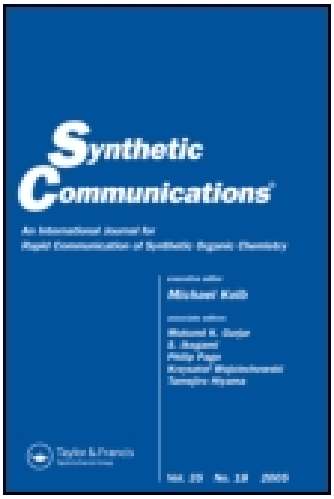

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SOLVENT-FREE AMINATION OF SECONDARY BENZYLIC ALCOHOLS WITH N-NUCLEOPHILES CATALYZED BY $FeCl_3$

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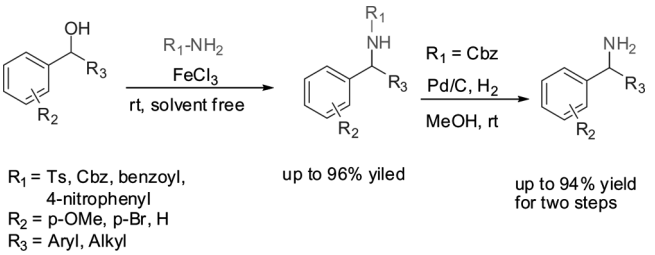
GRAPHICAL ABSTRACT



Abstract *A general, simple, and environmentally friendly method for the direct amination of secondary benzyl alcohols with amides or 4-nitroaniline is described. This method has been applied to a variety of substrates, and the reaction proceeded smoothly at room temperature under solvent-free conditions. $CbzNH_2$ was proved to be very useful in the direct preparation of the benzylic amines from corresponding alcohols.*

Keywords Amination; benzyl alcohols; benzyl amines; $FeCl_3$; solvent free

INTRODUCTION

Benzylic amines are of medicinal potential and are found in a number of biologically active compounds.[1,2] C–N bond formation is an important reaction for the synthesis of these kinds of amines. Generally, this transformation is carried out using alkyl halides in the presence of a stoichiometric amount of base. Although this method works well even on a large scale, often it is associated with significant drawbacks including unavailability of halogenated substrate, toxicity of halogenated substrates, the use of a strong base, and production of large amounts of salts as by-products. Thus, benzylic alcohols and their derivatives have received considerable

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attention as carbon electrophiles capable of reacting with various carbon, oxygen, and sulfur nucleophiles.[3] However, there are a very limited number of examples known with less nucleophilic nitrogen nucleophiles such as amides and electron-deficient aromatic amines.

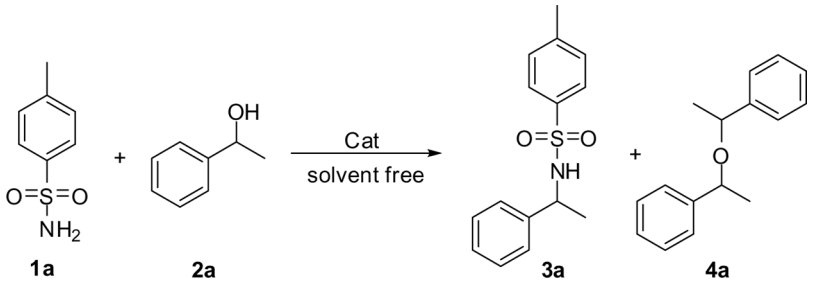
To the best of our knowledge, only a few Lewis acid–catalyzed amidation reactions of alcohols with primary amides have been described in the literature using $NaAuCl_4$,[4] H-montmorillonite,[5] $MoCl_5$,[6] $NbCl_5$,[7] $FeCl_3$,[8] and $Bi(OTf)_3$/KPF_6[9] among others.[10] More important, the solvents used for these reactions mainly were CH_2Cl_2,[4,6] CH_3NO_2,[8] CH_3CN,[9] and 1,4-dioxane,[5,9] which are too expensive and toxic for practical utility of these methods in the large-scale synthesis of differently substituted benzylic amides or amines.

Over the past few years, a significant amount of research has been directed toward the progress of new technologies for environmentally benign processes, and the development of new, general, efficient, ecofriendly catalytic procedures for amination reactions is desirable. Environmental concerns about solvent-based chemistry have stimulated a renewed interest in the study of chemical reactions under solvent-free conditions.[11]

In this context, we report herein that $FeCl_3$ is an efficient catalyst for the amination reactions of secondary benzylic alcohols with nitrogen nucleophiles under solvent-free conditions.

