An oxidatively-activated safety catch linker for solid phase synthesis†

Stephen G. Davies,* Duncan A. B. Mortimer, Andrew W. Mulvaney, Angela J. Russell, Hjalmar Skarphedinsson, Andrew D. Smith and Richard J. Vickers

Received 7th February 2008, Accepted 21st February 2008
First published as an Advance Article on the web 14th March 2008
DOI: 10.1039/b802204f

A *N*-benzyl-4-amino-2,2-dimethylbutanoic acid-based system has been developed as a new oxidatively activated safety catch linker for reaction monitoring and optimisation on solid support. The CAN promoted oxidative debenzylation of the tertiary *N*-benzylamine moiety, followed by concomitant cyclisation and release of alcohols and amines has been demonstrated both in solution phase model studies and on the solid phase. The linker system has been applied to the solid phase synthesis of a collection of phenol derivatives, and to the demonstration of the attachment and release of a chiral auxiliary from a solid support.

Introduction

Solid phase organic synthesis is an important strategy that has been widely applied to the parallel synthesis of large arrays of structurally similar molecules for high throughput screening in pharmacological assays.[1] The advancement of simple, selective and high yielding cleavage strategies is of paramount importance for the success of this approach.[2,3] Within this field, the safety catch principle, first introduced by Kenner *et al.*,[4] describes a linker that is stable to a derivatisation sequence before being selectively activated and subsequently releasing the desired product into solution. Numerous safety catch linkers have been developed and used to release a variety of functional groups into solution.[3,5–7] This strategy has been applied to a range of systems,[7] and even to the development of *in vivo* drug delivery systems that require enzyme activation.[8] Although a wide range of simple linkers and cleavage strategies for alcohols[9] and amines[10,11] have been developed, relatively few safety catch linkers have been described for the anchoring and release of alcohols.

We have previously shown that *N*-benzyl tertiary amines are susceptible to chemoselective *N*-debenzylation with CAN,[11] and considered this reaction ideal for the development of a novel oxidatively cleavable linker system for applications in solid phase synthesis. At the onset of these investigations, a number of features were incorporated into the linker design to enhance its stability under a range of reaction conditions yet facilitate cleavage and release from the resin. *gem*-Dimethyl substitution α- to the carbonyl group was incorporated to simultaneously protect against nucleophilic attack, render the carbonyl non-enolisable and promote 5-exo-trig cyclisation after oxidative cleavage using the Thorpe–Ingold effect,[12] giving the solid phase bound γ-lactam and releasing the product into solution (Fig. 1).

In this manuscript we demonstrate model studies in solution towards this goal, describe the realisation of this strategy on solid phase, its application to the parallel synthesis of a number of phenol derivatives, and preliminary investigations into its evaluation as an analytical tool in solid phase asymmetric synthesis.

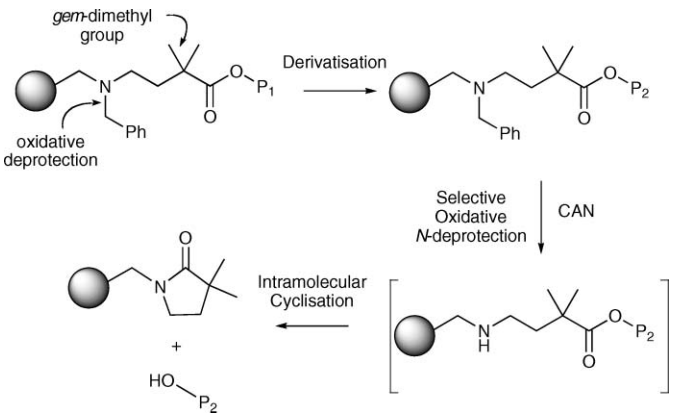


Fig. 1 Proposed oxidatively activated safety catch linker system.

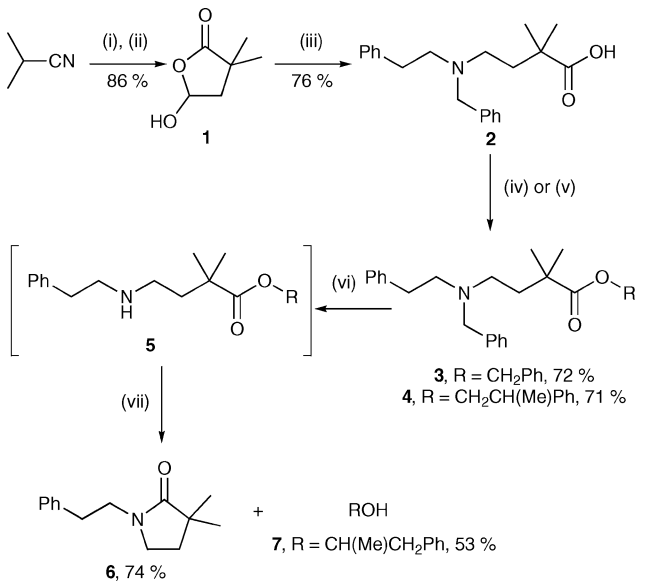
Results and discussion

Model solution phase studies

Initial studies focused upon the demonstration of this oxidatively cleavable linker strategy on a model solution phase system. Dihydrofuranone **1** was identified as a key intermediate in this sequence, and was prepared in two steps following literature protocols from commercially available *iso*-butyronitrile, reliably giving **1** in multi-gram quantitities. Installation of the oxidatively activated linker section was achieved by reductive amination of dihydrofuranone **1** with *N*-benzyl-*N*-phenylethylamine, affording acid **2** in good yield. Coupling of acid **2** with benzyl alcohol and 2-phenyl-propan-1-ol **7** using EDCI and HOBt gave the esters **3** and **4** in 72% and 71% yield respectively. The oxidative *N*-debenzylation and cyclisation of **3** with CAN, followed by heating at reflux gave quantitative conversion to lactam **6** after removal of benzyl alcohol *in vacuo*. *N*-Debenzylation of ester **4** with CAN followed by aqueous NaOH afforded amino ester **5**. Subsequent reflux in toluene to promote cyclisation and alcohol release gave a 50 : 50 mixture of **6** and **7**, with chromatographic purification giving lactam **6** in 74% yield and alcohol **7** in 53% yield (Scheme 1).

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: steve.davies@chem.ox.ac.uk

† Electronic supplementary information (ESI) available: Further experimental details. See DOI: 10.1039/b802204f



Scheme 1 *Reagents and conditions:* (i) LDA (1 eq.), THF, bromoacetaldehyde diethyl acetal (1 eq.), Δ, 16 h; (ii) HCl : AcOH : H_2O (20 : 10 : 5), Δ, 16 h; (iii) *N*-benzyl-*N*-phenylethylamine, MeOH, TMOF, 2 h rt then $NaBH_4$, 0 °C, 1 h, then rt, 16 h; (iv) Benzyl alcohol (3 eq.), EDCI, HOBt, DIPEA, CH_2Cl_2, rt, 16 h; (v) 1-phenyl-propan-2-ol **7** (3 eq.), EDCI, HOBt, DIPEA, CH_2Cl_2, rt, 16 h; (vi) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h, then NaOH (2 M, aq.); (vii) toluene, Δ, 16 h.

To probe the efficiency of this linker system in solution phase the coupling and subsequent cyclo-release of a range of amines was investigated. Activation of acid **2** with EDCI and HOBt and addition of benzylamine **18**, (*R*)-α-methylbenzylamine (*R*)-**19**, *N*-benzyl-*N*-methylamine **20** or *N*-benzylpiperazine **21** gave the corresponding amides **8–11** in moderate to good yields. However, treatment of acid **2** with *N*-benzyl-*N*-ethylamine under the same conditions only returned starting acid **2**. Treatment of acid **2** with 4-aminopiperidine was observed to give complete conversion to the secondary amide **13**, with none of the corresponding tertiary amide observed, demonstrating the capability of the linker to discriminate between primary and secondary amines.

