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COMMUNICATION

Selective Catalytic Hoffmann N-Alkylation of Poor Nucleophilic Amines and Amides with Catalytic Amounts of Alkyl Halides

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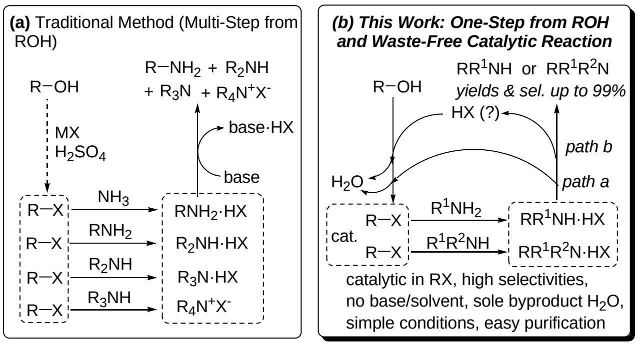
Using only catalytic amounts of alkyl halides in the reactions of poor nucleophilic amines/amides and alcohols led to a selective Hoffmann N-alkylation reaction catalytic in alkyl halides, providing a practical and efficient method for practical synthesis of *mono*- or *di*-alkylated amines/amides in high selectivities. This new method avoids the use of large amounts of bases, alkyl halides, and solvents, and generates water as the only byproduct. Preliminary mechanistic studies showed that alkyl halides are key intermediates/catalysts regeneratable in the reaction cycle.

Nitrogen-containing compounds play important roles in all fields of chemistry, among which amine and amide derivatives are the most fundamental chemicals as they are usually the starting materials for the synthesis of other useful organonitrogen blocks. The reaction of ammonia/amines and alkyl halides,[1] namely the Hoffmann N-alkylation reaction discovered by A. W. Hoffmann in 1850,[1a] is included in all text books as the basic method for amine derivative synthesis (Scheme 1a).[1c] However, this method requires excess amounts of the active and toxic alkyl halides, produces a mixture of amines and ammonium salts as the byproducts, and is thus low in selectivity and atom economy, which also resulted in tedious product separation and purification problems. The Gabriel reaction initiated by S. Gabriel in 1887 was later developed as a more selective method for preparation of primary amines,[1c,2] but the requirement of multi steps and large amounts of bases and the production of large amounts of waste salts make the method low in atom and reaction efficiency. More recently, Jung and co-workers developed a selective preparation of secondary amines from primary amines using CsOH as the base[3] by taking advantage of the “Cesium Effect”.[3,4] However, the method requires pre-activated 4Å molecular sieves, anhydrous solvents, and excess amounts of alkyl halides and pre-dried CsOH, and is thus less practical from synthetic point of view.

Scheme 1. (a) Traditional Hoffmann N-Alkylation Reaction and (b) Catalytic Hoffmann N-Alkylation Reaction.



Recently the reaction of amides and imines affording Mannich-type adducts, used to be stoichiometric in silicon enolates, was made catalytic in trialkylsilyl triflate by the Kobayashi group in 2011;[5] while the Mitsunobu reaction was also made catalytic in phosphine by Aldrich and co-workers in 2015.[6] To our knowledge, Hoffmann N-alkylation reactions catalytic in alkyl halides have not been described yet. Herein we report an advance of the research by describing a selective catalytic Hoffmann N-alkylation reaction (Scheme 1b), in which, by using only catalytic amounts of alkyl halides, the reactions of primary and secondary amines/amides with primary and secondary alcohols can produce *mono*- or *di*-alkylated amines/amides in high selectivities under transition metal-, base- and solvent-free conditions, generating meanwhile water as the only byproduct.

