Chemoselective debenzylation of *N*-benzyl tertiary amines with ceric ammonium nitrate

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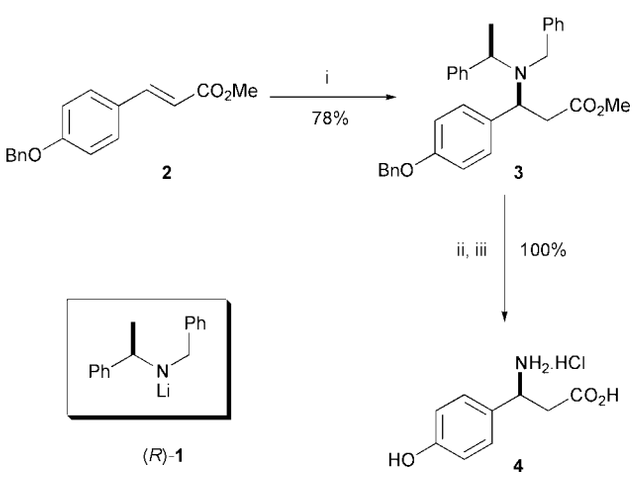
Treatment of a range of *N*-benzyl tertiary amines with aqueous ceric ammonium nitrate results in *N*-debenzylation to afford the corresponding secondary amine. Chemoselective mono-*N*-debenzylation of *N*-benzyl tertiary amines is shown to occur in the presence of *N*-benzyl amides, *O*-benzyl ethers, *O*-benzyl esters, *O*-benzyl phenolates and *S*-benzyl ethers.

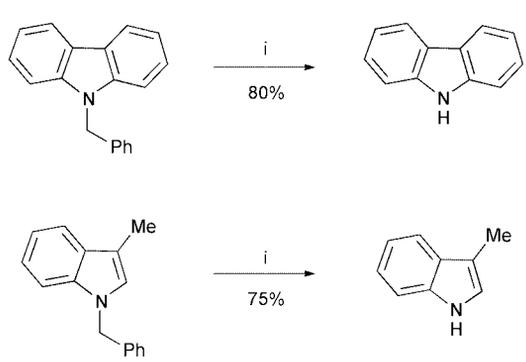
Introduction

The benzyl moiety is one of the most commonly employed protecting groups for heteroatom functionality in organic synthesis due to its ease of introduction and inherent stability. A variety of methodologies have been investigated for benzylic deprotection,[1] with removal *via* catalytic hydrogenolysis being the most widely used pathway, particularly for the deprotection of *N*-benzyl amines,[2] *O*-benzyl ethers,[3] *O*-benzyl esters,[4] and *O*-benzyl phenolates.[5] Indeed, the susceptibility of *N*-benzyl deprotection upon hydrogenolysis has been extensively used within our laboratory for the asymmetric synthesis of homochiral β-amino acid derivatives.[6] For example, addition of (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **1** to (*E*)-methyl 3-(4-benzyloxyphenyl)prop-2-enoate **2** proceeds to give (3*S*, α*R*)-methyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-benzyloxyphenyl)propanoate **3** in >95% de and 78% yield. Hydrogenolysis of **3** to remove the *N*-benzyl amine and *O*-benzyl ether protecting groups and subsequent ester hydrolysis enables isolation of the homochiral hydrochloride salt of β-tyrosine **4** in excellent yield (Scheme 1).[7]



Scheme 1 *Reagents and conditions*: i. (*R*)-**1**, −78 °C, THF then NH_4Cl (aq); ii. $Pd(OH)_2$/C, MeOH, H_2; iii. HCl (aq).

Although global heteroatom benzylic deprotection can be readily achieved *via* hydrogenolysis, there are only a few examples where chemoselective debenzylation of a perbenzylated substrate has been employed as a deprotection strategy. Thus, while methodology has been developed for the selective deprotection of *O*-benzyl esters in the presence of *N*-benzyl amines using Pd-catalysed transfer hydrogenation,[8] complementary methodology for the chemoselective removal of an *N*-benzyl group remains relatively unexplored. We have observed that in some cases it is possible to control hydrogenolytic deprotection of tertiary amino β-amino esters so that selective removal of the *N*-benzyl group in preference to the *N*-(α-methylbenzyl) group can be achieved.[9] While Pearlman's catalyst[10] and transfer hydrogenation[11] have also been shown in selected cases to promote *N*-debenzylation in the presence of *O*-benzyl ethers, an oxidative method of *N*-debenzylation of tertiary amines would be useful as an alternative to reductive hydrogenation. Although CAN and DDQ have been widely used as oxidative agents for the deprotection of methoxy-substituted benzylic protecting groups of alcohol,[12] amine[9, 13] and amide functionalities,[14] oxidative methods of benzylic cleavage which do not contain mesomerically donating substituents are rare. These include the report by Banerji *et al.* who have recently shown that certain *N*-benzyl heterocycles can be debenzylated upon treatment with $TiCl_3$–Li–I_2 in THF in high yield (Scheme 2).[15] Similarly, related oxidative approaches have



Scheme 2 *Reagents and conditions*: i. $TiCl_3$, Li, THF then I_2, RT.

shown that TPAP,[16] CuBr–LiO^{t}Bu,[17] Co(II)–^{t}BuOOH[18] and PhIO–$RuCl_2(PPh_3)_3$[19] all have the capacity to oxidise secondary benzylic amines to imines in high yields (Fig. 1).

Towards this aim, preliminary communications upon the ability of CAN in aqueous MeCN to facilitate the chemoselective *N*-debenzylation of tertiary *N*-benzyl amines have

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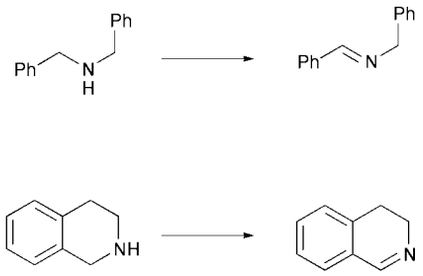


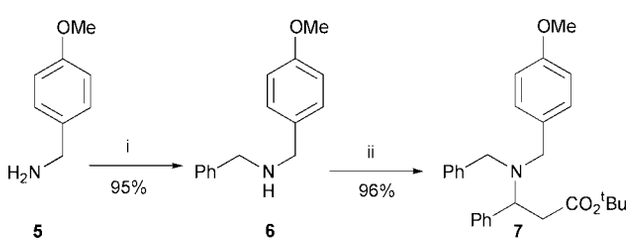
Fig. 1

been reported by ourselves[20] and others,[21] and we now report herein our results, delineating the scope and limitations of this versatile transformation.

Results and discussion

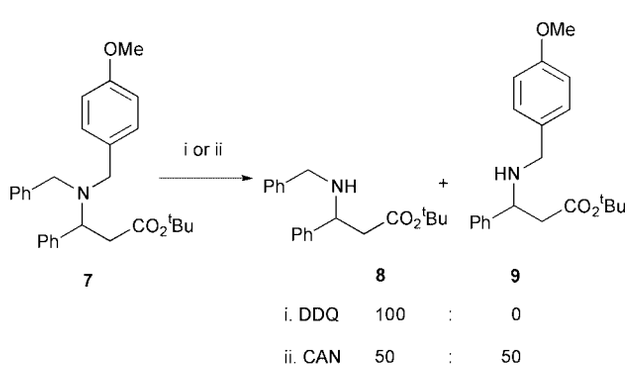
N-Debenzylation of tertiary *N*-benzyl β-amino esters

As part of our continuing programme towards extending the versatility of our lithium amide conjugate addition methodology, a novel debenzylation reaction of tertiary *N*-benzyl amines was observed during oxidative deprotection of *tert*-butyl 3-[*N*-benzyl-*N*-(4-methoxybenzyl)amino]-3-phenylpropanoate **7**. Tertiary amine **7** was prepared *via* deprotonation with *n*-BuLi of *N*-benzyl-*N*-(4-methoxybenzyl)amine **6** (prepared by reductive amination of 4-methoxybenzylamine **5** with benzaldehyde) at −78 °C and subsequent addition to *tert*-butyl cinnamate to give β-amino ester **7** in excellent yield (Scheme 3).



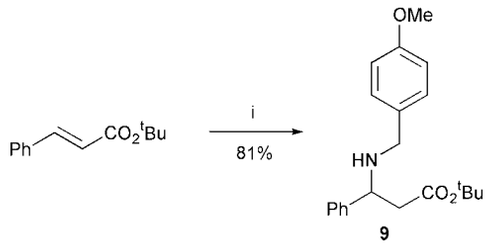
Scheme 3 *Reagents and conditions*: i. PhCHO, EtOH, Δ then $NaBH_4$; ii. *n*-BuLi then *tert*-butyl cinnamate, THF, −78 °C.

