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COMMUNICATION

Highly Selective sp^3 C-N Bond Activation of Tertiary Anilines Modulated by Steric and Thermodynamic Factors

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A highly selective sp^3 C-N cleavage of tertiary anilines was achieved using TBN/TEMPO catalyst system. When *N,N*-diaklylanilines (alkyl, benzyl) were employed, the N-CH_3 bond was selectively cleaved via radical C-H activation. While allyl group was installed, totally reverse selectivity was observed. It is worth noting that solvent effect is also crucial to obtain high reaction efficiency and selectivity.

The C–N bond, as one of the most abundant chemical bonds, is ubiquitous in organic synthetic intermediates, biomolecules, drugs and natural products. Therefore, considerable efforts were devoted to construction of C-N bond for synthesis of amines, amides and other nitrogen-containing compounds. [1] In contrast, due to the high C–N bond dissociation energy and its inherently inert reactivity, the cleavage of C–N bond still remain a great challenge in synthetic society. Recently, with the development of transition-metal catalyzed activation of inert chemical bonds, such as C–H, [2] C–C [3] and C–O bonds,[4] C-N bond activation has become one of the hottest topic in organic chemistry.[5-8] Generally, two kinds of transition-metal-catalyzed C-N cleavage were investigated extensively: (1) oxidative addition of transition-metal to C – N bond, (2) formation of imine or iminium species. Based on these strategies, various C-N bonds were activated to facilitate useful and applicable transformations, in which the nitrogen-containing substrates were utilized as nitrogen and/or carbon sources for the synthesis of the desired products. [6-10]
Among them, cleavage of sp^3 C-N bond is highly desirable. Pioneered by Trost's work in 1980, [8a] a series of activation of allylic amines were achieved, [8] in which the C-N bond was activated by low-valent metal via oxidative addition (Fig. 1, eq 1). Since 2012, Huang and co-workers developed a series of C-N bond activation in aminals initiated by oxidative addition between the aminal and Pd(0) complex (Fig. 1, eq 2). [9] It is worth noting that in these work, both the aminomethyl moiety and the amino nucleophile could be successfully incorporated into the desired products without any atom loss. Different from above strategies, Huang also established a new way for oxidative C-N bond activation in tertiary amines promoted by C-H activation in 2011. [10a] In this transformation, the C-N bond was cleaved via an iminium-type intermediate. Using the same strategy, [10] Lei reported an elegant palladium/copper-catalysed domino process of tertiary anilines, constructing 3-methyleneindolin-2-one skeleton in good yields (Fig. 1, eq 3). [10b] Recently, Jiao and co-workers also achieved a Rh-catalyzed aerobic oxidative cyclization of anilines, alkynes, and CO, in which the C-N bond of tertiary anilines was efficiently cleaved. [10e]

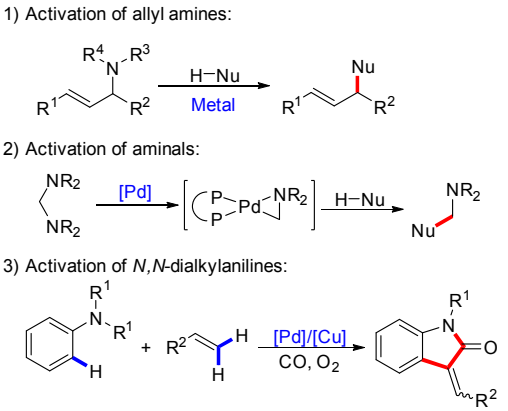

Fig. 1 Activation of sp^3 C-N bond.

From these work, we can see that activation of C-H bond adjacent to nitrogen is a candidate to trigger further C-N bond cleavage. However, these methods suffered from shortcomings, such as high reaction temperature, using of transition metals and poor site-selectivity. With the

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† Electronic Supplementary Information (ESI) available: Experimental details and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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development of radical C-H activation, [11] we wondered whether C-N cleavage could be achieved under mild conditions, especially avoiding using of transition metals (metal free).

