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Green and Scalable Aldehyde-Catalyzed Transition Metal-Free Dehydrative *N*-Alkylation of Amides and Amines with Alcohols

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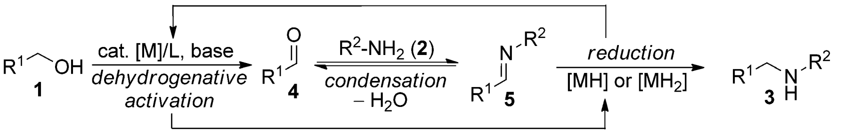
Abstract: In contrast to the borrowing hydrogen-type *N*-alkylation reactions, in which alcohols were activated by transition metal-catalyzed anaerobic dehydrogenation, the addition of external aldehydes was accidentally found to be a simple and effective protocol for alcohol activation. This interesting finding subsequently led to an efficient and green, practical and scalable aldehyde-catalyzed transition metal-free dehydrative *N*-alkylation method for a variety of amides, amines, and alcohols. Mechanistic studies revealed that this reaction most possibly proceeds *via* a simple but interesting transition metal-free relay race mechanism.

Keywords: alcohols; aldehyde catalysis; amides; amines; N-alkylation; relay race mechanism; transition metal-free conditions

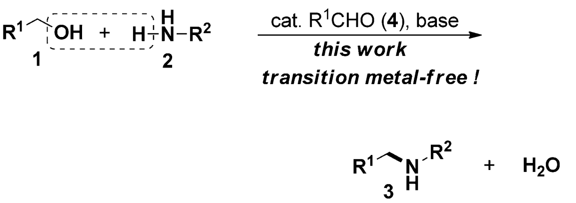
Regarding the fundamental principles of a green transformation,[1] advantageous synthetic methods avoiding mutagenic and waste-producing reagents are of extraordinary interest in both academic and industrial work.[1,2] Recently, the transition metal-catalyzed dehydrative *N*-alkylation of amines and amides using alcohols as the greener alkylating reagents, namely the borrowing of hydrogen or hydrogen autotransfer methodology [Eq. (1)],[3–8] has become a useful way to achieve versatile amine and amide derivatives, which are known as key moieties in pharmaceuticals, bioactive molecules, and natural products.[3,9] However, despite the recent progresses, drawbacks still remain and many challenges have not yet been effectively addressed in the existing methods. For example, since the initial dehydrogenative alcohol activation to aldehydes and hydridometal species is a thermodynamically unfavourable process, preformed noble metal complexes or addition of capricious ligands for catalyst activation were usually required under inert atmosphere protection, which is not only expensive, not readily accessible and toxic, but can be severe drawbacks of the methods, especially in pharmaceutical, biochemical and industrial applications. Therefore, the development of efficient, economic, lowly toxic, even transition metal-free processes is still an urgent and challenging task in the field.

Although transition metal-free *N*-alkylation reactions were already known[3d,10] before the emergence of the metal-catalyzed reactions in 1981,[4] they require even harsher reaction conditions than the metal-catalyzed methods,[3–8] such as very high temperature (>200 °C, even to 400 °C), high pressure, the use of large excess amounts of alcohols or amines, strong basic conditions by using large amounts of bases, long reaction times, and suffer from the problems of low yields and low selectivities of the products. To overcome these disadvantages, various transition metal-catalyzed methods were later reported.[3–8] Consequently, there still remains much room for improvement over the known methods. A direct solution to the problems seems vague; one of the best ways may be adopting the more economic and less toxic metal catalysts such as Cu and Fe,[6,7,11,12] or using recyclable heterogeneous catalysts,[8] or by developing more stable catalysts that can be used under less demanding aerobic conditions.[7,12] However, many of



(1)

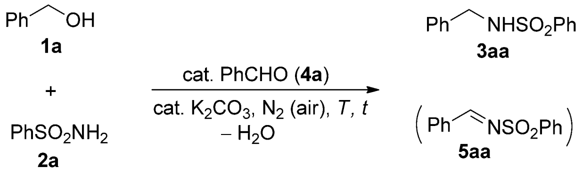
the reactions still have to use a large excess alcohols, amines, or bases, and require high temperatures and long reaction times.[6–8,11] Herein we report an advance in the field by disclosing a green and efficient, practical and scalable aldehyde-catalyzed transition metal-free dehydrative *N*-alkylation reaction of amides and amines with alcohols [Eq. (2)].[13]



