CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201303296

Nucleophilic Attack of α-Aminoalkyl Radicals on Carbon–Nitrogen Triple Bonds to Construct α-Amino Nitriles: An Experimental and Computational Study

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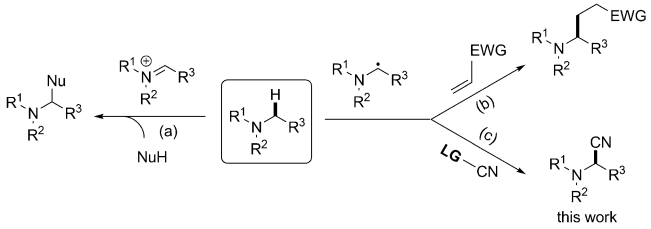
Abstract: A new reactivity pattern of α-aminoalkyl radicals, involving nucleophilic attack on C≡N triple bonds under thermal conditions, has been developed to construct α-amino nitriles. In contrast to previous C–H functionalization of tertiary amines involving α-aminoalkyl radicals, this methodology does not require the use of photocatalytic conditions or a transition-metal catalyst. Inexpensive and nontoxic phenylacetonitrile was chosen as cyano source for this α-aminonitrile forming reaction. A plausible mechanism is proposed based upon experimental and computational results. An α-aminoalkyl radical intermediate and benzoyl cyanide have been shown to be key intermediates in this green and mild radical process. Nucleophilic attack of the α-aminoalkyl radical on the C≡N bond of PhCOCN followed by an elimination step forms the desired α-aminonitrile and an acyl radical.

Keywords: density functional calculations · radical reactions · reaction mechanisms · reactive intermediates · synthetic methods

Introduction

C–H functionalization[1] of tertiary amines has drawn much attention in recent years as a powerful strategy to construct various α-substituted amines, which are important synthetic intermediates for generating nitrogen-containing compounds.[2] Currently, two methods are routinely employed to synthesize α-functionalized tertiary amines. The first involves generation of iminium ion intermediates through oxidation of tertiary amines, which has been developed by the groups of Murahashi,[3] Li,[4] and others[5] (Scheme 1a). Very recently, an elegant functionalization of tertiary amines via iminium ion intermediates formed in situ through visible-light photoredox catalysis has also been reported.[6]

The second type of α-C–H bond functionalization of tertiary amines takes advantage of nucleophilic α-aminoalkyl radicals (Scheme 1b).[7] Yoshida et al. reported the addition of α-amino alkyl radicals to various double bonds bearing an electron-withdrawing group based on the reduction of a "cation pool".[7a,b] Related studies by the group of Nagaoka revealed a radical hydroxyalkylation of the C–H bond adjacent to the nitrogen atom by using Et_3B/air.[7c] MacMillan and co-workers described a photoredox-catalyzed α-amino C–H arylation reaction that proceeds through a radical process.[7d] Recently, the groups of Nishibayashi,[7e–g] Reiser and Pandey,[7h] and Yoon[7i] have independently reported the visible-light-mediated addition of α-amino alkyl radicals to various α,β-unsaturated systems. In 2012, tandem α-alkylation/cyclization of N-benzyl carbamates with nonactivated olefins was established by Mancheño and co-workers.[7j]



Scheme 1. α-C–H bond functionalization of tertiary amines.

Despite the remarkable success of the radical strategy outlined above, its usual reliance on photocatalytic/electrochemical conditions and the requirement for C=C bonds bearing electron-poor groups limit its utility in synthetic chemistry. Therefore, a new process that can be applied to a broader range of electrophiles under thermal conditions is highly desirable. Herein, we report a mechanistically interesting and metal-free[8,9] process to construct synthetically important α-amino nitriles[10] (Scheme 1c). To the best of our knowledge, this represents the first example of nucleophilic attack of α-aminoalkyl radicals on C≡N bonds under thermal conditions, although ketone-nitrile reductive cou-

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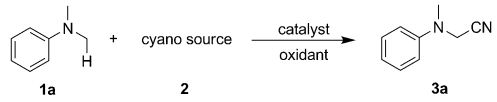
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303296.

pling mediated by SmI_2 constitutes a valuable method with which to form α-hydroxy ketone derivatives.[11,12]

Results and Discussion

The reaction conditions for oxidative cyanation[13] of *N*,*N*-dimethylaniline (**1a**) was extensively screened with tetrabutylammonium iodide (TBAI) as catalyst and *tert*-butyl hydroperoxide (TBHP) as primary oxidant (Table 1).[14] When

Table 1. Optimization of reaction conditions.[a]



