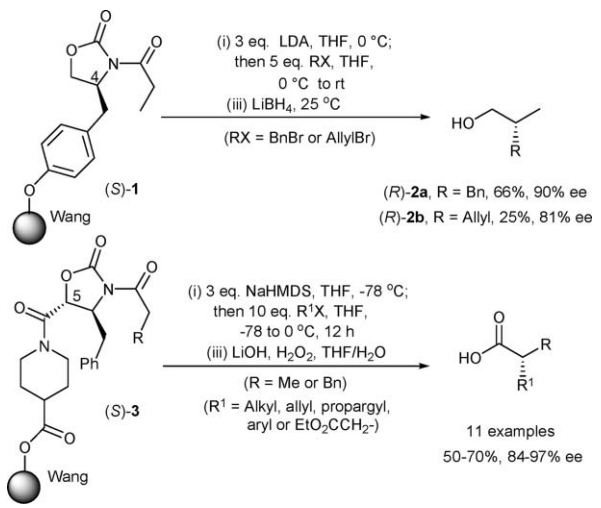
A cleavable linker strategy for optimising enolate alkylation reactions of a polymer-supported Evans' oxazolidin-2-one†

Rachel Green,[a] Andrew T. Merritt[b] and Steven D. Bull*[a]

Received (in Cambridge, UK) 11th September 2007, Accepted 13th November 2007
First published as an Advance Article on the web 29th November 2007
DOI: 10.1039/b713966g

A cleavable linker strategy has been used to optimise the enolate alkylation reactions of a recyclable L-tyrosine derived polymer-supported oxazolidin-2-one for the asymmetric synthesis of a series of chiral α-alkyl acids.

A number of polymer-supported Evans' oxazolidin-2-ones have been developed for asymmetric synthesis,[1] however their use for asymmetric enolate alkylation reactions has proven to be problematic.[2] For example, Burgess and Lim initially reported that alkylation of the lithium enolate of an L-tyrosine derived Wang-supported *N*-propionyloxazolidin-2-one (*S*)-**1** with five equivalents of benzyl bromide at 0 °C, followed by treatment with $LiBH_4$, gave 2-methyl-3-phenylpropan-1-ol (*R*)-**2a** in 66% yield and 90% ee (Scheme 1).[3] However, they described that extended reaction times led to alcohol (*R*)-**2a** in lower ee and reduced yield, with losses in diastereocontrol dependent on the amount of base used, and lower yields being due to "loss of the propionyl group from the oxazolidin-2-one prior to cleavage". Furthermore, alkylation of the lithium enolate of (*S*)-**1** with allyl bromide, followed by $LiBH_4$ cleavage, afforded chiral alcohol (*R*)-**2b** in lower 81% ee and a much poorer 25% yield.[3]



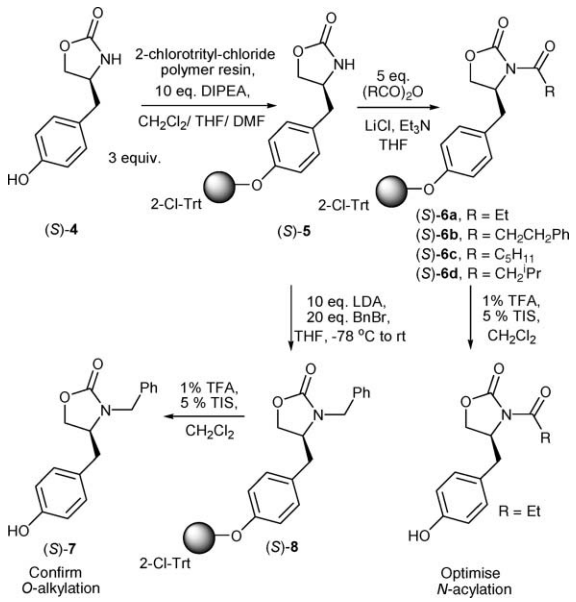
Scheme 1 Enolate alkylation reactions of L-tyrosine derived polymer (*S*)-**1** and phenylnorstatine derived polymer (*S*)-**3**.

