Electrophilic Amination of Organometallic Reagents: Recent Discoveries and Mechanistic Insights

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Abstract: Electrophilic amination constitutes a unique strategy for the synthesis of C–N bonds. One often-overlooked example of this type of process involves the reaction of organometallic nucleophiles with electrophilic nitrogen sources to yield aryl and alkyl amine derivatives. Such transformations are mechanistically intriguing and have the potential to drastically alter the logic by which nitrogen-containing compounds are synthesized.

Keywords: Amination, C–N bonds, electrophilic nitrogen, mechanism, organometallic reagents, umpolung.

INTRODUCTION

Methods for the synthesis of C–N bonds have received significant attention owing to the myriad of natural and unnatural products containing the amino functional group [1]. Traditional methods for the synthesis of amines largely involve the attack of nucleophilic nitrogen sources on electrophilic species. These include classical S_N2 and reductive amination methods in addition to transition metal-catalyzed Buchwald-Hartwig-type cross-couplings [2]. An alternative "umpolung" approach involving nucleophilic attack on an electrophilic nitrogen source has been known since 1938 [3], but until recently, remained largely unexplored. This strategy is the retrosynthetic complement to standard nucleophilic amination, and as a result, has the potential to greatly impact the evolution of chemical methods for the synthesis of nitrogen functionality.

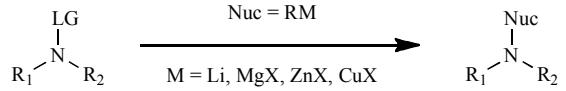


Fig. (1).

The power of this approach has already been realized using amines and enolates as the nucleophilic component, however, electrophilic amination of organometallics is a much more nascent field [4]. As this area of research has grown, intriguing mechanistic insights have been revealed. Ultimately, these fundamental discoveries may lead to the development of practical methods for the reaction of organometallic species with $R_1R_2N^+$ synthons (Fig. **1**), and thus, transform the way we envision constructing C–N bonds.

Reagents for the electrophilic amination of organometallics can be divided into two classes: those that involve nucleophilic attack occurring formally at an sp^2-hybridized nitrogen (Fig. **2a**) and those that result in attack occurring at an sp^3-hybridized center (Fig. **2b**). This brief review will initially explore reactions of the former class of electrophiles before discussing the latter along with their potential advantages.

ATTACK ON sp^2-HYBRIDIZED ELECTROPHILES

Aryl organomagnesium as well as aryl and alkyl organozinc reagents have been shown to add to diazene electrophiles of general structure **1** [5]. Additions to di-*tert*-butyl azodicarboxylate and arylazo tosylates afford primary and secondary amines, respectively, after manipulation of the intermediate hydrazino compounds (Scheme **1**). Interestingly, attack on the unsymmetrical arylazo tosylates occurs regioselectively at the nitrogen bearing the aryl

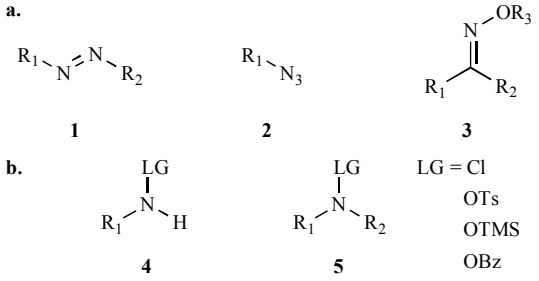
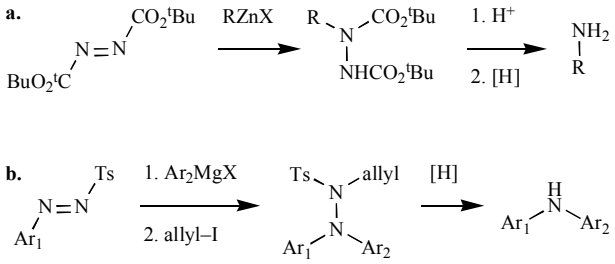


Fig. (2).

group, presumably due to the polarization of the unsymmetrical azo group. Functional groups such as aryl halides and triflates can be tolerated under these electrophilic amination conditions, thus highlighting the complementarity of these methods to Buchwald-Hartwig-type cross-couplings [2]. While appealing, these methods require additional steps to convert the initially formed hydrazines to the corresponding 1° and 2° amines. However, the ability to perform the addition reaction as well as the subsequent N–N bond reduction [6] in a single reaction vessel would serve to facilitate the application of this chemistry.



