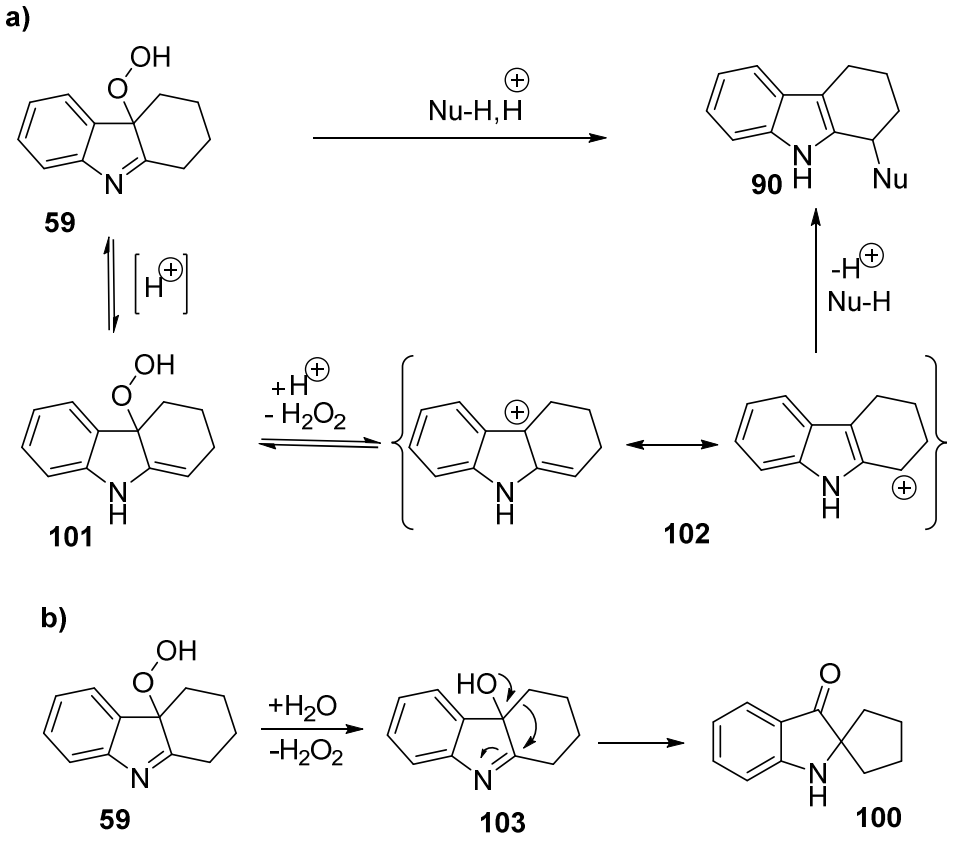
Table 30: Screening of iron catalysts[a]



Entry	Catalyst (5 mol%)	Aniline 91 (Remaining, %)	Product 99 (%)
1[b]	$Fe(OTf)_3$	90	10 (8)
2	$FeCl_2$	100	Traces
3	$K_4Fe(CN)_6$	100	0
4	$FePO_4$	100	0
5	$FeBr_3$	100	0
6	$FeCl_3$	93	7
7	$Fe(NO_3)_3.9H_2O$	91	9
8	$Fe(OAc)_2$	100	0
9	Iron acetylacetonate	100	0
10	$K_4Fe(CN)_6$	100	0
11	$FePO_4$	100	0
12	$(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$	100	0
13	$FeBr_2$	100	0
14	$(C_5H_5)Fe(CO)_2I$	100	0

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of CH_3CN were used. Yields were determined by ^1H NMR based upon the conversion of *p*-nitroaniline (**91**). [b]: The numbers in brackets represent isolated yield

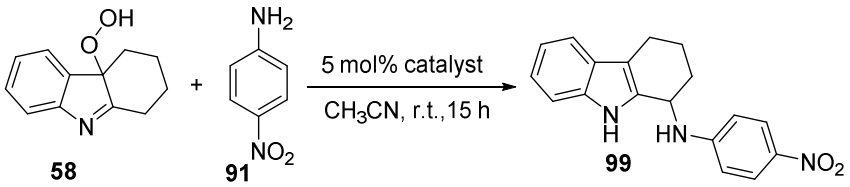
The new C–N bond was selectively formed in the 1-position of the saturated ring. The regiochemistry was unambiguously confirmed with the help of ^{1}H NMR spectroscopy. A plausible reaction mechanism is shown in Scheme 57a. It involves the acid catalyzed tautomerism of imine **59** to enamine **101**. Then the removal of H_2O_2 leads to the carbocation **102** which is then attacked by nucleophile to afford the rearomatized coupling product **90**. The possible mechanism for the formation of spiro product **100** involves the hydrolysis of peroxide **59** to generate alcohol **103**. Potentially with iron catalysts the alcohol **103** can also form by the decomposition of peroxide **59**.[79-80] The alcohol **103** further undergoes 1,2-rearrangement to afford spiro product **100**.[50, 85]



Scheme 57: Plausible mechanism for the coupling of peroxide 59 with aniline 91 and for the formation of spiro product 100

I, then, screened few other Lewis and Brønsted acids. By using PTSA as catalyst, 5% of the desired coupling product **99** could be observed (Table 31, entry 1). $Bi(OTf)_3$ and $Sc(OTf)_3$ also afforded the coupling product **99** in comparable yields to $Fe(OTf)_3$ (Table 31, entry 2-3). Decomposition of peroxide **59** was observed by using MsOH as catalyst (Table 31, entry 4). In all these reactions, in addition to the formation of unidentified by products, spiro product **100** (Scheme 57b) was always observed.

Table 31: Further screnning of acids

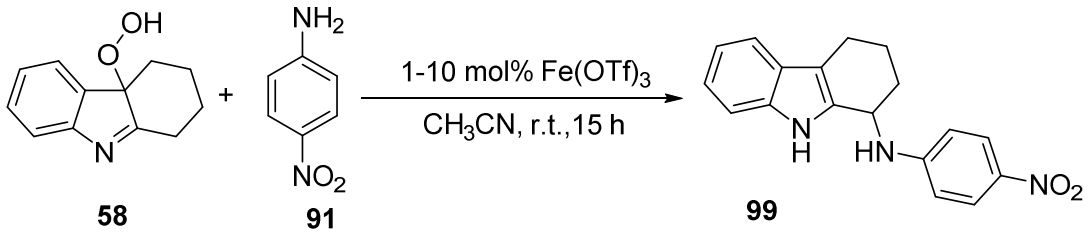


Entry	Catalyst (5 mol%)	Aniline 91 (Remaining, %)	Product 99 (%)
1	PTSA	95	5
2	$Bi(OTf)_3$	90	10
3	$Sc(OTf)_3$	92	8
4	MsOH	100	0

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of CH_3CN were used. Yields were determined by ^1H NMR based upon the conversion of *p*-nitroaniline **91**.

In order to further improve the outcome of the reaction, a screening of the loading of catalyst was then performed. No change in the yield of the product **99** could be observed by decreasing the loading of $Fe(OTf)_3$ to 3 mol% (Table 32, entry 1).

Table 32: Screening of catalyst loading and variation in the procedure[a]



58 **91** **99**

Entry	$Fe(OTf)_3$ (mol%)	Product 99(%)
1	3	10
2	1	1
3	10	0
4[b]	5	3
5[b]	0.5	7
6[b]	1	6
7[c]	5	8
8[c]	1	5

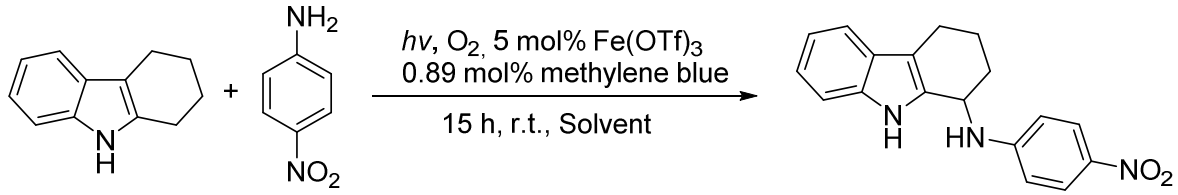
[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of CH_3CN were used. Yields were determined by ^1H NMR based upon the conversion of *p*-nitroaniline (**91**). [b]: Dropwise addition of *p*-nitroaniline. [c]: Dropwise addition of peroxide **59**

However, the further lowering of the loading of $Fe(OTf)_3$ to 1 mol% resulted in the significant decrease of the yield of the desired coupling reaction (Table 32, entry 2). The reaction did not afford the desired product **99** and decomposition of peroxide **59** was observed when catalyst loading was increased to 10 mol% (Table 32, entry 3). Further efforts with dropwise addition of the coupling partners using different concentrations of the catalyst were also not helpful (Table 32, entry 4-8).

After the proof of the principle for the coupling of peroxide **59** with aniline **91**, I decided to optimize the reaction conditions by performing the two-step reaction (isolation of peroxide **59** and then subjecting it to coupling conditions) in one pot fashion (*in situ* formation and coupling of peroxide **59** with aniline **91** under acidic conditions). Initially, methylene blue was selected as sensitizer and 500 watt lamp

was used as source of visible light.

Table 33: Screening of solvents for one pot coupling of 58 with 91[a]



58 **91** **99**

Entry	Solvent	Carbazole 58 (%)[b]	Product 99 (%)
1	CH_3CN	100	0
2	CH_3CN+MeOH (1:1)	85	0
3	DMF	100	0
4	DMSO	90	5
5	Toluene	100	0
6	DCM	100	0
7	MeOH	0	32
8[c]	MeOH	0	40
9	AcOH	100	0
10[d]	AcOH	0	40

[a] 0.49 mmol **58**, 0.49 mmol **91**, 10 mL solvent and 0.014 mg/mL (1.4 mg) methylene blue was used. Yields were determined by 1H NMR based upon the conversion of aniline **91**. [b] During the conversions of carbazole **58**, it was converted to product **99** and other unknown products. [c] The reaction was performed at 0 °C [d] no catalyst was used.

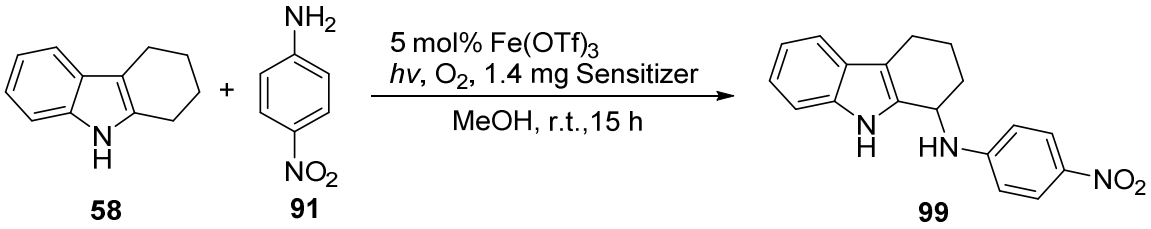
For this purpose, I screened different solvents (Table 33). Presumably, due to the quenching of singlet oxygen[50b] by the Lewis basic sites of DMSO, DMF and acetonitrile, the oxidation of carbazole **58** to related hydroperoxide **59** was not possible in these solvents (Table 33, entry 1-4).

In addition, the oxidation of carbazole **58** was also not observed using Toluene and DCM as solvents (Table 33, entry 5-6). Gratifyingly in methanol as solvent, carbazole **58** was completely consumed and 32% of the intermediate peroxide **59** was converted to desired coupling product **99** and the remaining peroxide **59** was decomposed to other unidentified products (Table 33, entry 7). The yield of the reaction was further increased to 40% when the reaction was performed at 0°C in methanol as solvent showing that temperature also plays an important role in this reaction (Table 33, entry 8). The combination of $Fe(OTf)_3$ with acetic acid was not suitable for the oxidation of **1** (Table 33, entry 9). However, when the reaction was performed in the absence of $Fe(OTf)_3$, using AcOH as solvent; without any other additional catalyst, an improved yield of 40% of the product **99** was observed. However, due to the freezing point (16-17 °C) of acetic acid, the reaction could not be performed at reduced temperatures using AcOH as solvent.

As it was easy to perform reaction at room temperature and multiple reactions could be performed simultaneously, therefore, I first decided to further optimize the different parameters at room temperature using methanol as solvent. I intended to screen different temperatures after adjusting all other parameters like sensitizer, ratio of coupling partners, loading of suitable catalyst and concentration of solution.

I, next, wanted to observe the effect of the nature of sensitizer on the outcome of the reaction. For this reason, I next screened different sensitizers (Table 34). All the screened sensitizers afforded the desired product in comparable yields. However, slightly improved yields were obtained by using 9,10-dicyanoanthracene and iron phthalocyanine as sensitizers (Table 34, entry 1 & 6).

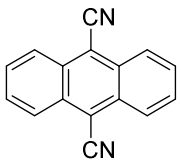
Table 34: Screening of sensitizers[a]



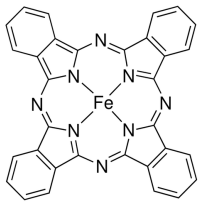
58 **91** **99**

Entry	Sensitizer	Carbazole 58 (%)	Aniline 91 (%)	Product 99 (%)
1	9,10-dicyanoanthracene	0	64	36
2	Tetraphenylporphyrin	0	77	23
3	Phthalocyanine	0	67	33
4	Zinc phthalocyanine	0	67	33
5	Copper phthalocyanine	0	66	34
6	Iron phthalocyanine	0	65	35
7	Methylene blue	0	68	32
8	Tris(bipyridine)ruthenium(II) chloride hexahydrate	0	70	30

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 10 mL MeOH and 1.4 mg of sensitizer were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**



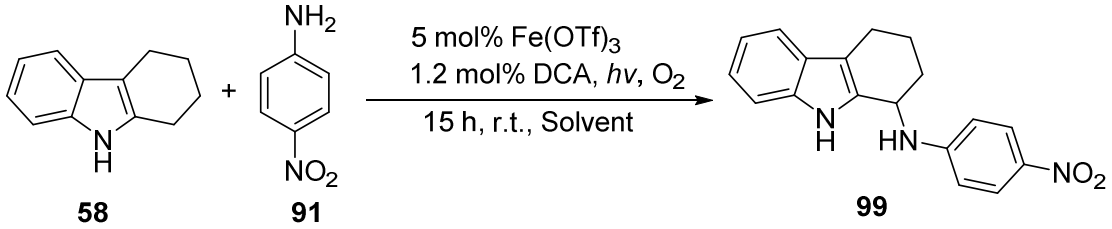
9,10-dicyanoanthracene (DCA)



Iron phthalocyanine (FePc)

Having selected 9,10-dicyanoanthracene (DCA) as standard sensitizer, I again screened the same solvents (Table 35, entry 1-6) as for Table 33 and similar results were obtained.

Table 35: Screening of solvents by using DCA as sensitizer[a]



58 **91** **99**

Entry	Solvent	Carbazole 58 (%)	Aniline 91 (%)	Product 99 (%)
1	CH_3CN	50	50	0
2	CH_3CN+MeOH (1:1)	35	45	5
	DMF	50	50	0
4	Toluene	50	50	0
5	DCM	50	50	0
6	**MeOH**	**0**	**64**	**36**
7	*n*-BuOH	50	50	0
9	*Tert*-BuOH	50	50	0
11	*n*-PrOH	100	100	0
8	*Iso*-PrOH	35	45	5
10	EtOH	0	38	12
12	**AcOH**	**0**	**60**	**40**

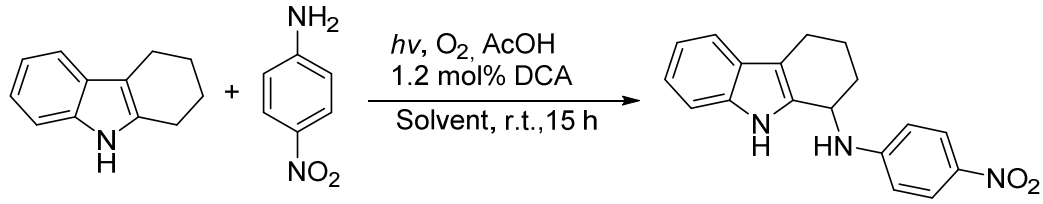
[a]: 0.49 mmol **58**, 0.49 mmol **91**, 10 mL solvent and 1.4 mg of DCA were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

Based on the remarkable results obtained in methanol, some other alcoholic solvents were also tested for the desired transformation. Unfortunately, all of them gave the desired product in inferior yields as compared with methanol (Table 35, entry 7-10). AcOH, again, was proved to be the better solvent and yield of 40% of product **99** was obtained (Table 35, entry 11).

As the best yield was obtained using acetic acid as solvent (Table 35, entry 12), and second best result was obtained by using methanol as solvent and $Fe(OTf)_3$

as catalyst (Table 35, entry 6), I tested different concentrations of acetic acid as catalyst in methanol which was used as solvent (Table 36, entry 1-7). The yield of the product **99** was increased by increasing the concentration of acetic and again the best yield was obtained when acetic acid was used as solvent without any additional catalyst (Table 36, entry 7). In order to test the efficiency of other carboxylic acids, the reaction was also performed by using propionic acid as solvent, without any additional catalyst. Although full conversion of carbazole **58** was observed, yet, it was found to be completely ineffective for the desired coupling reaction (Table 36, entry 8). The formed peroxide **59** was decomposed to a mixture of unidentified products containing spiro product **100** as major by product.

Table 36: Screening of different concentrations of acetic acid in methanol[a]



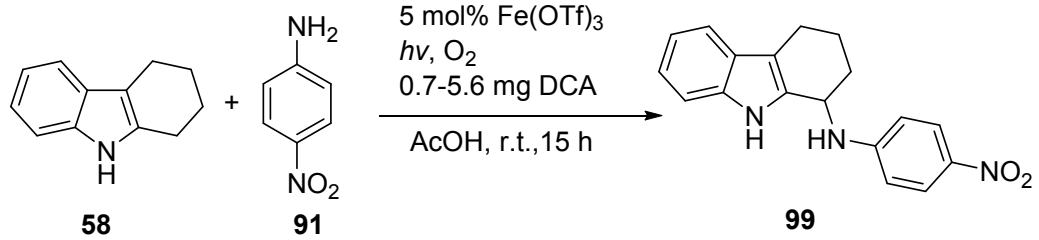
58 **91** **99**

Entry	AcOH(%)	MeOH (mL)	Aniline 91 (%)	Product 99 (%)
1	5	10	89	11
2	10	10	90	10
3	50	10	78	22
4	100	10	70	30
5	500	10	70	30
6	5 mL	5	68	32
7	10 mL	0	60	40
8[b]	10 mL	0	100	0

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 10 mL solvent and 1.4 mg of DCA were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b] Propionic acid as solvent

In order to observe the effect of the loading of sensitizer on the outcome of reaction, I tested different concentrations of DCA which was used as sensitizer (Table 37). I found that concentration of sensitizer also played an important role for the desired transformation and 0.14 mg/mL of sensitizer (Table 37, entry 3) was found to be optimal for the reaction. Any modification of concentration from this value decreased the yield of product **99**.

Table 37: Variation in the concentration of sensitizer[a]



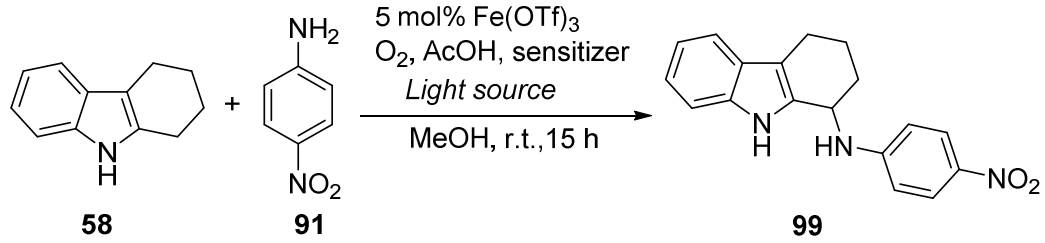
58 **91** **99**

Entry	Sensitizer (mg/mL)	Carbazole 58(%)	Aniline 91(%)	Product 99(%)
1	0.07	0	72	28
2	0.10	0	73	27
3	0.14	0	64	36
4	0.28	0	70	30
5	0.42	0	75	25
6	0.56	0	78	22

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

During my efforts for the optimization of the reaction, I found that iron phthalocyanine gave similar yields under day light, without the need for any additional source of light (Table 38, entry 1).

Table 38: Variation of the source of light[a]

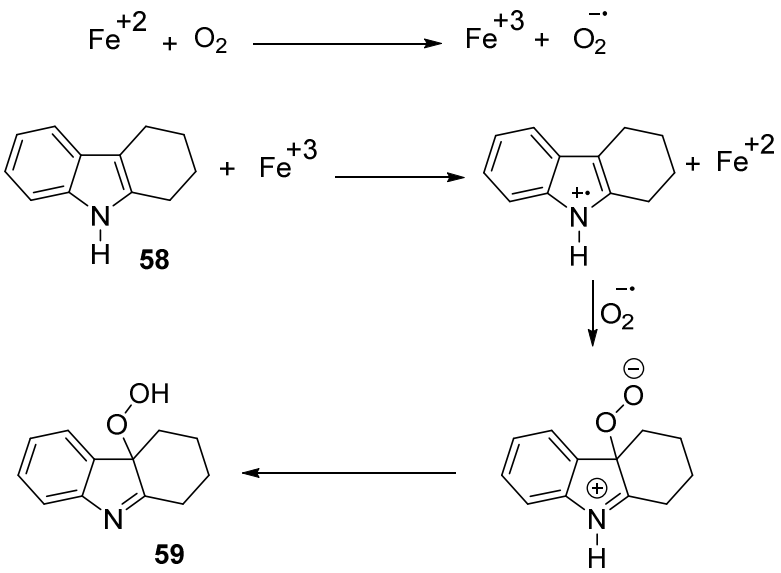


58 **91** **99**

Entry	Light	Sensitizer	Carbazole 58(%)	Aniline 91(%)	Product 99(%)
1	Day Light	FePc	0	64	36
2	Day Light	DCA	100	100	0
3	Day Light	ZnPc	100	100	0
4	Day Light	CuPc	100	100	0
5	Covered with aluminium Foil	FePc	16	74	26
6	23 Watt lamp	FePc	0	64	36

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 10 mL MeOH and 1.4 mg of sensitizer was used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

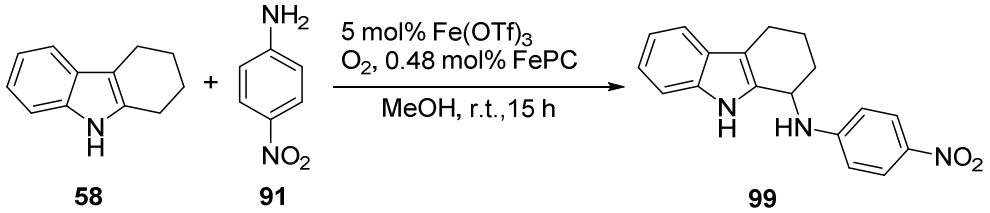
This result was very striking for us. I performed the reaction with DCA without the use of any light source but no conversion of carbazole **58** was observed (Table 38, entry 2). I also performed the reaction by using copper phthalocyanine and zinc phthalocyanine as sensitizer under day light (Table 38, entry 3-4). But once again, no conversion of carbazole **58** was observed. In order to completely prevent the irradiation of the reaction mixture, I covered the reaction with aluminium foil and then performed the reaction by using iron phthalocyanine as sensitizer. The reaction proceeded albeit in slight lower yield (Table 38, entry 5). These results showed that the use of light is not necessary for the oxidation of carbazole **58** in the presence of iron phthalocyanine as sensitizer and reaction might proceed through single electron transfer (SET) mechanism (Scheme 58).[85] This discovery was very interesting for us. As it was very easy to perform the reaction without using light, therefore I decided to perform of further optimization studies using FePc as sensitizer.



Scheme 58: Proposed radical mechanism for the formation of peroxide 59

Next, I wanted to find the appropriate molar ratio of the two coupling partners (Table 39). Presumably, due to the deactivation of the catalyst by aniline **91**, the yield of the product was decreased by increasing the molar ratio of aniline **91** (Table 39, entry 1-3). There was a slight increase in the yield of product **99** by increasing the ratio of carbazole **58** (Table 39, entry 4-5). Since all the carbazoles are not commercially available, I decided to further optimize the yield by using 1:1 ratio of the two coupling partners. I, then, performed the reaction by changing the loading of the catalyst. The yield of product **99** dropped significantly by further increasing or decreasing the concentration of catalyst (Table 39, entry 6-8). Therefore 5 mol% of $Fe(OTf)_3$ was found to be optimal for this reaction.

Table 39: Variation in molar ratio of coupling partners and loading of catalyst[a]



58 **91** **99**

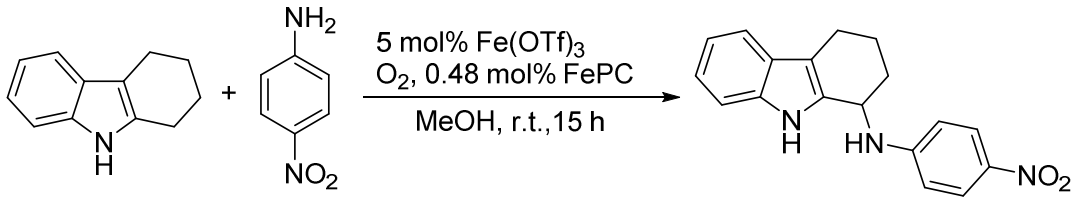
Entry	$Fe(OTf)_3$ (mol%)	Carbazole 58 (equiv.)	Aniline 91 (equiv.)	Product 99 (%)
1	5	1.0	1.0	36
2	5	1.0	1.5	22
3	5	1.0	2.0	14
4	5	1.5	1.0	41
5	5	2.0	1.0	38
6	1	1.0	1.0	5
7	3	1.0	1.0	23
8	10	1.0	1.0	10

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

In search for improving the yield of the reaction, the reaction was also performed by varying the concentration of the reagents (Table 40). By increasing the concentration to 0.33 M of each of the aniline **91** and also of carbazole **58**, the time for the full conversion of carbazole **58** was increased to 60h and poor yield of product **99** was achieved. Control experiment showed that the product **99** was decomposed over time under acidic conditions. So, I concluded that because of the decomposition of formed product **99**, the longer reaction time and higher catalyst loading was not suitable for the desired reaction. In order to avoid the decomposition of product **99**, the 1reaction was performed by reducing the loading of catalyst to 1 mol% (Table 40, entry 3). However, further decrease in the yield of product **99** was observed. I, then, rationalized that the dilution of the reaction media might be helpful in accelerating the photooxidation of **58** to peroxide **59** thus avoiding the decomposition of product **99** (Table 40, entry 4). The progress of the reaction was controlled at regular intervals. It was found that with this increase

in dilution (decrease in the concentration), the reaction was completed in 15h. However, the overall yield of product **99** was decreased to 30% (Table 40, entry 4).

Table 40: Variation in concentration coupling partners[a]



58 **91** **99**

Entry	MeOH (mL)	Concentration of 58&91 (mol/L)	Aniline 91 remaining	Product 99(%)
1	10	0.049	64	36
2[b]	1.5	0.33	80	20
3[b,c]	1.5	0.33	90	10
4	20	0.024	70	30

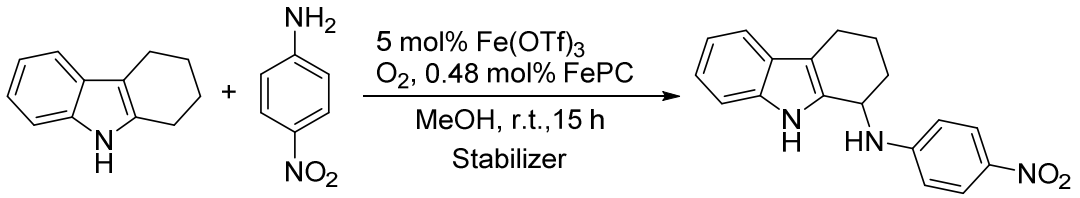
[a]: 0.49 mmol **58** and 0.49 mmol **91** were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b] Complete conversion of carbazole **58** was achieved in 60 h. [c] 1 mol% of catalyst was used used

These results show that there are different factors which influence the reaction. On one hand, in order to accelerate the oxidation of **1** to **2** and minimize the decomposition of **4**, high dilution is required. On the other hand, the catalyst loading should be kept at the optimal concentration value for the success of coupling step. Any deviation from the optimal value of concentration and loading of reagents results in the formation of the product **99** in lowered yields. A concentration of 0.049 M of each coupling partner and 5 mol% loading of $Fe(OTf)_3$ seems to be the suitable for this reaction so far.

As it was assumed that reaction proceeds through the formation of cationic intermediates (Scheme 57), therefore, I realized that the yield of the desired reaction reaction might increase if I could manage to stabilize these possible intermediates. Therefore, different additives were tested. However, the addition of these stabilizers was also found to be ineffective in increasing the yield of product **99** (Table 41). The addition of TBAF, $LiClO_4$ and CuBr resulted in the complete

decomposition of carbazole **58** (Table 41, entry 1-3). The yield was decreased to 20% by the addition of water (Table 41, entry 4) and TBABr (Table 41, entry 5) did not show any effect on the yield of product **99**.

Table 41: Addition of stabilizers[a]



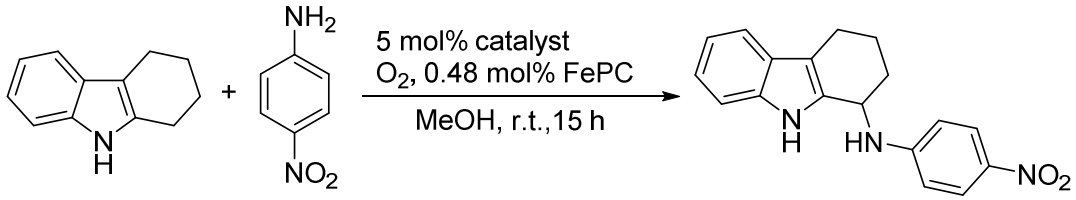
58 **91** **99**

Entry	Stabilizer (1.0 equiv.)	Aniline 91 remaining	Product 99(%)
1	TBAF	100	0
2	$LiClO_4$	100	0
3	CuBr	100	0
4	H_2O	80	20
5	TBABr	63	37

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg FePC and 10 mL of MeOH were used. Yields were determined by ^1H NMR based upon the conversion of aniline **91**

After finding an appropriate concentration of coupling partners, catalyst and sensitizer, and suitable amount of solvent required for the reaction I further screened other catalysts (Table 42). Among different Lewis acids, only $Yb(OTf)_3$ afforded the product **99** in 35% yield (Table 42, entry 11). Most of the used Brønsted acidic catalysts gave inferior yields as compared with iron triflate (Table 42, entry 12). However relatively good yields were obtained by using TFA and PTSA (Table 42, entry 6-7,11).

Table 42: Screening of catalysts[a]



58 **91** **99**

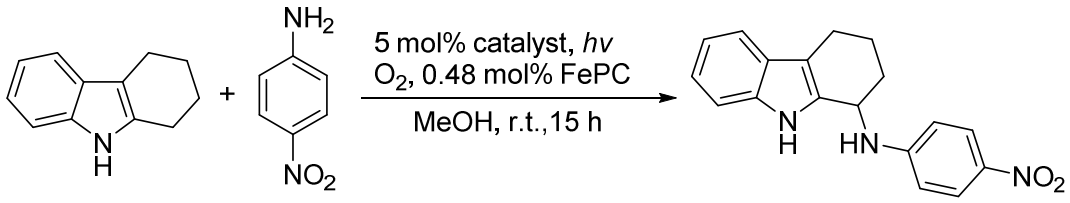
Entry	Catalyst	Aniline 91 (%)	Product 99 (%)[a]
1	AcOH	89	11
2	Ti(*i*PrO$_4$)	100	0
3	$MgCl_2$	84	16
4	$RuCl_3$	74	26
5	$Zn(OTf)_2$	70	30
6	TFA	72	28
7	PTSA	73	27
8	$FeCl_2$	100	0
9	$Bi(OTf)_3$	78	22
10	$FeCl_3$	85	15
11	$Yb(OTf)_3$	65	35
12	$Fe(OTf)_3$	64	36

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg FePc and 10 mL MeOH was used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

Being encouraged from the result of PTSA and TFA, I screened other Brønsted acids. I found that yield of the product **99** increases by increasing the strength of acid upto pKa value of -0.25 (Table 43, entry 1-5) and further increase in the strength of acid decreases the yield of product **99** (Table 43, entry 5-6). This general trend is not respected by PTSA which gave higher yield despite being stronger than MsOH. I further increased the loading of the TFA and PTSA to 10 mol%. The yield was increased to 41% by increasing the concentration of TFA but the increase the loading of PTSA was detrimental for the reaction and yield was

decreased to 24% (Table 43, entry 8-9).

Table 43: Screening of Brønsted acids[a]



58 **91** **99**

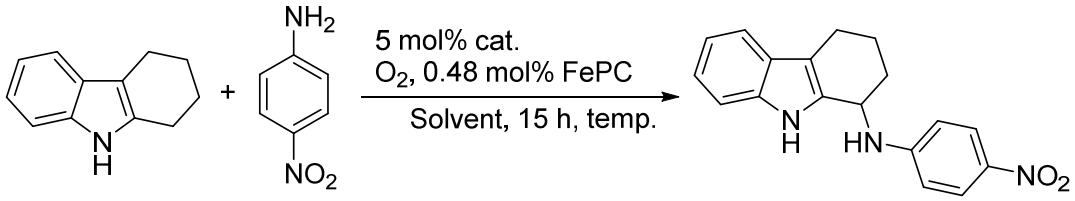
Entry	Catalyst	pKa (H_2O)	Aniline 91(%)	Product 99(%)
1	AcOH	4.76	89	11
2	4-nitro benzoic acid	3.41	88	12
3	DPP	2	78	22
4	TCA	0.65	83	17
5	TFA	-0.25	72	28
6	MsOH	-2.6	63	14
7	PTSA	-2.8	73	27
8[b]	TFA	-0.25	59	41
9[b]	PTSA	-2.8	76	24

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg of FePC and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: 10 mol% of catalyst was added

In order to find an appropriate temperature for the desired reaction, I at first performed the reaction at different temperatures by using a combination of methanol and iron triflate (Table 44). The decrease in temperature showed a positive effect on the reaction and -40 °C was found to be optimal temperature for the desired reaction (Table 44, entry 4). A further decrease in temperature was not helpful for the desired transformation (Table 44, entry 4-5). The reaction was also performed at 0°C by using AcOH as solvent, without any additional catalyst. The yield was slightly improved from 40% (using AcOH at room temperature) to 42% (Table 44, entry 6). Because of freezing point of AcOH (16-17 °C), the reaction could not be performed at further reduced temperatures by using AcOH

as solvent of reaction.

Table 44: Screening of temperature[a]



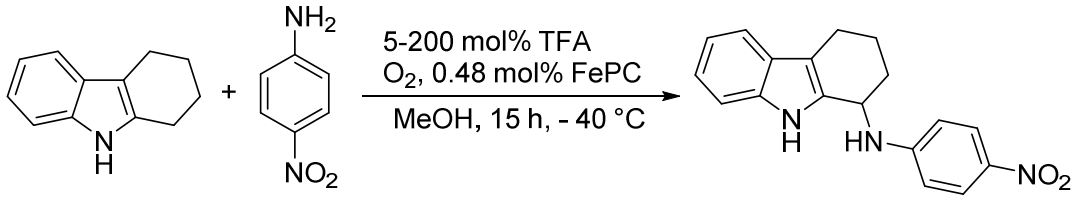
58 **91** **99**

Entry	Solvent	Temp.	Catalyst	Aniline 91(%	Product 99 (%)
1	MeOH	r.t.	$Fe(OTf)_3$	64	36
2	MeOH	0°C	$Fe(OTf)_3$	58	42
3	MeOH	-20°C	$Fe(OTf)_3$	58	42
4	MeOH	-40°C	$Fe(OTf)_3$	54	46
5	MeOH	-78°C	$Fe(OTf)_3$	57	43
6	AcOH	0°C	--	58	42

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of methanol were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

The reaction was then also performed at -40°C by using different concentrations of TFA in methanol (Table 45). By increasing the concentration of TFA to 10 mol%, the yield of product **99** was increased to 50% (Table 45, entry 2). Any further increase in the loading of TFA was detrimental for the reaction. The yield of product **99** was decreased to 15% by using 20 mol% of TFA and complete decomposition of carbazole **58** was observed by further increase in the loading of TFA (Table 45, entry 3-6). Since good yield had been obtained by using $Zn(OTf)_2$ (Table 42, entry 5), I decided to use combination of TFA and $Zn(OTf)_2$. However, this combination did not help in improving the yield (Table 45, entry 7-8).

Table 45: Variation in concentration of TFA at -40°C[a]



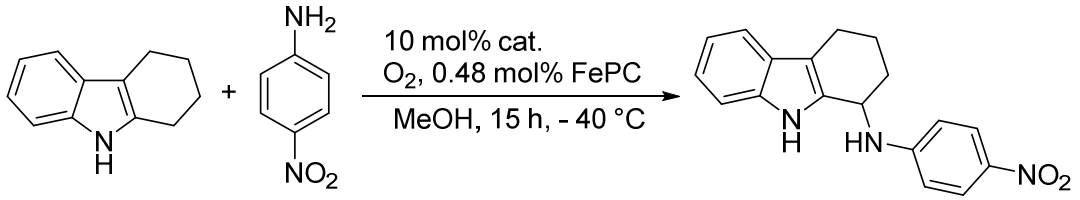
58 **91** **99**

Entry	TFA (mol%)	Aniline 91 (%)	Product 99 (%)
1	5	59	39
2	**10**	**50**	**50**
3	20	85	15
4	50	100	0
5	100	100	0
6	200	100	0
7[b]	5	60	40
8[b]	10	59	39

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91** [b] 5 mol% $Zn(OTf)_2$ was also added

I then screened different other catalysts at -40°C (Table 46). But, no improvement in the yield of product **99** was observed. Among different mineral acids, HNO_3 (pKa=-0.25) afforded better yields (Table 45, entry 4). The use of stronger acids (MsOH, TfOH) could not improve the yield (Table 45, 10-12).

Table 46: Screening of catalysts at -40°C[a]



58 **91** **99**

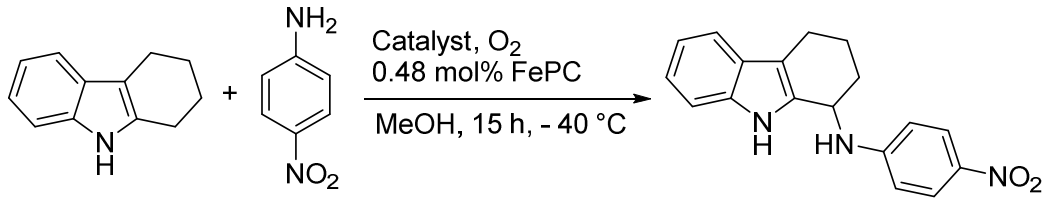
Entry	Catalyst	Aniline 91 (%)	Product 99 (%)
1	Saccharin	89	10
2		63	37
3		55	45
4	HNO_3	50	50
5	H_3PO_4	62	38
6	H_2SO_4	90	10
7	TFA	50	50
8	Picric acid	70	30
9	$Fe(OTf)_3$	54	46
10	MsOH	75	25
11[b]	MsOH	66	34
12	TfOH	80	20

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg FePC and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: 5 mol% of MsOH was used.

In order to stabilize possible cationic intermediates which might be formed during the progress of the reaction, it was decided to use a waek base in combination with TFA. The use of the mixture of acid-base as catalyst of the reaction was also not effective for the desired transformation. The yield was significantly decreased by using PTMS (Pyridinium trifluoromethanesulfonate), PPTS (Pyridinium *p*-toluenesulfonate) and dimethyl amine.HCl (DMIH) (Table 47, entry 1-3). The

combination of 10 mol% of TFA and 5 mol% of base was also not suitable (Table 47, entry 4-5).

Table 47: Use of mixture of acids and bases at -40°C[a]



58 **91** **99**

Entry	Catalyst	TFA (mol%)	Aniline 91(%)	Product 99(%)
1[b]	PTMS	0	65	35
2[c]	PPTS	0	70	30
3[d]	DMIH	0	64	36
4[e]	Pyridine	10	60	40
5[e]	Triethyl amine	10	58	42

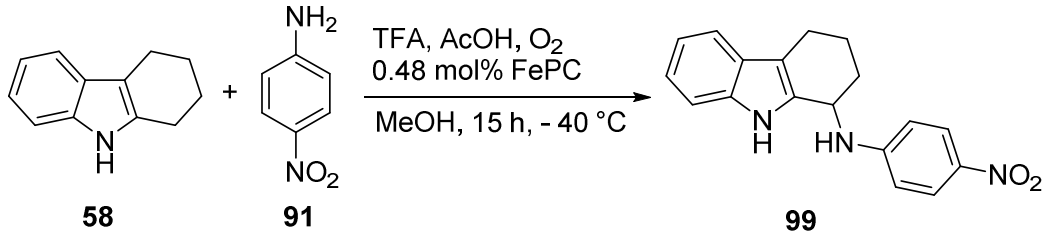
[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: 10 mol% of Pyridinium trifluoromethanesulfonate (PTMS) was used**.** [c]: 10 mol% Pyridinium *p*-toluenesulfonate (PPTS) was used. [d]: 10 mol% of dimethyl amine.HCl (DMIH) was used. [e]: 10 mol% of TFA + 5 mol% of base was used

Until now the carbazole **58**, off-white in color, purchased from sigma aldrich was used for the studies. Aftert receiving a new batch of carbazole **58** from Sigma Aldrich, I performed the reaction under similar (Table 45, entry 2) conditions (FePc as sensitizer, 10 mol% TFA as catalyst and methanol as solvent). The reaction was completed in 22h and the yield of the product **99** (27%) was significantly lower than that observed previously (50% of the product **99**). After comparing the old and new batches of carbazole **58**, I found that new batch was grey colored and reaction mixture turns light black after dissolving carbazole **58** in methanol or toluene. Next, I performed reaction after receiving **58** from Acros Organics and Alfa Aesar and again poor yield of the product **99** was obtained. These poor yields were attributed to the dark yellow color of starting material **1**. In order to see the effect of color of carbazole **58** on the oxidation of carbazole to form peroxide **59**, I performed the photooxidation reaction of **58** in toluene.

It was found that the formation of the hydroperoxide **59** was also slowed down and complete oxidation of **58** was obtained in 15 h instead of 3 h. Therefore, the poor yields of product **99** were attributed to the dark yellow color of the unknown impurity present in starting material **1**. After column chromatography, most of the yellow and black colored byproducts were adsorbed on the column and comparatively less colored tetrahydrocarbazole **58** was eluted. The reaction was then performed by using this purified carbazole **58** (same conditions as in Table 46, entry 7) and an improved yield of 37% of product **99** was obtained. The off-white colored carbazole **58** was not furthermore available from sigma aldrich, therefore, from now onwards the reactions were performed by using this self purified carbazole **58**.

In order to further optimize the yield, I performed the reaction by using a mixture of methanol with acetic acid. Initially the ratio of methanol and acetic acid was kept constant and concentration of TFA was changed. The yield of product **99** was slightly increased by decreasing the loading of TFA (Table 48, entry 1-3). An increase in the concentration of sensitizer (FePC) was found to be detrimental for the reaction and yield was decreased to 35% (Table 48, entry 4). The reaction was then performed by using 1.0 equiv. of acetic acid and by changing the concentration of TFA. An improved yield of 47% was obtained by using acetic acid (1.0 equiv.) and 10 mol% TFA (Table 48, entry 6). The yield was decreased by further decreasing the concentration of acetic acid (Table 48, entry 7).

Table 48: Variation in the ratio of AcOH and TFA[a]



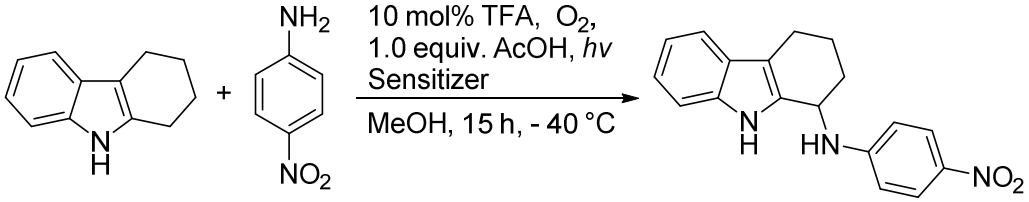
58 **91** **99**

Entry	Acetic Acid	MeOH (mL)	TFA (mol %)	Product 99(%)
1	2.5 mL	7.5	10	42
2	2.5 mL	7.5	5	46
3	2.5 mL	7.5	3	46
4[b]	2.5 mL	7.5	5	35
5	1.0 equiv.	10	5	41
6	**1.0 equiv.**	**10**	**10**	**47**
7	0.25 equiv.	10	10	33

[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 mL of solvent were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91** [b]: 2.8 mg of FePC was used

By using these optimized conditions (Table 48, entry 6), I again, screened some other sensitizers. The yield was improved to 54% by using $P(tPfc)(OH)_2$ (Table 49, entry 1).[86] There was a slight decrease in the yield of **4** by decreasing the concentration of $P(tPfc)(OH)_2$ (Table 49, entry 2). Slightly lowered yield was observed by using tris bipyridine ruthenium chloride as sensitizer. Methylene blue and TPP were not able to oxidize carbazole **58** under these conditions and mainly starting materials were found after 15 h of reaction time (Table 49, entry 3-5).

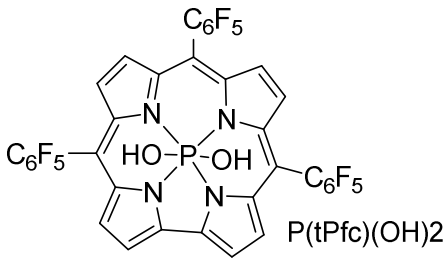
Table 49: Further Screening of sensitizers[a]



58 **91** **99**

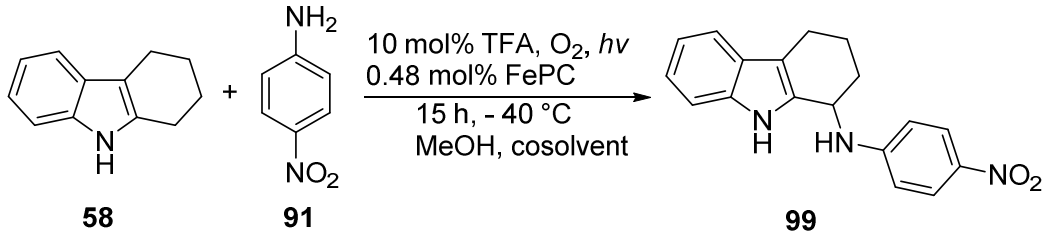
Entry	Sensitizer	Product 99 (%)
1	$P(tPfc)(OH)_2$	54
2[b]	$P(tPfc)(OH)_2$	53
3	TPP	02
4	Tris bipyridine ruthenium chloride	47
5[c]	Methylene blue	0

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg sensitizer and 10 mL of MeOH were used. Yields were determined by ^1H NMR based upon the conversion of aniline **91**. [b]: 0.7 mg of $P(tPfc)(OH)_2$ was used. [c]: No conversion of **58** was observed



As it was very easy to perform the multiple reactions by using FePc as sensitizer, therefore I investigated the influence of a cosolvent in combination with methanol using FePc as sensitizer of choice (Table 50). Complete conversion of carbazole **58** and poor yields of the product **99** were obtained by using different co-solvents (Table 50, entry 1-6). However, low but clean conversion of **58** to **99** was observed with combination of dimethyl sulfide (DMS) with methanol (Table 50, entry 7).

Table 50: Testing of mixtures of solvents[a]



58 **91** **99**

Entry	Cosolvent	Ratio (MeOH:CoSolvent)	Product 99 (%)
1	DCM	1:1	7
2	*N*-Methyl-2-pyrrolidone	1:1	20
3	Tetrachloroethane	1:1	0
4	Cyclohexene	1:1	0
5	Nitromethane	1:1	18
6	Benzene	1:1	2
7	Dimethyl sulfide	1:1	16
8[b]	Dimethyl sulfide	1:1	32
9[c]	Dimethyl sulfide	1:1	0
10	Carbon disulfide	1:1	36
11	Carbon disulfide	1:0.6	34
12	Carbon disulfide	1:0.2	32

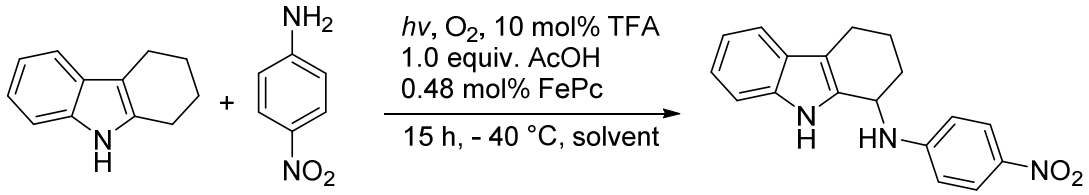
[a]: 0.49 mmol **58**, 0.49 mmol **91** and 10 solvent (overall) were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: yield was measured after 7 days. [c]: P(tPfc)$(OH)_2$ was used as sensitizer

In order to get complete conversion of carbazole **58**, the reaction was allowed to stir for further 7 days and there was no significant increase in the yield of product **99** (Table 50, entry 8). The slow conversion of carbazole **58** can be attributed to the deactivation of sensitizer by Lewis basic site of DMS.

I, next, performed the reaction by using $P(tPfc)(OH)_2$ as sensitizer and surprisingly no conversion of carbazole **58** was observed (Table 50, entry 7-9). Comparatively better yield (36%) of product **99** was obtained by using carbon disulfide as cosolvent (Table 50, entry 10). The yield could not be improved by further varying the ratio of two solvents (Table 50, entry 10-12).

As the use of acetic acid was found to be helpful for optimizing the yield, therefore, acetic acid was added to the mixture of MeOH:CDS which was used in different ratios (Table 51, entry 1-3). By increasing the ratio of carbon disulfide (CDS), the yield of product **99** was decreased. FePc was completely insoluble in carbon disulfide (CDS) and only starting materials were observed when the reaction was performed in carbon disulfide (CDS) without methanol (Table 51, entry 4).