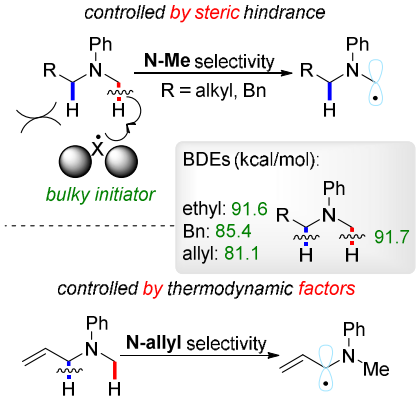
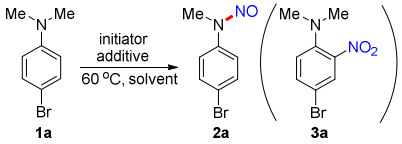


Fig. 2 Selectivity control of sp^3 C-N bond activation (this work).

It is well-known that the sp^3 C-H bond adjacent to nitrogen is relatively active and can readily undergo homolytic cleavage (via oxidative deprotonation, H-abstraction, etc) to the corresponding free radical. In our previous research on radical C-H functionalization, [12] various sp^3 C-H bond adjacent to nitrogen could be smoothly oxidized under radical cation induced aerobic conditions, and in some cases, C-N cleavage process occurred. [12d-e] Encouraged by these results, we questioned whether the C-N bond in tertiary amines could also be broken via radical mediated mechanism. However, how to generate the α-amino radical intermediate selectively is a long-standing challenging problem in radical chemistry, in which the site selectivity is controlled by the balance of various factors, such as thermodynamic driving force, bond dissociation energy (BDE), steric hindrance, polarity matching effect,[13] solvent effect and so on. Recently, significant progress on site-selective functionalization was achieved through the application of radical hydrogen atom transfer (HAT). [14] For example, Murphy reported a site-selective and contra-thermodynamic HAT reaction of trialkylamines, in which functionalization on N-CH_3 group was favored by using the bulky radical cation of DABCO. [14c] Very recently, MacMillan also described a polarity-match-based selective sp^3 C–H alkylation via the combination of photoredox, nickel and HAT catalysis, steering by the conventional BDE-driven model.[14d] However, for tertiary anilines, the C-H bonds of methyl and methylene groups are both electron-rich (hydridic), and furthermore, the BDE difference is very subtle (91.7 vs 91.6 kcal/mol, Fig. 2), [15] which are not competent to achieve highly selective transformations. Consequently, we questioned whether a sterically bulky radical initiator could be employed to surmount the influence of BDE and thermodynamic stability on the site-selectivity, providing a radical intermediate on the less hindered position (Fig. 2). If this idea is feasible, the selective C-N bond cleavage could be fulfilled by further iminium intermediate formation and following decomposition. Herein, we report an efficient approach to highly selective sp^3 C-N activation of tertiary anilines using *tert*-butyl nitrite (TBN)/TEMPO catalyst system, in which the site-selectivity is readily modulated by steric hindrance and thermodynamic factors (Fig. 2).

Table 1. Optimization of reaction conditions



1a **2a** **3a**

Entry	Solvent	Initiator	TEMPO	Yield (%) [a]
1	MeCN	$TBPA^{+\cdot}$ [b]	none	N. R.
2	MeCN	TBHP [c]	none	N. R.
3	MeCN	TEMPO [c]	-	N. R.
4	MeCN	TBN [d]	none	53 (29) [e]
5	DCE	TBN [d]	none	44 (28)[e]
6	$CHCl_3$	TBN [d]	none	33 (51)[e]
7	MeCN	TBN [d]	none	47 (24)[e]
8	MeCN	TBN [d]	none	49 (28)[e]
9	MeCN	TBN [d]	1 eq	93 [f] (93) [g]
10	MeCN	TBN [d]	0.2 eq	92 (<5%) [e, g]
11	MeCN	TBN [d]	0.1 eq	93 (<5%) [e, g]
12	MeCN	TBN [d]	0.1 eq	94 (<5%) [e, g, h]
13	1,4-dioxane	TBN [d]	0.1 eq	84 (7%) [e, g, h]
14	MeCN	TBN [d]	0.2 eq	trace [h, i]

[a] Yield of crude product ^{1}HNMR using 1,3,5-trimethoxyl-benzene as internal standard. [b] In the presence of 10 mol % $TBPA^{+\cdot}$. [c] 1 equivalent of the initiator and in the case of TBHP, 10 mol % of CuBr was added. [d] 1.5 equivalent of TBN was added. [e] Yields in parentheses is the nitro-products. [f] Under O_2. [g] Under air. [h] Room temperature. [i] Under argon atmosphere.

