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The advent of electrophilic hydroxylamine-derived reagents for the direct preparation of unprotected amines

Valentina C. M. Gasser, † Szabolcs Makai † and Bill Morandi *

Electrophilic aminating reagents have seen a renaissance in recent years as effective nitrogen sources for the synthesis of unprotected amino functionalities. Based on their reactivity, several noble and non-noble transition metal catalysed amination reactions have been developed. These include the aziridination and difunctionalisation of alkenes, the amination of arenes as well as the synthesis of aminated sulfur compounds. In particular, the use of hydroxylamine-derived (N–O) reagents, such as PONT ($PivONH_3OTf$), has enabled the introduction of unprotected amino groups on various different feedstock compounds, such as alkenes, arenes and thiols. This strategy obviates undesired protecting-group manipulations and thus improves step efficiency and atom economy. Overall, this feature article gives a recent update on several reactions that have been unlocked by employing versatile hydroxylamine-derived aminating reagents, which facilitate the generation of unprotected primary, secondary and tertiary amino groups.

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1 Introduction

The introduction of amino groups is one of the most important tasks in organic synthesis, as numerous bioactive compounds contain nitrogen atoms. More than 90% of the top 100 small molecule therapeutics sold in 2020 possess at least one C–N bond.[1] Catalytic amination reactions represent a powerful toolbox to forge these bonds and create valuable building blocks from easily accessible hydrocarbon feedstocks. An emerging approach in this research area is the use of electrophilic nitrogen reagents to generate useful aminated products. However, modulating groups, such as electron-withdrawing moieties, are often critical to controlling the reactivity of the precursor and the active aminating species. The common issue

Laboratorium für Organische Chemie ETH Zürich, Vladimir-Prelog-Weg 3, HCI, Zürich 8093, Switzerland. E-mail: morandib@ethz.ch
† These authors contributed equally to this work.

Valentina C. M. Gasser

Valentina Gasser studied at the ETH Zürich (2011–2018), where she obtained her MSc degree in Chemistry and carried out research in the groups of Prof. P. Chen and Prof. E. M. Carreira. She joined the group of Prof. R. Sarpong (UC Berkeley) for her Master's thesis in the United States. After an industrial placement at Givaudan in Process Research in Zürich, CH, she joined the Morandi group as a doctoral candidate at ETH Zürich. Her research focus lies in iron-catalysed amination reactions. She is active in projects that strive to achieve more diversity, equity and inclusion in academia.

Szabolcs Makai

Szabolcs Makai studied at the Ludwig-Maximilians University in Munich, Germany (2012–2018), where he obtained his MSc degree in Chemistry. After research stays in the groups of Prof. D. Trauner (LMU Munich), Prof. S. V. Ley (University of Cambridge) and an industrial placement at Novartis in Basel, CH, he joined the Morandi group for his Master's thesis. He continued as doctoral candidate within the same group at ETH Zurich where he is focusing on iron-catalysed amination reactions. During his PhD studies, he conducted an industrial placement at Syngenta Crop Protection in Stein, CH.

among these methods is that the installed amino functionality bears hard to cleave protecting groups, such as sulfonamides. Their removal requires an additional step and operates usually under harsh reaction conditions, creating challenges in downstream functionalisation, thus limiting the step- and atom economy of the overall amination reaction. Obviating the installation of this protecting group would greatly streamline the way an amine is introduced in a synthetic sequence.

Recently, our group, among others, has been involved in the development of Fe catalysed amination reactions that allow the direct installation of unprotected amines into abundant feedstock compounds, such as alkenes, arenes and thiols. A key advance in establishing these reactions was the development and use of bench-stable, protonated hydroxylamine derivatives which exhibit sufficient reactivity to access the desired product in an unprotected form.[2] A key reagent, *O*-pivaloylated hydroxylammonium reagent **R7** ($PivONH_3OTf$), has played a particularly enabling role in our research group.[3] This reagent was initially reported by Guimond and Fagnou as a convenient building block to introduce an *O*-acyl hydroxamic acid directing group.[4] Its protonated form prevents a facile rearrangement to the more stable *N*-hydroxy amide and thus makes the reagent an ideal NH_2^+ surrogate.[5] We recently disclosed a reliable scale-up synthesis of this reagent on a decagram scale.[6] This reagent has also become commercially available, further facilitating its use in preparative reactions. In this review, the acronym PONT (PivONH$_3$OTf, *O*-pivaloyl hydroxylammonium triflate) is used to describe this reagent. Besides PONT, other important hydroxylamine-derived (N–O) reagents as well as related N–X reagents, are presented within this review (Fig. 1).[7–10]

The aim of this feature article is to present the evolution of the field of unprotected amine preparation through the use of electrophilic nitrogen reagents. The focus lies in the specific areas of interest of our research group along with important literature precedent as well as contemporary methods. We will begin with recent advances in the field of alkene amination (Section 2.1), continue with methods for the amination of aromatic C–H bonds (Section 2.2) and conclude with a section on the amination of sulfur-containing moieties (Section 2.3). To complement our non-comprehensive article, the readers are referred to excellent reviews on catalytic aminations for extended reading.[11–17]

Bill Morandi

Bill Morandi studied at the ETH Zurich (2003–2008), earning a BSc in Biology and an MSc in Chemical Biology. After a PhD with Prof. Erick M. Carreira, he moved in 2012 to CalTech to work with Prof. Robert H. Grubbs as a postdoctoral fellow. From 2014 to 2018, he was an independent Max Planck Research Group Leader at the Max-Planck-Institut für Kohlenforschung (Mülheim, Germany), before subsequently returning to ETH Zürich as a Professor in 2018. He is currently Full Professor of Synthetic Organic Chemistry and heads the Institute of Organic Chemistry (Laboratorium für Organische Chemie) at ETH Zürich.

2 Introduction of nitrogen through electrophilic reagents

2.1 Amination of alkenes

Alkenes represent an important class of feedstock hydrocarbons suitable to react with hydroxylamine-derived aminating reagents. Practical ways to combine alkenes with electrophilic aminating reagents proceed through aziridination[37] or difunctionalisation strategies.[38] By applying the latter, an additional moiety is directly installed at the vicinal position relative to the amino group, thereby enabling the construction of densely functionalised target molecules. This distinguishes difunctionalisations from hydroamination reactions, which are not covered in this article.[28,39–42]

2.1.1 Aziridination of alkenes. Two seminal reports from Hamelin[43] and Bottaro[44] independently showed the inherent reactivity of *N*-unprotected, *O*-arylsulfonyl reagents **R2** (*O*-(mesitylsulfonyl)hydroxylamine, MSH) and **R3** (*O*-(tosyl)hydroxylamine, $TsONH_2$) to afford unprotected aziridines. Three decades later, a collaborative work between the groups of Ess, Kürti and Falck disclosed an improved protocol which uses safer[45] *O*-aryl reagent **R10** (*O*-(2,4-dinitrophenyl)hydroxylamine, DPH) (Scheme 1A).[46] The Rh catalysed reaction proceeds mildly with broad functional group tolerance on both activated and unactivated alkenes. Using a methylated DPH reagent allowed the installation of *N*-methyl aziridines.

