Synthesis and evaluation of a new polymer-supported pseudoephedrine auxiliary for asymmetric alkylations on solid phase†

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A polymer-supported pseudoephedrine auxiliary linked to the support through nitrogen, has been developed for use in asymmetric alkylations on solid phase.

The development of immobilised chiral auxiliaries for asymmetric library synthesis remains a relatively under-developed area.[1] Our interest in the development of new linkers[2] for synthesis, has led us to evaluate ephedrine[3] and pseudoephedrine chiral resins[4] for solid phase, asymmetric synthesis. These chiral linking units tether substrates to the polymer support and control the stereochemistry of reactions carried out on the substrate (Fig. 1).

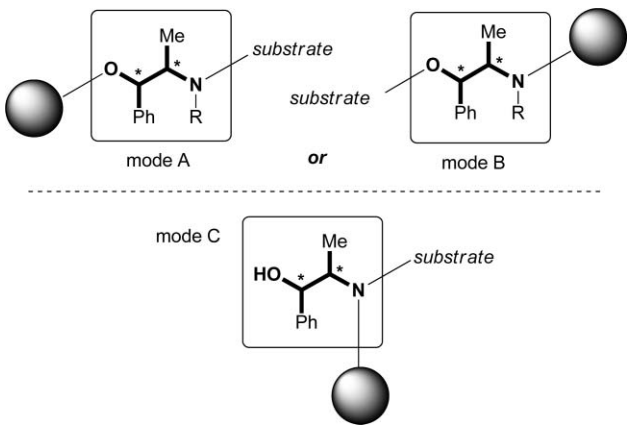


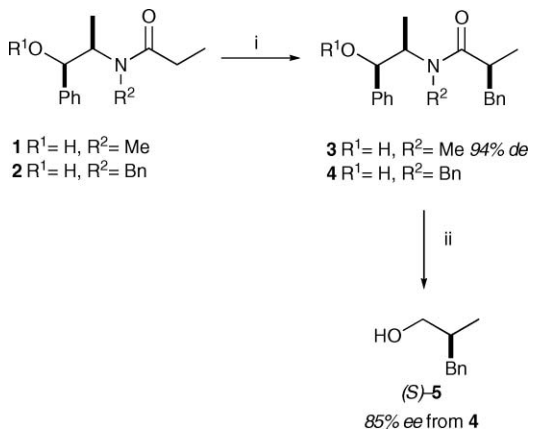
Fig. 1 Ephedrine and pseudoephedrine chiral resins.

Oxazolidinones remain the most extensively explored supported auxiliary,[1,5] however, ephedrine and pseudoephedrine resins present attractive, complementary systems that might be expected to have greater stability and therefore recyclability.[3,4]

We have described a Sm(II)-mediated, asymmetric catch and release approach to γ-butyrolactones that involves intermolecular radical additions to α,β-unsaturated esters attached to resin through an ephedrine chiral linker[3] (*mode B*). Myers' pseudoephedrine chiral auxiliary[6] continues to evolve as a valuable tool for a range of asymmetric transformations.[7] We have also reported the application of a pseudoephedrine resin (*mode A*) in Myers-type asymmetric alkylations on solid phase,[4] and have demonstrated the potential of the approach for asymmetric library synthesis.

Although immobilisation of pseudoephedrine through oxygen (*mode A*) using Merrifield resin can be achieved in one-step,[4] this simple approach to immobilisation does not permit hydrolytic cleavage of enantiomerically enriched carboxylic acids from the auxiliary[8] although alcohols and ketones can be prepared (80–93% ee). We felt that a pseudoephedrine resin bearing a free hydroxyl group, attached to the polymer support through nitrogen (*mode C*) (Fig. 1), would address this shortcoming. Here we describe the design, synthesis and evaluation of an improved pseudoephedrine auxiliary attached to the support through nitrogen.

