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RESEARCH ARTICLE

Design and Scalable Synthesis of *N*-Alkyl-Hydroxylamine Reagents for the Direct, Iron-Catalyzed Installation of Medicinally Relevant Amines

Eric Falk,[a] Szabolcs Makai,[a] Tristan Delcaillau,[a] Laura Gürtler,[a] and Bill Morandi*[a]

In memory of Kilian Muñiz

[a] E. Falk, S. Makai, T. Delcaillau, L. Gürtler, Prof. Dr. B. Morandi
Laboratorium für Organische Chemie
ETH Zürich
Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland
E-mail: bill.morandi@org.chem.ethz.ch

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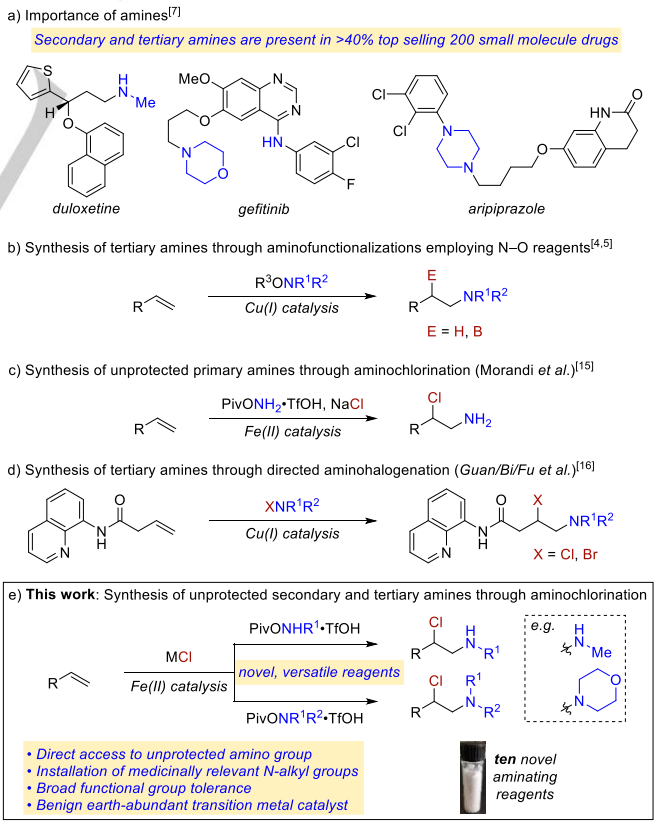
Abstract: Secondary and tertiary alkylamines are privileged substance classes which are often found in pharmaceuticals and other biologically active small molecules. Herein, we report their direct synthesis from alkenes through an aminative difunctionalization reaction enabled by iron catalysis. A family of ten novel hydroxylamine-derived aminating reagents were designed for the installation of several medicinally relevant amine groups, such as methylamine, morpholine and piperazine, through the aminochlorination of alkenes. The methodology displays an excellent functional group tolerance, and a broad scope of alkenes was converted to the corresponding products, including several drug-like molecules. Besides aminochlorination, the installation of other functionalities through aminoazidation, aminohydroxylation and even intramolecular carboamination reactions, is demonstrated, further highlighting the broad potential of these new reagents for the discovery of novel amination reactions.

Introduction

Densely functionalized aliphatic amines are prevalent in natural products, pharmaceuticals and other small molecules with biological functions (Scheme 1a).[1] Intermolecular aminofunctionalizations of alkenes are powerful tools for the synthesis of this privileged substance class from simple hydrocarbon feedstocks.[2] However, the majority of the reported aminofunctionalizations introduce the amine in a protected form (e.g. tosyl, nosyl) because these methods often require an electron-deficient nitrogen to enhance the electrophilicity of the aminating species involved.[3] In contrast, and despite their synthetic utility, electron-rich alkylamino sources are mostly unreactive in those cases, often preventing the development of efficient and useful intermolecular aminofunctionalization reactions. In a notable exception, an umpolung approach which features migratory insertion of alkenes into M−X bonds (M = Cu, Ni, Zr; X = B, C, H), followed by a nucleophilic attack of this alkyl-metal species on a hydroxylamine derivative, has led to synthetically attractive examples of intermolecular aminoboration,[4] hydroamination[5] and carboamination[6] of unactivated olefins (Scheme 1b). Given the synthetic relevance of alkylamines in medicinal chemistry,[7] the installation of further functionalities *via* intermolecular aminofunctionalization reactions remains a central goal in synthetic chemistry.

