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Cobalt-catalyzed benzylic C–H amination via dehydrogenative-coupling reaction

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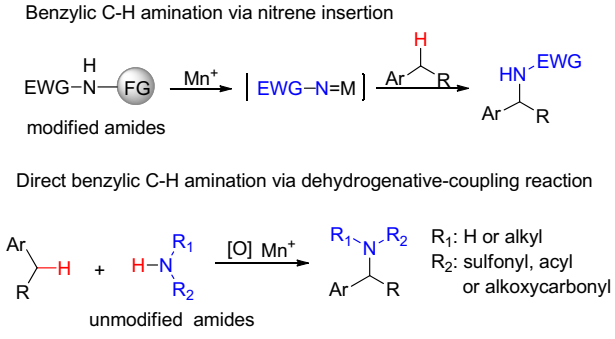
ABSTRACT

An efficient direct benzylic C–H amination via dehydrogenative-coupling by using an inexpensive catalyst/oxidant ($CoBr_2$/^{t}BuOO^{t}Bu) system is described. Various unmodified amides including primary or secondary sulfonamides, carboxamides, and carbamates preformed well with benzylic hydrocarbons with moderate to good yields.

1. Introduction

Amines are abundant in natural and synthetic products and play a key role in many biologically active compounds, such as amino acids and alkaloids. The methods for the introduction of amino groups range from the classical transformations, including nucleophilic substitution and reductive amination, to modern amination methodologies such as Buchwald–Hartwig C–N coupling,[1] Chan–Lam C–N coupling,[2] Ullmann-type amination,[3] and alkene hydroamination.[4] These methods have the disadvantages that they always require pre-installation of reactive functional groups and often proceed under relatively harsh conditions. Therefore, the direct amination of C–H bonds with high efficiency and selectivity is of great potential synthetic utility. In the past two decades, significant progresses have been achieved within the C–H bond aminations fields,[5] particularly with regard to the reactions between allylic or benzylic hydrocarbons and modified amides or amines, such as ArI=NTs,[5f,6,7] chloramine-T,[8] bromamines-T,[9] tosyloxycarbamates,[10] and arylazides,[11] which act as nitrene precursors (Scheme 1). In spite of the great efforts, limits still remain as follows: (1) to obtain these compounds, functionalization of the corresponding amides or amines are necessary; (2) as a consequence of the metal–nitrenoid intermediate, nitrogen source is restricted to primary amide species; (3) carboxamides, the most common amide species, have scarcely been employed in C–H amination. Although a few recent reports[12] have addressed these questions to some extent, it still lacks a simple system, that is, applicable to most amides, such as primary or secondary sulfonamides, carboxamides, and carbamates. Thus, additional effective and inexpensive amination strategies, which would be applicable to most primary and secondary amides, are highly desirable.



Scheme 1. Catalyzed C–H aminations.

Dehyrogenative-coupling reaction has provided a foundation for the next generation of chemical syntheses with an eye on green chemistry and has been applied to generate C–C bonds directly from the coupling of C–H and C–H bonds.[13] To our knowledge, C–N bond formations via dehydrogenative-coupling were seldom reported.[14] In this paper, we wish to report a general method for the direct dehydrogenative amination of benzyl C–H bonds (Scheme 1). By using an inexpensive catalyst/oxidant ($CoBr_2$/^{t}BuOO^{t}Bu) system, benzyl hydrocarbon could react smoothly with several kinds of unmodified primary and secondary amides, such as sulfonamides, carboxamides, and carbamates.

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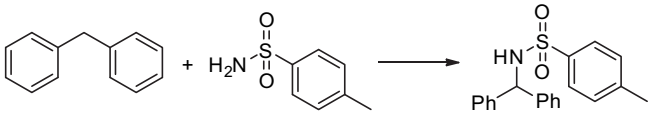
2. Results and discussion

