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Access to Secondary Amines through Hydrogen Autotransfer Reaction Mediated by KO^{t}Bu

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Dedicated to our colleague Prof. Douglas B. Grotjahn

We report herein an *N*-alkylation reaction of amines with alcohols through a hydrogen autotransfer reaction. Unlike other catalytic systems containing transition metals or additives, potassium tertiary butoxide was found to be a unique and effective catalyst for synthesizing secondary amines. The role of the K^+ ion and the reaction intermediates were studied under control experiments and by theoretical calculations. The reaction was found to be general and tolerates a series of functional groups, providing a convenient method to synthesize *N*-alkylated compounds.

Introduction

Alkylated amines and their derivatives are prevalent moieties found in various natural products and have wide applications in agrochemicals,[1] pharmaceuticals,[2] and material science (Figure 1).[3] Although several methods are available in the literature, for synthesizing alkyl-amines including reductive methods,[4] carbon–nitrogen cross-coupling reactions,[5] *N*-alkylation with an alkyl halide,[6] etc. most of these reports suffer from drawbacks such as long and tedious reaction protocol,[7] requirement of expensive alkyl halides as alkylating agents,[8] generations of the stoichiometric amount of waste,[9] low atom efficiency,[10] narrow substrate scope,[11] and over alkylation.[12] To avoid over-alkylation, a route via imine followed by hydrogenation is well appreciated for a long time. Though, the limited availability of aldehydes in nature enforced us to find an alternate pathway starting with alcohol as the alkylating agent.

Hydrogen autotransfer reaction is an extremely useful strategy for alcohol transformation via the dehydrogenation-hydrogenation pathway.[13] In general, the hydrogen autotransfer reaction proceeds with the activation of one of the reactants via the borrowing of two hydrogen atoms from it followed by a condensation reaction and finally the return of borrowed hydrogen to the reaction intermediate to form the product (Scheme 1). This methodology employs alcohols directly as alkylating agents and has been widely used to construct carbon-carbon and carbon-heteroatom bonds with water as the only byproduct.[14]

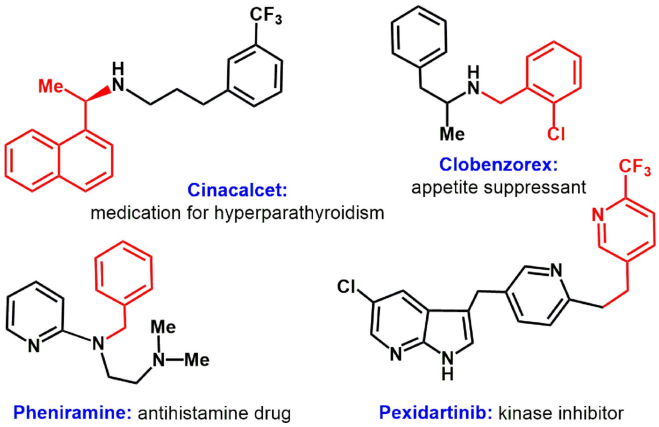
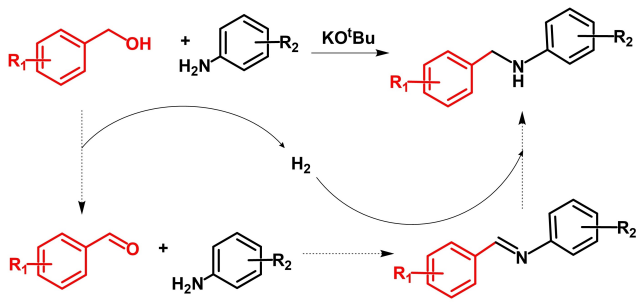


Figure 1. Selected examples of pharmaceutically important *N*-alkylated amines.

During the hydrogen borrowing reaction between benzyl alcohol and aniline, an initial dehydrogenation of the alcohol



Scheme 1. Current work.

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results in the formation of the corresponding aldehyde, which then undergoes condensation with an amine to form imine, followed by hydrogenation of the intermediate imine into *N*-alkylated amine (Scheme 1). As the reactant alcohol acts as the hydrogen donor this process does not require an external hydrogen source. The selective *N*-alkylation of primary amines using alcohols via the borrowing hydrogen strategy is recognized as an efficient and benign method of obtaining secondary amines.

Extensive research has been carried out to explore the *N*-alkylation reaction via the hydrogen borrowing method catalysed by precious metals e.g., Au,[15] Ir,[16] Ru,[17] Pd.[18] Then the focus was shifted to the inexpensive and more abundant, first-row transition metal as catalyst.[19] As a result, since the last decade, several hydrogen borrowing reactions have been reported employing Cu,[20] Mn,[21] Fe,[22] Co,[23] Ni[24] and Zn[25] as catalysts which offer an easy and straightforward route for *N*-alkylation starting with alcohol as the reactant (Scheme 2).