Table 51: Variation in the ratio of two solvents in presence of AcOH[a]



58 **91** **99**

Entry	Methanol (mL)	CDS (mL)	Aniline 91 (%)	Product 99 (%)
1	5	5	64	36
2	3	7	66	34
3	1	9	68	32
4[b]	0	10	100	0

[a]: 0.49 mmol **58**, 0.49 mmol **91**, 1.4 mg FePC and 10 mL of MeOH were used. Yields were determined by 1H NMR based upon the conversion of aniline **91**. [b]: No oxidation of carbazole **58** (FePc was completely insoluble)

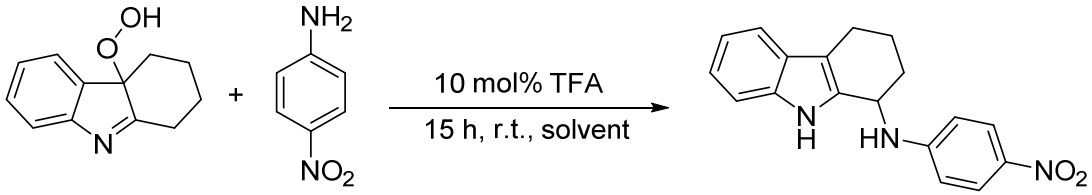
5.3.2.2 Summary

These studies prove the feasibility of one pot C–H functionalization of carbazole **58** through phtochemically generated hydroperoxide. FePc was found to be a suitable sensitizer for the desired transformation. The reaction proceeded at the same rate and similar yield of the product **99** was obtained under day light using FePc as sensitizer. Therefore, the use of special source of light was not necessary. Better yields of the desired coupling product **99** (47%) were obtained by using a combination of methanol as solvent and TFA/AcOH as catalyst. The use AcOH as solvent, without any additional catalyst, was also found to be suitable for the desired transformation and smiliar yields (42% of product **99**) as with combination of TFA, AcOH/MeOH were obtained.

5.3.2.3 Development of two step method:

It was next decided to perform the reaction in two steps (isolation of peroxide **59** and then subjecting it to reaction conditions for substitution). For this purpose, optimization was performed by using purified peroxide **59**. Since, according to the previous studies (section 5.3.2.1, 5.3.2.2), TFA was found to be the most suitable catalyst, therefore I screened different solvents by using TFA as catalyst. Poor yields were obtained in comparatively less polar solvents (Table 52, entry 1-3). In ethyl acetate the desired product was delivered in 65%. The use of highly polar solvents was beneficial and the desired product was obtained in better yields (Table 52, entry 5-7). Methanol was found to be superior to all the tested solvents which afforded the coupling product in 77% yield (Table 52, entry 7).

Table 52: Screening of solvents (two step method) [a]



59 **91** **99**

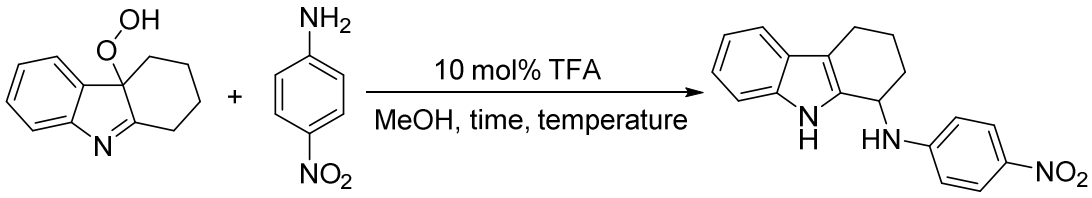
Entry	Solvent	Aniline 91 (%)	Product 99 (%)
1	CH_3CN	86	14
2	Toluene	77	23
3	$CHCl_3$	83	17
4	EtOAc	35	65
5[b]	DMSO	34	66
6[b]	DMF	56	44
7[b]	MeOH	25	77
8[b,c]	MeOH	25	75

[a]: 0.49 mmol **59**, 0.49 mmol **91**, 10 mL MeOH, a: Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b] Reaction was completed in 4 h. [c] Isolated yield

Next, I performed the reaction at different temperatures (Table 53). The yield of the reaction was not significantly affected by varying the temperature between

0° C–40 °C. Room temperature was found to be optimal for the reaction (Table 53, entry 1-3). However, there was significant loss in reactivity when temperature was decreased to -40 °C (Table 53, entry 4).

Table 53: Screening of temperatures (Two step method)[a]



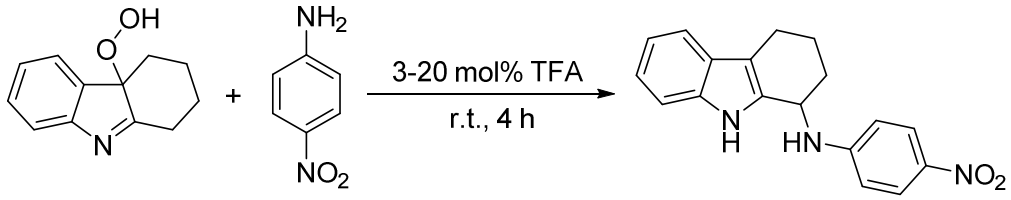
59 **91** **99**

Entry	Temp. (°C)	Time (h)	Aniline 91 (%)	Product 99 (%)
1	r.t.	4	25	75
2	40	3	30	70
3	0	15	35	65
4	-40	15	80	20

[a]: 0.49 mmol **59**, 0.49 mmol **91** and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**

The reaction was then performed by varying the loading of catalyst (Table 54). The yield of the reaction was decreased by decreasing the loading of TFA to 3 mol% (Table 54, entry 1-2).

Table 54: Screening of catalyst loading (Two step method)[a]



59 **91** **99**

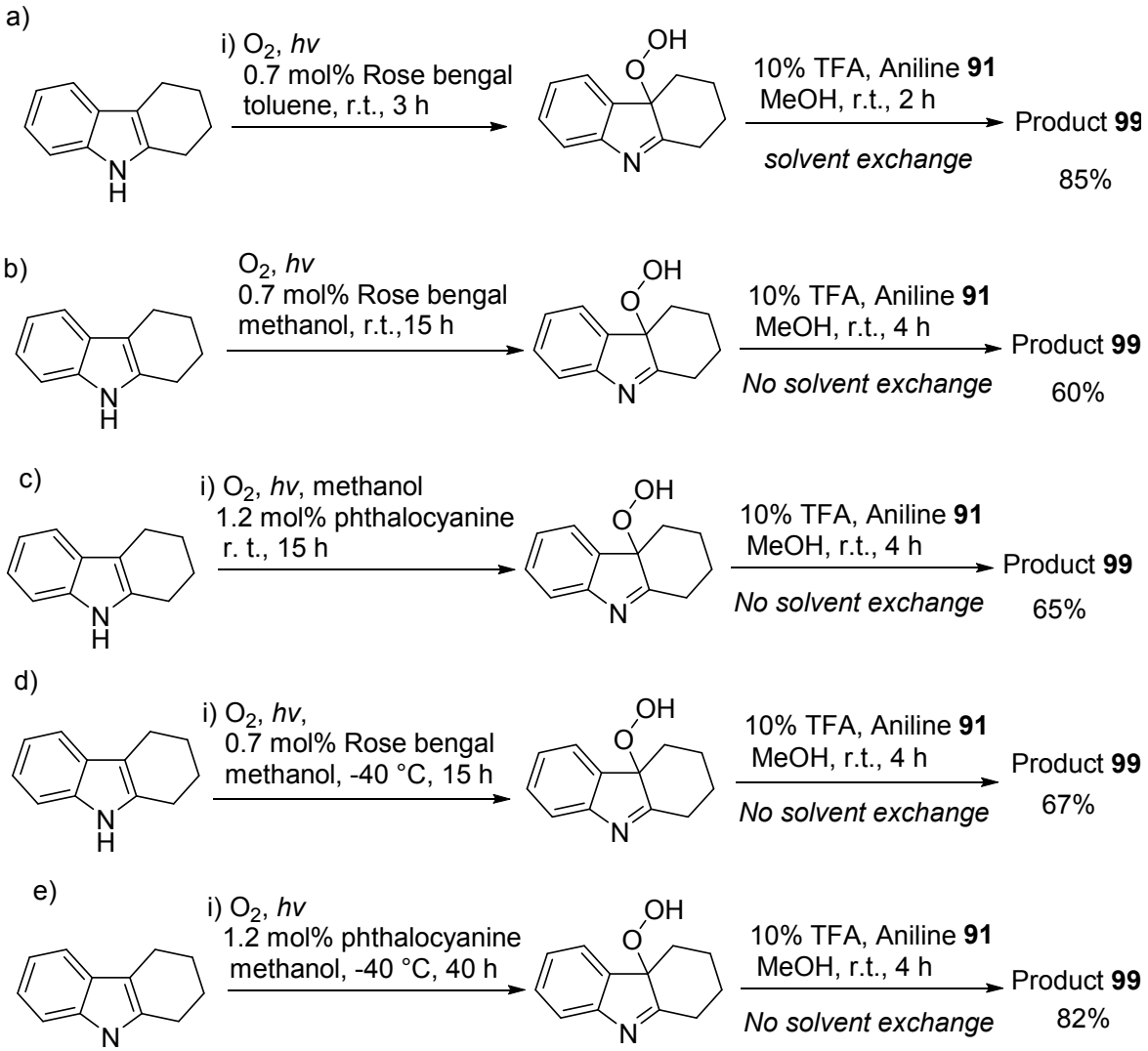
Entry	Catalyst (mol%)	Aniline 91 (%)	Product 99 (%)
1	3	40	60
2	5	34	66
3	10	24	76
4	20	30	70
5[b]	10	14	86

[a]: 0.49 mmol **59**, 0.49 mmol **91** and 10 mL of MeOH were used. Yields were determined by ^{1}H NMR based upon the conversion of aniline **91**. [b]: 0.5 mL methanol was used and reaction time was 2 h

The increase in the loading of TFA was also detrimental and the yield of product **99** was decreased by increasing the loading of the catalyst to 20 mol% (Table 54, entry 4). However, the yield of product **99** was further increased to 86% when reaction was performed at higher substrate concentrations (Table 54, entry 5).

The reaction could also be performed in a one pot, two step fashion with similar yields by exchanging the solvent after the oxidation step (Scheme 59, entry a). The aniline **91** and catalyst (10 mol% TFA) were added after the oxidation of carbazole **58** to peroxide **59** and after the exchange the solvent. In order to provide an efficient one pot method without the need to change solvent, I investigated the photooxidation of carbazole **58** in methanol by using varoius sensitizers. However, a complex mixture of products was obtained by using TPP, DCA and methylene blue as sensitizers. ^{1}H NMR spectrum looked comparatively cleaner and less byproducts were formed when rose bengal and phthalocyanine were used as sensitizers. Therefore, I added catalyst and aniline **91** to the reaction mixture after the full conversion of carbazole **58** to peroxide **59** and good yields of product **99** were obtained at room temperature (Scheme 59, entry b, c). Fascinated by such good reaction outcome, I performed the same reaction by decreasing the temperature of reaction to -40°C (Scheme 59, entry d, e). By using

rose bengal as sensitizer, the yield was improved to 67% and photooxidation of carbazole **58** was completed in 15 h (Scheme 59, entry d). Phthalocyanine gave a slower but very clean reaction profile for the conversion of carbazole **58** to intermediate peroxide **59** in 40 h at -40°C and the yield of the product was improved to 82% (Scheme 59, entry e).

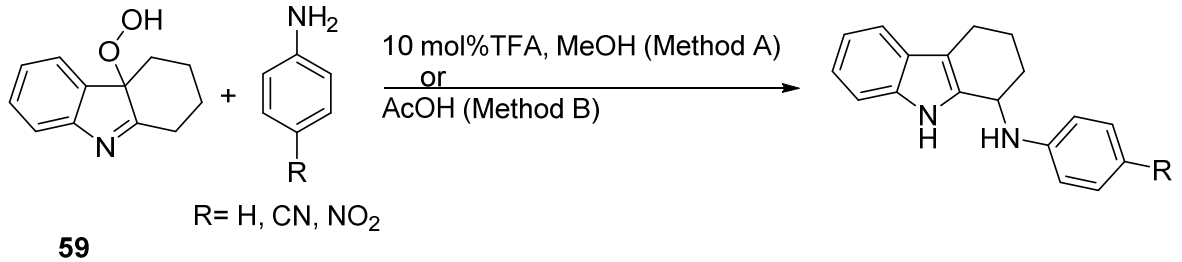


Scheme 59: Development of one pot method; (a) a one-pot method with solvent exchange; (b-e) a one-pot method without solvent exchange using rose bengal and phthalocyanine as sensitizers at room temperature and at -40°C.

As the hydroperoxide **59** can be conveniently isolated by simple filtration and stored at room temperature, therefore, I have mostly studied the reaction in two separate steps.

Using this isolated hydroperoxide **59** I next investigated the scope of aniline reagent in the transformation. Excellent yields were achieved with anilines (**105**&**91**) having strongly electron withdrawing groups (Table 55, entries 2-3). However, poor yields were obtained with aniline (**104**). The reaction of peroxide **59** with aniline gave only 10% of the coupling product (Table 55, entry 1).

Table 55: Effect of the nature of the substituent on the reactivity of aniline[a]



R= H, CN, NO_2

59

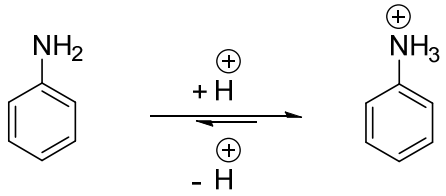
Entry	R	Method A yield (%) (Product)	Method B yield (%) (Product)
1	H (**104**)	10 (**106**)	60 (**106**)
2	CN (**105**)	80 (**107**)	80 (**107**)
3	NO_2 (**91**)	86 (**99**)	30 (**99**)

[a]: 0.49 mmol **59**, 0.49 mmol **91** and 10 mL of solvent (MeOH or AcOH) were used. Yields were determined by ^{1}H NMR based upon the conversion of used aniline.

It should be noted that rose bengal is not stable against acid. Because of its decomposition, the pink color of rose bengal disappears under acidic conditions. With all the reactions using aniline **91** as nucleophile the pink color of rose bengal, already present in traces in isolated peroxide **59**, disappeared immediately after the addition of TFA. The reaction of hydroperoxide **59** with aniline gave only 10% of the coupling product. Careful observation showed that color of rose bengal did not disappear after the addition of 10 mol% of TFA suggesting that free acid was not available in the reaction medium.

Increased catalyst loading was beneficial, as the concentration of free acid avaiable for protonation of peroxide moiety inceases by increasing the loading of catalyst, upto an optimal value of 40% TFA which delivered the coupling product in 40% yield. Further increase in catalyst loading was detrimental for the reaction and peroxide **59** was decomposed to unwanted products. The problem was solved by using AcOH as solvent without any additional catalyst which afforded the desired coupling with an improved yield of 60% (Table 55).

It is suggested that, because of the basicity of anilines, an equilibrium is established between protonated anilines and unprotonated anilines. In case of aniline, without any electron withdrawing group, the equilibrium mainly lies on the right hand side and results in the deactivation of catalyst (Scheme 60). An increase in loading of TFA or use of AcOH as solvents increases the availability of free acid for activating the peroxide **59** and giving desired coupling product.



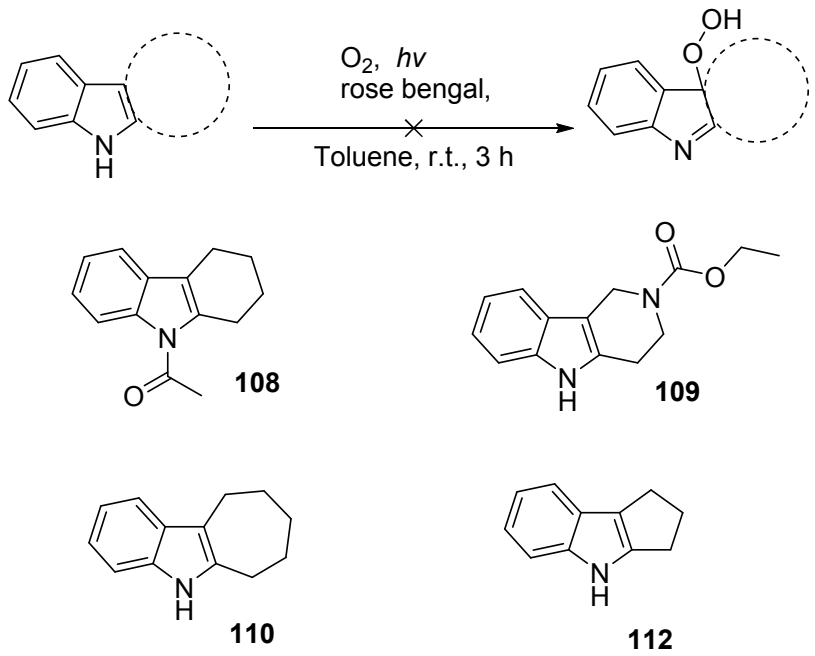
Deactivation of cat. and nucleophile

Scheme 60 : Deactivation of catalyst by aniline

In general, the use of acetic acid (Method B) was found to be suitable for the coupling of unsubstituted aniline while the use of methanol/TFA (Method A) was preferred for the coupling of electron poor anilines with hydroperoxide **59** (Table 55).

Having optimized conditions in hand, I then focused the attention on substrate scope (Scheme 61). For this reason I first introduced acyl group on the nitrogen of carbazole. However, due to the electron withdrawing nature of acyl group, there was no conversion of **108** under these conditions.

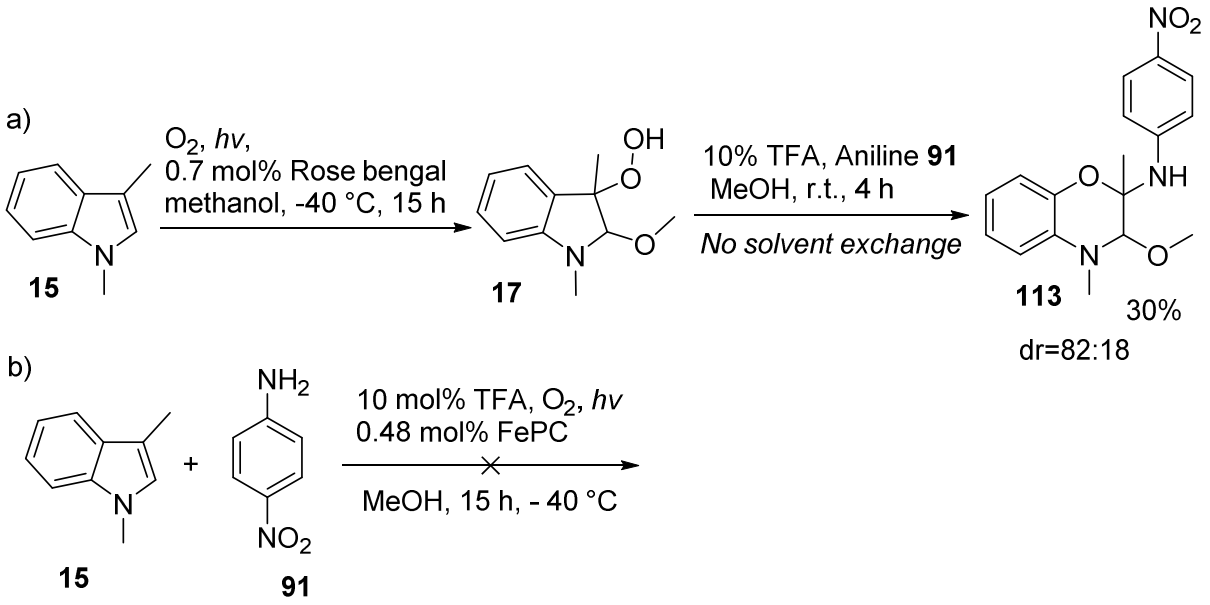
Presumably on the account of significant change in the electronic properties of molecule, no oxidation of carboloine **109** was observed by using standard conditions (Scheme 61).



Scheme 61: Failing Substrates under Standard conditions

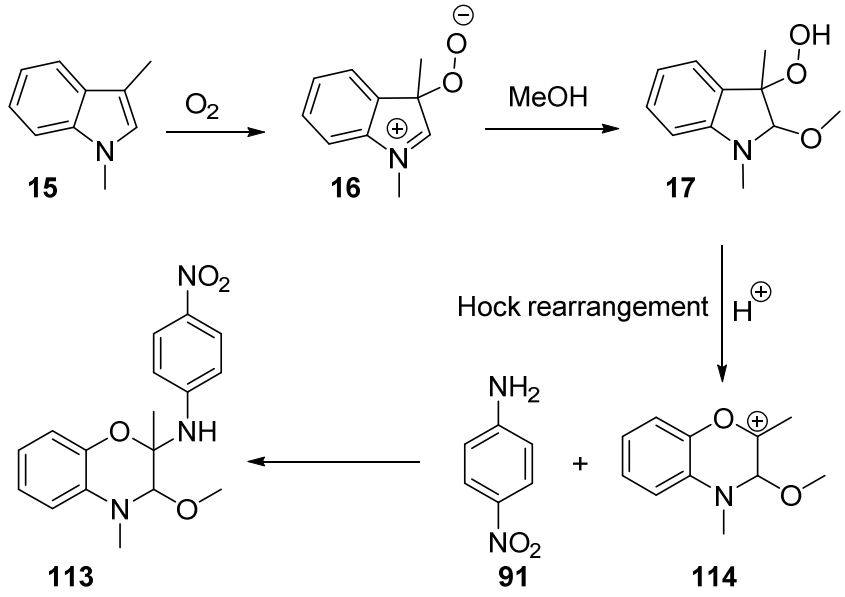
Indole **110** and **112** derivatives with an annulated saturated seven membered ring and five membered ring respectively did not yield the desired products, probably due to the reported instability of the corresponding hydroperoxide.[87]

1,3-dimethyl indole (**15**) was subjected to photooxidation conditions.[58] The indole was completely consumed after 15h. However because of the unstability of the formed peroxide, it could not be detected at room temperature and was completely decomposed (Scheme 62a). Therefore the photooxidation reaction was performed in methanol at -40°C and after the full conversion of 1,3-dimethylindole (**15**), the catalyst and aniline **91** were added to the reaction mixture (Scheme 62b). The intermediate peroxide **17** was converted to product **113** after Hock rearrangement and trapping of intermediate cation with aniline **91** (see Scheme 63). The product **113** was a mixture of two diastereomers with ratio of 82:18. However, only the major diastereomer could be isolated after purification. In order to improve the efficiency of the reaction, the reaction was also perfomed in one pot fashion (Scheme 62c). However, no oxidation of the indole was observed and only the starting materials were recovered.



Scheme 62: Photooxidation and coupling of 1,3-dimethyl indole (15)

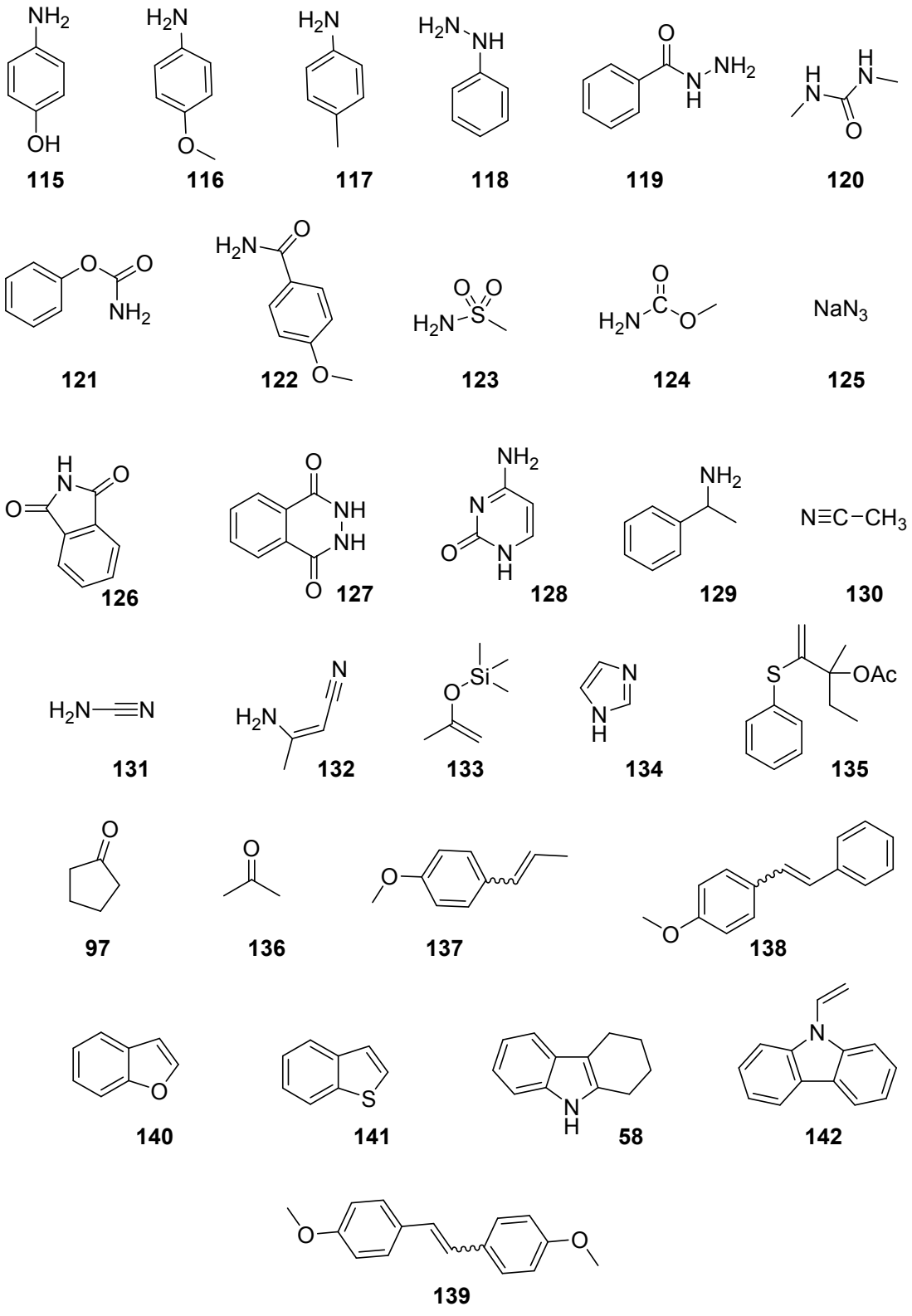
The plausible mechanism involves the oxidation of indole **15** to zwitterion **16** which is then trapped by methanol to give peroxide **17** (Scheme 63).



Scheme 63: Proposed mechanism for the coupling of indole 14 with aniline 91

It is then converted to carbocation **114** under acidic conditions as a result of Hock rearrangement. The carbocation **114** further reacts with aniline **91** to afford the observed product **113**.

The scope of the coupling reaction reaction using peroxide **59** was then investigated. A variety of other nitrogen based and carbon based nucleophiles were tested by using both methods *i.e*. 10 mol% TFA in MeOH (Method A) and AcOH as solvent without any additional catalyst (Method B) one by one (Scheme 64). The introduction of electron donating group on the aniline ring was detrimental for the reaction and the desired product was not observed (Scheme 64, nucleophile **115**-**117**). It was assumed that an increase in the nucleophilicity also increases the basicity of nucleophile and then as a result of acid base reaction the nucleophile is deactivated. In agreement to this logical conclusion, phenyl hydrazine (**118**) and phenyl hydrazide (**119**) were also not reactive under these conditions (Scheme 64, nucleophile **118**-**119**). Other nitrogen based nucleophiles having an alectron withdrawing group adjacent to nitrogen were also tested (Scheme 64, nucleophile **120**-1**34**). Surprisingly, none of them gave the desired coupling product. It is possible that the desired products are formed but they are not stable under these conditions. In general, coupling products decompose slowly under acidic conditions. The nucleophile **135**, taken from Prof. Dr. Valentin Ananikov belonging to Russian Academy of Sciences, Leninsky Prospekt 47, Moscow 119991, was also not active. On the other hand the optimized reaction conditions were also not suitable for the coupling of different carbon based nucleophiles (Scheme 64, nucleophile **97**-**142**). It seems that because of their poor nucleophilicity these carbon based nucleophiles are not suitable for the transformation.



Scheme 64: Failed nucleophiles

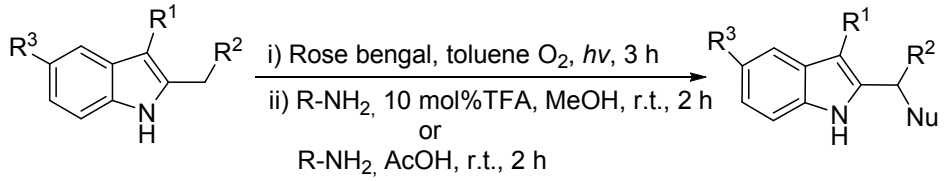
2-methyl indole, which is more nucleophilic than ketones, alkenes, furan and thiophene, was also tested.[88] Interestingly, moderate yield of the desired coupling product were obtained (further details about this reaction will be discussed later in next section 5.3.3).

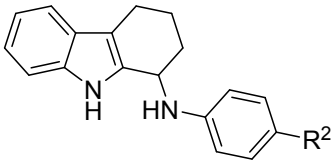
However, a wide range of anilines having different substituents could be coupled with peroxide **59**. Excellent yields were achieved with anilines having electron withdrawing groups (Scheme 65, compound **99**, **107**) while unsubstituted and halogen substituted anilines (compound **106**, **143**) gave good yields. The reaction of chloro tetrahydrocarbazole with *o*-nitroaniline was possible with slightly lower yields (Scheme 65, compound **144**).

Saccharin, being acidic itself, afforded the coupling product **145** with hydroperoxide **59** in good yields without any additional catalyst. Tetrahydroquinoline and indoline derivatives yielded the coupling products **146**-**149** in good to excellent yields.

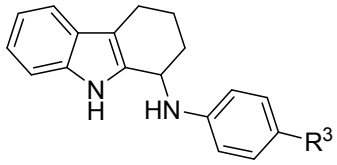
The reaction was also performed by introducing different substituents to the carbazole substrate. The formation of the corresponding hydroperoxides was not hampered by the introduction of different halogen and alkyl substituents in the tetrahydrocarbazole structure. However the rate of formation of the corresponding hydroperoxide was slowed down after the introduction of strong electron withdrawing groups (like -CN) in the aromatic ring of tetrahydrocarbazole. For 2,3 dialkyl substituted indoles, the oxidation was achieved at reduced temperatures.

The reaction of 3-methyl-tetrahydrocarbazole hydroperoxide and 3-phenyl-tetrahydrocarbazole hydroperoxide with *p*-nitroaniline (**91**) and *p*-cyanoaniline (**105**) resulted in the formation of diastereomers with the ratio of 83:17, 91:9 and 65:35 respectively (Scheme 65, compounds **150**-**152**). The major diastereomers were purified by column chromatography and the relative configuration of the alkyl group and aniline nucleophile was determined as *trans* with the help of ^{1}H NMR (see experimental section).

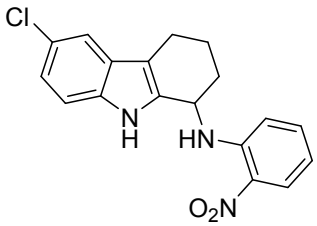




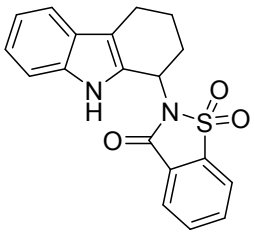
R^2= NO_2, **99**, 86%[a]
R^2= CN, **107**, 80%[a]



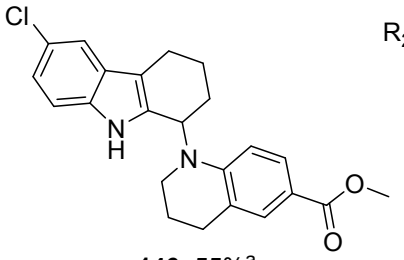
R=F, **143**, 65%[b]
R=H, **106**, 60%[b]



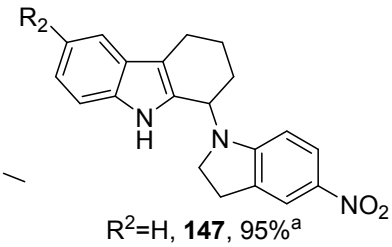
144, 55%[a]



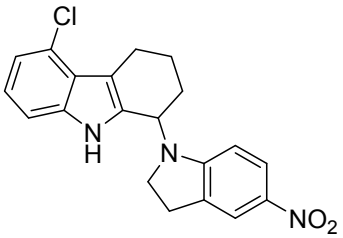
145, 52%[c]



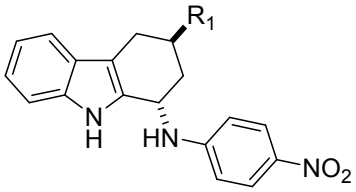
146, 55%[a]



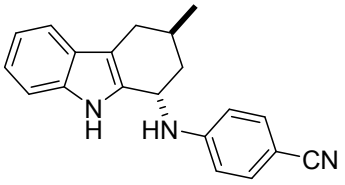
R^2=H, **147**, 95%[a]
R^2=F, **148**, 55%[a]



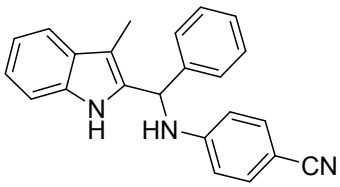
149, 70%[a]



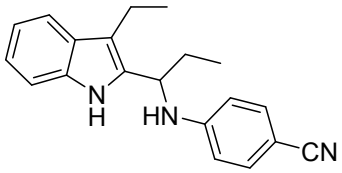
R^1= Me, **150**, dr 83:17, 67%[a]
R^1= Ph, **151**, dr 91:09 67%[a]



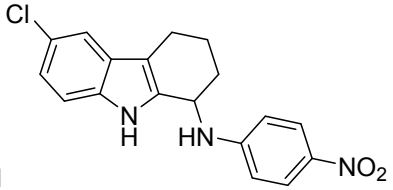
152, dr 65:35, 80%[a]



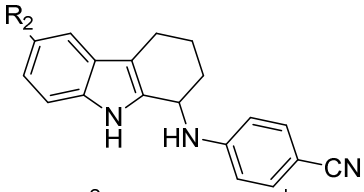
153, 67 %[b]



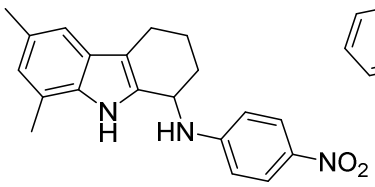
154, 60 %[b]



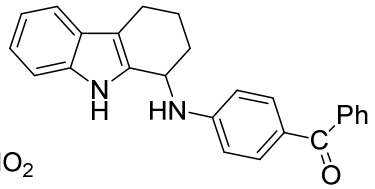
R^2= Cl, **155**, 85%[a]



R^2= CN, **156**, 50%[b]
R^2= Cl, **157**, 88%[b]
R^2= Br,**158**, 80%[b]



159, 86%[a]



160, 70%[b]

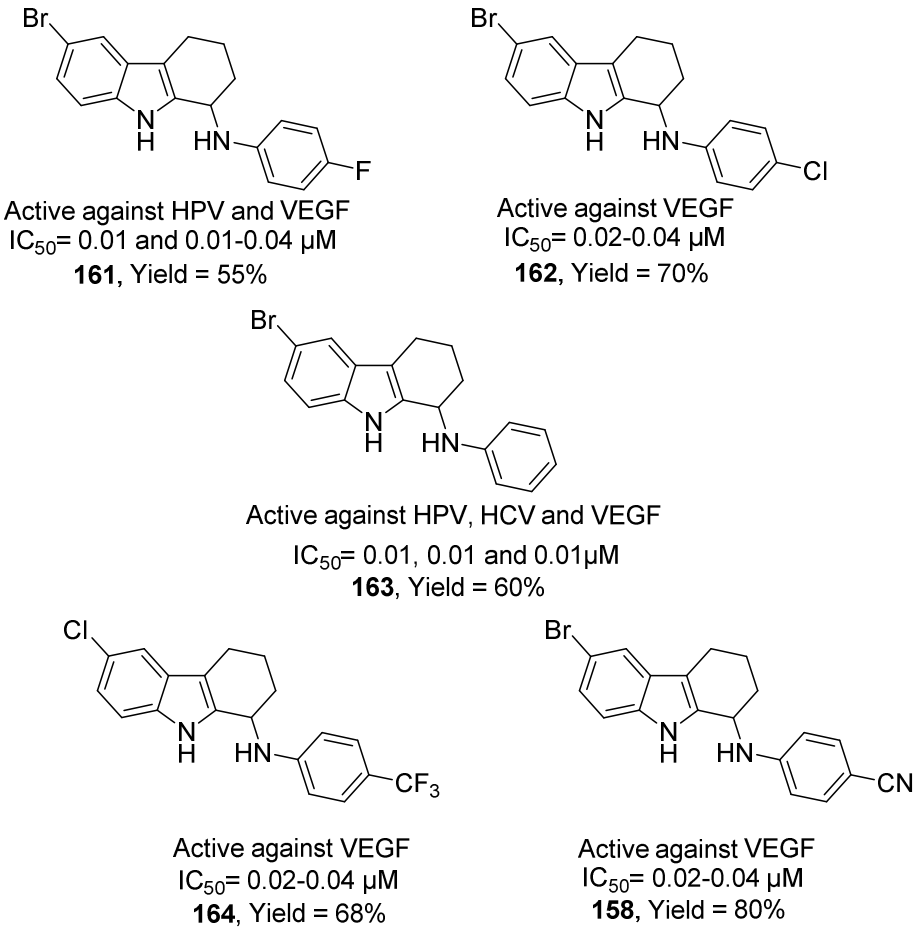
Scheme 65: Scope of the reaction; (a): General procedure A: MeOH, Nu-H (1.0 equiv.), 10mol% TFA, r.t., 2 h (b): General procedure B: Nu-H (1.0 equiv.), AcOH, r.t., 2 h (c): MeOH, Nu-H (1.0 equiv.), r.t., 3 h, no additional catalyst

The presence of six membered ring is not necessary for the coupling reaction. By introducing benzyl group group at indole C-2, the reaction proceeds in good yields (Scheme 65, compound **153**). The transformation can also tolerate extended alkyl chains at indole C-2 and C-3 positions. 2-Propyl-3-ethyl indole afforded the coupling product with *p*-cyanoaniline in 60% yield (Scheme 65, compound **154**). Similarly many other products (Scheme 65, compound **155-160**) bearing different substituents could be formed in excellent using these methods.

Importantly, the reaction does not require any aqueous workup. The solvent is directly evaporated after full conversion of peroxide **59** (or other peroxides) and the products are purified by column chromatography. In many cases the product precipitates in pure form and no chromatography is needed.

Some other salient features of the reaction are noteworthy: 1) tetrahydrocarbazole and its derivatives can be easily converted to the corresponding hydroperoxides by using oxygen and catalytic amounts of rose bengal in 3 hours in quantitative yield, 2) the reaction proceeds smoothly at room temperature, 3) the reaction requires only cheap acid, no expensive metal catalyst is required, 4) the coupling reaction is normally completed in 2-3 hours, 5) the reaction is air- and moisture tolerant.

It was also proved that the developed method could also be applied to the synthesis of biological active compounds which were known to be effective for the treatment of Human papillomaviruses (HPVs)[67a] and Hepatitis C virus (HCV)[67b] or as inhibitor for vascular endothelial growth factor (VEGF).[89]



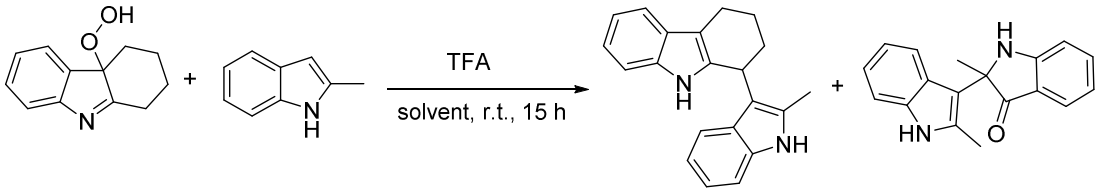
Scheme 66: Application of the developed method, Method B, for the synthesis of known pharmaceutically active compounds

5.3.3 Extension of the scope of reaction by using DMSO as solvent:

I, next, also wanted to extend the scope of the developed reaction to other nucleophiles. For this reason I subjected 2-methyl indole (**165**) to the reaction conditions, using AcOH as solvent (Table 56, entry 1). The desired coupling product **166** was obtained albeit in poor yield. The product **167** formed by the dimerization of indole **165** was observed as major byproduct (Table 56). Slightly better yields were obtained by using combination of methanol and TFA (Table 56, entry 2). Yield of product **166** was further improved to 48% by using DMF as solvent and TFA as catalyst (Table 56, entry 3). However, the formation of dimer **167** was always found to be the competing reaction.[90]

During the structural analysis of peroxide **59** by ^{1}H NMR, it was observed that it was reduced to alcohol **103** in DMSO-d_6 (see Scheme 69 for structure of alcohol **103**) and the formed alcohol **103** was also stable in DMSO.

Table 56: Screening of solvents[a]



59 **165** **166** **167**

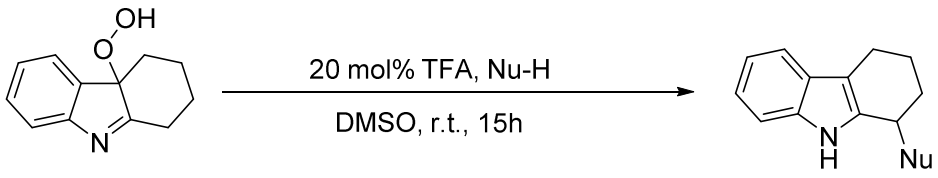
Entry	Solvent	TFA (mol%)	166 (%)	167 (%)
1	AcOH	-	15	35
2	MeOH	10	41	14
3	DMF	10	48	20
4	DMSO:MeOH	10	86	4
5[b]	DMSO:MeOH	10	95	4

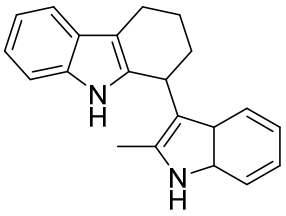
[a]: 0.49 mmol **59**, 0.49 mmol **165** and 2 mL of solvent was used. Yields were determined by ^{1}H NMR using internal standard. [b]: 1.5 equiv. 2-methyl indole was used

For this reason, I rationalized that use of DMSO can be helpful because it can help to avoid the oxidation of indole by reducing the peroxide **59** and formed hydrogen peroxide respectively. Based upon this assumption, a mixture of DMSO:MeOH with a ratio of 1:1 was used and excellent yields of the coupling product **166** could be achieved (Table 56, entry 4).

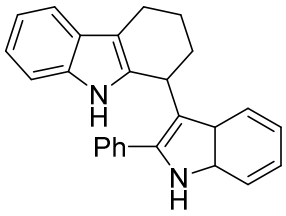
The reaction was then applied to the coupling of 2-phenyl indole with peroxide **59**. The reaction proceeded smoothly to afford the desired coupling product **168** in excellent yield (Scheme 67). However, the reaction works only with 2-substituted indoles and poor yields were obtained when reaction was applied to other indoles without substituent at C-2 position.

For nucleophiles, other than indoles, the use of methanol as cosolvent was not helpful and DMSO was used as the only solvent for the reaction. Different failed nucleophiles under the previously developed conditions could be successfully coupled using DMSO as solvent. For example the use of *p*-methoxy aniline as nucleophile afforded the desired coupling products **169** in good yield (Scheme 67). 1,3-Dimethyl urea and thiophenol could also be coupled with peroxide **59** to furnish the desired coupling products **170** and **171** respectively (Scheme 67). The acylated product **172** was obtained in good yields by using 1:1 mixture of DMSO:AcOH without any additional catalyst. The acetate group could potentially be displaced by other nucleophiles to get synthetically useful products.[69] The reaction was then also applied to the coupling of 1-naphthyl amine and 57% yield of the coupling product **173** was obtained (Scheme 67).

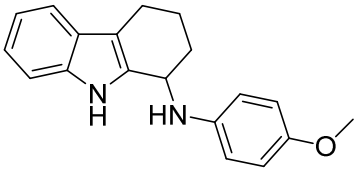




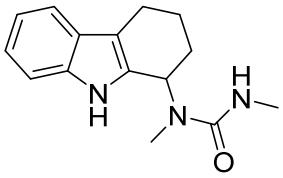
166, 91%[h,d]



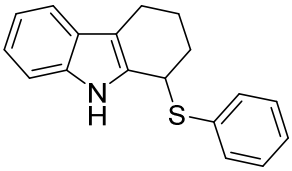
168, 79%[h,d]



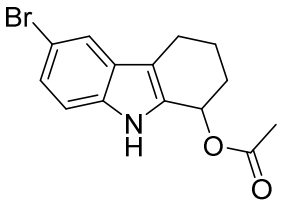
169, 44%[a]



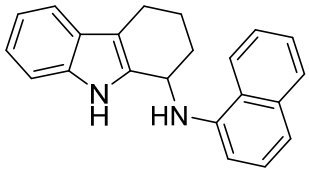
170, 65%[b]



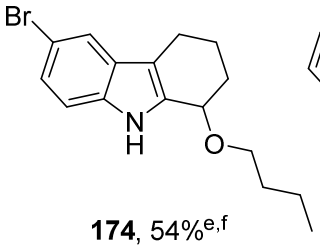
171, 65%[a]



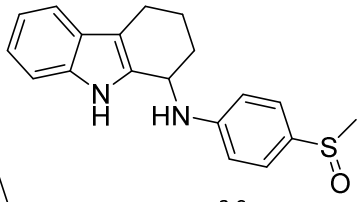
172, 40%[g]



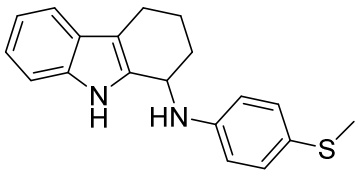
173, 57%[b]



174, 54%[e,f]



176, 58%[a,c]



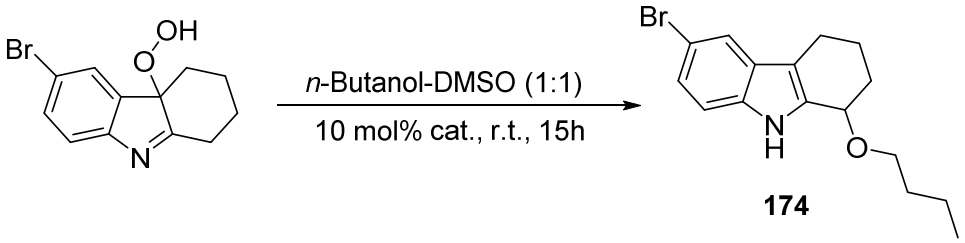
177, 74%[b]

Scheme 67: Scope of the reaction, a: 1.0 equiv. of nucleophile was used, b: 5.0 equiv. of nucleophile was used, c: AcOH was used as solvent without any additional catalyst, d: 1:1 ratio of methanol and DMSO was used as solvent, e: 1:1 ratio of n-butanol and DMSO was used as solvent, f: 10 mol% PTSA was used as catalyst, g: 1:1 ratio of AcOH and DMSO was used as solvent without any additional catalyst, h: 1.5 equiv. of nucleophile was used

However, the coupling of peroxide **59** with *n*-butanol under these conditions gave only 15% of the desired coupling product **174**. The yield was slightly improved to 20% by using 1:1 mixture of DMSO and *n*-butanol as solvent (Table 57, entry 1). In order to optimize the yield, some other catalysts were screened and PTSA was

found to be the optimal one affording ^{1}H NMR yield of 60% (Table 57, entry 10).

Table 57: Screening of catalysts[a]

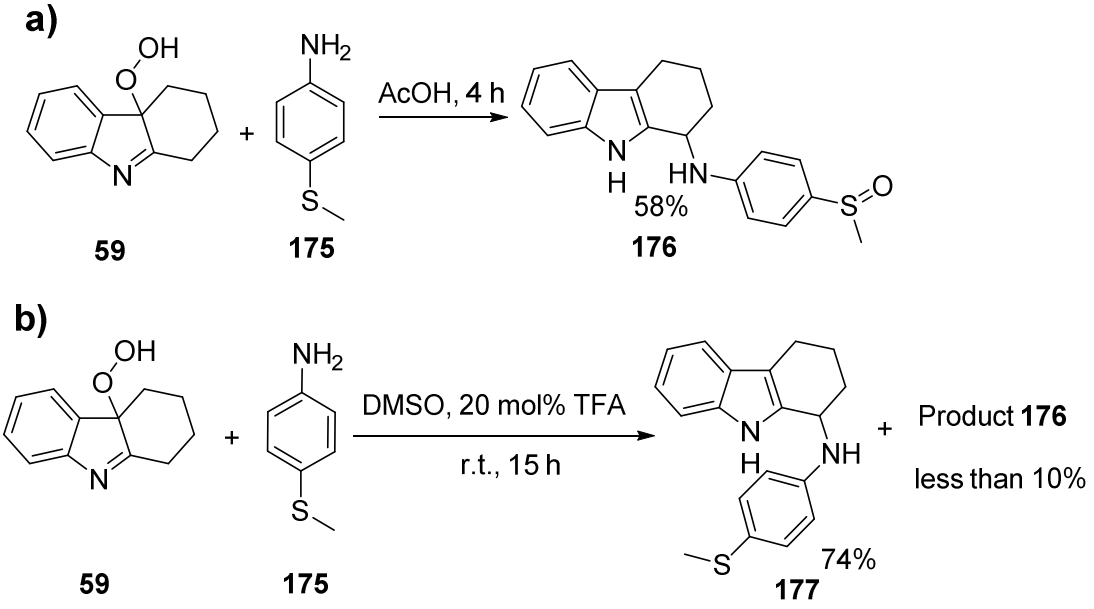


174

Entry	Catalyst	Product 174 (%)
1	TFA	20
2	$Fe(OTf)_3$	25
3	$FeBr_3$	06
4	MsOH	50
5	TCAA	00
6[b]	MsOH	52
7	HCl	00
8	HNO_3	48
9	$HClO_4$	53
10	PTSA	60

[a]: 1:1 mixture of DMSO:*n*-BuOH (1 mL:1 mL) was used as solvent. Yields were determined by ^{1}H NMR using internal standard. [b]: 5 mol% of MsOH was used as catalyst

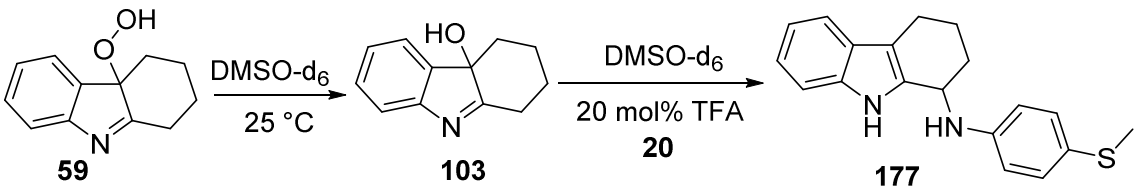
The coupling of 4-(Methylthio)aniline (**175**) with hydroperoxide **59** was performed by using AcOH as solvent without any additional catalyst (Scheme 68a). The structure elucidation confirmed the formation of the product **176** in which the sulfide group of aniline has been oxidized to sulfoxide (Scheme 68a).