(2)

Recently, by employing the borrowing hydrogen strategy, several transition metal-catalyzed *N*-alkylation methods, mainly benzylation reactions, were reported for the synthesis of useful sulfonamide and amine derivatives [Eq. (1)].[5–8] In contrast, we accidentally found that air played a crucial role in a Rh-catalyzed reaction,[12a] which subsequently led to the discovery of an air-promoted metal-catalyzed aerobic alkylation method and an interesting mechanism analogous to the relay race game.[12] We also proposed that metal-catalyzed aerobic alcohol oxidation should be a new way of alcohol activation/aldehyde generation,[12,14] which unfortunately it seems has not been generally recognized by the field so far.[3–8,12,14] During our further efforts to develop more preferable catalysts, we accidentally noticed that the reaction of alcohols and sulfonamides could be driven to completion by merely adding catalytic amounts of the intermediate aldehydes [Eq. (2), $R^2 = RSO_2$], which implied that *the lone aldehyde can catalyze the reaction efficiently to completion without any transition metal catalysts!*[13] Thus, simply heating a solvent-free mixture of benzyl alcohol **1a**, benzenesulfonamide **2a**, benzaldehyde **4a** (10–20 mol%), and K_2CO_3 (10–20 mol%) at 100–135 °C could efficiently lead to high conversions of **2a** to product **3aa** in high selectivities (Table 1). As shown, reactions with neither aldehyde nor base did not occur at all (runs 5–7), and reactions using lesser amounts of aldehyde and/or base were accordingly less efficient.[15] Worth noting is that the reactions conducted under air could also give equally good results (yields in parenthesis) with those under nitrogen (yield outside the parenthesis), showing that air does not affect the reaction at all. Therefore, inert atmosphere protection can be avoided and operations and conditions of the reaction can be simplified greatly by employing this new catalytic method.

Table 1. Screening and optimization of the reaction conditions.[a]



Run	**4a**, K_2CO_3 (mol%)	T, t	**3aa** [%][b]
1	20, 20	100 °C, 36 h	69 (57)
2	20, 20	120 °C, 16 h	99 (99)
3[c,d]	20, 20	120 °C, 16 h	99 (99)
4	10, 10	120 °C, 16 h	88 (80)
5[c]	0, 10	120 °C, 16 h	NR (NR)
6[c,e]	10, 0	120 °C, 16 h	NR (NR)
7[c]	0, 0	120 °C, 16 h	NR (NR)
8	10, 10	135 °C, 17 h	99 (99)
9[c,d]	10, 10	135 °C, 17 h	99 (99)

[a] The mixture of **1a** (1.3 equiv.), **2a** (3 mmol), **4a**, and K_2CO_3 (AR grade of 99.56% purity was used unless otherwise noted) was sealed under N_2 or air in a 20-mL Schlenk tube and then heated. The reaction was then monitored by TLC and/or GC-MS.

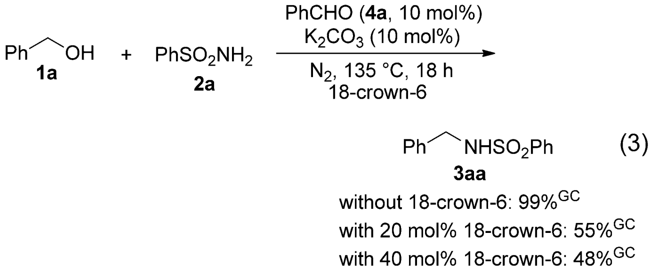
[b] Conversions of **2a** to **3aa** are based on GC analysis. The GC conversions obtained from the reactions under nitrogen are shown outside the parenthesis (those under air are shown in the parenthesis). Usually none or < 0.5% **5aa** was detected by GC (**3aa**/**5aa** > 99/1).

[c] To avoid contamination of **1a** by slight amounts of **4a**, redistilled absolute **1a** (100% purity) was used. NR: no reaction.