1a 2 3a

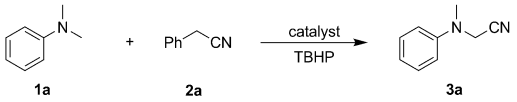
Entry	Catalyst	Cyano source	Oxidant	Yield [%][b]
1	TBAI	$PhCH_2CN$	TBHP	84
2	TBAI	NaCN	TBHP	10
3	TBAI	TMSCN	TBHP	10
4	TBAI	MeCN	TBHP	n.d.
5	–	$PhCH_2CN$	TBHP	n.d.
6	TBAI	$PhCH_2CN$	–	n.d.
7	KI	$PhCH_2CN$	TBHP	n.d.
8	Bu_4NBr	$PhCH_2CN$	TBHP	n.d.
9	$PdCl_2$	$PhCH_2CN$	TBHP	n.d.
10	$CuBr_2$	$PhCH_2CN$	TBHP	n.d.
11	TBAI	$PhCH_2CN$	Oxone	n.d.
12	TBAI	$PhCH_2CN$	TBP	<10
13	TBAI	$PhCH_2CN$	H_2O_2	n.d.
14	TBAI	4-NO_2-$PhCH_2CN$	TBHP	35
15	TBAI	4-OMe-$PhCH_2CN$	TBHP	89[c]
16	TBAI	TsCN	TBHP	<5
17	TBAI	CCl_3CN	TBHP	<5
18	TBAI	$PhCH_2CN$	TBHP	65[d]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.25 mmol), TBAI (0.01 mol), oxidant (2.5 mmol), H_2O (1.5 mL), *t*BuOH (0.5 mL), 60 °C, 36 h. [b] Isolated yield; n.d. = not detected. [c] Detected by GC. [d] **1a** (10 mmol) was used.

phenylacetonitrile (**2a**) was used as cyano source, the desired α-amino nitrile **3a** was obtained in high yield (84%; Table 1, entry 1). In contrast to previous oxidative cyanation of tertiary amines,[15] the methodology was distinguished by the fact that it did not require photocatalytic conditions, expensive transition-metal catalysts, or toxic cyano sources. In fact, cyanide anions such as NaCN and TMSCN (Table 1, entries 2 and 3), which are frequently used as nucleophiles to attack iminium ion intermediates in α-amino nitrile synthesis, were found to be poor cyano donors for **1a**, suggesting that a different mechanism was involved in this TBAI/TBHP system. Both TBAI and TBHP were essential for α-amino nitrile formation under our conditions (Table 1, entries 5 and 6). Replacement of TBAI by other catalysts, including organocatalysts and transition-metal catalysts, did not lead to the desired product (Table 1, entries 7–10). Notably, when other common oxidants were used for this transformation, again, no significant amount of product **3a** was detected (Table 1, entries 11–13). Substituent effect on the phenyl ring of phenylacetonitrile was further investigated. The use of 4-nitrophenylacetonitrile as cyano source led to formation of the desired product **3a** in 35% yield (Table 1, entry 14). In sharp contrast, when 4-methoxyphenylacetonitrile was used as cyano source, product **3a** was achieved in high yield detected by GC (89%; Table 1, entry 15). Unfortunately, its purification was very difficult due to the presence of some uncharacterized byproducts. Considering the expense and operational simplicity, phenylacetonitrile was chosen as cyano source in subsequent investigations. Other cyano sources, such as TsCN and CCl_3CN, did not lead to the desired product (Table 1, entries 16 and 17). Notably, this α-amino nitrile formation reaction could be scaled up to 10 mmol, generating the desired product **3a** in 65% yield (Table 1, entry 18).

To ascertain the identity of the active intermediates that result from TBAI/TBHP, we screened a series of iodine-containing reagents to see whether they could similarly catalyze the oxidative cyanation of *N*,*N*-dimethylaniline (**1a**). None of the I(0)–I(V) species tested could drive the reaction enough to produce substantial amounts of the α-amino nitrile product **3a** (Table 2). In particular, we found no evi-

Table 2. Investigations on the reaction mechanism by screening various iodine reagents.[a]



