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Asymmetric solution-phase mixture aldol reaction using oligomeric ethylene glycol tagged chiral oxazolidinones

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Abstract

Sorting tags are oligomeric structures that can be used as protecting groups or chiral auxiliaries enabling solution-phase mixture syntheses of multiple tagged compounds in one pot and allowing for facile and predictable chromatographic separation of products at the end of synthetic sequences. Perfluorinated hydrocarbon and oligomeric ethylene glycol (OEG) derivatives are known classes of sorting tags. Herein we describe the preparation of OEGylated chiral oxazolidinones and their use in asymmetric solution-phase mixture aldol reactions. Through the use of such oxazolidinones based on tyrosine four different individually tagged aldol adducts were obtained as a mixture, chromatographically demixed, detagged, and it was shown that these processes gave the desired aldol products in good yield and enantioselectivity.

Keywords

Solution-Phase Mixture Synthesis
Oligomeric Ethylene Glycol
Evans Aldol Reaction
Oxazolidinone
Sorting Tag

Introduction

Drawbacks associated with solid-phase organic synthesis have prompted a search for alternative methods for the generation of libraries of structurally diverse compounds. Such methods include liquid phase organic synthesis[1a,b] along with solution-phase strategies such as the generation of indexed combinatorial libraries[2a-c] and approaches involving the use of phase tags such as precipitons,[3a-c] boronic acid derivatives,[4] and fluorous synthesis.[5a-g] Among these alternative methods fluorous synthesis is particularly important as it provides for a reliable strategy, termed Fluorous Mixture Synthesis (FMS),[6a-i] allowing for the mixture synthesis of target structures and their separation into individual products at the end of the synthetic sequence. This is accomplished through labelling of each substrate with a fluorocarbon sorting tag of unique chain length, taking mixtures of these tagged substrates through a number of synthetic steps, and separation (i.e. demixing) of these tagged substrates by chromatography with a fluorous stationary phase where substrate elution order is dictated by the chain length of the sorting tag.

We have discovered that oligomeric ethylene glycol (OEG) derivatives can also be used as sorting tags.[7a,b] OEG tags allow for the orderly and predictable demixing of a mixture of tagged substrates through chromatography on regular silica gel where elution times are directly proportional to OEG chain length (Figure 1).[7a] Demixing efficiency can be further enhanced by addition of lithium salts to silica gel (i.e. complexation chromatography).[7a] OEG tags are particularly noteworthy because they are separable under orthogonal chromatographic conditions with respect to fluorous tags. This chromatographic orthogonality allows for double tagging of substrates through which a larger number of parallel solution-phase reactions can be carried out in the same reaction vessel compared to the use of a single class of sorting tag.[7c-d]

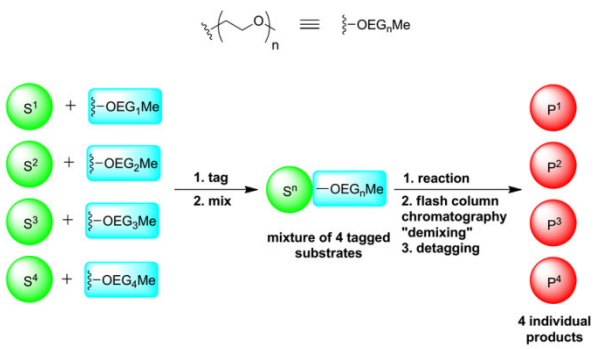
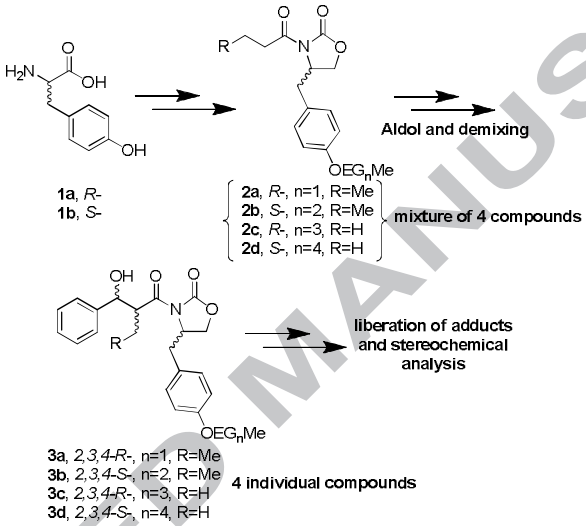


Figure 1. Principle of solution-phase mixture synthesis using OEG-based sorting tags.

The aldol reaction is a very important method for C-C bond formation. Use of chiral oxazolidinones (i.e. Evans auxiliaries) as chiral auxiliaries for asymmetric aldol reactions has been a seminal contribution to this area.[8a-c] The high synthetic value of Evans auxiliaries made the preparation and application of OEG tagged chiral oxazolidinones an attractive target for us. Chiral oxazolidinones derived from tyrosine were of particular interest as they allow for straightforward derivatization with OEGs through etherification. In this communication we would like to report on the preparation and application of OEG tagged chiral oxazolidinones derived from tyrosine.

