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Overcoming Intrinsic Diastereoselection using Polyleucine as a Chiral Epoxidation Catalyst

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Abstract: The use of polyleucine in the diastereoselective, catalyst-controlled epoxidation of enantiomerically pure γ-heterosubstituted-α,β-unsaturated ketones (**1**), to yield the corresponding α,β-epoxy-γ,δ-(isopropylidene)dioxy carbonyl compounds, is described.

Many reagents and catalysts enable enantioselective synthesis, but only a few are powerful enough to control reactions of chiral compounds so as to overcome intrinsic diastereoselection in both the matched and mismatched sense.[1] One such system involves the well-known Katsuki-Sharpless epoxidation of γ-heterosubstituted allylic alcohols.[2] Elsewhere it has been reported that polyleucine acts as a highly versatile enantioselective epoxidation catalyst.[3] Herein we extend this powerful methodology by demonstrating epoxidation of γ-heterosubstituted-α,β-unsaturated carbonyl compounds (bearing a chiral centre in the γ-position), using polyleucine as a chiral catalyst to overwhelm the intrinsic diastereofacial preference exhibited by the chiral substrate.

The dioxolane (4*S*)-**1** was chosen as a substrate for this investigation. Using the recently reported silica gel-supported sodium metaperiodate methodology,[4] one pot oxidative cleavage of 1,2:5,6-diisopropylidene-D-mannitol with subsequent olefination using phenylcarbonylmethylene triphenylphosphorane afforded (*S*)-**1** in 97 % yield (ratio of isomers *E*:*Z* = 2 : 1). The *E*/*Z*-mixture was separated by flash chromatography and the isomers studied individually with respect to polyleucine-catalysed oxidation.

Epoxidation of the *E*-isomer (4*S*)-**1** under biphasic conditions[3a] (UHP/DBU/THF) in the absence of polyleucine gave the isomeric epoxides **2** (*syn*) and **3** (*anti*) in the ratio of 1 : 2.2. As expected from earlier work, immobilised poly-D-leucine (i-PDL) was the matched catalyst providing **3** in excellent diastereoselectivity (1 : 30 and 1 : 20), using two protocols.[3] However, polymer-control of the diastereoselectivity was not impressive in the mismatched case using immobilised poly-L-leucine (i-PLL) as the chiral catalyst. It is noteworthy that the rate of the background reaction is relatively fast yet the polyamino acids still exert a significant control, particularly in the matched case. In an attempt to decrease the rate of the background reaction, the reaction temperature was lowered. Percarbonate conditions[3b] ($Na_2CO_3 1.5H_2O_2$/DME/H_2O) responded best to the lower temperature, resulting in a much improved diastereoselectivity in the mismatched case using i-PLL (3.8 : 1)(see Table 1). Recrystallisation of the diastereomerically enriched epoxides **2** and **3** provided single diastereomers[5] (for the physical parameters of compound **3** see reference 9; compound **2** had mp 64 °C, $[\alpha]_D = -35.9^\circ$ [*c* 1, $CHCl_3$]). Proof of the *anti*-diastereoselectivity of the matched case was obtained from crystal structure analysis.[6]

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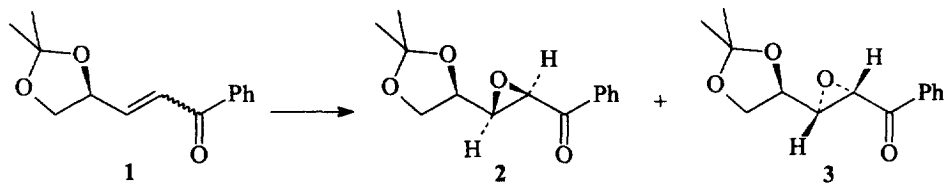


Scheme 1.

Table 1: Influence of Polyleucine on the Epoxidation of *E*-1

Temperature	Catalyst	Time	2 : 3[d]	Matching	Isolated yield
20 °C	None[a]	5 h	1 : 2.2	-	93 %
20 °C	i-PDL[a]	5 h	1 : 30	matched	95 %
20 °C	i-PLL[a]	5 h	1 : 1	mismatched	92 %
20 °C	None[b]	30 min	1 : 2.7	-	94 %
20 °C	i-PDL[b]	30 min	1 : 20	matched	97 %
20 °C	i-PLL[b]	30 min	2.4 : 1	mismatched	96 %
0 to –3 °C	None[b]	24 h	1 : 3.0	5 % sm[c] left	94 %
0 to –3 °C	i-PDL[b]	24 h	1 : 34	matched	97 %
0 to –3 °C	i-PLL[b]	24 h	3.8 : 1	mismatched	98 %

a) UHP, DBU, THF, 20 °C. b) $Na_2CO_3.1.5\ H_2O_2$, DME:H_2O (2:1). c) sm: starting material. d) determined by HPLC. i-PDL: immobilised poly-D-leucine; i-PLL: immobilised poly-L-leucine.