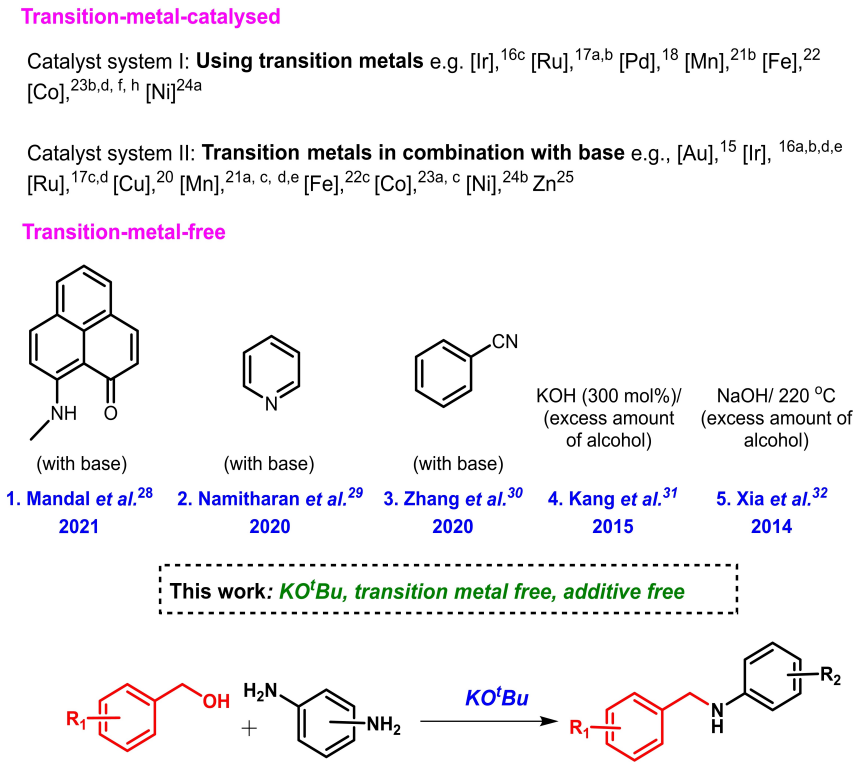
Although the hydrogen autotransfer reactions have several economical and operational benefits, the requirement of transition metal catalysts is one of the severe drawbacks, considering that heavy transition metals are rare, expensive, and toxic in nature. Moreover, metal contamination in the final product is one of the serious limitation of using transition metals as catalysts.[26] Additionally, discarded catalysts wastes often cause environmental pollution and arehazardous to the marine ecosystem.[27]

Thus, transition metal-free *N*-alkylation gains significant importance in overcoming the aforesaid challenges.[28–33] Recently, Mandal and coworkers showed that phenalenyl ligand could imitate the role of transition metals in storing and transferring hydrogen molecules leading to the alkylation of anilines by alcohols via borrowing hydrogen method.[28] Similarly, Namitharan and coworkers used pyridine as efficient biomimetic hydrogen shuttles for a transition-metal-free direct *N*-alkylation.[29] Likewise, Hu and coworkers found nitriles mediated cascade *N*-alkylation reaction of amines by alcohols.[30] Nevertheless, the existing reports possess significant difficulties like very high reaction temperatures,[31] requirements of excess amounts of inorganic bases,[32] and additives.[33]

On the other hand, an interesting report by Berkessel and coworkers showed the role of KO^{t}Bu in ketones hydrogenation.[34] Additionally, Grubbs and coworkers reports KO^{t}Bu-catalysed dehydrogenative silylation of aromatic heterocycles.[35] In the last few years, several methodologies were reported employing KO^{t}Bu as a dehydrogenating agent for various transformations.[35,36] Inspired by these unique approaches, we recently reported potassium tertiary butoxide-mediated acceptorless dehydrogenation alcohol in 2-aryl quinazoline synthesis.[37] With our continued interest in transition metal-free reactions, we report here the direct use of potassium tertiary butoxide in hydrogen-borrowing reactions between primary amines and alcohols.

Results and Discussion

To optimize the reaction conditions, the reaction was studied with various reaction parameters such as reaction temperature, time, solvents, and the amount of base used, and the results are



Scheme 2. State of the art in direct *N*-alkylation reactions using alcohol as alkylating agent.

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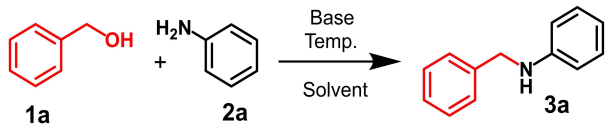
summarized in Table 1. The maximum yield of the product was obtained when benzyl alcohol (0.75 mmol), aniline (0.5 mmol), KO^{t}Bu (0.5 mmol), in toluene (2 mL) were stirred in argon atmosphere for 24 h, under refluxing condition using heating block at 130 °C (Table 1, entry 3). Deviation from a standard condition with respect to reaction time and temperature generates a lower yield of the product (Table 1, entries 1, 2, 4). Though the reaction smoothly undergoes in toluene, a polar hydrocarbon solvent, it fails to initiate in DMF, a polar protic solvent that effectively solvates the cation (Table 1, entry 12). Surprisingly it has been observed that the similar base NaO^{t}Bu failed to initiate the reaction (Table 1, entry 6). Furthermore, a weaker base such as KOH gave only 39% of the product (Table 1, entry 7), whereas only trace amount of product was obtained when NaOH was used as base (Table 1, entry 8).

