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Asymmetric Epoxidation of *cis*-Alkenes Mediated by Iminium Salts: Highly Enantioselective Synthesis of Levcromakalim

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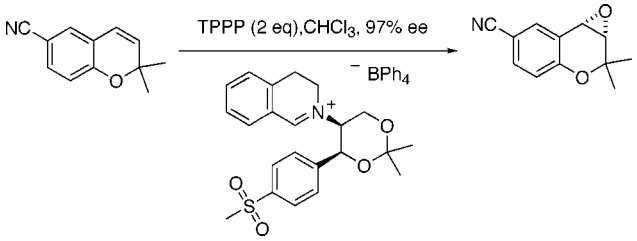
ABSTRACT



A range of *cis*-substituted olefins has been epoxidized with a new dihydroisoquinolinium salt catalyst, using tetraphenylphosphonium monoperoxysulfate as the stoichiometric oxidant, giving ee's of up to 97%. The reaction has been used as the key step in an enantioselective synthesis of the antihypertensive agent levcromakalim.

Asymmetric epoxidation of alkenes is an extremely powerful synthetic tool. Recently organocatalysis, that is, catalysis by small organic molecules involving no metal atoms, has received increasing attention,[2] and a good deal of this has been focused on asymmetric epoxidation by dioxiranes.[3] Several fructose-derived dioxiranes, e.g., **1**, have emerged as useful mediators in asymmetric epoxidations.[4] Enantioselectivity is good to excellent; catalyst loadings, however, remain high. Oxaziridinium salts generated, for example, by oxidation of iminium salts are useful electrophilic oxidants for alkene epoxidation,[5] and the iminium salts may be used catalytically; effective catalyst loadings can be as low as 0.1 mol %. Enantiomeric excesses obtained using chiral iminium salt catalysts have, however, until recently[6] been limited to around 70% at best.

Catalytic use of iminium salts has required the presence of oxone as the stoichiometric oxidant, and water must also be present in the reaction medium for oxone solubility. We have recently reported a nonaqueous system for epoxidation by oxaziridinium salt catalysts, which uses tetraphenyl

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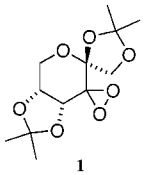
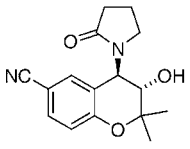
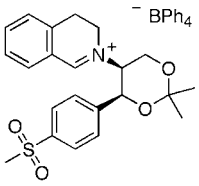
phosphonium monoperoxysulfate (TPPP) as the primary oxidant.[7] This oxidant is soluble in a variety of organic solvents, and reactions can be performed over a range of temperatures in the absence of water. Herein we report the use of chloroform as the preferred solvent for the epoxidation of several *cis*-alkenes using this system and the highly enantioselective synthesis of the antihypertensive agent levcromakalim **2** using this epoxidation as a key step.



1



2

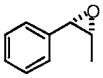
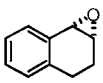
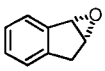
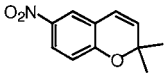
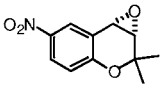
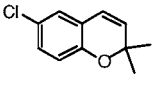
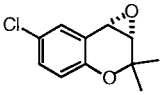
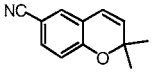
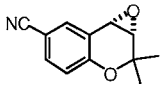


3

Iminium salt **3** is one of our more enantioselective and reactive epoxidation catalysts in the nonaqueous system for *trans*- and trisubstituted alkene substrates. For example, *trans*-stilbene, usually a very poor substrate under our standard aqueous conditions,[6] is epoxidized with 67% ee in the presence of iminium salt **3** in chloroform solution to give the (+)-(*R*,*R*) configured epoxide as the major enantiomer. Several *cis*-alkenes were subjected to the same reaction conditions (Table 1). Good enantiomeric excesses were also observed for *cis*-*β*-methyl styrene (70% ee) and dihydronaphthalene (82% ee). The level of enantioselectivity observed was remarkable given that the corresponding reaction carried out under our standard aqueous conditions with oxone afforded dihydronaphthalene oxide in only 45% ee. The enantiomeric excess for epoxidation of indene is somewhat lower (61% ee) but is still much higher than other reported ee's for this epoxidation mediated by oxaziridinium salts. Epoxidation of the non-aryl *cis*-hept-2-ene produced epoxide with quantitative conversion but with low ee. Electron-deficient alkenes are also poor substrates. It is interesting to note that the enantiomeric excesses of epoxides generated in chloroform are superior to those of epoxides generated in acetonitrile.

We next turned our attention to the epoxidation of benzopyran substrates. We were delighted to observe excellent enantioselectivities in the epoxidations of 6-nitro, 6-chloro-, and 6-cyano-2,2-dimethylbenzopyrans (Table 1). The epoxidation of 6-cyano-2,2-dimethylbenzopyran [9] was

Table 1. Catalytic Asymmetric Epoxidation of Various *cis*-Alkenes Using TPPP in $CHCl_3$ [a,8]

Alkene	Epoxide	Yield/ %[b]	ee/ %[c,d]	Config[e]
		85	70 (53)	(+)-1*S*,2*R*
		89[f]	82 (56)	(–)-1*S*,2*R*
		83	61	(+)-1*S*,2*R*
		52	88	(–)-1*S*,2*S*
		76	93	(–)-1*S*,2*S*
		59	97 (80)	(–)-1*S*,2*S*

[a] Epoxidation conditions: iminium salt **3** (10 mol %), TPPP (2 equiv), $CHCl_3$, −40 °C, 24 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by ^{1}H NMR spectroscopy in the presence of (+)-Eu(hfc)$_3$ (0.1 molar equiv) or by chiral HPLC on a Chiracel OD column. [d] Numbers in parentheses refer to the ee obtained when acetonitrile was employed as reaction solvent. [e] The absolute configurations of the major enantiomers were determined by comparison of the sense of optical rotation with values reported in the literature. [f] Reaction time of 17 h.

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(8) In a control experiment formation of epoxide was not observed upon treatment of 1,2-dihydronaphthalene with TPPP in chloroform even after 48 h at 0 °C.

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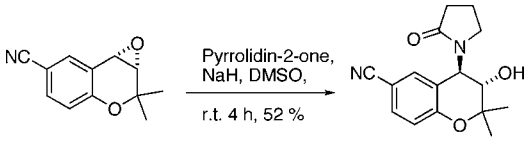
of particular interest, as ring opening of the epoxide unit with a variety of nucleophiles affords compounds with significant biological activity,[10] including the antihypertensive agent levcromakalim ((−)-cromakalim) **2** (Scheme 1).[11]

Scheme 1. Synthesis of Levcromakalim



4 **2**

In this case, the corresponding (*S*,*S*)-epoxide **4** was formed in 97% ee and 59% yield. This is the highest ee yet reported for asymmetric epoxidation mediated by oxaziridinium salts. Treatment of the epoxide **4** with pyrrolidin-2-one under the conditions described by Evans afforded the (−)-(3*S*,4*R*) enantiomer of **2** in 52% yield.[12]

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Supporting Information Available: Full experimental detail. This material is available free of charge via the Internet at http://pubs.acs.org.

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