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Iminium Salt Catalysts for Asymmetric Epoxidation: The First High Enantioselectivities

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ABSTRACT



A highly enantioselective iminium salt catalyst has been prepared and tested in the catalytic asymmetric epoxidation of unfunctionalized alkenes, giving up to 95% ee, the highest ee yet reported for iminium salt-catalyzed epoxidation. Catalyst loadings as low as 0.1 mol % may be used.

Chiral epoxides are extremely useful building blocks for asymmetric synthesis,² and the development of effective systems for asymmetric epoxidation has received considerable attention.³ Oxaziridinium salts, e.g., **1**, generated for

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example by oxidation of iminium salts, are useful electrophilic oxidants for olefin epoxidation. Since the first oxaziridinium salts were described by Lusinchi in 1976⁴ and the corresponding iminium salts subsequently shown to catalyze epoxidation in the presence of oxone,⁵ several other groups have sought to design selective asymmetric catalysts in this area.⁶ Enantiomeric excesses have, however, been limited to ca. 70% at best, and few substrate types invoke even this level of enantioselectivity. Recent reports by Yang and Armstrong utilize acyclic chiral iminium salts generated

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in situ from chiral amines and aldehydes, but enantiomeric excesses are again moderate and catalyst loadings high.⁷

Our own approach to chiral iminium salt catalysts differs from previous investigations, where the exocyclic group attached to the nitrogen atom of the iminium unit has invariably been methyl or ethyl.



We reasoned that positioning of asymmetric centers in an exocyclic substituent on the iminium nitrogen atom, as in 2, would bring these controlling asymmetric elements of the catalyst nearer to the site of oxygen transfer and should therefore increase the ee induced in an epoxidation reaction.⁸



We have recently reported a new family of much more reactive catalysts, in which the dihydroisoquinolinium moiety has been replaced by a biphenyl structure fused to a sevenmembered ring azepinium salt.⁸ The catalyst **3**, derived, as is **2**, from 5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane **4**, induces complete conversion of alkenes to epoxides in only 10 min at 0 °C. A binaphthalene-fused azepinium salt catalyst, achiral at the nitrogen substituent, has also been described, and gave 71% ee for phenylcyclohexene oxide and 45% ee for α -methylstilbene oxide.⁶ Lacour has reported catalysis of epoxidation by oxone with the iminium salt of **3** but using an enantiomerically pure TRISPHAT counterion and dichloromethane/water as the solvent system.⁹

We describe herein several new azepinium salt catalysts, derived from (+)- and (-)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane 4^{10} and (-)-isopinocampheylamine $5^{11,12}$



moieties, and fused to (*R*)- or (*S*)-binaphthalene units. These catalysts are directly prepared, in good yields, from the bromomethyl carbaldehyde intermediate **6**, which we prepare in turn from commercial (*R*)- or (*S*)-(1,1')-binaphthalenyl-2,2'-diol (Binol) (Scheme 1, Table 1).

Table 1. Cyclocondensation of Primary Amines 4 and 5 with the Bromoaldehyde 6

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bromoaldehyde	amine	product	yield (%)
(<i>R</i>)	4	7a	66
(S)	ent-4	ent- 7a	64
(S)	4	7 b	63
(<i>R</i>)	5	7c	71
(S)	5	7d	73

With the new catalysts in hand, we were able to test their effectiveness in several epoxidation reactions. Initially, we screened the catalysts with our usual test substrates, 1-phenylcyclohexene, α -methylstilbene, and triphenylethylene (Table 2).

Catalyst **7a** showed the best reaction profile, being not only the most reactive but also the most enantioselective



iminium salt epoxidation catalyst yet discovered. For example, in the presence of 7a, 1-phenycyclohexene oxide was produced in 69% yield with an unprecedented 91% ee in

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⁽¹²⁾ The HPLC conditions used for analysis of 1-phenyldihydronaphthalene were: Chiracel OD column, flow rate 1.0, hexane/IPA 90:10, retention times (1S,2R) 9.78 min (major isomer), (1R,2S) 11.81 min (minor isomer).

Table 2. Asymmetric Epoxidation of Unfunctionalized AlkenesMediated by Catalysts $7\mathbf{a}-\mathbf{d}^a$

alkene	catalyst	time/h	yield/ % ^b	ee/ %°	config ^d
			70	70	
	7 a	0.20	69	91	(-)1S, 2S
Ph	ent-7a	0.20	66	88	(+)1R, 2R
	7 b	2.0	54	78	(+)1R,2R
	7 c	2.0	40	53	(-)1 <i>S</i> ,2 <i>S</i>
	7 d	2.0	44	58	(+)1 <i>R</i> ,2 <i>R</i>
	7 a	0.40	58	49	(–)1 <i>S</i> ,2 <i>S</i>
Ph	7 b	4.0	<5%	_	-
Me	7 c	4.0	<5%	-	_
	7 d	4.0	<5%	-	_
	7 a	0.50	60	12	(+)- <i>S</i>
Ph Ph	7 b	4.0	<5%	_	_
FII	7 c	4.0	<5%	_	_
	7 d	4.0	<5%	_	_

^{*a*} Conditions: iminium salt (5 mol %), oxone (2 equiv), Na₂CO₃ (4 equiv), MeCN/H₂O (1:1), 0 °C. ^{*b*} Isolated yields. ^{*c*} Enantiomeric excesses were determined by ¹H NMR spectroscopy in the presence of (+)-Eu(hfc)₃. ^{*d*} Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature.

under 20 min, while the other catalysts (apart from *ent*-**7a**, the enantiomer of **7a**) were less selective and gave more sluggish reactions. The isopinocamphenyl moiety offers little enantiocontrol, leading to epoxides with only moderate ees. The poor reactivity of catalysts **7b**-**d** is highlighted by the attempted epoxidations of α -methyl stilbene and triphenyl ethylene, where poor conversions were observed after 4 h. Catalyst **7a**, however, afforded complete conversion to the corresponding epoxides in a much shorter time and an isolated yield of ca. 60%, although the ees were low to moderate. In a control reaction of 1-phenylcyclohexene in the absence of catalyst, epoxide was generated in less than 1% yield after 8 h.