[a]*Department of Chemistry, University of Bath, Claverton Down, Bath, UK BA2 7AY. E-mail: s.d.bull@bath.ac.uk*
[b]*GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b713966g

These results were clearly inferior to those reported previously for alkylation of lithium enolates of related *N*-propionyl-oxazolidin-2-ones in 'solution phase'.[4] This prompted Kotake *et al.* to propose that the poor diastereocontrol observed for (*S*)-**1** might be a result of the oxazolidin-2-one being attached to polymer *via* its stereodirecting C_4-benzyl group. Therefore, they prepared new types of Wang-supported *N*-acyloxazolidin-2-one (*S*)-**3**, whose oxazolidin-2-one fragments were attached to polymer *via* their remote C_5-positions, leaving an unhindered C_4-benzyl group free for stereocontrol. This strategy proved successful, with lithium[5] and sodium[6] enolates of a range of *N*-acyloxazolidin-2-ones (*S*)-**3** being used in asymmetric enolate alkylation reactions to afford eleven chiral α-alkyl acids in 84–97% ee and 50–70% yield.[6] Their polymers could be recycled with no loss of stereocontrol, although a decrease in yield of chiral acids produced between each reaction cycle was observed.[5]

We were unconvinced that the poor performance of (*S*)-**1** in enolate alkylation reactions was due to the oxazolidin-2-one being attached to polymer *via* its stereodirecting C_4-benzyl substituent, since this hypothesis failed to explain why diastereoselectivity was dependent on both the length of reaction and the amount of base present. Furthermore, L-tyrosine derived polymer-supported oxazolidin-2-ones had been used previously in other types of asymmetric transformation to afford different classes of chiral product in high de.[1]

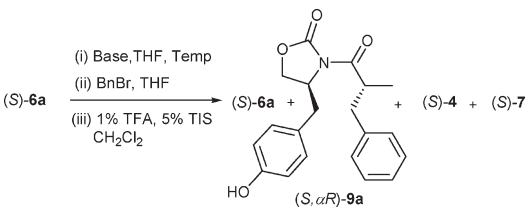
Consequently, we decided to investigate the enolate alkylation reactions of an L-tyrosine derived oxazolidin-2-one attached to polymer-support *via* an orthogonally cleavable linker that would enable polymer-supported intermediates to be identified as required. Therefore, 2-chlorotrityl chloride resin was treated with three equivalents of oxazolidin-2-one (*S*)-**4**[7] and ten equivalents of diisopropylethylamine (DIPEA) in CH_2Cl_2–THF–DMF, to give *O*-linked-*NH*-oxazolidin-2-one polymer (*S*)-**5** with a reproducible loading of 0.96–1.16 mmol g^{-1}. The exclusive formation of (*S*)-**5** was confirmed *via* its treatment with ten equivalents of LDA and twenty equivalents of BnBr in THF at −78 °C, which gave polymer (*S*)-**8** that was cleaved with 1% trifluoroacetic acid (TFA)–5% triisopropylsilane (TIS) in CH_2Cl_2 to afford *N*-benzyloxazolidin-2-one (*S*)-**7** as a single product, with no *O*-benzyloxazolidin-2-one being present. The *N*-propionylation reaction of polymer (*S*)-**5** was also optimised using this TFA cleavage approach, which revealed that five equivalents of propionic anhydride, Et_3N and LiCl in THF were required to ensure complete conversion of (*S*)-**5** to *N*-propionyl polymer (*S*)-**6a**. These conditions were then employed to prepare a series of four *N*-acyloxazolidin-2-one polymers (*S*)-**6a–d** with loadings of between 0.91–1.15 mmol g^{-1} (Scheme 2).



Scheme 2 Formation and *N*-acylation of 2-chlorotrityl polymer-supported oxazolidin-2-one (*S*)-**5**.

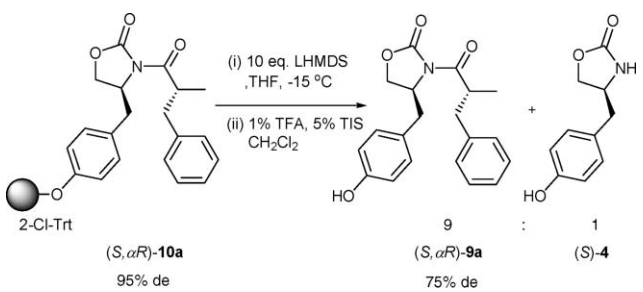
The enolate alkylation reaction of (*S*)-**6a** was then investigated, *via* treatment with varying amounts of base,[8] at different temperatures, using different amounts of benzyl bromide, followed by subsequent TFA cleavage to determine product ratios (Table 1). These results revealed that a competing enolate decomposition pathway was occurring on polymer support to afford significant amounts of *NH*-oxazolidin-2-one (*S*)-**5**, and small amounts of *N*-benzyloxazolidin-2-one (*S*)-**8**.[9] Whilst the amount of (*S*)-**5** formed could be reduced to 15% by carrying out the reaction at −15 °C, this lower temperature required excess base and/or extended reaction times to ensure complete consumption of (*S*)-**6a**. However, changing to these conditions resulted in a significant reduction in both the de and yield of (*S*,α*R*)-**10a**.

