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Borrowing hydrogen methodology for the conversion of alcohols into N-protected primary amines and in situ deprotection

Gareth W. Lamb [a], Andrew J. A. Watson [a], Katherine E. Jolley [a], Aoife C. Maxwell [b], Jonathan M. J. Williams [a,*]

[a] Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK
[b] GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage SG1 2NY, UK

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ABSTRACT

Alcohols have been converted into a range of protected amines including sulfonamides and *N*-alkylbenzylamine derivatives. Representative examples of deprotection to afford primary amines are also provided.

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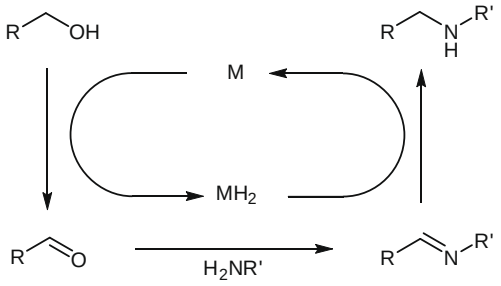
The alkylation of amines by alcohols using the borrowing hydrogen strategy provides an alternative approach to the synthesis of amines.[1] Water is the only reaction by-product, and traditional alkylating agents, including potentially mutagenic alkyl halides, are avoided. The metal-catalysed pathway involves the temporary removal of hydrogen from an alcohol to form an aldehyde, which undergoes imine formation prior to return of the hydrogen to generate a new C–N bond (Scheme 1).

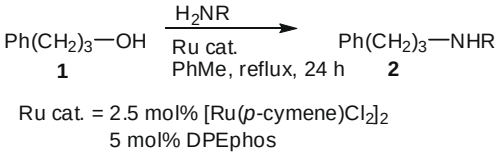
There have been several iridium[2] and ruthenium[3] complexes, which have been shown to be effective for the alkylation of amines by alcohols, including our own contributions using [Ru(*p*-cymene)Cl_2]$_2$ in the presence of a diphosphine ligand.[4] We were interested in exploiting this chemistry for the direct formation of N-protected primary amines, and report our findings in this Letter. Protected primary amines can either undergo further transformation elsewhere in the substrate or be deprotected to give primary amines. The use of ammonia for the direct conversion of alcohols into primary amines has recently been reported, although imine formation and other oxidative reactions were observed as byproducts in some cases.[5]

Initially, we chose to examine the use of alkylamines such as benzylamines for the conversion of 3-phenylpropanol **1** into the corresponding N-protected primary amines **2**. The reactions were performed using the [Ru(*p*-cymene)Cl_2]$_2$/DPEphos combination, in toluene at reflux for 24 h (Scheme 2).

The amine alkylation worked well in most cases. Benzylamine (entry 1) and singly branched analogues (entries 2 and 3) afforded the alkylated products with complete conversion, although the N-alkylation of tritylamine gave a lower conversion (entry 4), presumably for steric reasons. Methoxy-substituted (entry 5) and dimethoxy-substituted (entries 6 and 7) benzylamines also gave complete conversion into the alkylated product, as did the use of the *p*-methoxyaniline. The isolated yields were more variable, principally due to the separation of secondary amine from small amounts of tertiary amine byproduct, formed by over-alkylation. However, for the alkylation of 1-phenylethylamine, only monoalkylation was observed, leading cleanly to the secondary amines.



Scheme 1. The use of alcohols as alkylating agents by borrowing hydrogen.



Scheme 2. Formation of N-protected primary amines from alcohols.

* Corresponding author. Tel.: +44 1225 383 942; fax: +44 1225 386 231.
E-mail address: j.m.j.williams@bath.ac.uk (J.M.J. Williams).