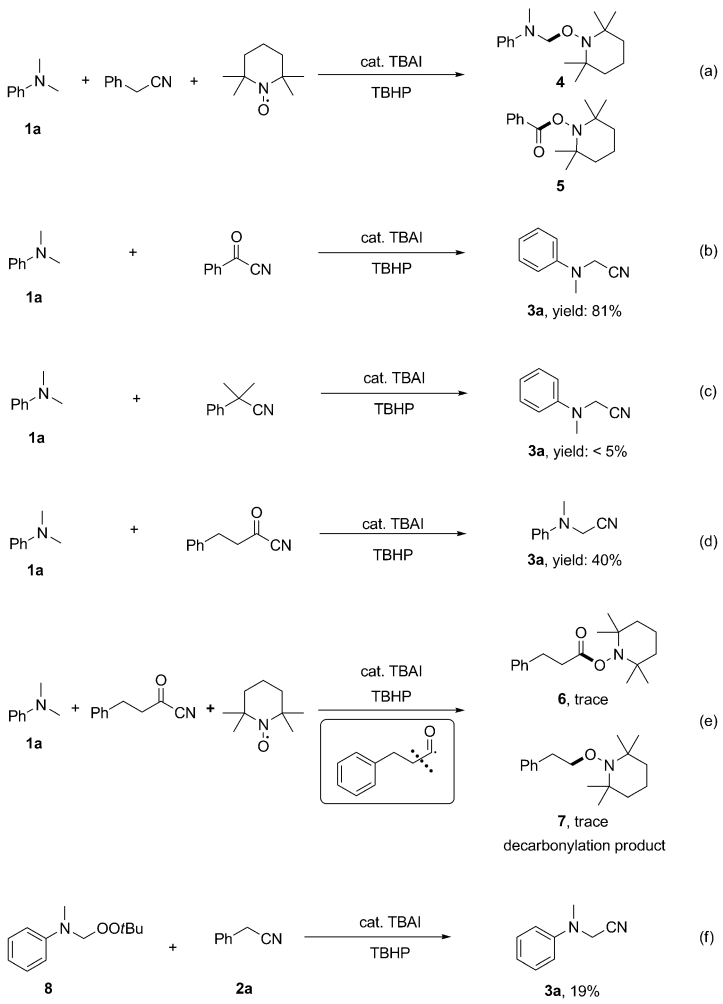
1a 2a 3a

Entry	Catalyst	Yield [%][b]
1	I_2	<5
2	IBr	<5
3	NIS	<5
4	$PhI(OAc)_2$	<5
5	$NaIO_3$	<5
6	I_2 (20 mol%), Bu_4NOH (1.0 equiv)	<5[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), catalyst (0.01 mol), TBHP (2.5 mmol), H_2O (1.5 mL), *t*BuOH (0.5 mL), 60 °C, 36 h. [b] Isolated yield. [c] $[Bu_4N]^+[IO]^-$ generated in situ.

dence that hypoiodite, which Ishihara et al.[16] showed could be generated in situ from iodine and Bu_4NOH, had any appreciable impact on the yield of **3a** (Table 2, entry 6). These findings implied that this cyanation reaction likely involved a *t*BuO$^\bullet$ and/or *t*BuOO$^\bullet$ radical intermediate that was generated from TBHP[14] rather than an oxidizing iodine species.

Further mechanistic studies revealed that adding 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger resulted in a sharp decrease in the yield of **3a** and gave rise to small amounts of α-aminoalkyl radical adduct **4** and PhC(O)$^\bullet$ radical adduct **5**, which not only confirmed our earlier speculation of the involvement of radical intermediates, but also hinted at benzoyl cyanide as the cyano donor (Scheme 2a). Substituting benzoyl cyanide for phenylacetonitrile led to the identical product **3a** in high yield (Scheme 2b). In addition, no significant amount of α-amino



Scheme 2. Investigations on the reaction mechanism.

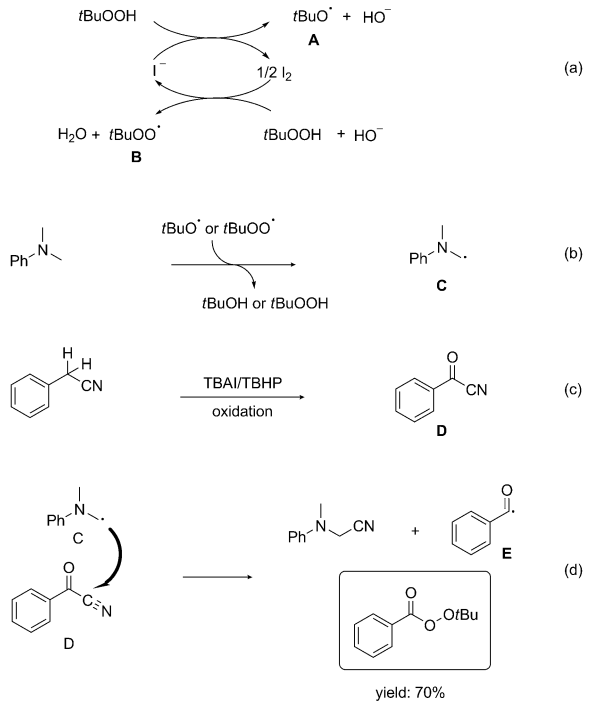
nitrile **3a** was achieved when α,α-dimethylphenylacetonitrile was used as the cyano source (Scheme 2c).

