Dissertation zur Erlangung des Doktorgrades

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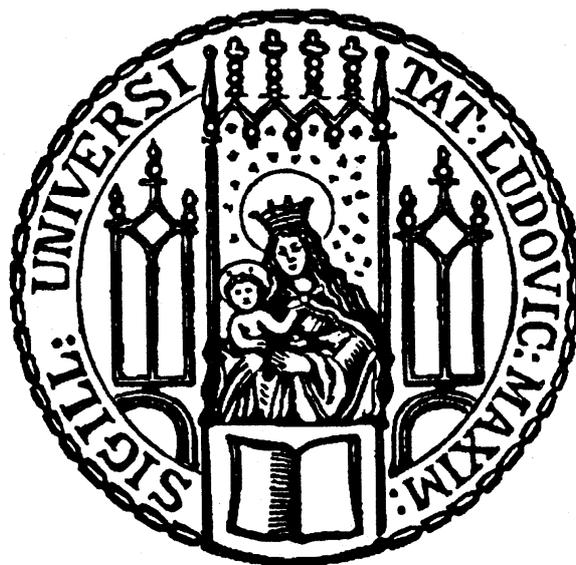
Catalyzed and Non Catalyzed Oxidative

Functionalization of Tertiary Amines

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aus

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Erklärung

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Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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"Der Wille zum System ist ein Mangel an Rechtschaffenheit"

(Friedrich Nietzsche)

Danksagung

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0.1   Iron-catalyzed Generation of α-Amino Nitriles from Tertiary Amines

A combination of iron(II) chloride as catalyst, trimethylsilyl cyanide as source of cyanide ions, and *tert*-butyl hydroperoxide as oxidant enables the conversion of aromatic tertiary amines into α-amino nitriles under mild conditions, as described by Han.[1] In this work the iron-catalyzed generation of α-amino nitriles was expanded to benzylic and aliphatic tertiary amines (Scheme 0.1). Chemoselective transformation of *N*-methyl groups into their corresponding α-amino nitriles was achieved in the presence of *N*-benzyl and *N*-alkyl groups.
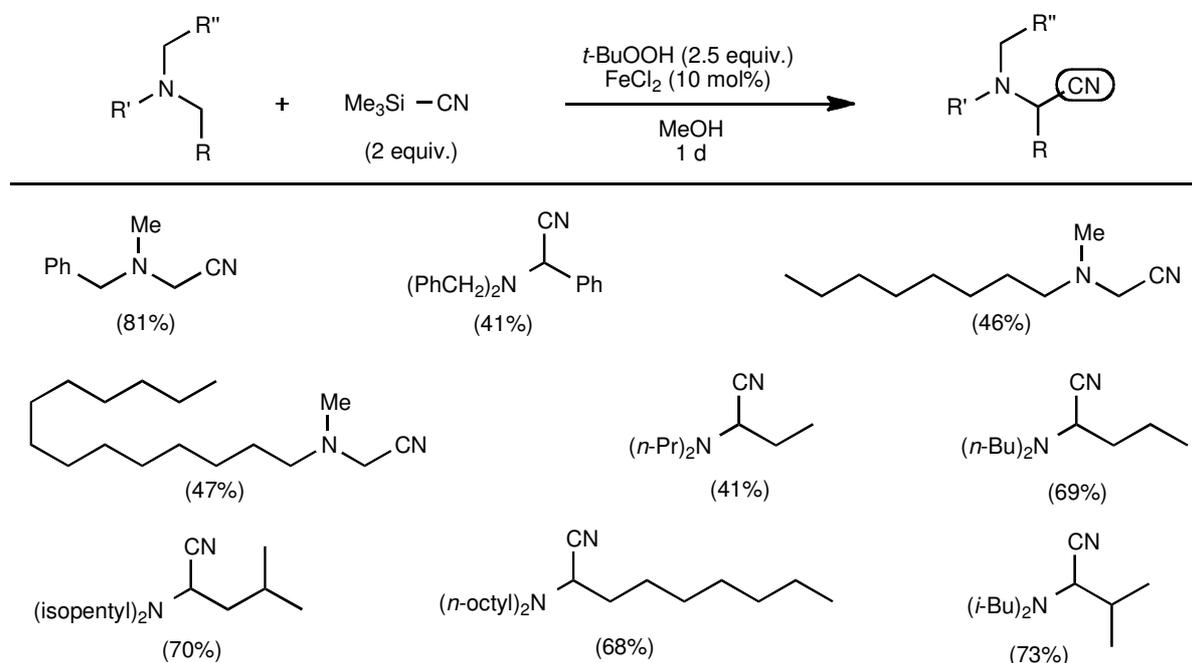
Scheme 0.1: FeCl₂-catalyzed oxidative α-cyanations of benzylic and aliphatic tertiary amines.

[1]   W. Han, A. R. Ofial, *Chem. Commun.* **2009**, 5024-5026.

Furthermore, *N,N*-dialkylanilines PhNR$_2$ with R = Et, Bu, Bn furnished the alkyl-(aryl)aminoacetonitriles PhN(R)CH$_2$CN as the main products accompanied by α-amino nitriles generated by ordinary α-cyanation of the aniline PhNR$_2$.

The formation of PhN(R)CH$_2$CN was rationalized by oxidative degradation of *N,N*-dialkylanilines to *N*-alkylanilines, their condensation with formaldehyde, generated by oxidation of the solvent methanol, and final trapping of the thus formed iminium ions by cyanide (Scheme 0.2).

R   R
[O] →→ R   R
CN$^-$ → R   R

tertiary amine   iminium ion **A**

hydrolysis | –RCHO

CH$_3$OH

[O] / solvent oxidation

HCHO

secondary amine **B**

iminium ion **E**

CN$^-$
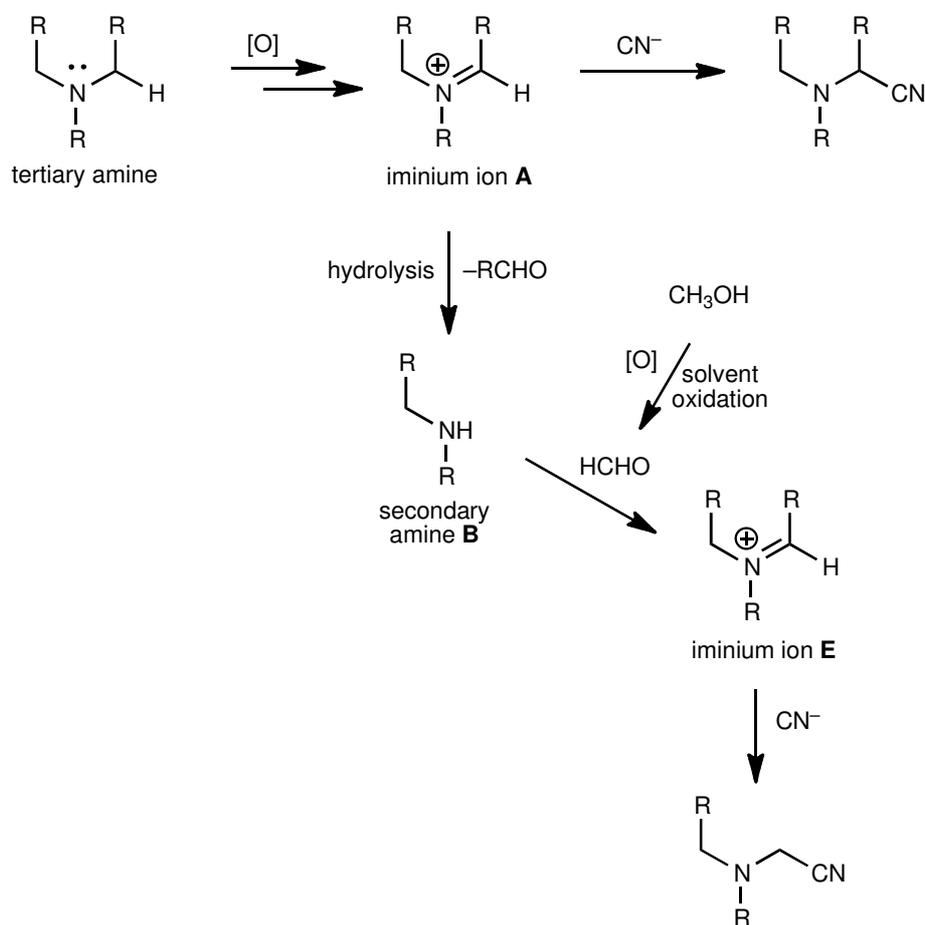
Scheme 0.2: Oxidative dealkylation of tertiary amines by FeCl$_2$ as the catalyst and *tert*-butyl hydroperoxide as the oxidant and subsequent trapping of the secondary amine intermediates.

Isotopic labeling of the methylene unit that originated from the solvent methanol allowed to proof the solvent participation in this reaction as given in Scheme 0.3.
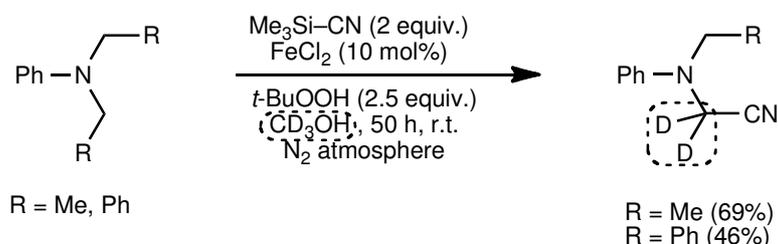
Scheme 0.3: Dealkylative cyanomethylation of *N,N*-dialkylanilines in CD$_3$OH.

0.2 Sequential Oxidative α-Cyanation/Anti-Markovnikov Hydroalkoxylation of Allylamines

In recent years, the Ofial Group developed iron-catalyzed oxidative α-cyanations of a variety of tertiary amines. This work describes the development of an iron-catalysed α-cyanation of tertiary allylamines that is coupled with a subsequent chemo- and regioselective addition of alcohols to the π-system of the vinyl-substituted α-amino nitrile to yield 2-amino-4-alkoxybutanenitriles under mild conditions (Scheme 0.4).

1a (R = H)	2a (21% after 4h)	3a (86% after 16 h)
1b (R = Me)		3b (85% after 14 h)
1c (R = OMe)		3c (93% after 14 h)
1d (R = Br)		3d (67% after 19 h)
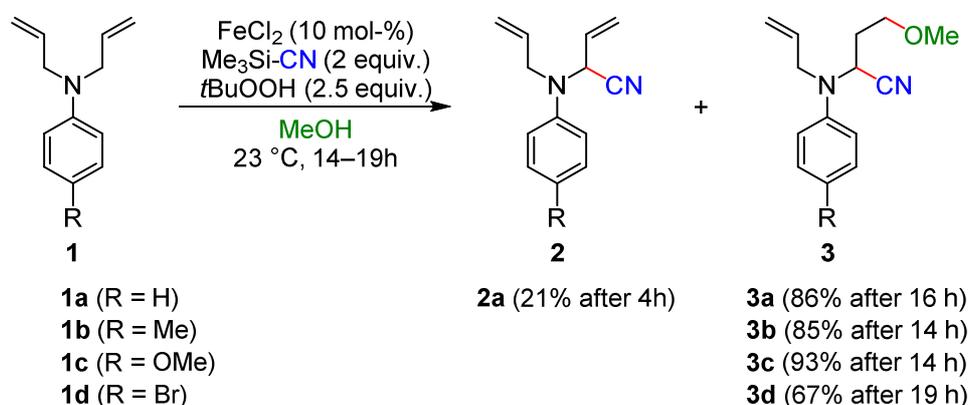
Scheme 0.4: Sequential oxidative cyanation/hydroalkoxylation of *N,N*-diallylamines.

While the ordinary cyanation product was isolated in low yield (21%) when the reaction was worked-up after 4 h reaction time, the product of addition of methanol to the corresponding 2-amino-4-alkoxybutanenitrile was obtained in 86% yield after 16 h. Reactions with *N*-allyl-*N*-ethylaniline and triallylamine showed that the scope of the oxidative α-cyanation/hydroalkoxylation can be extended to mono- and triallyl-substituted amines (Scheme 0.5). Employing *N*-allyl-*N*-methylaniline as the substrate, the corresponding amino nitrile was formed exclusively.
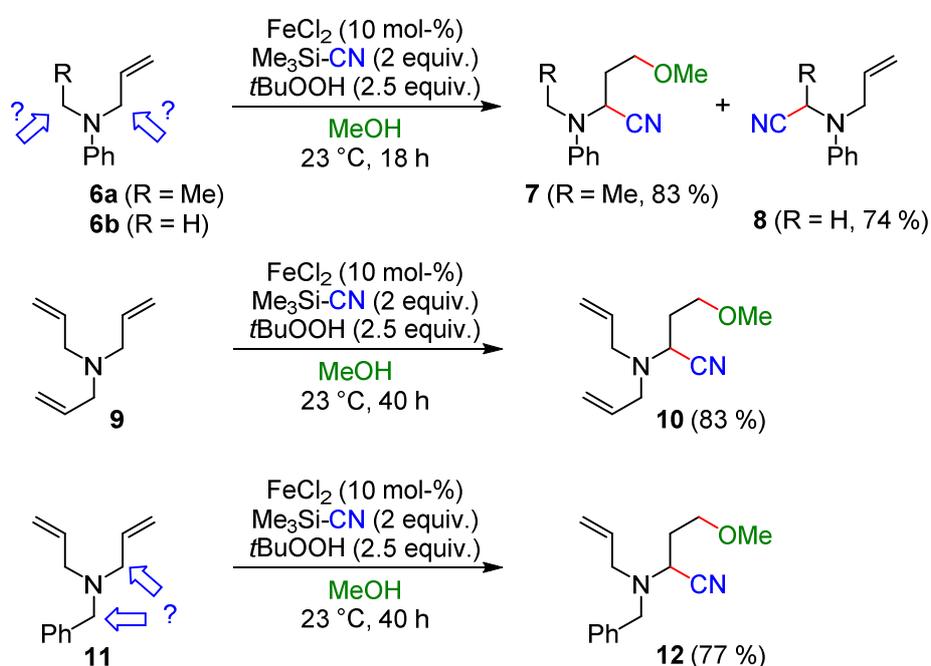
Scheme 0.5. Oxidative cyanation/hydroalkoxylation of the mono-allylamines, triallylamine and *N,N*-diallylbenzylamine.

Further studies indicated, that the α-cyanation is followed by a Michael-type addition of the alcohol (Scheme 0.6).
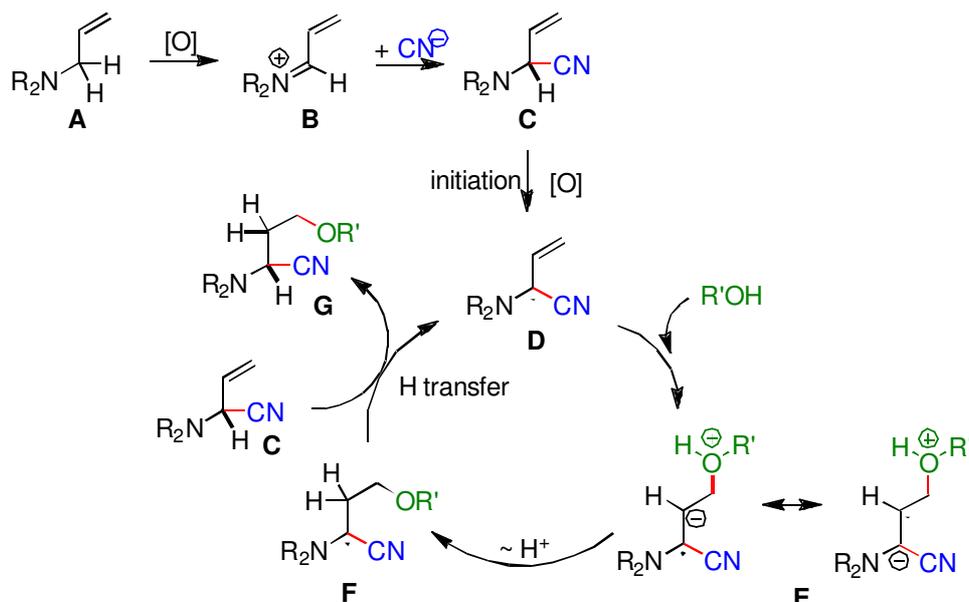
Scheme 0.6: Suggested mechanism for the oxidative C1-cyanation of the *N*-allyl group with subsequent anti-Markovnikov hydroalkoxylation.

0.3 Potassium Thiocyanate as Source of Cyanide for the Oxidative α-Cyanation of Tertiary Amines

Oxidation at the sulfur of the safe-to-handle potassium thiocyanate released cyanide units that were trapped in the presence of co-oxidized tertiary amines to form α-amino nitriles. These cyanations worked in aqueous solutions and did not require a catalyst, nor did they form toxic byproducts (Scheme 0.7).
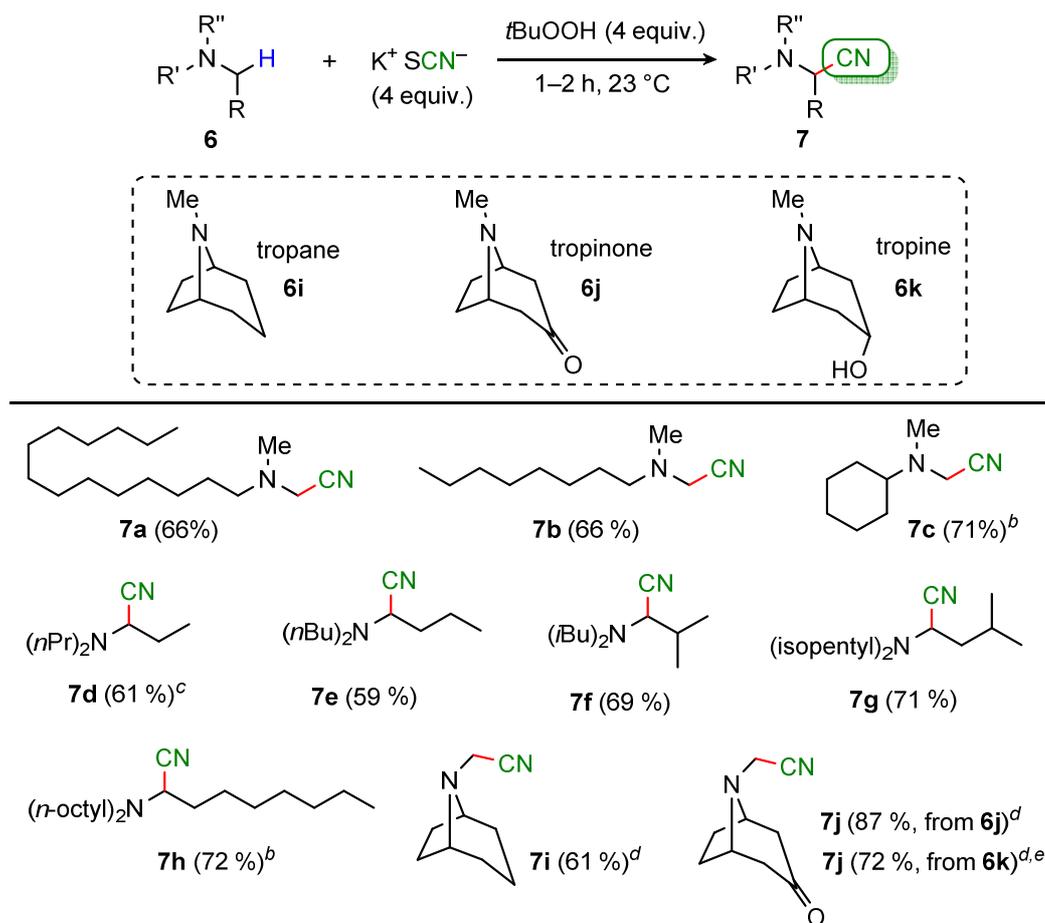
Scheme 0.7: Generation of α-amino nitriles from tertiary amines and potassium thiocyanate.

[a] Reaction conditions: amine (1 mmol), KSCN (4 equiv.), aq tBuOOH (70 % (w/w), 4 equiv.), ambient temperature (ca. 23 °C); yields refer to isolated products after column chromatography. [b] A 4.5 M solution of tBuOOH in CH$_2$Cl$_2$ was used as oxidant. [c] With MeCN as solvent (0.5 mL). [d] With MeCN as solvent (2 mL) at 50 °C. [e] With 5 equiv. of tBuOOH.

N,N-Dialkylanilines did not undergo oxidative α-cyanation at ambient temperature. After heating the reaction mixtures for 1 h to 80 ºC, oxidative cyanation at one of the NMe groups of para-substituted N,N-dimethylanilines produced the corresponding α-amino nitriles (Scheme 0.8).

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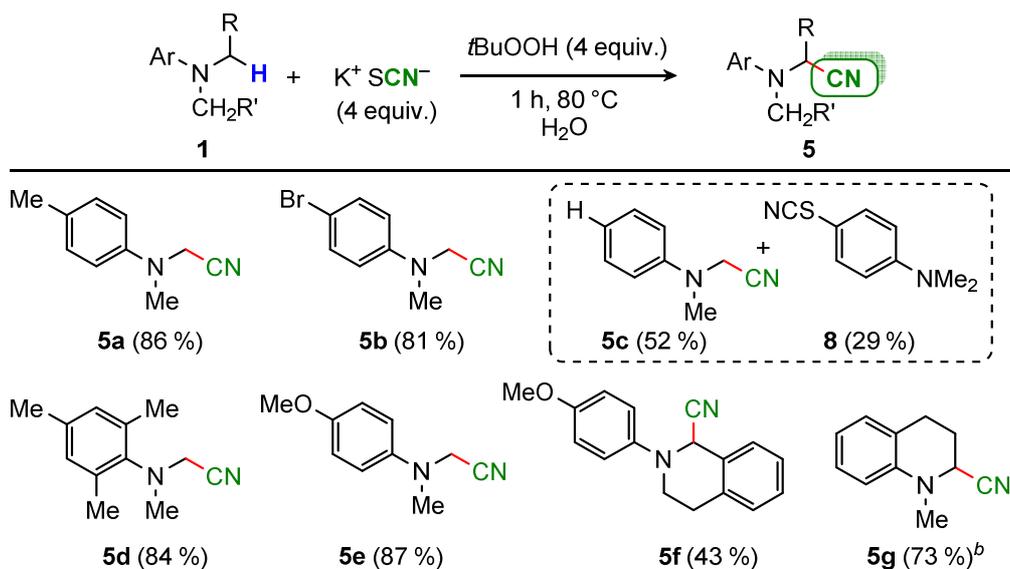
Scheme 0.8: Generation of α-amino nitriles from anilines and potassium thiocyanate.

In this work both the electrophile and the nucleophile were generated in situ from oxidizable precursors. The sulfur of SCN^- is used as a sacrifical group that safeguards the toxic nucleophile CN^- until its active form is released under the reaction conditions.

0.4 Direct Conversion of Tertiary *N*-Methyl Amines to *N*-Boc Protected Amines

The direct oxidative conversion of *N*-methyl into *N*-Boc groups would be an attractive method to generate *N*-Boc protected tertiary amines. As summarized in Scheme 0.9 a series of seven tertiary methyl amines underwent selective oxidation to form *N*-Boc protected amines. However, the method suffers from low functional group tolerance and small substrate scope.
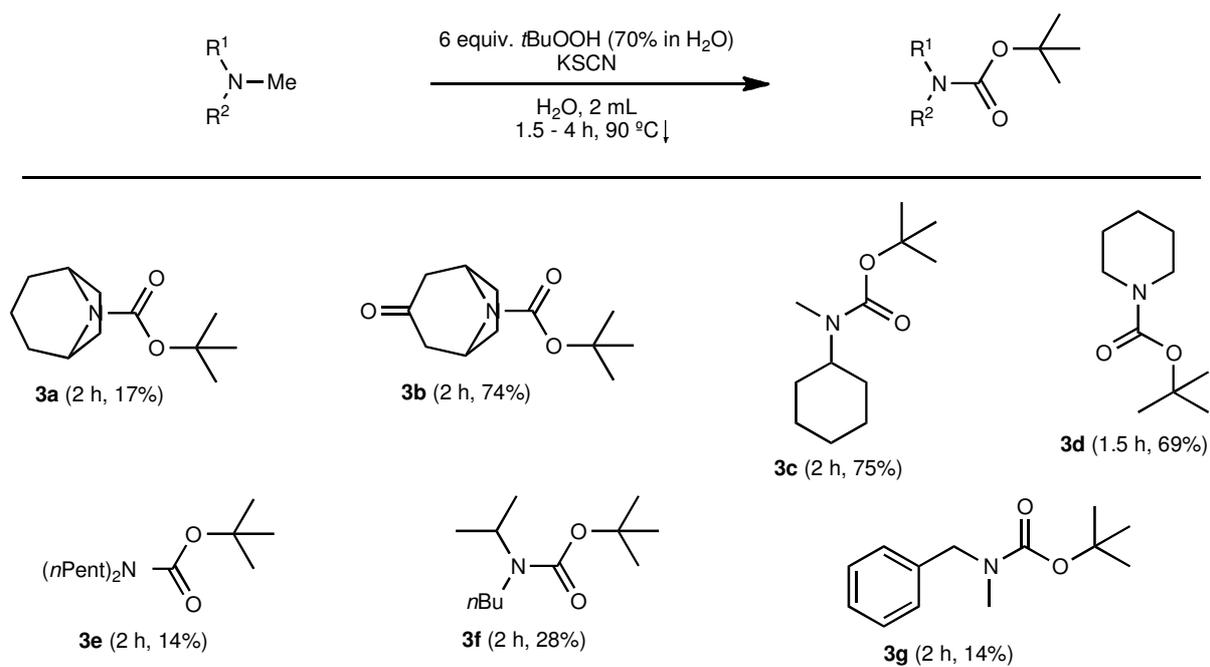
Scheme 0.9: Direct transformation of *N*-methyl into *N*-Boc groups.

3a (2 h, 17%)

3b (2 h, 74%)

3c (2 h, 75%)

3d (1.5 h, 69%)

3e (2 h, 14%)

3f (2 h, 28%)

3g (2 h, 14%)

1 Introduction

1.1 General

The formation of new C–C and C–X bonds is one of the major challenges in synthetic chemistry. The classical approach to control reactivity and target regioselectivity in such reactions uses molecules with already functionalized entities C–Y. After being installed in the substrate, the C–Y group subsequently undergoes reactions with appropriate reagents to form new C–C or C–X bonds selectively. As an alternative strategy, the direct transformation of ubiquitous C–H bonds of organic molecules has recently moved to center (Scheme 1).[1]
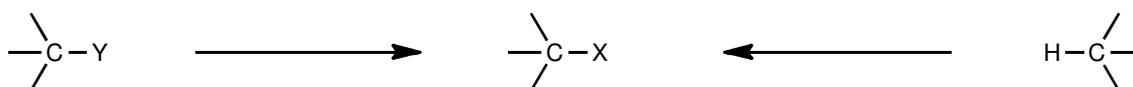
Scheme 1.1: General scheme for the introduction of functional groups (X) into organic molecules.

The direct functionalization of alkyl, alkenyl and aryl C–H bonds implies two fundamental challenges in organic and organometallic chemistry. Due to the numerous C–H bonds in nearly all organic molecules, selectivity is a very important issue. For effective applications, only a certain C–H bond has to undergo activation, rather than several C–H bonds in the same molecule. To achieve high selectivity, several strategies have been developed, such as the use of directing group effects, intramolecular chelation effects, using one substrate in excess,[2a,b] electronic effect-regulated substrates,[2b,c] or steric effect-regulated substrates. [2d,e,f]

The inert nature of many C–H bonds bears the second challenge for useful synthetic applications. A bond dissociation energy of about 400-440 kJ/mol,[3] characterizes alkyl C–H bonds as strong and robust, furthermore these bonds are localized and unpolarized.[1b,3] Bond dissociation energies of about 340-380 kJ/mol are described for C–H bonds adjacent to nitrogen atoms in tertiary amines.[3] Transition metal catalysts have turned out as efficient C–H bond activating agents via insertion into C–H bonds to form C–M bonds.[2g-l] These C–M bonds, formed as intermediates in the catalytic circle, are significantly more reactive than their C–H counterparts and can subsequently be transformed into the desired products.

Transition metal catalysis, therefore, is one of the most powerful and versatile tools in organic chemistry. In the past decades, transition metal catalysts, such as palladium,[4] ruthenium,[5] rhodium,[6] iridium,[7] gold[8] and platinum[9] have shown powerful abilities. Among the transition metal catalysts, palladium is well known to be the most versatile catalyst in organic synthesis.[10] The increase of prices for many transition metals brought the need to focus on cheaper alternatives.

Iron is not only one of the least toxic but also one of the most abundant metals in nature.[11] It is not an accidental occurance, that iron, from ancient times[12a] to todays industrial importance,[12b] played an essential role in the progress of human societies.[12c] To the present day, iron catalysis has revealed a huge potential and covers almost the full scope of transformations which are relevant in organic synthesis.[13]

1.2 Iron catalyzed carbon-carbon bond formation via C–H functionalization

1.2.1 General

One of the major goals in C–H activation is the development of resource efficient and sustainable synthetic applications. Thus it is inspiring, that various iron compounds are incorporated in biological systems, such as cytochrome P-450. Hence, catalytic chemistry based on cytochrome P-450 modeling is well-documented.[14] Iron catalyzed C–H bond functionalization meets the requirements of high efficiency and sustainable synthetic processing.[13]

In particular, the iron-catalyzed functionalizations of $C(sp^3)$–H bonds is a versatile synthetic strategy to avoid the use of prefunctionalized substrates.[14] This chapter will give a short overview on iron-catalyzed carbon-carbon bond forming reactions via C–H bond functionalization, where at least one reaction center is an sp^3 hybridized carbon.

1.2.2 Iron catalyzed C–H / C–metal cross coupling reactions on $C(sp^3)$–H bonds

Organometallic reagents are reliable and versatile tools in organic synthesis. They play an important role in many synthetic strategies, including the field of C–H bond functionalizations.

The Kumaraswarmy group developed a direct oxidative coupling of allylstannanes with tetrahydroisoquinolines (Scheme 1.2).[15] Readily available iron(III) chloride hexahydrate was used as catalyst and aqueous *t*BuOOH as oxidant.
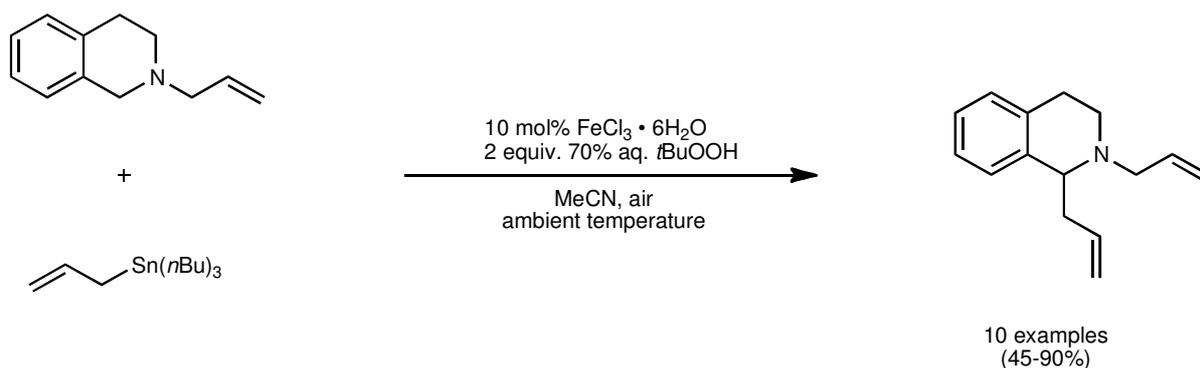
Scheme 1.2: Iron-catalyzed oxidative coupling of allylstannanes with tetrahydroisoquinolines.[15]

The authors proposed a tentative mechanism, where initial activation by $FeCl_3$–tBuOOH generates a metal coordinated iminium intermediate and intermolecular nucleophilic addition to this iminium ion leads to the observed product.[15]

The reaction substrates included morpholines, pyrrolidines and *N*-methylanilines. The method provided products, which are suitable for ring closing metathesis.

