

Solid Phase Aldol and Conjugate Addition Reactions Using Evans' Oxazolidinone Chiral Auxiliary

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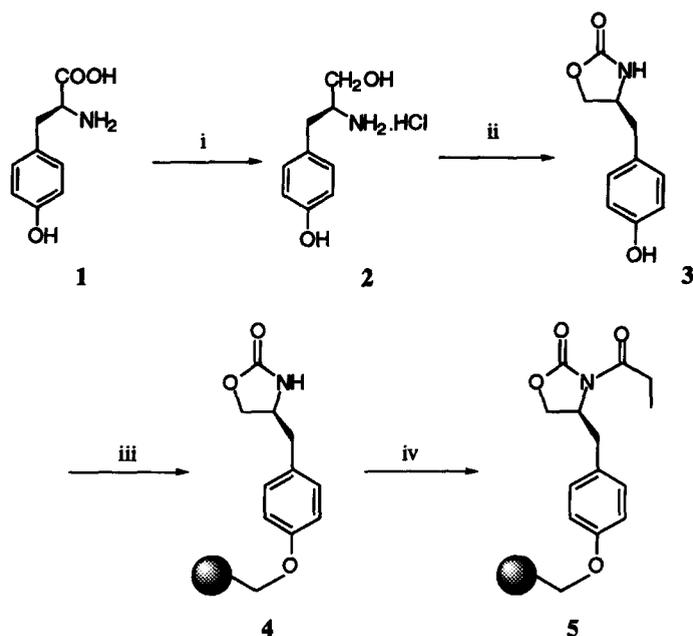
Abstract: Resin-supported Evans' chiral auxiliary is used in an aldol and a conjugate addition reaction on solid phase. The experiments show that solid-phase asymmetric reactions can reproduce the high enantiomeric excesses observed in solution phase reactions and also highlight specific problems associated with working on resin. © 1998 Elsevier Science Ltd. All rights reserved.

A continuing challenge in solid phase chemistry is to adapt solution phase reactions to work well on resin.¹ As confidence in the generality of solid phase chemistry has grown, so more challenging aspects of synthetic chemistry such as asymmetric synthesis are being developed on resin.² In this area, one of the most important chiral auxiliaries is the oxazolidinone introduced by Evans.³ This has been used *inter alia* for asymmetric alkylations, aldol⁴ and conjugate addition reactions.⁵ A soluble boron enolate derived from acylated Evans' chiral auxiliary has been used in an aldol reaction with a resin-bound aromatic aldehyde.⁶ A resin-bound Evans' auxiliary has been used in alkylation reactions,⁷ and most recently in an aldol reaction, although the enantiomeric excess obtained was not reported.⁸ In this paper we report a simple approach for attaching Evans' chiral auxiliary to resin, and its use in solid phase aldol and conjugate addition reactions. The enantiomeric excesses observed in both reactions are comparable with the corresponding solution phase reactions.

Preparation of the Resin-supported Evans' Auxiliary

The preparation of resin-supported Evans' auxiliary is shown in Scheme 1. *L*-Tyrosine was reduced to *L*-tyrosinol using borane-dimethyl sulfide complex,⁹ which was immediately converted to its hydrochloride salt **2**. Treatment of the salt **2** with saturated aqueous sodium bicarbonate regenerated *L*-tyrosinol, which was converted to oxazolidinone **3** by heating with diethyl carbonate. The oxazolidinone **3** was attached directly onto hydroxymethyl resin under Mitsunobu conditions.¹⁰ The FTIR spectrum of **4** showed bands at 3447 cm⁻¹ (m, N-H) and 1758 cm⁻¹ (s, C=O).

To acylate the auxiliary, it was first treated with *n*-BuLi twice. This involved draining away the excess reagent from the first treatment before a fresh batch of THF and *n*-BuLi was added. After draining the second batch of *n*-BuLi, the resin was resuspended in THF and the propionyl chloride was added. The propionylated auxiliary **5** was characterised by FTIR spectroscopy, showing bands at 1776 (s, C=O of oxazolidinone), and 1709 cm⁻¹ (s, C=O). Derivatised resin **5** has previously been prepared by using the phenolate of the propionylated auxiliary to displace chloride from Merrifield resin.⁷ The approach we describe here is shorter and uses milder conditions.¹¹



