Exploring Substrate Scope of Shi-Type Epoxidations

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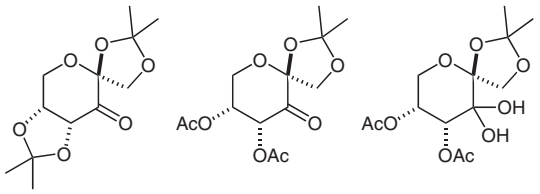
Abstract: Enantioselective epoxidations of alkenes (12 examples) were achieved using a Shi-type carbohydrate-derived hydrate and Oxone. The chiral platform provided by the catalyst tolerates a wide range of substituents providing high yields and enantioselectivities (80–95.5% ee). However, styrene derivatives were only converted with poor selectivities (11–26% ee).

Key words: alkenes, asymmetric catalysis, organocatalysis, ligands, epoxidations

Asymmetric alkene epoxidation is a powerful route to chiral epoxides,[1] which are useful synthetic intermediates for the asymmetric synthesis of complex molecules[2] or chiral catalysts.[3] Chiral dioxiranes, generated in situ from chiral ketones and potassium peroxomonosulfate ($KHSO_5$), are practically unrivalled in the epoxidation of unfunctionalised *trans* and trisubstituted alkenes.[1b,d,4] The development by Shi and co-workers of carbohydrate-derived ketones[4a–4c] and $KHSO_5$ (Oxone) as the stoichiometric oxidant is perhaps the most efficient of these methodologies and the fructose derivative **1** is the most well known of these catalysts (Figure 1).[5]



1 **2** **3**

Figure 1 Shi's standard catalyst **1**, diester fructose derivative **2** and hydrate **3**

The diester fructose derivative **2** is even more attractive in terms of robustness and substrate scope in the asymmetric epoxidation of alkenes: Shi has reported its use in the epoxidation of α,β-unsaturated esters,[6] and our group[7] has extended its use to unfunctionalised alkenes using low catalyst loadings.[8] Furthermore, we have developed a selective and efficient preparation method for both diester **2** and its hydrate **3** and recently reported that hydrate **3** shows the same high catalytic activity as its parent compound **2** in epoxidation studies of a model *trans* alkene.[7]

The currently accepted model for epoxidations mediated by **1** is based on Shi's analysis of the stereochemistry of the produced epoxides. A chiral dioxirane derived from ketone **1** has two diastereomeric oxygens and on the basis of sterical arguments the equatorial oxygen is likely to be the more accessible one for olefin approach, with the major enantiomer resulting via a spiro transition state.[5] Singleton and Wang have recently supported this analysis through the use of experimental kinetic isotope effects (KIE) and DFT calculations.[9] We have recently reported a study via isotopic labelling studies that further, experimentally, supports this model of dioxirane-mediated epoxidations.[10] Our results revealed several key aspects about the origin of the stereoinduction. Namely, the epoxidation process comprises highly stereoselective attack of the β face of **2** by HSO_5^-, oxygen transfer from the dioxirane to the alkene proceeds predominately through approach of the *Si*-alkene face onto the β face of dioxirane and that attack of the most hindered face of the dioxirane by the alkene does not take place to any measurable extent.

Preliminary epoxidation studies of a model *trans* alkene showed that hydrate **3** was at least as useful a chiral catalyst as ketone **1**.[7] We thus sought to perform an in depth study of the catalytic properties and substrate scope of hydrate **3**. Described herein is the application of this compound as a mediator in the asymmetric epoxidation of unfunctionalised alkenes (Scheme 1 and Table 1).

The epoxidations (Scheme 1) were carried out under standard conditions,[12] organoaqueous media with 10 mol% of compound **3** at 0 °C, as this offered a good balance between conversion and selectivity.[7] The pH value was a key parameter in dioxirane-catalysed epoxidations,[5] hence the optimal pH value for epoxidation with **3** was investigated using *trans*-stilbene (**4a**) as a test substrate. The pH values from 9 to 10 were obtained by simultaneously adding aqueous K_2CO_3 and a solution of Oxone in pH 6 buffer (see footnote a in Table 1).[13] Lower conversions were observed at pH 10 (39% yield) than at pH 9 (55% yield). Conversely, enantioselectivity improved with higher pH (89% and 95% ee, respectively). The lower stability of the oxidant at higher pH values may account for these low conversions. In order to overcome this problem, the amount of Oxone was doubled while the pH value was fixed at 10. As expected, a higher conversion was achieved (63% yield; Table 1, entry 1). The best yield (95%) and enantioselectivity (95.5% ee) of all the tested conditions was obtained by switching from catalytic to