This transformation was further improved and resulted in variations where more inexpensive aminating reagents[47,48] and non-noble metal catalysts, such as copper and iron,[49,50] could be used instead.

Recently, an elegant organocatalytic version of this transformation was presented by the Kürti group (Scheme 1B).[51] The key intermediate proved to be the corresponding oxaziridine, which was generated *in situ* from **R1** (hydroxylamine-*O*-sulfonic acid, HOSA) and a catalytic amount of an electron-deficient ketone. This unusual N–O reagent transferred an NH equivalent to an alkene in a concerted fashion, mechanistically reminiscent of an epoxidation with dioxiranes. This similarity was further exploited in the induction of enantioselectivity when using a chiral ketone.[52]

Another notable example of transition-metal free *N*-methylaziridination was developed by Bower and co-workers using an *in situ* Boc-deprotected *O*-sulfonyl hydroxylamine reagent.[53]

Further references for exemplary intramolecular[54–58] transformations and those that afford the nitrogen in a protected[59–63] form or from enones[64] are given, albeit not discussed in greater detail in this article.

2.1.2 Aminohalogenation of alkenes. Despite very early initial reports[65–67] about 2-haloamines and their synthesis from

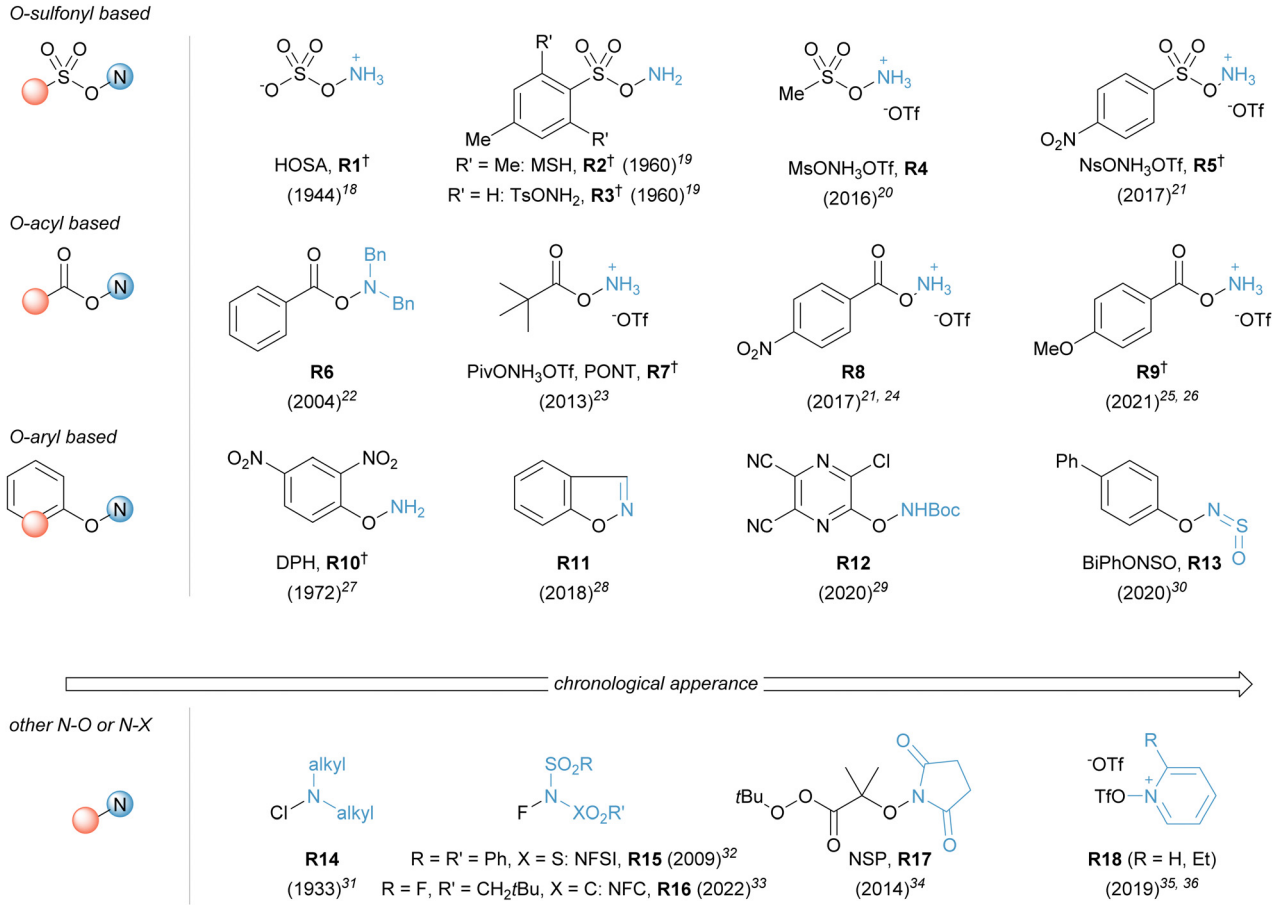
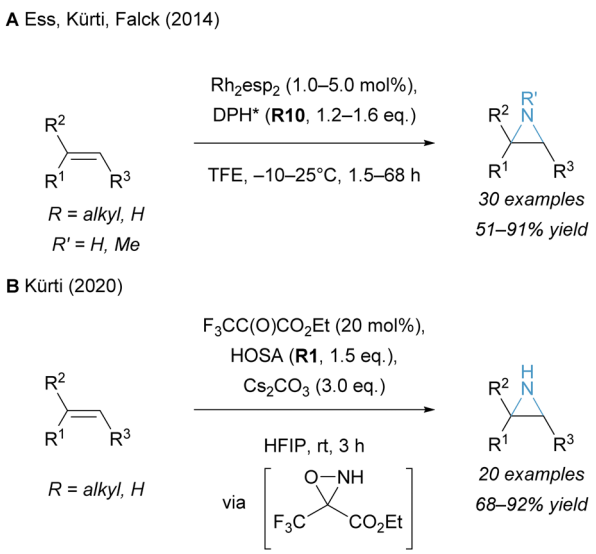


Fig. 1 Selected N–X based reagents in electrophilic amination reactions ordered according to their core structure. Year of their first reported application in brackets.[18–36] Reagents with known *N*-substituted congeners are marked with a dagger.