To validate our hypothesis, we commenced our studies by attempting the C-N cleavage of *N,N*-dimethylaniline **1a** under different reaction conditions, and the results were compiled in Table 1. Firstly, some bulky radical initiators such as $TBPA^{+\cdot}$ (tris(4-bromophenyl)aminiumhexachloroantimonate), TBHP/CuBr and TEMPO were tested (entries 1-3). Unfortunately, no desired reaction occurred. After extensive survey of literatures, [16] TBN was declared to liberate the NO_2 and *tert*-butoxyl radicals in the presence of dioxygen. These radicals might abstract a hydrogen atom from the hydridic C-H bond to produce the corresponding carbon-centered free radical. Therefore, the model reaction was conducted in the presence of TBN (1.5 eq) and dioxygen. To our satisfaction, the reaction proceeded extremely fast, and the substrate **1a** was fully consumed, providing a complicated mixture. By GC-MS analysis, not only C-N cleaved product **2a**, but also nitration compound **3a** were detected (entry 4-8), together with other unidentified compounds. Encouraged by these promising

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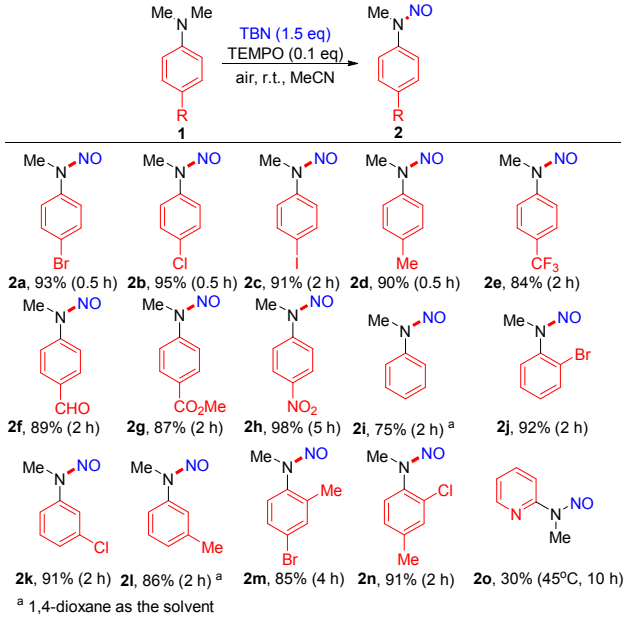
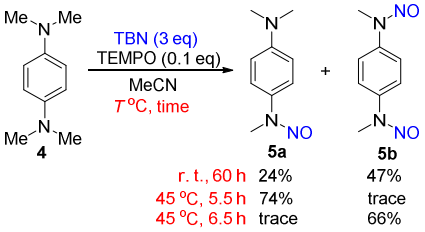
results, one equivalent of TEMPO was added into the reaction mixture to intercept the generated radical intermediate, and avoid possible side reactions. [17] It turns out that in the presence of TEMPO, the reaction was singularized, affording the desired nitrosamine in 93% yield (entry 9). After further optimization of catalyst loading and reaction temperature (entries 9-12), 1.5 equivalent of TBN and 0.1 equivalent of TEMPO at room temperature under air atmosphere were found the best reaction conditions, and the *N*-nitrosoaniline **2a** was obtained in 94% yield (entry 12). 1,4-Dioxane was also an alternative solvent, giving **2a** in a slightly decreased yield (entry 13). In the absence of dioxygen, no reaction occurred, implying that both TBN and dioxygen are crucial to initiate the C-H and consecutive C-N activation (entry 14).