To initiate our study of the amination of benzylic hydrocarbons, diphenylmethane **1a** and tosylamine ($TsNH_2$) **2a** were chosen as substrates to optimize the reaction conditions, and the results were summarized in Table 1. Firstly, the reaction was conducted by using $FeCl_3$ as the catalyst and di-*tert*-butyl peroxide (DTBP) as the oxidant, but no desired product was detected. However, when $FeCl_3$ was replaced with $CoBr_2$ as the catalyst, we were pleased to find that the amination product **3a** could be obtained in 66% isolated yield (Table 1, entry 2). Other oxidant including *tert*-butyl hydroperoxide (TBHP) and H_2O_2 were not effective (entries 3 and 4). $CuBr_2$ and $FeBr_3$ also facilitated the reaction, but were less efficient than $CoBr_2$ under the same conditions (entries 5–7). Unexpectedly, other easily-available cobalt salts, such as $CoCl_2$, $Co(OAc)_2$, and hydrated $CoBr_2$ were found to be inactive (entries 8–10). Solvents also significantly affected the reaction, and no product could be obtained in polar solvents, such as DMF and Dioxane (entries 11 and 12). Meanwhile, non-polar solvents, such as ethyl acetate, toluene, *p*-xylene, 1,2-dichloroethane (DCE), and 1,1,2-trichloroethane (TCE) were good for the reaction (entries 13–17). When TCE, a higher boiling point solvent, was used, the reaction could be carried out at 120 °C in a shorter reaction time and gave **3a** with 73% yield (entry 17). In the absence of a catalyst, no product was observable (entry 18), thus providing the evidence that cobalt is involved in the catalytic cycle.

Table 1
Direct amination of diphenyl methane with tosylamine[a]



1a **2a** **3a**

Entry	Catalyst	Oxidant	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)
1	$FeCl_3$	DTBP	DCE	90	72	N.D.
2	$CoBr_2$	DTBP	DCE	90	72	66
3	$CoBr_2$	H_2O_2	DCE	90	72	N.D.
4	$CoBr_2$	TBHP	DCE	90	72	N.D.
5[c]	$CoBr_2$	DTBP	DCE	90	48	60
6[c]	$CuBr_2$	DTBP	DCE	90	48	23
7[c]	$FeBr_3$	DTBP	DCE	90	48	54
8[c]	$CoCl_2$	DTBP	DCE	90	48	N.D.
9[c]	$Co(OAc)_2$	DTBP	DCE	90	48	trace
10[c]	$CoBr_2 \cdot 6H_2O$	DTBP	DCE	90	48	N.D.
11[d]	$CoBr_2$	DTBP	DMF	90	48	N.D.
12[d]	$CoBr_2$	DTBP	Dioxane	110	48	N.D.
13[d]	$CoBr_2$	DTBP	EA	70	48	58
14[d]	$CoBr_2$	DTBP	Toluene	110	28	53
15[d]	$CoBr_2$	DTBP	*p*-Xylene	120	28	61
16[d]	$CoBr_2$	DTBP	DCE	90	48	55
17[d]	$CoBr_2$	DTBP	TCE	120	28	73
18[d]	None	DTBP	TCE	120	28	N.D.

[a] General conditions: **1a** (1.5 mmol, 3 equiv), **2a** (0.5 mmol, 1 equiv), oxidant (2 equiv), solvent (2 mL), catalyst (20 mol %).
[b] Isolated yields.
[c] Compound **1a** (1.5 equiv).
[d] Compound **1a** (2.5 equiv). (DTBP=di-*tert*-butyl peroxide, DCE=$ClCH_2CH_2Cl$, TCE=Cl_2CHCH_2Cl).

Additives are often found to play important roles in organic reactions. We tested the use of several polar solvent molecules as the additives for the reaction. As shown in Table 2, the addition of 10 mol % of water, ethanol or dioxane only slightly affected the reaction, and similar yields were obtained in comparison with the reaction without an additive (entries 2–4). To our delight, acetic acid could greatly promote the reaction, and the yield sharply increased to 93% (entry 5). Although it is difficult to provide a mechanistic rational for the observed improvements at the present stage, the fact that good results were obtained with 0.5 equiv of acetic acid relative to cobalt suggests that monocarboxylate-bridged cobalt(II) complexes could be involved as reported by others.[15]

Table 2
Effect of additives in the preparation of **3a** under the optimized conditions[a]

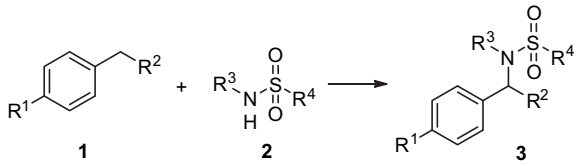
Entry	Additive	Yield[b] (%)
1	None	72
2	H_2O	73
3	Ethanol	79
4	Dioxane	70
5	Acetic acid	93

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.5 mmol), DTBP (2 equiv), $CoBr_2$ (20 mol %), additive (0.1 equiv), in 1 mL of $CHCl_2CH_2Cl$, 120 °C, 28 h.
[b] Isolated yields.