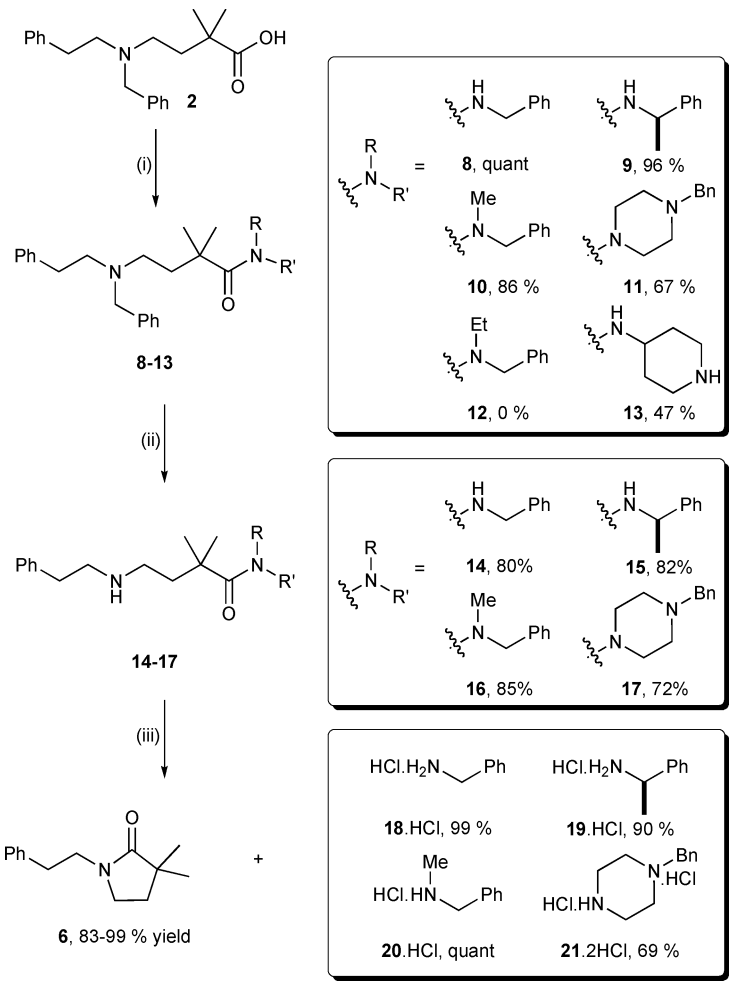
Treatment of **8** with CAN resulted in chemoselective *N*-debenzylation, giving amine **14** in 80% isolated yield, with subsequent reflux in toluene and treatment of the crude product mixture with HCl, followed by aqueous work-up, allowing the isolation of benzylamine hydrochloride **18**·HCl in 99% yield and lactam **6** in 97% yield. The application of this protocol to amides **9** and **10** also proved efficient, giving the corresponding amine hydrochlorides **19**·HCl and **20**·HCl in excellent yields, with no *N*-debenzylation of the intermediate *N*-methyl-*N*-benzylamide **16**, consistent with previous observations.[11] Treatment of **11** with CAN allowed the selective mono *N*-debenzylation of the acyclic tertiary amino group in the presence of the *N*-benzylpiperazine group to give **17**, again consistent with previous observations,[11] with subsequent reflux in toluene and treatment with HCl affording *N*-benzylpiperazine hydrochloride **21**·HCl in 69% yield. This process also proceeds without racemisation of (*R*)-**19**, as its specific rotation {$[\alpha]_D^{22}$ +2.6 (*c* 1.0, H_2O)}, was identical to an authentic sample, and consistent with the literature value {lit.[13] $[\alpha]_D^{22}$ +2.3 (*c* 2.9, H_2O)} (Scheme 2).

As a final solution phase model, the introduction of a reaction step capable of introducing diversity in a subsequent solid phase library was investigated. To this end, esterification of acid **2** to the corresponding 4-iodophenyl ester was investigated, as it was envisaged that derivatisation could be achieved by Suzuki coupling. Activation and esterification of acid **2** was achieved through treatment with EDCI and HOBt with excess 4-iodophenol, giving the desired 4-iodophenyl ester **22** in 82% yield. Suzuki coupling of ester **22** with phenylboronic acid using 20 mol% of $Pd_2(dba)_3$ gave the biaryl ester **23** (ν_{max} 1748 cm^{-1}) with complete conversion; the identity of biaryl ester **23** was unambiguously confirmed by treatment of acid **2** with excess 4-phenylphenol **24** under standard coupling conditions, giving **23** in 71% isolated yield after chromatography. To complete the model solution phase studies, *N*-debenzylation of ester **23** was accomplished by treatment with CAN (5 eq.) in THF : H_2O (8 : 1) and subsequent treatment with neutral alumina promoted spontaneous cyclisation in this case affording a 50 : 50 mixture of the lactam **6** and 4-phenylphenol **24**. Chromatographic purification facilitated their separation, giving lactam **6** (ν_{max} 1682 cm^{-1}) in 96% yield and 4-phenylphenol **24** in 92% yield (Scheme 3).

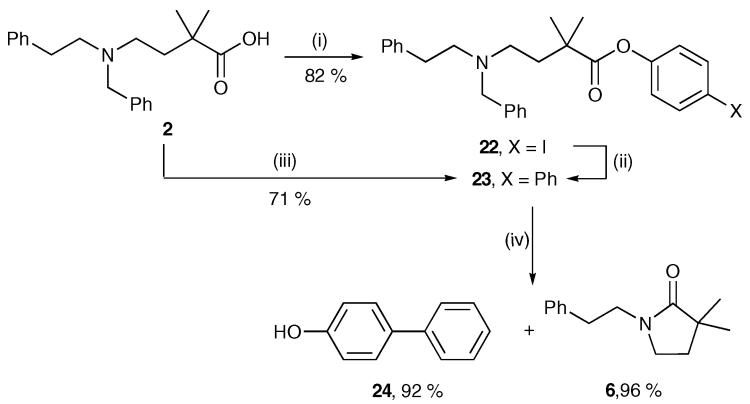
Solid phase synthesis: model studies

Having successfully demonstrated the concept of an oxidatively activated cleavage system in a model solution phase system, efforts were directed towards its adaptation to the solid phase. An approach designed to allow the loading of the polymer to be determined unambiguously was followed. Reductive amination of dihydrofuranone **1** with *N*-benzyl-*N*-butenylamine gave acid **25** in 81% yield, with subsequent esterification giving the corresponding 4-phenylphenol ester **26** (ν_{max} 1745 cm^{-1}) in 92% yield. Grafting of ester **26** to the polymer with bromopolystyrene resin using a Suzuki–Miyaura cross coupling was next investigated. Treatment of ester **26** with 9-BBN at 0 °C, followed by the addition of prewashed bromopolystyrene resin (Argonaut Technologies,[14] polymer loading: 3.22 mmol g^{-1}) with 9% $Pd(OAc)_2$ and DPPF gave, after subsequent washing, the solid supported ester **27** (ν_{max} 1748 cm^{-1}). To determine the polymer loading, ester **27** was saponified by treatment with LiOH in THF : H_2O (8 : 1) under reflux, giving both 4-phenylphenol **24** and polymer supported acid **28** (ν_{max} 1713 cm^{-1}) in quantitative yield, consistent with a polymer loading of 1.73 mmol g^{-1} (Scheme 4). The designed enhanced stability of the ester towards basic hydrolysis, conferred by the *gem*-dimethyl substitution α- to the carbonyl, is illustrated by the forcing conditions necessary for complete saponification.

The ability of **27** to undergo debenzylation and cyclo-release from the solid support was next investigated. Treatment of **27** with 5 equivalents of CAN in THF : H_2O (8 : 1), followed by washing, gave a yellow resin that was dried *in vacuo* to a constant mass. IR investigations of this polymer revealed the presence of an ester bond (ν_{max} 1746 cm^{-1}), allowing its assignment as **29**. Investigations in the solution phase model system had demonstrated that intermediates such as **29** undergo cyclisation under mild conditions and a base promoted cyclisation to lactam **30** at rt was therefore investigated. Treatment of **29** with CH_2Cl_2 : NEt_3 (5 : 1) gave 4-phenylphenol **24** in 78% yield after work-up, with IR investigations of the remaining resin indicating complete conversion of **29** (ν_{max} 1746 cm^{-1}) to the polymer bound lactam **30**



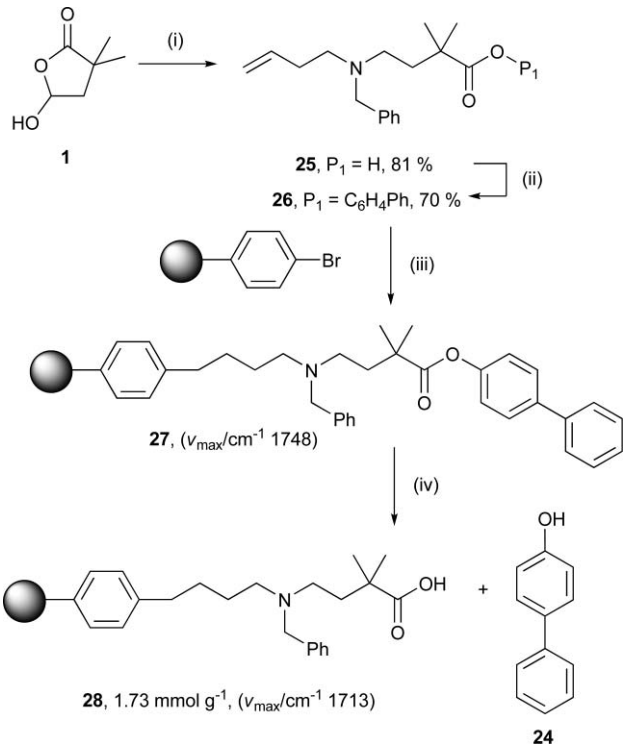
Scheme 2 *Reagents and conditions:* (i) amine (3–4 eq.), EDCI, HOBt, DIPEA, CH_2Cl_2 or DMF, rt, 16 h; (ii) CAN (5 eq.), THF : H_2O (8 : 1), rt 16 h, then NaOH (2 M, aq.); (iii) Δ, toluene, 48 h then HCl.