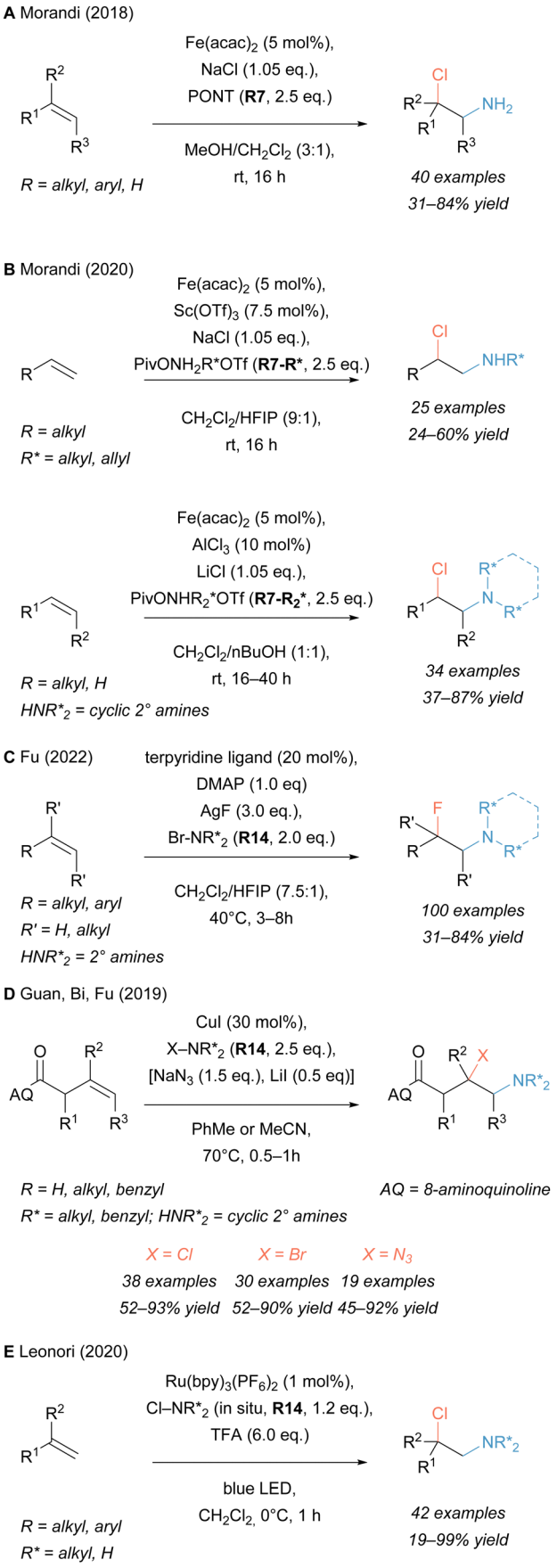


Scheme 1 Unprotected, direct aziridination of alkenes. esp: α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

alkenes, it was only a decade ago that aminohalogenation reactions experienced a renaissance seen with the development of a series of catalytic reactions.[68–70] Several of them were based on using *N*-sulfonamide reagents and consequently led to the installation of *N*-sulfonyl protected amino motifs. An additional deprotection step was required to liberate the free amine, often employing harsh conditions.[71–73] In contrast, extensive work by Xu and co-workers showed that *O*-benzyl hydroxylamine-derived reagents were suitable for the introduction of *N*-carbamate protected β-haloamines under Fe catalysis.[74,75]

An Fe catalyst was used by our group for developing a mild aminochlorination reaction (Scheme 2A).[76] Benign sodium chloride served as the halogen source, whereas the unprotected amino group was introduced by the use of *O*-pivaloylated hydroxylammonium reagent PONT (**R7**). The aminochlorination reaction proceeded under ambient conditions and transformed a wide range of vinyl arenes and unactivated, aliphatic alkenes with excellent Markovnikov selectivity to the desired 2-chloroamines. Several functional groups were tolerated (*e.g.* free alcohols, alkynes and N-heterocycles). Downstream derivatisations showed facile transformation to a broad range of products like aziridines and divergent reduction of the 2-chloroamine to either linear or branched primary amines.

Recent work by our group expanded the scope of this reaction to unprotected secondary and tertiary amino groups



Scheme 2 Unprotected aminohalogenation of alkenes. Acac: acetylacetonate.

by developing new, structurally related, *N*-alkylated hydroxylammonium reagents **R7-R*** and **R7-R_2*** to introduce medicinally relevant amino groups (Scheme 2B).[77] Importantly, these reagents could be synthesised on a multigram scale and were isolated as stable, crystalline solids.

The application of those novel reagents in aminochlorination reactions led to the synthesis of a broad range of densely functionalised amines. Furthermore, it was shown that these reagents can partake in other difunctionalisation reactions, such as aminohydroxylation, aminoazidation and a tethered carboamination reaction.[77]

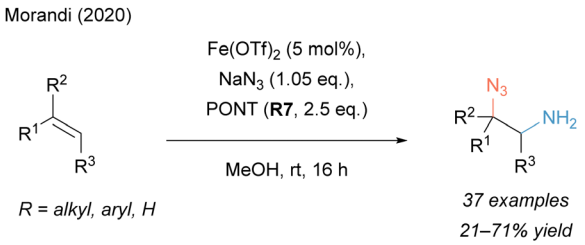
Among aminofunctionalisation reactions, the installation of fluoride along with an unprotected amine on unactivated alkenes has posed a long term challenge.[78,79] Recently, the Fu lab reported the synthesis of tertiary 2-fluoroamines from alkenes in a silver mediated transformation using terpyridine ligands (Scheme 2C).[80]

A different approach towards the construction of tertiary β-(pseudo)haloamines (X = Cl, Br, N_3) was disclosed by a collaboration between the groups of Guan, Bi, and Fu (Scheme 2D).[81] A suitably positioned 8-aminoquinoline directing group assisted the Cu catalysed activation of the olefin in β,γ-position. In that process, *N*-haloamines **R14** provided both the amino group and the halide. With the addition of exogenous azide, aminoazidation was observed which resulted in the first report of a one-step, unprotected aminoazidation for tertiary amine synthesis. The reaction allowed the installation of several amines but always required a bulky directing group, thus limiting its scope.

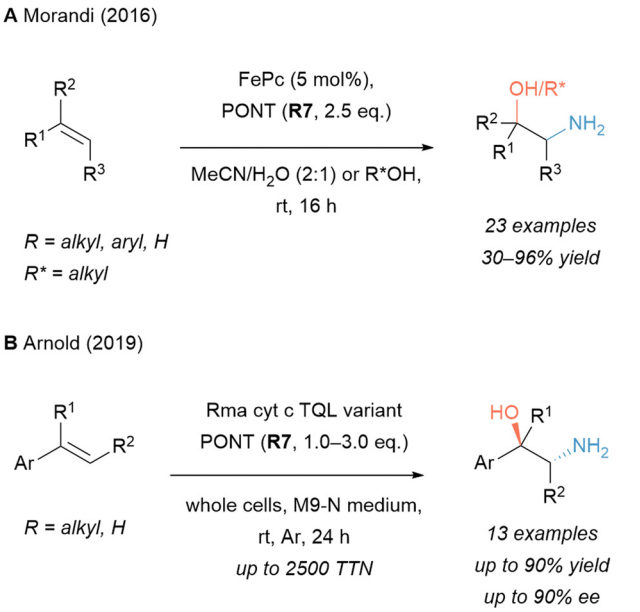
An *N*-chloroamine based strategy for the synthesis of a wide range of diamines from alkenes was described by Leonori and co-workers (Scheme 2E).[82] In a one-pot reaction, an amine was first *N*-chlorinated before being added across an olefin *via* a photochemical, radical aminochlorination reaction. The resulting 2-chloroamines could be transformed in the same pot into an aziridinium intermediate, which was prone to open with various *N*-nucleophiles to yield heterodiamines. This protocol elegantly combines the broad functional group tolerance of the aminochlorination step with the wide range of easily accessible secondary amino nucleophiles. However, this transformation showed limitations when a sterically less demanding amine was used as the initial nitrogen source. In those cases, an alternative amino surrogate might be preferred (*e.g.* *N*-substituted hydroxylammonium reagents, *vide supra*).[77]

Recent work by other groups presents additional examples for the construction of heterodiamines *via* an aziridinium intermediate.[83–85]

2.1.3 Masked diamination of alkenes. A direct approach to vicinal diamines with distinguishable amino groups is the installation of a masked amino motif on an alkene along with an amino group.[86] Examples for such a masked amino moiety could be, for example, an orthogonally protected amine,[87–91] a thiocyanate,[92] or an azido group. Theoretically, both nitrogen groups could be masked in an identical way,[93–96] however, challenging regioselective unmasking renders this approach less appealing.[97]



Scheme 3 Unprotected aminoazidation of alkenes.