Methods which provide direct access to unprotected primary and secondary alkylamines from simple alkenes are highly attractive for the step-economical and protecting-group-free synthesis of bioactive molecules.[8] Compared to the synthesis of unprotected primary amines from unsaturated compounds, in which significant advancement has been achieved over the recent



Scheme 1. Context of this work. Piv = pivalate, trimethylacetyl. Tf = triflyl, trifluoromethanesulfonyl.

years,[9] the direct synthesis of unprotected secondary amines from simple hydrocarbon feedstocks remains underdeveloped.[5g,10-12] Broadly applicable, intermolecular catalytic methods for the direct synthesis of unprotected secondary amines from alkenes are limited to isolated examples of hydroamination[5g,10] and aziridination.[11] It is important here to note that secondary amines can also be challenging to access using traditional synthetic routes, such as reductive amination and alkylation, because an overreaction can be difficult to prevent.[13] Considering that the majority of aliphatic amines present in biologically active compounds are either secondary or tertiary, the extension of the scope of intermolecular aminofunctionalizations to unprotected secondary as well as tertiary amines is highly desirable.[14]

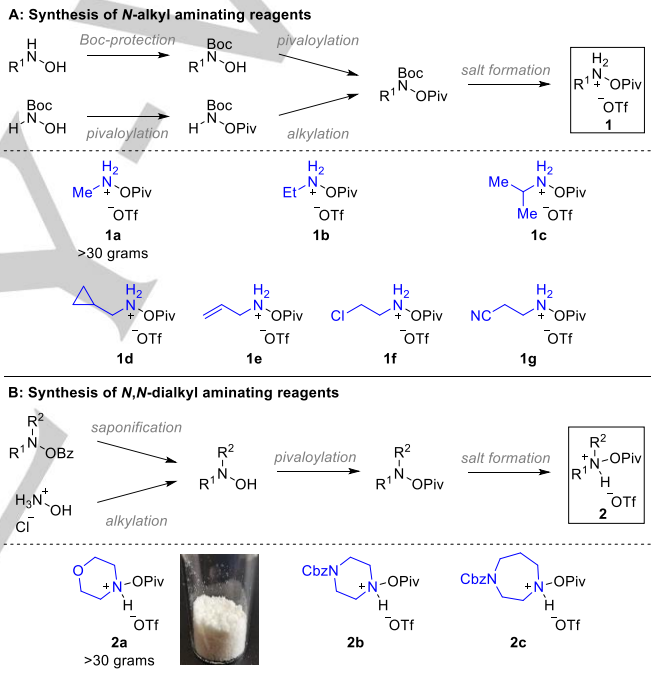
The aminohalogenation of alkenes provides a complementary approach to the synthesis of important amines. The resulting products are versatile building blocks for the rapid synthesis of a plethora of derivatives. Recently, we reported an iron-catalyzed aminochlorination of alkenes delivering versatile unprotected 2-chloroamines which could be further derivatized to useful functionalized primary amines (Scheme 1c).[15] Unfortunately, this chemistry could not be readily extended to the synthesis of secondary and tertiary amines because of the unavailability of the corresponding reagents and the lack of suitable reaction conditions (*vide infra*). Shortly after our report, a directed intermolecular aminohalogenation of unactivated alkenes was reported by Guan, Bi and Fu (Scheme 1d).[16] While this reaction allows for the installation of highly functionalized tertiary alkylamines employing mild reaction conditions, the requirement for a suitably positioned directing group severely limits its generality. Furthermore, unprotected secondary amines are not accessible through this transformation. In light of these limitations,[17] the development of a new family of bench-stable hydroxylamine reagents bearing medicinally relevant alkyl groups appears crucial to fill an important gap in this research area and enable the development of a general, catalytic aminochlorination of unbiased alkenes.

Herein, we report the scalable syntheses of ten novel, versatile aminating reagents bearing medicinally relevant substitution patterns. We present their application in an iron-catalyzed intermolecular aminative difunctionalization of unactivated alkenes to directly access unprotected secondary as well as tertiary 2-chloro-*N*-alkylamines (Scheme 1e).[18] The broad substrate scope includes unactivated mono- and disubstituted alkenes bearing unprotected polar functional groups often found in biologically active molecules. The versatility of these new reagents is further demonstrated in three additional examples of aminofunctionalizations, clearly showing their broad potential in catalytic aminations.