As expected,[22] treatment of β-amino ester **7** with DDQ showed selective cleavage of the 4-methoxy-substituted *N*-benzyl group, furnishing the known *tert*-butyl 3-(*N*-benzylamino)-3-phenylpropanoate **8**[23] and 4-methoxybenzaldehyde. However, treatment of β-amino ester **7** with CAN (2.1 eq.) remarkably gave a 50:50 mixture of the two possible cleavage products *N*-benzyl **8** and *tert*-butyl 3-*N*-(4-methoxybenzylamino)-3-phenylpropanoate **9** (Scheme 4). The identity of



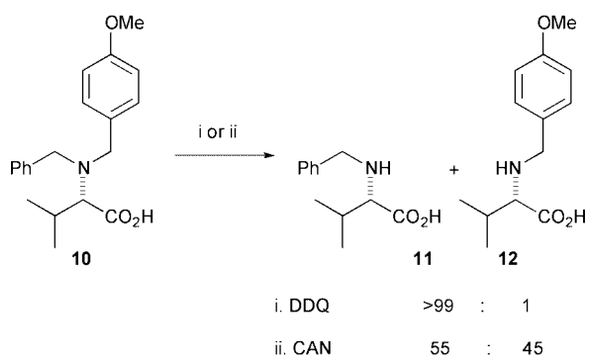
Scheme 4 *Reagents and conditions*: i. DDQ (1.2 eq.), DCM–H_2O (5:1), RT; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

secondary amine **9** was confirmed unambiguously by synthesis *via* conjugate addition of lithium 4-methoxybenzylamide to *tert*-butyl cinnamate in 81% yield (Scheme 5).



Scheme 5 *Reagents and conditions*: i. lithium 4-methoxybenzylamide (1.6 eq.), −78 °C, THF.

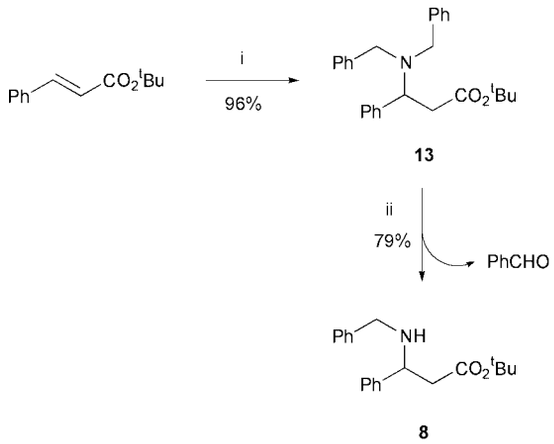
The complete lack of selectivity for deprotection of tertiary amine **7** with CAN is in sharp contrast to its well established use for the deprotection of the 4-methoxy-substituted benzylic group of *N*-4-methoxybenzyl-*N*-benzyl amides[24] and *O*-methoxybenzyl ethers in the presence of *O*-benzyl ethers.[25] This lack of selectivity implies oxidation at the tertiary nitrogen centre, rather than at the arene ring, since the outcome of the reaction is unaffected by arene substitution. Similar ratios of products have been noted recently by Metz *et al.*[21] for the DDQ or CAN promoted debenzylation of *N*-benzyl-*N*-(4-methoxybenzyl)amine **10**, which furnished a 55:45 ratio of *N*-benzyl **11** to *N*-(4-methoxybenzyl) **12** upon treatment with CAN (Scheme 6).



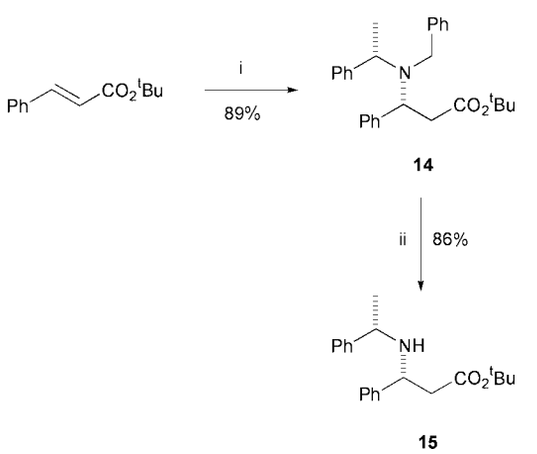
Scheme 6 *Reagents and conditions*: i. DDQ (1.5 eq.), DCM–H_2O (10:1), 0 °C; ii. CAN (2.1 eq.), MeCN–H_2O (4:1), 0 °C.

The susceptibility of the unsubstituted *N*-benzyl group to undergo oxidative cleavage by CAN suggested that this benzylic deprotection would be applicable for the debenzylation of other tertiary *N*-benzyl amines. Consequently the generality of this protocol was fully investigated for a range of β-amino esters. The *N*-debenzylation of β-amino esters with three benzylic *N*-protecting groups was the initial subject of this investigation. Thus, *tert*-butyl 3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate **13**, which contains two *N*-benzylic and one α-substituted-*N*-benzylic group, was prepared by addition of lithium dibenzylamide to *tert*-butyl cinnamate in 96% yield. Treatment of **13** with CAN (2.1 eq.) in aqueous acetonitrile resulted in mono-debenzylation to afford exclusively, by ^1H NMR spectroscopic analysis of the crude reaction mixture, the known secondary amine **8**. Secondary amine **8** was isolated in 79% yield after chromatography to remove benzaldehyde (Scheme 7).

Similarly, *N*-debenzylation of homochiral tertiary amine (3*R*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate **14**, which contains one *N*-benzylic and two α-substituted *N*-benzylic protecting groups, gave exclusively the known (3*R*,α*S*)-*tert*-butyl 3-(*N*-α-methylbenzylamino)-3-phenylpropanoate **15** upon treatment with CAN (2.1 eq.). Secondary amine **15** was isolated in 86% yield after chromatography. Since **15** was a single diastereoisomer, the specific rotation of (3*R*,α*S*)-**15** {$[\alpha]_D^{23}$ −15.8 (*c* 1.0, $CHCl_3$); lit.[26] $[\alpha]_D^{21}$ −16.3 (*c* 1.45, $CHCl_3$)} provides confirmation that the stereochemical integrity of **15** is not compromised by the CAN mediated *N*-benzylic deprotection (Scheme 8).

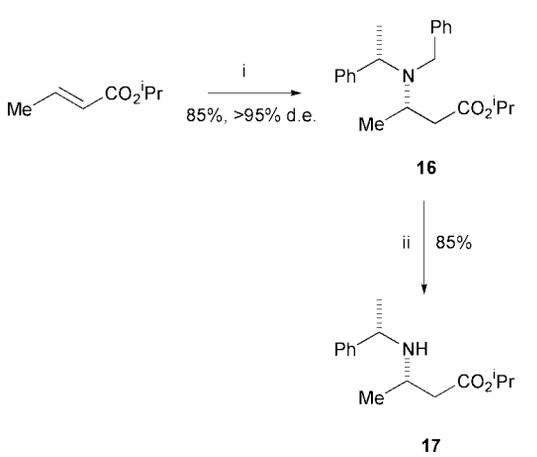


Scheme 7 *Reagents and conditions*: i. $(Bn)_2NLi$ (1.6 eq.), THF, −78 °C; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.



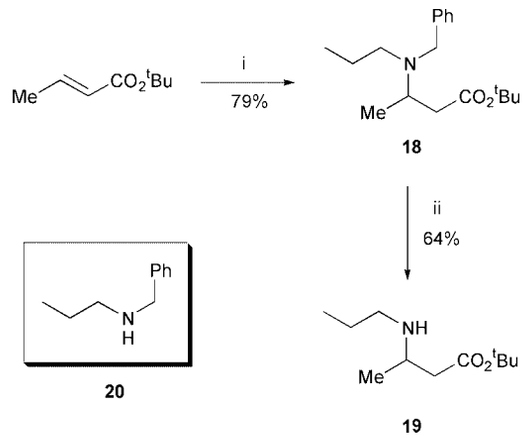
Scheme 8 *Reagents and conditions*: i. (*S*)-**1** (1.6 eq.), THF, −78 °C; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

Extension of this oxidative *N*-benzyl cleavage methodology to the deprotection of tertiary amines containing two *N*-benzylic groups was next demonstrated. Thus, (3*S*,α*S*)-isopropyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate **16** was prepared in 85% yield and >95% de by addition of (*S*)-**1** to isopropyl crotonate. Treatment of β-amino ester **16** with CAN (2.1 eq.) proceeded with selective *N*-benzyl cleavage to furnish (3*R*,*aS*)-isopropyl 3-(*N*-α-methylbenzylamino)butanoate **17** in 85% yield (Scheme 9).



Scheme 9 *Reagents and conditions*: i. (*S*)-**1** (1.6 eq.), THF, −78 °C; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

Finally, tertiary amine *tert*-butyl 3-(*N*-propyl-*N*-benzylamino)butanoate **18** containing only one *N*-benzyl group was prepared in 79% yield by addition of the lithium amide of *N*-benzyl-*N*-propylamine **20** to *tert*-butyl crotonate. Treatment of **18** with aqueous CAN (2.1 eq.) gave the debenzylated secondary amine **19** in 64% yield, the slightly lower isolated yield for this debenzylation reaction being attributed to the volatility of **19** (Scheme 10).

