# Resin type can have important effects on solid phase asymmetric alkylation reactions

**Kevin Burgess* and Dongyeol Lim**

*Department of Chemistry, Texas A & M University, College Station, TX 77843-3255, USA*

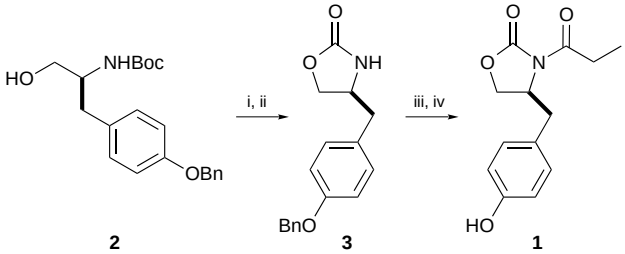
**A new *N*-propionylated oxazolidinone 1 is prepared; asymmetric alkylations of this auxiliary proceed with varying yields and enantioselectivities when supported on Merrifield, Wang and TentaGel R PHB resins.**

Techniques for solid phase organic syntheses[1] are pivotal for the development of combinatorial methods and other approaches to high throughput syntheses.[2–4] Asymmetric reactions on a solid phase have not been widely explored so far, yet they have potential advantages for some applications.[5] Supported chiral auxiliaries, for instance, can be recovered by filtration, and could potentially be recycled.

Two issues that need to be addressed for syntheses and applications of supported chiral auxiliaries are, first, how the auxiliary will be linked to the solid phase and, second, which solid phase will be used. At least two approaches to these problems have been reported. Leznoff initiated this area of research in studies wherein chiral amines were *O*-linked to Merrifield resin; condensations of these supported amines with cyclohexanone gave imines which were then deprotonated and *C*-methylated with high stereoselectivities.[6] More recently, Kurth and co-workers have attached pyrrolidine-based auxiliaries to Merrifield resin and used them in allylation/iodolactonization sequences.[7–9] Neither of these studies, however, embraced auxiliaries that are widely used in contemporary organic syntheses, and some of the supports that are now favoured for solid phase reactions. Here we describe an oxazolidinone **1** that can be conveniently linked to polymeric materials, and demonstrate that the choice of resin is important with respect to applications of the supported-auxiliary.

Synthesis of the oxazolidinone **1** began with commercially available Boc-Tyr(Bn) which was easily reduced to the corresponding alcohol **2** ($Pr^iOCOCl$, $NEt_3$, THF, then $NaBH_4$, $H_2O$). Removal of the *N*-protecting group and reaction with phosgene gave oxazolidinone **3** (Scheme 1). This material was then *N*-propionylated and subjected to hydrogenolysis to give the desired auxiliary **1**.

One of the attractive features of oxazolidinone **1** is that the phenolic hydroxy group is available for attachment to polymers. For Merrifield's resin this was accomplished *via* nucleophilic displacement of the benzylic chloride (3 equiv. of **1**, $Bu^tOK$, catalytic 18-crown-6/$Bu_4NI$, DMF, 75 °C, 3.5 d).[9] However, for the Wang and TentaGel resins Mitsunobu couplings[10] were used (3 equiv. of **1**, $EtO_2CNNCO_2Et$, $PPh_3$, 20 h).[11–13] Loadings of the auxiliary on the resins were difficult to determine accurately; after some experimentation, the following method was developed. The functionalized resins were reacted with lithium benzyloxide, and the benzyl propionate produced was quantified using HPLC and NMR. On the basis of these measurements it was calculated that approximately 30% of the available reactive sites on the Merrifield resin were coupled with the auxiliary under the conditions described above. For the Wang and TentaGel resins the corresponding loadings were 56 and 60% respectively.



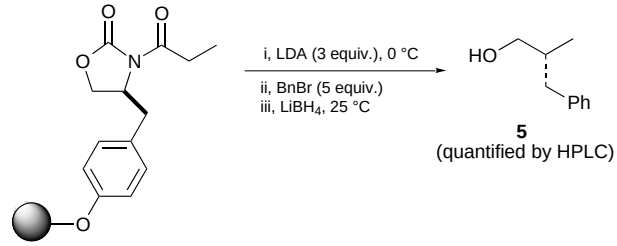

**2** **3** **1**

**Scheme 1** *Reagents and conditions*: i, HCl, $Et_2O$–EtOAc, 25 °C, 15 h (93%); ii, $COCl_2$, KOH–$K_2CO_3$ (aq), MePh, 0–25 °C, 12 h (98%); iii, $(EtCO)_2O$, LiCl, $NEt_3$, THF, −78–25 °C, 18 h (93%); iv, $H_2$, cat. Pd–C, MeOH–EtOAc, 25 °C, 12 h (96%)

Deprotonation of the supported oxazolidinones **4** with LDA in THF then reaction with benzyl bromide was chosen as a model transformation. These reactions were followed by IR (KBr disc). With Wang resin for instance, the supported oxazolidinones **4** had carbonyl stretches at 1704 and 1785 $cm^{-1}$. Benzylation of this material shifted the IR bands to 1701 and 1778 $cm^{-1}$. Hydrolytic cleavage of the benzylated propionate produced resin with a single carbonyl stretch at 1743 $cm^{-1}$, corresponding to the supported auxiliary. IR spectra of similar, but unsupported, auxiliaries have carbonyl stretches at *ca*. 1752 $cm^{-1}$.