Results and Discussion

Design and scalable synthesis of novel aminating reagents

Our initial goal was to develop suitable aminating reagents which, ideally, can be obtained from commercially available starting materials in a minimal number of steps and are stable to ambient conditions. We targeted the preparation of reagents bearing some of the most common motifs found in bioactive compounds, such as a *N*−Me, piperazine or morpholine. Gratifyingly, we were able to employ two robust and general 3-step sequences from commercially available hydroxylamine derivatives for the synthesis of *N*-alkyl aminating reagents (Scheme 2A).[19,20] The synthetic methods are scalable, do not require specialized equipment and would likely be applicable to the synthesis of a much larger library of reagents. To prove the generality of this approach, we prepared seven novel mono-alkylated reagents, most of them on a gram scale. This includes the single-batch preparation of 33 grams of the *N*−methyl reagent **1a**. Additionally, a series of tertiary alkyl amine reagents were also readily synthesized through similar 3-step sequences starting from easily accessible hydroxylamine derivatives (Scheme 2B).[19,20] The morpholine reagent **2a** was prepared on a 101 mmol (34 grams) scale, further demonstrating the scalability of this synthetic route. Due to the versatility of hydroxylamine-derived compounds in organic synthesis, these new reagents have broad potential for the development of new amination reactions, even beyond the aminative difunctionalizations of alkenes reported in this work.[21]

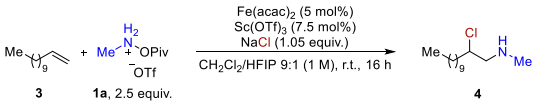


Scheme 2. Synthesis of a novel family of aminating reagents. Boc = *tert*-butyloxycarbonyl. Bz = benzyl. CBz = carboxybenzyl.

N-Alkylaminochlorination of alkenes

Based on our research interests in the synthesis of unprotected, primary amino alcohols, 2-azidoamines and 2-chloroamines under iron-catalysis,[15,22] and the general interest in radical amination reactions,[23] we set out to investigate conditions for the synthesis of unprotected secondary 2-chloro-*N*-alkylamines from alkenes using this novel series of reagents. We identified two potential challenges which could prevent the desired reactivity: (1) The increased steric bulk of the required aminating reagents could prevent a productive reactivity with the iron catalyst and (2) the presence of electron-donating alkyl substituents significantly increases the electron density at the nitrogen center which, in turn,

Table 1. Selected optimization results[a]