Scheme 4 Selected aminooxygenation reactions of alkenes with hydroxylamine derived reagents. tfa: trifluoroacetate; Ns: *p*-nitrobenzenesulfonamide; Pc: phthalocyanine.

Considering an azido group as a masked amine resulted in several recent reports of aminoazidation reactions which are either intramolecular[98–101] or afford the amine in a protected form, such as a bissulfonamide.[102–105] An ideal masked diamine however would consist of one free amino function.

Based on the results of our aminochlorination reaction, we envisioned that the very same aminating agent (PONT, **R7**) might be capable to facilitate the formation of unprotected, 2-azidoamines in combination with sodium azide (Scheme 3).[106] The same regioselectivity as in the aminochlorination reaction, *i.e.* the amino group being introduced at the less substituted carbon, was observed under iron catalysis and an extensive investigation of the alkene scope revealed that even a complex olefin-containing tripeptide and a polyene probe could be aminated with excellent chemoselectivity. The utility of the resulting 2-azidoamines was demonstrated in subsequent independent transformations of both nitrogen functionalities and the synthesis of important diamino structures, such as triazoles, diamines, ureas and azidopiperidines. Its practicality was further showcased by applying the methodology in the (formal) synthesis of three bioactive molecules. Preliminary mechanistic experiments hinted towards a radical pathway without the involvement of a subsequent carbocationic intermediate.

2.1.4 Aminohydroxylation of alkenes. Besides 1,2-diamines, 1,2-amino alcohols are prevalent structures in bioactive molecules as well as catalysis.[107] Their synthesis from alkenes was pioneered by Sharpless and co-workers using chloramine-T as a nitrogen source to install the amine in its sulfonamide-protected form using an Os catalyst.[108]

Following up on Cu and Fe catalysed work by Yoon and co-workers,[109–111] the Xu lab reported an aminooxygenation reaction yielding carbamate protected amines.[112,113] In an Fe catalysed reaction with pybox ligands, an *N*-carbamate and an *O*-acyl group were introduced in a variety of alkenes and dienes. Enantioselectivity could also be induced when using a chiral box or pybox ligand. Despite not yielding the unprotected amino alcohol as the primary product, this can be easily revealed by subsequent hydrolysis.

This concept to introduce an *O*-acyl group as an oxygen surrogate in aminooxygenation reactions has been a recurring strategy.[114–116]

In 2016, our group disclosed an aminohydroxylation reaction which afforded *N*- and *O*-unprotected aminoalcohols from styrenes and 1,1-disubstituted alkenes (Scheme 4A).[117,118] A key element of this transformation was the use of a robust Fe catalyst (iron phthalocyanine, FePc) and PONT (**R7**) to deliver an unprotected amine. The aqueous solvent mixture served as a source of the hydroxyl group in the process. Alternatively, the use of an alcoholic medium led to *O*-alkylated products. The reaction found application in a synthetic route of drug molecules which started from cashew nut shell liquid as renewable, green feedstock.[119] Recently, a collaboration between our group and the groups of Neese and DeBeer revealed important mechanistic features of this reaction.[120]

Inspired by the structural similarities between the Pc ligand and the structure of hemoproteins, the Arnold group developed an asymmetric variant of the aminohydroxylation reaction of vinyl arenes (Scheme 4B).[121] Opting for a haemoprotein, a very thermostable *Rhodotermus marinus* cytochrome C enzyme was selected as a starting point for directed evolution. A bioengineered catalyst was created which resulted in excellent enantioselectivity and total turnover numbers (TTN) of up to 2500 in the asymmetric aminohydroxylation of alkenes with PONT (**R7**) as the aminating reagent.

2.2 Intermolecular aromatic C–H amination

The rise of novel hydroxylamine-derived aminating reagents in the last 20 years has also paved the way for innate C–H amination reactions catalysed by noble as well as non-noble transition metals. Early reports of innate C(sp^2)–H amination were limited in scope, partly because the aromatic substrate was used in excess.[12] Further development unlocked the synthesis of free primary anilines under mild conditions. In addition to innate C–H aminations, methodologies have also emerged that target the functionalization of arenes at the *ortho*-, *meta*- and *para*-position.

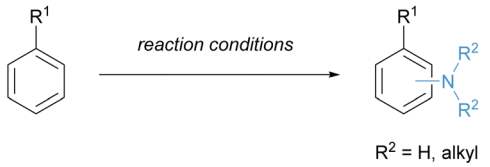
2.2.1 Noble metal-catalysed aromatic C–H amination. A seminal report in the area of innate C–H amination with

only 1 equivalent of arene was disclosed by the Ritter group in 2013.[122] They employed an amine-*N*-oxide-ligated palladium complex, combined with a Ag co-catalyst, for the generation of a wide range of sulfonamides. Glorius and co-workers realised the Rh(III) catalysed amination of arenes possessing a pyridine or *O*-methyl hydroxamic acid directing group by employing an *N*-Boc-protected hydroxylamine-derived aminating reagent.[123] In 2016, Kürti and Falck reported the generation of free primary and *N*-alkyl arylamines catalysed by a rhodium complex. This reaction is proposed to proceed *via* a metal–nitrenium intermediate.[124] An example of the Rh catalysed, *para*-selective C–H amination of alkoxyarenes was reported by the Kawabata group in 2018.[125]

2.2.2 Earth-abundant metal-catalysed aromatic C–H amination. Earth-abundant metals such as Na, Al, Ti, Fe, Ni, Cu, or Hg have been known to promote innate arene C–H amination for several decades. One of the first amination strategies employing an N–X reagent was the reaction of hydroxylamine *O*-sulfonic acid (HOSA, **R1**) with arenes in the presence of aluminium chloride, developed by Keller in 1944 and Bennett in 1961 (Scheme 5).[126,127] Other early examples of innate aromatic C–H amination with hydroxylamine-derived reagents include homolytic aromatic amination reactions involving amino radical cations generated from N–Cl substrates in a strongly acidic environment (H_2SO_4) or mediated by Na(I), Ti(IV), Fe(II), Cu(I), Ni(II), and Hg(I) salts, as reported by Bock and Minisci.[128–131] The utility of these early reports remained limited due to the excess of arene employed, and the need of Brønsted or Lewis acids.