In the literature, dehydrative N-alkylation reactions of amines/amides with alcohols can be achieved mainly by the transition metal-catalyzed borrowing hydrogen and hydrogen autotransfer methodology[7] or Lewis/Brönsted acids- or transition metal-mediated/catalyzed direct nucleophilic substitution reactions.[8] The former method usually requires noble metal catalysts to fulfill the anaerobic dehydrogenative activation of the alcohols,[7] whereas the latter one is mainly limited to more active alcohols such as secondary arylmethanols, allylic and propargylic alcohols.[8] In the past few years, our group also focused on dehydrative N- and C-alkylation reactions[9,10]

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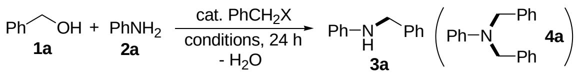
Electronic Supplementary Information (ESI) available: Experimental details, product characterization, details of the control experiments, and copies of ^{1}H NMR, ^{13}C NMR and HRMS spectra of the products. See DOI: 10.1039/x0xx00000x using the greener alcohols as the alkylating reagents,[7,8] especially that externally-added aldehydes or ketones could be regenerated to work as the catalysts.[10] Since alkyl halides can also be produced from alcohols by halogenation,[1c] we hypothesized that if alkyl halides can be regenerated *in situ* from alcohols and then recycled to react with amines, a catalytic Hoffmann N-alkylation reaction could possibly be achieved by using only catalytic amounts of alkyl halides (Scheme 1b). Although we have successfully developed an alkyl halides-catalyzed O-alkylative etherification reaction of alcohols for symmetrical and unsymmetrical dialkyl ether synthesis[10e] and tried many times on the corresponding alkyl halide-catalyzed N-alkylation reactions, these initial attempts failed. We thus reckoned the reason that such a transformation have not be realized so far since Hoffmann's report[1a] is most probably because the amine substrates and the alkylated amine products, with the latter being more basic and more nucleophilic, may readily transform the alkyl halides into corresponding ammonium salts, and hence terminate the reaction (Scheme 1a).

Table 1. Condition Screening for Catalytic N-Benzylation of Aniline.

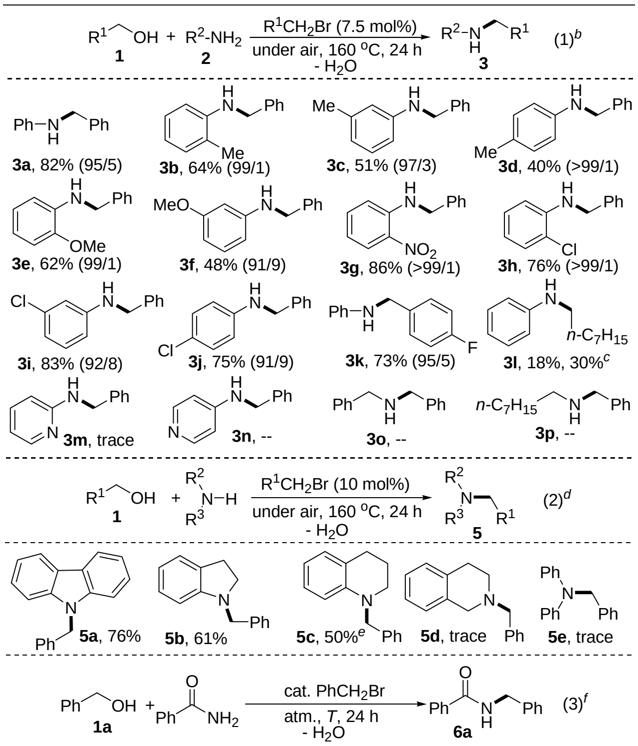


run	**1a**/**2a** (mmol)	X (mol%)	atm., T (°C)	**3a**%;[a] **3a**/**4a**[b]
1[c]	1.5/1	Br (5)	N_2, 120	trace
2	3/2	Br (5)	N_2, 150	76; 91/9
3	3/2	Br (10)	N_2, 150	90; 72/28
4	2/4	Br (10)	N_2, 150	94; 92/8
5	2/3	Br (7.5)	N_2, 150	50; 98/2
6	2/3	Br (7.5)	N_2, 160	94; 95/5
7	***2/3***	***Br (7.5)***	***air, 160***	***94 (82); 95/5***
8	2/3	Cl (7.5)	air, 160	(63)
9	2/3	--	air, 160	--