Scheme 68: Coupling of peroxide 59 with thioaniline 175 in AcOH and DMSO

By performing the reaction with a mixture of AcOH and DMSO, a mixture of two different products **176** and **177**, with ratio of approximately 1:1, in overall moderate yield was observed. The formation of product **176** could be suppressed by using DMSO as the only solvent and TFA as catalyst. By increasing the concentration of aniline **175** (5.0 equivalents), excellent yield of the coupling product **177** could be isolated (Scheme 68b).

In order to answer the question if hydroperoxide **59** is first reduced to alcohol **103** and then the coupling proceeds, or first step is the coupling of peroxide **59** with aniline **175**, followed by the reduction of H_2O_2 with DMSO, the reaction was performed in two separate steps. The peroxide **59** was first reduced to alcohol **103** in DMSO and then the formed alcohol **103** was coupled with methyl-thioaniline **175** in DMSO using 20 mol% TFA as catalyst (Scheme 69).



Scheme 69: Studying the reduction of peroxide 59 followed by coupling step at 25 °C. 0.048 mmol of peroxide 59, 0.048 mmol of alcohol 103, 0.0096 mmol of TFA and 0.24 mmol of aniline 175 were used.

The progress of each reaction was controlled at regular time intervals. The peroxide **59** was not completely reduced to the alcohol **103** even after 24h. The coupling step thioaniline **175** with alcohol **103** was faster and was completed in 3.5 h as compared to 8.5 h with peroxide **59**.

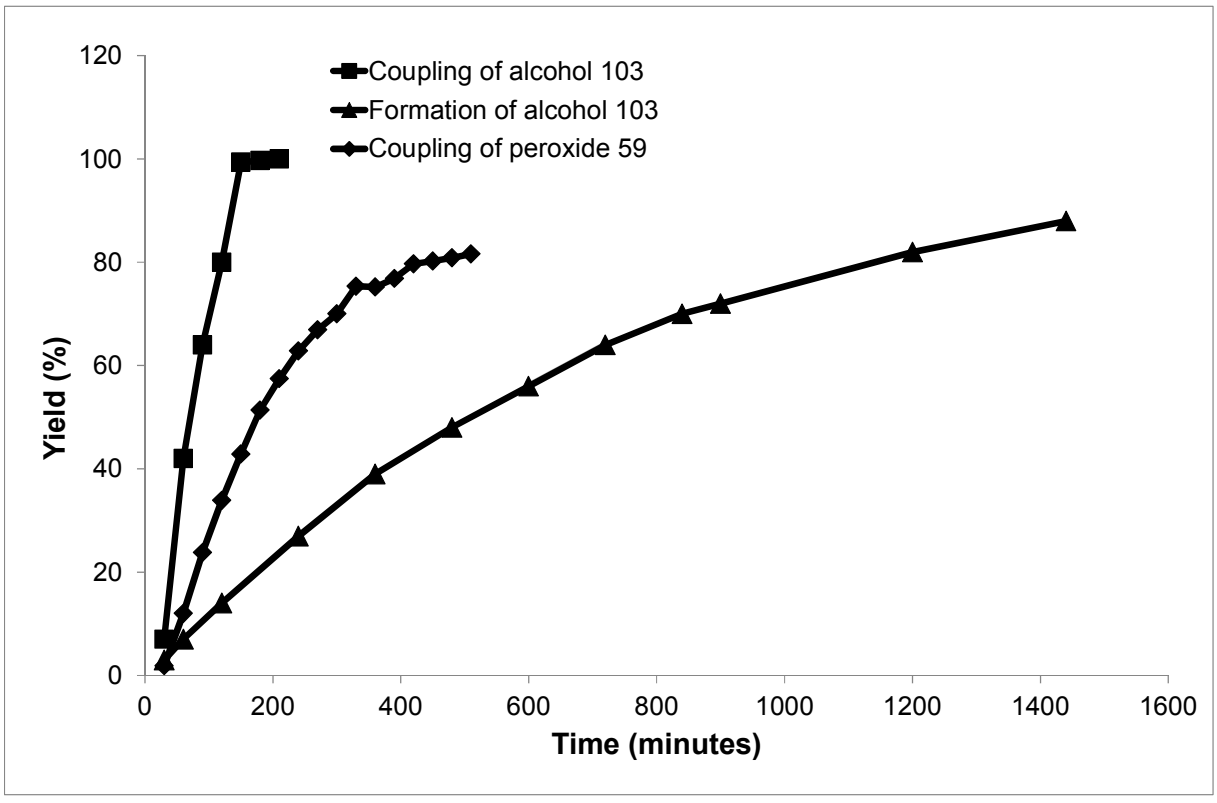


Figure 5: Time taken for the reduction of peroxide 59 and for the coupling of alcohol 103 and peroxide 59 with aniline 175 in separate reactions. 0.048 mmol of peroxide 59, 0.048 mmol of alcohol 103, 0.0096 mmol of TFA and 0.24 mmol of aniline 175 were used. The reactions were performed at 25 °C in NMR tube using DMSO-d_6 as solvent

From these experiments, It could be concluded that the coupling of peroxide **59** with thioaniline **175** could proceed *via* alcohol **103** which could be formed *in situ* by DMSO. However, as the coupling step by using peroxide **59** as starting material was faster than the reduction of peroxide **59** to alcohol **103** therefore it was assumed that coupling mainly proceeds directly from peroxide **59**. The formed H_2O_2 could then be reduced by DMSO.

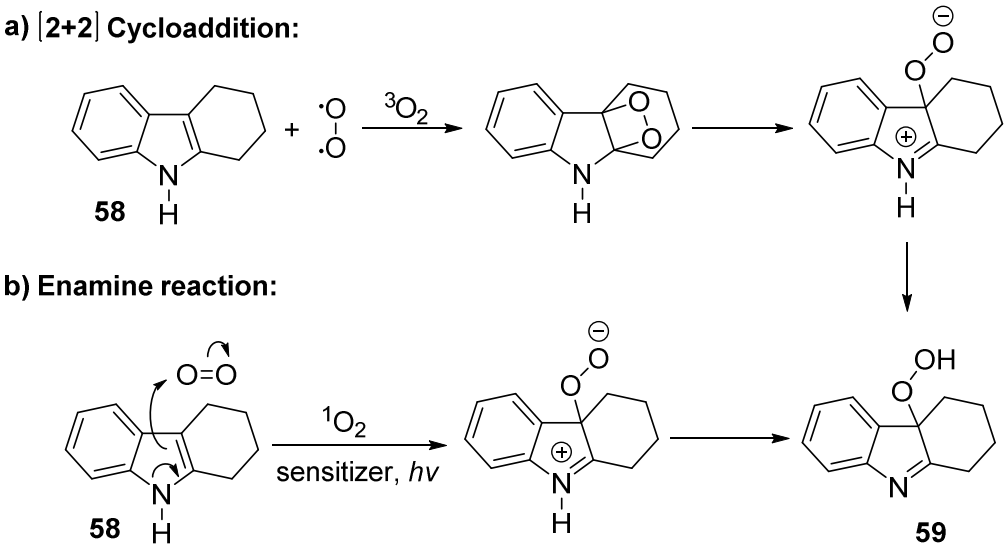
5.3.3 Summary:

In summary, I have developed a practical one pot method for the C–H functionalization of tetrahydrocarbazole derivatives *via* intermediate hydroperoxides with the aid of oxygen, visible light and catalytic amounts of cheap acid and sensitizer. The reaction is practically simple, proceeds at room temperature and affords the coupling products in good to excellent yields. I have also synthesized some representative pharmaceutically active compounds. The formation of peroxide with oxygen followed by the acid catalyzed substitution of H_2O_2 can be an interesting new field in organic synthesis. Potentially, different other organic molecules could be accessible by oxidative coupling reactions in this way. Therefore, the applications of this method towards the synthesis of other complex molecules and natural products is anticipated.

5.4 Mechanistic studies on the C–H functionalization of tetrahydrocarbazole *via* photochemically generated hydroperoxides

5.4.1 Mechanistic Studies of the formation of hydroperoxide

The reaction of singlet oxygen with indole derivatives gives rise to peroxides.[51d, 51e, 57]. The photooxidation of tetrahydrocarbazole **58** with molecular oxygen[11, 12] using toluene as solvent and rose bengal as sensitizer affords hydroperoxide **59** in quantitative yields. However, the mechanism for the formation of this peroxide is still not clear.

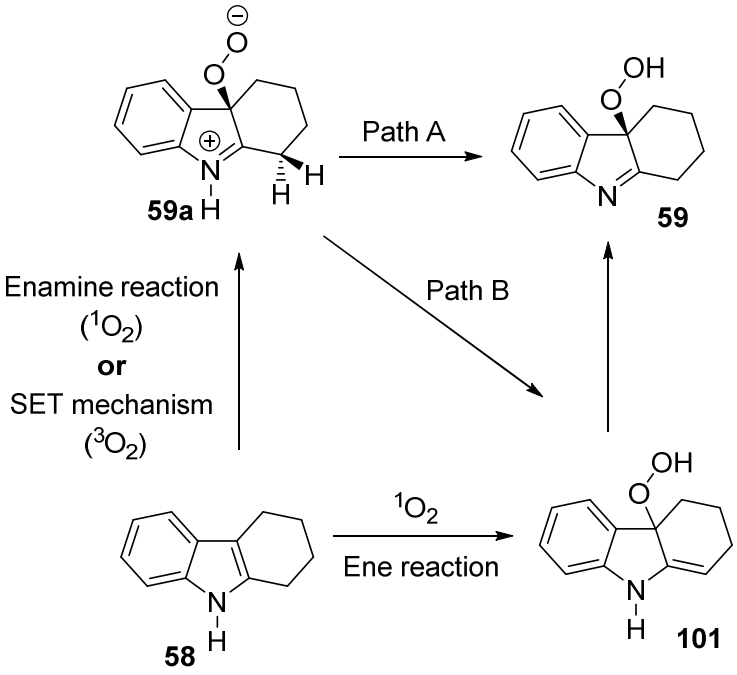


Scheme 70: Possible pathways for the formation of peroxide 59

One possible pathway might be the formation of dioxetane by concerted [2+2] cycloaddition. This dioxetane can then rearrange to give peroxide **59** (Scheme 70a). However, this approach has been found to be forbidden for electron rich enamines.[13] The introduction of hydroperoxide moiety by the photooxidation of *N*-protected indoles has been proposed to take place by enamine type reaction which yields zwitter ionic intermediates (Scheme 70b).[1-3, 14-17]

There are two possible reactions which can give peroxide **59** *i.e*. i) ene reaction through allylic proton at C-1 carbon and ii) Single electron tranfer (SET)[85, 91] or enamine type reaction (Scheme 71). The ene reaction of carbazole **58** with singlet oxygen would generate enamine peroxide **101** which can further tautomerize to peroxide **59**. On the other hand zwitterion **59a** can be formed by the enamine type reaction of carbazole **58** with singlet oxygen or through single electron transfer mechanism.[85] The negatively charged oxygen can either abstract proton from C–H bond (Scheme 71, Path B) or from *N–H* bond (Scheme 2, Path A). I rationalized that the negatively charged oxygen of zwitterion can easily access one of the allylic hydrogen at C-1 as compared to planar hydrogen at nitrogen (Scheme 71). This abstraction would result in the formation of enamine. Formation of this kind of intermediate enamine has also been suggested before during the photooxidation of 1,2,3-trimethyl indole in aprotic solvents.[14]

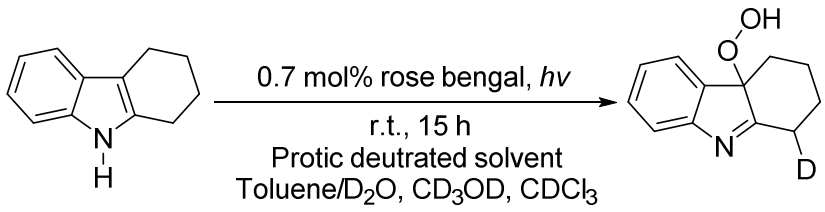
Therefore, it was decided to investigate the possibility of the formation of enamine **2b** over the course of the reaction. It was realized that the tautomerism of enamine **2b** to peroxide **59** in protic deuterated solvents could result in the incorporation deuterium in the formed peroxide **59** (Scheme 71).



Scheme 71: Abstraction of proton (path A) versus abstraction of C–H proton (path B) and singlet oxygen ene reaction

Therefore, the photooxidation of carbazole **58** was performed in different protic deuterated solvents. As toluene was a suitable solvent for the photooxidation of carbazole **58** to peroxide **59**, therefore at first, a mixture of toluene with D_2O, CD_3OD and $CDCl_3$ in different ratios was used for the photooxidation reaction (Table 58, entry 1-4). These reactions provided the peroxide **59** in quantitative yields, however, no incorporation of deuterium was observed in the formed peroxide. The reaction was then performed in $CDCl_3$ without the use of toluene. Again the reaction worked in quantitative yield and there was no incorporation of deuterium in the formed peroxide (Table 58, entry 5). The reaction was also performed in CD_3OD. However, there was poor conversion of carbazole **58** and formed peroxide could not be isolated (Table 58, entry 6-7).

Table 58: Incorporation of deuterium in deuterated solvents[a]



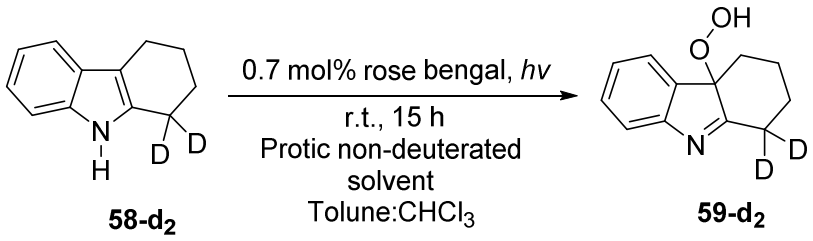
58 **59-d_1**

Entry	Toluene (mL)	D_2O (mL)	CD_3OD (mL)	$CDCl_3$ (mL)	D (%)
1	9.5	0.5	-	-	0
2	9.5	-	0.5	-	0
3	8.0	-	2.5	-	0
4	5.0	-	-	5	0
5	-	-	-	10	0
6[b]	-	-	10.0	-	-
7[b]	-	-	10.0	-	-

[a]: 0.49 mmol **58** and 10 mL of solvent was used. [b]: Reaction was performed at -78°C with phthalocyanine as sensitizer and formed peroxide was decomposed on purification

In order to further confirm these results, tetrahydrocarbazole **58**-d_2 was synthesized and subjected to the reaction conditions for the formation of hydroperoxide **59**-d_2 (Table 59, entry 1-2). Peroxide **59**-d_2 was formed in quantitative yields but again there was no change in the content of deuterium before and after the reaction.

Table 59: Change in the content of deuterium



58-d_2 **59-d_2**

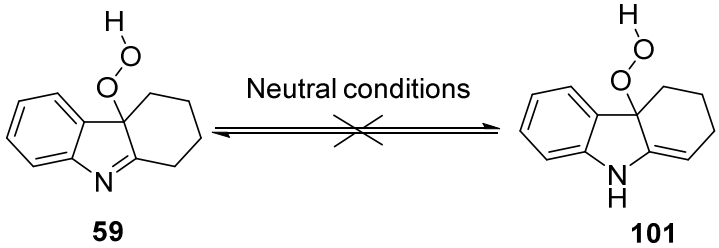
Entry	Toluene (mL)	Chloroform (mL)[c]	Yield[a]	Change in D (%)
1[b]	10	0	Quant.	0
2[b]	8	2	Quant.	0

[a]: 0.49 mmol **1** and 10 mL of solvent was used. [b] Incorporation of hydrogen

These results suggested that:

i) Reaction does not proceed through ene reaction and path B of enamine type reaction (Scheme 71).

ii) The formed imine is highly stable and does not exist in equilibrium with enamine under neutral conditions (Scheme 72).

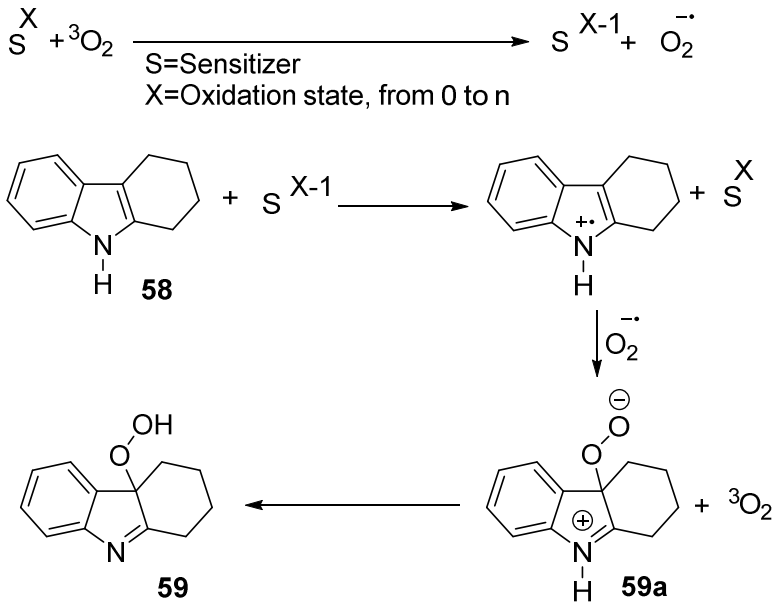


59 **101**

Scheme 72: Lack of tautomerism under neutral conditions

Based upon these results, it is suggested that zwitterion **59a** formed during the reaction abstracts the proton from nitrogen and is converted to peroxide **59**.

Exclusion of path B suggests that the reaction of tetrahydrocarbazole with singlet oxygen to furnish peroxide **59** could either proceed through enamine type reaction or radical reaction (Scheme 73).

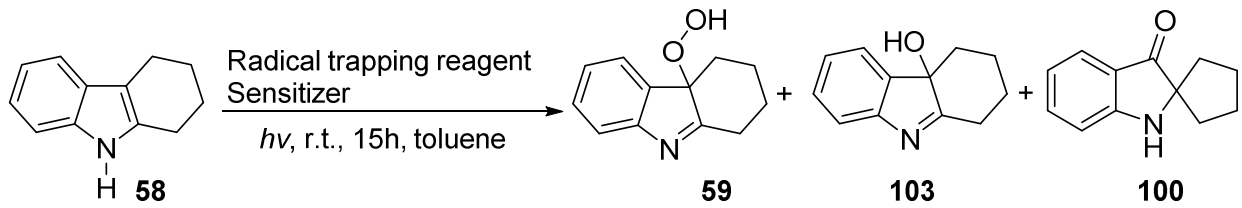


Scheme 73: Proposed radical mechanism for the formation of peroxide 59

In order to inhibit or trap the possible radical intermediates, the photooxygenation reaction was then performed by using BHT and TEMPO (Table 60, entry 3-6). Rose bengal and FePc were used as sensitizers. In the absence of any radical quencher the full conversion of carbazole **58** was achieved in 3-4 h (Table 60, entry 1-2). In case of rose bengal as sensitizer, carbazole **58** was quantitatively converted to peroxide **59**. However, FePc afforded a mixture of peroxide **59**, alcohol **103** and spiro product **100** (Table 60, entry 1). The alcohol **103** and spiro product **100** might arise from peroxide **59** through reduction with iron.[79] By using rose bengal in combination with BHT and TEMPO, the photoxygenation reaction was extremely slow (<1% conversion after 15 h) and starting materials were recovered after 15 h of reaction time (Table 60, entry 3-4).

Similar results were obtained by using the combination of FePc and BHT. The slow conversion might arise from the quenching of singlet oxygen with Lewis basic sites of radical trapper.[50b] However, the combination of FePc with TEMPO gave slow but complete conversion of carbazole **58** to peroxide **59** and products **100** and **103** (Table 60, entry 6). No product arising from the combination of carbazole **58** and TEMPO was observed. The formation of products arising from the photooxygenation of carbazole **58** and the absence of any product arising from TEMPO suggest that reaction does not proceed through radical mechanism. However, it is also possible that intermediate radicals react faster with oxygen than with TEMPO. Therefore, more investigations are needed in order to find the real mechanism behind the formation of peroxide **59**.

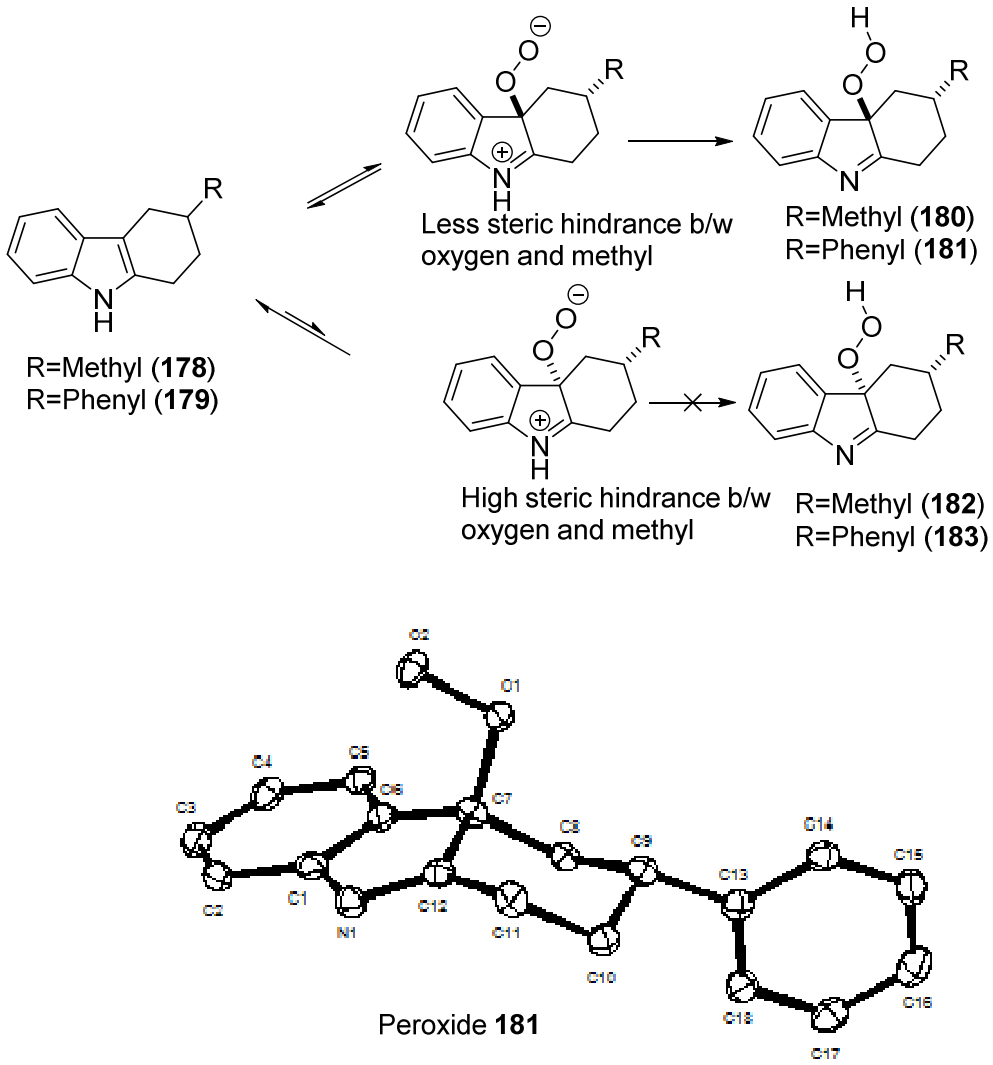
Table 60: Use of radical trapping reagents in the photooxygenation reaction[a]



Entry	Sensitizer	Radical trapping reagents	Result
1[b]	FePc	-	Complex mixture of products **59**, **103** and **100**
2[b]	Rose bengal	-	**59** (in quantitative yield)
3	Rose bengal	BHT	Extremely slow formation of **59**
4	Rose bengal	TEMPO	No Rxn
5	FePc	BHT	Extremely slow formation of **59**, **103** and **100**
6	FePc	TEMPO	Complex mixture of products **59**, **103** and **100**

[b] 1.4 mg of sensitizer was used. 10 mL of toluene was used. [b] Full conversion of carbazole **58** was obtained in 3-4 h

When 3-phenyl tetrahydrocarbazole **178** and 3-menyl tetrahydrocarbazole **179** were irradiated with visible light under the reaction conditions, only one diastereomer of corresponding peroxide was formed exclusively from both of these starting materials (Scheme 74). The structure of these diastereomers was confirmed by X-ray crystallography and it was found that the peroxide group and the methyl and phenyl group were *trans* to each other (Scheme 74). It is postulated that zwitterion intermediate in which methyl, phenyl group and peroxide group are *cis* to each other is highly unstable because of the steric hindrance between the two groups and does not lead towards the product. It loses molecular oxygen to regenerate aromatic starting material.[75] It is also possible that because of the steric hindrance between incoming oxygen molecule and methyl group of carbazole **178** and **179**, even the zwitterionic intermediate is not formed. Therefore, the only formed products are the products **180** and **181** in which these groups are *trans* to each other.



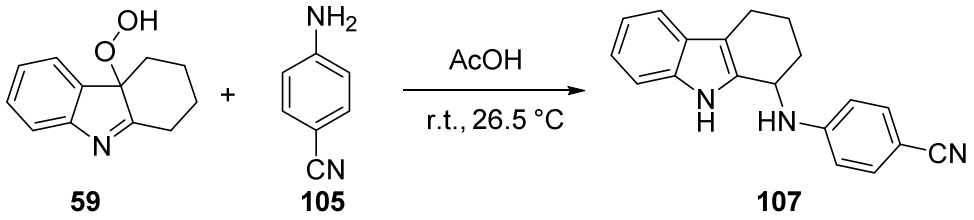
Scheme 74: Explanation for the formation of one diastereomer and X-ray structure of peroxide 181. For X-ray structure of peroxide 180 and other related information see section 9

5.4.2 Mechanistic Studies for the substitution reaction

Brønsted acid catalyzed aerobic oxidative coupling of different indole derivatives (*via* hydroperoxides) with nitrogen based nucleophiles has been discussed in the previous chapter (For detail see section 5.3.2.3 and section 5.3.3).

The coupling of derivatives of tetrahydrocarbazole **184** with different nucleophiles has been discussed before.[68-69, 92] The generally proposed rationale for these coupling reactions is the formation of enamine **186** (Scheme 76a) which further reacts with a nucleophile to form the product **187**. However, detailed mechanistic studies in this area are lacking. I have experienced that deep understanding of a reaction mechanism can help in the further development of the method.[47b]

Here, I present detailed mechanistic studies for the coupling of peroxide **59** with aniline **105** in AcOH to give product **107**.

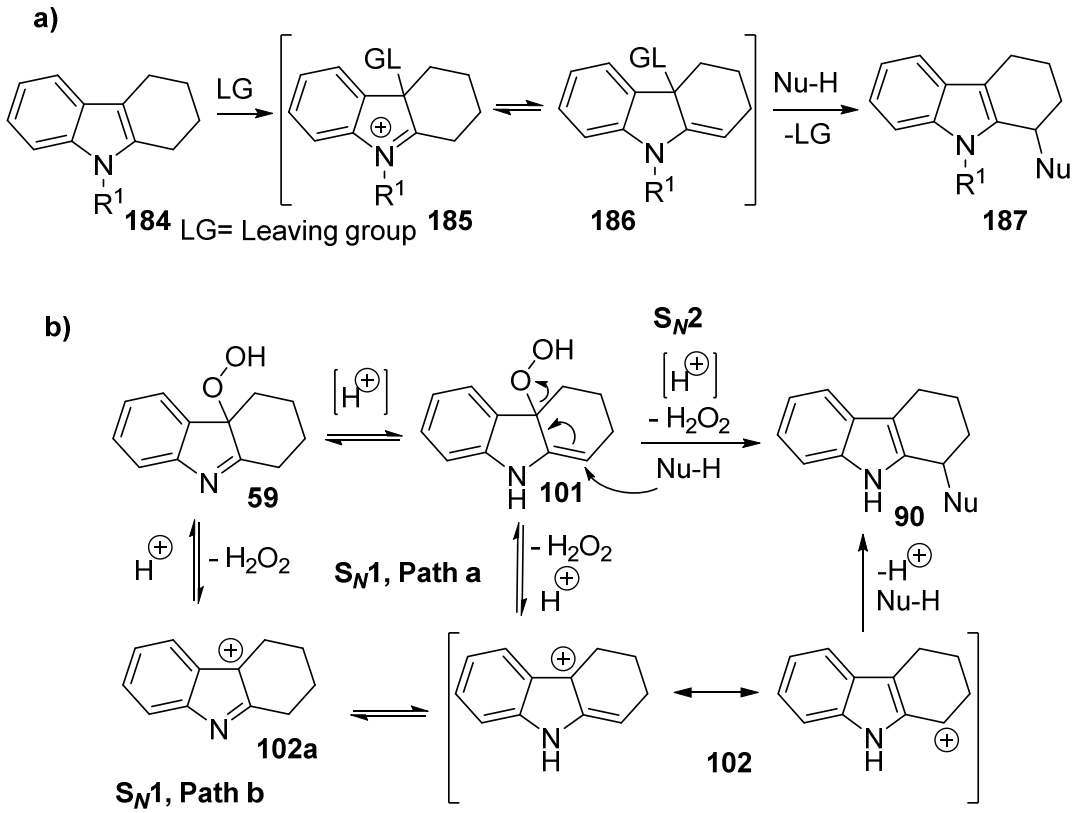


59 **105** **107**

Scheme 75: Acid catalysed coupling reaction of peroxide 59 with *p*-cyanoaniline (105).

The possible scenario for this acid catalyzed substitution reaction involves the protonation of peroxide **59** followed by substitution with aniline **105** through S_N1 or S_N2 mechanism (Scheme 76b). Furthermore, the are two possibilities for S_N1 reaction *i.e*. path a and path b. In path a, imine **59** tautomerizes to enamine **101** and then the cleavage of H_2O_2 takes place to afford cation **102** while path b involves the cleavage the of H_2O_2 from imine **59** to give carbocation **102a** and then this cation **102a** tautomerizes to give allylic cation **102**.

The first task was to distinguish between S_N1 and S_N2 mechanisms (Scheme 76b). Kinetic studies appear to be the most suitable tool to determine the order of reaction with respect to each substrate, peroxide **59** and aniline **105**, and hence distinguish between these two possibilities of S_N1 and S_N2 mechanism (Scheme 76b).



Scheme 76: a) Generally suggested mechanism for the coupling of tetrahydrocarbazole derivatives with different nucleophiles where R^1 is protecting group and R^2 is leaving group. b) Possible pathways (S_N1 *vs* S_N2) for the developed coupling reaction

To determine the order of reaction in aniline **105**, the concentration of peroxide **59** was kept constant and the reactions were performed by using different concentrations of aniline **105**, with the aniline **105** always being in excess of peroxide **59** (Figure 6). The reaction mixtures were quenched by a base to stop the reaction at determined intervals. The concentration of product **107** was calculated from the product of the fractional conversion and the initial concentration of the limiting reagent **105**. As the kinetics are the reflection of reaction mechanism, therefore, an accurate measurement of kinetics is important for investigating the mechanism of a reaction.[93] Therefore, for each value of concentration, the reaction was repeated at least two times, conversion of aniline **105** and concentration of coupling product **107** were measured at regular intervals by ^{1}H NMR and then the average values were taken for further calculations.

A graph plotted between the concentration of product **107** (y-axis) and time (x-axis) showed that the reaction was slowed down and poor yields of the product were obtained by increasing the concentration of aniline **105** (Figure 6). This negative effect of the concentration of aniline **105** on the rate of the reaction could be attributed to the weakly basic nature of the aniline **105**, which decreases the overall acidity of the system and thereby slows down the activation of peroxide **59** towards the substitution reaction.

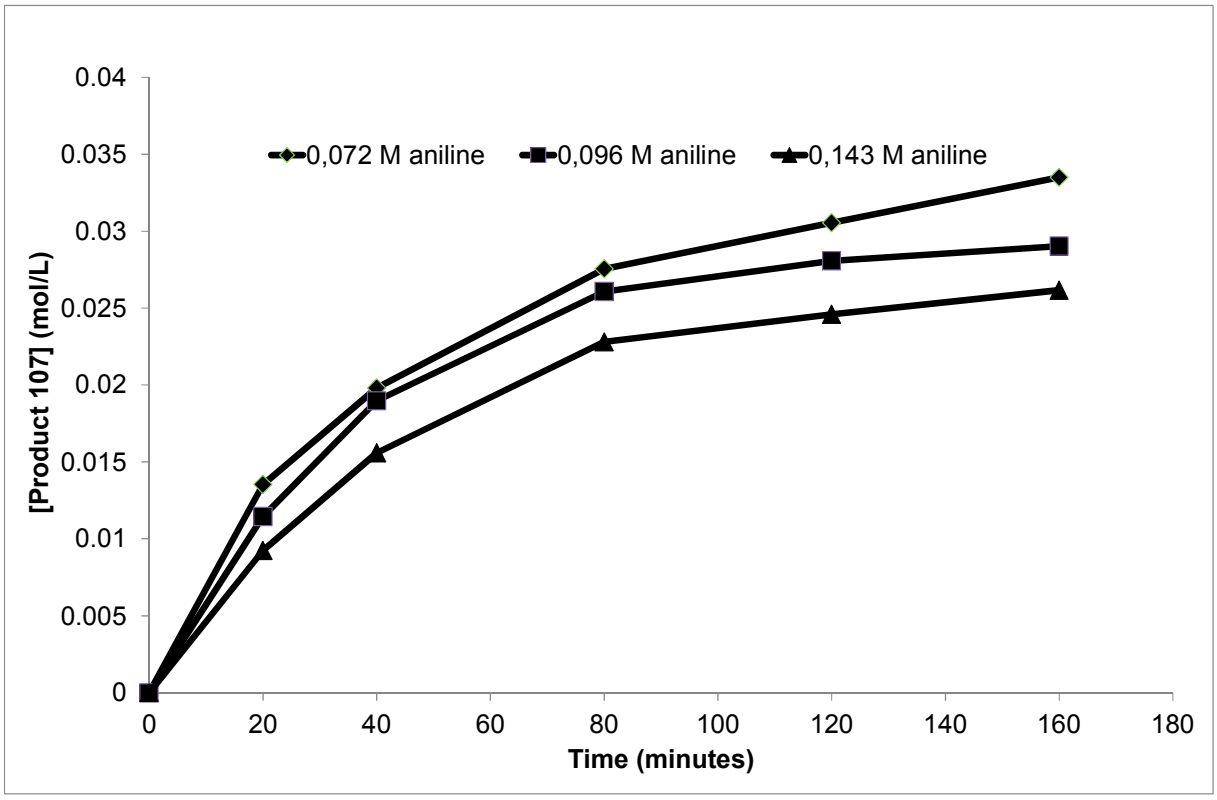


Figure 6: Reaction progress profile of product concentration versus time using different concentrations of aniline 105 (0.072 M to 0.143 M) under identical conditions keeping the concentration of peroxide 59 (0.048 M) constant. The reactions were performed in acetic acid as solvent, without any additional catalyst at 26.5 °C and at 275 rpm speed of stirrer. The concentration of coupling product was measured by ^{1}H NMR at regular intervals.

A polynomial curve of third order was fitted to the conversion versus time profile. Subsequently, the reaction rate was derived by taking the first derivative of this curve.

The reaction rate was then plotted versus the concentration of peroxide. This plot of rate *vs* concentration is also called as "graphical rate equation"(Figure 7).[93] As the concentration of peroxide **59** decreases over time, plotting the concentration of peroxide **59** as x-axis means that the reaction progresses from right to left. The graph clearly shows that reaction rate is slowed down by increasing the concentration of aniline **105** and full conversion of limiting substrate (peroxide **59**) was not achieved.

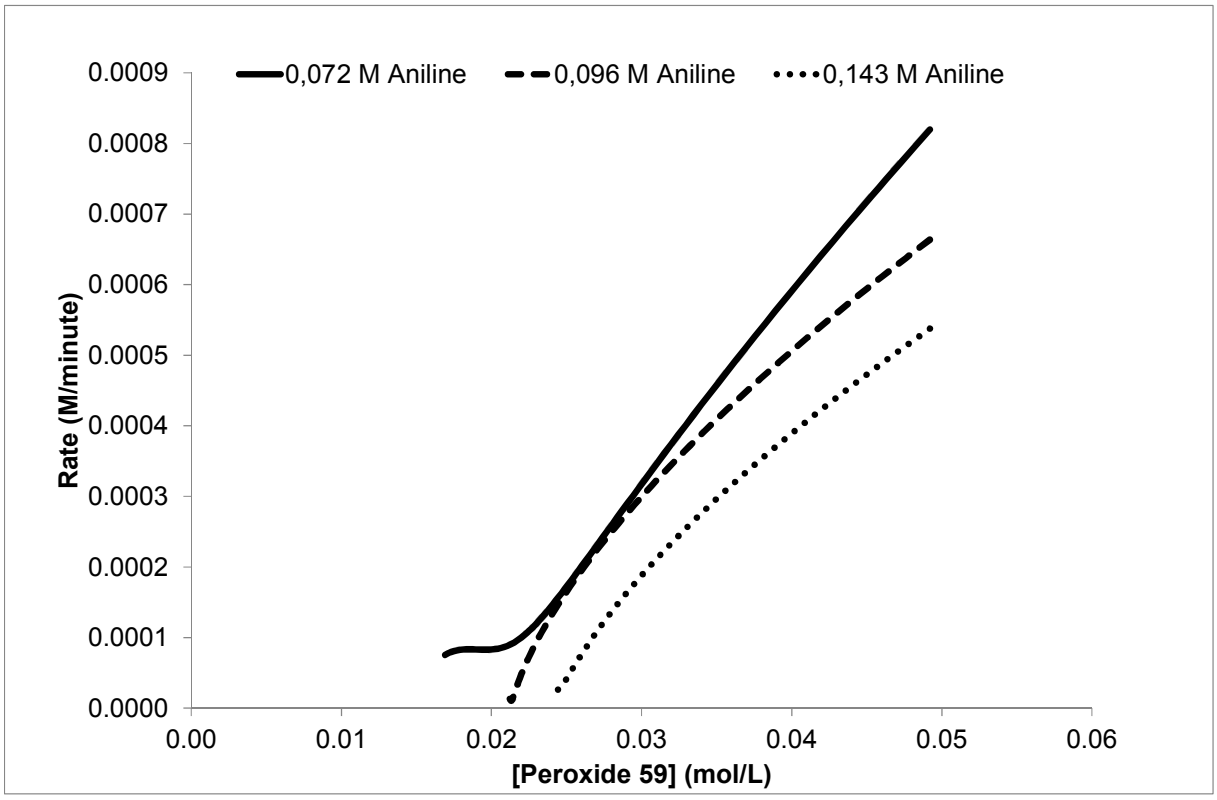


Figure 7: Rate of reaction versus concentration of peroxide 59 at different concentrations of aniline 105

The order of reaction, *x*, in aniline **105** can be determined from a plot of rate/[aniline **105**]^{x} versus [peroxide **59**] by searching the value of *x* that causes all rate curves to overlay with each other.[93] The best graphical overlay of lines belonging to different concentrations of aniline **105** was obtained when value of x was taken as - 0.5, showing that reaction was of negative order (-0.5) with respect to aniline **105** (Figure 8).

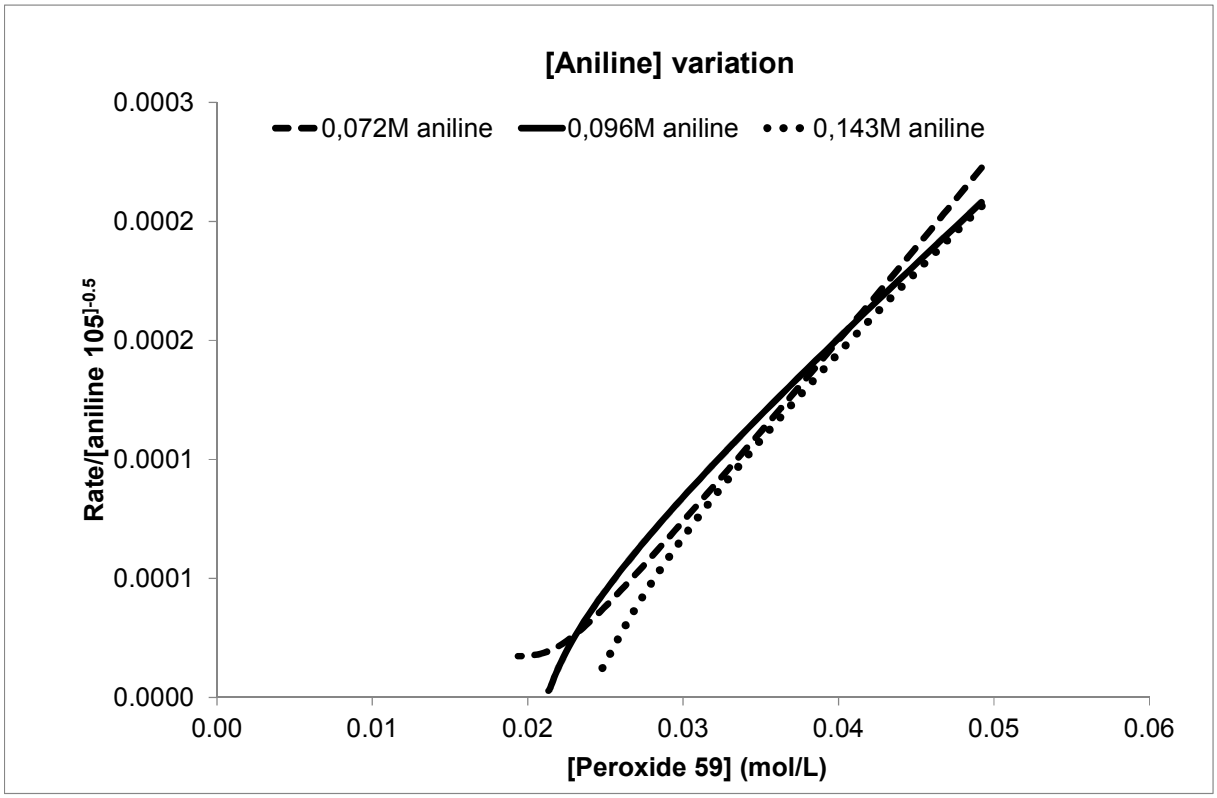


Figure 8: A graph plotted between rate/[aniline 105]$^{-0.5}$ versus [peroxide 59].

Next, the reaction was performed by varying the concentration of peroxide **59** keeping the concentration of aniline **105** constant (Figure 9). For these experiments, the peroxide **59** was used in equimolar amounts or in excess compared to the aniline **105**.

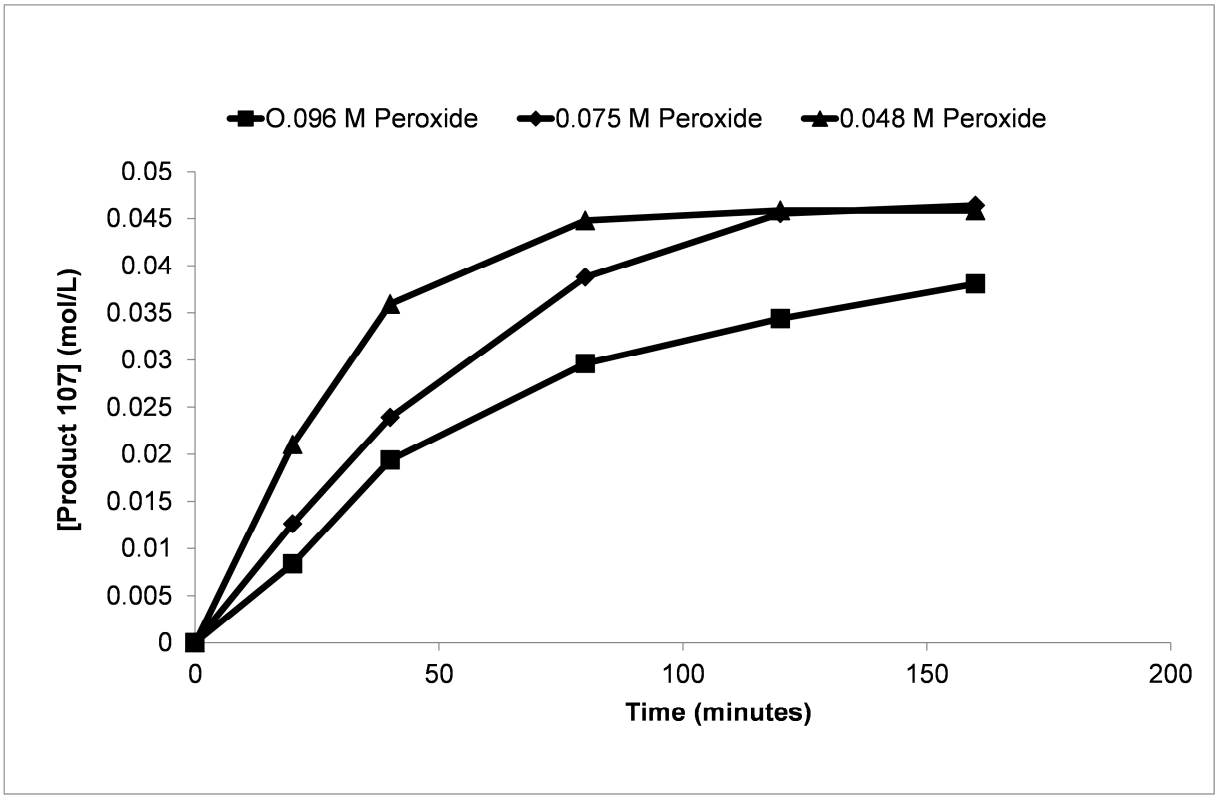


Figure 9: Reaction progress profile of increase in product concentration versus time using different concentrations of peroxide 59 (0.048 M to 0.096 M) under identical conditions keeping the concentration of aniline 105 (0.048 M) constant. The reactions were performed in acetic acid as solvent, without any additional catalyst at 26.5 °C and at 275 rpm speed of stirrer. The concentration of coupling product was measured by ^{1}H NMR at regular intervals.

It was found that, in contrast to the previous analysis, the rate of reaction increases by increasing the concentration of peroxide **59** and the limiting substrate, aniline **105**, is almost completely consumed. This means that rate of reaction positively depends upon the concentration of peroxide **59**.

This observation was further confirmed by plotting the rate of reaction versus the concentration of aniline **105** (Figure 10). It is obvious from the graph that reaction rate is increased by increasing the concentration of peroxide **59**.

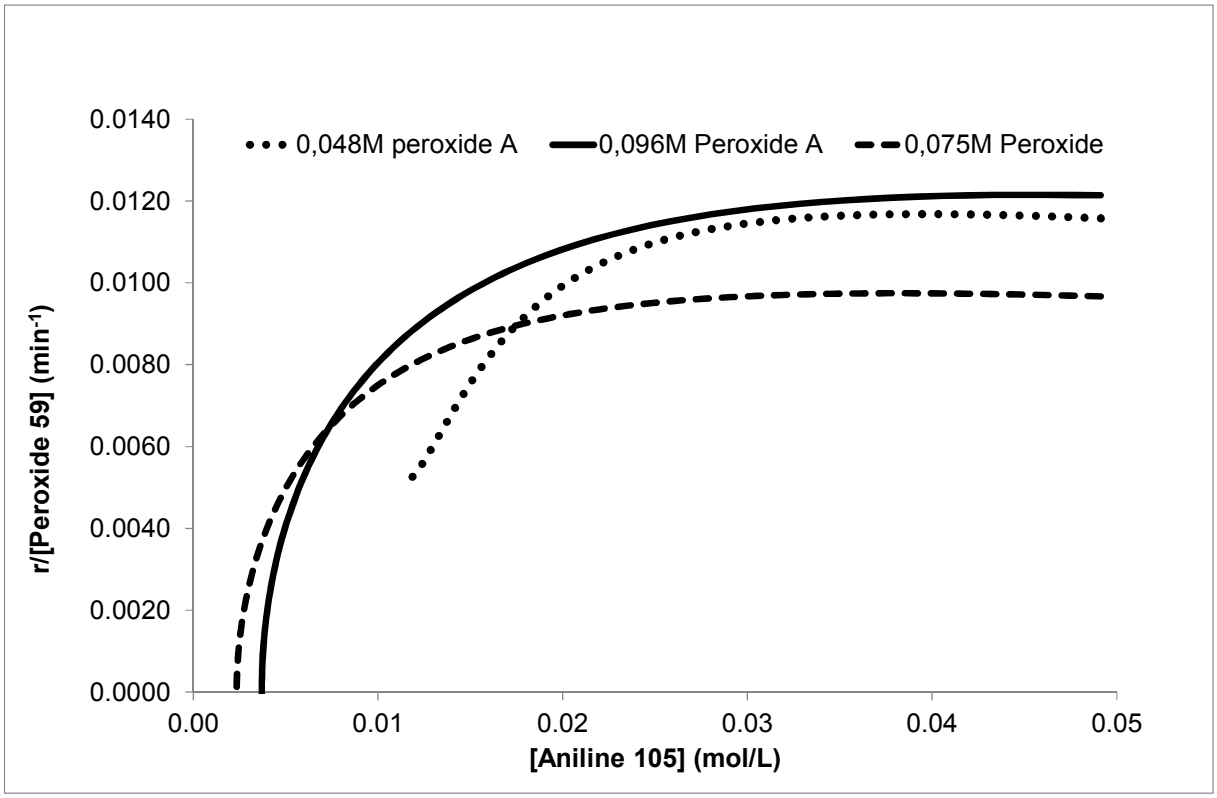


Figure 10: Reaction of reaction *vs* concentration of aniline 105 at varying concentrations of peroxide 59.

Next, a graph was plotted between r/[peroxide **59**]^{x} and [aniline **105**] (Figure 11). It was found that reaction curves overlay to a certain extent when the value of *x* was taken as 1.