Catalyst **7a** was subsequently used to epoxidize several other olefins. Again the reactivity of the catalyst at (5 mol %) was good, but a wide range of ees was observed (Table 3). 1-Phenyl-3,4-dihydronaphthalene was epoxidized with very high enantioselectivity (95% ee and 66% yield after 35 min). *para*-Phenylstyrene oxide was produced with 29% ee, the highest reported ee for epoxidation of a terminal alkene using iminium salt catalysis.

Table 3.	Asymmetric Epoxidation of Various Alkenes
Mediated	by Catalyst 7a ^a

alkene	time/h	yield/ % ^b	ee/ %°	config ^d
Ph Ph	0.45	58	20	(–)-S,S
\frown +	0.25	63	25	(–)-1 <i>S</i> ,2 <i>S</i>
	0.30	60	17	(–)-1 <i>S</i> ,2 <i>R</i>
Ph	0.35	66	95	(-)-1 <i>S</i> ,2 <i>R</i>
ОН	2.0	67	38	(-)-2 <i>S</i> ,3 <i>S</i>
Ph	1.0	70	29	(+)-S

^{*a*} Conditions: iminium salt (5 mol %), oxone (2 equiv), Na₂CO₃ (4 equiv), MeCN/H₂O (1:1), 0 °C. ^{*b*} Isolated yields. ^{*c*} Enantiomeric excesses were determined by ¹H NMR spectroscopy in the presence of (+)-Eu(hfc)₃ or by chiral HPLC using a Chiracel OD column.¹² ^{*d*} Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature.

With a number of successful epoxidation substrates established for catalyst **7a**, several cycloalkenes, of varying ring sizes, were submitted to the asymmetric epoxidation reaction (Table 4). Reactions were carried out using just 1

Table 4. Effect of Ring Size on the Epoxidation of Several Cycloalkenes with Catalyst $7a^{a}$

alkene	time/h	yield/ % ^b	ee/ %°	config ^d
Ph	5.0	52	55	(–)-1 <i>S</i> ,2 <i>S</i>
Ph	1.1	64	91	(–)-1 <i>S</i> ,2 <i>S</i>
Ph	5.0	57	76	(-)-1 <i>S</i> ,2 <i>S</i>

^{*a*} Conditions: iminium salt (1 mol %), oxone (2 equiv), Na₂CO₃ (4 equiv), MeCN/H₂O (1:1), 0 °C. ^{*b*} Isolated yields. ^{*c*} Enantiomeric excesses were determined by ¹H NMR spectroscopy in the presence of (+)-Eu(hfc)₃. ^{*d*} Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature.

mol % catalyst **7a**. Again, good conversions to epoxides were achieved, and, interestingly, the five- and seven-membered ring cycloalkenes were less reactive than was 1-phenyl-cyclohexene. The reactions were much more sluggish, and enantioselectivities were poorer than those observed for 1-phenylcyclohexene: 1-phenylcyclopentene oxide was formed in 55% ee and 1-phenylcycloheptene in 76% ee.

Using 1-phenylcyclohexene as a test substrate, we also conducted a catalyst loading study of 7a, with catalyst loadings ranging from 0.1 to 5 mol % (Table 5). We were delighted and extremely surprised to observe high levels of asymmetric induction with low catalyst loadings. We have

Table 5. Catalyst Loading Study on the Epoxidation of 1-Phenylcyclohexene with Catalyst $7a^{a}$

[7a] (mol %)	time (h)	yield (%) b	ee (%) ^c	$configuration^d$
5.0	0.2	69	91	(-)-(1 <i>S</i> ,2 <i>S</i>)
1.0	1.1	64	91	(-)-(1 <i>S</i> ,2 <i>S</i>)
0.5	2.0	65	91	(-)-(1 <i>S</i> ,2 <i>S</i>)
0.1	6.0	68	88	(-)-(1 <i>S</i> ,2 <i>S</i>)

^{*a*} Conditions: Oxone (2 equiv), Na₂CO₃ (4 equiv), MeCN/H₂O (1:1), 0 °C. ^{*b*} Isolated yields. ^{*c*} Enantiomeric excesses were determined by ¹H NMR spectroscopy in the presence of (+)-Eu(hfc)₃. ^{*d*} Absolute configurations of the major enantiomers were determined by comparison of optical rotation with those reported in the literature.

previously reported that it is possible to use just 0.5 mol % catalyst, but a loss in enantioselectivity is commonly observed. In this case, however, catalyst loadings can be so low that effective epoxidation of 1.0 g of 1-phenylcyclohexene, with 68% yield and 88% ee, can be achieved using just 5 mg of catalyst (0.1 mol %).

Catalyst **7a** gives the highest ees ever reported for iminium salt-catalyzed epoxidation and for several substrates is the most enantioselective iminium salt catalyst known. It is also the most active iminium salt catalyst that we have discovered and is effective at remarkably low catalyst loading. Generally, organic catalysts require high catalyst loadings, and decomposition of the catalyst is often observed. In the case of catalyst **7a**, the enantioselectivity appears to be independent of catalyst loading down to 0.5 mol %; decreasing the amount of catalyst merely increases the reaction time.

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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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