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Enantioselective organocatalytic epoxidation using hypervalent iodine reagents

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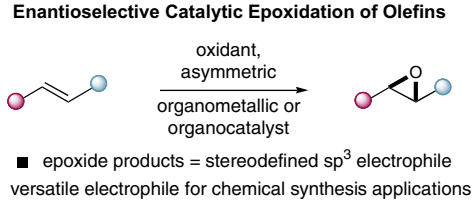
Abstract—A rare example of a hypervalent iodine reagent participating in a 1,4-heteroconjugate addition reaction is reported for the organocatalytic, asymmetric epoxidation of α,β-unsaturated aldehydes using imidazolidinone catalyst **1**. Development of an 'internal syringe pump' effect via the slow release of iodosobenzene from an iminoiodinane source provides high levels of reaction efficiency and enantiomeric control in the asymmetric epoxidation of electron-deficient olefins. ^{15}N NMR studies were conducted to elucidate the reaction pathways that lead to catalyst depletion in the presence of prototypical oxidants. These NMR studies also provided the mechanistic foundation for the application of iminoiodinanes as an internal slow release oxidant to circumvent these catalyst depletion pathways.

1. Introduction

The enantioselective catalytic oxidation of olefins is arguably one of the most powerful transformations known to practitioners of chemical synthesis.[1] Indeed, since the invention of the Sharpless asymmetric epoxidation,[2] there has been an ever-increasing demand for catalyst-controlled processes that allow efficient and predictable access to enantioenriched oxiranes. Significant efforts to expand the scope of such catalytic epoxidations have been made via the seminal contributions of Jacobsen[3] and Katsuki[4] using metal-ligated systems for the electrophilic delivery of oxygen. Complementary to these established organometallic strategies, Shi,[5] Denmark,[6] Yang,[7] and Armstrong[8] have developed an elegant organocatalytic approach that relies upon a ketone-derived dioxirane catalyst for the asymmetric epoxidation of trisubstituted and 1,2-*trans*-disubstituted alkenes. These epoxidation methods are applicable to several olefin classes; however, they do not encompass the enantioselective epoxidation of electron-deficient olefins.



Existing technologies for the enantioselective epoxidation of olefins[9] via LUMO-lowering activation have been founded upon the Weitz–Scheffer reaction,[10] wherein a nucleophilic chiral peroxide adds to an enone or enal (Fig. 1). This strategy of hydroperoxide delivery via a homogeneous chiral metal complex has been adopted and developed by Enders[11] in a stoichiometric manner and in a catalytic approach by Jackson[12] and Shibasaki.[13] Alternatively, asymmetric phase transfer agents have been utilized to transport a reactive oxo-species to olefin substrates as epitomized in the work of Roberts[14] using polyamino acids and in the cinchona alkaloid-derived salts of Lygo[15] and Corey.[16]

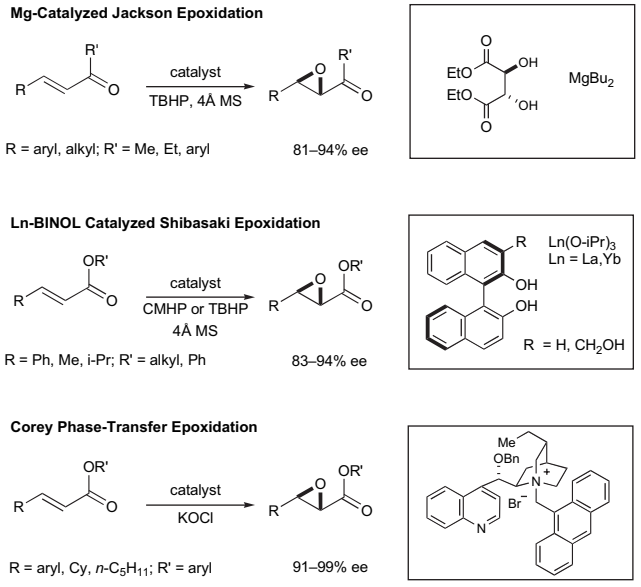


Figure 1. General methods for catalytic nucleophilic epoxidations.