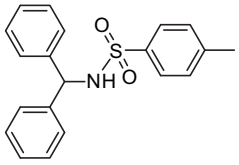
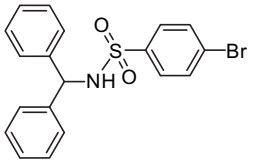
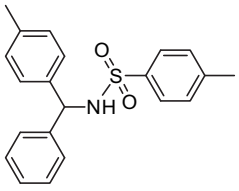
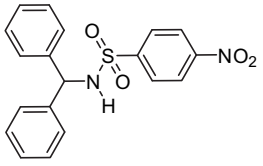
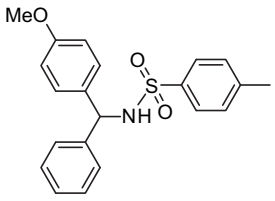
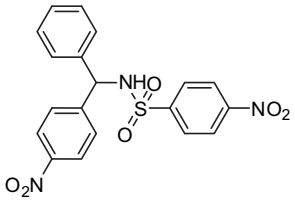
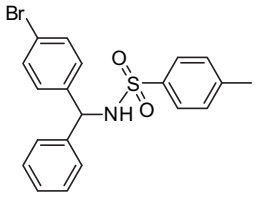
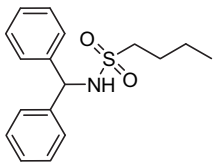
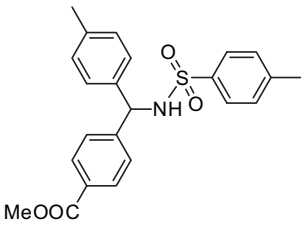
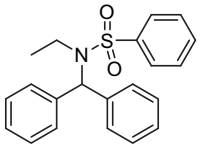
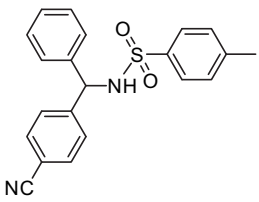
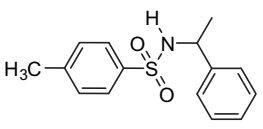
The substrate scopes of the direct benzylic C–H amination were subsequently expanded by using various hydrocarbons and sulfonamides. As shown in Table 3, the direct amination at benzyl position of several diphenylmethane derivatives with various sulfonamides proceeded smoothly with moderate to high yields (Table 3, **3a**–**f**). Electronic effect played an important role in the reaction, and the diphenylmethane substrates with electron-withdrawing groups on the phenyl ring (**3d**, **3f**) gave lower yields than those with electron-donating groups. We speculated that the electron-withdrawing groups might destabilize the proposed benzyl cation species. From the reactions employing different sulfonamides, it was also found that the sulfonamides with electron-withdrawing groups gave harshly decreased yields of the products (**3i**, **3j**). This might be due to the decreased electron density on the nitrogen atom caused by the electron-withdrawing group. The reaction between a diphenylmethane and a sulfonamide in which both are substituted with an electron-withdraw group was also tested, and very low yield was observed (**3k**). We found that the reaction was also applicable to an alkyl sulfonamide and a secondary sulfonamide, albeit moderate yields were obtained. *n*-Butyl sulfonamide and *N*-ethyl tosylamide could react with diphenylmethane and gave the corresponding products in 57% and 30% yields, respectively (**3l**, **3m**). Besides diarylmethanes, the less active but simpler substrates, such as ethylbenzene could undergo the direct amination with up to 90% yields by using ethylbenzene as the solvent (**3n**, **3o**). For the substrate with a tertiary benzylic C–H bond, no amination product was observed under the same conditions (**3p**).

We further found that carboxamides and carbamates were also suitable for the direct amination process. Diphenylmethane could react with several benzamides and furoylamide to give the corresponding products with up to 96% yields (Table 4, **5a**–**e**). The electronic properties of the benzyl substrates seemed important for the reaction outcome. The substrate with an electron-donating group reacted well and gave an excellent yield of 97% (**5f**), while an electron-withdrawing group greatly retarded the reaction (58%, **5g**). Ethylbenzene and its analogs also reacted smoothly with benzamides to give moderate to good yields (**5h**–**n**). Similar to that described above for the diphenylmethanes, the electro-deficient ethylbenzene derivatives gave the corresponding products also with lower yields (**5k**, **5l**). A carbamate was found to be an excellent candidate for the reaction, which gave the amination product in 94% yield (**5o**). This was the first example of direct intermolecular amination using an unmodified carbamate. Remarkably, secondary carboxamides also provided good yields (**5p**, **5q**), which were