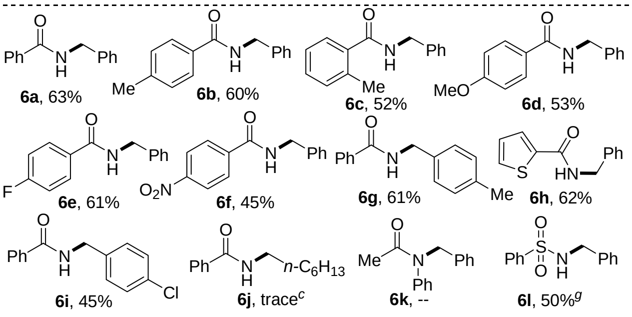
[a] GC yields (isolated yields in parenthesis) of **3a** based on limiting substrate. [b] Selectivities determined by GC-MS analysis. [c] In normal solvents such as dioxane, toluene, DMF, DMSO, etc.

We then turned our attention to poor nucleophilic amines/amides such as the anilines and amides. As shown in Table 1, solvent effect was initially evaluated in the reaction of benzyl alcohol (**1a**) and aniline (**2a**) with 5 mol% $PhCH_2Br$ at 120 °C under N_2. Only trace product could be detected (run 1). In great contrast, when a similar reaction was performed without any solvent, a good yield of the product with a high selectivity of the *mono*-alkylated **3a** (91%) could be obtained at 150 °C (run 2). Further condition screening showed that higher catalyst loading (10 mol%) led to lower selectivity (run 3) and higher **2a**/**1a** ratio to higher **3a** selectivity (run 4). Thus, the highest selectivity of 98% was obtained by using 7.5 mol% $PhCH_2Br$ with a **2a**/**1a** ratio of 3/2 (run 5), with the product yield further improved to 94% by running the reaction at 160 °C (run 6). We also tested the same reaction in air. It also afforded **3a** with the same high yield and high selectivity (run 7), showing that inert atmosphere protection is not necessary and operation of the reactions could be greatly simplified. In comparison, $PhCH_2Cl$ is much less active, giving **3a** in a lower yield (run 8). Moreover, no reaction was observed without the catalyst (run 9), revealing the significant role of alkyl halides in the reaction.

Table 2. Catalytic N-Alkylation of Primary and Secondary Amines and Amides with Primary Alcohols.[a]



run	cat. (mol%)	atm., *T* (°C)	**6a**%	run	cat. (mol%)	atm., *T* (°C)	**6a**%
(1)	10~20	air, 150	trace~13	***(3)***	***40***	***air, 170***	***63***
(2)	40	air, 150	37	(4)	40	N_2, 170	62



[a] Isolated yields based on limiting substrates. [b] **1** (2 mmol), **2** (3 mmol). Selectivities shown in parenthesis determined by GC-MS analysis. [c] RI used as the catalyst. [d] **1** (1.5 mmol), secondary amine (1 mmol). [e] 20 mol% catalyst. [f] **1** (2.4 mmol), amide (2 mmol). [g] 40 mol% TBAI added.

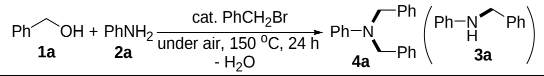
Above optimized conditions were then applied to other amines, amides, and alcohols to extend the scope of the catalytic N-alkylation method. With substituted anilines (Table 2, eq. 1), both electron-rich and -deficient ones, including those with sterically more bulky *ortho*-substituents, afforded the target *mono*-alkylated anilines in high selectivities, with the yields of the electron-deficient ones (**3g-k**) generally higher than those of the electron-rich ones (**3b-f**). In contrast, aliphatic alcohols were less reactive, giving only low yields of the product even using corresponding alkyl iodide as the catalyst (**3l**). Pyridyl and aliphatic amines were not reactive under present conditions.

No reaction occurred or only trace products were detected (**3m**-**p**).