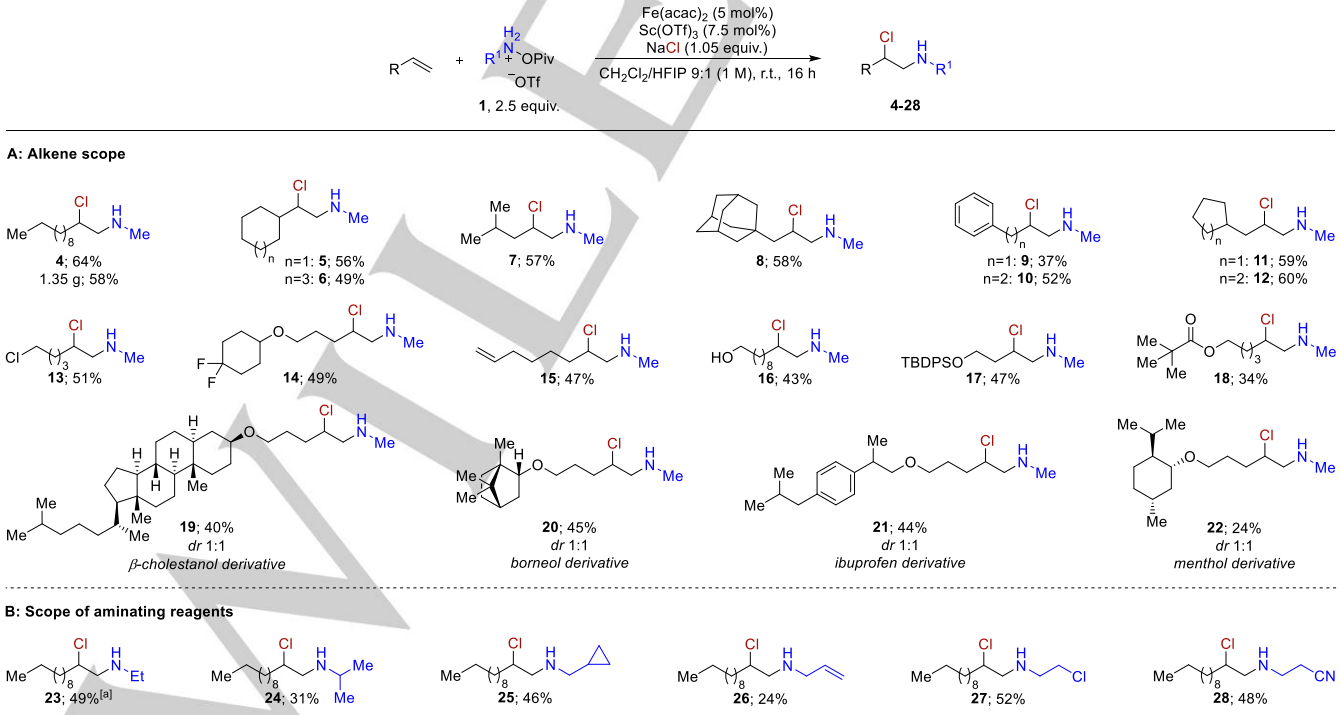


Entry	Deviation from standard conditions	Yield[b]
1	CH_2Cl_2/MeOH 1:3, no LA	0
2	MeOH instead of HFIP, no LA	26
3	TFE instead of HFIP, no LA	4
4	No LA	50
5	**None**	**62**
6	$AlCl_3$ instead of $Sc(OTf)_3$	60
7	No Fe	0
8	Under air	28
9	No LA, under air	51

[a] Reaction conditions: 1-dodecene (0.20 mmol), **1a** (0.50 mmol), $Fe(acac)_2$ (5 mol%), $Sc(OTf)_3$ (7.5 mol%), NaCl (0.21 mmol), CH_2Cl_2/HFIP 9:1 (0.20 mL) at r.t., 16 h, inert atmosphere. [b] Yields in % obtained by ^{1}H NMR using trichloroethylene as internal standard. acac = acetylacetonate. TFE = 2,2,2-trifluoroethanol.

could decrease the electrophilicity of the aminating species.[24] Due to its prevalence in biologically active molecules, we decided to utilize the installation of *N*-methylamine as a benchmark reaction for the optimization of the reaction conditions. Importantly, simple extension of our previous procedure for the synthesis of unprotected, primary 2-chloroamines[15] did not result in any product formation (Table 1, entry 1), clearly highlighting the challenges of developing this process. We thus started our investigations by evaluating different iron catalysts, chloride salts and solvents. Increasing the ratio of dichloromethane to methanol allowed the *N*-methylaminochlorination of 1-dodecene (**3**) to occur with low yield (Entry 2). Encouraged by numerous reports discussing the unique properties of fluorinated alcohols, especially their ability to increase the lifetime of radical cations, we investigated their use as co-solvents in our reaction (Entries 3 & 4).[25] We were pleased to find that a combination of dichloromethane and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) led to a significant improvement of the yield. Inspired by a report of Newcomb, in which they demonstrated the beneficial effect of Lewis acids (LA) on dialkylaminyl radical reactions, we also evaluated different Lewis acids as additives in our reaction.[26] Gratifyingly, the addition of Lewis acids did indeed reproducibly increase the yield of our reaction (Entries 5 & 6). $Sc(OTf)_3$ proved to be optimal as the addition of 7.5 mol% $Sc(OTf)_3$ significantly increased the yield of the benchmark reaction. If a simpler reaction setup is desired, the reaction can be performed under air without the addition of a Lewis acid to afford **4** in moderate yield (Entry 9).

We then investigated the alkene scope of the reaction (Scheme 3A). Sterically congested alkyl groups such as cyclohexyl (**5**), isopropyl (**7**) or adamantyl (**8**) in close proximity to the alkene were all tolerated. In products bearing an acidic C−H bond at the β-position relative to the chloride, no elimination of HCl was observed (**9**). Alkenyl halides, such as chlorides (**13**) and fluorides (**14**) could undergo methylaminochlorination. Dienes (**15**) were



Scheme 3. Substrate scope of the *N*-alkylaminochlorination reaction. Yields are of isolated products; diastereomeric ratio (*dr*) determined by NMR. Reaction conditions: Alkene (0.50 mmol), **1** (1.25 mmol), $Fe(acac)_2$ (5 mol%), $Sc(OTf)_3$ (7.5 mol%), NaCl (0.525 mmol), CH_2Cl_2/HFIP 9:1 (0.50 mL) at r.t., 16 h, inert atmosphere. [a] 40 hours reaction time. TBDPS = *tert*-butyldiphenylsilyl.