Table 1. Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Solvent	Base	Temperature (°C)	Time(h)	Isolated Yield (%)[b]
1	Toluene	KO^{t}Bu	130	8	43
2	Toluene	KO^{t}Bu	130	12	57
3	Toluene	KO^{t}Bu	130	24	91
4	Toluene	KO^{t}Bu	100	24	61
5	Toluene	KO^{t}Bu	130	24	45[c]
6	Toluene	NaO^{t}Bu	130	24	Trace[d]
7	Toluene	KOH	130	24	39
8	Toluene	NaOH	130	24	Trace
9	Toluene	Cs_2CO_3	130	24	10
10	Toluene	K_2CO_3	130	24	Trace
11	Toluene	$KHCO_3$	130	24	Trace
12	DMF	KO^{t}Bu	130	24	Trace
13	H_2O	KO^{t}Bu	100	24	Trace
14	^{t}amyl alcohol	KO^{t}Bu	130	24	Trace
15	Toluene	KO^{t}Bu	130	24	Trace[d]
16	Toluene	KO^{t}Bu	130	24	86[e]

[a] Reaction conditions: benzyl alcohol (0.75 mmol), aniline (0.5 mmol), base (0.5 mmol), solvent (2 mL) stirred under argon atmosphere for required time using a preheated heating block; [b] Yields refer to those of pure products characterized by ^{1}H NMR, and ^{13}C NMR spectroscopic data; [c] using 0.25 mmol of KO^{t}Bu; [d] along with 2 mmol of 18-crown-6 ether; [e] along with 2 mmol of TEMPO.

To confirm the role of potassium ions in this reaction, metal-ion trapping experiments using 18-crown-6 ether have been performed (Table 1, entry 15). The reaction was completely arrested in the presence of excess 18-crown-6 ether which indicates the crucial role of potassium ions in the reaction pathway. This confirms the significant role of K^+ ions in the present reaction. In addition, to check any possible metal contamination,[38] *i.e.* the leading force of the reaction, ICP-OES (Inductively Coupled Plasma Optical Emission Spectroscopy) of each chemical used was performed and only rather insignificant 1.8, 1.3, 0.1, 0.8 ppm level of copper, nickel, manganese and silver ions were detected,[39] while other metal ions are below the detection level. To completely rule out the possible impurity effect, we carried out two similar reactions using new glassware and stirring bars under standard reaction conditions, where we intentionally added a catalytic amount of transition metal salts (0.1 mg of $NiCl_2$, $CuSO_4$, $PdCl_2$, $RuCl_3$) into one of the reaction mixtures. After 8 h of the reaction, we found the yield of the product was comparable in both cases, indicating the insignificant role of those metal ions in the reaction.

In general, the reactions were very clean, giving the corresponding *N*-benzylaniline in high yields. To further explore the scope of this strategy, a wide variety of substituted anilines and benzyl alcohols were chosen as substrates and the results are summarized in Table 2. It is observed that the reaction was uniform regardless of the nature of substituents on the aromatic ring. The substrate containing electron-releasing functional groups e.g. –Me and –OMe as substituents gave very high yields of the products (Table 2, entries **3b**, **3e**, **3g**, **3h** and **3i**). The easily reducible functionalities such as –OAll, –$COCH_3$, –NO_2, remained unaffected (Table 2, entries **3f**, **3m** and **3o**). Additionally, hydrolyzable functional groups such as –CN is well tolerated under the present reaction conditions (Table 2, **3n**). Furthermore, the reaction was smoothly performed with the reactants containing halogen functionalities e.g. –Br, –Cl and –F (Table 2, entries **3c**, **3d**, **3j**, **3k** and **3l**) and furnished good to the excellent yield of the products. Moreover, we found that chloro-substituted benzyl alcohols were slightly less reactive (Table 2, entries **3c** and **3d**). However no dehalogenation product was detected. Then, vulnerable moiety e.g. O-benzyl (Table 2, entry **3p**) also provided a good yield of the product. Surprisingly, aliphatic alcohols, which readily undergo alcohol dimerization under hydrogen borrowing reaction conditions,[19] showed satisfactory performance in the present reaction strategy (Table 2, entries **3r**, **3s**, and **3t**). Heterocyclic moieties also gave good results (Table 2, entries **3q** and **3t**). And also unexpectedly, the reaction with aliphatic amines was sluggish and when reaction was carried between aliphatic amines or benzylamine with benzyl alcohol in the presence of excess of KO^{t}Bu we obtained the corresponding imine as the product (SI).

