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Direct β-C(sp^3)−H Functionalization of Aliphatic Amines to α,β-Unsaturated Imines, Aldehydes, and Chromenes

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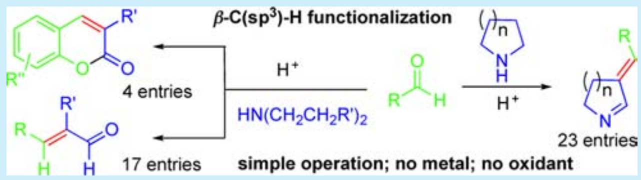
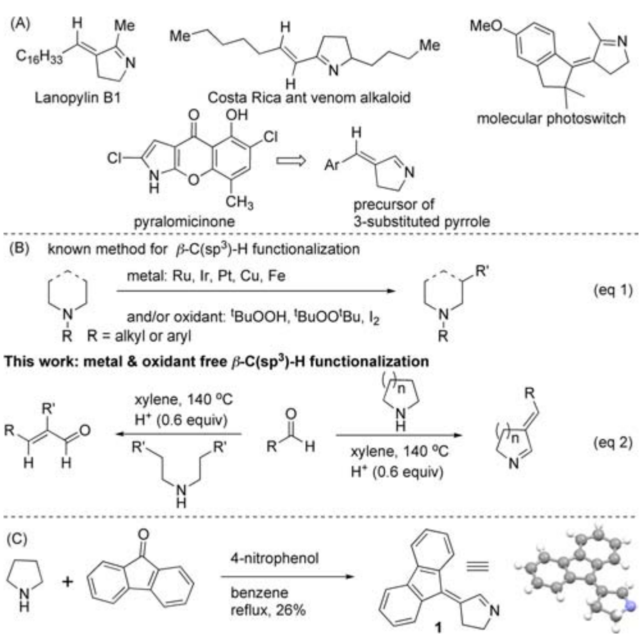
Ⓢ *Supporting Information*

ABSTRACT: A metal-free method for direct β-C(sp^3)−H functionalization of aliphatic amine was developed. The method is based on a reaction that yields enamine directly from the corresponding aliphatic amine, which otherwise requires the aid of metallic reagent and/or external oxidant. The reaction is operationally simple, general, and highly efficient in functionalizing both cyclic and acyclic amines. Structurally diverse unsaturated imines were obtained from *N*-heterocycles, while acyclic amines provided 2-alkyl cinnamaldehyde and benzopyran derivatives with excellent *E*/*Z*-selectivity.



Aliphatic amines with varied functionalization are key structural motifs of many biologically important molecules of natural and synthetic origin.[1] In this regard, α,β-unsaturated imines are of particular interest because they can participate in different reactions, producing various functionalized amines.[2] Moreover, different bioactive molecules are decorated with this moiety (Scheme 1A). The relevant examples include a class of natural products having an α,β-unsaturated pyrroline unit, lanopylin B1 and their derivatives, acting as a human lanosterol synthase inhibitor.[3] A similar structural motif was found in the alkaloid isolated from the venom of the Costa Rican ant.[4] Further, α,β-unsaturated pyrrolines are direct precursors of the β-substituted pyrrole derivatives, and thus, these can be used for the syntheses of pyrrole-based natural products.[5] In addition to biological significance, the α,β-unsaturated pyrroline moiety is also very important in material chemistry in the context of the development of biomimetic molecular photoswitches.[6]

Scheme 1. (A) Natural and Synthetic α,β-Unsaturated Imines; (B) β-C(sp^3)−H Functionalization of Aliphatic Amine; (C) First Result for Metal- and Oxidant-Free β-C(sp^3)−H Functionalization



Various synthetic methodologies were developed for the preparation of functionalized aliphatic amines.[7] Direct C−H functionalization of suitable saturated amines has become the method of choice in synthesis.[8] This strategy provides products with desired complexity, in a single step, avoiding the additional step(s) to preactivate or prefunctionalize the substrates. In this context, α-C−H functionalization of amine has dominated the field.[7,8] On the other hand, although indirect pathways are known for the preparation of β-functionalized amine,[9] reports on direct functionalization of more challenging β-C(sp^3)−H bonds are very few.[10] Reactions primarily using metal- and/or oxidant-based reagent/catalyst were employed to achieve direct β-C(sp^3)−H functionalization of amines (Scheme 1B). Moreover, removal of the *N*-protecting group, which is essential in metal-mediated C−H functionalization, is required for further application of functionalized amines. The known reaction on β-C−H functionalization without metal and oxidant necessitates the use of suitably prefunctionalized amine as substrate.[11] Development of novel methodology that operates under metal- and oxidant-free conditions for direct β-functionalization of aliphatic amine is desirable. Herein, we report a metal- and oxidant-free novel method for direct β-C(sp^3)−H functionalization of aliphatic amines. Cyclic aliphatic secondary amines produced α,β-unsaturated imines, while α,β-unsaturated aldehydes and chromenes were obtained from acyclic amines.