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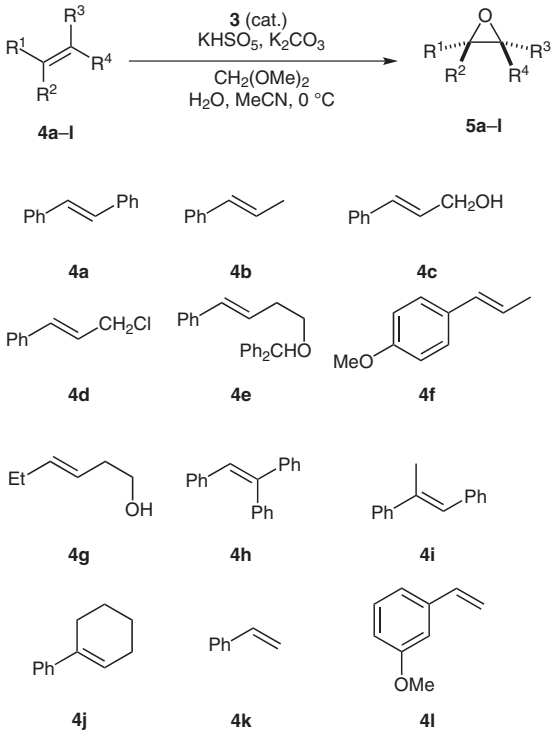

Scheme 1 Epoxidations mediated by hydrate **3** as the precatalyst

substoichiometric amounts of hydrate **3** (30 mol%, entry 2). However, we considered reaction conditions involving catalytic amounts of **3**, lower amounts of Oxone and lower pH values to be optimal in terms of atom economy (i.e. amounts of catalyst used and waste generated), hence they were chosen for the study of the epoxidation of several alkenes. Though for some difficult cases the pH value, the amount of catalyst or Oxone were increased. The results are summarised in Table 1.

The hydrate-derived species **3** effectively catalysed the epoxidation of a variety of *trans*-aryl-disubstituted olefins (Table 1, entries 1–8), providing ee values ranging from 83% to 95.5%. Species **3** was found to be comparable to Shi's diester fructose derivative **2** for a number of alkenes (**4a**,**c**,**g**,**h**).[7] Olefin substrates with a wide range of groups, such as aryl or alkyl substituents, benzyloxy ethers, hydroxymethyl or chloromethyl substituents were tolerated. Under the same experimental conditions, the epoxidation of diaryl-substituted alkenes proceeded with the highest selectivity, followed by arylalkyl-substituted alkenes and, lastly, dialkyl-substituted alkenes (cf. entries 2, 4 and 9 in Table 1). Several trisubstituted olefins (Table 1, entries 10–12) were also epoxidised with high selectivity. However, disappointingly, the epoxidation of styrenes by **3** showed only poor selectivities (entries 13 and 14), though conversions remained high, under all tested conditions. In all cases, where known, the absolute configurations of the obtained products are in agreement with the currently accepted mechanism of epoxidation by chiral dioxiranes derived from ketone **1**.[5]

Table 1 Epoxidations Mediated by Hydrate **3** as Precatalyst

Entry	Alkene	Reaction conditions[a]	Yield (%)[b]	ee (%)[c]
1	**4a**	**3** (10 mol%), Oxone (3.2 equiv), K_2CO_3 (6.8 equiv)	63	93.5 (*R*,*R*)-**5a**
2	**4a**	**3** (30 mol%), Oxone (3.2 equiv), K_2CO_3 (6.8 equiv)	95	95.5 (*R*,*R*)-**5a**
3	**4b**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	60	83 (*R*,*R*)-**5b**
4	**4b**	**3** (30 mol%), Oxone (3.2 equiv), K_2CO_3 (6.8 equiv)	83	89 (*R*,*R*)-**5b**
5	**4c**	**3** (10 mol%), Oxone (3.2 equiv), K_2CO_3 (6.8 equiv)	89	86 (*R*,*R*)-**5c**
6	**4d**	**3** (30 mol%), Oxone (3.2 equiv), K_2CO_3 (6.8 equiv)	80	90 (*R*,*S*)-**5d**
7	**4e**[11]	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	52	90[d] **5e**
8	**4f**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	99	83[e] **5f**
9	**4g**	**3** (30 mol%), Oxone (1.6 equiv), K_2CO_3 (7.2 equiv)	n.d.[f]	80 (*R*,*R*)-**5g**
10	**4h**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	52	92 (*R*)-**5h**
11	**4i**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	41	83 (*R*,*R*)-**5i**
12	**4j**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	82	92 (*R*,*R*)-**5j**
13	**4k**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	99	26 (*R*)-**5k**
14	**4l**	**3** (10 mol%), Oxone (1.6 equiv), K_2CO_3 (2.4 equiv)	99	11[g] **5l**

[a] Oxone and base were simultaneously added during a period of 2 h. The reaction mixture was further stirred at 0 °C for 16 h. The pH values were increased throughout the addition period from 6 to ca. 9 when K_2CO_3 (2.4 equiv) was used, and to ca. 10 in the other cases.
[b] Isolated material.
[c] Enantiomeric excesses.
[d] Unreported epoxide, configuration was assumed to be *R*,*R*.
[e] Configuration was assumed to be *R*,*R*.
[f] Not determined (**5g** was distilled together with the solvent during the workup).
[g] Configuration assumed to be *R*.