Keywords: Epoxidation; Organocatalysis; Enantioselective; Iodosobenzene.
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Most recently, Jørgensen and co-workers[17] have demonstrated the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes using iminium catalysis. In these elegant studies, a variety of enals rapidly underwent asymmetric epoxidation using hydrogen peroxide as the stoichiometric oxidant in the presence of a proline-derived catalyst. In this publication, we further demonstrate the use of our chiral imidazolidinone salts as iminium activation catalysts for the asymmetric epoxidation of α,β-unsaturated aldehydes. This transformation provides rapid access to enantio-enriched 1,2-*trans*-formyl epoxides, an ambiphilic class of electrophile of known value in chemical synthesis.[18]

In 2002, we initiated studies to develop a novel organocatalytic strategy for the asymmetric epoxidation of electron-deficient olefins based upon the activation principle of iminium catalysis. Having demonstrated the capacity of chiral amines to function as asymmetric catalysts and building on previous successes in cycloadditions and 1,4-conjugate additions,[19] it was anticipated that a nucleophilic oxygen that incorporated a suitable leaving group could add with enantiofacial selectivity to an iminium-activated α,β-unsaturated aldehyde (Fig. 2). Subsequent enamine formation followed by intramolecular trapping of the pendent electrophilic oxygen with concomitant expulsion of the oxygen-tethered leaving group should then produce an oxirane (Fig. 3). At the outset of these studies, we felt that the proposed cyclization step had good precedent given related

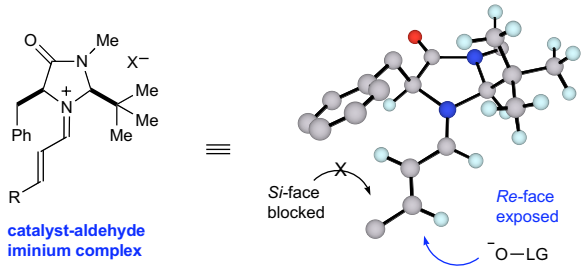


Figure 2. Rationale of catalyst-controlled enantioselectivity utilizing an MM3-2 model of the catalyst.

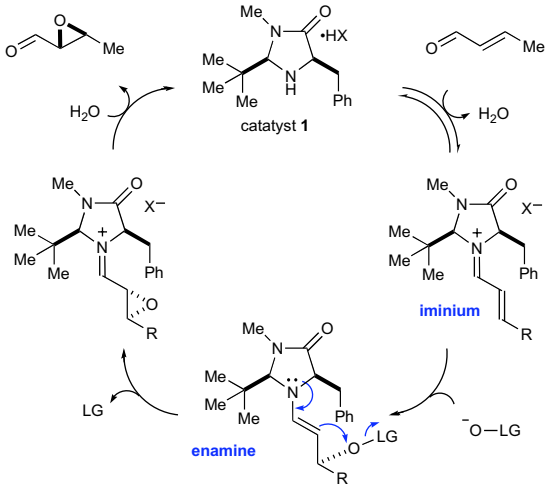


Figure 3. Proposed organocatalytic cycle for oxirane formation and the generation of an α,β-epoxy aldehyde.

cyclopropanation studies that were ongoing in our laboratory.[19a] In that methodology, a pendent thionium moiety functions as a suitable leaving group for intramolecular enamine cyclization to yield three-membered carbocycles. With this in mind, we recognized that an analogous epoxidation mechanism would rely on the judicious selection of an ambiphilic oxygen source that could function as a viable nucleophile for the conjugate addition step, yet would be suitably electrophilic (via incorporation of an electronegative leaving group (LG)) to enable intramolecular enamine oxidation and oxirane formation.