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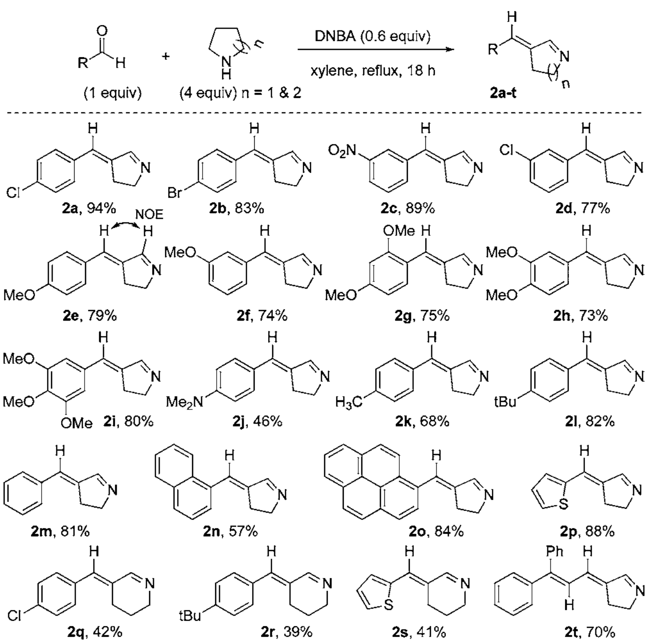
During the development of direct α-C−H arylation of amine,[12] we reacted pyrrolidine in the presence of 9-fluorenone and *p*-nitrophenol in refluxing benzene (Scheme 1C). However, we observed that, instead of the desired C−H arylated product, compound **1** was formed with 26% yield. We realized that the reaction will provide the opportunity to achieve direct β-C−H functionalization of aliphatic amines under simple reaction conditions without using metal- or oxidant-based reagents or catalyst. Furthermore, the method will have potential to provide privileged structures in a single step without using preoxidized or prefunctionalized substrates. Therefore, we investigated the reaction further. Reaction conditions varying the additives, solvents, reaction times, and temperatures were examined to optimize the reaction of *p*-chlorobenzaldehyde with pyrrolidine (see the Supporting Information, Table S1). The best yield (94%) of desired product **2a** was obtained in a reaction of aldehyde with pyrrolidine (4 equiv) in the presence of 3,5-dinitrobenzoic acid (DNBA, 0.6 equiv) in refluxing xylene. The isolated product was found to have the double bond exclusively with *E*-configuration.

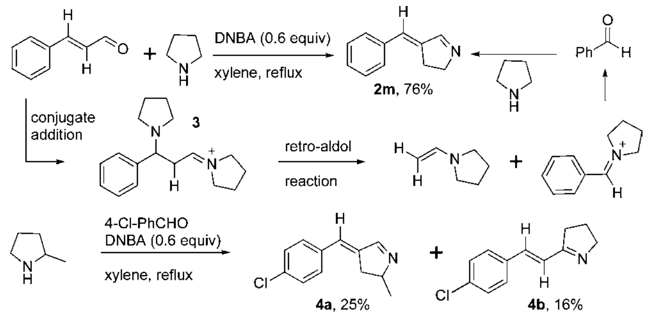
The optimized reaction conditions were employed to investigate the substrate scope of the reaction. Various aldehydes containing a wide range of functional groups were reacted with different *N*-heterocycles providing structurally diverse α,β-unsaturated imines **2a−t** (Scheme 2). Aldehydes

Scheme 2. Scope in Synthesis of α,β-Unsaturated Imines



with or without an electron-donating or electron-withdrawing substituent in the aryl moiety were equally efficient in providing corresponding β-functionalized amines. Moreover, the reactions worked well with aryl aldehydes having substituents irrespective of their position *ortho*, *meta*, and *para* to aldehyde moiety. Heteroaromatic aldehyde also provided the desired imine **2p** with excellent yield (88%). Lower yields of imine derivatives (**2q−s**) were obtained by functionalizing piperidine.[13] Similarly, cinnamaldehyde derivative was also employed successfully to obtain conjugated imine **2t** with very good yield. To our surprise, dehomologation occurred, producing pyrroline **2m** with 76% yield, while cinnamaldehyde was reacted with pyrrolidine under the standard reaction conditions (Scheme 3).