Vishwakarma and co-workers reported a $C(sp^3)$–H activation of the α-position of aliphatic ethers by an iron(III) oxide catalyzed coupling with Grignard or organolithium reagents (Scheme 1.3).[16]
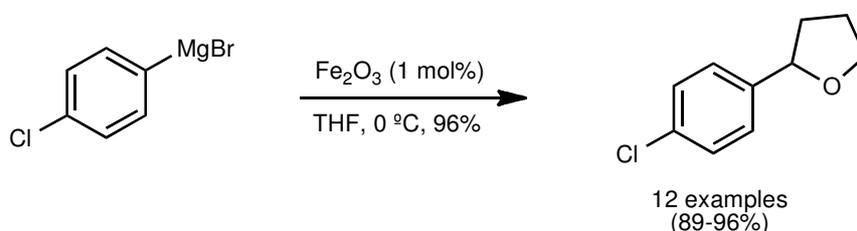
Scheme 1.3: Iron-catalyzed coupling of arylmagnesium halides with tetrahydrofuran.[16]

In 2010 Nakamura and co-workers reported an unconventional iron-catalyzed C–H activation.[17] The α-positions in cyclic and acyclic tertiary amines were arylated or alkenylated by Grignard or organozinc reagents under Fe(acac)$_3$ catalysis (Scheme 1.4).
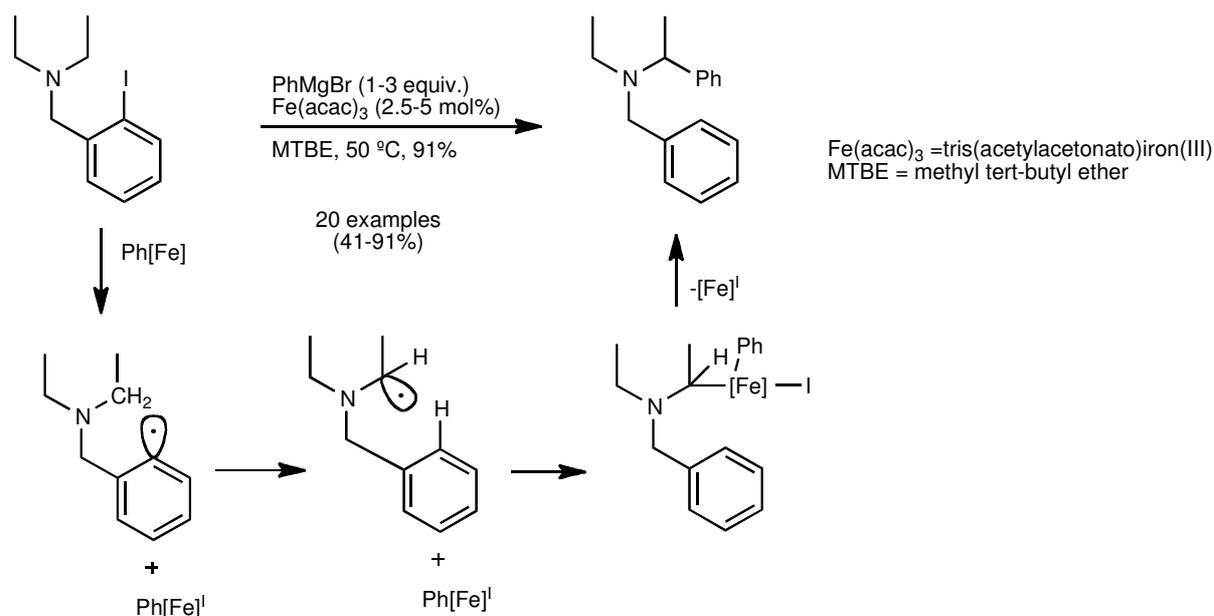
Scheme 1.4: Proposed mechanism of the iron-catalyzed C–C bond formation at α-position of aliphatic amines via C–H activation.[17]

The authors assumed that the reductive generation of an aryl radical from the iodoarene is followed by hydrogen abstraction from the α-position of the tertiary amine. The stabilized alkyl radical adjacent to the nitrogen could undergo oxidative addition to an aryliron complex and reductive elimination leads to C–C bond formation.[17]

1.2.3 C–C bond formation via cross-dehydrogenative-coupling

Among various methods to form carbon-carbon bonds, the direct coupling of of two C–H bonds would be the most efficient and straightforward method, by avoiding the use of organo halides or organometallic reagents.[13a] The construction of C–C bonds by direct formation from two C–H bonds under oxidative conditions was named as the cross-dehydrogenative-coupling (CDC).[18]

The first iron-catalyzed CDC reaction was reported by C.-J. Li and co-workers in 2007 (Scheme 1.5).[19]

R^1 = alkyl   R^3 = aryl
R^2 = alkyl   R^4 = aryl, alkyl, alkoxy

10-88%
18 examples
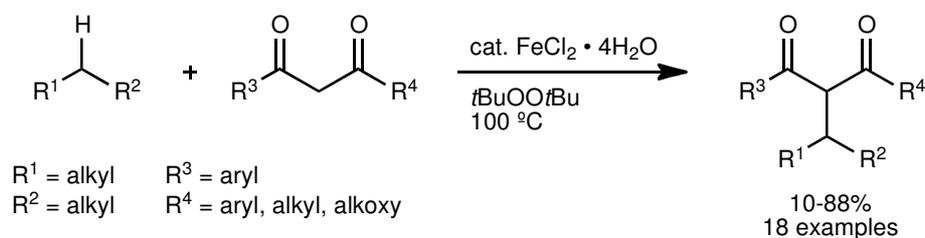
Scheme 1.5: Iron-catalyzed direct alkylation of 1,3-dicarbonyl compounds.[19]

The suggested mechanism for this reaction is given in Scheme 1.6. Li et al. assume, that the alkoxy radical derives from the iron-catalyzed decomposition of the peroxide. The radical species would then react with cyclohexane to give a cyclohexyl radical, whereas the alkoxy-iron complex would react with the β-keto ester to form a Fe enolate. The cyclohexyl radical would be able to react with the enolate to form the alkylated β-keto ester, and regeneration of Fe(II) restarts the catalytic cycle.[19]
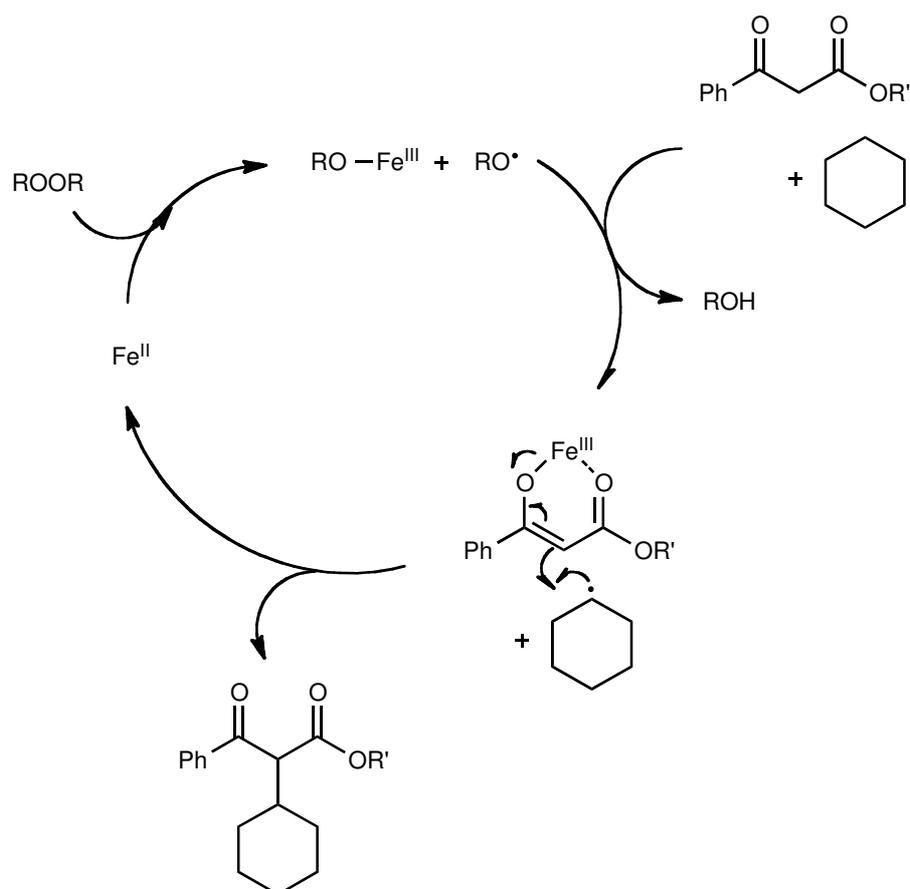
Scheme 1.6: Mechanism for the Fe-catalyzed alkylation of 1,3-dicarbonyl compounds as suggested by Li et al.[19]

The concept of cross-dehydrogenative-coupling is a growing field of scientific interest and some research effort has been invested to investigate the potential of this reactions. The CDC reactions are commonly classified according to different hybridizations of the both carbon reaction centers.[13a]

1.2.3.1 CDC between C(sp^3) and C(sp) bonds

A cross-dehydrogenative-coupling between sp^3 and sp C–H bonds was described by Volla and Vogel in 2009 (Scheme 1.7).[20] A direct alkynylation of C(sp^3)–H bonds adjacent to the N atom of both aromatic and aliphatic tertiary amines with terminal

alkynes was realized. The reaction was carried out without using a solvent in the presence of $FeCl_2$ as a catalyst and tBuOOtBu as an oxidant. A silyl group was applied for protecting one side of the terminal alkyne. After removing the protecting group Volla and Vogel were able to perform a second cross-dehydrogenative-coupling between the terminal alkyne and N,N-dimethyloctan-1-amine.
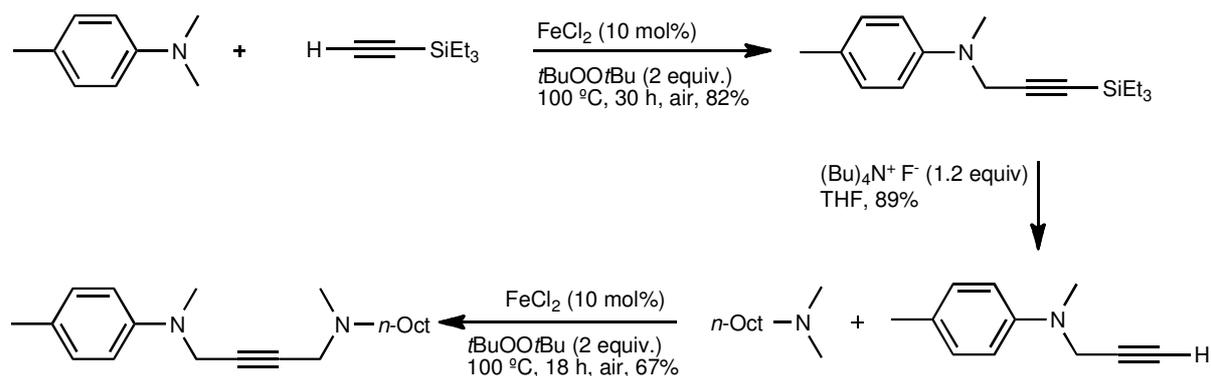
Scheme 1.7: Subsequent $FeCl_2$-catalyzed oxidative couplings with two different tertiary amines.[20]

As a mechanistic explanation the authors suggested the generation of iminium ions by iron catalyzed single electron transfer reactions. The iminium ions were then quenched by alkynyl anions, derived from the iron-acetylide indermediates, to form the desired products.[20]

1.2.3.2 CDC between $C(sp^3)$ and $C(sp^2)$ bonds

With the iron-catalyzed arylation of diphenylmethanes, Shi and co-workers reported a cross-dehydrogenative-coupling between sp^3 and sp^2 C–H bonds (Scheme 1.8).[21]
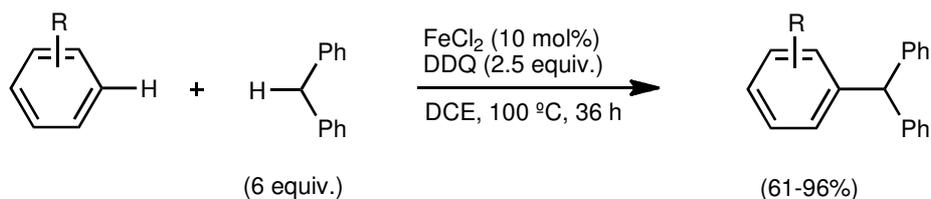
DCE = 1,2-dichloroethane
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Scheme 1.8: Iron-catalyzed cross-dehydrogenative-coupling of aryl C–H bonds with benzylic C–H bonds.[21]

Various electron-rich arenes and different diarylmethanes were suitable substrates with good regioselectivity, controlled by the electronic properties of the arenes. With the more electron rich arenes, double CDC reactions were also observed.[21] Aliphatic substrates were beyond the reactions scope.

1.2.3.3 CDC between two C(sp^3) bonds

A method for the CDC reaction of a single 1,3-dicarbonyl compound with different ethers was discovered by the group of Z. Li in 2008.[22b] With double alkylation of the methylene group from the methyl moiety of *N*,*N*-dimethylaniline Z. Li and co-workers reported a cross-dehydrogenative-coupling between two C(sp^3)–H bonds in 2009 (Scheme 1.9).[22a]

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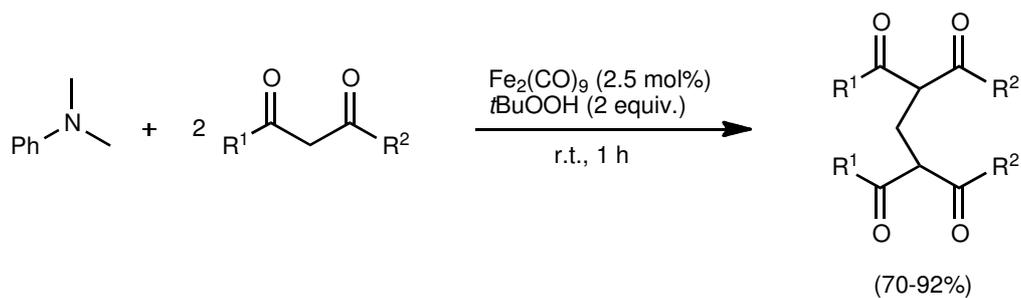
Scheme 1.9: Iron-catalyzed CDC of *N*-methyl amines with 1,3-dicarbonyl compounds.[22a]

I) Synthesis of the suggested reaction intermediate **A**.
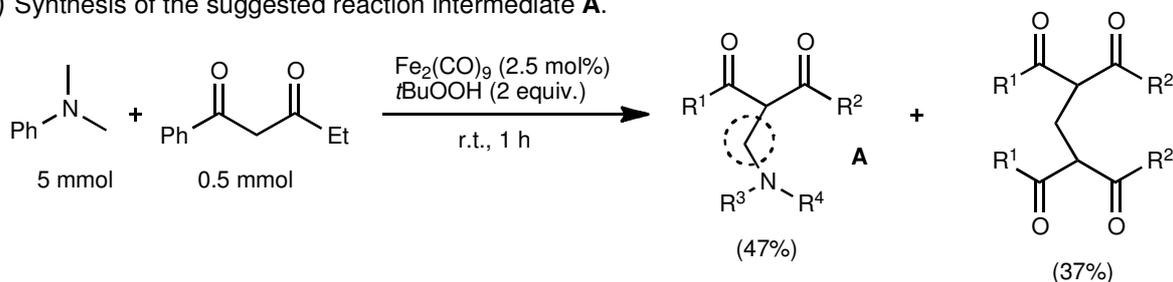
II) Proposed mechanism for the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds.
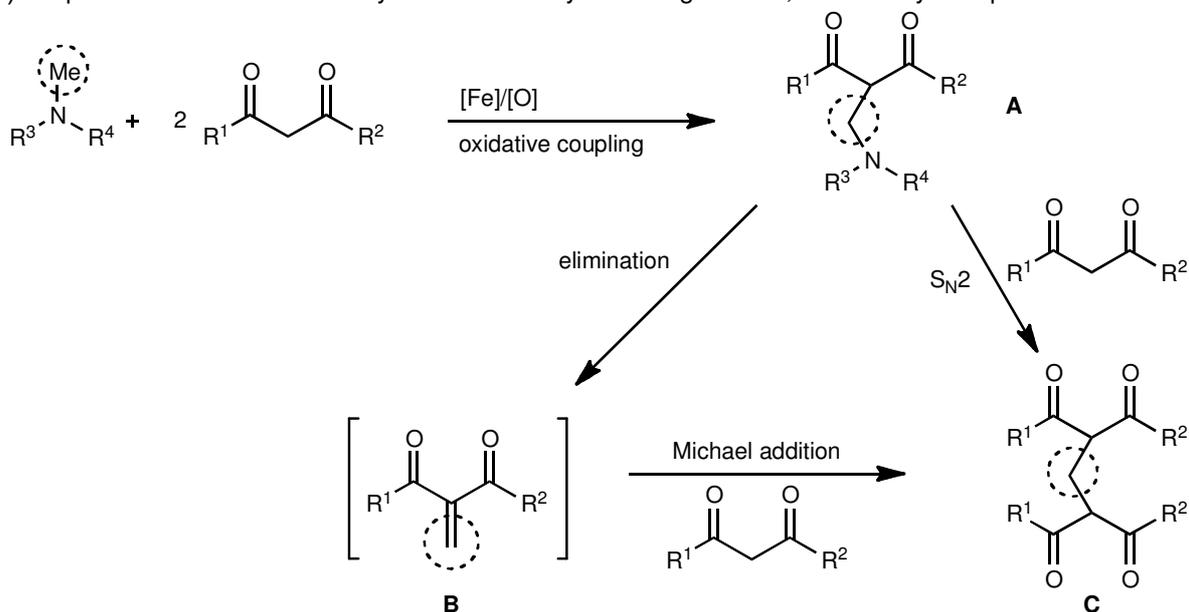
Scheme 1.10: Mechanistic study and suggested pathways for the iron-catalyzed CDC of *N*-methyl amines with 1,3-dicarbonyl compounds.[22a]

The authors reported, that the oxidative coupling product **A** was isolated in 47% yield together with 37% of **C** in the presence of 10 equivalents of *N,N*-dimethylaniline (Scheme 1.10 **I**).[22a] The isolated intermediate **A** was subjected to standard reaction conditions and **C** was obtained in 91% yield. Due to this result, the authors suggested that the oxidative coupling product **A** is most likely a possible intermediate for the reaction (Scheme 1.10 **II**).[22a] The product **C** is formed by either a nucleophilic substitution or a tandem Cope elimination / Michael addition via an intermediate **B**.[22a] Hence, Z. Li and co-workers pointed out that the reaction of 1,3-dicarbonyl compounds with formaldehyde (the presence of formaldehyde in this reaction was proven by a Nash test, for details see ref [22a]), which was generated *in situ* via iron-catalyzed oxidative *N*-demethylation, would also afford the methylene-bridged bis-1,3-dicarbonyl product **C**.[22a]

In 2013 Doyle and co-workers described an iron-catalyzed CDC reaction between sp^3 hybridized C–H bonds of aniline derivatives and sp^3 or sp^2 C–H bonds of several types of nucleophiles (Scheme 1.11).[23]
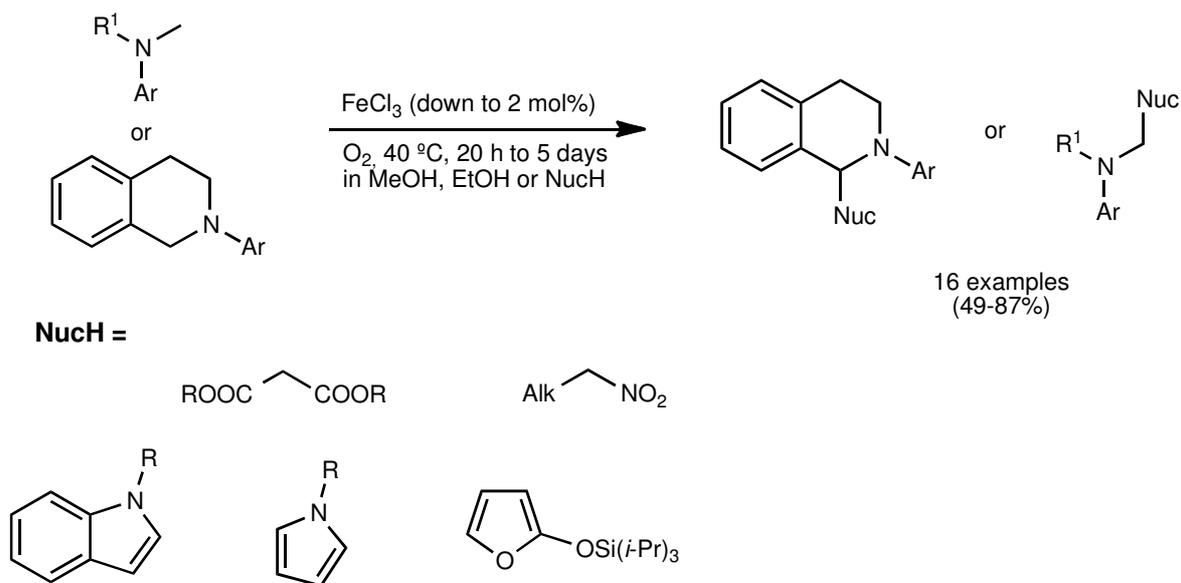
Scheme 1.11: FeCl$_3$ catalyzed oxidative coupling of tertiary amines with various nucleophiles.[23]

The Doyle group proposed a general mechanism for transition metal catalyzed oxidative N,N-dialkyanilines with *tert*-butyl hydroperoxide (TBHP).[24] The TBHP radical is the major oxidant in the rate-determining single electron transfer (SET) step that is followed by competing backward SET and irreversible heterolytic cleavage of the carbon–hydrogen bond at the α-position to nitrogen. A second SET completes the conversion of *N,N*-dimethylaniline to an iminium ion that is subsequently trapped by the nucleophilic solvent or the oxidant prior to formation of the product (Scheme 1.12).[24]
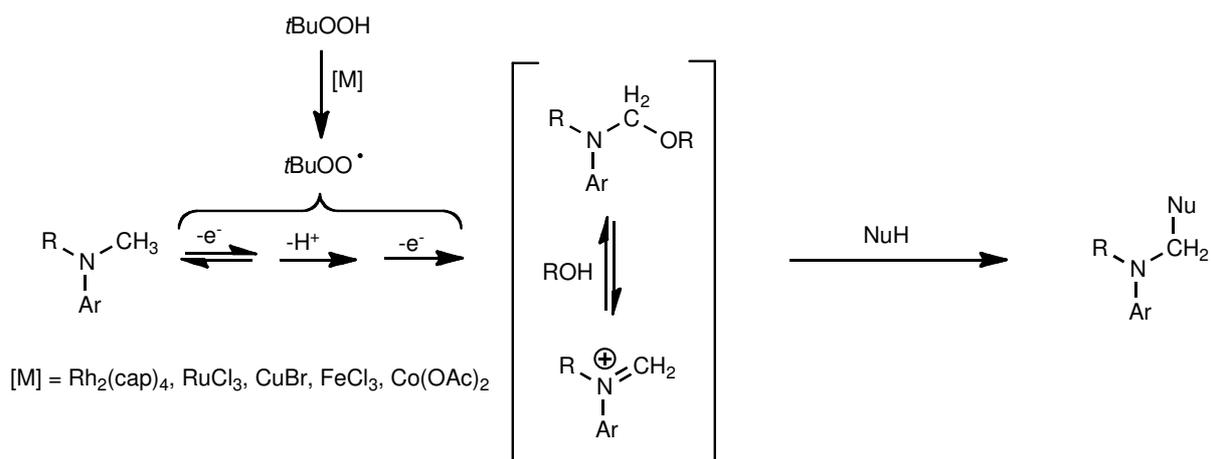
Scheme 1.12: General mechanism of oxidative Mannich reactions with TBHP, suggested by Doyle et al.[24]

In summary, iron-catalyzed cross-dehydrogenative-coupling has been demonstrated to be an attractive and versatile tool for the formation of C–C bonds under oxidative conditions. In the presence of simple and affordable catalysts like iron salts and cheap oxidants such as hydrogen peroxide, oxygen and TBHP the functionalization of various sp^3 C–H bonds by other C–H bonds can be performed without the need of prefunctionalized reagents such as halides, pseudohalides or metals.

1.3 Cyanides

1.3.1 General

Nitriles are important building blocks in organic chemistry, their applications include the synthesis of many products, such as dyes, herbicides, pesticides and drugs.[25] Furthermore, the nitrile group serves as a platform for the generation of functional groups, like amino, amidino, tetrazolidino, amido groups, aldehydes or carboxylic acids.[26a]

Their importance in organic chemistry and the demand for a safe to handle synthesis of nitriles has triggered research towards employing less toxic or completely non-toxic cyanide sources.[26b] This chapter gives a short overview on the methods applied for the cyanation of organic compounds. It moves from common nitrile syntheses to more recent synthetic strategies highlighting less toxic cyanide surrogates.

1.3.2 Prussic acid and potassium cyanide – classical approaches on the synthesis of nitriles

The classical pathways to synthesize arylnitriles are the Sandmeyer reaction[27] and the Rosenmund-von Braun reaction (Scheme 1.13).[28]

Sandmeyer reaction

$$Ar-N_2^{\oplus} \; X^{\ominus} \quad \xrightarrow[\text{60 - 100 ºC}]{\text{CuCN}} \quad Ar-CN$$

Rosenmund-von Braun reaction
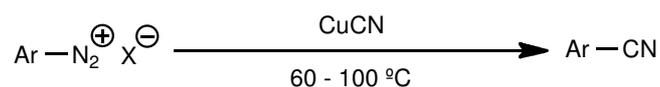
$$Ar-X \quad \xrightarrow[\text{polar solvent, 60 - 100 ºC}]{\text{CuCN}} \quad Ar-CN$$
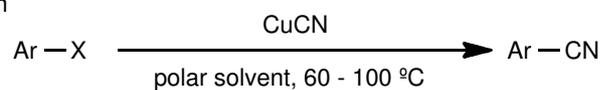
(X = I, Br)

Scheme 1.13: Classical reactions for the synthesis of aryl nitriles.

With the need of stoichiometric amounts of CuCN and their relatively harsh reaction conditions, both reactions tend to have significant disadvantages. Avoiding these problems, alternative reactions have been developed to synthesize nitriles.[29] Especially transition metal catalysis has turned out to be a promising tool to synthesize nitriles.[30] In industry the standard method to generate aliphatic nitriles is the nickel catalyzed hydrocyanation where HCN gas is used as a cyanide source (Scheme 1.14).[31]
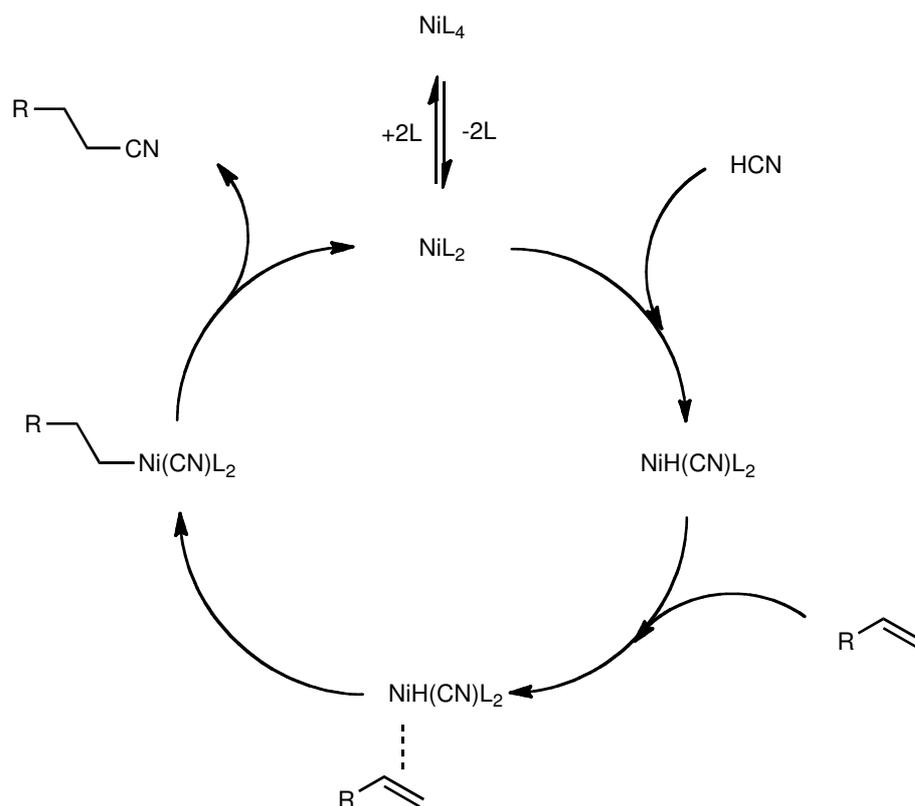
Scheme 1.14: Hydrocyanation reaction.[31]

Other metal or metalloid bound cyanide sources have been successfully employed in transition metal catalyzed nitrile synthesis, such as KCN, [32] NaCN, [33] Zn(CN)$_2$, [34] trimethylsilylcyanide(TMSCN)[35] and K$_4$[Fe(CN)$_6$][36] (Scheme 1.15).
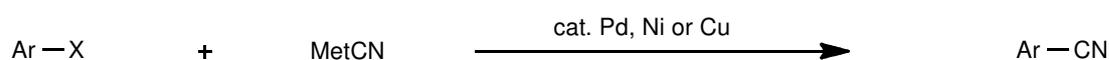
X = I, Br, Cl, OTf

MetCN = KCN, NaCN, Zn(CN)$_2$, TMSCN, K$_4$[Fe(CN)$_6$]

Scheme 1.15: Transition metal catalyzed synthesis of aryl nitriles.[37]

However, the described methods tend to have severe disadvantages. In particular expensive transition-metal catalysts are needed, which require careful regulation of

the cyanide concentration, to avoid the formation of inert metal-cyanide complexes.[38] And nevertheless, most of these methods still suffer from the disadvantage to require highly toxic cyanide sources.

1.3.3 Cyanohydrins as source of cyanides in organic synthesis

The development of non-toxic cyanide sources has been object of research in recent years. Cyanohydrins have been used as surrogates of highly toxic CN-salts. In particular acetone cyanohydrin has been successfully applied as a cheap and relatively save alternative cyanide source. [39]

In 2003, Beller and co-workers described the first Pd-catalyzed cyanation of aryl halides using acetone cyanohydrin as the CN-source (Scheme 1.16).[40] To avoid poisoning of the catalyst, acetone cyanohydrin was added continuously in small amounts over the whole reaction time. [38c,41]
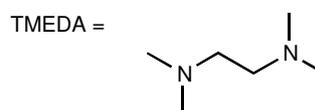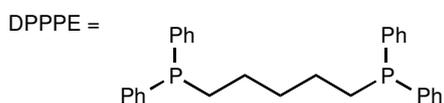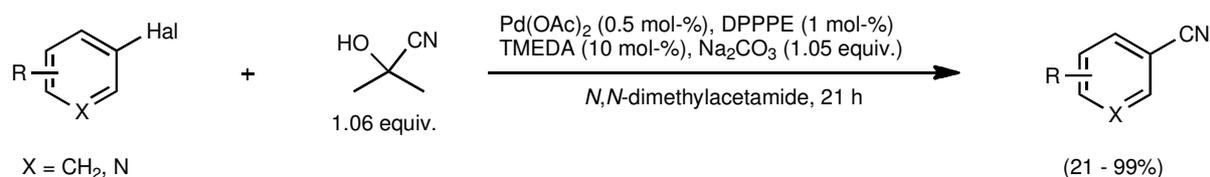
Scheme 1.16: Pd-catalyzed cyanation of aryl halides.[41]

Cyclohexanone cyanohydrin as CN-source was employed by the Taran group in 2010 to furnish a Pd-catalyzed decarboxylative cyanation of arene carboxylic acids (Scheme 1.17). [42]
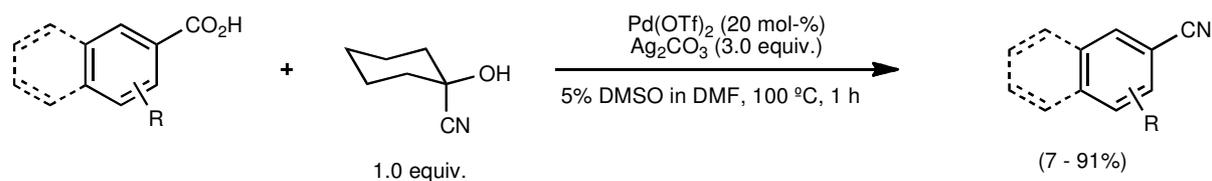
Scheme 1.17: Decarboxylative cyanation of arene carboxylic acids.[42]

In order to avoid deactivation of the Pd-catalyst, Beller's method was adapted, and cyclohexanone cyanohydrin was slowly added over the whole reaction time.

A direct, ruthenium catalyzed cyanation of tertiary aryl amines employing acetone cyanohydrin as CN-source was reported by Sain and co-workers in 2011 (Scheme 1.18).[43] A remarkable feature of the described method is the application of acetone cyanohydrin both as CN-source and solvent.
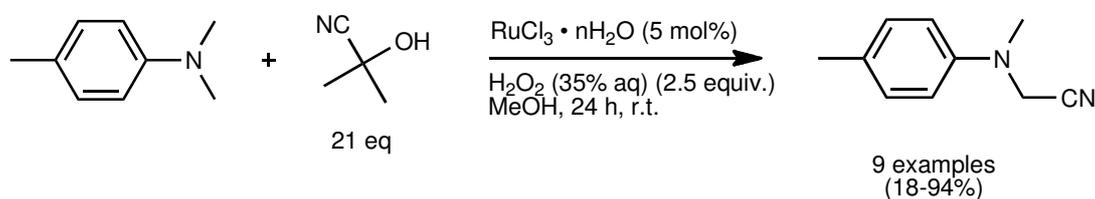
Scheme 1.18: Ru- catalyzed cyanation of tertiary amines.[43]

Though cyanohydrins seem to be an alternative source for cyanide ions, their production requires highly toxic CN-salts. Their status as less-toxic surrogates for KCN and NaCN is therefore questionable.

1.3.4 Solvents as direct source of cyanides

A method using the solvent as CN-source, was reported by Cheng and co-workers already in 1998. In these Pd- or Ni-catalyzed reactions, compared to acetone cyanohydrin much less toxic alkyl nitriles, such as acetonitrile were used as cyanide source (Scheme 1.19).[35]

R² = CH₃, 100%
      CH₃CH₂, 61%
      CH₃(CH₂)₂, 50%
      PhCH₂, 97%
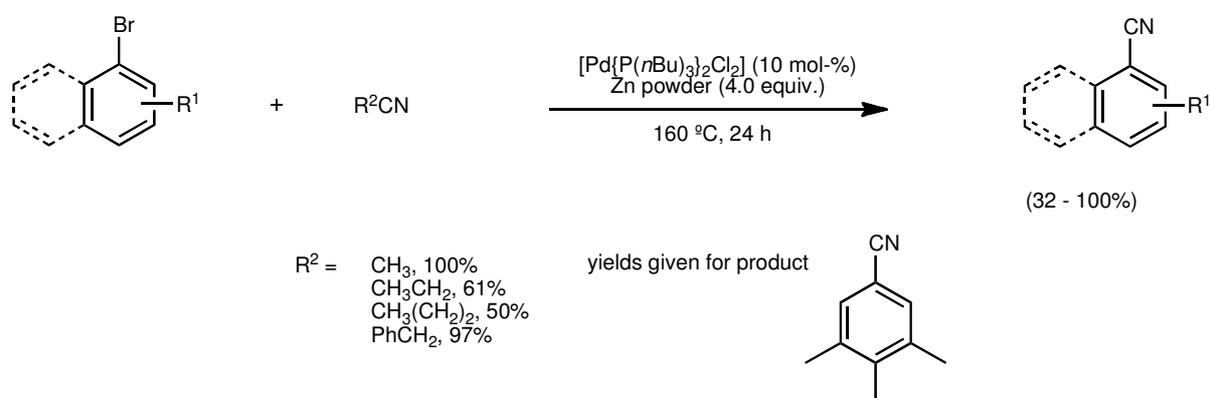
Scheme 1.19: Pd- catalyzed cyanation of aryl halides.[35]

1.3.5 *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide as a less toxic CN-source

Beller and co-workers explored another pathway for the generation of aryl nitriles, employing *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as an easy to provide CN-source.[44]

The synthesis of NCTS was first published in 1949 by Frederick Kurzer.[45] This N-bound cyanide source can easily be furnished without using any toxic CN-salts (Scheme 1.20).
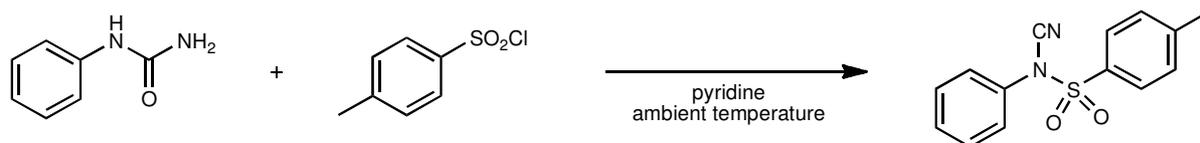
Scheme 1.20: Synthesis of NCTS by F. Kurzer.[45]

In 2011, the Beller group developed a Rh-catalyzed cyanation method in which NCTS and aryl boronic acids reacted to aryl nitriles (Scheme 1.21).[44a] The proposed mechanism suggests, that no HCN is generated within the catalytic cycle (Scheme 1.22).[44a]
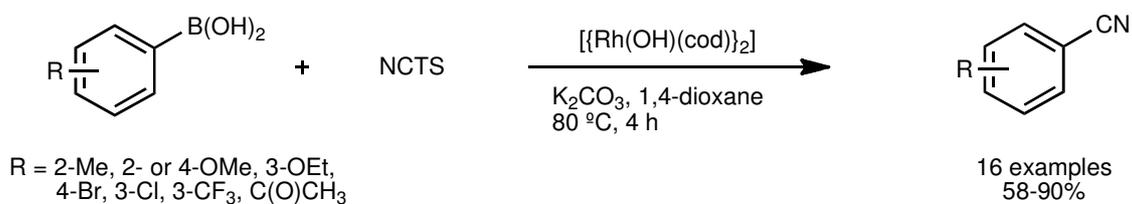
Scheme 1.21: Rh-catalyzed cyanation of aryl boronic acids using NCTS as CN-source.[44a]
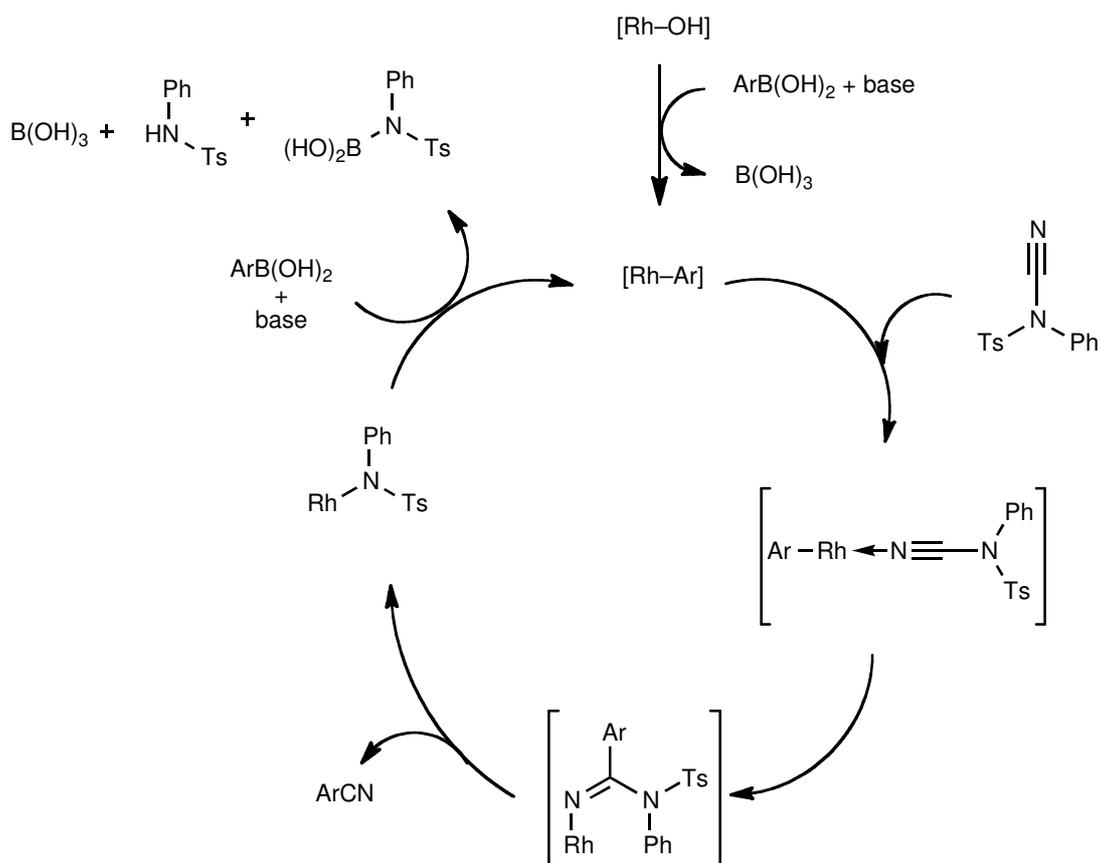
Scheme 1.22: Suggested mechanism for the Rh-catalyzed cyanation of boronic acids.[44a]

Furthermore, NCTS was employed by Beller and co-workers in an electrophilic cyanation of aryl-Grignard-reagents[44b] Aryl nitriles were generated through addition of NCTS to the lithiated aryl bromides (Scheme 1.23).[46, 44b]
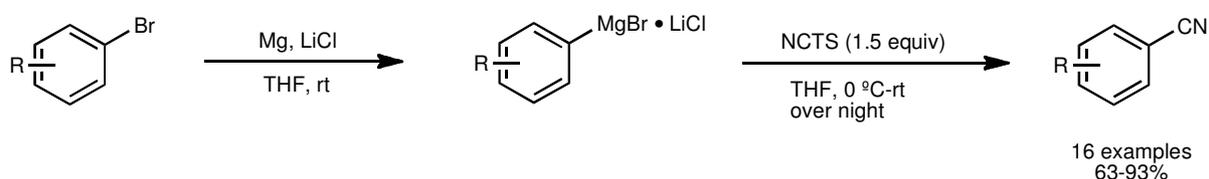
Scheme 1.23: Cyanation of aryl bromides by NCTS.[44b]