RESULTS AND DISCUSSION

The amidation reaction of 1-phenylethanol (**2a**) with 4-methylbenzenesulfonamide (**1a**) was chosen as model reaction to find the best reaction conditions (Scheme 1). First, different kinds of catalyst were tested in this reaction, and the results are summarized in Table 1 (entries 1–7). Brønsted acid and *p*-methylbenzenesulfonic acid were examined and only traces of benzylic amine (**3a**) were afforded (Table 1, entry 1). Except for $FeCl_3$ (Table 1, entry 7), other Lewis acids, such as $Yb(OTf)_3$, $YbCl_3$, $AlCl_3$, $TiCl_4$, $InCl_3$, and $FeCl_3 \cdot 6H_2O$ all had poor results (Table 1, entries 2–6). Thus, $FeCl_3$ was the best choice for this reaction. Using $FeCl_3$ as catalyst, different reaction times were tested, and the results showed that 4 h was enough for this reaction (Table 1, entries 7–9). Meanwhile, the temperature was also examined, and the high temperature was proved to be fit for the formation of by-product **4a** (Table 1, entries 7 and 10–13). The reactions were carried out at room



Scheme 1. Amidation reaction of 1-phenylethanol with Ts-NH_2.

Table 1. Optimization of the amination reaction

Entry[a,b]	Catalyst	Catalyst loading (mol%)	Time (h)	Temp (°C)	Yield[c] (%)
1	TsOH	20	4	rt	Trace
2	$Yb(OTf)_3$	20	4	rt	Trace
3	$YbCl_3$	20	4	rt	Trace
4	$TiCl_4$	20	4	rt	Trace
5	$InCl_3$	20	4	rt	Trace
6	$FeCl_3 \cdot H_2O$	20	4	rt	Trace
7	$FeCl_3$	20	4	rt	85
8	$FeCl_3$	20	1	rt	60
9	$FeCl_3$	20	8	rt	85
10	$FeCl_3$	20	4	40	80
11	$FeCl_3$	20	4	60	50
12	$FeCl_3$	20	4	80	Trace
13	$FeCl_3$	20	4	100	Trace
14	$FeCl_3$	1	4	rt	Trace
15	$FeCl_3$	2	4	rt	Trace
16	$FeCl_3$	5	4	rt	Trace
17	$FeCl_3$	10	4	rt	20
18	$FeCl_3$	30	4	rt	80

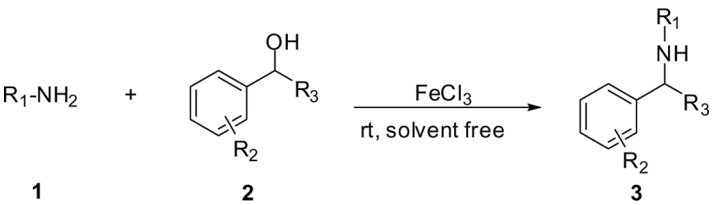
[a]Reaction condition: 4-methylbenzenesulfonamide (1.2 mmol), 1-phenylethanol (1 mmol).
[b]4-Methylbenzenesulfonamide was ground before use.
[c]Isolated yield.

temperature for 4 h, with different amounts of catalyst, and the most suitable catalyst/substrate ratio seems to be 0.2 (Table 1, entries 7 and 14–18).

Having established the reaction conditions, we further explored the generality and efficiency of the $FeCl_3$-catalyzed direct amination of various nucleophiles such as *p*-toluenesulfonamide, benzamide, benzyl carbamate, and 4-nitroaniline with benzylic alcohols (Scheme 2). In general, the reaction proceeded smoothly for all cases in good to excellent yields within a very short period of time with complete selectivity. The results are summarized in Table 2.

First, *p*-toluenesulfonamide was treated with different benzylic alcohols (Scheme 3), and the yields of the products were associated with the stability of the carbon cations formed in this reaction (Table 2, entries 1–5).

As a first example, benzylic alcohol **2b** was treated with *p*-toluenesulfonamide in the presence of a catalytic amount of $FeCl_3$ (20 mol%) at room temperature to give the corresponding amidated product **3b** in 80% yield within 4 h (Table 2, entry 1).