Scheme 1.

As with diazene-based electrophiles, organoazides will undergo addition of organometallics to form intermediates that can be cleaved to reveal the desired amine products [7]. Trost and Pearson have demonstrated that azidomethylphenyl sulfide (**6**) will react regioselectively with Grignard reagents to form triazene structures [8]. Such intermediates can be converted to the corresponding protected amines following acylation and N–N bond cleavage. More recently, Hoffmann and co-workers observed that reaction of **6** with an optically active Grignard reagent occurred with complete retention of configuration (Scheme **2b**) [9].

Retention of stereochemical configuration in this transformation is noteworthy because electrophilic amination of Grignard reagents could proceed via either a polar mechanism or a single electron transfer (SET) process. A polar mechanism would be expected to

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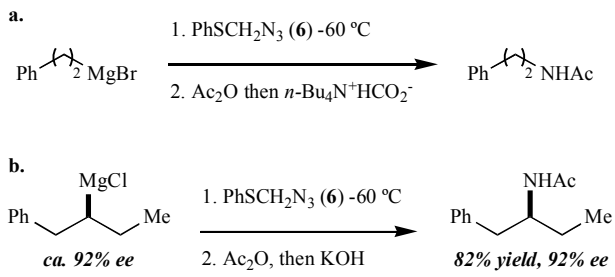
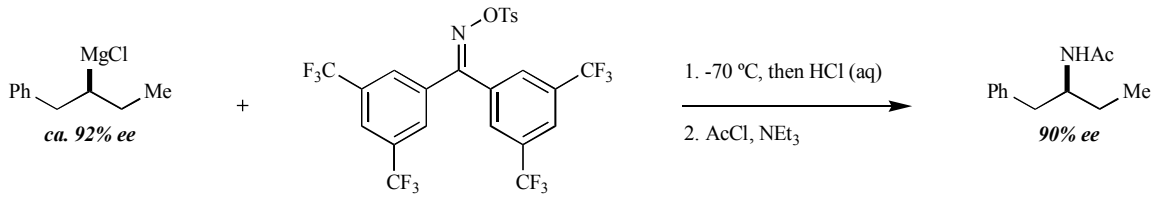


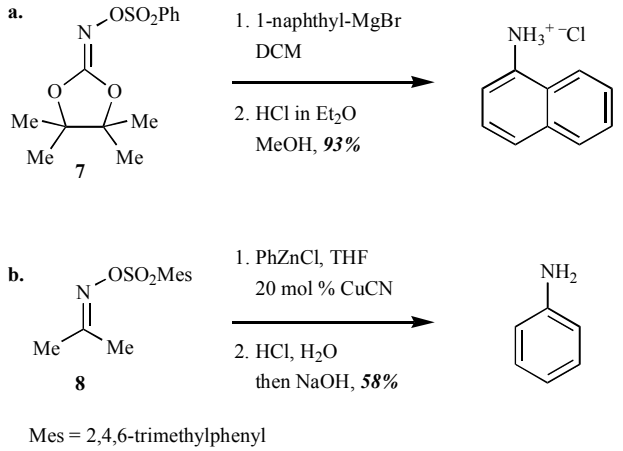
Scheme 2.