Scheme 1. (i) $\text{BH}_3\cdot\text{SMe}_2$ (3 eq.), $\text{BF}_3\cdot\text{OEt}_2$ (1.2 eq.), THF, reflux, 18 h; 5 M aq. NaOH, reflux, 24 h, then 6 M aq. HCl (83%); (ii) sat. aq. NaHCO_3 ; $(\text{EtO})_2\text{CO}$ (4 eq.), K_2CO_3 (20 mol%), 125–130 °C, 8 h (86%); (iii) hydroxymethyl resin, DEAD (5 eq.), Ph_3P (5 eq.) for 5 eq. of **3**, THF, 0 °C, 1 h, then 25 °C, 72 h (iv) *n*-BuLi (10.5 eq.), THF, -78 °C, 1 h, twice; EtCOCl (12.6 eq.), THF, -78 °C, 6 h.

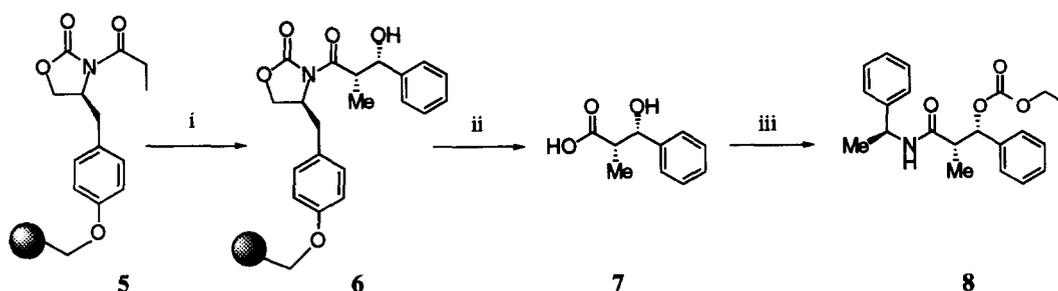
Aldol Reaction

The propionylated resin **5** was enolised using *n*-dibutylboron triflate and triethylamine (Scheme 2). It was found that using 1.5 equivalents of *n*-dibutylboron triflate resulted in only a 20% conversion to the aldol product, due to incomplete formation of the boron enolate. One advantage of solid phase chemistry is the option to use excess of the soluble reagents to drive reactions to completion. However in this aldol reaction that option appeared to be compromised by a report that a reversal of stereochemistry is observed if two equivalents of *n*-dibutylboron triflate are present.¹² To circumvent such problems, the formation of the enolate was first driven to completion by using an excess of *n*-dibutylboron triflate (13 equivalents) and triethylamine. The excess reagents were then drained away. Thereafter the resin was resuspended in dichloromethane and cooled to -78 °C before benzaldehyde was added to form **6**.

The cleavage of the aldol product from the resin was problematic. In solution, removal of the chiral auxiliary is best achieved with lithium peroxide,¹³ however treatment of **6** under these cleavage conditions gave product that was heavily contaminated with unidentifiable impurities. These impurities appear to be derived from the resin as they are found when well-washed unloaded hydroxymethyl or Wang resin is treated (and retreated) under these cleavage conditions. Consequently the cleavage of the aldol product from the chiral auxiliary was attempted with lithium hydroxide in THF, conditions which work well in solution but are also reported to cause partial endocyclic cleavage of the auxiliary.¹³ Under these conditions a much cleaner product **7** was obtained (94% purity by HPLC using a SEDEX evaporative light scattering detector).

Only the *syn* diastereoisomer of the acid **7** was detected by ^1H NMR spectroscopy, corresponding to a diastereomeric excess in the aldol reaction of greater than 98%. This result is identical to that reported by Evans for the solution phase reaction.⁴ The yield of acid **7** from resin-bound auxiliary **4** was 63%, based on the initial loading of chiral auxiliary on the resin.¹⁰ The yield reported for the solution phase reactions, from propionylation of the auxiliary to cleavage of the aldol product, was 75–80%.⁴ The acid **7** was derivatised with

