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Base mediated cascade amidination/*N*-alkylation of amines by alcohols

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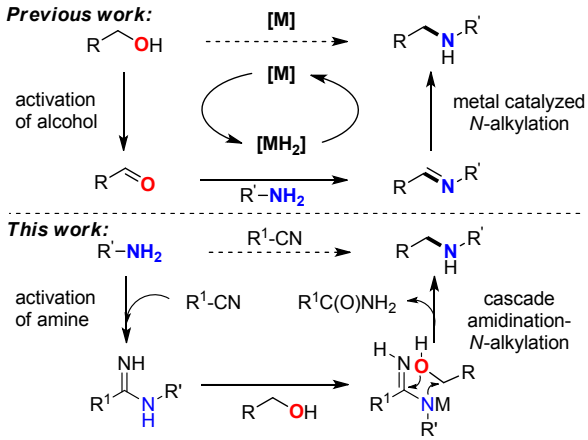
A base-mediated cascade amidination/*N*-alkylation reaction of amines by alcohols has been developed. Nitriles has been identified as an efficient and benign water acceptor reagent for the first time in the *N*-alkylation. Notably, the procedure tolerates a series of functional groups, such as methoxyl, halo, vinyl and hetero groups, providing a convenient method to construct the different substituted diamino compounds, ^{15}N labeled amine and could scaled up to 1 mol scale offered 138.7 g desired product in good yield in one-pot. Mechanistic studies provided strong evidence of amidination of amines with nitriles facilitated by *t*-BuOK.

As one of the most important fundamental structural motifs, amines has been considered as a privileged structure in natural products, bioactive molecules and functional materials.[1] As such, the development of efficient procedures toward these molecules is of great significance to chemical and material science and has attracted plenty of attention over the past decades.[2]

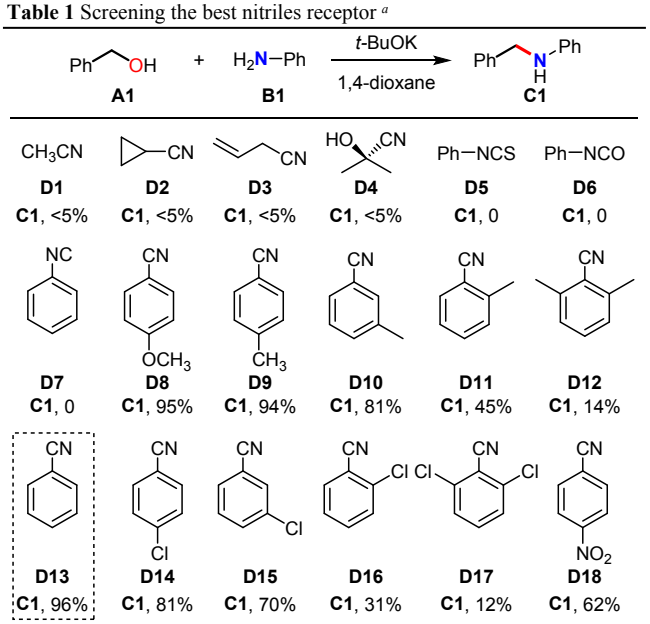


Scheme 1 State of the art and the reaction described here.

Metal catalyzed borrowing of hydrogen methodology (BH/HA) has become appealing way to offered versatile amines, which on account of the sustainable green features of the readily available alcohol substrates (its could abundant supply from indigestible lignocellulose biomass degradation) and advantages over the halide substrates.[3] Mechanistically, metal catalyzed *N*-alkylation functionalization is a thermodynamically unfavorable procedure, because of initial dehydrogenative alcohol converted to active hydridometal species and aldehyde.[4] Therefore, complex catalysts or capricious ligands are in most cases required to sustain the catalytic cycle, which generally are not readily accessible, manipulations and toxic (Scheme 1, top).[5] Thus, the development of efficient, economic, even metal catalyst or ligand free processes is still a challenging task in this field. One attractive approach to circumvent this problem is to employ the sole base or organic additive for realizing *N*-alkylation transformation.