The most straight-forward approach to the preparation of a pseudoephedrine resin, immobilised through nitrogen, involves the *N*-alkylation of norpseudoephedrine using Merrifield resin. To examine whether such a system would be viable, *N*-benzylpseudoephedrine amide **2**, a solution model for an amide immobilised through nitrogen, was prepared[9] and alkylated (Scheme 1). Myers' system **1**[6] is also included for comparison.



Scheme 1 *Reagents and conditions*: (i) LDA 2.1 equiv., LiCl 6 equiv., THF −78 °C to rt then BnBr added at 0 °C, 88% (for **4**); (ii) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 75%.

Alkylation of **2** using Myers' conditions gave **4** in 88% yield. The relative stereochemistry of **4** was confirmed by X-ray crystallography.[10] Reduction of **4** with lithium amidotrihydroborate gave (*S*)-**5** in 75% yield and in 85% ee. Thus the exchange of the *N*-methyl group in Myers' pseudoephedrine auxiliary for a larger benzyl substituent, led to a small drop in selectivity (~9% ee).

To evaluate this simple approach on solid phase, Merrifield resin was treated with norpseudoephedrine hydrochloride **6**[11] to give pseudoephedrine resin **7** (~0.88 mmol g^{-1}). Acylation then gave amide **8** that upon alkylation and reductive cleavage gave (*S*)-**5** in 56% overall yield but only 45% ee (Scheme 2).

Not only does the proximity of the polymer backbone appear to interfere with the diastereoselectivity of the alkylation step

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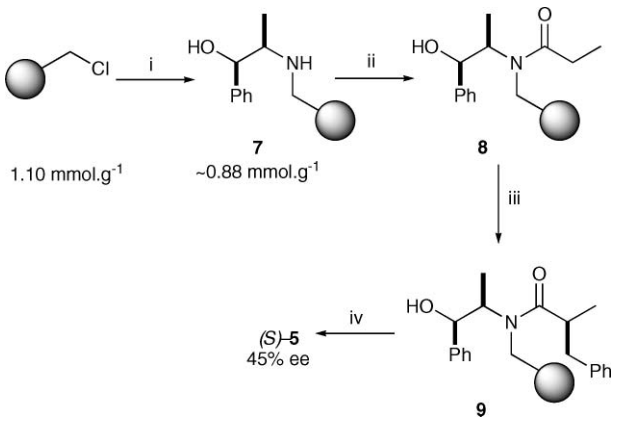
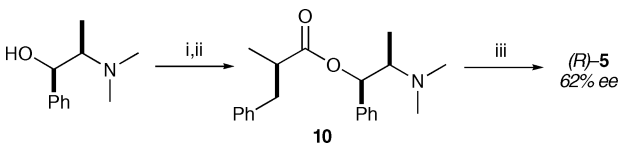


Scheme 2 *Reagents and conditions*: (i) **6**, Et_3N, DMF, 50 °C; (ii) propionic anhydride, THF, Et_3N, rt; (iii) LDA. LiCl, THF, −78 °C to rt then BnBr, THF, 0 °C to rt; (iv) LDA, $BH_3{\cdot}NH_3$, THF, 56% overall (based on loading of **7**).