One could argue that nucleophilic substitution of acyl cyanide by TEMPO,[17] instead of direct coupling between PhC(O)• radical and TEMPO, could also reasonably form adduct **5**. To offer more compelling evidence, further experiments were carried out to test the involvement of acyl radicals in this α-amino nitrile formation reaction. Employing 3-phenylpropanoyl cyanide as a cyano source led to formation of product **3a** in moderate yield (Scheme 2d). When the reaction of **1a** with 3-phenylpropanoyl cyanide was performed in the presence of TEMPO, in addition to the expected $PhCH_2CH_2C(O)$• radical adduct **6**, we also detected adduct **7**, which was formed from $PhCH_2CH_2$• radical and TEMPO (Scheme 2e). These results suggest that the $PhCH_2CH_2C(O)$• radical generated in situ and subsequent decarbonylation process[18] is involved in this transformation.

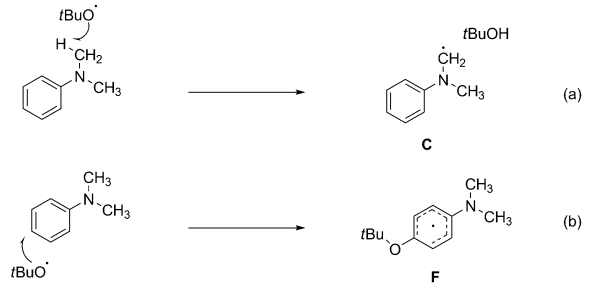
Transition-metal-catalyzed α-C–H functionalization of tertiary amines by using TBHP as oxidant has been elegantly investigated by several groups.[3a,f,4a–d,5c–e,h,j–l] According to pioneering studies by Klussmann et al.[5j] and Doyle et al.,[5l] these processes generally entail an α-amino peroxide precursor that can subsequently convert into an iminium ion intermediate when aided by a transition-metal catalyst. However, iminium ions might not play a major role in the formation of **3a** due to the absence of any metal ions in our catalytic system. This was confirmed by the finding that α-amino peroxide derivative **8** fared poorly as a substrate in our reaction (Scheme 2f).

Scheme 3 provides an overview of our proposed radical-mediated mechanism for the α-cyanation of tertiary amines. A catalytic redox cycle involving TBHP and TBAI first gave rise to both *t*BuO• (**A**) and *t*BuOO• (**B**; Scheme 3a),[19,20] which could then abstract the α-hydrogen of the tertiary amine to afford α-aminoalkyl radical intermediate **C** (Scheme 3b). In addition to **C**, benzoyl cyanide (**D**) could also be formed in situ due to the oxidative environment involved (Scheme 3c). Finally, nucleophilic attack of α-aminoalkyl radical **C** on the C≡N bond of PhCOCN (**D**) and subsequent elimination leads to the desired product and a PhC(O)• radical (**E**; Scheme 3d). It is noteworthy that the PhC(O)• radical (**E**) could be trapped by *t*BuOO• (**B**), providing the *tert*-butyl peroxybenzoate as a byproduct, which was verified by experiment.

The complexity of the above mechanism and the many reactive species it involves renders the reaction system susceptible to multiple alternative pathways contributing to potential side reactions. To explore these possibilities, (U)B3LYP calculations[21] were performed on the α-amino nitrile formation reaction by using the Gaussian 09 suite.[22] The 6-31+G(d,p) basis set was used for geometry optimization and the 6-311++G(d,p) basis set[23] was employed for single point energy calculation of the optimized structures. For *t*BuO• (**A**, two competing mechanistic routes, a) α-H abstraction of $PhN(CH_3)_2$, and b) aromatic radical addition to its *para*-position, were assessed and compared (Scheme 4). Calculations indicated that the former reaction pathway is much more favorable than the latter in terms of both kinetic and thermodynamic profiles (Figure 1). Therefore, α-aminoalkyl radical **C**, resulting from H-atom abstraction, would be expected to participate in the subsequent reactions. In addition, the cal-



Scheme 3. Proposed reaction mechanism.



Scheme 4. Two reaction pathways between tBuO$^\bullet$ and $PhN(CH_3)_2$.

culated energy barrier for abstraction of an α-H from $PhN(CH_3)_2$ by tBuOO$^\bullet$ (**B**) was revealed to be much higher than for tBuO$^\bullet$ (**A**; see Scheme S1 and Figure S1 in the Supporting Information), which is at least partially attributable to the lower spin density of the former species around its terminal oxygen (0.68 vs. 0.87 e).

We then similarly analyzed three possible reaction routes between tBuO$^\bullet$ (**A**) and another reactant, $PhCH_2CN$ (**2a**), which were a) H-atom abstraction from the methylene group, b) the addition of tBuO$^\bullet$ to the cyano group, and c) the addition of tBuO$^\bullet$ to the benzene ring (Scheme 5). The energy profiles of these three reaction pathways are summarized in Figure 2. Calculations indicated that hydrogen abstraction was exothermic by 26.1 kcal mol^{-1} and had the smallest activation energy demand of the three reaction pathways at only 1.5 kcal mol^{-1}.[24] The two alternative addition reaction pathways could therefore not compete with the H-atom abstraction reaction pathway.