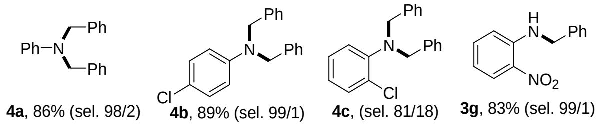
This method could also be applied to base-free N-alkylation of secondary amines (Table 2, eq. 2). Thus, the reactions of carbazole and indoline with **1a** afforded good yields of the products with 10 mol% catalyst (**5a**-**b**). The reaction of tetrahydroquinoline was less efficient, but could give a moderate yield of the product with more catalyst (**5c**). Other secondary amines such as tetrahydroisoquinoline and diphenylamine were not reactive at present (**5d**-**e**).

Inspired by above successful results, the more demanding N-alkylation of amides was then investigated (Table 2, eq. 3). Initially, only low yields of **6a** were obtained from the reaction of **1a** and benzamide (eq. 3, run 1). Different to anilines, no *di*-alkylation byproduct was detected in this reaction, possibly due to the much lower nucleophilicity of the benzamide. By increasing the catalyst loading and enhancing the reaction temperature (runs 2-3), a much higher yield of **6a** could be obtained with 40 mol% $PhCH_2Br$ at 170 °C (run 3). The same result could also be obtained under N_2 (run 4), revealing again that inert atmosphere protection is not necessary. The reactions of electron-rich and -deficient amides and alcohols, including those more bulky ones and a heteroaromatic one, proceeded smoothly to afford the target alkylated amides in moderate yields (**6b**-**i**). An aliphatic alcohol and a secondary amide were also tested, but they were not reactive (**6j**-**k**). The sulfonamide is even less reactive under the same conditions, giving only trace amount of **6l**, with a 50% yield obtained when 40 mol% TBAI was added.

Table 3. Catalytic N,N-Dibenzylation of Anilines.[a]



run	**1a/2a**	cat. (mol%)	**4a**%	**4a/3a**	run	**1a/2a**	cat. (mol%)	**4a**%	**4a/3a**
(1)	3/1	5	(88)	23/77	(4)	4/1	10	(>99)	94/6
(2)	3/1	10	(95)	77/23	***(5)***	***4/1***	***15***	***86 (>99)***	***98/2***
(3)	4/1	5	(>99)	87/13					



4a, 86% (sel. 98/2) **4b**, 89% (sel. 99/1) **4c**, (sel. 81/18) **3g**, 83% (sel. 99/1)

[a] Isolated yields (GC yields in parenthesis) of **4** based on **2**. Selectivities determined by GC-MS analysis.

Since more aniline and controlled catalyst loadings led to selective *mono*-alkylation (Table 1), reverse conditions promisingly providing a selective N,N-*di*-alkylation reaction were then tested (Table 3). With 5 mol% catalyst and 3 equiv. **1a**, the reaction still gave mainly *mono*-alkylated **3a** (run 1). More catalyst and **1a** gave *di*-alkylated **4a** in much higher selectivities (runs 2-4). The highest 98% selectivity and a high isolated yield of **4a** were then obtained by using 4 equiv. **1a** and 15 mol% catalyst (run 5). Electron-deficient anilines reacted efficiently to give *di*-alkylated products in a high selectivity (**4b**). An *ortho*-substituted one gave the product in a lower selectivity due to steric effect of the *ortho*-group (**4c**). *mono*-Alkylated **3g** was still the major product in the reaction of *o*-nitroaniline, most possibly due to the weak nucleophilicity of the amino moiety attributed to the *ortho*-nitro group.