An electrophilic cyanation, using NCTS, was also reported by Wang and co-workers in 2011 (Scheme 1.24). [47]
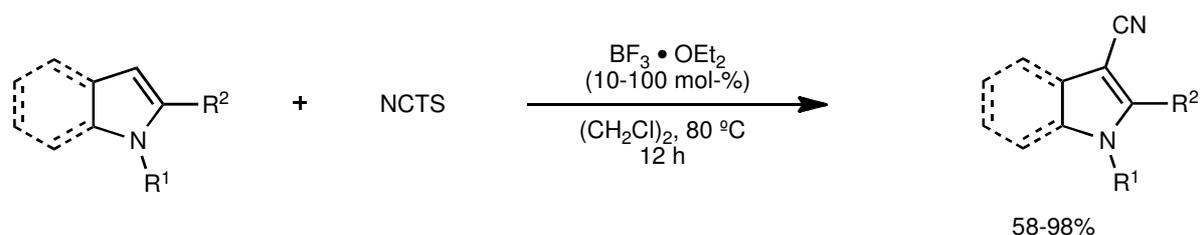
Scheme 1.24: Cyanation of indoles and pyrroles using NCTS.[47]

1.3.6 Multi component cyanide sources

Another approach to achieve the cyanation of organic molecules without the use of toxic CN salts is given in the concept of "combined" cyanide sources. Herein, the reaction partner cyanide is generated in situ from two separate molecules, which are less toxic and easy to handle.[35]

N,N-Dimethylformamide (DMF) is a commonly used solvent in organic chemistry. It has also been shown to be a very versatile precursor for the generation of several functional groups, such as O, CO, NMe_2, $CONMe_2$, Me and CHO.[48]

In 2009, Jia and co-workers disclosed the development of a CN-source by a Pd-catalyzed direct cyanation of 2-phenylpyridines employing DMF and aqueous ammonia(Scheme 1.25).[49]

A similar method was employed by Kim and Chang for the Cu-catalyzed reaction of DMF and aqueous ammonia in 2010.[50]
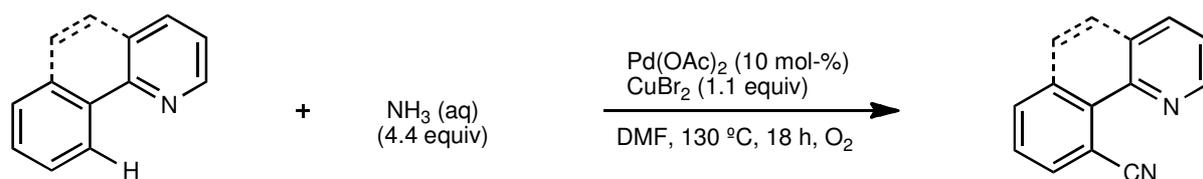
Scheme 1.25: Direct cyanation of 2-phenylpyridines with DMF and ammonia.[49]

Formation of the cyanide was investigated by using both isotopically labeled DMF and ammonia and a mechanism shown in Scheme 1.26 was proposed. [51]
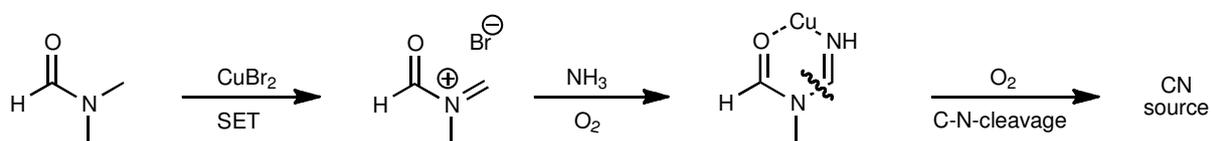
Scheme 1.26: Proposed mechanism for the generation of cyanide from DMF and ammonia.[51]

The authors suggested, that a Cu(II)-mediated single-electron transfer takes place first, converting DMF to an iminium species, which reacts with ammonia to afford an amidine intermediate.[35,51] The C–N bond cleavage of amidine was assumed to proceed under the employed oxidative conditions, thus releasing the cyano moiety.[35,51]

Cheng and co-workers reported the direct Pd-catalyzed cyanation of indoles by using dimethylsulfoxide (DMSO) and ammonium bicarbonate as the combined CN-source (Scheme 1.27). [52]
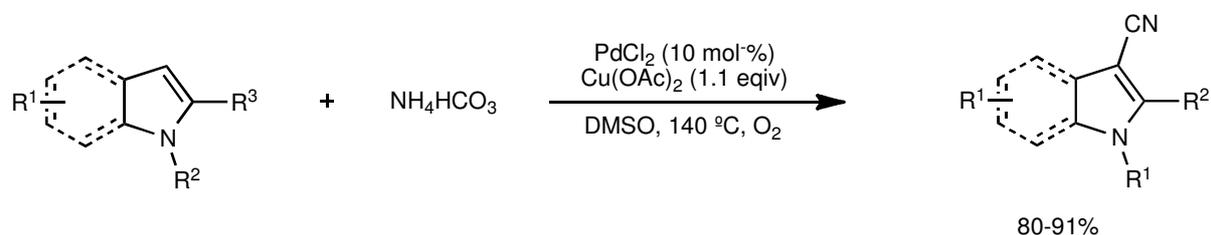
Scheme 1.27: Direct cyanation of hetero arenes using DMSO and NH$_4$HCO$_3$.[52]

Cheng and co-workers could also achieve the direct Cu-catalyzed cyanation of aryl halides by using DMF and ammonium bicarbonate.[53]

A mixture of DMF and ammonium iodide was employed by Chang and co-workers to achieve direct cyanation of aryl and alkenyl boronic acids.[54] The scope of this method also comprised the direct cyanation of electron rich arenes (Scheme 1.28).[54]

$$Ar-B(OH)_2 \quad + \quad NH_4I \quad \xrightarrow[\text{DMF, 130 ºC, 18 h, O}_2]{\substack{\text{Cu(NO}_3)_2 \bullet 3\,H_2O\ (2.0\ equiv) \\ \text{HOAc (2.0 equiv)}}} \quad \begin{array}{c} Ar-CN \\ \text{59-99\%} \end{array}$$
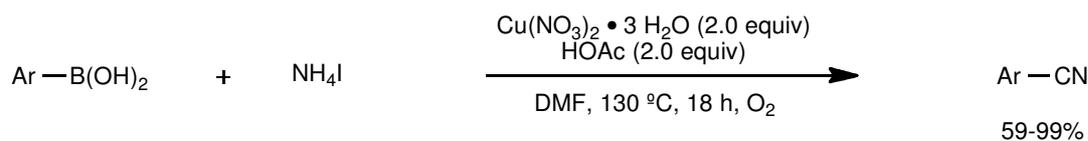
Scheme 1.28: Direct cyanation of electron rich arenes using NH_4I and DMF.[54]

In 2011, Ding and Jiao described the Pd-catalyzed direct cyanation of indoles by using only DMF as the CN-source.[55] The work of Bhanage et al. also described the in situ generation of cyanide just employing formamides (Scheme 1.29).[56]

$$Ar-X \quad + \quad \underset{H}{\overset{O}{\|}}\!\!-\!\!NH_2 \quad \xrightarrow[\text{140 ºC, 48 h, N}_2]{\substack{\text{Pd(OAc)}_2\ (5\ \text{mol-\%}) \\ \text{xantphos (10 mol-\%)} \\ \text{POCl}_3\ (2.0\ \text{equiv})}} \quad \begin{array}{c} Ar-CN \\ \text{53-93\%} \end{array}$$

X=I, Br

xantphos
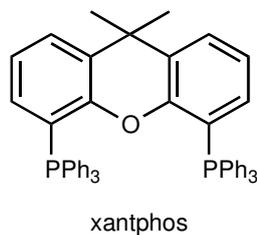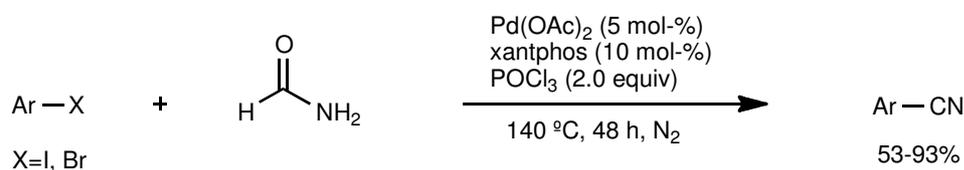
Scheme 1.29: Cyanation of aryl halides using formamide.[56]

The postulated mechanism for a Pd-catalyzed cyanation of aryl halides is shown in Scheme 1.30.[56] The authors suggested that cyanation of aryl halides with

formamide may generate benzamide as an intermediate that undergoes the sequential dehydration, thus leading to benzonitrile products.[56]
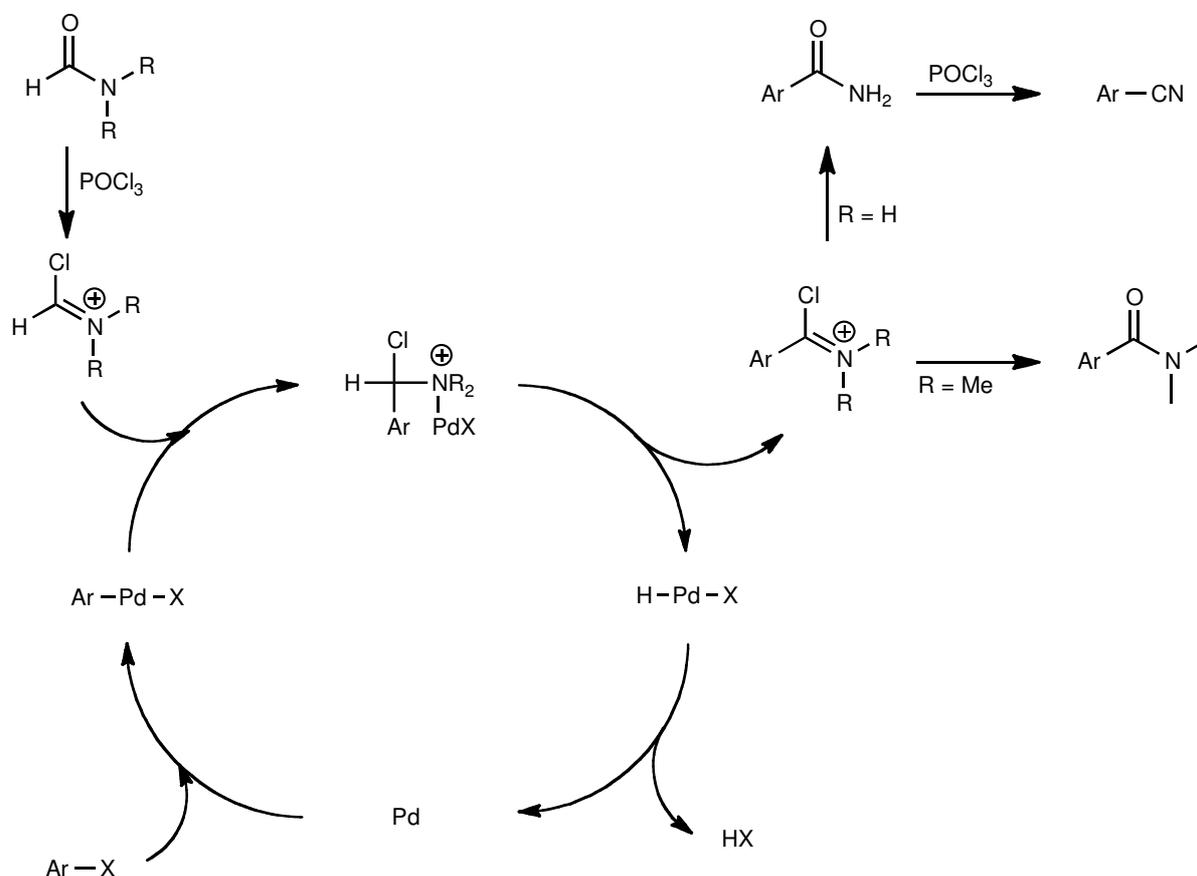
Scheme 1.30: Postulated mechanism for a Pd-catalyzed cyanation of aryl halides.[56]

1.3.7 Potassium thiocyanate – an approach from the 19th century

Although some efforts were taken to investigate new metal free and less toxic cyanide sources, like developing "combined" CN-sources, it is surprising that the very simple thiocyanate has not been in focus of research.

In 1857 Hugo Schiff reported the generation of benzonitrile from benzoyl chloride and potassium thiocyanate.[57] Edmund A. Letts discovered in 1872 that benzoic acid and potassium thiocyanate reacted to give benzonitrile (Scheme 1.31).[58]
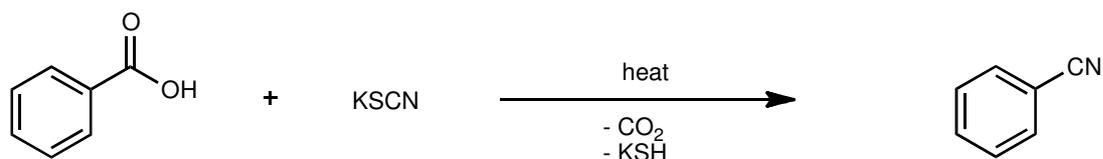
Scheme 1.31: Letts nitrile synthesis.[58]

Improving the Letts reaction by using the zinc(II) salt of the acid, done by E. E. Reids, was the last major improvement of the application of thiocyanates as CN-sources for a long time.[59]

In 2006 Zhang and Liebeskind described a Pd-catalyzed cross coupling reaction of benzyl thiocyanates with arylboronic acids (Scheme 1.32).[60]

R = (hetero) aryl, alkenyl

TC = thiophene-2-carboxylate
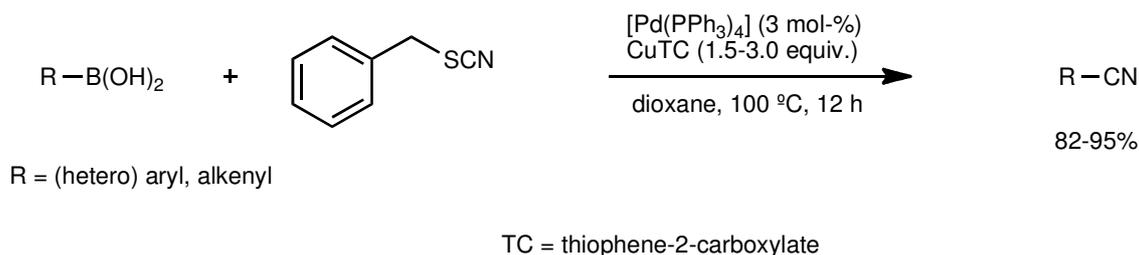
Scheme 1.32: Cyanation of aryl- and alkenylboronic acids with benzylthiocyanate.[60]

Scheme 1.33 shows the proposed mechanism, for the reaction of aryl- and alkenylboronic acids with benzylthiocyanate. [60,61]

The authors suggested that the cyanation may start with an oxidative addition of benzoyl thiocyanate to Pd^0,[35,61] followed by the transmetallation from boron to palladium and then reductive elimination. Additionally, it was suggested that the copper additive acts as a thiophilic reagent agent to enhance the polarization of the palladium-thiolate bond, while simultaneously providing borophilic activation by coordination of carboxylate to the boron atom.[35,61]
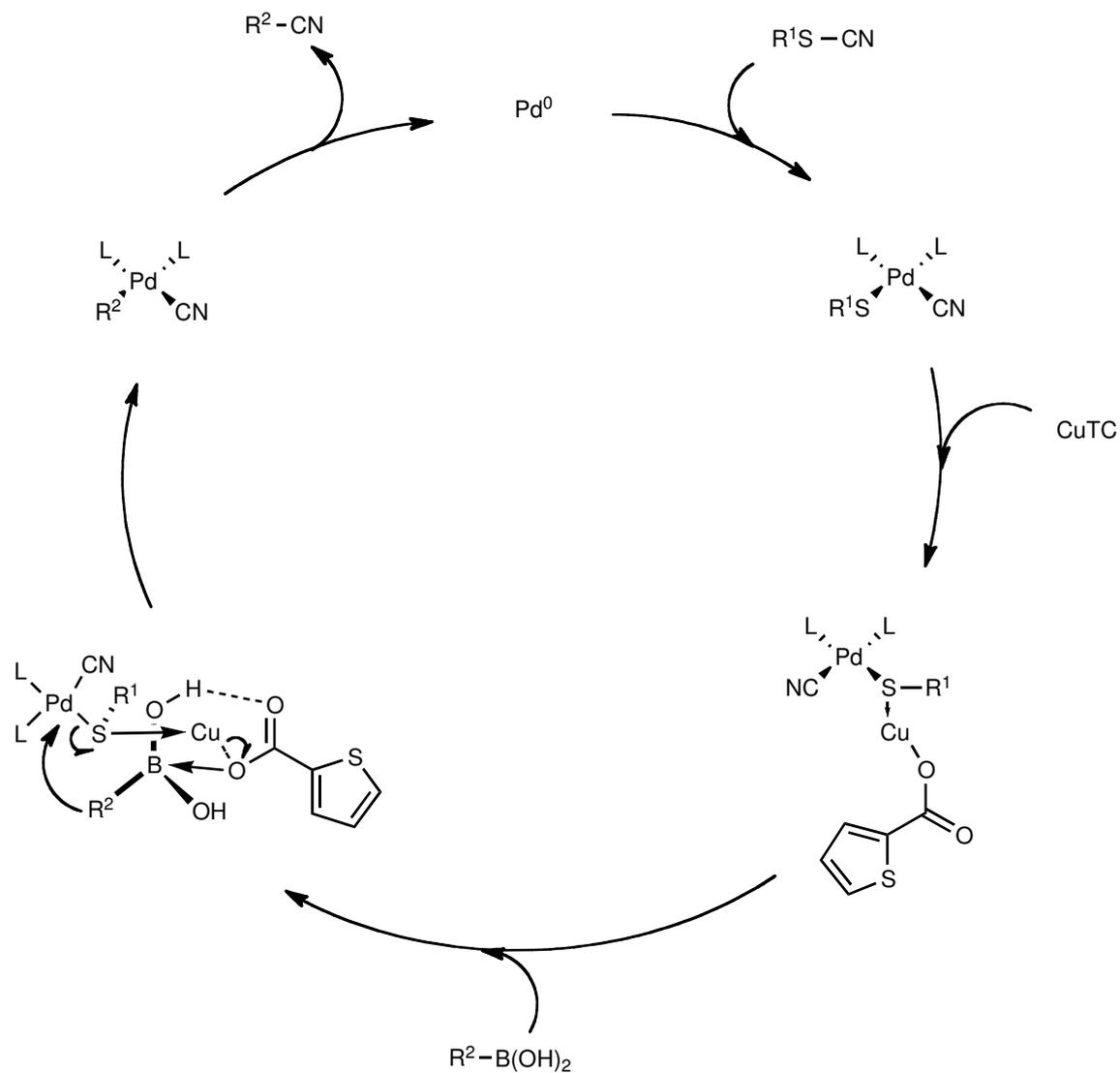
Scheme 1.33: Proposed mechanism, for the reaction of aryl- and alkenylboronic acids with benzyl thiocyanate.[61]

1.4 Objectives

Nitrogen-containing compounds can frequently be found among natural products, biological active molecules and therapeutic drugs.[25] Therefore, functionalization of nitrogen-containing compounds has attracted considerable attention.[26b,35] In particular the nitrile group serves as a very versatile building block for the generation of functional groups.[26a]

An iron catalyzed cyanation of tertiary aryl amines was developed by Wei Han in 2009 (Scheme 1.34).[62]
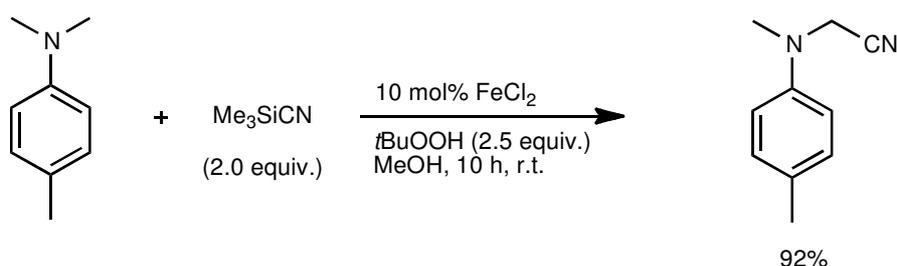
Scheme 1.34: Cyanation of a tertiary aryl amine by Wei Han.[62]

One aim of this Thesis was the expansion of the substrate scope of the α-cyanation to aliphatic and allyl substituted amines. Further studies should explore the selectivity of this reaction as well as possibilities for its application beyond the scope of a simple cyanation. Especially the exploration of multi step reactions was in the focus. The use of tertiary allyl amines would provide the option to combine α-cyanations with additions on alkenes in a one-pot synthesis (Scheme 1.35).
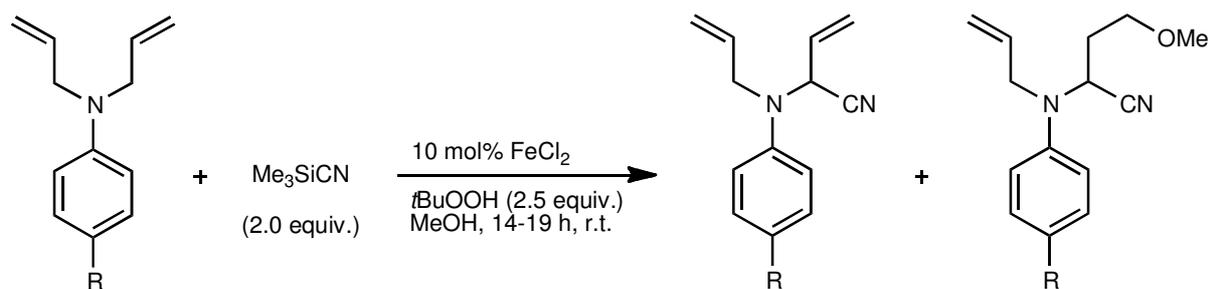
Scheme 1.35: Multi step reaction which combines α-cyanations with additions on alkenes.

Most methods for the synthesis of nitriles suffer from the disadvantage to require highly toxic cyanide sources. The development of non-toxic cyanide sources has therefore been subject of research in the last years. However, most of the cyanide sources reported as non-toxic alternative still have a significant level of toxicity (Table 1.1).

Table 1.1: Toxicity of different CN sources used for oxidative α-cyanations of tertiary amines.[73]

Compound	LD50[a] [mg·kg^{-1}]		Danger Pictograms[a]
NaCN	1.67	(intramuscular, rabbits),	
	4.3	(intraperitoneal, rats)	
	4.8	(oral, rats)	
	10.4	(dermal, rabbits)	
KCN	4	(intraperitoneal, rats),	
	7.5	(oral, female rats),	
	14.3	(dermal, rabbits)	
malononitrile	19	(oral, mice)	
acetone cyanohydrin	15.8	(dermal, rabbits)	
	18.7	(oral, rats)	
ethyl cyanoformate		no data available	
trimethylsilyl cyanide		no data available	
trimethylsilyl azide[b]		no data available	
benzoyl cyanide	37.6	(oral, rats)	
benzyl cyanide	270	(oral, rats)	
	270	(dermal, rabbits)	
potassium thiocyanate	854 (oral, rats)		

[a] According to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS Classification) compounds with LD$_{50}$ < 300 mg kg^{-1} are classified as toxic (data from MSDS sheets by Sigma-Aldrich, Steinheim, Germany, Dec. 12th, 2014). [b] Trimethylsilyl azide (N source) and 1,2-dichloroethane (C source) were used as a combined source of CN, see ref 7a-c in Chapter 4.

One major goal of this Thesis was the development of a most simple and versatile method for the cyanation of tertiary amines, which employs an easy to access and non-toxic cyanide source. This could be achieved with the employment of potassium thiocyanate as described in Chapter 4.

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2

Iron-Catalyzed Generation of α-Amino Nitriles from Tertiary Amines

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2.1 Introduction

The direct transformation of ubiquitous CH bonds of organic molecules has recently moved to the center of synthetic organic chemistry.[1] In many cases, heteroatoms in the substrate cause a differentiation of the intrinsic reactivities of the CH bonds in their vicinity and facilitate selective reactions without the extra steps needed for the prefunctionalization of a certain position in the substrate.[2] In particular, CH bonds adjacent to the nitrogen atom of amines can be oxidatively functionalized with high selectivity as shown by the rapid development of cross dehydrogenative couplings (CDC) and related reactions in the past decade that were often exemplified by using tetrahydroisoquinolines or *N,N*-dimethylanilines as substrates. [3,4]

According to recent mechanistic studies, a sequence of electron–proton–electron transfer reactions and final interception by nucleophilic solvent or oxidant converts tertiary amines in the presence of transition metal catalysts and oxidants to hemiaminals or *N,O*-acetals which are in equilibrium with iminium ions (Scheme 2.1).[5,6] Trapping of the electrophilic iminium ions with a variety of nucleophiles has been exploited,[3-5,6a] e.g., for alkynylations,[7] (hetero)arylations,[8] phosphonations,[9] reactions with enolizable nucleophiles[10] and many other α-functionalizations of tertiary amines. [11]
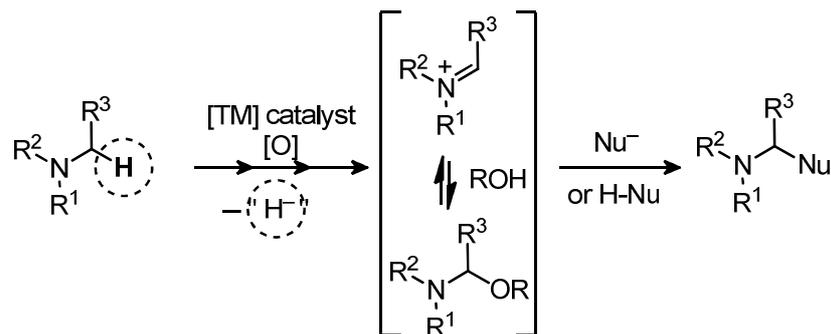
R[1] = aryl or alkyl, R[2] = alkyl, R[3] = H, alkyl or aryl
OR = OMe (from solvent MeOH), OH (from H_2O, oxidation side product)
     or OOtBu (from oxidant)

Scheme 2.1. Transition metal (TM)-catalyzed oxidative α-functionalization of tertiary amines.

In recent years α-cyanation has evolved to an often studied test reaction for the oxidative α-functionalization of tertiary amines.[12-15] The thus generated α-amino nitriles are highly interesting synthetic targets owing to their versatility as intermediates in organic transformations and occurrence in natural products.[16] Numerous transition metals (Ru,[17] Cu,[18] V,[19] Au,[20] Mo,[21] Co[22]) without or with ligands have been employed as catalysts for the amine cyanation in combination with peroxides or molecular oxygen as oxidants. Cheap sodium or potassium cyanide worked excellently as cyanide sources, but efforts were also undertaken to use less toxic cyanation reagents, such as trimethylsilyl cyanide,[23] cyanohydrins,[24] ethyl cyanoformate,[25] or malononitrile.[18]

Iron is not only one of the least toxic but also one of the least expensive metals that possesses the ability to catalyze direct CH transformations.[26,27] Iron-containing heme and non-heme enzymes are catalysts for a variety of oxidative reactions,[28,29] and structurally related phthalocyanine- and oligopyridine-complexed iron(II) salts

efficiently catalyze oxidative cyanations of tertiary amines.[30,31] However, designed ligands are not prerequisites for the catalytic activity of iron salts.[32-37]

We reported recently that various α-amino nitriles can be synthesized selectively and under mild conditions by oxidizing tertiary amines with catalytic amounts of iron salts and *tert*-butyl hydroperoxide as oxidant.[34a] The conversion of *N,N*-dimethyl-*p*-toluidine (**1a**) to 2-[methyl(*p*-tolyl)amino]acetonitrile (**2a**) was used to optimize the catalyst system for the α-cyanation of *N,N*-dialkylanilines. We found that **2a** was formed in optimum yield of 92% from **1a** and trimethylsilyl cyanide (2 equiv.) when catalytic amounts of FeCl$_2$ (10 mol%) were combined with 2.5 equiv. of *tert*-butyl hydroperoxide as oxidant in methanol (Scheme 2.2).[34a]
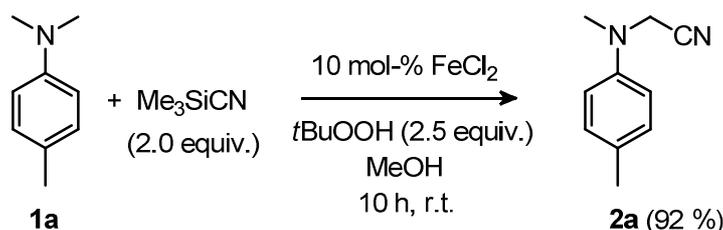
Scheme 2.2. FeCl$_2$-catalyzed α-cyanation of **1a** with trimethylsilyl cyanide and *tert*-butyl hydroperoxide.[34a]

The optimized reaction conditions were generally applicable for the oxidative cyanation of ring-substituted anilines and cyclic *N*-phenylamines and allowed the isolation of the α-functionalized amines **2a–l** (Scheme 2.3).[34a] Biscyanation in α- and α′-positions to the nitrogen of *N*-phenylpyrrolidine with 4 equiv. of trimethylsilyl cyanide gave **2l′** that was characterized by X-ray crystallography.[34b]

2a (X = 4-Me, 92 %) **2f** (X = 4-Br, 78 %)
2b (X = 3-Me, 89 %) **2g** (X = 2-Br, 85 %)
2c (X = 2-Me, 76 %) **2h** (X = 3-NO$_2$, 80 %)
2d (X = H, 90 %)   **2i** (X = 4-NO$_2$, 45 %)
2e (X = 4-OMe, 87 %)

2j (X = H, 85 %)
2k (X = OMe, 83 %)   **2l** (82 %)   **2l'** (54 %)
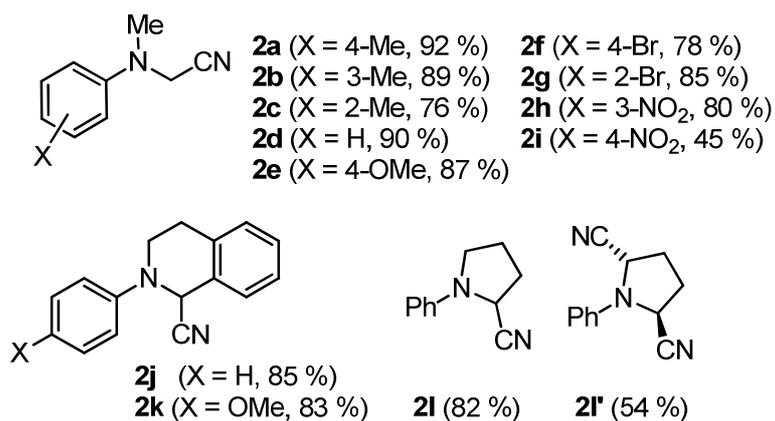
Scheme 2.3. α-Amino nitriles obtained by FeCl$_2$-catalyzed cyanations of aniline derivatives with trimethylsilyl cyanide and *tert*-butyl hydroperoxide.[34]

We have now extended the scope of this cyanation reaction with regard to functional group tolerance and amines used. Furthermore, we show that oxidative degradation of *N,N*-dialkylanilines to *N*-alkylanilines can be combined with solvent oxidation to establish an unprecedented access to amino-substituted acetonitriles.

2.2. Results and Discussion

2.2.1. Iron-Catalyzed Cyanations of Aromatic and Aliphatic Tertiary Amines

Table 2.1 shows that a series of *N,N*-dialkylated anilines underwent α-cyanation under the standard reaction conditions defined in Scheme 2.2. The presence of an *N*-naphthyl substituent resulted in a slight retardation of the oxidative cyanation at the dimethylamino moiety. Nevertheless, *N,N*-dimethyl-1-naphthylamine (**3**) was converted in good yield of 72% to 2-[methyl(naphth-1-yl)amino]acetonitrile (**4**).

The cyanations of methyl-, methoxy-, bromo-, and nitro-substituted anilines (Scheme 2.3) already showed that several functional groups are tolerated as ring substitutents in the *N,N*-dimethylanilines (Scheme 2.3).[34a] Furthermore, the linkage of a *p*-ethoxycarbonyl or a *p*-benzoyl group to the aniline substrate was compatible with the cyanation reaction and gave acceptable yields of **6** (74%) and **8** (85%), respectively.

Although two dimethylamino groups are available in Michler's ketone **9**, only one of them was cyanated under the standard reaction conditions. Probably the connection of the two dimethylamino groups through conjugated sp^2-hybridized carbon atoms decreases the reactivity of the remaining NMe_2 group after oxidation and functionalization of the first NMe_2 group.

Separation of the conjugated systems by a methylene group, as in bis[4-(dimethylamino)phenyl]methane (**11**), resulted in undisturbed and independent reactivity of both dimethylamino units of **11** which led to the symmetrical bis-cyano product **12** in 68% yield when the reaction was performed with a moderately increased amount of cyanating agent (3.0 equiv. of trimethylsilyl cyanide used instead of 2.0 equiv.). Oxidation or competing cyanation of the CH_2 group in the benzylic position was not observed.[38]

Table 2.1. FeCl$_2$-catalyzed oxidative α-cyanations of *N,N*-dialkylated anilines.

Entry	Amine		Conditions[a]	Products (Yield [%])[b]	
1	(1-naphthyl)NMe$_2$	**3**	10 mol-% FeCl$_2$, 24 h		**4** (72 %)
2	EtO$_2$C–C$_6$H$_4$–NMe$_2$	**5**	20 mol-% FeCl$_2$, 24 h, reflux		**6** (74 %)
3	PhC(O)–C$_6$H$_4$–NMe$_2$	**7**	20 mol-% FeCl$_2$, 24 h, reflux		**8** (85 %)
4	Me$_2$N–C$_6$H$_4$–C(O)–C$_6$H$_4$–NMe$_2$	**9**	20 mol-% FeCl$_2$, 24 h, reflux		**10** (74 %)
5	Me$_2$N–C$_6$H$_4$–CH$_2$–C$_6$H$_4$–NMe$_2$	**11**	15 mol-% FeCl$_2$, 15 h[c]		**12** (68 %)
6	tris(4-NMe$_2$-phenyl)methane	**13**	15 mol-% FeCl$_2$, 24 h[c]		**14** (61 %)
7	Ph–morpholine	**15**	10 mol-% FeCl$_2$, 16 h		**16** (92 %)
8	Ph–N(Et)Me	**17**	10 mol-% FeCl$_2$, 14 h		**18a** (93 %)
9	R = Me	**19a**	10 mol-% FeCl$_2$, 50 h	**20a** (22 %) +	**18a** (67 %)
10	R = *n*Pr	**19b**	10 mol-% FeCl$_2$, 50 h	**20b** (27 %) +	**18b** (62 %)
11	R = Ph	**19c**	10 mol-% FeCl$_2$, 50 h	**20c** (34 %) +	**18c** (47 %)
12	(mesityl)N(CH$_2$CN)Me	**21**	15 mol-% FeCl$_2$, 72 h, reflux[d]		**22** (72 %)

[a] *Reaction conditions*: amine (1.0 mmol), trimethylsilylcyanide (2.0 mmol), *t*-BuOOH (2.5 mmol), MeOH (2.0 mL), room temperature (22±1 °C). [b] Yield of isolated product after column chromatography on SiO$_2$. [c] In the presence of 3.0 mmol trimethylsilyl cyanide and 3.0 mmol *t*-BuOOH. [d] Oxidant *t*-BuOOH replaced by O$_2$ (1 atm).

Upon oxidation at the central CH unit tris[4-(dimethylamino)phenyl]methane **13** could easily form one of the most stable carbocations, crystal violet (pK_{R+} = 9.36).[38] However, analogous to the behaviour of **11**, **13** was oxidized exclusively at the dimethylamino substituents as indicated by the subsequent three-fold cyanation to **14** (61% yield) when 3.0 equiv. of trimethylsilyl cyanide were used.

As previously shown for *N*-phenylpyrrolidine (Scheme 2.3),[34a] the strategy of oxidative cyanation can also be employed for generating carbonitrile derivatives of *N*-phenylated cyclic amines. The morpholine moiety has rarely been demonstrated to be able to undergo oxidative α-functionalization at a heterocyclic CH bond adjacent to the nitrogen.[15d] To our delight, oxidative cyanation of 4-phenylmorpholine (**15**) gave 4-phenylmorpholine-3-carbonitrile (**16**) in an excellent yield of 92%.

The chemoselective oxidative cyanation of *N*-ethyl-*N*-methylaniline (**17**) to the 2-aminoacetonitrile **18a** (93% yield) illustrates that oxidation at the *N*-methyl group is highly preferred over a competing process at an NCH$_2$ of the *N*-ethyl group, in agreement with previous reports[17b,18,25b,30,31] and the order of kinetic acidities of laser flash photolytically generated amine radical cations (Ph_2NCH_3 > $Ph_2NCH_2CH_3$, from radical cation deprotonations with acetate ions).[40]

Surprisingly low yields of the expected α-amino nitriles **20a–c** were obtained for aniline derivatives **19a–c** that do not carry a methylated amino group. The α-cyanated products **20a–c** (22–34% yield) were accompanied by the aminoacetonitrile derivatives **18a–c**, which could be isolated in useful yields between 47 and 67%.