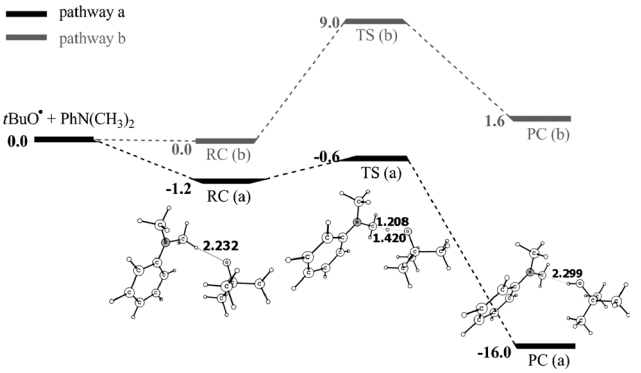
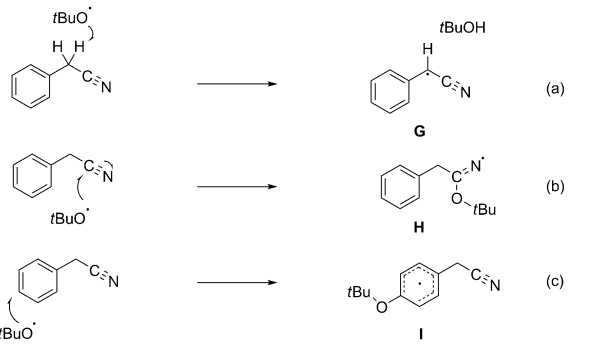


Figure 1. Energy profiles of the two reaction pathways between tBuO$^\bullet$ and $PhN(CH_3)_2$ calculated at the (U)B3LYP/6-311++G(d,p)//(U)B3LYP/6-31+G(d,p) level of theory (ΔH(0 K), in kcal mol^{-1}). Bond lengths are shown in Å.



Scheme 5. Three possible reaction pathways between tBuO$^\bullet$ and $PhCH_2CN$.

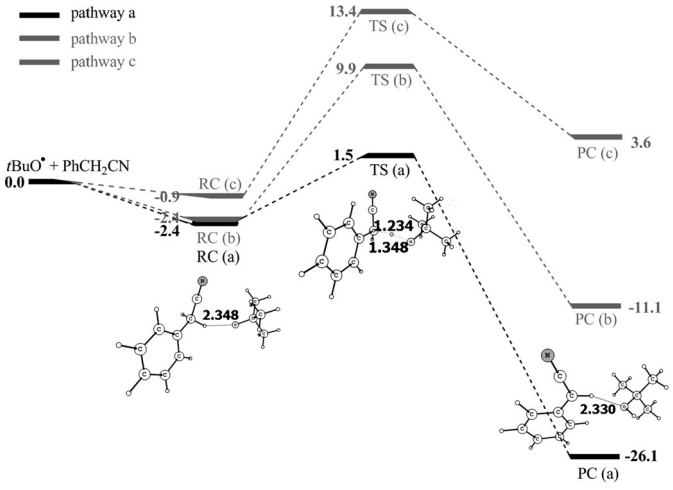
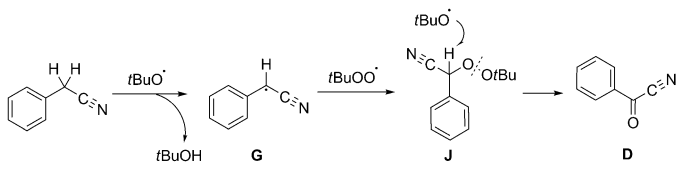


Figure 2. Energy profiles of three reaction pathways between tBuO$^\bullet$ and $PhCH_2CN$ calculated at the (U)B3LYP/6-311++G(d,p)//(U)B3LYP/6-31+G(d,p) level of theory (ΔH(0 K), in kcal mol^{-1}). Bond lengths are shown in Å.

Computational studies also provided a rather convenient but nevertheless convincing explanation for the generation of PhCOCN (**D**), an experimentally verified intermediate

that proved crucial for both product formation and mechanistic deduction. Following α-H abstraction, radical **G** might combine with *t*BuOO• (**B**) to afford a closed-shell intermediate **J**, which could then undergo a second α-H abstraction, this time by *t*BuO• (**A**), to eventually give **D** (Scheme 6).



Scheme 6. In situ generation of PhCOCN (**D**) through a radical process.

