A mild and efficient method for formation of C–N bond from benzyl alcohols and sulfonamide, carboxamide, 4-nitroanline and azide catalysed by $SnCl_4$

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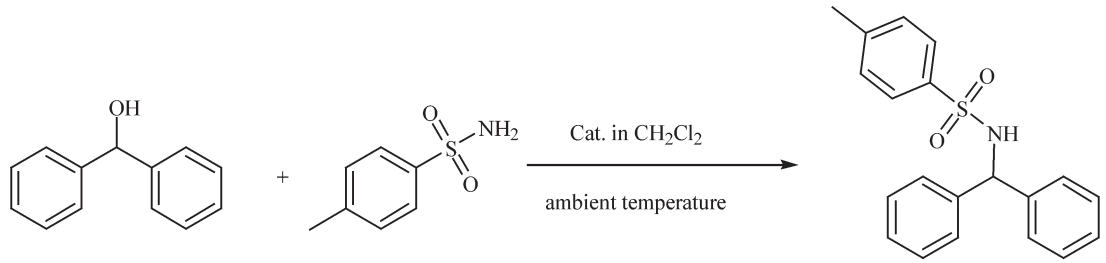
A mild and efficient method for the formation of C–N bonds is reported with $SnCl_4$ as an inexpensive catalyst. With 10 mol% of $SnCl_4$, the direct substitution reaction of secondary benzyl alcohols with a sulfonamide, a carboxamide, 4-nitroaniline and an azide proceeds well in good to excellent yields at room temperature.

Keywords: C–N bond formation, benzyl alcohol, *p*-toluenesulfonamide, *p*-nitroaniline, tetramethylsilylazide

The formation of C–N bonds is an important reaction in organic synthesis.[1] The traditional method for formation of C–N bonds always produces stoichiometric amounts of salt waste in the derivatisation of the alcohol and C–N bond formation steps.[2,3] Recently the direct catalytic substitution of alcohols with *N-nucleo*philes has aroused interest due to its atomic economy and environmental advantages.[2–6] Several catalysts have been developed for this transformation in the literature, such as $NaAuCl_4$,[4] H-montmorillonite,[5] Bi $(OTf)_3/KPF_6$,[3] $CoCl_5$ [6] and $FeCl_3$. [2] But the in these cases, high reaction temperatures, complex catalytic systems or expensive metals are usually involved. In line with our efforts on the methodologies of construction of C-X bonds,[7–10] we report here a mild and efficient method for formation of C–N bond from benzylic alcohols and *N-nucleo*philes catalysed by $SnCl_4$.

We took the reaction between benzhydryl alcohol **1a** and *p*-toluenesulfonamide **2a** as an example for the investigation of catalysts for the formation of the C–N bond from alcohols and *N*-nucleophiles (Scheme 1). $ZnCl_2$ was applied in this reaction first, but no desirable product was found at room temperature or at reflux (Entries 1, 2 in Table 1). $AlCl_3$ was then tried, and 50% yield of **3a** was given at room temperature, but the high reaction temperature could not improve the yield of **3a** (entries 3, 4 in Table 1). $SnCl_4$ is an inexpensive Lewis acid and has been applied as the catalyst for the Ferrier rearrangement,[11] glycosylation reaction[12] and C–C bond construction.[13] Here we found $SnCl_4$ (10 mol% of the alcohol) in CH_2Cl_2 could efficiently catalyse the direct substitution reaction between **1a** and **2a** to give **3a** in 95% yield within 16 hours at room temperature (Entry 5 in Table 1). Moreover, $BF_3{\cdot}OEt_2$ could only catalyse this reaction with 77% yield which was less than the yield in the case of $SnCl_4$ (entry 6 in Table 1). Other Lewis acid catalysts such as $FeCl_3{\cdot}6H_2O$ and $Fe_2(SO_4)_3{\cdot}xH_2O$ did not catalyse this reaction (entries 7–9 in Table 1).

Based on the results in Table 1, applications of the $SnCl_4$-catalysed direct substitutions with secondary benzyl alcohols and other *N*-nucleophiles were attempted (Table 2). The *N*-nucleophiles, including 4-nitroaniline, carboxamide, azide



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

Scheme 1 the catalytic reaction between benzhydryl alcohol and *p*-toluenesulfonamide.

