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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 8115–8117

Asymmetric epoxidation of *cis*-β-methylstyrenes catalyzed by *N*-aryl substituted oxazolidinone-containing ketones. A beneficial substituent effect

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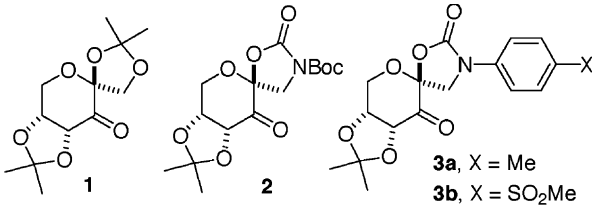
Received 29 July 2004; revised 20 August 2004; accepted 20 August 2004
Available online 17 September 2004

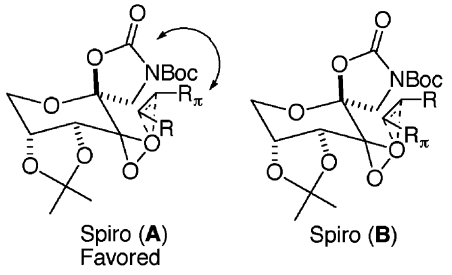
Abstract—Asymmetric epoxidation of substituted *cis*-β-methylstyrenes using *N*-aryl substituted oxazolidinone-containing ketones as catalysts shows that substituents on the phenyl group of the olefin have significant positive effects on the enantioselectivity of the epoxidation, indicating a beneficial interaction between the phenyl group of the olefin and the phenyl group of the ketone catalyst.

Asymmetric epoxidation of olefins is an important method for synthesizing optically active epoxides. Great success has been achieved for the epoxidation of allylic alcohols,[1] the metal-catalyzed epoxidation of unfunctionalized olefins,[2] and the nucleophilic epoxidation of electron-deficient olefins.[3] In recent years, chiral dioxiranes have been shown to be powerful asymmetric epoxidation agents.[4–6] In our earlier studies, we have shown that fructose-derived ketone **1** (Scheme 1) gives high enantioselectivity for the epoxidation of *trans*- and trisubstituted olefins.[7] Subsequently, we have found that ketone **2**, resulting from the replacement of the spiro ketal of ketone **1** with an oxazolidinone, provides encouragingly high ee's for the epoxidation of *cis*-olefins and styrenes.[8] Our earlier studies suggest that the asymmetric induction is likely due to an attraction between the R_π group and the oxazolidinone moiety of the ketone catalyst in the transition state (Scheme 2). This electronic interaction was further illustrated by our recent studies with *N*-aryl substituted oxazolidinone ketone **3**.[9] To further probe this interaction, we have investigated the epoxidation of various substituted *cis*-β-methylstyrenes and have found that the olefin substituent has a significant effect on the enantioselectivity of the epoxidation. Herein we wish to report our preliminary efforts on this subject.



Scheme 1.

The epoxidation was initially investigated using ketone **3a** as catalyst. Subjecting *cis*-β-methylstyrene to the epoxidation conditions with 10 mol% of ketone **3a** at −10 °C gave (1*R*,2*S*)-*cis*-β-methylstyrene oxide with 99% conversion and 84% ee (Table 1, entry 1).[10] The epoxidation of *cis*-β-methylstyrene with **3a** was found



Scheme 2.

Keywords: Asymmetric epoxidation; Chiral dioxirane; Chiral ketone; Phenyl–phenyl interaction.
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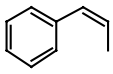
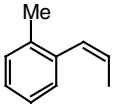
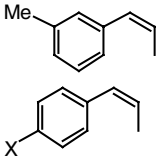
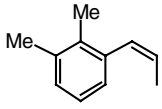
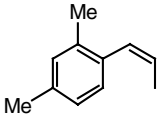
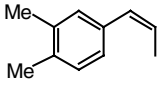
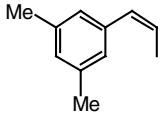
doi:10.1016/j.tetlet.2004.08.124

Table 1. Asymmetric epoxidation of olefins catalyzed by ketones **3a** and **3b**

Entry	Substrate	Ketone **3a**[a]		Ketone **3b**[b]	
		Conv. (%)[c]	ee (%)[c]	Conv. (%)[c]	ee (%)[c]
1		99	84	100	90
2		86	88	80	92
3		94	91	100	93
4	X = Me	100	88	96	92
5	X = Et	87	90	91	93
6	X = F	99	87	100	91
7	X = Cl	79	92	90	95
8	X = Br	82	93	86	96
9	X = CN	94	96	98	96
10	X = NO_2	86	98	91	97
11		72	92	100	97
12		75	91	97	96
13		97	91	100	94
14		98	92	100	94