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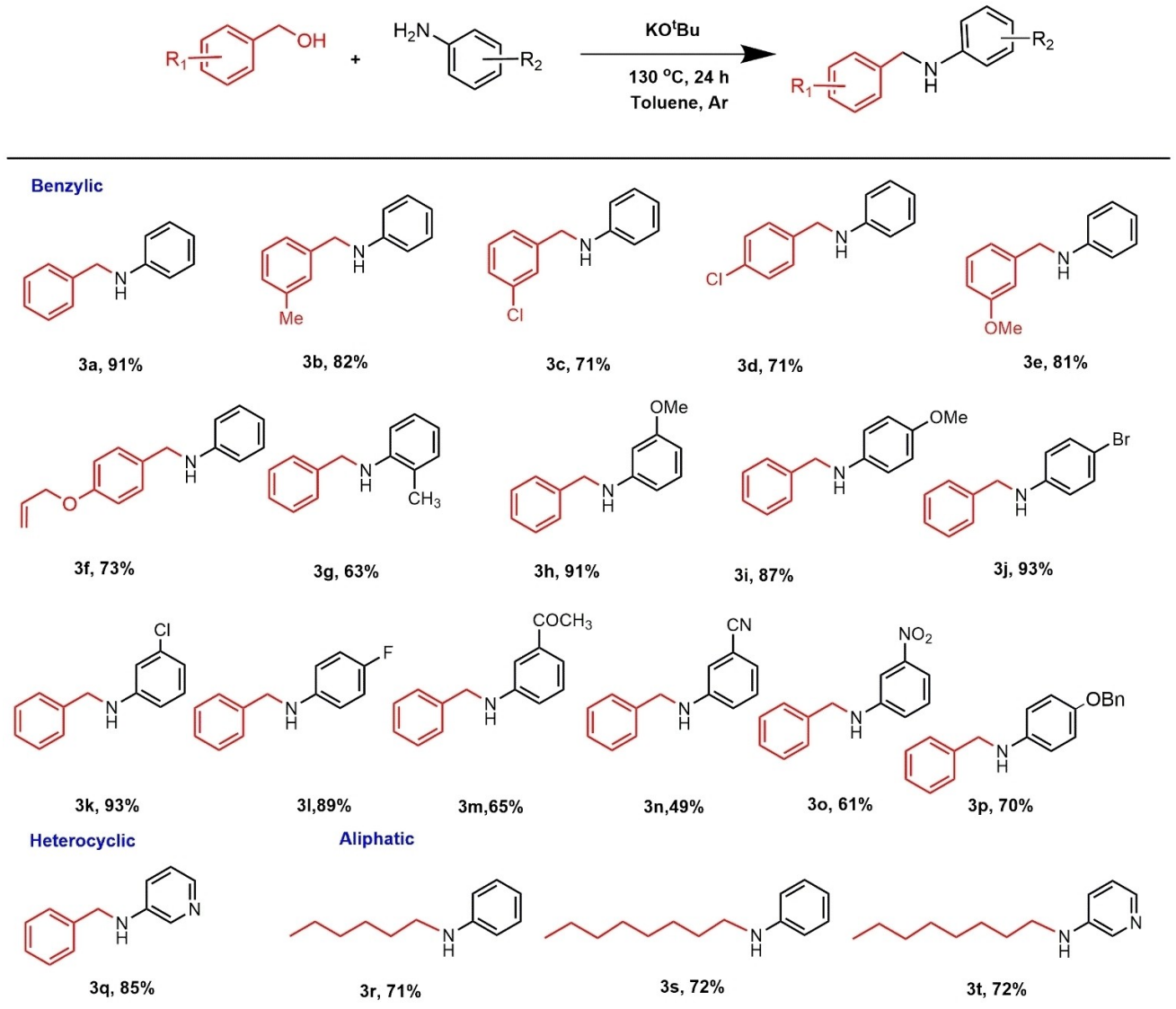
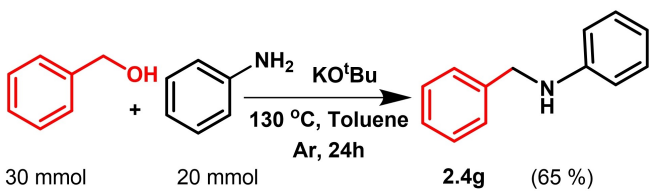
Table 2. Substrate scope for *N*-alkylation.



[a] Reaction conditions: benzyl alcohol (0.75 mmol), aniline (0.5 mmol), KO^{t}Bu (0.5 mmol), toluene (2 mL) stirred under argon atmosphere for 24 h using a preheated heating block, [b] Yields refer to those of pure products characterized by ^{1}H NMR, and ^{13}C NMR spectroscopic data.

The gram-scale utility of the reaction was validated (Scheme 3) using 20 mmol of aniline as substrate and gave 65% yield of the corresponding product (vs 91% in 0.5 mmol scale).

To investigate the mechanistic pathway for the reactions, a series of control experiments were carried out and reported in Figure 2, Table 1. To check whether the reaction follows the free radical pathway we performed the reaction in the presence of TEMPO (Table 2, entry 16). We observed no appreciable change in yield, and this ruled out the possibility of the free radical pathway. To understand the reaction intermediate, the reaction stopped after 12 h (instead of 24 h required for full completion) and the liquid crude products are analyzed by NMR spectroscopy (Scheme 4, eq 1 and Figure S4, in SI). The presence of benzaldehyde, imine, and *N*-benzyl-aniline along with the reactant used was identified in the crude reaction mixture. Moreover, the presence of hydrogen gas was identified by gas chromatography (Figure S7, in SI) during the reaction. Obviously, when we carried out the reaction with benzaldehyde instead of benzyl alcohol, we were unable to detect the desired product and the reaction stopped only at the imine stage



Scheme 3. Gram scale synthesis.