Table 3
Direct benzylic C–H amination between aromatic hydrocarbons and sulfonamides[a,b]

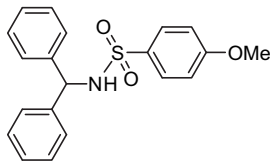
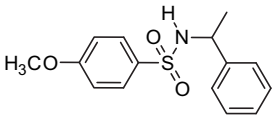
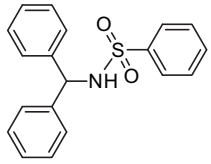
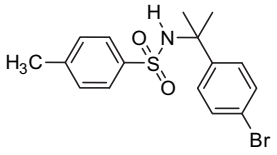


1 **2** **3**

Product	Yields (%)	Product	Yields (%)
 **3a**	93	 **3i**	57
 **3b**	81	 **3j**	44
 **3c**	82	 **3k**	23
 **3d**	65	 **3l**	57
 **3e**	55	 **3m**	30
 **3f**	64	 **3n**	90[c]

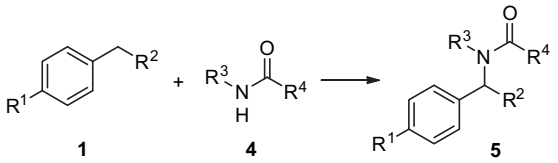
(*continued on next page*)

Table 3 (*continued*)

Product	Yields (%)	Product	Yields (%)
 **3g**	83	 **3o**	86[c]
 **3h**	87	 **3p**	0[c]

[a] Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), 1,1,2-trichloroethane (1 mL), DTBP (2 equiv), acetic acid (10 mol %), 120 °C, 28 h, unless otherwise noted.
[b] Isolated yields.
[c] Alkyl benzene (1 mL) was used as solvent.

Table 4
C–H amination with various carboxamides and carbamates[a,b]



1 **4** **5**

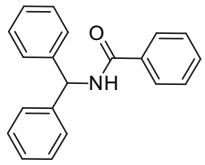
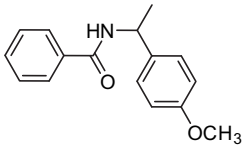
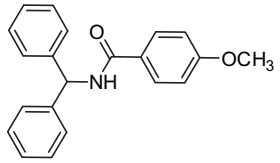
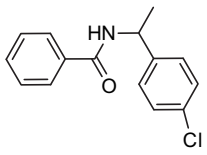
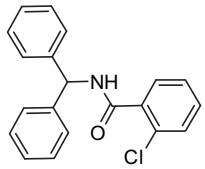
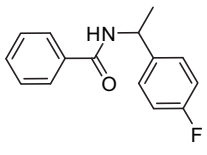
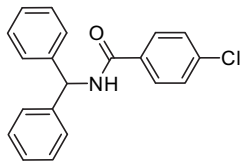
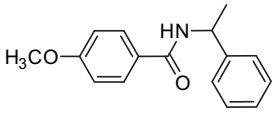
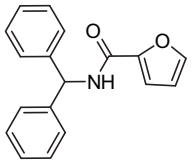
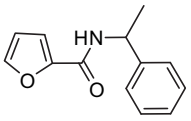
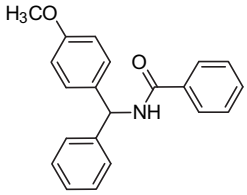
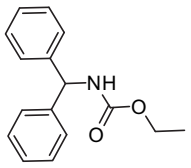
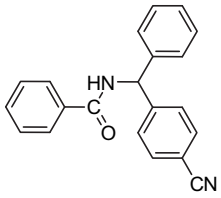
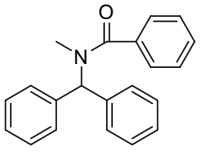
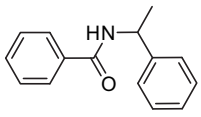
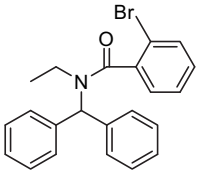
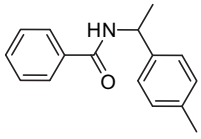
Product	Yields (%)	Product	Yields (%)
 **5a**	96	 **5j**	70[c]
 **5b**	86	 **5k**	44[c]
 **5c**	96	 **5l**	64[c]
 **5d**	50	 **5m**	87[c]

