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Direct Access to Primary Amines from Alkenes by Selective Metal-Free Hydroamination

*Yi-Dan Du, Bi-Hong Chen, and Wei Shu**

Dedicated to the 100th anniversary of Chemistry at Nankai University

Abstract: *Direct and selective synthesis of primary amines from easily available precursors is attractive yet challenging. Herein, we report the rapid synthesis of primary amines from alkenes via metal-free regioselective hydroamination at room temperature. Ammonium carbonate was used as ammonia surrogate for the first time, allowing for efficient conversion of terminal and internal alkenes into linear, α-branched, and α-tertiary primary amines under mild conditions. This method provides a straightforward and powerful approach to a wide spectrum of advanced, highly functionalized primary amines which are of particular interest in pharmaceutical chemistry and other areas.*

Aliphatic primary amines serve as substructure in a wide variety of drug molecules, textiles, agrochemicals, and materials as well as precursors for secondary, tertiary amines, and other functional groups.[1–3] Significant numbers of molecules among the top-200 best-selling drugs are aliphatic amine derivatives (Figure 1a).[2c] Thus, primary amines are extremely important in chemistry and material sciences, but the selective synthesis is challenging due to their high reactivity.[1,4] Classical means to access aliphatic primary amines include S_N2 substitution of alkyl (pseudo)halides with excess ammonia,[5] Gabriel reaction,[6,7] Staudinger reaction,[8] and reduction of alkyl nitro groups,[9] nitriles,[10] oximes or imines[11] (Figure 1b). While these methods are well-established, they suffer from some of the following limitations: 1) Selectivity over primary, secondary, and tertiary amines is difficult to control. 2) Limited to linear and α-branched primary amines, more sterically demanding α-tertiary primary amines are inaccessible. 3) Tedious multistep process is employed. 4) Harsh reaction condition is needed. 5) Advanced and/or toxic precursors are required. To date, general and modular assembly of aliphatic amines from easily available and abundant functional groups in a selective and step-economic fashion is highly desirable. Alkenes are easily available and manufactured on very large scale during petroleum refining. In addition, the orthogonal reactivity of alkenes over other polar functional groups provides opportunities for accessing molecular complexity and late-stage functionalization.[12] In light of these benefits, metal-catalyzed alkene hydroamination has been extensively studied for decades with tremendous advances.[13,14] Methods for the intermolecular coupling of unactivated alkenes with amine source to generate aliphatic primary amines are currently unknown.[15]

In 2018, Buchwald's group reported an elegant example of a two-step procedure via copper-catalyzed hydroamination of olefins to primary amines, using isoxazole electrophiles as latent amine equivalent.[16] This reaction led to benzylic primary amines from styrenes and linear primary amines from aliphatic olefins.[17] Due to the steric hindrance and low bonding affinity of tri- and tetra-substituted alkenes to the metal center, sterically demanding α-tertiary primary amines are inaccessible.[18] Recently, Knowles' group reported a seminal work on photocatalytic coupling of primary or secondary amine with alkenes, providing a facile approach to secondary or tertiary aliphatic amines, respectively (Figure 1c).[19] These protocols produce an aminium radical cation intermediate through single electron oxidation of primary or secondary amines, and are thus not applicable to the direct synthesis of primary amines. A general and straightforward method for the direct synthesis of primary amines from alkenes with a nontoxic and cost-effective ammonia source, in particular, for more challenging α-branched and α-tertiary primary amines remains an unmet challenge. Several factors have

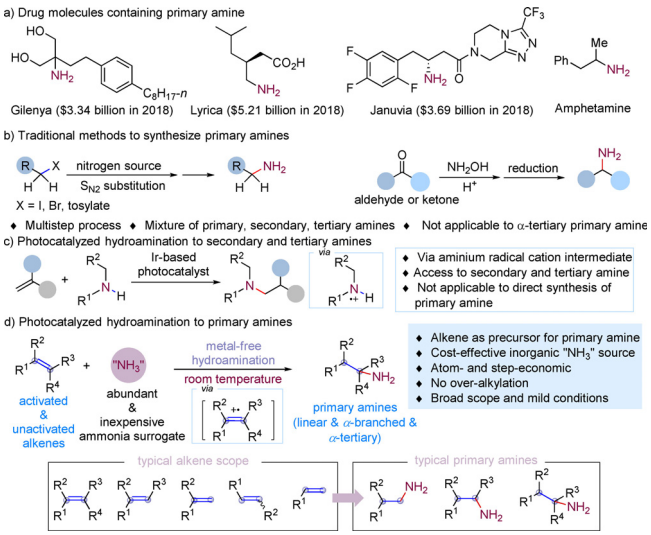

Figure 1. Significance of primary amines and reaction development.