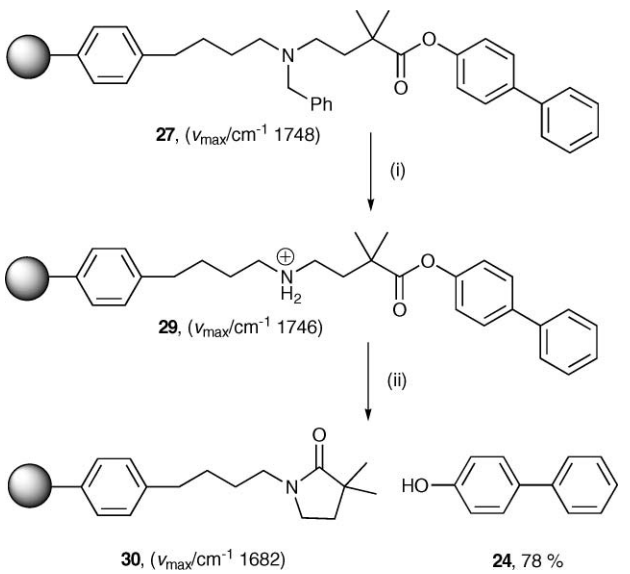
Scheme 3 *Reagents and conditions:* (i) 4-iodophenol (5 eq.), EDCI (1.5 eq.), HOBt (2 eq.), DIPEA (3 eq.), CH_2Cl_2, rt, 16 h; (ii) phenylboronic acid (2 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (2.5 eq.), DMF, rt, 24 h; (iii) 4-phenylphenol (4 eq.), EDCI (2.5 eq.), HOBt (2 eq.), DIPEA (4 eq.), CH_2Cl_2, rt, 16 h; (iv) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h then Al_2O_3.

(ν_{max} 1682 cm^{-1}) (Scheme 5). Although base promoted cyclisation and release from the polymer support incurs another reaction step in this strategy, this could be beneficial for product purity as it allows its controlled release into solution. Furthermore, this allows the inorganic CAN residues to be washed from the polymer matrix before product release, preventing any undesired side reactions with the released product.

Having demonstrated the use of the linker system for the release of 4-phenylphenol **24** from the solid phase, the utility of this protocol for the attachment and release of benzylamine **18** was

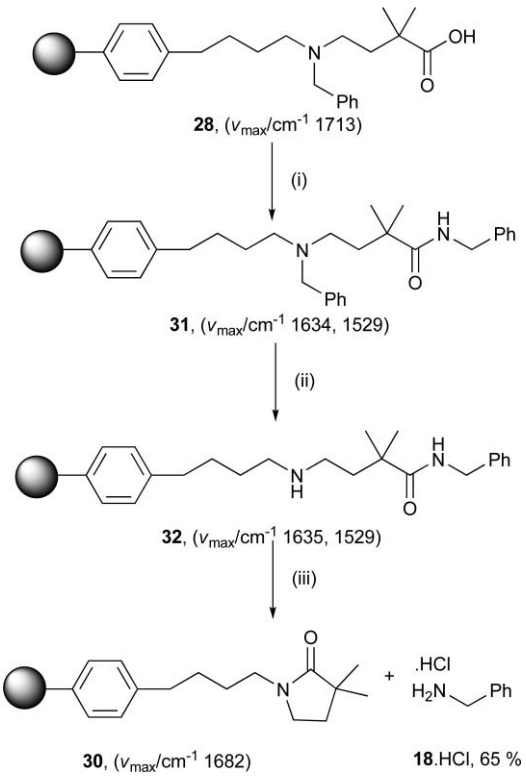


Scheme 4 *Reagents and conditions:* (i) *N*-benzyl-*N*-butenylamine, MeOH, TMOF, $NaBH_4$; (ii) HOC_6H_4Ph (3 eq.), EDCI (2 eq.), HOBT (2 eq.), CH_2Cl_2, rt; (iii) phenylboronic acid (5 eq.), $Pd(OAc)_2$ (9 mol%), DPPF (0.11 eq.), K_2CO_3 (5 eq.), DMF, 70 °C, 48 h; (iv) LiOH (10 eq.), THF : H_2O (8 : 1), Δ.



Scheme 5 *Reagents and conditions:* (i) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h; (ii) CH_2Cl_2 : NEt_3 (5 : 1), rt, 30 min.

investigated. Solid supported carboxylic acid **28** was activated with DIC–HOBt and treated with excess benzylamine **18** (6 eq.) to afford the polymer supported *N*-benzylamide **31** that exhibited similar IR properties (ν_{max} 1634 cm^{-1}, 1529 cm^{-1}) to the solution phase analog **8** (ν_{max} 1643 cm^{-1}, 1529 cm^{-1}). Treatment of **31** with CAN followed by aqueous NaOH gave a polymer **32** (ν_{max} 1635 cm^{-1}, 1529 cm^{-1}), which was heated in toluene to promote cyclisation, resulting in complete conversion to lactam **30** (ν_{max} 1682 cm^{-1}). The released amine was subsequently converted to its hydrochloride salt **18**·HCl and isolated in 65% yield (Scheme 6).

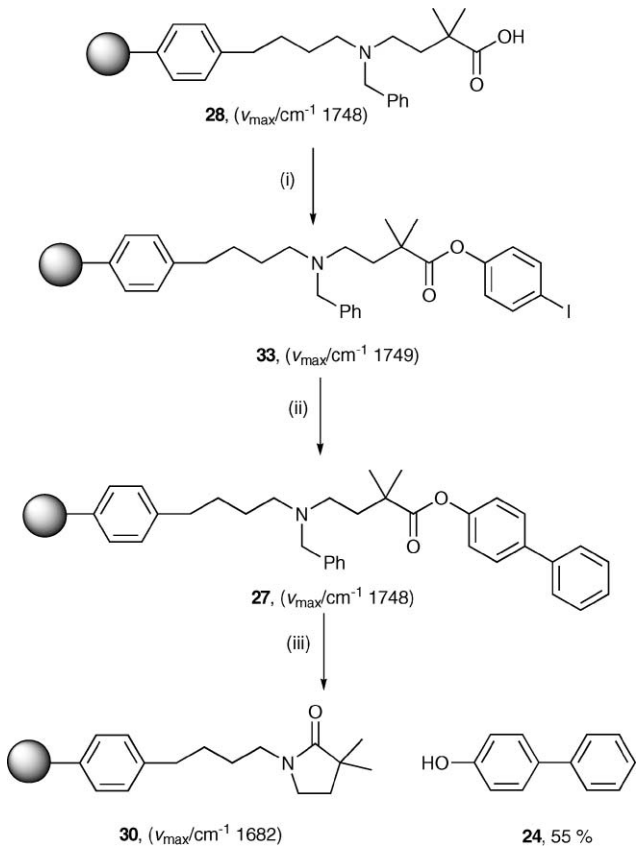


Scheme 6 *Reagents and conditions:* (i) benzylamine **18** (6 eq.), DIC (3 eq.), HOBt (3 eq.), DIPEA (6 eq.), CH_2Cl_2, rt, 16 h; (ii) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h, then NaOH (2 M, aq.); (iii) Δ, toluene, 48 h.

