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# Asymmetric epoxidation of a geminally-disubstituted and some trisubstituted enones catalysed by poly-L-leucine

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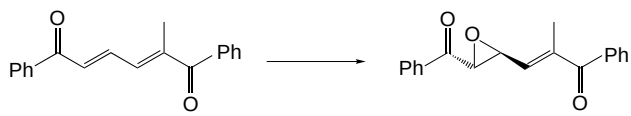
**Abstract**—Epoxidation of a range of enones derived from tetralone or related cyclic ketones, employing poly-L-leucine, urea–$H_2O_2$ and DBU in *iso*-propyl acetate is reported. The corresponding epoxides were isolated in 63–85% yield and 59–96% ee. 

There is widespread interest in the use of synthetic peptides as catalysts and ligands in stereoselective synthesis.[1] The seminal work of Juliá and Colonna showed that *E*-chalcone [PhCOCH=CHPh] can be oxidised in a stereoselective manner using a triphasic reaction medium, comprising aqueous $H_2O_2$, a water-immiscible organic solvent and an insoluble polyamino acid, typically poly-L-alanine, to give the corresponding epoxide in high enantiomeric excess.[2,3] These and other workers subsequently showed that a range of *E*-disubstituted enones including alkyl, aryl and extended conjugated systems could be converted into optically active oxiranes using this strategy.[4,5] More recently we have demonstrated that, using the triphasic conditions and Aliquat® 336 as an additive, even the less reactive phenyl-*E*-styrylsulphone is oxidised to the corresponding epoxide (61% yield over 4 days) albeit with modest stereoselectivity (21% ee). However electrophilic olefins possessing other substitution patterns have been tried without success; for example, acyclic trisubstituted enones proved inert under the triphasic reaction conditions.

Recently, we introduced a new, non-aqueous, biphasic reaction protocol for the Juliá–Colonna oxidation[6] comprising urea–$H_2O_2$, DBU and poly-L-leucine immobilised on a polystyrene support (*i*-PLL).[7] Even under these more powerful oxidation conditions, trisubstituted enones proved to be unreactive.[8] The effect of placing a simple alkyl unit in the α-position of the enone on the reactivity under the biphasic conditions is clearly illustrated in Scheme 1. Oxidation of the diene **1** produced epoxide **2** (70% yield, 92% ee) as the only isolated product, thus leaving the unreacted olefin available for further functionalisation.[9]

In this paper we show that conformationally-restricted tetralones **3a**–**f**[10] and related compounds **3g**,**h** undergo




**1** **2**

**Scheme 1.** *Reagents and conditions*: Urea–$H_2O_2$, DBU, *i*-PLL, THF, 10 h, 70%.

**Table 1.** Oxidation of enone **3a** (0.24 mmol) to the epoxide **4a**

| Entry | *i*-PLL (mg) | Oxidant (mmol) | Base (mmol) | Solvent ($cm^3$) | Time (h) | Conversion (%) [ee (%)] |
|---|---|---|---|---|---|---|
| i | 100 | 30% aq. $H_2O_2$ (1.76) | 4 M NaOH (0.8) | Toluene (0.8) | 168 | 100 [74] |
| ii | 100 | Urea–$H_2O_2$ (0.3)[a] | DBU (0.6)[a] | THF (0.8) | 55 | 100 [62] |
| iii | 100 | Urea–$H_2O_2$ (0.3)[a] | DBU (0.6)[a] | EtOAc (0.8) | 80 | 72 [70] |
| iv | 200 | Urea–$H_2O_2$ (0.12)[a] | DBU (0.2)[a] | *i*-PrOAc (1.6) | 90 | 100 [84] |

[a] Amount indicated added every 12 h.

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| | | |
|---|---|---|
| **3a** | R=Ph; n=1 | **4a** |
| **3b** | R=*p*-Br-$C_6H_4$; n=1 | **4b** |
| **3c** | R=*p*-$NO_2$-$C_6H_4$; n=1 | **4c** |
| **3d** | R=Me; n=1 | **4d** |
| **3e** | R=*t*Bu; n=1 | **4e** |
| **3f** | R=H; n=1 | **4f** |
| **3g** | R=Ph; n=0 | **4g** |
| **3h** | R=Ph; n=2 | **4h** |

**Scheme 2.** *Reagents and conditions*: Enone (0.24 mmol), *i*-PLL (200 mg), urea–$H_2O_2$ (0.12 mmol every 12 h), DBU (0.20 mmol every 12 h), *iso*-propyl acetate (1.6 $cm^3$).[11]

asymmetric epoxidation using *i*-PLL as the catalyst. Thus, under the Juliá–Colonna triphasic conditions, tetralone **3a** was slowly transformed into the epoxide **4a** (Table 1, entry i). The analogous biphasic reaction was faster but slightly less stereoselective (Table 1, entry ii). Changing the solvent to ethyl acetate (Table 1, entry iii) or *iso*-propyl acetate gave improved stereoselectivity and the reaction was optimised for the latter solvent, resulting in a slower addition of oxidant to a more dilute solution containing an increased amount of catalyst (Table 1, entry iv).