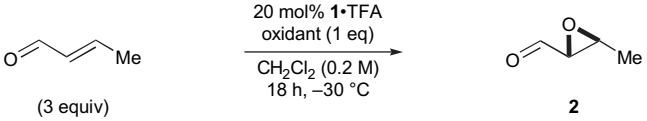
2. Results and discussion

2.1. Preliminary investigations

Our studies began with an investigation to define potential oxygen sources that would participate in the requisite 1,4-heteroconjugate addition/enamine cyclization. Initial experiments were performed with crotonaldehyde and a variety of commercially available oxidants in the presence of catalyst **1**·trifluoroacetic acid (TFA) salt. To our delight, the desired 2,3-epoxyaldehyde product (**2**) was readily accessed using a variety of oxygen sources (Table 1). Implementation of *m*-CPBA provided the epoxide product **2** with encouraging selectivity levels (Table 1, entry 3, 73% ee); however, studies to define the utility of this reagent (solvent, temperature) resulted in little improvement in overall enantiocontrol. The use of peroxides, such as *tert*-butyl hydrogen peroxide and hydrogen peroxide[20] also provided the desired oxirane with notable enantioselectivities (Table 1, entries 4 and 5). However, attempts to employ such oxidants with less reactive substrates (such as cinnamaldehyde) resulted mainly in the production of the catalyst *N*-oxide derivative, a catalyst depletion pathway that significantly reduces reaction efficiency. Unfortunately, bleach and pyridine *N*-oxide were not found to be viable reagents for this process (Table 1, entry 6).

We next examined the use of hypervalent λ^3-iodanes as potential oxidants for this organocatalytic Weitz–Scheffer reaction. While iodosobenzene is routinely employed as an oxygen transfer agent in metal-oxo mediated epoxidations,[21]

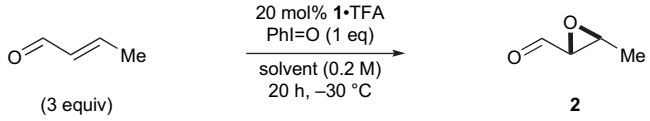
Table 1. Initial survey of oxygen sources for epoxidation



Entry	Oxidant	% Conversion[a]	% ee[b]
1	Pyridine *N*-oxide	NR	—
2	OXONE®	NR	—
3	*m*-CPBA	34	73
4	*t*-BuOOH[c]	35	69
5	H_2O_2[d]	9	59
6	NaOCl[e]	9	0
7	PhI=O	43	72

[a] Conversion determined by GC relative to methyl benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] Used as 5 M solution in decane.
[d] Used as a 50% solution in water.
[e] Used as a 5.25% solution in water.

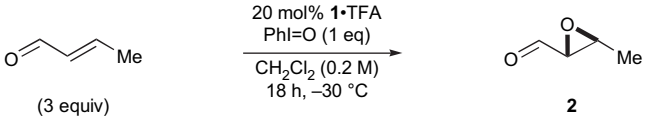
Table 2. Effect of solvent on the epoxidation reaction



Entry	Solvent	ε[a]	% Conversion[b]	% ee[c]
1	DMF (10% H_2O)	—	87	25
2	MeCN	36.6	55	33
3	Acetone	21.0	41	42
4	CH_2Cl_2	8.9	50	80
5	THF	7.5	14	76
6	THF (10% H_2O)	—	12	75
7	$CHCl_3$	4.8	45	82
8	Ether	4.3	29	63
9	Toluene	2.4	63	64

[a] See Ref. 38.
[b] Conversion determined by GC relative to tridecane.
[c] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

Table 3. Effect of acid co-catalyst on the epoxidation reaction



Entry	HX	pK_a	% Conversion[a]	% ee[b]
1	TfOH	−14	74	87
2	$HClO_4$	−10	68	88
3	*p*-TSA[c]	−2.6	50	76
4	TFA	−0.3	42	72
5	DCA[d]	1.3	27	72
6	CNA[e]	2.5	27	69