[*] Dr. Y.-D. Du, B.-H. Chen, Prof. Dr. W. Shu
Shenzhen Grubbs Institute, Department of Chemistry, and Guangdong Provincial Key Laboratory of Catalysis
Southern University of Science and Technology
Shenzhen 518055, Guangdong (P. R. China)
E-mail: shuw@sustech.edu.cn

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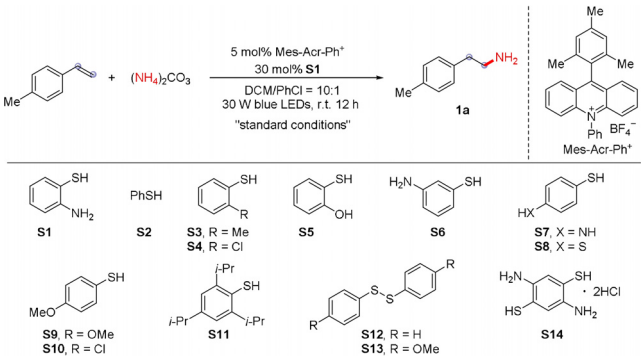
impeded the development of primary amine synthesis from alkenes via photocatalysis: 1) Identification of a proper ammonia source. 2) A primary amine is more electron-rich than the parent ammonia source, and thus prone to be oxidized prior to the ammonia surrogate. 3) A primary amine is more nucleophilic than the parent ammonia source and prone to undergo multifold alkylation reactions to give a mixture of secondary and tertiary amines. A seminal work by Nicewicz postulated that alkenes could undergo single electron oxidation to radical cation intermediates, leaving massive chemical space to further elaborate alkenes with weak nucleophiles.[20] Unfortunately, this strategy is not applicable to aliphatic amine synthesis due to the high reductive potential of aliphatic amines compared to alkenes. Herein, we developed the direct synthesis of primary amines from alkenes under mild conditions using readily available and cost-effective precursors (Figure 1d). The identification of a latent ammonia surrogate as well as the catalytic conditions is the key to the success of this process. This metal-free protocol tolerates tetra-, tri-, di-, and mono-substituted alkenes with various electronic and steric patterns, allowing for the primary amine synthesis to proceed at room temperature with exclusive regioselectivity.

To test our hypothesis for the regioselective synthesis of primary amines from alkenes, 4-methylstyrene was used as the model substrate to evaluate the reaction conditions. After extensive optimization of reaction parameters,[21] we identified the use of 5 mol% of Mes-Acr-Ph$^+$ ($E^*_{red} = +2.20$ V) and 30 mol% of 2-aminothiophenol as catalyst, ammonium carbonate as ammonia source in DCM/PhCl = 10:1 under blue LED irradiation at room temperature as the optimal reaction conditions, affording the desired primary amine **1a** as single regioisomer in 75% isolated yield (Table 1, entry 1). We found the use of ammonium carbonate as the ammonia surrogate was the key to the success of this transformation, probably due to the proper release rate of ammonia during the reaction course. The use of other ammonium salts as ammonia surrogate could also form **1a**, albeit with inferior efficiency (see Tables S1 and S7). The choice of hydrogen atom donor had a substantial impact on the efficiency of this transformation (Table 1, entries 2–14). After evaluation of a wide variety of thiophenol derivatives (**S1**–**S14**), we found that 2-aminothiophenol (**S1**) provided the optimal result. Other thiophenol derivatives delivered primary amine **1a** with diminished yields (Table 1, entries 3–11). Phenyl disulfide derivatives could also catalyze the desired transformation to give **1a**, albeit in lower yields (Table 1, entries 12 and 13). Dithiophenol could also mediate the reaction, furnishing **1a** in 67% yield (Table 1, entry 14). A 2-amino group may interact with thiol to facilitate the hydrogen atom transfer. No desired primary amine **1a** was observed in the absence of thiol (Table 1, entry 15). The use of chlorobenzene as co-solvent significantly enhanced the outcome of the hydroamination reaction. Other tested solvents, such as hexanes, acetonitrile, tetrahydrofuran, ether, or trifluorotoluene also afforded hydroamination product **1a** in good yields (Table 1, entries 16–21). Control experiments revealed that both photocatalyst and light irradiation are required for the reaction (Table 1, entry 22).[21]