The calculated energy barrier of the α-H abstraction from **J** induced by *t*BuO• was shown to be only 0.8 kcal mol^{-1}, suggesting that the formation of the PhCOCN intermediate (**D**) was plausible (Figure 3).

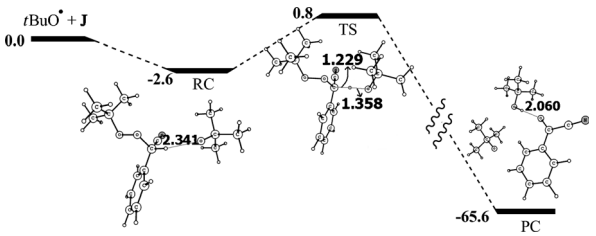
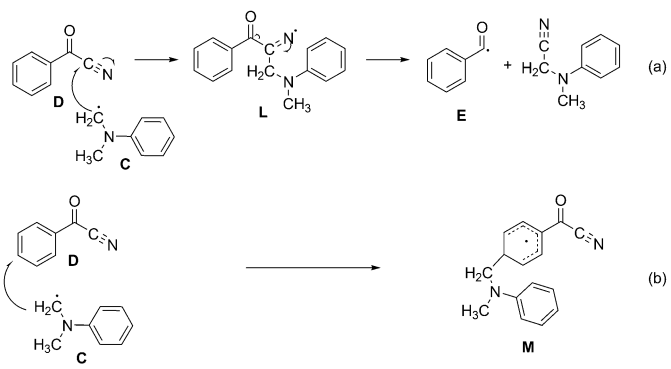


Figure 3. Energy profiles of the H-abstraction reaction between *t*BuO• and **J** calculated at the (U)B3LYP/6-311++G(d,p)//(U)B3LYP/6-31+G(d,p) level of theory (ΔH(0 K), in kcal mol^{-1}). Bond lengths are shown in Å.

The final phase of our proposed mechanism begins with attack of the α-aminoalkyl radical **C** on the cyano group in PhCOCN to give imine radical intermediate **L** (Scheme 7), the activation energy of which was estimated to be 4.7 kcal mol^{-1}. Inspection of the spin density of **L** revealed the unpaired electron to be mainly localize around the terminal nitrogen site. The adduct **L** can then undergo elimination reaction to form the final α-amino nitrile product and the PhC(O) radical. The energy of the transition state (TS) in the elimination step is 2.8 kcal mol^{-1} higher than that of the TS in the first addition step, which indicates that elimination is the rate-limiting step in the production of α-amino nitrile (Figure 4).

Another complicating factor that needs to be considered is the competition between the cyano group and the benzene ring as the site of radical addition. Computational studies revealed that the former (cyano group) would be more favorable,[25] because it requires 3.6 kcal mol^{-1} less energy than the latter (Figure 4).



Scheme 7. Two possible reaction pathways between $PhNCH_3CH_2^{\bullet}$ radical (**C**) and PhCOCN (**D**).

Although both experimental and computational results present convincing evidence that supports a radical mechanism, we found that the use of NaCN could result in a yield of up to 10% of **3a** (Table 3, entry 1), suggesting that an iminium ion mechanism seemed at least feasible under some conditions. In contrast to **1a**, when cyanation of 1-phenylpyrrolidine was performed by using $PhCH_2CN$ as cyano source, the yield of product **3b** decreased remarkably (50 vs. 84%; Table 3), perhaps due to increased steric hindrance. It should be noted that the ionization energy (IE) of radical **O** is 9.8 kcal mol^{-1} lower than that of radical **C**, indicating that it is much easier for radical **O** to be oxidized to the corresponding iminium ion intermediates **P** in the presence of TBHP. Consequently, the yield of product **3b** through an ionic process increases in comparison with **3a** (40 vs. 10%).

The calculated IE of radical **Q** is 15.3 kcal mol^{-1} lower than that of radical **C** (116.6 vs. 131.9 kcal mol^{-1}), suggesting that radical **Q** could be easily oxidized to the corresponding iminium ion intermediate. As anticipated, the ionic cyanation reaction proceeds smoothly, leading to the desired product **3c** in 54% yield (Table 3, entry 3).