Epoxidation of the *Z*-isomer (4*S*)-**1** is stereoconvergent with respect to its *E*-isomer, thus once again affording the epoxides **2** and **3**. Biphasic epoxidation of *Z*-(4*S*)-**1** in the absence of catalyst very rapidly afforded **3** as the major diastereomer, with i-PDL appreciably enhancing the diastereoselectivity in the matched sense. In the mismatched case the slight intrinsic control is completely overturned by i-PLL to give a *syn*/*anti* ratio of 3.6 : 1 and 4.0 : 1 using the biphasic reaction conditions at 20 °C and –30 °C respectively (see Table 2).

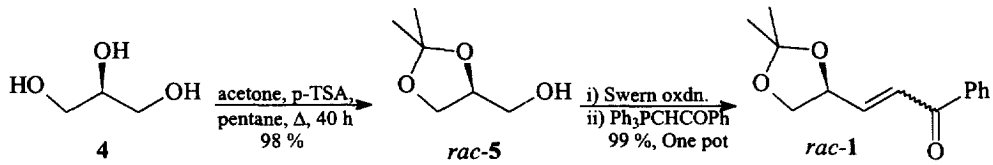
Table 2: Influence of Polyleucine on the Epoxidation of (*Z*)-1

Temperature	Catalyst	Time	2 : 3[d]	Matching	Isolated yield
20 °C	None[a]	50 min	1 : 1.3	-	92 %
20 °C	i-PDL[a]	35 min	1 : 8.0	matched	91 %
20 °C	i-PLL[a]	35 min	3.6 : 1	mismatched	94 %
-30 °C	i-PLL[a]	18 h	4.0 : 1	mismatched	90 %

a) and d) As for Table 1. i-PDL: immobilised poly-D-leucine; i-PLL: immobilised poly-L-leucine.

Furthermore, epoxidation of a mixture of geometric isomers of (4*S*)-**1** (*E*:*Z*; 2:1) with matched catalyst (i-PDL) under biphasic protocol at 20 °C, afforded a **2** : **3** diastereomer ratio of at least 1 : 17, thus, in a synthetic sense obviating the necessity to separate the Wittig olefination *E*/*Z* mixture.

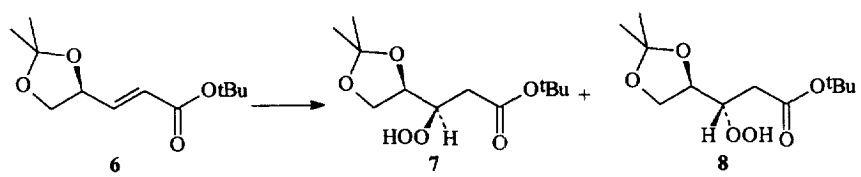
Racemic enone *rac*-**1** was prepared from glycerol (**4**) as shown in Scheme 2. Swern oxidation of the acetonide *rac*-**5** was low yielding and problematic.[7] However, a one pot Swern oxidation and Wittig olefination afforded the stable dioxolane *rac*-**1**, in excellent yield (99 % from *rac*-**5**, *E*:*Z* = 1 : 1).



Scheme 2.

Epoxidation of the racemic *E*-isomer *E-rac*-**1** under percarbonate conditions without polyleucine at 0 °C favoured the *anti* epoxide in a ratio of 1 : 3.0. Careful analysis of the reaction mixture resulting from a poly-L-leucine catalysed epoxidation, under the same conditions, revealed a matched **2** : **3** ratio of 1 : 37 for the (4*R*)-enantiomer of **1**, and confirmed a mismatched ratio of 3.9 : 1 for (4*S*)-**1** (*cf* last entry Table 1). The increase in the matched diastereoselectivty for i-PLL compared to i-PDL was attributed to the greater enantiopurity of the natural L-leucine (in comparison to the unnatural D-leucine) used in the preparation of leucine *N*-carboxyanhydride prior to polymerisation.

In an attempt to expand the polyleucine methodology to the epoxidation of α,β-unsaturated esters, the corresponding dioxolane **6** was synthesised by Wittig olefination of (4*R*)-2,2-dimethyl-1,3-dioxolan-4-carbaldehyde with *t*-butoxycarbonylmethylene triphenylphosphorane. Attempted substrate controlled epoxidation of (4*R*)-**6** afforded the unexpected hydroperoxy compounds **7** and **8** with an excellent diastereoselectivity in favour of the *syn* isomer **7** (15.7 : 1). The ratio of diastereoisomers was obtained from the integration of the sharp signal of the hydroperoxy proton in the ^{1}H-NMR spectrum and the stereochemistry of the major diastereomer was based on literature precedent for additions of alkoxides to γ-alkoxyalkenoates, which have been shown to proceed with *syn*-diastereoselectivity.[8] Attempted polyleucine controlled epoxidation of **6** afforded the same hydroperoxides with a lowering in the diastereoselectivity and negligible matching or mismatching (see Table 3). The *syn*-hydroperoxide **7**[9] is currently under investigation as a chiral oxidation reagent.



Scheme 3.