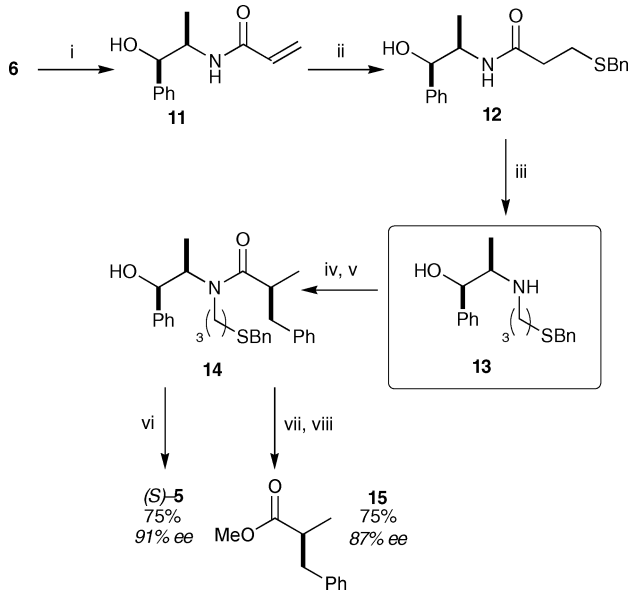
but the bulk of the support hinders *N*-acylation and may lead to competing *O*-acylation. For example, extended treatment of **7** with propionic anhydride gave a resin (ν(C=O) 1628 cm^{-1}, ν (C=O) 1738 cm^{-1}), that upon alkylation and cleavage, gave (*S*)-**5** in 15% ee. To add support to the hypothesis that over-acylation was effecting the diastereoselectivities observed, *N*-methylpseudoephedrine was acylated and alkylated to give **10**. Reduction then gave the opposite enantiomer (*R*)-**5** in 62% ee, clearly showing that *O*-acylation and ester alkylation would be expected to lead to an erosion of product enantiomeric excess when preparing (*S*)-**5** (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) propionic anhydride, THF, Et_3N, rt; (ii) LDA, LiCl, THF −78 °C to rt then BnBr added at 0 °C; (iii) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 53% overall.

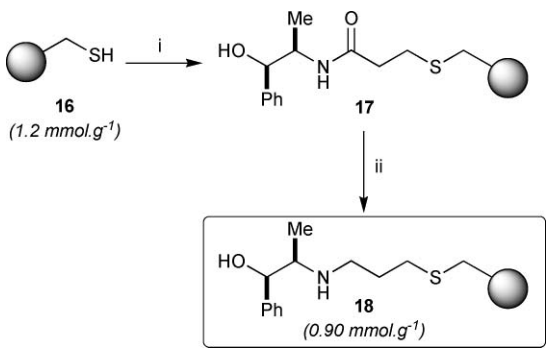
From these model studies it was clear that linkage to the support through a longer spacer unit would be a necessary feature of an effective pseudoephedrine auxiliary immobilised through nitrogen. Aware of the need for a synthetically, straight-forward approach, we investigated a new immobilisation strategy in solution. Norpseudoephedrine **6** was converted to acrylamide **11** and the Michael addition of benzylthiolate was used to mimic an immobilisation step involving a benzylthiol resin. Resulting amide **12** was then reduced to **13**, a solution model for a pseudoephedrine resin linked to the polymer support through nitrogen *via* a three carbon spacer (Scheme 4). Pleasingly, acylation with propionic anhydride, alkylation with benzyl bromide and reductive cleavage gave (*S*)-**5** in good overall yield and in 91% ee (*cf.* 94% ee using Myers' system in solution). Importantly, hydrolytic cleavage of the auxiliary and esterification of the resultant acid, gave **15** in 75% yield and 87% ee (Scheme 4).

Satisfied that this linker system would allow access to enantiomerically enriched carboxylic acid derivatives by hydrolysis, we prepared a polymer-supported analogue of pseudoephedrine derivative **13**. Norpseudoephedrine acrylamide **11** was immo-



Scheme 4 *Reagents and conditions*: (i) TMSCl, NEt_3, CH_2Cl_2, 0 °C, 1 h then acryloyl chloride, rt, 2 h, then citric acid, MeOH, 64%; (ii) BnSH, NaH, THF, 0 °C, 60%; (iii) $BH_3{\cdot}$THF, Δ, THF, 92%; (iv) propionic anhydride, CH_2Cl_2, Et_3N, rt, 72%; (v) LDA, LiCl, THF −78 °C to rt then BnBr added at 0 °C, 65%; (vi) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt, 75%; (vii) 9 N H_2SO_4, dioxane, Δ, 100%; (viii) $TMSCHN_2$, toluene–MeOH, rt, 75%.