One noteworthy finding was that substituting $PhCH_2CN$ for NaCN as the cyano donor in the above reaction pro-

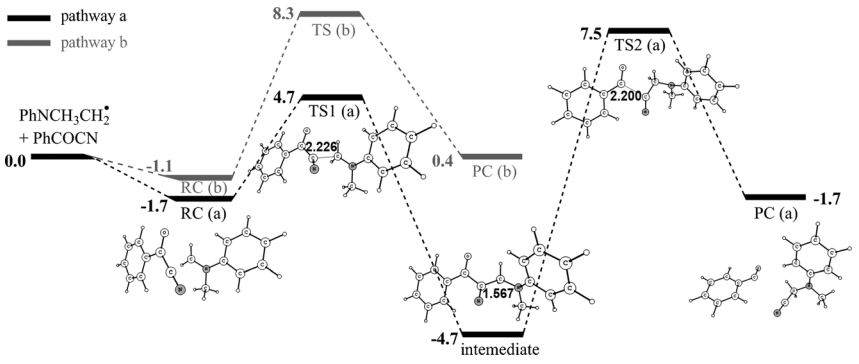
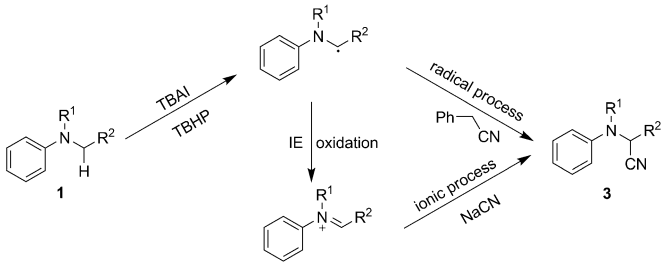


Figure 4. Energy profile of two reaction pathways between $PhNCH_3CH_2^{\bullet}$ radical and PhCOCN calculated at the (U)B3LYP/6-311++G(d,p)//(U)B3LYP/6-31+G(d,p) level of theory (ΔH(0 K), in kcal mol^{-1}). Bond lengths are shown in Å.

Table 3. Calculated ionization energies (IE) of radicals at the (U)B3LYP/6-311++G-(d,p)//(U)B3LYP/6-31+G(d,p) level of theory and the implication of the yield in radical and ionic processes.[a]



Entry	α-Aminoalkyl	IE [kcal mol^{-1}]	Iminium cation	Product	Yield ($PhCH_2CN$) [%][b]	Yield (NaCN) [%][b]
1	C	131.9	N	3a	84	10
2	O	122.1	P	3b	50	40
3	Q	116.6	R	3c	–	54
4	Q	–	–	3b	55	–

[a] Reaction conditions: **1a** (0.5 mmol), TBAI (0.01 mol), TBHP (2.5 mmol), H_2O (1.5 mL), *t*BuOH (0.5 mL), 60 °C, 36 h. [b] $PhCH_2CN$ (1.25 mmol) was used. [c] NaCN (1.25 mmol) was used.

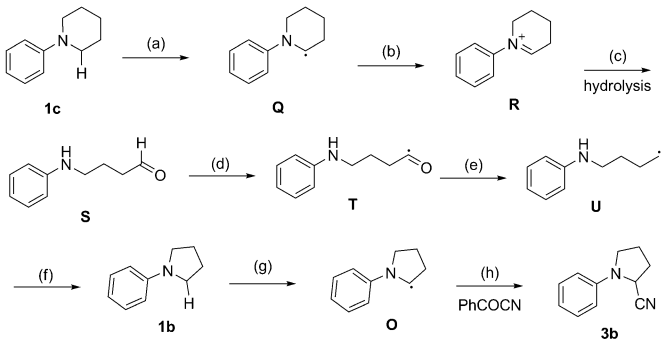
duced ring-contraction product **3b** in 55% yield (Table 3, entry 4). We proposed a plausible mechanism for this unexpected product as shown in Scheme 8. Basically, the radical intermediate **Q** that was generated from TBAI/TBHP-promoted α-H abstraction of **1c** (step a) could be oxidized to form a cyclic iminium species **R** (step b), which, following hydrolysis and ring opening, could be converted into aldehyde **S**. The terminal hydrogen of **S** could be abstracted to produce acyl radical **T**, which then leads to the formation of radical **U** through decarbonylation (step e). The latter radical undergoes cyclization (step f), hydrogen abstraction (step g), and eventually reacts with PhCOCN (step h) to afford **3b**. To verify our hypothesis, we capatured the reaction intermediates with TEMPO and generated a variety of α-aminoalkyl, acyl, and alkyl radical adducts, which could all be easily derived from intermediates at different stages of the proposed mechanism (Scheme 9).

We then subjected a series of differently substituted tertiary amines to the nitrile-forming reaction by using the optimized set of conditions, to explore the scope of the approach. The reactions all provided the corresponding α-amino nitrile products in moderate to high yields as summarized in Table 4. Notably, cyanation of tertiary amines containing two chemically unequivalent α-C–H bonds was found to occur selectively on the primary C–H (products **3d–h**). Furthermore, halogen substituents on the aromatic ring did not appear to interfere with the C–H functionalization (products **3k**, **3m**, and **3n**), allowing further synthetic manipulations such as transition-metal-catalyzed cross-coupling reactions. When *N*,*N*-dibutylaniline was used as reaction partner, no significant amount of α-amino nitrile **3o** was observed, perhaps due to increased steric interference.

