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Direct Alkylation of Amines with Alcohols Catalyzed by Base

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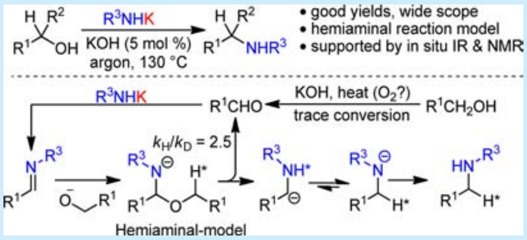
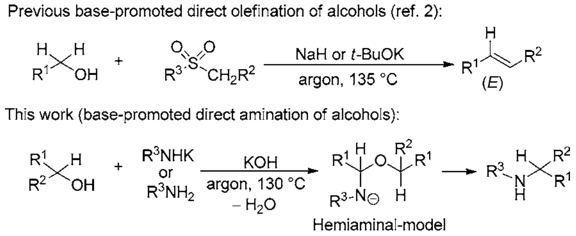
Supporting Information

ABSTRACT: A base-catalyzed/promoted transition-metal-free direct alkylation of amines with alcohols has been developed, giving the desired amines in generally high yields from either aromatic or aliphatic alcohols. On the basis of the ^1H NMR and in situ IR (React-IR) monitoring experiments, isotope-labeling experiments, as well as control experiments, a novel "hemiaminal" model is proposed to understand the mechanism, which explains the formation of the "extra" aldehyde in the reaction.



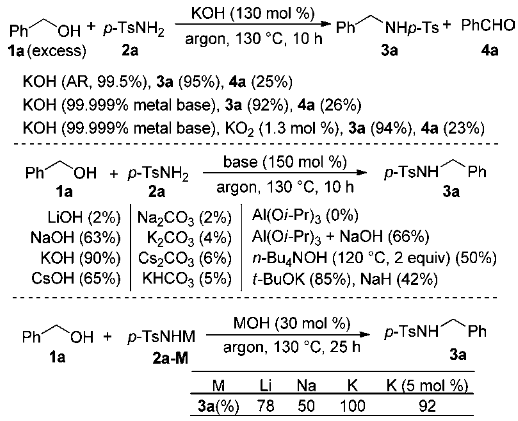
Self-hydride-transferring oxidation–reduction strategy[1] has been well utilized in the transition-metal-catalyzed direct alkylation of amines with alcohols for its atom-economic synthesis based on a self-hydride transferring coupling strategy.[2,3] In this process, no extra hydrogen sources are needed. The metal-catalyzed direct alkylation of amines has been well-established by catalysts such as Ru,[4] Rh,[5] Pd,[6] Fe,[7] Ni,[8] etc. In principle, a transition-metal-free process could be promising to avoid the problems (metal residue, high costs, etc.) caused by metal catalysts. In this paper, we report a base-promoted direct alkylation of amines with alcohols under transition-metal-free conditions (Scheme 1, bottom). A mechanistic study based on experimental evidence was also performed.

Scheme 1

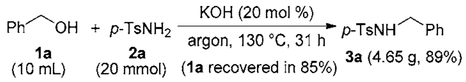


In our investigation on the transition-metal-catalyzed oxidative coupling of benzyl alcohol **1a** with p-$TsNH_2$ **2a**, we noticed that, without catalysts, the reaction also worked well (Scheme 2). In the ICP-AES (inductively coupled plasma atomic emission spectroscopy, an elemental analytical technique) tests, transition metals such as Pd, Ru, and Cu were not observed. Highly pure (99.999% metal bases) KOH did not change the results. *t*-BuOK afforded **3a** in high yield as well, while carbonates gave trace conversions.[9b,12] Use of deprotonated **2a** led to a decrease in stoichiometric base to 30 mol %. Potassium hydroxide proved to be the optimized base, and only 5 mol % of KOH afforded the desired product **3a** in 92% yield. "Extra" aldehyde **4a** could be generated in the reaction conditions,[10,11] increasing from <0.1% in the starting material to 25% in the reaction mixture (Scheme 2).

Scheme 2. Effect of Bases and Metal Cations



When a catalytic amount of KOH was used as catalyst, the direct amination of alcohols with various potassium sulfonamides **2**-K afforded target products generally in high to excellent yields (Scheme 3). For example, benzyl alcohol reacted with different potassium sulfonamides to afford the corresponding sulfonyl amines **3** in high yields (**3a**, **3i**, **3j**, **3k**). The heteroaryl alcohols also gave the desired products in high to excellent yields (**3b** and **3c**). In all examples, extra alcohol starting materials could be recycled. A gram-scale benzylation of **2a** with benzylic alcohol gave more than 4 g of **3a** in 89% isolated yield (eq 1).