A series of preliminary reactions showed the number of equivalents of base and the reaction times had a significant effect on the enantiomeric excess. It was also observed that reactions on the TentaGel resin were faster than on the Merrifield and Wang supports. Consequently, a series of experiments were performed in which 3 equiv. of LDA were added to the heterogeneous auxiliary at 0 °C. For the Merrifield and Wang resins, benzyl bromide was added after 30 min, allowed to react at 0 °C for 30 min, then for a systematically varied time at 25 °C. For the TentaGel based system, benzyl bromide was added after 20 min, and allowed to react for various times at 0 °C. The results of these studies are summarized in Fig. 1.

Fig. 1 shows that the yield of alcohol **5** reaches a maximum in the initial stages of the reaction, then decreases. For the TentaGel resin, the maximum yield is observed at short reaction times and decreases more precipitously as the reaction time is extended than for either the Merrifield or the Wang resins. Throughout, the HPLC traces of the material cleaved from the support show only one UV active product, hence the reduction in the yield is not due to formation of supported impurities with UV chromophores. Decreased yields could, however, be due to




**4a** Merrifield
**b** Wang
**c** TentaGel

**5**
(quantified by HPLC)

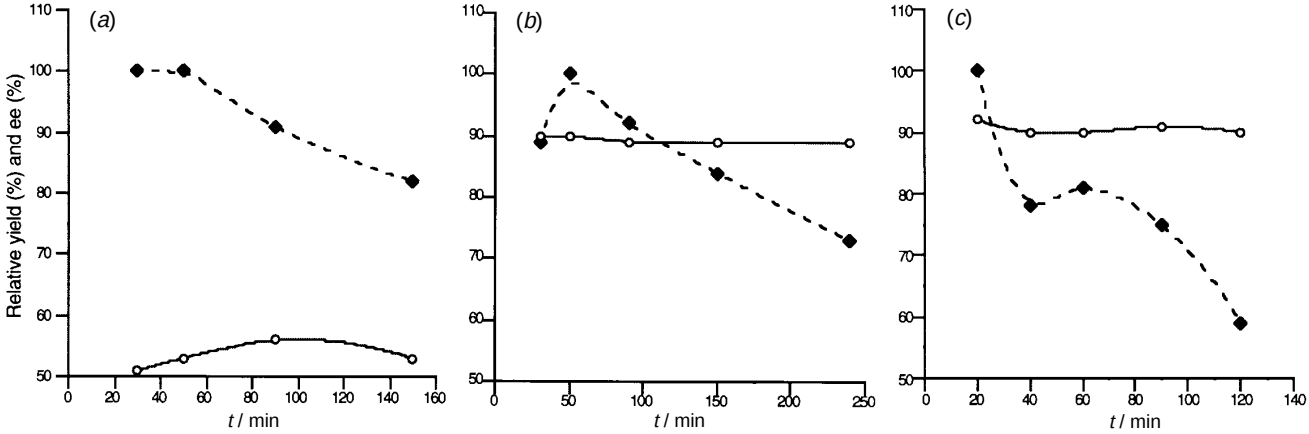
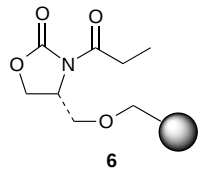



**Fig. 1** Percent yield (relative to the maximum for that reaction (◆) and enantiomeric excess (○) profiles for benzylation of the supported auxiliary **4** on (*a*) Merrifield, (*b*) Wang and (*c*) Tentagel R PHB resins. For conditions, see text.

**Table 1** Asymmetric alkylation reactions of the Wang-supported oxazolidinone **4b**

| | Reaction conditions | | | | |
|---|---|---|---|---|---|
| Alkylating agent | Equiv. LDA | Time/h at 0 °C | Time/h at 25 °C | Yield[a] (%) | Ee[b] (%) |
| BnBr | 3 | 0.5 | 0.33 | 66 | 90 |
| BnBr | 2 | 1.0 | 12 | 39 | 86 |
| $CH_2CHCH_2Br$ | 3 | 0.5 | 0.33 | 25 | 81[c] |
| $CH_2CHCH_2Br$ | 2 | 2.0 | 15 | — | 88 |
| $BnOCH_2Cl$ | 3 | 0.5 | 0.33 | 12 | 71[d] |
| $BnOCH_2Cl$ | 2 | 2.5 | 14 | 20 | 76[d] |

[a] For the alkylation and cleavage steps combined, determined by analytical HPLC using phenylpropanol as an internal standard. Authentic racemic products were prepared by solution phase syntheses and identified by $^1H$ and $^{13}C$ NMR spectroscopy. [b] Determined by analytical HPLC using a ChiralCel OD column. [c] Yields and ees were determined by using a chiral GC column prepared 'in house'. [d] Errors were relatively high because HPLC resolution of the enantiomers on a ChiralCel OD did not give baseline separation.