Recently, we have identified that *t*-BuOK can deal with alcohols to generate alkoxide species and manganese-catalyzed olefination of alkyl-substituted *N*-heteroarenes with alcohols.[6] These results together with our progress on the use of alcohols as the replacement of sustainable green substrates for *N*-alkylation,[7] prompted us to envision that amines might be transformed to amidines for circumvent the inherent necessary in the metal catalyzed alkylation with catalyst stabilized by ligand for activated alcohols to maintain catalytic cycle.[8] Specifically, we postulated that the metathesis process of the intermediate amidine generated *in situ* from the amine with nitrile under the base promoted to alcohol gave the desired product, realizing nitriles as a water acceptor for sustain the transformation (Scheme 1, bottom). Moreover, to the best of our knowledge, there is no reaction system dealing with nitriles as water acceptor for the *N*-alkylation has been disclosed. Herein, we describe the first base mediated amidination/*N*-alkylation of amines by alcohols that employs nitriles as an efficient benign water acceptor.

Table 1 Screening the best nitriles receptor [a]



[a] Reaction conditions: **A1** (1.0 mmol), **B1** (0.5 mmol), **D** (0.8 mmol), *t*-BuOK (0.8 mmol), 1,4-dioxane (2.0 mL), 120 °C, N_2, 15 h. Yield of **C1** determined by GC-analysis.

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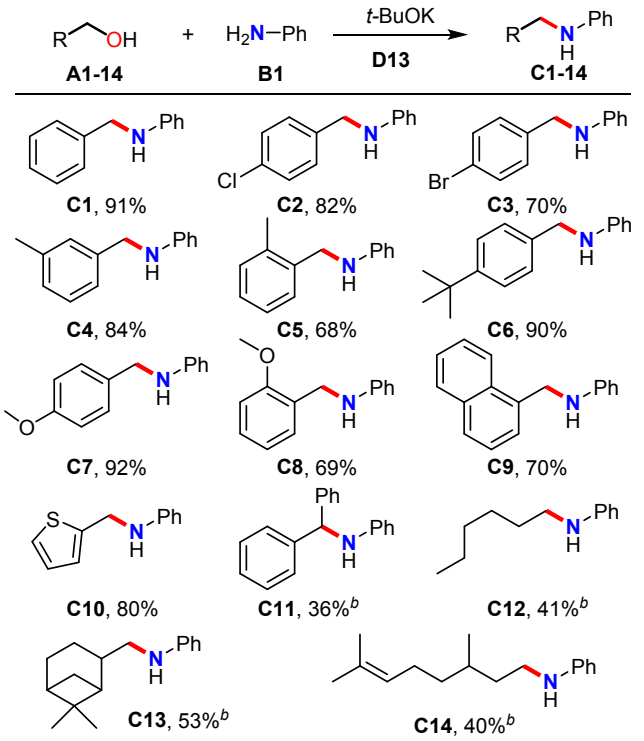
To probe the validity of our hypothesis, we examined the possibility of the *N*-alkylation of aniline by phenyl methanol with various nitriles as water acceptor (Table 1). After finding initial reaction conditions, different organic compounds with the groups contain of 'CN' were tested to find the most active nitriles. Only a trace amount of the desired **C1** was detected with alkyl substituted nitriles (**D1-D4**). Isothiocyanatobenzene, isocyanatobenzene or isocyanobenzene as the acceptor, the alkylation product was unfounded. Nitriles functionalized with the aromatic groups (**D8-D18**) gave the better yields of **C1**. Further investigation revealed that the reactivity was affected by the electronic and steric nature of the substituted groups of aromatic nitriles, and the sequence activity was electron-donating > withdrawing groups; *para* > *meta* > *ortho*. Thus benzonitrile was chosen as the relatively cheap acceptor. In addition, the best yield of **C1** was obtained after thoroughly optimization of the reaction parameters (type of base, amount of base, type of solvent, substrate ratio, reaction temperature and time) with **D13**.[9]

