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An efficient $FeCl_3$-catalyzed amidation reaction of secondary benzylic and allylic alcohols with carboxamides or *p*-toluenesulfonamide

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Abstract

A simple, inexpensive, environmentally friendly and high yielding amidation reaction of benzylic and allylic alcohols with primary amides using a catalytic amount of $FeCl_3$ (5 mol %) is described. Direct substitution of various amides such as benzamide, sulfonamide, acetamide and acrylamide is reported, and this method also works on a large scale in high yield.

Keywords: Ferric chloride; Amidation reactions; Alcohols; Atom-economical; Inexpensive

C–N bond formation is an important reaction in organic synthesis. Hence, the development of simple, efficient and environmentally friendly C–N bond forming reactions is of paramount importance in organic synthesis. Among the various methods for the construction of C–N bonds,[1] transition metal catalyzed substitution reactions of derivatives of alcohols with nitrogen nucleophiles such as amines/amides is one of the most efficient and reliable methods.[2] However, these methods produce stoichiometric amounts of salt waste both in derivatization of the alcohols and the C–N bond formation steps. Thus, in view of the demand for efficient, economic and environmentally viable processes for the direct catalytic substitution of alcohols[3] with nitrogen nucleophiles, a method for the formation of C–N bonds, which is salt-free, highly atom-economic,[4] environmentally friendly with water as the only byproduct is highly desirable. Although a number of C–N bond forming reactions by direct substitution of alcohols with amines catalyzed by transition metals have been reported,[5] the use of weak nitrogen nucleophiles such as amides which are easily available are extremely rare and require high temperatures.[6] Moreover, amide-containing compounds are very useful in organic synthesis and in biology.[7]

To our knowledge, only a few Lewis acid catalyzed amidation reactions of alcohols with primary amides have been described in the literature using $NaAuCl_4$,[8a] H–Montmorillonite,[8b] $MoCl_5$[8c] and a combination of $Bi(OTf)_3$[3a] with KPF_6 as additive. However, the use of expensive and toxic catalysts limit the practical utility of these methods in the large scale synthesis of differently substituted benzylic and allylic amides, despite the importance of the corresponding benzylic and allylic amines in fine chemicals and pharmaceutical industries.[9] Furthermore, the substrate generality is limited. Therefore, development of a more practical and economical method for direct substitution of primary amides with benzylic or allylic alcohols is highly desirable for the synthesis of such compounds.

Recently, we reported two very efficient methods for the direct catalytic substitution of alcohols with various nucleophiles using the inexpensive and environmentally friendly Lewis acid $FeCl_3$.[10] Herein, we report the $FeCl_3$-catalyzed direct substitution of benzylic and allylic alcohols with various carboxamides or *p*-toluenesulfonamide (Scheme 1).

To establish the reaction conditions we initially examined C–N bond formation between benzyl amide **2** and benzhydrol **1** in the presence of $FeCl_3$.[11] The reaction

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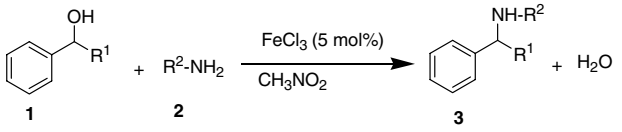
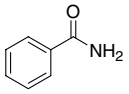
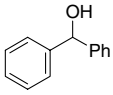
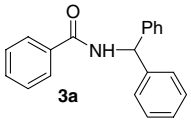
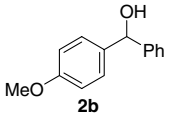
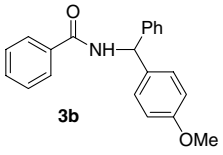
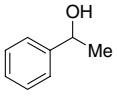
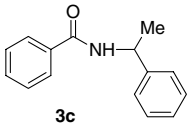
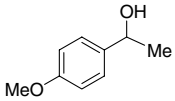
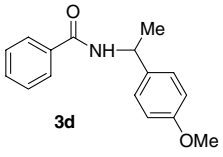
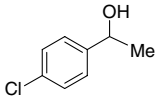
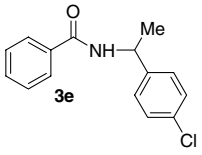
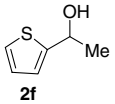
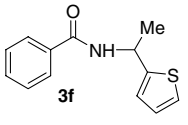
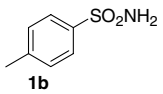
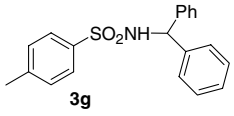
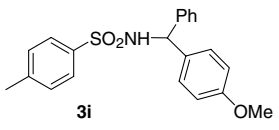


