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The Preparation and First Application of a Polymer-Supported "Evans" Oxazolidinone.

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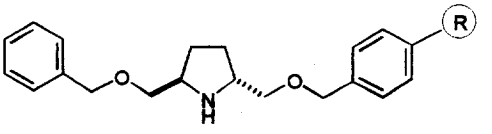
Abstract: The preparation of a polymer-supported "Evans" oxazolidinone is described, and its use as a chiral auxiliary is demonstrated by the synthesis of a chiral α-alkyl carboxylic acid (e.e. 96%).

Over recent years there has been increasing interest in solid phase organic synthesis (SPOS),[1] mainly due to the emergence of combinatorial chemistry as an approach to the lead compounds required in drug discovery programmes.[2] As the field of medicinal chemistry has progressed, the importance of chirality in drug design has become a major factor for consideration.

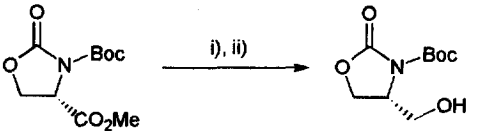
We are currently investigating the development of polymer-supported chiral auxiliaries for use in the solid phase (possibly combinatorial) synthesis of a wide range of optically active organic compounds. Kurth has recently reported the synthesis of optically active 3,5-disubstituted-γ-butyrolactones using the polymer-supported C_2-symmetric amine (1) as chiral auxiliary.[3] Unfortunately the preparation of such C_2-symmetric systems can be lengthy, which may limit their use compared to other chiral auxiliary systems.[4]



(1)

In this communication we wish to report the preparation of a novel, polymer-supported chiral auxiliary based on the "Evans oxazolidinones". The oxazolidinones are arguably the most successful of the chiral auxiliary systems currently available for asymmetric transformations based on acyl group reactivity. The range of reaction types currently amenable to stereocontrol using oxazolidinones includes: enolate alkylation[5], enolate oxidation[6], enolate halogenation[7], enolate amination[8], enolate acylation[9], aldol reactions[10] and Diels-Alder reactions.[11] The desired chiral products may be deprotected by mild, non-destructive hydrolysis to yield the optically pure products as either acids, esters or alcohols[5] and regenerate the auxiliary in optically pure form for re-use.

Our initial target, compound (**2**), was accessed from L-serine following the methods of Sibi.[12] Reduction of the ester group was achieved using sodium borohydride in ethanol[13] to yield the desired alcohol (**3**) in 66% yield as highlighted in Scheme 1.

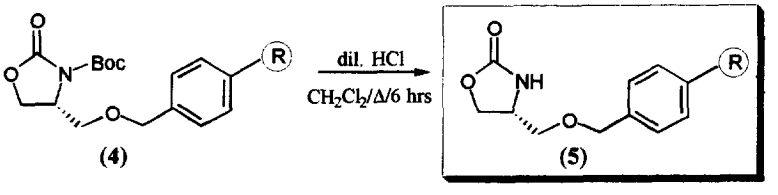


(**2**) (**3**)

i) $NaBH_4$, EtOH, 0 °C; ii) NH_4Cl (sat. aq.)

Scheme 1.