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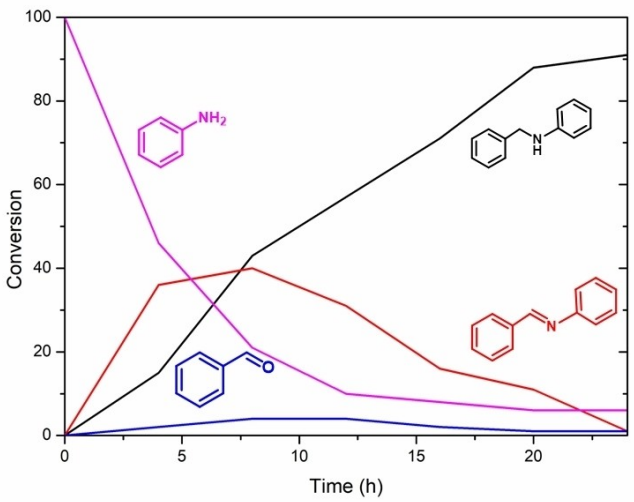
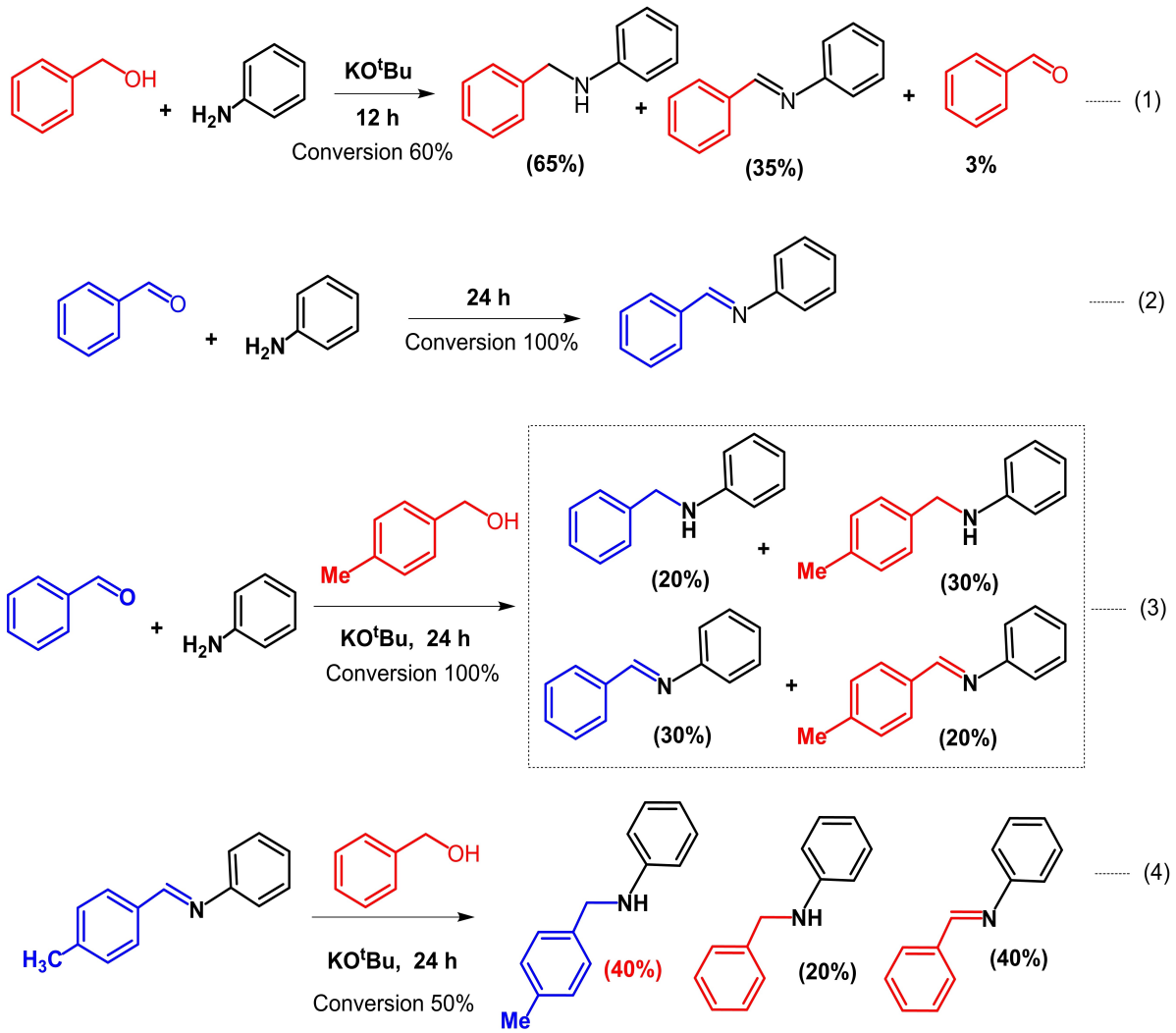


Figure 2. Conversion with time plot.

(Scheme 4, eq 2). This confirms the role of benzyl alcohol as a hydrogen donor. Furthermore, in a crossover experiment using benzyl alcohol and *p*-anisaldehyde as substrate (Scheme 4, eq 3 and Figure S5, in SI) we obtained two sets of products. To further verify this, we carried out the reaction using imine (4a) and 4-methylbenzyl alcohol (Scheme 4, eq 4). The result confirms that imine is one of the major intermediates along with aldehyde.