Table 1 Direct catalytic reaction of benzhydryl alcohol with *p*-toluenesulfonamide with different Lewis acid catalysts

Entry	Catalyst[a]	Reaction time /h	Temperature	Yield of **3a**[b]/%
1	$ZnCl_2$	24	RT	0
2	$ZnCl_2$	24	Reflux	0
3	$AlCl_3$	24	RT	50
4	$AlCl_3$	24	Reflux	45
5	$SnCl_4$	16	RT	95
6	$BF_3{\cdot}OEt_2$	16	RT	77
7	$FeCl_3{\cdot}6H_2O$	24	RT	0
8	$FeCl_3{\cdot}6H_2O$	24	Reflux	0
9	$Fe_2(SO_4)_3{\cdot}xH_2O$	24	Reflux	**0**

RT, Room temperature.
[a] 10 mol% catalyst was used. [b] Isolated yield.

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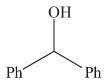
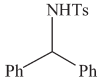
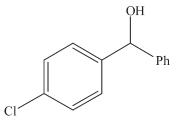
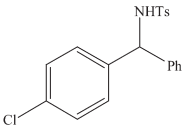
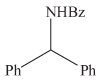
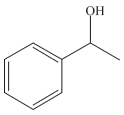
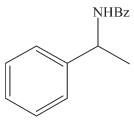
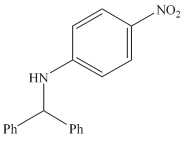
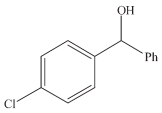
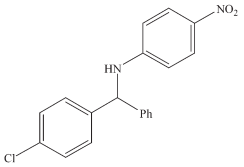
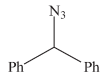
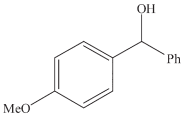
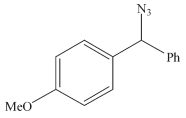
Table 2 The direct substitution reactions of alcohols with *N*-nucleophiles catalysed by $SnCl_4$ at room temperature

Entry	Alcohol	Nucleophile	Product	Time /h	Yield[a]/%
1	 **1a**	$TsNH_2$ **2a**	 **3a**	16	95
2	 **1b**	$TsNH_2$ **2a**	 **3b**	18	85
3	 **1c**	$TsNH_2$ **2a**	 **3c**	16	69
4	 **1a**	$BzNH_2$ **2b**	 **3d**	16	93
5	 **1b**	$BzNH_2$ **2b**	 **3e**	18	71
6	 **1a**	4-$NO_2C_6H_4NH_2$ **2c**	 **3f**	16	88
7	 **1a**	4-$NO_2C_6H_4NH_2$ **2c**	 **3g**	16	85
8	 **1a**	$TMSN_3$ **2d**	 **3h**	16	91
9	 **1d**	$TMSN_3$ **2d**	 **3i**	10	90

[a] Isolated yield.

were also investigated for this direct amidation reaction, and good to excellent yields of product were obtained (entries 4–10 in Table 2). Additionally, benzhydryl alcohols with electron-withdrawing groups or electron-donating groups and benzyl alcohols also reacted smoothly with the *N*-nucleophiles with good yields (entries 2, 3, 5, 7, 9, in Table 2). It was also established that in the absence of $SnCl_4$ no products were formed from the benzyl alcohol with aniline, benzylamine, benzamide nor TMS azide after 24h at ambient temperatures.

In brief, a mild and efficient method for formation of C–N bond is reported with $SnCl_4$ as a catalyst. With 10 mol% of $SnCl_4$, the direct substitution reaction of secondary benzyl alcohols with a sulfonamide, a carboxamide, amines and an azide proceeded well in good yields at room temperature. The further application of this method to the efficient synthesis of designed drugs is now being undertaken in our laboratory.

Experimental

Melting points were measured in a Kofler micro-melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr with frequency in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in ppm downfield from the internal standard tetramethylsilane. All reagents were obtained from commercial sources and used without further purification.

The direct substitution reaction of alcohols and N-*nucleophile*: A mixture of $SnCl_4$ (0.1 mmol), alcohol **1** (1 mmol), and *N*-nucleophile **2** (1.2 mmol) in CH_2Cl_2 (10 mL) was stirred under air at room temperature for 16 h until complete consumption of alcohol as judged by TLC. Then saturated $NaHCO_3$ (10 mL) was added into the reaction mixture. After the conventional workup, the residue of the organic phase was purified by column chromatography (petroleum ether/ ethyl acetate) to give products **3**.