[d] Virgin glassware and stirring bar, absolute **1a** and **4a**, and 4N grade K_2CO_3 (99.992% purity) were used.

[e] Traces **5aa** derived from the added **4a** and **2a** were detected.

Since the influences of metal impurities in catalysts, additives, or substrates and the determination of the active catalytic species are currently key concerns in many metal-catalyzed or metal-free reactions,[16] and since there were no corresponding studies in the early transition metal-free *N*-alkylation reactions,[3d,10] whether transition metal catalysts are indeed not required in present reactions remains to be elucidated. As illustrated below, it can be demonstrated unequivocally that the reaction is indeed transition metal-free. Firstly, both the aldehyde and base were found to be essential. Their combination is so crucial that no reaction occurred at all with neither of them (Table 1, runs 5–7). Accordingly, aldehyde and base loadings affected the reaction rates greatly (Table 1) so that more amounts of them unexceptionally led to faster reactions and/or lower reaction temperatures (runs 1–3) and *vice versa*.[15] Secondly, screening of the bases also revealed their key function in the reaction, in which K_2CO_3 was still found to be the best one regarding efficiency, selectivity, economy and ease of handling.[15] Thirdly, control reactions using virgin glassware and stirring bar, 4N K_2CO_3 (99.992% purity), and absolute benzyl alcohol **1a** and benzaldehyde **4a** (runs 3 and 9) also gave the same good results as those with AR K_2CO_3 (runs 2 and 8),[17] both under air and under nitrogen, revealing that the 100 times purer 4N K_2CO_3 has the same catalytic activity as the trace transiton metal-contaminated AR K_2CO_3 in the same reaction. In addition, more control reactions using 4N K_2CO_3 (10 mol%), 4-cholobenzaldehyde (**4f**) as the catalyst (10 mol%), and various metal catalysts as the additives (1 mol%) in the reactions of 4-cholobenzyl alcohol (**1f**) and **2a** were also carried out to investigate the influences of transition metal catalysts on the reaction.[15] The results only revealed that the metal catalysts were ineffective in promoting the aldehyde-catalyzed reactions, indicating that the aldehyde alone is the best catalyst for the reaction. On the contrary, obvious retardance of the aldehyde-catalyzed reactions and lower yields of the product were observed when only catalytic amounts of 18-crown-6 was added as the additive [Eq. (3)], which should be attributed to the well-known strong complexation ability of 18-crown-6 with the potassium cation.[18] The addition of 18-crown-6 may result in a lower concentration of the free potassium cation in the reaction media, and consequently lower activity in the reaction. The above results reflected clearly the significant role of the alkali bases in promoting the reactions rather than the transition metal catalysts or the metal impurities. Based on the above findings, the possibilities of transition metal-catalyzed processes due to metal contamination in the substrates, catalysts, or bases can be eliminated.



(3)

The optimized conditions were then applied to various amides, amines and alcohols to extend the scope of the method by using corresponding aldehydes (R^1CHO, **4**) as the catalysts (Table 2). As investigated, various sulfonamides and benzylic alcohols, including the sterically more hindered ones (runs 4, 11, 14, 16), heteroaromatic ones (runs 9, 17), aliphatic sulfonamides (runs 18–20), and those with reactive functional groups (runs 5–8, 13, 14, 16, 17, 20) gave efficiently the target products in good to high yields. Similarly, sulfinamides (runs 21–23) and various heteroaromatic and aromatic amines (runs 24–40), all important building blocks in pharmaceuticals and bioactive molecules, also reacted efficiently with the alcohols to give high yields of the target products under similar conditions by using NaOH or CsOH as the better alkali bases. The method's synthetic potential is also exemplified by the efficient preparation of apyrabactin **3ah** (run 16),[9i] which used to be obtained from the corrosive, instable, and more expensive sulfonyl chloride.

