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Iron Catalysis: Rust-Free Future

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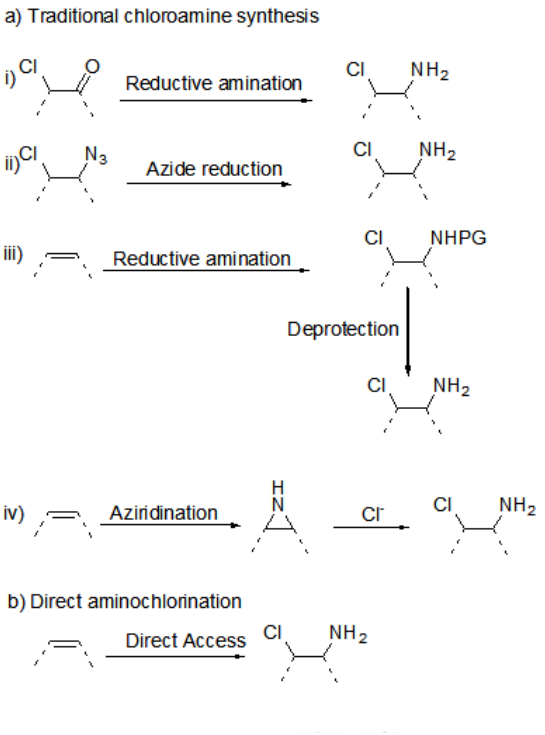
Abstract: The addition of nitrogen to carbon compounds is generally a laborious process. To prevent undesired reactivity of nitrogen generally it needs protection, and sometimes removal of protecting group can be difficult, and also use of protection-deprotection strategy is contrary to the ideality of organic transformations from the point of step- and atom-economy. Legnani et al. reported a resourceful method to add simple NH_2 to alkenes from a hydroxylamine derivative directly which is highlighted herein. A simple iron-catalyzed aminochlorination of alkenes using table salts as chloride source proceeds through a radical mechanism, where it is poised for a wide variety of further functionalization options.

The second most abundant metal on earth is Iron. It is a group 8 and period 4 element with electronic configuration [Ar] $3d^6 4s^2$. Iron as a metal is rarely found in nature because it oxidizes readily in the presence of oxygen and moisture to their corresponding oxide (commonly known as rust). The preferred oxidation state of iron is +2 and +3. Iron is the most common element on the Earth and thus is relatively cheap. Although the 2nd and 3rd-row transition metals have a long and developed history of achieving high yields and enantioselectivity for a large number of reactions compare to 1st row transition metals, the low price and novel reactivity of iron catalysts open up a new horizon in the field of catalysis for the valuable organic transformations.[1]

In order to live a beautiful and daily healthy life in people's daily lives we have to constantly fight various illnesses. The role of drugs is very important in relieving the diseases. Primary amines are necessary constituents of bioactive compounds and adaptable intermediates in the synthesis of drug and agrochemicals.[2] The classical synthesis of primary amine depends on reductive amination, the dehydrogenative coupling of alcohols, allylic amination, or azide or nitrile reduction. These traditional methods depend on the attachment of a polar group in the starting material, also have limits for the necessity of protection –deprotection of nitrogen, activation of olefin with an aryl group, or generation of hazardous azide intermediates (Scheme 1). Therefore, the preparation of primary amine from easily accessible alkenes is a challenging task. Herein, I have highlighted a recent effort to develop a highly efficient

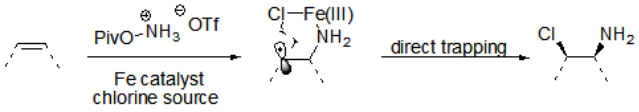
method for the aminochlorination of inactivated alkenes to achieve unprotected primary amine derivatives.[3]



Scheme 1: Comparison of selectivity in traditional chloroamine synthesis and direct aminochlorination.

A catalytic approach leads to both the desired unprotected amine group, preferably at the more demanding primary position, and a flexible electrophile at the secondary position which might prove especially useful for the synthesis of important compounds. In an ideal world, these products can be accessed through the usage of an easy protocol, cheaper reagents, and an Earth-abundant metallic catalyst. In precept, the unprotected 2-chloroalkylamines might behave as an amphoteric aminated building blocks. These apparently unstable compounds have hardly been reported in the literature[4], and the limited feasible synthetic methods to get them commonly depend on the direct chlorination of amino alcohols[5] or through the ring-opening reactions of NH-aziridines.[6] Occasionally, using stoichiometric protocols the aminochloro alkane derivatives protected by a tosyl (Ts) group can be accessed from alkenes, but these protocols are not perfect due to the difficult selective cleavage of the Ts group in the presence of the chloride and the absence of regioselectivity, in addition to poor scope and yield.[7–12] Bach et al. reported an intramolecular aminochlorination using iron-catalyst, however the products are chloro-substituted oxazolidinones instead of unprotected 2-chloroalkylamines.[13–15]

A proposed mechanism for the reaction contains three key features (Scheme 2). First, the formation of nitrogen centered radicals from the amine source in the presence of iron (II) catalyst. Second, generation of putative unstable radical intermediate[16] from the addition of a nitrogen-centered radical on a C=C double bond. Third, the rapid chlorine atom transfer from the amine-bound iron(III) complex[17] to form the desired product and regeneration of the iron(II) catalyst. The facile hemolytic substitution of the carbon radical with the iron bound chlorine atom certainly opens new vistas in iron-catalysis.