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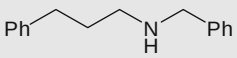
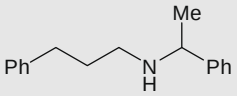
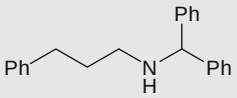
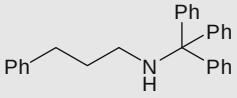
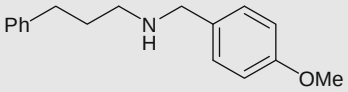
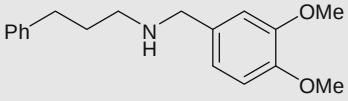
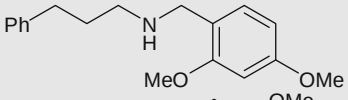
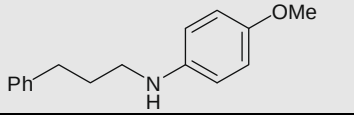
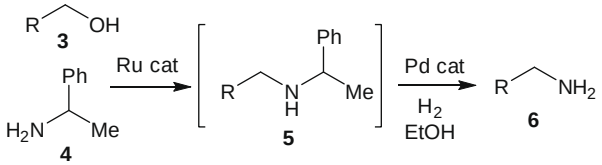
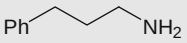
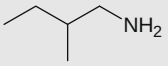
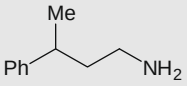
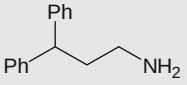
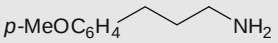
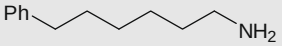
Table 1
Formation of protected amines **2**[a]

Entry	Amine product	Conv.[b] (%)
1		100 (57)
2		100 (85)
3		100 (79)
4		60 (54)
5		100 (60)
6		100 (54)
7		100 (60)
8		100

[a] Reaction conditions; 2.5 mol % $[Ru(p\text{-cymene})Cl_2]_2$, 5 mol % DPEphos, alcohol **1** (1 mmol), amine (1 mmol), toluene, 110 °C, 24 h. DPEphos = bis(2-diphenylphosphinophenyl)ether.
[b] Conversion was determined by analysis of the ^1H NMR spectra. Figures in parentheses are isolated yields.

Table 2
Alkylation of 1-phenylethylamine **4** and hydrogenolysis to give primary amines **6**[a]



Entry	Primary amine product	Yield[b] (%)
1		83[c]
2		68
3		52
4		75
5		54
6		65

[a] Reaction conditions; 2.5 mol % $[Ru(p\text{-cymene})Cl_2]_2$, 5 mol % DPEphos, alcohol **1** (1 mmol), amine (1 mmol), toluene, 110 °C, 24 h, then Pd/C (10 mol %), EtOH, HCl (6 M), H_2 (1 atm), 65 °C, 14 h.[8]
[b] Isolated yield over two steps from the corresponding primary alcohols.
[c] Isolated as the free amine—all others as the HCl salt.

All of the amine-protecting groups shown in Table 1 have been reported to be removed relatively easily.[6] We chose to investigate the use of the 1-phenethyl protection (entry 2) for a range of other substrates, and to couple this with in situ deprotection. Therefore, alcohols **3** were coupled with 1-phenethylamine **4** to give the protected primary amines **5**, which were then hydrogenolysed by addition of Pd/C (10 wt %) and ethanol to the reaction mixture, followed by heating under 1 atm of hydrogen.[7] The so-formed primary amines **6** were obtained in good yields (Table 2). We were unable to identify conditions where the ruthenium catalyst used for the N-alkylation was able to effect hydrogenolysis.

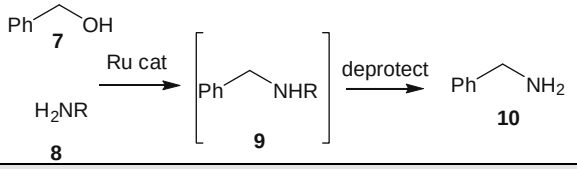
The overall transformation of alcohol was observed by NMR to lead to the primary amine very selectively, although the isolated yields were somewhat variable. For entry 1, the amine was isolated by acid/base extraction, and was obtained in good yield. For the other examples, the product was isolated by crystallisation of the hydrochloride salt (the HCl salts were insufficiently soluble in the aqueous layer).