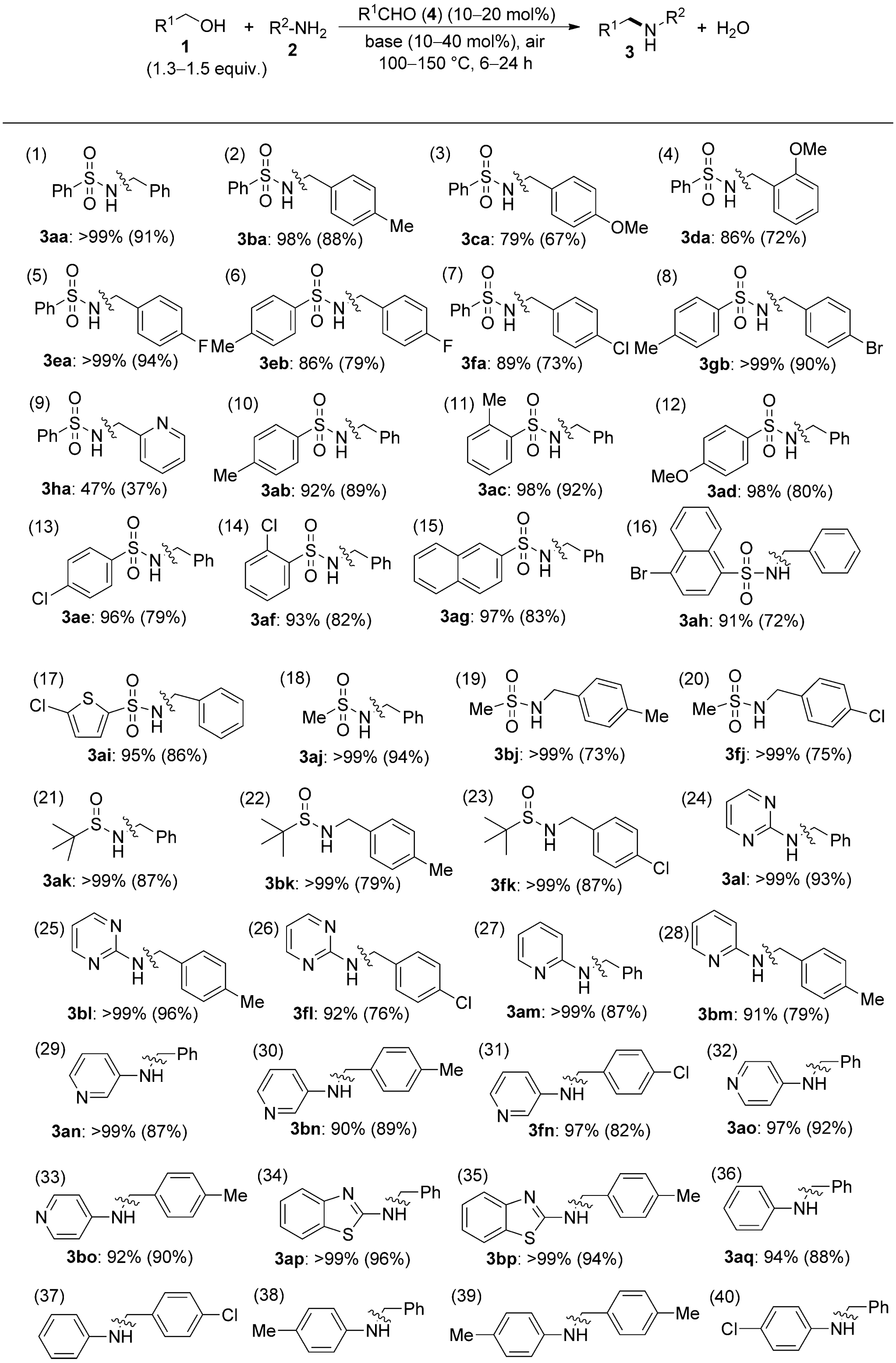
It should be mentioned that, during the extension of the substrates, the base was again found to be crucial for the reaction's efficiency as we have observed during the conditions screening. Thus, by carefully screening the base effect and by using the best base for each substrate, the reactions were very efficient and usually afforded high yields of the products. For example, it was found that NaOH is the best base for sulfinamides and heteroaromatic amines and CsOH for aromatic amines. Although the reasons for these differences, the relationship between the basicity of the bases and the acidity of the N−H bonds, as well as the choice of a right base for a given substrate remain to be clarified, the above results revealed again that the alkali cations played key roles in the reactions, supporting again that the reactions are most possibly transition metal-free. In contrast, as revealed by the literature reports,[5–8] possibly because no base optimizations were conducted in many of the metal-catalyzed reactions, the metal catalysts would then play a more significant role when the less effective bases were used. On the contrary, in the present reactions, by choosing the right base and using aldehydes as the catalyst, the use of transition metal catalysts and inert atmosphere protection can be avoided, while still retaining similarly high reaction efficiencies. This also reveals an advantage of the method over the metal-catalyzed reactions.