Scheme 3.

occur stereospecifically, while an SET process would likely result in significant, if not complete, stereo-erosion [10]. Interestingly, Hoffmann has made a similar observation using an electrophilic oxime reagent of type **3** (Scheme **3**), again suggesting that a polar mechanism is operative. This result is particularly provocative because it suggests the possibility of an S_N2 reaction occurring at an sp^2-hybridized atom [11].

The energetic barrier associated with an S_N2 displacement at an sp^2-hybridized atom might be expected to be significant. As a result, undesired side reactions such as nucleophilic addition to the oxime, α-deprotonation, and Beckmann rearrangement could become competitive. Accordingly, Narasaka and co-workers developed **7**, a nitrogen source that is not prone to such undesired side reactions (Scheme **4a**) [12]. Similarly, Erdik and co-workers found acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime (**8**) to be suitable for the electrophilic amination of organozinc reagents. Reactions with **8**, however, only took place in the presence of a catalytic amount of CuCN (Scheme **4b**) [13]. While experiments using stereodefined Grignard reagents suggest that these nucleophiles undergo electrophilic amination through a polar process, the same experiments were not performed with zinc cyanocuprates. As a result, the possibility that zinc cyanocuprates react through an SET pathway cannot be discounted.



Mes = 2,4,6-trimethylphenyl

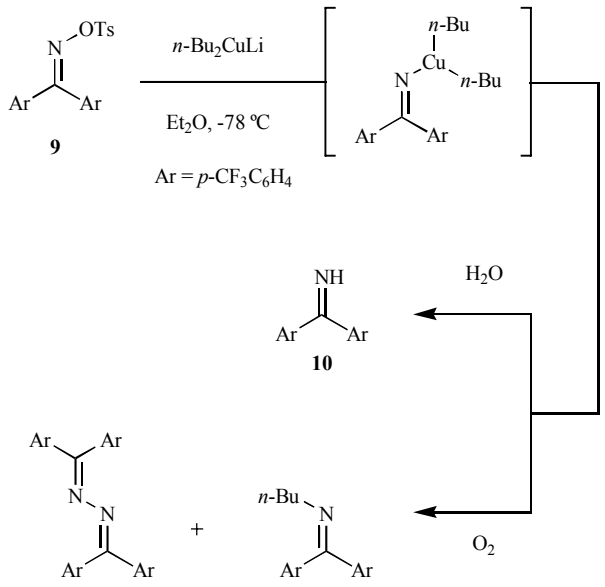
Scheme 4.

The examples highlighted above together with Hoffman's earlier observations (see Schemes **2** and **3**) prompted a more systematic study of the mechanism by which substitution at sp^2-hybridized nitrogens occurs [14]. Hammett analysis of reactions between **8** and either Grignard reagents or zinc cyanocuprates revealed that electrophilic amination was accelerated when either type of organometallic was substituted with electron-donating substituents. However, the magnitude of the ρ-values for these processes differed significantly (−2.94 and −0.84 for Grignard reagents and zinc cyanocuprates, respectively). Erdik and Ömür have suggested that this result reflects a change in mechanism between the two types of reactions. Both classes of organometallics exhibit nucleophilic character, though Grignard reagents are significantly more reactive in this regard. Currently, it is believed that Grignard reagents react with *O*-sulfonyl oximes through direct S_N2 displacement, while reactions using zinc cyanocuprates operate by way of an oxidative addition/reductive elimination pathway [14].

Theoretical evidence for an intramolecular S_N2 displacement at an sp^2-hybridized nitrogen atom has been provided by Nakamura and co-workers [15]. Post-Hartree-Fock *ab initio* calculations (MP2(FC)/6-31G*) indicate that an S_N2 mechanism for this process is energetically feasible with an activation barrier of only 8.8 kcal mol^{-1}. In fact, related S_N2 reactions at sp^2-hybridized carbon centers have also been studied and are supported by theory [16]. Nevertheless, it would seem that more experimental evidence is needed to make definitive statements about the mechanism of Grignard substitution at the nitrogen atom of an *O*-sulfonyl oxime. Complete inversion at the nitrogen center of a stereo-defined unsymmetrically substituted ketoxime would lend credence to this mechanistic proposal, but to the best of my knowledge, such an experiment has not been described.