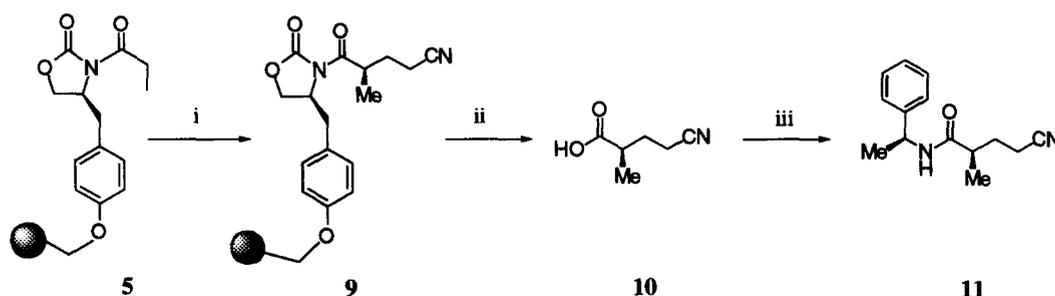
(*S*)-1-phenylethylamine¹⁴ to form the amide **8** which was shown to be a single diastereoisomer by HPLC, under conditions which gave baseline resolution from the amide of the enantiomer **7**. This establishes the high enantioselectivity of this reaction on resin.



Scheme 2. (i) *n*-Bu₂BOTf (13 eq.), Et₃N (14.8 eq.), CH₂Cl₂, 0 °C, 2 h; PhCHO (16.4 eq.), CH₂Cl₂, -78 °C, 3 h, then 0 °C, 3 h; pH 7 aq. phosphate buffer - MeOH (1:2), 0 °C, 1 h; (ii) LiOH (11.7 eq.), THF, 0 °C, 6 h, then aq. HCl; (iii) ClCO₂Et (2.2 eq.), Et₃N (3.0 eq.), CH₂Cl₂, 0 °C, then (*S*)-1-phenylethylamine (1.1 eq.), 0 °C, 1 h, 25 °C, 24 h.

Conjugate Addition

There have been several reports of conjugate addition reactions on resin, only a few of which involve a carbon nucleophile,¹⁵ and none with asymmetric control. We therefore explored the use of propionylated Evans' chiral auxiliary **5** for asymmetric conjugate addition on solid phase using acrylonitrile as the electrophile (Scheme 3).⁵ The propionyl group in **5** was first enolised using excess TiCl₃(*Oi*-Pr) and diisopropylethylamine (DIPEA), after which the excess reagents were drained away. The resin was then resuspended in dichloromethane and acrylonitrile was added. The conjugate addition reaction proceeded smoothly to form **9**, which was cleaved using lithium hydroxide to release **10**.¹⁶



Scheme 3. (i) TiCl₃(*Oi*-Pr) (5 eq.), DIPEA (6 eq.), CH₂Cl₂, 0 °C, 3 h; CH₂=CHCN (10 eq.), CH₂Cl₂, 0 °C, 24 h; sat. aq. NH₄Cl, 0 °C, 1 h; (ii) LiOH (5 eq.), THF, 0 °C, 6 h, then aq. HCl; (iii) ClCO₂Et (1.1 eq.), Et₃N (1.5 eq.), CH₂Cl₂, 0 °C, then (*S*)-1-phenylethylamine (1.1 eq.), 0 °C, 1 h, 25 °C, 24 h.

In order to determine the enantiomeric excess of **10** it was converted to the amide **11** using (*S*)-1-phenylethylamine.¹⁴ The diastereomeric composition was determined by ¹H NMR spectroscopy to be 89:11, the major product being **11**. The crude yield of **10** isolated from resin was 52% based on the loading of chiral auxiliary **5**.¹⁰ Minor impurities were evident in the ¹H NMR spectrum. In the corresponding solution phase

study, the acid **10** was not cleaved from the auxiliary. The diastereomeric ratio for the addition product (corresponding to **9**) was 98:2.⁵

Our study has demonstrated that asymmetric aldol and conjugate addition reactions in solution can be reproduced on solid phase with little or no loss of enantiomeric or diastereomeric selectivity. The experiments highlight the need to adopt a flexible approach in experimental design, for example by choosing a resin that is compatible with certain reagents, and selecting other reagents to be compatible with the resin.

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10. The loading capacities of hydroxymethyl polystyrene resin used were 0.79 mmol/g for the aldol reaction, 1.49 mmol/g for the Michael addition. The attachment of the chiral auxiliary was quantitative as determined by nitrogen analysis.
11. The chiral auxiliary was also attached to Wang resin. However under the Lewis acidic conditions used for the aldol reaction (enolisation with *n*-dibutylboron triflate and triethylamine), partial cleavage of the auxiliary from the resin was observed. This was not a problem with the auxiliary attached to hydroxymethyl resin **5**.
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16. A conjugate addition reaction using ethyl vinyl ketone precomplexed with titanium tetrachloride as the Michael acceptor was unsuccessful. The insolubility of the titanium complex in dichloromethane prevented it penetrating the resin.