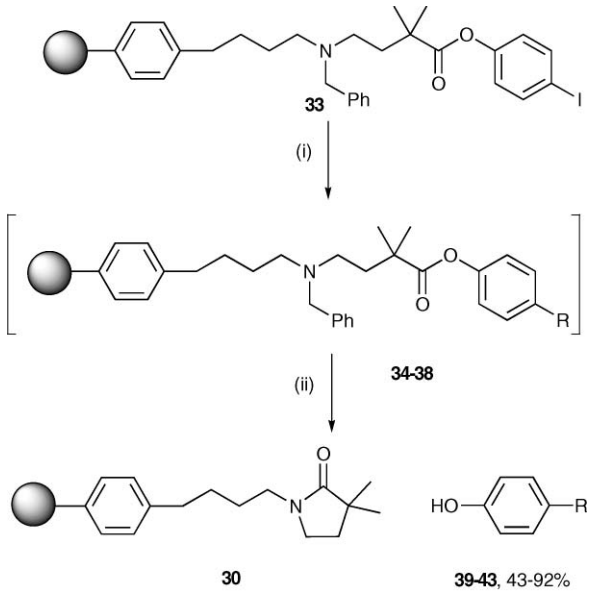
Cross-coupling reactions and cyclo-release on solid phase: library synthesis

Further studies focused upon the performance of cross coupling reactions on the solid phase to prepare 4-phenylphenol **24**. Treatment of polymer bound carboxylic acid **28** with DIC–HOBt and 4-iodophenol (10 eq.) gave quantitative conversion by mass to the desired 4-iodophenyl ester resin **33** (ν_{max} 1749 cm^{-1}). Suzuki coupling of 4-iodophenyl ester resin **33** with phenylboronic acid at 70 °C and subsequent treatment of the product resin **27** with 5 equivalents of CAN afforded 4-phenylphenol **24** in 55% isolated yield. Significantly, under these optimised conditions, no 4-iodophenol was detected upon cyclorelease indicating complete conversion, with IR analysis of the residual resin indicating the presence of the polymer-supported lactam **30** (ν_{max} 1682 cm^{-1}) (Scheme 7).

Following these successful solid phase transformations, attention turned to the preparation of a small pilot library of phenols including biphenols **42** and **43** and terphenol **39** that have been evaluated as ligands for the β-estrogen receptor in an analogous library synthesis of 4-hydroxy biphenyls.[15] A diverse range of arylboronic acids incorporating electron donating and withdrawing substituents were chosen for this Suzuki coupling strategy, whose products were anticipated to be tolerant towards oxidative debenzylation with CAN and subsequent cyclo-release



Scheme 7 *Reagents and conditions:* (i) 4-iodophenol (10 eq.), DIC (3 eq.), HOBt (4 eq.), DIPEA (8 eq.), CH_2Cl_2, rt, 16 h; (ii) phenylboronic acid (5 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (5 eq.), DMF, 70 °C, 48 h; (iii) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h, then CH_2Cl_2 : NEt_3 (5 : 1), rt, 30 min.



	R	Yield (%)	HPLC purity (%)
39		51	92
40	CHO	79	90
41	CHO	74	91
42	OMe	43	89
43	F_3C	74	59

Scheme 8 *Reagents and conditions:* (i) aryl boronic acid $(HO)_2BR$ (5 eq.), $Pd_2(dba)_3$ (0.2 eq.), K_2CO_3 (5 eq.), DMF, 70 °C, 48 h; (ii) CAN (5 eq.), THF : H_2O (8 : 1), rt, 16 h, then CH_2Cl_2 : NEt_3 (5 : 1), rt, 30 min.

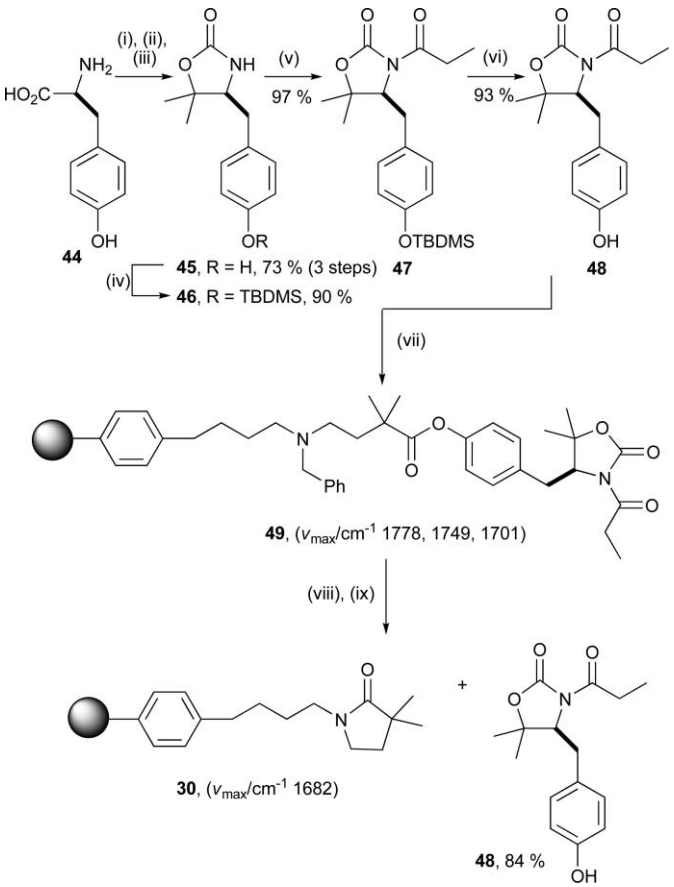
from the safety catch linker. Under standard conditions, treatment of resin **33** with a range of arylboronic acids under Pd catalysis and treatment of the resulting resins **34–38** with CAN gave the desired phenols **39–43** in 43–92% isolated yield and in generally high HPLC purity (Scheme 8).

Towards an oxidatively cleavable solid supported chiral auxiliary system

Having demonstrated the applicability of this safety catch protocol to the solid phase synthesis of a small number of phenol derivatives, subsequent studies were directed towards the incorporation of a chiral auxiliary into the safety catch linker. Oxazolidin-2-one based chiral auxiliaries have found widespread use in solution phase asymmetric synthesis due to their efficiency in a broad range of stereoselective manipulations[16] and their accessibility from readily available α-amino acids.[17] Much effort has been made to immobilise oxazolidine-2-one based chiral auxiliaries on polymer supports,[18] with Burgess having shown that a tyrosine derived oxazolidinone requires a Wang linker as the optimal support.[19] This tyrosine derived oxazolidinone has since been applied to a range of stereoselective transformations on solid phase including aldol reactions, conjugate addition, Diels–Alder and 1,3-dipolar cycloadditions,[20] although these reactions are difficult to optimise due to problems in reaction monitoring.[19] Calmès *et al.* first demonstrated in 2001 that a suitable labile linker system could be used to allow cleavage of a chiral auxiliary attached to the solid phase at any point in the reaction sequence, allowing simple and straightforward reaction monitoring, thus facilitating optimisation.[21] This concept has contemporaneously been applied by us,[22] and recently by Bull *et al.*[23] to the development of a labile linker for an oxazolidinone derived solid-supported chiral auxiliary. The safety catch linker described herein was also proposed to be a suitable system for application in the optimisation of such solid phase asymmetric transformations.

Tyrosine derived SuperQuat 5,5-dimethyloxazolidinone **45** was therefore prepared following our established literature procedure in 73% yield.[24] *O*-Silylation of **45** gave **46** in 90% yield after recrystallisation, with subsequent deprotonation with *n*-BuLi and acylation with propanoyl chloride affording *O*-TBDMS protected **47** in 97% yield (88% over two steps). Silyl deprotection of **47** with TBAF in THF subsequently afforded the *N*-propanoyl SuperQuat **48** in 93% yield. SuperQuat **48** was next readily attached to the solid supported carboxylic acid **28** using standard protocols, with IR analysis of the resin **49** revealing three bands in the carbonyl region {ν_{max} 1778 cm^{-1} (endocyclic), 1749 cm^{-1} (ester) and 1701 cm^{-1} (exocyclic)}. The debenzylation and cyclorelease protocol was

then examined, with treatment of **49** with CAN (5 eq.), followed by washing with THF and water to remove inorganic residues. The desired cyclisation was promoted by treatment with NEt_3 in CH_2Cl_2, affording *N*-propanoyl SuperQuat **48** in 84% yield, thus demonstrating that the ester linkage may be selectively cleaved in the presence of the *N*-acyloxazolidinone to release the chiral auxiliary into solution (Scheme 9).



Scheme 9 *Reagents and conditions:* (i) $SOCl_2$, MeOH, Δ then Boc_2O, $NaHCO_3$, EtOH, rt; (ii) MeMgBr (5 eq.), THF, −78 °C to rt; (iii) ^{t}BuOK, THF, Δ; (iv) TBDMSCl, imidazole, CH_2Cl_2, rt, 24 h; (v) *n*-BuLi, −78 °C, THF, then CH_3CH_2COCl; (vi) TBAF, THF, 1 h; (vii) **28**, EDCI, HOBt, DIPEA, CH_2Cl_2, 20 h; (viii) CAN (5 eq.), THF : H_2O (8 : 1), rt, 5 h; (ix) CH_2Cl_2 : NEt_3 (5 : 1), rt, 30 min.