Table 4. Catalytic N-Alkylation of Amines and Amides with Secondary and Tertiary Alcohols.[a]

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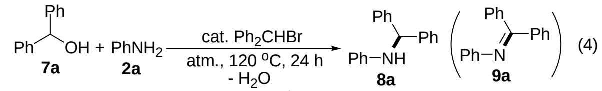
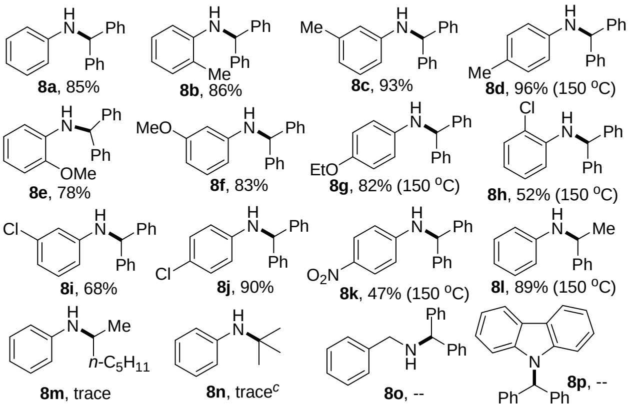


run	**7a/2a**	cat. (mol%)	atm.	**8a**%	**8a/9a**[b]	run	**7a/2a**	cat. (mol%)	atm.	**8a**%	**8a/9a**[b]
(1)	2/2	5	air	(81)	74/36	***(3)***	***2/3***	***10***	***N_2***	***85 (94)***	***>99/1***
(2)	2/3	5	N_2	(76)	>99/1	(4)	2/3	--	N_2	--	

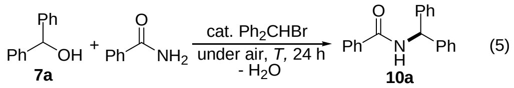


8a, 85% **8b**, 86% **8c**, 93% **8d**, 96% (150 °C)

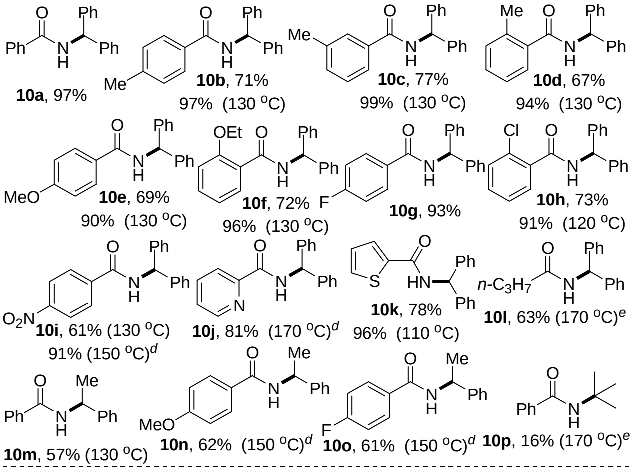
8e, 78% **8f**, 83% **8g**, 82% (150 °C) **8h**, 52% (150 °C)

8i, 68% **8j**, 90% **8k**, 47% (150 °C) **8l**, 89% (150 °C)

8m, trace **8n**, trace[c] **8o**, -- **8p**, --



run	cat. (mol%)	T (°C)	**10a**%	run	cat. (mol%)	T (°C)	**10a**%
(1)	10~20	90~170	95~97	(3)	10	80	61
(2)	***10***	***90***	***97***	(4)	--	90	--

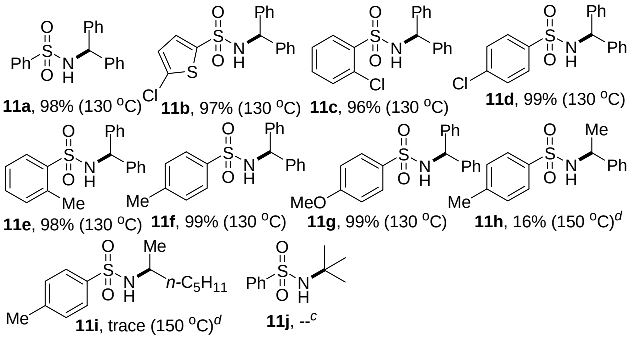


10a, 97% **10b**, 71% 97% (130 °C) **10c**, 77% 99% (130 °C) **10d**, 67% 94% (130 °C)

10e, 69% 90% (130 °C) **10f**, 72% 96% (130 °C) **10g**, 93% **10h**, 73% 91% (120 °C)