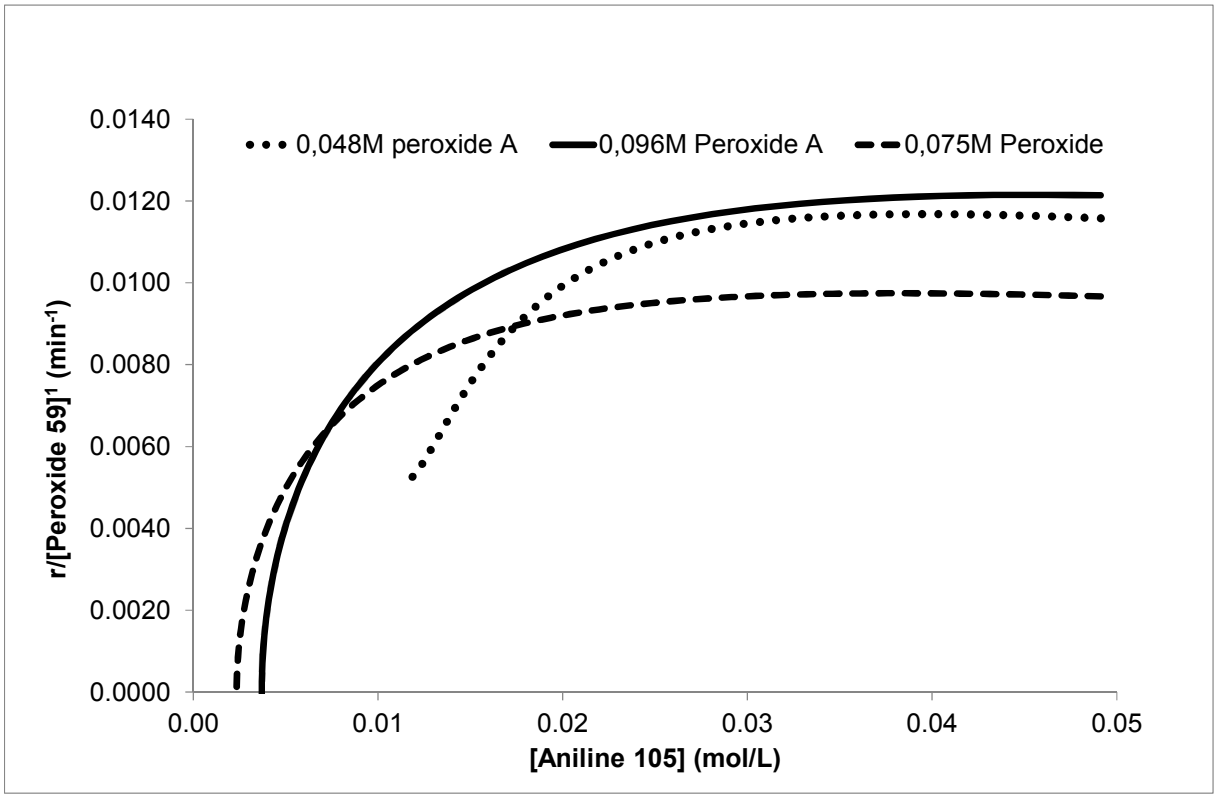
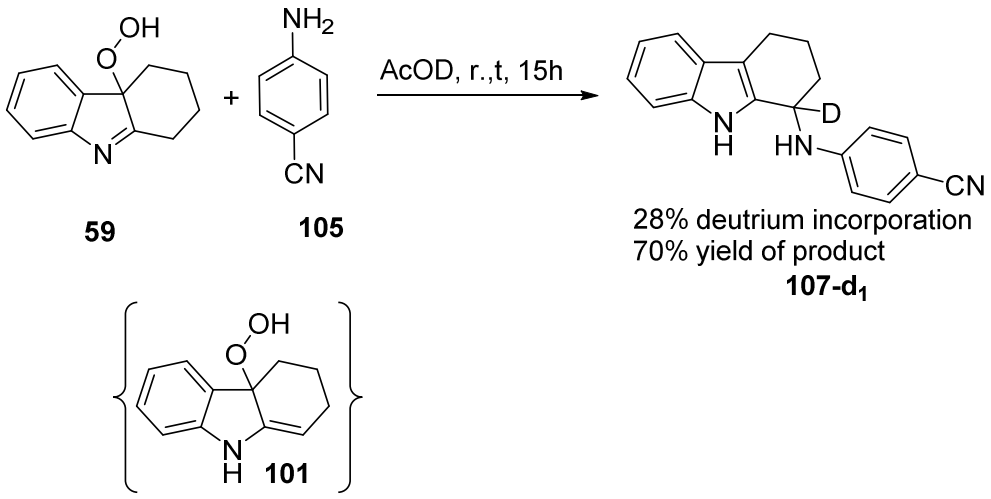


Figure 11: A graph plotted after curve fitting between rate/[peroxide 59]^1 versus [aniline 105] showing an overlay of lines belonging to different concentrations of peroxide 59 when the order of reaction was taken as 1.0.

The studies show that the reaction is approximately first order in peroxide **59** and negative or zero order in aniline **105**, thereby suggesting a S_N1-type mechanism.

$$\text{Rate of reaction} \approx [\text{Aniline } \mathbf{105}]^{-0.5}\,[\text{Peroxide } \mathbf{59}]^{1.0} \qquad \text{Equation 1}$$

Next I wanted to know how the postulated intermediate **13b** (Scheme 76b) was formed during the course of the reaction. For this purpose, the reaction was performed in deuterated acetic acid. It was found that there was an incorporation of 28% deuterium in the coupling product **107-d$_1$** (Scheme 77).

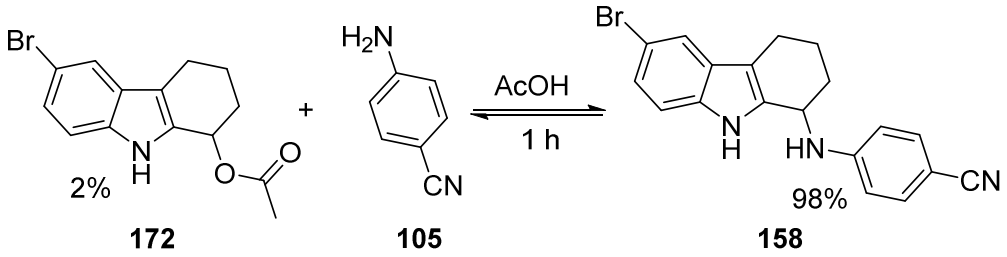


Scheme 77: Evidence for the formation of enamine

This partial incorporation of deuterium in the product **107** at position-1 under the reaction conditions (Scheme 77) suggests that an equilibrium between imine **59** and enamine **101** is established prior to the formation of allylic cation **102** (see Scheme 76 for structure of cation **102**) under acidic conditions. The attempts to observe enamine **101** with the help of NMR spectroscopy were unsuccessful. This and the relatively low incorporation of deuterium suggests that the formed enamine is highly reactive and rapidly reacts under acidic conditions to afford the coupling product **107-d_1** before complete equilibrium H-D exchange can be achieved achieved.

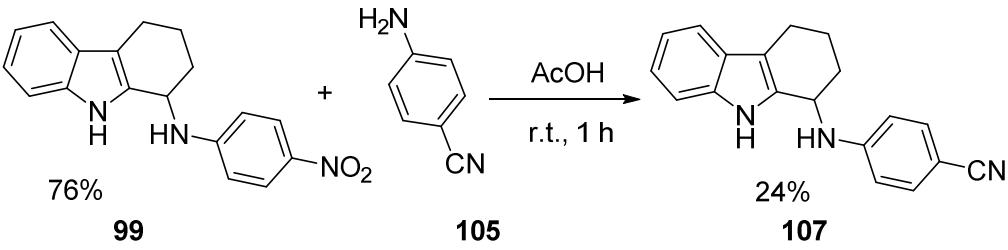
During the ^{1}H NMR analysis of the reaction mixture some additional signals were observed. These signals disappeared when the solvent was evaporated under vacuum. These signals seemed to arise from the coupling of carbazole **58** with acetic acid. But this product was unstable and could not be isolated for characterization. However, the acylated product **172** arising from 6-bromo tetrahydrocarbazole could be isolated and characterized supporting the proposed structure.

This isolated product **172** was then subjected to reaction conditions (Scheme 78). The ^{1}H NMR anaylysis of the reaction mixture showed that 98% of product **172** reacted with **105** under acidic conditions in one hour to give product **158**.



Scheme 78: Conversion of acylated product 172 to the product 158

This result proves that the intermediate allylic cation **102** can be trapped by a solvent molecule to form an acylated product such as **172**. This product can then undergo substitution reaction by an external nucleophile. In order to investigate the stability of the coupling products of carbazole **58** with nitrogen nucleophiles, the isolated coupling product **99** was subjected to reaction conditions in the presence of another nucleophile **105** (Scheme 79). It was found that the 24% of product **99** was converted to product **107** in one hour. Similar results were obtained when **107** was subjected to reaction conditions by using *p*-nitroaniline (**91**) as external nucleophile.

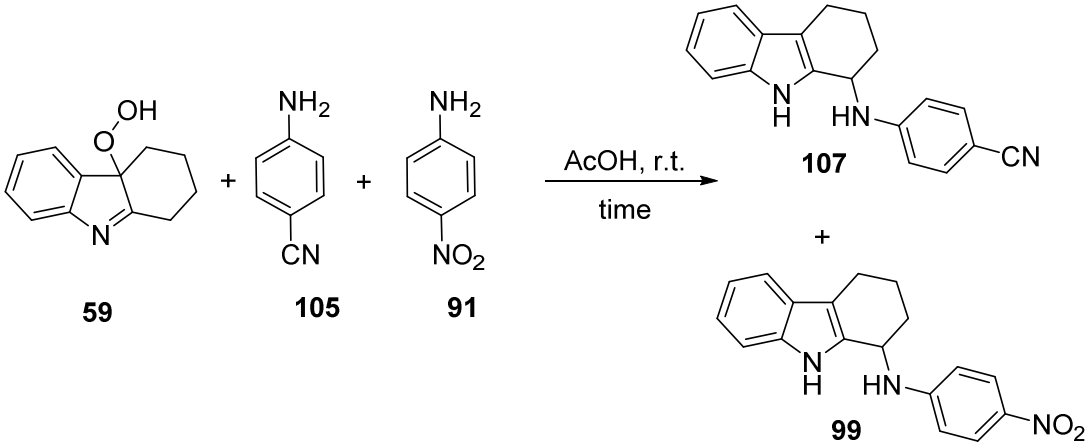


Scheme 79: Equilibrium between the coupling products

A competition experiment between *p*-cyano- and *p*-nitroaniline in the reaction with hydroperoxide **59** gave a mixture of products **107** and **99** (Table 61). Initially product **99** was observed in slight excess over product **107**.

However, over the course of the reaction an equilibrium was established between product **107** and **99** and both products were observed in 1:1 ratio after 15 h.

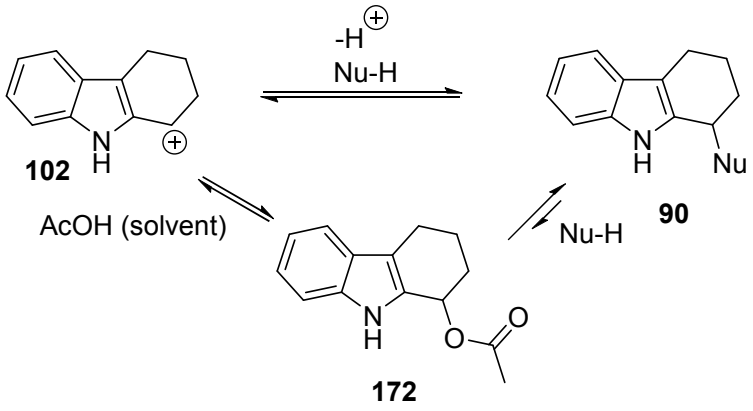
Table 61: Competition experiment between *p*-cyanoaniline (105) and *p*-nitroaniline (91)[a]



Entry	Time (h)	Overall conversion	107 (%)	99 (%)
1	0.6	26	47	53
2	5	62	47	53
3	15	60	50	50

[a] 0.49 mmol of peroxide **59**, 0.49 mmol of aniline **105**, 0.49 mmol of aniline **91** and 10 mL of AcOH were used. The yields of the coupling products was measured by ^{1}H NMR at regular intervals

All these results (Scheme 78, Scheme 79, Table 61) suggest that the C-N bond is labile under the reaction conditions and that an equilibrium is established between the formed coupling products and allylic cation **102** (Scheme 80).



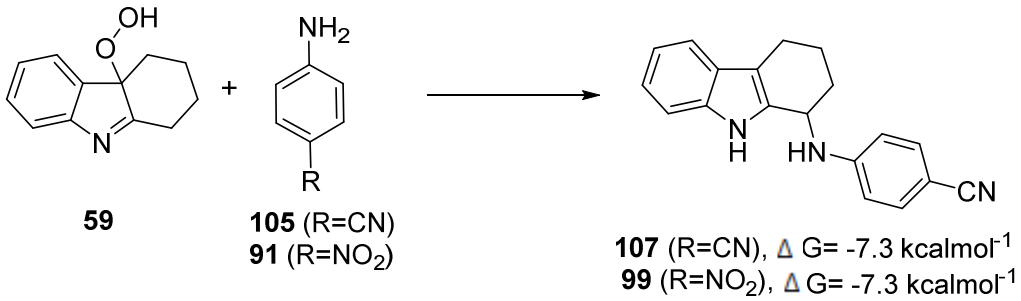
Scheme 80: Equilibrium between different products

The attention was then turned to the detection of H_2O_2, which would be liberated according to the proposed mechanism. The reaction mixture was analyzed for the coupling of peroxide **59** with aniline **105** after complete consumption of peroxide **59**. To this light yellow colored reaction mixture was added an acidic aqueous solution of $K_2Cr_2O_7$. Owing to the presence of H_2O_2, the solution turned to blue (formation of $CrO(O_2)_2$).[47b, 94] The control experiments showed that this method was not sensitive to the purified hydroperoxide **59**, in accordance to the previous observations in our research group.[47b]

Computational studies (In collaboration with Dr. Martin Breugst, Department für Chemie, Universität zu Köln)

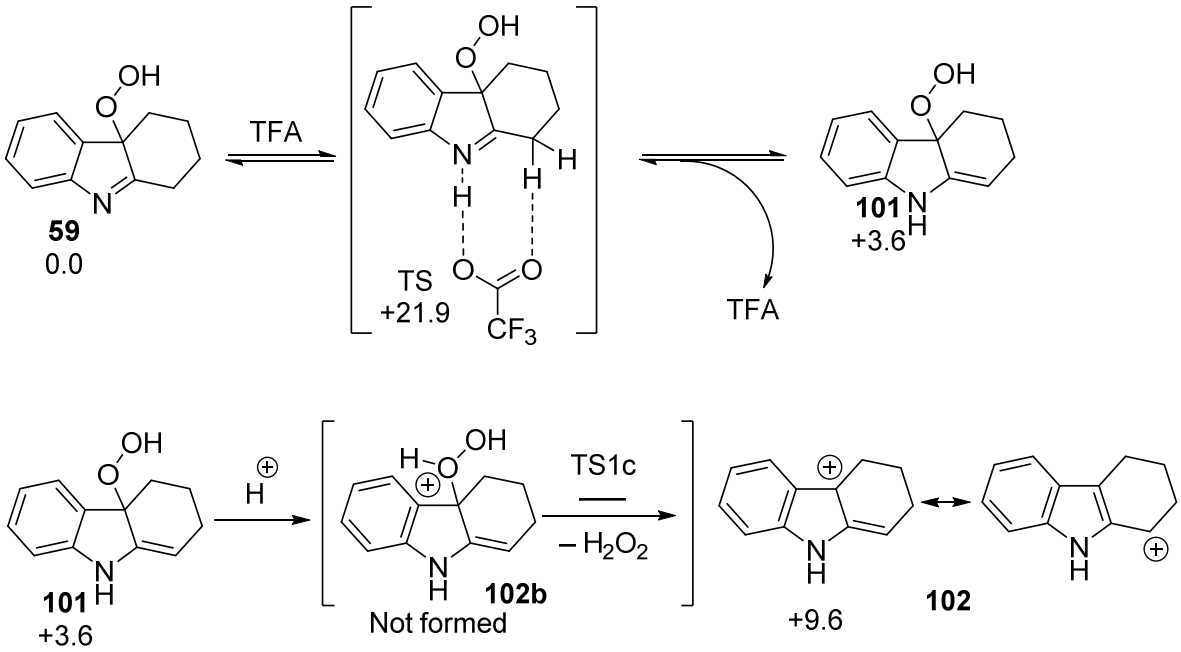
The computational approach also allows to study intermediates that are too unstable to be observed experimentally. Therefore, in order to get further information about the mechanism of reaction and possible intermediates before the formation of desired product, it was decided to collaborate with Dr. Martin Breugst, Department für Chemie, Universität zu Köln, for computational studies. All the Computational studies were performed by Dr. Martin Breugst. Although all the experiments during mechanistic studies were performed in acetic acid as solvent yet it has also been shown in previous section that similar results are obtained in methanolic solution with trifluoroacetic acid as Brønsted acid using *p*-cyanoaniline (**105**) as nucleophile and peroxide **59** as electrophile. During computational studies, in methanol as solvent, direct solvent participation especially in proton transfer reactions, was somewhat less likely due to the lower acidity. Therefore, it was decided to use methanol as the solvent and trifluoroacetic acid as Brønsted acid for the computational studies. Furthermore, for the the computational investigations *p*-nitroaniline (**91**) was employed as nucleophile instead of the cyanoaniline **105**.

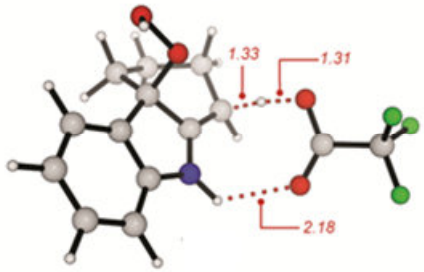
During previous studies (Section 5.3.2.3) it has already been shown that both nucleophiles behave similarly in reactivity. Further validation of their comparable reactivities came from their almost equal reaction free energies for the combinations with peroxide **59** (Scheme 81).



Scheme 81: Overall thermodynamics for the reactions of the differently substituted anilines 91 and 105 and tetrahydrocarbazole peroxides (59) [in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM (MeOH)].

Computational studies showed that the nitrogen atom is the most basic centre of peroxide **59**. Acid promoted tautomerization leads to intermediate **101**. A proton shuttle mechanism *via* trifluoroacetic acid was suggested for the tautomerization of **59** to enamine **101** (Scheme 82). Additionally, these studies also showed that the initial tautomerization of imine **59** to enamine **101** is the rate limiting step. Followed by the formation of enamine **101**, the protonation of the oxygen atom of **101** results in an immediate C–O bond cleavage to yield carbocation **102** in a concerted fashion without the formation of peroxide **102b** (Scheme 82). Furthermore, the conversion of **102b** to **102** without any energy barrier also explained why a complete equilibrium H-D exchange was not achieved during the reaction in Scheme 77.

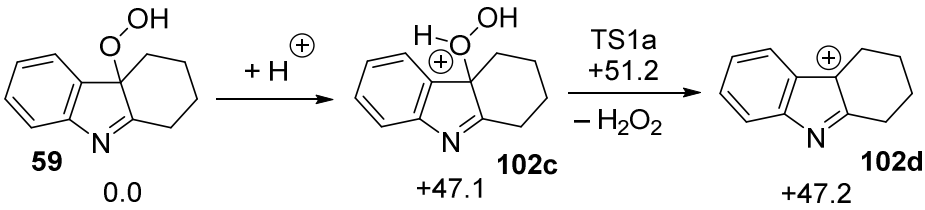




Transition state for conversion of imine **59** to enamine **101**

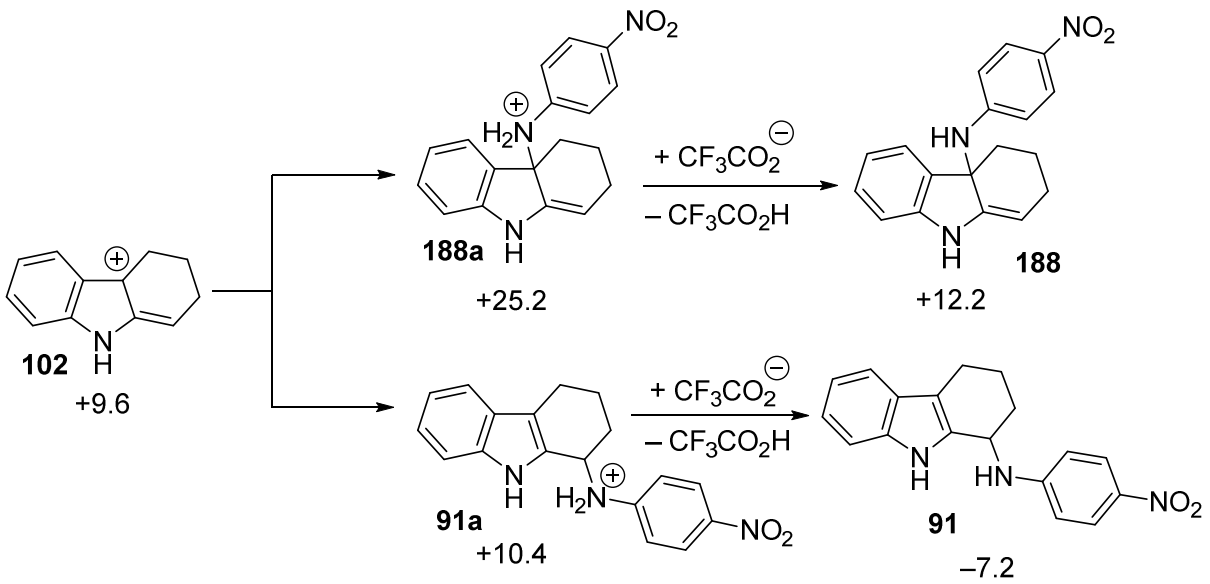
Scheme 82: Possible pathway for the formation of cation 102 [in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM(MeOH)].

The higher energies for the transition states and intermediates for the formation of cation **102a**, a possible intermediate before the formation of cation **102**, render the formation of cation **102** through path suggested in Scheme 83 highly unlikely



Scheme 83: Unfavourable pathway for hydrogen peroxide dissociation from protonated peroxides [in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM(MeOH)].

Furthermore, the transition states energies could be obtained for the nucleophilic attack of *p*-nitroaniline (**91**) on both ends of the aza allyl cation **102**. The attack at the indole substructure yields the ammonium ion **188a** (Scheme 84).



Scheme 84: Different pathways for the nucleophilic attack of *p*-nitroaniline (91) on the allyl cations 102 [free energies in kcal mol^{-1} with respect to peroxide 59, M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM(MeOH)].

The attack at the cyclohexene substructure results not only in the more stable ammonium ion **91a** but also proceeds through the more favourable transition state **TS2b** (Figure 12). The formation of thermodynamically more stable product **99** explains the exclusive C–H amination in 1-position of the tetrahydrocarbazole **58** scaffold.

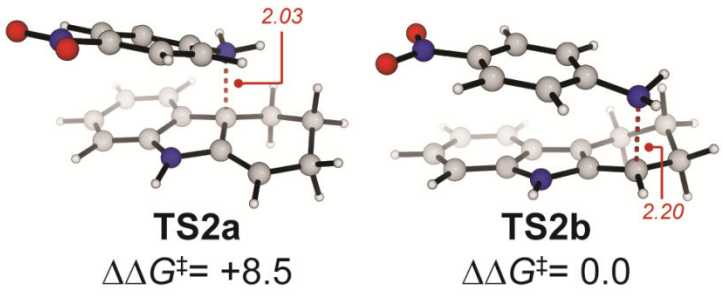
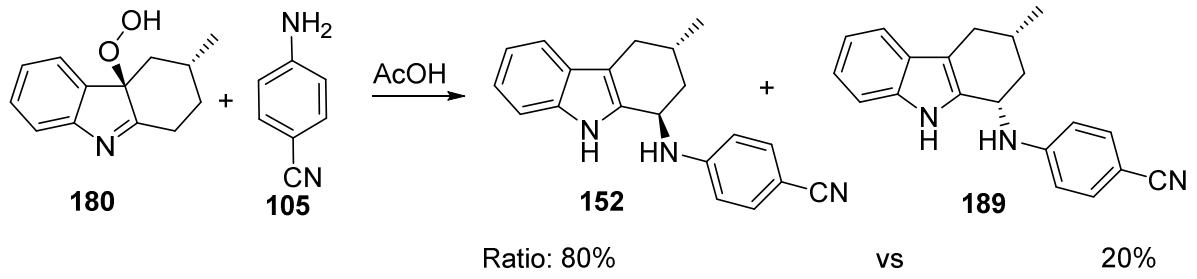


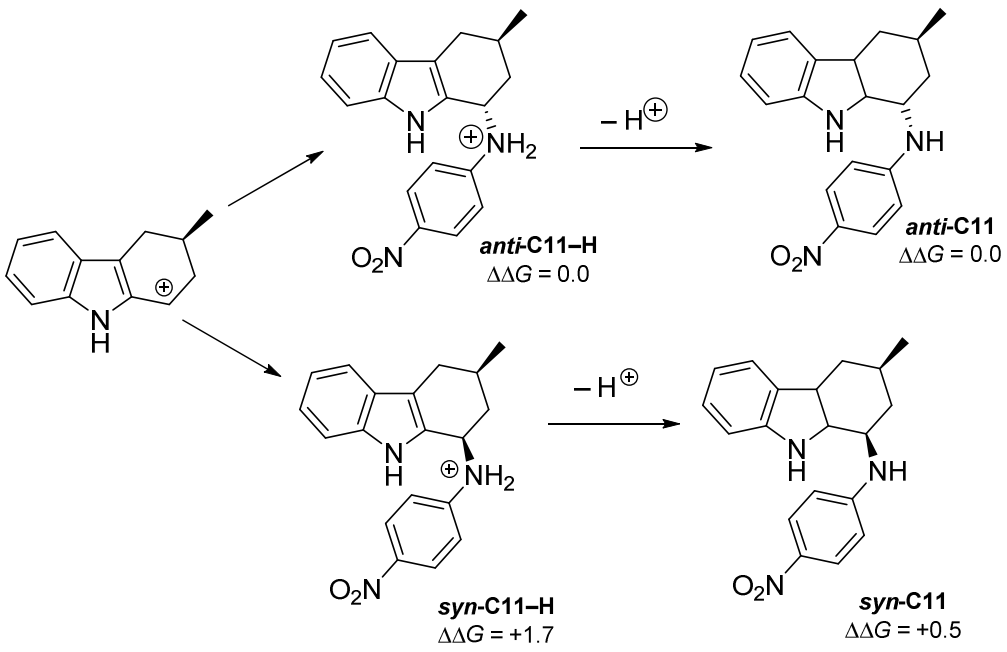
Figure 12: Transition states for the nucleophilic attack of *p*-nitroaniline (91) on the allyl cation 102, relative activation free energies (in kcal mol–1) and selected bond lengths (in Å) [M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM(MeOH)].

Finally it was interesting to know which factors control the diastereoselectivity observed in the transformation of the peroxide **180** and the aniline **105** to desired product (Scheme 85).



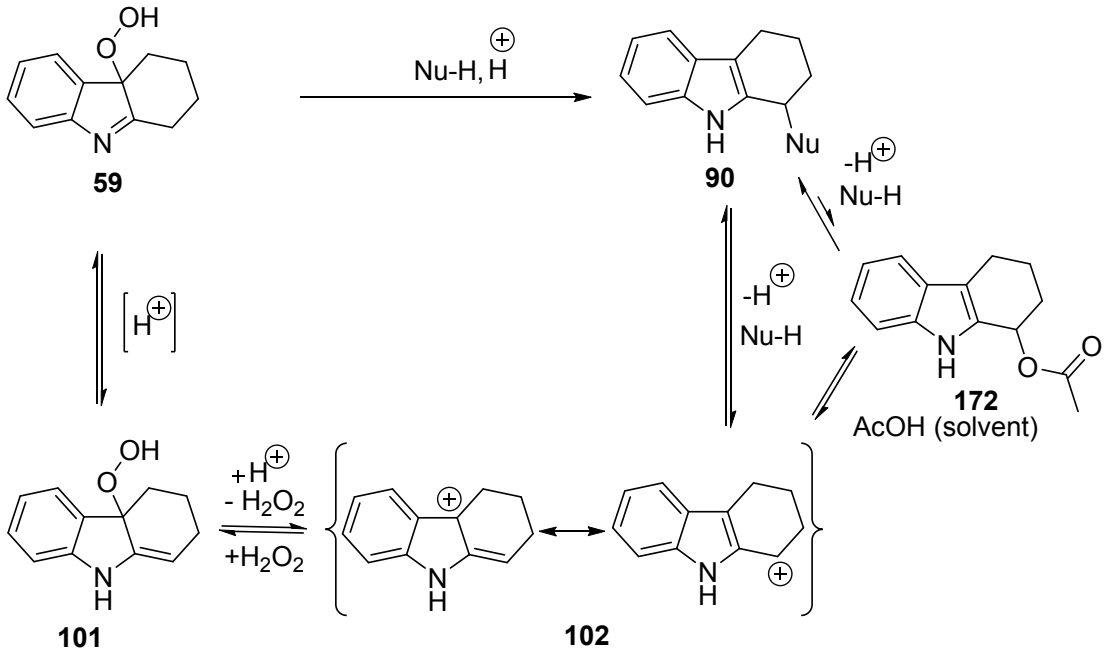
Scheme 85: Preferred formation of *trans*-diastereomer

Relative free energies for the transition states for the stereo-determining step as well as for the protonated and neutral substitution products were also calculated. In all cases, the structures with an *anti*-orientation of the nucleophile and the methyl group were preferred over their *syn*-analogues. The calculated diastereoselectivity (3.9:1) based on the different activation free energies is in very good agreement with the experimentally observed ratio of 4.0:1.



Scheme 86: Relative differences in free energies for the nucleophilic attack of aniline 91 on the chiral carbocation [in kcal mol^{-1}, M06-2X-D3/def2-TZVPP/IEFPCM//M06-2X-D3/6-31+G(d,p)/IEFPCM(MeOH)].

Based on all the aforementioned observations, it is suggested that the acid catalyzed tautomerism of imine **59** to enamine **101** followed by the cleavage of peroxide moiety gives carbocation **102**. The trapping of this resonance stabilized allylic cation **102** by the nucleophile or by the solvent gives the coupling products **90** and **14** respectively. These products **14** and **90** exist in equilibrium. The equilibrium mainly lies towards the product **90**. The evaporation of the solvent shifts the equilibrium and leads to the exclusive formation of the desired product (Scheme 87).



Scheme 87: Proposed mechanism of the reaction

5.4.3 Summary

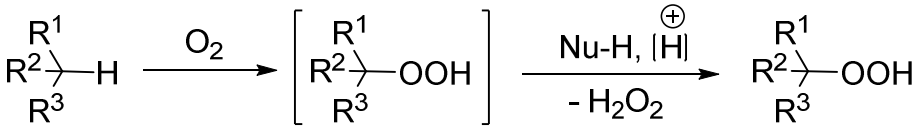
In summary, the combined experimental and computational investigations of the coupling reaction of peroxide **59** supported the substitution of hydrogen peroxide *via* an S_N1 mechanism. The exclusive C–H amination in 1-position of the tetrahydrocarbazole scaffold could be explained by an acid-catalyzed tautomerization of the imine form of the hydroperoxide to its enamine isomer. These investigations could be helpful for other reactions with tetrahydrocarbazole derivatives. Computational investigations indicate that the rate limiting step is this initial tautomerization, which is in excellent agreement with the experimental studies. The mechanistic studies support the concept of C–H functionalization *via* intermediate peroxides and could be helpful in further extensions of this strategy towards other substrates.

6 Summary and conclusion of this thesis

This Ph.D. thesis describes the development of methods for the C–H functionalization of different substrates *via* intermediate hydroperoxides with the aid of oxygen, visible light and catalytic amounts of cheap acid and a sensitizer.

Organic hydroperoxides have rarely been used as electrophiles for coupling with different nucleophiles.[42] Previous studies in our research group with xanthene suggested that the hydroperoxide moiety could be substituted with different nucleophiles under specific acidic conditions.[42b, 42g]

Peroxides are formed by autooxidation in air, therefore it was interesting to find out if the C–H functionalisation of organic molecules could be achieved by using these peroxides as leaving groups (Scheme 88). As oxygen would be the only oxidant, therefore this concept could be very attractive for green chemistry.[70]

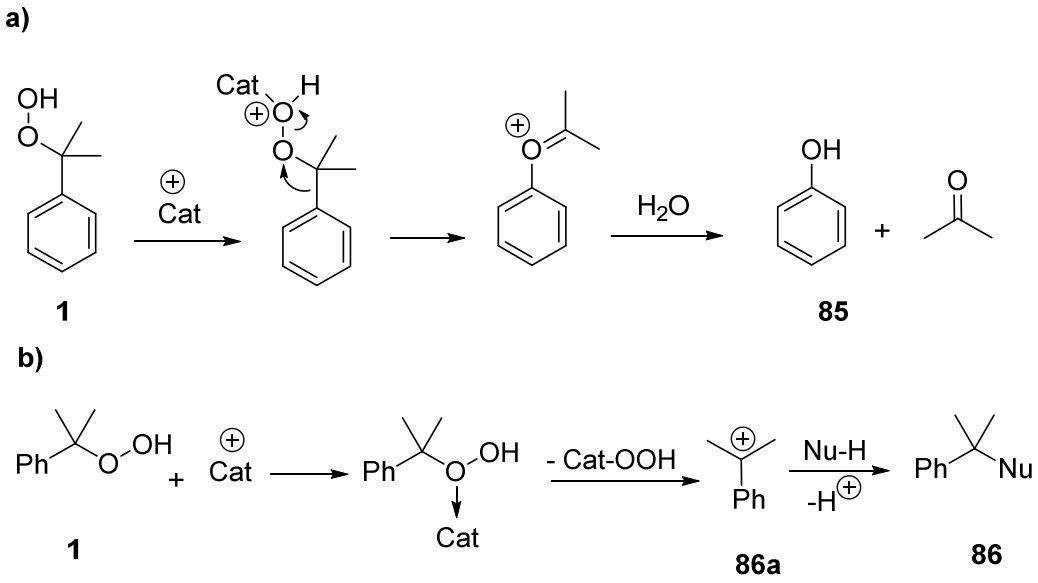


Scheme 88: Concept of C–H functionalization *via* Intermediate Peroxides

In order to explore the feasibility of this concept, two substrate classes were selected for this thesis. Before investigating the concept of C–H functionalisation *via* intermediate peroxides using these two classes, it was decided to get deeper insight into the reactivity of hydroperoxides in general by choosing the commercially available and relatively stable cumene hydroperoxide **1** as a test substrate.

Cumene hydroperoxide (**1)** is known to rearrange and produce phenol and acetone under acidic conditions.[76] I wanted to investigate the possibility of nucleophilic substitution of cumene hydroperoxide (**1**), and the effect of different catalysts and solvents on the path of the reaction (Scheme 89).[44, 77]

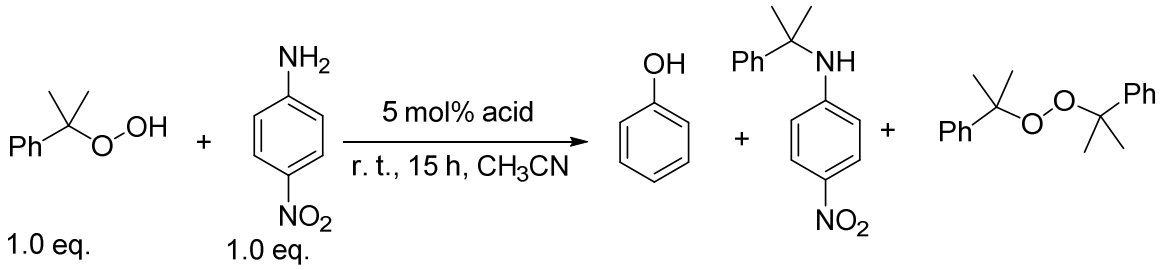
Moreover, in order to get close to the definition of an ideal green reaction,[70] I was keen to achieve the required transformation by catalytic amounts of environmentally benign, abundant and inexpensive catalysts.



Scheme 89: Selective protonation of oxygen: (a) Suggested mechanism for Hock rearrangement (b) and nucleophilic substitution

In order to observe the effect of different catalysts on the path of reaction initially acetonitrile was selected as solvent and different catalysts were screened. A selection of the most interesting results is shown in Table 62. It was found that iron catalysts favor the substitution reaction (Table 62, entry 4) while phenol was obtained as major product of the reaction by using Brønsted acids as catalysts (Table 62, entry 5-6). A mixture of products in different ratios was obtained by using other Lewis acids (Table 62, entry 1-3). The absolute hardness[13] of few Lewis acids was also calculated and no real corelation between the hardness of an acid and its selectivity for substitution was observed. It was concluded, in contrast to a previous theory by Minisci *et al*.,[44] the selectivity of different Lewis acids towards nucleophilic substitution or Hock rearrangement could not be explained through the HSAB principle.

Table 62: Comparison of selected Lewis and Brønsted acids on the reactivity of peroxide 1[a]

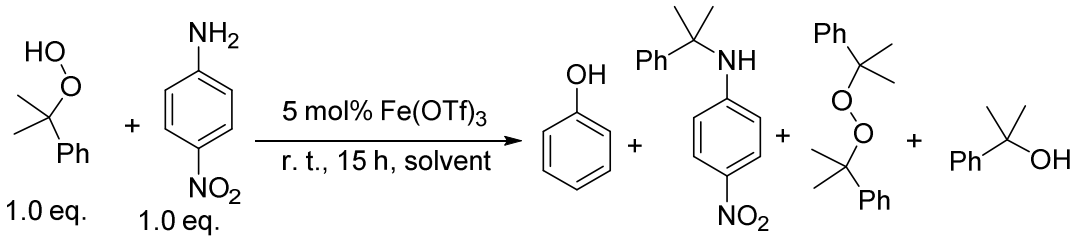


Entry	Catalyst	Cons. (%)	85 (%)	92+93 (%)	Hardness (eV)	S[b]Re:Sub (%)
1	$Sc(OTf)_3$	51	32	4+15	12.28	63:37
2	$Bi(OTf)_3$	80	64	3+13	12.30	80:20
3	$In(OTf)_3$	72	56	3+13	13.82	78:22
4	$Fe(OTf)_3$	100	0	30+70	15.24	00:100
5	MsOH	100	74	4+12	-	82:18
6	TfOH	100	86	3+11	-	86:14

[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of acetonitrile were used. Yields determined by ^{1}H NMR based upon the overall conversion of peroxide **1** alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

In order to find the effect of solvent on the reactivity of peroxide **1**, $Fe(OTf)_3$ was selected as catalyst and different solvents were screened (Table 63). The solvent played an important role and path of the reaction was completely changed by changing the solvent of the reaction under exactly the same conditions. For example acetonitrile favored the formation of substitutuion products while the rearrangement to phenol was the major pathway of the reaction by using acetone as solvent. Combination of $Fe(OTf)_3$ and methanol exclusively favored the formation of alcohol **94**.

Table 63: Screening of solvents by using $Fe(OTf)_3$ as catalyst[a]



Entry	Solvent	Cons.[a] (%)	85[a] (%)	92+93[a] (%)	94 (%)	S[b]Re:Sub (%)
1	CH_3CN	100	0	30+70	0	0:100
2	Acetone	84	60	3+3	18	91:09
3	MeOH	100	0	0	100	--

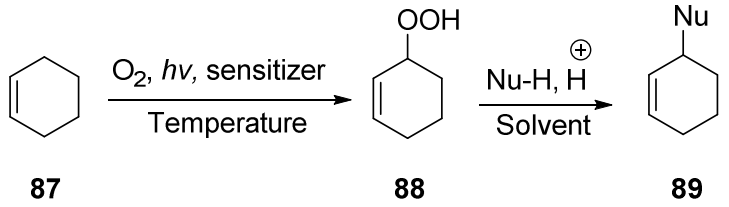
[a] 0.49 mmol of **1** and 0.49 mmol of **91** were used. 10 mL of solvent were used. Yields determined by ^{1}H NMR based upon the overall conversion of peroxide **1** alcohol **94** already present in the solution. [b] Selectivity Rearrangement:Substitution

The reactivity of hydroperoxide **1** was also tested under previously developed conditions. [42b, 45] It was found that suitable combination of solvent and catalyst is required to activate each hydroperoxide and get the desired selectivity.

In conclusion, the reaction can be guided to the desired direction *i.e*. Hock rearrangement or nucleophilic substitution by using a suitable combination of an acid catalyst and a solvent. The combination of acetonitrile with iron catalysts is suitable to get S_N products while strong Brønsted acids like MsOH favour the formation of phenol.

Cross coupling reactions with allylic substrates are very useful in the synthesis of complex molecules, but only few aerobic allylic C–H functionalizations are known.[72] It was decided to start the studies with cyclohexene (**87**) as a test substrate. The choice of cyclohexene (**87**) was driven not only by its commercial availability, but also from the possibility to avoid the complication arising from the regiochemistry of the peroxidation.

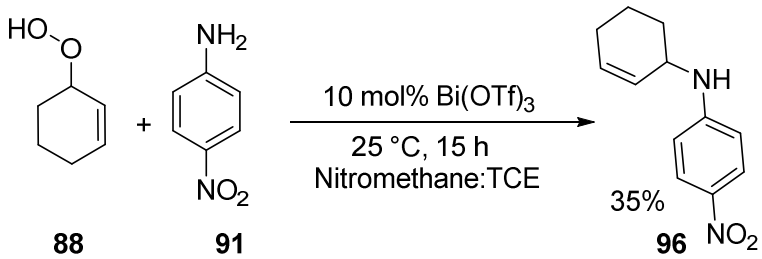
Strategy of the project was to introduce the hydroperoxide moiety in the cyclohexene substrate by an ene reaction with the aid of oxygen, a sensitizer and light and then substitute it with different nucleophiles under acidic conditions (Scheme 90).



Scheme 90: Project Idea

The generally used method for the formation of peroxide **88** requires the use of base[73] which is not compatible with the planned acidic conditions for substitution. I wanted to develop a method which could be compatible with acidic conditions

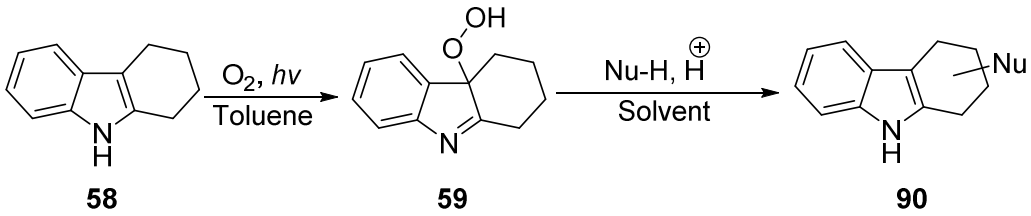
After optimization studies it was found that the yield of peroxide **88** could be improved to 75% by using visible light and molecular oxygen in the presence of TPP as sensitizer and chloroform as solvent. For the coupling of peroxide **88**, aniline **91** was chosen as nucleophile. After screening of solvents, a mixture of nitromethane and 1,1,2,2-tetrachloroethane was found to be suitable for the coupling step. Among different screened acids, Lewis acids gave better results than Brønsted acids and the highest isolated yield of 35% was obtained by using $Bi(OTf)_3$ as catalyst.



Scheme 91: Acid catalysed coupling of peroxide 88 with aniline 91

Although the yield of the coupling product **96** could not be further improved, these results prove that the peroxide moiety can be, in general, used as leaving group. After getting further motivation from this project, I wanted to try other organic hydroperoxides and get further experience about the reactivity of peroxides.

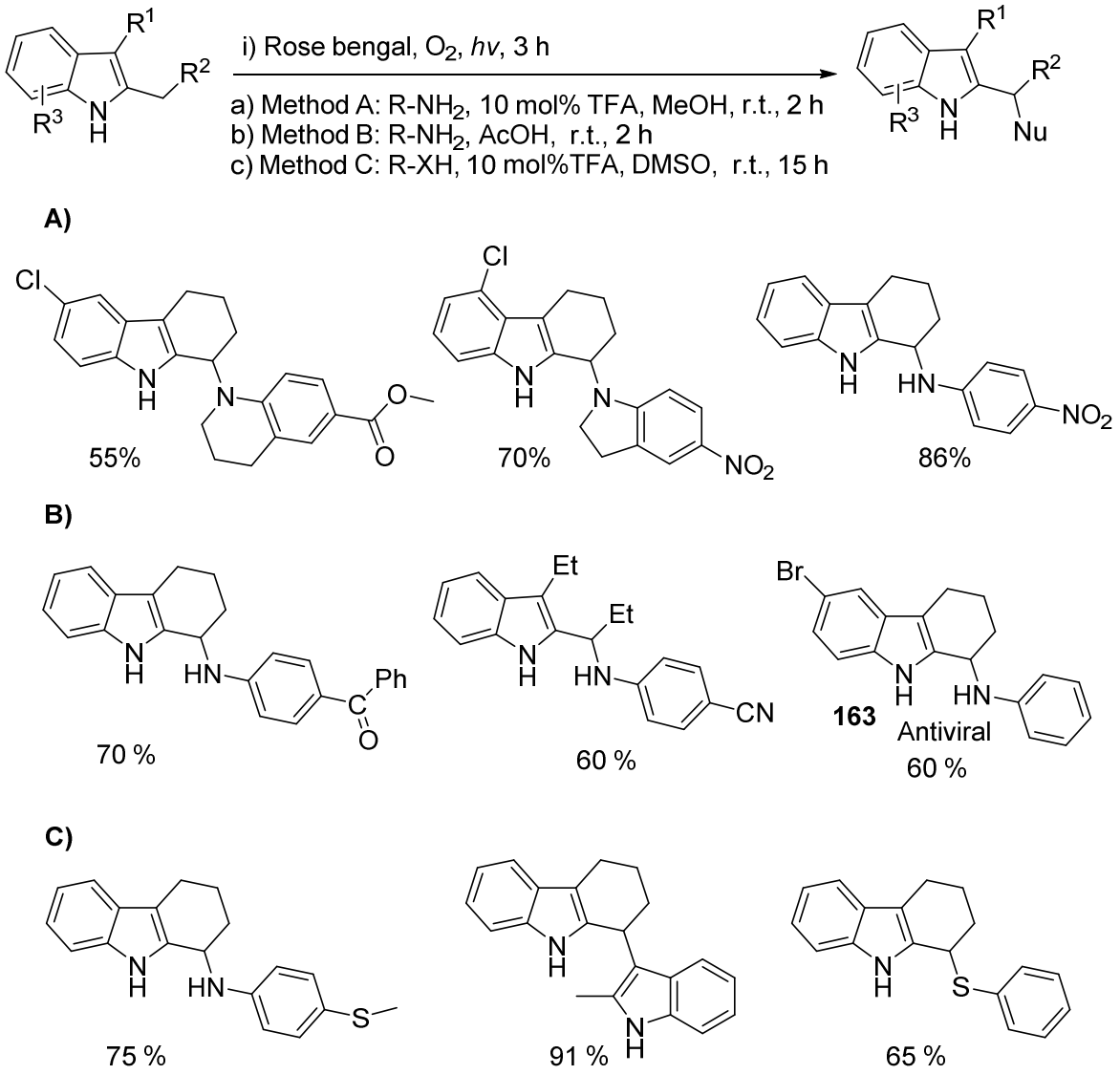
The photooxidation of tetrahydrocarbazole (**58**) under an atmosphere of oxygen[50] using toluene as solvent and rose bengal as sensitizer yields carbazole hydroperoxide **59** in quantitative yields (Scheme 92).[64-65] The formed peroxide **59** can be isolated from the reaction mixture *via* precipitation and stored at room temperature for several months without any decomposition. Additionally, the indolic core is present in a large number of biological active compounds.[95] For these reasons, tetrahydrocarbazole was selected as substrate for coupling reactions (Scheme 92).



58 **59** **90**

Scheme 92: Project Idea for the functionalization of tetrahydrocarbazole 58

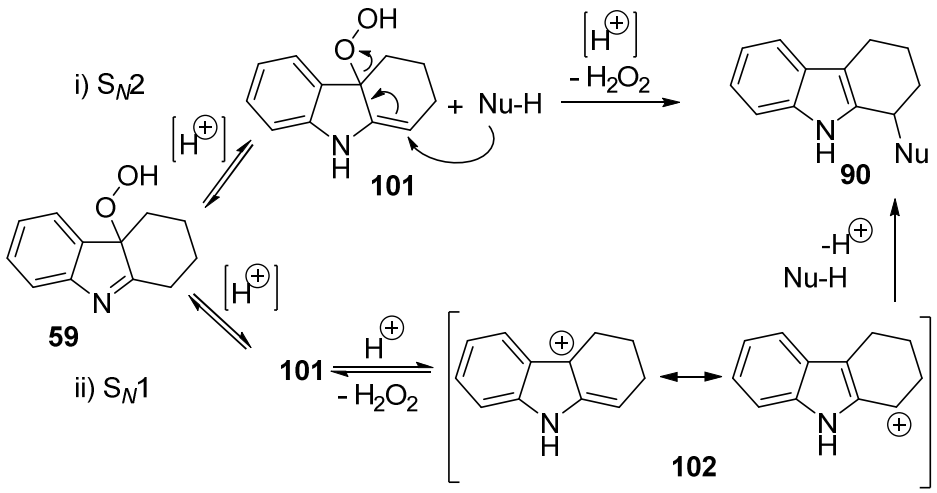
After careful optimization, a practical method for the C–H functionalization of tetrahydrocarbazole **58** derivatives *via* intermediate hydroperoxides with the aid of oxygen, visible light and catalytic amounts of cheap Brønsted acid and sensitizer has been developed (Scheme 93). In general, the use of methanol/TFA (Method A) was preferred for the coupling of electron poor anilines with hydroperoxide **59** while the use of acetic acid as solvent (Method B) was found to be suitable for the coupling of aniline and halogen substituted anilines. For anilines having moderately electron withdrawing groups, both methods are equally effective. Anilines bearing electron donating groups were found to be completely unreactive and poor yields were obained with 2-methyl indole under these conditions.



Scheme 93: Examples for the coupling of tetrahydrocarbazole derivatives with different nuleophiles

The combination of DMSO/TFA (Method C) was found to be suitable for the coupling of electron rich anilines and indoles with carbazole peroxide **59**. It was found that DMSO has the ability to reduce hydroperoxides to corresponding alcohols, thus avoiding the unwanted oxidation of nucleophiles and coupling products. The reactions are practically simple, proceeds at room temperature and afford the coupling products in good to excellent yields. The reaction has also been applied to the synthesis of representative biologically active compounds like compound **163** (Scheme 93).