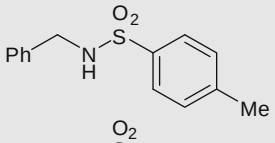
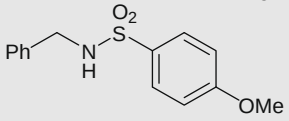
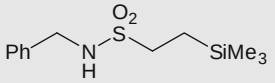
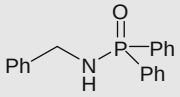
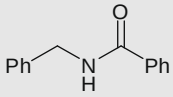
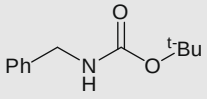
The use of benzyl-protecting groups was anticipated to lead to problems for the conversion of benzyl alcohols into benzylamines, due to the difficulty of selectively removing the correct benzyl group from intermediates of the type $ArCH_2NHCH_2Ar'$.[9] We therefore considered the use of alternative amine protecting groups involving amides and related groups. The coupling of benzyl alcohols **7** with a range of sulfonamides was successful (Table 3, entries 1–3) as well as with diphenylphosphinamide (entry 4), although we were unable to achieve coupling of an amide (entry 5) or a carbamate (entry 6) under these conditions. We have previously reported that sulfonamides can be alkylated by alcohols using $[Ru(p\text{-cymene})Cl_2]_2$ in the presence of DPEphos.[4c,10] However, optimisation studies showed that the reactions could be performed successfully using triphenylphosphine in place of DPEphos. These reactions were performed at 150 °C in xylene, although essentially complete conversion was also obtained for the alkylation of both *p*-toluenesulfonamide and trimethylsilylethanesulfonamide (SES amide) with benzyl alcohol when the reaction was performed in toluene at 110 °C. Diphenylphosphinamide was alkylated with 90% conversion under the milder conditions.

The reactions were also repeated with an in situ deprotection of the sulfonamide or phosphinamide. For entries 1 and 2, this was achieved using Mg/MeOH,[11] where the overall conversion of benzyl alcohol into benzylamine was superior for the *p*-methyl-substituted arylsulfonamide (entry 1) compared with the *p*-methoxy-substituted variant (entry 2). For the SES amide in entry 3, CsF in DMF[12] was used for the deprotection, and for entry 4, treatment with acetic acid/formic acid/water (2:2:1) was used.[13] All of these procedures allowed for the conversion of benzyl alcohol into benzylamine without isolation of the protected intermediate.

Since the trimethylsilylethanesulfonamide group is one of the most readily removed sulfonamides,[14] we investigated further reactions with sulfonamide **11**. Various alcohols were converted into the corresponding SES-protected amines in good yields, and in the alkylation/deprotection sequence, the primary amine could be obtained in good yield without isolation of the intermediate sulfonamide (Table 4). Typical procedures for deprotections are provided.[8,15]

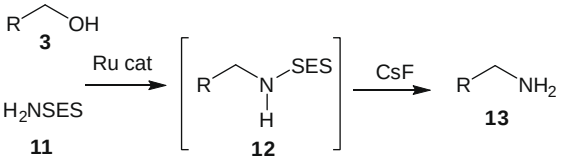
Table 3
Conversion of benzyl alcohol into benzylamine via amination and deprotection

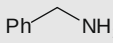
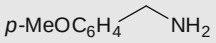
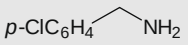
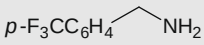
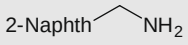
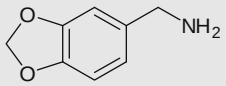


Entry	Intermediate **9**	Yield **9**[a] (%)	Yield **10**[b] (%)
1		84	86
2		92	45
3		87	74
4		71	90
5		0	—
6		0	—

[a] Isolated yield of the protected amine **9**. 2.5 mol % [Ru(*p*-cymene)Cl_2]$_2$, 10 mol % PPh_3, 10 mol % K_2CO_3, alcohol **7** (1 mmol), sulfonamide or phosphinamide (1 mmol), xylene, 150 °C, 24 h.
[b] Isolated yield of benzylamine **10** (as its HCl salt) over the two-step, one-pot amination/deprotection sequence. Crude protected amine reacted with; Mg (20 mmol), MeOH, 80 °C, 24 h (entries 1 and 2). CsF (10 mmol), DMF, 110 °C, 48 h (entry 3). $MeCO_2H/HCO_2H/H_2O$ (2:2:1), 80 °C, 24 h (entry 4).