10i, 61% (130 °C) 91% (150 °C)[d] **10j**, 81% (170 °C)[d] **10k**, 78% 96% (110 °C) **10l**, 63% (170 °C)[e]

10m, 57% (130 °C) **10n**, 62% (150 °C)[d] **10o**, 61% (150 °C)[d] **10p**, 16% (170 °C)[e]



11a, 98% (130 °C) **11b**, 97% (130 °C) **11c**, 96% (130 °C) **11d**, 99% (130 °C)

11e, 98% (130 °C) **11f**, 99% (130 °C) **11g**, 99% (130 °C) **11h**, 16% (150 °C)[d]

11i, trace (150 °C)[d] **11j**, --[c]

[a] Isolated yields (GC yields in parenthesis) based on limiting substrates. [b] Selectivities determined by GC-MS analysis. [c] RI used as the catalyst. [d] 20 mol% catalyst. [e] 40 mol% catalyst.

Above catalytic N-alkylation method could also be applied to secondary alcohols. Initially, the reaction of **2a** and benzohydrol

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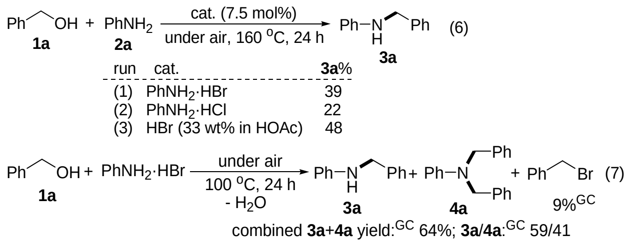
(**7a**) under air gave a mixture of the target product **8a** and an imine byproduct **9a** (eq. 4, run 1), which is most possibly formed by aerobic oxidation of **7a** to the corresponding ketone and subsequent condensation reaction with the aniline. No *di*-alkylation product was detected most possibly due to the steric effects of the secondary alcohol. Then, by performing the reaction under N_2 and increasing the catalyst loading (runs 2-3), a high yield of the product was obtained in the highest selectivity of >99%. No reaction was observed either without the catalyst (run 4). This method was then extended to other anilines and alcohols. The reactions of electron-rich and –deficient anilines and 1-phenylehtanol gave good to high yields of the products with some at higher temperatures (**8b**-**l**). Although we tried many times, the reactions of aliphatic secondary and tertiary alcohols, aliphatic and secondary amines were not successful under similar conditions (**8m**-**p**).

The reaction of amides with secondary alcohols was then tested, which was found to be more efficient than the reactions with primary alcohols (Table 2, eq. 3), giving almost quantitative yields of the product at above 90^{o}C (Table 4, eq. 5, runs 1-2). The reaction was less efficient below 90^{o}C (run 3) and no reaction occurred at all without the catalyst (run 4). Electron-rich and –deficient and heteroaryl amides also gave quantitative yields of the products with some requiring higher temperatures and more catalysts (**10b**-**k**). This method was also applicable to aliphatic amides and other secondary alcohols, giving moderate yields of the products (**10l**-**o**). Tertiary alcohol like *t*-BuOH also reacted with benzamide, albeit the yield was not high at present (**10p**). Different to the preceding unsuccessful reactions with primary alcohols, the reactions of sulfonamides with benzohydrol were very efficient, giving almost quantitative yields of the products at 130 ^{o}C (**11a**-**g**). In contrast, no reaction occurred at all without the catalyst. Moreover, the reactions with other secondary and tertiary alcohols were not efficient. Only a low yield of the product could be obtained or trace products detected at present (**11h**-**j**).

