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Molybdenum(V) chloride-catalyzed amidation of secondary benzyl alcohols with sulfonamides and carbamates☆

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Abstract—A general and selective method for the direct amidation of secondary benzyl alcohols with both sulfonamides and carbamates is described. This method has been applied to a variety of substrates and the reaction proceeded smoothly at room temperature in the presence of 5 mol % molybdenum(V) chloride to give the desired products in good yields.
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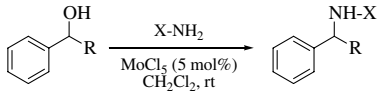
Benzylic amines are of medicinal potential[1] and are found in a number of biologically active compounds such as sertraline (antidepressant), cetirizine hydrochloride (histamine H-receptor) and SNC80 (an opioid receptor agonist).[1c–e] Literature methods for the synthesis of such compounds include introduction of an amine via reductive amination of ketones[2] or the addition of an organometallic compound to an imine.[3,4] Alternatively, substitution of a hydroxyl group is also known with amine nucleophiles, which generally require pre-activation of the hydroxyl group due to their poor leaving ability.[5] Most of these methods also work equally well for non-benzylic alcohols. Therefore, the selective and direct substitution of alcohols with amine nucleophiles is an attractive goal.

In recent years, benzylic alcohols and their derivatives have received considerable attention as carbon electrophiles capable of reacting with various carbon, oxygen and sulfur nucleophiles.[6] To the best of our knowledge there is a very limited number of examples known with less nucleophilic nitrogen nucleophiles such as sulfonamides and carbamates. The catalysts/reagents employed for these examples are $NaAuCl_4$,[7] H–montmorillonite,[8] $Bi(OTf)_3/KPF_6$[9] amongst others.[6a,10] Herein we report a simple procedure for the direct amidation of secondary benzylic alcohols with sulfonamides or carbamates in the presence of 5 mol % of molybdenum(V) chloride[11] that augments existing methods for the transformations (Scheme 1).

As a first example, benzylic alcohol **1a** was treated with *p*-toluenesulfonamide ($TsNH_2$) in the presence of catalytic molybdenum(V) chloride (5 mol %) in dichloromethane at room temperature to give the corresponding amidated product **2a** in 90% yield within 5 h (Table 1, entry 1). The reaction of **1a** with benzenesulfonamide was also successful (Table 1, entry 2). With this success, we were interested to test the nucleophilic substitution reaction with benzyl carbamate ($CbzNH_2$). Thus, the reaction of **1a** with $CbzNH_2$ in the presence of 5 mol % $MoCl_5$ in CH_2Cl_2 proceeded easily to provide the corresponding Cbz-protected amine **2c** in 90% yield (Table 1, entry 3). Similarly, the catalytic system was also effective for the amidation of **1a** with *t*-butyl carbamate ($BocNH_2$) (Table 1, entry 4). To further explore this $MoCl_5$-catalyzed direct amidation of benzylic alcohols, various substrates were studied and the results are summarized in Table 1. Benzylic alcohols such as benzhydrol **1b** and 1-phenylethanol **1c** were reacted with both *p*-toluenesulfonamide and benzyl carbamate under the described reaction conditions to provide the corresponding amide products **2e–h** in good yields (Table 1,



R= alkyl or aryl or alkynyl; X= $PhSO_2$ or Ts or Cbz or Boc

Scheme 1.

Keywords: Molybdenum(V) chloride; Amidation; Benzyl alcohol; Sulfonamide; Carbamate.
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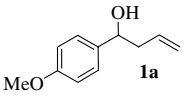
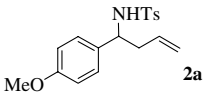
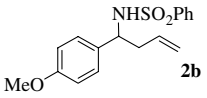
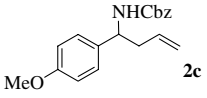
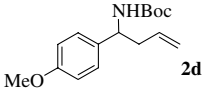
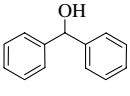
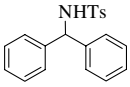
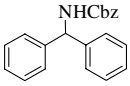
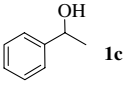
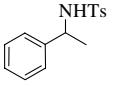
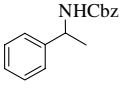
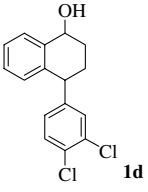
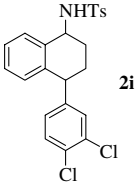
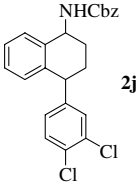
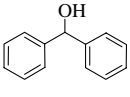
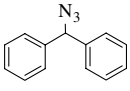
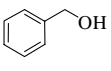
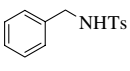
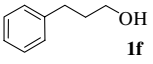
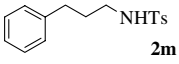
Table 1. $MoCl_5$-catalyzed amidation of secondary benzyl alcohols