Table 1: Optimization of the reaction conditions.[a]



Entry	Variation from "standard conditions"	Yield [%][b]
1	none	79 (75)
2	**S2** instead of **S1**	22
3	**S3** instead of **S1**	15
4	**S4** instead of **S1**	traces
5	**S5** instead of **S1**	40
6	**S6** instead of **S1**	18
7	**S7** instead of **S1**	42
8	**S8** instead of **S1**	19
9	**S9** instead of **S1**	34
10	**S10** instead of **S1**	16
11	**S11** instead of **S1**	18
12	**S12** instead of **S1**	8
13	**S13** instead of **S1**	32
14	**S14** instead of **S1**	67
15	no thiol	0
16	hexanes instead of PhCl	57
17	EtOAc instead of PhCl	64
18	CH_3CN instead of PhCl	53
19	THF instead of PhCl	74
20	Et_2O instead of PhCl	65
21	$PhCF_3$ instead of PhCl	73
22	no photocatalyst/light	0

[a] The reaction was performed with 0.11 mmol of *para*-methylstyrene with 1.65 mmol of $(NH_4)_2CO_3$ in DCM (20 mL) and chlorobenzene (2.0 mL) under irradiation with a 30 W blue LED at ambient temperature for 12 h; DCM = dichloromethane, THF = tetrahydrofuran. [b] Yield was determined by ^{1}H NMR analysis of the crude mixture using PhTMS as internal standard. Isolated yield in parentheses.

With the optimized reaction conditions in hand, we set out to explore the scope of this transformation. The reaction conditions could be applied to a wide variety of alkenes with diverse substitution patterns and varied electronic properties, delivering a broad spectrum of primary amines with sophisticated and advanced functional groups (Figures 2–4). Due to purification issues, some primary amines were isolated in a protected form. This method could be employed to synthesize linear primary amines (Figure 2a). Terminal styrenes with different substitution patterns on the aromatic ring were all good substrates for this reaction, giving the corresponding β-aryl ethyl amines in good yields (**1a**–**1g**). 1-Alkyl-substituted styrenes could be applied to this reaction, furnishing various β-aryl long-chain aliphatic primary amines in good yields (**1h**–**1l**). 1,1-Cycle-substituted alkenes could be efficiently transformed into corresponding primary amines in good yields (**1m**–**1o**). The β-thiazole-substituted ethyl amine

