ORGANIC LETTERS

2002
Vol. 4, No. 26
4583−4585

Evaluation of a Pseudoephedrine Linker for Asymmetric Alkylations on Solid Phase

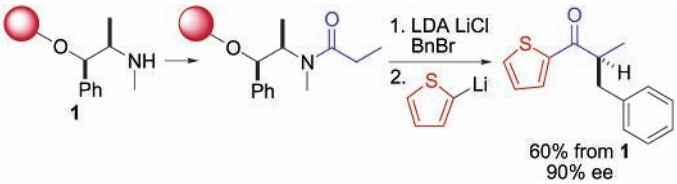
Panee C. Hutchison,[†] Tom D. Heightman,[‡] and David J. Procter*,[†]

Department of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow, G12 8QQ, United Kingdom, and GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom

davidp@chem.gla.ac.uk

Received September 10, 2002

ABSTRACT



Immobilized pseudoephedrine amides have been conveniently prepared by attachment of pseudoephedrine to Merrifield resin and acylation on nitrogen. Deprotonation and alkylation of the resin bound amides proceeds smoothly. Products were cleaved from the resin to give ketones and alcohols in high enantiomeric excess and moderate to good overall yield.

Although the use of a supported chiral auxiliary was first reported 30 years ago, the efficient, asymmetric synthesis of chiral compounds using solid phase auxiliaries is still a relatively underdeveloped area.[1] Oxazolidinone-based auxiliaries have been most commonly employed; however, these auxiliaries must be prepared, either on or off resin, prior to use, and their efficient recycling has yet to be described. In addition, in one example, the attachment of an oxazolidinone-based auxiliary to a solid support was problematic due to side reactions. This has recently led to confusion over the exact nature of an immobilized oxazolidinone auxiliary.[2]

Our interest in the development of new solid-phase, linker technologies[3] has led us to consider readily available and inexpensive ephedrine and pseudoephedrine derivatives as "*chiral linkers*" for solid-phase synthesis. These linkers would allow substrates to be linked to resin and control the stereochemistry of reactions carried out on the substrate. Importantly, the "one-step" attachment of the commercially available ephedrine or pseudoephedrine unit to resin through either oxygen or nitrogen should be straightforward leading to robust ether or amine linkages (Figure 1).

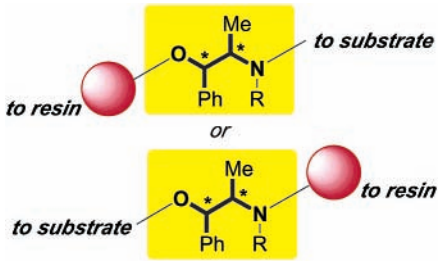


Figure 1. Ephedrine and Pseudoephedrine Chiral Links.

In this Letter, we describe the first application of this strategy in an adaptation of Myers' pseudoephedrine auxiliary approach for the asymmetric alkylation of amide enolates.[4]

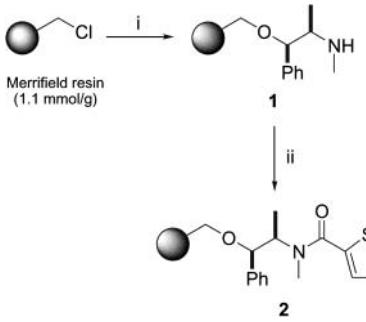
(1*R*,2*R*)-Pseudoephedrine was attached to Merrifield resin by adapting Welch's procedure for O-benzylation.[5] The

[†] University of Glasgow.
[‡] GlaxoSmithKline.