Scheme 3. Unusual Reactivity of Cinnamaldehyde and Reaction of 2-Methylpyrrolidine



Retro-aldol reaction is proposed to rationalize this observation.[14] In the presence of excess pyrrolidine, cinnamaldehyde probably participated in conjugate addition to provide β-amino iminium ion derivative **3**. Subsequently, **3** underwent retro-aldol reaction forming benzaldehyde or its corresponding iminium ion, which reacted with pyrrolidine under standard reaction conditions providing pyrroline **2m**.

The reaction with 2-substituted pyrrolidine was investigated next. Accordingly, *L*-proline was reacted with *p*-chlorobenzaldehyde under optimized reaction conditions. However, decarboxylation occurred and compound **2a** (10%) was isolated along with other undesired derivatives (Scheme S1, eq 1). On the other hand, two regioisomeric conjugated imines **4a** and **4b** were obtained from 2-methyl pyrrolidine (Scheme 3).

With the success in functionalizing aliphatic *N*-heterocycles, we turned our attention to acyclic saturated secondary amines as the potential substrates for β-C−H functionalization. We set the first reaction of *N*,*N*-dibutylamine with *p*-chlorobenzaldehyde under the reaction conditions optimized for *N*-heterocycles. However, the homologated unsaturated aldehyde **6a** was isolated with 50% yield instead of desired unsaturated imine **5** (Scheme 4 and Scheme S2). Unsaturated aldehydes were widely used in organic synthesis for the preparation of bioactive natural and unnatural compounds.[15] Specially, 2- alkyl-substituted cinnamaldehyde derivatives find direct application in the perfume and cosmetic industry.[16] Syntheses of these compounds, primarily via cross-aldol reaction, remained inefficient due to the associated undesired self-condensation and polymerization reaction.[17] These complications could be potentially avoided during their syntheses via this operationally simple method utilizing amine as the formal aldol donor. Therefore, we looked further to optimize (Table S2) and investigate the scope of the reaction. Different dialkylamines were reacted with various aldehydes providing structurally diverse 2-alkylated cinnamaldehyde derivatives **6a−q** (Scheme 4). Many of them can be considered as potential aroma substances for use in the fragrance industry. In particular, hexyl cinnamal (**6l**) is a natural aroma found in the essential oil of chamomile and used in perfume. This compound was prepared from benzaldehyde and dioctylamine in a single step without using metal- or oxidant-based reagents. Conjugated aldehydes were found to have thermodynamically more stable *E*-geometry in the double bond. However, mixtures of *E*- and *Z*-isomers were found for aldehyde **6g** and dienals **6p** and **6q**. Interestingly, coumarin and/or chromene-2-ol derivatives

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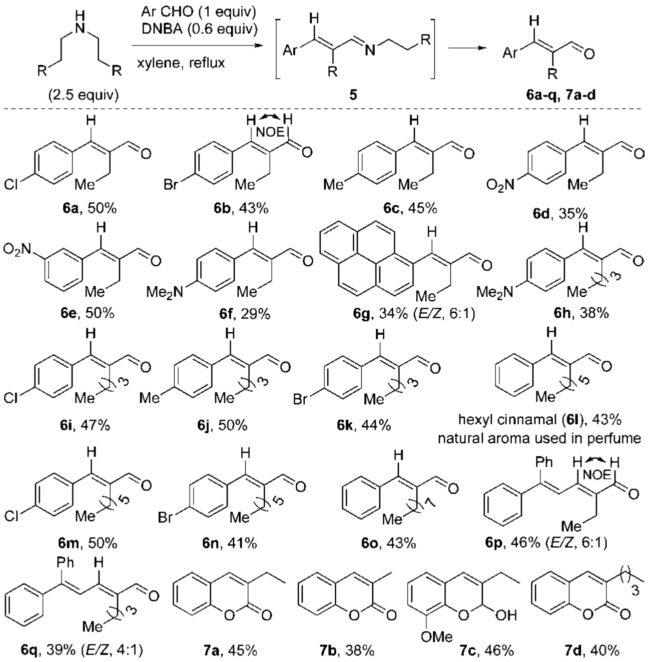
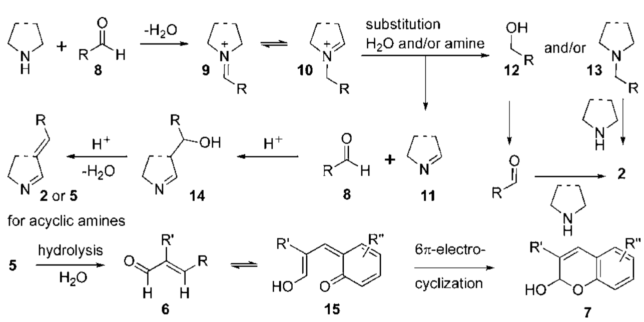
Scheme 4. Scope in Synthesis of 2-Alkylated Cinnamaldehyde