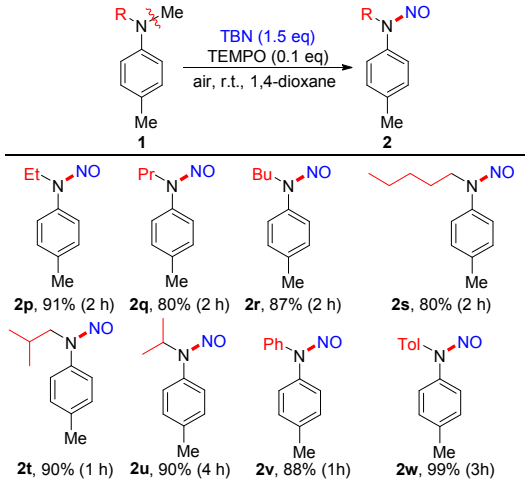


Scheme 1. Reaction scope on anilines



Scheme 2. Sequential cleavage of *p*-phenylenediamine derivative

With the best reaction conditions established, the substituents on aniline varied to evaluate the functional group tolerance (Scheme 1). In general, the *N,N*-dimethylanilines with both electron-withdrawing and -donating groups on the phenyl ring were well tolerated with good to excellent yields under this protocol. Aniline derivatives substituted with the halogens Cl, Br and I afforded the corresponding *N*-nitrosoanilines in excellent yields (**2a-c**). A comparable yield was obtained for the substrate with methyl group (**2d**). Electron-withdrawing groups, such as CF_3, CHO and CO_2Me, did not exert negative effect on the C-N bond cleavage, providing the desired products (**2e-g**) in high yields with slightly elongated reaction time. It is worth noting that aniline with aldehyde group, which is susceptible under oxidative conditions, could also afford the desired product **2f** in 89%, implying good functional group tolerance of this mild reaction conditions. Even nitro group substituted aniline gave the desired product **2h** in 98% yield. *N,N*-dimethylanilines bearing *ortho*- and *meta*-substituents underwent smooth reactions, giving the desired products in 86% to 92% isolated yields (**2j-l**). Importantly, for substrate **1i** and **1l**, 1,4-dioxane as the solvent was crucial to avoid nitration side-products. [18] When 2,4- disubstituted *N,N*-dimeylanilines were employed as the substrates, the reaction also took place smoothly to furnish the desired product in high yields (**2m-n**). The reaction of N,N-dimethylpyridin-2-amine was also tested under the standard reaction conditions, and different from aniline derivatives, this substrate exhibited lower reactivity, providing the corresponding demethylation product in 30% yield at 45 °C.



Scheme 3. C-N bond cleavage of unsymmetric anilines

As one reviewer's suggestion, the reactivity of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine **4** was also evaluated (Scheme 2). Under the standard conditions, a mixture of **5a** and **5b** were isolated. At higher temperature, the mononitrosation product **5a** was isolated in 74% yield with trace amount of **5b**. Interestingly, when the reaction time was extended to 6.5 h, dinitrosation product **5b** was obtained in 66% yield and only trace amount of mononitrosation product was detected. These results show that in this substrate, the C-N bond cleavage occurred stepwise, and the control of reaction time is essential to achieve higher selectivity.

Having succeeded in the C-N bond activation of symmetric *N,N*-dialkylanilines, we decided to apply this methodology to more challenging substrates. Then, the reactions of unsymmetric *N,N*-dialkylanilines were performed to test the selectivity of this C-N activation. However, when the reaction of *N*-ethyl-*N*-methylaniline was conducted in MeCN, a mixture was obtained, in which the N-CH_3 cleavage was favored (ratio:

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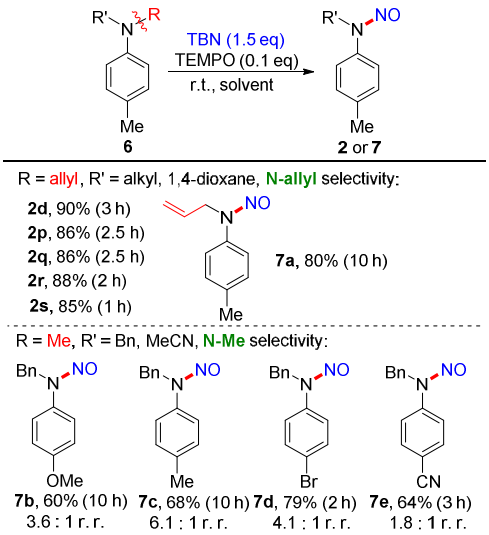
6 : 1; for details, see ESI). To our delight, when 1,4-dioxane was chosen as the reaction solvent, excellent selectivity was achieved, giving the demethylation product **2p** in 91% yield (Scheme 3). [19] Similar selectivity was also observed for *n*-propyl, *n*-butyl and *n*-pentyl, yielding the expected products **2q-2s** in 80%, 87% and 80% yields, respectively. Bulky group did not decrease the reaction efficiency, and *N*-nitrosoaniline **2t** was obtained in 90%. Significantly, *N*-iso-propylaniline underwent the selective C-N cleavage quite well, and the N-CH_3 bond was cleaved exclusively (**2u**), supporting the steric hindrance controlled site-selectivity. Several diphenylamine derived substrates, such as **1v** and **1v**, were also compatible with this process to afford the desired products **2v–2w** in high yields. For products **2u** and **2v**, two sets of signals were observed in ^{1}H and ^{13}C NMR. It is attributed to that *N*-nitrosamines can exhibit syn and anti-orientations due to the restricted rotation of the N–N bond. [16g]