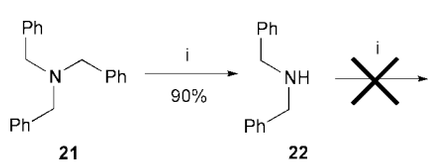


Scheme 10 *Reagents and conditions*: i. **20** (1.6 eq.), *n*-BuLi (1.55 eq.), THF, −78 °C; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

The selective *N*-debenzylation of β-amino esters with CAN has been shown to be a facile process. The transformation proceeds without racemisation of branched benzylic centres, indicating its utility in asymmetric synthesis.[27]

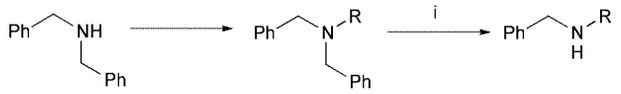
N-Debenzylation of *N*-benzyl tertiary amines

In order to examine further the scope and limitations of this methodology, tertiary *N*-benzyl amine tribenzylamine **21** was subjected to the CAN deprotection conditions. Clean monodebenzylation of **21** occurred to afford dibenzylamine **22** and benzaldehyde, with dibenzylamine **22** being isolated in 90% yield after chromatography. The selectivity of this oxidative deprotection for tertiary *N*-benzyl amines and not secondary *N*-benzyl amines was confirmed *via* treatment of dibenzylamine **22** with CAN which returned starting material in quantitative yield (Scheme 11).



Scheme 11 *Reagents and conditions*: i. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

To probe further the range of functionality which could be tolerated within the parent *N*-benzyl tertiary amine substrate, a series of tertiary *N*,*N*-dibenzyl-*N*-alkylamines **23**–**28**[28] (Table 1) was subjected to treatment with CAN (2.1 eq.) as shown in Scheme 12. For tertiary *N*-propyl **23**, *N*-butyl **24** and *N*-hexyl **25** *N*,*N*-dibenzylamines the mono-deprotection reaction was facile, returning the secondary *N*-benzyl-*N*-alkylamines **20**, **29** and **30** in 54–72% yield after purification. The sterically hindered *N*,*N*-dibenzyl-*N*-*tert*-butylamine **26** also underwent *N*-debenzylation with CAN, giving *N*-benzyl-*N*-*tert*-butylamine **31** in 68% yield. Attempted deprotection of the *N*-Me- and *N*-Et-substituted tertiary dibenzylamines **27** and **28** proved unsuccessful under these reaction conditions, with no evidence for the formation of secondary amines **32** and **33** even upon treatment with excess CAN and extended reaction times.[29] Similarly the CAN debenzylation protocol did not facilitate deprotection of cyclic tertiary *N*-benzyl amines, since treatment of *N*-benzylpiperidine **34**, *N*-benzylproline ethyl ester **35** and *N*-benzylpiperidin-4-one **36** with aqueous CAN showed no

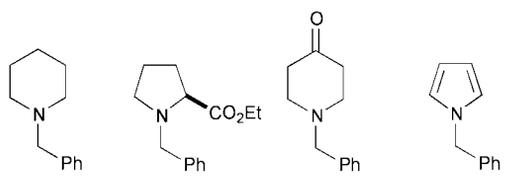


23-28 **20, 29-31**

Scheme 12 *Reagents and conditions*: i. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

Table 1 *N*-Debenzylation of *N*,*N*-dibenzyl-*N*-alkylamines

	R		Yield (%)
23	Pr	**20**	69
24	Bu	**29**	72
25	Hex	**30**	54
26	^{t}Bu	**31**	68
27	Me	**32**	—
28	Et	**33**	—



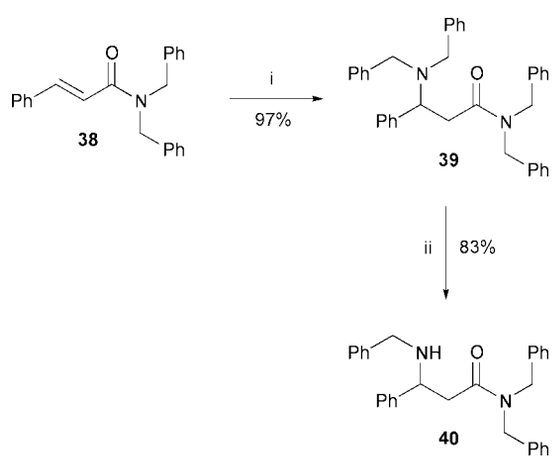
34 **35** **36** **37**

Fig. 2 Compounds inert to *N*-debenzylation with CAN.

reaction, only returning starting materials, while *N*-benzylpyrrole **37** polymerised under the reaction conditions (Fig. 2).

Chemoselective *N*-debenzylation studies

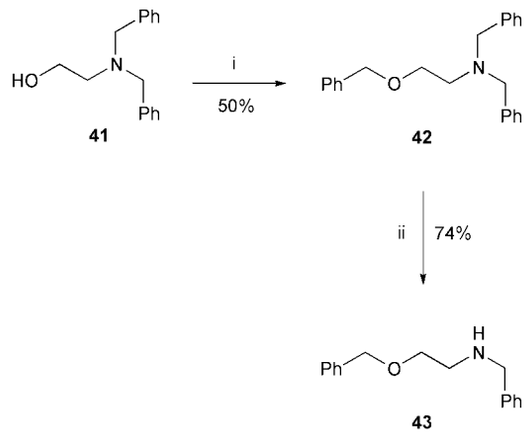
The susceptibility of *N*-benzyl tertiary amines to undergo mono-*N*-debenzylation with CAN led to an investigation of the chemoselectivity of this transformation. Initial studies in this area concentrated upon the debenzylation of *N*-benzyl tertiary amines in the presence of an *N*-benzyl amide. Thus, *N*,*N*-dibenzyl-3-dibenzylamino-3-phenylpropionamide **39** was prepared by addition of lithium dibenzylamide to *N*,*N*-dibenzylcinnamide **38**. Treatment of β-amino amide **39** with CAN (2.1 eq.) resulted in mono-*N*-debenzylation of the amine functionality, furnishing secondary amine *N*,*N*-dibenzyl-3-benzylamino-3-phenylpropionamide **40** in 83% yield (Scheme 13).



38 **39** **40**

Scheme 13 *Reagents and conditions*: i. $N(Bn)_2Li$ (1.6 eq.), THF, −78 °C; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

Similarly, debenzylation of a tertiary *N*,*N*-dibenzylamine which contained an *O*-benzyl ether functionality was studied. Thus, dibenzyl(2-benzyloxyethyl)amine **42** was prepared *via* benzylation of 2-(dibenzylamino)ethanol **41** with BnBr in THF. Treatment of perbenzylated **42** with CAN resulted in chemoselective *N*-deprotection to afford the mono-*N*-debenzylated secondary amine **43**, leaving the *O*-benzyl ether moiety intact (Scheme 14).



41 **42** **43**

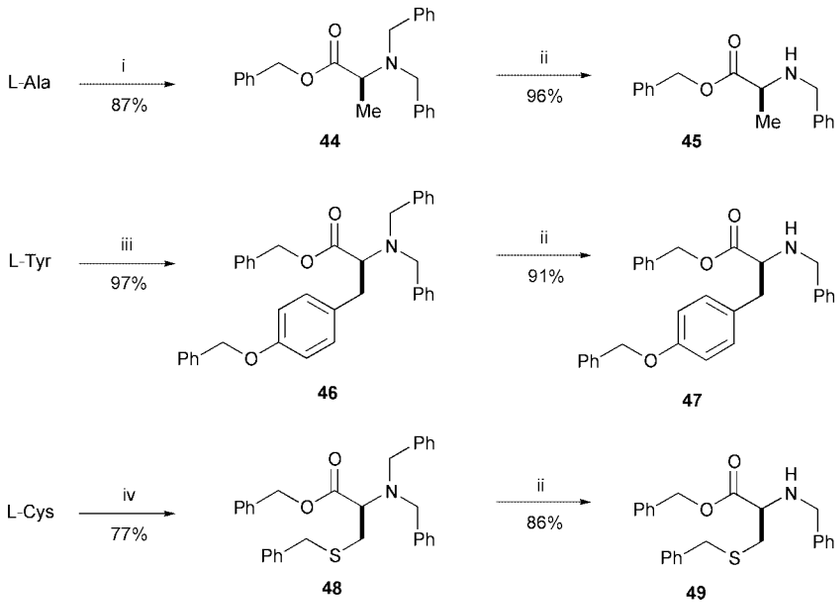
Scheme 14 *Reagents and conditions*: i. KO^{t}Bu, 18-crown-6, BnBr, THF; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT.

This methodology was further extended to the mono-*N*-deprotection of perbenzylated amino acid derivatives **44**, **46** and **48**, in order to ascertain the chemoselectivity of this process in the presence of *O*-benzyl esters, *O*-benzyl phenolates and *S*-benzyl ethers. Thus, L-Ala, L-Tyr and L-Cys were perbenzylated by treatment with K_2CO_3 and BnBr to afford **44**, **46** and **48** in good yield. Reaction of (2*S*)-benzyl 2-dibenzylaminopropanoate **44** gave (*2S*)-benzyl 2-benzylaminopropanoate **45** {$[a]_D^{23}$ −38.6, *c* 1.0, MeOH; lit.[30] (*ent*) $[a]_D^{25}$ +40.4, *c* 1.0, MeOH} leaving the benzyl ester intact. Furthermore, oxidative *N*-debenzylation of the amino functionality of (2*S*)-benzyl 3-(4-benzyloxyphenyl)-2-dibenzylaminopropanoate **46** and (2*R*)-benzyl 3-benzylsulfanyl-2-dibenzylaminopropanoate **48** gave secondary amines (2*S*)-benzyl 3-(4-benzyloxyphenyl)-2-benzylaminopropanoate **47** {$[a]_D^{24}$ −8.3, *c* 1.2, $CHCl_3$} and (2*R*)-benzyl 3-benzylsulfanyl-2-benzylaminopropanoate **49** {$[a]_D^{23}$ −21.9, *c* 1.1, $CHCl_3$} respectively in excellent isolated yields, leaving both the *O*-benzyl and *S*-benzyl protecting groups intact (Scheme 15).