The optimised conditions were utilised to investigate the oxidation of a family of related compounds (Scheme 2 and Table 2). Placing a substituent such as bromine on the benzylidene group had little effect, the epoxide **4b** being obtained in good yield (Table 2, entry ii) while the product **4c** having an excellent enantiomeric excess was obtained from the *p*-nitrobenzylidene derivative **3c** (Table 2, entry iii). After recrystallisation from dichloromethane/hexane the enantiomer of **4b** could not be detected by HPLC analysis and the absolute configuration of this pure sample of **4b** was confirmed by X-ray crystallography (Fig. 1).[12]

Replacement of the aryl moiety by a methyl group was well tolerated with the enone **3d** being transformed with good stereoselectivity (92% ee) into the

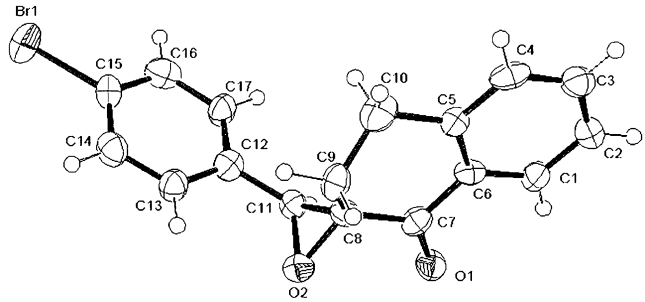


**Figure 1.** Structure of compound **4b**.

epoxide **4d** (Table 2, entry iv). In contrast, the *tert*-butyl compound **3e** was oxidised slowly (8 days) to give the epoxide **4e** of somewhat lower ee (Table 2, entry v). The α-methylene compound **3f** was oxidised rapidly (7 h) to give the corresponding epoxide **4f** in good enantiomeric excess (Table 2, entry vi). This is one of the rare examples where a geminally disubstituted enone is oxidised using the Juliá–Colonna methodology.[5]

The effect of changing the size of the ring annealed to the phenyl group was also investigated. For example, the indanone derivative **3g** was oxidised, furnishing the epoxide **4g** with good stereoselectivity (Table 2, entry vii). However, oxidation of the benzosuberone derivative **3h** was much less satisfactory taking one week to produce epoxide **4h** of modest enantiomeric excess (Table 2, entry viii). Seemingly the more flexible seven-membered ring renders this substrate less amenable to polyleucine-catalysed epoxidation.

In summary, the newly developed biphasic conditions for the Juliá–Colonna oxidation serve to convert tetralones and analogous compounds to the corresponding epoxides with good to excellent enantioselectivity.[14]

However, the new protocol is still not effective for stereoselective oxidation of endocyclic enones; for example, the 'tethered' chalcone 3-phenylinden-1-one forms epoxide under the biphasic conditions but the product is racemic.

**Table 2.** Epoxidation of enones **3a–h** to give the epoxides **4a–h**

| Entry | Substrate | Time (h) | Product | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| i | **3a** | 90 | **4a** | 76 | 84[a] |
| ii | **3b** | 72 | **4b** | 81 | 82[a] |
| iii | **3c** | 78 | **4c** | 85 | 96[a] |
| iv | **3d** | 60 | **4d** | 66 | 92[a] |
| v | **3e** | 192 | **4e** | 63 | 83[a] |
| vi | **3f** | 7 | **4f** | 64 | 94[b] |
| vii | **3g** | 48 | **4g** | 72 | 88[a] |
| viii | **3h** | 168 | **4h** | 74 | 59[a] |

[a] Determined by HPLC using a Chiralpak® AD column (eluent: 10% *i*-PrOH in hexane, UV detection at 254 nm) using racemic epoxides[13] as standards.

[b] Determined by $^1H$ NMR in the presence of the chiral shift reagent Eu(hfc)$_3$.

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11. For the oxidation of **3f**, oxidant and base were added after 0.5, 1, 3 and 6 h.
12. Crystal data of **4b**: $C_{17}H_{13}BrO_2$, $M=329.21$, $T=213(2)$ K, $\lambda=0.71073$ Å, orthorhombic $P2_12_12_1$, $a=8.0308(9)$, $b=8.9960(11)$, $c=19.876(3)$ Å, $V=1435.9(3)$ Å$^3$, $Z=4$, $\rho_{calcd}=1.523$ mg m$^{-3}$, $\mu$(Mo K$\alpha$)$=2.777$ mm$^{-1}$, $R_1$ ($F>4\sigma F$)$=0.051$, $wR_2$ (all data)$=0.120$. Data were collected on a Stoe IPDS diffractometer and the structure was refined on $F^2$ using all data (SHELX-97). The absolute structure was determined unambiguously (absolute structure parameter −0.04(2)).
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