To our surprise, when using dialkylanilines containing only N-CH_2R positions, the C-N cleavage process were seriously disturbed by nitration on phenyl ring, in which less bulky substrates shown slightly higher preference to undergo C-N cleavage (see ESI). These results also supported that the reaction efficiency was strongly affected by the steric hindrance over thermodynamic stability of the radical intermediate and BDEs. To enhance the BDE-driven model counteracting the steric congestion (for the BDE of allyl C-H bond, see Fig. 2), the reaction of allyl group substituted anilines were investigated under the standard conditions (Scheme 4). Consistent with our prediction, when the allyl group was installed on nitrogen, reverse site-selectivity was observed. No matter methyl group and other alkyl groups existed, the C-N cleavage occurred exclusively on N-allyl bond, providing the *N*-nitrosoanilines in 85% to 90% yields (**2d-s**). Critical to the success of this reaction was the use of 1,4-dioxane as the solvent, which avoided the formation of demethylation products (see ESI). Interestingly, when diallyl group substituted starting material **6a** was employed, only one allyl group was efficiently cleaved (**7a**). To further verify this steric hindrance modulated site-selectivity, the reactions of a series of *N*-methyl-*N*-benzylanilines were investigated under the standard reaction conditions. Although BDE of the benzylic C-H bond is lower than the methylic one (85.4 vs 91.7 kcal/mol, Fig. 2), [15] preference to N-Me selectivity was observed (**7b-e**). We reason that this abnormal selectivity is attributed to the fact that benzyl group is more sterically encumbered than allyl group. Differently, for *N*-benzylanilines, MeCN as the solvent gave higher site-selectivity, favoring N-Me cleavage (see ESI for details). The exact reason remains unknown.



Scheme 4. C-N activation of *N*-allyl and benzylanilines

To gain some preliminary understanding of the reaction mechanism, a series of control experiments were carried out under the standard conditions (Scheme 5). First, in the absence of TBN and dioxygen, respectively, no reaction occurred (eq 1 and 2), suggesting that the reaction was initiated by the TBN derived free radicals. To confirm the existence of NO_2 radical, one equivalent of styrene was added to the reaction solution, and the corresponding nitrostyrene was detected by GC-MS (eq 3). [16d] From the above results, we assume that the C-N bond cleavage might probably be enabled by intermolecular HAT between TBN derived free radicals and *N,N*-dialkylanilines. Then, an intramolecular KIE experiment was conducted (eq 4), affording KIE value in 6.44. This KIE value indicated that the C-H bond cleavage might be engaged in the rate-determining step. Next, a HRMS experiment of the reaction mixture was performed (eq 5), and to our delight, the signal at m/z 197.9910 (calcd for $C_8H_9BrN^+$, 197.9913) was detected. This signal is related to the mass of an iminium intermediate, verifying that the C-N bond might be cleaved through the decomposition of this iminium intermediate. Interestingly, we also detected trace amount of TEMPO oxoammonium (calcd for $C_8H_{18}NO^+$, 156.1383; found, 156.1390), which might be derived from oxidation of TEMPO radical. To determinate the real catalyst, the C-N activation reaction of aniline **1r** was performed in the presence of TEMPO oxoammonium (eq 6). However, no reaction occurred. While in the presence of TBN (1.5 eq), the desired product **2r** was detected in 23% ^{1}H NMR yield (eq 7). These results supported that the C-N bond cleavage is promoted by TBN, and excluded the participation of TEMPO oxoammonium.