While traditional protecting group strategies rely upon the inherent orthogonal chemical reactivity of protecting groups to establish selective heteroatom deprotection, it is proposed that the strategy of global benzylic heteroatom protection and subsequent chemoselective deprotection reported herein is an alternative protecting group strategy which will find increased use in organic synthesis.

Conclusion

In conclusion, we have demonstrated that the CAN mediated *N*-debenzylation protocol proceeds in uniformly good yields for acyclic *tri*-, *di*- and *mono*-*N*-benzyl tertiary amines that do not contain *N*-Me or *N*-Et substituents, with preferential cleavage of unbranched *N*-benzylic substituents over α-branched *N*-benzylic substituents. *N*-Benzyl secondary amines are inert to further oxidation. The CAN mediated *N*-deprotection is chemoselective, enabling *N*-benzyl deprotection in the presence of *N*-benzyl amide, *O*-benzyl ether, *O*-benzyl ester, *O*-benzyl phenolate and *S*-benzyl ether functionalities. Competitive experiments with tertiary *N*-benzyl-*N*-4-methoxybenzyl-substituted amines indicate that the outcome of the reaction is unaffected by arene substitution, implying initial single electron oxidation by CAN at the tertiary nitrogen centre of the amino nitrogen rather than at the arene ring of the *N*-benzyl substituent. Further mechanistic studies within this area are currently ongoing to delineate the reaction mechanism of this remarkable transformation.



Scheme 15 *Reagents and conditions*: i. K_2CO_3, BnBr, DMF; ii. CAN (2.1 eq.), MeCN–H_2O (5:1), RT; iii. K_2CO_3, BnBr, EtOH; iv. K_2CO_3, BnBr, DMF–H_2O.

Experimental

General

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of nitrogen using standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. Ceric ammonium nitrate (A.C.S. grade) was used as supplied. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using 7% ammonium molybdate in 10% sulfuric acid–ethanol, iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 ml. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

Representative procedure 1: for lithium amide additions

n-Butyllithium (1.55 eq.) was added dropwise to a stirred solution of secondary amine (1.6 eq.) in anhydrous THF at −78 °C and stirred for thirty minutes under nitrogen. A solution of the α,β-unsaturated ester (1.0 eq.) in anhydrous THF was added dropwise *via* cannula and stirred at −78 °C for two hours before the addition of saturated aqueous ammonium chloride and warmed to RT. The resultant solution was partitioned between brine and 1:1 DCM–Et_2O and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 2: for CAN debenzylation

CAN (2.1 eq.) was added portionwise to a stirred solution of the substrate (1.0 eq.) in MeCN–H_2O (5:1) and stirred at RT. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and stirred vigorously for ten minutes before extracting with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* before purification by column chromatography.

Preparation of *N*-benzyl-*N*-(4-methoxybenzyl)amine[31] 6

Based upon a literature procedure,[32] benzaldehyde (5.57 g, 52.5 mmol, 1.05 eq.) and 4-methoxybenzylamine **5** (6.86 g, 50 mmol, 1.00 eq.) were heated at reflux in EtOH (100 ml) before the addition of $NaBH_4$ (3.18 g, 84 mmol, 1.60 eq.) at 0 °C and warmed to RT. After work-up, concentration *in vacuo* gave **6** as a yellow oil (10.8 g, 95%) which was subsequently used without further purification. δ_H (200 MHz, $CDCl_3$) 1.72 (1H, br s, N*H*), 3.76, 3.81 (2 × 2H, s, NCH_2 × 2), 3.82 (3H, s, O*Me*), 6.87–6.91 (2H, m, *Ph*), 7.27–7.37 (7H, m, *Ph*).

Preparation of *tert*-butyl 3-[*N*-benzyl-*N*-(4-methoxybenzyl)-amino]-3-phenylpropanoate 7

Following representative procedure 1, *n*-butyllithium (1.6 M, 4.74 ml, 7.6 mmol), **6** (1.78 g, 7.8 mmol) in THF (15 ml) and *tert*-butyl cinnamate (1.0 g, 4.9 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 12:1) **7** as a colourless oil (2.04 g, 96%). R_f 0.25; $C_{28}H_{33}NO_3$ requires C 77.9; H 7.7; N 3.25; found C 77.5; H 7.5, N 3.2%; ν_{max}/cm^{-1} (film) 2974, 2828 (C–H), 1738 (C=O), 1512, 1456 (OMe bend), 1255 (Ph–O), 1156 (C–O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, $CO_2C(Me)_3$), 2.72 (1H, dd, $J_{2A,2B}$ 14.4, $J_{2A,3}$ 8.6, C(2)H_A), 2.99 (1H, dd, $J_{2B,2A}$ 14.4, $J_{2B,3}$ 6.9, C(2)H_B), 3.26 and 3.68 (2 × 2H, ABq, NCH_2 × 2), 3.80 (3H, s, O*Me*), 4.27 (1H, app t, J 7.8, C(3)*H*), 6.85 (2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe), 7.21–7.38 (12H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 30.0, 37.2, 53.2, 53.7, 55.2, 59.0, 80.4, 113.6, 126.9, 127.2, 128.0, 128.2, 128.7, 128.8, 130.0, 131.7, 138.5, 139.9, 158.6, 171.1; *m/z* APCI$^+$ 432.3 (MH$^+$, 100%), 376.2 (MH$^+$ − C_4H_8, 20%).

Deprotection of 7 with DDQ

DDQ (131 mg, 0.58 mmol, 1.2 eq.) was added to a solution of **7** (200 mg, 0.48 mmol, 1.0 eq.) in DCM–H_2O (5:1) (3 ml) and stirred overnight at RT. The solution was poured onto saturated aqueous sodium bicarbonate solution (20 ml), extracted with DCM (3 × 60 ml), dried and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture and comparison with authentic ^{1}H NMR spectra of *tert*-butyl 3-(*N*-benzylamino)-3-phenylpropanoate **8** and *tert*-butyl 3-(*N*-4-methoxybenzylamino)-3-phenylpropanoate **9** indicated the selective cleavage of the 4-OMe substituted benzyl group to give **8** and 4-methoxybenzaldehyde.

Deprotection of 7 with CAN

Following representative procedure 2, CAN (536 mg, 0.98 mmol, 2.1 eq.) was added to **7** (200 mg, 0.47 mmol, 1.0 eq.) in MeCN–H_2O (5:1) (6 ml) at RT. Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction mixture and comparison with authentic ^{1}H NMR spectra of **8** and **9** indicated a 50:50 mixture of secondary amines **8** and **9**.

Preparation of *tert*-butyl 3-(*N*-4-methoxybenzylamino)-3-phenylpropanoate 9

Following representative procedure 1, *n*-butyllithium (1.6 M, 2.38 ml, 3.8 mmol), 4-methoxybenzylamine **5** (538 mg, 3.92 mmol) in THF (10 ml) and *tert*-butyl cinnamate (0.5 g, 2.45 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 2:1) **9** as a colourless oil (673 mg, 81%). R_f 0.3; $C_{21}H_{27}NO_3$ requires C 73.9; H 8.0; N 4.1; found C 73.5; H 7.75; N 4.0%; ν_{max}/cm^{-1} (film) 3330 (NH), 2924, 2839 (C–H), 1726 (C=O), 1514, 1458 (OMe bend), 1245 (Ph–O), 1151 (C–O); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $CO_2C(Me)_3$), 1.91 (1H, br s, N*H*), 2.53 (1H, dd, $J_{2A,2B}$ 15.2, $J_{2A,3}$ 5.3, C(2)H_A), 2.64 (1H, dd, $J_{2B,2A}$ 15.2, $J_{2B,3}$ 8.7, C(2)H_B), 3.56 (2H, ABq, NCH_2), 3.80 (3H, s, O*Me*), 4.06 (1H, dd, $J_{3,2B}$ 8.7, $J_{3,2A}$ 5.3, C(3)*H*), 6.84 (2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe), 7.25–7.38 (7H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 28.0, 44.2, 50.7, 55.2, 59.0, 80.6, 113.7, 127.3, 128.5, 129.3, 132.4, 142.7, 158.5, 171.1; *m*/*z* APCI$^+$ 342.2 (MH$^+$, 60%), 364.2 (MNa$^+$, 10%), 286.2 (MH$^+$ − C_4H_8, 100%).