While evidence for the S_N2 reaction of Grignard reagents with **8** is largely theoretical, the oxidative addition/reductive elimination pathway for lithium dialkylcuprates is supported experimentally. For instance, the reaction of lithium dibutylcuprate with **9** provided imine **10** in high yield upon aqueous workup (Scheme **5**). This formal reduction of the N–O bond could have proceeded through the protonation of a putative Cu(III) intermediate. Furthermore, if instead O_2 was bubbled through the reaction mixture, reductive elimination could be induced to give both the desired butyl imine and the homo-coupled hydrazone, thus lending additional support for the intermediacy of a Cu(III) species.

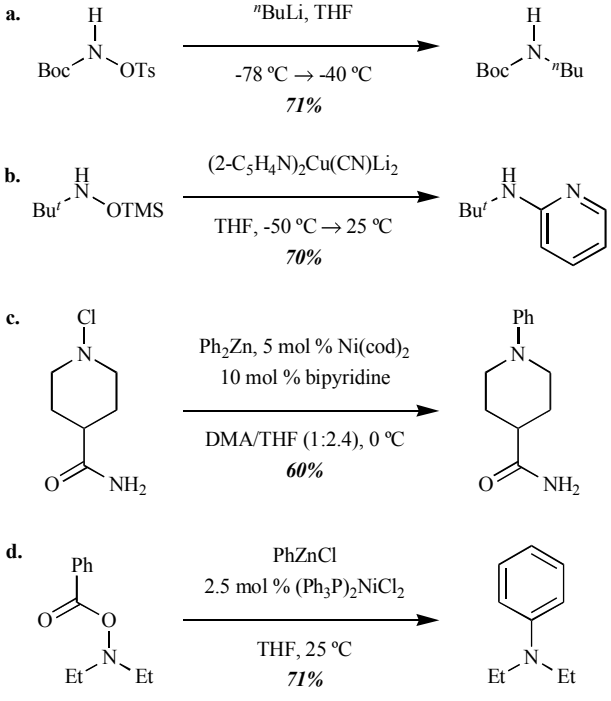
Although several of the mechanistic details by which various organometallic species react with reagents such as **7, 8,** and **9** remain ambiguous, it is clear that the nature of the nucleophile can greatly influence the reaction pathway. Regardless, these substituted oximes belong to a class of electrophiles (Fig. **2a**) with many inherent disadvantages. First, such sp^2-hybridized electrophilic aminating reagents require subsequent manipulations to unveil the desired amine products, and as a consequence, syntheses that utilize them suffer from poor atom and step economy. Second, their use is generally limited to the synthesis of primary amines. Fortunately, an alternative approach for preparing functionalized amines involving the use of electrophilic sp^3-hybridized nitrogen sources (see Fig. **2b**) does not suffer from these problems. The details of such processes, with a specific focus on reaction mechanism, will be discussed in the next portion of this review.



Scheme 5.

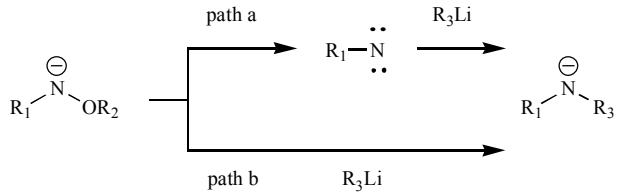
ATTACK ON sp^3-HYBRIDIZED ELECTROPHILES

The reaction of organometallic reagents with electrophilic sp^3-hybridized nitrogen sources has been shown to yield protected primary amines in addition to the more challenging to access secondary and tertiary amines (Scheme **6**) [17]. These electrophiles can possess various leaving groups including chlorides, alkoxides, sulfonates, and benzoates. Furthermore, this class of electrophilic aminating reagents can be subdivided based on the mechanism by which they undergo substitution. This distinction is highly dependent on whether or not the electrophile contains at least one ionizable proton at nitrogen.



