

Chemoselective oxidative debenzoylation of tertiary *N*-benzyl aminesSteven D. Bull,<sup>a</sup> Stephen G. Davies,<sup>\*a</sup> Garry Fenton,<sup>b</sup> Andrew W. Mulvaney,<sup>a</sup> R. Shyam Prasad<sup>a</sup> and Andrew D. Smith<sup>a</sup><sup>a</sup> The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY.

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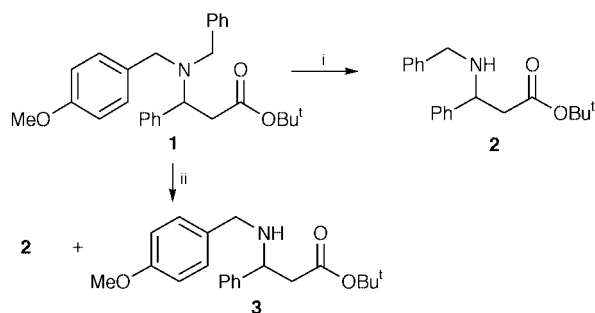
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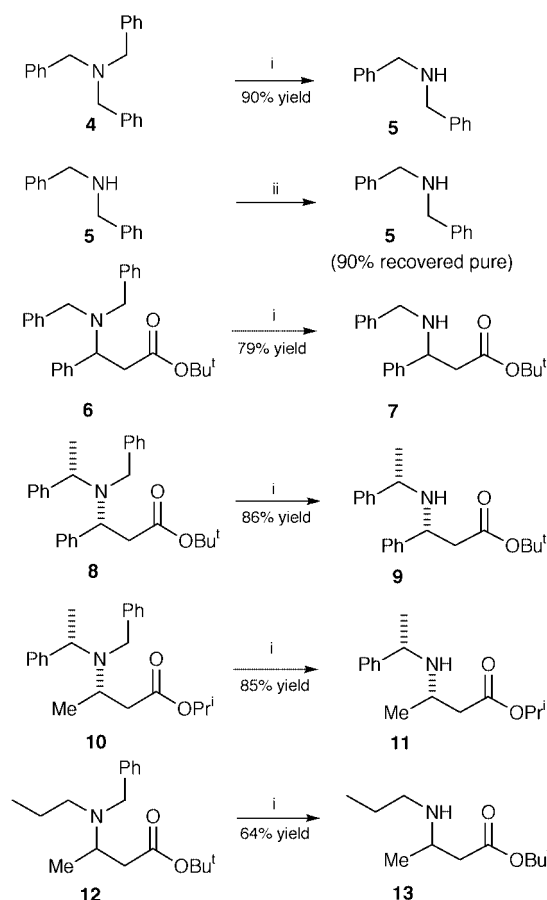
Treatment of tertiary amines containing one or more *N*-benzyl protecting groups with aqueous ceric ammonium nitrate results in clean *N*-debzoylation to afford the corresponding secondary amine.

Differentially protected homochiral lithium amide additions to  $\alpha,\beta$ -unsaturated esters have proved to be an extremely versatile route for the asymmetric synthesis of homochiral  $\beta$ -amino acids and  $\beta$ -lactams.<sup>1–3</sup> In the course of studies directed towards extending the versatility of this lithium amide methodology, the synthetic applications of a novel debenzoylation reaction observed when *tert*-butyl 3-[benzyl(4-methoxybenzyl)amino]-3-phenylpropionate **1** was treated with aqueous ceric ammonium nitrate (CAN) are reported herein. Thus, while treatment of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted as expected in smooth cleavage of the 4-methoxybenzyl protecting group to afford *tert*-butyl 3-benzylamino-3-phenylpropionate **2**, treatment of **1** with 2.1 equiv. of CAN in CH<sub>3</sub>CN–H<sub>2</sub>O afforded a 50:50 mixture of the monodeprotected products **2** and *tert*-butyl 3-(4-methoxybenzylamino)-3-phenylpropionate **3** (Scheme 1). It is noteworthy that in both cases the isolated products were those resulting from cleavage of the primary benzylic amine; the secondary benzylic centre ( $\beta$ -centre) remained unaffected under these conditions. This lack of selectivity for deprotection of tertiary amine **1** is in direct contrast to the well-established use of CAN for the orthogonal deprotection of 4-methoxybenzyl ethers in the presence of *O*-benzyl ethers.<sup>4</sup>