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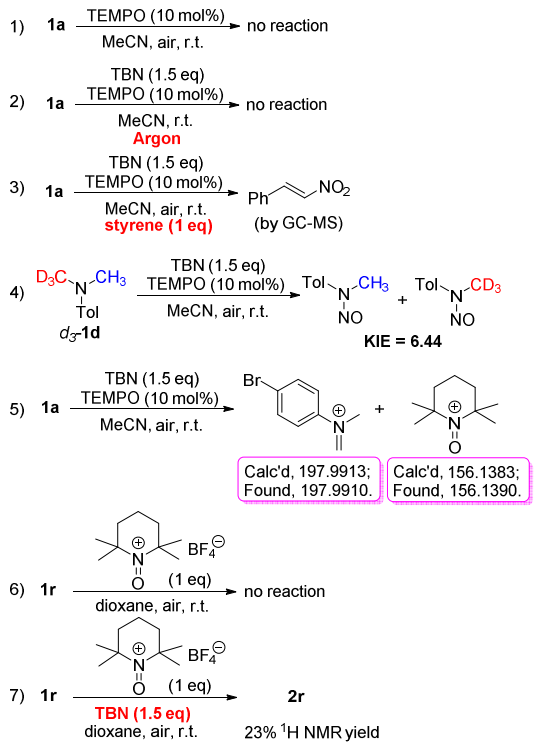
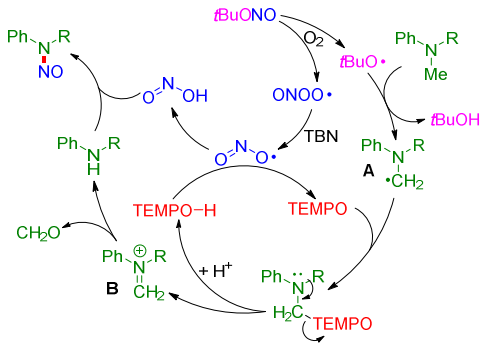


Scheme 5. Control experiments

Based on the experimental results and previous reports related to TBN, a possible mechanism was proposed for this novel C-N activation/N-N formation process (Scheme 6). Supported by strong literature precedent, [16] we believed that a peroxynitrite radical and *tert*-butoxyl radical were formed by aerobic cleavage of the N-O bond of TBN. The bulky *tert*-butoxyl radical preferred to abstract a hydrogen from the less crowed N-Me site, providing an α-amino radical **A** (**N-Me selectivity**). When allyl group exists, the thermodynamic factors overcome the steric effect, generating a more stable α-amino radical (**N-allyl selectivity**). In the presence of TEMPO, the generated α-amino radical intermediate was trapped, and after elimination of TEMPOH, an iminium intermediate **B** was afforded. Decomposition of the iminium ion released an *N*-alkylaniline with expelling of formaldehyde. Concurrent with the formation of intermediate **B**, the NO_2 radical, which was generated from the secondary reaction between the peroxynitrite radical and TBN, abstracts a hydrogen atom from TEMPOH to regenerated TEMPO, together with nitrous acid. Finally, a classical *N*-nitrosation between *N*-alkylaniline and the nitrous acid occurred, giving the *N*-nitrosamine derivatives in high yields.



Scheme 6. Proposed mechanism.

Conclusions

In summary, we developed an efficient catalyst system to achieve selective C-N bond activation. This reaction is initiated by radical sp^3 C-H bond activation, whose selectivity is well modulated by steric hindrance and thermodynamic factors. In the case of *N,N*-dialkylanilines with bulkier substituents (alkyl, Bn, etc), the N-CH_3 bond cleavage was highly preferred. When allyl group was installed on nitrogen, the BDE of the C-H bond adjacent to nitrogen was obviously lowered, and thoroughly reverse selectivity was observed. It should be pointed out that the site-selectivity of C-H/C-N activation is affected by various factors, such as thermodynamic driving force, BDE, steric hindrance, polarity matching effect, solvent effect and so on, and the overall outcome is the result of synergism of these effects. Compared with traditional method of transition-metal enabled C-N bond activation, this reaction is featured by mild reaction conditions (room temperature and air atomosphere), high efficiency (up to 99% yield), good functional group tolerance (halogens, CF_3, CHO, CO_2Me, etc.) and greener catalyst system (metal free). Further applications and more variants of this C-N activation are still underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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