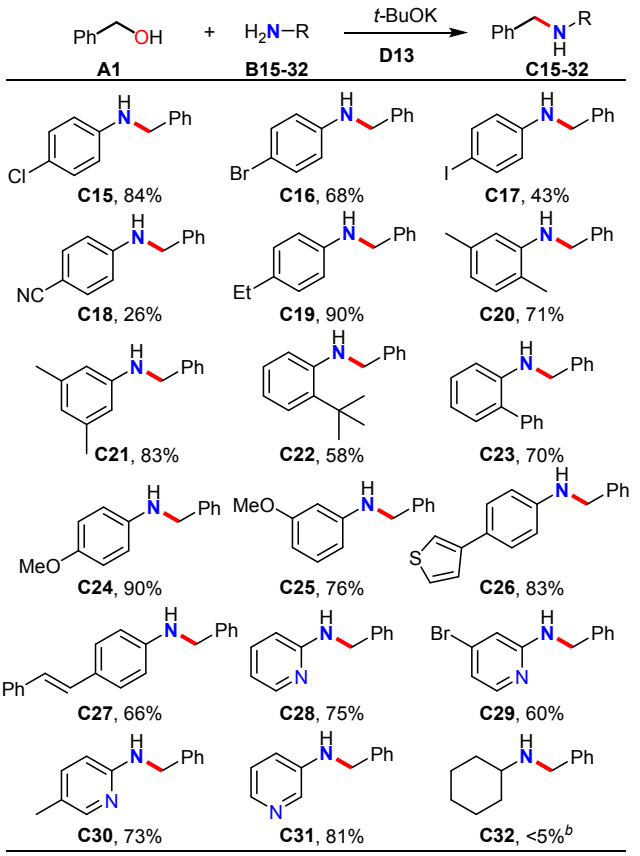
Table 2 *N*-alkylation of aniline with various alcohols [a]



[a] Reaction conditions: **A1-14** (1.0 mmol), **B1** (0.5 mmol), **D13** (0.8 mmol), *t*-BuOK (0.8 mmol), 1,4-dioxane (2.0 mL), 120 °C, N_2, 15 h. Isolated yield. [b] **A** (2.0 mmol), **D13** (1.0 mmol), 130 °C, 48 h.

With the optimized *N*-alkylation conditions in hand, initially, we examined the substrate scope of alcohols for the synthesis of *N*-substituted anilines (Table 2). Alcohols containing various electron rich and inefficient aromatic functional groups reacted smoothly to produce the corresponding products in good to high yields. The aryl halide substituent remained intact during this reaction (**C2**, **C3**), providing the *N*-alkylation adducts in high yields and a useful handle for further elaboration. The orientation of substituents on the aromatic ring system of alcohols had an obvious impact on the efficacy of the transformation, affording **C5** and **C8** in decrease yields. Naphthalen-1-amine was surveyed and the reaction proceeded to give **C9** in 70% yield. Heterocyclic **C10** could be obtained in good yield under standard conditions. **C11** was isolated in reasonable yield with biphenyl methanol substrate. Furthermore, aliphatic alcohols were less reactive and acceptable amount products **C12-C14** were formed when the reaction was conducted at high temperature for extension of reaction time.

Table 3 *N*-alkylation of phenyl methanol with various amines [a]



[a] Reaction conditions: **A1** (1.0 mmol), **B15-32** (0.5 mmol), **D13** (0.8 mmol), *t*-BuOK (0.8 mmol), 1,4-dioxane (2.0 mL), 120 °C, N_2, 15 h. Isolated yield. [b] **A1** (3.0 mmol), **D13** (2.0 mmol), *t*-BuOK (2.0 mmol), 150 °C (carried out in the autoclave), 48 h.

Subsequent, investigation of the scope regarding the amines was undertaken in Table 3. For most of the substituted anilines, the transformation proceeded smoothly to offer the corresponding products in moderate to excellent yields. The conversion could be compatible with a wide range of functional groups such as halo, cyano, alkyl, alkyloxy and thienyl groups, showing that the present reaction had a good functional groups tolerance. Lower yields were obtained substituted with electron-withdrawing groups than electron-donating ones on aromatic ring. Halide groups particularly, even iodo, survived well in the standard procedure, leading to corresponding adducts **C15-C17** in acceptable to good yields. The orientation of substituents of amines had slight impact on the efficacy of the conversion, affording the **C20, C22** and **C23** in decrease yields. Interestingly, the (*E*)-4-styrylaniline reacted rendering the target amine **C27** in