In conclusion, we have developed a novel, oxidatively activated safety catch linker system that has been applied to the solid phase synthesis of a range of phenols. The attachment and release of a chiral auxiliary from the solid phase using this linker system has also been demonstrated. Current studies are underway to apply this methodology to a range of asymmetric protocols on the solid phase.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen or argon before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[25] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or Na_2SO_4 as stated. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded on either a Perkin-Elmer Paragon 1000 FT-IR spectrometer or a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz), AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz), Bruker DPX 250 (^{1}H: 250 MHz) or Varian 200 (^{1}H: 200 MHz) spectrometers in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. The field was locked by external referencing to the relevant deuteron resonance. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Reverse-phase HPLC was carried out on a Gilson instrument comprising of Gilson 306 pumps, Gilson 811C dynamic mixer, Gilson 806 manomeric module with automated injection on a Gilson 215 liquid handler, configured with a Gilson 819 valve actuator. Separations were performed on a Hypersil® Elite C18 column (5 μm particle size, 150 × 4.6 mm). All experiments were performed under gradient elution with deionised H_2O (containing 0.1% TFA) and MeCN, starting from 95% H_2O, 5% MeCN to 5% H_2O, 95% MeCN over 8 minutes then isocratic for 4 minutes. The flow rate was 1.0 mL min^{-1}. Detection was at λ 220, 254 and 290 nm with a Gilson 170 Diode Array Detector with equipment control and data collection managed by Gilson Unipoint LC software version 3.01. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyaniline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General experimental procedures

Representative Procedure 1: carbodiimide coupling reactions in solution. To a solution of the requisite carboxylic acid in CH_2Cl_2 or DMF was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred at room temperature for 16 hours. The

resulting solution was partitioned with 10% aqueous HCl and then 2 M aqueous NaOH. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* before purification as described.

Representative Procedure 2: CAN oxidation in solution. CAN (5.0 eq.) was added to a stirred solution of the requisite tertiary amine (1.0 eq.) in THF : H_2O (8 : 1) or MeCN : H_2O (5 : 1) and stirred for 16 hours at room temperature. The reaction was quenched with either a 2 M aqueous solution of NaOH or saturated aqueous bicarbonate solution ($NaHCO_3$) and extracted into ether or CH_2Cl_2. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the resulting crude product purified as described.

Representative Procedure 3: carbodiimide coupling reactions on polymer support. To a suspension of the requisite carboxylic acid in CH_2Cl_2 was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred at room temperature for 16 hours. The resin was transferred to a sintered funnel, washed repeatedly with DMF, MeOH and CH_2Cl_2 then dried to a constant mass *in vacuo.*

Representative Procedure 4: Suzuki couplings on polymer support. To a stirred suspension of the polymer supported 4-iodophenyl ester (1.0 eq.) in DMF, boronic acid (4.0 eq.) and K_2CO_3 (5.0 eq.) was added Pd_2dba_3 (0.20 eq.) in 2 or 3 portions over 36 hours at 70 °C. The resin was transferred to a sintered funnel, washed repeatedly with DMF, water, THF and CH_2Cl_2 and then dried to a constant mass *in vacuo.*

Representative Procedure 5: CAN oxidation on polymer support. CAN (5.0 eq.) was added to a stirred suspension of the requisite resin (1.0 eq.) in THF : H_2O (8 : 1). After stirring for 16 hours the resin was transferred to a sintered funnel and washed repeatedly with THF, water, THF and CH_2Cl_2. The resin was then treated with CH_2Cl_2 : NEt_3 (5 : 1) and the filtrate was concentrated *in vacuo.* The resulting residue was filtered through a plug of silica (EtOAc eluent) and the solvent removed *in vacuo.* The resin was dried *in vacuo* to a constant mass.

2″-Phenylprop-1″-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]butanoate (4). Following Representative Procedure 1, to a stirred solution of **2** (544 mg, 1.67 mmol, 1.0 eq.), 2-phenylpropan-1-ol **7** (0.701 mL, 5.02 mmol, 3.0 eq.), HOBt (452 mg, 3.35 mmol, 2.0 eq.) and DIPEA (0.878 mL, 5.02 mmol, 3.0 eq.) in CH_2Cl_2 (20 mL) was added EDCI (481 mg, 2.51 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and washed with 10% aqueous HCl (30 mL) and 2 M aqueous NaOH solution (30 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography on silica gel (EtOAc : petrol, 1 : 9) afforded the title compound **4** as a colourless oil (525 mg, 71%); ν_{max}/cm^{-1} (film) 1726; δ_H (400 MHz, $CDCl_3$) 1.12 (6H, s, CMe_2), 1.31 (3H, d, *J* 7.0, C(3″)H_3), 1.71–1.75 (2H, m, C(3)H_2), 2.44–2.48 (2H, m, C(4)H_2), 2.64–2.79 (4H, m, C(1′)H_2 and C(2′)H_2), 3.04–3.13 (1H, m, C(2″)*H*), 3.62 (2H, s, NCH_2Ph), 4.06–4.22 (2H, m, C(1″)H_2), 7.16–7.47 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1, 25.3, 33.5, 37.2, 39.0, 41.3, 49.5, 55.4, 58.4, 69.2, 125.9, 126.6, 126.8, 127.3, 128.2, 128.3, 128.4, 128.8, 139.5, 140.6, 143.2, 177.5; *m*/*z* (ESI$^+$) 444 (MH$^+$, 100%); HRMS $C_{30}H_{38}NO_2$ (MH$^+$) requires 444.2903; found 444.2905.

***N*-(2′-Phenylethyl)-3,3-dimethyl-pyrrolidin-2-one 6 and 2-phenylpropan-1-ol (7).** Following Representative Procedure 2, CAN (494 mg, 0.903 mmol, 5.0 eq.) was added to a stirred solution of **4** (80 mg, 0.181 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (6 mL). After 3 hours the mixture was partitioned with 2 M aqueous NaOH solution (5 mL) and ether (20 mL). The aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford 2″-phenylprop-1″-yl 2,2-dimethyl-4-[*N*-(2′-phenylethyl)amino]butanoate **5**. The crude residue was refluxed in toluene for 16 hours. The solvent was removed and separation by column chromatography on silica gel (EtOAc : petrol, 1 : 9–4 : 6, stepwise elution) afforded 2-phenylpropan-1-ol **7** (13 mg, 53%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.9, CH_3CHPh), 2.93–3.01 (1H, m, CH_3C*H*Ph), 3.72 (2H, d, *J* 6.8, CH_2OH), 7.20–7.40 (5H, m, *Ph*); further elution afforded **6** as a colourless oil (29 mg, 74%); ν_{max}/cm^{-1} (film) 1685; δ_H (400 MHz, $CDCl_3$) 1.08 (6H, s, CMe_2), 1.77 (2H, t, *J* 6.8, C(4)H_2), 2.85 (2H, t, *J* 7.4, C(2′)H_2), 3.12 (2H, t, *J* 6.8, C(5)H_2), 3.54 (2H, t, *J* 7.4, C(1′)H_2), 7.20–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5, 33.7, 34.2, 40.5, 43.9, 44.1, 126.4, 128.4, 128.7, 138.8, 179.4; *m*/*z* (ESI$^+$) 218 (MH$^+$, 100%); HRMS $C_{14}H_{20}NO$ (MH$^+$) requires 218.1545; found 218.1548.

***N*-Benzyl-2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]-butanamide (8).** Following Representative Procedure 1, to a stirred solution of **2** (3.20 g, 9.83 mmol, 1.0 eq.), benzylamine **18** (3.22 mL, 29.5 mmol, 3.0 eq.), HOBt (2.66 g, 19.7 mmol, 2.0 eq.) and DIPEA (6.88 mL, 39.3 mmol, 4.0 eq.) in CH_2Cl_2 (100 mL) was added EDCI (2.45 g, 12.8 mmol, 1.3 eq.). The resulting solution was stirred for 16 hours then washed with 10% aqueous HCl (150 mL) and 2 M aqueous NaOH solution (150 mL), then dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography on silica gel (MeOH : $CHCl_3$, 2 : 98) afforded the title compound **8** as a yellow viscous oil (4.08 g, 100%); ν_{max}/cm^{-1} (film) 3351, 1643, 1529; δ_H (400 MHz, $CDCl_3$) 1.20 (6H, s, CMe_2), 1.76 (2H, t, *J* 7.4, C(3)H_2), 2.55 (2H, t, *J* 7.4, C(4)H_2), 2.65–2.76 (4H, m, C(1′)H_2 and C(2′)H_2), 3.63 (2H, s, NCH_2Ph), 4.40 (2H, d, *J* 5.4, NHCH_2Ph), 6.65 (1H, t, *J* 5.4, N*H*CH$_2$Ph), 7.12–7.47 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.1, 33.1, 37.6, 41.5, 43.5, 49.6, 55.4, 58.4, 125.9, 126.9, 127.4, 127.8, 128.2, 128.3, 128.7, 128.7, 129.0, 138.8, 139.1, 140.4, 177.3; *m*/*z* (ESI$^+$) 415 (MH$^+$, 100%); HRMS $C_{35}H_{35}N_2O$ (MH$^+$) requires 415.2749; found 415.2754.