In addition, the mechanism of the coupling reaction of peroxide **58** with aniline **105** in acetic acid as solvent without any additional catalyst has also been investigated. The possible scenario for this acid catalyzed substitution reaction involved the protonation of peroxide **59** followed by substitution with aniline **105** *via* S_N1 or by S_N2 mechanism. Kinetic studies were used to distinguish between these two possibilities (Scheme 94)

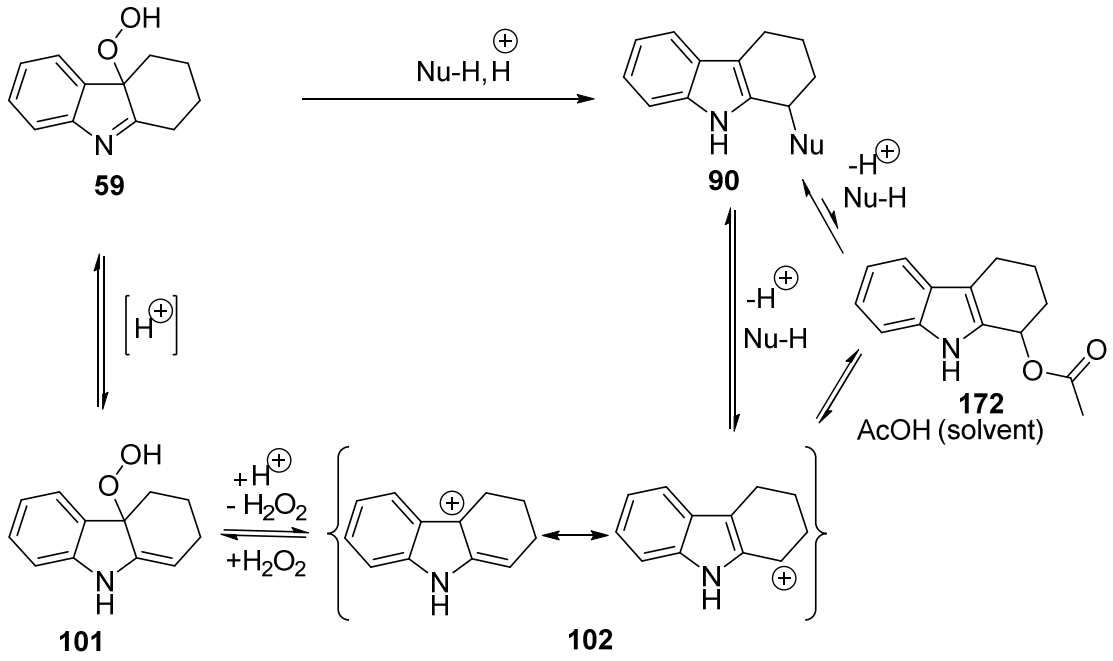


Scheme 94: Possible pathways (S_N1 vs S_N2) for the developed coupling reaction

The kinetic studies supported the S_N1 mechanism. Computational studies, performed by Dr. Martin Breugst, also indicated that the initial tautomerization of imine **59** to enamine **101** was the rate determining step. Furthermore, the presence of an enamine intermediate could also be confirmed by deuterium incorporation experiments.

Different control experiments showed that coupling products are formed reversibly. Furthermore, the presence of H_2O_2, which should be liberated according to the proposed mechanism, was confirmed by using acidic solution of $K_2Cr_2O_7$.[47b, 94]

In conclusion, the following mechanism of the coupling reaction can be suggested (Scheme 95).



Scheme 95: Proposed mechanism of the reaction

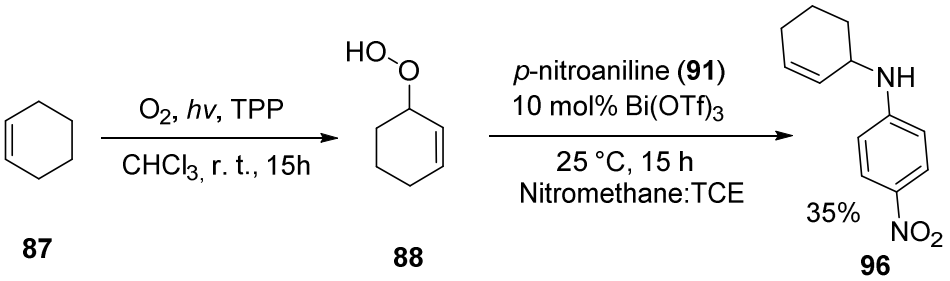
Acid-catalyzed tautomerization of imine form of hydroperoxide **59** leads to its enamine isomer **101**. Protonation followed by the loss of hydrogen peroxide results in the formation of a stabilized allylic cation. Trapping of this resonance stabilized allylic cation **102** by the nucleophile or by the solvent gives the coupling products **172** and **90** respectively. These products **172** and **90** exist in equilibrium. The evaporation of the solvent gives desired product exclusively. Computational investigations were in complete agreement with the experimental studies. The mechanistic studies support the concept of C–H functionalization *via* intermediate peroxide and could be helpful in further extensions of this strategy towards other substrates.

7 Outlook

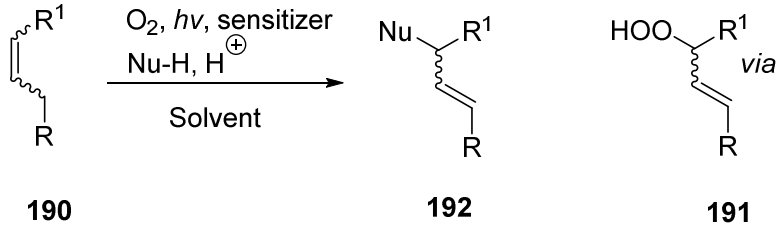
Hydroperoxides are often formed by the aerobic oxidation of organic molecules. The functionalization of C–H bond *via* intermediate peroxides (CHIPS) represents an appealing strategy for more sustainable chemistry.

Cross coupling reactions through allylic C–H activation[71] is an attractive but very challenging technique and very few aerobic allylic C–H activations are known.[72] It has been shown that allylic activation of cyclohexene (**87**) could be achieved *via* photochemically generated intermediate peroxide (**88**) in moderate yields (Section 4.2). The substitution of the peroxide moiety in (**88**) with nucleophiles turned out to be the real challenge in this methodology.

Proof of principle conditions:



Desirable future extension:



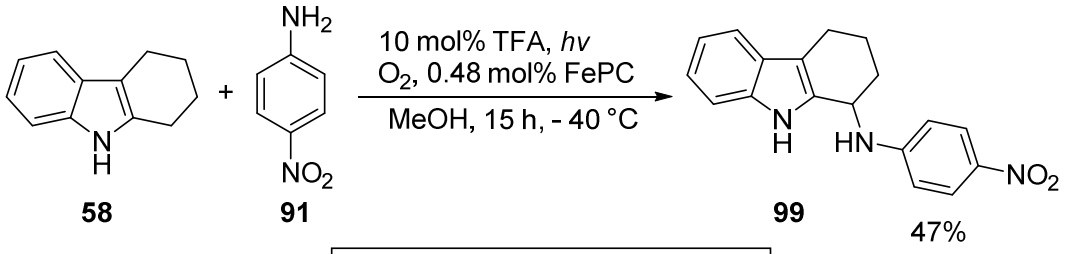
Scheme 96: Proof of principle for allylic C–H activation *via* intermediate peroxide and desirable future work

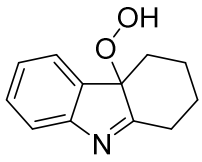
Unfortunately, the yield of product **96** could not yet be improved beyond 35% (Scheme 96). A direction for the further development of this method is the search for a suitable combination of an acid catalyst and solvent which favors the coupling of peroxide **88** with aniline **91**. The yield of the reaction can also be improved by stabilizing the possible intermediate cations finding suitable additive.

After finding suitable conditions for coupling step, the reaction can then be performed in one pot *i*.e. *in situ* formation of intermediate peroxide followed by substitution under same conditions. Many sensitizers are not stable against acidic conditions. While performing reaction in one pot, it might also be important to find a sensitizer which is stable against acidic conditions and also facilitates the oxidation of the alkene to the corresponding hydroperoxide under reaction conditions. After finding suitable conditions for one pot coupling, the scope of the reaction can then be extended to other substrates.

A one pot method (Scheme 97) for the C–H amination of tetrahydrocarbazole **58** *via* intermediate hydroperoxide **58** with the aid of oxygen, visible light and catalytic amounts of a cheap Brønsted acid and a sensitizer has been developed (Section 5.3.2.1, section 5.3.2.2). The moderate yield of the coupling product could be obtained under optimized reaction conditions.

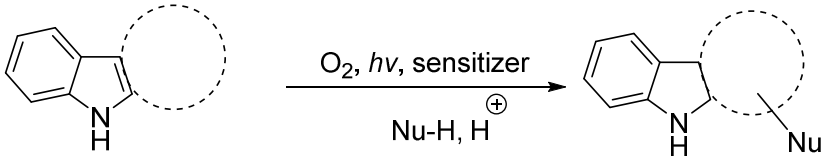
Proof of principle conditions:





59
Isolable intermediate peroxide

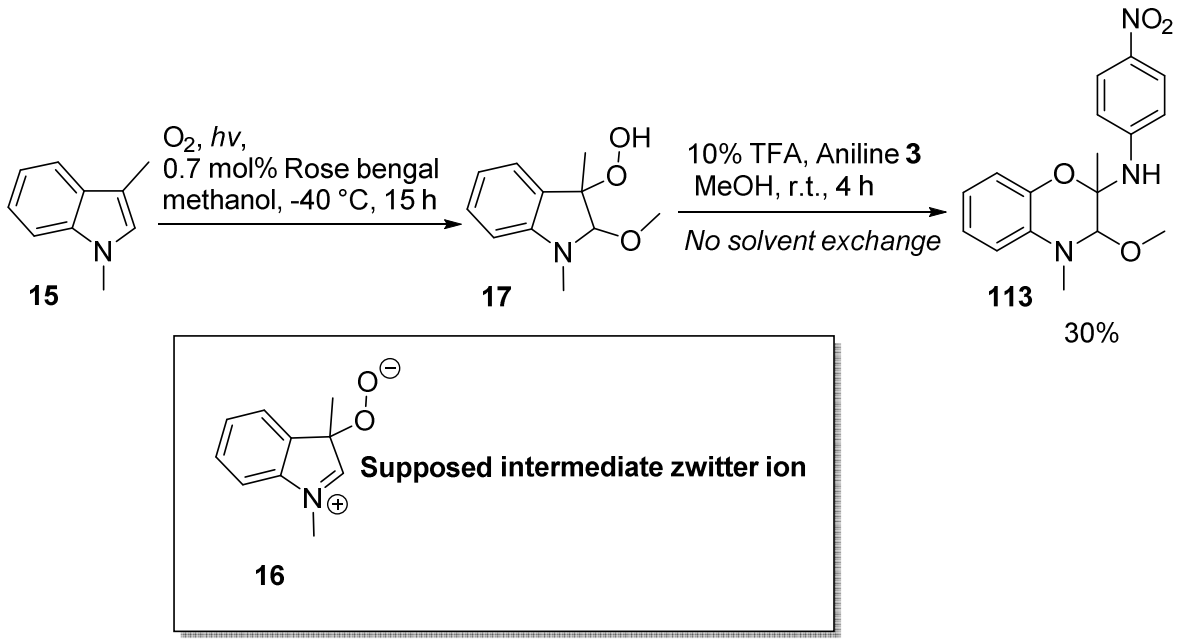
Desirable future extension:



Scheme 97: Proof of principle for C–H functionalization of indole derivatives *via* photochemically generated hydroperoxides

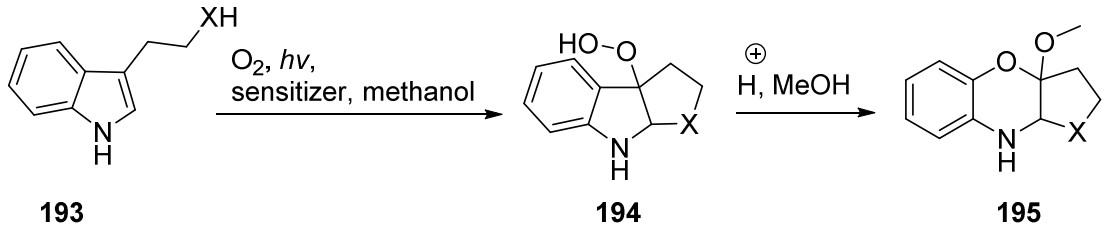
The reactions proceeded in excellent yields by using the isolated peroxide and subjecting it to reaction conditions. It was also found that the coupling products slowly decompose under acidic conditions over the course of the reaction. Therefore it is assumed that the slow oxidation of carbazole **58** under reaction conditions is the main problem associated with the further development of the one-pot methodology. The problem can be solved by finding appropriate conditions, especially regarding the choice of the sensitizer, that help in accelerating the rate of reaction and in stabilizing the formed product. Alternatively, other carbon based nucleophiles which might give rise to stable coupling products as result of C-C bond formation, can also be used The developed methodology can then be applied to other indoles (Scheme 97).

During the efforts to extend the scope of reaction, it was found that photoinduced oxidation of 1,3-dimethyl indole (**15**), followed by treatment with an acid catalyst and aniline **91**, led to the formation of product **113**. Based on literature precedents,[60, 96] it is suggested that 1,3-dimethyl indole (**15**) was converted to intermediate **17** that could be formed after the trapping of zwitter ionic **16** with methanol. Under acidic conditions, the peroxide **17** underwent a Hock rearrangement and a substitution reaction with *p*-nitroaniline (**91**) to give product **113**.



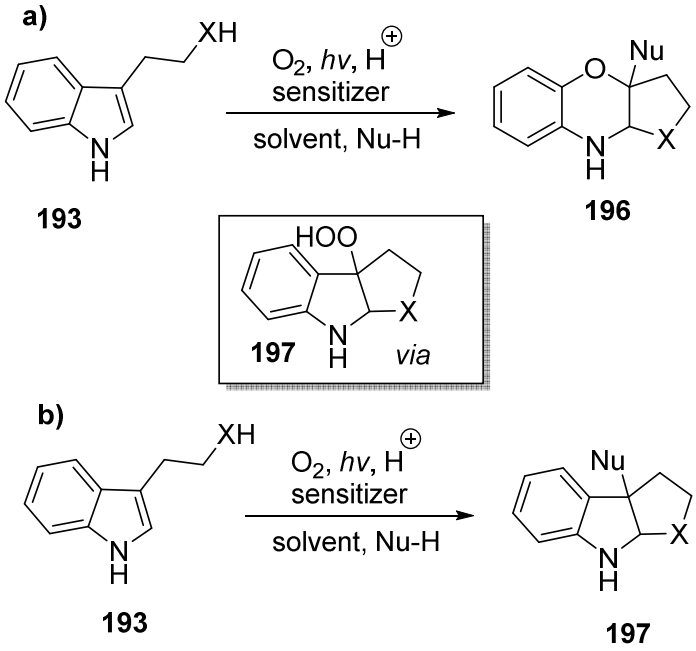
Scheme 98: Formation of product 113 through the Hock rearrangement and substitution of photochemically generated peroxide

Saito *et al*. have also reported that photoinduced oxidation of different tryptamine, tryptophol and tryptophan derivatives leads towards the formation of tricyclic peroxides **194** through the intramolecular trapping of formed intermediate zwitter ions. Under acidic conditions in methanol as solvent, the formed peroxides **194** rearrange and combine with methanol to give compound **195**.[60, 96]



Scheme 99: Literature precedent for the formation of 195 type compounds

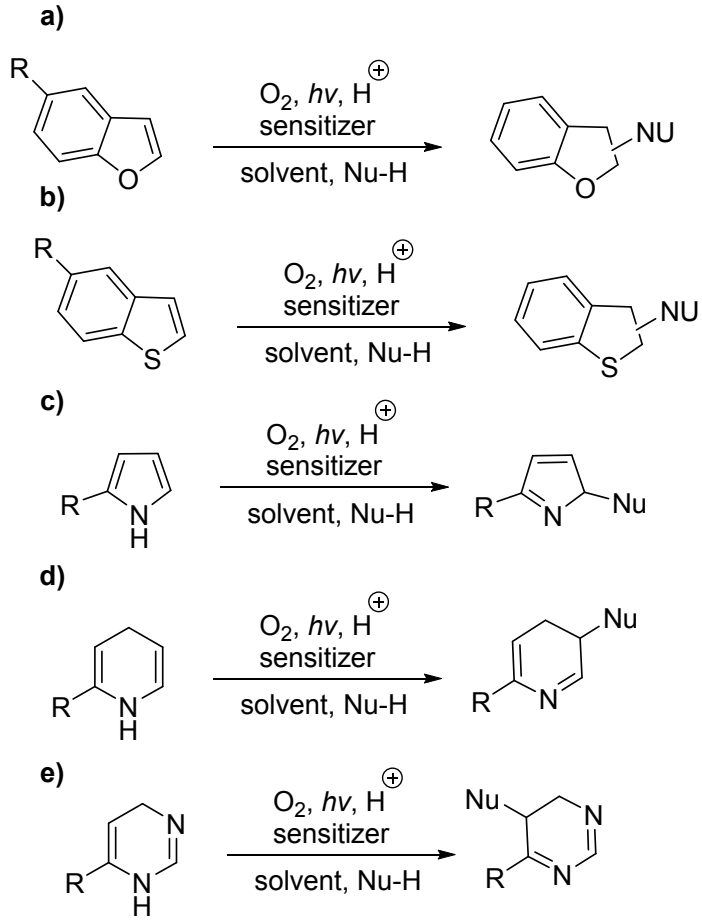
1-4-Benzoxazines are pharmacetically important compounds.[97] Based on results discussed in this thesis (Scheme 98) and previous work by saito *et al*. (Scheme 99), it should be possible to develop a one pot method which can potentially give access to benzoxazines like **196** (Scheme 100). The very first potential challenge will be to find a sensitizer that is stable under acidic conditions and is also suitable for the oxidation of starting material to corresponding hydroperoxide.



Scheme 100: Suggested future work on photo induced cyclization and substitution reactions

Similary, tricyclic compounds like **197** are core structure of a number of natural alkaloids.[98] It has already been shown that catalyst and solvent play an important role during substitution reaction of organic peroxides. Using a hydroperoxide as starting material (Chapter 1), the reaction could be guided to Hock rearrangements or nucleophilic substitutions by using a suitable combination of solvent and catalyst. Therefore, another direction for future research work might be the search to suitable conditions that facilitate the direct substitution of peroxide moiety, without rearrangement, to give compounds like **197**. The successful development of this methodology can facilitate the synthesis of many polycyclic natural alkaloids.[98]

Singlet oxygen is also know to react with a large variety of heterocycles and giving rise to different peroxides.[51d, 51e] For example, furans, thiofurans, pyrroles, 1,4-dihydropyridines and 1,4-dihydropyrimidines (Scheme 101, a-e respectively) have been reported to react with singlet oxygen and form peroxides. Mostly the formed peroxides are unstable and can not be isolated. However, a one pot method *i.e*. *in situ* formation and substitution of peroxide, might potentially allow the use of these intermediate peroxides for coupling reactions. As different peroxides behave differently, it might be necessary to find suitable reaction conditions for each class of molecules separately. The stability and reactivity of intermediate peroxides is also affected by the presence of substituents,[51d, 51e] therefore it might also be useful to use a substituent that facilitates the coupling of intermediate peroxides with desired nucleophiles.



Scheme 101: Further extension of the concept of "C–H functionalization *via* intermediate peroxides" to other classes of heterocycles

8 Experimental part

8.1 General experimental conditions

Unless otherwise indicated, all reagents and solvents were purchased from commercial distributors and used as received.

Solvents (toluene, hexanes, ethyl acetate, dichloromethane, methanol) used for column chromatography were of technical grade and used after distillation in a rotary evaporator.

TLC was used to check the reactions for full conversion and was performed on Macherey-Nagel Polygram Sil G/UV254 and Macherey-Nagel Polygram Alox N/UV254 thin layer plates. TLC spots were visualized by UV-light irradiation.

Flash column chromatography was carried out using Merck Silica Gel 60 (40-63 µm) and Alox. Yields refer to pure isolated compounds.

^{1}H and ^{13}C NMR spectra were measured with Bruker AV 600, AV 500 and AV 400 spectrometers. All chemical shifts are given in ppm downfield relative to TMS and were referenced to the solvent residual peaks.[99] 1H NMR chemical shifts are designated using the following abbreviations as well as their combinations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, app. = apparent. For ^{13}C NMR data the following abbreviations are used: p = primary (CH_3), s = secondary (CH_2), t = tertiary (CH), q = quaternary (C).

High resolution mass spectra were recorded with a Bruker APEX III FTICR-MS or a Finnigan SSQ 7000 quadrupole MS or a Finnigan MAT 95 double focusing sector field MS instrument.

Computational Details

All the computational studies were performed by Dr. Martin Breugst. For all intermediates of the C–H functionalization of tetrahydrocarbazole **58**, the conformational space was explored using the OPLS-2005 force field and a modified Monte Carlo search routine implemented in MacroModel version 9.8. An energy cut-off of 20 kcal mol^{-1} was used for the conformational analysis, and structures with heavy-atom RMSDs less than 1 Å after the initial force field optimization were considered to be the same conformer. The remaining structures where subsequently optimized with the meta-hybrid M06-2X functional, Grimme's

D3 dispersion correction (zero-damping), and the double-ζ

basis set 6-31+G(d,p). Solvation by methanol was accounted for by using the integral equation formalism polarizable continuum model (IEFPCM) for all calculations (optimizations, frequencies, and single-point energies). Polarizable continuum models do not have a large impact on the calculated frequencies, but might be necessary for the location of transition states in some cases. Vibrational analysis verified that each structure was a minimum or a transition state. Following the intrinsic reaction coordinates (IRC) confirmed that all transition states connected the corresponding reactants and products on the potential energy surface. Thermal corrections were calculated from unscaled harmonic vibrational frequencies at the same level of theory for a standard state of 1 mol L–1 and 298.15 K. Entropic contributions to the reported free energies were calculated from partition functions evaluated with Truhlar's quasiharmonic approximation. This method uses the same approximations as the usual harmonic oscillator approximation except that all vibrational frequencies lower than 100 cm–1 are set equal to 100 cm–1 to correct for the breakdown of the harmonic oscillator approximation for low frequencies. Electronic energies were subsequently obtained from single-point calculations employing the M06-2X functional with the large triple-ζ def2-TZVPP basis set, IEFPCM for methanol, and Grimme's D3 dispersion correction. An ultrafine grid corresponding to 99 radial shells and 590 angular points was used throughout this investigation for numerical integration of the density. The reported free energies refer to the lowest-energy conformer and are almost identical to those obtained from Boltzmann-averaged ensembles. All DFT calculations were performed with Gaussian 09.

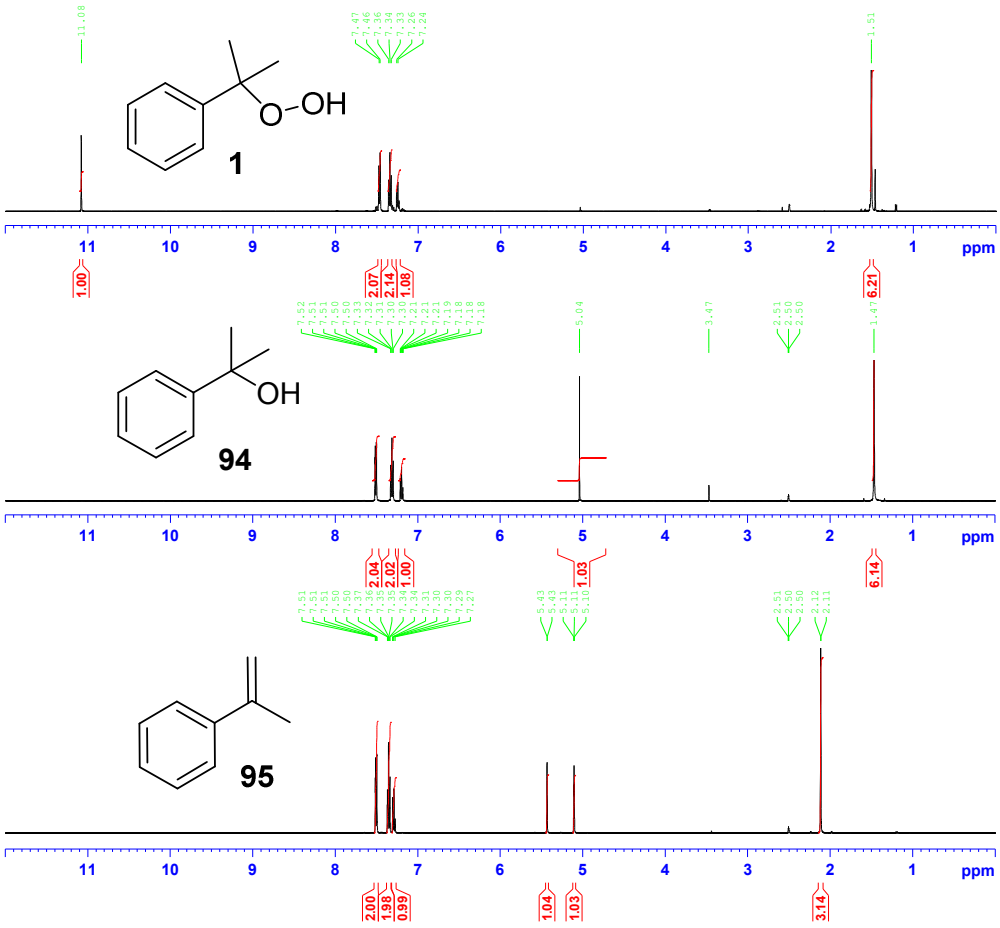
8.2 Study on the reactivity of cumene hydroperoxide used as model substrate

8.2.1 General procedure for performing different reactions

The desired amount of cumene hydroperoxide was dissolved in desired solvent (10 ml). To this reaction mixture was added the required amount of *p*-nitroaniline (**91**) followed by the addition of catalyst. After specific time, a sample was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

8.2.2 Comparison of spectra for the measurement of yield

^{1}HNMR of all the possible products arising from the decomposition of cumene hydroperoxide was measured in DMSO-d_6 (Figure 13).



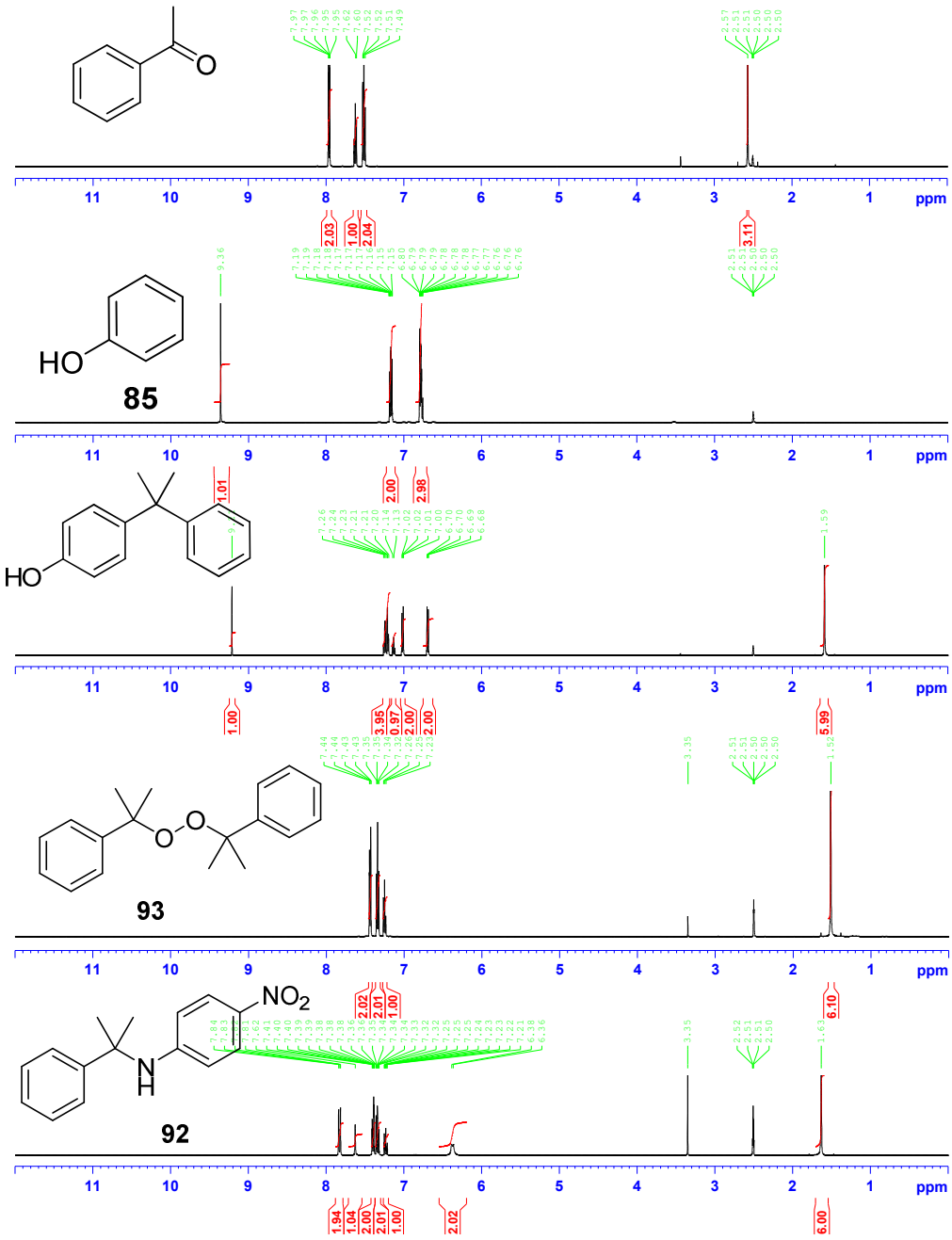


Figure 13: An overlay of ^{1}H NMR of possible products after decomposition of cumene hydroperoxide (1)

For the measurement of relative yields of the products of a reaction, a small portion of reaction mixture was diluted with DMSO-d_6 and ^{1}H NMR was measured. Then, the ^{1}H NMR of this crude reaction mixture was compared with the ^{1}H NMR spectra of all the possible products of cumene hydroperoxide. From the ratio of signals of different products, relative yields were calculated. Normally under the conditions, phenol (**85**), coupling product (**92**) cumyl dimer (**93**), and cumyl alcohol (**94**) were mainly formed. In the reaction mixture, signals of the products were

slightly shifted. With careful observation, it was possible to identify the signal of each product. For example in Figure 14 and Figure 15, the signals at 1.47 ppm, 1.51 ppm and at 1.63 ppm belong to cumene hydroperoxide **1**, dicumyl peroxide **93** and coupling product **92** respectively.

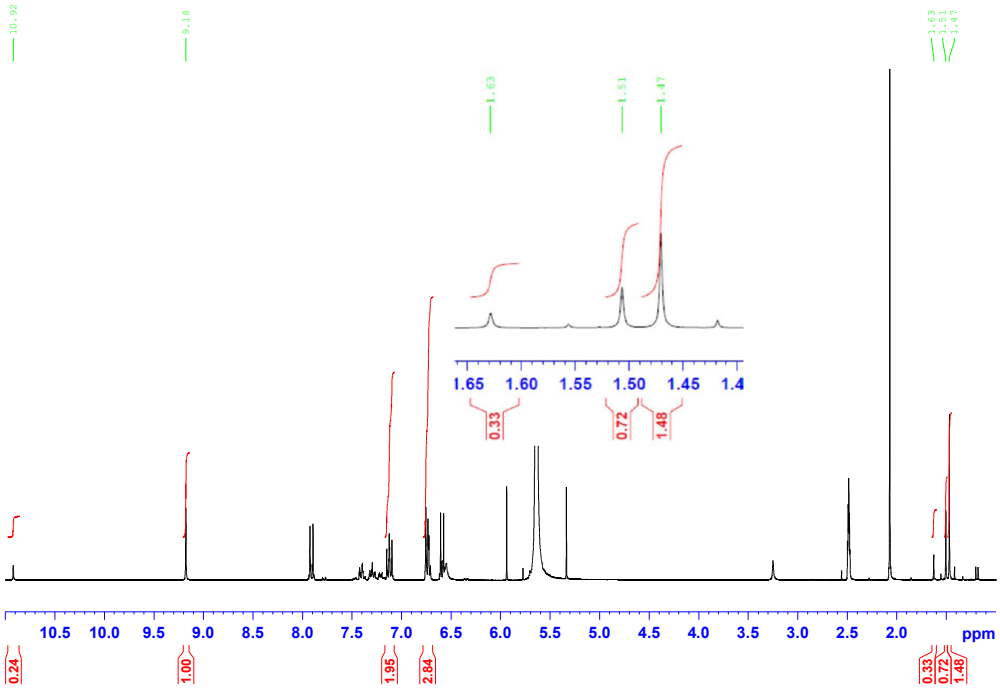


Figure 14: ^{1}H NMR in DMSO of reaction mixture

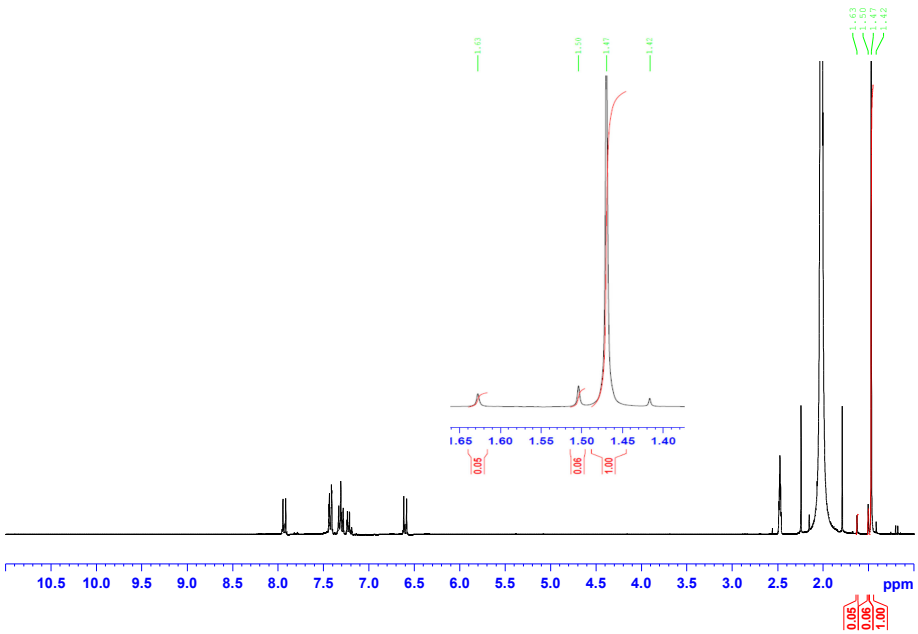


Figure 15: ^{1}H NMR in DMSO of reaction mixture

Performing the reaction by changing different acid catalysts in acetonitrile as solvent

Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (10 ml). To this reaction mixture was added the *p*-nitroaniline (67.4 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of 5 mol% of desired catalyst. The reaction mixture was then allowed to stir at room temperature for 15 h. After 15h, a sample (0.1 mL) was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

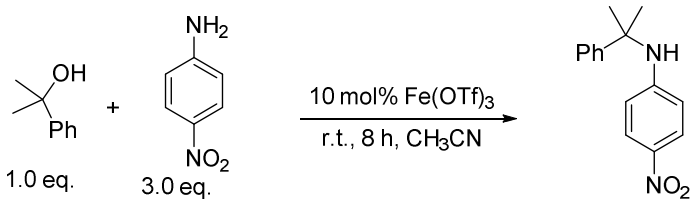
Performing the reaction by changing different solvents with one specific catalyst (representative example with $Fe(OTf)_3$)

Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in desired solvent (10 ml). To this reaction mixture was added the *p*-nitroaniline (67.4 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of 5 mol% of $Fe(OTf)_3$ (12.3 mg, 0.0245 mmol, 0.05 equiv.). The reaction mixture was then allowed to stir at room temperature for 15 h. After 15h, a sample (0.1 mL) was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products. Similarly other reactions were performed by changing the catalysts and solvents and yields were measured.

(Data for Figure 3a, Section 5.1.2): Control reaction by using 1.47 mmol (excess) of *p*-nitroaniline and 0.49 mmol of cumene alcohol:

Cumene alcohol (68.3 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (10 ml). To this reaction mixture was added the *p*-nitroaniline (202.2 mg, 1.47 mmol, 3.0 equiv.) followed by the addition of $Fe(OTf)_3$ (24.6 mg, 0.049 mmol, 0.1 equiv.). The reaction mixture was then allowed to stir at room temperature for 8 h. The progress of the reaction was measured at different time intervals. After specific time, a sample (0.1 mL) was taken from the reaction mixture and was diluted with d_6-DMSO. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

Table 64: Control reaction by using excess of *p*-nitroaniline compared with alcohol 94



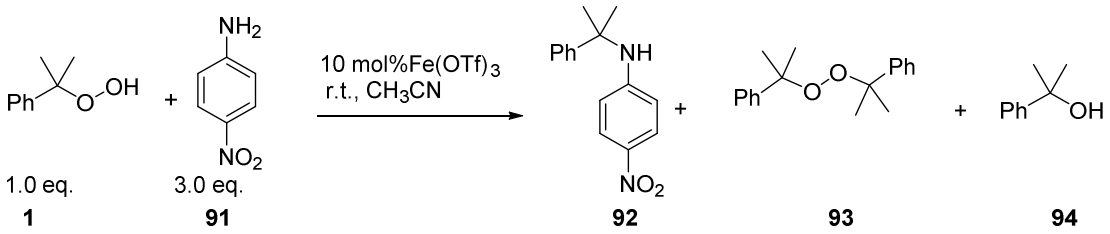
Entry	Cons. (%)[a]	Time (h)	92 (%)
1	80	0.5	80
2	87	3	87
3	88	22	88
4	88	22	88

[a] Yields determined by ^{1}H NMR.

Data for Figure 3b, Section 5.1.2: Control reaction by using 1.47 mmol (excess) of *p*-nitroaniline and 0.49 mmol of cumene hydroperoxide:

Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (10 ml). To this reaction mixture was added the *p*-nitroaniline (202.2 mg, 1.47 mmol, 3.0 equiv.) followed by the addition of $Fe(OTf)_3$ (24.6 mg, 0.049 mmol, 0.1 equiv.). The reaction mixture was then allowed to stir at room temperature for 8 h. The progress of the reaction was measured at different time intervals. After specific time, a sample (0.1 mL) was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

Table 65: Control reaction by using excess of *p*-nitroaniline compared with peroxide 1



1.0 eq. 3.0 eq.

1 **91** **92** **93** **94**

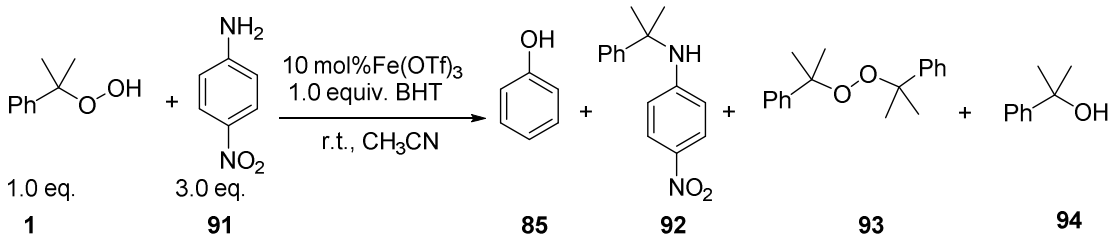
Entry	Cons. (%)[a]	Time (h)	92 (%)	93 (%)	94 (%)
1	41	1	23	7	11
2	53	3	38	12	7
3	87	5	59	18	10
4	89	8	60	20	9

[a] Yields determined by ^{1}H NMR.

Data for Scheme 52, Section 5.1.2: Control reaction by using BHT as radical trapper

Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (10 ml). To this reaction mixture was added the *p*-nitroaniline (202.2 mg, 1.47 mmol, 3.0 equiv.) and BHT (107.8 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of $Fe(OTf)_3$ (24.6 mg, 0.049 mmol, 0.1 equiv.). The reaction mixture was allowed to stir at room temperature for 5 h. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

Table 66: Control reaction by using excess of *p*-nitroaniline compared with peroxide 1



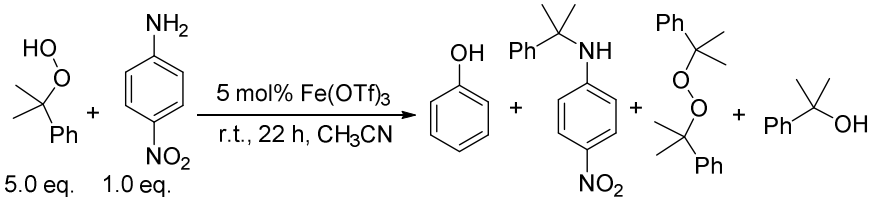
Entry	Cons. (%)	Time (h)	92 (%)	93 (%)
1	53	3	40	13
2	84	5	60	14

[a] Yields determined by ^{1}H NMR.

Data for Figure 4a, Section 5.1.2: Control reaction by using 2.45 mmol of cumene hydroperoxide and 0.49 mmol of *p*-nitroaniline:

Cumene hydroperoxide (452.5 µL, 2.45 mmol, 5.0 equiv.) was dissolved in desired solvent (10 ml). To this reaction mixture was added the *p*-nitroaniline (67.4 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of 5 mol% of $Fe(OTf)_3$ (12.3 mg, 0.0245 mmol, 0.05 equiv.). The reaction mixture was then allowed to stir at room temperature for 22 h. The progress of the reaction was measured at different time intervals. After specific time, a sample (0.1 mL) was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

Table 67: Control reaction by using 2.45 mmol of cumene hydroperoxide



1 **91** **85** **92** **93** **94**

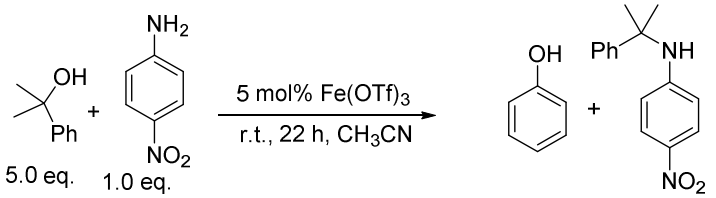
Entry	Cons. (%)	Time (h)	92 (%)	93 (%)	94(%)
1	60	3	4	50	6
2	71	5	3	62	6
3	95	22	3	85	7

[a] Yields determined by ^{1}H NMR.

Data for Figure 4b, Section 5.1.2: Control reaction by using 2.45 mmol of cumene alcohol and 0.49 mmol of *p*-nitroaniline:

Cumene alcohol (341.5 µL, 2.45 mmol, 5.0 equiv.) was dissolved in desired solvent (10 ml). To this reaction mixture was added the *p*-nitroaniline (67.4 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of 5 mol% of $Fe(OTf)_3$ (12.3 mg, 0.0245 mmol, 0.05 equiv.). The reaction mixture was then allowed to stir at room temperature for 22 hours. The progress of the reaction was measured at different time intervals. After specific time, a sample (0.1 mL) was taken from the reaction mixture and was diluted with d_6-DMSO. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products.

Table 68: Control reaction by using 2.45 mmol of cumene alcohol



94 **91** **85** **92**

Entry	Cons. (%)	Time (h)	92 (%)	94 (%)
1	20	3	20	80
2	20	5	20	80
3	20	22	20	80

[a] Yields determined by ^{1}H NMR.

Procedure of reaction for Scheme 52, Section 5.1.2: Control reaction by using 2.45 mmol of cumene hydroperoxide without using *p*-nitroaniline

Cumene hydroperoxide (452.5 µL, 2.45 mmol, 5.0 equiv.) was dissolved in desired solvent (10 ml). To this reaction mixture was added 5 mol% of $Fe(OTf)_3$ (12.3 mg, 0.0245 mmol, 0.05 equiv.). The reaction mixture was then allowed to stir at room temperature. The progress of the reaction was measured after 10 minutes. A sample (0.1 mL) was taken from the reaction mixture and was diluted with DMSO-d_6. After measuring the ^{1}H NMR of the reaction mixture, the comparative ratio of different products was measured by comparing the signals belonging to these products. The cumene hydroperoxide was quantitatively converted to phenol after 10 minutes.

8.2.3 Calculation of absolute hardness of Lewis acids

Absolute hardness[78] = Ionization energy - Electron affinity/2

Sn^{+4} (Tin)

Ionization energy = 40.7 ev[100]

Electron affinity = 1.112070 ev[101]

Hardness = 19.79

Hf^{+4} (Hafnium)

Ionization energy = 33.30 ev[102]

Electron affinity = 1.112070 ev[103]

Hardness = 16.09

Fe^{+3} (Iron)

Ionization energy = 30.643 ev[100]

Electron affinity = 0.151 ev[104]

Hardness = 15.2445

Sc^{+3} (Scandium)

Ionization energy = 24.75 ev[100]

Electron affinity = 0.189 ev[105]

Hardness = 12.2805

In^{+3} (Indium)

Ionization energy = 28.03 ev[100]

Electron affinity = 0.38392 ev[106]

Hardness = 13.82

Bi^{+3} (Bismuth)

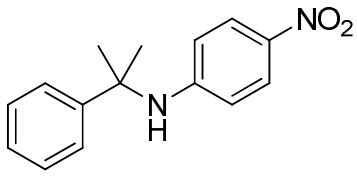
Ionization energy = 25.56 ev[100]

Electron affinity = 0.942362 ev[107]

Hardness = 12.308

8.2.4 Synthesis and characterization of the coupling products

4-nitro-N-(2-phenylpropan-2-yl)aniline (92):



Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (10 ml). To this reaction mixture was added the *p*-nitroaniline (202.2 mg, 1.47 mmol, 3.0 equiv.) followed by the addition of $Fe(OTf)_3$ (24.6 mg, 0.049 mmol, 0.1 equiv.). After 24 h, the solvent was reduced to dryness and the resulting solid was purified by column chromatography (alox, hexane/ethylacetate 90:10) to afford the desired product as yellow solid. Yield: 75%.

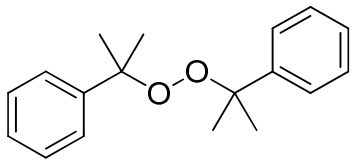
Rf = 0.60 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d6): δ 7.82 (dd, J = 7.8 Hz, J = 1.2 Hz, 2H), 7.62 (s, 1H), 7.40-7.37 (m, 2H), 7.30 (m, 2H), 7.23 (tt, J = 7.0 Hz, J = 1.6 Hz, 1H), 6.37 (d, J = 8.0 Hz, 2H), 1.63 (s, 6H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 153.2 , 146.5, 136.0, 129.0, 127.0, 125.8, 125.5, 113.4, 56.2, 30.2, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{18}H_{17}N_3O_2Na_1$ $[M+Na]^+$: 279.110398; found: 279.110535.

(peroxybis(propane-2,2-diyl))dibenzene (dicumyl peroxide) (93):



Cumene hydroperoxide (90.5 µL, 0.49 mmol, 1.0 equiv.) was dissolved in acetonitrile (3 ml). To this reaction mixture was added the phenol (46.06 mg, 0.49 mmol, 1.0 equiv.) followed by the addition of $FeCl_2$ (3.14 mg, 0.025 mmol, 0.05 equiv.). After 15 h, the solvent was reduced to dryness and the resulting solid was purified by column chromatography (alox, hexane/ethylacetate 90:5) to afford the desired product as a colorless liquid in quantitative yield

Rf = 0.90 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.43 (dd, J = 8.3 Hz, J = 0.9 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 7.3 Hz, 2H), 1.51 (s, 6H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 145.6 , 127.8, 126.8, 125.3, 81.5, 26.7, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{22}O_2Na_1$ [M+Na]+: 293.151202; found: 293.150927.

8.3 Allylic C–H functionalization *via* photochemically generated hydroperoxides

8.3.1 General procedures

General procedure for optimizing the yield of cyclohexe hydroperoxide

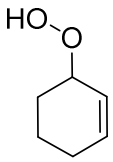
Cyclohexene (0.49 mmol) was dissolved in the desired solvent (10 mL) at room temperature. To this solution was added the desired sensitizer (1.4 mg) followed by the addition of an additive (if used). The resulting reaction mixture was irradiated with visible light under an oxygen atmosphere for 15 h. The yield of hydroperoxide was determined by ^{1}H NMR based upon the conversion of cyclohexene.

General procedure for optimizing the yield of coupling product

Cyclohexene hydroperoxide (55.8 mg, 0.49 mmol, 1.0 equiv.) was dissolved in a desired solvent (10 ml). To this reaction mixture was added the required amount of *p*-nitroaniline followed by the addition of catalyst. After a specific time, a sample (1 mL) was taken from the reaction mixture and was quenched with an aqueous saturated solution of $NaHCO_3$. The product was then extracted into the organic phase by using ethyl acetate as solvent (5 mL). The organic phase was reduced to dryness and yield of the coupling product was measured based upon the conversion of *p*-nitroaniline.