Table 1 Investigating enolate alkylation reactions of (*S*)-**6a** using TFA cleavage to examine product ratios



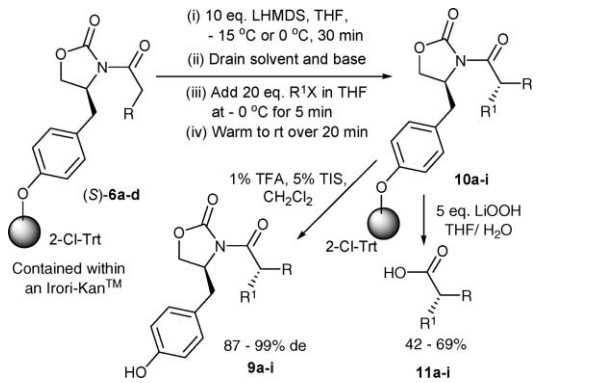
Reaction conditions	Ratio of products from TFA cleavage reaction			
	6a	**9a**	**4**	**7**
3 eq. LDA, 0 °C; 5 eq. BnBr, 30 min	26	33 (85% de)	41	0
3 eq. LHMDS, −15 °C; 5 eq. BnBr, 30 min	20	62 (85% de)	15	3
3 eq. LHMDS, −15 °C; 5 eq. BnBr, 12 h	0	58 (76% de)	42	0
10 eq. LHMDS, −15 °C; 20 eq. BnBr, 12 h	0	57 (68% de)	38	5

In order to explain these results we proposed that base catalysed epimerisation of (*S*,α*R*)-**10a** was responsible for the poor de in these reactions, rather than poor diastereoselectivity in the initial enolate alkylation reaction. In order to confirm this hypothesis, diastereoisomerically pure (*S*,α*R*)-**10a** (>95% de)[10] was treated with ten equivalents of LHMDS for 12 h at −15 °C, followed by cleavage with TFA, which gave epimerised (*S*,α*R*)-**9a** (75% de) and *NH*-oxazolidin-2-one (*S*)-**4** in a ratio of 9 : 1 (Scheme 3). Therefore, it was clear that excess LHMDS could deprotonate (*S*,α*R*)-**10a** resulting in an enolate that was either protonated to afford (*S*,α*R*)-**10a** in inferior de, or decomposed to regenerate (*S*)-**5**, thus explaining the erosion in de and yield of recovered (*S*,α*R*)-**9a** over time. Consequently, it was decided to modify the reaction conditions so that the excess LHMDS responsible for generating the enolate of (*S*,α*R*)-**10a** would be removed before addition of benzyl bromide, thus preventing any excess LHMDS from being available to epimerise (*S*,α*R*)-**10a**. Therefore, (*S*)-**6a** was encased in an IRORI mini-Kan™ and treated with ten equivalents of LHMDS in THF at −15 °C (or 0 °C) for 30 min, before the solvent/excess LHMDS was removed *via* cannula. The resultant polymer was then re-suspended in THF at −15 °C (or 0 °C), and treated with twenty equivalents of benzyl bromide in pre-chilled THF at −15 °C (or 0 °C). TFA cleavage of the resultant resin revealed that (*S*,α*R*)-**9a** had been formed in 70–75% yield and in a much improved >95% de, along with 20–25% *NH*-oxazolidin-2-one (*S*)-**4** and 0–5% *N*-benzyloxazolidin-2-one (*S*)-**7**. All attempts to optimise these conditions further in an attempt to reduce the amount of (*S*)-**5** formed proved unsuccessful. Therefore, these conditions were used for reaction of the lithium enolates of 150 mg batches of *N*-acyloxazolidin-2-ones (*S*)-**6a–d** with a range of electrophiles (benzyl bromide, methyl iodide and allyl iodide) to afford nine α-alkylated resins **10a–i**. Twenty milligrams of each resin **10a–i** were then cleaved with 1% TFA and the cleavage products analysed *via* HPLC, which revealed that complete consumption of *N*-acyloxazolidin-2-ones (*S*)-**6a–d** had occurred to afford α-alkylated products **9a–i** in good 87–99% de (Table 2). The remaining resin **10a–i** (approx. 130 mg) was then hydrolysed using five equivalents of LiOOH[11] in THF–H_2O to afford their corresponding chiral α-alkyl acids **11a–i** in acceptable 42–69% yields (calculated over three steps for *N*-acylation, enolate alkylation and side-chain cleavage) (Table 2). The enantiomeric excess of chiral acid (*R*)-**11a** was determined as 97% ee *via* chiral HPLC analysis, which was identical in value to the diastereoisomeric excess of (*S*,α*R*)-**9a** of 97% de, thus confirming that LiOOH hydrolysis of (*S*,α*R*)-**10a** had occurred without racemisation. Consequently, it was concluded that the ee values of α-alkyl-acids