***N*-Benzyl-2,2-dimethyl-4-[*N*-(2′-phenylethyl)amino]butanamide (14).** Following Representative Procedure 2, CAN (6.15 g, 11.2 mmol, 5.0 eq.) was added to a stirred solution of **8** (929 mg, 2.24 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (90 mL). After 16 hours the mixture was partitioned between 2 M aqueous NaOH solution (100 mL) and ether (200 mL). The aqueous layer was extracted with ether (200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography on silica gel (MeOH : $CHCl_3$, 2 : 98–3 : 7, stepwise elution) afforded the title compound **14** as a colourless oil (579 mg, 80%); ν_{max}/cm^{-1} (film) 3339, 1641, 1532; δ_H (400 MHz, $CDCl_3$) 1.20 (6H, s, CMe_2), 1.72 (2H, t, *J* 7.4, C(3)H_2), 2.21 (1H, br s, N*H*), 2.62 (2H, t, *J* 7.4, C(4)H_2), 2.69–2.82 (4H, m, C(1′)H_2 and C(2′)H_2), 4.40 (2H, d, *J* 5.6, NHCH_2Ph), 6.97 (1H, t, *J* 5.6, N*H*CH$_2$Ph), 6.97–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.2, 36.0, 40.3, 41.5, 43.6, 45.6, 50.9, 126.2, 127.3, 127.7, 128.5, 128.6,

128.7, 138.7, 139.6, 177.5; *m/z* (ESI$^+$) 325 (MH$^+$, 100%); HRMS $C_{21}H_{29}N_2O$ (MH$^+$) requires 325.2280; found 325.2278.

***N*-(2′-Phenylethyl)-3,3-dimethyl-pyrrolidin-2-one (6) and benzylamine hydrochloride (18·HCl).** **14** (210 mg, 0.648 mmol, 1.0 eq.) was refluxed in toluene (20 mL) for 16 hours. The organic layer was washed with 10% aqueous HCl (10 mL). The organic layer was concentrated *in vacuo.* The resultant residue was partitioned between CH_2Cl_2 (20 mL) and the retained aqueous layer. The organic layer was washed with 10% aqueous HCl (10 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **6** (136 mg, 97%) with identical physical and spectroscopic properties to those described above. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford benzylamine hydrochloride **18**·HCl as a white crystalline solid (92 mg, 99%); mp 258–260 °C (lit.[26] 261–262 °C); δ_H (200 MHz, CD_3OD) 4.16 (2H, s, NCH_2Ph), 7.45–7.52 (5H, m, *Ph*).

4″-Iodophenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)-amino]butanoate (22). Following Representative Procedure 1, to a stirred solution of **2** (1.50 g, 4.61 mmol, 1.0 eq.), 4-iodophenol (5.08 g, 23.1 mmol, 5.0 eq.), HOBt (1.25 g, 9.23 mmol, 2.0 eq.) and DIPEA (2.42 mL, 13.8 mmol, 3.0 eq.) in CH_2Cl_2 (60 mL) was added EDCI (1.33 g, 6.92 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours then washed with 10% aqueous HCl (60 mL) and 2 M aqueous NaOH solution (60 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography on silica gel (MeOH : $CHCl_3$, 2 : 98) afforded the title compound **22** as a colourless oil (1.99 g, 82%); ν_{max}/cm^{-1} (film) 1752; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, s, CMe_2), 1.88–1.92 (2H, m, C(3)H_2), 2.58–2.62 (2H, m, C(4)H_2), 2.75–2.84 (4H, m, C(1′)H_2 and C(2′)H_2), 3.66 (2H, s, NCH_2Ph), 6.65–6.68 (2H, m, *Ar*), 7.16–7.57 (10H, m, *Ph*), 7.70–7.72 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.4, 33.5, 37.3, 41.6, 49.4, 55.6, 58.5, 89.5, 123.8, 125.9, 126.9, 128.3, 128.8, 128.8, 138.4, 139.4, 140.5, 150.8, 175.9; *m/z* (ESI$^+$) 528 (MH$^+$, 100%); HRMS $C_{27}H_{31}NO_2$ (MH$^+$) requires 528.1400; found 528.1403.

4″-Biphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]-butanoate (23).

Method A. Following Representative Procedure 1, to a stirred solution of **2** (326 mg, 1.00 mmol, 1.0 eq.), 4-phenylphenol **24** (683 mg, 4.00 mmol, 4.0 eq.), HOBt (271 mg, 2.00 mmol, 2.0 eq.) and DIPEA (0.702 mL, 4.00 mmol, 4.0 eq.) in CH_2Cl_2 (25 mL) was added EDCI (481 mg, 2.50 mmol, 2.5 eq.) portionwise over 24 hours. The resulting solution was washed with 10% aqueous HCl (25 mL) and 2 M aqueous NaOH solution (25 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography on silica gel (EtOAc : petrol, 1 : 9–2 : 8, stepwise elution) afforded the title compound **23** as a white waxy solid (341 mg, 71%); ν_{max}/cm^{-1} (film) 1748; δ_H (400 MHz, $CDCl_3$) 1.37 (6H, s, CMe_2), 1.95–1.99 (2H, m, C(3)H_2), 2.67–2.71 (2H, m, *C*(4)H_2), 2.79–2.88 (4H, m, C(1′)H_2 and C(2′)H_2), 3.75 (2H, s, NCH_2Ph), 7.03–7.05 (2H, m, *Ar*), 7.21–7.62 (17 H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 33.3, 37.2, 41.5, 49.4, 55.5, 58.4, 121.7, 125.4, 125.9, 126.9, 127.1, 127.2, 128.0, 128.2, 128.2, 128.7, 128.8, 138.7, 139.3, 140.3, 140.4, 150.2, 176.2; *m/z* (ESI$^+$) 478 (MH$^+$, 100%); HRMS $C_{33}H_{36}NO_2$ requires (MH$^+$) 478.2746; found 478.2740.

Method B. To a stirred solution of **22** (393 mg, 0.746 mmol, 1.0 eq.), K_2CO_3 (257 mg, 1.86 mmol, 2.5 eq.) and phenylboronic acid (182 mg, 1.49 mmol, 2.0 eq.) in DMF (20 mL) was added portionwise over 20 hours $Pd_2(dba)_3$ (136 mg, 0.149 mmol, 0.20 eq.). After 24 hours the solvent was removed *in vacuo* and the resulting residue partitioned between water (40 mL) and CH_2Cl_2 (80 mL). The aqueous layer was extracted with CH_2Cl_2 (80 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil (247 mg). Attempted purification by column chromatography (EtOAc : petrol, 1 : 9–2 : 8) afforded a mixture, inseparable by column chromatography, of dibenzylideneacetone and **23**, with identical physical and spectroscopic properties to those described above.

***N*-(2′-Phenylethyl)-3,3-dimethyl-pyrrolidin-2-one (6) and 4-phenylphenol (24).** CAN (419 mg, 0.765 mmol, 5.0 eq.) was added to a solution of **23** (73 mg, 0.153 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (4 mL) and the resulting mixture stirred for 16 h. Filtration through a small plug of aluminium oxide (neutral) using EtOAc as the eluting solvent afforded a *ca.* 50 : 50 mixture of **6** and **24**. Separation by column chromatography on silica gel (EtOAc : petrol, 2 : 98–8 : 2, stepwise elution) afforded lactam **4** as a colourless oil (32 mg, 96%) with identical physical and spectroscopic properties to those described above. Further elution afforded 4-phenylphenol **24** as a white crystalline solid (24 mg, 92%); mp 158–160 °C (lit.[27] 166–167 °C); δ_H (400 MHz, $CDCl_3$) 4.89 (1H, br s, O*H*), 6.89–6.96 (2H, m, *Ar*), 7.27–7.58 (7H, m, *Ar*).

4‴-Biphenyl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)-butyl]amino}butanoate (27).