Experimental results clearly indicate that KO^{t}Bu has a significant role in the hydrogenation dehydrogenation step. To enlighten the role of KO^{t}Bu, we performed Density Functional Theory (DFT) calculations (Figure 3). As in our previous work,[37] the reaction begins with the formation of complex **1** ($\Delta G = -7.0$ kcal/mol) between a molecule of benzyl alcohol and KO^{t}Bu. Next, the benzyl alcohol is oxidized to benzaldehyde **3** ($\Delta G = 1.7$ kcal/mol) via a six-membered ring transition state **TS 1→2** ($\Delta G^{\ddagger} = 26.5$ kcal/mol) and releasing hydrogen into the solution. Meanwhile, a molecule of aniline is deprotonated by KO^{t}Bu forming **4**, which easily reacts with benzaldehyde to form the potassium carbinolamine **6** ($\Delta G = 5.7$ kcal/mol).



Scheme 4. Control experiments (Reaction conditions: all the reactions are carried out under argon atmosphere at 130 °C in toluene medium, selectivities are calculated from the respective ^{1}H NMR spectra and given in the brackets).

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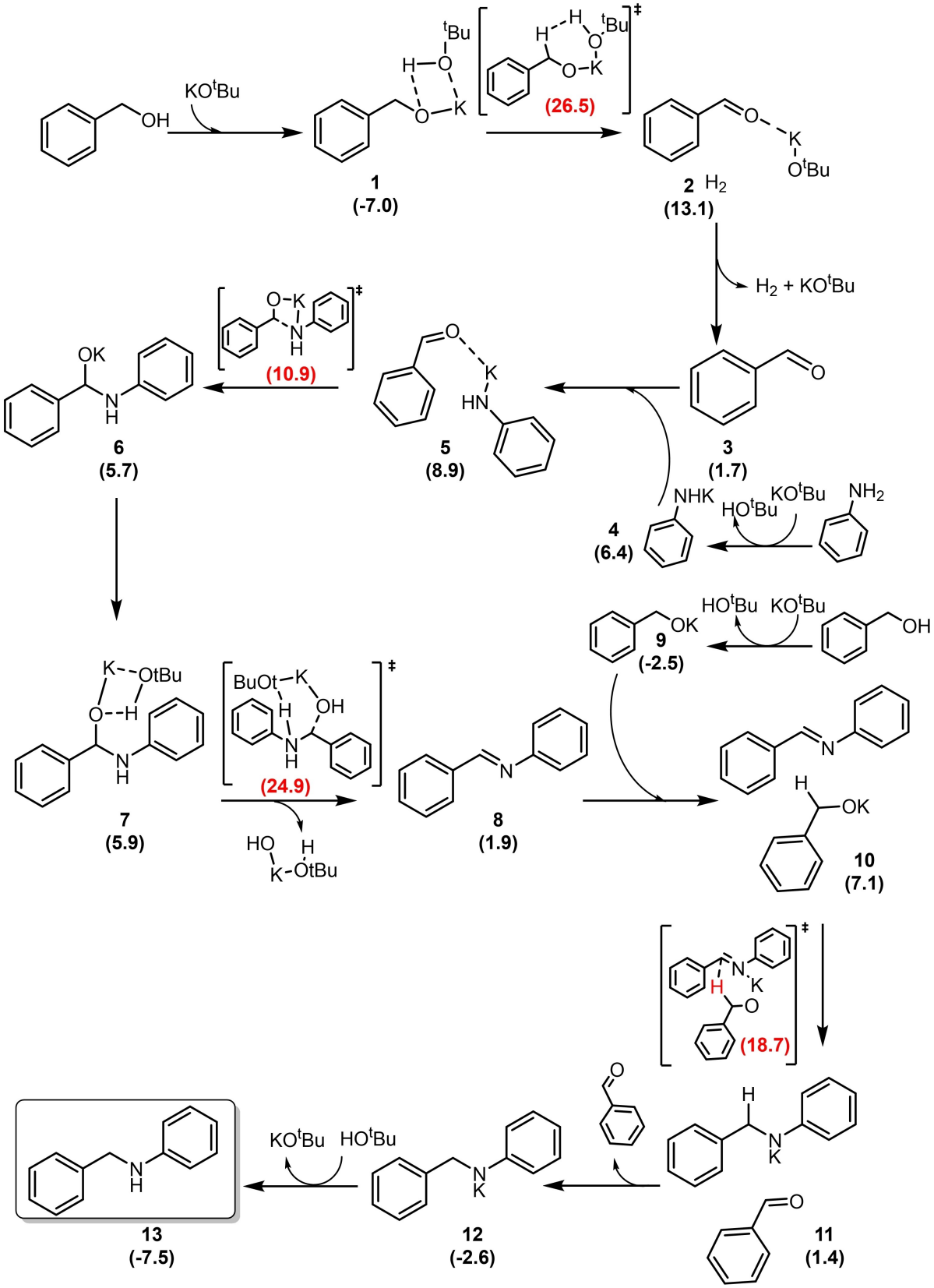

Figure 3. Reaction mechanism of amine formation starting from benzyl alcohol and aniline via an alcohol dehydrogenation strategy promoted by potassium tertiary butoxide (relative Gibbs energies in kcal/mol) at the M06-D3/def2-TZVPP(smd)//BP86-D3/def2-SVP level of theory.