Scheme 3 Epimerisation of (*S*)-**10a** using excess LHMDS.

Table 2 De values of chiral *N*-α-alkyloxazolidin-2-ones **9a**–**i** and yields of chiral acids **11a**–**i**



Reactants (polymer/R^1X)	De of TFA cleavage products **9a**–**i**	Yield of chiral acids **11a**–**i**
6a/BnBr	(*S*,α*R*)-**9a**, 97% de	(*R*)-**11a**, 69%
6a/AllylBr	(*S*,α*R*)-**9b**, 92% de	(*R*)-**11b**, 61%
6b/MeI	(*S*,*S*)-**9c**, 87% de	(*S*)-**11c**, 45%
6c/MeI	(*S*,*S*)-**9d**, 95% de	(*S*)-**11d**, 53%
6c/BnBr	(*S*,α*R*)-**9e**, 90% de	(*R*)-**11e**, 48%
6c/AllylBr	(*S*,α*R*)-**9f**, 99% de	(*R*)-**11f**, 58%
6d/MeI	(*S*,*S*)-**9g**, 90% de	(*S*)-**11g**, 42%
6d/BnBr	(*S*,*S*)-**9h**, 99% de	(*S*)-**11h**, 52%
6d/AllylBr	(*S*,*S*)-**9i**, 99% de	(*S*)-**11i**, 60%

11b–**i** were identical to the de values of their corresponding α-alkyloxazolidin-2-ones **9b**–**i**.

We then demonstrated that the polymer could be efficiently recycled by carrying out four sequential polymer-supported asymmetric enolate alkylation reactions (comprising *N*-acylation, alkylation and side chain cleavage) on the *same* batch of resin (*S*)-**5**. Characterisation of the α-alkyloxazolidin-2-ones **10** produced in these consecutive enolate alkylation reactions was achieved by cleaving 20 mg portions of resin with 1% TFA and analysing the cleavage products by ^{1}H NMR spectroscopy. This revealed that the *same* batch of resin (*S*)-**5** could be recycled four times to afford chiral α-alkyl-acids (*R*)-**11a** (69%, 95% de for (*S*,α*R*)-**9a**), (*S*)-**11g** (45%, 87% de for (*S*,*S*)-**9g**), (*S*)-**11c** (43%, 89% de for (*S*,*S*)-**9c**) and (*R*)-**11a** (38%, 96% de for (*S*,α*R*)-**9a**) respectively, with no losses in diastereocontrol when compared to results obtained using 'fresh' resin (*S*)-**5** (see Table 2). Indeed, the first and fourth reaction cycles produced α-benzyl propionic acid (*R*)-**11a** with essentially identical de values of 95% and 97% de respectively. However, the yield of chiral α-alkyl acids produced after each progressive reaction cycle did decrease, with the fourth reaction cycle producing (*R*)-**11a** in only 38% yield, which was much lower than the 69% yield produced in the first reaction cycle using virgin polymer. ^{1}H-NMR spectroscopic analysis of the *NH*-oxazolidin-2-one (*S*)-**5** obtained from cleavage of 20 mg portions of resin at the end of each reaction cycle (after LiOOH hydrolysis) revealed increasingly complex spectra, that we propose are a result of progressive accumulation of small amounts of different *N*-alkyloxazolidin-2-ones formed from the enolate decomposition pathway of each reaction cycle.