Oxygen is an attractive, atom-economic, and environmentally benign ("green") oxidant.[41] As detailed in the Supporting Information for the formation of **2a–g**, it was possible to replace the oxidant *tert*-butyl hydroperoxide by molecular oxygen in several cases. However, when the FeCl$_2$-catalyzed cyanations of anilines **1a–g**

under aerobic conditions are compared with the analogous reactions in which oxidation is achieved with a 5.5 M decane solution of *tert*-butyl hydroperoxide,[34] it becomes obvious that using the organic peroxide is the superior method because the yields of α-amino nitriles **2a**–**g** were generally higher (+8 to +30 %), and in several reactions room temperature was sufficient, whereas the analogous reaction under aerobic conditions required heating to reflux temperature of the solvent. Only for electron-rich anilines, may the aerobic version of the iron-catalyzed α-cyanation be a practical alternative, as exemplified by the conversion of *N,N*-dimethylmesidine (**21**) to **22** (Table 2.1, entry 12).

Table 2.2 summarizes our results for α-cyanations of benzylic and aliphatic tertiary amines that were carried out at ambient or even lower temperature. Oxidative cyanations at benzylamines showed that oxidation at NCH_3 groups is preferred over oxidizing $C(sp^3)H$ bonds of NCH_2Ph. *N,N*-Dimethylbenzylamine (**23**) reacted at 0 °C selectively to furnish **24** in a yield of 81%. The cyanation of tribenzylamine (**25**), a substrate that does not contain a NCH_3 group, was much less efficient and gave **26** in only a moderate yield of 41%.

Table 2.2. FeCl$_2$-catalyzed oxidative α-cyanations of benzylic and aliphatic tertiary amines.[a]

Entry	Amine		Products (Yield [%])[b]	
1	Ph⌒NMe$_2$	**23**	Ph⌒N(Me)⌒CN	**24** (81 %)[c]
2	(PhCH$_2$)$_3$N	**25**	(PhCH$_2$)$_2$N–CH(CN)Ph	**26** (41 %)[d]
3	⌒⌒⌒NMe$_2$	**27**	⌒⌒⌒N(Me)⌒CN	**28** (46 %)
4	⌒⌒⌒NMe$_2$	**29**	⌒⌒⌒N(Me)⌒CN	**30** (47 %)
5	(nPr)$_3$N	**31**	(nPr)$_2$N–CH(CN)CH$_2$CH$_3$	**32** (48 %)
6	(nBu)$_3$N	**33**	(nBu)$_2$N–CH(CN)CH$_2$CH$_2$CH$_3$	**34** (69 %)
7	(isopentyl)$_3$N	**35**	(isopentyl)$_2$N–CH(CN)CH$_2$CH(CH$_3$)$_2$	**36** (70 %)
8	(n-octyl)$_3$N	**37**	(n-octyl)$_2$N–CH(CN)⌒⌒⌒	**38** (68 %)
9	(iBu)$_3$N	**39**	(iBu)$_2$N–CH(CN)CH(CH$_3$)$_2$	**40** (73 %)

[a] *Reaction conditions*: amine (1.0 mmol), trimethylsilyl cyanide (2.0 mmol), *t*-BuOOH (2.5 mmol), FeCl$_2$ (10 mol%), MeOH (2.0 mL), room temperature (22±1 °C). [b] Yield of isolated product after column chromatography on SiO$_2$. [c] Reaction at 0 °C. [d] With 15 mol% of FeCl$_2$.

The versatility of the FeCl$_2$-catalyzed oxidative cyanation of amines is further underscored by the fact that purely aliphatic tertiary amines can be used as substrates (Table 2.2, entries 3–9). The tertiary amines **27** and **29** with an unbranched alkyl substituent at NMe$_2$ reacted selectively at the methyl groups to give amino nitriles **28** (46% yield) and **30** (47% yield), respectively. Furthermore, a

series of trialkylamines **31**, **33**, **35** and **37** was converted to the α-amino nitriles **32**, **34**, **36**, and **38**, respectively, in useful yields.

Interestingly, even the sterically demanding triisobutylamine **39** was cyanated with high efficiency to **40** (73% yield). Precipitation from water delivered crystals of **40** that could be characterized by X-ray structure analysis (Figure 2.1). Details of the crystal structure of **40** are reported in section 2.4 and ref.[42]
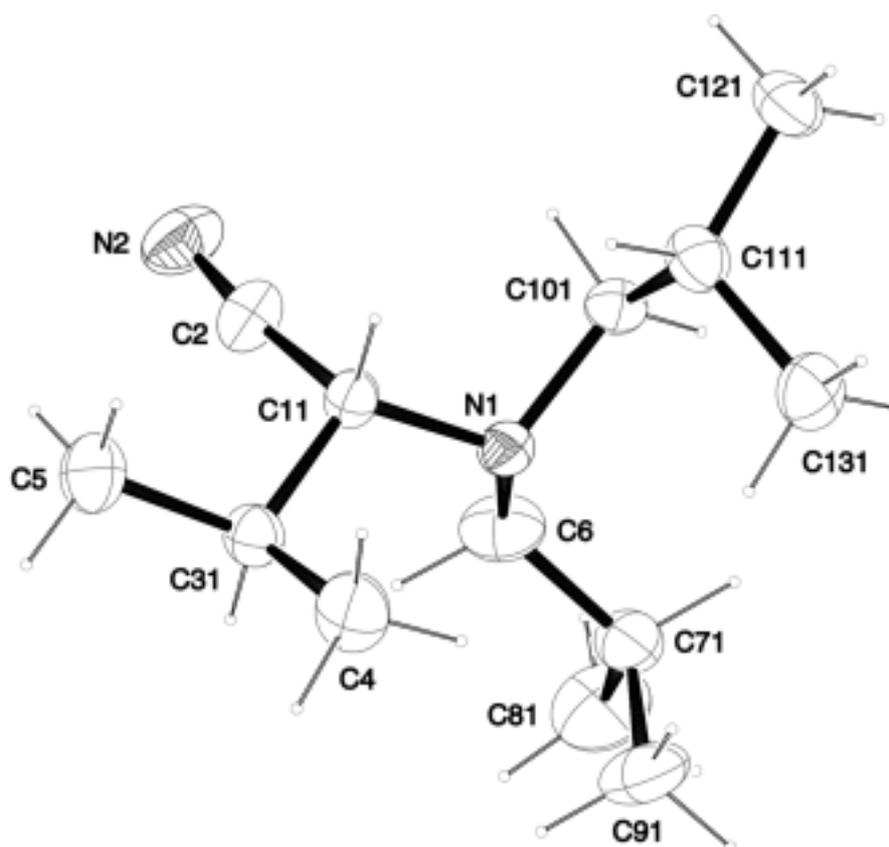
Figure 2.1. X-ray structure of **40** [as the molecules crystallized disordered a split model was applied (sof ratio 0.72/0.28), the Figure shows the main component only, thermal ellipsoids are drawn at the 50% probability level].[42]

2.2.2 Solvent Participation in the Formation of Aminoacetonitriles 18 from *N,N*-Dialkylanilines

It is well known that degradation of tertiary amines can occur under oxidative reaction conditions. For example, hydrolysis of the intermediate iminium ions (**A**) by water, that is unavoidably generated during oxidation, can produce secondary amines (**B**) and aldehydes (Scheme 2.4). [43-45]
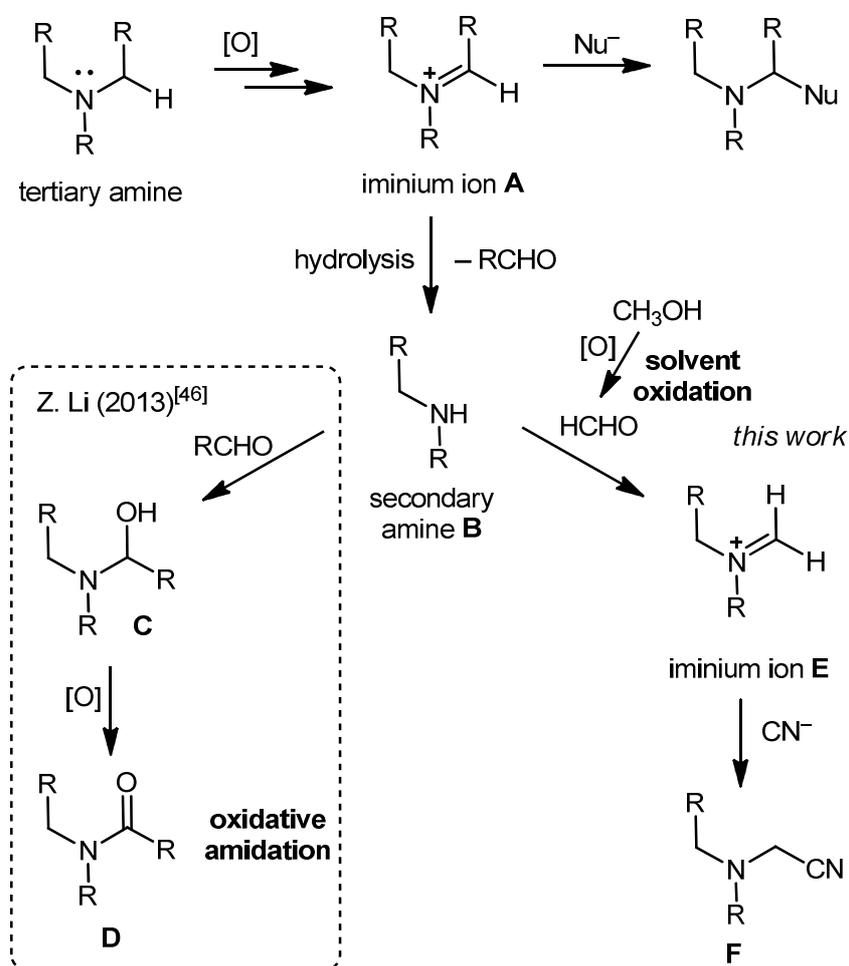
Scheme 2.4. Oxidative dealkylation of tertiary amines by $FeCl_2$ as the catalyst and *tert*-butyl hydroperoxide as the oxidant and subsequent electrophilic trapping of the secondary amine intermediates.

We suspected that the aminoacetonitriles **18a–c** (Table 2.1, entries 9–11) could originate from amines **B**. Recently, Z. Li and co-workers reported that *in situ* generated secondary amines **B** could be trapped by added aldehydes (in acetonitrile solution), and an iron-catalyzed oxidation of the thus formed aminols **C** by excess *tert*-butyl hydroperoxide furnished a variety of amides **D**.[46]

Accordingly, hydrolysis of **A** to **B** becomes infeasible under water-free reaction conditions. Efficient removal of water from the reaction mixture by molecular sieves[47] during the oxidative cyanation of **19a** with trimethylsilyl cyanide (Scheme 2.5), therefore, entirely changed the product selectivity from prevailing **18a** (Table 2.1, entry 9) to clear preference for **20a**.
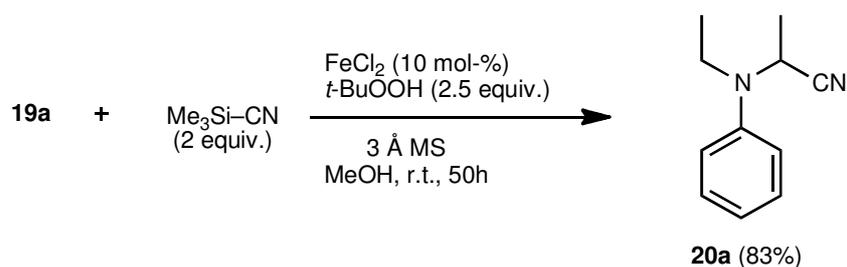
Scheme 2.5. Oxidative iron-catalyzed cyanation of **19a** with trimethylsilyl cyanide in methanol under water-free conditions.

We also speculated that the solvent could participate as a reagent, in accord with Bolm's report that iron catalysis enables the oxidation of methanol to formaldehyde under reaction conditions very similar to ours.[48] Furthermore, as shown in Scheme 2.6, isotope scrambling was observed by Ratnikov and Doyle in the rhodium-catalyzed oxidative Mannich reaction of **2a**-*d*6 with **41** that was carried out in the presence of an excess of formaldehyde (37% aqueous solution).[48] The formation of

42 illustrates that formaldehyde is involved in a fast equilibration at the stage of *N,O*-acetals before the potent nucleophile **41** can trap the intermediate iminium ions.
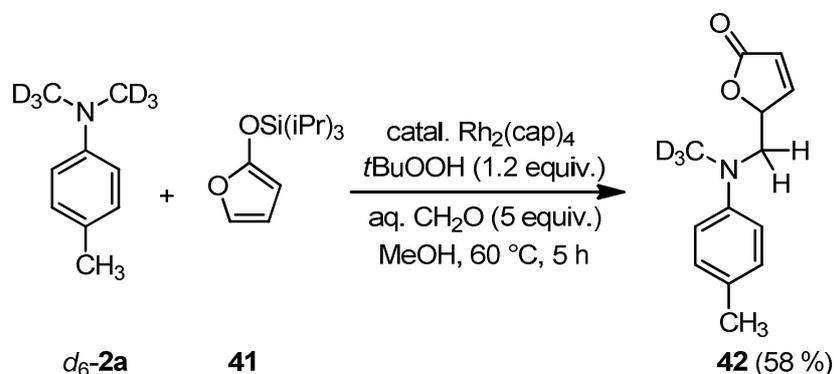
Scheme 2.6. Oxidative Mannich reaction of **2a**-d_6 with siloxyfuran **41** catalyzed by di-rhodium caprolactame [Rh$_2$(cap)$_4$, 1 mol%] (from ref.[6a]).

As sketched in Scheme 2.4, oxidation of the solvent methanol would provide formaldehyde that is capable of forming iminium ion **E** upon reaction with the amine **B**. Cyanide trapping of the iminium ion **E** would lead to the observed major products **18a–c** (or **F** in Scheme 2.4).

Isotopic labelling of the methylene unit that originates from the solvent methanol would allow for testing this hypothesis. We repeated, therefore, the reactions that converted **19a** and **19c** to the mixtures of **20a/18a** and **20c/18c**, respectively, under the previously employed reaction conditions but now with methanol-d_3 as the solvent and isolated the corresponding aminoacetonitriles **18a'** and **18c'** in yields of 69 and 46%, respectively (Scheme 2.7).
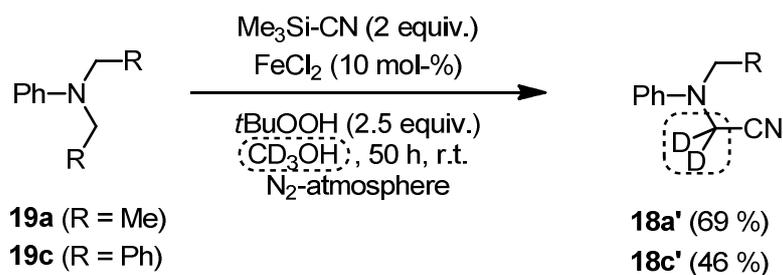
Scheme 2.7. Dealkylative cyanomethylation of **19a** and **19c** in CD$_3$OH.

Figure 2.2 shows a comparison of the ^{1}H NMR spectra of the products obtained from the oxidative cyanation of **19c** in either CH$_3$OH (Figure 2.2a) or CD$_3$OH (Figure 2.2b). Obviously the singlet at δ = 4.53 ppm, that corresponds to the resonance of the protons of the benzylic NCH$_2$ group, remained unaffected by the change of the reaction medium from CH$_3$OH to CD$_3$OH. However, the resonance of the cyanated NCH$_2$ group (δ = 4.08 ppm) was extinguished almost completely in the ^{1}H NMR spectrum of **18c'**. It can be derived from the integral for this singlet that >98% of the isolated **18c'** contained a CD$_2$ group that originated from the oxidized solvent CD$_3$OH.

a) **18c** from the reaction of **19c** in CH₃OH
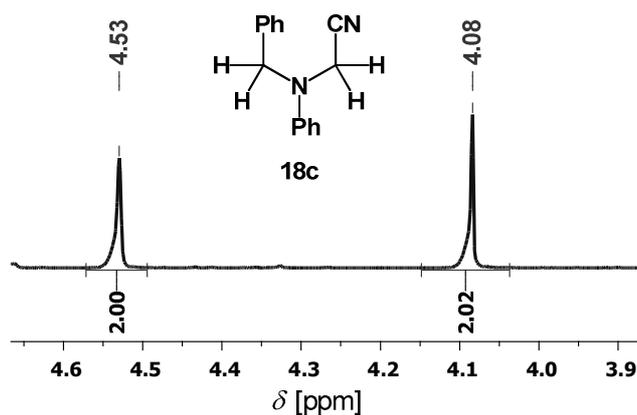
b) **18c'** from the reaction of **19c** in CD₃OH
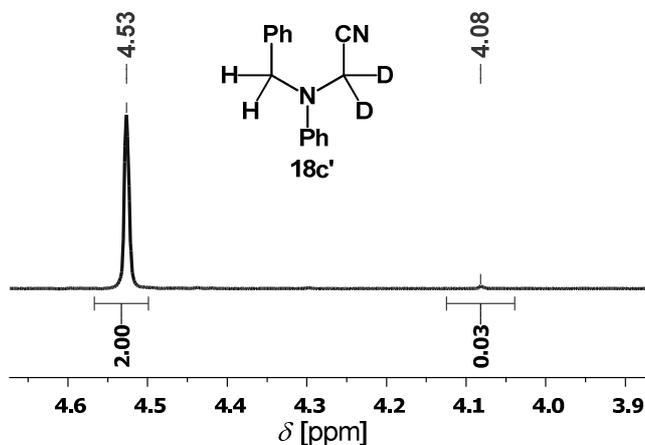
Figure 2.2. Oxidative cyanation of *N,N*-dibenzylaniline **19c**: a) ¹H NMR spectrum of **18c** obtained from the reaction **19 c** in CH₃OH (see Table 2.1, entry 11 for reaction conditions); b) ¹H NMR spectrum of **18c'** obtained from the reaction **19c** in CD₃OH (see Scheme 2.7 for reaction conditions).

Analogously, the cyanated NCH_2 group of **18a** (singlet at δ = 4.14 ppm) was replaced in **18a'** by a CD_2 group with >97% probability (see the section 2.4 for the ¹H NMR spectra of **18a** and **18a'**). As a consequence, the sequence of reaction steps proposed in Scheme 2.4 is corroborated by the results of the oxidative cyanations in deuterated methanol.

2.3 Conclusions

In summary, structurally diverse α-amino nitriles were synthesized from tertiary amines by using $FeCl_2$ as the catalyst and *tert*-butyl hydroperoxide as the oxidant. Oxidative α-functionalization could also be achieved for some substrates (**1a**–**g**, **21**) when the organic peroxide was replaced by molecular oxygen (1 atm) as the oxidant. $C(sp^3)H$ bonds adjacent to the nitrogen of *N,N*-dimethylanilines, benzylic and aliphatic amines were selectively cleaved and converted to CN moieties by trapping the intermediate iminium ions with the cyanide ion source trimethylsilyl cyanide in methanol.

Oxidative dealkylation with subsequent cyanomethylation under participation of the solvent methanol was the main reaction path for *N,N*-dialkylanilines $PhNR_2$ with R = Et, Bu, Bn. Iron-catalyzed methanol oxidation to formaldehyde may explain on the one hand that hyperstoichiometric amounts (in relation to the amine) of *tert*-butyl hydroperoxide are required as the oxidant. On the other hand, it contributes to the understanding why methanol plays such a unique role as a solvent in oxidative α-functionalizations of tertiary amines: Methanol does not only solubilize the reagents but also acts as a nucleophile that intercepts the intermediate iminium ions to generate *N,O*-acetals as a safe reservoir from which the electrophilically reactive iminium ions can be re-generated by thermal or acid-catalyzed equilibrium reactions.[5,49] In addition, methanol helps to avoid oxidative dealkylation of tertiary amines, which would give rise to by-products (secondary amines and products thereof), in reactions which actually aim to generate α-functionalized tertiary amines. Although *N,N*-dimethyl-substituted anilines belong to standard compounds for testing the reaction conditions of CDC reactions at tertiary amines, **3**–**11** participation of the solvent methanol in its oxidized form has probably remained undiscovered because

of two reasons: (a) the formation of products identical to those that are obtained by direct oxidative α-functionalization and (b) the use of catalysts that were unable to catalyze the oxidation of methanol to formaldehyde with *tert*-butyl hydroperoxide.[6a] Using methanol-d_3 as a probe revealed that the solvent participates productively to generate the 2,2-dideuterated 2-aminoacetonitriles **18′** which may be useful as a cost effective synthetic platform for generating d_2-derivatives of 1,2-diamines, amino acids or tetrahydroquinolines.[16b,17b]

2.4   Experimental Section

In order to identify my contribution to this multiauthor publication, this Experimental Section covers exclusively those experiments, which were performed by me.

General. All reactions were carried out under an atmosphere of dry nitrogen. [1]H (300 or 400 MHz) and [13]C (75.5 or 100.6 MHz) NMR spectra of solutions in CDCl$_3$ were recorded on 300 or 400 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals ($δ_H$ 7.26 and $δ_C$ 77.16 ppm).[S2] Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond).

Materials. Commercially available tertiary amines were used as received. *N,N*-Dimethyl-*p*-anisidine was prepared according to a literature procedure.[S3] Trimethylsilyl cyanide (98 %, Acros) and *tert.*-butyl hydroperoxide (5.5 M solution in decane, purum, Aldrich) were purchased.

The following iron and copper salts were used: Iron(II) acetate (anhydrous, 97 %, Strem), iron(III) acetylacetonate (99.9 %, Aldrich), iron(III) bromide (99 %, ABCR), iron(II) chloride (98 %, Aldrich), iron(III) chloride (anhydrous, 97 %, Grüssing), iron(III) chloride hexahydrate (99 %), iron(II) fluoride (anhydrous, 99 %, Strem),

[S2]   G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176-2179.

[S3]   J. A. Hodges, R. T. Raines, *Org. Lett.* **2006**, *8*, 4695-4697.

iron(II) gluconate hydrate (purum p.a., Fluka), iron(II) sulfate (99 %), copper(I) bromide (98 %, Acros), and copper(II) bromide (> 99%, Acros).

The following amines were purchased from commercial suppliers: N-phenyl-morpholine (**11**, 98 %, ABCR), N,N-diethylamine (**15a**, 99 %, Acros), N,N-dibutylamines (**15b**, 97 %, Aldrich), N,N-dibenzylamine (**15c**, 99 %, ABCR), dimethyloctylamine (**21**, 98 %, ABCR), dimethyltetradecylamine (**23**, >95 %, techn., Aldrich), triisobutylamine (**25**, 98 %, ABCR),

N-Ethyl-*N*-methyl-aniline (**13**) was prepared by heating a solution of *N*-methylaniline (3.25 mL, 30 mmol), EtBr (3.8 mL, 51 mmol) and NEt$_3$ (10.4 mL, 75 mmol) in MeCN (30 mL) to reflux for 16 h. After allowing the reaction mixture to cool to ambient temperature, the suspension was filtrated, poured on brine (50 mL), and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic phases were washed with water and dried (MgSO$_4$). After evaporating the solvent, the crude material was distilled in the vacuum (65 °C/0.01 mbar) to give **13** (3.4 g, 84 %) as a colorless liquid.

General Procedure A (FeCl$_2$/*t*BuOOH/N$_2$ atmosphere): Under an atmosphere of dry N$_2$, a Schlenk flask was charged with iron(II) chloride (10 mol %, 13 mg). The tertiary amine (1.0 mmol), trimethylsilyl cyanide (2.0 mmol, 0.27 mL), and MeOH (2.0 mL) were added successively by syringe. To the mixture was added dropwise *tert*-butyl hydroperoxide (2.5 mmol, 0.47 mL, 5.5 M solution in decane) over a period of 5 min. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl or Na$_2$CO$_3$ solution (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic phases were combined, dried (MgSO$_4$), and the volatile components were evaporated in a

rotary evaporator. The crude product was purified by column chromatography on silica gel (*n*-pentane/diethyl ether = 15:2, v/v).

4-Phenylmorpholine-3-carbonitrile (16)

Following *General Procedure A*, 4-phenyl-morpholine **15** (188 mg, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 16 h to give **16** (173 mg, 92 %) as a colorless solid; mp 98.3-98.5 °C.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 3.28–3.31 (m, 2 H), 3.71-3.80 (m, 1 H), 3.92 (dd, *J* = 11.6 Hz, *J* = 2.9 Hz, 1 H), 4.08-4.19 (m, 2 H), 4.41-4.43 (m, 1 H), 6.97-7.07 (m, 3 H), 7.32-7.39 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 45.7, 51.2, 67.1, 68.3, 116.1, 117.5, 122.8, 129.8, 148.5 ppm; analysis calcd for C$_{11}$H$_{12}$N$_2$O: C, 70.19; H, 6.43; N, 14.88; found C, 69.92; H, 6.43; N, 14.76.

2-(Ethyl(phenyl)amino)acetonitrile (18a)

Following *General Procedure A*, *N*-ethyl-*N*-methylaniline **17** (145 µL, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 14 h to give **18a** (149 mg, 93 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref[17a].

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 3.45 (q, *J* = 7.2 Hz, 2 H), 4.14 (s, 2 H), 6.85-6.94 (m, 3 H), 7.30-7.35 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 12.3, 39.6, 46.4, 115.0, 116.5, 119.9, 129.6, 147.0 ppm.

2-(Ethyl(phenyl)amino)propanenitrile (20a) and 2-(Ethyl(phenyl)amino)-acetonitrile (18a)

Following *General Procedure A*, *N,N*-diethylaniline **19a** (160 µL, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 50 h. The crude product mixture was

separated by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:2) to give **20a** (38 mg, 22 %) and **18a** (107 mg, 67 %), both as colorless viscous liquids.

20a: Known compound; the NMR spectroscopic data agree with those given in ref[14c]. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.19 (t, J = 7.1 Hz, 3 H), 1.57 (d, J = 7.2 Hz, 3 H), 3.28-3.42 (m, 2 H), 4.48 (q, J = 7.2 Hz, 1 H), 6.97-7.00 (m, 3 H), 7.29-7.33 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 14.0, 18.7, 43.7, 48.4, 119.1, 119.6, 121.9, 129.5, 146.9 ppm; v (neat/ATR probe) 3061, 2977, 2936, 1597, 1579, 1498, 1450, 1377, 1353, 1259, 1197, 1129, 1080, 1036, 789, 749, 691 cm^{-1}; HRMS (EI) calcd for C$_{11}$H$_{14}$N$_2$ m/z 174.1157, found m/z 174.1157.

18a: Known compound; the NMR spectroscopic data agree with those given in ref[17a]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.26 (t, J = 7.1 Hz, 3 H), 3.45 (q, J = 7.1 Hz, 2 H), 4.15 (s, 2 H), 6.86-6.94 (m, 3 H), 7.29-7.35 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 12.3, 39.6, 46.4, 115.1, 116.5, 120.0, 129.6, 147.0 ppm; HRMS (EI) calcd for C$_{10}$H$_{12}$N$_2$ m/z 160.0995, found m/z 160.0997; v (neat/ATR probe) 3061, 3042, 2975, 2929, 1599, 1577, 1503, 1377, 1347, 1274, 1243, 1185, 1129, 1075, 1038, 1011, 975, 910, 871, 795, 749, 731, 690 cm^{-1}.

2-(Ethyl(phenyl)amino)propanenitrile (20a)

Analogous to *General Procedure A* but with added molecular sieves (3 Å, 4–8 mesh, 270 mg), **19a** (160 μL, 1.00 mmol) reacted with Me$_3$SiCN (270 μL, 2.00 mmol) for 50 h in dry methanol. The crude product mixture was separated by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:2) to give **20a** (144 mg, 83 %) as colorless viscous liquids. The proton NMR spectrum proved purity and identity of **20a**.

2,2-Dideuterio-2-(ethyl(phenyl)amino)acetonitrile (18a')

Following *General Procedure A*, *N,N*-diethylaniline **19a** (160 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 50 h in CD_3OH (2 mL). The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 15:2) to give **18a'** (112 mg, 69 %) as a colorless viscous liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.25 (t, J = 7.1 Hz, 3 H), 3.42 (q, J = 7.1 Hz, 2 H), 4.06 (s, 0.06 H), 6.78-6.86 (m, 3 H), 7.21-7.26 ppm (m, 2H); ^{2}H NMR (CCl_4/$CDCl_3$, 61.4 MHz): δ = 4.07 ppm (s); ^{13}C NMR (CCl_4/$CDCl_3$, 100.6 MHz): δ = 12.7, 46.5, 115.62, 115.65, 120.5, 129.7, 147.2 ppm; v (neat/ATR probe) 3062, 2975, 2934, 1599, 1576, 1503, 1370, 1350, 1267, 1203, 1096, 992, 788, 748, 690 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}D_2N_2$ *m/z* 162.1121, found *m/z* 162.1122.

2-(Butyl(phenyl)amino)pentanenitrile (20b) and 2-(Butyl(phenyl)amino)-acetonitrile (18b)

Following *General Procedure A*, *N,N*-dibutylaniline **19b** (225 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 50 h. The crude product mixture was separated by column chromatography (SiO_2, pentane/Et_2O = 30:1 → 15:1) to give **20b** (62 mg, 27 %) and **18b** (117 mg, 62 %), both as colorless viscous liquids.

20b: Known compound; the NMR and IR spectroscopic data agree with those given in ref[14c]; ^{13}C multiplicities are based on gHSQC experiments ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.93 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.33-1.63 (m, 6 H), 1.82-1.90 (m, 2 H), 3.16-3.32 (m, 2 H), 4.29 (t, J = 7.8 Hz, 1 H), 6.95-7.01 (m, 3 H), 7.27-7.34 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.6 (q), 14.0 (q), 19.4 (t), 20.4 (t), 30.2 (t), 34.3 (t), 49.1 (t), 54.3 (d), 119.05 (s), 119.18 (d), 121.7 (d), 129.4 (d), 147.8 (s) ppm; v (neat/ATR probe) 3061, 2958, 2932, 2872, 1597, 1498, 1465, 1377,

1281, 1257, 1219, 1179, 1134, 1112, 1037, 993, 931, 748, 692 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}N_2$ m/z 230.1778, found m/z 230.1794.

18b: ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.97 (t, J = 7.3 Hz, 3 H), 1.34-1.46 (m, 2 H), 1.56-1.69 (m, 2 H), 3.32-3.37 (m, 2 H), 4.15 (s, 2 H), 6.84-6.92 (m, 3 H), 7.27-7.33 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 14.1, 20.4, 29.4, 40.2, 52.0, 115.0, 116.4, 119.9, 129.6, 147.4 ppm; v (neat/ATR probe) 3060, 3041, 2957, 2929, 2871, 1599, 1577, 1503, 1457, 1428, 1367, 1347, 1252, 1220, 1180, 1041, 924, 868, 747, 690 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}N_2$ m/z 188.1308, found m/z 188.1305.

2-(Benzyl(phenyl)amino)-2-phenylacetonitrile (20c) and 2-(Benzyl(phenyl)amino)acetonitrile (18c)

Following *General Procedure A*, *N*,*N*-dibenzyl-aniline **19c** (273 mg, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 50 h. The crude product mixture was separated by column chromatography (SiO$_2$, pentane/Et$_2$O = 8:1) to give **18c** (104 mg, 47 %) as a colorless viscous liquid and a mixed fraction of **19c** and **20c**. Pure **20c** (101 mg, 34 %) could then be crystallized from pentane/Et$_2$O = 5:1; mp 133.0-133.5 °C (ref.[51] mp 134 °C, from EtOH).

20c: ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 4.28-4.40 (m, 2 H), 5.65 (s, 1 H), 6.86-6.96 (m, 3 H), 7.13-7.23 (m, 7 H), 7.28-7.33 (m, 3 H), 7.46-7.49 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 54.0, 58.7, 116.8, 119.9, 122.5, 127.5, 127.7, 127.8, 128.7, 129.1, 129.2, 129.3, 133.5, 137.6, 147.4 ppm; v (neat/ATR probe) 3061, 3025, 2922, 2852, 1597, 1581, 1494, 1465, 1452, 1379, 1337, 1264, 1253, 1219, 1121, 1070, 1027, 938, 921, 909, 761, 746, 724, 692 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{18}N_2$ m/z 298.1465, found m/z 298.1459.

18c: Known compound; the ^{1}H NMR spectroscopic data agree with those given in ref[52]. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 4.08 (s, 2 H), 4.53 (s, 2 H), 6.95-7.00 (m, 3 H), 7.32-7.39 (m, 7 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 39.7, 55.9, 115.8, 115.9, 120.8, 127.8, 128.0, 129.0, 129.7, 136.9, 148.1 ppm; v (neat/ATR probe) 3062, 3029, 2925, 2852, 1598, 1579, 1503, 1495, 1452, 1426, 1357, 1221, 1199, 1168, 1027, 960, 937, 869, 749, 729, 690 cm^{-1}; HRMS (EI) calcd for C$_{15}$H$_{14}$N$_2$ m/z 222.1151, found m/z 222.1156.

2-(Benzyl(phenyl)amino)-2,2-dideuterio-acetonitrile (18c')

Following *General Procedure A*, N,N-dibenzyl-aniline **19c** (273 mg, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 50 h in CD$_3$OH (2 mL). The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 8:1) to give **18c'** (103 mg, 46 %) as a colorless viscous liquid.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 4.08 (s, 0.03 H), 4.53 (s, 2 H), 6.95-7.00 (m, 3 H), 7.31-7.40 ppm (m, 7 H); ^{2}H NMR (CCl$_4$/CDCl$_3$, 46.1 MHz): δ = 4.07 ppm (s); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 55.8, 115.8, 115.9, 120.8, 127.8, 128.0, 129.0, 129.7, 137.0, 148.1 ppm; v (neat/ATR probe) 3062, 3029, 2925, 2854, 1598, 1578, 1502, 1452, 1351, 1297, 1246, 1203, 1069, 1028, 990, 940, 909, 892, 812, 748, 726, 690 cm^{-1}; HRMS (EI) calcd for C$_{15}$H$_{12}$D$_2$N$_2$ m/z 224.1277, found m/z 224.1275.

2-(Benzyl(methyl)amino)acetonitrile (24)

Following *General Procedure A*, benzyl-dimethylamine **23** (152 µL, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 24 h at 0 °C to furnish **18** (129 mg, 81 %). Known compound; the NMR spectroscopic data agree with those given in ref[12a,53].

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 2.44 (s, 3 H), 3.45 (s, 2 H), 3.61 (s, 2 H), 7.26-7.37 ppm (m, 5 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 42.5, 44.3, 60.3, 114.7, 127.9, 128.7, 129.1, 137.1 ppm; ν (neat/ATR probe) 3064, 3031, 2983, 2949, 2842, 2231, 1496, 1454, 1416, 1371, 1327, 1125, 1037, 1027, 983, 840, 740, 698 cm^{-1}; HRMS (EI) calcd for C$_{10}$H$_{12}$N$_2$ m/z 160.1000, found m/z 160.0996.

2-(Dibenzylamino)-2-phenylacetonitrile (26)

Analogous to *General Procedure A*, tribenzylamine **25** (290 mg, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) and FeCl$_2$ (15 mol %) for 24 h to furnish **26** (128 mg, 41 %). Known compound; the NMR spectroscopic data agree with those given in ref[12a,53].

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.45 (d, ^2J = 13.6 Hz, 2 H), 3.91 (d, ^2J = 13.6 Hz, 2 H), 4.94 (s, 1 H), 7.28-7.44 (m, 13 H), 7.60-7.62 ppm (m, 2 H); ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 55.1, 57.4, 115.5, 127.77, 127.79, 128.7, 128.89, 128.93, 134.0, 137.8 ppm; ν (neat/ATR probe) 3061, 3033, 2925, 2803, 2235, 1493, 1452, 1372, 1113, 1076, 1027, 966, 924, 744, 694 cm^{-1}; HRMS (EI) calcd for C$_{22}$H$_{20}$N$_2$ m/z 312.1626, found m/z 312.1606.

2-(Methyl(octyl)amino)acetonitrile (28)

Following *General Procedure A*, dimethyl-octylamine **27** (205 µL, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 26 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **28** (84 mg, 46 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref[54].

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.85-0.89 (m, 3 H), 1.25-1.29 (m, 10 H), 1.42-1.48 (m, 2 H), 2.36 (s, 3 H), 2.43-2.47 (m, 2 H), 3.54 ppm (s, 2 H); ^{13}C NMR (CDCl$_3$, 75.5

MHz): δ = 14.2, 22.8, 27.2, 27.4, 29.3, 29.5, 31.9, 42.1, 45.1, 56.0, 114.7 ppm; v (neat/ATR probe) 2924, 2854, 2803, 1681, 1458, 1378, 1321, 1159, 1105, 1043, 950, 860, 834, 723 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{22}N_2$ m/z 182.1778, found m/z 182.1786.

2-(Methyl(tetradecyl)amino)acetonitrile (30)

Following *General Procedure A*, dimethyl-tetradecylamine **29** (305 µL, 1.00 mmol) reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 26 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **30** (125 mg, 47 %) as a colorless viscous liquid.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.85-0.89 (m, 3 H), 1.25 (br s, 22 H), 1.43-1.49 (m, 2 H), 2.36 (s, 3 H), 2.43-2.48 (m, 2 H), 3.54 ppm (s, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 14.2, 22.8, 27.2, 27.5, 29.5, 29.6, 29.68, 29.72, 29.77, 29.79, 29.81, 32.1, 42.1, 45.2, 56.0, 114.6 ppm; v (neat/ATR probe) 2922, 2852, 1683, 1466, 1377, 1319, 1042, 909, 860, 732 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{34}N_2$ m/z 266.2717, found m/z 266.2714.