**6**

loss of the propionyl group from the oxazolidinone prior to cleavage.[14] Consistent with this, the IR stretch for the supported amide at 1701 $cm^{-1}$ diminishes with reaction time. Throughout, the measured enantiomeric excesses of the product **5** vary by ±3%; this fluctuation is probably within experimental error. However, in other experiments it was observed that after longer reaction times the enantiomeric excess of the product decreases measurably.

Overall, the data in Fig. 1 indicate that in terms of yield, enantiomeric excess and preservation of yield after extended reaction times, Wang resin is the preferred support. It is also cheaper than TentaGel resin, and has a higher loading capacity. Several more reactions were therefore performed using Wang resin and the results are summarized in Table 1. Yields and enantiomeric excesses obtained for benzyl bromide were superior to those obtained with other electrophiles. However, the results for these other electrophiles probably could be improved *via* optimization studies of the type carried out for the benzylation reactions.

After this work was complete, but before these studies were submitted for publication, other researchers reported the preparation of an oxazolidinone **6**, supported on Merrifield resin.[15] One alkylation reaction of this material was described (2 equiv. LDA, THF, 0 °C, then 2 equiv. BnBr; deprotonation and alkylation time unspecified), and that benzylation product (isolated as the acid) had an enantiomeric excess of 96%. We would have anticipated that the structural differences between auxiliaries **6** and **4** would be such that the tyrosine derivative **4** would give higher diastereoselectivities. In fact, **4** on Merrifield resin in our study gave stereoselectivities that are markedly inferior to those reported for **6** on the same resin, a result that we find surprising.

Overall, we conclude that optimization of these solid phase alkylation reactions is more difficult than for the corresponding solution phase reactions; the support has a marked effect and different resins may be most suitable for different oxazolidinones and electrophiles. Generally, solid phase reactions are more difficult to study than transformations in solution because they are more difficult to monitor. In addition, this work shows that resin type can be a significant variable that can further complicate the process of optimization.

We thank Dr Aroonsiri Shitangkoon for help with the chiral chromatography. Financial support for this research was obtained from The National Institutes of Health and The Robert A. Welch Foundation, and K. B. thanks the NIH for a Research Career Development Award and the Alfred P. Sloan Foundation for a fellowship. NMR facilities were provided by the NSF *via* the chemical instrumentation programme.

## References

1 L. A. Thompson and J. A. Ellman, *Chem. Rev.*, 1996, **96**, 555.
2 M. A. Gallop, R. W. Barrett, W. J. Dower, S. P. A. Fodor and E. M. Gordon, *J. Med. Chem.*, 1994, **37**, 1233.
3 E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor and M. A. Gallop, *J. Med. Chem.*, 1994, **37**, 1385.
4 N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki and J. Steele, *Tetrahedron*, 1995, **51**, 8135.
5 M. Reggelin and V. Brenig, *Tetrahedron Lett.*, 1996, **37**, 6851.
6 C. R. McArthur, P. M. Worster, J.-L. Jiang and C. C. Leznoff, *Can. J. Chem.*, 1982, **60**, 1836.
7 X. Beebe, N. E. Schore and M. J. Kurth, *J. Am. Chem. Soc.*, 1992, **114**, 10061.
8 H.-S. Moon, N. E. Schore and M. J. Kurth, *Tetrahedron Lett.*, 1994, **35**, 8915.
9 H.-S. Moon, N. E. Schore and M. J. Kurth, *J. Org. Chem.*, 1992, **57**, 6088.
10 D. L. Hughes, *Org. React.*, 1992, **42**, 335.
11 L. S. Richter and T. R. Gadek, *Tetrahedron Lett.*, 1994, **35**, 4705.
12 T. A. Rano and K. T. Chapman, *Tetrahedron Lett.*, 1995, **36**, 3789.
13 V. Krchnak, Z. Flegelova, A. S. Weichsel and M. Lebl, *Tetrahedron Lett.*, 1995, **36**, 6193.
14 D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
15 S. M. Allin and S. J. Shuttleworth, *Tetrahedron Lett.*, 1996, **37**, 8023.

*Received, 19th December 1996; Com. 6/08524E*