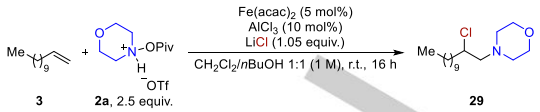
only mono-aminated, even though an excess of aminating reagent was used, a result best explained by the precipitation of the ammonium product after the initial amination. Free primary alcohols (**16**) and acid labile groups such as silyl ethers (**17**) were also suitable substrates. Synthetically relevant functional groups like esters (**18**) further expanded the scope of this transformation. Even a β-cholestanol derivative, which is poorly soluble in many organic solvents, afforded the desired product (**19**). Borneol, ibuprofen and menthol derivatives (**20**-**22**) were all converted to their *N*-methylaminated analogs. Collectively, these substrates show that the reaction could be used for late-stage functionalization. Styrenes only afforded the product in low yields, despite the fact that high conversion of the alkene starting material could be observed. This behavior is probably caused by undesired radical oligomer- and polymerization under the reaction conditions. To demonstrate the robustness and applicability of the new reaction on a preparative scale, we further showed that the method can produce gram amounts of the 2-chloroamine **4** in a similar yield under otherwise identical reaction conditions.

The applicability of the other new reagents **1b**-**1g** was next explored (Scheme 3B). All reagents were compatible with the reaction, including the sterically demanding isopropylamine reagent. A cyclopropyl in close proximity did not undergo ring-opening and afforded the corresponding cyclopropylmethylamine (**25**) in moderate yield. Remarkably, preliminary experiments showed that allylamine can be installed (**26**) with no subsequent amination of the double bond. This result, when combined with the observation made above that monoamination selectively occurred on a diene substrate, suggests that aminated compounds (products or reagents) are likely protonated under the reaction conditions and thus are not soluble enough to react with the active aminating species. This phenomenon leads to a high chemoselectivity for the amination of double bonds located on non-aminated compounds.

N,*N*-Dialkylaminochlorination of alkenes

Aminative difunctionalizations of alkenes installing tertiary amines are better developed compared to the installation of unprotected secondary amines.[4-6,16,23h-j] However, due to significant limitations in alkene scope, the discovery of a broadly applicable method remains desirable. Hence, we began to expand our methodology to the installation of tertiary amines using the reagents **2a**-**2c** presented above. An investigation of iron catalysts, additives, chloride salts and solvents revealed again a strong dependence on the solvent mixture. Surprisingly, the use of HFIP as co-solvent led to a complete shutdown of the reactivity in this case (Table 2, entry 1). Instead, a combination of dichloromethane and *n*-butanol was found to be ideal (Entry 2). Lewis acids were again found to be beneficial for the reaction, of which $AlCl_3$ proved to be optimal (Entry 3). Furthermore, substituting NaCl with LiCl increased the yield of the reaction significantly (Entries 4 & 5). Without any alkali metal chloride salt, the desired product was still obtained in 10% yield (Entry 6). $AlCl_3$ can thus also serve as a chloride source for the reaction besides its primary function as Lewis acid.[27]

Table 2. Selected optimization results[a]