Entry	Benzyl alcohol	Carbamate/sulfonamide	Reaction time (h)	Product[a]	Yield[b] (%)
1	 **1a**	$TsNH_2$	5	 **2a**	90
2	**1a**	$PhSO_2NH_2$	6	 **2b**	88
3	**1a**	$CbzNH_2$	5	 **2c**	90
4	**1a**	$BocNH_2$	8	 **2d**	85
5	 **1b**	$TsNH_2$	10	 **2e**	84
6	**1b**	$CbzNH_2$	12	 **2f**	89
7	 **1c**	$TsNH_2$	10	 **2g**	82
8	**1c**	$CbzNH_2$	8	 **2h**	84
9	 **1d**	$TsNH_2$	12	 **2i**	70
10	**1d**	$CbzNH_2$	10	 **2j**	72
11	 **1b**	$TMSN_3$	4	 **2k**	92
12	 **1e**	$TsNH_2$	24	 **2l**	0[c]
13	 **1f**	$TsNH_2$	24	 **2m**	0[c]

[a] All the products were characterized by ^1H, ^{13}C NMR and mass spectra.
[b] Isolated yields.
[c] No reaction either at room temperature or at 40 °C.

entries 5–8). Entries 9 and 10 (Table 1) demonstrate the conversion of alcohol **1d** to sertraline derivatives **2i** and **2j**. In addition, we observed that the reaction of benzhydrol with azidotrimethylsilane ($TMSN_3$) was also successful furnishing the corresponding azide **2k** in 92% yield (Table 1, entry 11). However, the reaction of pri-

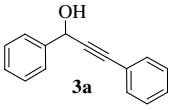
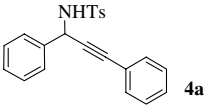
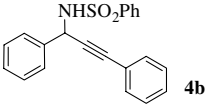
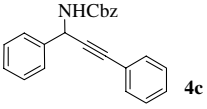
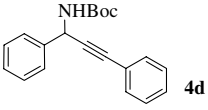
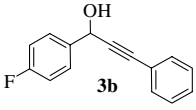
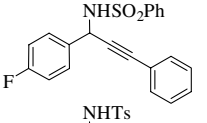
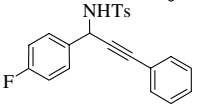
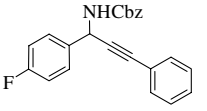
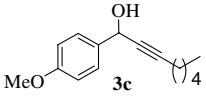
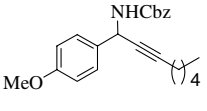
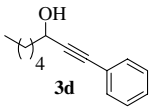
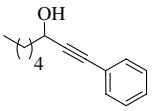
mary benzyl alcohol **1e** or non-benzylic alcohol **1f** with *p*-toluenesulfonamide was unsuccessful (Table 1, entries 12 and 13).

Next, we sought to extend this methodology to the direct amidation of propargyl alcohols an important transformation.[6b,c,9,12] Accordingly, the reaction of propargylic alcohol **3a** with sulfonamides and carbamates, namely, $TsNH_2$, $PhSO_2NH_2$, $CbzNH_2$ and $BocNH_2$ in the presence of $MoCl_5$ (5 mol %) gave the corresponding amide derivatives **4a–d** in good yields (Table 2, entries 1–4). Similarly, propargylic substrates **3b** and **3c** also underwent facile nucleophilic substitution with $TsNH_2$ and $CbzNH_2$ (Table 2, entries 5–8). However, the reaction of propargylic alcohol **3d** with *p*-toluenesulfonamide failed to give the desired product **4i** after 24 h at room temperature or at 40 °C (Table 2, entry 9). The results from the above reactions clearly demonstrate that the direct amidation with sulfonamides or carbamates was successful only in the case of propargyl alcohols generated from aromatic aldehydes, and not with the propargyl alcohols generated from aliphatic aldehydes. This may be due to the benzylic nature of the former alcohols.[13]

As described above, molybdenum(V) chloride (5 mol %) in CH_2Cl_2 presents itself as an effective catalyst for the direct amidation of benzylic alcohols with sulfonamides and carbamates. In addition to good yields, mild reaction conditions and an operational simplicity makes this newly developed method of broad synthetic utility.

General experimental procedure: To a stirred solution of benzylic alcohol (1 mmol) in dichloromethane (5 mL) was added sulfonamide or carbamate (1 mmol) and 5 mol % $MoCl_5$. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC analysis. After the reaction was complete (for reaction time, see Tables 1 and 2), the mixture was evaporated in vacuo. The residue was purified by

Table 2. $MoCl_5$-catalyzed amidation of secondary benzyl/propargyl alcohols

Entry	Benzyl alcohol	Carbamate/sulfonamide	Reaction time (h)	Product[a]	Yield[b] (%)
1	 **3a**	$TsNH_2$	8	 **4a**	88
2	**3a**	$PhSO_2NH_2$	10	 **4b**	86
3	**3a**	$CbzNH_2$	8	 **4c**	85
4	**3a**	$BocNH_2$	12	 **4d**	82
5	 **3b**	$PhSO_2NH_2$	10	 **4e**	86
6	**3b**	$TsNH_2$	7	 **4f**	89
7	**3b**	$CbzNH_2$	9	 **4g**	87
8	 **3c**	$CbzNH_2$	8	 **4h**	78
9	 **3d**	$TsNH_2$	24	 **4i**	0[c]