2-(Dipropylamino)butanenitrile (32): Following *General Procedure A*, tripropylamine **31** (0.19 mL, 1.0 mmol) reacted with Me$_3$SiCN (0.270 µL, 2.00 mmol) for 24 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 40:1) to give **32** as a colorless viscous liquid; yield: 81 mg (48%); known compound;[55] multiplicities of ^{13}C resonances are based on gHSQC experiments.

^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.89 (t, J = 7.4 Hz, 6 H), 1.04 (t, J = 7.4 Hz, 3 H), 1.36–1.59 (m, 4 H), 1.65–1.86 (m, 2 H), 2.31–2.40 (m, 2 H), 2.46–2.55 (m, 2 H), 3.47 (t, J = 7.8 Hz, 1 H); 13C NMR (CDCl3, 75.5 MHz): δ = 10.9 (q), 11.8 (q), 21.3 (t), 25.5

(t), 53.8 (t), 56.6 (d), 118.7 (s); IR (neat/ATR probe): v = 2963, 2936, 2875, 2821, 1464, 1382, 1341, 1301, 1261, 1191, 1178, 1068, 1014, 944, 864, 805 cm^{-1}; HR-MS (EI): m/z=168.1601, calcd. for $C_{10}H_{20}N_2$: 168.1621.

2-(Dibutylamino)pentanenitrile (34): Following *General Procedure A*, tributylamine **33** (0.24 mL, 1.0 mmol) was reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 27 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O=40:1) to give **34** as a colorless viscous liquid; yield: 145 mg (69%); known compound; the 1H NMR spectroscopic data agree with those given in ref.[56] ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.89–0.97 (m, 9 H), 1.21–1.54 (m, 10 H), 1.66–1.75 (m, 2 H), 2.30–2.38 (m, 2 H), 2.52–2.62 (m, 2 H), 3.58 (t, J=7.7 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 13.6, 14.1, 19.4, 20.5, 30.4, 34.1, 51.6, 54.5, 118.7; IR (neat/ATR probe): v = 2958, 2932, 2873, 2823, 1467, 1379, 1309, 1261, 1170, 1116, 1091, 877, 801, 741 cm^{-1}; HR-MS (EI): m/z = 210.2106, calcd. for $C_{13}H_{26}N_2$: 210.2091.

2-(Diisopentylamino)-4-methylpentanenitrile (36): Following *General Procedure A*, triisopentylamine **35** (0.29 mL, 1.0 mmol) was reacted with Me$_3$SiCN (270 µL, 2.00 mmol) for 27 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O=45:1) to give **36** as a colorless viscous liquid; yield: 177 mg (70%); ^{1}H NMR (CDCl$_3$, 300 MHz): δ=0.89 (d, J=2.9 Hz, 6 H), 0.91 (d, J = 3.0 Hz, 6 H), 0.94 (d, J = 6.6 Hz, 6 H), 1.29–1.36 (m, 4 H), 1.53–1.66 (m, 4 H), 1.83 (sept, J = 6.7 Hz, 1 H), 2.28–2.37 (m, 2 H), 2.56–2.66 (m, 2 H), 3.65 (t, J = 7.8 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 22.2, 22.4, 22.5, 23.2, 24.8, 26.2, 37.2, 40.8, 50.1, 52.9, 118.8; IR (neat/ATR probe): v = 2956, 2930, 2870, 1468, 1386, 1368, 1261, 1169, 1132, 1088, 971, 920, 818 cm^{-1}; HR-MS (EI): m/z = 252.2561, calcd. for $C_{16}H_{32}N_2$: 252.2560.

2-(Dioctylamino)nonanenitrile (38): Following *General Procedure A,* tri-*n*-octylamine **39** (0.45 mL, 1.0 mmol) was reacted with Me₃SiCN (270 µL, 2.00 mmol) for 28 h. The crude product was purified by column chromatography (SiO₂, pentane/Et₂O=110:1) to give **38** as a colorless viscous liquid; yield: 258 mg (68%); ^{1}H NMR (CDCl₃, 300 MHz): δ = 0.85–0.90 (m, 9 H), 1.23–1.75 (m, 36 H), 2.28–2.59 (m, 4 H), 3.55 (t, J = 7.7 Hz, 1 H); ^{13}C NMR (CDCl₃, 75.5 MHz): δ = 14.17, 14.20, 22.7, 22.8, 26.2, 27.4, 28.1, 29.1, 29.2, 29.4, 29.6, 31.9, 32.0, 32.1, 51.9, 54.7, 118.7; IR (neat/ATR probe): v = 2955, 2924, 2855, 1466, 1378, 1154, 1100, 722 cm⁻1; HR-MS (EI): m/z = 378.3956, calcd. for $C_{25}H_{50}N_2$: 378.3969.

2-(Diisobutylamino)-3-methylbutanenitrile (40)

Following *General Procedure A,* triisobutylamine **39** (240 µL, 1.00 mmol) reacted with Me₃SiCN (270 µL, 2.00 mmol) for 24 h. The crude product was crystallized from H₂O to give **40** (154 mg, 73 %) as colorless crystals, mp. 61.0–61.5 °C. Known compound; the NMR spectroscopic data agree with those given in ref[12a]; ^{13}C multiplicities are based on gHSQC experiments.

^{1}H NMR (CDCl₃, 300 MHz): δ = 0.88 (d, J = 6.6 Hz, 6 H), 0.93 (d, J = 6.4 Hz, 6 H), 1.03 (d, J = 6.5 Hz, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.64-1.74 (m, 2 H), 1.88-1.96 (m, 1 H), 2.12 (dd, J = 12.9 Hz, J = 10.3 Hz, 2 H), 2.24 (dd, J = 12.9 Hz, J = 4.3 Hz, 2 H), 3.07 ppm (d, J = 10.7 Hz, 1 H); ^{13}C NMR (CDCl₃, 75.5 MHz): δ = 19.9 (q), 20.5 (q), 20.8 (q), 21.1 (q), 26.3 (d), 29.4 (d), 60.9 (t), 63.0 (d), 117.8 (s) ppm; v (neat/ATR probe) 2955, 2867, 2811, 1467, 1386, 1367, 1281, 1198, 1170, 1123, 1084, 1065, 979, 932, 884, 867, 811 cm⁻¹.

X-ray crystal structure analysis of 40

The data collection was performed on a Bruker IμS diffractometer (MoKα radiation, 200 K). The structure was solved by direct methods with SIR97[57] and refined with SHELXL-97.[58]

CCDC 933149 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
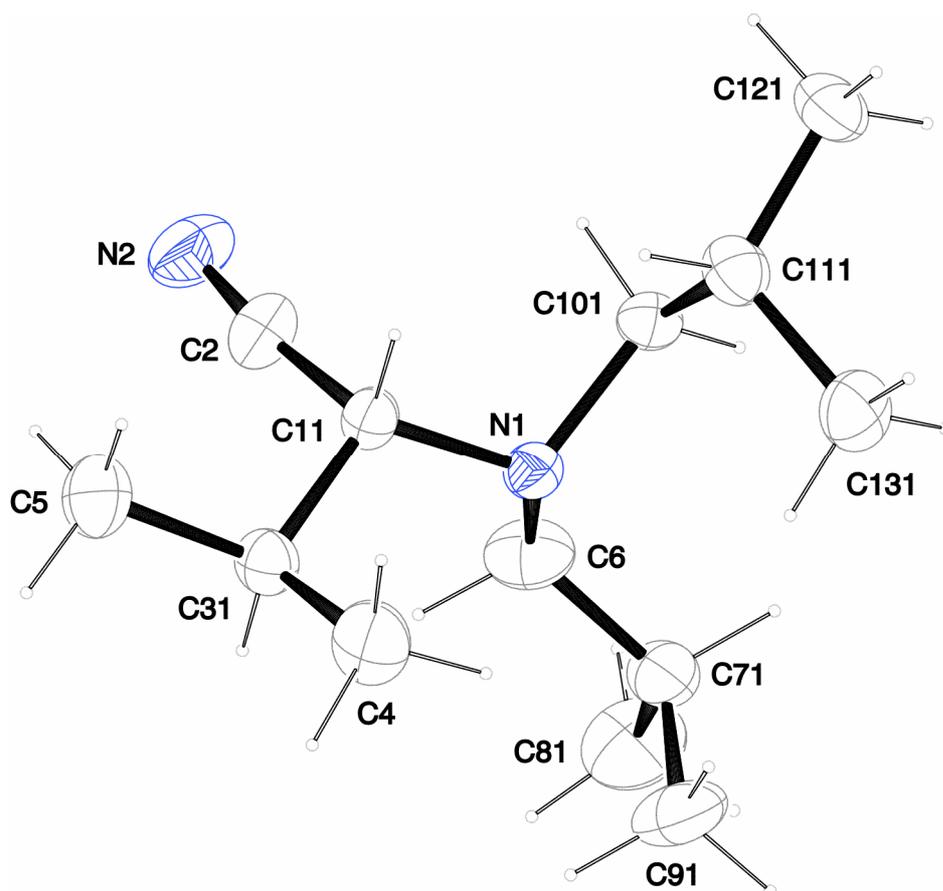
Molecule disordered, split model applied, sof ratio 0.72/0.28. The figure shows the main component only. Split atoms of the minor part have been refined isotropically.

2-(Diisobutylamino)-3-methylbutanenitrile (40). Crystallographic data:

	40
net formula	$C_{13}H_{26}N_2$
M_r/g mol^{-1}	210.359
crystal size/mm	0.257 × 0.256 × 0.105
crystal system	monoclinic
space group	$P2_1/c$
a/Å	12.6577(17)
b/Å	9.8704(12)
c/Å	11.7460(16)
α/°	90
β/°	97.131(4)
γ/°	90
V/Å^3	1456.2(3)
Z	4
calc. density/g cm^{-3}	0.95952(20)
μ/mm^{-1}	0.056
absorption correction	multi-scan
transmission factor range	0.9125–0.9801
refls. measured	8097
R_{int}	0.0317
mean $\sigma(I)/I$	0.0325
θ range	2.62–25.08
observed refls.	1718
x, y (weighting scheme)	0.0767, 0.6119
hydrogen refinement	constr
refls in refinement	2550
parameters	183
restraints	0
$R(F_{obs})$	0.0590
$R_w(F^2)$	0.1769
S	1.020
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.247
min electron density/e Å^{-3}	–0.258

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3

Sequential Oxidative α-Cyanation/Anti-Markovnikov Hydroalkoxylation of Tertiary Allylamines

3.1 Introduction

Additions to alkenes are atom-economic reactions that are used by synthetic chemists in academia and industry to introduce a broad variety of functional groups into hydrocarbons.[1] However, only a limited number of methods exist so far for anti-Markovnikov additions of alcohols to simple aliphatic olefins. Arnold studied the photosensitized generation of alkene radical cations,[2] which were trapped with alcohols to provide anti-Markovnikov adducts.[3] Since then, only a few related examples for photochemically induced anti-Markovnikov alcohol additions have been reported, all of which use 1-aryl- or 1,1-diarylalkenes as reaction partners (Scheme 1a).[4-6] General methods for intermolecular anti-Markovnikov hydroalkoxylations under mild and practical conditions are still lacking because of a shortage of applicable catalytic processes,[7] in particular with catalysts based on earth-abundant elements such as iron.[8-10]

According to the methylenology principle[11] Michael additions of alcohols at intrinsically nucleophilic CC double bonds could be mediated by linking the electron-rich π-system with an electron-accepting group through a radical center. As C-centered radicals are efficiently stabilized by captodative effects,[12] vinyl-substituted α-amino nitriles would be ideal substrates for testing this approach.

Introduction of nitrile groups at C-H bonds adjacent to the nitrogen of tertiary amines has recently been achieved with several catalyst-oxidant combinations and various cyanide sources.[13-15] Hence, allylamines may serve as potential precursors for vinyl-substituted α-amino nitriles. Indeed, it has been reported that allylamines can be used in oxidative α-cyanations under various conditions[16,17] (Scheme 1b). The few examples show, however, that oxidation occurrs preferentially at aliphatic or benzylic

α-positions of the amines,[17a-c] and only Mizuno and co-workers detected small amounts of α-cyanated products that originated from reaction at the allyl group.[17d,18]

(a) anti-Markovnikov hydroalkoxylation of 1-aryl alknes via alkene radical cations:
(Arnold, 1973)
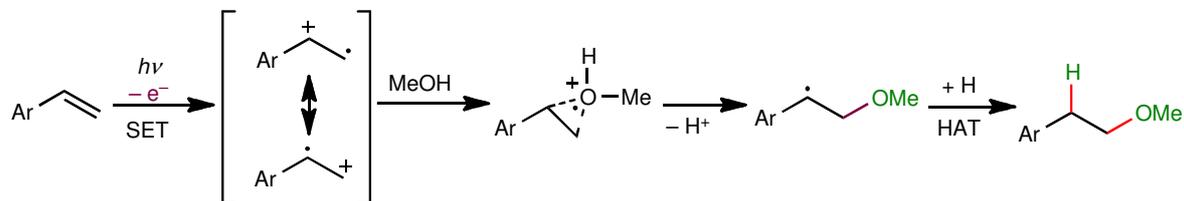
(b) Oxidative α-cyanations of allyl-substituted tertiary amines:
(Lambert, 2011)[b]   (Lingaiah, 2012 / Nageswar, 2012)[b]

(Mizuno, 2013)[b]

(44% total yield)

67 : 29 : 4
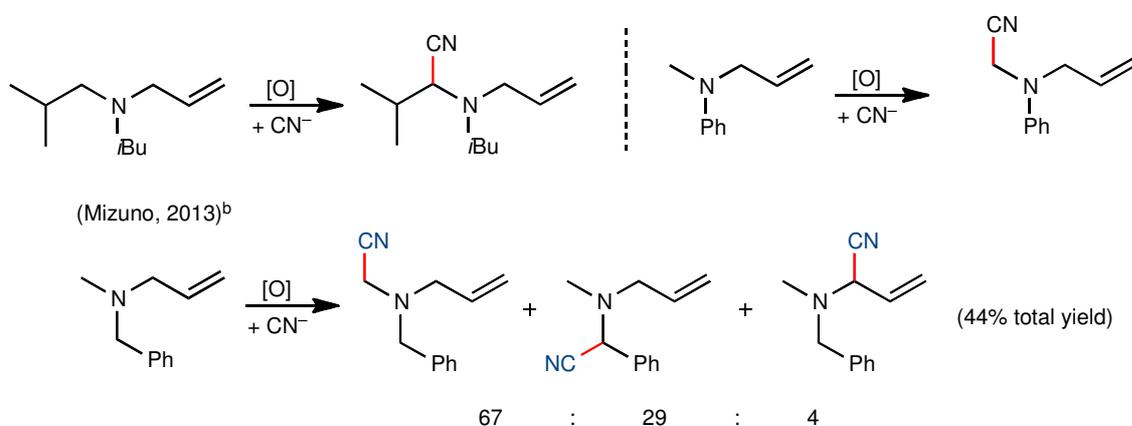
(c) This work: Oxidative α-cyanation/anti-Markovnikov hydroalkoxylation of allylamines:

Scheme 3.1. Direct anti-Markovnikov additions of alcohols to alkenes[a] and oxidative α-cyanations of allylamines. [a]SET, single electron transfer, HAT, hydrogen atom transfer. [b]For reaction conditions see notes in ref 17.

In recent years, we have developed iron-catalyzed oxidative α-cyanations of a variety of tertiary amines.[19,20] Here, we report that FeCl$_2$-catalysed direct α-cyanations at tertiary allylamines in allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double bonds of the initially generated α-amino nitriles (Scheme 3.1c).

3.2 Results and discussion

In recent years, we have developed iron-catalyzed oxidative α-cyanations of a variety of tertiary amines.[19,20] Here, we report that $FeCl_2$-catalysed direct α-cyanations at tertiary allylamines in allylic position are followed by anti-Markovnikov additions of alcohols across the vinylic CC double bonds of the initially generated α-amino nitriles (Scheme 1c).

Monitoring the oxidative cyanation of *N*,*N*-diallylaniline **1a** under our standard conditions in methanol [10 mol-% $FeCl_2$, 2 equiv of Me_3SiCN, 2.5 equiv of *t*BuOOH (5.5 M in decane), dry N_2 atmosphere, ambient temperature][19c,21] by GC-MS indicated that significant amounts of the α-cyanation product **2a** accumulated in the reaction mixture only during the initial phase of the reaction. The cyanation product **2a** was accompanied by generation of compounds with a molecular mass of **2a**·MeOH. While, **2a** was isolated in low yield (21%) when the reaction was worked up after 4 h reaction time, the product of addition of methanol to **2a** was obtained in 86% yield after 16 h (Scheme 3.2). 2D-NMR spectroscopic characterization of **2a**·MeOH showed the presence of a terminal methoxy group, in agreement with structure **3a**. *N*,*N*-diallylanilines **1b,c** with electron donating *p*-methyl (σ_p = -0.17)[22] or *p*-methoxy (σ_p^- = -0.27)[22] substituents at the phenyl rings analogously gave 2-anilino-4-methoxybutanenitriles **3b,c** in yields of 85% and 93%, respectively. The electron-withdrawing *p*-bromo-substituted aniline **1d** (σ_p^-(Br) = 0.25)[22] gave **3d** in a moderate yield of 67%.
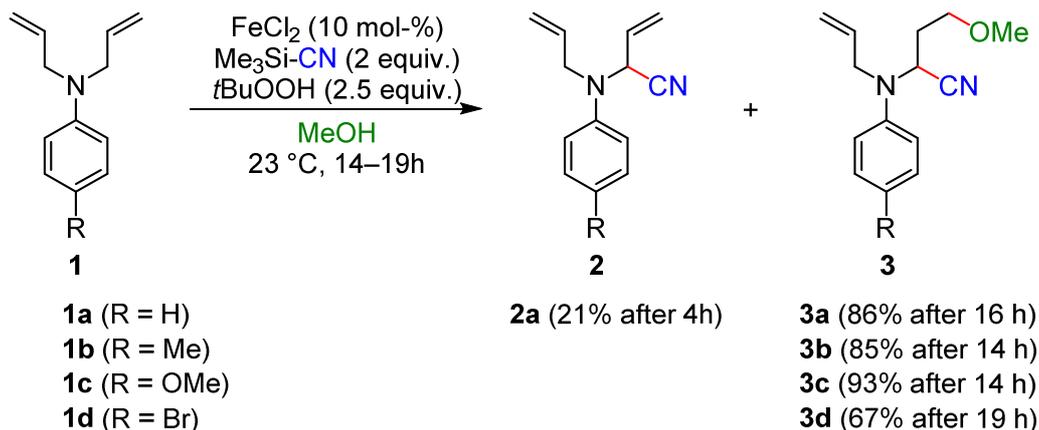
Scheme 3.2. Sequential Oxidative Cyanation/Hydroalkoxylation of *N,N*-Diallylanilines **1a-d** (yields refer to isolated products after chromatographic purification).

Changing the solvent from CH_3OH to CD_3OD for the reaction of **1a** under otherwise identical conditions of Scheme 3.2 yielded the d_3-methyl ether **3a'** in 88% yield.

While the ^1H and ^{13}C NMR spectra of **3a'** indicate a quantitative OCD_3 incorporation, the methylene group at C3 of the 4-methoxybutanenitrile branch shows a ca. 42% uptake of D (see experimental section). Because of fast H/D exchange between CD_3OD and *t*BuOOH under the conditions applied, it is presently not possible to unequivocally assign the source of the H or D that adds to the C3 position.

To rationalize the selective anti-Markovnikov addition of methanol, we suggest that iron-catalyzed oxidation converts the allyl-substituted amines **A** into α,β-unsaturated iminium ions **B**, which are then trapped by kinetically controlled attack of cyanide ions at the iminium carbon (Scheme 3.3).[23] Further oxidation of the intermediate α-amino nitriles **C** generates the donor/acceptor-substituted radicals **D**, which enter a

radical chain reaction. In accord with the methylenology principle,[11] radicals **D** show reactivity comparable to the π-electron-deficient acrylonitriles. Therefore, Michael-type addition of alcohols to the terminal C-4 may generate intermediates **E**, in which the negative charge is delocalized and efficiently stabilized by the electron-withdrawing cyano group. Fast proton transfer converts **E** to radicals **F**, which benefit from captodative stabilization.[12] Deuteration at C2 in product **3a'** was not observed (see above). Therefore, we conclude that O-H groups of *t*BuOOH or C–H of methanol do not act as hydrogen atom donors towards radicals **F**. The catalytic cycle may be closed, however, by direct or indirect hydrogen atom transfer[24] from α-amino nitriles **C** to radicals **F** to generate the final products **G** as well as the radicals **D** that take part in the next cycle of the radical chain reaction. On the basis of the quantum-chemically calculated radical stabilisation energies (RSEs),[25] transfer of a hydrogen atom from **C** to radical **F** is thermodynamically feasible and exothermic by 38 kJ mol^{-1} (in the gas phase, for details see experimental section).
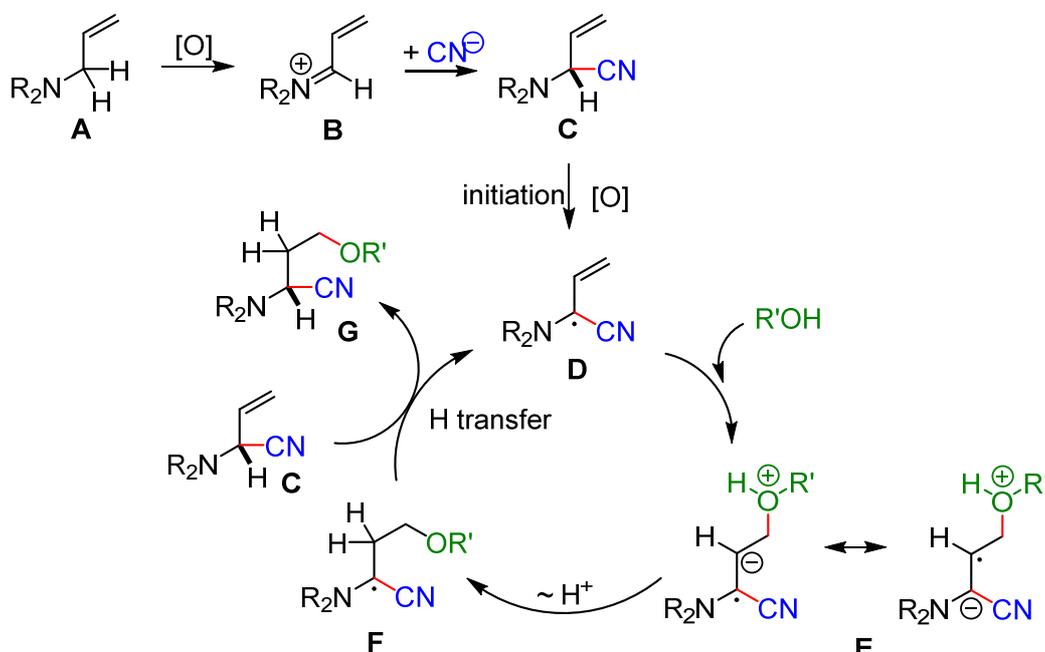
Scheme 3.3. Suggested mechanism for the oxidative C1-cyanation of the *N*-allyl group with subsequent anti-Markovnikov hydroalkoxylation.

Both radicals **D** and **F** involved in the proposed catalytic cycle are unusually stable in absolute terms, which implies weak C-H bonds in the closed shell parent systems **C** and **G**. On the basis of bond dissociation energies (BDEs), the relevant C-H bond of **2a** (+310 kJ/mol) is slightly weaker than that of 2-phenlymalononitrile (+322 ± 4 kJ/mol, from ref 26), which was successfully used as the H atom donor in intra-molecular hydroetherifications.[5g,6a] The relevant C-H bond of **2a** is also weaker than in reaction product **3a** (+348 kJ/mol), and much weaker than the allylic C-H bond in propene (+369 kJ/mol)[27] or the α-C-H bond in the glycine-derivative (+364 kJ/mol) depicted in Scheme 3.4.[25,28] Interestingly, the α-C-H bond in **3a** is of comparable strength as the O-H bond in tBuOOH (BDE = +353 ± 9 kJ/mol, from ref 29).

BDE (C–H) (kJ/mol):   310   346   322   364   369
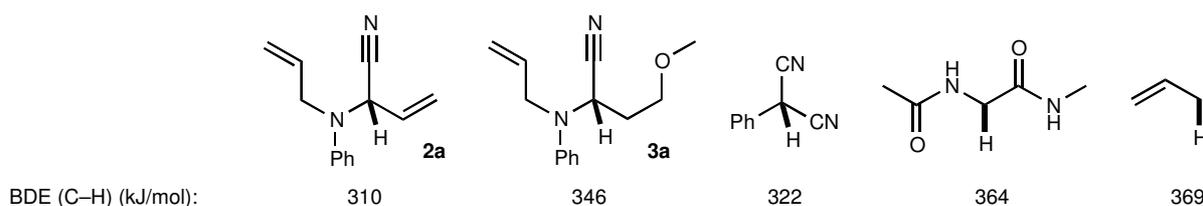
Scheme 3.4. Comparison of C-H bond dissociation energies (BDEs) in α-amino nitriles **2a** and **3a** with those in structurally analogous compounds and in 2-phenylmalononitrile.

When ethanol was used as the solvent instead of methanol, the 4-ethoxy-substituted 2-aminobutanenitrile **4** (68%) was obtained from **1a** by the cyanation/hydroalkoxylation sequence (Scheme 3.5).
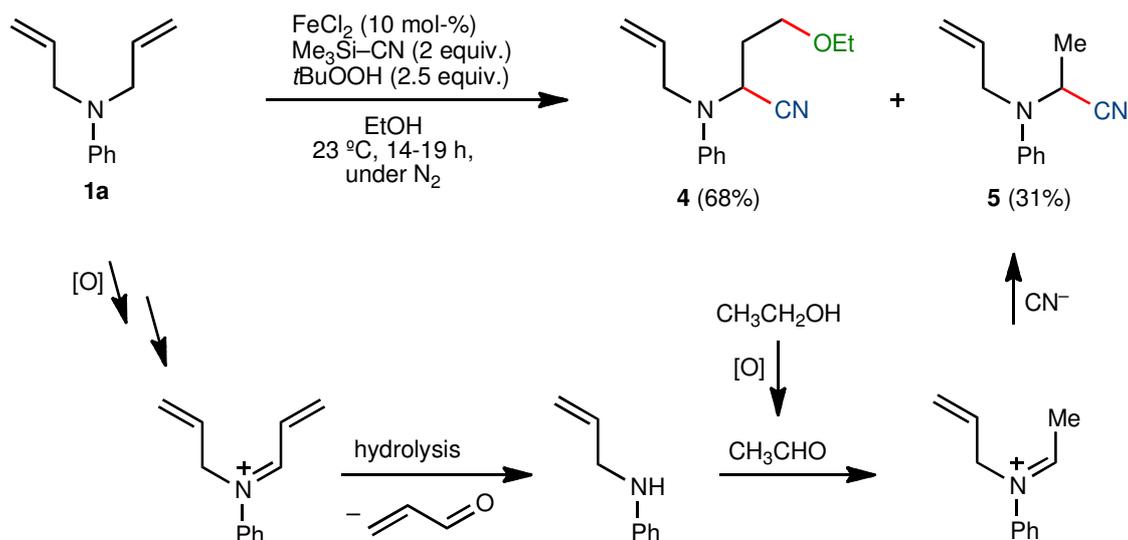
Scheme 3.5. Oxidative Cyanation of *N,N*-Diallylaniline in Ethanol (yields refer to isolated products after separation and purification by column chromatography).

Ethyl ether **4** was accompanied by the 2-aminopropanenitrile **5** (31 % isolated yield), whose formation is rationalized in analogy to the previously described oxidative dealkylation/cyanomethylation of *N,N*-dialkylanilines in methanol:[19c] Oxidative degradation of **1a** via hydrolysis of the intermediate α,β-unsaturated iminium ions forms *N*-allylaniline, which condenses with acetaldehyde, generated by oxidation of the solvent ethanol,[30] to yield iminium ions, which are finally trapped by cyanide to yield **5** (Scheme 3.5).

Reactions with *N*-allyl-*N*-ethylaniline (**6a**) and triallylamine (**9**) showed that the scope of the oxidative α-cyanation/hydroalkoxylation can be extended to mono- and triallyl-substituted amines (Scheme 3.6). Preferred cyanation of the NMe group of *N*-allyl-*N*-methylaniline (**6b**) to yield the α-amino nitrile **8** is in agreement with previous reports[17b-d] and allows one to derive the reactivity order NMe > *N*-allyl > NEt for the regioselectivity of these oxidative α-functionalization of *N,N*-disubstituted anilines. This reactivity order differs from Lambert's observation of a preferred hydride transfer from the aliphatic group of allyl-diisobutylamine to tropylium ions.[17a] Our

reactivity order also differs from that for relative rates for the deprotonation of laser-flash photolytically generated amine radical cations by acetate, k_{rel} = 2.7 (*N*-allyl) > 1 (NMe) > 0.24 (NEt), which were explained by stereoelectronic effects in the preferred transition state conformation.[31] One consequence of the chemoselectivity NMe > *N*-allyl of the oxidative functionalisation step is that this preference makes NMe groups in tertiary amines incompatible with the α-cyanation/anti-Markovnikov hydroalkoxylation sequence because the α-cyanation is directed to the N-methyl group.
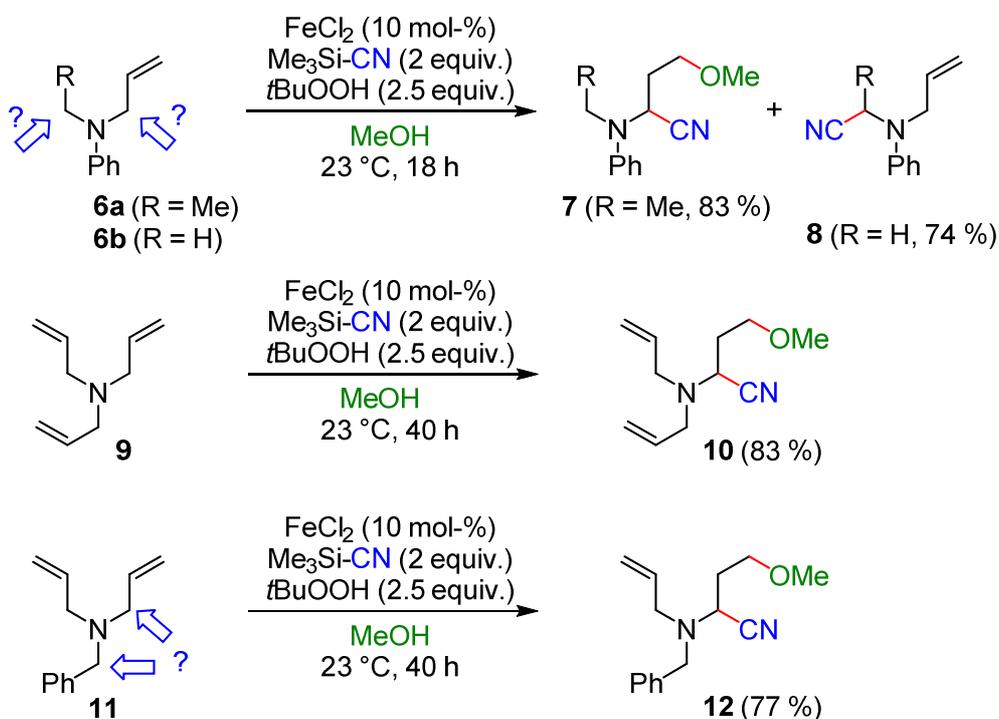
Scheme 3.6. Oxidative Cyanation/Hydroalkoxylation of the Monoallylamines **6a,b**, Triallylamine (**9**) and *N,N*-Diallylbenzylamine (**11**) (All reactions under dry N$_2$ atmosphere. Yields refer to isolated products after chromatographic purification)

Whereas a 7-fold preference for *N*-benzyl over *N*-allyl reactivity was found by Mizuno,[17d] we succeeded in preparing methyl ether **12** from *N*,*N*-diallylbenzylamine **11** under our reaction conditions.

3.3. Conclusion

In conclusion, an iron-catalysed α-cyanation of tertiary allylamines has been developed that is coupled with a subsequent chemo- and regioselective addition of alcohols to the π-system of the vinyl-substituted α-amino nitrile intermediate. Thus, this reaction combines three components[32] in one pot to yield 2-amino-4-alkoxybutanenitriles under mild conditions. Such ether-functionalized derivatives may further extend the rich synthetic versatility of α-amino nitriles.[33] Detailed studies of the mechanism including further characterisation of highly stabilised radicals of structural type **D**, as well as broadening the scope of this novel type of anti-Markovnikov hydroalkoxylation are currently underway.

3.4 Experimental section

In order to identify my contribution to this multiauthor publication, this Experimental Section covers exclusively those experiments, which were performed by me.

3.4.1. General

All reactions were carried out under an atmosphere of dry nitrogen. ^{1}H (300 or 400 MHz) and ^{13}C (75.5 or 100.6 MHz) NMR spectra of solutions in CDCl$_3$ were recorded on 300 or 400 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.26 and δ_C 77.16 ppm).[34] Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Signal assignments are based on gCOSY and gHSQC experiments. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond).

Materials. Triallylamine (Aldrich), iron(II) chloride (98%, Aldrich), trimethylsilyl cyanide (98%, Acros), *tert.*-butyl hydroperoxide (5.5 M solution in decane, purum, Aldrich) and d_4-methanol (99.80% D, Euriso-Top) were purchased. Allylanilines and allylamines were synthesized according to literature procedures.[35,36]

3.4.2. Oxidative α-cyanation/hydroalkoxylation of tertiary allylamines

General Procedure. Under an atmosphere of dry N$_2$, a Schlenk flask was charged with iron(II) chloride (10 mol%, 13 mg). The tertiary allylamine (1.0 mmol), trimethylsilyl cyanide (2.0 mmol, 0.27 mL), and MeOH (2.0 mL) were added

successively by syringe. To the mixture was added dropwise *t*BuOOH (2.5 mmol, 0.46 mL, 5.5 M solution in decane) over a period of 5 min. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel.

2-(Allyl(phenyl)amino)but-3-enenitrile (2a)

Following the *General Procedure*, *N*,*N*-diallylaniline **1a** (173 mg, 1.00 mmol) reacted with Me_3SiCN and *t*BuOOH for 4 h. The crude product was purified by column chromatography (SiO_2, pentane/CH_2Cl_2 = 3:2) to give **2a** (42 mg, 21%) as a colorless liquid.

2a
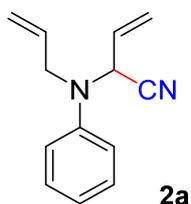
^{1}**H NMR** (300 MHz, $CDCl_3$): δ = 3.77–3.90 (m, 2 H), 5.09–5.27 (m, 3 H), 5.41–5.45 (m, 1 H), 5.64–5.70 (m, 1 H), 5.75–5.90 (m, 2 H), 6.87–6.93 (m, 3 H), 7.20–7.26 (m, 2 H).

^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ = 52.2 (CH_2), 55.3 (CH), 116.4 (C), 117.56 (CH), 117.61 (CH_2), 120.4 (CH_2), 121.3 (CH), 129.4 (CH), 131.0 (CH), 134.5 (CH), 147.4 (C).

HRMS (EI, 70 eV): *m*/*z* [M]$_+$· Calcd for $[C_{13}H_{14}N_2]^{+ \cdot}$ 198.1152; Found 198.1147.

2-(Allyl(phenyl)amino)-4-methoxybutanenitrile (3a)

Following the *General Procedure*, *N*,*N*-diallylaniline **1a** (173 mg, 1.00 mmol) reacted with Me_3SiCN and *t*BuOOH for 16 h. The crude product was purified by column chromatography (SiO_2, pentane/CH_2Cl_2 = 3:2) to give **3a** (198 mg, 86%) as a colorless liquid.

3a
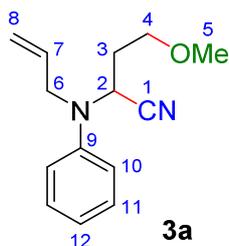
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.18 (m, 2 H, 3-H), 3.36 (s, 3 H, 5-H), 3.51–3.55 (m, 2 H, 4-H), 3.85–4.00 (m, 2 H, 6-H), 4.76 (t, *J* = 7.7 Hz, 1 H, 2-H), 5.19–5.33 (m, 2 H, 8-H), 5.83–5.95 (m, 1 H, 7-H), 6.93–7.01 (m, 10-H and 12-H), 7.26–7.32 (m, 11-H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 32.6 (CH_2, C-3), 49.9 (CH, C-2), 52.8 (CH_2, C-6), 58.9 (CH_3, C-5), 67.7 (CH_2, C-4), 117.5 (CH_2, C-8), 118.0 (CH, C-10), 118.6 (C, C-1), 121.3 (CH, C-12), 129.3 (CH, C-11), 134.6 (CH, C-7), 147.7 (C, C-9).

ν (neat/ATR probe): 2959, 2929, 2874, 1495, 1453, 1363, 1189, 1116, 913, 731, 698 cm^{-1}.

HRMS (EI, 70 eV): *m*/*z* [M]$^{+\cdot}$ Calcd for [$C_{14}H_{18}N_2O$]$^{+\cdot}$ 230.1414; Found 230.1414.