R^1 = alkyl, aryl or allyl
R^2 = PhCO, Ts, CH_3CO or CH_2=CHCO

Scheme 1. $FeCl_3$-catalyzed amidation of benzylic/allylic alcohols.

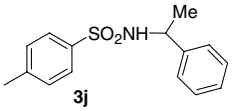
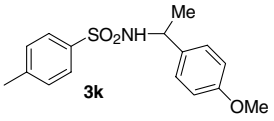
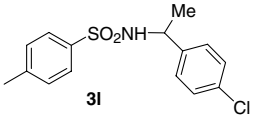
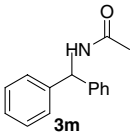
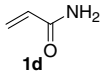
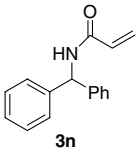
proceeded in the presence of a catalytic amount of $FeCl_3$ (5 mol %) in nitromethane under reflux and the desired substituted amide **3a** was obtained in 98% yield, without the removal of moisture and air. We investigated this reaction with several solvents including acetonitrile, tetrahydrofuran, dichloroethane, nitromethane and methylene chloride; however, the reaction did not proceed in methylene chloride and tetrahydrofuran even under refluxing

Table 1
$FeCl_3$-catalyzed substitution of various alcohols **2** with amides **1**[a]

Entry	Nucleophile	Alcohol	Product	Time (h)	Temp (°C)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	1	Reflux	98
2	**1a**	 **2b**	 **3b**	1	Reflux	98
3	**1a**	 **2c**	 **3c**	2	Reflux	55
4	**1a**	 **2d**	 **3d**	3	rt	85
5	**1a**	 **2e**	 **3e**	3	Reflux	65
6	**1a**	 **2f**	 **3f**	1	80	56
7	 **1b**	**2a**	 **3g**	2	Reflux	98
8	**1b**	**2b**	 **3i**	1	Reflux	82

(*continued on next page*)

Table 1 (*continued*)

Entry	Nucleophile	Alcohol	Product	Time (h)	Temp (°C)	Yield[b] (%)
9	**1b**	**2c**	 **3j**	1	Reflux	84
10	**1b**	**2d**	 **3k**	1	rt	84
11	**1b**	**2e**	 **3l**	2	Reflux	96
12	 **1c**	**2a**	 **3m**	4	Reflux	94
13	 **1d**	**2a**	 **3n**	3	Reflux	85

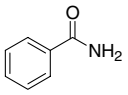
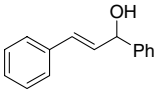
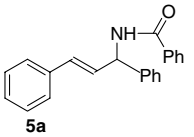
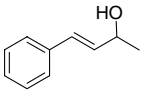
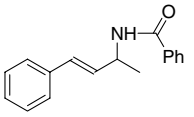
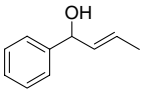
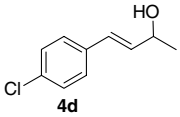
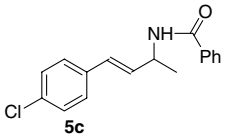
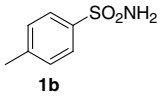
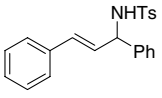
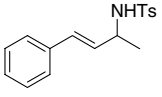
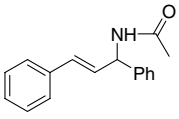
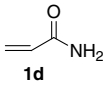
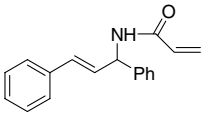
[a] Reaction condition: nucleophile **1** (1 mmol), alcohol **2** (1 mmol), $FeCl_3$ (0.5 mmol), nitromethane (3.5 mL).
[b] The yield refers to pure isolated product characterized from spectral data.