10.1021/ol0268788 CCC: $22.00
Published on Web 12/04/2002

loading at this stage was determined by conversion of **1** to the thiophene carboxamide **2** followed by sulfur elemental analysis of the resin. In Myers' original pseudoephedrine auxiliary approach, deprotonation generates a dianion as the hydroxyl on the auxiliary is also deprotonated during enolization. The lithium alkoxide on the auxiliary has been implicated in attempts to rationalize the diastereoselectivity of the alkylation reactions.[6]

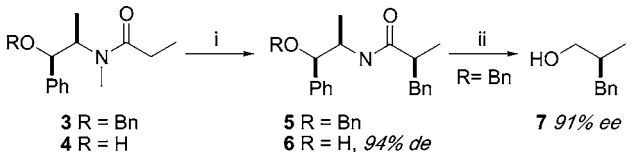
Scheme 1[a]



[a] Reagents and conditions: (i) KH, (1*R*,2*R*)-pseudoephedrine, THF, 18 h; resultant solution was then added to resin in THF, rt. (ii) Thiophene carbonyl chloride, NEt_3, CH_2Cl_2, rt.

Clearly in our approach, as the hydroxyl group of pseudoephedrine acts as a link to the solid support, formation of an analogous dianion is not possible. To ensure that high diastereoselectivites would still be observed in alkylations of our system, *O*-benzylpseudoephedrine amide **3**, a solution-phase model for an immobilized amide, was prepared and alkylated (Scheme 2).

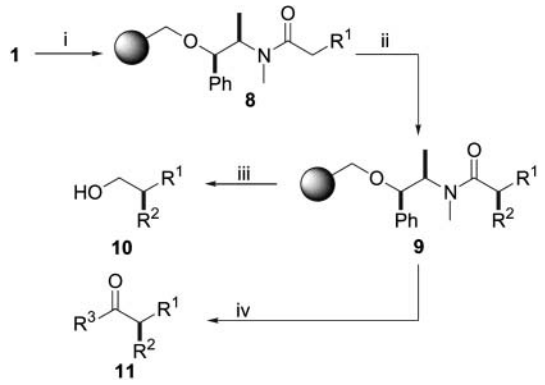
Scheme 2[a]



[a] Reagents and conditions: (i) LDA (2.1 equiv), LiCl (6 equiv), THF, from −78 °C to rt; BnBr was then added at 0 °C, 86%. (ii) LDA (3.9 equiv), $BH_3{\cdot}NH_3$, THF, from 0 °C to rt, 55%.

Crucially, only slightly lower diastereoselectivity (91% de) was observed in the case of the *O*-benzylpseudoephedrine amide **3**, compared to the analogous Myers-type substrate **4** (94% de).[7] Assured that linkage to the resin through oxygen should not greatly effect the diastereoselectivity of alkylation reactions, we performed acylation of pseudoephedrine resin **1** (anhydride or acid chloride, NEt_3 CH_2Cl_2, rt) to give the corresponding resin-bound pseudoephedrine amides **8** (ν_{max} 1635−1645 cm^{-1}).[8] Amides **8** were then deprotonated and alkylated to give adducts **9** (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (i) Propionic anhydride/valeric anhydride/phenylacetyl chloride, NEt_3, CH_2Cl_2, rt. (ii) LDA (6.2 equiv), LiCl (36 equiv), THF, from −78 °C to rt; BnBr/BuI (4.5 equiv) was then added at 0 °C. (iii) LDA (1.2 equiv), $BH_3{\cdot}NH_3$ (1.2 equiv), from −78 °C to rt; mixture was added to resin at 0 °C and allowed to warm to rt. (iv) R^3Li, Et_2O, from −78 °C to 0 °C.

Myers' has shown that the auxiliary group can be removed from pseudoephedrine amides, using a variety of methods to give carboxylic acids, primary alcohols, ketones, and