8.3.2 Synthesis and characterization of starting materials and coupling products

3-hydroperoxycyclohex-1-ene (88)



Cyclohexene (0.49 mmol) was dissolved in 10 mL chloroform at room temperature. To this solution was added TPP (1.4 mg) followed by the addition of $NiCl_2$ (0.025 mmol, 3.25 mg). The resulting reaction mixture was irradiated with visible light under oxygen atmosphere. After 15 h, the solvent was evaporated and the crude product was purified *via* column chromatography (Alox, hexane/ethylacetate 80:20) to afford the desired product as oil, Yield: 60%

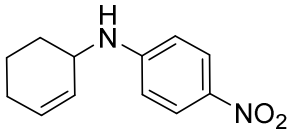
R_f = 0.20 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d_6): 11.04 (s, 1H), 5.93-5.90 (m, 1H), 5.72-5.69 (m, 1H), 4.28-4.27 (m, 1H), 2.03-1.97 (m, 2H), 1.83-1.76 (m, 1H), 1.67-1.57 (m, 2H), 1.55-1.47 (m, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): *δ* 132.5, 125.1, 76.8, 26.1, 24.8, 18.1, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{16}H_{10}O_2Na_1$ $[M+Na]^+$: 137.057299; found: 137.057390

***N*-(cyclohex-2-en-1-yl)-4-nitroaniline (96)**



Cyclohexene hydroperoxide (55.8 mg, 0.49 mmol, 1.0 equiv.) was dissolved in a 1:1 mixture of nitromethane and 1,1,2,2-tetrachloroethane (overall 10 ml solvent). To this reaction mixture was added the *p*-nitroaniline (202.2 mg, 1.47 mmol, 3.0 equiv.) followed by the addition of $Fe(OTf)_2$ (17.3 mg, 0.049 mmol, 0.1 equiv.). After 15 h at 25 °C, the reaction mixture was quenched with aqueous saturated solution of $NaHCO_3$. The product was then extracted into the organic phase by using ethyl acetate as solvent (3x30 mL). The organic phase was then dried over $MgSO_4$, reduced to dryness and the resulting solid was purified by column

chromatography (alox, hexane/ethylacetate 90:10) to afford the desired product as yellow solid. Yield: 34%. Rf = 0.50 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d$_6$): 7.98 (d, *J* = 9.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 9.4 Hz, 2H), 5.90-5.86 (m, 1H), 5.67-5.64 (m, 1H), 4.10 (broad m, 1H), 2.04-1.97 (m, 2H), 1.90-1.84 (m, 1H), 1.74-1.68 (m, 1H), 1.64-1.50 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d$_6$): *δ* 153.6, 135.4, 130.1, 127.4, 126.2, 46.9, 28.1, 24.4, 19.2, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{12}H_{14}N_2O_2Na_1$ $[M+Na]^+$: 241.094746; found: 241.094660

8.4 C–H functionalization of tetrahydrocarbazole derivatives *via* photochemically generated hydroperoxides

8.4.1 Synthetic procedures

Synthesis of tetrahydrocarbazole derivatives

The different tetrahydrocarbazole and indol derivatives were synthesized by Fischer Indole Synthesis using standard procedures.[108]

General procedure for the synthesis of hydroperoxides:

The desired substrate (1g) was dissolved in toluene (100 ml). To this solution was added rose bengal (2mg). The resulting reaction mixture was irradiated with a 23 watt lamp under an O_2 atmosphere. The progress of the reaction was controlled with ^{1}H NMR. After the full conversion of the substrate, the precipitated solid was filtered to afford the desired product in quantitative yields. All the hydroperoxides looked pink because of the presence of rose bengal.

Reaction of hydroperoxides with *N*–H nucleophiles

Method A (MeOH/TFA), for the coupling of electron poor anilines

The hydroperoxide (0.49 mmol, 1.0 equiv.) was dissolved in methanol (0.5 ml). To this reaction mixture was added the desired nucleophile (0.49 mmol, 1.0 equiv.) followed by the addition of TFA (3.7 µL, 0.049 mmol, 0.1 equiv.). After 2-4 h, the solvent was reduced to dryness and the resulting solid was purified by column chromatography or by recrystallization.

Method B (AcOH), for the coupling of plain and halogenated anilines

The hydroperoxide (0.49 mmol, 1.0 equiv.) was dissolved in acetic acid (0.5 ml). To this reaction mixture was added the desired nucleophile (0.49 mmol, 1.0 equiv.). After 2-4 h, the solvent was reduced to dryness and the resulting solid was purified by column chromatography or by recrystallization.

Method C (DMSO:MeOH/TFA) for the coupling of indoles with peroxide

The hydroperoxide (0.49 mmol, 100 mg) was dissolved in 1:1 mixture of DMSO and methanol (1mL+1mL). To this reaction mixture was added 10 mol% TFA and was allowed to stir for 15h at room temperature. The solvent was then evaporated under reduced pressure and the crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/triethylamine 80:15:5) to afford the desired product.

Method D (DMSO/TFA) (for the coupling of electron rich anilines and other nucleophiles with peroxide)

The hydroperoxide (0.49 mmol, 100 mg) was dissolved in DMSO (2 mL) To this reaction mixture was added desired nucleophile (1.0-5.0 equivalent) followed by the addition of 20 mol% TFA and was allowed to stir for 15h at room temperature. The solvent was then evaporated under reduced pressure and the crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/triethylamine) to afford the desired product.

8.4.2 Comparison of two-step and one-pot methods

Two-step method: The hydroperoxide **59** was synthesized in toluene as described above and employed in the coupling step as a purified compound. Using this procedure, a yield of 86% over two steps was achieved for the coupling of tetrahydrocarbazole **58** and *p*-nitroaniline (**91**).

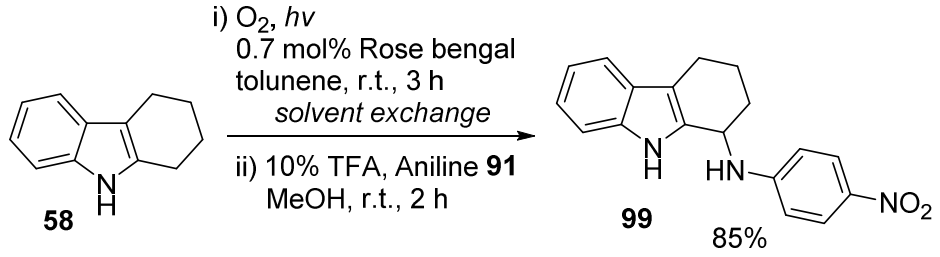
One-pot method with exchange of solvent: after synthesis of the peroxide **59** in toluene according to the procedure described above, toluene is removed under vacuum and the resulting mixture is directly employed in the next step. Using this procedure, a yield of 85% over two steps was achieved for the coupling of tetrahydrocarbazole **58** and *p*-nitroaniline (**91**).

One-pot method without change of solvent:

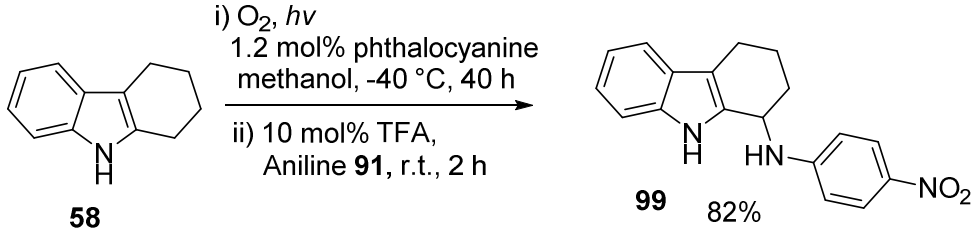
The indole derivative (0.49 mmol) was dissolved in methanol (10 ml). To this solution was added phthalocyanine (2 mg). The resultant reaction mixture was irradiated with a 500 watt lamp under an atmosphere of oxygen for 40 hours at -40°C. The progress of the reaction was controlled by ^{1}H NMR. After full conversion of the substrate, aniline (1.0 equiv.) and trifluoroacetic acid (10 mol%)

was added and the mixture was stirred at ambient temperature. After 3 hours, the solvent was reduced to dryness and the resulting solid was purified by column chromatography or by recrystallization. Using this procedure, a yield of 82% was achieved for the coupling of tetrahydrocarbazole **58** and *p*-nitroaniline (**91**).

a) One pot method with exchange of solvent



e) One pot method without exchange of solvent



Scheme 102: Comparison of a, One-pot, two-step protocol exchanging the solvent without isolation of hydroperoxide 59. b, One-pot, two-step protocol in methanol without need to exchange the solvent.

8.4.3 Determination of the position of new C-N bond

To determine the structure of the coupling products and unambiguously distinguish it from all the other possible isomers, a detailed NMR analysis of product **99** was performed. With the help of ^{15}N–HMBC, it was possible to assign the hydrogen atoms directly connected to nitrogen (Figure 16). The correct regioisomer was confirmed by Nuclear Overhauser effect spectroscopy (NOESY), which showed the long range coupling of indolic *N*–H with the aniline *N*–H and methyne C–H (Figure 17).

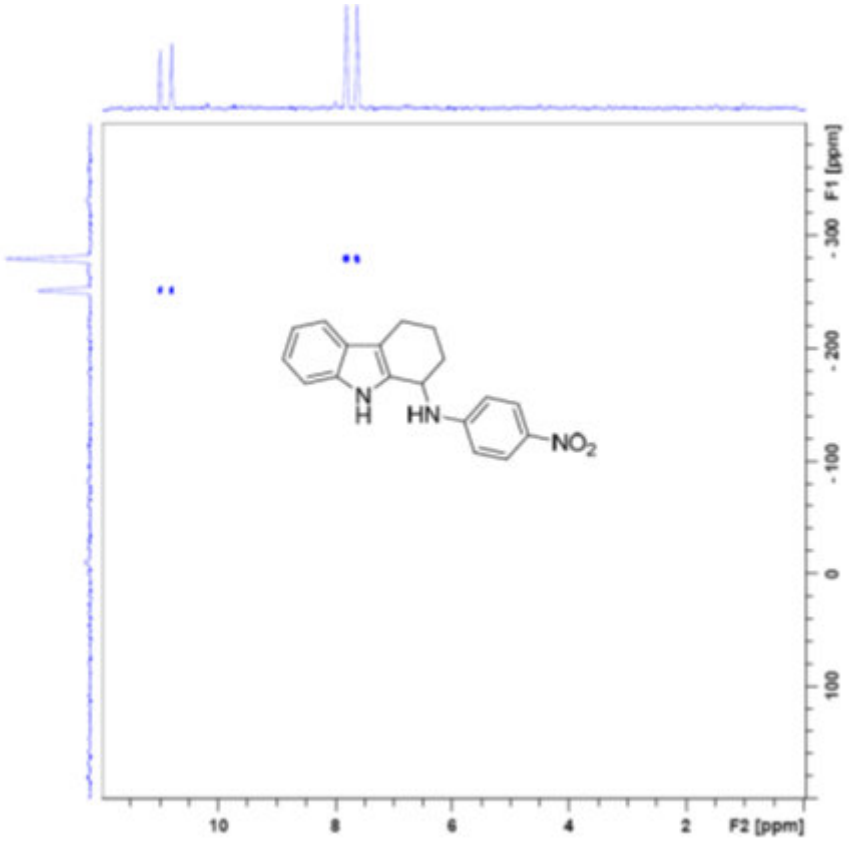


Figure 16: ^{15}N–HMBC of 99 in DMSO (to find the hydrogens directly connected with nitrogen)

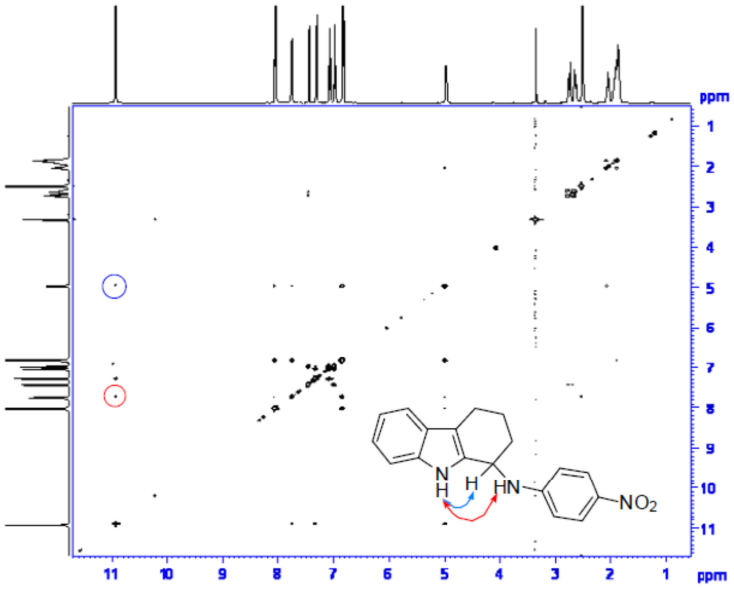


Figure 17: NOESY of 99 in DMSO (to determine the position of the new C-N bond)

8.4.4 Determination of the relative configuration of the major diastereomer for (1*R*,3*S*)-*N*-(4-nitrophenyl)-3-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine (151)

The reaction of phenyl substituted tetrahydrocarbazole hydroperoxide with *p*-nitroaniline led to the formation of two diastereomers with a ratio of 85:15. It was possible to isolate the major diastereomer by column chromatography. The configuration of the major diastereomer was determined by assigning all protons by H,H-COSY, HMBC and HSQC and determining the coupling constants between Ha- Hb/Hc and Hd- Hb/Hc and Hd-He/Hf (Figure 18, Figure 19,Table 69).

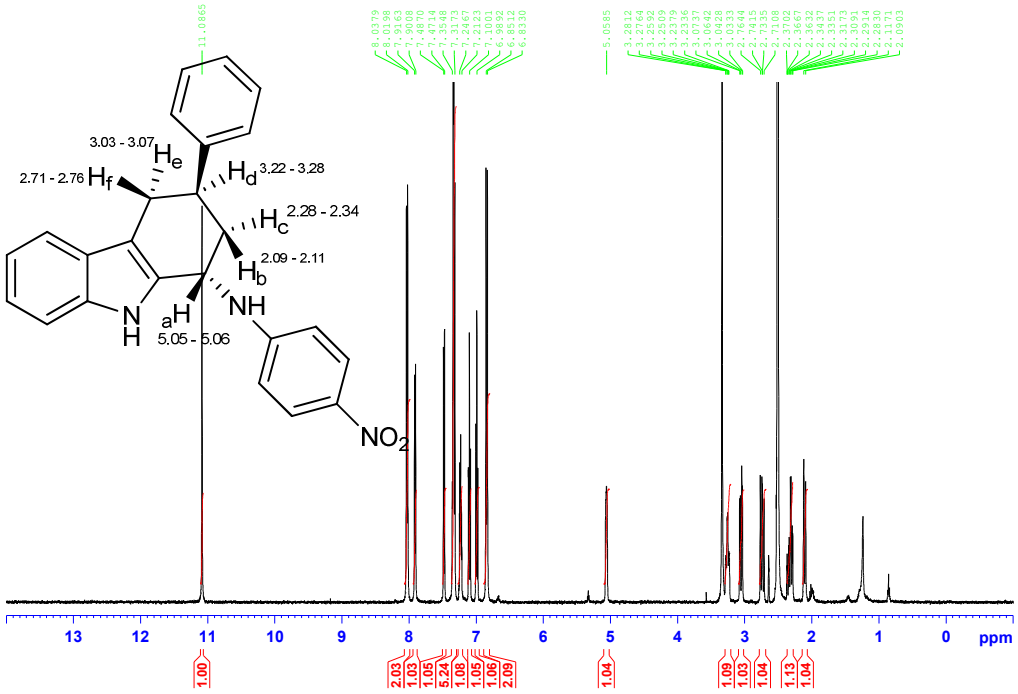


Figure 18: ^{1}H NMR in DMSO of the major diastereomer of 151

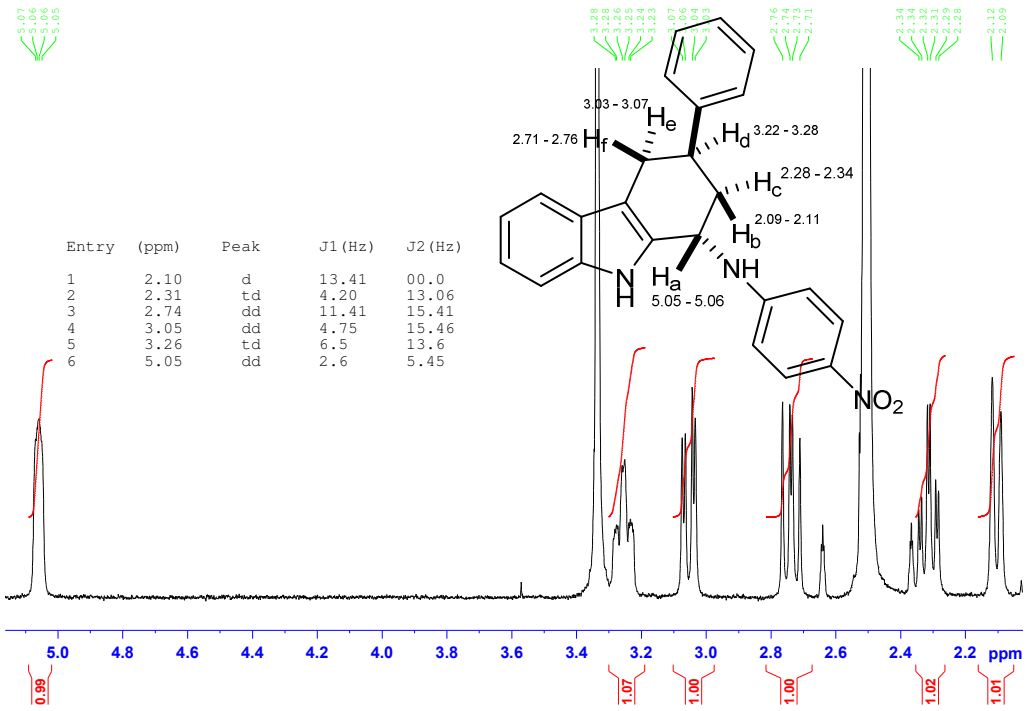
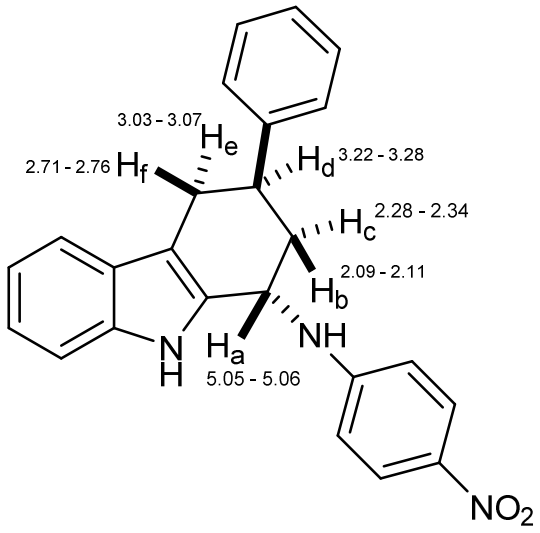


Figure 19: Expansion of ^{1}H NMR in DMSO of the major diastereomer of 151

Table 69: Chemical shifts and coupling constants for the major diastereomer of 151



Entry	Proton	Chemical shift (ppm)	Multiplicity	Coupling constant (*J*, Hz)
1	b	2.09-2.11	d	13.4
2	c	2.28-2.34	td	13.1, 4.2
3	f	2.71-2.76	dd	15.4, 11.4
6	e	3.03-3.07	dd	15.5, 4.7
7	d	3.22-3.28	tdd	13.9, 4.9, 2.9
8	a	5.05	m	<6

[a] ^{1}H NMR was measured in DMSO-d_6

Proton H_b shows a broad doublet at 2.09-2.11 ppm with a coupling constant value of 13.4 Hz (geminal coupling with H_c) (Figure 18, Figure 19, Table 69). The additional coupling of Hb with Hd and Ha can be observed in H,H-COSY sopectrum (Figure 20). Ha shows a multiplet at 5.05 ppm, however, by carefully examining the spectra it can be seen that the coupling constant is not greater than 6 Hz which proves the equatorial-axial and equatorial-equatorial relation of Ha with Hb and Hc respectively.

The absence of an axial-axial coupling constant between Ha and Hb/Hc and the presence of an axial-axial coupling constant between H_d-H_b/H_c and H_d-H_e/H_f indicates that the aniline substituent is in an axial position and the phenyl ring in an equatorial one. Accordingly, the relationship between phenyl and aniline substituents is *trans*.

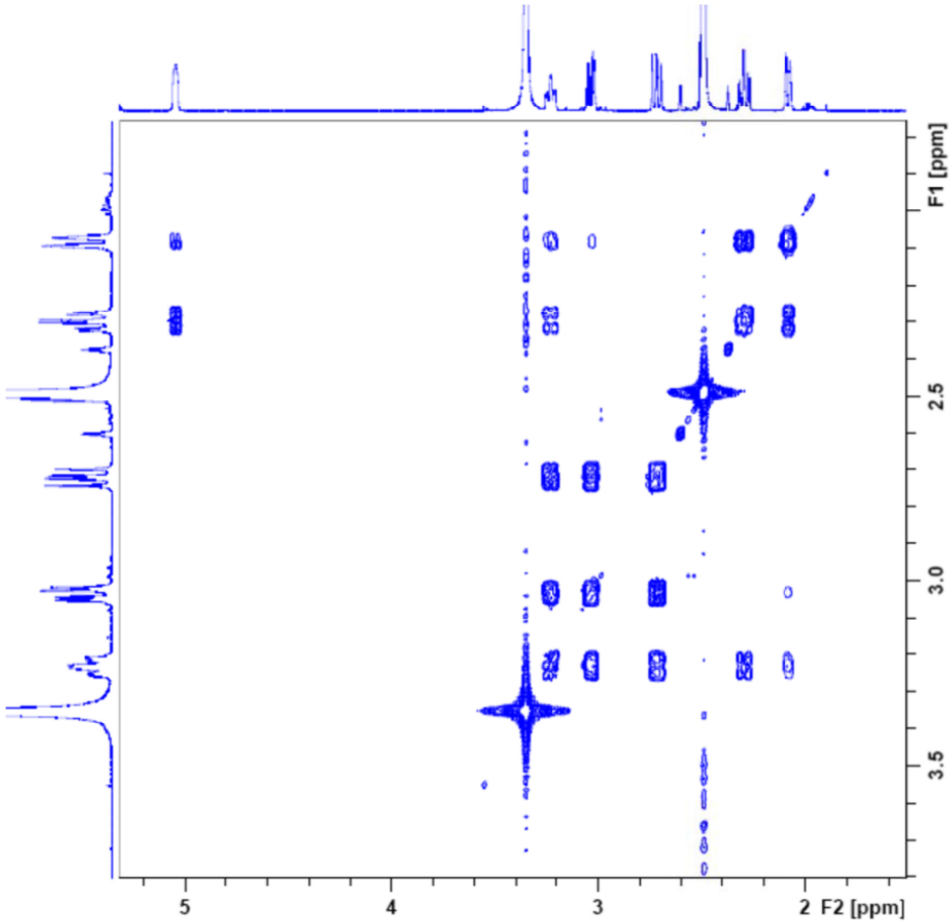


Figure 20: Expansion of H,H COSY in DMSO of the major diastereomer of 151.

The relative configuration of the major diastereomer of **152** was determined in the same way.

8.4.6 Reduction of hydroperoxides to alcohols in DMSO-d6

A reduction of the hydroperoxide group in peroxide **59** and its derivatives to the alcohol was observed in DMSO by measuring the ^{1}H NMR spectra at different time intervals. For example, the chloro tetrahydrocarbazole hydroperoxide was completely reduced to the corresponding alcohol after 72 hours in DMSO-d6 (Figure 21). This generally caused problems of obtaining clean ^{13}C NMR spectra, since these required longer acquisition times. Alternative solvents were less suited for the characterization of the hydroperoxides, either because the solubility was too low, decomposition reactions occurred or the hydroperoxide group was not detectable.

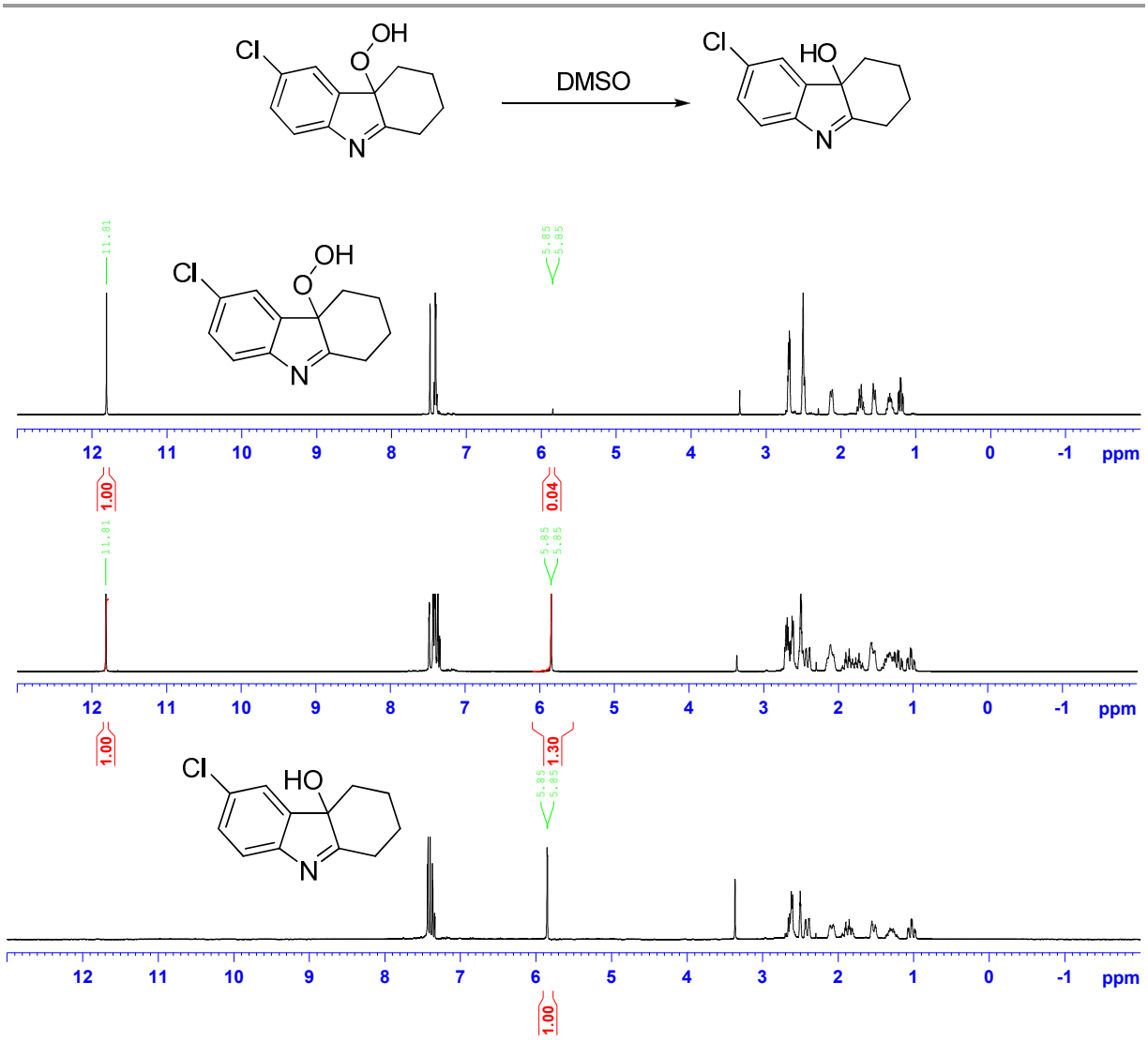
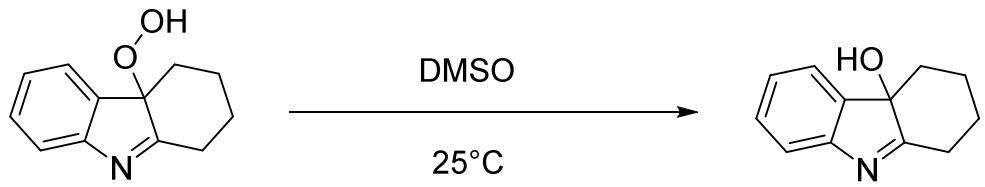


Figure 21: Reduction of a chlorotetrahydrocarbazole hydroperoxide in DMSO-d_6

Data for Figure 5, Section 5.3.3: Reduction of peroxide 59

Hydroperoxide (**59**, 6.25 mg, 0.03 mmol) was dissolved in deutrated DMSO (0.6 mL) in NMR tube at 25 °C. The progress of the reduction of peroxide **59** to alcohol **103** was measured at regular intervals.

Table 70: Reduction of peroxide 59 to alcohol 103 in DMSO



59 **103**

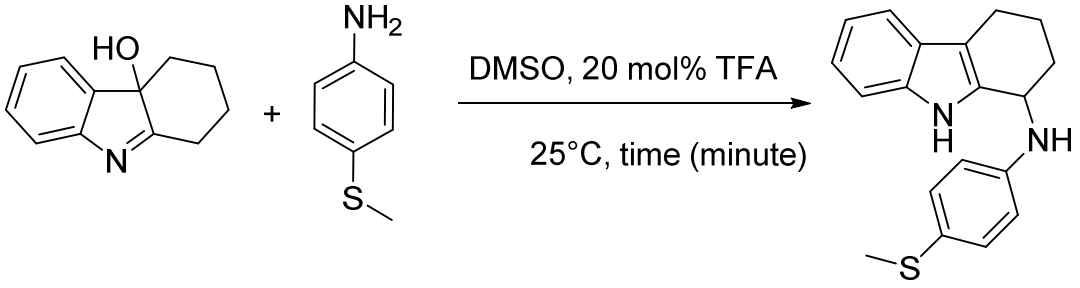
Entry	Time (minutes)	Peroxide 59	Alcohol 103
1	30	97	3
2	60	93	7
3	120	86	14
4	240	73	27
5	360	61	39
6	480	52	48
7	600	44	56
8	720	36	64
9	840	30	70
10	900	28	72
11	1200	18	82
12	1440	12	88

[a] ^{1}H NMR was measured in DMSO at regular intervals in NMR tube at 25 °C

Data for Figure 5, Section 5.3.3: Coupling of alcohol 103 with 4-methyl thioaniline (175)

Alcohol **103** (0.048 mmol, 9.16 mg, 1.0 equiv) was dissolved in DMSO-d_6 in NMR tube at 25 °C. To this solution was added thioaniline **175** (0.24 mmol, 29.9 uL, 5.0 equiv) followed by the addition of 20 mol% TFA. The progress of the coupling reaction was measured at regular intervals.

Table 71: Coupling of alcohol 103 with 4-methyl thioaniline (175)



103 **175** **177**

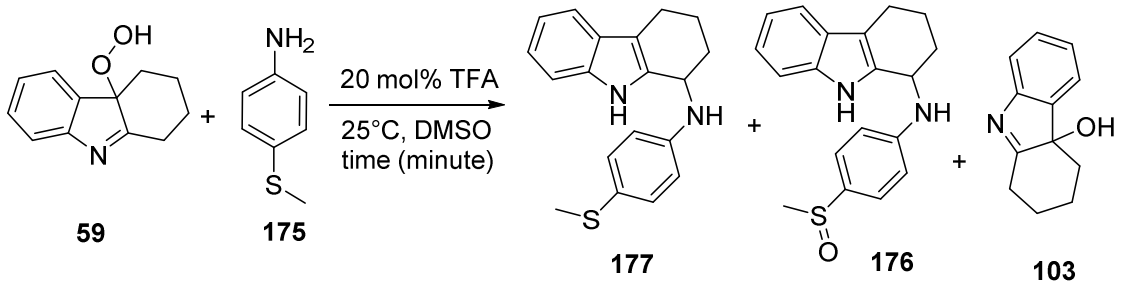
Entry	Time (minutes)	Alcohol 103	Product 177
1	30	93	7
2	60	58	42
3	90	36	64
4	120	20	80
5	150	0,6	99,4
6	180	0,3	99,7
7	210	0	100

[a] ^{1}H NMR was measured in DMSO at regular intervals at 25 °C

Data for Figure 5, Section 5.3.3: Coupling of peroxide 59 with 4-methyl thioaniline (175)

Peroxide (0.048 mmol, 10 mg, 1.0 equiv) was dissolved in DMSO-d_6 in NMR tube at 25 °C. To this solution was added thioaniline **175** (0.24 mmol, 29.9 uL, 5.0 equiv) followed by the addition of 20 mol% TFA. The progress of the coupling reaction was measured at regular intervals.

Table 72: Coupling of Peroxide 59 with 4-methyl thioaniline 175



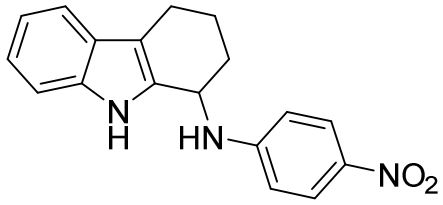
59 **175** **177** **176** **103**

Time (minutes)	Peroxide 59	Product 177	Product 176	Alcohol 103
30	94	2	0	4
60	80	12	1	7
90	68	24	2	6
120	57	34	3	5
150	48	43	6	4
180	39	51	7	2
210	32	57	9	1
240	27	63	9	1
270	22	57	11	1
300	17	70	12	0
330	13	74	12	0
360	11	75	13	0
390	8	77	14	0
420	6	79	14	0
450	5	80	14	0
480	4	81	15	0
510	3	81	15	0

[a] ^{1}H NMR was measured in DMSO at regular intervals at 25 °C

8.4.7 Synthesis and characterization of the coupling products

N-(4-nitrophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (99):



Synthesized according to Method A, Rf = 0.60 (hexane/ethy acetate 70:30).

Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Yellow solid, Yield: 86%.

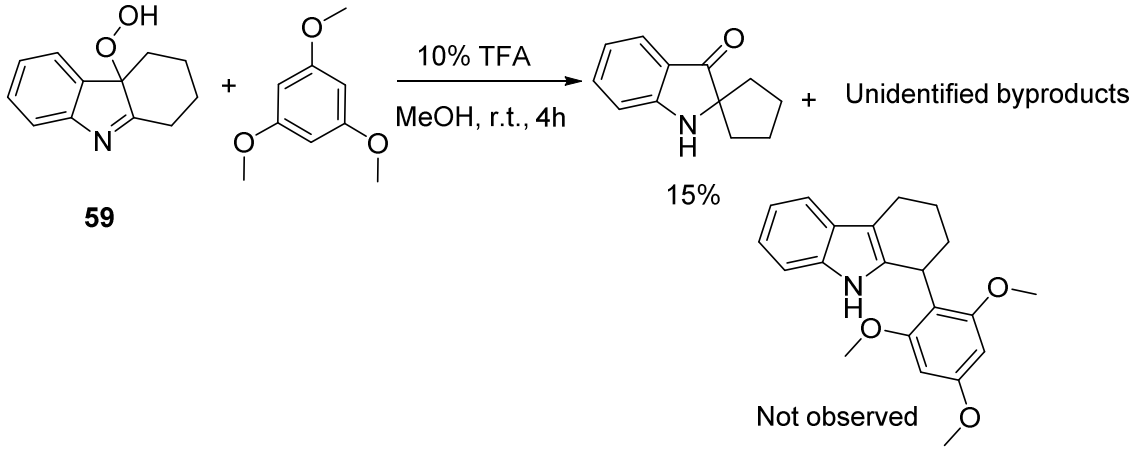
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.9 Hz, 2H), 4.98-4.96 (m, 1H), 2.76-2.72 (m, 1H), 2.66-2.60 (m, 1H), 2.07-2.02 (m, 1H), 1.93-1.84 (m, 3H), ppm;

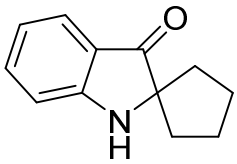
^{13}C NMR (125 MHz, DMSO-d_6): *δ* 153.6 , 136.0, 135.5, 133.0, 126.4, 126.3, 121.2, 118.2, 118.0, 111.1, 110.7, 45.6, 29.2, 20.6, 19.6 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{18}H_{17}N_3O_2Na_1$ $[M+Na]^+$: 330.121296; found: 330.120960.

Spiro[cyclopentane-1,2'-indolin]-3'-one (100)

Trimethoxy benzene (0.48 mmol, 1.0 equiv.) was dissolved in AcOH (10 mL) at room temperature. To this reaction mixture was then added hydroperoxide **59** (0.48 mmol, 1.0 equiv.) followed by the addition of 10 mol% TFA. The reaction mixture was then allowed to stir at room temperature for 4 h. The solvent was then evaporated and the spiro product was purified by column chromatography (Silica gel (hexane/ethylacetate/triethylamine 90:5:5)) to afford the spiro product as yellow solid. R_f = 0.65, Yield: 15%



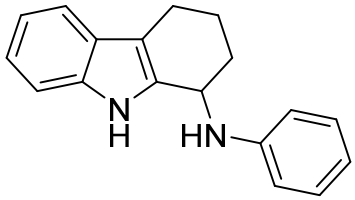


^{1}H NMR (500 MHz, DMSO-d_6): δ 7.53 (s, 1H), 7.44-7.39 (m, 2H), 6.83-6.80 (m, 1H), 6.69-6.66 (m, 1H), 1.83-1.79 (m, 6H), 1.63-1.60 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 204.6, 160.5, 136.9, 123.7, 118.7, 116.9, 111.9, 73.5, 37.1, 24.9 ppm;

HR-MS (ESIneg) m/z: M-H calcd. for $C_{12}H_{12}N_1O_1$ $[M-H]^-$: 186.092439; found: 186.092480.

***N*-phenyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (106):**



Synthesized according to Method B, Rf = 0.78 (hexane/ethy acetate 70:30).

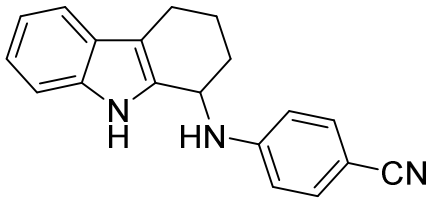
Purification: The crude product was purified *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as white solid, Yield: 60%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.84 (s, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.10 (t, J = 7.5 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.73 (d, J = 8.1 Hz, 2H), 6.54 (t, J = 7.3 Hz, 1H), 5.92 (d, J = 8.8 Hz, 1H), 4.78-4.76 (m, 1H), 2.73-2.69 (m, 1H), 2.64-2.59 (m, 1H), 2.0-1.91 (m, 2H), 1.86-1.77 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 147.8, 136.0, 134.8, 128.9, 126.6, 120.8, 118.0, 117.7, 15.6, 112.6, 111.0, 110.0, 45.8, 28.9, 20.8, 19.8, ppm;

HR-MS (ESIneg) m/z: M+ calcd. for $C_{18}H_{17}N_2$ [M-H]-: 261.139722; found: 261.139424

4-(2,3,4,9-tetrahydro-1*H*-carbazol-1-ylamino)benzonitrile (107):



Synthesized according to Method B, Rf = 0.62 (hexane/ethy acetate 70:30).

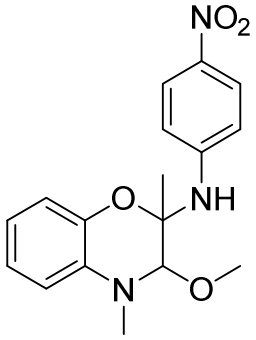
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, white solid, Yield: 80%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.89 (s, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.05 (t, J = 7.2 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 4.88-4.87 (m, 1H), 2.75-2.70 (m, 1H), 2.64-2.59 (m, 1H), 2.02-1.96 (m, 1H), 1.95-1.90 (m, 1H), 1.87-1.80 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.2 , 136.0, 133.5, 133.3, 126.4, 121.0, 120.6, 118.1, 117.8, 111.1, 110.5, 95.4, 45.2, 28.9, 20.6, 19.6 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{19}H_{17}N_3Na_1$ [M+Na]+: 310.131469; found: 310.131446

3-methoxy-2,4-dimethyl-N-(4-nitrophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-amine (113)



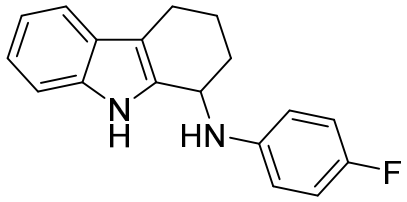
1,3-dimethyl indole (0.49 mmol) was dissolved in methanol (10 ml). To this solution was added rose bengal (2 mg). The resultant reaction mixture was irradiated with a 500 watt lamp under an atmosphere of oxygen for 15 hours at -40°C. The progress of the reaction was controlled by ^{1}H NMR. After full conversion of the substrate, *p*-nitroaniline (1.0 equiv.) and trifluoroacetic acid (10 mol%) was added and the mixture was stirred at ambient temperature. After 8 hours, the solvent was reduced to dryness and the resulting solid was purified by by recrystallization to afford the major diatereomer in 30% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96 (d, J = 9.3 Hz, 2H), 7.28 (d, J = 9.7 Hz, 1H), 7.02 (d, J = 9.7 Hz, 2H), 6.88-6.82 (m, 2H), 6.68-6.61 (m, 2H), 5.08 (d, J = 9.6 Hz, 1H), 3.19 (s, 3H), 2.88 (s, 3H), 1.45 (s, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 154.1, 140.0, 136.4, 133.3, 126.0, 122.3, 117.2, 116.2, 111.9, 97.8, 69.1, 48.7, 36.1, 18.6, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{17}H_{19}N_3O_4Na_1$ [M+Na]+: 352.126777; found: 352.126853

N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (143):



Synthesized according to Method B, Rf = 0.79 (hexane/ethy acetate 70:30).

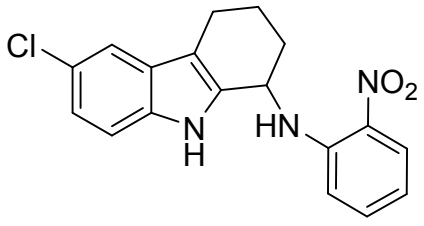
Purification: The crude product was purified *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as white solid, Yield: 65%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 6.97-6.92 (m, 3H), 6.73 (dd, J = 8.9 Hz, J = 4.6 Hz, 2H), 5.88 (d, J = 8.9 Hz, 1H), 4.74-4.71 (m, 1H), 2.73-2.68 (m, 1H), 2.64-2.59 (m, 1H), 1.98-1.93 (m, 2H), 1.86-1.77 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 155.0, 153.2, 144.5, 136.0, 134.8, 126.6, 120.8, 118.0, 117.7, 115.3, 115.1, 113.4, 113.3, 111.0, 110.0, 46.3, 28.8, 20.8, 19.8 ppm;

HR-MS EI (DE) m/z: M+ calcd. for $C_{18}H_{17}N_2F_1$ [M]+: 280.137580; found: 280.137313

6-chloro-N-(2-nitrophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (144):



Synthesized according to Method A, Rf = 0.55 (hexane/ethy acetate 70:30).

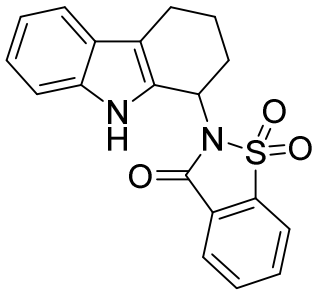
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, yellow solid, Yield: 55%;

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.20 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (s, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.77 (t, J = 7.7 Hz, 1H), 5.22 (d, J = 5.7 Hz, 1H), 2.76-2.73 (m, 1H), 2.64-2.61 (m, 1H), 2.16-2.15 (m, 1H), 1.99-1.88 (m, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 144.2, 136.8, 134.8, 134.6, 131.3, 127.6, 126.3, 123.1, 121.3, 117.5, 115.8, 114.8, 112.7, 111.1, 46.2, 29.3, 20.2, 20.1 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{16}N_3O_2Cl_1Na_1$[M+Na]+: 364.082326; found: 364.082303

Synthesis of 1-saccharinyl-2,3,4,9-tetrahydro-1H-carbazole (145):



Synthesized according to Method A (without TFA), Rf = 0.50 (hexane/ethy acetate 70:30).

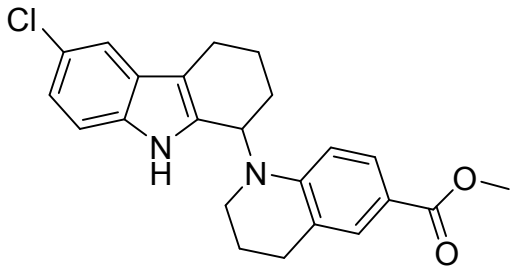
Purification: The desired product was precipitated by using a mixture of hexane/ethyl acetate. Yield: 52%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.80 (s, 1H), 8.28 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.05 (t, J = 7.6 Hz, 1H), 8.00 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.54 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 5.71 (t, J = 7.6 Hz, 1H), 2.71 (m, 2H), 2.44 (q, J = 8.3 Hz, 1H), 2.28-2.26 (m, 1H), 2.19-2.18 (m, 1H), 1.96-1.90 (m, 1H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 158.2 , 136.9, 136.2, 135.5, 135.0, 129.7, 126.6, 124.9, 121.2, 121.1, 118.3, 118.0, 111.7, 111.1, 47.6, 28.4, 22.2, 20.2 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{19}H_{16}N_2O_3S_1Na_1$ $[M+Na]^+$: 375.077386; found: 375.077706

Methyl 1-(6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-yl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (146):



Synthesized according to Method A, Rf = 0.48 (hexane/ethy acetate 70:30).

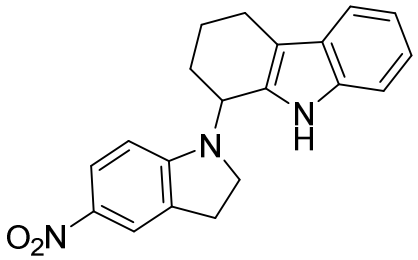
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. White solid, Yield: 55%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.07 (s, 1H), 7.63 (m (br), 1H), 7.56 (s, 1H), 7.45 (s 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.03 (dd, J = 8.5 Hz, J = 1.1 Hz, 1H), 6.98 (m, br, 1H), 5.40 (m, br, 1H), 3.75 (s, 3H), 3.04-2.91 (m, 2H), 2.75-2.66 (m, 4H), 2.09-1.70 (m, 6H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 166.3, 134.6, 130.2, 129.0, 127.9, 122.9, 121.8, 120.7, 117.1, 115.3, 112.5, 109.7, 109.6, 51.1, 27.7, 21.8, 20.8, 20.3, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{23}H_{23}Cl_1N_2O_2Na_1$ $[M+Na]^+$: 417.134022; found: 417.134037

1-(5-nitroindolin-1-yl)-2,3,4,9-tetrahydro-1*H*-carbazole (147):



Synthesized according to Method A, Rf = 0.63 (hexane/ethy acetate 70:30).

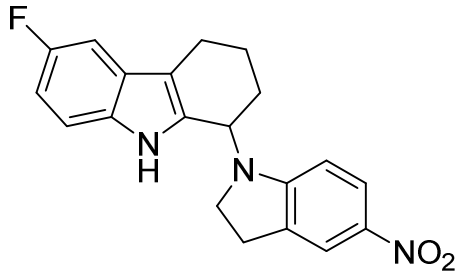
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Orange solid, Yield: 95%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.90 (s, 1H), 7.97 (dd, J = 8.9 Hz , J = 2.4 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.97 (t, J = 7.8 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 5.21-5.19 (m, 1H), 3.68-3.63 (q, J = 18.7 Hz , J = 9.3 Hz, 1H), 3.47-3.41 (q, J = 17.8 Hz , J = 8.8 Hz, 1H), 3.05 (t, J = 8.6 Hz, 2H), 2.70-2.64 (m, 2H), 2.09-2.02 (m, 2H), 1.91-1.85 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 156.5 (q), 136.3 (q), 136.2 (q), 131.5 (q), 130.7 (q), 126.6 (q), 126.4 (t), 121.1 (t), 120.1 (t), 118.3 (t), 118.0 (t), 111.6 (q), 111.1 (t), 104.0 (t), 49.9 (t), 48.8 (s), 26.3 (s), 26.1 (s), 21.9 (s), 20.4 (s) ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{19}N_3O_2Na_1$ [M+Na]+: 356.136948; found: 356.137207.

6-fluoro-1-(5-nitroindolin-1-yl)-2,3,4,9-tetrahydro-1H-carbazole (148):



Synthesized according to Method A, Rf = 0.58 (hexane/ethy acetate 70:30).

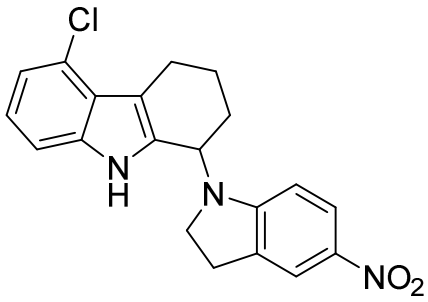
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Orange solid, Yield: 55%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.01 (s, 1H), 7.97 (dd, J = 8.9 Hz , J = 2.3 Hz, 1H), 7.87 (s, 1H), 7.25 (dd, J = 8.8 Hz, J = 4.5 Hz, 1H), 7.18 (dd, J = 9.8 Hz, J = 2.4 Hz, 1H), 6.89 (td, J = 9.2 Hz, J = 2.4 Hz, 1H), 6.53 (d, J = 8.9 Hz, 1H), 5.22-5.19 (m, 1H), 3.65 (q, J = 9.3Hz, 1H), 3.41 (q, J = 8.8 Hz, 1H), 3.06 (t, J = 8.7 Hz, 2H), 2.62-2.61 (m, 2H), 2.06-2.03 (m, 2H), 1.94-1.82 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 157.6, 156.5, 155.7, 136.4, 133.8, 132.9, 130.7, 128.8, 128.1, 126.9, 126.8, 126.4, 125.3, 120.2, 112.0, 111.9, 111.8, 109.1, 108.9, 104.0, 102.9, 102.7, 49.9, 48.7, 26.3, 25.9, 21.8, 20.3 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{20}H_{18}F_1N_3O_2Na_1$ $[M+Na]^+$: 374.127526; found: 374.127686

5-chloro-1-(5-nitroindolin-1-yl)-2,3,4,9-tetrahydro-1H-carbazole (149):



Synthesized according to Method A, Rf = 0.60 (hexane/ethy acetate 70:30).

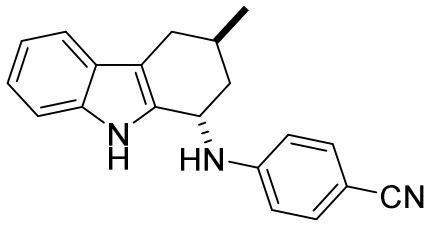
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, Orange solid, Yield: 70%;

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.34 (s, 1H), 7.97 (dd, J = 8.9 Hz , J = 1.8 Hz, 1H), 7.84 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 6.49 (d, J = 8.9 Hz, 1H), 5.16-5.15 (m, 1H), 3.68-3.62 (q, J = 9.2 Hz, 1H), 3.48-3.42 (q, J = 8.8 Hz, 1H), 3.05 (t, J = 8.6 Hz, 2H), 2.74-2.67 (m, 2H), 2.08-1.92 (m, 2H), 1.86-1.85 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 156.4, 136.0, 133.1, 132.8, 130.8, 128.6, 126.5, 121.0, 120.0, 119.4, 117.1, 115.6, 113.2, 103.7, 49.3, 49.2, 26.4, 26.2, 21.2, 20.4 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{18}N_3Cl_1O_2Na_1$ [M+Na]+: 390.097970; found: 390.097825

4-((1*R*,3*S*)-3-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-ylamino)benzonitrile (150):



Synthesized according to Method A, Rf = 0.50 (hexane/ethy acetate 70:30).