[a] Conversion determined by GC relative to benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] *p*-Toluenesulfonic acid.
[d] Dichloroacetic acid.
[e] Cyanoacetic acid.

its oxidative properties generally derive from the electrophilic character of the hypervalent iodine. However, there are a few reported cases in which iodosobenzene has been found to possess sufficient ylide character to participate in nucleophilic addition via the oxygen center.[22] Given the remarkable lability of the phenyliodonio moiety (~10^6 times better leaving group than triflate),[21] we postulated that the use of hypervalent λ^3-iodanes might enable a rapid ring closure from the electrophilic character of the hypervalent iodine and thereby minimize the intervention of a reversible oxo-conjugate addition (an equilibrium process that would diminish kinetic enantiocontrol). Moreover, we presumed that the oxidation byproduct, iodobenzene, would have no deleterious impact on the organocatalytic cycle (Fig. 3).

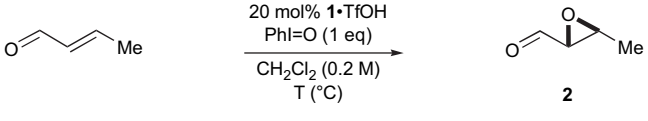
Indeed, exposure of crotonaldehyde to iodosobenzene in the presence of catalyst **1**·TFA provided epoxide **2** with encouraging levels of enantiocontrol (Table 1, entry 7, 72% ee). A survey of reaction media (Table 2) revealed that high dielectric solvents typically enabled superior efficiencies while lower dielectric systems provided higher asymmetric induction. Balancing this apparent dichotomy, CH_2Cl_2 and $CHCl_3$ demonstrated useful efficiencies while maintaining optimal enantioselectivity (Table 2, entries 4 and 7, 80–82% ee). On this basis, we selected halogenated media for further exploratory studies.

The impact of the Brønsted acid co-catalyst component on this organocatalytic epoxidation was next examined. As revealed in Table 3, an apparent correlation was observed between reaction conversion/enantiocontrol and the pK_a of the acid co-catalyst. More specifically, stronger acids, such as TfOH and $HClO_4$, provided the epoxide adduct with useful selectivities and yields (entries 1 and 2, pK_a −10 to −14, 87–88% ee), while acids with higher pK_a rendered poor conversions (entries 5 and 6, pK_a 1.3–2.5, 27% conversion). This trend can be rationalized on the basis that the stronger acid co-catalyst enables a higher equilibrium content of the catalyst–substrate iminium adduct thereby increasing the rate of addition–cyclization sequence.[23] Moreover, the observed enantioselectivity is likely to track reaction efficiency given the traditional requirements for the catalyst-controlled pathway to kinetically out-compete the non-catalyzed (racemic) process.

The influence of temperature on this epoxidation protocol was next investigated (Table 4). As expected on the basis of Boltzman distributions, a significant improvement in enantioselectivity was realized by lowering the reaction temperature. More surprising, however, was the accompanying increase in reaction efficiency with the same temperature trend. Subsequent studies (vide infra) have revealed that lower temperatures are essential to avoid detrimental reaction pathways such as catalyst oxidation and substrate decomposition.

Having established what we believed to be the optimal oxidation conditions, we next examined the scope of the olefin component in this organocatalytic oxirane formation. As revealed in Table 5, α,β-unsaturated aldehydes that incorporate alkyl group substituents are susceptible to iodosobenzene epoxidation with good efficiency and enantioselectivities (entries 1–3, 80–93% ee). To our disappointment, however, substrates that form more stabilized iminium species with catalyst **1** (such as cinnamaldehyde, entry 4) demonstrated diminished conversion and lower levels of asymmetric induction. At this juncture we hypothesized that a catalytic cycle wherein the 1,4-oxygen addition step is rate determining would be consistent with these findings. Moreover, we rationalized that implementation of a more nucleophilic iodosobenzene source should therefore provide an increase