(1) Carbohydrate-based auxiliaries: (a) Kawana, M.; Emoto, S. *Tetrahedron Lett.* **1972**, *48*, 4855. Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 160. (b) Oertel, K.; Zech, G.; Kunz, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1431. Chiral amines: (c) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 221. McArthur, C. R.; Worster, P. M.; Jiang, J.-L.; Leznoff, C. C. *Can. J. Chem.* **1982**, *60*, 1836. Evans oxazolidinones: (d) Allin, S. M.; Shuttleworth, S. J. *Tetrahedron Lett.* **1996**, *37*, 8023. (e) Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785. (f) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777. (g) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655. (h) Winkler, J. D.; McCoull, W. *Tetrahedron Lett.* **1998**, *39*, 4935. (i) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 1265. Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313. Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron*: *Asymmetry* **2002**, *13*, 333. Pyrrolidine-based auxiliaries: (j) Moon, H.-s.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088. Moon, H.-s.; Schore, N. E.; Kurth, M. J. *Tetrahedron Lett.* **1994**, *35*, 8915. Oppolzer's camphorsultam: (k) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. Oxazolines: (l) Colwell, A. R.; Duckwall, L. R.; Brooks, R.; McManus, S. P. *J. Org. Chem.* **1981**, *46*, 3097. Hydrazine auxiliaries: (m) Enders, D.; Kirchhoff, J. H.; Köbberling, J.; Peiffer, T. H. *Org. Lett.* **2001**, *3*, 1241. Alcohol auxiliary: (n) Akkari, R.; Calmes, M.; Mai, N.; Rolland, M.; Martinez, J. *J. Org. Chem.* **2001**, *66*, 5859. Sulfinamide auxiliary: (o) Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127. α-Hydroxyvaline auxiliary: (p) Savinov, S. N.; Austin, D. J. *Org. Lett.* **2002**, *4*, 1419.

(2) Bew, S. P.; Bull, S. D.; Davies, S. G. *Tetrahedron Lett.* **2000**, *41*, 7577.

(3) McKerlie, F.; Procter, D. J.; Wynne, G. *Chem. Commun*. **2002**, 584.

(4) (a) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (d) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428. (e) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322.

(5) Näslund, J.; Welch, C. J. *Tetrahedron*: *Asymmetry* **1991**, *2*, 1123. In our hands, solution-phase benzylation of pseudoephedrine under these conditions was found to give less than 5% *N*-benzyl pseudoephedrine. Thus, similar high selectivity for O-alkylation is expected in the immobilization step.

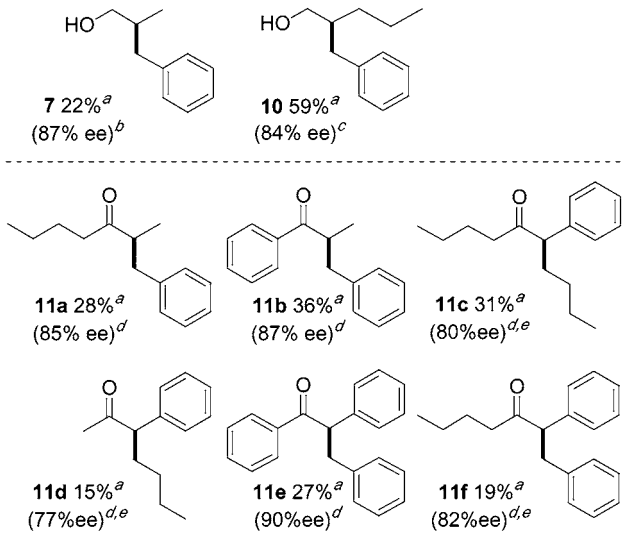
(6) For a discussion, see ref 4c.

(7) For the R = H series, diastereoselectivities were determined by conversion of **6** into the corresponding TMS ether and analysis by GCMS. For the R = Bn series, the diastereoisomeric purity of **5** was obtained indirectly from the enantiomeric excess of **7**.

aldehydes.[4c] In our solid-phase approach, the use of different cleavage strategies allows us to introduce further diversity into our collection of compounds during the cleavage process.

One disadvantage of simple immobilization through the hydroxyl group of the pseudoephedrine unit is that hydrolytic cleavage after alkylation, to give enantiomerically enriched carboxylic acids directly, is not possible using Myers' conditions. Myers has clearly shown that hydrolysis of pseudoephedrine amides proceeds through N−O acyl transfer followed by ester hydrolysis.[4c] This is obviously not possible if the hydroxyl is derivatized. We have, however, been successful in cleaving products from the resin to give primary alcohols and ketones: primary alcohols **7** and **10** were obtained by reduction of the immobilized pseudoephedrine amides with lithium amidotrihydroborate (LAB, LiH_2NBH_3),[9,4c] while ketones **11** were prepared by reaction of the starting amides with alkyllithium reagents (R^3Li, Et_2O/THF).[4c]

Moderate to good isolated yields are obtained for the three-step processes and products are obtained in good enantiomeric excess (Figure 2).[10,11] No extensive attempts to optimize the diastereoselectivity of the alkylation reactions on solid phase or the efficiency of the cleavage steps have yet been made.