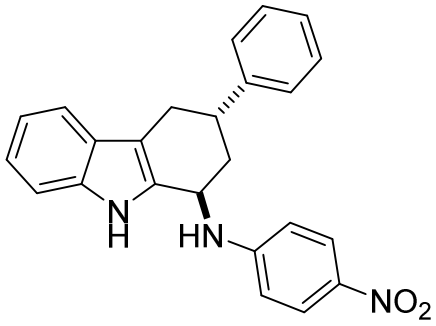
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, yielding a white solid as a mixture of diastereomers (trans:cis 65:35) in 80% yield. The ratio of diastereomers was determined by 1H-NMR analysis of the crude reaction mixture. The major diastereomer could be isolated *via* columnchromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) in 47% yield.

Major Diastereomer (*trans*): ^{1}H NMR (500 MHz, DMSO-d$_6$): 10.93 (s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 7.8, 1H), 7.27 (dt, J = 7.8, J = 0.8, 1H), 7.13 (d, J = 8.0, 1H), 7.06 (td, J = 8.1, J = 1.1, 1H), 6.96 (td, J = 7.9 Hz, J = 0.9, 1H), 6.79 (d, J =.8.9 Hz, 2H), 4.87-4.84 (m, 1H), 2.85 (dd, J = 15.3 Hz, J = 4.5 Hz, 1H), 2.21 (dd, J = 15.1, J = 10.5, 1H), 2.13-2.09 (m, 1H), 1.91 (d, J = 13.2 Hz, 1H), 1.67 (dt, J = 13.1 Hz, J = 4.4 Hz , 1H), 1.09 (d, J = 6.5 Hz, 3H) ppm;

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 150.9, 136.4, 133.4, 132.9, 126.2, 121.2, 120.7, 118.2, 117.9, 111.1, 110.9, 95.4, 44.7, 36.7, 29.3, 25.1, 21.6, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{19}N_3Na_1$ [M+Na]+: 324.147117; found: 324.146804

***N*-(4-Nitrophenyl)-3-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine (151):**



Synthesized according to Method A, reaction time was 12 h, Rf = 0.60 (hexane/ ethy acetate 70:30).

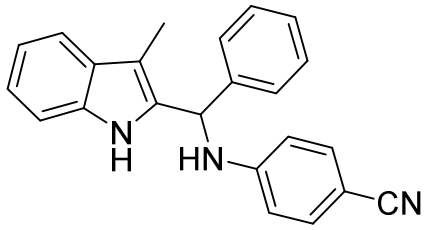
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, yielding a yellow solid as a mixture of diastereomers (trans:cis 91:09) in 67% yield. The ratio of diastereomers was determined by 1H-NMRanalysis of the crude reaction mixture. The major diastereomer could be isolated *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) in 45% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.08 (s, 1H), 8.03 (d J = 9.0 Hz, 2H), 7.91(d, J = 7.7, 1H), 7.48(d, J = 7.8, 1H), 7.35-7.31 (m, 5H), 7.24-7.21 (m, 1H), 7.10 (t, J =.8.1 Hz), 6.90 (t, J =.7.8 Hz), 6.84 (d, J = 9.1, 2H), 5.06-5.05 (m, 1H), 3.28-3.22 (m, 1H), 3.05 (dd, J = 15.4, J = 4.7, 1H), 2.74 (dd, J = 15.4, J = 11.3, 1H), 2.31 (dt, J = 13.0, J = 4.2, 1H), 2.10 (d, J = 13.4, 1H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 153.1, 145.9, 136.4, 135.7, 132.1, 128.4, 127.0, 126.8, 126.3, 126.2, 126.1, 121.5, 118.4, 118.1, 111.1, 111.0, 45.2, 36.34, 35.7, 29.3 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{24}H_{21}N_3O_2Na_1$ $[M+Na]^+$: 406.152595; found: 406.152717

4-((3-methyl-1H-indol-2-yl)(phenyl)methylamino)benzonitrile (153):



Synthesized according to Method B, Rf = 0.45 (hexane/ethy acetate 70:30).

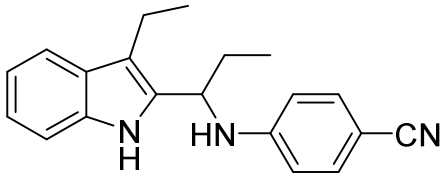
Purification: The crude product was purified *via* column chromatography (aluminium oxide, hexane/ethylacetate 90:10) to afford the desired product as white solid, Yield: 67%;

^{1}H NMR (500 MHz, DMSO-d6): δ 10.74 (s, 1H), 7.46-7.41 (m, 5H), 7.36 (t, J = 7.3 Hz, 2H), 7.32 (d, J = 5.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 8.1 Hz, 2H), 5.93 (d, J = 4.9 Hz, 1H), 2.24 (s, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 151.3, 140.7, 135.4, 134.4, 133.1, 128.6, 128.5, 127.3, 127.2, 120.9, 120.4, 118.2, 117.9, 112.9, 111.1, 106.1, 96.7, 53.8, 8.4 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{21}N_3Na_1$ [M+Na]+: 360.147112; found: 360.147287

4-(1-(3-ethyl-1H-indol-2-yl)propylamino)benzonitrile (154):



Synthesized according to Method B, Rf = 0.45 (hexane/ethy acetate 70:30).

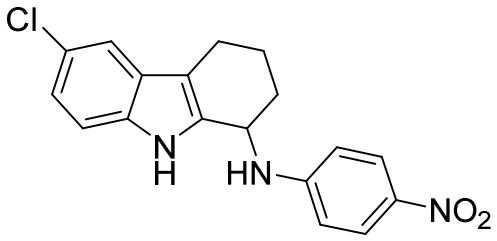
Purification: The crude product was purified *via* column chromatography (florisil, hexane/ethylacetate/triethylamine 90:10) to afford the desired product as white solid, Yield: 60%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.61 (s, 1H), 7.43 (d, J = 8.11 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 6.2 Hz, 1H), 6.6 (d, J = 6.7 Hz, 2H), 4.57 (q, J = 6.8 Hz, 1H), 2.80 (qd, J = 7.3 Hz , J = 3.3 Hz, 2H), 1.98 (s, J = 7.2 Hz, 1H), 1.86 (s, J = 7.2 Hz, 1H), 1.17 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.5, 135.4, 134.7, 133.1, 127.7, 120.5, 118.1, 118.0, 112.7, 112.3, 111.0, 96.0, 51.1., 28.7, 16.9, 15.7, 10.9 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{21}N_3Na_1$ [M+Na]+: 326.162768; found: 326.162661

6-chloro-N-(4-nitrophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (155):



Synthesized according to Method A, Rf = 0.49 (hexane/ethy acetate 70:30).

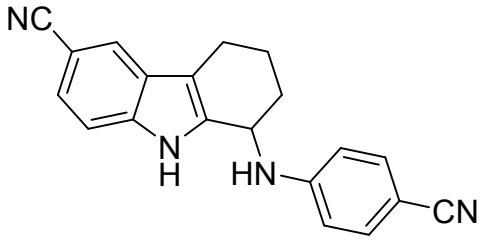
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Yellow solid, Yield: 85%.

1H NMR (500 MHz, DMSO-d_6): δ 11.16 (s, 1H), 8.04 (d, J = 7.5 Hz, 2H), 7.76 (d, J = 6.7 Hz, 1H), 7.41 (s, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 7.5 Hz, 2H), 4.89 (m, 1H), 2.70 (m, 1H), 2.63 (m, 1H), 2.04 (m, 1H), 1.91-1.85 (m, 3H) ppm;

13C NMR (125 MHz, DMSO-d_6): δ 153.6 , 135.7, 135.0, 134.5, 126.6, 126.3, 122.9, 121.1, 117.3, 112.6, 110.7, 45.6, 29.2, 20.4, 19.6 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{18}H_{16}N_3O_2Cl_1Na_1$[M+Na]$^+$: 364.082326; found: 364.082303

1-(4-cyanophenylamino)-2,3,4,9-tetrahydro-1H-carbazole-6-carbonitrile (156):



Synthesized according to Method B, reaction time was 12 h, Rf = 0.43 (hexane/ethy acetate 70:30).

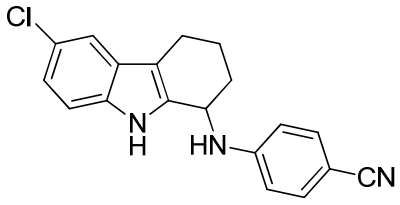
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. White solid, Yield: 50%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.56 (s, 1H), 7.99 (s, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.42 (q, J = 18.6 Hz, J = 8.4 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 4.94-4.92 (m, 1H), 2.76-2.73 (3, 1H), 2.66-2.63 (m, 1H), 2.04-1.99 (m, 1H), 1.91-1.82 (m, 3H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.2 , 137.9, 136.5, 133.5, 126.4, 123.9, 123.7, 120.9, 120.6, 112.3, 111.8, 100.1, 95.8, 45.2, 28.9, 20.3, 19.5 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{20}H_{16}N_4Na_1$ [M+Na]+: 335.126711; found: 335.126902

4-(6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-ylamino)benzonitrile (157):



Synthesized according to Method B, Rf = 0.60 (hexane/ethy acetate 70:30).

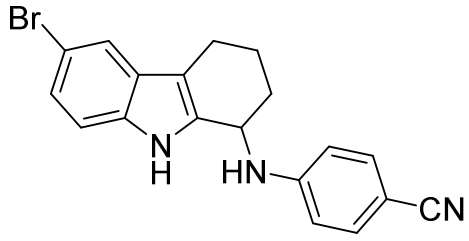
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. White solid, Yield: 88%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.12 (s, 1H), 7.48 (t, J = 8.5 Hz, 3H), 7.30 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.5 Hz, J = 1.8Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 4.90-4.88 (m, 1H), 2.71-2.68 (m, 1H), 2.62-2.58 (m, 1H), 2.03-1.98 (m, 1H), 1.94-1.87 (m, 1H) 1.83-1.81 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.2 , 135.6, 134.5, 133.4, 127.6, 122.8, 120.9, 120.6, 117.2, 112.6, 110.5, 95.6, 45.3, 29.0, 20.4, 19.7 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{19}H_{16}N_3Cl_1O_2Na_1$[M+Na]+: 344.092495; found: 344.092205

4-(6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-ylamino)benzonitrile (158):



Synthesized according to Method A, reaction time was 12 h, rf = 0.44 (EtOAc/Isohexane, 30:70).

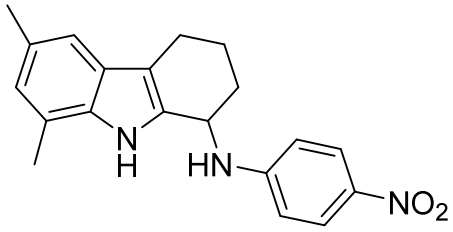
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Off white solid, Yield: 80%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.14 (s, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.16 (t, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.6 Hz, 2H), 4.88-4.90 (m, 1H), 2.68-2.71 (m, 1H), 2.58-2.61 (m, 1H), 1.98-2.03 (m, 1H), 1.89-1.92 (m, 1H), 1.81-1.83 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.2 (q), 135.4.0 (q), 134.7 (q), 133.4 (t), 128.4 (t), 123.5 (t), 120.7 (q), 120.2 (t), 113.0 (t), 110.8 (q), 110.5 (q), 95.7 (q), 45.3 (q), 29.0 (s), 20.4 (s), 19.7 (s) ppm;

HRMS-(EI) (m/z): M+ calcd for $C_{19}H_{16}Br_1N_3Na_1$, 388.041988; found 388.041996.

6,8-dimethyl-*N*-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-amine (159):



Synthesized according to Method A, R_f = 0.63 (hexane/ethy acetate 70:30).

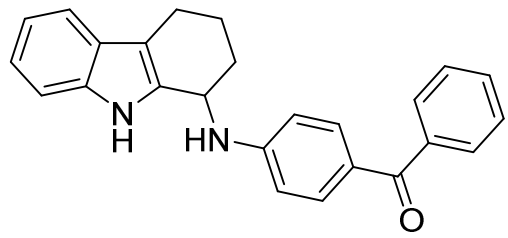
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate. Yellow solid, Yield: 86%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.52 (s, 1H), 4.91-4.90 (m, 1H), 3.00 (d, J = 15.8 Hz, 1H), 2.89-2.85 (m, 1H), 2.54 (s, 3H), 2.31 (s, 3H), 1.97-1.83 (m, 4H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 153.5, 136.6, 135.5, 131.5, 129.9, 129.1, 126.3, 123.3, 121.3, 111.0, 108.8, 45.6, 28.6, 23.1, 21.3, 19.8, 19.5, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{20}H_{21}N_3O_2Na_1$ $[M+Na]^+$: 358.152592; found: 358.152310

Phenyl (4-(2,3,4,9-tetrahydro-1H-carbazol-1-ylamino)phenyl)methanone (160):



Synthesized according to Method A, Rf = 0.62 (hexane/ethy acetate 70:30).

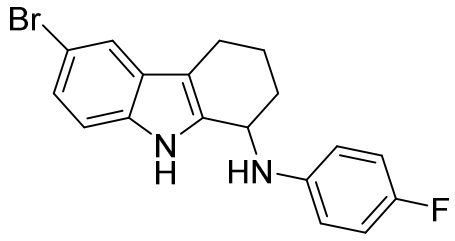
Purification: Over the course of the reaction, the precipitation of a large proportion of the desired coupling product was observed. The complete precipitation could be achieved by using a mixture of hexane/ethyl acetate, white solid, Yield: 70%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.91 (s, 1H), 7.64-7.58 (m, 5H), 7.53 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1 H), 7.18 (d, J= 8.3 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 4.93-4.92 (m, 1H), 2.76-2.71 (m, 1H), 2.65-2.61 (m, 1H), 2.05-1.84 (m, 4H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 193.3, 152.0, 139.0, 136.1, 133.6, 132.5, 131.1, 128.8, 128.2, 126.5, 123.7, 121.0, 118.2, 117.9, 111.1, 110.5, 45.5, 29.2, 20.7, 19.7, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{25}H_{22}N_2Na_1O_1$ $[M+Na]^+$: 389.162429; found: 389.162734

6-bromo-N-(4-fluorophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (161):



Synthesized according to Method B, reaction time was 12 h, Rf = 0.78 (hexane/ethy acetate 70:30).

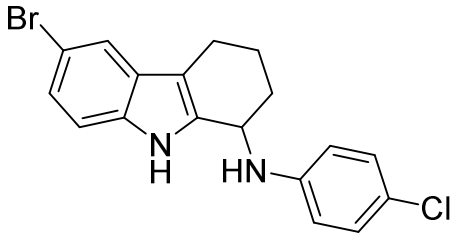
Purification: The crude product was purified *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as white solid, Yield: 55%;

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.09 (s, 1H), 7.58 (d, J = 1.7 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.14 (dd, J = 8.5 Hz, J = 1.8 Hz , 1H), 6.94 (t, J = 9.8 Hz, J = 8.9 Hz, 2H), 6.72 (dd, J = 4.59 Hz, J = 8.9 Hz, 2H), 5.91 (d, J = 8.8 Hz, 1H), 4.75-4.74 (m, 1H), 2.69-2.65 (m, 1H), 2.61-2.57 (m, 1H), 2.00-1.91 (m, 2H), 1.79-1.77 (m, 3H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 155.1, 153.3, 144.4, 136.7, 134.7, 128.5, 123.2, 120.1, 115.3, 115.2, 113.5., 113.4, 113.0, 110.6, 110.0, 46.4, 28.8, 20.5, 19.8 ppm;

HR-MS EI (ESIneg) m/z: M-H calcd. for $C_{18}H_{15}N_2F_1Br_1$ $[M-H]^-$: 357.040826; found: 357.040930.

6-bromo-N-(4-chlorophenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (162):



Synthesized according to Method B, reaction time was 12 h, Rf = 0.78 (hexane/ethy acetate 70:30).

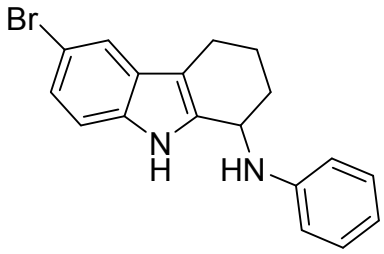
Purification: The crude product was purified *via* column chromatography (Aluminium oxide, hexane/ethylacetate 90:5) to afford the desired product as white solid, Yield: 70%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.15 (dd, J = 8.5 Hz, J = 1.9 Hz , 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.9 Hz, 2H), 6.23 (d, J = 8.8 Hz, 1H), 4.77-4.75 (m, 1H), 2.69-2.66 (m, 1H), 2.62-2.57 (m, 1H), 1.99-1.91 (m, 2H), 1.81-1.78 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 146.7, 136.3, 134.7, 128.6, 128.4, 123.2, 120.1, 118.9, 113.9, 113.0, 110.7, 110.1, 45.9, 28.8, 20.5, 19.8, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{16}Br_1Cl_1N_2$ $[M]^+$: 374.018554; found: 374.018317

6-bromo-N-phenyl-2,3,4,9-tetrahydro-1H-carbazol-1-amine (163):



Synthesized according to Method B, reaction time was 12 h, Rf = 0.79 (hexane/ethy acetate 70:30).

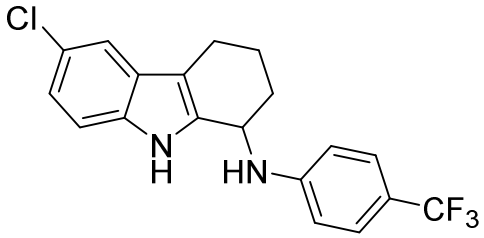
Purification: The crude product was purified *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as white solid, Yield: 60%

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.10 (s, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.26 (d, J=8.56 Hz, 1 H), 7.15 (dd, J= 8.51 Hz , J=1.90 Hz, 1 H), 7.10 (t, J = 7.4 Hz, 2H), 6.73 (d, J = 7.9 Hz, 2H), 6.56 (t, J = 7.3 Hz, 1H), 5.97 (d, J = 8.9 Hz, 1H), 4.79-4.77 (m, 1H), 2.70-2.66 (m, 1H), 2.62-2.57 (m, 1H), 2.02-1.93 (m, 2H), 1.85-1.77 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 147.8, 136.8, 134.7, 128.5, 123.1, 120.1, 115.8, 113.0, 112.6, 110.6, 110.0, 45.9, 28.9, 20.5, 19.9, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{17}Br_1N_2Na_1$ [M+Na]+: 363.046740; found: 363.046458

6-chloro-N-(4-(trifluoromethyl)phenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (164):



Synthesized according to Method B, Rf = 0.78 (hexane/ethy acetate 70:30).

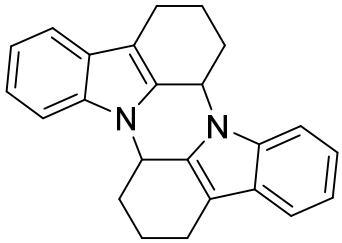
Purification: The crude product was purified *via* column chromatography (silica gel, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as white solid, Yield: 68%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (s, 1H), 7.46 (d, J = 1.9 Hz, 2H), 7.40 (d, J = 8.5 Hz, 1H),7.31 (d, J = 8.5 Hz, 1H), 7.05 (dd, J = 8.5 Hz, J = 2.0 Hz , 1H), 6.83 (t, J = 8.2 Hz, 3H), 4.88-4.86 (m, 1H), 2.71-2.67 (m, 1H), 2.63-2.61 (m, 1H), 2.02-1.99 (m, 1H), 1.94-1.92 (m, 1H), 1.85-1.81 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 150.7, 136.0, 134.5, 127.7, 126.3, 126.2, 125.2 (quatret), 122.8, 120.8, 117.2, 115.1 (quatret), 112.6, 111.7, 110.4, 45.5, 28.9, 20.5, 19.7, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{19}H_{16}Cl_1F_3N_2Na_1$ $[M+Na]^+$: 387.084631; found: 387.084784

1,2,3,8a,9,10,11,16a-octahydrodiindolo[3,2,1-de:3',2',1'-kl]phenazine



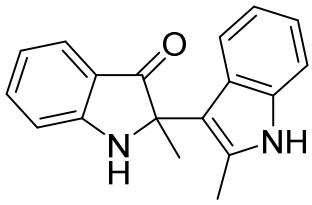
To a solution of carbazole alcohol in methanol was added 20 mol% TFA. The reaction mixture was then allowed to stir at room temperature for 2h. The precipitated solid was then filtered to give the desired dimer in 20% yield.

^{1}H NMR (500 MHz, $CDCl_3$-d1): δ 7.69 (d, J =.8.0 Hz, 1H), 7.54 (d, J =.7.2 Hz, 1H), 7.24-7.18 (m, 2H), 4.95-4.93 (m, 1H), 3.24-3.21 (m, 1H), 2.93-2.81 (m, 2H), 2.36-2.32 (m, 1H), 2.16-2.07 (m, 2H), ppm;

^{13}C NMR (125 MHz, $CDCl_3$-d1): δ 140.4, 134.3, 130.1, 121.9, 120.6, 118.7, 112.3, 111.5, 53.7, 31.3, 21.6, 20.1, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{24}H_{22}N_2Na_1$ [M+Na]+: 361.167516; found: 361.167750

2-methyl-2-(2-methyl-1H-indol-3-yl)indolin-3-one (167)



The product was observed in 4-35% yield during different optimization reactions.

Rf = 0.20 (hexane/ethy acetate 70:30).

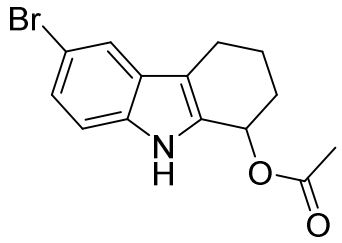
Purification: The crude product was purified recrystallization Yield: 4-35%

^{1}H NMR (500 MHz, DMSO-d6): δ 10.89 (s, 1H), 7.73 (s, 1H), 7.51-7.45 (m, 2H, 7.23 (dd, J = 10.9 Hz, 2H), 6.93 (t, J =.7.4 Hz, 1H), 6.88 (d, J =.8.2 Hz, 1H), 6.79 (t, J =.7.5 Hz, 1H), 6.72 (t, J =.7.2 Hz, 1H), 2.40 (s, 3H), 1.74 (s, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 203.9, 159.9, 137.4, 134.7, 133.0, 127.1, 124.4, 120.0, 118.3, 117.7, 116.9, 111.7, 110.4, 108.4, 66.2, 24.3, 13.9 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{16}N_2O_1$ [M]+: 276.126263; found: 276.126003

6-bromo-2,3,4,9-tetrahydro-1H-carbazol-1-yl acetate (172)



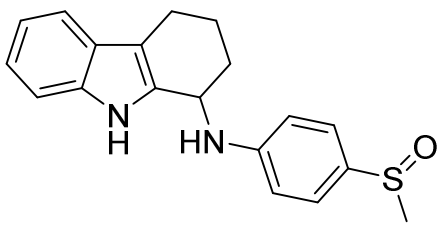
The bromohydroperoxide (0.49 mmol, 137.7 mg) was dissolved in 1:1 mixture of DMSO and acetic acid (1mL+1mL) and reaction mixture was allowed to stir for 25h at room temperature. The solvent was then evaporated under reduced pressure and the crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as yellow solid, Yield: 40%; Rf = 0.60 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d6): δ 10.98 (s, 1H), 7.62 (s, 1H), 7.30 (d, J = 8.6, 1H), 7.19 (dd, J =.7.7 Hz, J =.1.5 Hz), 5.93 (dd, J =.4.1 Hz, 1H), 2.58-2.53 (m, 1H), 2.05 (s, 3H), 2.03-1.92 (m, 2H), 1.85-1.84 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 170.2, 134.8, 132.7, 127.8, 124.2, 120.7, 113.5, 112.2, 110.9, 64.8, 29.1, 21.0, 20.1, 19.1 ppm;

HR-MS (EI(DE)) m/z: M^+ calcd. for $C_{14}H_{14}N_1O_2Br_1$ $[M+Na]^+$: 307.020806; found: 307.021103

N-(4-(methylsulfinyl)phenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (158)



The hydroperoxide (0.49 mmol, 1.0 equiv.) was dissolved in methanol (10 ml). To this reaction mixture was added the 4-methyl thioaniline (0.49 mmol, 1.0 equiv. 60,96 µL) followed by the addition of TFA (7.5 µL, 0.098 mmol, 0.2 equiv.). After 15 h, the solvent was reduced to dryness and the resulting solid was purified by

recrystallization.

Rf = 0. 15 (hexane/ethy acetate 70:30).

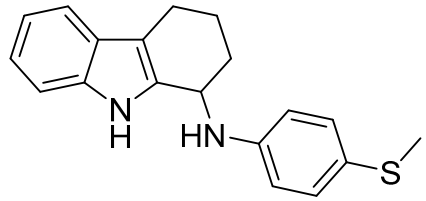
Purification: The crude product was purified recrystallized to afford the desired product as white solid, Yield: 58%;

^{1}H NMR (500 MHz, DMSO-d6): 10.87 (s, 1H), 7.42 (d, J = 8.3, 3H), 7.29 (d, J = 8.0, 1H), 7.04 (t, J =.7.4 Hz), 6.96 (t, J =.7.3 Hz), 6.86 (d, J = 8.4, 2H), 6.67 (d, J = 8.2, 1H), 4.86-4.84 (m, 1H), 2.73-2.70 (m, 1H), 2.64-2.60 (m, 4H), 2.0-1.81 (m, 4H) ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 172.0, 150.2, 136.0, 134.1, 130.5, 126.5, 125.5, 121.0, 118.1, 117.8, 112.2, 111.1, 110.3, 45.6, 43.0, 29.0, 20.7, 19.7, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{19}H_{20}N_2O_1S_1Na_1$ [M+Na]+: 347.118854; found: 347.118820

N-(4-(methylthio)phenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (177)



Synthesized accoerding to general Method D. 5.0 equivalent of 4-methyl thioaniline was used as nucleophile.

Rf = 0.60 (hexane/ethy acetate 70:30).

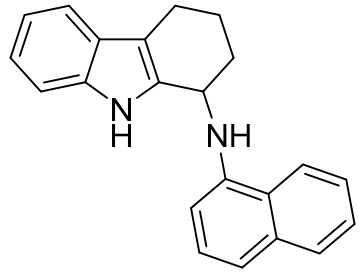
Purification: The crude product was purified recrystallized to afford the desired product as white solid, Yield: 74

^{1}H NMR (500 MHz, DMSO-d6): 10.87 (s, 1H), 7.42 (d, J = 8.3, 3H), 7.29 (d, J = 8.0, 1H), 7.04 (t, J =.7.4 Hz), 6.96 (t, J =.7.3 Hz), 6.86 (d, J = 8.4, 2H), 6.67 (d, J = 8.2, 1H), 4.86-4.84 (m, 1H), 2.73-2.70 (m, 1H), 2.64-2.60 (m, 4H), 2.0-1.81 (m, 4H) ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 172.0, 150.2, 136.0, 134.1, 130.5, 126.5, 125.5, 121.0, 118.1, 117.8, 112.2, 111.1, 110.3, 45.6, 43.0, 29.0, 20.7, 19.7, ppm;

HR-MS (EI(DE)) m/z: M+ calcd. for $C_{19}H_{20}N_2S_1$ [M]+: 308.134719; found: 308.134535

N-(naphthalen-1-yl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (173)



Synthesized accoerding to general Method D. 5.0 equivalent of naphthalen-1-amine was used as nucleophile.

Rf = 0.60 (hexane/ethy acetate 70:30).

Purification: The crude product was purified *via* column chromatography (Alox,

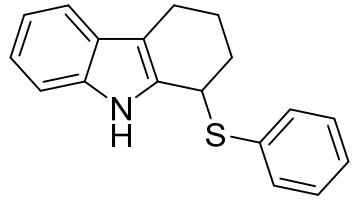
Iso hexane/ethylacetate/Et3N 89:10:1) to afford the desired product as white solid, Yield: 57%;

^{1}H NMR (500 MHz, DMSO-d_6): 10.81 (s, 1H), 8.27 (d, J = 8.5, 1H), 7.76 (d, J = 7.7, 1H), 7.45-7.41 (m, 2H), 7.35-7.29 (m, 3H), 7.14 (d, J =.8.1 Hz, 1H), 7.06-7.02 (m, 1H), 6.98-6.95 (m, 1H), 6.79 (d, J =.7.6 Hz, 1H), 6.28 (d, J =.8.3 Hz, 1H), 5.05-5.02 (m, 1H), 2.78-2.65 (m, 2H), 2.15-2.00 (m, 3H), 1.88-1.82 (m, 1H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 143.1, 136.1, 135.0, 134.2, 127.8, 126.8, 125.5, 123.8, 123.3, 122.2, 120.7, 118.0, 117.7, 115.5, 111.2, 110.2, 103.7, 46.7, 28.7, 20.8, 20.5,ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{22}H_{20}N_2Na_1$ [M+Na]+: 335.151868; found: 335.151555

1-(phenylthio)-2,3,4,9-tetrahydro-1H-carbazole (171)



Synthesized accoerding to general Method D. 1.0 equivalent of benzenethiol was used as nucleophile.

Rf = 0.70 (hexane/ethy acetate 70:30).

Purification: The crude product was purified *via* column chromatography (Alox,

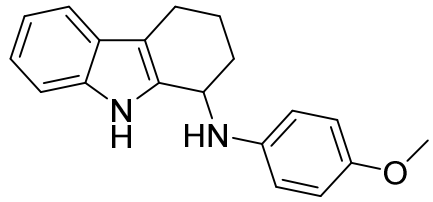
Iso hexane/ethylacetate/Et_3N 89:10:1) to afford the desired product as white solid, Yield: 65%

^{1}H NMR (500 MHz, DMSO-d_6): 10.94 (s, 1H), 7.50-7.46 (m, 2H), 7.40-7.25 (m, 5H), 7.10-7.04 (m, 1H), 6.99-6.93 (m, 1H), 4.74-4.72 (m, 1H), 2.69 (dt, J =.16.1 Hz, J =.4.4 Hz, 1H), 2.60 (dd, J =.8.0 Hz, J =.5.7 Hz, 1H), 2.15-1.92 (m, 3H), 2.15-1.92 (m, 3H), 1.84-1.79 (m, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 136.1, 135.2, 132.0, 130.7, 129.1, 126.7, 126.4, 121.3, .118.2, 117.8, 111.1, 111.0, 41.6, 29.6, 20.4, 19.3, ppm;

HR-MS (EI(DE)) m/z: M+ calcd. for $C_{18}H_{17}N_1S_1$ [M]+: 279.108171; found: 279.108209

N-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1H-carbazol-1-amine (169)



Synthesized accoerding to general Method D. 5.0 equivalent of 4-methoxy aniline was used as nucleophile.

Rf = 0.60 (hexane/ethy acetate 70:30).

Purification: The crude product was purified *via* column chromatography (Alox,

hexane/ethylacetate/Et_3N 79:20:1) followed by recrystallization using a mixture of MTBE and pentane at -40 °C to afford the desired product as white solid, Yield:

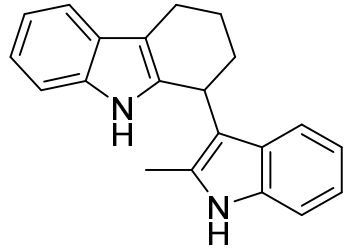
44%

^{1}H NMR (500 MHz, DMSO-d_6): 10.83 (s, 1H), 7.40 (d, J =.7.6 Hz, 1H), 7.29 (d, J =.7.9 Hz, 1H), 7.04-7.01 (m, 1H), 6.96-6.93 (m, 1H), 6.75-6.69 (m, 4H), 5.45 (d, J =.9.3 Hz, 1H), 4.70-4.68 (m, 1H), 3.65 (s, 3H), 2.72-2.67 (m, 1H), 2.63-2.59 (m, 1H), 1.97-1.93 (m, 2H), 1.84-1.75 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 150.7, 142.0, 136.0, 135.2, 126.6, 120.7, 118.0, 117.7, 114.6, 113.9, 111.1, 110.0, 55.2, 46.8, 28.9, 20.8, 19.9, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for C19H20N2O1Na1 [M+Na]+: 315.146784; found: 315.146547

1-(2-methyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1H-carbazole (166)



Synthesized accoerding to general Method C.

Rf = 0.50 (hexane/ethy acetate 70:30).

Purification: The crude product was purified *via* column chromatography (Alox,

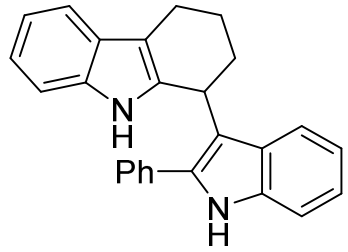
hexane/ethylacetate/Et_3N 79:20:1) to afford the desired product as white solid, Yield: 91%;

^{1}H NMR (500 MHz, DMSO-d_6): 10.80 (s, 1H), 10.26 (s, 1H), 7.43-7.41 (3, 1H), 7.25 (d, J =.8.1 Hz, 1H), 7.16-7.14 (m, 1H), 6.96-6.85 (m, 4H), 6.71 (t, , J =.7.1 Hz, 1H), 4.41-4.39 (m, 1H), 2.81-2.79 (m, 2H), 2.63 (s, 3H), 2.15-1.95 (m, 3H), 1.86-1.82 (m, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 137.0, 135.9, 135.2, 132.0, 127.4, 127.0, 119.9, 119.6, 117.9, 117.8, 117:7; 117:3; 112:0; 110:8; 110:3; 108:4; 32:0; 31.4; 22.8; 21.0; 11.3, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{21}H_{20}N_2Na_1$ $[M+Na]^+$: 323.151864; found: 323.151734

1-(2-phenyl-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-carbazole (168)



Synthesized accoerding to general Method C.

Rf = 0.40 (hexane/ethy acetate 70:30).

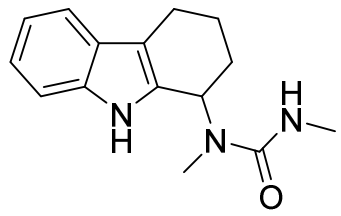
Purification: The crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/Et_3N 79:20:1) to afford the desired product as white solid, Yield: 79%;

^{1}H NMR (500 MHz, DMSO-d_6): 11.27 (s, 1H), 10.24 (s, 1H), 7.68 (d, J =.7.7 Hz, 2H), 7.54 (t, J =.7.8 Hz, 2H), 7.43-7.40 (m, 2H), 7.36-7.34 (m, 1H), 7.11-7.09 (m, 1H), 7.00-6.97 (m, 1H), 6.94-6.90 (m, 2H), 6.81 (d, J =.7.7 Hz, 1H), 6.70 (t, J =.7.2 Hz, 1H), 4.85 (t, J =.7.2 Hz, 1H), 2.85-2.77 (m, 2H), 2.19-2.09 (m, 3H), 1.81-1.77 (m, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 137.0, 136.3, 136.0, 135.6, 132.9, 128.7, 128.6, 127.6, 127.1, 127.0, 121.0, 119.9, 119.4, 118.4, 117.8, 117.3 113.0, 111.2, 110.8, 108.3, 32.2, 32.1, 23.3, 20.9, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{26}H_{22}N_2Na_1$ [M+Na]+: 385.167516; found: 385.167520

1,3-dimethyl-1-(2,3,4,9-tetrahydro-1H-carbazol-1-yl)urea (170)



Synthesized accoerding to general Method D. 5.0 equivalent of 1,3 dimethyl urea was used as nucleophile.

Rf = 0.10 (hexane/ethy acetate 50:50).

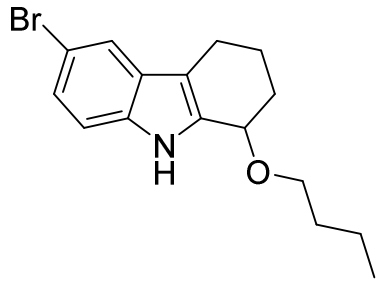
Purification: The crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/Et_3N 79:20:1) followed by washing with water (3 x 5 mL) to afford the desired product as white solid, Yield: 65%;

^{1}H NMR (500 MHz, DMSO-d_6): 10.71 (s, 1H), 7.36 (d, J =.7.8 Hz, 1H), 7.25 (d, J =.7.9 Hz, 1H), 7.00 (d, J =.7.5 Hz, 1H), 6.93 (d, J =.7.4 Hz, 1H), 6.35 (d, J =.4.3 Hz, 1H), 5.53-5.51 (m, 1H), 2.67-2.57 (m, 5H), 2.00-1.98 (m, 1H), 1.91-1.87 (m, 1H), 1.77-1.66 (m, 2H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 158.4, 136.2, 133.5, 126.8, 120.6, 118.1, 117.6, 111.6, 111.0, 49.5, 29.2, 27.8, 27.3, 22.3, 20.4, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{15}H_{19}N_3O_1Na_1$ $[M+Na]^+$: 280.142034; found: 280.141866

6-bromo-1-butoxy-2,3,4,9-tetrahydro-1H-carbazole (174)



The bromohydroperoxide (0.49 mmol, 137.7 mg) was dissolved in 1:1 mixture of DMSO and n-butanol (1mL+1mL) followed the addition of 10 mol% PTSA. The reaction mixture was allowed to stir for 15h at room temperature. The solvent was then evaporated under reduced pressure and the crude product was purified *via* column chromatography (Alox, hexane/ethylacetate/triethylamine 90:5:5) to afford the desired product as yellow solid, Yield: 54%; Rf = 0.60 (hexane/ethy acetate 70:30).

Rf = 0.80 (hexane/ethy acetate 70:30).

^{1}H NMR (500 MHz, DMSO-d_6): 11.01 (s, 1H), 7.57 (d, J =.1.8 Hz, 1H), 7.28 (d, J =.8.5 Hz, 1H), 7.00 (dd, J =.8.6 Hz, J =.1.9 Hz, 1H), 4.52-4.51 (m, 1H), 3.62-3.58 (m, 1H), 3.56-3.52 (m, 1H), 2.68-2.64 (m, 1H), 1.92-1.86 (m, 3H), 1.76-1.72 (m, 1H), 1.55-1.50 (m, 2H), 1.39-1.32 (sextet, J =.7.5 Hz , 2H), 0.89 (t, J =.7.4 Hz , 3H), ppm;

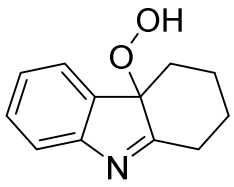
^{13}C NMR (125 MHz, DMSO-d_6): δ 135.8, 134.9, 128.1, 123.5, 120.4, 113.1, 110.7, 110.2, 69.8, 67.7, 31.8, 28.7, 20.3, 19.2, 18.9, 13.8, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{16}H_{20}N_1O_1Br_1$ $[M]^+$: 321.072838; found: 321.072548

8.4.8 Synthesis and characterization of hydroperoxides

Low solubility and stability (in acidic and basic solvents) are the main problems associated with these hydroperoxides. DMSO was found to be a suitable solvent for the measurement of NMR spectra. However, in DMSO these hydroperoxides are reduced to the corresponding alcohol (see above). Therefore, it was not possible to measure clean carbon spectra for some of these compounds.

4a-hydroperoxy-2,3,4,4a-tetrahydro-1H-carbazole (59)



Synthesized according to the general procedure for the synthesis of hydroperoxides.

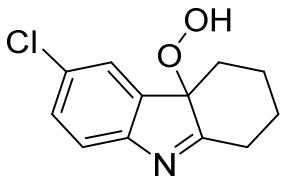
Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d6): *δ* 11.66 (s, 1H), 7.42 (dd, *J* = 10.2 Hz *, J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.4 Hz , 1H), 2.71-2.68 (m, 2H), 2.50-2.47 (m, 1H), 2.13(d, *J* = 13.5 Hz, 1H), 1.76 (ddt, *J* = 27.0 Hz, *J* = 13.5 Hz, *J* = 3.5 Hz, 1H), 1.55 (d, *J* = 13.4 Hz, 1H), 1.39-1.29 (m, 1H), 1.17 (dt, *J* = 14.2 Hz, *J* = 4.1 Hz, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d6): *δ* 184.1, 153.9, 138.9, 129.1, 125.0, 122.7, 119.7, 91.1, 35.3, 29.2, 27.9, 20.3, ppm;

HR-MS EI (DE) m/z: M^+ calcd. for $C_{12}H_{13}N_1O_2[M]^+$: 203.094626; found: 203.094831

6-chloro-4a-hydroperoxy-2,3,4,4a-tetrahydro-1H-carbazole



Synthesized according to the general procedure for the synthesis of hydroperoxides.

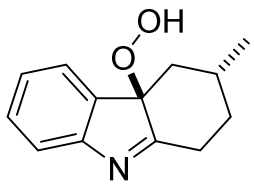
Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d6): *δ* 11.80 (s, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.43-7.40 (m, 2H), 2.71-2.69 (m, 2H), 2.50-2.49 (m, 1H), 2.13(d, *J* = 12.0 Hz, 1H), 1.74 (qt, *J* = 13.5 Hz, *J* = 3.5 Hz, 1H), 1.55 (d, *J* = 13.4 Hz, 1H), 1.39-1.30 (m, 1H), 1.20 (dt, *J* = 14.2 Hz, *J* = 4.1 Hz, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d6): *δ* 185.2, 152.7, 141.1, 129.8, 129.0, 123.2, 121.0, 91.4, 35.1, 29.3, 27.9, 20.2 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{12}H_{12}N_1O_2Cl_1Na_1$ $[M+Na]^+$: 260.044876; found: 260.044990

4a-hydroperoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole (180)



Synthesized according to the general procedure for the synthesis of hydroperoxides.

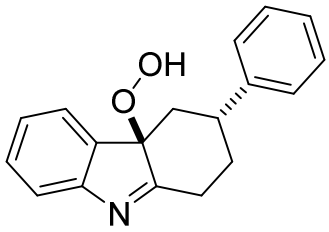
Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d_6): *δ* 11.77 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.34 (dt, , *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 2.76 (dt, , *J* = 13.2 Hz, *J* = 5.4 Hz 1H), 2.65-2.62 (m, 1H), 2.41(d, *J* = 14.4 Hz, 1H), 2.08-2.06 (m, 2H), 1.09 (dq, *J* = 13.4 Hz, *J* = 4.1 Hz, 1H), 0.94 (d, *J* = 14.4 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): *δ* 184.3, 154.0, 138.8, 129.1, 125.1, 122.6, 119.7, 91.2, 42.9, 36.1, 28.5, 26.9, 20.4, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{13}H_{15}N_1O_2Na_1$ $[M+Na]^+$: 240.099500; found: 240.099752

4a-hydroperoxy-3-phenyl-2,3,4,4a-tetrahydro-1*H*-carbazole (181)



Synthesized according to the general procedure for the synthesis of hydroperoxides.

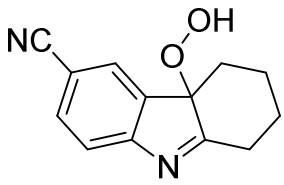
Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.77 (s, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.34 (dt, , J = 7.5 Hz, J = 1.0 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 2.76 (dt, , J = 13.2 Hz, J = 5.4 Hz 1H), 2.65-2.62 (m, 1H), 2.41(d, J = 14.4 Hz, 1H), 2.08-2.06 (m, 2H), 1.09 (dq, J = 13.4 Hz, J = 4.1 Hz, 1H), 0.94 (d, J = 14.4 Hz, 1H), 0.89 (d, J = 6.5 Hz, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 183.3, 154.1, 144.0, 138.5, 139.3, 128.4, 127.0, 126.3, 125.2, 122.9, 119.8, 91.1, 41.4, 38.1, 35.5, 28.9, ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{18}H_{17}N_1O_2Na_1$ [M+Na]+: 302.115151; found: 302.115128

4a-hydroperoxy-2,3,4,4a-tetrahydro-1H-carbazole-6-carbonitrile



Synthesized according to the general procedure for the synthesis of hydroperoxides, but using a 500 watt halogen lamp at -40°C.

Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.88 (s, 1H), 7.1 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 2.77-2.74 (m, 2H), 2.53-2.52 (m, 1H), 2.16 (d, J = 11.9 Hz, 1H), 1.75 (q, J = 10.2 Hz, 1H), 1.57 (d, J = 13.0 Hz, 1H), 1.41-1.32 (m, 1H), 1.20 (dt, J = 14.2 Hz, J = 4.0 Hz, 1H), ppm;

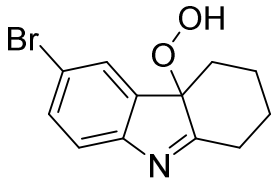
^{13}C NMR (125 MHz, DMSO-d_6): δ 188.9, 157.6 140.0, 134.6, 126.5, 120.8, 119.1, 107.5, 93.3, 29.5, 27.9, 20.1 ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{13}H_{12}N_2O_2Na_1$ [M+Na]+: 251.07097; found: 251.079211

6-bromo-4a-hydroperoxy-2,3,4,4a-tetrahydro-1*H*-carbazole

Synthesized according to the general procedure for the synthesis of hydroperoxides.

Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.



^{1}H NMR (500 MHz, DMSO-d_6): δ 11.78 (s, 1H), 7.41 (dd, J = 8.1 Hz, J = 4.5 Hz , 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.16 (t, J = 9.0 Hz, 1H), 2.70-2.67 (m, 2H), 2.50-2.46 (m, 1H), 2.12 (d, J = 12.2 Hz, 1H), 1.74 (q, J = 13.5 Hz, 1H), 1.56 (d, J = 13.2 Hz, 1H), 1.38-1.30 (m, 1H), 1.20 (dt, J = 14.2 Hz, J = 4.0 Hz, 1H), ppm;

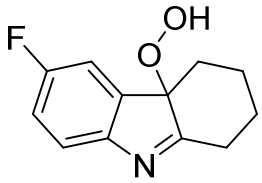
^{13}C NMR (125 MHz, DMSO-d_6): δ 184.5, 184.4, 161.3, 159.4, 150.0, 141.1, 141.0, 120.6, 120.5, 115.4, 115.2, 110.9, 110.6, 91.4, 35.1, 29.2, 27.9, 20.2, ppm;

HR-MS (ESIpos) m/z: M^+ calcd. for $C_{12}H_{12}Br_1N_1O_2Na_1$ $[M+Na]^+$: 303.994376; found: 303.994445

6-fluoro-4a-hydroperoxy-2,3,4,4a-tetrahydro-1*H*-carbazole:

Synthesized according to the general procedure for the synthesis of hydroperoxides.

Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

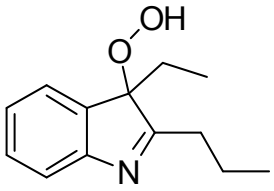


^{1}H NMR (500 MHz, DMSO-d_6): δ 11.81 (s, 1H), 7.61 (s , 1H), 7.54 (d, J = 8.10 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 2.69 (dd, J = 8.7 Hz, J = 3.7 Hz, 2H), 2.50-2.48 (m, 1H), 2.12 (d, J = 12.3 Hz, 1H), 1.74 (q, J = 13.5 Hz, 1H), 1.55 (d, J = 13.1 Hz, 1H), 1.36-1.32 (m, 1H), 1.21 (dt, J = 14.2 Hz, J = 3.8 Hz, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 185.0, 153.0, 141.4, 131.9, 125.9, 121.5, 118.1, 91.4, 35.1, 29.2, 27.8, 20.2, ppm;

HR-MS EI(DE) m/z: M+ calcd. for $C_{12}H_{12}F_1N_1O_2$ [M]: 221.08507; found: 221.085092

3-ethyl-3-hydroperoxy-2-propyl-3*H*-indole:



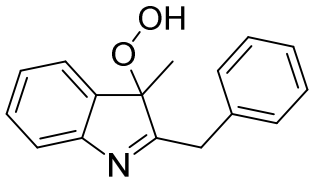
Synthesized according to the general procedure for the synthesis of hydroperoxides but using a 500 watt halogen lamp at -40°C.

Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.60 (s, 1H), 7.38-7.35 (m, 2H), 7.33 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.20 (td, J = 7.3 Hz, J = 0.90 Hz, 1H), 2.60 (dt, J = 17.9 Hz, J = 7.3 Hz, 1H), 2.40 (dt, J = 18.0 Hz, J = 7.4 Hz, 1H), 1.94-1.89 (m, 1H), 1.80-1.70 (m, 3H), ppm;

HR-MS (CI(DE)) m/z: M+ calcd. for $C_{16}H_{15}N_1O_2Na_1$ [M+H]+: 220.133752; found: 220.133523

Synthesis of 2-benzyl-3-hydroperoxy-3-methyl-3*H*-indole:



Synthesized according to the general procedure for the synthesis of hydroperoxides but using 500 watt halogen lamp at -40°C.

Purification: The crude product was purified by simple filtration as pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d6): δ 11.81 (s, 1H), 7.42 (d, J = 7.1 Hz, 1H), 7.36-7.30 (m, 6H), 7.26-7.19 (m, 2H), 3.94 (q, J = 16.0 Hz, 2H), 3.04 (s, 3H), ppm;

^{13}C NMR (125 MHz, DMSO-d6): δ 184.7, 153.2, 138.6, 136.6, 129.7, 129.3, 128.1, 126.3, 125.5, 122.5, 119.8, 92.7, 34.4, 19.0 ppm;

HR-MS (ESIpos) m/z: M+ calcd. for $C_{16}H_{15}N_1O_2Na_1$ [M+Na]+: 276.099501; found: 276.099676

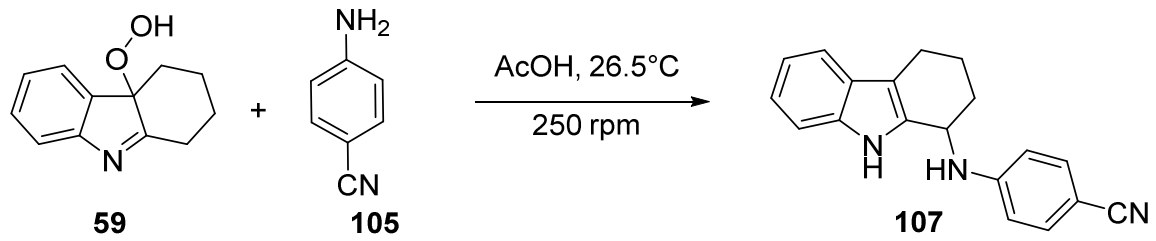
8.5 Mechanistic studies on the C–H functionalization of tetrahydrocarbazole *via* photochemically generated hydroperoxides

8.5.1 Determination of the order of reaction

In order to find the order of reaction with respect to nucleophile (*p*-cyanoaniline, **105**) and electrophile (carbazole hydroperoxide, **59**), different reactions were performed by varying the concentration of both substrates one by one. For determining the order of reaction with respect to peroxide **59**, the concentration of aniline **105** was kept constant (0.05 M) and the concentration of peroxide **59** was varied (0.05M, 0.08 M, and 0.10 M). For determining the order of reaction with respect to aniline **105**, the concentration of peroxide **59** was kept constant (0.05 M) and the concentration of aniline **105** was varied (0.07 M, 0.10 M, and 0.14 M). For each concentration of nucleophile **105** and electrophile **59**, the progress of the reaction was checked at different time intervals.