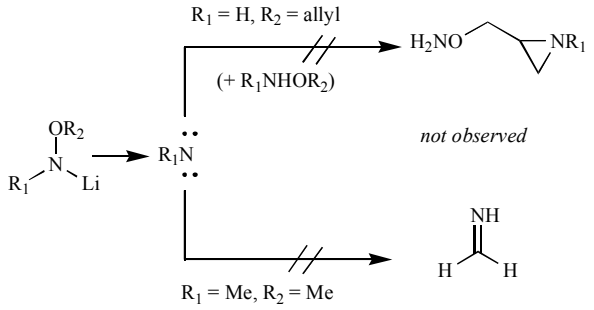
Scheme 6.

The mechanistic details by which reagents with the general structures R_1HN–LG (**4**) and R_1R_2N–LG (**5**) react with organometallics have been the subject of numerous reports (*vide infra*). One of the more interesting mechanistic subtleties involves the reaction of alkyl lithiums with *O*-substituted hydroxylamines bearing at least one proton on nitrogen (**4**). Electrophilic aminations of this type require two equivalents of organolithium reagent, presumably due to initial deprotonation of the hydroxylamine. The resulting lithium alkoxyamide can then either undergo α-elimination to form a highly reactive nitrene that is intercepted by a second equivalent of organometallic reagent (Scheme **7**, path a), or it can undergo direct substitution (Scheme **7**, path b). The latter mechanistic proposal is particularly intriguing, and somewhat counterintuitive, because it involves carbanion attack at a center that is formally anionic.



Scheme 7.

Beak and co-workers have published several studies on the mechanism of RHN–LG substitution with organometallic reagents, and they have concluded that free nitrenes are not intermediates on the reaction coordinate [18]. Several pieces of evidence support this conclusion. First, byproducts characteristic of reactions involving nitrenes were not observed. These include aziridines when *O*-allyl hydroxylamine is used as a starting material, or products resulting from a 1,2-hydrogen migration in reactions with *N*-methylmethoxyamine (Scheme **8**) [19]. Second, endocyclic restriction tests along with deuterium labeling studies suggest that the nucleophile and leaving group prefer to be disposed 180º from each other in the transition state.



Scheme 8.

Theoretical calculations have provided several explanations as to why substitution by a formal anion at a negatively charged sp^3-hybridized nitrogen would proceed as the favored pathway [20]. First, calculations suggest that the N–O bond of the lithium alkoxyamide (LiNHOR) is significantly more polarized than that of the neutral hydroxylamine (NH_2OR). Theory also suggests that a lithium-bridged structure is responsible for the lengthening of the N–O bond (Fig. **3b**) [21]. In addition, the aggregation state of the reactants is likely to play a large role in facilitating this reaction. Examples of such complex-induced proximity effects (CIPE) are well known [22]. Furthermore, these effects can often be disrupted by the addition of hexamethylphosphoramide (HMPA) as a cosolvent due to its strong propensity to coordinate lithium. An experiment where an electrophilic amination is performed in the presence of HMPA would be quite informative and shed some light on the importance of these putative aggregates.