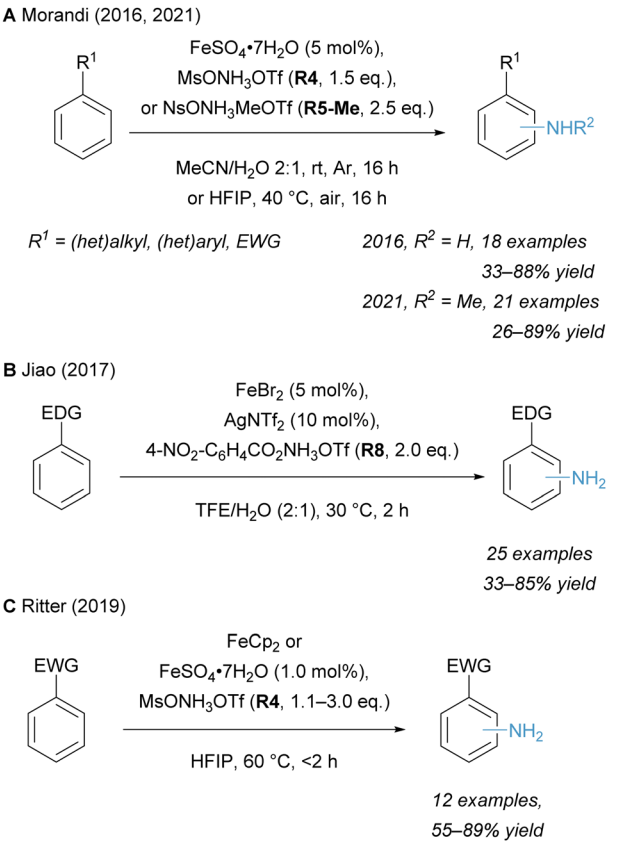
In recent years, significant progress has been made in Fe catalysed amination reactions, employing hydroxylamine-derived aminating reagents and using arenes as the limiting reagent. A mild procedure for the imidation of (hetero)arenes, catalysed by ferrocene and employing *N*-succinimidyl perester (NSP, **R17**) as the aminating reagent, was reported by Baran and co-workers in 2014.[34] This strategy proceeding *via* a radical pathway enabled the reaction to work on a wider range of substrates (including various heteroarenes) than previously reported methods, yet it still required a deprotection step of the succinimide to unmask the free amine. The innate Fe catalysed arene C–H amination to generate free anilines was published by our group in 2016 using the hydroxylamine-derived reagent $MsONH_3OTf$ (**R4**) (Scheme 6A).[20] The use of an earth-abundant metal under mild conditions enabled the direct access to a plethora of primary anilines and is a more cost-efficient method for analogous Rh catalysed transformations. This amination strategy was also subsequently applied in the total synthesis of di- and sesquiterpenoids by the Dong group in 2020.[132] We also reported the Fe catalysed C–H amination for the synthesis of *N*-methylanilines from simple arenes using electrophilic aminating reagent $NsONH_2MeOTf$ (**R5-Me**).[133] More recently, the Xu and Huang groups reported the C–H amination of (hetero)arenes under photoredox catalysis to form protected trifluoromethylamines.[134]

With the development of new Fe catalysed innate C–H amination reactions a variety of new aminating reagents was introduced, each tailored for different kinds of transformations. In 2017, Jiao and co-workers introduced a new aminating reagent $4\text{-}NO_2\text{–}C_6H_4CO_2NH_3OTf$ (**R8**), which enabled the Fe catalysed C–H amination of electron-rich and -neutral arenes as well as heteroarenes (Scheme 6B).[21] Mechanistic studies



	Keller (1944), Bennett (1961)	Bock (1965)	Minisci (1984)
mediator	$AlCl_3$	$AlCl_3$, $FeSO_4•7H_2O$, CuCl, $NiCl_2$, etc.	$FeSO_4•7H_2O$
aminating reagent	HOSA (**R1**)	Cl–N(alkyl)$_2$ (**R13**)	HOSA (**R1**)
R^1	EDG, EWG	EDG, EWG	EDG
solvent	Ar–R^1	nitroalkanes	AcOH/H_2O 2:1
temperature	95–105 °C	80–100 °C	40 °C
reaction time	30 min	6–10 h	2 h
scope	7 examples	9 examples	5 examples
yield	1–51% yield	5–60% yield	21–90% yield

Scheme 5 Early examples of innate C–H arene amination.

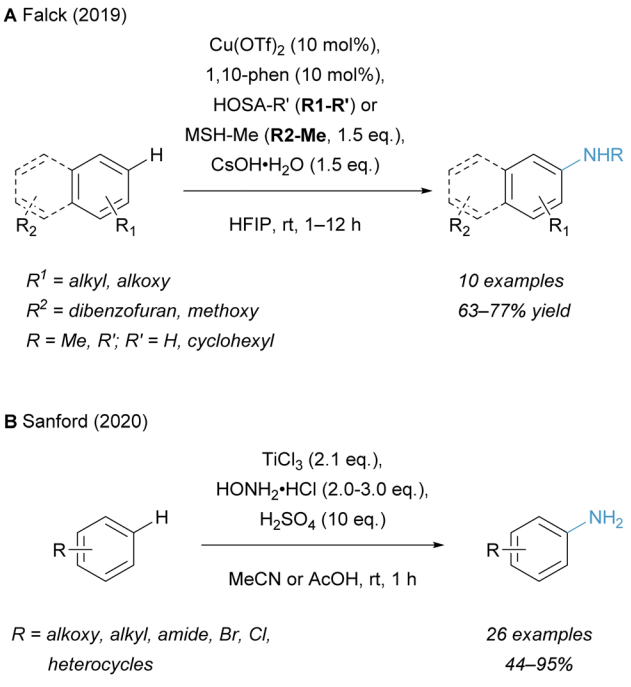


Scheme 6 Fe catalysed C–H amination of arenes.