[a] All the products were characterized by ^1H, ^{13}C NMR and mass spectra.
[b] Isolated yields.
[c] No reaction either at room temperature or at 40 °C.

column chromatography on silica gel using ethyl acetate and hexanes as eluent to give the corresponding amidated products.[14]

Acknowledgements

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13. A close look at the literature reveals the fact that, the hydroxyl substrates, which successfully participated were also flanked on one side by a phenyl group and on the other side with an acetylenic group. See Refs. 6a,c,9,13.
14. Spectral data for representative new products; (**2a**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (d, $J = 8.3$ Hz, 2H), 7.1 (d, $J = 8.3$ Hz, 2H), 6.93 (d, $J = 8.3$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 2H), 5.57–5.43 (m, 1H), 5.04–4.96 (m, 2H), 4.27 (dd, $J = 6.8$, 13.6 Hz, 1H), 3.71 (s, 3H), 2.51–2.39 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 143.1, 137.7, 133.4, 132.6, 129.4 (2C), 127.9 (2C), 127.3 (2C), 119.1, 113.8 (2C), 56.9, 55.3, 42.0, 21.6; HRMS (ESI) calcd for $C_{18}H_{21}NO_3SNa$: 354.1139 $[M+Na]^+$, found: 354.1153 $[M+Na]^+$. Compound **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, $J = 7.55$ Hz, 2H), 7.45–7.4 (m, 1H), 7.34–7.28 (m, 2H), 6.92 (d, $J = 8.3$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 2H), 5.58–5.44 (m,1H), 5.3 (d, $J = 6.79$ Hz, 1H), 5.04 (d, $J = 6.04$ Hz, 1H), 4.99 (s, 1H), 4.31 (dd, $J = 7.55$, 14.35 Hz, 1H), 3.71 (s, 3H), 2.51–2.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 140.7, 133.4, 132.5 (2C), 128.9 (2C), 127.9 (2C), 127.3 (2C), 119.4, 113.9 (2C), 56.9, 55.4, 42.0; HRMS (ESI) calcd for $C_{17}H_{19}NO_3SNa$: 340.0983 $[M+Na]^+$, found: 340.0984 $[M+Na]^+$. Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.21 (m, 5H), 7.13 (d, $J = 8.3$ Hz, 2H), 6.78 (d, $J = 8.3$ Hz, 2H), 5.71–5.56 (m, 1H), 5.12–5.0 (m, 4H), 4.69 (br s, 1H), 3.75 (s, 3H), 2.54–2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 155.8, 136.6, 134.2, 134.0, 128.6 (2C), 128.3 (3C), 127.6 (2C), 118.5, 114.1 (2C), 66.9, 55.4, 54.2, 41.2; HRMS (ESI) calcd for $C_{19}H_{21}NO_3Na$: 334.1419 $[M+Na]^+$, found: 334.1411 $[M+Na]^+$. Compound **2d**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (d, $J = 9.14$ Hz, 2H), 6.80 (d, $J = 8.3$ Hz, 2H), 5.78–5.53 (m, 1H), 5.16–4.98 (m, 2H), 4.90–4.73 (m, 1H), 4.70–4.53 (m, 1H), 3.78 (s, 3H), 2.49 (br t, $J =$ 5.81 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 155.0, 134.5, 134.3, 127.5 (2C), 118.2, 114.0 (2C), 79.6, 55.4, 55.3, 41.4, 28.5 (3C); HRMS (ESI) calcd for $C_{16}H_{23}NO_3Na$: 300.1575 $[M+Na]^+$, found: 300.1574 $[M+Na]^+$. Compound **4c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, $J = 6.59$ Hz, 2H), 7.46–7.39 (m, 3H), 7.35–7.24 (m, 10H), 5.91 (d,$J = 8.7$ Hz, 1H), 5.28 (br d, $J =$ 7.8 Hz, 1H), 5.12 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 139.4, 136.3, 131.9 (2C), 128.9 (2C), 128.7, 128.7 (2C), 128.5, 128.4 (2C), 128.3 (2C), 127.1 (3C), 122.5, 87.1, 85.2, 67.3, 47.6; HRMS (ESI) calcd for $C_{23}H_{19}NO_2Na$: 364.1313 $[M+Na]^+$, found: 364.1308 $[M+Na]^+$. Compound **4d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.19 (m, 10H), 5.85 (br d, $J = 8.3$ Hz, 1H), 5.01 (br d, $J = 7.55$ Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 139.7, 131.9 (2C), 128.8 (2C), 128.6, 128.4 (2C), 128.1, 127.1 (2C), 122.7, 87.6, 84.9, 80.3, 47.0, 28.5 (3C); HRMS (ESI) calcd for $C_{20}H_{21}NO_2Na$: 330.1469 $[M+Na]^+$, found: 330.1474 $[M+Na]^+$.