Due to the precipitation of coupling product **107**, a separate reaction was performed for measuring the concentration of coupling product **107** at each specific time interval. At the end of reaction, the reaction mixture was diluted with 50 mL ethyl acetate. An aliquot (5 mL) of this homogenous mixture was taken and added to a cooled (- 25°C) aqueous saturated solution of NaOH. The solvent was then evaporated and yield of the coupling product **107** was determined by ^{1}H NMR based upon the conversion of aniline **105**. Using this yield of product **107** at different intervals, concentration of the coupling product **107** was calculated. Concentration of coupling product = [Initial concentration of limiting substrate]/100x coupling product **107** (%) at specific time interval). A representative example is given below.

Table 73: Concentration of 107 at different intervals



59 **105** **107**

Entry	Time	107(%)	[107] mol/L
1	0	0	0
2	20	17.0	0,0083
3	40	39.4	0,0193
4	80	60.2	0,0296
5	120	70.0	0,0343
6	160	77.4	0,0380

[a]: Reaction progress profile of increase in concentration of product **107** with time using 0.049 M peroxide **59** and 0.049 M aniline **105**. The concentration of coupling product was measured by ^{1}H NMR at regular intervals at 26.5 °C and at 275 rpm speed of stirrer.

Then a graph was plotted between time (x-axis) and concentration of coupling product (y-axis).

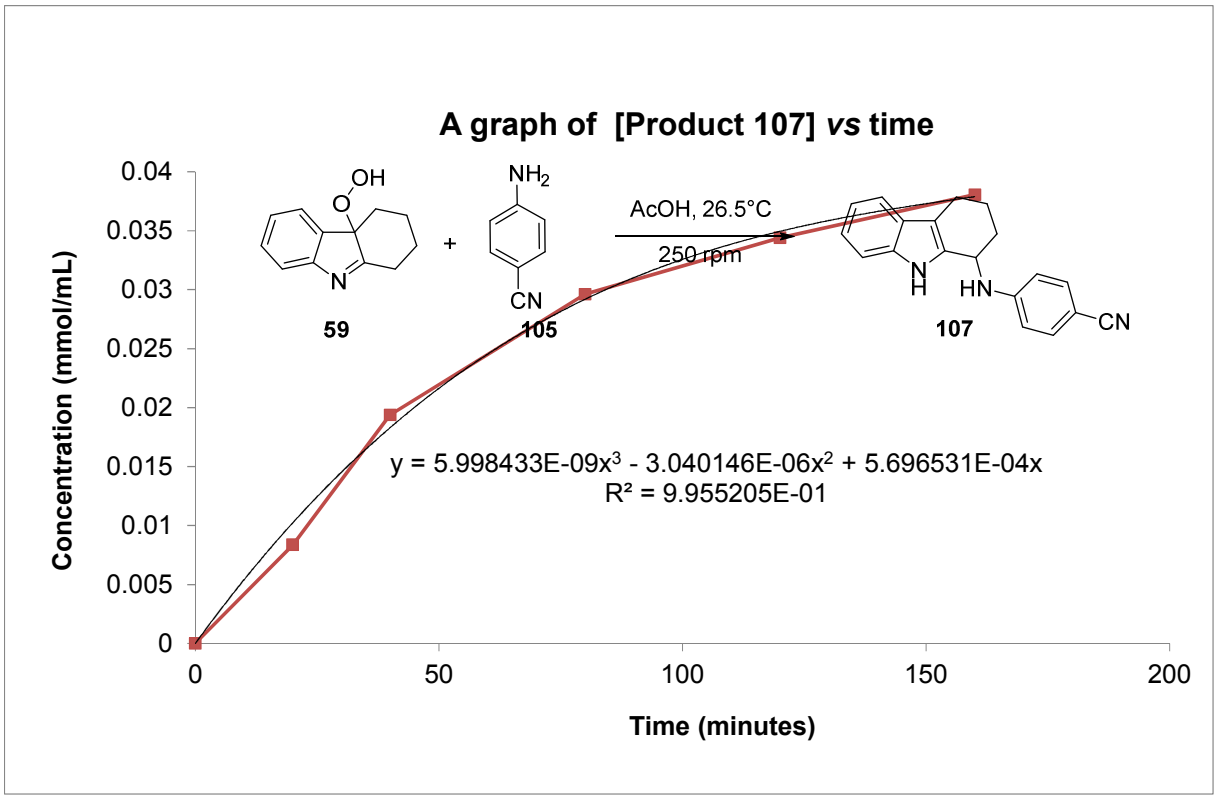


Figure 22: Change in the concentration of product with time

Curve fitting was performed by taking the first derivative of the equation.

$$y = 5{,}998433E\text{-}09x3 - 3{,}040146E\text{-}06x2 + 5{,}696531E\text{-}04x$$

A polynomial curve of third order was fitted to the average conversion versus time profile, the first derivative of which then gave the reaction rate profile of Figure 23.

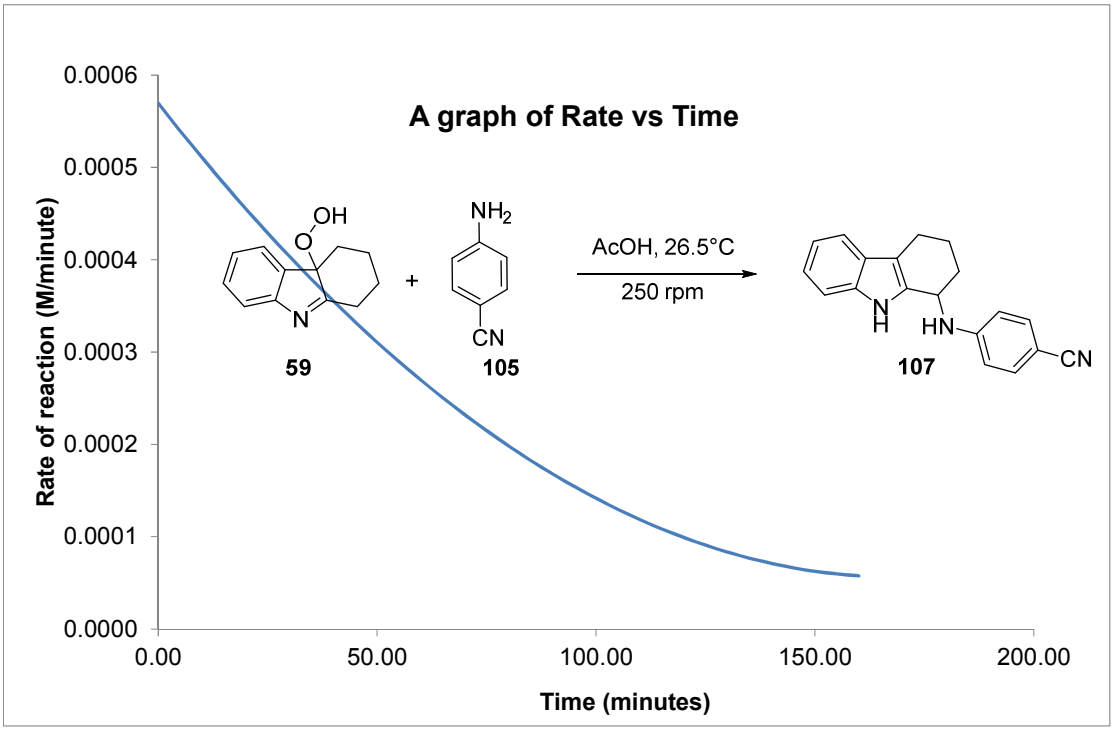


Figure 23: Change in the rate of reaction with time

Curve fitting was performed by taking the first derivative of the equation.

y = 5,998433E-09x3 - 3,040146E-06x2 + 5,696531E-04x

Equation for finding concentration of aniline at any specific time:

Concentration of aniline **105** = Initial concentration of aniline **105** - concentration of coupling product **107** at specific time (Equation 1)

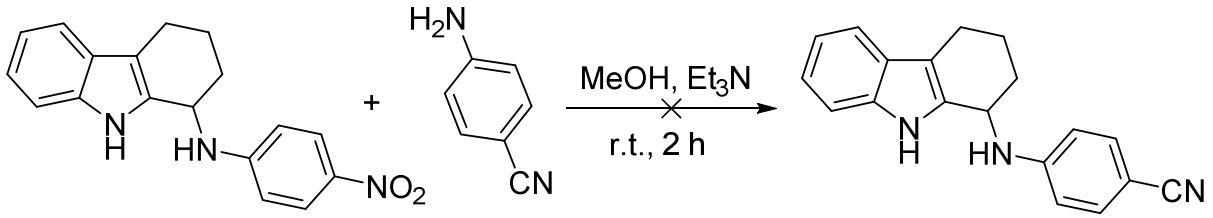
Equation for finding concentration of peroxide 5 at any specific time:

[Peroxide **59**] = Initial concentration of peroxide **59** -(initial concentration of aniline **105** - concentration of aniline **105** at specific time) (Equation 2)

8.5.2 Representative procedure for performing kinetic studies:

The *p*-cyanoaniline (0.48 mmol, 1.0 equiv.) was dissolved in acetic acid (10 ml) at 26.5°C and 250 rpm speed of magnetic stirrer. To this reaction mixture was then added hydroperoxide **59** (0.48 mmol, 1.0 equiv.). The progress of the reaction was checked at different time intervals. Due to the precipitation of coupling product **107**, a separate reaction was performed for measuring concentration of coupling product at each specific time interval. At the end of reaction, the reaction mixture was diluted with 50 mL ethyl acetate. An aliquot (5 mL) of this homogenous mixture was taken and added to cooled (-25°C) aqueous solution of NaOH. After extraction, triethylamine (1 mL) was added into the organic phase. The solvent was then evaporated and yield of the coupling product was determined by ^{1}H NMR based upon the conversion of aniline **105**. Similarly, the yield of product **107** was calculated at different intervals for different combinations of concentrations of both coupling partners.

8.5.3 Control experiment for exchange of one nucleophile with another nucleophile under basic conditions

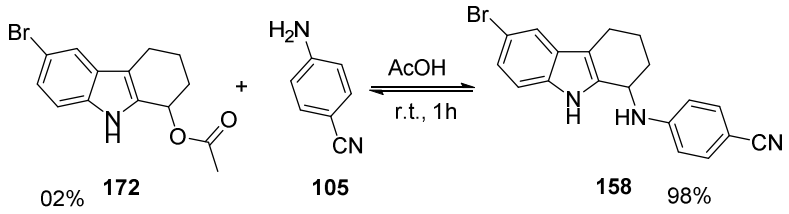


99 **105** **107**

The product **99** (0.19 mmol, 1.0 equiv. 58.3 mg) was dissolved in 4 mL methanol. To this was added triethylamine (1 mL) followed by the addition of nucleophile **105** (0.19 mmol, 1.0 equiv. 21.42 mg). The reaction mixture was allowed to stir at room temperature for 2 h. In order to dissolve the precipitated solid, the reaction mixture was diluted with ethyl acetate (20 mL).

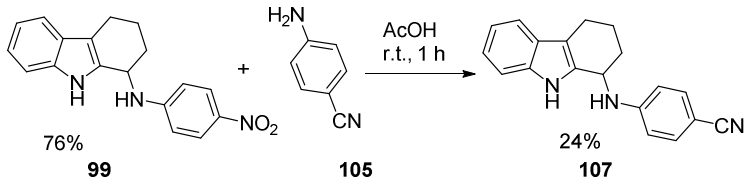
An aliquot (5 mL) of this homogenous mixture was taken and added to cooled (-25°C) aqueous solution of NaOH. After extraction, triethylamine (1 mL) was added into the organic phase. The solvent was then evaporated and ratio of products was measured by 1H NMR. The ^{1}H NMR did not show any conversion of product **99** to product **107**. It was found that product **99** was stable under basic conditions and no exchange of nucleophile was observed.

8.5.4 Exchange of solvent with external nucleophile under reaction conditions



The product **172** (0.19 mmol, 1.0 equiv. 60 mg) was dissolved in 4 mL acetic acid. To this was added nucleophile **105** (0.19 mmol, 1.0 equiv. 21.42 mg). The reaction mixture was allowed to stir at room temperature for 1h. In order to dissolve the precipitated solid, the reaction mixture was diluted with ethyl acetate (20 mL). A sample (5 mL) taken from this homogenous mixture was quenched with saturated aqueous solution of NaOH (cooled at -25 °C). After extraction, 1 mL of triethyl amine was added to organic phase. The resulting organic phase was evaporated and ratio of products was measured by ^{1}H NMR. It was found that 98% of product **172** was converted to product **158** after 1 h.

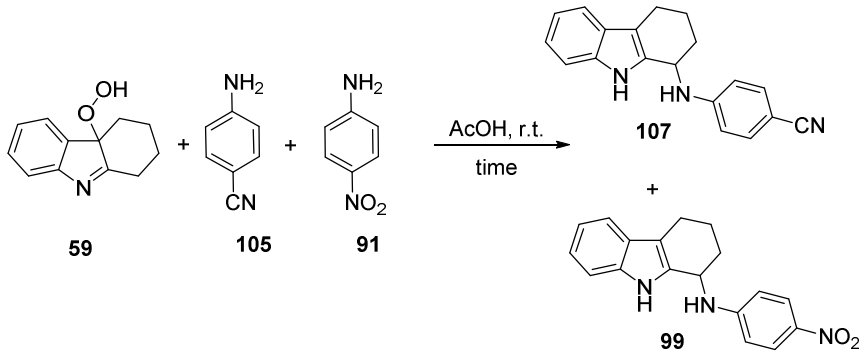
8.5.5 Exchange of one nucleophile with another nucleophile under reaction conditions



The product **99** (0.19 mmol, 1.0 equiv. 58.3 mg) was dissolved in 4 mL acetic acid. To this was added nucleophile **105** (0.19 mmol, 1.0 equiv. 21.42 mg). The reaction mixture was allowed to stir at room temperature for 1 h.

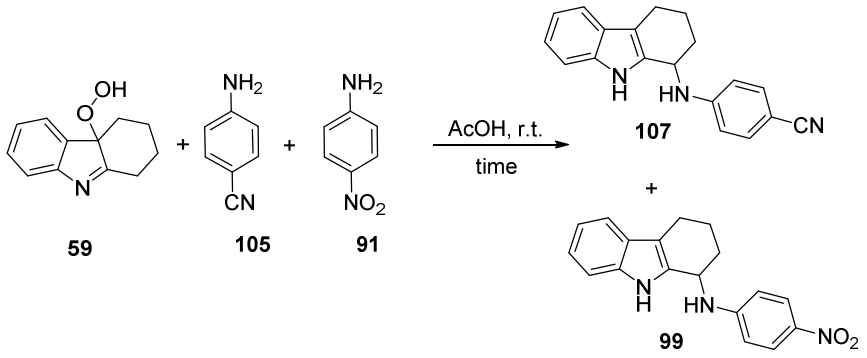
In order to dissolve the precipitated solid the reaction mixture was diluted with ethyl acetate (20 mL). A sample (5 mL) taken from this homogenous mixture was quenched with saturated aqueous solution of NaOH (cooled at -025 °C). After extraction, 1 mL of triethyl amine was added to organic phase. The resulting organic phase was evaporated and ratio of products was measured by ^{1}H NMR.

8.5.6 Experiment to find the stability of coupling products and reactivity of nucleophiles



The *p*-cyanoaniline (0.49 mmol, 1.0 equiv. 58.0 mg) and *p*-nitroaniline (0.49 mmol, 1.0 equiv. 67.4 mg) was dissolved in acetic acid (10 ml) at room temperature. To this reaction mixture was then added hydroperoxide (0.49 mmol, 1.0 equiv., 100 mg). The progress of the reaction was checked at different time intervals. Due to the precipitation of coupling product, a separate reaction was performed for measuring concentration of coupling product at each specific time interval. At the end of reaction, the reaction mixture was diluted with 50 mL ethyl acetate. An aliquot (5 mL) of this homogenous mixture was taken and added to ice cooled aqueous solution of NaOH. After extraction, triethylamine (1 mL) was added into the organic phase. The solvent was then evaporated and overall conversion of the two anilines (**105** and **91**) and ratio of coupling products **107** and **99** was determined by ^{1}H NMR based upon the conversion of aniline **107** and aniline **99**.

Table 74: Competition between aniline 91 and aniline 105



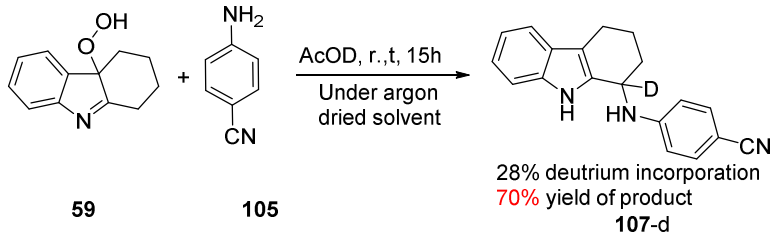
Entry	Time (h)	Overall conversion	4 (%)	13 (%)
1	0.6	26	47	53
2	5	62	47	53
3	15	60	50	50

The yields of the coupling products was measured by ^{1}H NMR at regular intervals

8.5.7 Detection of H_2O_2

p-cyanoaniline (0.49 mmol, 57.88 mg. 1.0 equiv.) was dissolved in 5 mL AcOH. To this reaction mixture was then added peroxide **59** (0.49 mmol, 57.88 mg. 1.0 equiv.) and the reaction mixture was stirred at room temperature for 4 h. 100 µL of yellow colored 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_2SO_4 (2.5 M) and 5mL peroxide free diethyl ether. The sample was gently mixed for 20 seconds. The reaction mixture turned blue (from yellow) indicating the presence of H_2O_2 in the sample of reaction mixture.

8.5.8 Indirect prove for the existence of enamine-imine equilibrium



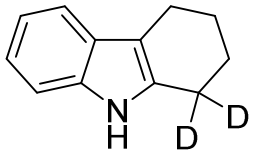
p-cyanoaniline (**105**, 0.49 mmol, 57.88 mg. 1.0 equiv.) was dissolved in 0.5 mL deuterated AcOD. The reaction mixture was stirred under argon for 4 h. The solvent was then evaporated by applying high vacuum. Again 0.5 mL of AcOD was added and reaction mixture was stirred for 1h. The solvent was again removed under high vacuum. In another flask, carbazole hydroperoxide (**59**, 0.49 mmol, 100 mg. 1.0 equiv.) was dissolved in 1mL deuterated methanol and stirred over moleculer sieves (5 A°) for 10 minutes. The solution of methanol was then transferred to the other flask containing *p*-cyanoaniline (**105**) through Pasteur pipette fitted with a plug of cotton. The vacuum was again applied to evaporate the methanol. These processes of adding deuterated solvents to both reagents were performed for exchanging all the proton attached to hetero atoms by deuterium in order to make the system free of protons. Deuterated AcOD (5 mL) was added and the reaction mixture was allowed to stir under an argon atmosphere at room temperature for 15 h. The solvent was then evaporated by rotary evaporator. The reaction mixture was dissolved in 10 mL methanol (a sample was immediately taken from this homogenous mixture, the solvent was removed and a ^{1}H NMR spectrum was measured to determine the ratio of C-D(H) vs aromatic C–H protons of aniline, an incorporation of 30% of deuterium was observed) and stirred for 60 minutes and the solvent was then evaporated (3x10 mL, process was repeated three times).

The product **107**-d was then purified through recrystallization by using a mixture of ethyl acetate and pentane. The ratio of the NH proton (and aromatic C–H protons of aniline) vs deuterium was measured. The comparison of ratios (before crystallization (30%) and after crystallization (28%) were similar and 28% incorporation of deuterium was observed. Yield of purified product=70%.

Stirring the product **107** in deuterated AcOD did not show any incorporation of deuterium.

8.5.8 Synthesis and characterization of products

1 2,3,4,9-tetrahydro-1H-carbazole-1,1-d_2 (58-d_2)



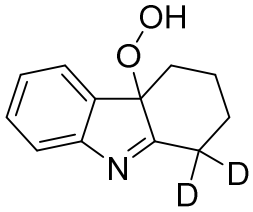
The product was synthesized by Fischer Indole Synthesis using standard procedures. [108] The solution of phenyl hydrazine (9.85 mmol, 0.97 mL) and cyclohexanone (9.78 mmol, 1 mL) was stirred in deutrated acetic acid for 4 h. The solvent was then evaporated and the desired product was purified by using column chromatography (Alox, Isohexane/EtOAc (80:20)). Yield of purified product=70%

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.58 (s, 1H), 7.31-7.30 (m, 1H), 7.22-7.21 (m, 1H), 6.97-6.95 (m, 0.84H), 6.91-6.88 (m, 0.89H), 2.69-2.65 (m, 0.56H), 2.50-2.47 (t, J = 5.9 Hz, 2H), 1.81-1.77 (m, 4H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 135.6, 134.3-134.2 (m, 1C), 127.2, 119.9-119.7 (m, 1C), 117.9-119.8 (m, 1C), 117.0-116.9 (m, 1C), 110.4-110.3 (m, 1C), 108.0 (m, 1C), 22.9-22.0 (m, 3c), 20.6, ppm;

HR-MS EI (ESI neg) m/z: M-H calcd. for $C_{12}H_{13}N_1O_2[M-H]^+$: 172.110078; found: 172.110100

4a-hydroperoxy-2,3,4,4a-tetrahydro-1H-carbazole-1,1-d_2 (59-d_2)



The deutated tetrahyrocarbazole (500 mg) was dissolved in toluene (50 ml). To this solution was added rose bengal (1mg). The resultant reaction mixture was irradiated with 23 watt lamp under O_2 atmosphere.

The progress of the reaction was controlled with ^{1}H NMR. After full conversion of the substrate, the precipitated solid was filtered to afford the desired product in quantitative yield.

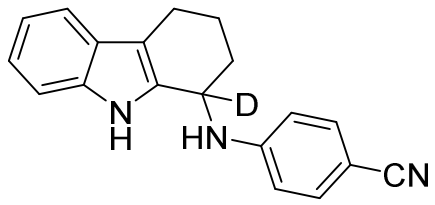
Purification: The crude product was purified by simple filtration as a pink solid in quantitative yield.

^{1}H NMR (500 MHz, DMSO-d_6): *δ* 11.64 (broad s, 1H), 7.42-7.38 (m, 2H), 7.34-7.31 (m, 0.84H), 7.20-7.17 (tm, 0.89H), 2.69-2.65 (m, 0.56H), 2.50-2.46 (m, 1H), 2.11-2.08 (m, 1H), 1.79-1.71 (m, 1H), 1.55-1.52 (m, 1H), 1.33-1.28 (m, 1H), 1.17 (dt, *J* = 14.2 Hz, *J* = 4.1 Hz, 1H), ppm;

^{13}C NMR (125 MHz, DMSO-d_6): *δ* 184.1, 153.9, 138.9, 129.1-129.0 (m, 1C), 125.0-124.9 (m, 1C), 122.7-122.6 (m, 1C), 119.7-119.6 (m, 1C), 91.1 (m, 1C), 35.4-35.3 (m, 1C), 29.3-27.8 (m, 1c), 27.8, ppm;

HR-MS EI (ESIpos) m/z: M^+ calcd. for $C_{12}H_{11}N_1O_2D_2[M+Na]^+$: 228.096402; found: 228.096480

2 4-((2,3,4,9-tetrahydro-1H-carbazol-1-yl-1-d)amino)benzonitrile (107-d_1)



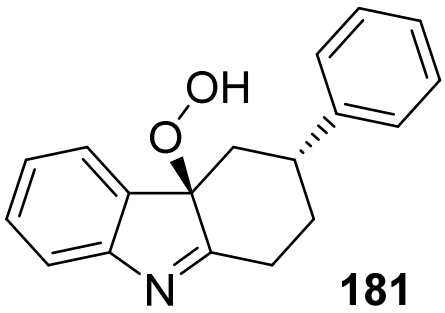
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.87 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 7.06-7.04 (m, 1H), 6.97-6.95 (m, 1H), 6.81 (d, J = 8.9 Hz, 2H), 4.88-4.86 (m, 0.71H), 2.74-2.70 (m, 1H), 2.64-2.59 (m, 1H), 2.01-1.96 (m, 1H), 1.94-1.90 (m, 1H), 1.87-1.80 (m, 2H) ppm;

^{13}C NMR (125 MHz, DMSO-d_6): δ 151.3 , 136.1, 133.6, 133.4, 126.5, 121.1, 120.7, 118.2, 117.9, 111.1, 110.6, 95.5, 45.3, 45.0 (t, 17.96 Hz), 29.0, 20.7, 19.7, ppm;

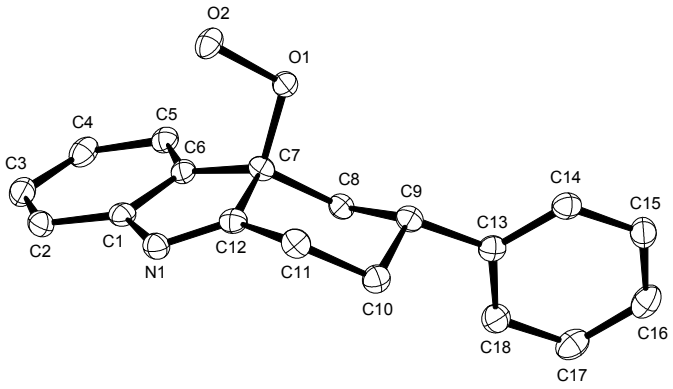
HR-MS (ESIneg) m/z: M- calcd. for $C_{19}H_{16}D_1N_3$ $[M-H]^-$: 287.141248; found: 287.141590

9 X-Ray crystal structure data

4a-hydroperoxy-3-phenyl-2,3,4,4a-tetrahydro-1*H*-carbazole (181)



181



Crystal data and structure refinement

Identification code	8089	
Empirical formula	$C_{18}\ H_{17}\ NO_2$	
Color	colourless	
Formula weight	279.33 g mol^{-1}	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	RHOMBOHEDRAL	
Space group	R3, (no. 146)	
Unit cell dimensions	a = 20.1974(7) Å	α= 90°.
	b = 20.1974(7) Å	β= 90°.
	c = 8.9778(3) Å	γ= 120°.
Volume	3171.69(19) Å3	

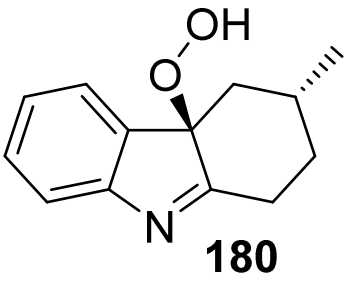
Z	9
Density (calculated)	1.316 Mg m^{-3}
Absorption coefficient	0.684 mm^{-1}
F(000)	1332 e
Crystal size	0.28 x 0.12 x 0.11 mm^3
θ range for data collection	4.38 to 67.09°.
Index ranges	-24 ≤ h ≤24, -24≤ k ≤ 24, -10 ≤ l ≤ 10
Reflections collected	29884
Independent reflections	2478 [Rint = 0.0432]
Reflections with I>2σ(I)	2432
Completeness to θ = 67.09°	99.6 %
Absorption correction	Gaussian
Max. and min. transmission	0.95 and 0.86
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2478 / 1 / 193
Goodness-of-fit on F2	1.060
Final R indices [I>2σ (I)]	R_1 = 0.0280 wR_2 = 0.0694
R indices (all data)	R_1 = 0.0284 wR_2 = 0.0697
Absolute structure parameter	-0.14(16)
Largest diff. peak and hole	0.137 and -0.143 e $Å^{-3}$

Bond lengths [Å] and angles [°].

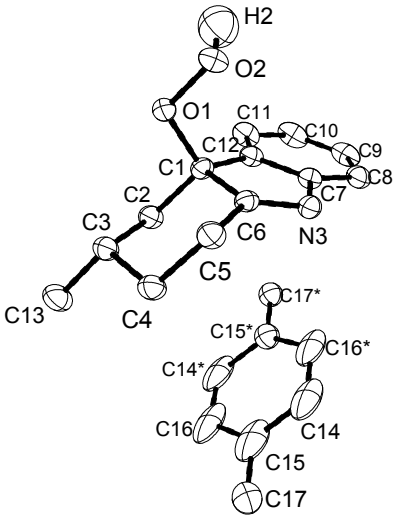
O(1)-C(7)	1.4368(17)	O(1)-O(2)	1.4703(13)
N(1)-C(12)	1.2871(18)	N(1)-C(1)	1.4405(18)
C(1)-C(2)	1.380(2)	C(1)-C(6)	1.397(2)
C(2)-C(3)	1.397(2)	C(3)-C(4)	1.387(2)
C(4)-C(5)	1.399(2)	C(5)-C(6)	1.374(2)
C(6)-C(7)	1.5032(19)	C(7)-C(8)	1.5262(19)
C(7)-C(12)	1.5289(19)	C(8)-C(9)	1.5417(19)
C(9)-C(13)	1.5126(19)	C(9)-C(10)	1.5439(19)
C(10)-C(11)	1.547(2)	C(11)-C(12)	1.489(2)
C(13)-C(14)	1.392(2)	C(13)-C(18)	1.396(2)
C(14)-C(15)	1.395(2)	C(15)-C(16)	1.383(2)
C(16)-C(17)	1.385(2)	C(17)-C(18)	1.390(2)
C(7)-O(1)-O(2)	106.99(9)	C(12)-N(1)-C(1)	107.18(12)
C(2)-C(1)-C(6)	121.79(13)	C(2)-C(1)-N(1)	126.92(13)
C(6)-C(1)-N(1)	111.29(12)	C(1)-C(2)-C(3)	117.38(14)
C(4)-C(3)-C(2)	121.10(14)	C(3)-C(4)-C(5)	120.75(14)
C(6)-C(5)-C(4)	118.25(13)	C(5)-C(6)-C(1)	120.63(12)
C(5)-C(6)-C(7)	132.33(13)	C(1)-C(6)-C(7)	107.02(12)
O(1)-C(7)-C(6)	113.06(11)	O(1)-C(7)-C(8)	104.69(10)
C(6)-C(7)-C(8)	117.00(12)	O(1)-C(7)-C(12)	112.23(11)
C(6)-C(7)-C(12)	100.41(11)	C(8)-C(7)-C(12)	109.64(11)
C(7)-C(8)-C(9)	111.01(11)	C(13)-C(9)-C(8)	112.05(11)
C(13)-C(9)-C(10)	112.27(12)	C(8)-C(9)-C(10)	109.64(11)
C(9)-C(10)-C(11)	111.29(12)	C(12)-C(11)-C(10)	109.54(11)
N(1)-C(12)-C(11)	126.82(13)	N(1)-C(12)-C(7)	113.91(12)

C(11)-C(12)-C(7)	119.08(12)	C(14)-C(13)-C(18)	118.32(13)
C(14)-C(13)-C(9)	120.33(13)	C(18)-C(13)-C(9)	121.35(13)
C(13)-C(14)-C(15)	120.88(14)	C(16)-C(15)-C(14)	120.22(14)
C(15)-C(16)-C(17)	119.37(14)	C(16)-C(17)-C(18)	120.58(14)
C(17)-C(18)-C(13)	120.62(14)		

4a-hydroperoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole (180)



180



Crystalized from toluene

Crystal data and structure refinement.

Identification code	7911sadabs
Empirical formula	$C_{33}\ H_{40}N_2O_4$
Color	colourless
Formula weight	528.67gmol^{-1}
Temperature	100 K
Wavelength	1.54178 Å
Crystal system	MONOCLINIC
Space group	p 21/n, (no. 14)
Unit cell dimensions	a = 8.5281 (6) Å α= 90°.
	b = 9.9904 (7) Å β= 93.279(3)°.
	c = 16.8671(12) Å γ = 90°.
Volume	1434.71(18) Å3
Z	2
Density (calculated)	1.224 Mg m^{-3}

Absorption coefficient	0.635 mm^{-1}
F(000)	568 e
Crystal size	0.30 x 0.08 x 0.05 mm^3
θ range for data collection	5.15 to 67.13°.
Index ranges	-10 ≤ h ≤ 10, -10≤ k ≤11, -20≤ l ≤ 20
Reflections collected	60969
Independent reflections	2526 [Rint = 0.0738]
Reflections with I>2σ (I)	2338
Completeness to θ = 67.13°	98.7 %
Absorption correction	Gaussian
Max. and min. transmission	0.97587 and 0.89942
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2526 / 0 / 198
Goodness-of-fit on F^2	1.065
Final R indices [I>2σ(I)]	R_1 = 0.0464 w R_2 = 0.1070
R indices (all data)	R_1 = 0.0494 w R_2 = 0.1096
Largest diff. peak and hole	0.258 and -0.344 e $Å^{-3}$

Selected bond lengths [Å] and angles [°].

C(1)-O(1)	1.4262(18)	C(1)-C(12)	1.508(2)
C(1)-C(6)	1.524(2)	C(1)-C(2)	1.533(2)
C(2)-C(3)	1.534(2)	C(3)-C(4)	1.530(2)
C(3)-C(13)	1.530(2)	C(4)-C(5)	1.543(2)
C(5)-C(6)	1.479(2)	C(6)-N(3)	1.288(2)
C(7)-C(8)	1.385(2)	C(7)-C(12)	1.393(2)
C(7)-N(3)	1.437(2)	C(8)-C(9)	1.395(3)
C(9)-C(10)	1.387(3)	C(10)-C(11)	1.396(3)

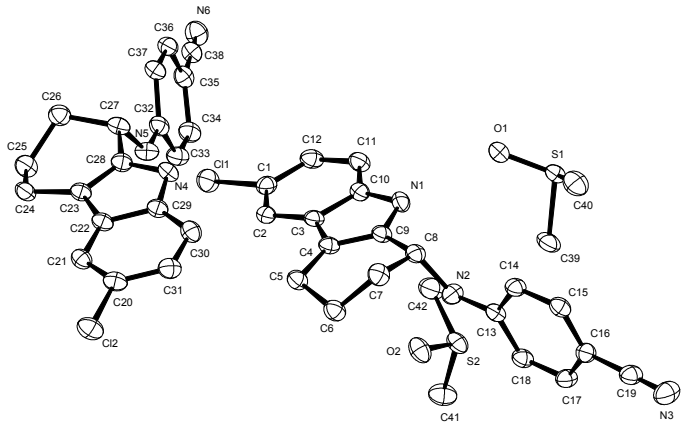
C(11)-C(12)	1.379(2)	C(14)-C(15)	1.396(4)
C(15)-C(17)	1.251(5)	C(15)-C(16)	1.393(4)
C(17)-H(17A)	0.83(5)	C(17)-H(17B)	0.94(4)
C(17)-H(17C)	1.08(5)	O(1)-O(2)	1.4688(15)
O(2)-H(2)	0.97(3)		

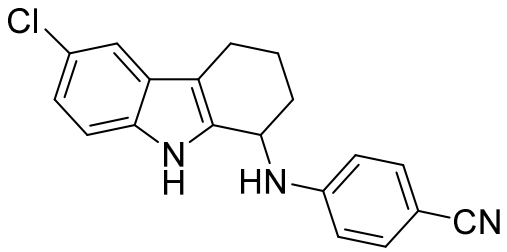
O(1)-C(1)-C(12)	116.05(12)	O(1)-C(1)-C(6)	112.33(12)
C(12)-C(1)-C(6)	100.27(12)	O(1)-C(1)-C(2)	104.62(12)
C(12)-C(1)-C(2)	115.04(12)	C(6)-C(1)-C(2)	108.56(12)
C(1)-C(2)-C(3)	112.28(13)	C(4)-C(3)-C(13)	110.71(13)
C(4)-C(3)-C(2)	110.31(13)	C(13)-C(3)-C(2)	110.32(14)
C(3)-C(4)-C(5)	112.83(13)	C(6)-C(5)-C(4)	107.98(12)
N(3)-C(6)-C(5)	126.93(13)	N(3)-C(6)-C(1)	113.90(13)
C(5)-C(6)-C(1)	118.60(13)	C(8)-C(7)-C(12)	122.00(15)
C(8)-C(7)-N(3)	126.74(14)	C(12)-C(7)-N(3)	111.20(13)
C(7)-C(8)-C(9)	117.62(16)	C(10)-C(9)-C(8)	120.52(16)
C(9)-C(10)-C(11)	121.36(16)	C(12)-C(11)-C(10)	118.22(17)
C(11)-C(12)-C(7)	120.27(15)	C(11)-C(12)-C(1)	132.44(15)
C(7)-C(12)-C(1)	107.18(13)	C(17)-C(15)-C(16)	120.7(3)
C(17)-C(15)-C(14)	120.4(3)	C(16)-C(15)-C(14)	118.8(3)

C(15)-C(17)-H(17A)	103(3)	C(15)-C(17)-H(17B)	106(3)H(17A)-
C(17)-H(17B)	111(4)	C(15)-C(17)-H(17C)	114(2)
H(17A)-C(17)-H(17C)	110(4)	H(17B)-C(17)-H(17C)	113(3)
C(6)-N(3)-C(7)	107.42(12)	C(1)-O(1)-O(2)	106.67(10)
O(1)-O(2)-H(2)	100.7(15)		

Symmetry transformations used to generate equivalent atoms.

4-((6-chloro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl)amino)benzonitrile





Crystal data and structure refinement.

Identification code	7642
Empirical formula	$C_{21}H_{22}ClN_3OS$
Color	colourless
Formula weight	399.93gmol^{-1}
Temperature	100 K
Wavelength	1.54178 Å
Crystal system	TRICLINIC
Space group	$P\bar{1}$, (no. 2)

Unit cell dimensions	a = 10.3396(3) Å	α= 83.171(2)°
	b = 11.1324(3) Å	β= 75.762(2)°
	c = 18.1230(5) Å	γ = 89.106(2)°
Volume	2007.42(10) Å3	
Z	4	
Density (calculated)	1.323 Mg m^{-3}	
Absorption coefficient	2.777 mm^{-1}	
F(000)	840 e	
Crystal size	0.33 x 0.30 x 0.08 mm^3	
θ range for data collection	2.53 to 64.60°	
Index ranges	-10 ≤ h α 11, -12≤ k ≤ 13, -21 ≤ l ≤ 21	
Reflections collected	41515	
Independent reflections	6514 [Rint = 0.0823]	
Reflections with I>2σ (I)	5028	
Completeness to θ = 64.60°	96.5 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.87 and 0.60	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6514 / 0 / 491	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2σ(I)]	R_1 = 0.0414	wR^2 = 0.0946
R indices (all data)	R_1 = 0.0622	wR^2 = 0.1051
Largest diff. peak and hole	0.238 and -0.368 e $Å^{-3}$	

Bond lengths [Å] and angles [°]

C(1)-C(2)	1.378(4)	C(1)-C(12)	1.399(4)
C(1)-Cl(1)	1.750(2)	C(2)-C(3)	1.407(3)
C(3)-C(10)	1.413(3)	C(3)-C(4)	1.431(3)
C(4)-C(9)	1.366(3)	C(4)-C(5)	1.503(3)
C(5)-C(6)	1.531(4)	C(6)-C(7)	1.527(4)
C(7)-C(8)	1.531(4)	C(8)-N(2)	1.466(3)
C(8)-C(9)	1.491(3)	C(9)-N(1)	1.377(3)
C(10)-N(1)	1.376(3)	C(10)-C(11)	1.390(3)
C(11)-C(12)	1.388(4)	C(13)-N(2)	1.360(3)
C(13)-C(18)	1.407(4)	C(13)-C(14)	1.415(3)
C(14)-C(15)	1.381(4)	C(15)-C(16)	1.393(4)
C(16)-C(17)	1.406(4)	C(16)-C(19)	1.442(4)
C(17)-C(18)	1.376(4)	C(19)-N(3)	1.151(3)
C(20)-C(21)	1.375(4)	C(20)-C(31)	1.404(4)
C(20)-Cl(2)	1.750(3)	C(21)-C(22)	1.402(3)
C(22)-C(29)	1.422(3)	C(22)-C(23)	1.429(4)
C(23)-C(28)	1.363(4)	C(23)-C(24)	1.503(3)
C(24)-C(25)	1.541(4)	C(25)-C(26)	1.525(4)
C(26)-C(27)	1.537(4)	C(27)-N(5)	1.468(3)
C(27)-C(28)	1.493(3)	C(28)-N(4)	1.382(3)
C(29)-N(4)	1.372(3)	C(29)-C(30)	1.389(4)
C(30)-C(31)	1.385(4)	C(32)-N(5)	1.360(3)
C(32)-C(33)	1.407(4)	C(32)-C(37)	1.408(4)
C(33)-C(34)	1.372(4)	C(34)-C(35)	1.401(4)
C(35)-C(36)	1.391(4)	C(35)-C(38)	1.440(4)

C(36)-C(37)	1.377(4)	C(38)-N(6)	1.151(3)
C(39)-S(1)	1.783(3)	C(40)-S(1)	1.783(3)
C(41)-S(2)	1.781(3)	C(42)-S(2)	1.783(3)
O(1)-S(1)	1.5132(19)	O(2)-S(2)	1.5002(19)
C(2)-C(1)-C(12)	123.1(2)	C(2)-C(1)-Cl(1)	119.0(2)
C(12)-C(1)-Cl(1)	117.9(2)	C(1)-C(2)-C(3)	117.8(2)
C(2)-C(3)-C(10)	119.0(2)	C(2)-C(3)-C(4)	133.8(2)
C(10)-C(3)-C(4)	107.2(2)	C(9)-C(4)-C(3)	106.3(2)
C(9)-C(4)-C(5)	123.0(2)	C(3)-C(4)-C(5)	130.7(2)
C(4)-C(5)-C(6)	110.1(2)	C(7)-C(6)-C(5)	111.8(2)
C(6)-C(7)-C(8)	112.1(2)	N(2)-C(8)-C(9)	109.1(2)
N(2)-C(8)-C(7)	113.2(2)	C(9)-C(8)-C(7)	108.5(2)
C(4)-C(9)-N(1)	110.5(2)	C(4)-C(9)-C(8)	125.9(2)
N(1)-C(9)-C(8)	123.5(2)	N(1)-C(10)-C(11)	129.8(2)
N(1)-C(10)-C(3)	107.6(2)	C(11)-C(10)-C(3)	122.5(2)
C(12)-C(11)-C(10)	117.8(2)	C(11)-C(12)-C(1)	119.9(2)
N(2)-C(13)-C(18)	119.6(2)	N(2)-C(13)-C(14)	122.4(2)
C(18)-C(13)-C(14)	118.0(2)	C(15)-C(14)-C(13)	120.3(2)
C(14)-C(15)-C(16)	121.0(2)	C(15)-C(16)-C(17)	119.2(2)
C(15)-C(16)-C(19)	120.9(2)	C(17)-C(16)-C(19)	119.9(2)
C(18)-C(17)-C(16)	119.9(2)	C(17)-C(18)-C(13)	121.5(2)
N(3)-C(19)-C(16)	179.2(3)	C(21)-C(20)-C(31)	122.7(2)
C(21)-C(20)-Cl(2)	119.2(2)	C(31)-C(20)-Cl(2)	118.1(2)
C(20)-C(21)-C(22)	118.4(2)	C(21)-C(22)-C(29)	118.8(2)
C(21)-C(22)-C(23)	134.3(2)	C(29)-C(22)-C(23)	106.9(2)
C(28)-C(23)-C(22)	106.5(2)	C(28)-C(23)-C(24)	123.4(2)
C(22)-C(23)-C(24)	130.0(2)	C(23)-C(24)-C(25)	109.5(2)

C(26)-C(25)-C(24)	111.4(2)	C(25)-C(26)-C(27)	112.4(2)
N(5)-C(27)-C(28)	108.4(2)	N(5)-C(27)-C(26)	112.8(2)
C(28)-C(27)-C(26)	108.2(2)	C(23)-C(28)-N(4)	110.6(2)
C(23)-C(28)-C(27)	126.1(2)	N(4)-C(28)-C(27)	123.3(2)
N(4)-C(29)-C(30)	130.4(2)	N(4)-C(29)-C(22)	107.7(2)
C(30)-C(29)-C(22)	121.9(2)	C(31)-C(30)-C(29)	118.5(2)
C(30)-C(31)-C(20)	119.7(2)	N(5)-C(32)-C(33)	119.2(2)
N(5)-C(32)-C(37)	122.7(2)	C(33)-C(32)-C(37)	118.1(2)
C(34)-C(33)-C(32)	121.1(2)	C(33)-C(34)-C(35)	120.3(2)
C(36)-C(35)-C(34)	118.9(2)	C(36)-C(35)-C(38)	120.7(2)
C(34)-C(35)-C(38)	120.3(2)	C(37)-C(36)-C(35)	121.1(2)
C(36)-C(37)-C(32)	120.3(2)	N(6)-C(38)-C(35)	178.0(3)
C(10)-N(1)-C(9)	108.4(2)	C(13)-N(2)-C(8)	124.7(2)
C(29)-N(4)-C(28)	108.3(2)	C(32)-N(5)-C(27)	123.9(2)
O(1)-S(1)-C(39)	105.25(12)	O(1)-S(1)-C(40)	105.74(13)
C(39)-S(1)-C(40)	97.94(14)	O(2)-S(2)-C(41)	106.74(13)
O(2)-S(2)-C(42)	106.19(13)	C(41)-S(2)-C(42)	97.38(14)

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11 Appendix

11.1 Erklärung

Ich versichere, dass ich Dvon mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit- einschließlich Tabellen, Karten und Abbildungen-, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie noch nicht veröffentlicht worden ist, sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn PD. Dr. Martin Klußmann betreut worden.“

Mülheim an der Ruhr, September 2014

Bisher sind folgende Teilpublikationen veröffentlicht worden:

- **N. Gulzar**, K. M. Jones, H. Konnerth, M. Breugst, M. Klussmann, "Experimental and computational studies on the C-H amination mechanism of tetrahydrocarbazoles via hydroperoxides" *Chem. Eur. J.*, **2014**, submitted
- **N. Gulzar**, B. Schweitzer-Chaput, M. Klussmann, "Oxidative coupling reactions for the functionalisation of C-H bonds using oxygen" *Catal. Sci. Technol.,* **2014**, DOI: 10.1039/C4CY00544A.
- **N. Gulzar**, M. Klussmann, "Synthesis of antiviral tetrahydrocarbazole derivatives by photochemical and acid-catalyzed C-H functionalization via intermediate peroxides" *J. Vis. Exp.*, **2014**, doi:10.3791/51504.
- **N. Gulzar**, M. Klußmann, "Aerobic C-H amination of tetrahydrocarbazole derivatives via photochemically generated hydroperoxides" *Org. Biomol. Chem.*, **2013**, 11, 4516–4520.

11.2 Lebenslauf

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Projekterfahrung/Promotion
03.2011-11 2014

Promotion in der Organischen Chemie (Organische Synthese, Homogene Katalyse, Methodenentwicklung)
Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr
Titel: C–H Funktionalisierung über photochemisch erzeugte Hydroperoxide: Methodenentwicklung und Mechanistische Studien
Doktorvater: PD Dr. Martin Klußmann
Forschungsthemen

- Entwicklung neuer Verfahren für die nachhaltige Synthese von heterozyklischen **pharmazeutischen Wirkstoffen**
- Mechanistische Studien von Reaktionen mit Hydroperoxiden

Fachvorträge/In- und Ausland
03.2011-10.2014

- Posterpräsentation in einem Video Zeitschrift (*J. Vis. Exp.*, **2014**)
- Posterpräsentation auf der Sitzung des Fachbeirats **2014**, Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr
- **Vortrag** und Posterpräsentation auf dem 4. JungChemikerForum **2013**, Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr
- Posterpräsentation auf dem 14. Tetrahedron Symposium **2013**, **Seoul, SüdKorea**
- Posterpräsentation auf der 18. ORCHEM Konferenz **2012**, Weimar
- Posterpräsentation auf der Sitzung des Fachbeirats **2011**, Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr

Erfahrungen und Fähigkeiten

- **Arbeit in einem internationalen Team**
- Zusammenarbeit mit Chemielaboranten, Doktoranden und Postdoktoranden
- **Kooperation mit anderen Wissenschaftlern**
- zeiteffiziente und selbständige Arbeitsweise
- Lösen von komplexen Fragestellungen durch gründliches Analysieren
- Schreiben von Wissenschaftlichen Publikationen
- Betreuung von studentischen Praktikanten und Auszubildenden

M.Sc. Studien/Inland 10.2008-10.2010	**Master of Science in Chemie** Technische Universität Braunschweig, Deutschland Note 2,0 ECTS (European Credit Transfer System) **Masterarbeit in der Organischen Chemie** **Betreuer**: Prof. Dr. Thomas Lindel, Institut für Organische Chemie **Forschungsthemen (Heterozyklische Naturstoffsynthese)** ➢ Arbeiten zur Synthese des marinen Naturstoffs Caulerpin ➢ Synthese des Naturstoffs Flustrabromin
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Industrieerfahrung/Ausland 07.2006-09.2006	**Praktikum** Batala Pharmaceutical, 23/B, S-I-E#2. Gujranwala, Pakistan, ➢ Rohstoffanalyse ➢ Fertigproduktanalyse
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Publikationen

- **N. Gulzar**, K. M. Jones, H. Konnerth, M. Breugst, M. Klussmann, "Experimental and computational studies on the C-H amination mechanism of tetrahydrocarbazoles via hydroperoxides" *Chem. Eur. J.*, **2014**, submitted
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- **N. Gulzar**, M. Klußmann, "Aerobic C-H amination of tetrahydrocarbazole derivatives via photochemically generated hydroperoxides" *Org. Biomol. Chem.*, **2013**, 11, 4516–4520.
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- P. John, I. U. Khan, S. T. Sheikh, **N. Gulzar**, Aziz-Ur-Rehman "Anodizing of aluminum with improved corrosion properties" *J. Chem. Soc. Pak.*, **2010**, 32, 46.
- P. John, I. U. Khan, S. T. Sheikh, **N. Gulzar** and A. Rehman,"Enhancing Pitting Corrosion Resistance of Aluminium by Anodizing Process" *Asian J. Chem.*, **2013**, 25(7), 3815.
- P. John, I. U. Khan, S. T. Sheikh, **N. Gulzar** and A. Rehman, "Improving Pitting Corrosion Resistance of Aluminum by Anodizing Process" *J. Chem. Soc. Pak.*, **2013**, 35(1), 72.

Patente

- **N. Gulzar**, M. Klußmann, Process for the preparation of substituted indole derivatives, PCT Int. Appl. (2014), **WO 2014016296 A1 20140130** und Eur. Pat. Appl. (2014), **EP 2690091 A1 20140129.**

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