Moreover, products obtained by this new method are rather clean since small amounts of the organic impurities, mainly the slight excess of alcohols and aldehydes, can be readily removed by vacuum distillation, rendering the method particularly promising for large-scale preparations at the lowest cost. Indeed, several 50-mmol scale reactions of **1** and **2** readily afforded good yields of pure **3** (72–77% isolated yields) by simply recrystallizing the crude products.[15] Although substrate scope of the method remains to be fully investigated, all the above results revealed its potential generality and broad utility in the green synthesis of the amine and amide derivatives.

All the above results also indicated that the mechanism of the aldehyde-catalyzed *N*-alkylation reactions should be interesting. Since no transition metal catalysts are involved, a new mechanism different to the metal-catalyzed borrowing hydrogen process[3–8] should be responsible for the present reactions (Scheme 1).[19]

Firstly, base was found to promote the dehydrative condensation of amides/amines **2** with aldehydes **4** to

Table 2. Extension of the substrate scope.[a]



(1) **3aa**: >99% (91%)
(2) **3ba**: 98% (88%)
(3) **3ca**: 79% (67%)
(4) **3da**: 86% (72%)
(5) **3ea**: >99% (94%)
(6) **3eb**: 86% (79%)
(7) **3fa**: 89% (73%)
(8) **3gb**: >99% (90%)
(9) **3ha**: 47% (37%)
(10) **3ab**: 92% (89%)
(11) **3ac**: 98% (92%)
(12) **3ad**: 98% (80%)
(13) **3ae**: 96% (79%)
(14) **3af**: 93% (82%)
(15) **3ag**: 97% (83%)
(16) **3ah**: 91% (72%)
(17) **3ai**: 95% (86%)
(18) **3aj**: >99% (94%)
(19) **3bj**: >99% (73%)
(20) **3fj**: >99% (75%)
(21) **3ak**: >99% (87%)
(22) **3bk**: >99% (79%)
(23) **3fk**: >99% (87%)
(24) **3al**: >99% (93%)
(25) **3bl**: >99% (96%)
(26) **3fl**: 92% (76%)
(27) **3am**: >99% (87%)
(28) **3bm**: 91% (79%)
(29) **3an**: >99% (87%)
(30) **3bn**: 90% (89%)
(31) **3fn**: 97% (82%)
(32) **3ao**: 97% (92%)
(33) **3bo**: 92% (90%)
(34) **3ap**: >99% (96%)
(35) **3bp**: >99% (94%)
(36) **3aq**: 94% (88%)
(37) **3fq**: 67% (65%)
(38) **3ar**: >99% (97%)
(39) **3br**: 86% (79%)
(40) **3as**: 98% (89%)

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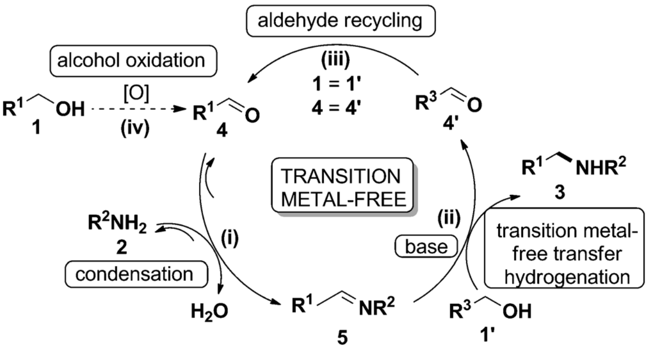
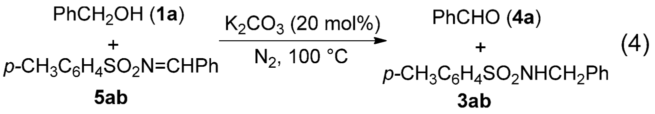
[a] See the Supporting Information (Table S1) for detailed procedures and conditions. GC conversions of **2** to **3** are shown out of the parenthesis. Isolated yields based on **2** are shown in the parenthesis. **3**/**5** ratios >99/1 as determined by GC.