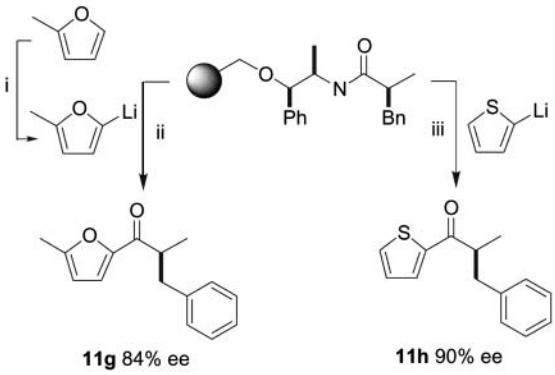


[a] isolated yields based on the loading of **1** and for 3 steps.
[b] ee was determined by chiral GC (see supporting information).
[c] ee was determined by the method outlined in ref 10.
[d] ee was determined by the procedure outlined in ref 11.
[e] ee of the product lowered due to some enolization on cleavage.

Figure 2.

The use of readily available heteroaryllithiums in the cleavage step allows efficient access to heteroaromatic ketones and illustrates the potential of our approach for the generation of libraries of enantiomerically enriched compounds (Scheme 4).[11]

Scheme 4[a]



[a] Reagents and conditions: (i) ^{n}BuLi (1.0 equiv), THF, −25 °C. (ii) Heteroaryllithium (4.8 equiv) was added to resin (1.0 equiv) at −78 °C and then warmed to 0 °C, 47% for three steps from **1**. (iii) Thienyllithium (4.8 equiv) was added to resin (1.0 equiv) at −78 °C and then warmed to 0 °C, 60% for three steps from **1**.

In summary, inexpensive pseudoephedrine can be conveniently immobilized on Merrifield resin in a single step, through a robust ether link. The first asymmetric alkylations on amides immobilized via this pseudoephedrine linker have been carried out. Cleavage of products from the resin gives primary alcohols and ketones in moderate to good overall yield and good enantiomeric excess. We are currently developing methods for cleavage that will allow access to other classes of enantiomerically enriched products and are examining the recycling of the chiral resin. In addition, we are applying pseudoephedrine and ephedrine linkers to other asymmetric processes on solid phase.

Acknowledgment. We thank the University of Glasgow for the award of a University Scholarship to P.C.H and GlaxoSmithKline for a CASE award to P.C.H. We also thank Prof. Philip Hodge for suggesting the thiophene carboxamide method for the determination of loading. Finally, we acknowledge Mr. J. Gall from the NMR Spectroscopy Laboratory at the University of Glasgow for technical assistance.

Supporting Information Available: Experimental procedures and full characterization data for **1**−**3**, **5**, **7**−**10**, and **11a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0268788

(8) In some IR spectra, extremely faint *ester* carbonyl stretches could also be seen. This is in agreement with previous observations regarding high selectivity in the O-alkylation of pseudoephedrine (see ref 5).

(9) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

(10) Enantiomeric excess of alcohol **10** was determined by preparation of both the (*R*)- and (*S*)- Mosher's esters and analysis by ^{19}F NMR.

(11) Enantiomeric excess of ketones **11a**−**f** and **11h** was determined by reduction of the ketones with $LiAlH_4$, esterification with both (*R*)- and (*S*)-Mosher's acids and analysis of the resultant diastereoisomeric mixtures of esters by ^{19}F NMR (see ref 4c). Enantiomeric excess of **11g** was determined by chiral HPLC.