2-(Allyl(phenyl)amino)-4-(d_3-methoxy)butanenitrile (3a')

Following the *General Procedure* using CD_3OD as solvent, *N,N*-diallylaniline **1a** (173 mg, 1.00 mmol) reacted with Me_3SiCN and *t*BuOOH for 16 h. The crude product was purified by column chromatography (SiO_2, pentane/CH_2Cl_2 = 3:2) to give **3a'** (205 mg, 88%) as a colorless liquid.

3a'
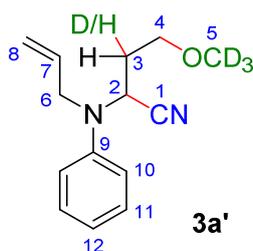
^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.04–2.20 (m, 1.6 H, 3-H), 3.50–3.55 (m, 2 H, 4-H), 3.84–4.00 (m, 2 H, 6-H), 4.73–4.78 (m, 1 H, 2-H), 5.18–5.33 (m, 2 H, 8-H), 5.82–5.95 (m, 1 H, 7-H), 6.92–7.01 (m, 10-H and 12-H), 7.26–7.31 (m, 11-H).

^{2}H NMR (61.4 MHz, CDCl$_3$): δ = 3.33 (s, 3 D, 5-D), ca. 2.13 (m, 0.4 D, 3-D).

^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 32.3 (t, $^1J_{C,D}$ = 20.0 Hz, CHD, C-3) and 32.6 (CH$_2$, C-3), 49.86/49.92 (CH, C-2), 52.79/52.80 (CH$_2$, C-6), 58.1 (sept, $^1J_{C,D}$ = 21.5 Hz, CD$_3$, C-5), 67.55/67.60 (CH$_2$, C-4), 117.5 (CH$_2$, C-8), 118.0 (CH, C-10), 118.6 (C, C-1), 121.3 (CH, C-12), 129.4 (CH, C-11), 134.6 (CH, C-7), 147.8 (C, C-9).

HRMS (EI, 70 eV): m/z [M]$^{+\cdot}$ Calcd for [C$_{14}$H$_{15}$^{2}H$_3$N$_2$O]$^{+\cdot}$ 233.1602; Found 233.1617.

2-(Allyl(*p*-tolyl)amino)-4-methoxybutanenitrile (3b)

Following the *General Procedure*, *N,N*-diallyl-4-methylaniline **1b** (187 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH in decane for 14 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 3:2) to give **3b** (208 mg, 85%) as a colorless liquid.

3b
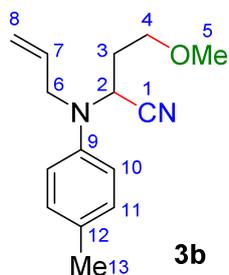
^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.98–2.20 (m, 2 H, 3-H), 2.30 (s, 3 H, 13-H), 3.36 (s, 3 H, 5-H), 3.47–3.60 (m, 2 H, 4-H), 3.80–3.95 (m, 2 H, 6-H), 4.64 (t, *J* = 7.7 Hz, 1 H,

2-H), 5.18–5.33 (m, 2 H, 8-H), 5.81–5.93 (m, 1 H, 7-H), 6.94–6.97 (m, 2 H, 10-H), 7.09–7.13 (m, 2 H, 11-H).

^{13}**C NMR** (75.5 MHz, CDCl$_3$): δ = 20.6 (CH$_3$, C-13), 32.6 (CH$_2$, C-3), 50.6 (CH, C-2), 53.4 (CH$_2$, C-6), 58.9 (CH$_3$, C-5), 67.8 (CH$_2$, C-4), 117.6 (CH$_2$, C-8), 118.6 (C, C-1), 119.6 (CH, C-10), 129.9 (CH, C-11), 131.7 (C, C-12), 134.8 (CH, C-7), 145.4 (C, C-9).

ν (neat/ATR probe): 2925, 2875, 1616, 1514, 1455, 1385, 1239, 1219, 1183, 1117, 990, 921, 866, 806, 727 cm^{-1}.

HRMS (EI, 70 eV): *m/z* [M]$^{+\cdot}$ Calcd for [C$_{15}$H$_{20}$N$_2$O]$^{+\cdot}$ 244.1571; Found 244.1576.

2-(Allyl(4-methoxyphenyl)amino)-4-methoxybutanenitrile (3c)

Following the *General Procedure*, *N,N*-diallyl-4-methoxyaniline **1c** (203 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 14 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 3:2) to give **3c** (242 mg, 93%) as a colorless liquid.
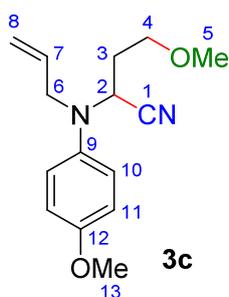
^{1}**H NMR** (300 MHz, CDCl$_3$): δ = 1.88–2.14 (m, 2 H, 3-H), 3.35 (s, 3 H, 5-H), 3.45–3.60 (m, 2 H, 4-H), 3.68–3.85 (m, 2 H, 6-H), 3.78 (s superimposed with resonances of 6-H, 3 H, 13-H), 4.43 (t, *J* = 7.8 Hz, 1 H, 2-H), 5.14–5.31 (m, 2 H, 8-H), 5.75–5.88 (m, 1 H, 7-H), 6.83–6.86 and 7.06–7.09 (2 m, 2 × 2 H, 10-H and 11-H).

^{13}**C NMR** (75.5 MHz, CDCl$_3$): δ = 32.6 (CH$_2$, C-3), 51.9 (CH, C-2), 54.9 (CH$_2$, C-6), 55.6 (CH$_3$, C-13), 58.9 (CH$_3$, C-5), 67.9 (CH$_2$, C-4), 114.5 (CH, C-10 or C-11), 118.0 (CH$_2$, C-8), 118.7 (C, C-1), 123.8 (CH, C-10 or C-11), 134.8 (CH, C-7), 141.1 (C, C-9), 156.3 (C, C-12).

ν (neat/ATR probe): 2931, 2834, 1509, 1462, 1244, 1214, 1181, 1117, 1036, 917, 866, 834, 731 cm^{-1}.

HRMS (EI, 70 eV): m/z [M]$^{+\cdot}$ Calcd for [C$_{15}$H$_{20}$N$_2$O$_2$]$^{+\cdot}$ 260.1520; Found 260.1504.

2-(Allyl(4-bromophenyl)amino)-4-methoxybutanenitrile (3d)

Following the *General Procedure*, *N,N*-diallyl-4-bromoaniline **1d** (252 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 19 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 3:2) to give **3d** (207 mg, 67%) as a yellow liquid.
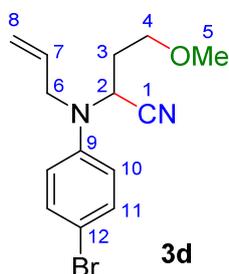

^{1}**H NMR** (300 MHz, CDCl$_3$): δ = 2.02–2.20 (m, 2 H, 3-H), 3.35 (s, 3 H, 5-H), 3.49–3.53 (m, 2 H, 4-H), 3.82–3.97 (m, 2 H, 6-H), 4.73 (t, J = 7.7 Hz, 1 H, 2-H), 5.19–5.30 (m, 2 H, 8-H), 5.78–5.91 (m, 1 H, 7-H), 6.83–6.86 (m, 2 H, 10-H), 7.35–7.38 (m, 2 H, 11-H).

^{13}**C NMR** (75.5 MHz, CDCl$_3$): δ = 32.4 (CH$_2$, C-3), 49.7 (CH, C-2), 52.4 (CH$_2$, C-6), 58.9 (CH$_3$, C-5), 67.4 (CH$_2$, C-4), 113.5 (C, C-12), 117.8 (CH$_2$, C-8), 118.2 (C, C-1), 119.2 (CH, C-10), 132.1 (CH, C-11), 133.9 (CH, C-7), 146.6 (C, C-9).

ν (neat/ATR probe): 2929, 2877, 2831, 1590, 1493, 1458, 1385, 1236, 1183, 1116, 1081, 998, 918, 866, 808, 731, 648 cm^{-1}.

HRMS (EI, 70 eV): m/z [M]$^{+\cdot}$ Calcd for [C$_{14}$H$_{17}$^{79}BrN$_2$O]$^{+\cdot}$ 308.0519; Found 308.0522.

2-(Allyl(phenyl)amino)-4-ethoxybutanenitrile (4) and 2-(allyl(phenyl)amino)-propanenitrile (5)

Following the *General Procedure* using EtOH as solvent, *N,N*-diallylaniline **1a** (173 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 16 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 3:2) to give **4** (166 mg, 68%) as a colorless liquid and **5** (58 mg, 31%) as a colorless liquid.
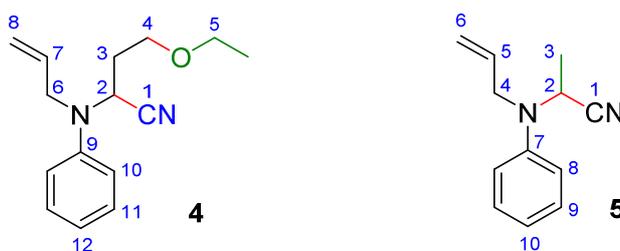
Analytical data for **4**: **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 1.21 (t, J = 7.0 Hz, 3 H, 5-CH$_3$), 2.03–2.23 (m, 2 H, 3-H), 3.45–3.59 (m, 4 H, 4-H and 5-H), 3.85–4.01 (m, 2 H, 6-H), 4.79 (t, J = 7.7 Hz, 1 H, 2-H), 5.19–5.34 (m, 2 H, 8-H), 5.83–5.95 (m, 1 H, 7-H), 6.92–7.01 (m, 10-H and 12-H), 7.26–7.32 (m, 2 H, 11-H).

^{13}C NMR (75.5 MHz, CDCl$_3$): δ = 15.1 (CH$_3$, 5-CH$_3$), 32.6 (CH$_2$, C-3), 49.8 (CH, C-2), 52.6 (CH$_2$, C-6), 65.3 (CH$_2$, C-4), 66.5 (CH$_2$, C-5), 117.4 (CH$_2$, C-8), 117.9 (CH, C-10), 118.6 (C, C- 1), 121.1 (CH, C-12), 129.2 (CH, C-11), 134.5 (CH, C-7), 147.7 (C, C-9).

ν (neat/ATR probe): 2975, 2930, 2867, 1598, 1502, 1377, 1236, 1172, 1110, 990, 915, 749, 732, 692 cm^{-1}.

HRMS (EI, 70 eV): m/z [M]$^{+\cdot}$ Calcd for [C$_{15}$H$_{20}$N$_2$O]$^{+\cdot}$ 244.1570; Found 244.1569.

Analytical data for **5**: **¹H NMR** (300 MHz, CDCl$_3$): δ = 1.58 (d, *J* = 7.2, 3 H, 3-H), 3.85–4.00 (m, 2 H, 4-H), 4.56 (q, *J* = 7.2 Hz, 1 H, 2-H), 5.20–5.35 (m, 2 H, 6-H), 5.85–5.97 (m, 1 H, 5-H), 6.96–7.00 (m, 3 H, H-8 and H-10), 7.26–7.33 (m, 2 H, H-9).

¹³C NMR (75.5 MHz, CDCl$_3$): δ = 18.6 (CH$_3$, C-3), 47.4 (CH, C-2), 53.0 (CH$_2$, C-4), 117.4 (CH$_2$, C-6), 118.4 (CH, C-8), 119.3 (C, C-1), 121.7 (CH, C-10), 129.4 (CH, C-9), 134.9 (CH, C-5), 147.7 (C, C-7).

HRMS (EI, 70 eV): *m/z* [M]$^{+\cdot}$ Calcd for [C$_{12}$H$_{14}$N$_2$]$^{+\cdot}$ 186.1152; Found 186.1163.

2-(Ethyl(phenyl)amino)-4-methoxybutanenitrile (7) Following the *General Procedure*, *N*-allyl-*N*-ethylaniline **6a** (161 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 18 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 2:1) to give **7** (181 mg, 83%) as a colorless liquid.
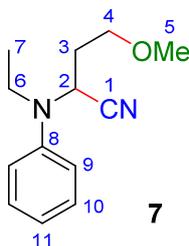

¹H NMR (300 MHz, CDCl$_3$): δ = 1.19 (t, J = 7.1 Hz, 3 H, 7-H), 2.02–2.19 (m, 2 H, 3-H), 3.26–3.43 (m, 2 H, 6-H), 3.36 (s superimposed with resonances of 6-H, 3 H, 5-H), 3.49–3.59 (m, 2 H, 4-H), 4.67 (t, J = 7.7 Hz, 1 H, 2-H), 6.94–7.02 (m, 3 H, 9-H and 11-H), 7.26–7.33 (m, 2 H, 10-H).

¹³C NMR (75.5 MHz, CDCl$_3$): δ = 13.7 (CH$_3$, C-7), 32.6 (CH$_2$, C-3), 43.7 (CH$_2$, C-6), 50.7 (CH, C-2), 59.0 (CH$_3$, C-5), 67.7 (CH$_2$, C-4), 118.7 (CH, C-9), 118.9 (C, C-1), 121.5 (CH, C-11), 129.5 (CH, C-10), 147.2 (C, C-8).

ν (neat/ATR probe): 2977, 2929, 2875, 1598, 1502, 1385, 1248, 1190, 1116, 1014, 910, 862, 750, 730, 693, 647 cm^{-1}.

HRMS (EI, 70 eV): m/z [M]$^{+\cdot}$ Calcd for [C$_{13}$H$_{18}$N$_2$O]$^{+\cdot}$ 218.1414; Found 218.1411.

2-(Allyl(phenyl)amino)acetonitrile (8) Following the *General Procedure*, *N*-allyl-*N*-methylaniline **6b** (147 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 18 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 2:1) to give **8** (128 mg, 74%) as a colorless liquid. Known compound, the NMR spectroscopic data agree with those given in lit.[37]
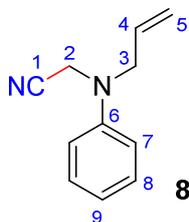
^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 3.97 (d, J = 5.6 Hz, 2 H, 3-H), 4.15 (s, 2 H, 2-H), 5.28–5.38 (m, 2 H, 5-H), 5.85–5.95 (m, 1 H, 4-H), 6.89–6.95 (m, 3 H, 7-H and 9-H), 7.30–7.34 (m, 2 H, 8-H).

^{13}**C NMR** (100.6 MHz, CDCl$_3$): δ = 39.4 (CH$_2$, C-3), 54.6 (CH$_2$, C-2), 115.3 (CH, C-7), 116.1 (C, C-1), 118.6 (CH$_2$, C-5), 120.3 (CH, C-9), 129.6 (C, C-8), 133.0 (CH, C-4), 147.5 (C, C-6).

2-(Diallylamino)-4-methoxybutanenitrile (10)

Following the *General Procedure*, triallylamine **9** (137 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 40 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 2:3) to give **10** (161 mg, 83%) as a colorless liquid.

10
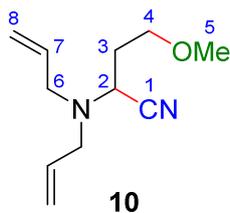
^{1}**H NMR** (300 MHz, CDCl$_3$): δ = 1.95–2.04 (m, 2 H, 3-H), 2.88–2.96 (m, 2 H, 6-H$_a$), 3.32–3.40 (m, 2 H, 6-H$_b$), 3.32 (s superimposed with resonances of 6-H$_b$, 3 H, 5-H), 3.42–3.55 (m, 2 H, 4-H), 3.98 (t, J = 7.8 Hz, 1 H, 2-H), 5.16–5.30 (m, 4 H, 8-H), 5.70–5.83 (m, 2 H, 7-H).

^{13}**C NMR** (75.5 MHz, CDCl$_3$): δ = 31.9 (CH$_2$, C-3), 50.3 (CH, C-2), 54.5 (CH$_2$, C-6), 58.9 (CH$_3$, C-5), 68.0 (CH$_2$, C-4), 117.8 (C, C-1), 118.5 (CH$_2$, C-8), 134.9 (CH, C-7).

ν (neat/ATR probe): 3082, 2981, 2931, 2814, 1644, 1450, 1420, 1189, 1116, 994, 920, 732 cm^{-1}.

HRMS (EI, 70 eV): m/z [M-H]$^-$ Calcd for [C$_{11}$H$_{17}$N$_2$O]$^-$ 193.1346; Found 193.1333.

2-(Allyl(benzyl)amino)-4-methoxybutanenitrile (12) Following the *General Procedure*, *N,N*-diallyl-benzylamine **11** (187 mg, 1.00 mmol) reacted with Me$_3$SiCN and *t*BuOOH for 40 h. The crude product was purified by column chromatography (SiO$_2$, pentane/CH$_2$Cl$_2$ = 2:3) to give **12** (188 mg, 77%) as a colorless liquid.

12
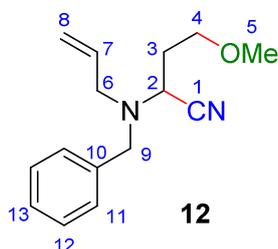
^{1}**H NMR** (400 MHz, CDCl$_3$): δ = 1.91–1.97 (m, 2 H, 3-H), 2.87–2.93 (m, 1 H, 6-H$_a$), 3.19 (s, 3 H, 5-H), 3.20–3.43 (m, 4 H, 4-H, 6-H$_b$ and 9-H$_a$), 3.86–3.91 (m, 2 H, 2-H

and 9-H$_b$), 5.12–5.15 (m, 2 H, 8-H), 5.21–5.26 (m, 1 H, 7-H), 7.18–7.29 (m, 5 H, 11-H, 12-H and 13-H).

^{13}**C NMR** (100.6 MHz, CDCl$_3$): δ = 31.9 (CH$_2$, C-3), 50.3 (CH, C- 2), 54.6 (CH$_2$, C-6), 55.5 (CH$_2$, C-9), 58.8 (CH$_3$, C-5), 68.0 (CH$_2$, C-4), 117.7 (C, C- 1), 118.8 (CH$_2$, C-8), 127.6, 128.6, 128.7 (3 × CH, C-11, C-12 and C-13), 134.8 (CH, C-7), 138.1 (C, C-10).

HRMS (EI, 70 eV): m/z [M-H]$^-$ Calcd for [C$_{15}$H$_{19}$N$_2$O]$^-$ 243.1503; Found 243.1490.

3.4.3. Preparation of tertiary allylamines 1a-d, 6a, b, and 11

According to a procedure reported in lit.[35]: In a 500 mL round-bottom flask equipped with a reflux condenser and a stir bar, aniline (50 mmol), allyl bromide (12.1 g, 100 mmol), and Na$_2$CO$_3$ (5.40 g, 51 mmol) were added to aqueous ethanol (200 mL, EtOH/H$_2$O = 4/1). The reaction mixture was refluxed overnight. The crude product was poured on saturated aq. NaHCO$_3$ (50 mL) and extracted with Et$_2$O (3 × 50 mL). The combined organic layers were washed with H$_2$O (2 × 50 mL), dried over MgSO$_4$, and the solvent was evaporated in the vacuum. The crude product was distilled over KOH to provide the corresponding diallylaniline.

N,N-**Diallylaniline (1a):** 6.2 g (71%). Known compound, the NMR spectroscopic data agree with those given in lit.[38]: ^{1}**H NMR** (300 MHz, CDCl$_3$): δ = 3.99-4.02 (m, 4 H), 5.22-5.30 (m, 4 H), 5.89-6.01 (m, 2 H), 6.77-6.81 (m, 3 H), 7.28-7.31 (m, 2 H).
^{13}**C NMR** (75.5 MHz, CDCl$_3$): δ = 52.9, 112.5, 116.1, 116.4, 129.2, 134.2, 148.8.

N,N-**Diallyl-4-methylaniline (1b):** 6.7 g (71%). Known compound, the NMR spectroscopic data agree with those given in lit.[38]: ^{1}**H NMR** (300 MHz, CDCl$_3$): δ =

2.29 (s, 3 H), 3.93-3.95 (m, 4 H), 5.17-5.26 (m, 4 H), 5.84-5.97 (m, 2 H), 6.67-6.70 (m, 2 H), 7.05-7.08 (m, 2 H). **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 20.3, 53.1, 112.8, 116.0, 125.6, 129.7, 134.4, 146.8.

***N,N*-Diallyl-4-methoxyaniline (1c):** 3.5 g (34%). Known compound, the NMR spectroscopic data agree with those given in lit.[38]: **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 3.77 (s, 3 H), 3.88-3.89 (m, 4 H), 5.16-5.24 (m, 4 H), 5.82-5.93 (m, 2 H), 6.71-6.74 (m, 2 H), 6.82-6.85 (m, 2 H). **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 53.7, 55.9, 114.6, 114.8, 116.2, 134.7, 143.6, 151.7.

***N,N*-Diallyl-4-bromoaniline (1d):** 3.5 g (28%). Known compound, the NMR spectroscopic data agree with those given in lit.[38]: **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 3.89-3.92 (m, 4 H), 5.14-5.20 (m, 4 H), 5.78-5.90 (m, 2 H), 6.56-6.59 (m, 2 H), 7.25-7.28 (m, 2 H). **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 53.0, 108.2, 114.1, 116.3, 131.8, 133.5, 147.7.

***N*-Allyl-*N*-ethylaniline (6a)** from *N*-ethylaniline (6.1 g, 50 mmol), allyl bromide (4.8 mL, 40 mmol), and Na$_2$CO$_3$ (4.2 g, 40 mmol) as described above to the preparation of **1a**-**d**. The crude product was purified by vacuum distillation from CaH$_2$: 4.8 g (74%). Known compound, the NMR spectroscopic data agree with those given in lit.[39]: **^{1}H NMR** (300 MHz, CDCl$_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 3.46 (q, J = 7.1 Hz, 2 H), 3.96-3.99 (m, 2 H), 5.19-5.29 (m, 2 H), 5.88-6.00 (m, 1 H), 6.74-6.79 (m, 3 H), 7.26- 7.31 (m, 2 H). **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 12.4, 44.8, 52.8, 112.2, 115.9, 116.0, 129.3, 134.6, 148.3.

***N*-Allyl-*N*-methylaniline (6b)** from *N*-methylaniline (5.4 g, 50 mmol), allyl bromide (4.8 mL, 40 mmol), and Na$_2$CO$_3$ (4.2 g, 40 mmol) as described above for the

preparation of **1a**-**d**. The crude product was purified by vacuum distillation from CaH$_2$: 4.0 g (68%). Known compound, the NMR spectroscopic data agree with those given in lit.[39]: **^{1}H NMR** (400 MHz, CDCl$_3$): δ = 2.97 (s, 3 H), 3.94-3.96 (m, 2 H), 5.16-5.23 (m, 2 H), 5.83-5.93 (m, 1 H), 6.73-6.78 (m, 3 H), 7.24-7.27 (m, 2 H). **^{13}C NMR** (100.6 MHz, CDCl$_3$): δ = 38.1, 55.4, 112.6, 116.3, 116.5, 129.2, 134.0, 149.6.

_N,N_-Diallyl-benzylamine (11) from benzylamine as described above for the preparation of **1a**-**d**. The crude product was purified by vacuum distillation from CaH$_2$: 5.7 g (61%). Known compound, the NMR spectroscopic data agree with those given in lit.[38]: **^{1}H NMR** (300 MHz, CDCl$_3$, Me$_4$Si): δ = 3.00 (dt, J = 6.3 Hz, J = 1.4 Hz, 4 H), 3.49 (s, 2 H), 5.03-5.14 (m, 4 H), 5.73-5.87 (m, 2 H), 7.14-7.26 (m, 5 H). **^{13}C NMR** (75.5 MHz, CDCl$_3$): δ = 56.6, 57.7, 117.4, 126.9, 128.3, 129.0, 136.0, 139.6.

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4

Potassium Thiocyanate as Source of Cyanide for the Oxidative α-Cyanation of Tertiary Amines

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4.1. Introduction

Oxidation of thiocyanate salts can be directed in a way that cyanide ions accumulate. This cyanide formation is of interest in mining industries where waste waters and tailings with high concentrations of thiocyanate salts are generated during the cyanidation of sulfur-containing metal ores. Several technical oxidation processes have, therefore, been developed for the recycling of CN^- from SCN^- with the goal to minimize costly loss of cyanide during the treatment of the ores as well as to reduce deleterious effects of SCN^- on aquatic ecosystems.[1,2] Also in organisms, peroxidases can catalyze the oxidative degradation of thiocyanate to cyanide.[3] Such peroxidase activities, for example, complicate the correct forensic analysis of human tissue[3d–f] and disturb the relation of blood cyanide concentration with the amount of excreted hydrogen cyanide in breath.[3c] Furthermore, peroxidase-catalyzed production of CN^- from SCN^- has been discussed to contribute to the metabolic formation of toxic dicyano aurate (I) in patients treated with medicinal gold complexes.[3g] In addition, the mechanism of the pH dependent thiocyanate oxidation by H_2O_2 to form cyanide according to equation 1 has been studied in some detail.[4]

$$3\ H_2O_2 + SCN^- \rightarrow HSO_4^- + HCN + 2\ H_2O \qquad (1)$$
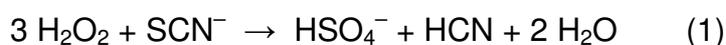
4.2. Results and Discussion

We had previously shown that CH-cyanation adjacent to the nitrogen of a broad range of tertiary amines can be achieved by using $FeCl_2$ as the catalyst, tBuOOH as the oxidant and Me_3SiCN as the CN source.[5] We then hypothesized that, under analogous reaction conditions, combining oxidizable SCN^- salts with oxidizable tertiary amines could provide an access to α-amino nitriles[6] which is particularly appealing because a non-toxic CN source could be used (Scheme 4.1 and Table 4.1, experimental section).[5,7–10]

Scheme 4.1. Synthesis of α-Amino Nitriles by Oxidative Coupling of Cyanide with Tertiary Amines (DCE = 1,2-dichloroethane).
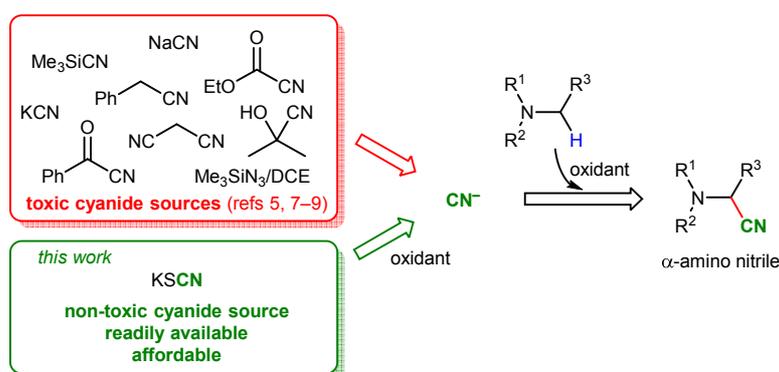
The reaction of *N,N*-dimethyl-*p*-toluidine (**1a**) with 2 equivalents of potassium rhodanide in the presence of catalytic amounts of $FeCl_2$ (10 mol-%) and 2.5 equivalents of tBuOOH produced neither the thiocyanated amine **2a** nor the thermodynamically more stable isothiocyanate isomer **2a'** (Scheme 2, upper part). Instead, a mixture of *N*-methyl-*p*-toluidine (**3a**), *N*-methyl-*N*-(*p*-tolyl)formamide (**4a**) and the α-amino nitrile **5a** formed with low selectivity (ratio in the crude product: 33/24/43, as determined by GC-MS analysis).

Scheme 4.2. Formation of α-Amino Nitriles **5a** and **7a** by Oxidative Coupling of KSCN with the Amines **1a** and **6a**[a]
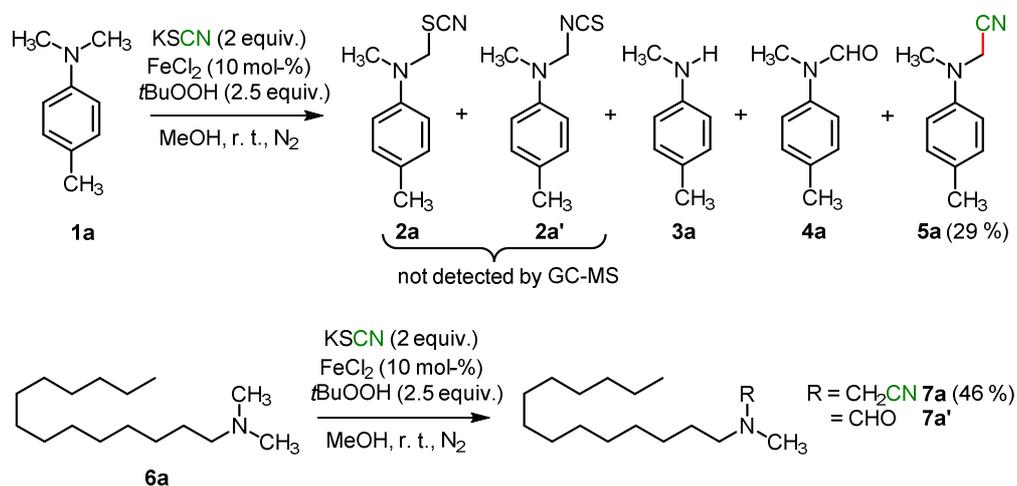
[a] 5.5 M tBuOOH in decane was used as the oxidant.

The presence of **5a** in the crude product mixture confirmed that not only the aniline derivative **1a** but also the thiocyanate ion was oxidized under the reaction conditions. After purification by column chromatography **5a** was obtained in 29 % yield. Analogously, and even more promising, the oxidative cyanation of dimethyltetradecylamine (**6a**) with KSCN generated α-amino nitrile **7a** in an isolated yield of 46 % (Scheme 4.2, lower part). N-Methyl-N-tetradecyl-formamide (**7a'**) was formed as a by-product of the oxidation of **6a**, but the selectivity for the formation of **7a** (ratio in the crude product: **7a/7a'** = 84/16, as determined by GC-MS) was already encouraging. Further optimization of the cyanation of amine **6a** by thiocyanate was carried to improve the practicability and selectivity of the reaction (Table 4.1).

Entries 1-2 of Table 4.1 show that exclusion of moisture did not affect the yield of **7a**, which enabled us to continue working without a protecting N_2 atmosphere.

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Increasing the excess of thiocyanate from 2 to 3 equivalents slightly increased the yield of **7a** from 47 to 51 % (entry 3). After changing the solvent of the oxidant tBuOOH from decane to water, the yield of **7a** remained unaffected while the reaction time could be reduced from 16 h to 5 h (entry 4). Surprisingly, the yield of **7a** decreased gradually when the amount of $FeCl_2$ was increased from 10 over 20 to 100 mol-% (entries 4-6), which led us to study the oxidative cyanation reaction in absence of $FeCl_2$. Comparison of entry 7 with entries 4-6 shows that $FeCl_2$ was not necessary for the formation of **7a** from **6a** and KSCN. We, therefore, continued the optimization without using a catalyst.

Owing to the consumption of the oxidant tBuOOH by interaction with the amine *and* the thiocyanate ions, a further increase of the amount of the oxidant seemed to make sense. Thus, the use of 4 equiv. of tBuOOH was beneficial for the yield of **7a** (57 %, entry 8) and further shortened the reaction time from 6 h to 3 h. Similar yields of **7a** (57-61 %) were obtained after comparable reaction times (3 to 4 h) when the reaction was carried out in methanol, acetonitrile, or water. However, the fastest conversion of **6a** to **7a** was achieved when the reactants were not diluted by any added solvent, which reduced the reaction time from 3 h (entries 8-10) to 45 min (entry 11). Further increase of the excess of potassium thiocyanate or the oxidant tBuOOH slightly improved the isolated yields of **7a** (entries 12 and 14). An optimum of 66 % for the yield of **7a** was found at a reaction time of 90 min when 4 equiv. of tBuOOH and 4 equiv. of KSCN were used (entry 13). Under the conditions of entry 13 also the selectivity **7a**/**7a'** had increased to 95/5 in favour of the cyanation product **7a** (GC-MS of the crude material). Hence, entry 13 was defined as standard for testing the scope of the double oxidative cyanation with further amines.

Table 4.1. Optimization of the Oxidative α-Cyanation of Dimethyltetradecylamine (**6a**) by Potassium Thiocyanate[a]

Entry	FeCl$_2$ [mol-%]	Solvent	Equiv. KSCN	Oxidant/conditions	Yields of 7a [%]
1	10	MeOH	2	tBuOOH[b]/under N$_2$, 16 h	46
2	10	MeOH	2	tBuOOH[b]/air, 16 h	47
3	10	MeOH	3	tBuOOH[b]/air, 16 h	51
4	10	MeOH	3	aq tBuOOH[c]/air, 5 h	51
5	20	MeOH	3	aq tBuOOH[c] /air, 6 h	50
6	100	MeOH	3	aq tBuOOH[c] /air, 6 h	43
7	—	MeOH	3	aq tBuOOH[c] /air, 6 h	52
8	—	MeOH	3	aq tBuOOH[d] /air, 3 h	57
9	—	MeCN	3	aq tBuOOH[d] /air, 3 h	60
10	—	H$_2$O	3	aq tBuOOH[d] /air, 4 h	61
11	—	—	3	aq tBuOOH[d] /air, 45 min	61
12	—	—	4	aq tBuOOH[d] /air, 45 min	62
13	**—**	**—**	**4**	**aq tBuOOH[d]/air, 1.5 h**	**66**
14	—	—	5	aq tBuOOH[e]/air, 45 min	64

[a] At ambient temperature (ca. 23 °C), solvent volume: 2 mL; yields refer to isolated product after column chromatography. [b–e] Oxidants: [b] 2.5 equiv. of tBuOOH (5.5 M solution in decane); [c] 2.5 equiv. of aqueous tBuOOH (= 70/30 w/w mixture of tBuOOH and water). [d] 4 equiv. of aq tBuOOH; [e] 6 equiv. of aq tBuOOH.

As summarized in Scheme 4.3, a series of aliphatic tertiary amines **6** was selectively α-cyanated to form **7a-h**. Reactions of dimethylalkylamines RNMe$_2$ led to formation

of 2-amino acetonitriles **7a**,**b** because of a selective cyanation at the NMe groups. Efficient oxidation of the well water-soluble amines cyclohexyldimethylamine (**6c**) and tripropylamine (**6d**) under standard conditions generated the corresponding amides instead of α-cyanated amines.[11] Cyanation of **6c** by KSCN could be achieved, however, by using a 4.5 M solution of *t*BuOOH in dichloromethane, which is a milder oxidizing agent as compared with 70 % aq *t*BuOOH and provides a lower solubility for KSCN than purely aqueous reaction mixtures. Alternatively, small volumes of acetonitrile can be added to the reaction mixture when aq *t*BuOOH is used. In this way, **7d** was obtained from **6d** in a moderate yield of 61 %.

Scheme 4.3. Generation of α-Amino Nitriles from Tertiary Amines and Potassium Thiocyanate[a]
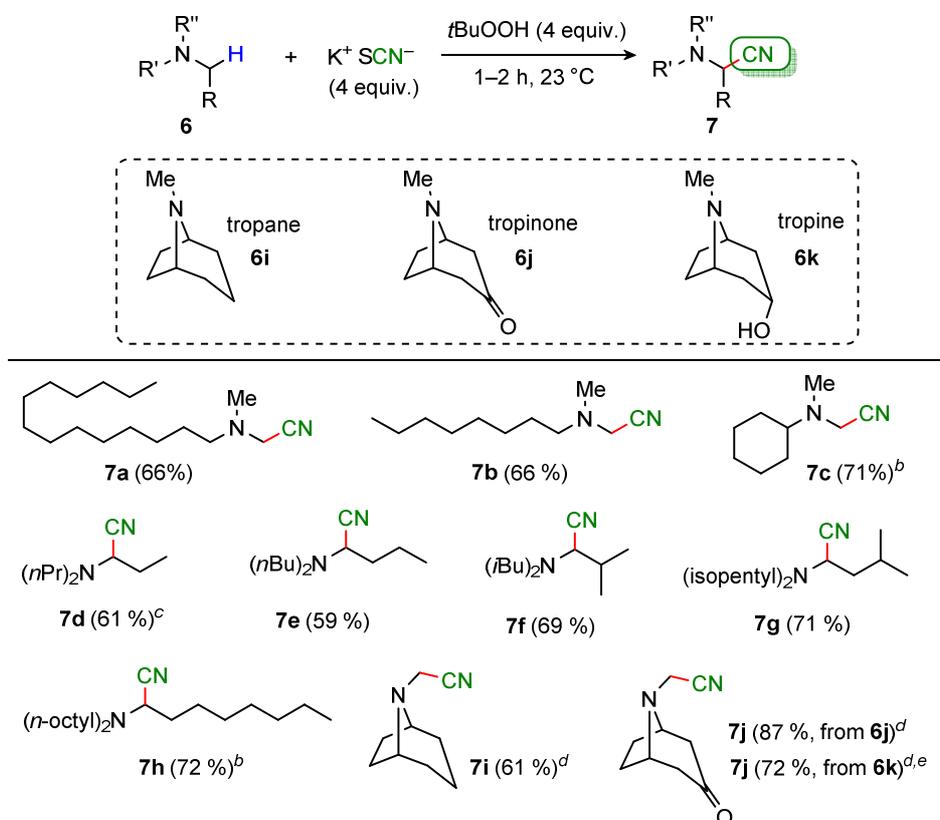
[a] Reaction conditions: amine (1 mmol), KSCN (4 equiv.), aq tBuOOH (70 % (w/w), 4 equiv.), ambient temperature (ca. 23 °C); yields refer to isolated products after column chromatography. [b] A 4.5 M solution of tBuOOH in CH_2Cl_2 was used as oxidant. [c] With MeCN as solvent (0.5 mL). [d] With MeCN as solvent (2 mL) at 50 °C. [e] With 5 equiv. of tBuOOH.