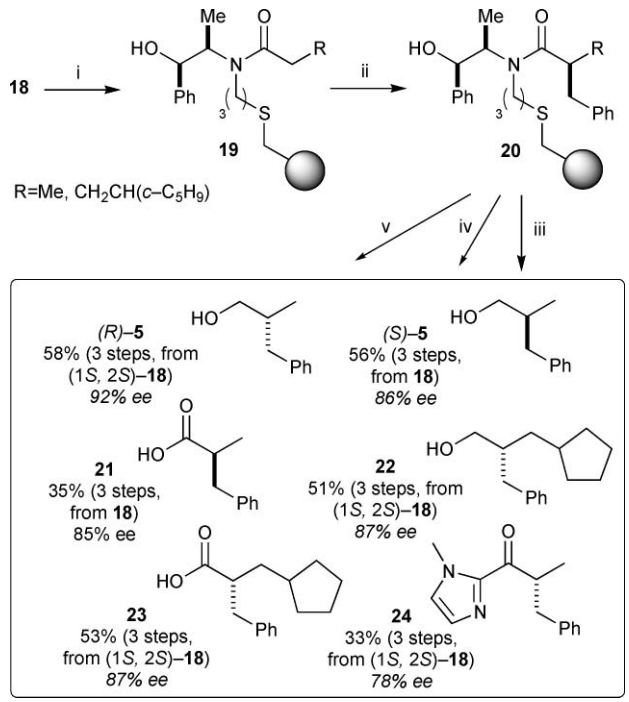
bilised using Merrifield-based thiol resin **16**[12] by addition to a suspension of the resin and NaH in THF. Amide **17** was then reduced with borane to give **18** (Scheme 5). Microanalysis of **18** indicated a loading of 0.90 mmol g^{-1}.



Scheme 5 *Reagents and conditions*: (i) NaH, THF, **11**; (ii) $BH_3{\cdot}$THF, THF.

Pseudoephedrine resin **18** (and its enantiomer, (1*S*,2*S*)-**18**) was evaluated by carrying out the unoptimised synthesis of a small collection of alcohols, acids and a ketone. Acylation of **18** with propionic anhydride and 3-cyclopentyl propionic acid (activated with pivaloyl chloride) followed by alkylation with benzyl bromide gave immobilised adducts **20**. Reductive cleavage gave the expected alcohols (*S*)-**5**, (*R*)-**5** and **22** in 86–92% ee (*NB* The level of selectivity observed in the synthesis of alcohol (*R*)-**5** is essentially the same as that observed using Myers' solution auxiliary[6e]). Pleasingly, hydrolysis using tetra-*n*-butylammonium hydroxide in *t*-BuOH and water gave the carboxylic acids **21** and **23** with similar selectivities. Finally, ketone **24** was prepared in somewhat lower enantiomeric excess due to some epimerisation

during cleavage.[13] All yields are for isolated products obtained after 3 steps. No attempt was made to optimise the cleavage reactions and we conclude that the chemistry of pseudoephedrine resin **18** is relatively robust (Scheme 6).

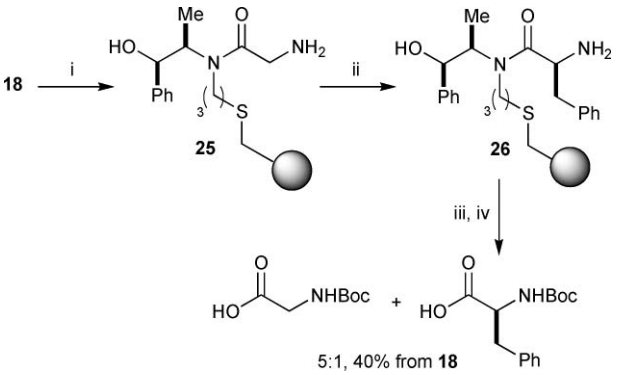


Scheme 6 *Reagents and conditions*: (i) TMSCl, Et_3N, THF then propionic anhydride, THF, Et_3N, rt *or* 3-cyclopentyl propionic acid and pivaloyl chloride in MeCN and THF, then TBAF, THF; (ii) LDA, LiCl, THF −78 °C to rt, BnBr, 0 °C to rt; (iii) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C to rt; (iv) *n*-Bu_4NOH, *t*-BuOH, H_2O, THF, Δ; (v) 1-methylimidazole, *n*-BuLi, THF −78 °C to rt then *i*-Pr_2NH.