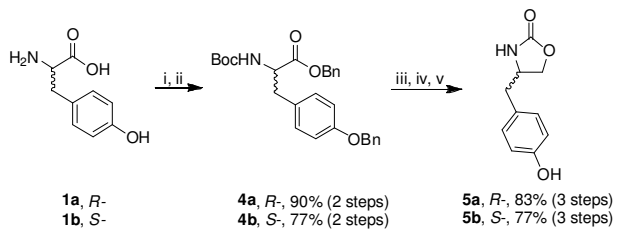
The objectives of this study were: *i*. The preparation of acylated-OEGylated chiral oxazolidinones **2a**-**d** starting from **1a**-**b**; *ii*. Execution of mixture solution-phase aldol reactions of **2a**-**d** with benzaldehyde; *iii*. Demonstration of demixing of the products using chromatography on normal phase silica; *iv*. Stereochemical analysis of the aldol products thus formed (**3a**-**d**) to establish the efficacy and suitability of these OEGylated chiral oxazolidinones for asymmetric mixture aldol reactions. Structures **2a**-**d** were targeted because they would maximize the chromatographic resolution of products **3a**-**d**. Aldol reactions with benzaldehyde were selected since the resulting aldol adducts are known and thus would allow for facile assessment of the utility of OEGylated chiral oxazolidinones (Scheme 1).



Scheme 1. Objectives of this study.

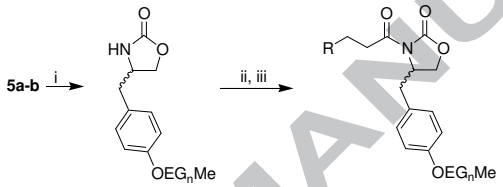
Results and Discussion

While a number of routes could be considered for the preparation of tyrosine based chiral oxazolidinones, we found the method developed by Green *et al.* to be particularly convenient and high yielding.[9] Boc protection of *R*- and *S*-tyrosine (**1a**-**b**) followed by benzylation afforded the globally protected amino acids (**4a**-**b**) in good yields. $LiAlH_4$ reduction of **4a**-**b**, NaH mediated oxazolidinone formation, and removal of the benzyl protecting group through hydrogenation afforded chiral oxazolidinones **5a**-**b** in good yields as well (Scheme 1). The optical rotation of **5b** (-11.2°) matched the values reported in the literature. The optical rotation of **5a** (+11.2°) was, as expected, the opposite of **5b** (Scheme 2).



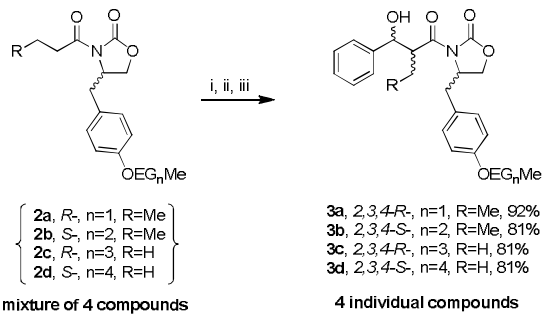
Scheme 2. i. Boc_2O, dioxane:H_2O (1:1), TEA, 20 °C, 20 h; **ii.** BnBr, K_2CO_3, Bu_4NI, DMF, rt, 2 d; **iii.** $LiAlH_4$, THF, 0 °C to rt, 2 h; **iv.** NaH, THF, rt, 24 h; **v.** Pd/C, H_2, rt, 24 h.

OEGylation of oxazolidinones **5a**-**b** was accomplished with acceptable yields through Cs_2CO_3/KI mediated etherification with OEG-chlorides of varying chain lengths. Thus the *R*- isomers were tagged with OEG-1 and OEG-3 (**6a**, **6c**) and the *S*- isomers were tagged wth OEG-2 and OEG-4 (**6b**, **6d**). **6a**-**b** and **6c**-**d** were acylated in good yields with, respectively, butyryl and propionyl chloride using *n*-BuLi to give **2a**-**d** (Scheme 3).[8]



Scheme 3. i. Cs_2CO_3, KI, Cl-OEG_nMe, DMF, 60 °C, 24 h; **ii.** *n*-BuLi, THF, -78 °C, 20 min.; **iii.** RCH_2CH_2COCl, THF, -78 °C, 30 min.

With **2a**-**d** in hand, mixture aldol reactions of these OEG-tagged substrates with benzaldehyde were carried out. Enolization of a mixture of **2a**-**d** using Bu_2BOTf (1.8 eq.) and NEt_3 (1.9 eq.), and subsequent addition of benzaldehyde afforded a mixture of OEG-tagged aldol products **3a**-**d**. This mixture was demixed using silica gel flash column chromatography (Scheme 4). It is remarkable that it was possible to separate 9 compounds (4 products, 4 starting materials, and excess benzaldehyde) with good purity in a single run. Demixing was also demonstrated using normal phase HPLC and a chromatogram for this separation is provided in Figure 2 (for chromatographic parameters see Table SI-1, Supporting Information). Product elution times in either case were-as expected-directly proportional to bound OEG chain length.