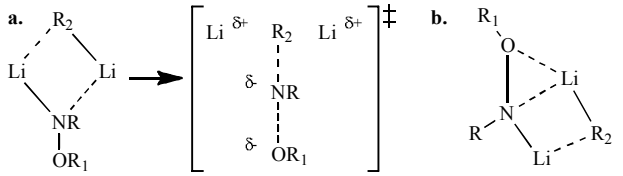
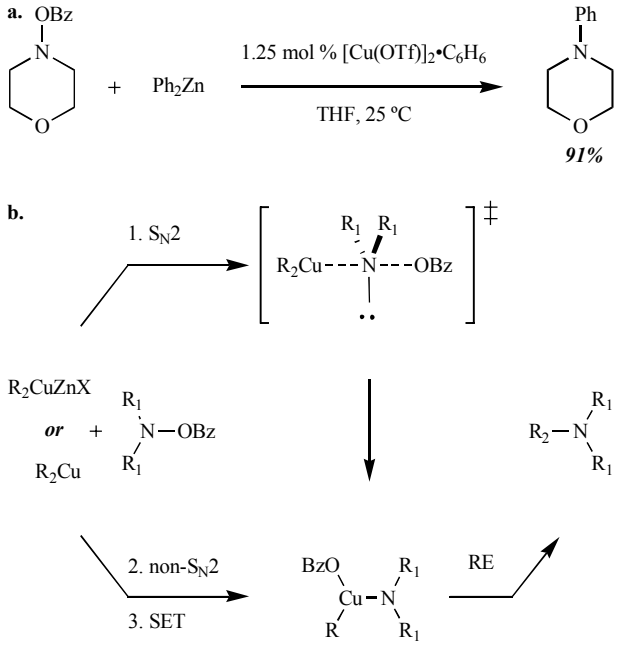


Fig. (3). (**a**) Original transition structure for hydroxylamine substitution as proposed by Beak [18d] (**b**) Transition structure supported by *ab initio* S.C.F. M.O. calculations.

Whereas *O*-alkyl hydroxylamines seem to require activation toward nucleophilic attack by initial deprotonation and subsequent bridging of the N–O bond, *N,N*-dialkyl hydroxylamines possessing good leaving groups (such as sulfonate or benzoate) require no such activation. These latter reagents have become popular electrophiles used in the synthesis of tertiary amines [17d,h-j].

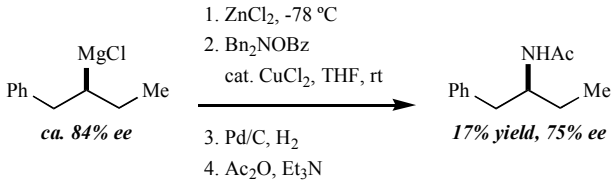
Initial kinetic studies on the reaction of *O*-(mesitylsulfonyl)-*N,N*-dimethylhydroxylamine with Grignard reagents has revealed a first order dependency on Grignard reagent [23]. In addition, the negative ρ and $\Delta S^{\ddagger}$ values obtained from Hammett and Eyring analyses, respectively, are consistent with a direct S_N2 pathway.

In contrast, the Cu-catalyzed amination of alkyl zinc reagents with *O*-(benzoyl)-*N,N*-dialkylhydroxylamines, recently reported by Johnson and co-workers [17j] (Scheme **9a**), is likely to proceed by a mechanism involving initial oxidative addition to the N–O bond followed by reductive elimination to form product [24]. The first step, oxidative addition between the organocopper species and the *O*-(benzoyl)-*N,N*-dialkylhydroxylamine, can potentially occur through several distinct mechanisms, such as direct S_N2 displacement by the Cu complex, σ-complexation followed by concerted insertion into the N–O bond, or SET-mediated oxidative addition (Scheme **9b**).



Scheme 9.

The first piece of evidence in support of oxidative addition occurring through an S_N2 mechanism was the fact that only 9% racemization was observed when Hoffmann's stereodefined organometallic reagent was employed (Scheme **10**) [24a]. Johnson and Campbell claim that significantly greater racemization would be expected if radical species were involved, and this contention is supported by the work of Hoffmann and co-workers [10]. Furthermore, the degree of stereoerosion was comparable to a related reaction involving the conjugate addition of a cuprate to an enone [25]. Both the electrophilic amination and the conjugate addition required Mg to Zn and Zn to Cu transmetallation steps, suggesting that these manipulations could be the common source of stereoerosion. However, it should be noted that 9% stereoerosion is still significantly greater than what is observed for related reactions using Grignard reagents (Schemes **2** and **3**). Therefore, it cannot be discounted that polar and SET mechanisms are operating concurrently, thus giving rise to less than ideal retention of configuration.