conditions. The reactions did proceed in dichloroethane and acetonitrile at reflux, but they were very sluggish. The best results were achieved using nitromethane in terms of time and yields.

Encouraged by these initial results, we next investigated the amidation reactions of a number of amides including benzamide, *p*-toluenesulfonamide, acetamide and acrylamide with several structurally diverse benzylic alcohols. The results are summarized in Table 1. In general, the reactions proceeded efficiently with various substituted secondary benzylic alcohols and primary amides in very good to excellent yields within very short period of time. The present method was equally effective for benzylic alcohols bearing electron-donating and weak electron-withdrawing groups such as methoxy and chloride (Table 1, entries 2, 4, 5, 8, 9 and 11). Aliphatic primary amides such as acrylamide and acetamide also underwent smooth amidation with benzhydrol **2a** and gave the desired products in 85% and 94% yields, respectively (Table 1, entries 12 and 13), which have not been reported previously by other methods.[8] Furthermore, this reaction was also applied to thiophene derivative **2f** (Table 1, entry 6), but a slightly lower yield of product was obtained. Various functional groups such as methoxy, chloride, tosyl, acetyl, benzoyl and acryl tolerated the reaction conditions. Although this reaction was highly efficient for secondary benzylic alcohols, benzyl alcohol itself did not react under these conditions even on prolonged heating. In all cases, selective monosubstitution of the amide occurred even when using excess alcohols. We also investigated this reaction on a large scale (5.43 mmol) synthesis of **3a**, which afforded the product in a similar 97% yield.[11]

To extend the scope of this methodology, the direct substitution of structurally varied allylic alcohols with amides was investigated. All the reactions proceeded smoothly in the presence of 5 mol % $FeCl_3$ in nitromethane at room temperature (Table 2) in good yields with complete selectivity within a short period of time. Amide **1a** reacted under similar reaction conditions with two regio-isomeric allylic alcohols **4b** and **4c** and furnished the single product **5b** regioselectively in good yield (Table 2, entries 2 and 3). This clearly reflects the formation of the same, delocalized allylic cation intermediate from each of the alcohols, followed by nucleophilic attack by the amide to produce product **5b** (S_N1 mechanism involved). Both steric and electronic factors are responsible for the regioselective formation of **5b**. Similar regioselectivity was also observed in the reactions of *p*-toluenesulfonamide with alcohols **4b** and **4c** to afford the corresponding aminated product **5e** in good yields (Table 2, entries 6 and 7). So, the present

Table 2
$FeCl_3$-catalyzed substitution of various allylic alcohols **4** with amides **1**[a]

Entry	Nucleophile	Alcohol	Product	Time (h)	Temp (°C)	Yield[b] (%)
1	 **1a**	 **4a**	 **5a**	2	rt	85
2	**1a**	 **4b**	 **5b**	1.5	rt	68[c]
3	**1a**	 **4c**	**5b**	3	rt	48[c]
4	**1a**	 **4d**	 **5c**	3	rt	50[c]
5	 **1b**	**4a**	 **5d**	2	rt	60
6	**1b**	**4b**	 **5e**	1	rt	65[c]
7	**1b**	**4c**	**5e**	2.5	rt	80
8	 **1c**	**4a**	 **5f**	3	rt	76
9	 **1d**	**4a**	 **5g**	3	rt	67

[a] Reaction conditions: nucleophile **1** (1 mmol), alcohol **2** (1 mmol), $FeCl_3$ (0.5 mmol), nitromethane (3.5 mL) and the product was extracted with ethyl acetate.
[b] The yield refers to pure isolated product characterized from spectral data.
[c] The reaction was performed using 1.5 equiv of amide.

method is also useful for the synthesis of structurally varied allylic amides.