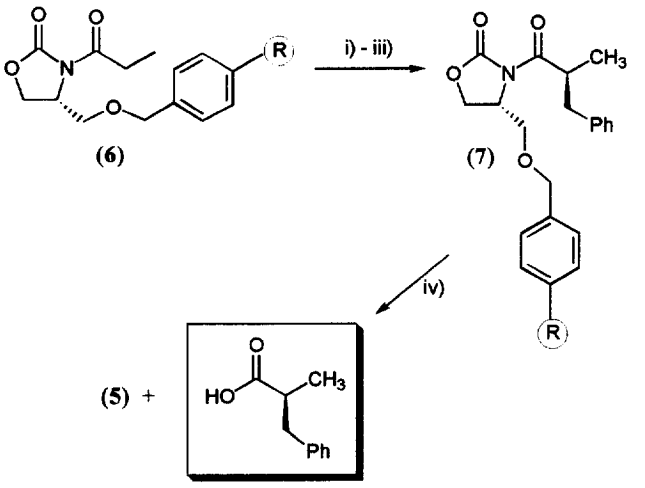
The hydroxyl group was required to act as a "handle" for coupling of (**3**) to a suitably functionalised polymer support. We chose to employ Merrifield's resin,[14] reasoning that the bulky benzyl substituent would provide a high degree of steric bias in future asymmetric syntheses. The potassium alkoxide was generated by addition of 1.5 equivalents of potassium hydride to a stirred solution of (**3**) in DMF at 0°C. After 2 hours the resulting alkoxide was transferred to a suspension of DMF-swollen Merrifield's resin (1 molar equivalent) containing a catalytic amount of 18-crown-6; the reaction mixture was heated to 80°C and stirred at this temperature for 5 days. Filtration of the resin, washing successively with DMF, MeOH, THF and Et_2O furnished the polymer-supported *N*-protected oxazolidinone (**4**), as evidenced by FTIR spectroscopy [KBr, 1749 (C=O), 1685 (C=O), 1601 cm^{-1} (Ar)]. Removal of the Boc protecting group was accomplished using traditional methods,[15] and could be followed by disappearance of the FTIR band corresponding to the Boc-carbonyl group at 1685 cm^{-1}.



(**4**) (**5**)

Scheme 2.

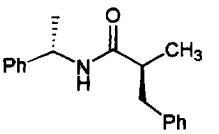
Thus, preparation of the desired polymer-supported oxazolidinone was accomplished in only 5 steps. In order to investigate the potential of our novel polymer-supported reagent we were required to produce an *N*-acyl derivative such as (**6**). Following a recent report by Ager,[16] this was accomplished using triethylamine/DMAP (10%)/propionic anhydride in THF solvent under reflux for 4 days. FTIR analysis of the resin revealed a new carbonyl band corresponding to the *N*-propionyl side chain (1652 cm^{-1}).



i) LDA (2 eq.), THF, 0°C; ii) $PhCH_2Br$ (2 eq.); iii) NH_4Cl (sat. aq.); iv) $LiOH.H_2O$, THF, H_2O.

Scheme 3.

THF-swollen resin (**6**) was treated with lithium diisopropylamide to give, presumably, the chelated *Z*-enolate[5] which was quenched by addition of benzyl bromide (Scheme 3). Treatment of alkylated resin (**7**) with lithium hydroxide monohydrate in THF/water (3:1) for 12 hours furnished the desired α-alkylated carboxylic acid (**8**) in 42% yield (based on loading of the original Merrifield polymer) and regenerated the polymer-supported chiral auxiliary (**5**), which was isolated simply by filtration. The ^{1}H-NMR spectrum of (**8**) was consistent with previously reported spectra.[17] The absolute configuration of (*S*)-(+)-(**8**) was determined by comparison of previously reported data for the specific optical rotation of the known compound.[18] The induced stereochemistry is as expected from the usual transition state models suggested for alkylation of *Z*-enolates derived from *N*-acyl oxazolidinones.[5] An e.e. of 96% was determined by conversion of the acid to the corresponding (*S*)-α-methylbenzylamine-derived amide (**9**) for NMR assay,[19] as described by Vedejs.[20]



(**9**)

In summary, we report the first synthesis of a polymer-supported oxazolidinone and have demonstrated the potential for carrying out typical acyl group chemistry on such a system. Further investigations are underway to establish the extent and possible limitations of Evans' chemistry with polymer-supported auxiliaries.

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18. (*S*)-(+)-(**8**): $[\alpha]_D^{22}$ = + 23.81 (*c* 5.5, EtOH), [lit[17]: $[\alpha]_D$ = + 17.7, (*c* 2.37, EtOH)]. A value of + 28.6 (*c* 1, $CHCl_3$) has been reported by Davies and co-workers.[21]
19. The e.e. value was determined by integration of the doublet signals observed for the methyl groups in both the major and minor diastereoisomer products (major isomer: δ 1.29 (3H, d, *J* 7.8), 1.40 (3H, d, *J* 7.8); minor isomer: δ 1.34 (d, *J* 7.8) [only one doublet for minor isomer visible, second signal obscured by other resonances in the crude reaction mixture].
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