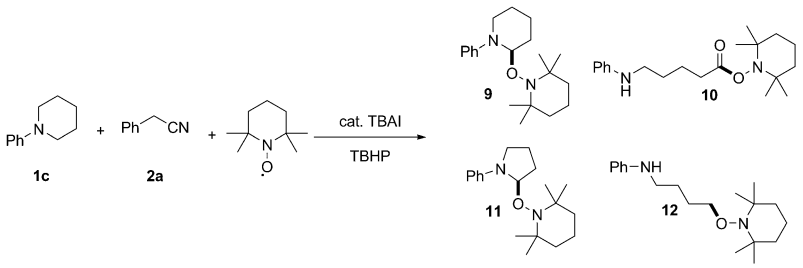
Conclusion

A novel reactivity pattern of α-aminoalkyl radicals, involving nucleophilic attack on the carbon–nitrogen triple bond of PhCOCN and subsequent elimination of $PhC(O)^{\bullet}$ radical, has been realized for the first time under thermal conditions.

In contrast to previous C–H functionalization of tertiary amines, this methodology did not involve photocatalytic conditions or transition-metal catalysts. Inexpensive and nontoxic $PhCH_2CN$ was

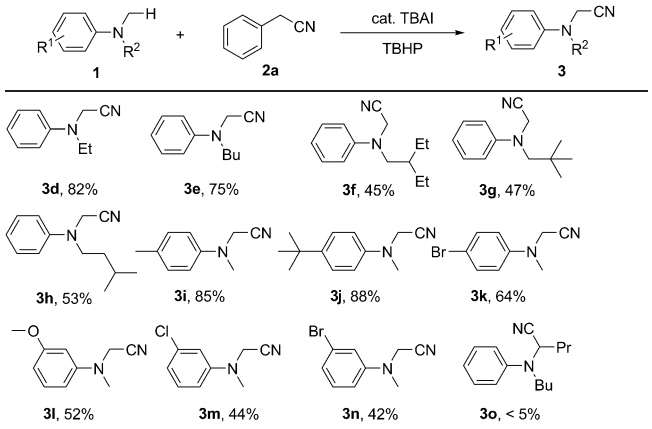


Scheme 8. Proposed mechanism for the cyanation of 1-phenylpiperidine by using $PhCH_2CN$.



Scheme 9. Detection of reaction intermediates.

Table 4. Scope of tertiary amines.[a]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.25 mmol), TBAI (0.01 mol), TBHP (2.5 mmol), H_2O (1.5 mL), *t*BuOH (0.5 mL), 60 °C, 36 h.

used as cyano source for the construction of α-amino nitriles. Based upon the experimental and computational results, a plausible mechanism has been proposed. The α-aminoalkyl radical intermediate **C** was generated in situ, aided by *t*BuO$^{\bullet}$ radical (**A**). In addition to **C**, benzoyl cyanide (**D**) was also formed under the oxidative conditions. Finally, nucleophilic attack of α-aminoalkyl radical **C** on the C≡N bond of PhCOCN (**D**) and subsequent elimination of the PhC(O)$^{\bullet}$ radical (**E**) provided the desired α-amino nitrile. It is noteworthy that ring-contraction product **3b** was achieved when 1-phenylpiperidine was submitted to the reaction conditions using $PhCH_2CN$ as cyano donor. The unusual characteristics of the α-aminoalkyl radical will be further explored in our laboratory, especially with respect to its use with electrophiles other than PhCOCN.

Experimental Section

General procedure: Bu_4NI (0.01 mmol) and tertiary amine (0.5 mmol) were added to a test tube and H_2O (1.5 mL), *t*BuOH (0.5 mL), phenylacetonitrile (1.25 mmol, 142 μL), and TBHP (70% in H_2O, 2.5 mmol, 342 μL) were added by using a syringe. The reaction mixture was stirred at 60 °C for 36 h, then the reaction was quenched (consumption of residual TBHP) by the addition of saturated Na_2SO_3 solution and extracted with ethyl acetate. The organic layer was combined and dried with Na_2SO_4. Removal of solvent followed by flash column chromatographic purification afforded products.

Acknowledgements

This project was funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and NSFC (21072142, 21272165).

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[24] The *t*BuO$^{\bullet}$ may undergo β-cleavage to yield a methyl radical and acetone. The calculated energy barrier for this step is 11.9 kcal mol^{-1} at the (U)B3LYP/6–311++G(d,p)//(U)B3LYP/6-31+G(d,p) level of theory, which is much higher in energy than the studied intermolecular H-abstraction reactions.

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Received: August 22, 2013
Published online: November 22, 2013