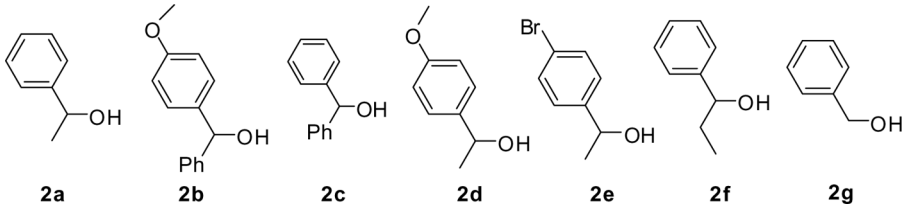
Scheme 2. Solvent-free amination of the benzylic alcohols with different N-nucleophiles catalyzed by $FeCl_3$.

Table 2. Amination of secondary benzylic alcohols with N-nucleophiles catalyzed by $FeCl_3$ under solvent-free conditions

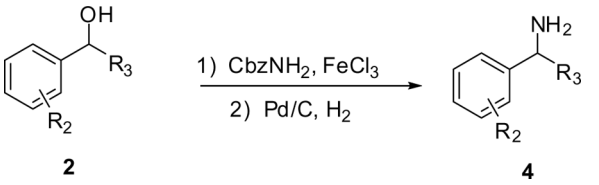
Entry[a]	R_1	Alcohols (**2**)	Temp. (°C)	Product(**3**)	Yield (%)[b]
1	Ts (**1a**)	**2b**	rt	**3b**	80
2	Ts (**1a**)	**2c**	60[c]	**3c**	90
3	Ts (**1a**)	**2d**	rt	**3d**	70
4	Ts (**1a**)	**2e**	rt	**3e**	51
5	Ts (**1a**)	**2f**	rt	**3f**	52
6	Benzoyl (**1b**)	**2b**	60[c]	**3g**	80
7	Benzoyl (**1b**)	**2c**	60[c]	**3h**	90
8	Benzoyl (**1b**)	**2d**	rt	**3i**	65
9	Cbz (**1c**)	**2b**	60[c]	**3j**	80
10	Cbz (**1c**)	**2c**	60[c]	**3k**	96
11	Cbz (**1c**)	**2d**	rt	**3l**	90
12	4-Nitrophenyl (**1d**)	**2a**	rt	**3m**	46
13	4-Nitrophenyl (**1d**)	**2b**	60[c]	**3n**	75
14	4-Nitrophenyl (**1d**)	**2c**	60[c]	**30**	80
15	4-Nitrophenyl (**1d**)	**2d**	rt	**3p**	91
16	4-Nitrophenyl (**1d**)	**2f**	rt	**3q**	40
17	Boc (**1e**)	**2c**	60[c]	**3r**	Trace
18	Ph (**1f**)	**2c**	rt	**3s**	Trace
19	Ts (**1a**)	**2g**	rt	**3t**	Trace

[a]Reaction condition: nucleophile (1.2 mmol), benzylic alcohols (1 mmol), $FeCl_3$ (20 mol%), room temperature.
[b]Isolated yield.
[c]When the reactants were both solid, they were ground together and warmed to 60 °C.

The reaction of **1a** with other benzylic alcohols was also successful (Table 2, entries 2–5). With this success, we were interested in testing the nucleophilic substitution reaction with benzamide. Thus, the reaction of benzylic alcohols with benzamide in the presence of 20 mol% $FeCl_3$ proceeded easily to provide the corresponding amides with a yield of up to 90% (Table 2, entries 6–8). Similarly, the catalytic system was also effective for the amidation of **2c** with benzyl carbamate, which provided the corresponding Cbz-protected amines up to 96% yield (Table 2, entries 9–11). Finally, other N-nucleophiles, such as 4-nitroaniline, were also successfully tested, allowing the introduction of aniline-based moieties at the benzylic position (Table 2, entries 12–16). When *t*-butyl carbamate ($BocNH_2$) and aniline were introduced, traces of products were afforded (Table 2, entries 17 and 18). When the less reactive benzylic



Scheme 3. Chemical structure of the benzylic alcohols used in amination reactions.



2 **4**

Scheme 4. Direct access to benzylic amines.

Table 3. Two-steps methods to the synthesis of benzyl amines

Entry	Alcohol (**2**)	Compound (**4**)	Yield(%)[a] two steps
1	**2b**	**4b**	78
2	**2c**	**4c**	94
3	**2d**	**4d**	88

[a]Isolated yield.

alcohol **2g** was tested with **1a**, almost no reaction was carried out in the model conditions (Table 2, entry 19).

However, when two components of the reactants were both solid particles, the reaction must be carried out at a higher temperature to get excellent yield, which might due to the homogeneous mixing after the melting of the two components (Table 2, entries 2, 6, 7, 10, 13, and 14).