Oxidative photo-generation of iminium ions from amines and subsequent trapping with trimethylsilyl cyanide has been reported to be an efficient method for the cyanation of a series of alkaloids.[9a] As tropinone (**6j**) was reported to undergo iron-catalyzed oxidative amidations by aldehydes with tBuOOH as the oxidant,[12] we set out to investigate whether cyanation of **6j** is possible with the reagent combination

*t*BuOOH/KSCN. We found that neither tropane (**6i**) nor **6j** were converted under the standard conditions at ambient temperature. However, heating the acetonitrile solutions of **6i** and **6j** with KSCN and *t*BuOOH at 50 °C resulted in the selective formation of the α-amino nitriles **7i** and **7j** in 61 and 87 % yield, respectively. In a gram scale experiment, 10 mmol of tropinone (**6j**) gave **7j** in 85 % yield. Crystals suitable for x-ray single crystal analysis were grown by slow evaporation of the solvent from a CH_2Cl_2 solution of **7j**.[13]

The cyanated alkaloid **7j** was also obtained from tropine (**6k**), which demonstrates that the secondary alcohol group of **6k** is oxidized to a ketone under the reaction conditions. The corresponding cyanation of atropine, which carries a primary hydroxyl group, however, turned out to be beyond the scope of the *t*BuOOH/KSCN cyanation method in this work.

We then studied the behavior of *N,N*-dialkylanilines under our reaction conditions (Scheme 4.4). After heating the reaction mixtures for 1 h at 80 °C, oxidative cyanation at one of the NMe groups of *para*-substituted *N,N*-dimethylanilines produced the corresponding α-amino nitriles **5a,b,d,e** with yields of 81 to 87 %. Cyanation of the *N*-(*p*-anisyl)tetrahydroisoquinoline (**1f**) was less efficient, but still gave solely the product of the cyanation reaction **5f** in 43 % yield. Only in the reaction with the parent *N,N*-dimethylaniline (**1c**), the formation of the α-amino nitrile was accompanied by the thiocyanation of the aromatic ring: After separation by column chromatography, **5c** and **8** were obtained in 52 and 29 % yield, respectively. The formation of **8** is in accord with a recent report by Khazaei, Zolfigol, and co-workers that *N,N*-dialkylanilines react with KSCN and 30% aq. H_2O_2 to yield *para*-thiocyanated anilines.[14]

In contrast to the regioselectivity observed for **6a-c**, 1-methyl tetrahydroquinoline (**1g**) did not undergo cyanation at the NCH_3 group after warming at 50 °C for 2 h but

was selectively cyanated at the NCH$_2$ group to give **5g**. Competing thiocyanation of the electron-rich aromatic ring of **1g** was not observed.

Scheme 4.4. Generation of α-Amino Nitriles from Anilines and Potassium Thiocyanate[a]
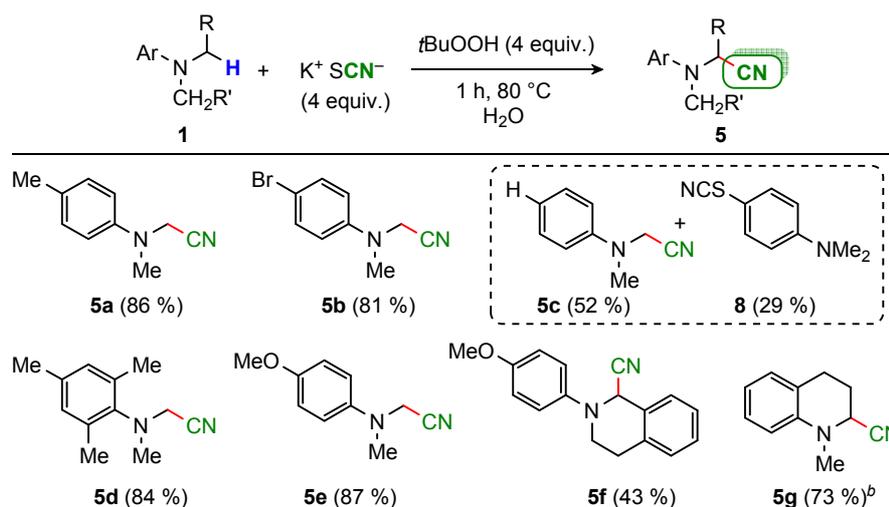
[a] Reaction conditions: aniline (1 mmol), KSCN (4 equiv.), 70% aq *t*BuOOH (4 equiv.), water (2 mL), 80 °C; yields refer to isolated products after column chromatography. [b] With MeCN as solvent (2 mL) at 50 °C for 2 h.

Oxidation of SCN$^-$ by H$_2$O$_2$ has been described to generate OSCN$^-$ (or HOSCN) as a first intermediate that is easily further oxidized to finally yield SO$_4^{2-}$ as the sulfur-containing product.[4d] Repeating the experiment in Table 1, entry 13, with subsequent treatment of the reaction solution with BaCO$_3$/HCl led to precipitation of a colorless powder that was collected by filtration and analyzed by x-ray powder diffraction, which clearly showed that BaSO$_4$ had precipitated (see Supporting Information) and thus clarified the fate of sulfur upon oxidation of SCN$^-$ by *t*BuOOH.

The important role of radical intermediates in the initial steps of the oxidative cyanation reactions in Schemes 4.3 and 4.4 is revealed by the ability of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT, 2.5 equiv.) to completely suppress the conversion of the tertiary amine **6a** (Scheme 4.5) under reaction conditions similar to those of Table 4.1, entries 9 or 13.

Scheme 4.5. Attempted Cyanation of **6a** in the Presence of the Radical Scavenger BHT
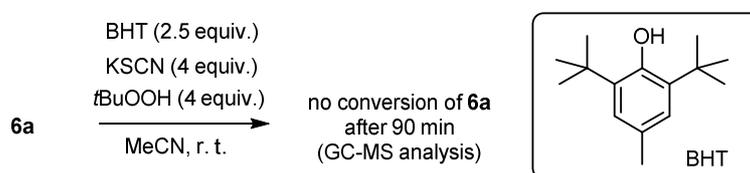
The regioselective formation of the α-amino nitriles **7a**-**c,i,j** shows that oxidation at the methyl group adjacent to the nitrogen of the amine is highly preferred over a competing process at an NCH_2R or $NCHR_2$ group, which agrees with previous reports[5c,7h,i,k,o,u,z] but is just the opposite of the expectation based on the stabilities of structurally related amino-stabilized alkyl radicals or iminium ions. The reactivity order $NCH_3 > NCH_2R \gg NCHR_2$ agrees, however, with the regioselective photoadditions of tertiary amines to singlet stilbene[15a,b] as well as with relative rates for the deprotonation of laser-flash photolytically generated amine radical cations by acetate,[15c] which both have been rationalized by stereoelectronic effects in the preferred transition state conformation.[15] We assume, therefore, that stereoelectronic effects during the deprotonation of the amine radical cations (Scheme 4.6) also control the regioselectivities under our reaction conditions.

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Scheme 4.6. Oxidation of Tertiary Amines by Subsequent Electron-Proton-Electron Transfers
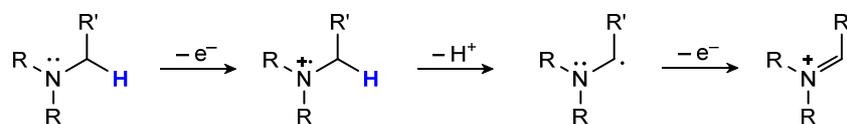
In oxidative couplings one of the substrate nucleophiles is converted to an electrophilic species that is then trapped by the other nucleophile.[16] In this work *both the electrophile and the nucleophile were generated in situ from oxidizable precursors*. The sulfur of SCN^- is used as a sacrificial group that safeguards the toxic nucleophile CN^- until its active form is released under the reaction conditions. To the best of our knowledge, this concept has only been applied once before: Wan and co-workers have recently obtained α-amino nitriles from benzyl cyanide and tertiary amines with *t*BuOOH as the oxidant.[7aa] In that reaction, *t*BuOOH oxidized the benzyl cyanide to benzoyl cyanide and the tertiary amines to α-aminoalkyl radicals. Experimental and theoretical investigations led Wan and coworkers to propose that the radical intermediates then attack the CN triple bond of PhCOCN to form imine radical intermediates that eliminate a phenacyl radical to yield the α-amino nitriles. Whether analogous radical processes also operate in the oxidative removal of sulfur from SCN^- remains to be clarified. Alternatively, the intermediate α-aminoalkyl radicals could be further oxidized by *t*BuO· or HO· to yield iminium ions which are trapped by cyanide ions that are generated by oxidation of thiocyanate ions as suggested in equation 2.

$$3\ t\text{BuOOH} + H_2O + SCN^- \rightarrow HSO_4^- + HCN + 3\ t\text{BuOH} \qquad (2)$$

4.3 Conclusion

In summary, simultaneous oxidation of tertiary amines and thiocyanate ions by *tert*-butylhydroperoxide in various solvents generated α-amino nitriles under mild conditions without the use of catalysts or toxic CN sources. Contributing to a development of synthetic chemistry that is friendly to the environment and hazard-free to men, potassium thiocyanate is used for the first time in organic synthesis to replace toxic cyanation reagents.[10,17] It is also worth mentioning that the waste products of the presented reactions (that is, H_2O, $KHSO_4$, *t*BuOH or KOCN from over-oxidation of KSCN) are unproblematic with regard to safety and environmental aspects.[18]

4.4   Experimental Section

All reactions were carried out under air atmosphere. ^{1}H (300 or 400 MHz) and ^{13}C (75.5 or 100.6 MHz) NMR spectra of solutions in $CDCl_3$ were recorded on 300 or 400 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.26 and δ_C 77.16).[19] Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The numbers of attached hydrogen atoms (C, CH, CH_2, or CH_3) were derived from additional gHSQC data. HRMS was performed on a mass spectrometer with sector field detector. Infrared spectra of neat substances were recorded on a FT-IR spectrometer equipped with an ATR probe (diamond).

Potassium thiocyanate (99%) and aqueous tBuOOH (70 wt % tBuOOH in H_2O) were purchased.

Commercially available tertiary amines were used as received: Dimethyltetradecylamine (technical, ≥95%), dimethyl-n-octylamine (95%), cyclohexyldimethylamine (98%), tropinone (99%), tropane (98%), tripropylamine (≥98%), tributylamin (puriss. p.a., ≥99%), triisobutylamine (98%), triisopentylamine (≥95%), tri-n-octylamine (96%), tropine (98 %), *N*,*N*,4-trimethylaniline (99 %), *N*,*N*,2,4,6-pentamethylaniline (98 %), 4-bromo-N,N-dimethylaniline (98 %), dicyclohexylmethylamine (97%), and *N*,*N*-dimethylaniline (99 %).

N,*N*-Dimethyl-*p*-anisidine was prepared as described in ref.[20] and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline was obtained by following a procedure reported in ref.[21] Reductive formylation of quinoline with formic acid furnished 1-formyl-1,2,3,4-tetrahydroquinoline that was subsequently reduced with $LiAlH_4$ to 1-methyl-1,2,3,4-tetrahydroquinoline.[22]

Experimental Procedure A.

A 10 mL round-bottom flask was charged with KSCN (0.40 g, 4.0 mmol) and the tertiary amine (1.0 mmol). Then aqueous tBuOOH (70 wt % tBuOOH in H_2O, 0.55 mL, 4.0 mmol) or a 4.9 M solution of tBuOOH in CH_2Cl_2 (0.75 mL, 4.0 mmol) was added successively by syringe over a period of 5 min, and the suspension was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured on brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

Experimental Procedure B.

KSCN (0.40 g, 4.0 mmol) and the tertiary amine (1.0 mmol) were dissolved in MeCN (2 mL). Then aqueous tBuOOH (70 wt % tBuOOH in H_2O, 0.55 mL, 4.0 mmol) was added successively by syringe. The solution was stirred at 50 °C for the indicated time. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

Experimental Procedure C.

KSCN (0.40 g, 4.0 mmol) and the N,N-dialkylated aniline (1.00 mmol) were poured on water (2.00 mL), and aqueous tBuOOH (70 wt % tBuOOH in H_2O, 0.55 mL, 4.0 mmol) was added by syringe. The solution was stirred at 80 °C for 1 h. After allowing

the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography.

2-(Methyl(tetradecyl)amino)acetonitrile (7a).

Following *General Procedure A*, dimethyl-tetradecylamine **6a** (0.30 mL, 0.99 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **7a** (174 mg, 66 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.86–0.90 (m, 3 H), 1.26 (br s, 22 H), 1.40–1.47 (m, 2 H), 2.35 (s, 3 H), 2.41–2.46 (m, 2 H), 3.53 (s, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 14.3, 22.8, 27.3, 27.6, 29.5, 29.6, 29.72, 29.74, 29.80, 29.82, 29.83, 32.1, 42.2, 45.3, 56.0, 114.8.

2-(Methyl(octyl)amino)acetonitrile (7b).

Following *General Procedure A*, dimethyl-octylamine **6b** (0.20 mL, 0.97 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **7b** (117 mg, 66 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.85–0.90 (m, 3 H), 1.27–1.29 (m, 10 H), 1.42–1.47 (m, 2 H), 2.35 (s, 3 H), 2.41–2.46 (m, 2 H), 3.52 (s, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 14.2, 22.8, 27.3, 27.6, 29.4, 29.5, 31.9, 42.2, 45.3, 56.0, 114.8.

2-(Cyclohexyl(methyl)amino)acetonitrile (7c).

Following *General Procedure A*, *N,N*-dimethylcyclohexylamine **6c** (0.15 mL, 1.00 mmol) reacted with KSCN and *t*BuOOH (4.9 M in CH_2Cl_2) for 1.5 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 1:1) to give **7c** (108 mg, 71 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[23]. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.11–1.34 (m, 4 H), 1.59–1.92 (m, 6 H), 2.29–2.39 (m, 1 H), 2.40 (s, 3 H), 3.58 (s, 2 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 25.2, 25.9, 30.1, 39.2, 42.6, 61.3, 116.1; IR (neat/ATR probe): v = 2923, 2850, 1660, 1448, 1436, 1421, 1292, 1268, 1232, 1180, 1128, 994, 896, 810, 724, 715 cm^{-1}.

2-(Dipropylamino)butanenitrile (7d).

Analogous to *General Procedure A*, tripropylamine **6d** (0.19 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH in acetonitrile (0.5 mL) for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 40:1) to give **7d** (103 mg, 61 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, *J* = 7.3 Hz, 6 H), 1.04 (t, *J* = 7.4 Hz, 3 H), 1.38–1.56 (m, 4 H), 1.70–1.86 (m, 2 H), 2.31–2.40 (m, 2 H), 2.46–2.55 (m, 2 H), 3.47 (t, *J* = 7.8 Hz, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 10.9, 11.8, 21.3, 25.5, 53.8, 56.6, 118.7.

2-(Dibutylamino)pentanenitrile (7e).

Following *General Procedure A*, tributylamine **6e** (0.24 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 2 h. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O = 40:1) to give **7e** (124 mg, 59 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with

those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.88-0.96 (m, 9 H), 1.27–1.51 (m, 10 H), 1.65–1.74 (m, 2 H), 2.29–2.38 (m, 2 H), 2.51–2.61 (m, 2 H), 3.57 (t, J = 7.7 Hz, 1 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 13.6, 14.1, 19.4, 20.5, 30.4, 34.1, 51.6, 54.5, 118.7.

2-(Diisobutylamino)-3-methylbutanenitrile (7f).

Following *General Procedure A*, triisobutylamine **6f** (0.24 mL, 1.0 mmol) reacted with KSCN and aq tBuOOH for 1.5 h. The crude product was crystallized from H$_2$O to give **7f** (145 mg, 69 %) as colorless crystals, mp. 61.0–61.5 °C. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.88 (d, J = 6.6 Hz, 6 H), 0.92 (d, J = 6.5 Hz, 6 H), 1.03 (d, J = 6.5 Hz, 3 H), 1.10 (d, J = 6.7 Hz, 3 H), 1.62–1.76 (m, 2 H), 1.85–1.98 (m, 1 H), 2.12 (dd, J = 12.9 Hz, J = 10.3 Hz, 2 H), 2.24 (dd, J = 12.9 Hz, J = 4.2 Hz, 2 H), 3.06 (d, J = 10.8 Hz, 1 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 19.9 (CH$_3$), 20.5 (CH$_3$), 20.8 (CH$_3$), 21.1 (CH$_3$), 26.3 (CH), 29.4 (CH), 60.9 (CH$_2$), 63.0 (CH), 117.8 (C), the numbers of attached hydrogen atoms were derived from additional gHSQC data.

2-(Diisopentylamino)-4-methylpentanenitrile (7g).

Following *General Procedure A*, triisopentylamine **6g** (0.29 mL, 0.95 mmol) reacted with KSCN and aq tBuOOH for 2 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 45:1) to give **7g** (170 mg, 71 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.89 (d, J = 2.9 Hz, 6 H), 0.91 (d, J = 3.0 Hz, 6 H), 0.93 (d, J = 6.6 Hz, 6 H), 1.25–1.36 (m, 4 H), 1.53–1.66 (m, 4 H), 1.83 (sept, J = 6.7 Hz, 1 H), 2.28–2.37 (m, 2 H), 2.56–2.66 (m, 2 H), 3.66 (t, J = 7.7

Hz, 1 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 22.2, 22.45, 22.52, 23.2, 24.8, 26.2, 37.2, 40.8, 50.1, 52.9, 118.8.

2-(Dioctylamino)nonanenitrile (7h).

Following to *General Procedure A*, tri-*n*-octylamine **6h** (0.45 mL, 1.0 mmol) reacted with KSCN and *t*BuOOH (4.9 M in CH$_2$Cl$_2$) for 1.5 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 110:1) to give **7h** (273 mg, 72 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.86–0.90 (m, 9 H), 1.23-1.45 (m, 34 H), 1.66–1.73 (m, 2 H), 2.30–2.36 (m, 2 H), 2.51–2.58 (m, 2 H), 3.55 (t, J = 7.8 Hz, 1 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 100.6 MHz): δ 14.20, 14.24, 22.76, 22.81, 26.2, 27.4, 28.2, 29.1, 29.2, 29.5, 29.6, 31.9, 32.0, 32.1, 51.9, 54.7, 118.8.

2-((1R,5S)-8-Azabicyclo[3.2.1]octan-8-yl)acetonitrile (7i).

Following *General Procedure B*, tropane **6i** (0.14 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc = 5:4) to give **7i** (96 mg, 61 %) as a colorless viscous liquid. Known compound, ref.[24]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.34–1.78 (m, 8 H), 1.93–1.97 (m, 2 H), 3.27–3.29 (m, 4 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 16.2 (CH$_2$), 26.1 (CH$_2$), 31.0 (CH$_2$), 41.0 (CH$_2$), 60.5 (CH), 117.9 (C), the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (neat/ATR probe): v = 2929, 2871, 1476, 1456, 1431, 1341, 1331, 1313, 1255, 1219, 1168, 1134, 1111, 1069, 1057, 1038, 980, 942, 874, 849, 821, 768, 720 cm^{-1}.

2-((1R,5S)-3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (7j) from tropinone (6j).

Potassium thiocyanate (4.0 g, 40 mmol) and tropinone **6j** (1.4 g, 10 mmol) were dissolved in acetonitrile (20 mL) and heated at 50 °C. The reaction was started by slow injection of aq *t*BuOOH (5.5 mL, 40 mmol, within ca. 5 min). The reaction mixture was then stirred at 50 °C for another 2.5 h, during which the mixture became more and more opaque. After allowing the reaction mixture to cool at ambient temperature, the suspension was poured on brine (60 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried (MgSO$_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (pentane:ethyl acetate = 4:5) to give **7j** (1.4 g, 85 %) as a colorless solid (mp. 64.5–65 °C). Crystals suitable for x-ray single crystal analysis were obtained by slow evaporation of a dichloromethane solution of **7j**.[13] Known compound, ref.[9a]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.63–1.71 (m, 2 H), 2.09–2.13 (m, 2 H), 2.22–2.27 (m, 2 H), 2.61–2.68 (m, 2 H), 3.50 (s, 2 H), 3.59–3.60 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 27.5 (CH$_2$), 40.2 (CH$_2$), 48.7 (CH$_2$), 59.7 (CH), 117.3 (C, CN), 208.1 (C, C=O), the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (neat/ATR probe): v = 2955, 2886, 1709, 1473, 1411, 1341, 1234, 1194, 1152, 1134, 1101, 1008, 905, 842, 776, 726 cm^{-1}.

2-((1R,5S)-3-Oxo-8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (7j) from tropine (6k).

Analogous to *General Procedure B*, tropine **6k** (0.14 mL, 0.99 mmol) reacted with KSCN and 5 equiv. of aq *t*BuOOH (0.69 mL, 5.00 mmol) for 2 h. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc = 4:5) to give **7j** (118

mg, 72 %) as colorless crystals. ^{1}H and ^{13}C NMR spectra agree with those of **7j** that was obtained from **6j**.

2-(Methyl(p-tolyl)amino)acetonitrile (5a).

Following *General Procedure C*, *N,N*,4-trimethylaniline **1a** (0.14 mL, 0.97 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 6:1) to give **5a** (133 mg, 86 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5a]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.33 (s, 3 H), 2.97 (s, 3 H), 4.12 (s, 2 H), 6.80–6.85 (m, 2 H), 7.14–7.17 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 20.4, 39.4, 42.7, 115.3, 115.6, 129.7, 130.0, 145.7.

2-((4-Bromophenyl)(methyl)amino)acetonitrile (5b).

Following *General Procedure C*, 4-bromo-*N,N*-dimethylaniline **1b** (0.20 g, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 20:1) to give **5b** (182 mg, 81 %) as a colorless solid. Known compound; the NMR spectroscopic data agree with those given in ref.[5a]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.98 (s, 3 H), 4.14 (s, 2 H), 6.70–6.75 (m, 2 H), 7.37–7.42 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 39.4, 42.3, 112.7, 115.2, 116.5, 132.4, 146.9.

2-(Methyl(phenyl)amino)acetonitrile (5c) and *N,N*-dimethyl-4-thiocyanatoaniline (8).

Following *General Procedure C*, *N,N*-dimethylaniline **1c** (0.13 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 1 h. The product mixture was separated by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:1→15:2) to give **5c** and **8**.

2-(Methyl(phenyl)amino)acetonitrile (5c):

76 mg (52 %), colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5a]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.01 (s, 3 H), 4.15 (s, 2 H), 6.87–6.98 (m, 3 H), 7.32–7.37 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 39.2, 42.2, 114.8, 115.6, 120.1, 129.5, 147.8.

_N,N_-Dimethyl-4-thiocyanatoaniline (8):

52 mg (29 %), colorless solid, mp 73-73.5 °C. Known compound; the NMR spectroscopic data agree with those given in ref.[14,25]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.99 (s, 6 H), 6.66–6.69 (m, 2 H), 7.39–7.45 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 40.3, 106.7, 112.7, 113.3, 134.6, 151.8.

2-(Mesityl(methyl)amino)acetonitrile (5d).

Following _General Procedure C_, _N,N_,2,4,6-pentamethylaniline **1d** (0.18 mL, 1.0 mmol) reacted with KSCN and aq _t_BuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **5d** (158 mg, 84 %) as a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5c]. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.27 (s, 3 H), 2.29 (s, 6 H), 2.95 (s, 3 H), 3.93 (s, 2 H), 6.86 (s, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 19.0, 20.8, 40.4, 44.1, 117.7, 129.8, 136.0, 137.0, 144.3.

2-((4-Methoxyphenyl)(methyl)amino)acetonitrile (5e).

Following _General Procedure C_, 4-methoxy-_N,N_-dimethylaniline **1e** (0.15 g, 0.99 mmol) reacted with KSCN and aq _t_BuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give **5e** (151 mg, 87 %) as

a colorless viscous liquid. Known compound; the NMR spectroscopic data agree with those given in ref.[5a] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.92 (s, 3 H), 3.78 (s, 3 H), 4.07 (s, 2 H), 6.88 (s, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 40.0, 44.0, 55.7, 114.9, 115.5, 117.8, 142.3, 154.4.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (5f). Following *General Procedure C*, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **1f** (0.24 g, 1.0 mmol) reacted with KSCN and aq tBuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:2) to give **5f** (114 mg, 43 %) as a colorless solid. Known compound; the NMR spectroscopic data agree with those given in ref.[5a] ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.88–2.96 (m, 1 H), 3.10–3.22 (m, 1 H), 3.39–3.48 (m, 1 H), 3.54–3.61 (m, 1 H), 3.79 (s, 3 H), 5.36 (s, 1 H), 6.88–6.94 (m, 2 H), 7.06–7.11 (m, 2 H), 7.20–7.33 (m, 4 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 28.8, 45.0, 55.66, 55.68, 114.9, 117.7, 121.1, 126.8, 127.2, 128.8, 129.6, 129.8, 134.5, 142.7, 155.8.

1-Methyl-1,2,3,4-tetrahydroquinoline-2-carbonitrile (5g).

Following *General Procedure B*, 1-methyl-1,2,3,4-tetrahydroquinoline **1g** (0.15 g, 1.0 mmol) reacted with KSCN and aq tBuOOH for 1 h. The crude product was purified by column chromatography (SiO$_2$, pentane/ Et$_2$O = 7:1) to give **5g** (125 mg, 73 %) as a colorless viscous liquid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.24–2.34 (m, 2 H), 2.80–2.88 (m, 1 H), 3.02 (s, 3 H), 3.11–3.24 (m, 1 H), 4.28–4.31 (m, 1 H), 6.73–6.85 (m, 2 H), 7.05–7.21 (m, 2 H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75.5 MHz): δ 24.2 (CH$_2$), 25.6 (CH$_2$), 38.2 (CH$_3$), 51.8 (CH), 112.6 (CH), 118.2 (CH, CN), 119.0 (CH$_2$), 121.8 (C), 127.6 (CH), 129.1 (CH), 143.4 (C) the numbers of attached hydrogen atoms were derived from additional gHSQC data; IR (ATR): ν = 3022, 2937, 2895, 2846, 2820, 1601,

1579, 1494, 1474, 1446, 1362, 1313, 1264, 1208, 1172, 1133, 1118, 1093, 1067, 1044, 1036, 995, 932, 831, 800, 746, 704 cm^{-1}. HRMS (EI, 70 eV) m/z: [M]$^{+\cdot}$ Calcd for [C$_{11}$H$_{12}$N$_2$]$^{+\cdot}$ 172.0995; Found 172.0985.

Formation of *N,N*-Dicyclohexylformamide.

Following *General Procedure A*, *N,N*-dicyclohexylmethylamine (0.21 mL, 0.98 mmol) reacted with KSCN and aq *t*BuOOH for 1.5 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 2:1) to give *N,N*-dicyclohexylformamide (174 mg, 85 %) as a colorless solid; mp 61–62 °C. Known compound (mp 62.5-63.5 °C).[26] ^{1}H NMR (CDCl$_3$, 600 MHz): δ 1.05–1.80 (m, 20 H), 2.99–3.03 (m, 1 H), 3.87–3.91 (m, 1 H), 8.16 (s, 1 H, CHO); ^{13}C{^{1}H} NMR (CDCl$_3$, 150.6 MHz): δ 25.3, 25.4, 25.9, 26.3, 30.4, 34.7, 52.4, 54.9, 161.7.

Precipitation of BaSO$_4$.

A 10 mL flask was charged with KSCN (0.40 g, 4.0 mmol) and the amine **6a** (0.30 mL, 1.0 mmol). Then aq *t*BuOOH (0.55 mL, 4.0 mmol) was added successively by syringe over a period of 5 min. The resulting suspension was stirred at room temperature for 1.5 h. At the end of the reaction, the reaction mixture was poured on deionized water (20 mL), and extracted with CH$_2$Cl$_2$ (3 × 20 mL). To the aqueous layer was poured in a 100 mL Erlenmeyer flask, and BaCO$_3$ (1.0 g) and 2 м HCl (3 mL) were added. A colorless precipitate formed, which was separated by filtration and dried at 67 ºC to give BaSO$_4$ (340 mg, 1.5 mmol) as a colorless powder that was analyzed by x-ray powder diffraction. Reflections of the precipitated solid agreed with those for BaSO$_4$.[27]
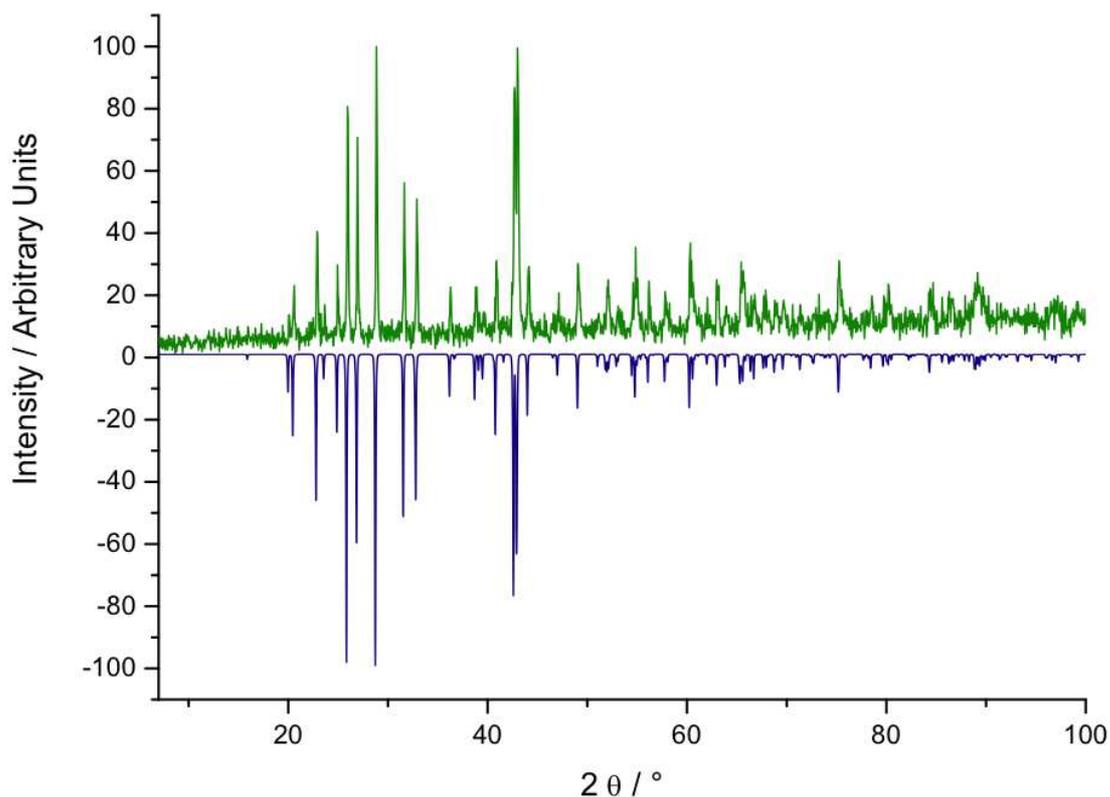
Figure 4.1. Reflections of the precipitated solid (upper line in green) agree with those that were previously determined for barite (BaSO$_4$, lower line in blue, data from ref.[27]).

Reaction of 6a in Presence of Radical Scavenger 2,6-Di-*tert*-butyl-4-methylphenol (BHT).

A mixture of KSCN (0.40 g, 4.0 mmol), the amine **6a** (0.30 mL, 1.0 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (0.55 g, 2.5 mmol) was dissolved in MeCN (2.00 mL) and aq *t*BuOOH (0.55 mL, 4.0 mmol) was added successively by syringe. The resulting suspension was stirred at room temperature for 1.5 h. Subsequently, the reaction mixture was poured on brine (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). Analysis of the crude product mixture with GC/MS showed only signals of the substrate **6a**.

X-ray Crystal Structure Analysis of 7j

The data collection was performed on a Bruker IµS diffractometer (MoKα radiation, 200 K). The structure was solved by direct methods with SIR97[28] and refined with SHELXL-97.[29]

CCDC 1027029 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
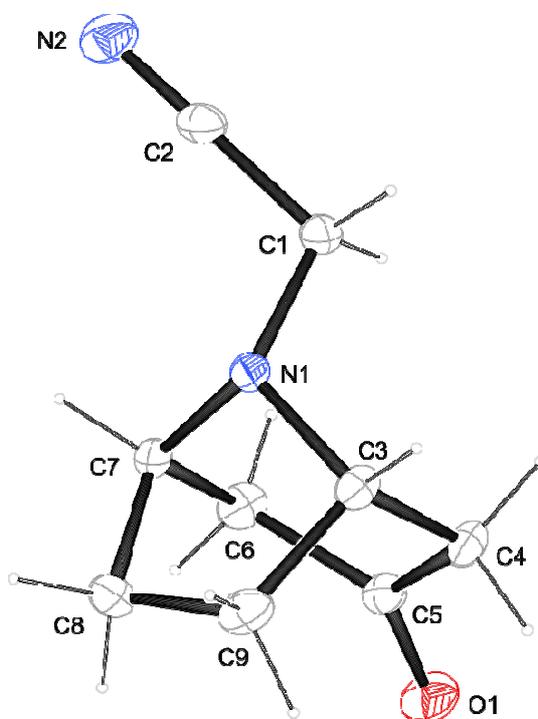

Figure 4.2. X-ray structure of **7j** (thermal ellipsoids are shown on the 50 % probability level). d(C1-N1) = 145.88(18) pm, d(C1-C2) = 146.8(2) pm, d(C2-N2) = 113.7(2) pm, d(C5-O1) = 121.22(18) pm, (N2-C2-C1) = 179.41(15)°.

Table 4.2. Crystallographic data of **7j**

net formula	$C_9H_{12}N_2O$
M_r/g mol^{-1}	164.204
crystal size/mm	$0.130 \times 0.100 \times 0.060$
T/K	173(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.6807(5)
b/Å	7.3529(6)
c/Å	17.0246(13)
α/°	90
β/°	90
γ/°	90
V/Å^3	836.29(11)
Z	4
calc. density/g cm^{-3}	1.30420(17)
μ/mm^{-1}	0.087
absorption correction	multi-scan
transmission factor range	0.9291–0.9585
refls. measured	21210
R_{int}	0.0383
mean σ(I)/I	0.0157
θ range	3.02–26.36
observed refls.	1608
x, y (weighting scheme)	0.0336, 0.1928
hydrogen refinement	constr
Flack parameter	1.4(16)
refls in refinement	1723
parameters	109
restraints	0
$R(F_{obs})$	0.0310
$R_w(F^2)$	0.0761
S	1.090
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.149
min electron density/e Å^{-3}	–0.152

Absolute structure unknown, no anomalous scatterer.

Toxicity of different CN sources used for oxidative α-cyanations of tertiary amines

Table 4.3. Toxicity of different CN sources used for oxidative α-cyanations of tertiary amines (in references 5, 7–9 of the main text)

Compound	LD50[a] [mg·kg^{-1}]		Danger Pictograms[a]
NaCN	1.67	(intramuscular, rabbits),	
	4.3	(intraperitoneal, rats)	
	4.8	(oral, rats)	
	10.4	(dermal, rabbits)	
KCN	4	(intraperitoneal, rats),	
	7.5	(oral, female rats),	
	14.3	(dermal, rabbits)	
malononitrile	19	(oral, mice)	
acetone cyanohydrin	15.8	(dermal, rabbits)	
	18.7	(oral, rats)	
ethyl cyanoformate		no data available	
trimethylsilyl cyanide		no data available	
trimethylsilyl azide[b]		no data available	
benzoyl cyanide	37.6	(oral, rats)	
benzyl cyanide	270	(oral, rats)	
	270	(dermal, rabbits)	
potassium thiocyanate	854 (oral, rats)		

[a] According to the Globally Harmonized System of Classification and Labeling of Chemicals (GHS Classification) compounds with LD50 < 300 mg kg–1 are classified as toxic (data from MSDS sheets by Sigma-Aldrich, Steinheim, Germany, Dec. 12th, 2014). [b] Trimethylsilyl azide (N source) and 1,2-dichloroethane (C source) were used as a combined source of CN, see ref 7ac of the main text.

4.5 References

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10. Only toxic CN sources with LD_{50} < 300 mg/kg (oral, rats) have been used in refs 5, 7–9 (see also Table 4.2 in the experimental section).

11. Also Cy_2NMe was oxidized by aq *t*BuOOH/KSCN at ambient temperature to give *N*,*N*-dicyclohexylformamide in a yield of 85 % (see experimental section).