In summary, hydrate **3** has been found to be comparable to Shi's diester fructose derivative **2** in epoxidations involving Oxone and we have expanded the substrate scope catalysed by **3**-derived species for a number of structurally varied alkenes. Current efforts are directed towards exploiting this methodology towards epoxidations of more difficult substrates, such as styrenes and tetrasubstituted alkenes.

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(8) Diacetate **2** is a very effective as epoxidation catalyst using 10 mol% of catalyst loading. Loading for Shi's catalysts usually ranges from 20 mol% to 30 mol%. See refs. 4a–c.

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(11) Compound **4e** (0.37 g, 46% yield) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.40 (m, 15 H), 6.48 (dt, 1 H, *J* = 16.0, 1.3 Hz), 6.28 (dt, 1 H, *J* = 16.0, 6.9 Hz), 5.42 (s, 1 H), 3.62 (t, 2 H, *J* = 6.9 Hz), 2.60 (qd, 2 H, *J* = 6.9, 1.3 Hz). ^{13}C NMR: δ = 142.4, 137.7, 131.6, 128.5, 128.4, 127.4, 127.3, 127.2, 127.0, 126.0, 83.7, 68.7, 33.6.
The asymmetric epoxidation of alkene **4e** to give (+)-**5e** was carried out by the general procedure (see ref. 12).
Compound 5e (0.15 g, 52% yield); white solid; mp 56 °C; $[\alpha]_D^{25}$ +28.53 (*c* 0.12, CH_2Cl_2). IR: 2871–3066, 1599, 1491, 1097, 1037, 855 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.36 (m, 15 H), 5.36 (s, 1 H), 3.69 (d, 1 H, *J* = 1.9 Hz), 3.65 (t, 2 H, *J* = 6.0 Hz), 3.13 (td, *J* = 5.6, 1.9 Hz), 2.02 (td, 2 H, *J* = 5.6, 6.0 Hz). ^{13}C NMR: δ = 142.3, 142.3, 137.8, 128.6, 128.5, 128.2, 127.6, 127.6, 127.3, 127.1, 127.0, 125.7, 84.0, 65.7, 61.1, 58.8, 33.1. HRMS: *m*/*z* calcd for $C_{23}H_{22}O_2Na$: 353.1517; found: 353.1520. Enantiomeric excess was determined by HPLC using a chiral stationary phase (Chiracel OD-H column), eluent: hexane–*i*-PrOH (95:5); flow: 0.8 mL/min; l = 216 nm; t_R (major) = 10.8 min; t_R (minor) = 11.7 min.

(12) **General Procedure for the Epoxidation of Alkenes**: The corresponding alkene (2.22 mmol) and the required amount of catalyst **3** (10–30 mol%) were dissolved in MeCN–dimethoxymethane (44 mL, 1:2). A pH 6 buffer solution (8 mL), tetrabutylammonium hydrogen sulfate (35 mg, 0.10 mmol) was slowly added with stirring and the mixture was cooled to the desired temperature. The flask was equipped with two syringe pumps; one of them was filled with a solution of Oxone (3.62–6.82 mmol) in pH 6 buffer (14 mL) and the other one with a solution of K_2CO_3 (5.33–16.06 mmol) in H_2O (14 mL). The two solutions were added dropwise over a 2 h period (syringe pump). The solution was stirred at 0 °C for the corresponding reaction time. The mixture was diluted with H_2O (40 mL) and extracted with the appropriate organic solvent [**5a** and **5h**: hexane (4 × 40 mL); **5b–g**,**i–l**: CH_2Cl_2 (4 × 40 mL)]. The combined organic fractions were collected and washed with brine (50 mL), dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude material was purified by flash chromatography on SiO_2·Et_3N (2.5%). Enantioselectivity was determined by chiral chromatography and the configuration of epoxides was established by comparison with either reported elution order or optical rotation if reported data was available. For **5a**, HPLC; Chiralpak AD.[14] For **5b**,[15] **5j**,[16] and **5k**,[17] GC: gamma dex. For **5c**[18] and **5h**,[19] HPLC; Chiralcel OD. For **5d**, HPLC; Chiralcel OD-H.[20] For **5f**,[21] HPLC: Chiralcel AD-H. For **5l** GC: gamma dex.

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