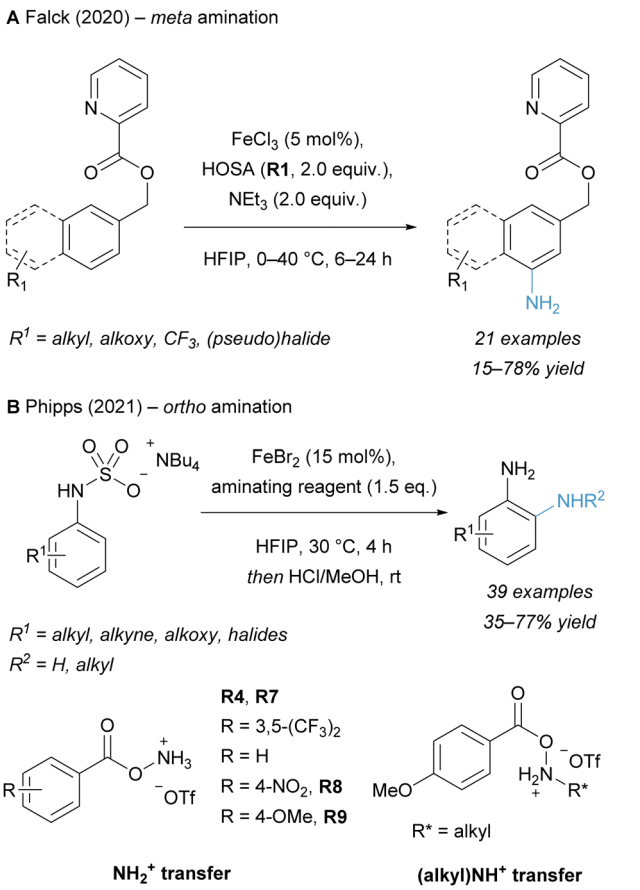
suggest that the transformation is enabled *via* the formation of an amino radical species. While only electron-rich or -neutral substrates were suitable for the generation of primary anilines, Ritter and co-workers realised the amination of electron-poor arenes in 2019 by modifying our previously reported conditions.[16] Hexafluoroisopropanol (HFIP), which disrupts ion pairing through hydrogen bonding interactions, proved to be essential for the successful C–H amination of these more inert substrates (Scheme 6C).[135]

Notable aminating strategies utilising non-noble transition metals, other than iron, have been developed in recent years. In 2019, the group of Falck employed catalytic $Cu(OTf)_2$ for the synthesis of free primary and secondary anilines (Scheme 7A).[49] This offers a cost-effective alternative to the established methodologies with Rh catalysts. An alternative $TiCl_3$-mediated amination strategy for the synthesis of free primary amines from arenes was reported by Sanford and co-workers in 2020 (Scheme 7B).[136] This protocol complements Minisci's originally reported conditions by using the arene as the limiting reagent and provides an expanded substrate scope.

2.2.3 Regioselective aromatic C–H amination. A challenge that has been partially addressed in recent years is the regioselective C–H amination of arenes. A highly *meta*-selective arene C–H amination strategy, assisted by a picolinate directing group, was reported by Falck and co-workers in 2021 (Scheme 8A).[137] One of the most recent advances in generating *ortho*-substituted primary amines over *meta*- or *para*-substituted ones is the regioselective arene *ortho*-amination of sulfamate-protected anilines developed by Phipps and co-workers (Scheme 8B). This directing group can easily be deprotected under acidic conditions.[25] This work makes use of



Scheme 7 Arene C–H amination reactions using Cu(II) and Ti(III) salts.

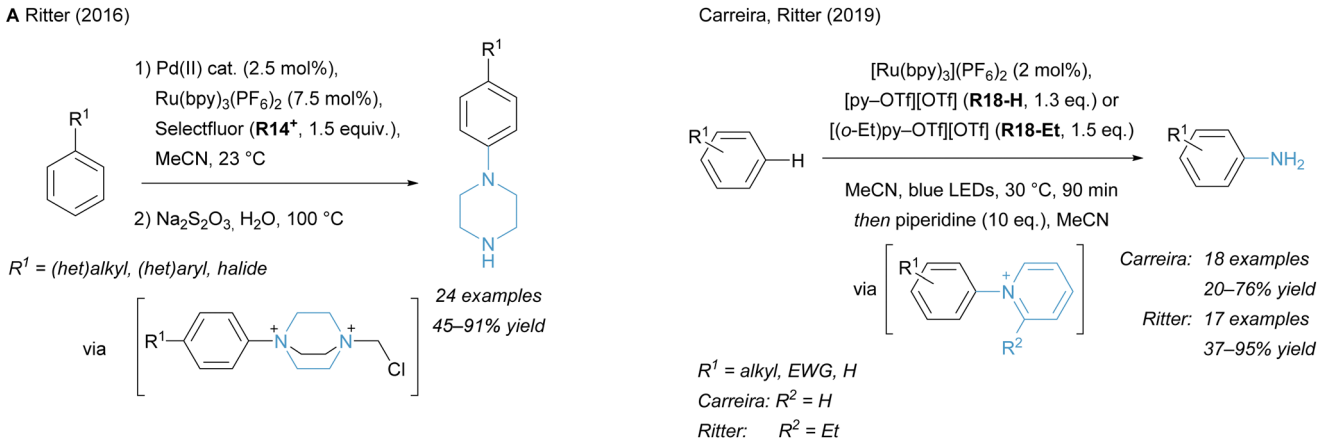


Scheme 8 Fe catalysed regioselective arene C–H amination at the *ortho*- and *para*-position.

electrostatic and hydrogen bonding interactions between the aminium radical cation generated from a wide range of known and novel reagents (**R4**, **R7–R9**) and the anionic arene sulfamate substrate in HFIP.

Several reports have been published to achieve the *para*-selective C–H amination of arenes using photoredox catalysis. These reactions, proceeding *via* the formation of highly electrophilic aminium radicals from *N*-haloamines, have been reported by the groups of Ritter (Scheme 9A)[138] and Leonori (Scheme 9B)[139] to generate *para*-substituted aryl piperazines and other tertiary amines. In the former report, selectfluor is used and thus necessitates a reduction step to unmask the diazoniabicyclo[2.2.2]octane salts into free piperazines. Therefore, a general protocol for the *para*-selective synthesis of free primary anilines *via* C–H amination with a broad substrate scope is still lacking.

2.2.4 Arylpyridinium ions as reactive intermediates in innate C–H amination reactions. The direct access of unprotected primary amines *via* arylpyridinium intermediates has also attracted the attention of several research groups. A photocatalytic approach was independently developed by the Carreira and Ritter groups in 2019, in which the direct C–H amination of arenes is enabled *via* photocatalytically generated pyridyl radical cations (Scheme 10).[35,36]



Scheme 9 Regioselective, photocatalysed arene C–H amination in *para*-position.

Scheme 10 C–H amination of arenes *via* arylpyridinium intermediates.