This unexpected reaction implies oxidation at the tertiary nitrogen atom rather than at the arene ring since the outcome of the reaction is unaffected by arene substitution and therefore should be equally applicable to debenzoylation of simple tertiary benzylamines. Thus, treatment of tribenzylamine **4** with CAN gave dibenzylamine **5** in 90% yield after chromatographic purification to remove benzaldehyde.<sup>5</sup> The chemoselectivity of this oxidative debenzoylation protocol for tertiary amines was confirmed by treating dibenzylamine **5** with excess CAN (10 equiv.), which resulted in essentially quantitative recovery of starting material. Treatment of tertiary amine **6**, which contains two *N*-benzylic and one  $\alpha$ -substituted *N*-benzylic groups, resulted in chemoselective monodebenzoylation to afford ex-



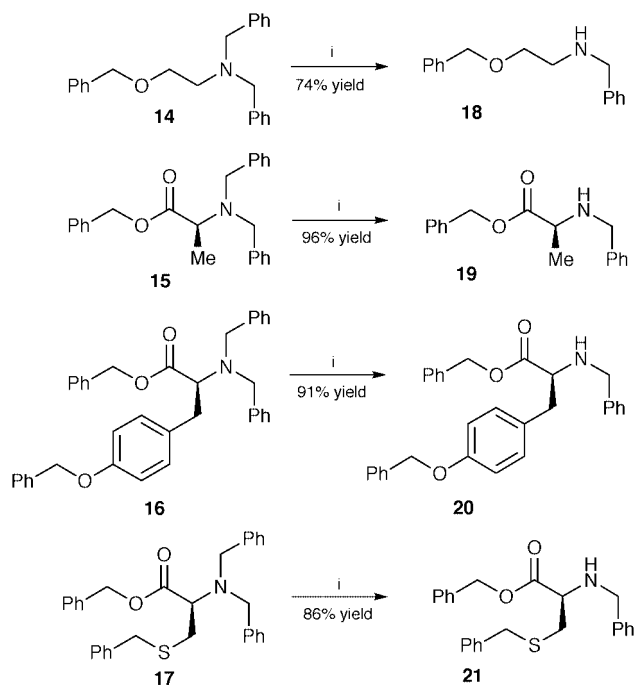
**Scheme 1** Reagents and conditions: i, DDQ, CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O (5:1); ii, CAN (2.1 equiv.), CH<sub>3</sub>CN–H<sub>2</sub>O (5:1).



**Scheme 2** Reagents and conditions: i, CAN (2.1 equiv.), CH<sub>3</sub>CN–H<sub>2</sub>O (5:1); ii, CAN (10.0 equiv.), CH<sub>3</sub>CN–H<sub>2</sub>O (5:1).

clusively secondary amine **7** in 79% isolated yield. Similarly, *N*-debzoylation of homochiral tertiary amine **8**, which contains one *N*-benzylic and two  $\alpha$ -substituted *N*-benzylic protecting groups, occurred without epimerisation, to afford homochiral secondary amine **9** {[ $\alpha$ ]<sub>D</sub> –15.8 (c 1.0, CHCl<sub>3</sub>); lit.<sup>2</sup> –16.3 (c 1.5, CHCl<sub>3</sub>)} in 86% isolated yield. Extension of this methodology to the deprotection of tertiary amines containing either two or one benzylic groups was also demonstrated *via* treatment of tertiary amines **10** and **12** to afford secondary amines **11** {[ $\alpha$ ]<sub>D</sub> –46.4 (c 1.0, CHCl<sub>3</sub>)} and **13** in 85 and 64% isolated yield respectively (Scheme 2). The lower isolated yield for amine **13** was a result of its inherent volatility, however, no other product was detected in the <sup>1</sup>H NMR spectrum obtained from the crude reaction mixture.