Preparation of *tert*-butyl 3-(*N*,*N*-dibenzylamino)-3-phenylpropanoate[33] 13

Following representative procedure 1, *n*-butyllithium (2.5 M, 3.0 ml, 7.6 mmol), dibenzylamine (1.54 g, 7.8 mmol) in THF (10 ml) and *tert*-butyl cinnamate (1.0 g, 4.9 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 20:1) **13** as a white solid (1.90 g, 96%). R_f 0.3; δ_H (200 MHz, $CDCl_3$) 1.34 (9H, s, $CO_2C(Me)_3$), 2.72 (1H, dd, $J_{2A,2B}$ 14.4, $J_{2A,3}$ 8.5, C(2)H_A), 3.00 (1H, dd, $J_{2B,2A}$ 14.4, $J_{2B,3}$ 7.1, C(2)H_B), 3.27 and 3.72 (2 × 2H, ABq, NCH_2 × 2), 4.28 (1H, dd, $J_{3,2A}$ 8.5, $J_{3,2B}$ 7.1, C(3)*H*), 7.19–7.41 (15H, m, *Ph*).

Preparation of *tert*-butyl 3-(*N*-benzylamino)-3-phenylpropanoate[23] 8

Following representative procedure 2, CAN (1.15 g, 2.1 mmol) was added to **13** (400 mg, 1.0 mmol) in MeCN–H_2O (5:1) (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 2:1) to give **8** as a colourless oil (246 mg, 79%). δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, $CO_2C(Me)_3$), 2.14 (1H, br s, N*H*), 2.58 (1H, dd, $J_{2A,2B}$ 15.2, $J_{2A,3}$ 5.3, C(2)H_A), 2.69 (1H, dd, $J_{2B,2A}$ 15.2, $J_{2B,3}$ 8.7, C(2)H_B), 3.64 (2H, ABq, NCH_2), 4.13 (1H, dd, $J_{3,2B}$ 8.7, $J_{3,2A}$ 5.3, C(3)*H*), 7.24–7.43 (10H, m, *Ph*).

Preparation of (3*R*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate[34] 14

Following representative procedure 1, *n*-butyllithium (1.6 M, 22.8 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (5.0 g, 23.5 mmol) in THF (20 ml) and *tert*-butyl cinnamate (3.0 g, 14.7 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 20:1) **14** as a colourless oil (5.45 g, 89%). $[\alpha]_D^{23}$ −4.0 (*c* 1.0, $CHCl_3$), lit.[35] (*ent*) $[\alpha]_D^{20}$ +3.9 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, $OC(Me)_3$), 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.45–2.60 (2H, m, C(2)H_2), 3.68 (2H, ABq, NCH_2), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.41 (1H, dd, $J_{3,2A}$ 9.5, $J_{3,2B}$ 5.6, C(3)*H*), 7.20–7.49 (15H, m, *Ph*).

Preparation of (3*R*,α*S*)-*tert*-butyl 3-(*N*-α-methylbenzylamino)-3-phenylpropanoate[26] 15

Following representative procedure 2, CAN (1.10 g, 2 mmol) was added to **14** (346 mg, 0.83 mmol) in MeCN–H_2O (5:1) (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 5:1) to give **15** as a yellow oil (234 mg, 86%). R_f 0.25; $[\alpha]_D^{23}$ −15.8 (*c* 1.0, $CHCl_3$); lit.[26] $[\alpha]_D^{23}$ −16.3 (*c* 1.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.5, C(α)*Me*), 1.42 (9H, s, $CO_2C(Me)_3$), 1.91 (1H, br s, N*H*), 2.59 (1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 6.2, C(2)H_A), 2.68 (1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 7.9, C(2)H_B), 3.70 (1H, q, *J* 6.5, C(α)*H*), 4.21 (1H, dd, $J_{3,2B}$ 7.9, $J_{3,2A}$ 6.2, C(3)*H*), 7.22–7.36 (10H, m, *Ph*).

Preparation of (3*S*,α*S*)-isopropyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 16

Following representative procedure 1, *n*-butyllithium (2.5 M, 1.26 mmol, 0.5 ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (250 mg, 1.30 mmol) in THF (3 ml) and isopropyl crotonate (104 mg, 0.81 mmol) in THF gave, after purification by column chromatography on silica gel (hexane–Et_2O 15:1) **16** as a colourless oil (234 mg, 85%). $C_{22}H_{29}NO_2$ requires C 77.8; H 8.6; N 4.1%; found C 77.6; H 8.5; N 4.1%; $[\alpha]_D^{24}$ +4.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 1727 (C=O), 1151 (C–O); δ_H (300 MHz, $CDCl_3$) 1.12, 1.16 (2 × 3H, d, *J* 6.2, $OCH(Me)_2$), 1.34 (3H, d, *J* 6.9, C(α)*Me*), 2.07 (1H, dd, $J_{2A,2B}$ 14.2, $J_{2A,3}$ 8.6, C(2)H_A), 2.31 (1H, dd, $J_{2B,2A}$ 14.2, $J_{2B,3}$ 5.1, C(2)H_B), 3.39–3.50 (1H, m, C(3)*H*), 3.63 (1H, d, *J* 14.9, NCH_A), 3.76 (1H, d, *J* 14.9, NCH_B), 3.89 (1H, q, *J* 6.9, C(α)*H*), 4.89 (1H, septet, *J* 6.2, $OCH(Me)_2$), 7.18–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7, 21.8, 39.8, 49.7, 50.3, 53.8, 67.4, 126.6, 126.7, 127.8, 128.1, 128.2, 128.3, 142.0, 144.3, 172.1; *m*/*z* APCI$^+$ 340.2 (MH$^+$, 100%), 362.1 (MNa$^+$, 10%).

Preparation of (3*S*,α*S*)-isopropyl 3-(*N*-α-methylbenzylamino)-butanoate 17

Following representative procedure 2, CAN (1.38 g, 2.1 mmol) was added to **17** (340 mg, 1.0 mmol) in MeCN–H_2O (5:1) (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 3:1) to give **17** as a colourless oil (212 mg, 85%). R_f 0.3; $[\alpha]_D^{24}$ −46.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3339 (NH), 2978, 2932 (C–H), 1728 (C=O), 1109 (C–O); δ_H (400 MHz, $CDCl_3$) 1.05, 1.24, 1.33 (4 × 3H, d, C(α)*Me*, $OCH(Me)_2$ and C(4)H_3), 1.53 (1H, br s, N*H*), 2.32–2.42 (2H, C(2)H_2), 2.98 (1H, app sextet, *J* 6.2, C(3)*H*), 3.89 (1H, q, *J* 6.5, C(α)*H*), 5.02 (1H, septet, *J* 6.4, $OCH(Me)_2$), 7.21–7.33 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 21.4, 21.8, 24.5, 41.0, 47.9, 55.1, 67.5, 126.5, 126.8, 128.3, 146.0, 171.8; *m*/*z* APCI$^+$ 250.2 (MH$^+$, 100%), 272.2 (MNa$^+$, 20%), 145.9 (MH$^+$ − C_4H_8, 70%); HRMS (CI$^+$) $C_{15}H_{24}NO_2$ requires 250.1807; found 250.1808.

Preparation of *N*-benzyl-*N*-propylamine[36] 20

Based upon a literature procedure,[32] benzaldehyde (11.1 g, 105 mmol) and propylamine (5.91 g, 100 mmol) were heated at reflux in EtOH (50 ml) before addition of $NaBH_4$ (6.05 g, 160 mmol) at 0 °C and allowed to warm to RT. After work-up, concentration *in vacuo* gave **20** as a colourless oil (13.7 g,

92%) which was subsequently used without further purification. δ_H (200 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.49–1.63 (3H, m, N*H* and $NCH_2CH_2CH_3$), 2.61 (2H, t, *J* 7.0, $NCH_2CH_2CH_3$), 3.80 (2H, s, NCH_2Ph), 7.05–7.35 (5H, m, *Ph*).

Preparation of *tert*-butyl 3-(*N*-propyl-*N*-benzylamino)butanoate 18

Following representative procedure 1, *n*-butyllithium (1.6 M, 6.8 ml, 10.9 mmol), *N*-propyl-*N*-benzylamine **20** (1.68 g, 11.3 mmol, 1.6 eq.) in THF (15 ml) and *tert*-butyl crotonate (1.0 g, 7.03 mmol, 1.0 eq.) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 10:1) **18** as a colourless oil (1.62 g, 79%). ν_{max}/cm^{-1} (film) 2962, 2934 (C–O), 1726 (C=O), 1160 (C–O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.3, $NCH_2CH_2CH_3$), 1.05 (3H, d, *J* 6.7, C(4)H_3), 1.37–1.45 (2H, m, $NCH_2CH_2CH_3$), 1.46 (9H, s, $CO_2C(Me)_3$), 2.15 (1H, dd, $J_{2A,2B}$ 14.0, $J_{2A,3}$ 6.5, C(2)H_A), 2.32–2.36 (2H, m, $NCH_2CH_2CH_3$), 2.51 (1H, dd, $J_{2AB,2A}$ 14.0, $J_{2B,3}$ 7.0, C(2)H_B), 3.32 (1H, app sextet, *J* 7.0, C(3)*H*), 3.54 (2H, ABq, NCH_2Ph), 7.19–7.36 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 11.8, 14.7, 21.7, 28.1, 40.1, 51.9, 53.9, 52.1, 80.0, 126.5, 127.9, 128.6, 141.0, 172.1; *m*/*z* APCI$^+$ 292.2 (MH^+, 70%), 314.2 (MNa^+, 20%), 236.1 ($MH^+ - C_4H_8$, 100%); HRMS (CI^+) $C_{18}H_{30}NO_2$ requires 292.2277; found 292.2281.

