Asymmetric Epoxidation

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Regio- and Enantioselective Epoxidation of Dienes by a Chiral Dioxirane: Synthesis of Optically Active Vinyl *cis*-Epoxides**

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Optically active vinyl epoxides are very useful synthetic intermediates,[1] and enantioselective monoepoxidation of conjugated dienes presents an efficient approach to these compounds.[2,3] Enantioselective epoxidation of conjugated dienes using chiral (salen)Mn catalysts has been shown to proceed predominantly at the *cis*-olefin with high regioselectivity and high enantioselectivity.[3] In the case of acyclic dienes, the epoxidation gave optically active vinyl *trans*-epoxides as major products.[3a,b,d] Earlier, we reported that fructose-derived ketone **1** (Scheme 1) is effective for the regioselective epoxidation of conjugated dienes to provide vinyl *trans*- and trisubstituted epoxides with high *ee* values [Eq. (1)].[4,5] Nevertheless, an efficient synthesis of chiral vinyl *cis*-epoxides is still highly desirable.

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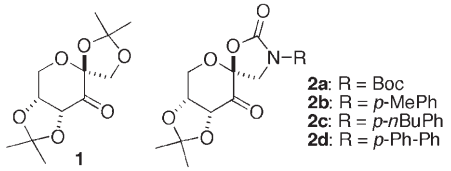
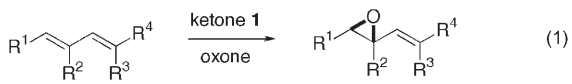
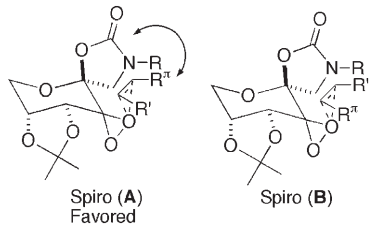
Supporting information for this article, including the characterization of epoxides and the data for the determination of the enantiomeric excesses of the epoxides, is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Boc = *tert*-butyloxycarbonyl.

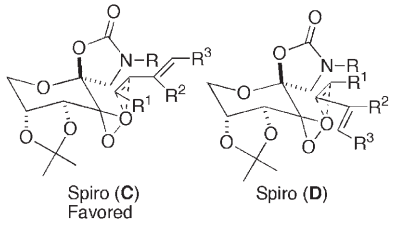


Recently, we found that oxazolidinone-containing ketone **2** provides high enantiomeric excesses for certain *cis*-olefins and styrenes.[6,7] Earlier studies suggest that spiro transition state **A** is favored over competing spiro **B** owing to an attraction between the R^{π} group of the olefin and the oxazolidinone moiety of the ketone catalyst (Scheme 2).[6,7]



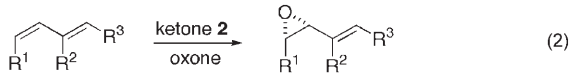
Scheme 2.

Up to this point, the R^{π} group has been primarily limited to aromatic groups. As part of our continuing efforts to further understand the interaction and expand the scope of this epoxidation, we examined the asymmetric epoxidation of conjugated dienes with ketone **2**. This study allows us to investigate whether alkenes can be effective directing groups to favor spiro transition state **C** (Scheme 3) and lead to the



Scheme 3.

synthesis of optically active vinyl *cis*-epoxides [Eq. (2)]. Herein, we report our preliminary efforts on this subject.



The epoxidation of conjugated dienes was carried out with ketone **2** as catalyst and oxone as oxidant. A variety of dienes are shown to be effective substrates, giving vinyl *cis*-epoxides with high *ee* values (Table 1).[8] The reactions were generally clean as judged by the ^{1}H NMR spectra of the crude reaction mixtures. The reactions were also stereospecific in that *cis*-olefins yielded only *cis*-epoxides, with no isomerization observed. The low isolated yields compared with the conversions in some cases were a result of the high sensitivity of vinyl epoxides towards flash column chromatography using silica gel.