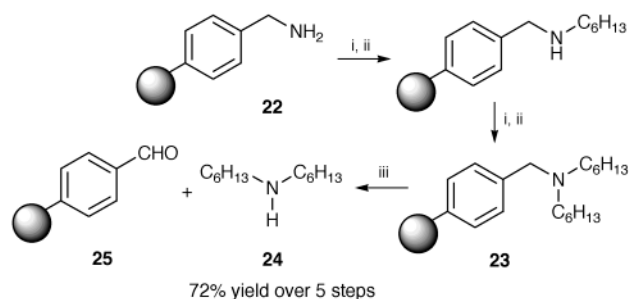
Since benzyl groups are commonly employed as protecting groups for other heteroatom functionality the chemoselectivity of this transformation was examined by carrying out the CAN-mediated tertiary amine debenzoylation protocol on a range of perbenzylated *N,N*-dibenzylamines which also contained ben-



**Scheme 3** Reagents and conditions: i, CAN (2.1 equiv.), CH<sub>3</sub>CN–H<sub>2</sub>O (5:1).

zyl ethers, benzyl esters, benzyl phenolates and benzyl thiolates. Thus, treatment of **14–17** resulted in clean *N*-deprotection to afford the mono-*N*-debenzylated secondary amines **18**, **19** {[ $\alpha$ ]<sub>D</sub> –38.6 (c 1.0); lit.<sup>6</sup> [ $\alpha$ ]<sub>D</sub> for *ent*-**19** 40.4 (c 1.0)}, **20** {[ $\alpha$ ]<sub>D</sub> –8.3 (c 1.2) and **21** {[ $\alpha$ ]<sub>D</sub> –21.9 (c 1.1)} in good to excellent isolated yields (Scheme 3).

With this chemoselective debenylation of tertiary amines in hand, the application of this novel cleavage protocol for solid phase synthesis was apparent. Thus, consecutive reductive alkylation<sup>7</sup> of aminomethyl polystyrene resin **22** with hexanal afforded polymer supported tertiary amine **23**, which was treated with CAN to afford dihexylamine **24** in 72% overall yield over the five steps (Scheme 4). This cleavage protocol constitutes a novel oxidative traceless linker synthesis of secondary amines on a solid support<sup>8</sup> and is of potential further utility in that cleavage of the secondary amine liberates formal polystyrene resin **25** ( $\nu_{\max}$  1700 cm<sup>-1</sup>; lit.<sup>9</sup> 1700 cm<sup>-1</sup>), thus affording the possibility of resin recycling.



**Scheme 4** Reagents and conditions: i, CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>CHO (5.0 equiv.), trimethyl orthoformate; ii, NaBH<sub>4</sub> (10.0 equiv.), DMF–EtOH (3:1); iii, CAN (5.0 equiv.), CH<sub>3</sub>CN–H<sub>2</sub>O (5:1), room temp.

In conclusion, treatment of *N*-benzyl tertiary amines with CAN results in smooth *N*-debenzylation to afford the corresponding secondary amines with complete chemoselectivity. While some *N*-debenzylation may be achieved under hydrogenolytic conditions in acid,<sup>10</sup> this novel debenylation under oxidative conditions adds considerable versatility to *N*-benzyl-

ation protection–deprotection methodology and to regeneration of polymer supports in combinatorial chemistry. Investigations are currently underway to determine the reaction mechanism of this transformation.

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- Representative protocol*: To a solution of *N*-benzylated tertiary amine (1 mmol) in CH<sub>3</sub>CN–H<sub>2</sub>O (5:1), at room temperature, was added CAN (2.1 equiv.) and the reaction mixture stirred for 2 h. The reaction mixture was neutralised with NaHCO<sub>3</sub> (aq), extracted with Et<sub>2</sub>O, dried (MgSO<sub>4</sub>), and the solvent and benzaldehyde removed *in vacuo* to afford a crude oil which was purified by chromatography to afford the desired secondary amine.
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