Preparation of *tert*-butyl 3-(*N*-propylamino)butanoate 19

Following representative procedure 2, CAN (1.97 g, 3.7 mmol, 2.1 eq.) was added to **18** (500 mg, 1.72 mmol, 1.0 eq.) in MeCN–H_2O (5:1) (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 2:1) to give **19** as a volatile colourless oil (221 mg, 64%). R_f (0.3); ν_{max}/cm^{-1} (film) 3337 (NH), 2967 (C–H), 1726 (C=O), 1153 (C–O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.09 (3H, d, *J* 6.4, C(4)H_3), 1.42–1.60 (2H, m, $NCH_2CH_2CH_3$), 1.44 (9H, s, $CO_2C(Me)_3$), 2.22 (1H, dd, $J_{2A,2B}$ 15.0, $J_{2A,3}$ 6.0, C(2)H_A), 2.36 (1H, dd, $J_{2B,2A}$ 14.0, $J_{2B,3}$ 6.5, C(2)H_B), 2.48–2.62 (2H, m, $NCH_2CH_2CH_3$), 3.03 (1H, m, C(3)*H*); δ_C (50 MHz, $CDCl_3$) 11.8, 20.5, 23.4, 28.1, 42.8, 49.0, 50.3, 80.3, 171.8; *m*/*z* APCI$^+$ 202.2 (MH^+, 10%), 146.1 ($MH^+ - C_4H_8$, 100%); HRMS (CI^+) $C_{11}H_{24}NO_2$ requires 202.1807; found 202.1806.

Preparation of dibenzylamine[37] 22

Following representative procedure 2, CAN (2.30 g, 4.2 mmol) was added to tribenzylamine **21** (575 mg, 2.0 mmol) in MeCN–H_2O (5:1) (6 ml) at RT. Following work-up, the residue was purified by column chromatography on silica gel (Et_2O) to give dibenzylamine **22** (354 mg, 90%). δ_H (200 MHz, $CDCl_3$) 3.88 (4H, s, 2 × NCH_2Ph), 7.10–7.35 (10H, m, *Ph*).

Preparation of *N*,*N*-dibenzyl-*N*-propylamine[38] 23

Based upon a literature procedure,[39] trimethyl orthoformate (4.0 g, 37.9 mmol), dibenzylamine (5.0 g, 25.3 mmol) and propionaldehyde (1.47 g, 25.3 mmol) were stirred at RT in MeOH (100 ml) at pH 6 prior to the portionwise addition of $NaBH_4$ (0.96 g, 25.3 mmol) at 0 °C. After sixteen hours, the reaction was concentrated *in vacuo*, washed with 10% aqueous citric acid and extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petrol 40–60–Et_2O 70:1) to give **23** (4.45 g, 74%) as a colourless oil. δ_H (200 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3, $CH_2CH_2CH_3$), 1.54 (2H, m, $CH_2CH_2CH_3$), 2.40 (2H, t, *J* 7.0, $NCH_2CH_2CH_3$), 3.57 (4H, s, 2 × NCH_2Ph), 7.20–7.42 (10H, m, *Ph*).

CAN mediated preparation of *N*-benzyl-*N*-propylamine 20

Following representative procedure 2, CAN (2.88 g, 5.26 mmol) was added to **23** (600 mg, 2.51 mmol) in MeCN–H_2O (5:1) (18 ml) at RT. Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 1:1 to neat Et_2O) to give **20** as a colourless oil (257 mg, 69% at 80% conversion) with identical spectroscopic properties to those described previously.

Preparation of *N*,*N*-dibenzyl-*N*-butylamine[40] 24

Based upon a literature procedure,[39] trimethyl orthoformate (4.0 g, 37.9 mmol), dibenzylamine (5.0 g, 25.3 mmol) and butyraldehyde (1.8 g, 25.3 mmol) were stirred at RT in MeOH (100 ml) at pH 6 prior to the portionwise addition of $NaBH_4$ (0.96 g, 25.3 mmol) at 0 °C. After sixteen hours, the reaction was concentrated *in vacuo*, washed with 10% aqueous citric acid, extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–Et_2O 70:1) to give **24** (4.85 g, 76%) as a colourless oil. δ_H (200 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, $CH_2CH_2CH_3$), 1.24–1.55 (2 × 2H, m, $CH_2CH_2CH_3$), 2.43 (2H, t, *J* 7.0, NCH_2CH_2), 3.57 (4H, s, 2 × NCH_2Ph), 7.20–7.40 (10H, m, *Ph*).

Preparation of *N*-benzyl-*N*-butylamine[41] 29

Following representative procedure 2, CAN (2.71 g, 4.94 mmol) was added to **24** (600 mg, 2.36 mmol) in MeCN–H_2O (5:1) (18 ml) at RT. Following work-up, the residue was purified by column chromatography on silica gel (gradient elution hexane–Et_2O 1:1 to neat Et_2O) to give **29** as a yellow oil (275 mg, 72% at 85% conversion). δ_H (200 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, $CH_2CH_2CH_3$), 1.29–1.59 (4H, m, $CH_2CH_2CH_3$), 2.64 (2H, t, *J* 7.2, NCH_2CH_2), 3.80 (2H, s, NCH_2Ph), 7.23–7.35 (5H, m, *Ph*).

Preparation of *N*,*N*-dibenzyl-*N*-hexylamine[42] 25

Based upon a literature procedure,[39] trimethyl orthoformate (2.4 g, 22.8 mmol), dibenzylamine (3.0 g, 15.2 mmol) and hexanal (1.83 ml, 15.2 mmol) were stirred in MeOH (50 ml) at pH6 prior to the portionwise addition of $NaBH_4$ (0.58 g, 15.2 mmol) at 0 °C. After five hours, the reaction was concentrated *in vacuo*, partitioned between Et_2O and H_2O, dried and concentrated *in vacuo* to give **25** (3.30 g, 77%) as a pale yellow oil. δ_H (200 MHz, $CDCl_3$) 0.95 (3H, t, *J* 6.7, CH_2CH_3), 1.24–1.60 (8H, m, $CH_2CH_2CH_2CH_2CH_3$), 2.49 (2H, t, *J* 7.1, NCH_2CH_2), 3.65 (4H, s, 2 × NCH_2Ph), 7.28–7.49 (10H, m, *Ph*).

Preparation of *N*-benzyl-*N*-hexylamine[43] 30

Following representative procedure 2, CAN (4.09 g, 7.46 mmol) was added to a stirred solution of **25** (1.0 g, 3.56 mmol) in MeCN–H_2O–THF (6:1:2) (45 ml) at RT. Following work-up, the residue was purified by Kugelrohr distillation (bp 200 °C, 20 mmHg) to give **30** (0.38 g, 54%) as a colourless oil. δ_H (200 MHz, $CDCl_3$) 0.92–0.98 (3H, m, CH_2CH_3), 1.35–1.62 (9H, m, $CH_2CH_2CH_2CH_2CH_3$ and N*H*), 2.70 (2H, t, *J* 7.2, NCH_2CH_2), 3.86 (2H, s, NCH_2Ph), 7.28–7.42 (5H, m, *Ph*).

Preparation of *N*,*N*-dibenzyl-*N*-*tert*-butylamine 26

Benzyl bromide (3.94 g, 23.0 mmol) was added dropwise to a stirred solution of K_2CO_3 (3.18 g, 23.0 mmol) and *tert*-butylamine (800 mg, 11.0 mmol) in THF–H_2O 1:1 (40 ml) at 0 °C and allowed to warm to RT. After sixteen hours the mixture was partitioned between H_2O and Et_2O (3 × 60 ml), dried and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the crude reaction showed a 2:1 ratio of *N*-benzyl-*N*-*tert*-butylamine to the required *N*,*N*-dibenzyl-*N*-*tert*-butylamine **26**. The crude material was triturated with DCM and *N*-benzyl-*N*-*tert*-butylamine was removed by filtration (555 mg, 30%). The filtrate was evaporated *in vacuo* and recrystallised from MeOH to afford **26** as colourless needles (812 mg, 29%), mp 65–66 °C.

$C_{18}H_{23}N$ requires C 85.3; H 9.15; N 5.55; found C 85.25; H 9.1; N 5.5%; δ_H (200 MHz, $CDCl_3$) 1.15 (9H, s, $C(CH_3)_3$), 3.72 (4H, s, 2 × $PhCH_2$), 7.10–7.40 (10H, m, Ph); δ_C (50 MHz, $CDCl_3$) 27.5, 54.4, 55.7, 126.3, 128.0, 128.5, 143.1; *m/z* APCI$^+$ 254 (MH^+, 60%), 198 ($MH^+ - C_4H_8$, 60%), 164 ($MH^+ - C_7H_6$, 100%), 108 ($MH^+ - C_4H_8 - C_7H_6$, 90%).