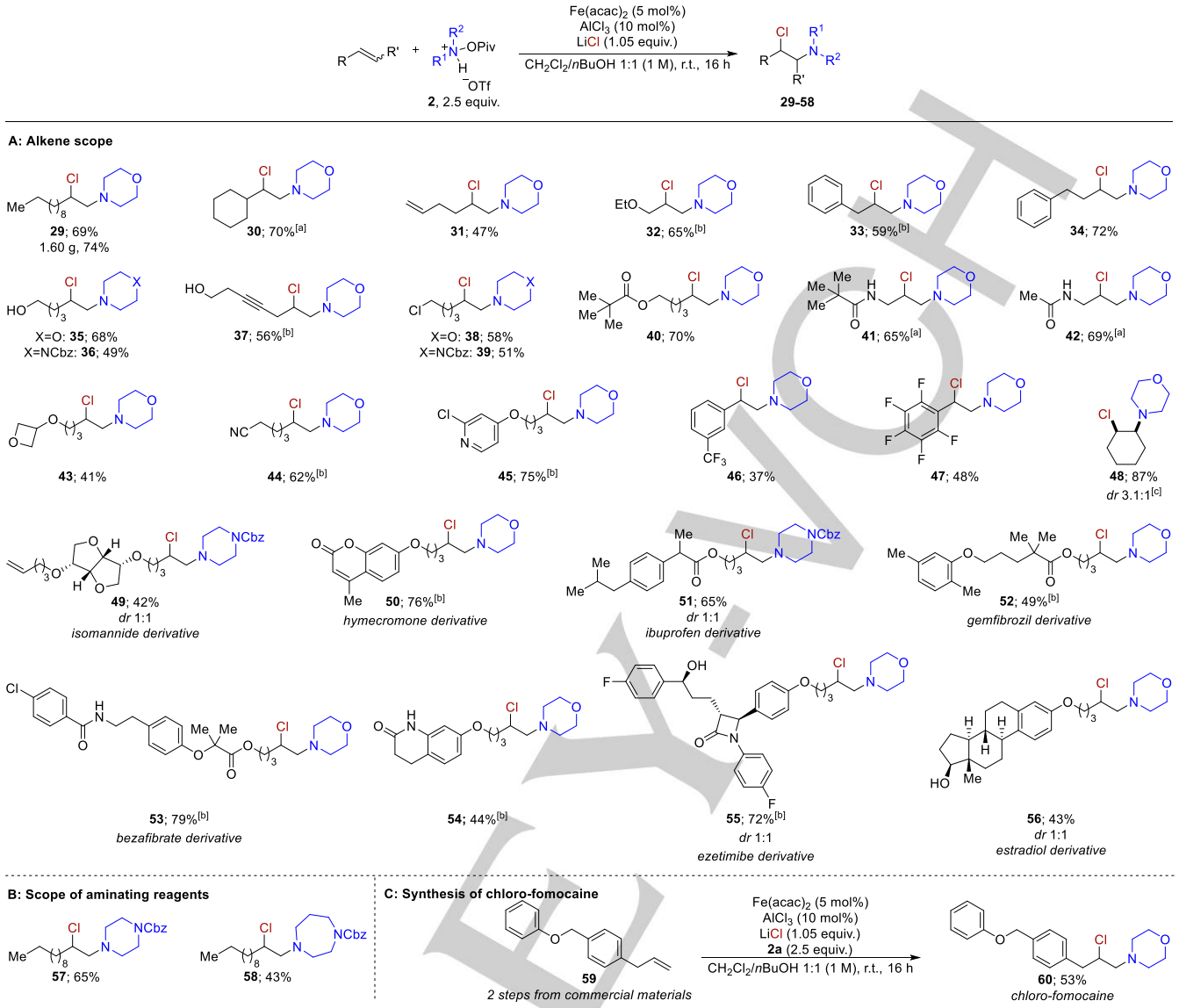


Entry	Deviation from standard conditions	Yield[b]
1	CH_2Cl_2/HFIP 9:1, no LA	0
2	No LA	38
3	**None**	**57**
4	NaCl instead of LiCl	39
5	NaCl, 7.5 mol% $Sc(OTf)_3$	24
6	No LiCl	10
7	No Fe	0
8	Under air	0

[a] Reaction conditions: 1-dodecene (0.20 mmol), **2a** (0.50 mmol), $Fe(acac)_2$ (5 mol%), $AlCl_3$ (10 mol%), LiCl (0.21 mmol), CH_2Cl_2/*n*BuOH 1:1 (0.20 mL) at r.t., 16 h, inert atmosphere. [b] Yields in % obtained by GC-FID using *n*-dodecane as internal standard.

We then set out to investigate the generality of the reaction on a range of alkenes (Scheme 4A). Aside from different carbon scaffolds, a broad variety of functional groups was found to be tolerated under the reaction conditions, such as ethers (**32**), free alcohols (**35**-**37**), aliphatic (**38**, **39**) as well as aryl halides (**45**, **47**), esters (**40**), amides (**41**, **42**) and nitriles (**44**). Again, dienes were selectively mono-aminated despite using an excess of aminating reagent (**31**). Remarkably, an alkene with an alkyne in close proximity reacted selectively, giving the 2-chloroamine **36** and leaving the alkyne untouched. Furthermore, heterocycles such as highly strained oxetanes (**43**) or pyridines (**45**) were compatible with this process as well. Alkenes with electron-poor aryl substituents (**46, 47**) as well as internal alkenes (**48**) were converted to the desired products, thus further expanding the scope of the transformation. Alkenes with more electron-rich aryl substituents only gave the product in low yields, presumably due to radical oligomer- and polymerization. Encouraged by the broad functional group tolerance, we investigated more challenging substrates of interest to medicinal chemistry. Several derivatives of pharmaceuticals or natural products were converted in moderate to good yields (**49**-**56**), highlighting the synthetic potential of this methodology for late-stage amination. The 2-chloroamine **29** was obtained on gram-scale in an even slightly higher yield than on small scale, demonstrating the preparative value of the methodology.