Table 4
Conversion of alcohols into primary amines via intermediate SES-protected amines



Entry	Product **13**	Yield **12**[a] (%)	Yield **13**[b] (%)
1		86	74
2		89	72
3		71	75
4		81	72
5		95	78
6		81	67

[a] Isolated yield of the protected amine **12** (as the HCl salt). 2.5 mol % [Ru(*p*-cymene)Cl_2]$_2$, 10 mol % PPh_3, 10 mol % K_2CO_3, alcohol **3** (1 mmol), sulfonamide **11** (1 mmol), xylene, 150 °C, 24 h.
[b] Isolated yield of primary amine **13** over the two-step, one-pot amination/deprotection sequence. Crude alkylated sulfonamides reacted with CsF (10 mmol), DMF, 110 °C, 48 h.

In summary, alcohols have been successfully converted into primary amines using ruthenium-catalysed borrowing hydrogen methodology coupled with deprotection of a range of N-protected intermediates.

Acknowledgements

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8. *Typical procedure for the alkylation of 1-phenylethylamine* **4** *with alcohols and subsequent deprotection.* To an oven-dried, nitrogen-purged carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (45.9 mg, 0.075 mmol) and DPEphos (80.8 mg, 0.150 mmol) were added primary alcohol (3 mmol), 1-phenylethylamine (3 mmol) and anhydrous toluene (3 mL). The reaction mixture was then heated to 110 °C for 24 h. The solvent was removed under vacuum, and the alkylated amine was isolated by column chromatography (SiO_2, EtOAc) or the crude material was cleaved in situ. After cooling to room temperature, Pd/C (10 wt %, 10% in Pd), EtOH (11 mL) and HCl (6 M, 1.1 mL) were added to the solution. The carousel tube was then purged with H_2 before heating to 65 °C for 14 h. The reaction mixture was cooled to room temperature, filtered to remove Pd/C, and concentrated under vacuum to a solid, which was recrystallised from by dissolving in minimal EtOH (approx. 2 mL) and addition of EtOAc (approx 20 mL).
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15. *Typical procedure for the formation of sulfonamides and their deprotection.*To an oven-dried, nitrogen-purged carousel tube containing $[Ru(p\text{-cymene})Cl_2]_2$ (15.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), and K_2CO_3 (14 mg, 0.1 mmol) were added primary sulfonamide (1 mmol), alcohol (1 mmol) and anhydrous xylene (1 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 10 min and then heated to 150 °C for 24 h. The solvent was removed under vacuum, and the alkylated sulfonamide was either isolated by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) or the crude material was cleaved in situ. Arylsulfonamides were cleaved by the addition of fresh Mg turnings (0.486 g, 20 mmol) and MeOH (5 mL) to the crude residue. This mixture was then heated at 80 °C for 24 h, and cooled to room temperature. After filtration, the clear solution was acidified using 1 M HCl in diethyl ether before reducing to dryness in vacuo. The resulting yellow solid was washed with CH_2Cl_2 to give the amine hydrochloride salt as a colourless solid. Trimethylsilylethanesulfonamides (SES) were cleaved by addition of CsF (0.152 g, 10 mmol) and DMF (2 mL) to the crude residue. This mixture was then heated at 110 °C for 48 h, cooled to room temperature, filtered and isolated as above. The phosphinamide (Table 3, entry 4) was cleaved by removal of the solvent in vacuo from the crude reaction mixture, addition of acetic acid (1 mL), formic acid (1 mL) and water (0.5 mL) and heating at 80 °C for 24 h. After removal of the solvent under vacuum, the resulting solid was washed with CH_2Cl_2 to give the amine hydrochloride salt as a colourless solid.