Preparation of *N*-benzyl-*N*-*tert*-butylamine[44] 31

Following representative procedure 2, CAN (1.15 g, 2.10 mmol) was added to **27** (253 mg, 1.00 mmol) in MeCN–H_2O (5:1) (14 ml) at RT. Following work-up, the residue was purified by column chromatography on silica gel (gradient elution hexane–Et_2O 1:1 to neat Et_2O) to give **31** as a yellow oil (111 mg, 68%). δ_H (200 MHz, $CDCl_3$) 1.23 (9H, s, $C(CH_3)_3$), 3.77 (2H, s, $PhCH_2$), 7.35–7.40 (5H, m, *Ph*).

Preparation of *N*,*N*-dibenzyl-*N*-methylamine[45] 27

Based upon a literature procedure,[46] formaldehyde (2 ml), dibenzylamine (985 mg, 5.0 mmol) and $NaBH_3CN$ (500 mg, 8.0 mmol) in MeCN (10 ml) gave **27** as a colourless oil (806 mg, 76%). δ_H (200 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 3.57 (4H, s, 2 × $PhCH_2$), 7.28–7.40 (10H, m, *Ph*).

Attempted CAN debenzylation of *N*,*N*-dibenzyl-*N*-methylamine 27

Following representative procedure 2, CAN (1.93 g, 3.52 mmol, 2.1 eq.) was added to **27** (354 mg, 1.68 mmol, 1.0 eq.) in MeCN–H_2O (5:1) (6 ml) at RT. Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed only starting material **27**.

Attempted CAN Debenzylation of *N*,*N*-dibenzyl-*N*-ethylamine 28

Following representative procedure 2, CAN (613 mg, 1.12 mmol, 2.1 eq.) was added to **28** (120 mg, 0.53 mmol, 1.0 eq.) in MeCN–H_2O (5:1) (6 ml) at RT. Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed only starting material **28**.

Preparation of *N*-benzylpiperidine[47] 34

Piperidine (537 mg, 6.31 mmol), potassium carbonate (435 mg, 3.15 mmol) and benzyl bromide (1.13 g, 6.63 mmol) were suspended in ethanol (20 ml) and stirred for 5 hours. The reaction mixture was filtered, concentrated *in vacuo*, redissolved in Et_2O, washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give **34** as a pale yellow oil (867 mg, 79%). δ_H (200 MHz, $CDCl_3$) 1.48 (2H, m, C(4)H_2), 1.62 (4H, m, C(3)H_2 and C(5)H_2), 2.42 (4H, t, *J* 4.5, C(2)H_2 and C(6)H_2), 3.52 (2H, s, $PhCH_2N$), 7.32–7.35 (5H, br s, *Ph*).

Preparation of *N*-benzylpyrrole[48] 37

Following a literature procedure,[49] benzyl bromide (1.97 g, 11.5 mmol) was added to pyrrole (670 mg, 10.0 mmol), potassium *tert*-butoxide (1.29 g, 11.5 mmol) and 18-crown-6 (264 mg, 1.0 mmol) in Et_2O (25 ml). After work-up, purification by Kugelrohr distillation (1 mmHg, 100 °C) yielded **37** as an amber oil (1.11 g, 71%). δ_H (200 MHz, $CDCl_3$) 5.15 (2H, s, NCH_2Ph), 6.28 (2H, t, *J* 2.0, pyrrole C*H*), 6.75 (2H, m, pyrrole C*H*), 7.20 (2H, d, *J* 8.1, *Ph*), 7.43 (3H, m, *Ph*).

Attempted oxidative debenzylation of *N*-benzylpiperidine 34

Following representative procedure 2, CAN (971 mg, 1.77 mmol) was added to **34** (100 mg, 0.57 mmol) in 5:1 MeCN–H_2O (6 ml). Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction showed only starting material (88 mg, 88% recovery).

Attempted oxidative debenzylation of (*S*)-*N*-benzylproline ethyl ester 35

Following representative procedure 2, CAN (1.15 g, 2.1 mmol) was added to **35** (233 mg, 1.0 mmol) in 5:1 MeCN–H_2O (6 ml). Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction showed only starting material (151 mg, 65% recovery). Repetition of the reaction with CAN (2.30 g, 4.20 mmol, 4.2 eq.) and stirring for 72 hours also returned only starting material.

Attempted oxidative debenzylation of *N*-benzylpiperidin-4-one 36

Following representative procedure 2, CAN (1.15 g, 2.10 mmol) was added to **36** (189 mg, 1.00 mmol) in 5:1 MeCN–H_2O (6 ml). Following work-up, ^{1}H NMR spectroscopic analysis of the crude reaction showed only starting material (130 mg, 69% recovery).

Attempted oxidative debenzylation of *N*-benzylpyrrole 37

Following representative procedure 2, CAN (1.90 g, 3.46 mmol) was added to **37** (259 mg, 1.65 mmol) in 5:1 MeCN–H_2O (6 ml). Following work-up, ^{1}H NMR spectroscopic analysis of the crude product showed a complex mixture of predominantly polymeric material.

Preparation of *N*,*N*-dibenzylcinnamide[50] 38

Dibenzylamine (18.1 g, 94.5 mmol, 2.1 eq.) was added dropwise to cinnamoyl chloride (7.5 g, 45 mmol, 1.0 eq.) in DCM (200 ml) at 0 °C and allowed to warm to RT over three hours. The resultant solution was partitioned between H_2O and DCM (3 × 100 ml), dried and concentrated *in vacuo* to give a crude yellow solid which was recrystallised (EtOH) to give **38** (12.4 g, 84%) as white needles. δ_H (200 MHz, $CDCl_3$) 4.64, 4.73 (2 × 2H, s, $N(CH_2Ph)_2$), 6.92 (1H, d, *J* 15.4, C(2)*H*), 7.22–7.51 (15H, m, *Ph*), 7.88 (1H, d, *J* 15.4, C(3)*H*).

Preparation of *N*,*N*-dibenzyl-3-dibenzylamino-3-phenylpropionamide 39

Following representative procedure 1, *n*-butyllithium (2.5 M, 4.0 ml, 10.0 mmol), dibenzylamine (2.02 g, 10.2 mmol) in THF (20 ml) and **38** (2.09 g, 6.38 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (pentane–Et_2O 4:1), **39** as a colourless oil (3.25 g, 97%), ν_{max}/cm^{-1} (film) 3028 (C–H), 1645 (C=O), 1494, 1452; δ_H (400 MHz, $CDCl_3$) 3.04 (2H, d, *J* 7.4, CH_2CO), 3.34, 3.75 (2 × 2H, d, *J* 14.0, $N(CH_2Ph)_2$), 4.28 (2H, ABq, $PhCH_2NCO$), 4.53 (3H, m, $PhCH_2NCO$ and $PhCHCH_2$), 7.03–7.42 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 36.04, 48.17, 49.96, 54.59, 60.76, 126.45, 126.85, 127.26, 127.31, 127.56, 128.11, 128.22, 128.30, 128.46, 128.60, 128.83, 128.88, 129.86, 136.49, 137.25, 138.62, 140.01, 171.28; *m/z* (APCI$^+$) 525 (MH^+, 100%); HRMS (CI$^+$) MH^+ $C_{37}H_{37}N_2O$ requires 525.2906, found 525.2912.

Preparation of *N*,*N*-dibenzyl-3-benzylamino-3-phenylpropionamide 40

Following representative procedure 2, CAN (2.34 g, 4.26 mmol) was added to **39** (1.06 g, 2.03 mmol) in MeCN–H_2O (5:1) (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (Et_2O–pentane 2:3) to give **40** as a colourless oil (733 mg, 83%). ν_{max}/cm^{-1} (film) 3324 (N–H), 3029 (C–H), 1639 (C=O), 1452; δ_H (400 MHz, $CDCl_3$) 2.55 (1H, br s, N*H*), 2.86 (2H, m, CH_2CO), 3.69 (2H, ABq, $NHCH_2Ph$), 4.39 (3H, m, $PhCH_2NCO$ and $PhCHCH_2$), 4.63 (2H, ABq, $PhCH_2$-NCO), 7.10–7.47 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 41.8, 48.1, 49.8, 51.7, 59.7, 126.4, 126.9, 127.4, 127.5, 127.6, 128.2, 128.3, 128.4, 128.6, 128.7, 129.0, 136.2, 137.1, 140.5, 143.1,

171.8; *m/z* (APCI$^+$) 435 (MH$^+$, 100%); HRMS (CI$^+$) MH$^+$ $C_{30}H_{31}N_2O$ requires 435.2436, found 435.2448.

Preparation of *N*,*N*-dibenzyl(2-benzyloxyethyl)amine 42

To a stirred solution of 2-(*N*,*N*-dibenzylamino)ethanol **41** (289 mg, 1.20 mmol) and 18-crown-6 (50 mg) in THF (6 ml) was added potassium *tert*-butoxide (161 mg, 1.44 mmol) at RT. After 30 minutes, benzyl bromide (308 mg, 1.80 mmol) was added and stirring was continued for a further 16 hours. The reaction mixture was then poured into water (20 ml), extracted with Et_2O (3 × 20 ml), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (pentane–Et_2O 9:1) gave **42** as a colourless oil (200 mg, 50%). δ_H (400 MHz, $CDCl_3$) 2.78 (2H, t, *J* 6.0, NCH_2CH$_2$O), 3.64 (2H, t, *J* 6.0, NCH$_2$CH_2O), 3.70 (4H, s, 2 × NCH_2Ph), 4.50 (2H, s, OCH_2Ph), 7.24–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 52.8, 58.9, 69.0, 73.0, 126.8, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.6, 128.8, 138.4, 139.7; *m/z* (APCI$^+$) 332 (MH$^+$); HRMS (CI$^+$) $C_{23}H_{25}NO$ requires 332.2014, found 332.2018.