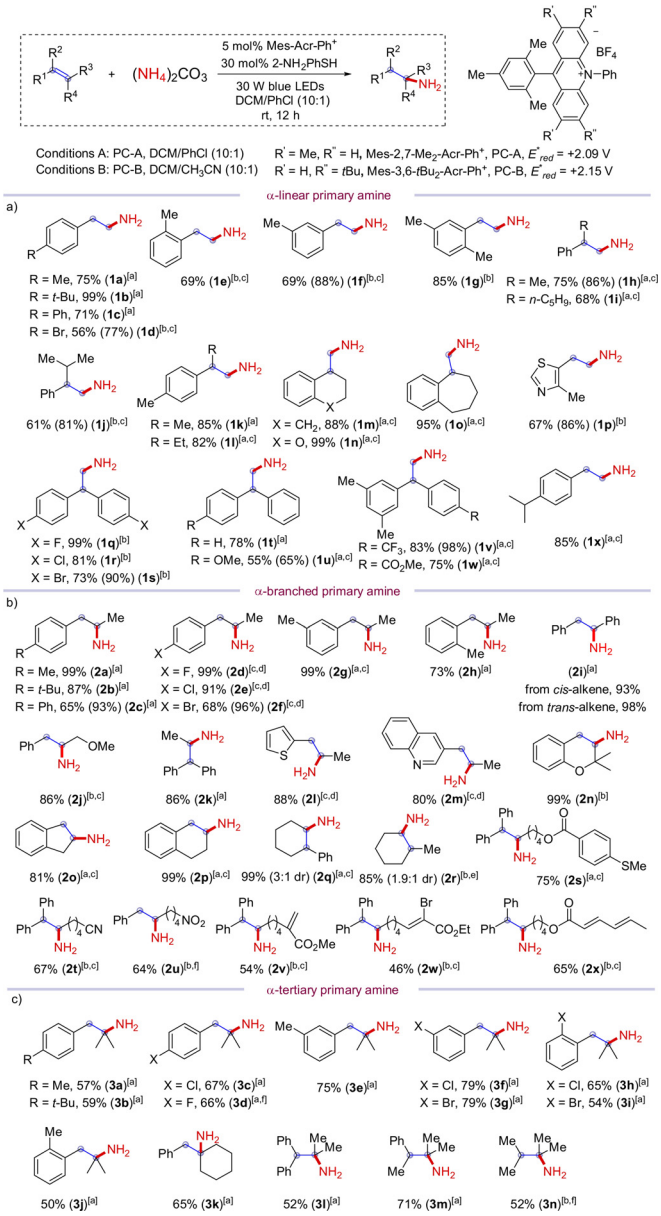


Figure 2. Scope of primary amine synthesis from selective hydroamination of alkene. [a] The reaction was conducted on 0.11 mmol scale under standard conditions. Isolated yield of free amine is shown unless otherwise noted. Yield in parentheses is based on the recovery of alkenes. Boc = *t*-butoxycarbonyl, Bz = benzoyl, Cbz = benzyloxycarbonyl. [b] Conditions B were used. [c] Isolated yield of NHBoc. [d] Conditions A were used. [e] Isolated yield of NHBz. [f] Isolated yield of NHCbz.

derivative **1p** was obtained in 86% yield. 1,1-Diaryl-substituted ethylenes with electron-rich or electron-poor substituents delivered β,β-bisaryl ethyl amines in excellent yields (**1q**–**1w**). 4-Isopropyl styrene delivered the primary amine **1x** in 85% yield, leaving the isopropyl group intact. This protocol was applicable to the synthesis of α-branched primary amines (Figure 2b). Internal alkenes, such as β-methyl styrenes with *para*-, *meta*-, *ortho*-substituents on the aromatic ring, could be converted to corresponding α-methyl primary amines in 73–99% yield (**2a**–**2h**). *cis*-1,2-Diphenylethene and *trans*-1,2-diphenylethene could be both transformed to **2i** under the reaction conditions in 93% and 98% yield, respectively. Methyl *trans*-cinnamyl ether could be converted to 2-aminoether **2j** in 86% yield. 1,1-Diphenyl propene could undergo hydroamination to give corresponding α-branched amine **2k** in 86% yield. Thiophene- and quinoline-substituted propenes were compatible under the reaction conditions, furnishing the heteroaryl-containing α-branched primary amines **2l** and **2m** in 88% and 80% yield, respectively. The 2-aminoether-bearing α-quaternary carbon center **2n** was obtained in 99% yield. Cyclic internal styrenes and aliphatic alkenes with di- or tri-substitutions could be converted to the corresponding aliphatic α-branched primary amines (**2o**–**2r**) in 81–99% yield. Notably, alkenes tethered with sulfide, cyanide, nitro, unsaturated ester, vinylbromide, or conjugated diene were all good substrates under the reaction conditions, affording corresponding primary amines in synthetically useful yields (**2s**–**2x**). α-Tertiary primary amines which are challenging to synthesize could be obtained using this mild method (Figure 2c). β,β-Dimethyl styrenes with *para*-, *meta*-, *ortho*-substituents on the aromatic ring could be successfully converted to corresponding α,α-dimethyl primary amines in moderate to excellent yields (**3a**–**3j**). Cyclohexyl-substituted styrene could be used to synthesize the bulky primary amine **3k** in 65% yield. Tetrasubstituted alkenes were also good substrates for this transformation, giving sterically congested primary amines **3l**–**3n** in synthetically useful yields.