(1)

With respect to the arylamines, the amines were used as starting materials directly; thus, excess KOH was used. Various

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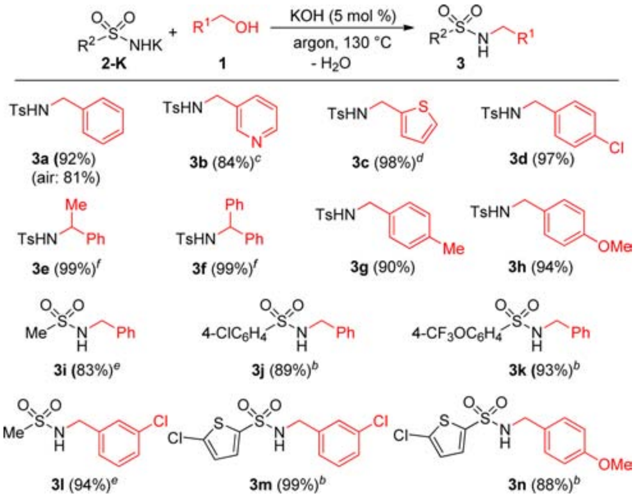
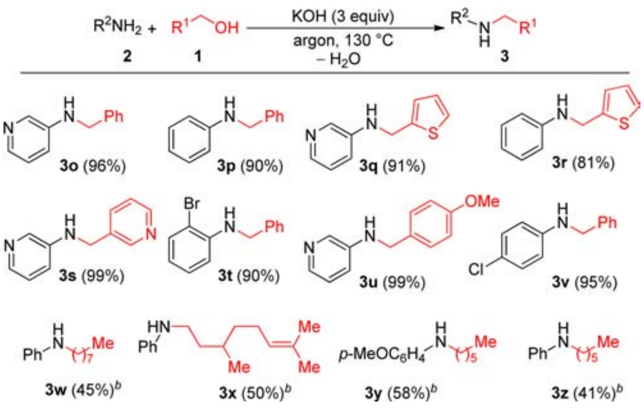
Scheme 3. Direct Alkylation of Sulfonamides with Alcohols[a]



[a]Reaction conditions: **1** (1 mL) and **2-K** (1 mmol), KOH (0.05 mmol), 130 °C, argon, isolated yield. [b]KOH (0.3 mmol). [c]KOH (0.2 mmol). [d]KOH (0.5 mmol). [e]KOH (0.4 mmol). [f]Using $TsNH_2$ instead of *p*-TsNHK, without KOH.

arylamines **2** reacted with alcohols **1** under the promotion of KOH, affording the target products **3o**−**v** in good to high yields (Scheme 4). Normally, a longer reaction time would be necessary for arylamination compared to the sulfonylamidation, despite the use of excess base. For the heteroarylamines, pyridin-3-amine afforded the corresponding amine products in excellent yields (**3o**, **3q**, **3s**, and **3u**). The aniline bearing a 2-bromo group could also give the product without loss of the bromo substituent (**3t**). The less active aliphatic alcohols could be applied in the direct alkylation of amines as well (**3w**−**z**).

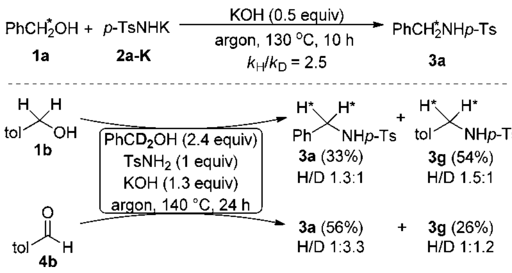
Scheme 4. Direct Alkylation of Arylamines with Alcohols[a]



[a]Reaction conditions: **1** (1 mL) and **2** (1 mmol), KOH (3 mmol), 130 °C, argon, isolated yield. [b]NaH instead of KOH, 160 °C.