Preparation of *N*-benzyl(2-benzyloxyethyl)amine[51] 43

Following representative procedure 2, CAN (397 mg, 0.73 mmol) was added to **42** (60 mg, 0.18 mmol) in 5:1 MeCN–H_2O (4 ml). Following work-up, the residue was purified by column chromatography on silica gel (gradient elution pentane–Et_2O 9:1 to 1:1) to give **43** (32 mg, 74%) as a colourless oil. δ_H (200 MHz, $CDCl_3$) 2.87 (2H, t, *J* 5.1, NCH_2CH$_2$OBn), 3.62 (2H, *J* 5.0, NCH$_2$CH_2OBn), 3.82 (2H, s, PhCH_2N), 4.53 (2H, s, OCH_2Ph) 7.21–7.43 (10H, m, *Ph*).

Preparation of (2*S*)-benzyl 2-dibenzylaminopropanoate[52] 44

L-Alanine (1.78 g, 20 mmol), anhydrous potassium carbonate (8.29 g, 60.0 mmol) and benzyl bromide (10.3 g, 7.13 ml, 60.0 mmol) were suspended in DMF (10 ml). After stirring for 3 days, the reaction mixture was decanted, the supernatant partitioned between Et_2O (100 ml) and water (100 ml) and the aqueous phase extracted with Et_2O (50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield **44** as an amber oil (6.28 g, 87%) which was utilised for debenzylation reactions without further purification. δ_H (200 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.0, CH_3), 3.55 (1H, m, CH$_3$CHN), 3.62 (2H, d, *J* 13.9, 2 × NCH_AH$_B$Ph), 3.84 (2H, d, *J* 14.0, 2 × NCH$_A$$H_B$Ph), 5.20 (2H, ABq, CO$_2CH_2$Ph), 7.10–7.51 (15H, m, Ph).

Preparation of (2*S*)-benzyl 2-benzylaminopropanoate[30] 45

Following representative procedure 2, CAN (385 mg, 0.70 mmol) was added to **44** (120 mg, 0.34 mmol) in 5:1 MeCN–H_2O (6 ml). Following work-up, the residue was purified by column chromatography on silica gel (pentane–Et_2O 3:2) to give **45** as a colourless oil (85 mg, 96%). $[\alpha]_D^{23}$ −38.6 (*c* 1.0, MeOH), lit.[30] *(ent)* $[\alpha]_D^{25}$ +40.4 (*c* 1.0, MeOH); δ_H (200 MHz, $CHCl_3$) 1.35 (3H, d, *J* 7.2, CH_3), 3.44 (1H, q, *J* 7.0, CHCH$_3$), 3.74 (2H, ABq, NCH_2Ph), 5.19 (2H, s, CO$_2$CH$_2$Ph), 7.30 (5H, m, Ph), 7.39 (5H, m, Ph).

Preparation of (2*S*)-benzyl 3-(4-benzyloxyphenyl)-2-dibenzylaminopropanoate[52] 46

Following a literature procedure,[52] L-tyrosine (1.81 g, 10 mmol), anhydrous potassium carbonate (6.10 g, 44.0 mmol) and benzyl bromide (7.20 g, 5.00 ml, 42.0 mmol) in EtOH (20 ml) gave, after purification by column chromatography on silica gel (40–60 petrol–EtOAc 9:1) **46** as a colourless oil (5.21 g, 97%). $[\alpha]_D^{23}$ −54.5 (*c* 0.85, $CHCl_3$), lit.[52] $[\alpha]_D^{25}$ −57.0 (*c* 1.5, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 3.02 (2H, m, ArCH_2CHCO$_2$), 3.52 (2H, d, *J* 14.0, 2 × NCH_AH$_B$Ph), 3.67 (1H, t, *J* 7.4, ArCH$_2$CHCO$_2$), 3.93 (2H, d, *J* 14.1, 2 × NCH$_A$$H_B$Ph), 5.08 (2H, s, PhC$H_2$OAr), 5.19 (2H, ABq, CO$_2CH_2$Ph), 6.89 (4H, m, O*Ar*) 7.11–7.52 (20H, m, *Ph*).

Preparation of (2*S*)-benzyl 3-(4-benzyloxyphenyl)-2-benzylaminopropanoate 47

Following representative procedure 2, CAN (190 mg, 0.35 mmol) was added to **46** (90 mg, 0.17 mmol) in 5:1 MeCN–H_2O (5 ml). Following work-up, the residue was purified by column chromatography on silica gel (gradient elution, 30–40 petrol–Et_2O 7:3 to 1:1) to give **47** as a gum (68 mg, 91%). $[\alpha]_D^{24}$ −8.3 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 3408 (N–H), 1732 (C=O), 1512, 1454 (C–O), 1242, 1160 (C–O); δ_H (400 MHz, $CDCl_3$) 1.94 (1H, br s, NH), 2.97 (2H, m, ArCH_2CH(CO)N), 3.60 (2H, t, *J* 6.9, CH(CO)N), 3.68 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 5.06 (2H, s, PhC$H_2$OAr), 5.12 (2H, ABq, CO$_2CH_2$Ph), 6.89 (2H, d, *J* 8.5 OAr), 7.07 (2H, d, *J* 8.5, OAr), 7.25–7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 38.9, 52.0, 62.2, 66.4, 69.9, 114.7, 127.1, 127.5, 128.0, 128.2, 128.4, 128.4, 128.5, 128.6, 129.3, 130.3, 135.6, 137.1, 139.5, 157.6, 174.5; HRMS (CI$^+$) MH$^+$ $C_{30}H_{30}NO_3$ requires 452.2226, found 452.2224.

Preparation of (2*R*)-benzyl 3-benzylsulfanyl-2-dibenzylaminopropanoate 48

L-Cysteine hydrochloride monohydrate (878 mg, 5 mmol), anhydrous potassium carbonate (3.801 g, 27.5 mmol) and benzyl bromide (3.591 g, 21 mmol) were suspended in DMF (20 ml) and water (10 ml) was added. After stirring for 5 days, the mixture was partitioned between Et_2O (100 ml) and water (100 ml) and the combined organic fractions washed with water (4 × 50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (30–40 petrol–Et_2O 9:1) gave **48** as a pale yellow oil (1.84 g, 77%). $[\alpha]_D^{22}$ −41.6 (*c* 1.8, $CHCl_3$); ν_{max}/cm^{-1} (film) 3017 (C–H), 1731 (C=O), 1490, 1454 (C–O), 1151 (C–O); δ_H (400 MHz, $CDCl_3$) 2.70 (1H, dd, $J_{1A,1B}$ 13.5, $J_{1A,2}$ 7.3, SC(1)H_AH$_B$C(2)N), 2.82 (1H, dd, $J_{1B,1A}$13.5, $J_{1B,2}$8.1, SC(1)H$_A$$H_B$C(2)N), 3.46 (2H, br s, SCH_2-Ph), 3.49 (2H, d, *J* 14.0, 2 × NCH_AH$_B$Ph), 3.61 (1H, app. t, *J* 7.7, SCH$_2$CHN), 3.86 (2H, d, *J* 13.7, 2 × NCH$_A$$H_B$Ph), 5.19 (1H, d, *J* 12.3, OCH_AH$_B$Ph), 5.30 (1H, d, *J* 12.3, OCH$_A$$H_B$Ph), 7.09–7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.7, 36.0, 54.5, 60.4, 66.3, 126.9, 127.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 129.0, 129.7, 135.9, 136.0, 137.9, 139.1, 171.2; HRMS (CI$^+$) MH$^+$ $C_{31}H_{32}NO_2S$ requires 482.2154; found 482.2159.

Preparation of (2*R*)-benzyl 3-benzylsulfanyl-2-benzylaminopropanoate 49

Following representative procedure 2, CAN (238 mg, 0.44 mmol) was added to **48** (100 mg, 0.21 mmol) in 5:1 MeCN–H_2O (3 ml). Following work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 3:1) to give **49** (70 mg, 86%) as a colourless oil. $[\alpha]_D^{23}$ −21.9 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 3412 (N–H), 3025 (C–H), 1728 (C=O), 1489, 1452 (C–O), 1152 (C–O); δ_H (400 MHz, $CDCl_3$) 2.39 (1H, br, s, NH), 2.76 (2H, m, SCH_2CH(CO)N), 3.51 (1H, t, *J* 6.5, CH(CO)N), 3.67 (2H, s, SCH_2Ph), 3.69 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 5.19 (2H, ABq, CO$_2CH_2$Ph), 7.21–7.54 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.0, 36.5, 51.9, 59.9, 66.8, 127.1, 127.3, 128.3, 128.4, 128.5, 128.6, 128.9, 135.5, 137.8, 139.1, 173.3; HRMS (CI$^+$) $C_{24}H_{26}NO_2S$ requires 392.1684; found 392.1689.

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