Some of the reaction trends are highlighted as follows. Regioselectivity for the epoxidation is dependent on the type of diene. For *cis*/*trans*-dienes, it was found that the *cis*-olefins were epoxidized preferentially with high regioselectivity.[9] The epoxide derived from the *trans*-olefin was only detected in one case (Table 1, entry 7). A conjugated triene (Table 1, entry 9) also proved to be an effective substrate. As expected, *cis*/trisubstituted dienes showed competition for epoxidation between the two olefins. The degree of trisubstituted olefin epoxidation varied depending on the steric and electronic properties of the diene. If the trisubstituted olefin was deactivated electronically and/or sterically, *cis*-olefin epoxidation was favored (Table 1, entries 10 and 11).

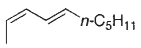
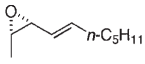
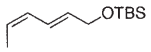
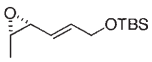
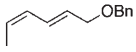
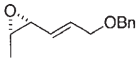
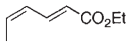
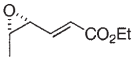
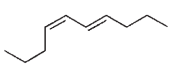
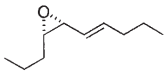
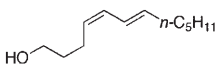
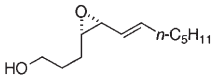
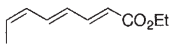
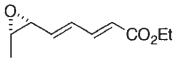
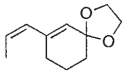
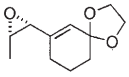
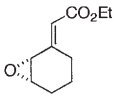
In most cases, no further epoxidation of vinyl *cis*-epoxides was found, presumably due to the deactivation of the olefin by the epoxide. For entry 8 in Table 1, bis(epoxide) was detected. In this case, the *ee* value of the mono(epoxide) did not change at different conversions, thus indicating that no significant kinetic resolution occurred during the reaction. However, for entry 10 in Table 1, it was found that the *ee* value of the vinyl epoxide increased with the conversion, which suggests that kinetic resolution may be occurring.

Changing the group on the 4-position of the aromatic ring of the catalyst had an effect on the enantioselectivity, likely due to additional interactions (possibly hydrophobic in nature) between this group and the substrate. The hydrophobic and hydrophilic nature of the R^1 and R^3 groups of the diene (Scheme 3) also have significant effects on the enantioselectivity of the epoxidation. Lower *ee* values were observed when the R^1 group was hydrophobic (Table 1, entry 7), presumably due to the increased hydrophobic interactions between the R^1 group and the N substituent of the catalyst in the competing spiro transition state **D** (Scheme 3). Conversely, higher *ee* values could be expected with more hydrophilic R^1 and/or more hydrophobic R^3 groups, thus further favoring spiro transition state **C** over **D** (for example, see Table 1, entry 8).

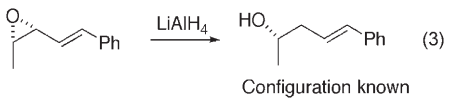
The stereochemistry of the epoxides shown in Table 1 is assigned on the basis of transition state spiro **C**. To further validate this model and the assigned stereochemistry, the absolute configurations of two representative examples (Table 1, entries 1 and 11) were determined [Eq. (3) and (4)] by converting the epoxide into a compound with known configuration.[10,11] The results in both cases support the initial assignment based on transition state spiro **C**.

In summary, we report that a conjugating olefin is an effective group for the attraction between the oxazolidinone of the catalyst and the substrate. A variety of conjugated

Table 1: Asymmetric epoxidation of dienes by ketone **2**.[a]

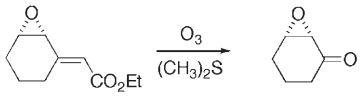
Entry	Diene	Epoxide	Ketone	Yield (Conv.) [%][b]	*ee* [%]
1			**2b**	66 (>95)[c,d]	85[e]
2			**2c**	47 (89)[f–h]	89[e]
3			**2d**	58 (100)[f,i]	92[j]
4			**2d**	64 (85)[f,g,k]	90[l]
5			**2d**	62 (98)[i]	90[l]
6			**2b**	64 (99)[i]	94[l]
7			**2d**	66 (88)[g,i,m,n]	76[l]
8			**2c**	80 (100)[c,f,i,o,p]	89[e]
9			**2b**	74 (99)[i]	94[l]
10			**2a**	61 (100)[f,i,q]	93[l]
11			**2b**	67 (>95)[c,i,r] [3b]	91[s]