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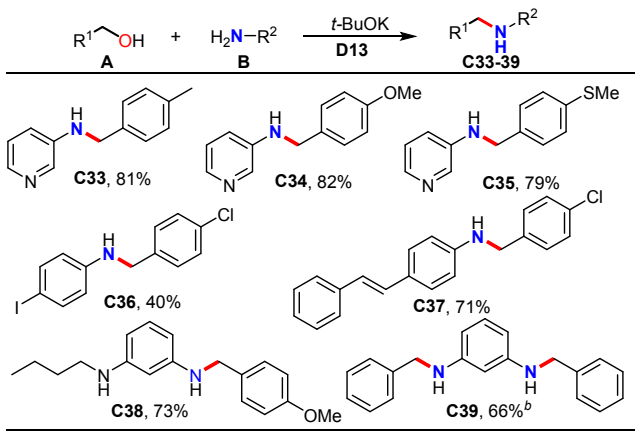
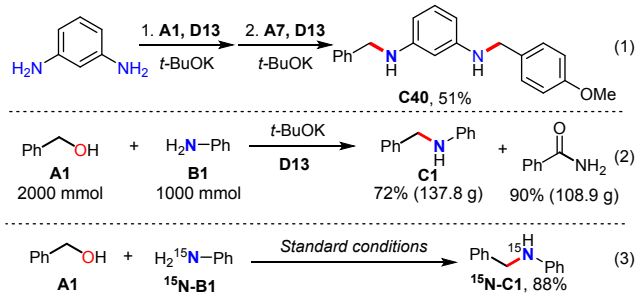
acceptable yield. Some heterocyclic moieties, including 2-pyridine, functionalization 2-pyridines and 3-pyridine, could be smoothly incorporated in the corresponding products **C28-C31**. Unfortunately, only trace amount of desired product was founded with aliphatic amine as partner even the reaction was even conducted under high temperature.

Table 4 *N*-alkylation of various alcohols with different amines [a]



[a] Reaction conditions: **A** (1.0 mmol), **B** (0.5 mmol), **D13** (0.8 mmol), *t*-BuOK (0.8 mmol), 1,4-dioxane (2.0 mL), 120 °C, N_2, 15 h. Isolated yield. [b] **A1** (3.0 mmol), **B1** (1.0 mmol), **D13** (2.0 mmol), 120 °C, 36 h.

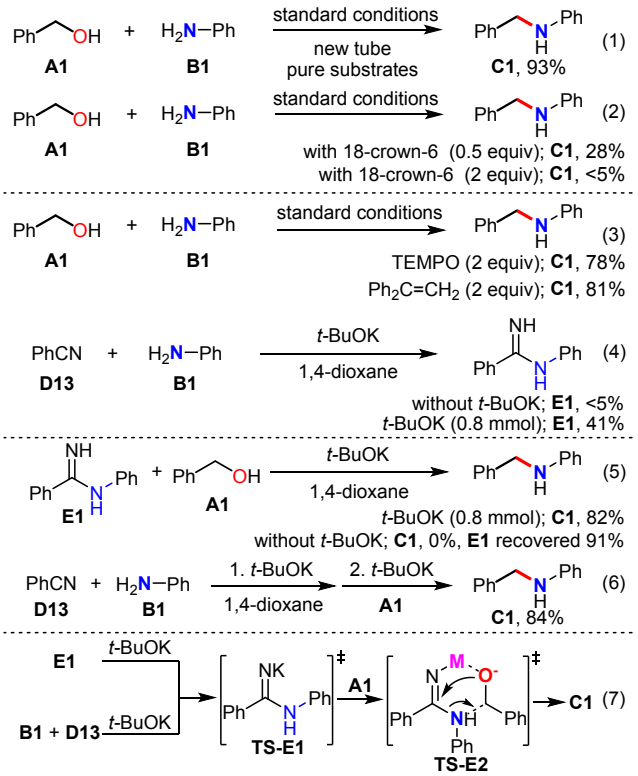
Furthermore, the *N*-alkylation of different substituent amines with various alcohols were also studied (Table 4). Alcohols bearing alkyl, alkyloxy and methylthio substituents derived from aromatic alcohols were effective substrates to react with pyridin-3-amine to provide the corresponding products **C33-C35** in good to high yields. Iodo and alkenyl substituted amines with (4-chlorophenyl)methanol underwent the *N*-alkylation process to give the desired products **C36-C37** in acceptable to good yields. Furthermore, the N^1-hexylbenzene-1,3-diamine reacted successfully rendering the target amine **C38** in good yield. Interestingly, double alkylation occurs when benzene-1,3-diamine was subjected to the present reaction, providing **C39** with double amino groups in 66% yield.



Scheme 2 Application of N-alkylation.

The cascade *N*-alkylation of benzene-1,3-diamine with **A1** and **A7** in the presence of appropriate amount of nitrile to form the **C40** in moderate yield, which can be used for to construct the different substituted diamino compounds and further transformations to complex amines molecules. Hereafter, we scaled up the transformation to 1 mol scale and product **C1** was recrystallized in 72% (137.8 g) with 90% (108.9 g) yield of byproduct benzamide. Subsequently, the ^{15}N-labeled *N*-benzyl aniline (**^{15}N-C1**) was formed when ^{15}N-labeled aniline was utilized, providing a convenient stratagy to incorporate ^{15}N into amine molecules (eq 3).