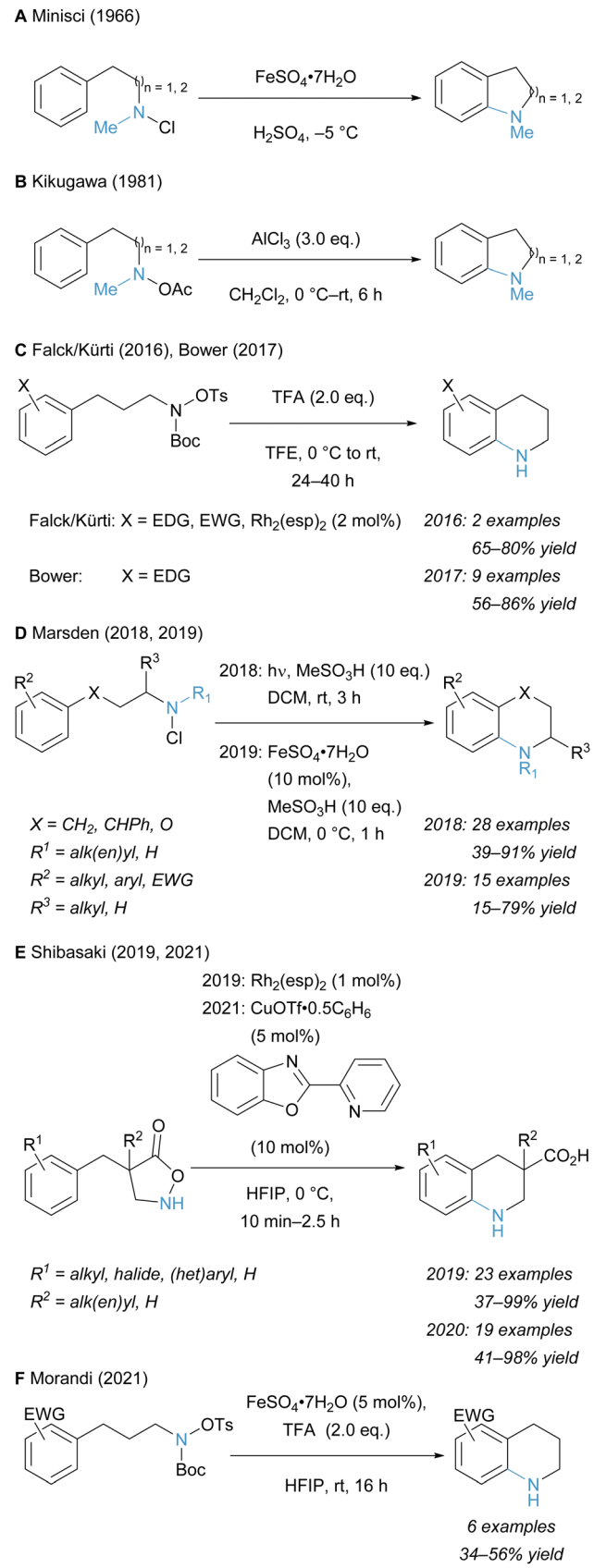
2.2.5 Intramolecular aromatic C–H amination. Heterocyclic compounds are extremely relevant in the pharmaceutical and agrochemical industry.[140] Several procedures for synthesizing indoles,[141,142] carbazoles,[143,144] indolines,[145,146] and benzazetidines[147] have been developed in the last decades *via* C–H arene amination. Next to these and the ones mentioned in the previous sections, another building block present in a wide range of biologically active natural and unnatural products is the tetrahydroquinoline motif.[148,149] The group of Minisci reported the intramolecular homolytic C–H amination by *N*-chloroamines (**R14**) in the presence of ferrous sulfate in concentrated sulphuric acid to afford indolines and tetrahydroquinolines already in 1966 (Scheme 11A).[129] The group of Kikugawa applied the $AlCl_3$-mediated intramolecular C–H arene amination to the synthesis of indolines and tetrahydroquinolines from alkylhydroxylamine derivatives in 1981 (Scheme 11B).[150]

These early examples laid the foundation for later advances in the generation of tetrahydroquinolines *via* C–H amination. In 2016, the Falck and Kürti groups developed an intramolecular Rh catalysed C–H amination of electron-rich and -poor arenes to afford several free tetrahydroquinolines. Thereafter, a metal-free procedure for the intramolecular C–H amination of electron-neutral as well as electron-rich arenes was developed by the Bower group (Scheme 11C). They propose that these substrates maintain sufficient nucleophilicity to approach the electrophilic amine moiety in an S_EAr fashion.[151] The Fe catalysed intramolecular C–H amidation of arenes for the generation of arylcarbamates was reported by Singh and co-workers in 2018. Mechanistic investigations and DFT calculations suggest a reaction pathway that likely proceeds *via* nitrene formation upon N–O bond cleavage.[152] The Marsden group reported the synthesis of tetrahydroquinolines from secondary alkylamines through the *in situ* formation of *N*-chloroamines with *N*-chlorosuccinimide (Scheme 11D). In the presence of methanesulfonic acid, these can undergo a light-mediated cyclization.[153] Their methodology was also applied in the synthesis of polycyclic substrates, whose skeleton is present in various complex alkaloids. Furthermore, continuous flow conditions drastically improved the efficiency of the reaction.[154] The same group reported the Fe catalysed intramolecular aromatic C–H amination of *N*-chloroamines with methanesulfonic acid to generate tertiary tetrahydroquinolines.[155]

The group of Shibasaki exploited the labile N–O bond of hydroxylamine-derived compounds and developed the Rh catalysed synthesis of novel β-amino acids, which were generated from initial N–O bond cleavage in the substrate, followed by intramolecular C–H arene amination of the liberated amine moiety (Scheme 11E).[156] With this method a variety of tetrahydroquinoline derivatives and spirocyclic β-amino acids could be prepared. An analogous protocol with a Cu catalyst was developed, thus enabling higher chemoselectivity than with the more reactive Rh catalyst. The reaction is proposed to proceed *via* a dicopper alkyl nitrene.[157]

The groups of Zhang, Chai, and Zhang developed the electrochemical cyclization of aryl sulfonamides to benzosultams *via* intramolecular aromatic C–H amination.[158]

In our recent publication on the Fe-mediated *N*-methylamination of arenes, we also reported the synthesis of electron-poor tetrahydroquinolines in the presence of trifluoroacetic acid in HFIP (Scheme 11F).[133] This procedure unlocks the functionalization of electron-poor arenes in a more cost-effective fashion compared to methods relying on the less abundant rhodium metal.[159]



Scheme 11 Synthesis of tetrahydroquinolines.

2.3 Amination of sulfur compounds

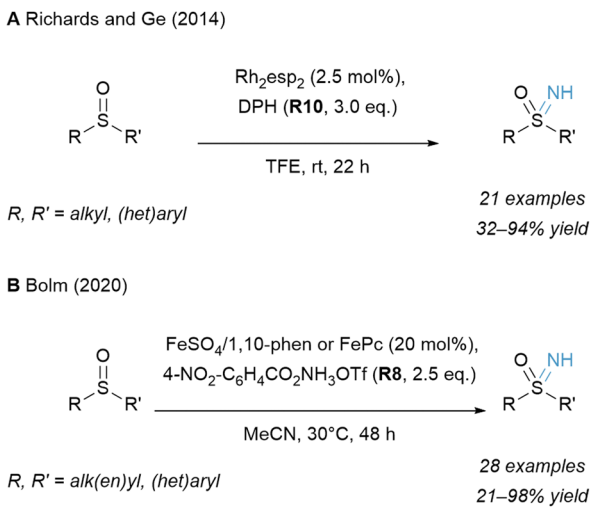
In addition to carbon nucleophiles, sulfur-bearing functionalities can be transformed with hydroxylamine-derived reagents to generate a variety of value-added aminated sulfur compounds.[160,161]

2.3.1 Sulfoximines. A prominent example of this transformation is the generation of sulfoximines from sulfoxides (Scheme 12).[162,163] In search of a safer alternative to hazardous reagents (*e.g.* **R2** (MSH)[164]) the group of Richards and Ge demonstrated the use of **R10** (DPH) in a Rh catalysed transformation (Scheme 12A) in 2014.[165] (Hetero)aromatic and aliphatic thioethers afforded the desired product in high yields, whereas steric bulk at the *ortho*-position hampered the reaction.