Scheme 4. i. 1.8 eq. Bu_2BOTf, 1.9 eq. NEt_3, CH_2Cl_2, 0 °C, 10 min; ii. PhCHO, CH_2Cl_2, -78 °C to 0 °C, 2 h; iii. Demixing using flash column chromatography on silica.

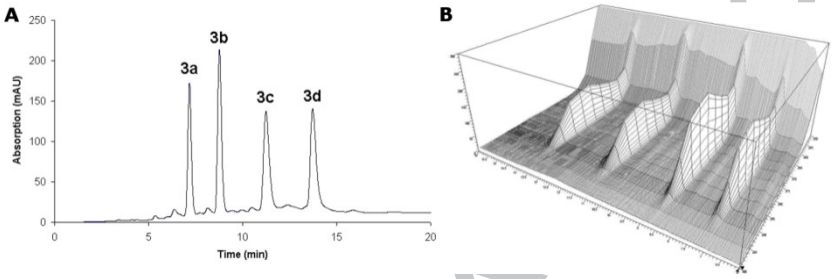
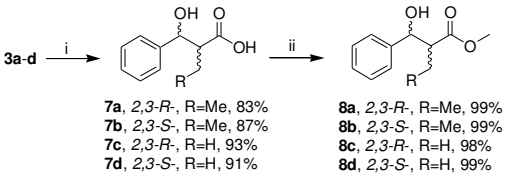


Figure 2. Panel A shows a normal phase HPLC chromatogram for a mixture of aldol adducts **3a**-**d** (Conditions: 250 x 4.6 mm Supelco Supelcosil silica column, gradient elution (1:1 EtOAc:hexanes for 5 min., then EtOAc to 5% IPA in EtOAc in 3 min.), 1 mL/min flow rate, UV-Vis detection). Panel B shows 2D-UV/Vis spectra demonstrating identical absorption profiles for the chromatographic peaks corresponding to **3a-d** (right to left).

Aldol products **7a**-**d** were liberated from the OEG-tagged chiral auxiliaries using LiOOH (LiOH mixed with H_2O_2).[10] To facilitate the stereochemical analysis of these products they were converted to the corresponding methyl esters **7a**-**d** through reaction with freshly prepared diazomethane (CH_2N_2). Both steps proceeded with good to excellent yields (Scheme 5).



Scheme 5. i. LiOH, H_2O_2, THF:H_2O (3:1), 0 °C, 2 h; ii. CH_2N_2, Et_2O, 0 °C, 1 h.

Relative and absolute stereochemical configurations, and enantiomeric purities of **7a**-**d** and **8a**-**d** were determined, respectively, using ^{1}H-NMR, optical rotation measurements, and chiral HPLC. α-β hydrogen spin-spin coupling constants (i.e. J_{AB}) as determined through ^{1}H-NMR indicated gauche conformations in all cases (i.e. J_{AB} < 6 Hz), thus it was inferred that *syn*-aldol products were obtained (Table SI-2, Supporting Information).[11] Optical rotation (i.e. $[\alpha]_D$) values for **7c**-**d** and **8a**-**d** matched those previously reported (Table SI-2, Supporting

Information),[12a-e] and it was concluded that products with the expected absolute configuration were obtained. Chiral HPLC analysis of **8a-d** revealed enantiomeric excess (i.e. % ee) values of 99% for **8a**, 98% for **8b**, 94% for **8c**, and 93% for **8d** (Table SI-4, Supporting Information).

In this study we have demonstrated the preparation of OEG-tagged chiral oxazolidinones and have used them in solution-phase mixture aldol reactions. The products obtained were easily demixed using silica gel flash column chromatography. As the chromatogram in Figure 2 shows, even using an extremely steep gradient excellent baseline resolution was observed between **3a-d**. Thus it is conceivable that it would be possible to demix more than 4 products using just 4 OEG tags. We have observed that OEG tags were compatible with all reaction conditions required in this work. Furthermore, aldol products were obtained in good yields and their stereochemical configurations were identical to what would be expected of the corresponding products of single component reactions. We believe that OEG-tagged protecting groups and chiral auxiliaries like **6a-d** will be important tools in the arsenal of chemists seeking to generate libraries of compounds through solution-phase mixture synthesis.

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Supplementary Information: Supplementary data (synthetic procedures, NMR data, and HPLC data) associated with this article can be found, in the online version, at …

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Highlights

- Oligomeric ethylene glycol (OEG) derivatives act as chromatographic sorting tags.
- Chiral oxazolidinones tagged with OEGs of varying length were synthesized.
- 4 aldol products were synthesized in one pot using tagged chiral oxazolidinones.
- Products were easily separated using silica gel flash column chromatography.
- Aldol products were obtained with good yield and enantioselectivity.

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Graphical Abstract