Method A. A solution of 9-BBN (42.5 mL, 21.3 mmol, 0.5 M in THF, 2.2 eq.) was added dropwise to a stirred solution of **26** (8.28 g, 19.3 mmol, 2.0 eq.) in THF (25 mL) at 0 °C. Stirring was continued for 1 hour at 0 °C and 4 hours at room temperature. Bromopolystyrene resin (3.00 g, 9.66 mmol, Argonout Technologies,[14] 3.22 mmol g^{-1}, 106 μm, 1.0 eq.) was washed repeatedly with DMF, THF and CH_2Cl_2 and dried *in vacuo* for 3 hours. The catalyst was prepared separately by the following procedure: DPPF (589 mg, 1.06 mmol, 0.11 eq.) was dissolved in DMF (20 mL), $Pd(OAc)_2$ (195 mg, 0.869 mmol, 0.090 eq.) was then added and the solution degassed before heating at 60 °C for 30 min. The hydroboration mixture was concentrated under reduced pressure to 5 ml and transferred to the flask containing the prewashed bromopolystyrene resin *via* cannula followed by K_2CO_3 (3.34 g, 24.2 mmol, 2.5 eq.). The catalyst was transferred to the resin suspension *via* cannula and the resulting mixture heated under nitrogen at 60 °C for 18 hours. The resin was transferred to a sintered funnel in DMF and washed with DMF, water, 0.2 M aqueous HCl, NEt_3, DMF, MeOH, THF, CH_2Cl_2, ether, THF and CH_2Cl_2. The resin was transferred to a round bottom flask, dried *in vacuo* to a constant mass (6.50 g) to afford **27**; ν_{max}/cm^{-1} (KBr) 1748.

Method B. Following Representative Procedure 4, to a stirred suspension of **33** (100 mg, 0.141 mmol, 1.0 eq.), K_2CO_3 (97 mg, 0.705 mmol, 5.0 eq.) and phenylboronic acid (69 mg, 0.56 mmol, 4.0 eq.) at 70 °C in DMF (3 mL) was added, $Pd_2(dba)_3$ (26 mg, 0.028 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant

mass to afford **27** (94 mg) with identical spectroscopic properties to those described above; loading 1.52 mmol g^{-1}.

Loading determination of 2,2-dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)butyl]amino}butanoic acid (28)

The resin **27** (6.50 g, 9.66 mmol, 1.0 eq.), as a suspension in THF : H_2O (8 : 1) (100 ml), was stirred at reflux with $LiOH{\cdot}H_2O$ (4.05 g, 17.1 mmol, 10.0 eq.) for 4 hours. The resulting resin was washed repeatedly with water and THF. The washings were collected and the THF removed *in vacuo.* The water layer was acidified with 10% aqueous HCl and repeatedly extracted with CH_2Cl_2 (3×). Evaporation of the solvent *in vacuo* afforded 4-phenylphenol **24** (1.65 g, 9.69 mmol) with identical physical and spectroscopic properties to those described above. The resin was further washed repeatedly with THF, DMF and 10% aqueous HCl, the pH was then adjusted to neutral with aqueous 2 M NaOH solution and again repeatedly washed with DMF, water and THF. The resin was dried *in vacuo* to a constant mass to afford **28** as a dark brown powder (5.60 g); ν_{max}/cm^{-1} (KBr) 1713; determined loading 1.73 mmol g^{-1}.

N-[4′-(4″-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and 4-phenylphenol (24)

CAN (1.25 g, 2.28 mmol, 5.0 eq.) was added to a stirred suspension of **27** (300 mg, ~0.456 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (3 mL). After 16 hours reaction time the resin was transferred to a sintered funnel and washed repeatedly with CH_2Cl_2, THF and water. The resin was dried *in vacuo* to a constant mass to afford the debenzylated product **29** as a pale yellow powder (315 mg); ν_{max}/cm^{-1} (KBr) 1746. Subsequently the resin (271 mg, ~0.392 mmol) was stirred in a mixture of CH_2Cl_2 : NEt_3 (5 : 1) (5 mL) for one hour and washed repeatedly with CH_2Cl_2 (20 mL, 3×). The combined organic layers were repeatedly washed with 10% aqueous HCl (50 mL, 3 ×). The organic layer was concentrated *in vacuo* to afford the desired 4-phenylphenol **24** (52 mg, 78%) with identical physical and spectroscopic properties to those described above; HPLC (MeCN–H_2O, 254 nm) >99%. The resin was dried *in vacuo* to a constant mass to afford **30** as a pale brown powder (209 mg); ν_{max}/cm^{-1} (KBr) 1682.

N-Benzyl-2,2-dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)butyl]amino}butanamide (31)

Following Representative Procedure 3, to a stirred suspension of **28** (500 mg, 0.865 mmol, 1.0 eq.), benzylamine **14** (0.566 mL, 5.19 mmol, 6.0 eq.), HOBt (351 mg, 2.56 mmol, 3.0 eq.) and DIPEA (0.904 mL, 5.19 mmol, 6.0 eq.) in CH_2Cl_2 (10 mL) was added DIC (0.406 ml, 2.56 mmol, 3.0 eq.). After 16 hours the resin was transferred to a sintered funnel and washed repeatedly with DMF, MeOH and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **31** as a pale brown powder (518 mg); ν_{max}/cm^{-1} (KBr) 3368, 1634, 1529; loading 1.68 mmol g^{-1}.

N-Benzyl-2,2-dimethyl-4-{*N*-[4′-(4″-polystyrenyl)butyl]amino}butanamide (32)

CAN (1.63 g, 2.96 mmol, 5.0 eq.) was added to a stirred suspension of **31** (355 mg, 0.593 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (13 mL). After 16 hours the resin was transferred to a sintered funnel and washed repeatedly with DMF, 2 M aqueous NaOH solution, water, MeOH and CH_2Cl_2. The resin was dried to a constant mass *in vacuo* to afford **32** as a pale brown powder (304 mg); ν_{max}/cm^{-1} (KBr) 3371, 1635, 1529; loading 1.98 mmol g^{-1}.

N-[4′-(4″-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and benzylamine hydrochloride (18·HCl)

The resin **32** (300 mg, 0.585 mmol) was stirred as a suspension in toluene (10 ml) and refluxed for 48 hours. The resin was transferred to a sintered funnel and washed repeatedly with toluene. To the combined organic washings was added 10% aqueous HCl. The solvents were removed *in vacuo* and the residue co-evaporated with MeOH to afford benzylamine hydrochloride **18**·HCl as a white crystalline solid (55 mg, 65%) with identical physical and spectroscopic properties to those described above. The resin was washed repeatedly with MeOH, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **30** as a dark brown powder (243 mg) with identical spectroscopic properties to those described above.

(*S*)-[4‴-(2‴-oxo-3‴-Propanoyl-5‴,5‴-dimethyl-oxazolidin-4‴-yl)-benzyl] 2,2-dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)butyl]amino}butanoate (49)

To a stirred suspension of **28** (500 mg, 0.865 mmol, 1.0 eq.), (*S*)-*N*-propanoyl SuperQuat **48** (959 mg, 3.46 mmol, 4.0 eq.), HOBt (467 mg, 3.46 mmol, 4.0 eq.) and DIPEA (0.603 mL, 6.92 mmol, 4.0 eq.) in CH_2Cl_2 (10 mL) was added EDCI (1.82 mL, 2.60 mmol, 3.0 eq.). After 20 hours the resin was transferred to a sintered funnel and washed repeatedly with CH_2Cl_2 and MeOH. The washings were collected and the solvent removed *in vacuo*, the resulting residue was partitioned between CH_2Cl_2 (50 ml) and 10% aqueous HCl (50 mL). The organic layer was washed with 10% aqueous HCl (50 mL). The organic layer was dried with Na_2SO_4 and the solvent removed *in vacuo* to afford recovered **48** (780 mg). The resin was further washed repeatedly with DMF, THF and CH_2Cl_2 and re-subjected to the same reaction protocol and work-up. The resin was dried *in vacuo* to a constant mass to afford **49** as a pale brown powder (659 mg). ν_{max}/cm^{-1} (KBr) 1778, 1749, 1701; loading 1.31 mmol g^{-1}.

N-[4′-(4″-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and (*S*)-3-propanoyl-4-(4′-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one (48)

CAN (538 mg, 0.983 mmol, 5.0 eq.) was added to a stirred suspension of **49** (150 mg, 0.197 mmol, 1.0 eq.) in THF : H_2O (8 : 1) (2 mL). After stirring for 5 hours the resin was transferred to a sintered funnel and washed repeatedly with THF, water, THF and CH_2Cl_2. The resin was then treated with CH_2Cl_2 : NEt_3 (5 : 1) (12 mL) and the filtrate was concentrated *in vacuo.* The resulting residue was partitioned between CH_2Cl_2 (10 ml) and 10% aqueous HCl (5 mL). The organic layer was washed with 10% aqueous HCl (5 mL), water (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **48** (46 mg, 84%); $[\alpha]_D^{22}$ −45.0 (*c* 1.0, $CHCl_3$); other physical and spectroscopic data was identical to that reported above. The resin was dried to a constant mass *in vacuo* (90 mg) to afford **30** with identical spectroscopic properties to those described above.