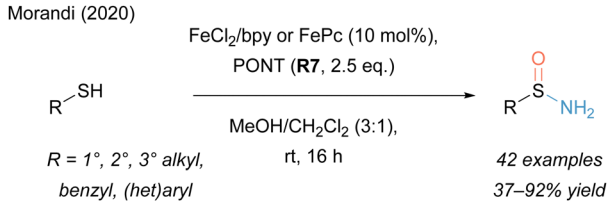
A more cost-effective method was disclosed a few years later by Bolm and co-workers (Scheme 12B).[166] An Fe based catalytic system with a phenanthroline (phen) or a phthalocyanine (Pc) ligand structure performed effectively. Though *O*-pivaloyl-substituted hydroxylammonium reagent PONT (**R7**) gave the desired product in good yield, the reaction could be further improved by switching to an *O*-benzoyl congener **R8** (4-NO_2–$C_6H_4CO_2NH_3OTf$).

2.3.2 Primary sulfinamides. Traditionally, the conversion of free thiols to sulfinamides can be achieved by a two-step protocol that used either sulfenamides[167] or sulfinates[168,169] as intermediates. A direct oxidative coupling approach with primary and secondary amines showed some over-oxidation of the sulfinamide group.[170]

Recently, our group reported that unprotected, primary sulfinamides could be selectively obtained in a mild Fe catalysed process under ambient conditions from thiols by employing PONT (**R7**) (Scheme 13).[171] This process allowed the use of a wide range of thiols: not only were thiophenols transformed in excellent yields, but also primary, secondary, tertiary as well as benzylic thiols all reacted to give the respective sulfinamide product without any overoxidation to sulfonamides.



Scheme 12 Amination of sulfoxides.



Scheme 13 Aminooxygenation of thiols. NCS: *N*-chlorosuccinimide; bpy: 2,2′-bipyridine.

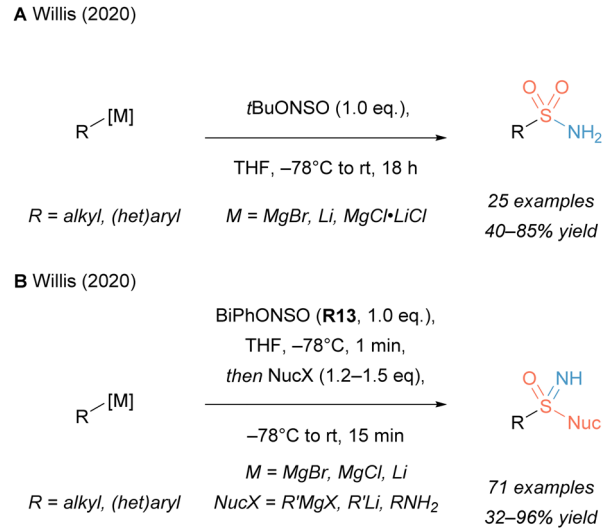
Considering related Fe catalysed transformations with this reagent (see Section 2.1), it is remarkable that alkene groups remained intact using this protocol.

A key mechanistic finding was that the aminating reagent acted beyond its usual function as a nitrogen source by also serving as an oxidant. The oxygen source could be traced back to the methanolic solvent system.

2.3.3 N–O reagents for C–S bond formation. Though various methods have been reported to transform thiols into primary, unprotected sulfonamides,[172–175] similar protocols employing a hydroxylamine-derived reagent are less known.

Recently, the laboratory of Willis has reported an example with a novel *N*-sulfinylhydroxylamine reagent that exhibits an N–O connectivity (Scheme 14A).[176] This electrophilic *O*-*t*Bu reagent (*t*BuONSO) already contained all the necessary atomic building blocks to generate a sulfonamide, including the sulfur core. The remaining C–S bond was then formed upon reaction with a strong carbon nucleophile such as a Grignard or organolithium species. Similarly, a novel *N*-silyl analogue was used to synthesise primary sulfinamides.[177]

O-Aryl reagent **R13** by contrast exhibits a weaker N–O bond and thus differs in reactivity (Scheme 14B).[30] The mechanistic experiments conducted by the group of Willis indicate that, upon attack of the first equivalent of an organometallic carbon nucleophile and loss of a phenolate, a sulfinyl nitrene species is formed. This could subsequently react further on the electrophilic sulfur with a different carbon or nitrogen nucleophile to yield unprotected sulfoximines and sulfonimidamides, respectively.



Scheme 14 Application of hydroxylamine-derived reagents for the construction of C–S bonds.

3 Conclusions and outlook

The reports discussed above clearly show that hydroxylamine-based reagents are a privileged class of electrophilic aminating species for the preparation of important amine building blocks. They are particularly attractive reagents enabling the direct synthesis of unprotected amines.

However, this should not discourage to envision new reagents which use the hydroxylamine handle to introduce transiently protected amines which can easily be deprotected. Recent examples are Fier's reagent (**R12**) for alpha-carbamation of pyridines[29] and an improved version of NFSI by the Hashimoto group (NFC, **R16**).[178]

In most cases, hydroxylamine-derived reagents exhibit scalable syntheses, air and temperature stability and a broad range of applications. Their practicality is further increased as they tend to be easy-to-handle solids with an extended shelf life. In contrast, *N*-chloro and *N*-bromo activated reagents suffer from low stability and availability. While methods directly using simple amines in photo-[179] or electrochemical[180,181] reactions have recently emerged for the formation of C–N bonds, solid hydroxylamine-derived reagents may represent a more convenient alternative for various applications. Especially in the case of low-molecular amino functions, hydroxylamine-derived reagents are less volatile and hazardous than their free amine and azide counterparts, making them ideal reagents for discovery projects and late-stage functionalisations. Moreover, their weak N–O bond enables facile and selective functionalisation under mild reaction conditions.

For all these reasons, it is important to further investigate methods to synthesise these reagents, especially with regard to developing new versatile methods for the construction of the N–O connectivity.[182] This, in turn, will provide access to more functionalised reagents which will bring about the design of new catalytic reactions.

A common limitation of several of the presented amination reactions employing N–O species is the use of perfluorinated reagents and/or solvents to achieve enhanced reactivity. It would be very desirable to find cheaper and environmentally more benign alternatives which mimic the special reactivity of *e.g.* hexafluoroisopropanol[183] to facilitate the application of these reactions on larger scales.

Another challenge in the field is that several synthetically useful transformations have remained elusive. For example, asymmetric transformations enabling the direct introduction of unprotected amines remain scarce, probably due to the additional challenges of controlling enantioselectivity in reactions that often involve radical intermediates.[184,185]

Finally, there is a clear need for additional mechanistic studies, particularly for reactions employing first-row transition

metals. A deeper understanding of these reactions could serve to improve their scope, as well as unlock completely new transformations.

In conclusion, we hope this feature article will serve as an inspiration for the future development of new transformations that will streamline the discovery and synthesis of important amines. Seeing the recent increase of reports in this research area, we are confident that the challenges mentioned above will be swiftly addressed by the synthetic community.

Conflicts of interest

There are no conflicts of interest to declare.

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