Table 3: Oxidation of 6 with urea-hydrogenperoxide and base, with and without polyleucine

Temperature	Catalyst	Time	7 : 8	Isolated yield
20 °C	None[a]	5 h	15.7 : 1	25 %[b]
20 °C	i-PDL[a]	5 h	2.4 : 1	40 %[c]
20 °C	i-PLL[a]	5 h	3.2 : 1	27 %[d]

a) As for Table 1. b) 33 % starting material recovered. c) 30 % starting material recovered. d) 35 % starting material recovered.

In summary, we have demonstrated, for a chiral γ-heteroatom substituted α,β-unsaturated enone, that polyleucine is a sufficiently powerful epoxidation catalyst to overcome intrinsic stereocontrol. This new finding allows the efficient synthesis of highly functionalised enantiomerically pure intermediates required

for elaboration towards natural products and other target molecules. Further work in extending this methodology and utilising the highly functionalised enantiomerically pure intermediates is in progress.

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3. a) Lasterra-Sánchez, M.E.; Roberts, S.M. *Current Organic Chemistry*, **1997**, *1*, 187, and references therein (for the biphasic conditions). b) Allen, J.V.; Drauz, K.; Ray, P.C.; Roberts, S.M. and Skidmore, J. unpublished results (for the percarbonate conditions).
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5. Analyses were conducted using a Chiralpak AD column (*Daicel Chemical Industries*), 0.46x25 cm; Eluent: ethanol-hexane (1:9); Flow rate: 1 cm^3min^{-1}; UV detection 254 nm; Retention time, **2**: R_t = 15 min.; **3**: R_t = 22 min. Starting from *rac*-**1**, the retention times for the products of *ent*-**1** epoxidation are, *ent*-**3**: 13 min.; *ent*-**2**: 35 min. Validation of the diastereomer ratios was obtained from UV-analysis of the enantiopure epoxides **2** and **3**, which afforded replicate chromatograms throughout the HPLC absorption range.
6. The crystal structure of **3** was provided by the E.P.S.R.C. X-Ray Crystallography Service, Department of Chemistry, University of Wales, Cardiff and the details will be reported in a full paper.
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8. Mulzer, J.; Kappert, M.; Huttner, G. and Jibril, I. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 704.
9. Analytical data for **3** and **7**:

   3: mp 65 °C (from ethyl acetate-hexane) (Found: C, 67.9; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5 %); $[\alpha]_D$ −12.5° ($CHCl_3$, *c* 1.0) $\nu_{max}(CHCl_3)/cm^{-1}$ 1694 (CO); δ_H (300 MHz, $CDCl_3$) 1.39 and 1.46 (2x3 H, 2xs, $C(CH_3)_2$), 3.25 (1 H, dd, *J* 5.4 and 1.8 Hz, H_3), 4.02 (1 H, dd, *J* 8.1 and 4.8 Hz, H_5), 4.09 (1 H, ddd, *J* 6.0, 5.4 and 4.8 Hz, H_4), 4.21 (1 H, dd, *J* 8.1 and 6.0 Hz, H_5), 4.23 (1 H, d, *J* 1.8 Hz, H_2), 7.51 (2 H, m, $2xH_1^3$), 7.63 (1 H, m, H_1^4), 8.04 (2 H, m, $2xH_1^2$); δ_C (75 MHz, $CDCl_3$) 25.1 and 26.6 ($C(CH_3)_2$), 55.6 (C_3), 59.2 (C_2), 67.0 (C_4), 75.3 (C_5), 110.4 ($C(CH_3)_2$), 128.4 ($2xC_1^3$), 128.9 ($2xC_1^2$), 134.1 (C_1^4), 135.5 (C_1^1) and 193.6 (C_1); *m*/z (CI) 249 $(M + H)^+$ and 266 $(M + NH_4)^+$.

   7: $\nu_{max}(CHCl_3)/cm^{-1}$ 3412 (br. OH), 1713 (ester CO) and 1362 (OO stretch); δ_H (300 MHz, $CDCl_3$) 1.35 and 1.43 (2 x 3H, 2 x s, $C(CH_3)_2$), 1.47 (9 H, s, $C(CH_3)_3$), 2.57 (1 H, dd, *J* 15.6 and 8.4 Hz, H_2), 2.69 (1 H, dd, *J* 15.6 and 3.9 Hz, H_2), 3.96 (1 H, dd, *J* 8.7 and 5.4 Hz, H_5), 4.11-4.23 (2 H, m, H_4 and H_5), 4.30 (1 H, ddd, *J* 8.4, 6.6 and 3.9 Hz, H_3) and 9.34 (1 H, s, OOH exchanged by D_2O); δ_C (75 MHz, $CDCl_3$) 25.1 and 26.4 ($C(CH_3)_2$), 27.96 ($C(CH_3)_3$), 36.33 (C_2), 67.0 (C_4), 75.5 (C_5), 81.5 ($C(CH_3)_3$), 82.8 (C_3), 109.6 ($C(CH_3)_2$) and 171.3 (C_1); *m*/z (CI) 246 (M^+– O), 229 (M^+– OOH), 247 (229 + NH_4^+) and 262 (M^+– OH + NH_3).