The enolate alkylation results described herein clearly demonstrate that the poor de values previously reported for L-tyrosine derived polymer-supported oxazolidin-2-ones are not a result of the chiral auxiliary being attached to polymer *via* its C_4-stereodirecting group. Furthermore, our new stepwise reaction protocol enables the cheap and readily available L-tyrosine derived polymer (*S*)-**5**[12] to be used for asymmetric enolate reactions with comparable levels of stereocontrol and performance to Kiso's phenylnorstatine derived polymer (*S*)-**3**.[13]

In conclusion, we have used a cleavable linker strategy to optimise the performance of a polymer-supported L-tyrosine derived oxazolidin-2-one for enolate alkylation reactions, thus enabling the asymmetric synthesis of a series of nine chiral α-alkyl acids. We anticipate that this type of cleavable linker approach will prove extremely useful for optimising the performance of other types of chiral auxiliary on polymer support.

We would like to thank the EPSRC (RG), GlaxoSmithKline (RG), the Royal Society (SDB) and the University of Sydney (SDB) for funding, and the mass-spectroscopic facility at Swansea for its assistance.

Notes and references

1 For an excellent review see: C. W. Y. Chung and P. H. Toy, *Tetrahedron: Asymmetry*, 2004, **15**, 387.
2 See: (*a*) S. M. Allin and S. J. Shuttleworth, *Tetrahedron Lett.*, 1996, **37**, 8023; (*b*) S. P. Bew, S. D. Bull and S. G. Davies, *Tetrahedron Lett.*, 2000, **41**, 7577; (*c*) S. P. Bew, S. D. Bull, S. G. Davies, E. D. Savory and D. J. Watkin, *Tetrahedron*, 2002, **58**, 9387; (*d*) S. M. Allin, C. A. Johnson and A. Timm, *Tetrahedron Lett.*, 2005, **46**, 2495.
3 K. Burgess and D. Lim, *Chem. Commun.*, 1997, 785.
4 (*a*) D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737; (*b*) D. L. J. Clive, K. S. Keshava Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. da Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze and J. R. Barrie, *J. Am. Chem. Soc.*, 1990, **112**, 3018.
5 T. Kotake, S. Rajesh, Y. Hayashi, Y. Mukai, M. Ueda, T. Kimura and Y. Kiso, *Tetrahedron Lett.*, 2004, **45**, 3651.
6 T. Kotake, Y. Hayashi, S. Rajesh, Y. Mukai, Y. Takiguchi, T. Kimura and Y. Kiso, *Tetrahedron*, 2005, **61**, 3819.
7 R. Green, P. J. M. Taylor, S. D. Bull, T. D. James, M. F. Mahon and A. Merritt, *Tetrahedron: Asymmetry*, 2003, **12**, 2619.
8 Although sodium enolates of *N*-acyloxazolidin-2-ones are more stable than lithium enolates (ref. 4*a*), using NaHMDS as a base gave no reduction in products arising from the enolate decomposition pathway.
9 S. D. Bull, S. G. Davies, S. Jones and H. J. Sanganee, *J. Chem. Soc., Perkin Trans. 1*, 1999, 387.
10 Diatereomerically pure polymer (*S*,α*R*)-**10a** (>95% de) was prepared *via* asymmetric synthesis of (4*S*)-4-(4-hydroxybenzyl)-3-((2*R*)-2-methyl-3-phenylpropionyl)oxazolidin-2-one in 'solution phase', followed by its attachment to 2-chlorotrityl resin.
11 TFA cleavage studies revealed that lower concentrations of LiOOH resulted in incomplete hydrolysis of polymers **10a**–**i**, whilst treatment with LiOH resulted in competing formation of endocyclic cleavage products, see: D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.*, 1987, **28**, 6141.
12 Polymer-supported oxazolidin-2-one (*S*)-**3** is prepared from the non-natural β-amino acid phenylnorstatine which is very expensive; (*R*,*R*)-*N*-Boc-**3** from CNH Technologies (1 g for £195.00), (*S*,*S*)-*N*-Boc-**3** from PepTech Corporation (1 g for £395.00).
13 It is surprising that polymers (*S*)-**3** do not suffer from problems associated with base-catalysed epimerisation of the α-stereocentres of their α-alkylated products, with reactions employing excess NaHMDS (or LDA) for enolate generation having been reported to afford chiral α-alkyl acids of up to 97% ee. See ref. 5 and 6.