Acknowledgements

The authors would like to thank the British Chevening Scholarship programme (H. S.) and New College, Oxford for a Junior Research Fellowship (A. D. S.).

References

1 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149; D. Obrecht, and J. M. Villalgordo, *Solid Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Elsevier Science Ltd., Oxford, 1998; F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Chichester, 2002.
2 For reviews see: J. Wills and S. Balasubramanian, *Curr. Opin. Chem. Biol.*, 2003, **7**, 346; F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091; I. W. James, *Tetrahedron*, 1999, **55**, 4855.
3 K. Gordon and S. Balasubramanian, *J. Chem. Technol. Biotechnol.*, 1999, **74**, 835.
4 G. W. Kenner;, J. R. McDermott and R. C. Sheppard, *J. Chem. Soc. D*, 1971, 636; for a review see:; P. Heidler and A. Link, *Bioorg. Med. Chem.*, 2005, **13**, 585.
5 A. Routledge, C. Abell and S. Balasubramanian, *Tetrahedron Lett.*, 1997, **38**, 1227; H. Glatz and W. Bannwarth, *Tetrahedron Lett.*, 2003, **44**, 149; M. Guo and L. Varady, *Tetrahedron Lett.*, 2002, **56**, 5611.
6 For reviews see: A. J. Wills and S. Balasubramanian, *Curr. Opin. Chem. Biol.*, 2003, **7**, 346; W. S. Wade, F. Yang and T. J. Sowin, *J. Comb. Chem.*, 2000, **2**, 266; K. Gordon and S. Balasubramanian, *J. Chem. Technol. Biotechnol.*, 1999, **74**, 835; M. Pátek and M. Lebl, *Biopolymers*, 1998, **47**, 353.
7 For select examples see: G. Subra, M. Amblard and J. Martinez, *Tetrahedron Lett.*, 2002, **43**, 9221; J. C. Kappel and G. Barany, *J. Comb. Chem.*, 2005, **7**, 78; S. Raghavan and A. Rajender, *Chem. Commun.*, 2002, **15**, 1572; S. Seeberger, R. J. Griffin, I. R. Hardcastle and B. T. Golding, *Org. Biomol. Chem.*, 2007, **5**, 132.
8 R. B. Greenwald, Y. H. Choe, C. D. Conover, K. Shum, D. Wu and M. Royzen, *J. Med. Chem.*, 2000, **43**, 475.
9 R. S. Garigipati, *Tetrahedron Lett.*, 1997, **38**, 6807; L. A. Thompson and J. A. Ellman, *Tetrahedron Lett.*, 1994, **35**, 9333; C. Gennari, S. Ceccarelli, U. Piarulli, K. Aboutayab, M. Donghi and I. Paterson, *Tetrahedron*, 1998, **54**, 14999; M. Reggelin, V. Brenig and R. Welcker, *Tetrahedron Lett.*, 1998, **39**, 4801; for a review see; N. H. Nam, S. Sardari and K. Parang, *J. Comb. Chem.*, 2003, **5**, 479.
10 M. F. Gordeev, D. V. Patel and E. M. Gordon, *J. Org. Chem.*, 1996, **61**, 924; A. V. Purandare and M. A. Poss, *Tetrahedron Lett.*, 1998, **39**, 935; I. A. Nash, B. W. Bycroft and W. C. Chan, *Tetrahedron Lett.*, 1996, **37**, 2625; K. H. Bleicher and J. R. Wareing, *Tetrahedron Lett.*, 1998, **39**, 4587; P. Forns, S. Sevilla, M. Erra, A. Ortega, N. de la Figuera Fernandez, D. Fernandez-Forner and F. Albericio, *Tetrahedron Lett.*, 2003, **44**, 6907; P. Conti, D. Demont, J. Cals, H. C. J. Ottenheijm and D. Leysen, *Tetrahedron Lett.*, 1997, **38**, 2915; R. L. Letsinger, M. J. Kornet, V. Mahadevan and D. M. Jerina, *J. Am. Chem. Soc.*, 1965, **86**, 5163; I. R. Marsh, H. Smith and M. Bradley, *Mol. Diversity*, 1997, **2**, 165; A. Routledge, T. Stock, S. L. Flitsch and N. J. Turner, *Tetrahedron Lett.*, 1997, **38**, 8287; K. Kaljuste and A. Unden, *Tetrahedron Lett.*, 1996, **37**, 3031; P. S. Furth, M. S. Reitman and A. F. Cook, *Tetrahedron Lett.*, 1997, **38**, 5403; W. Bannwarth, J. Huebscher and R. Barner, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1525; C. Kay, P. Murray, L. Sandow and A. B. Holmes, *Tetrahedron Lett.*, 1997, **38**, 6941; M. S. Congreve, C. Kay, J. J. Scicinski, S. V. Ley, G. Williams, P. J. Murray, S. C. McKeown and S. P. Watson, *Tetrahedron Lett.*, 2003, **44**, 4153; S. Kobayashi and Y. Aoki, *Tetrahedron Lett.*, 1998, **39**, 7345; J. H. Kirchhoff, S. Brase and D. Enders, *Tetrahedron Lett.*, 2001, **3**, 71; S. Brase, J. Köbberling, D. Enders, R. Lazny and M. Wang, *Tetrahedron Lett.*, 1999, **40**, 2105.
11 S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3765; S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad and A. D. Smith, *Chem. Commun.*, 2000, 337.
12 R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc., Trans.*, 1915, **107**, 1080; N. L. Allinger and V. Zalkow, *J. Org. Chem.*, 1960, **25**, 701.
13 B. Krzyzanowska and W. J. Stec, *Synthesis*, 1982, **4**, 270.
14 Now part of Biotage AB, Charlottesville, Virginia.
15 R. J. Edsall, H. A. Harris, E. S. Manas and R. E. Mewshaw, *Bioorg. Med. Chem.*, 2003, **11**, 3457.
16 For select examples see: D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; C. H. Heathcock, *Aldrichimica Acta*, 1990, **23**, 99; P. Pollock, J. Dambacher, R. Anness and M. Bergdahl, *Tetrahedron Lett.*, 2002, **43**, 3693; D. A. Evans, K. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238; For a review of the diversity of asymmetric synthesis that can be achieved using oxazolidinone auxiliaries see: D. J. Ager, I. Prakash and D. R. Schaad, *Aldrichimica Acta*, 1997, **30**, 3.
17 D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23.
18 For a recent review see: C. W. Y. Chung and P. H. Toy, *Tetrahedron: Asymmetry*, 2004, **15**, 387; for select examples see: S. M. Allin and S. J. Shuttleworth, *Tetrahedron Lett.*, 1996, **37**, 8023; S. M. Allin, C. A. Johnson and A. Timm, *Tetrahedron Lett.*, 2005, **46**, 2495; S. P. Bew, S. D. Bull and S. G. Davies, *Tetrahedron Lett.*, 2000, **41**, 7577.
19 K. Burgess and D. Lim, *Chem. Commun.*, 1997, 785.
20 A. V. Purandare and S. Natarajan, *Tetrahedron Lett.*, 1997, **38**, 8777; C. W. Phoon and C. Abell, *Tetrahedron Lett.*, 1998, **39**, 2655; J. D. Winkler and W. McCoull, *Tetrahedron Lett.*, 1998, **39**, 4935; G. Faita, A. Paio, P. Quadrelli, F. Rancati and P. Seneci, *Tetrahedron Lett.*, 2000, **41**, 1265.
21 R. Akkari, M. Calmès, N. Mai, M. Rolland and J. Martinez, *J. Org. Chem.*, 2001, **66**, 5859; R. Akkari, M. Calmès, D. Di Malta, F. Escale and J. Martinez, *Tetrahedron: Asymmetry*, 2003, **14**, 1223; R. Akkari, M. Calmès, F. Escale, J. Iapichella, M. Rolland and J. Martinez, *Tetrahedron: Asymmetry*, 2004, **15**, 2515; M. Calmès, R. Akkari, N. Barthes, F. Escale and J. Martinez, *Tetrahedron: Asymmetry*, 2005, **16**, 2179.
22 D. A. B. Mortimer, *PhD Thesis*, University of Oxford, 2002; S. D. Bull, S. G. Davies, and D. A. B. Mortimer, unpublished results.
23 R. Green, A. T. Merritt and S. D. Bull, *Chem. Commun.*, 2008, 508.
24 S. D. Bull, S. G. Davies, S. Jones, M. E. C. Polywka, R. S. Prasad and H. J. Sanganee, *Synlett*, 1998, 519.
25 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
26 E. Fabiano, B. T. Golding and M. M. Sadeghi, *Synthesis*, 1987, **2**, 190.
27 Y. Endo, K. Shudo and T. Okamoto, *J. Am. Chem. Soc.*, 1982, **104**, 6393.