Next, alkenes adjacent to heteroatoms were tested under the reaction conditions (Figure 3a). 2-Aminoalcohols and 1,2-diamines are common substructures in bioactive molecules and organic synthesis. Vinyl ether and enamine derivatives are well-tolerated under these reaction conditions, leading to diverse 2-aminoalcohol and 1,2-diamine structural motifs. 3,4-Dihydro-2*H*-pyran could undergo regioselective hydroamination to give 3-aminotetrahydropyran **4a** in 70% yield. Seven- and eight-membered cyclic silyl enol ethers could be tolerated in this reaction, giving medium-sized 2-aminosilylethers (**4b** and **4c**) in synthetic useful yields. Acyclic vinyl ethers are also good substrates in the reaction, delivering corresponding chain 2-aminoethers (**4d** and **4e**) in 76% and 72% yield, respectively. Free aminoalcohol **4f** could be obtained from *trans*-cinnamyl alcohol in 81% yield. Enamide derivatives could be applied to furnish 1,2-diamines containing one primary amine motif (**4g** and **4h**) in 72% and 98% yield, respectively.

To further demonstrate the robustness and utility of this protocol, we applied the reaction conditions to a series of natural product derivatives (Figure 3b). Estrone derivatives could undergo regioselective hydroamination to afford aminoether-bearing free phenol **5a** containing a primary amine and ketone **5b** bearing an α-linear primary amine in 65% and 80% yield, respectively. 3,4,6-Tri-*O*-benzyl-D-glucal could be successfully subjected to the reaction conditions and gave 2-amino-1,5-anhydro-2-deoxy-D-glucitol derivative **5c** in 70% yield. (*S*)-(−)-Terpineol was compatible with the reaction, giving the 3-amino-α,α,4-trimethyl-cyclohexanemethanol **5d** in 51% yield. Menthol-tethered vinyl ether could be incorporated into the reaction, giving menthol-containing 2-aminoether **5e** in 58% yield. 7-Methoxy-2,2-dimethylchromene

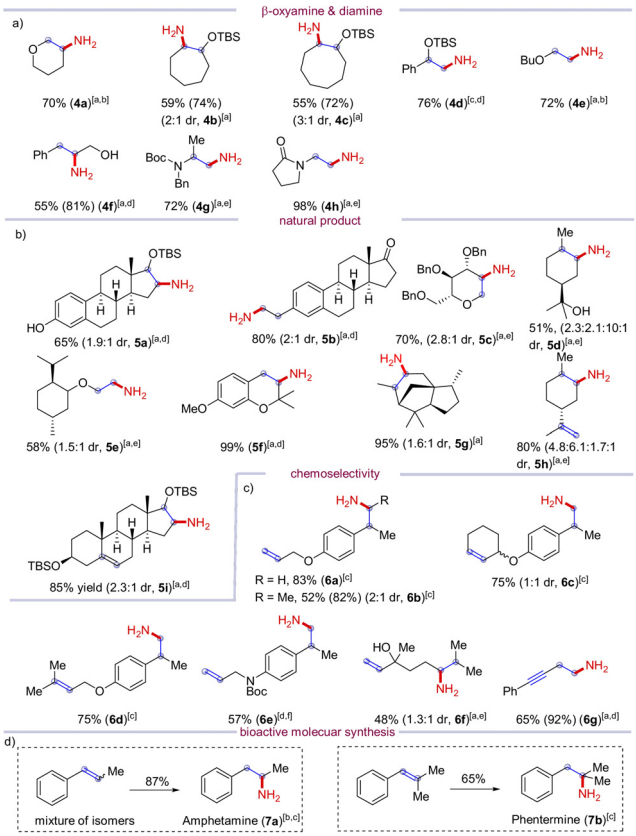


Figure 3. Synthetic application of the hydroamination reaction of alkenes. [a] The reaction was conducted on 0.11 mmol scale under Conditions B. Free primary amine was isolated unless otherwise noted. Yield based on the recovery of alkenes is shown in the parentheses. TBS = *t*-butyldimethylsilyl, Bn = benzyl. [b] Isolated yield of NHBz. [c] See Table 1, entry 1 for reaction conditions. [d] Isolated yield of NHBoc. [e] Isolated yield of NHCbz. [f] Conditions A were used.