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5

Direct Conversion of Tertiary N-Methyl Amines to N-Boc Protected Amines

5.1 Introduction

5.1.1 General

The modification of single functional groups in complex molecules or building blocks is a well known and widely used concept in organic chemistry. To achieve selective reactions only at a certain functional group it is often necessary to introduce protecting groups. The introduction and subsequent removal of protecting groups is, therefore, an important aspect when planning a synthetic strategy.[1]

Extensive research effort has been invested in the development of protecting groups applicable to nearly every type of functional groups, including amines, alcohols, 1,2-diols, carbonyl groups, carboxylic acids, alkenes and alkynes, amongst others.[1,2] The given possibility to get protection for most functional groups goes hand in hand with an abundance of protecting groups available, such as esters, benzyl protecting groups, organo silyl compounds, thioacetals, phosphates, alkyl ethers, alcoxyalkyl ethers, amongst others.[2] For an useful application in organic synthesis, with respect to ease of handling, simplicity, yield and cost of the process, a protecting group has to be choosen carefully.[1] Therefore the implementation and removal of protecting groups is still an important area of research.[3]

5.1.2 The Boc Protecting Group

The protection and deprotection of amino groups are important issues in organic synthesis.[1] The amino functionality is present in a wide range of compounds and hence the protection of amines is frequently needed in synthetic and especially medicinal chemistry.[2] The most simple method for the protection of amines is acylation.[4] But harsh reaction conditions are required to remove the protecting group to regain the amine functionality, which makes this method not suitable to handle multifunctional compounds.[4] Therefore, a protecting group that can be cleaved under mild reaction conditions is required. A very useful protecting group is the *tert*-butoxycarbonyl (Boc) group[1] introduced via commercially available di-*tert*-butyl-dicarbonate (Boc)$_2$O.[5] The Boc protecting group is suitable due to its stability under basic conditions as well as towards nucleophilic attacks and its removal by acid.[6]

A standard procedure for the introduction and removal of the Boc protecting group is given in Scheme 5.1. For the initial deprotonation of the amine 4-(*N,N*-dimethylamino)pyridine (DMAP)[7] or inorganic bases[8] are frequently used (Scheme 5.1a).

a) General scheme for the proctection of amines by the Boc protecting group.[1c,7,8]
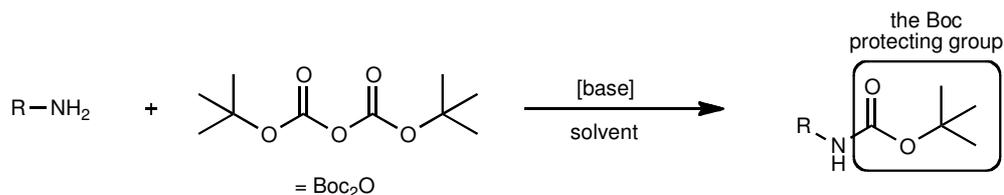
b) Detailed mechanism for the removal of Boc protecting groups by using aqueous acid.[1c]
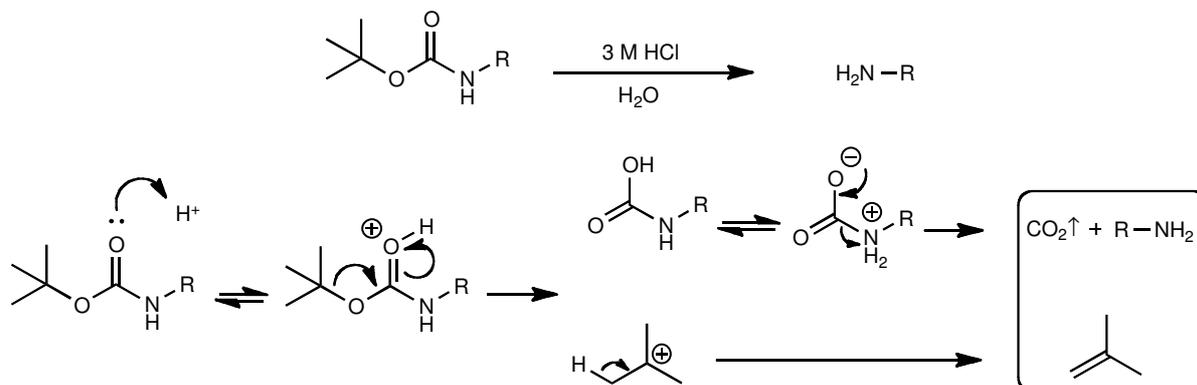
Scheme 5.1: Protection and deprotection of amines employing the Boc Protecting group.[1c]

Major disadvantages of this procedure are the long reaction time, toxic reagents and the formation of unwanted side products, such as isocyanates,[9] ureas,[7] and N,N-di-Boc[10] derivatives.

A strategy to avoid drawbacks occurring in base catalyzed Boc protections is the use of Lewis acids. Sharma and co-workers reported the $ZrCl_4$ mediated introduction of a Boc protecting group in 2004 (Scheme 5.2).[11]
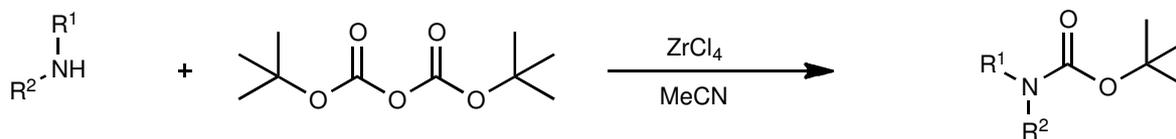

Scheme 5.2: $ZrCl_4$ mediated Boc protection of amines.[11]

This method avoids above mentioned disadvantages, but still $ZrCl_4$ is highly moisture sensitive and liberates fumes of hydrochloric acid. Other Lewis acids have been

employed for the Boc protection of amines, including $LiClO_4$,[12] $HClO_4$,[13] $Zn(ClO_4)_2 \cdot$ 6 H_2O,[14] $La(NO_3)_3 \cdot 6H_2O$[15] and $Cu(BF_4)_2$[16]. These reactions suffer from limited applicability and several disadvantages. Perchlorates are highly explosive compounds, most Lewis acids are deactivated by amines and vice versa, more than stoichiometric amounts are needed.[17] Further research has led to more suitable reagents for the implementation of the Boc protecting group, such as $HClO_4/SiO_2$,[13] Montmorillonite K10 or KSF,[18] I_2,[19] $H_3PW_{12}O_{40}$,[20] HFIP,[21] sulfamic acid,[22] Amberlyst 15,[23] and H_2O[24]. Employing most of these reagents is accompanied with certain difficulties and limitations, such as high costs, toxicity, corrosiveness, limited applications, deprotection of other protecting groups, and difficulties in the isolation of products.[2c]

The use of thiourea,[25a] thioglycoluril[25b] and guanidine hydrochloride[25c] in catalytic amounts published by Khaksar and co-workers showed an alternative pathway for metal free implementation of Boc protecting groups (Scheme 5.3).
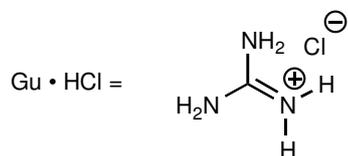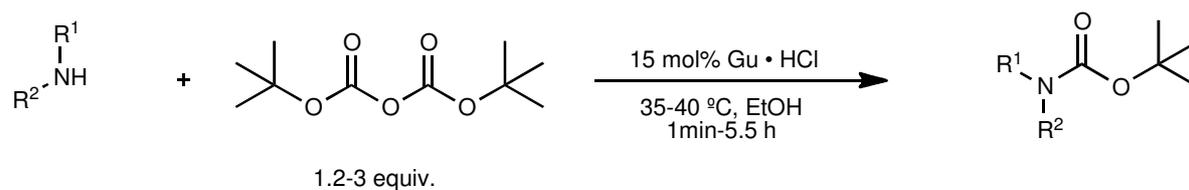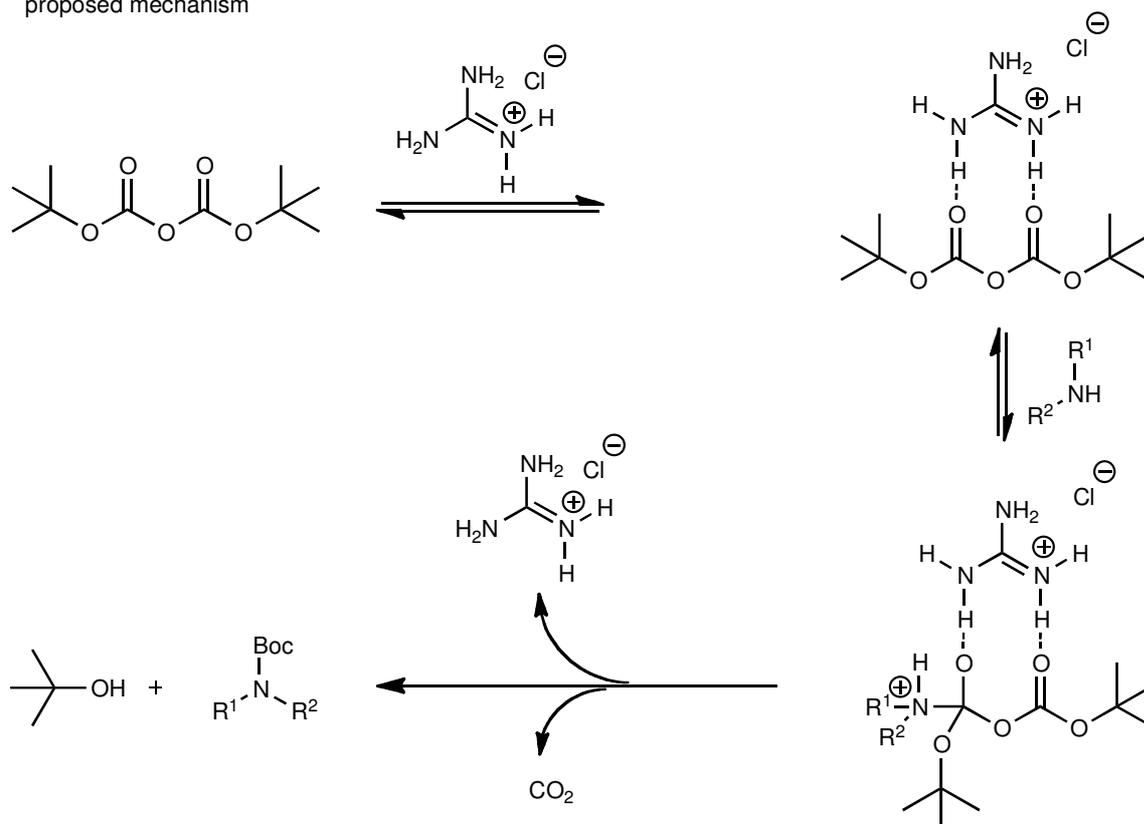
Scheme 5.3: Metal free Boc protection of amines using catalytic amounts of guanidine hydrochloride.[25c]

In 2012, Dighe and Jadhav published a microwave assisted Boc protection for amines, which does not require any reagent, catalyst, or solvent (Scheme 5.4).[26]
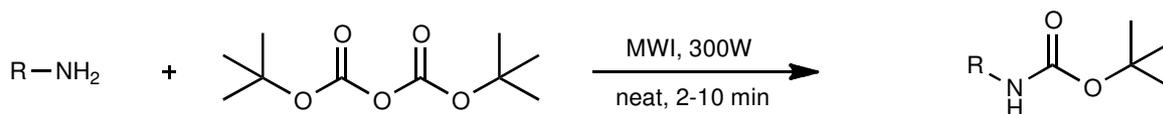
Scheme 5.4: Microwave assisted Boc protection of amines.[26] MWI, microwave irradiation.

However, the standard reagent for implementing the Boc protecting group, di-*tert*-butyl dicarbonate is a highly toxic compound and requires a laborious and dangerous synthesis. Another drawback of the use of Boc_2O is the utilization of just one Boc protecting group, while two *tert*-butoxycarbonyl fragments need to be employed. Scheme 5.5 describes a gram scale synthesis of Boc_2O.[27]

DABCO = 1,4-diazabicyclo[2.2.2]octane
DCM = dichloromethane
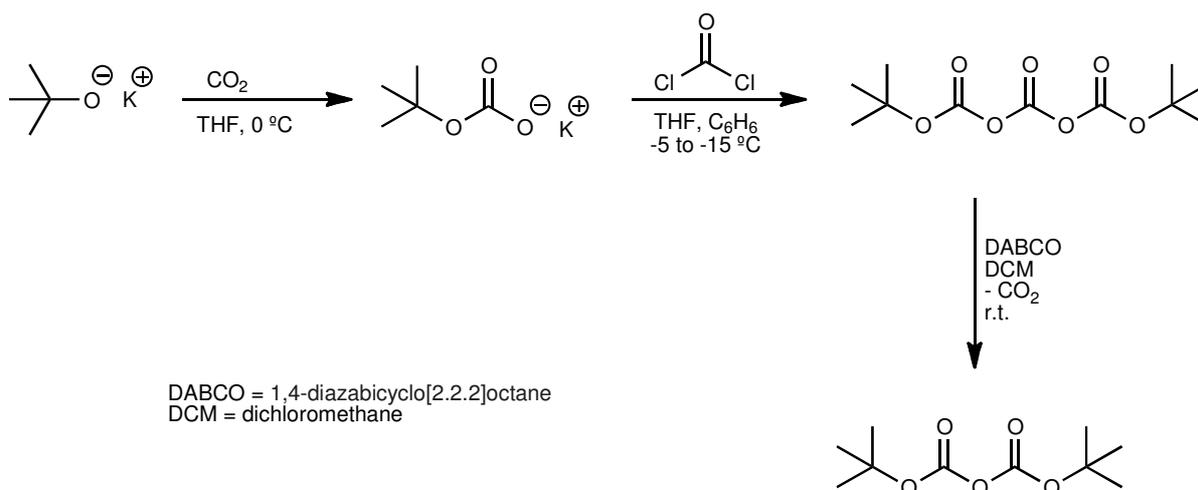
Scheme 5.5: Gram scale synthesis of Boc_2O.[27]

To avoid the use of highly toxic compounds and the production of waste, alternatives have been developed to introduce Boc protecting groups in a more economic way.

In 1977 Jampel and Wakselmann reported the Boc protection of amines by using 1-Boc-4-(dimethylamino)pyridinium tetrafluoroborate (Scheme 5.6).[28] A drawback is

the need of Boc$_2$O to synthesize 1-Boc-4-(dimethylamino)pyridinium tetrafluoroborate.[28]
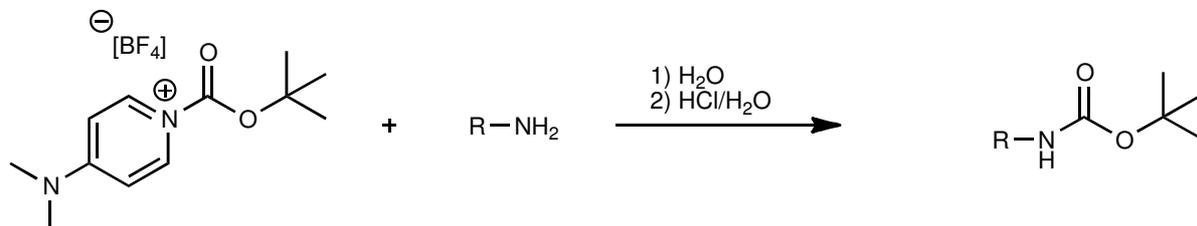
Scheme 5.6: Boc protection of amines by using 1-Boc-4-(dimethylamino)pyridinium tetrafluoroborate.[28]

Nine years later Barcelo and co-workers developed a method to introduce the Boc protecting group via 1-chloralkyl carbonates (Scheme 5.7).[29]
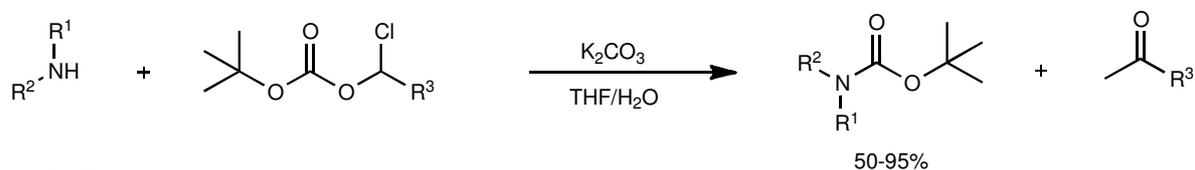
R^1, R^2, R^3 = aryl, alkyl

Scheme 5.7: Introduction of the Boc protecting group via 1-chloralkyl carbonates.[29]

With respect to constant research efforts on the use of protecting groups in organic synthesis, there is room for further improvement. Especially replacing Boc$_2$O by less toxic and more sustainable reagents for the introduction of Boc protecting groups can be a suitable field of activity.

### 5.1.3 Transforming *N*-methyl groups into amido functionalities

The transformation of *N*-methyl groups into amido functionalities is a common synthetic strategy in medicinal chemistry.[30] A standard protocol to obtain carbamates from tertiary methyl amines has been developed by the Olofson group.[31] This method is consisting of a two-steps dealkylation reaction, including substitution of the *N*-methyl group by employing α-chloroethyl chloroformate (ACE-Cl) (Scheme 5.8b).[31a] The use of chloroformate esters was established as a more efficient and versatile alternative compared to the dealkylation of tertiary amines with cyanogen bromide.[32] However, most chloroformate esters are highly toxic compounds and the preparation of carbamates from tertiary methyl amines still needs an additional third synthetic step.

Equipping tropinone with a Boc protecting group via demethylation by ACE-Cl is described by Gilbert and co-workers (Scheme 5.8a).[30a]

a) Introduction of the Boc protecting group via demethylation of tropinone.
   (Gilbert, 2004)[30a]

1) ACE-Cl, DCE, 80 ºC
2) MeOH, 50 ºC

3) Boc$_2$O, *i*PrOH, H$_2$O, NaOH, r.t.

yield not given
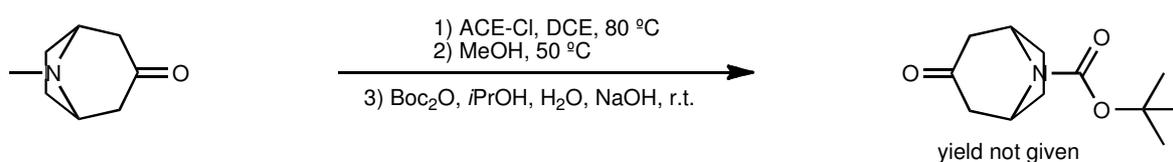
b) *N*-Demethylation of tropinone, according to the mechanism described by Olofson.[31a]

ACE-Cl
DCE, heat

MeOH
heat

•HCl + CO$_2$ +
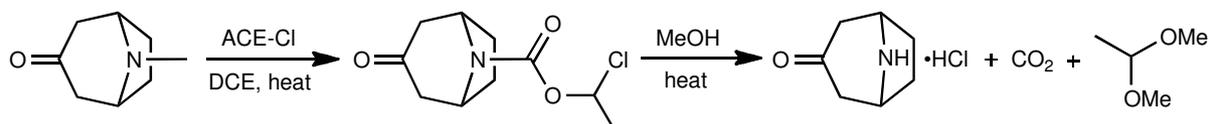
Scheme 5.8: Introduction of a Boc protecting group via demethylation of tropinone.[30a,31a]

5.2 Results and discussion

In our previous work, we described potassium thiocyanate as source of cyanide for the oxidative α-cyanation of tertiary amines.[33] The scope of this method included the successful cyanation of tropine (**1a**) and tropinone (**1b**). To our surprise, the reaction of **1a** and potassium thiocyanate furnished not only the expected 2-(8-azabicyclo[3.2.1]octan-8-yl)acetonitrile (**2a**) but also *tert*-butyl 8-azabicyclo[3.2.1]oct-ane-8-carboxylate (**3a**) in 34% yield as a side product (Scheme 5.10 **A**). Employing **1b** as the substrate, **2b** could be obtained in 87% yield, whereas the Boc protected tropinone **3b** was only generated in 10% yield (Scheme 5.9 **B**).
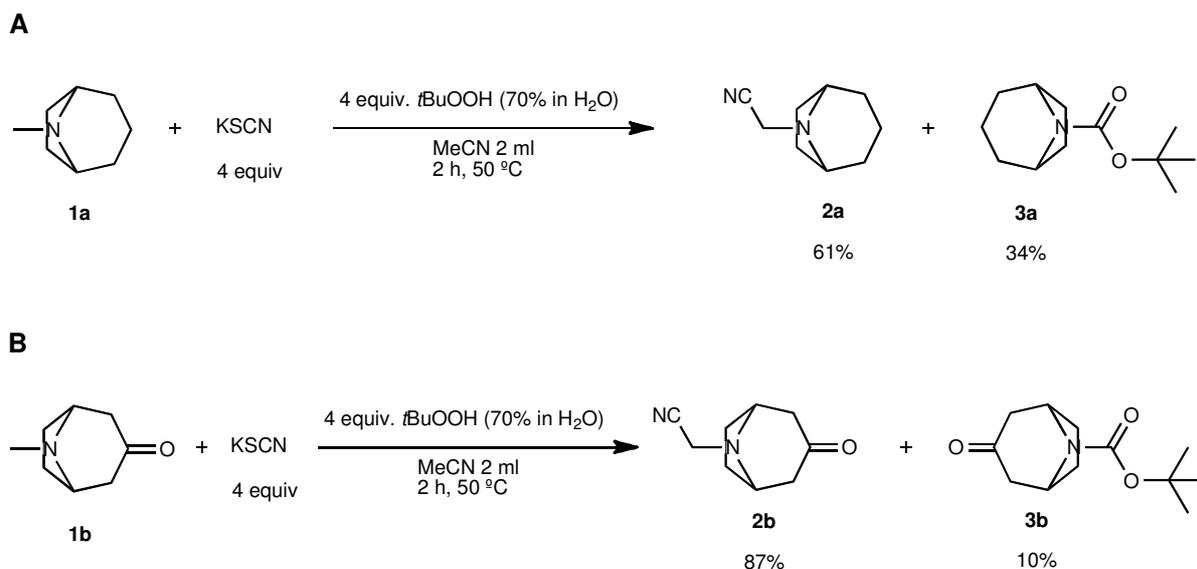
Scheme 5.9: **A**) Reaction of **1a** with KSCN and *t*BuOOH. **B**) Reaction of **1b** with KSCN and *t*BuOOH.

With gaining a reasonable yield of **3a** we were encouraged to undertake further investigations of this very simple Boc protection of an amine. Optimizing the method makes it necessary to completely reverse the selectivity of the reaction. Beginning

from the conversion of **1b** with a high selectivity for the cyanation product **2b** (Scheme 5.9 **B**), the method underwent further improvement.

Decreasing the excess of potassium thiocyanate as the cyanide source from 4 equivalents to 0.5 equivalents showed almost no impact to the selectivity of the reaction. An increase of the oxidizing agent *tert*-butylhydroperoxide from 4 to 6 equivalents was accompanied by a strong increase of the selectivity of the reaction towards product **3b**, but the cyanation still gave the major product. Applying higher temperatures moved the selectivity of the reaction slightly in the desired direction, but was not sufficient to establish **3b** as the major product. Switching the solvent from MeCN to a MeCN/water mixture combined with a silght increase of the potassium thiocyanate to 0.7 equivalents resulted in a one-to-one product ratio. Changing the solvent to water and further increasing the reaction temperature gave the Boc protected tropinone **3b** as the major product, still accompanied by the cyano product **2b**. Employing a temperature gradient from 90 ºC to ambient temperature finally gave **3b** in 74% yield, accompanied by formation of **2b** in less than 10% yield.

As summarized in Scheme 5.10 a series of tertiary methyl amines **1** underwent selective oxidation to form Boc protected **3a-g**. The conversion of **1d-f** afforded adjustment of the reaction conditions; Boc protection could be achieved, however, by using 0.5 equivalents of KSCN and constant heating to 80 ºC to give **3d-f** in moderate yields. In a gram scale synthesis, *N*-methyl-piperidine (**1d**) reacted with *t*BuOOH to give 1.2 g of **3d** in 69% yield. Transformation of *N,N*-dimethylbenzylamine (**1g**) took place with 0.3 eqivalents of KSCN and constant heating to 80 ºC to avoid the formation of cyanated **1g** as the major product. The Boc protected **3g** was obtained a poor yield of 14%.
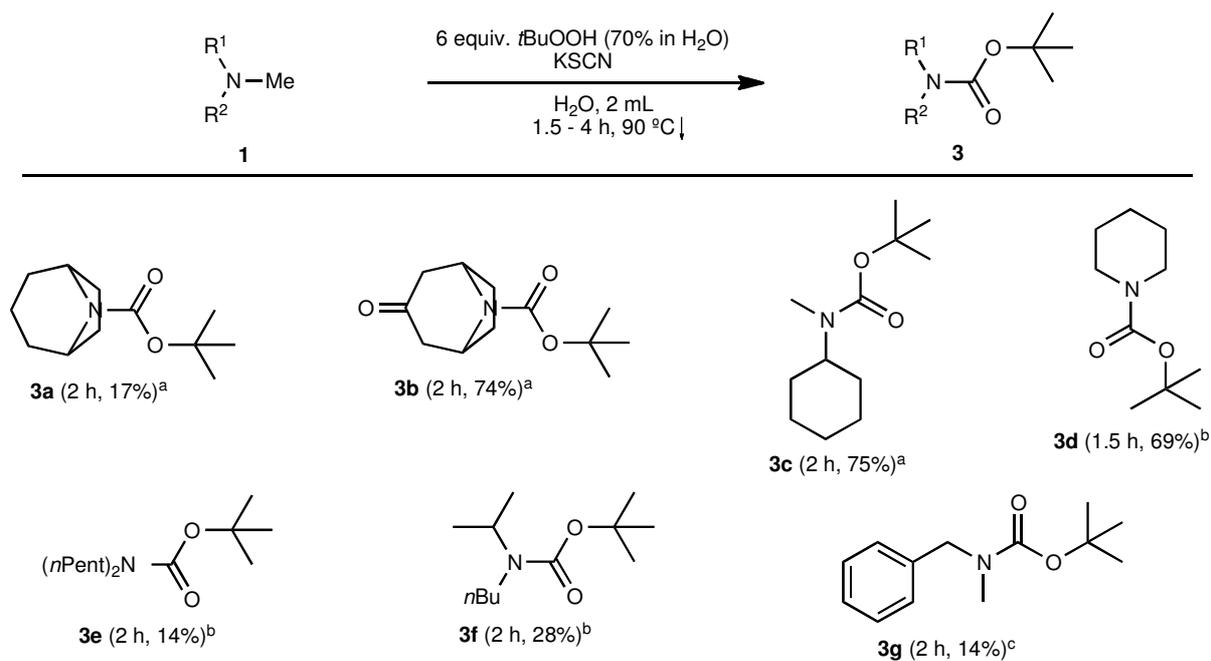
Scheme 5.10: KSCN mediated Boc protection of tertiary methyl amines. [a]Reaction conditions: amine (1 mmol), KSCN (0.7 equiv.), 70% aq tBuOOH (6 equiv.), water (2 mL), 90 ºC↓, yields refer to isolated products after purification. [b]With 0.5 equiv. KSCN and 80 ºC, in case of **3d**, 50 mmol of the amine were used. [c]With 0.3 equiv. KSCN and 80 ºC.

A total amount of further 18 tertiary methyl amines have been employed as substrates for the conversion of N-methyl- into Boc protecting groups, but did not undergo the desired transformation.

5.3 Conclusion

In summary, the direct oxidative conversion of N-methyl groups into Boc protecting groups at tertiary amines may illustrate a contribution for the implementation of Boc protecting groups into tertiary amines. However, the method suffers from low functional group tolerance and limited substrate scope.

5.4 Experimental section

All reactions were carried out under air atmosphere. ^{1}H (300 or 400 MHz) and ^{13}C (75.5, 101 or 151 MHz) NMR spectra of solutions in $CDCl_3$ were recorded on 300, 400 or 600 MHz NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.26 and δ_C 77.16).[34] Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The numbers of attached hydrogen atoms (C, CH, CH_2, or CH_3) were derived from additional gHSQC data. HRMS was performed on a mass spectrometer with sector field detector.

Potassium thiocyanate (99%) and aqueous tBuOOH (70 wt % tBuOOH in H_2O) were purchased.

Commercially available tertiary amines were used as received: Dimethyltetradecylamine (technical, ≥95%), cyclohexyldimethylamine (98%), tropinone (99%), tropane (98%), N,N,4-trimethylaniline (99%), dicyclohexylmethylamine (97%), N,N-dimethylbenzylamine (≥99%).

Experimental procedure A

KSCN (0.07 g, 0.7 mmol) and the tertiary amine (1.0 mmol) were dissolved in H_2O (2 mL). Then aqueous tBuOOH (70 wt % tBuOOH in H_2O, 0.85 mL, 6.1 mmol) was added by syringe. The solution mixture was put on a pre heated oil bath (90 °C) and was stirred for the indicated time without further heating. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over

MgSO$_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography or distillation.

Experimental procedure B

KSCN (0.05 g, 0.5 mmol) and the tertiary amine (1.0 mmol) were dissolved in H$_2$O (2 mL). Then aqueous tBuOOH (70 wt % tBuOOH in H$_2$O, 0.85 mL, 6.1 mmol) was added by syringe. The solution was stirred at 80 °C for the indicated time. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (20 mL), and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried over MgSO$_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography or distillation.

$tert$-Butyl 8-azabicyclo[3.2.1]octane-8-carboxylate (3a)

Following *General Procedure A*, tropane **1a** (0.14 mL, 1.0 mmol) reacted with KSCN and aq. tBuOOH for 2 h. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc = 12:1) to give $tert$-butyl 8-azabicyclo[3.2.1]octane-8-carboxylate **3a** (36.6 mg, 17 %) as a colorless liquid.

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 4.12 (m, *2 H*), 1.92 (m, *2 H*), 1.69 (m, *1 H*), 1.63 (m, *1 H*), 1.58 (m, *2 H*), 1.45 (s, *9 H*), 1.38 (m, *2 H*), 1.24 (m, *2 H*) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$): δ = 153.4, 78.8, 54.2, 31.0, 30.3, 28.5, 16.8 ppm.

HRMS (EI, 70 eV) m/z: [M]$^{+\cdot}$ Calcd for [C$_{12}$H$_{19}$NO$_3$]$^{+\cdot}$ 225.1365; Found 225.1359.

tert-Butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (3b)

Following *General Procedure A*, tropanone **1b** (0.14 g, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 2 h. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc = 10:1) to give *tert*-butyl 8-azabicyclo[3.2.1]octane-8-carboxylate **3b** (167 mg, 74 %) as a colorless liquid.

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 4.46 (m, *2 H*), 2.65 (m, *2 H*), 2.33 (d, *J* = 15.8 Hz, 2H),2.08 (s, *2 H*), 1.69-1.62 (m, *2 H*), 1.49 (s, *9 H*) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$): δ = 208.5, 153.3, 80.4, 53.3, 49.1, 29.5, 28.6 ppm.

HRMS (EI, 70 eV) *m*/*z*: [M]$^{+\cdot}$ Calcd for [C$_{12}$H$_{19}$NO$_3$]$^{+\cdot}$ 225.1365; Found 225.1359.

tert-Butyl cyclohexyl(methyl)carbamate (3c)

Following *General Procedure B*, *N*,*N*-dimethylcyclohexanamine **1c** (0.22 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 3 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:1) to give *tert*-butyl cyclohexyl(methyl)carbamate **3c** (160 mg, 75 %) as a colorless liquid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 2.70 (s, *3 H*), 1.77 (m, *4 H*), 1.65 (m, *5 H*), 1.45 (s, *9 H*), 1.33 (m, *2 H*) ppm.

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 155.7, 79.0, 68.2, 30.3, 28.5, 28.2, 25.8, 25.6 ppm.

HRMS (EI, 70 eV) *m*/*z*: [M]$^{+\cdot}$ Calcd for [C$_{12}$H$_{23}$NO$_2$]$^{+\cdot}$ 213.1729; Found 213.1730.

tert-Butyl piperidine-1-carboxylate (3d)

KSCN (2.5 g, 25 mmol) and *N*-methylpiperidine **1d** (6.5 mL, 50 mmol) were dissolved in H_2O (100 mL). Then aqueous *t*BuOOH (70 wt % *t*BuOOH in H_2O, 42.5 mL, 0.300 mol) was added by syringe. The solution was stirred at 80 °C for 4 h. After allowing the reaction mixture to cool to room temperature, the suspension was poured on brine (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation (82 °C, 0.06 mbar) and column chromatography (SiO_2, pentane/Et_2O = 15:1) to give *tert*-butyl-piperidine-1-carboxylate **3d** (6.8 g, 69 %) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.29 (m, *4 H*), 1.50 (m, *2 H*), 1.44 (m, *4 H*), 1.39 (s, *9 H*) ppm.

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.8, 79.0, 44.5, 28.4, 25.7, 24.4 ppm.

HRMS (EI, 70eV) *m/z*: [M]$^{+\cdot}$ Calcd for $[C_{10}H_{19}NO_2]^{+\cdot}$ 185.1416; Found 185.1409.

tert-Butyl dipentylcarbamate (3e)

Following *General Procedure B*, *N*-methyl-*N*-pentylpentan-1-amine **1e** (0.22 mL, 1.0 mmol) reacted with KSCN and aq *t*BuOOH for 3 h. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc = 40:1, pentane/EtOAc = 70:1) to give *tert*-butyl dipentylcarbamate **3e** (97 mg, 28 %) as a colorless liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.31 (t, *J* = 7.5 Hz, *4 H*), 1.57 (m, *2 H*), 1.44 (s, *9 H*), 1.29 (m, *2 H*), 1.27 (m, *2 H*), 0.90 (m, *6 H*) ppm.

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 152.6, 78.8, 47.0, 34.09, 28.5, 26.1, 22.3, 14.0 ppm.

HRMS (EI, 70 eV) m/z: [M]$^{+ \cdot}$ Calcd for [C$_{15}$H$_{31}$NO$_2$]$^{+ \cdot}$ 257.2355; Found 257.2341.

tert-Butyl butyl(isopropyl)carbamate (3f)

Following _General Procedure B_, _N_-isopropyl-_N_-methylbutan-1-amine **1f** (0.13 mg, 1.0 mmol) reacted with KSCN and aq tBuOOH for 2 h. The crude product was purified by column chromatography (SiO$_2$, pentane/EtOAc = 35:1) to give _tert_-butyl butyl(isopropyl)carbamate **3f** (45 mg, 14 %) as a colorless liquid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 4.05 (m, _1 H_), 2.95 (m, _2 H_), 1.49 (m, _2 H_), 1.39 (s, _9 H_), 1.19 (m, _2 H_), 1.05 (m, _6 H_), 0.85 (t, _J_ = 7.4 Hz, _3 H_) ppm.

^{13}C-NMR (101 MHz, CDCl$_3$): δ = 153.1, 79.7, 51.0, 28.6, 28.4, 26.4, 20.4, 13.9 ppm.

HRMS (EI, 70 eV) m/z: [M]$^{+ \cdot}$ Calcd for [C$_{12}$H$_{25}$NO$_2$]$^{+ \cdot}$ 215.1885; Found 215.1862.

tert-Butyl benzyl(isopropyl)carbamate (3g)

Following _General Procedure B_, _N_-benzyl-_N_-methylpropan-2-amine **1g** (0.22 mL, 1.0 mmol) reacted with KSCN and aq tBuOOH for 3 h. The crude product was purified by column chromatography (SiO$_2$, pentane/Et$_2$O = 15:1) to give _tert_-butyl-benzyl(isopropyl)carbamate **3g** (60 mg, 14 %) as a colorless liquid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.31 – 7.05 (m, _5 H_), 4.35 (s, _3 H_), 2.76 (s, _2 H_), 1.41 (s, _9 H_) ppm.

^{13}C-NMR (101 MHz, CDCl$_3$): δ = 155.1, 138.1, 128.5, 127.2, 79.7, 53.4, 33.9, 28.5 ppm.

HRMS (EI, 70 eV) m/z: [M]$^{+\cdot}$ Calcd for [$C_{13}H_{19}NO_2$]$^{+\cdot}$ 221.1416; Found 221.1438.

N-Methyl-N-pentylpentan-1-amine (1e)

Substrate **1e** *was synthesized according to a literature procedure*:[35] Dipentylamine (6.5 mL, 32 mmol), glacial acetic acid (7.4 mL, 128 mmol, 4 equiv.), formaldehyde (37% in H_2O, 3.6 mL, 48 mmol, 1.5 equiv.) and zinc dust (4.2 g, 64 mmol, 2 eqiv.) were dissolved in 64 mL H_2O. The reaction mixture was stirred for 21 h at 50 ºC. After allowing the reaction mixture to cool to room temperature, the suspension was poured on saturated Na_2CO_3 solution (50 mL), and extracted with ethylacetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by distillation to give N-methyl-N-pentylpentan-1-amine **1e** (3.7 g, 67%) as a colorless liquid.

^{1}H-NMR (200 MHz, CDCl$_3$): δ = 2.35 (t, *J* = 7.0 Hz, *4 H*), 2.22 (s, *3 H*), 1.44 (m, *4 H*), 1.21 (m, *8 H*), 0.83 (t, *J* = 6.7 Hz, *6 H*) ppm.

N-Isopropyl-N-methylbutan-1-amine (1f)

Substrate **1e** *was synthesized according to a literature procedure*:[35] N-methylpropan-2-amine (4.6 mL, 44.2 mmol), butylchloride (5.6 mL, 53.1 mmol, 1.2 eqiv.) and Na_2CO_3 (49 g, 354 mmol, 8 eqiv.) were dissolved in 70 mL of a MeCN/H_2O 1:1 solution. After refluxing for 2.5 h, the reaction mixture was poured on 45 mL saturated Na_2CO_3 solution, 100 mL H_2O were added and the suspension was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 200 mL) dried over $MgSO_4$, and the solvent was removed under reduced

pressure to give *N*-isopropyl-*N*-methylbutan-1-amine **1f** (0.68 g, 12%) as a slightly yellow liquid.

^{1}H NMR (200 MHz, CDCl$_3$) δ = 2.89-2.73 (m, 1H), 2.39-2.28 (m, 2H), 1.99 (s, 3H), 1.39 (m, 4H), 0.99 (d, *J* = 6.6 Hz, 6H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm.

5.5 References

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