Scheme 1. Proposed mechanism for the aldehyde-catalyzed transition metal-free *N*-alkylation reaction.

afford the intermediate imines **5** (Scheme 1, step i),[15] which is a classic organic reaction that can also occur without any additives.[20] In great contrast, base was then found to be indispensible in the subsequent transfer hydrogenation step (step ii). Thus, although no target reaction occurred at all without the base, the transfer hydrogenation of imines **5** by primary alcohols **1** became very efficient even at lower temperatures (such as 100 °C) once catalytic amounts of the base were added, giving high yields of product **3**.[15] In comparison, secondary alcohols were found to be inferior reducing reagents in the reaction than the primary alcohols, giving low yields of the product under similar conditions.[21] More importantly, as measured by NMR analysis, about 1 equiv. of the by-product aldehyde **4** (in molar ratio to product **3**) was also produced simultaneously [Eq. (4)],[15] implying that quantitative amounts of **4** could be regenerated in the transfer hydrogenation step, which should then be recycled (step iii) to undergo a new condensation with **2** to finish the catalytic cycle. Interestingly, as shown in Scheme 1, the process that the latter alcohol **1′** gives its own hydrogen atoms to the preceding alcohol **1** (in its imine form **5** *via* aldehyde **4**) with itself being oxidized to **4′**, and will then (also in the imine form) receive new hydrogen atoms from an even later alcohol in the next cycle is analogous to the relay race game, resembling the passing on of the relay baton between the runners.

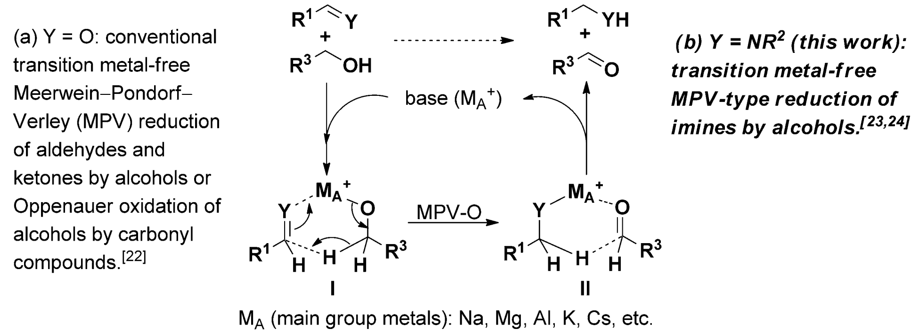


$$\begin{matrix}\text{PhCH}_2\text{OH }(\mathbf{1a})\\ +\\ p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{N=CHPh}\\ \mathbf{5ab}\end{matrix}\xrightarrow[\text{N}_2,\ 100\ ^\circ\text{C}]{\text{K}_2\text{CO}_3\ (20\ \text{mol\%})}\begin{matrix}\text{PhCHO }(\mathbf{4a})\\ +\\ p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHCH}_2\text{Ph}\\ \mathbf{3ab}\end{matrix}\qquad(4)$$

t:	**3ab**%$^{GC\ (NMR)}$	**4a**%$^{GC\ (NMR)}$	**4a/3ab**^{NMR}
4 h:	57 (72)	27 (70)	0.97/1.00
6 h:	66 (81)	29 (78)	0.96/1.00