More experiments were carried out for better understanding of the mechanism (Scheme 3). Initially, we examined a series of reaction conditions (ultra-pure substrates) using the new reaction tube, there was no impact on yield of **C1**, indicating this transformation should not involve a transition metal catalyzed process (eq 1). Furthermore, only trace amounts or low yield of the **C1** was obtained in the presence of 18-crown-6 (eq 2), attributing to the strong complexation ability of 18-crown-6 with the potassium cation.[10] In addition, **C1** was obtained in good yield when tetramethylpiperidin-1-oxyl or ethene-1,1-diyldibenzene were added into the standard reaction as radical scavenger, showing that this reaction should not be a free radical process (eq 3). These results demonstrated that the significant role of the base and nitrile in promoting this transformation the *N*-alkylation rather than metal catalysts or its impurities.



Scheme 3 Mechanistic investigations.

In addition, *N*-phenylbenzimidamide **E1** could be isolated 41% yield under the standard conditions, only trace amount of **E1** was detected in absence of base (eq 4). Further **E1** with **A1** could be transformed into **C1** in good yield at the same reaction conditions, but no reaction in absence of *t*-BuOK and **E1** could be recovered in high yield (eq 5). Meanwhile, **C1** was obtained in 84% yield by step by step reaction (eq 6). Furthermore, **E1** and byproduct benzamide were detected during the reaction, and the yield of **E1** and benzamide at different reaction times are outlined in Figure 1.[9] These results showed that *N*-phenylbenzimidamide **E1** (*in situ* form is **TS-E1**) may be the intermediate since the transformation of **E1** to **C1** *via* **TS-E2** was observed in Figure 1 and further confirmed our previous work.[7b]

Conclusions

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In summary, we have demonstrated an efficient protocol for the *t*-BuOK mediated cascade amidiation/*N*-alkylation of amines by alcohols. Importantly, the reaction employs nitriles as an inexpensive and benign water acceptor. Furthermore, this transformation is very practical, and a series of functional groups could be tolerated. As such, it represents a novel and simple method to access the different substituted monoamino, diamino compounds, ^{15}N labeled amine molecule and could scaled up to 1 mol scale. Further studies aimed at gaining a detailed mechanistic understanding of this *N*-alkylation and the application of base as the efficiently mediator in other transformations are currently in progress in our laboratory.

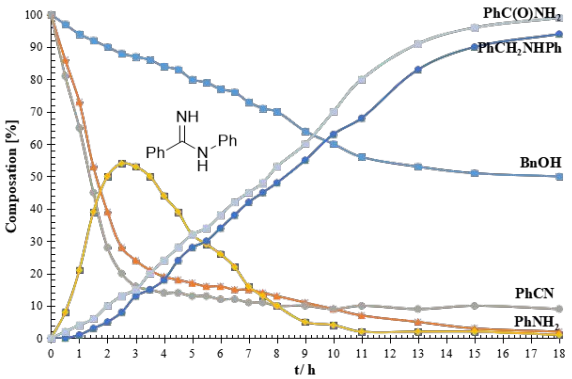

Figure 1 Distribution along with the reaction time.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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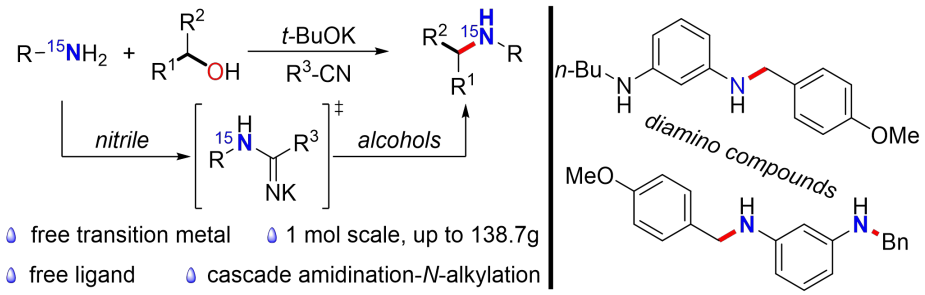

We have developed an efficient base mediated cascade amidination/*N*-alkylation of amines by alcohols with nitriles as a benign water acceptor reagent, providing a convenient method to construct the different substituted diamino compounds, ^{15}N labeled amine molecules and could scaled up to 1 mol scale.