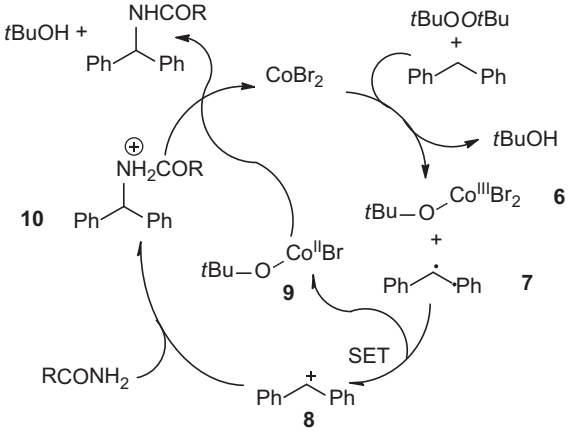
Table 4 (*continued*)

Product	Yields (%)	Product	Yields (%)
 **5e**	75	 **5n**	66[c]
 **5f**	97	 **5o**	94
 **5g**	58	 **5p**	60
 **5h**	84[c]	 **5q**	70
 **5i**	66[c]		

[a] Reaction conditions: **1** (1 mmol), **4** (0.5 mmol), 1,1,2-trichloroethane (1 mL), DTBP (2 equiv), acetic acid (10 mol %), 120 °C, 28 h, unless otherwise noted.
[b] Isolated yields.
[c] Relative substrate **1** (1 mL) was used as solvent.

higher than that given by the secondary sulfonamide. To our knowledge, there has been no report about the direct amination of hydrocarbons by using secondary carboxamides as the nitrogen source. In addition to the benzyl substrates, we also tested the reactivity of cyclohexene but only observed trace of allyl C–H amination product.

A tentative mechanism for the product formation is proposed in Scheme 2. The reaction between diphenylmethane and di-*tert*-butyl peroxide in the presence of $CoBr_2$ produced the Co(III) intermediate **6** and the diphenylmethane radical **7**.[13b,16,17] This benzylic radical was further oxidized to form the benzylic cation **8** through a single-electron transfer process.[13b,17] The subsequent nucleophilic addition of an amide would form the intermediate **10**, which upon proton abstraction by the reduced Co(II) intermediate **9** would deliver the coupling product and regenerate the catalyst.



Scheme 2. A tentative mechanism for the direct oxidative coupling of benzylic hydrocarbons with amides.

3. Conclusion

In summary, we have demonstrated a novel benzylic C–H amination strategy via dehydrogenative-coupling by using an inexpensive catalyst/oxidant ($CoBr_2$/^{t}BuOO^{t}Bu) system. The reaction could be applicable to various unmodified amides including primary or secondary sulfonamides, carboxamides, and carbamates.

4. Experimental

4.1. General

HRMS were performed on Bruker Daltonics Bio TOF mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in hertz.

4.2. General procedure for amination of benzylic hydrocarbons

Ethylbenzene (1 mL), or a solution of diphenylmethane (1 mmol) in trichloroethane (1 mL), was added to a mixture of amide (0.5 mmol), $CoBr_2$ (0.1 mmol) and AcOH (0.05 mmol) at room temperature, and DTBP (1 mmol) was then added. The resulting mixture was stirred at 120 °C for 28 h under air. After cooling to room temperature, the mixture was diluted with ethyl acetate (50 mL) and washed with water. The organic phase was dried over $MgSO_4$ and removed under reduced vacuum. The residue was purified by column chromatography eluting with ethyl acetate and hexane to afford the desired product.

Compound **3a**: 93%; slight yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J=8.0 Hz), 7.09–7.39 (m, 12H), 5.57 (d, 1H, J=7.2 Hz), 5.02 (d, 1H, J=6.8 Hz), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.5, 137.4, 129.4, 128.5, 127.6, 127.4, 127.2, 61.3, 21.5. HRMS (ESI) calcd for $C_{20}H_{18}NO_2S$ $(M-H)^-$ 336.1056; found 336.1045.

Compound **5a**: 96%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (t, 2H, J=7.2 Hz), 7.26–7.53 (m, 13H), 6.69 (d, br, 1H, J=7.2 Hz), 6.46 (d, 1H, J=8.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 141.5, 134.2, 131.7, 128.8, 128.6, 127.6, 127.5, 127.1, 57.5. HRMS (ESI) calcd for $C_{20}H_{17}NONa$ $(M+Na)^+$ 310.1208; found 310.1220.

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Supplementary data

Detailed experimental procedures and compound characterization. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.04.054.

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