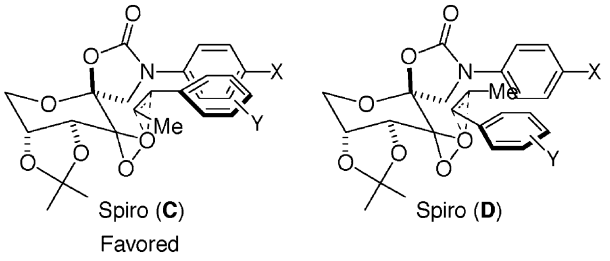
[a] All reactions were carried out with olefin (0.2 mmol), ketone **3a** (0.02 mmol), Oxone (0.197 g, 0.32 mmol), and K_2CO_3 (0.185 g, 1.34 mmol) in DME/DMM (3:1, v/v) (3 mL) and buffer (0.1 M K_2CO_3–AcOH, pH 9.3) (2 mL) at −10 °C (bath temperature). The reactions were stopped after 4 h.

[b] The reactions with ketone **3b** were carried out in a similar fashion to ketone **3a**. All reactions used 15 mol% of ketone except entries 11 and 12 where 20 mol% was used. For ketone **3b**, the epoxides (both *cis*- and *trans*-isomers) were isolated in 61–95% yield.

[c] The conversions and ee's were determined by chiral GC (Chiraldex B-DM). For entries 2–14, the olefin substrates contain 16–37% *trans*-isomers. The conversions indicated are those for *cis*-olefins.

to be stereospecific and no *trans*-β-methylstyrene oxide was formed during the reaction as judged by GC assays of the crude reaction mixture. Introducing a methyl group to *ortho*, *meta*, and *para* positions gave rise to a 4–7% ee increase (Table 1, entries 2–4).[11] Further studies with various *para* substituted *cis*-β-methylstyrenes showed that the ee's of the epoxides increased across the board from the electron-donating Me group to the electron-withdrawing NO_2 group (Table 1, entries 4–10). Up to 98% ee was attained with the NO_2 substituted olefin (Table 1, entry 10). The ee's also increased when two methyl groups were introduced at various positions (Table 1, entries 11–14). A similar trend was observed when the epoxidation was carried out with ketone **3b**, which contained an electron-withdrawing sulfone substituent on the phenyl group of the ketone catalyst.

The significant substituent effect observed with ketone **3** is rather interesting. The results suggest that there is an additional phenyl–phenyl interaction between the olefin and catalyst in the transition state aside from the attractive interaction between the phenyl group of the olefin and the oxazolidinone moiety of the catalyst (Scheme 3).[8,9] The crystal structure of **3a** shows that the phenyl group in this ketone is coplanar with the oxazolidinone.[9] Therefore, this phenyl–phenyl interaction is more likely to be an 'edge-to-face' interaction.[12] While electron-withdrawing groups on the phenyl group of the olefin



Scheme 3.

show a stronger effect, electron-donating groups can also enhance the interaction, suggesting that nonbonding interactions such as van der Waals forces and/or hydrophobic interactions could be involved in the phenyl–phenyl interaction in addition to electrostatic interactions.[12b] A precise understanding of the interaction for the current system awaits further studies.

In summary, asymmetric epoxidation of various substituted *cis*-β-methylstyrenes using *N*-aryl substituted oxazolidinone-containing ketones **3a** and **3b** has shown that the substituents on the phenyl group of the olefin have significant positive effects on the enantioselectivity of the epoxidation. These results reveal a beneficial interaction between the phenyl group of the olefin and the phenyl group of the ketone catalyst. Although the precise nature of this phenyl–phenyl interaction is not clear, such interactions could provide us additional opportunities to explore asymmetric induction. At the same time, the current epoxidation system could be used as a tool to further study such interactions. Synthetically, the observed beneficial substituent effect further enhances the practical aspect of ketone **3**, which is readily available from glucose.[9]

Acknowledgements

We are grateful to the generous financial support from the General Medical Sciences of the National Institutes of Health (GM59705-05), the Camille and Henry Dreyfus Foundation, and the Monfort Foundation (Colorado State University).

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