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This step involves the formation of complex **5** ($\Delta G =$ 8.9 kcal/mol) where the interaction between potassium cation and benzaldehyde activates the carbonyl group. Hence, the amine is added to the carbonyl group via **TS 5→6** ($\Delta G^{\ddagger} =$ 10.9 kcal/mol), where the carbon of the former carbonyl group switches from sp^2 to sp^3 hybridization. Next, the formation of imine **8** is favoured by the formation of intermediate **7** ($\Delta G =$ 5.9 kcal/mol) where intermediate **6** is complexed by the HO^{t}Bu formed previously.

From it, HO^{t}Bu transfers its proton to the KO moiety which favours the release of a KOH molecule and the deprotonation of the amine group through **TS 7→8** ($\Delta G^{\ddagger} =$ 24.9 kcal/mol). Once the imine **8** ($\Delta G =$ 1.9 kcal/mol) is formed, it can interact with the potassium alkoxide **9**, previously formed by the reaction of a molecule of benzyl alcohol with KO^{t}Bu, to form intermediate **10** ($\Delta G =$ 7.1 kcal/mol). In the next step, a formal KH molecule is added to the imine group through **TS 10→11** ($\Delta G^{\ddagger} =$ 18.7 kcal/mol) leading to the formation of **12** ($\Delta G =$ −2.6 kcal/mol) after the release of benzaldehyde from **11** ($\Delta G =$ 1.4 kcal/mol). Finally, the amine **13** ($\Delta G =$ −7.5 kcal/mol) is formed by exchange of the potassium with the proton of a HO^{t}Bu.

Furthermore, the imine hydrogenation mechanism proposed by Li *et al.*[31] has been further tested (Figure 4). Once intermediate **10** is formed, the imine can form hemiaminal **11** ($\Delta G =$ 7.7 kcal/mol) after potassium benzyl oxide attacks the electrophilic carbon of the imine via **TS 10→11a** ($\Delta G^{\ddagger} =$ 12.2 kcal/mol). In the presence of a base (e.g., benzyl oxide or *tert*-butoxide), the hemiaminal is then deprotonated through **TS 12a→13a** ($\Delta G^{\ddagger} =$ 20.9 kcal/mol with benzyl oxide and $\Delta G^{\ddagger} =$ 12.7 kcal/mol with *tert*-butoxide) after formation of intermediate **12a** ($\Delta G =$ −8.1 kcal/mol with benzyl oxide and $\Delta G =$ −13.4 kcal/mol with *tert*-butoxide). Next, ^{t}BuOH/BnOH is released from intermediate **13a** ($\Delta G =$ 14.6 kcal/mol with benzyl oxide and $\Delta G =$ 8.0 kcal/mol with *tert*-butoxide), while intermediate **14a** ($\Delta G =$ 9.3 kcal/mol with benzyl oxide and $\Delta G =$ 2.1 kcal/mol with *tert*-butoxide) releases a benzaldehyde molecule into solution via **TS 14a→15a** ($\Delta G^{\ddagger} =$ 19.2 kcal/mol with benzyl oxide and $\Delta G^{\ddagger} =$ 12.0 kcal/mol with *tert*-butoxide). Finally, intermediate **16a** ($\Delta G =$ 16.5 kcal/mol with benzyl oxide and $\Delta G =$ 9.2 kcal/mol with *tert*-butoxide) is formed and after a series of protonation steps the desired amine is obtained. Thus, since the kinetic cost is higher for this alternative mechanism from intermediate **10**, by at least 14.5 kcal/mol in the best scenario according to **TS 12a→13a** that defines the rds in Figure 4, we must rule out its existence.

With the results of Table 1 and Scheme 4 in mind, a comparative analysis of the nature of the base was also performed to have the lowest performance of the bases, compared to KO^{t}Bu. Thus, the countercation exchange with sodium, *i.e.* NaO^{t}Bu, increases the rds barrier by only 0.2 kcal/mol, but in addition the deprotonation of aniline becomes significantly more expensive, up to 6.0 kcal/mol. Going to K_2CO_3 the corresponding rds rises up 9.2 kcal/mol, but also 4.2 kcal/mol with KOH. Finally, with cesium, it also becomes more expensive by 1.5 kcal/mol with CsO^{t}Bu, but very interestingly, with CsOH there would be a lower kinetic effort of 4.6 kcal/mol.