We next investigated the reactivity of different aminating reagents **2a**-**2c**. As shown in Scheme 4B, all new *N*,*N*-dialkylamine reagents were compatible with this process. Medicinally important cyclic amines, such as morpholine (**29**) and piperazine (**57**), could be installed in good yields. The protected amino group was left intact in these reactions (**57**, **58**).



Scheme 4. Substrate scope of the *N*,*N*-dialkylaminochlorination reaction. Yields are of isolated products; *dr* determined by NMR. Reaction conditions: alkene (0.50 mmol), **2** (1.25 mmol), $Fe(acac)_2$ (5 mol%), $AlCl_3$ (10 mol%), LiCl (0.525 mmol), CH_2Cl_2/*n*BuOH 1:1 (0.50 mL) at r.t., 16 h, inert atmosphere. [a] 24 hours reaction time. [b] 40 hours reaction time. [c] *dr* determined by GC-FID.

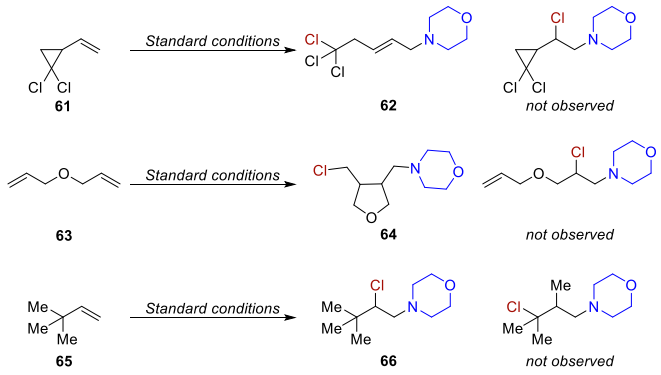
A chlorinated fomocaine analog could be obtained in only 3 steps from commercially available materials (Scheme 4C), further highlighting the synthetic utility of this methodology. The chlorine atom in β-position relative to the amine can potentially be used as a functional handle to facilitate the access to a broad variety of fomocaine analogs.

Control experiments

In recent work, our group hypothesized that the aminoazidation and aminochlorination of alkenes proceed *via* a carbon-centered radical.[15,22c] We thus assumed that the novel methodologies presented herein follow a similar mechanistic pathway. We decided to investigate the mechanism by conducting initial control experiments for the *N*,*N*-dialkylaminochlorination (Scheme 5). When we submitted 1,1-dichloro-2-vinylcyclopropane (**61**) to the standard aminochlorination conditions, we could obtain the ring-opened, chloroaminated product **62**. While vinylcyclopropanes are well known to undergo ring-opening in the presence of a carbon-centered radical,[28] there is also precedent for a cation-driven ring-opening of 1,1-dichloro-2-vinylcyclopropane.[29] Thus, we attempted to find stronger support for a radical mechanism. When diallyl ether was submitted to the reaction conditions for *N*,*N*-dialkylaminochlorination, the cyclized tetrahydrofuran derivative **64** could be isolated as the major product. Furthermore, during the aminochlorination of 3,3-dimethyl-1-butene, no 1,2-alkyl shift could be observed. Collectively, when combined with the carboamination reaction presented below (*vide infra*), these results are best explained by a stepwise mechanism proceeding *via* a carbon-centered radical intermediate.