Direct access to benzylic amines is also valuable in the context of the synthesis of bioactive products (Scheme 4). The purification of crude product over column chromatography, followed by the reduction of the Cbz-protected intermediates using Pd/C and H_2, afforded the desired methylamines in nearly quantitative yields. Thus, various benzylic amines have been successfully prepared using H_2 as the reducing agent in 78% to 94% yields, and the results are gathered in Table 3.

EXPERIMENTAL

Melting points were determined with an X-4 apparatus and are uncorrected. ^{1}H (400-MHz) and ^{13}C (100-MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. Mass (EI) spectra were recorded on a Micromass GCTTM mass spectrometer. All chemicals used were reagent grade and were used as received without further purification.

Representative Procedure for the Synthesis of Compound 3j

A mixture of (4-methoxyphenyl) (phenyl) methanol (**2b**, 1.0 mmol) and benzyl carbamate (**1c**, 1.2 mmol) was heated to 60 °C for 5 min until the reactant melted. Anhydrous $FeCl_3$ (30 mg, 20 mol%) was added in a single portion, and the reaction was continued until the reaction mixture solidified. The mixture was loaded onto a silica-gel column and chromatographed with petroleum ether/ethyl acetate (4:1) to

afford product **3j** as a white solid (273 mg, 0.80 mmol, 80%), mp 103–105 °C ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.32 (m, 6H), 7.32–7.24 (m, 4H), 7.17 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.96 (d, J = 6.0 Hz, 1H), 5.40 (Br s, 1H), 5.14 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0 155.6, 141.9, 136.4, 133.9, 128.6, 128.5, 128.2, 127.4, 127.1, 114.1, 67.0, 58.4, 55.3 ppm; HRMS (EI): m/z calcd. for $C_{22}H_{21}NO_3$ (M^+): 347.1521; found: 347.1506.

Representative Procedure for the Synthesis of Compound 4b

Pd-C 7%, (40 mg) was added to a solution of compound **3j** (173 mg, 0.5 mmol) in MeOH (10 mL). The mixture was stirred under a hydrogen atmosphere (1 bar) for 1.5 h, the catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (15 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to give pure product (4-methoxyphenyl)(phenyl)methanamine (4b) as a colorless oil (110 mg, quant yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 7.6 Hz, 2H), 7.30–7.35 (m, 4H), 7.24 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 5.18 (s, 1H), 3.98 (s, 3H), 2.08 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 145.8, 137.7, 128.4, 128.0, 126.9, 126.8, 113.8, 59.1, 55.2 ppm. HRMS (EI): m/z calcd. for $C_{14}H_{15}NO$ (M^+): 213.1154; found: 213.1153.

Selected Data

Benzyl (4-methoxyphenyl)(phenyl)methylcarbamate (3l). White solid; mp 83–85 °C; yield 224 mg (90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.30 (m, 5H), 7.25 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.06–5.17 (m, 2H), 5.00 (Br s, 1H), 4.83 (m, 1H), 3.81 (s, 3H),1.48 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 155.8, 136.5, 128.5, 128.2, 128.1, 127.2, 127.1, 114.0, 66.7, 58.3, 55.3, 22.3 ppm. HRMS (EI) m/z calcd. for $C_{17}H_{19}NO_3$ (M^+): 285.1365; found 285.1368.

N-(1-(4-methoxyphenyl)ethyl)-4-nitroaniline (3p). Milk-white solid; mp 125–127 °C; yield 246 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 9.2 Hz, Hz, 2H), 4.95 (br s, 1H), 4.57 (m, 1H), 3.80 (s, 3H), 1.56 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 152.4, 138.0, 135.2, 126.7, 126.2, 114.3, 111.8, 55.3, 52.7, 24.5 ppm. HRMS (EI): m/z calcd. for $C_{15}H_{16}N_2O_3$ (M^+): 272.1161; found: 273.1162.

CONCLUSION

In conclusion, we have developed an efficient procedure to obtain benzylic amines starting from the corresponding alcohols under solvent-free conditions. This methodology tolerates various benzylic alcohols bearing electron-donating but also mild electron-withdrawing groups. Several catalytic systems were compared, evidencing the higher selectivity of $FeCl_3$ over others. Among the nitrogen-based nucleophiles used, $CbzNH_2$ proved useful as an intermediate in the amidation–reduction sequence leading to the direct preparation of benzylic amines.

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