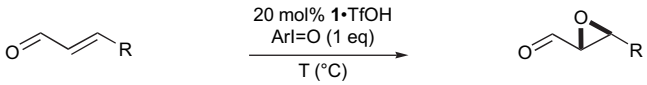
Table 4. Effect of temperature on reaction efficiency and selectivities



Entry	T (°C)	Time (h)	% Conversion[a]	% ee[b]
1	−20	18	49	83
2	−30	20	74	87
3	−40	15	98	89
4	−50	15	100	93

[a] Conversion determined by GC relative to benzyl ether.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).

Table 5. Organocatalytic epoxidations with iodosobenzene: initial studies



Entry	R	ArI=O	T (°C)	Time (h)	% Yield	% ee[a]
1	Me[b]	PhI=O	−50	10	100[d]	93
2	*n*-Pr[b]	PhI=O	−50	15	93[e]	88
3	*i*-Pr[c]	PhI=O	−40	15	86[e]	80
4	Ph[c]	PhI=O	−40	15	78[f]	73
5	CO_2Me	PhI=O	−50	15	45	85
6	*n*-Pr[b]	*p*-MePhI=O	−40	15	21	85

[a] Enantiomeric excesses were determined by chiral GC analysis (Chiraldex Γ-TA).
[b] Three equivalents of starting aldehyde in CH_2Cl_2 (0.075 M).
[c] One equivalent of aldehyde in $CHCl_3$ (0.25 M).
[d] Yield based on NMR analysis using benzyl ether as a standard.
[e] Yield based on isolation of corresponding epoxy alcohol.
[f] Stereochemical determination via correlation to literature, see Section 3.

in both reaction rate and enantioselectivity. To this end, *p*-Me iodosobenzene[24] was prepared and employed in an analogous epoxidation protocol (Table 5). Surprisingly, this more nucleophilic oxidant provided lower levels of reaction efficiency (Table 5, entry 5, 21% yield) in comparison to the less nucleophilic iodosobenzene (Table 5, entry 2, 93% yield). A subsequent ^{1}H NMR investigation has revealed that *p*-Me iodosobenzene rapidly participates in imidazolidinone oxidation, a catalyst depletion pathway that has a dramatic impact on overall catalyst efficiency and conversion (Fig. 4, Ar=*p*-MePh).[25] Intriguingly, ^{1}H NMR studies have also revealed that a slower variant of the same catalyst decomposition pathway is observed using iodosobenzene as the reaction oxidant (Fig. 4, Ar=Ph). At this stage, we presumed that the diminished enantioselectivities observed in the cinnamaldehyde epoxidation case (Table 5, entry 4) could be attributed to the intervention of a catalyst oxidation pathway that is competitive with the iminium-catalyzed addition–cyclization step. With respect to the relative capacities of iodosobenzene and *p*-Me iodosobenzene to function as catalyst oxidants, we have determined that the tolyl-derived system is more soluble in halogenated solvents than its polymeric phenyl iodide counterpart. As a result, the relative concentration of *p*-Me iodosobenzene in solution was found to be much higher, a scenario that dramatically increases the rate of catalyst oxidation and leads to greatly diminished conversions with this iodane. On this basis, we began to focus upon identifying alternative sources of hypervalent iodane, which could be employed to slowly generate reactive iodosobenzene monomer in situ, and in doing so function as a type of 'internal syringe pump'. In this manner, we hoped the imidazolidinone would partition exclusively towards iminium formation with the aldehyde substrate, thereby avoiding catalyst oxidation and depletion.