Control reactions were then investigated to help understanding the above successful catalytic Hoffmann N-alkylation reactions. As shown in eq. 6, hydrobromide[10] even hydrochloride salt of aniline ($PhNH_2{\cdot}HX$) was found capable of catalyzing the reaction to give considerable yields of **3a** (runs 1-2), revealing that these salts are active intermediates in the reactions (Scheme 1b). The reaction with catalytic amounts of HBr was also tested,[10] giving 48% **3a** (run 3). This yield, much lower than that of the standard reaction (Table 1), clearly showed that alkyl halides are far more effective than the corresponding haloid acids in the N-alkylation reactions. Moreover, a considerable amount of benzyl bromide (9%) was also detected in the reaction of $PhNH_2{\cdot}HBr$ and benzyl alcohol (eq. 7), implying that alkyl halides can be readily regenerated from the interaction of alcohols and ammonium salts (Scheme 1b, path a). Regeneration and recovery of the alkyl halides ultimately led to the catalytic N-alkylation process (Scheme 1b, path a). In addition, precipitate of $PhNH_2{\cdot}HBr$ salt was found instantly formed at the addition of HBr to aniline,[10] suggesting that the reaction with catalytic amounts of HBr (eq. 6, run 3) most likely proceeded with formation of $PhNH_2{\cdot}HBr$ and via a $PhNH_2{\cdot}HBr$-initiated process (eq. 6, run 1). This results also suggested that, even if free HBr may be generated in the reaction (Scheme 1, path b), it is most possibly trapped instantly by the amines to form the corresponding ammonium salts, which can then react with alcohols to give alkyl halides and catalyze the reaction to give alkylated products (eq. 7). On the other hand, since path b with liberation and loss of HBr can inevitably result in reduced reaction efficiency, although the possibility to undergo path b cannot be excluded completely at present, the reactions are more likely to proceed via path a (Scheme 1b) based on the experimental findings discussed above.



run	cat.	**3a**%
(1)	$PhNH_2{\cdot}HBr$	39
(2)	$PhNH_2{\cdot}HCl$	22
(3)	HBr (33 wt% in HOAc)	48

combined **3a**+**4a** yield:^{GC} 64%; **3a**/**4a**:^{GC} 59/41

Conclusions

In summary, by using only catalytic amounts of alkyl halides, a selective catalytic Hoffmann N-alkylation reaction of amines and amides with alcohols avoiding the use of transition metal catalysts, solvents, and large amounts of bases and alkyl halides can be achieved for efficient and green synthesis of *mono*- or *di*-alkylated amine/amide derivatives in high selectivities, generating no other wastes than the water as the only byproduct. Although the method is mainly suitable for poor nucleophilic amines/amides and more active benzylic alcohols at present, the current results revealed high potential of the method in synthesis for it provided new synthetic possibilities, and, there is still much space for improvement of the method by developing more active catalysts. Although the mechanism of the reaction is still remained to be elucidated in more depth in each cases, preliminary results clearly suggested that alkyl halides are key intermediates/catalysts that can be regenerated and recovered in the reaction cycle. Extension of the method such as developing new catalysts, to a wider scope of substrates, and deeper mechanistic understanding of the reactions are underway.

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11 The corresponding solid salt precipitated instantly once HBr was added to aniline. See ESI for details.

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Selective Catalytic Hoffmann N-Alkylation of Poor Nucleophilic Amines and Amides with Catalytic Amounts of Alkyl Halides

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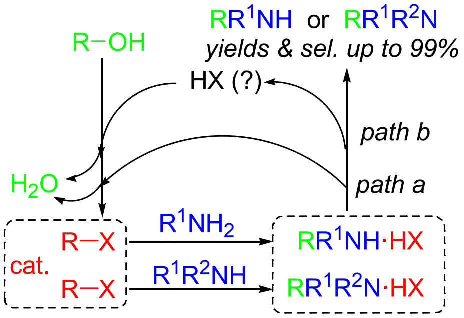

Selective Catalytic Hoffmann N-Alkylation Reaction:
catalytic in RX, high selectivities,
no base/solvent, sole byproduct H_2O,
simple conditions (under air) and
operation, easy purification

A selective Hoffmann N-alkylation reaction of amines/amides catalytic in alkyl halides is achieved, affording *mono*- or *di*-alkylated amines/amides in high selectivities by using alcohols as the alkylating reagents.