N-*benzhydryl*-p-*toluenesulfonamide* (**3a**): The physical data shown below were comparable to those reported.[4] m.p. 157–158 °C, Reported m.p.157°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J = 8.2 Hz, 2H), 7.21–7.07 (m, 12H), 5.61 (d, J = 7.2 Hz, 1H), 5.21 (d, J = 7.2 Hz, 1H), 2.5 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 142.6, 140.3, 132.5, 131.2, 130.5, 130.3, 130.1, 60.2, 23.1.

N-*[(4-Chloro-phenyl)-phenyl-methyl]-4-methyl-benzenesulfonamide* (**3b**): The physical data shown below were comparable to those reported.[14] m.p. 118–119 °C, Reported m.p. 119–120°C; ^1H NMR (400 MHz, $CDCl_3$), δ: 7.56 (d, J = 8.4 Hz, 2H), 7.24–7.03 (m, 11 H), 5.55 (d, J = 7.2 Hz, 1H), 4.96 (d, J = 7.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 139.8, 137.6, 137.0, 132.1, 128.9, 128.1, 127.9, 127.6, 126.5, 126.1, 126.3, 60.1, 19.9.

N-*(1-Phenyl)ethyl*-p-*toluenesulfonamide* (**3c**): The physical data shown below were comparable to those reported.[15] m.p. 81–82 °C, Reported m.p. 82–83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, J = 8.2 Hz, 2H), 7.19–6.95 (m, 7H), 5.34 (d, J = 7.2 Hz, 1H), 4.34 (m, 1H), 2.24 (s, 3H), 1.27 (d,, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 142.0, 141.2, 135.7, 127.1, 126.4, 126.0, 125.8, 125.0, 52.6, 22.9, 21.1.

N-*benzhydrylbenzamide* (**3d**): The physical data shown below were comparable to those reported.[16] m.p. 169–170 °C, Reported m.p. 170°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85–7.44 (m, 5H), 7.39–7.29 (m, 10H), 6.72 (d, J = 7.6 Hz, 1H), 6.48 (d, J = 7.6 Hz, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.5, 140.7, 133.2, 130.8, 128.1, 127.9, 127.7, 127.0, 126.6, 56.4.

N-*(1-Phenyl)ethylbenzamide* (**3e**): The physical data shown below were comparable to those reported.[17] m.p. 120–121°C, Reported m.p. 124°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73–7.68 (m, 2H), 7.40–7.15 (m, 8H), 6.52 (br, 1H), 5.43 (m, 1H), 1.63 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 142.9, 134.8, 130.9, 129.0, 127.9, 127.3, 126.8, 126.1, 50.0, 20.8.

N-*(4-nitrophenyl)-1,1'-diphenyl) methylamine* (**3f**): The physical data shown below were comparable to those reported.[4] m.p. 194–195°C, Reported m.p. 195°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.07–8.03 (m, 2H), 7.40–7.31 (m, 10H), 6.54–6.51 (m, 2H), 5.66 (d, J = 4 Hz, 1H), 5.02 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 152.7, 141.3, 139.1, 129.7, 128.5, 127.7, 127.0, 112.7, 63.1.

N-*(4-nitrophenyl)-1-phenyl-1'-(4-chlorophenyl)methylamine* (**3g**): The physical data shown below were comparable to those reported.[4] m.p. 120–121°C, Reported m.p. 121°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.8 Hz, 2H), 7.73–7.24 (m, 9H), 6.51 (d, J = 8.6 Hz, 2H), 5.52 (d, J = 4.8 Hz, 1H), 5.01 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.7, 140.1, 138.8, 138.1, 132.9, 129.3, 129.0, 128.1, 127.8, 126.3, 125.2, 110.8, 60.9.

1,1'-Diphenylazidomethane (**3h**): The physical data shown below were comparable to those reported.[4] ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52–7.40 (m, 10H), 5.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 69.7, 128.0, 129.3, 129.7, 140.7; IR (KBr) ν: 2119, 1620, 1521, 1450, 1300, 1170, 819, 697, 561 cm^{-1}; ESI-MS (*m/z*): 210.1 $(M+H)^+$.

1-Phenyl-1'-(4-methoxyphenyl)azidomethane (**3i**): The physical data shown below were comparable to those reported.[4] ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.21 (m, 9H), 5.68 (s, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.7, 139.7, 132.1, 129.7, 129.5, 128.9, 128.1, 113.7, 67.5, 55.1; IR (KBr) ν:2990, 2852, 2105, 1578, 1455, 1250, 1197, 901, 699, 532; ESI-MS (*m/z*): 240.1 $(M+H)^+$.

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