delivered chromene-derived primary amine **5 f** in quantitative yield. α-Cedrene underwent regioselective hydroamination to furnish corresponding primary amine **5g** in 95 % yield. (*R*)-Limonene and dehydroepiandrosterone are also tolerated in this reaction, furnishing corresponding primary amines **5h** and **5i** in 80 % and 85 % yield, respectively. It is noteworthy that the hydroamination selectively occurred on the internal alkene, and the terminal alkene remained intact, indicating complete chemoselectivity of this method over different alkenes. Inspired by this encouraging result, we further applied this protocol to chemoselective hydroamination over two different alkenes (Figure 3c), giving homoallylic primary amines in moderate to good yields (**6a–6 f**). Vinyl phenylacetylene was a good substrate for the reaction to undergo selective hydroamination on alkenes, giving homopropargyl primary amine **6g** in 92 % yield. 1-Substituted aliphatic alkenes are not reactive under the reaction conditions due to their high oxidative potentials ($E_{p/2} > 2.2$ V). Moreover, bioactive molecules phentermine (**7a**) and amphetamine (**7b**) could be synthesized from β-methyl styrene and β,β-dimethyl styrene in 87 % and 65 % yield (Figure 3d), which required multiple steps in traditional syntheses.[22,23]

To gain further insights into the reaction mechanism, we carried out a set of reactions to shed light on the reaction pathways (Figure 4). First, we conducted the radical clock reaction using **8** under standard conditions. Allylic primary amine product **9** was obtained in 82 % yield as a mixture of *Z*/*E* isomers, which could undergo the regioselective hydroamination followed by ring opening via radical intermediates **8-1** and **8-2**. Interestingly, α,β-dimethylstyrene **10** with different *Z*/*E* ratios gave the desired hydroamination product **11** in the same diastereomeric ratio (dr = 2:1), suggesting the reaction proceeded via the same radical intermediate **10-1**. The formation of **10-1** erases the *Z*/*E* information from **10**, followed by stereoselective hydrogen transfer to afford **11** in 81–83 % yield with identical diastereoselectivity. When geraniol derivative **12** was exposed to the standard conditions, aminocyclization product **13** was obtained in 32 % yield with 44 % conversion. The reaction may undergo a radical cascade cyclization mechanism via radical intermediates **12-1** and **12-2**. These two reactions both suggested the incorporation of radical intermediates in this reaction. To further confirm the pathway of this reaction, an alkene with an intramolecular alcohol **14**, which is difficult to be oxidized under the reaction conditions, was tested.[20a] When 5,5-diphenyl-4-penten-1-ol **14** was submitted to the reaction conditions, the intramolecular oxygen-trapped product **15** was exclusively detected in 88 % yield with or without ammonium carbonate. No intermolecular hydroamination product was detected. The result indicated the reaction went through single electron oxidation of an alkene moiety to give radical cation intermediate **14-1**, which was intramolecularly trapped by the alcohol moiety to give **14-2. 14-2** further extracted a hydrogen atom to deliver **15**. To further prove the existence of a radical cation intermediate, β-methyl 4-fluorostyrene **16** was subjected to the reaction conditions in the presence of TEMPO (2 equiv) under otherwise standard conditions. Hydroamination product **2 d** was not observed. Instead, the TEMPO adduct with alkene **17** was obtained in 51 % yield with 53 %

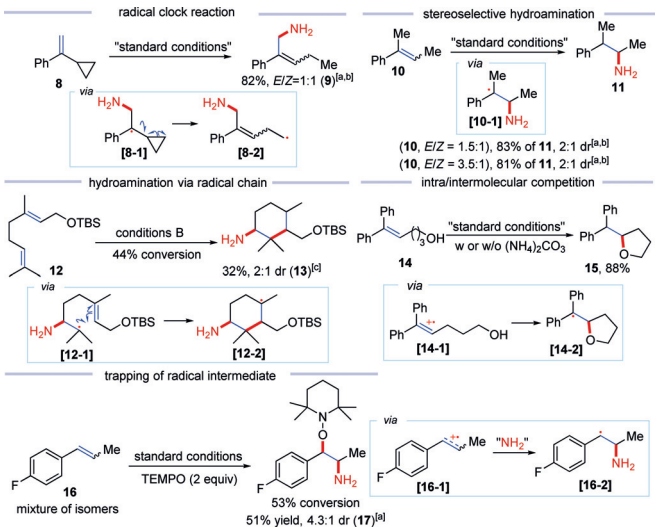


Figure 4. Mechanistic investigations of the reaction. [a] See Table 1, entry 1 for reaction conditions. [b] Isolated yield of NHBoc. [c] Isolated yield of free amine under conditions B.

conversion via the trapping of TEMPO with radical intermediate **16-2**, formed by amine attack via the radical cation intermediate **16-1**.