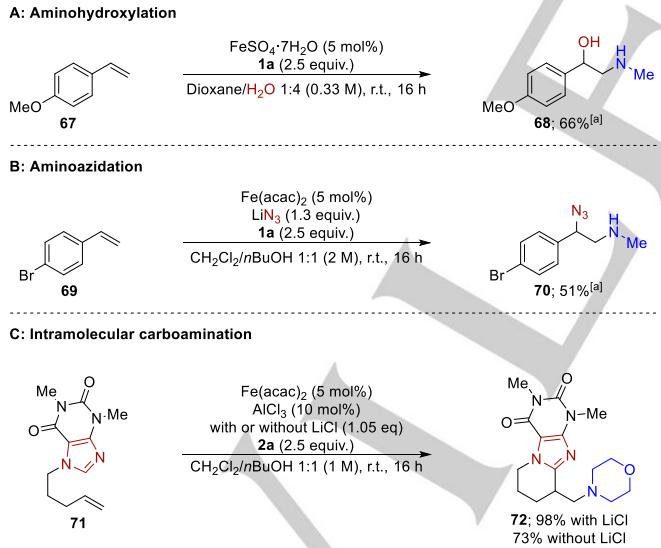
Versatile use of the new reagents in further aminofunctionalization reactions

Despite the broad synthetic applicability of 2-haloamines,[15,16] the direct installation of other functionalities beside chloride remains



Scheme 5. Control reactions.

highly attractive in terms of atom and step economy. We thus set out to examine, in preliminary experiments, whether our methodology can be diverted to other aminofunctionalizations. Based on our group's development of a protocol for the synthesis of unprotected, primary amino alcohols,[22a] we investigated the use of the new reagents in the synthesis of amino alcohols. After a minor re-optimization of the reaction conditions,[19] we were pleased to find that 4-methoxystyrene could be converted to the *N*-methylamino alcohol **68**, an *O*-methylated derivative of the naturally occurring synephrine, in moderate yield (Scheme 6A). Recently, our group also developed an aminoazidation reaction of alkenes to directly obtain primary, unprotected 2-azidoamines.[22c] We hence sought to use the new reagents to directly access 2-azidoamines. A preliminary, unoptimized result delivered the desired product **70** in 51% yield (Scheme 6B).



Scheme 6. Versatile use of the new reagents. Yields are of isolated products. [a] ^{1}H NMR yield.

Encouraged by those results, we began to investigate other aminative difunctionalizations. We reasoned that the proposed carbon-centered radical intermediate could possibly be trapped by a heteroarene in a new type of carboamination reaction.[30] Indeed, when we used an alkene substrate with a tethered theophylline unit (**71**), the cyclized product **72** was obtained in good yield (Scheme 6C). This natural product could thus be transformed in two steps (alkylation followed by carboamination) into a highly functionalized, polycyclic derivative. This result demonstrates the possibility to trap the carbon-centered radical in an intramolecular fashion, thus opening new horizons for the development of amination reactions using these novel reagents. Overall, the wide range of possible aminofunctionalizations demonstrated with these new reagents clearly highlights their broad synthetic potential in the preparation of bioactive molecules.

Conclusion

In conclusion, we have developed reliable and scalable synthetic routes to access a series of novel aminating reagents for the installation of several amine groups, such as methylamine, morpholine and piperazine, that are prevalent in pharmaceuticals and other biologically active small molecules. The reagents were employed in the direct synthesis of unprotected secondary as well as tertiary 2-chloroamines starting from a broad variety of unactivated, functionalized alkenes. The reactions proceed under mild conditions and are highly chemo- and regioselective. A benign and inexpensive iron salt serves as the catalyst. The versatility of the new reagents was further demonstrated in *N*-alkylaminohydroxylation and -azidation, as well as carboamination of alkenes.

Acknowledgements

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Keywords: amination • alkenes • difunctionalization • iron catalysis • protecting-group-free

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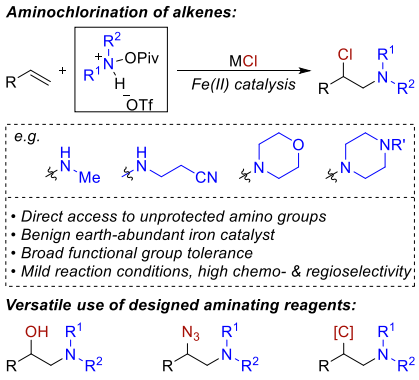

We report the direct synthesis of unprotected secondary and tertiary alkylamines from alkenes through an aminative difunctionalization reaction enabled by iron catalysis. A family of ten hydroxylamine-derived aminating reagents was designed for the installation of several medicinally relevant amine groups, such as methylamine, morpholine and piperazine, through the aminochlorination, -hydroxylation, -azidation and carboamination of alkenes.

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