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Chemoselective deprotection of tertiary benzylamines and reduction of carbon–carbon double bonds in the presence of benzyl and benzyloxymethyl ethers

Joginder S. Bajwa,* Joel Slade and Oljan Repič

Process R&D, Chemical and Analytical Development, Novartis Institute for Biomedical Research, 59 Route 10,
East Hanover, NJ 07936, USA

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Abstract

Catalytic transfer hydrogenation using 10% Pd–C in the presence of 1,4-cyclohexadiene as the hydrogen donor selectively debenzylates amines and reduces carbon–carbon double bonds while leaving benzyl and benzyloxymethyl ethers intact. © 2000 Elsevier Science Ltd. All rights reserved.

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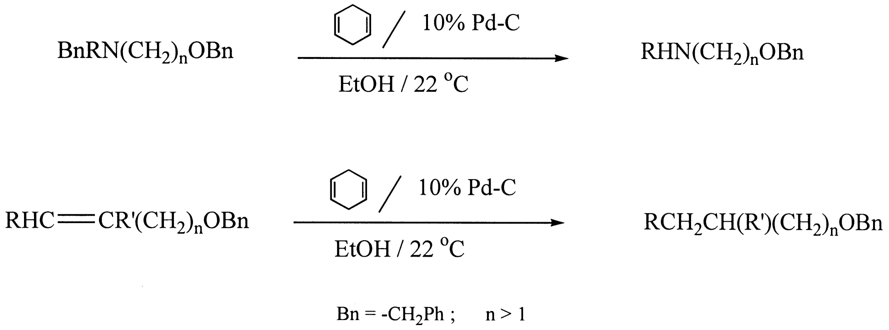
The use of catalytic transfer hydrogenation (CTH) has increased considerably in recent years,[1] and a large number of functional groups have been successfully reduced using a variety of hydrogen donors such as cyclohexene,[2,3] 1,4-cyclohexadiene,[4] formic acid,[5–7] ammonium formate,[8–10] hydrazine,[10,11] and sodium hydrogen hypophosphite.[10,12] However, despite the



Scheme 1.

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* Corresponding author. E-mail: joginder.bajwa@pharma.novartis.com

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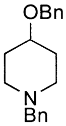
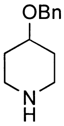
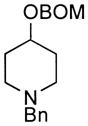
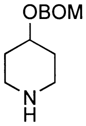
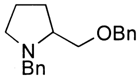
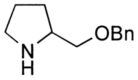
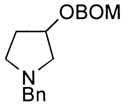
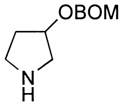
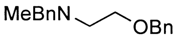
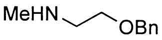
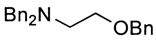
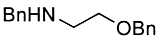
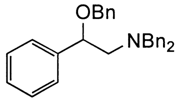
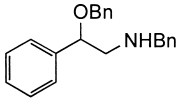
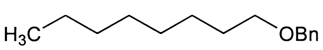
dramatic increase in the use of CTH, selective deprotection of *N*-benzylamines in the presence of benzyl ethers has not been reported to the best of our knowledge.[13] We would like to describe herein that CTH using 10% Pd–C in the presence of 1,4-cyclohexadiene as the hydrogen donor, selectively debenzylates amines and reduces carbon–carbon double bonds while leaving benzyl and benzyloxymethyl ethers intact (Scheme 1).

As illustrated in Table 1, *N*-debenzylation of tertiary amines proceeds selectively compared to *O*-debenzylation of benzyl ethers. It was found that the reactions were cleaner when carried out in

Table 1
Selective deprotection of benzylamines in the presence of benzyl ethers[a]

Entry	Substrate	Product[b]	Yield (%)[c]
1			72
2			73
3			69
4			66
5			70
6			70
7			40
8		No Reaction[d]	--

Bn = -CH$_2$Ph; BOM = -CH$_2$OCH$_2$Ph

[a] The reaction was carried out following the general procedure described in the text.

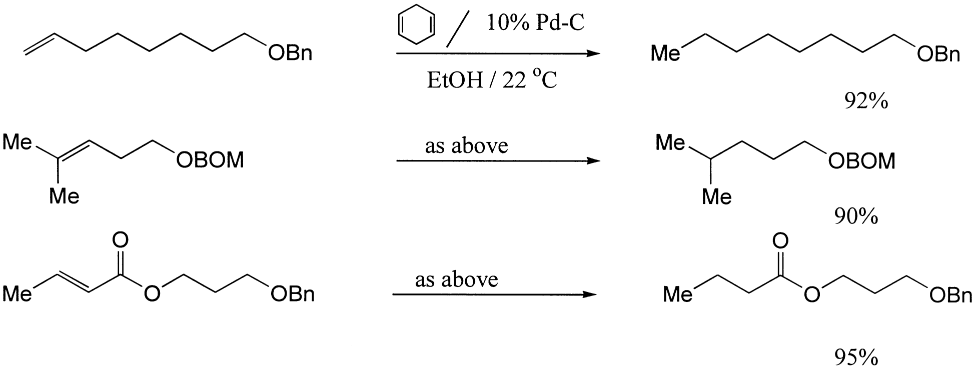
[b] All products were fully characterized by spectroscopic methods.

[c] Isolated yields.

[d] After 48 h.

the presence of acetic acid. It is worth noting that even prolonged reaction times failed to cleave any significant amount of the benzyl ether (entry 8). This selectivity is particularly surprising since it is generally assumed that *O*-debenzylation takes place with greater ease than does removal of an *N*-benzyl group.[14,15] Since hydrogenolysis of benzyl ethers is promoted by acids[16] and retarded by alkali bases,[17] selective *N*-debenzylations in the presence of benzyl ethers has been rationalized[13a] as being due to the basicity of the amine functionality present in the molecule. However, under our protocol, the reaction is run under acidic conditions, and we believe that the selectivity observed in the *N*-debenzylation in preference to the *O*-debenzylation is inherent in the unique source of hydrogen donor, 1,4-cyclohexadiene.

We next examined the synthetically attractive possibility of reducing carbon–carbon double bonds in the presence of benzyl and benzyloxymethyl ethers.[18] As shown in Scheme 2, isolated mono- and trisubstituted double bonds and conjugated double bonds were reduced to give products in good yields without affecting the benzyl or benzyloxymethyl ethers. These reactions were carried out without acetic acid.



Bn = $-CH_2Ph$; BOM = $-CH_2OCH_2Ph$

Scheme 2.

In summary, CTH using 1,4-cyclohexadiene as the hydrogen donor is a mild and efficient method for selective *N*-debenzylation of amines and reduction of carbon–carbon double bonds in the presence of benzyl and benzyloxymethyl ethers.

General procedure: To a stirred solution of benzylamine (1 mmol) in absolute ethanol (10 mL) and acetic acid (3 mmol) was added, under a nitrogen atmosphere, 10% Pd–C[19] (1:1 catalyst: substrate by weight) followed by 1,4-cyclohexadiene (0.43 mL, 5 mmol). After stirring the reaction mixture overnight (~16 h) the catalyst was removed by filtration through Celite, and the filtrate was evaporated to dryness under vacuum. The crude product was then purified by flash chromatography over silica gel using CH_2Cl_2:MeOH:NH_4OH (50:10:1) as the eluent.

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