(**7a−d**) with a *Z*-double bond were obtained on reaction with 2-hydroxyaryl aldehydes. As these compounds belong to an important class of heterocycles having biological importance,[18] salicylaldehyde derivatives were reacted with different dialkyl amines to obtain structurally diverse benzopyran derivatives (**7a−d**). 2-Alkylcoumarins were obtained from the reaction of salicylaldehyde, while *o*-vanillin gave chromene-2-ol as the major product.

On the basis of the experimental findings, a mechanistic proposal for the metal- and oxidant-free direct *β*-C−H functionalization of secondary amine is presented in Scheme 5. Aldehyde **8** condensed with secondary aliphatic amine

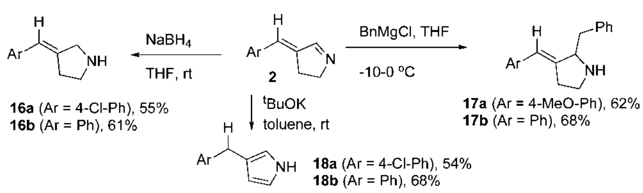
Scheme 5. Mechanistic Proposal for Direct *β*-C(sp^3)−H Functionalization



providing iminium ion **9**, which then rearranged to isomeric iminium ion **10**. Nucleophilic substitution reaction occurred at the benzylic or allylic position of **10** to release imine **11** and benzyl alcohol **12** or benzyl amine **13**. Subsequent reaction of enamine, formed from imine **11**, with aldehyde **8** provided the desired *α*,*β*-unsaturated imine **2** via intermediate alcohol **14**. For acyclic amine, the corresponding unstable imine **5** underwent hydrolysis providing conjugated aldehyde **6**. For salicylaldehyde-based substrates, the hydroxy group promoted intramolecular cyclization providing chromene-2-ol that underwent subsequent oxidation to coumarin derivatives **7**. Ring closing occurred either via thermal 6*π*-electrocyclization of *o*-quinone methide **15** or through intramolecular hemiacetalization (Scheme S2).[19] Attempts were made to isolate benzyl amine **13** as the support for the mechanistic proposal. Tertiary amine **6aa** corresponding to **13** was isolated along with the conjugated aldehyde **6a** (see Table S2). We thought that benzyl pyrrolidine **13** and benzyl alcohol **12**, which were not detected, probably reacted further, giving desired imine **2**. As a test for this, we found that, under the same reaction conditions, benzyl alcohol and benzyl pyrrolidine reacted separately in the presence of pyrrolidine to provide the desired imine **2m** (Scheme S1, eq 2 and 4). A considerable reduction of yield (to 46%) of **2a** was observed in a reaction performed under argon atmosphere (Table S1, entry 17). Therefore, the direct reaction of imine **11**, formed via aerial oxidation of pyrrolidine,[20] with aldehyde also contributed to the yield of **2** (Scheme S2). However, the experiment in the presence of radical inhibitor (BHT) did not show significant decrease in the yields of the desired product (Table S1).

Functionalized heterocycles obtained via this method can be further derivatized in a varied way to provide valuable products. For example, the imine functionality of **2** was reduced to afford allylic amines **16a** and**16b** (Scheme 6). Addition of

Scheme 6. Further Reactions of *β*-Functionalized Pyrrolidines



benzylmagnesium chloride furnished *α*,*β*-difunctionalized amines **17a** and **17b** with very good yields. Furthermore, valuable 3-substituted pyrrole derivatives **18a** and **18b** were obtained via base-mediated aromatization of the corresponding *β*-functionalized imines.

We have discovered a novel method for the direct *β*-C−H functionalization of aliphatic amines. Enamines were formed in situ directly from corresponding aliphatic amines without the aid of metal-based reagents and external oxidant. The method is general as it functionalizes both cyclic and acyclic saturated amines. Cyclic aliphatic amines provided biologically as well as synthetically important *α*,*β*-unsaturated imines with good to excellent yields and excellent *E*-selectivity. As the formal aldol donor, acyclic amine reacted with aldehyde under simple reaction conditions producing a series of 2-alkylcinnamaldehyde and chromen-2-ol/-one derivatives including natural aromas.

■ ASSOCIATED CONTENT

Supporting Information

Tables, additional schemes, experimental details, spectral data of all compounds, and X-ray data for compound **1** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01744.

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Notes

The authors declare no competing financial interest.

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