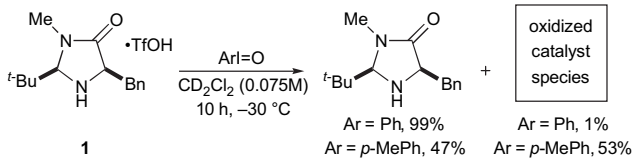


Figure 4. Mode of catalyst degradation when utilizing PhI=O and *p*-MePhI=O as the reagent in the epoxidation reaction.

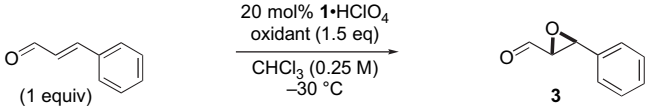
2.2. Secondary investigation: alternative iodosobenzene sources and the internal syringe pump effect

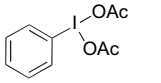
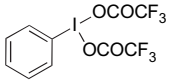
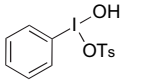
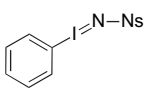
We next examined a range of hypervalent λ^3-iodane sources that we expected would slowly release iodosobenzene monomer when subjected to water or mild acid (Table 6). These studies were specifically performed with cinnamaldehyde with the anticipation that we might see an improvement in enantioselectivity with this substrate in comparison to analogous experiment with PhI=O (Table 5, entry 4, 73% ee). As revealed in Table 6, the use of commercially available diacetoxy iodosobenzene in the presence of water did indeed provide the desired epoxide with enhanced levels of enantiocontrol (entry 1, 84% ee); however, bis(trifluoroacetoxy) iodosobenzene and Koser's salt provided the oxirane **3** with poor efficiency (entries 2 and 3, 7–10% yield). Given that hypervalent I–N systems have been established to be less stable than the corresponding I–O class, we next examined the use of iminoiodanes as potential iodosobenzene surrogates in the presence of water or acid. To our great delight, exposure of cinnamaldehyde to [(nosylimino)iodo]benzene (NsNIPh) in the presence of catalyst **1** and 1 M acetic acid did indeed furnish epoxide **3** with excellent levels of conversion and enantiocontrol (entry 4, 100% conversion, 92% ee). It is noteworthy that arylsulfonylimino(aryl)iodanes are stable, easily storable compounds[21] that we have determined will function as controlled release iodosobenzene oxidants in the presence of acid or water (vide infra).

2.3. Epoxidation substrate scope

Having established the optimal oxidation conditions for epoxide formation, we next examined the scope of the α,β-unsaturated aldehyde component in this organocatalytic transformation. As revealed in Table 7, a variety of enal olefins can be successfully utilized with both high stereoselectivity and efficiency in the presence of NsNIPh. For example,

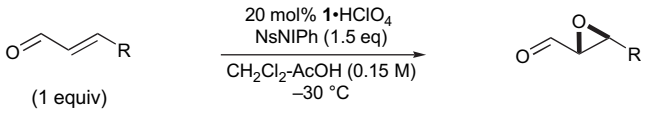
Table 6. Alternative iodosobenzene sources

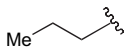
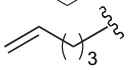
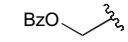
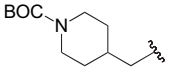
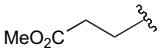
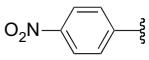
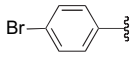


Entry	Oxidant	Additive	% Conversion[a]	% ee[b]
1		Water	68	84
2		Water	10	71
3[c]		Water	7	76
4		Water	71	80
		1 M AcOH	100	92

[a] Conversion determined by ^{1}H NMR analysis using MeOBn as a standard.
[b] Enantiomeric excess determined by chiral GC analysis (Chiraldex Γ-TA).
[c] Koser's salt = [(hydroxy)(tosyloxy)iodo]benzene.