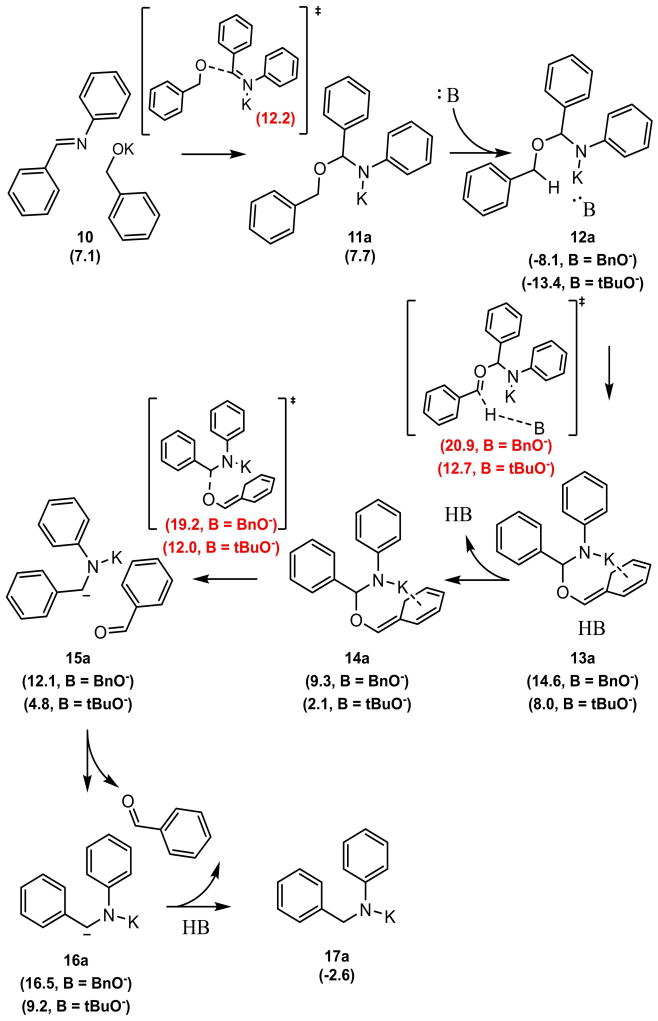

Figure 4. Alternative mechanism of imine hydrogenation via a hemiaminal intermediate (relative Gibbs energies in kcal/mol) at the M06-D3/def2-TZVPP(smd)//BP86-D3/def2-SVP level of theory.

In order to make a homonymous confrontation with Cs_2CO_3 the rds also worsened ostensibly, but still 2.1 kcal/mol better than with K_2CO_3, confirming the 10% yield for $CsCO_3$ whereas only traces for K_2CO_3. It should be noted that the potential multiplier effect of up to four base molecules is partially omitted here,[38,40] and the solvation with BnOH of the countercations, not only for computational savings, but to give a correct conformational validity. Take for instance, intermediate **1** would gain 11.5 kcal/mol with a BnOH molecule bonded to the potassium center. Overall, the results agree perfectly with the choice of KO^{t}Bu as the base with better performance, and could lead to enhance predictive catalysis actions on the same type of reaction.[41]

Conclusions

In conclusion, we have developed a convenient and efficient method to synthesize *N*-alkylated amine using inexpensive and readily available alcohol as the alkylating agent. Since this method does not require any transition metal-based catalyst,

the complexity associated with heavy metal contamination can be easily eliminated. Furthermore, this transformation is practical, and a series of functional groups could be tolerated. The present methodology has good functional group tolerance and offers general applicability to the synthesis of a variety of *N*-alkyl (including benzyl, heteroaryl and aliphatic) aromatic amines in good to excellent yields.

Experimental Section

Under argon atmosphere amine (0.5 mmol), alcohol (0.75 mmol), and 0.5 mmol of KO^{t}Bu were added to an oven-dried reaction vessel containing a magnetic bar. To this, 2.0 mL of toluene was added and the reaction mixture was stirred for 24 h in a preheated heating block (heating block temperature 130 °C). After completion of the reaction, the reaction vessel was cooled to room temperature, and diluted with 5 mL ethyl acetate. The reaction mixture was filtered using celite. Using a rotary vacuum evaporator, volatile impurities were removed under vacuum, and further purification of the product was carried out by column chromatography using silica gel as the stationary phase and hexane/ethyl acetate mixture as the eluent. The compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy.

We utilized the Gaussian16 suite of programs[42] to conduct static calculations based on Density Functional Theory (DFT). The BP86 functional developed by Becke and Perdew,[43] along with corrections for dispersion using Grimme's method (GD3 keyword in Gaussian16),[44] were employed. The molecular systems' electronic configurations were described using the double-ζ basis set with Ahlrichs' polarization scheme for main-group atoms (def2-SVP keyword in Gaussian).[45] Geometry optimizations were performed without imposing symmetry constraints, and the identified stationary points were confirmed through analytical frequency calculations. To account for the zero-point energies (ZPEs), the calculated frequencies were employed. Additionally, single-point calculations were performed at 130 °C using the M06-D3 functional[46] and the triple-ζ basis set def2-TZVPP. To incorporate solvent effects, we estimated the impact of amyl alcohol using the universal solvation model SMD developed by Cramer and Truhlar.[47] The reported Gibbs energies in our study encompass electronic energies obtained at the M06-D3/def2-TZVPP(smd)//BP86-D3/def2-SVP level of theory. These energies were corrected with zero-point energies, thermal corrections, and entropy effects computed at the BP86-D3/def2-SVP level.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary information file and from the corresponding author upon reasonable request.

Keywords: Transition-metal-free reactions · Hydrogen autotransfer · *N*-alkylation · Potassium *tert*-butoxide · Alcohols

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