Based on above findings and regarding that 4N K_2CO_3 also showed the same high catalytic activity as AR K_2CO_3 did in the reduction of imines **5** to products **3** by alcohols **1**,[15] the transfer hydrogenation step (Scheme 1, step ii) should be a transition metal-free process, also. As documented in the literature that have long been known, conventional transition metal-free Meerwein–Pondorf–Verley (MPV) reduction of aldehydes and ketones by alcohols or the Oppenauer oxidation of alcohols by carbonyl compounds is believed to proceed *via* six-membered cyclic transition states [Scheme 2 (a), Y = O].[22] Although the exact process and the transition states in the present transition metal-free transfer hydrogenation of imines still remain to be clarified, since no transition metal catalysts are involved in the reactions, eliminating the possibilities of the hydridometal species participated mechanisms, and that the cations of the main group metals M_A (K, Na, or Cs) play key roles to facilitate the reactions, it may by analogy be assumed that the present aldehyde-catalyzed transition metal-free *N*-alkylation reactions most probably proceed *via* similar six-membered cyclic MPV-type transition states [Scheme 2, (b), Y = NR^2].[23,24] To the best of our knowledge, this may be the first example of mild, efficient, and practical transfer hydrogenation of imines by alcohols *via* the transition metal-free MPV-type process.[3,22–25]

Besides, steps i + ii in Scheme 1 are similar to the well-documented reductive amination reactions.[26] Conventionally, carbonyl compounds were used as the substrates and large excess amounts of the hazardous gas hydrogen or waste-producing boron hydrides



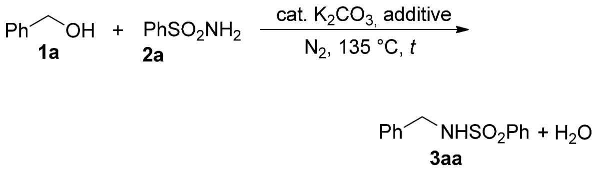
(a) Y = O: conventional transition metal-free Meerwein–Pondorf–Verley (MPV) reduction of aldehydes and ketones by alcohols or Oppenauer oxidation of alcohols by carbonyl compounds.[22]

(b) Y = NR2 (this work): transition metal-free MPV-type reduction of imines by alcohols.[23,24]

Scheme 2. Possible transition states involved in the transition metal-free transfer hydrogenation reactions.

were employed as the reducing reagents.[26] Differently, in the present method, by using alcohols **1** as the reducing reagent, the starting aldehydes **4** can be readily regenerated in quantitative amounts (Scheme 1, step ii) and will then circulate (step iii, **1**=**1′**, **4**=**4′**) in the catalytic cycle until the whole reaction is completed. Therefore, only catalytic amounts of the corresponding aldehydes **4** should be required in the reaction, which is in good accordance with the present aldehyde-catalyzed reactions. On the contrary, if a different aldehyde was added as the catalyst (step iii, **1**≠**1′**, **4**≠**4′**), a mixture of products could be obtained as we have also observed in corresponding control reactions.[15] These results not only revealed the advantages of the present method over some of the reductive amination reactions, but also strongly support the proposed mechanism.

Moreover, the proposed mechanism (Scheme 1) also indicated that, like aldehydes, the intermediate imines **5** that can give aldehydes **4** *via* transfer hydrogenation and will then be regenerated in next condensation step, should also be able to catalyze the reaction. Similarly, oxidants that can oxidize the alcohols to aldehydes (step iv) may also initiate the reaction effectively under similar conditions (steps iv+i+ii+iii). As shown in (Eq. (5)], the above hypothesis are indeed the cases as we have found out in the reactions using catalytic amounts of imine **5aa**, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), or PhI(OAc)$_2$ as the catalyst or initiators of the reaction, which further support the proposed mechanism from another angle.



(5)

1. PhSO$_2$N=CHPh (**5aa**, 10 mol%), K$_2$CO$_3$ (10 mol%), 18 h: 84%
2. TEMPO (20 mol%), K$_2$CO$_3$ (10 mol%), 24 h: 91%
3. PhI(OAc)$_2$ (20 mol%), K$_2$CO$_3$ (30 mol%), 24 h: 92%