Table 7. Enantioselective organocatalytic epoxidation: scope[a]



Entry	R	Time (h)	% Yield	% ee[b]
1	Me	10	88[c]	93
2		15	72	88
3		13	77	92
4		16	95[d]	92
5		15	89[e]	85
6		11	86	87
7		12	86	90
8		12	92[d]	92
9		6	89[d]	97
10		8	93[d]	93

[a] Products are single diastereomers, except in entry 1 (dr=1:7).
[b] Enantiomeric excess determined by chiral GC and SFC analysis.
[c] Yield determined by NMR analysis.
[d] $CHCl_3$ was used as solvent.
[e] Iodosobenzene was used as the oxidant at −40 °C.

the use of the previously problematic cinnamaldehyde system now provides the corresponding epoxide in 92% yield and 92% ee (entry 8). Moreover, electronic variation of the aryl ring substituents of this cinnamate system is well tolerated (entries 9 and 10, 89–92% yield, 92–97% ee). A variety of olefin components that incorporate alkyl substituents of varying steric demand can also be implemented (entries 1–3, 72–88% yield, 88–93% ee). It is important to note that functionalities that are often susceptible to oxidation (e.g., electron-deficient amines, electron-rich olefins) are compatible with NsNIPh, demonstrating its utility as a mild ambiphilic oxygen source (entries 4 and 6, 86–95% yield, 87–92% ee). It should also be noted that enals that incorporate electron-withdrawing groups (e.g., R=CO_2Me) do not provide the desired epoxide under these conditions. This issue was resolved by utilizing iodosobenzene as the oxidant as demonstrated in Table 5, entry 5.

2.4. Mechanistic studies

In an attempt to gain further insight into the inherent advantages of using NsNIPh in comparison to iodosobenzene in this organocatalytic epoxidation, various NMR studies were undertaken to examine (a) the controlled release of monomeric iodosobenzene from NsNIPh and (b) the subsequent effect of the monomeric iodosobenzene concentration on the rate of imidazolidinone catalyst oxidation.

2.4.1. ^{1}H NMR studies on the controlled release of monomeric iodosobenzene from NsNIPh. A low temperature ^{1}H NMR study (−30 °C) was performed to investigate the conversion of NsNIPh to monomeric iodosobenzene in the presence of deuterated chloroform and 1 M acetic acid (AcOD). As revealed in Figure 5, the sulfonamide (NsNIPh) does indeed undergo slow hydrolysis to provide a steady increase in the concentration of monomeric iodosobenzene over the course of 6 h. It is important to note that diacetoxy iodosobenzene (5%) and hemi-hydrolyzed nosyliodosobenzene (1%) were also present in the reaction solution.[26] In contrast, when the analogous ^{1}H NMR experiment was performed with oligomeric iodosobenzene, we observed the immediate formation of a relatively high concentration of iodosobenzene monomer (38%) that remained constant over the course of this 6-h study. Again, diacetoxy iodosobenzene (2%) was detected in this experiment. These NMR studies clearly demonstrate that the proposed slow release of monomeric iodosobenzene from NsNIPh ('internal syringe pump' effect) is not only feasible, but likely operational.

2.4.2. ^{15}N NMR studies on catalyst depletion as a function of oxidant concentration. To investigate the role of monomeric iodosobenzene concentration on catalyst depletion (via a variety of presumed amine oxidation pathways), we next turned to ^{15}N NMR studies. In this context, we first investigated the use of ^{15}N isotopically labeled imidazolidinone **4** as a catalyst for the epoxidation of cinnamaldehyde using (a) oligomeric iodosobenzene and (b) NsNIPh as the respective reaction oxidants. It should be noted that in both cases, reaction efficiencies and enantioselectivities were observed that were within experimental error of the corresponding results observed with catalyst having natural abundance nitrogen. With respect to catalyst depletion, we observed striking differences in both the rate and nature of imidazolidinone decomposition as a function of these two oxidants and presumably, therefore, the corresponding iodosobenzene monomer concentration. As illustrated in