Next, we set up a series of kinetic experiments to probe the kinetic behavior of this reaction (Figure 5).[21] The time course for the consumption of β,β-dimethylstyrene and the generation of corresponding primary amine **7b** is presented in Figure 5a. Hammett plot studies showed that the hydroamination reaction is sensitive to the substituent effects (Figure 5b). The Hammett slope ($\rho = -0.82$) shows positive charge buildup in the selectivity-determining transition state of the reaction and is more negative than typically observed for the generation of benzylic radicals. This is consistent with the mechanistic observations, suggesting the presence of the radical cation intermediates **14-1** or **16-1**.[24] Based on the experimental results and literature,[25] we propose the reaction mechanism depicted in Figure 5c. First, **PC** is activated to generate excited **PC*** by visible light irradiation. **PC*** interacts with the alkene via single electron oxidation to give radical cation intermediate **M1** in conjunction with reduced photocatalyst species **PC-1.** **M1** is trapped by ammonia released from ammonium carbonate to deliver intermediate **M2**. The stability of **M2** dominates the regioselectivity of the amine attack. **M2** can undergo HAT (hydrogen atom transfer) with 2-aminothiophenol to furnish protonated primary amine **M3** along with intermediate **M4.** **PC-1** can reduce **M4** to regenerate **PC** and 2-aminothiophenoxide **M5**, which can be protonated by **M3** to generate 2-aminothiophenol and primary amine product.

In summary, a straightforward and modular route to a wide variety of aliphatic primary amines from alkenes is presented here based on a metal-free hydroamination at room temperature. The use of cost-effective and easily available ammonium carbonate allows for the efficient conversion of terminal and internal alkenes with diverse substitution patterns into highly functionalized primary amines. Notably, the reaction demonstrates excellent selectivity over alkynes and different alkenes, leading to linear, α-branched, and α-tertiary primary amines selectively. The synthetic utility of this methodology is successfully demonstrated by the efficient synthesis of aminoalcohol derivatives, diamines, bioactive molecules, late-stage functionalization of natural products, as well as the rapid access to molecular complexity. Mechanistic investigations revealed the process underwent a radical cation intermediate. We anticipate this work will open a new avenue of employing alkenes as a general chemical handle for the practical synthesis of aliphatic primary amines in the context of both pharmaceuticals and natural product synthesis.

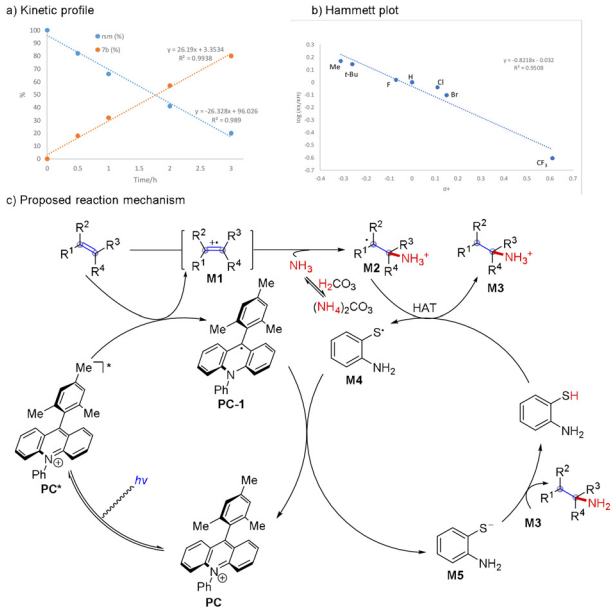


Figure 5. Kinetics investigations and proposed mechanism for the reaction.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkene · ammonium carbonate · hydroamination · metal-free · primary amines

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