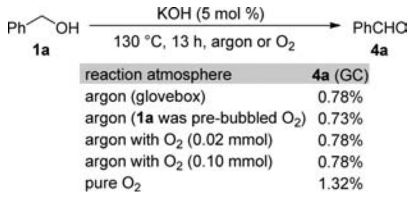
A first-order kinetic isotope effect was established as 2.5 for this direct alkylation of amines with alcohols, suggesting that the C−H cleavage step should be the rate-determining step (Scheme 5). When the mixture of $PhCD_2OH$ and *p*-$MePhCH_2OH$ was subjected to the reaction conditions, a mixture of products was obtained. The deuterium-labeling experiments showed that the hydride could transfer intermolecularly, which was further confirmed by the treatment of the mixture of $PhCD_2OH$ with *p*-MePhCHO.

Scheme 5. Deuterium-Labeling Experiments



The dehydrogenative oxidation of benzyl alcohol **1a** (with <0.1% of benzaldehyde **4a**) afforded 0.78% of **4a** (Scheme 6), which probably accelerated by trace amounts of O_2. Despite trace amounts of H_2 being detected by GC, the mechanism for dehydrogenative transformation of BnOH to PhCHO is unclear. Nevertheless, wherever **4a** appears, the trace amount of it is crucial for triggering the catalytic cycle.

Scheme 6. Effect of O_2 on Generation of 4a[a]

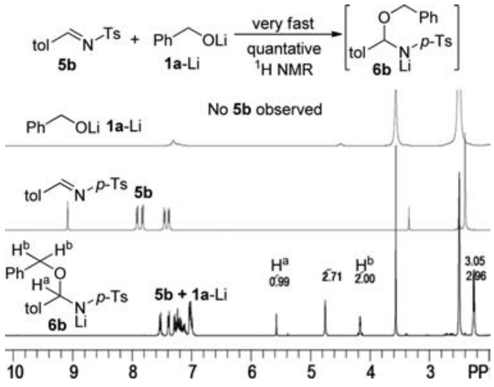


reaction atmosphere	**4a** (GC)
argon (glovebox)	0.78%
argon (**1a** was pre-bubbled O_2)	0.73%
argon with O_2 (0.02 mmol)	0.78%
argon with O_2 (0.10 mmol)	0.78%
pure O_2	1.32%

[a]Compound **1a** was sequentially degassed by bubbling argon for 2 h and then further degassed by freeze−pump−thaw method (in liquid N_2).

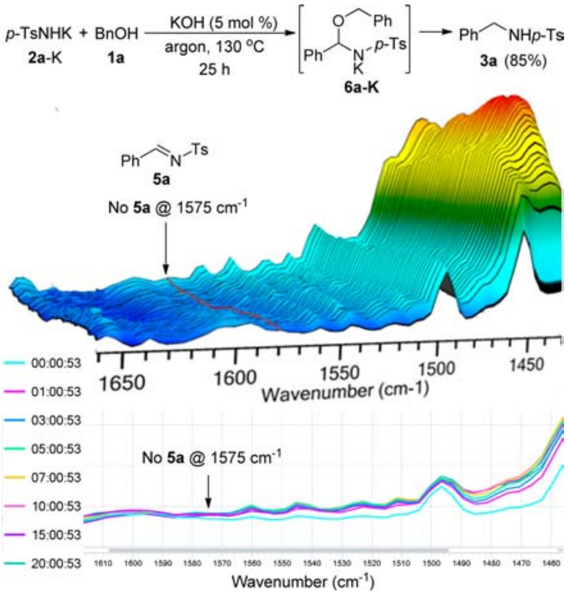
To investigate the possible hemiaminal intermediate in the reaction, deprotonated **1a** was added into the solution of imine **5b**. Upon the addition of **1a-Li**, **5b** completely disappeared, and intermediate **6b** was observed as the only compound from imine **5b** (Scheme 7), suggesting there was no observable imine **5b** to work as active intermediate for the O/M.P.V. (Oppenauer/Meerwein−Ponndorf−Verley) transition state. This observation was reasonable because imine **5b** is a very good electrophile and BnO^- is a good nucleophile. No imine **5a** was obsered by in situ IR in the reaction of **5a** with **1a** and amination of BnOH with TsNHK (Scheme 8). Intermediate **6a-Li** could be trapped by MeI to afford *N*-Me hemiaminal **7a** in 39% isolated yield (eq 2).