In summary, we have developed an efficient and scalable aldehyde-catalyzed dehydrative *N*-alkylation method for a variety of amides, amines, and alcohols. This method requires no transition metal catalysts, activating ligands, solvents, and inert atmosphere protection, but can efficiently afford the target amide and amine derivatives on a large-scale under milder conditions by using only the economic and readily available aldehydes and bases, and thus may become a green and practical method of choice for *N*-alkylation reactions. We also proposed a simple but interesting relay race mechanism for the transition metal-free *N*-alkylation reactions, which used to be unclear in the past.[3–8,10] The present results and conclusions not only support our previous studies,[12] but also indicate that, by using the right base and simply adding small amounts of aldehydes as the catalyst, the use of transition metal catalyst can be easily avoided. Since simple aldehyde-catalyzed reactions are still very rare up to date,[27] and due to the many obvious advantages, this aldehyde-catalyzed dehydrative alkylation method should be of potentially wide interest and broad utility in many fields. Further extensions and deeper mechanistic insights of the reactions are underway.

Experimental Section

Typical Procedure for Aldehyde-Catalyzed *N*-Alkylation of Amides and Amines with Alcohols

The mixture of benzyl alcohol **1a** (0.41 mL, 3.9 mmol, 1.3 equiv.), benzenesulfonamide **2a** (0.471 g, 3.0 mmol), K$_2$CO$_3$ (0.041 g, 0.3 mmol, 10 mol%), and absolute benzaldehyde **4** (30 μL, 0.3 mmol, 10 mol%) in a 20-mL Schlenk tube was sealed under air (or nitrogen) and then stirred at 135 °C for 18 h. After completion of the reaction as was monitored by TLC and/or GC-MS (>99% GC conversion), the mixture was quenched with ethyl acetate and the crude product purified by column chromatography using ethyl acetate and petroleum ether (60–90 °C) (v/v 15/1) as eluent, giving *N*-benzylbenzenesulfonamide **3aa**; isolated yield: 0.675 g (91%).

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[11] Unfortunately, we were unable to repeat the Fe-catalyzed method (ref.[6b]) by using absolute **1a** under inert conditions (see also the note in ref.[34] in our previous report of ref.[12b]). In our hands, by using FeCl$_2$ or FeCl$_3$ as the catalyst, which are known and used as Lewis acids, reactions of **1a** and **2a** in the absence of a base did not give **3aa**, but afforded dibenzyl ether as the major product, the typical product in acid-catalyzed reactions. When base was added, the ether was not observed, but no or only trace **3aa** could be detected.

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[13] Although facilitation of some reactions by aldehydes had been mentioned before (ref.[10c]), it was left unnoticed and ignored during the coming decades. Accordingly, aldehydes were not considered as the catalyst, and aldehyde addition was not taken as a method of alcohol activation in the past (refs.[3–8]).

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[17] See the Supporting Information for the original base purity reports containing the content data of the metal impurities.

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[19] The early transition metal-free *N*-alkylation reactions should proceed *via* a similar mechanism to the one we proposed, but it was not exactly clear and remained a hypothesis in the past since no corresponding studies on the reaction mechanism and the individual reactions have been carried out (refs.[3d,10]). On the other hand,

these early reports strongly support the proposals in our present study.

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[21] To further confirm the transfer hydrogenation step, we also attempted to user isopropyl alcohol as the hydrogen source to reduce **5aa** to **3aa** instead of the primary alcohols, but the reaction required a much higher temperature and longer reaction time, and gave only low yield of the product. See ref.[12f] for another example of less efficient transfer hydrogenation reaction by using a secondary alcohol as the reducing reagent.

[22] a) J. S. Cha, *Org. Process Res. Dev.* **2006**, *10*, 1032; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226; c) Ref.[3c]

[23] According to the mechanistic studies of the transfer hydrogenative reductions of carbonyl compounds and imines by alcohols, in certain cases, transition metal-catalyzed reactions may also proceed *via* the MPV-O mechanism without involving the hydridometal species. See refs.[3c,22b]

[24] Although it was held that benzyl alcohol can reduce imines to amines in the presence of KOH under harsh conditions (ref.[10]), it was a hypothesis only since no corresponding reactions were investigated to verify the transfer hydrogenation step. Moreover, in our present work, NaOH or CsOH that can be used in only catalytic amounts are found to be better bases than KOH in the cases of aromatic amines, and they lead to higher reaction efficiencies at much lower temperatures (see the Supporting Information for details).

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