Thus, we have demonstrated a simple $FeCl_3$-catalyzed direct amidation of benzylic and allylic alcohols with structurally varied primary amides under neutral reaction conditions in the presence of air and moisture. A thiophene system survived under these reaction conditions. No side products were isolated in any of the reactions. The reaction did not proceed at all without $FeCl_3$. Although the exact mechanism is uncertain at this moment, we have observed that the benzylic alcohols were first converted to the corresponding dimeric ether (catalyzed by $FeCl_3$) and then activated by the Lewis acid to produce the final product by nucleophilic substitution with the amide. Formation of an ether was not observed for allylic ethers. However, experimental observation can only be explained by considering the S_N1 mechanism operating for allylic alcohols. Further investigation on the reaction mechanism and the

scope of this reaction are currently underway in our laboratory.

The notable advantages of this method are the operational simplicity, direct use of alcohols and inexpensive and non-toxic $FeCl_3$ catalyst (5 mol %) which render this method an important alternative to previously reported methods. Moreover, this method can also be useful for the large scale synthesis of benzylic and allylic amide derivatives.

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References and notes

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11. *Representative experimental procedure*: To a stirred solution of benzamide **1a** (128 mg, 1 mmol) and benzhydrol **2a** (185 mg, 1 mmol) in dry nitromethane (3.5 mL) was added anhydrous $FeCl_3$ (8 mg, 0.05 mmol). The resulting reaction mixture was refluxed for 1 h. The reaction mixture was then concentrated under reduced pressure and loaded onto a silica gel column and chromatographed with petroleum ether/ ethyl acetate (4:1) to afford product **3a** (282 mg, 0.98 mmol, 98%) as a white solid, mp 170 °C (lit.[12] 170 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (d, $J = 7.7$ Hz, 1H), 6.68 (br s, 1H), 7.26–7.55 (m, 13H), 7.83 (d, $J = 7.5$ Hz, 2H).
Large scale synthesis of **3a**: A mixture of **1a** (1.00 g, 5.43 mmol), **2a** (658 mg, 5.43 mmol) and $FeCl_3$ (44 mg, 0.27 mmol) in nitromethane (6 mL) was refluxed for 1.5 h. Usual work-up and purification afforded a white solid **3a** (1.51 g, 5.27 mmol, 97%). Spectral data for new compounds are given below:
N-(4-Chlorophenylbut-3-en-2yl)benzamide (**5c**): White solid, mp 140 °C; IR (KBr) 3302, 1636, 1526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, $J = 3.3$ Hz, 3H), 4.95–5.00 (m, 1H), 6.11 (br s, 1H), 6.25 (dd, $J = 16.0$, 5.3 Hz, 1H), 6.54 (d, $J = 16.0$ Hz, 1H), 7.26–7.32 (m, 4H), 7.43–7.54 (m, 3H), 7.80 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 47.0, 127.0, 127.8, 128.7, 128.8, 128.9, 131.7, 133.4, 134.7, 135.3, 166.8; HRMS: m/z calcd for $C_{17}H_{16}ClNONa$: 308.0818; found, 308.0776.
N-(1,3-Diphenylprop-2-en-1-yl)acrylamide (**5g**): White solid, mp 123 °C; IR (KBr) 3238, 3055, 1656, 1614, 1547; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, $J = 11$ Hz, 1H), 5.88–5.96 (m, 2H), 6.11–6.21 (m, 1H), 6.33–6.41 (m, 2H), 6.57 (d, $J = 16$, 1H), 7.22–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.0, 126.7, 127.3, 127.4, 127.9, 128.7, 129.0, 130.7, 131.7, 136.5, 140.8, 164.7; MS m/z: calcd for $C_{18}H_{17}NONa$, 286.1208; found, 286.0687.
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