[a] All reactions were carried out at −10°C with diene (1 equiv), ketone (0.1–0.3 equiv), oxone (1.6 equiv), and K_2CO_3 (6.7 equiv) in DME/DMM (3:1, v/v) and buffer (0.1 M K_2CO_3/AcOH in 1×10^{-4} M aq. EDTA, pH 9.3) for 4 h, unless otherwise stated. TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl; Bn = benzyl; DME = 1,2-dimethoxyethane; DMM = dimethoxymethane; EDTA = ethylenediaminetetraacetic acid. [b] The conversion was determined by GC analysis of the crude reaction mixture. [c] The conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] 0.10 equiv catalyst used. [e] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ column). [f] Oxone and K_2CO_3 were added over 8 h. [g] 2.4 equiv oxone and 10.1 equiv K_2CO_3 were used. [h] 0.20 equiv catalyst used. [i] 0.25 equiv catalyst used. [j] Enantioselectivity was determined by chiral shift ^{1}H NMR spectroscopy with Eu(hfc)$_3$ (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate). [k] 0.30 equiv catalyst used. [l] Enantioselectivity was determined by Chiral GC (Chiraldex B-DM column). [m] Oxone and K_2CO_3 were added over 10 h. [n] 12:1 ratio of *cis*/*trans*-epoxides (regioselectivity) observed; the yield and *ee* for the *cis*-epoxide is given. [o] 0.96 equiv oxone and 4.0 equiv K_2CO_3 were used. [p] 10:1 ratio of mono/bis(epoxide)s observed; the yield and *ee* for the mono(epoxide) is given. [q] 1.8 equiv oxone and 4.0 equiv K_2CO_3 were used. [r] The isolated product is a mixture of *cis*-/trisubstituted epoxides (3.3:1); the *ee* value is given for the *cis*-epoxide. [s] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column).



(3)

Configuration known



(4)

Configuration known

dienes can be epoxidized with high enantioselectivity using glucose-derived catalysts **2a–d** and oxone as oxidant. The epoxidations are stereospecific and no isomerization is observed to give *cis*-epoxides exclusively from *cis*-olefins. The regio- and enantioselectivity of the reaction are dependent on the substitution pattern of the diene system. With this methodology, a variety of enantioenriched vinyl *cis*-epoxides are now readily available.

Experimental Section

Representative procedure for asymmetric epoxidation (Table 1, entry 6). Buffer (0.1 M K_2CO_3/AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3; 5 mL) and Bu_4NHSO_4 (0.0075 g, 0.02 mmol) were added with stirring to a solution of the diene (0.070 g, 0.50 mmol) and ketone **2b** (0.042 g, 0.125 mmol) in DME/DMM (3:1, v/v; 7.5 mL). The mixture was cooled to about −10°C (NaCl–ice bath temperature), and then a solution of oxone (0.20 M; 0.49 g, 0.80 mmol) in aqueous EDTA (4×10^{-4} M, 4.0 mL) and a solution of K_2CO_3 (0.84 M, 0.46 g, 3.36 mmol) in aqueous EDTA (4×10^{-4} M, 4.0 mL) were added dropwise simultaneously over a period of 4 h through a syringe pump. The reaction was then quenched with the addition of petroleum ether and extracted with a mixture (1:1, v/v) of petroleum ether/diethyl ether. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated, and the residue was purified by flash chromatography (the silica gel was buffered with 1% Et_3N in petroleum ether; petroleum ether/diethyl ether (1:0 to 19:1, v/v) was used as eluent) to give the *cis*-epoxide as a colorless oil (0.050 g, 64% yield, 94% *ee*).

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