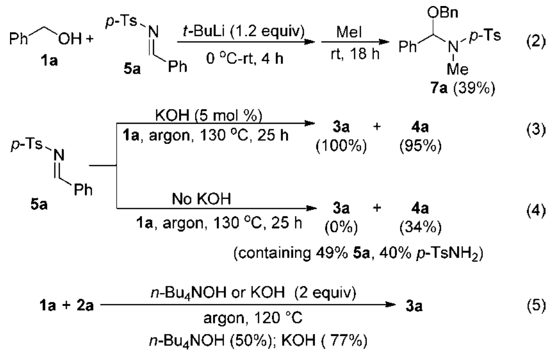
Scheme 7. Detecting Hemiaminal 6b by ^1H NMR



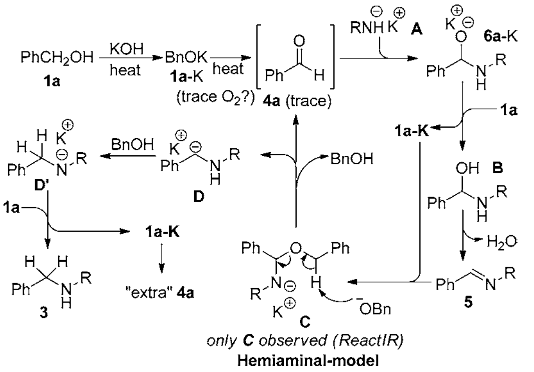
A hemiaminal working model was proposed on the basis of the experimental evidence (Scheme 9). First, the trace amount of

Scheme 8. Monitoring 5a by React-IR with KOH as Catalyst





Scheme 9. Working Model



benzaldehyde **4a** forms from **1a** (probably generated by the aid of trace amount of O_2, see details in Scheme 6), followed by the addition of **A** to form **6-K**, which is further protonated to **B**. The dehydration of intermediate **B** furnishes imine **5**, which is supported by the control reaction demonstrated in eq 3. Once imine **5** forms, it is simultaneously attacked by BnOK to afford hemiaminal **C**, supported by ^{1}H NMR and in situ IR monitoring (Schemes 7 and 8). **C** transforms to **D′** with the regeneration of aldehyde **4a**, which should be the rate-determining step since a KIE of 2.5 was observed (Scheme 5). The hemiaminal intermediate **C** is the only observable form from its imine precursor. The intermediate **C** is deprotonated by BnOK to form **D**. Finally, **D′** extracts a proton from **1a** to afford target amine product **3**. It should be pointed out that an additional 1 mol of BnOK forms in the last step, giving rise to the formation of some extra aldehyde. This extra aldehyde shows that aldehyde is an intermediate rather than a "catalyst" for this reaction.[9b]

In contrast, an O/M.P.V. redox model has been proposed in previous work, where aldehyde was considered as a "catalyst".[9b] In fact, imine **5b** disappeared immediately during mixing with deprotonated **1a** (Scheme 7); i.e., there was no observable imine intermediate in the reaction mixture, indicating too little imine to form the O/M.P.V. transition state. In the addition, K^+ is a very weak Lewis acid, and a stable transition state is difficult to obtain. However, n-Bu_4NOH alone instead of KOH could also give a moderate yield at 120 °C (n-Bu_4NOH decomposes at higher temperature) (eq 5), indicating that metal does not have to be necessarily involved in this reaction. Therefore, the O/M.P.V. working model could be ruled out thus far (Scheme 9).

In conclusion, a base-catalyzed/promoted direct amination of aromatic and aliphatic alcohols has been developed. Amounts of KOH as low as 5 mol % could promote the amination of alcohols in generally high yields. On the basis of the ^{1}H NMR and in situ IR-monitoring experiments, isotope-labeling experiments, as well as control experiments, a novel "hemiaminal" working model is proposed to understand the formation of the "extra" aldehyde which has not yet been wholly presented. The formation of extra aldehyde also proved that this reaction should not be "catalyzed" by aldehyde, as has been proposed before. Because n-Bu_4NOH alone could promote this reaction, a metal cation such as K^+ would not be necessary as a "Lewis acid" for this reaction. In addition, the transition-metal-free process, cheap base reagent, high efficiency, and direct amination of alcohols are all highlights of this method. This work is promising for large-scale manufacturing amines directly from various alcohols. The reaction model is also helpful for understanding the "direct" functionalization of alcohols under transition-metal-free conditions.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02685.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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(12) In highly concentrated solution (ref 9b), the reaction promoted by K_2CO_3 and 10 mol % of PhCHO gave a low yield of product together with 25% of aldehyde (repeated in our laboratory).

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