As pseudoephedrine resin **18** appeared to show a good correlation with Myers' solution auxiliary chemistry, we completed our study by assessing the utility of **18** for the solid phase synthesis of α-amino acids employing Myers' asymmetric alkylation of pseudoephedrine glycinamide.[6b,d,f] Immobilised glycinamide **25** was prepared by treatment of resin **18** with glycine methyl ester hydrochloride and triethylamine in THF.[6f] Unfortunately, exposure of **25** to the conditions for alkylation, hydrolytic cleavage with NaOH and Boc protection gave a 40% overall yield of *N*-Boc-glycine and *N*-Boc phenylalanine in a disappointing 5 : 1 ratio (Scheme 7). Attempts to improve the efficiency of the alkylation step have so far been unsuccessful.

While the alkylation of dianion intermediates generated from polymer-supported pseudoephedrine amides **19** proceeds satisfactorily, the efficient generation and alkylation of such intermediates from immobilised pseudoephedrine glycinamide **25** is more difficult and represents the current limit for the adaptation of Myers' chemistry to polystyrene supported derivatives. The use of other supports may resolve this problem.[14]

In conclusion, we have developed a polymer-supported pseudoephedrine auxiliary linked to the support through nitrogen. The auxiliary parallels Myers' solution chemistry more closely than the previously reported pseudoephedrine resin in that it allows direct access to enantiomerically enriched carboxylic acids in addition to alcohols and ketones.



Scheme 7 *Reagents and conditions*: (i) *O*-Me-glycine·HCl, *t*-BuOLi, THF, rt; (ii) LHMDS, LiCl, THF, 0 °C, BnBr 0 C to rt; (iii) 2 M NaOH, dioxane, H_2O, THF, Δ; (iv) Boc_2O, dioxane, H_2O, 0 °C to rt.

We acknowledge financial support from the EPSRC and Crystal Faraday (A. M. M. and J.-C. K).

Notes and references

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8 Myers has shown that hydrolysis of pseudoephedrine amides proceeds through *N*–*O* acyl transfer followed by ester hydrolysis (see ref. 6*e*).

9 *N*-Benzylpseudoephedrine amide **2** was prepared from norpseudoephedrine by *N*-benzoylation, $LiAlH_4$ reduction and acylation (63% overall).

10 CCDC reference number 632894. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700477j Crystal data for **4**. $C_{26}H_{29}NO_2$, M = 387.50, orthorhombic, a = 8.4065(12), b = 9.6892(14), c = 26.482(4) Å, U = 2157.0(5) Å^3, T = 100(1) °C, space

group $P2_12_12_1$ (no. 19), $Z = 4$, μ(MoKα)=0.074 mm^{-1}, $F(000) = 832$, 11625 measured reflections, 2557 unique reflections ($R_{int} = 0.0416$). Refinement was carried out on F^2 using all the data. The final $R1 = 0.0456$ for the 2402 reflections with $I > 2.00\ \sigma(I)$, w$R2 = 0.\ 0.1144$ for all the data.

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12 S. Kobayashi, I. Hachiya, S. Suzuki and M. Moriwaki, *Tetrahedron Lett.*, 1996, **37**, 2809.

13 It is known that epimerisation can sometimes occur in the synthesis of ketones from pseudoephedrine amides (Ref. 4 and 6*e*).

14 To investigate whether aggregation of the anionic species was an issue, we prepared **18** from commercial, *macroporous* thiol resin. Unfortunately, use of the rigid, highly cross-linked beads led to no improvement in the alkylation of the pseudoephedrine glycinamide intermediate.