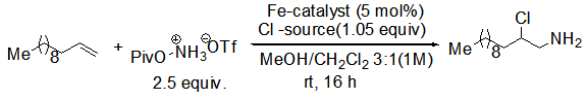


Scheme 2. Proposed mechanism.

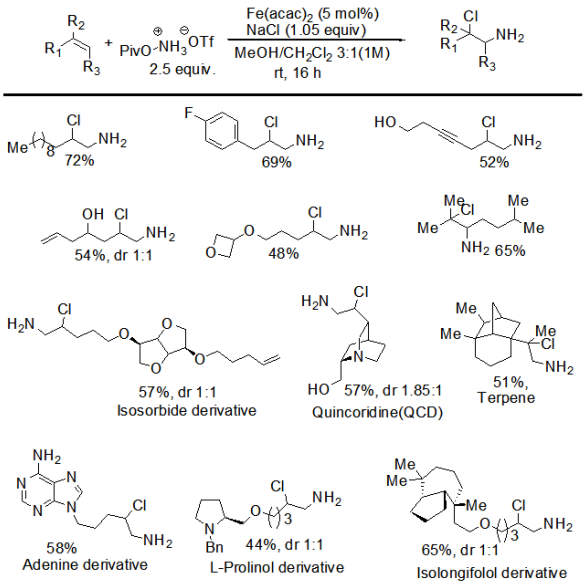
The optimal condition for the reaction was found when $Fe(acac)_2$ was used as a catalyst of choice, sodium chloride as a source of chloride, and a hydroxylamine-derived reagent as an amine source in a methanol-dichloromethane mixed solvent at room temperature (Table 1). Overall, this new approach to the challenge of selectivity in aminochlorination[18, 19] of alkenes offers a new avenue to access valuable aminochloro hydrocarbons under mild reaction conditions and using an economically profitable and environmentally benign iron catalyst. An impressive scope of this reaction,

as well as successful performance in more than two-gram scale, makes it attractive to the chemical community. The reaction is tolerant to a wide range of functional groups including unprotected polar functional groups (e.g. –CN, -OH and alkyne, etc.) that are traditionally problematic in transition metal catalysis giving the desired product in good yield (Scheme 3). Additionally, alkene compounds containing tertiary nitrogen center, tetrazole, oxetane, purine moieties also provide the corresponding products satisfactorily. The attractive feature of this reaction was the formation of the mono-functionalized product exclusively even in a case where more than one olefin double bonds were present in the substrate molecule. The entire basis of organic chemistry, and particularly organic synthesis, relies on selectivity that organic reactions can achieve. In broad terms, reaction selectivity can be described as the result of making a predominantly energetically favorable reaction path. Interestingly, the reaction is not restricted to mono-substituted alkenes, as both 1,1, and 1,2 di-substituted alkenes and even trisubstituted alkenes also provide the corresponding product in high yields. Unprotected 2-chloroalkylamine has unexplored reactivity and large synthetic utility, where it is poised for a wide variety of further functionalization options.

Table 1: Iron-catalyzed aminochlorination reaction

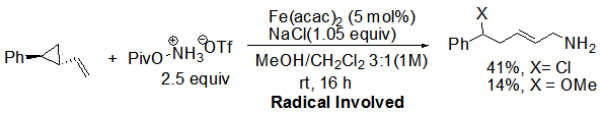


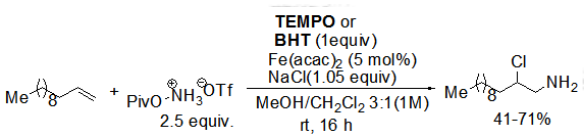
Entry	Catalyst	Catalyst loading	Chlorine source	Yield[%]
1	$FeCl_2$	1 equiv.		28
2	Fe(Phth)	5%	NaCl	0
3	$Fe(acac)_2$	5%	NaCl	72
4	$Fe(acac)_2$	5%	TMSCl	43



Scheme 3. Scope of the aminochlorination.

The chloro-group can be useful for various synthetic transformations which offer an avenue to access valuable organic compounds and synthetic intermediates. Furthermore, primary mechanistic investigation using one of the fastest radical clocks to detect the intermediacy of short-lived radical species approved the formation of radical intermediates, since the ring-opening product of cyclopropane was obtained and it was further supported by using radical scavenger TEMPO(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) or BHT (Butylated hydroxytoluene), did not influence on the reactivity of the alkene (Scheme 4). As cyclopropyl methyl radicals are known to readily undergo ring-opening,20 aminochlorination of alkenes follow the similar pathway. From the excerpt of these experiments, it is clear that, the rate constant of intramolecular chlorine atom transfer may be very faster.





Scheme 4. Radical trapping experiments.

Finally, economically cheap and simple iron –catalyzed aminochlorination reactions using a stable hydroxylamine derivative and sodium chloride under mild reaction conditions, like room temperature, under air and scope of reaction with a large variety of aliphatic and conjugated alkenes along with densely functionalized substrates provides 2-chloroalkyl amine products in high yields which opens a shiny door in iron catalysis. In this method, the excellent anti-Markovnikov regioselectivity with respect to the amino group was observed. The reactivity of 2-chloroalkyl amine towards various nucleophiles through the substitution of chlorine atom as well as electrophiles through the reaction of amino group allows facile access to linear or branched aliphatic amines, aziridines, azido amines, amino nitrile, homoallylic amines, and other valuable molecular scaffolds.

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