Scheme 10.

The fact that the Cu-catalyzed amination of alkyl zinc reagents with *O*-(benzoyl)-*N,N*-dialkylhydroxylamines proceeds with significant retention of configuration suggests that radicals are most likely not involved in the oxidative addition step. However, it does not distinguish between potential S_N2 and concerted mechanisms. Fortunately, these oxidative addition pathways can be differentiated based on their varying stereoelectronic requirements. For example, an intramolecular S_N2 reaction would have to proceed through a 6-*endo-tet* transition state (Fig. **4a**), which is disfavored according to Baldwin's rules. However, formation of a σ-complex (Fig. **4b**) followed by oxametalacyclopentane formation would be geometrically and stereoelectronically feasible according to Johnson and Campbell [24]. Therefore, an endocyclic restriction test was performed to determine which of these two scenarios was operative (Scheme **11**).

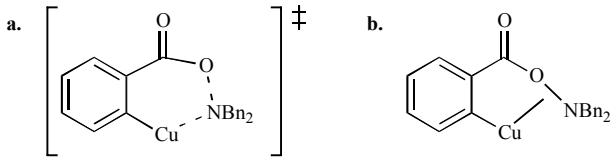
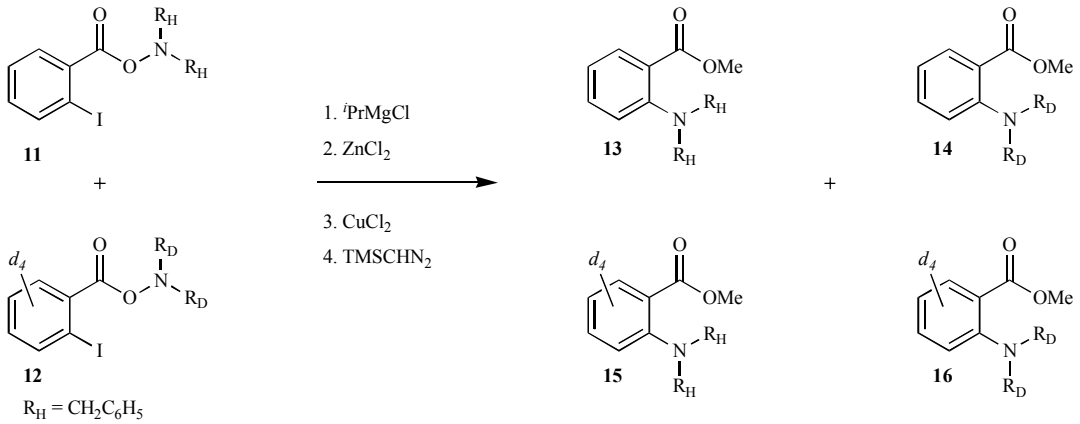


Fig. (4).

When the reaction was performed with differentially labeled starting materials (**11** and **12**), the crossover products (**14** and **15**) were obtained in a near statistical ratio along with the non-crossover products (**13** and **16**). This result strongly suggests that the reaction occurs intermolecularly presumably through an S_N2-like transition state [26]. These mechanistic insights could prove useful in the refinement of related electrophilic amination methodologies.

CONCLUSIONS

Detailed studies concerning the electrophilic amination of organometallic reagents have revealed many unexpected mechanistic curiosities such as direct S_N2 displacement at sp^2-hybridized centers and proximity-induced reaction of two negatively charged species. Only an understanding of such fundamental processes will enable these methods to move toward becoming practical approaches for the synthesis of amine-containing molecules. Although still in its infancy, the unique retrosynthetic disconnects that it affords coupled with its operational simplicity make the electrophilic amination of organometallic reagents a strategy with clear potential to greatly impact chemical synthesis.



Scheme 11.

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