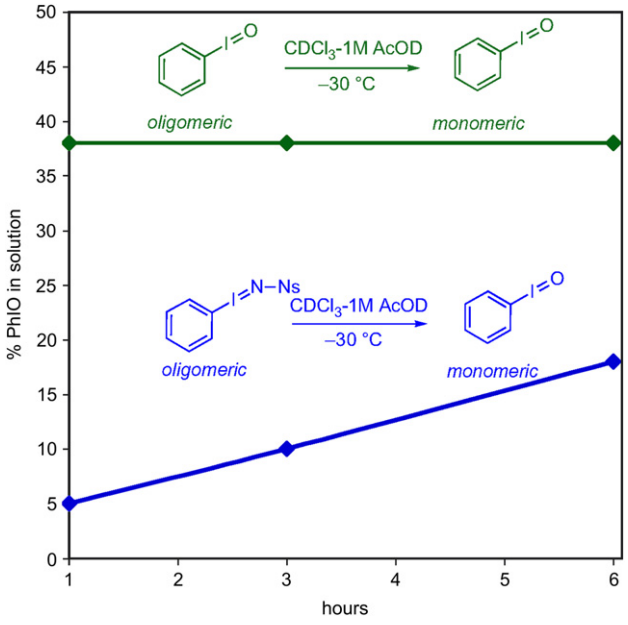


Figure 5. The solution content of monomeric iodosobenzene (PhIO) versus time as a function of iodane source.

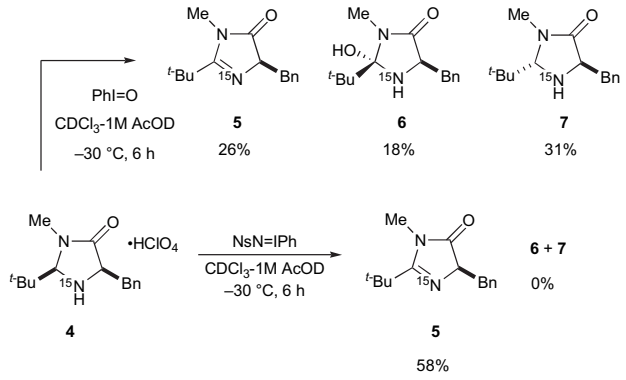


Figure 6. Mode of catalyst degradation when utilizing iodosobenzene or NsNIPh in the epoxidation of cinnamaldehyde as observed by ^{15}N NMR.

Figure 6, the use of oligomeric iodosobenzene leads to the formation of three catalyst-derived amines over the course of the reaction, namely imine **5**, aminol **6**, and the corresponding trans catalyst isomer **7**. In contrast, the analogous reaction that employs NsNIPh leads only to the formation of the corresponding imine **5** (Fig. 7). It should be noted that isolation and separate resubjection of catalyst derivatives **5**, **6**, and **7** to the outlined epoxidation conditions have confirmed that each of these amine species is catalytically inactive. More important, however, is that the rate of catalyst consumption appears to be a function of the source of monomeric iodosobenzene. As revealed in Figure 7, real time ^{15}N NMR studies performed on a low temperature epoxidation reaction with oligomeric iodosobenzene clearly demonstrates that the formation of imine **5** occurs within the first 20 min of the reaction protocol (Fig. 7a). Moreover, after 6 h there is almost complete conversion of the catalyst to amine derivatives **5**, **6**, and **7** (Fig. 7b). In contrast, the use of the slow release oxidant NsNIPh results in almost no formation of catalyst oxidation products after 20 min (Fig. 7c), and only imine adduct **5** is formed in observable quantities after 6 h (Fig. 7d). Notably, significant quantities of the active catalyst **4** remain after 6 h when NsNIPh is employed, highlighting that the 'internal syringe pump' concept is critical to achieving useful levels of catalyst efficiency within this epoxidation protocol.

In summary, we have further established iminium catalysis as a valuable strategy for asymmetric synthesis in the context of an enantioselective enal epoxidation protocol. This new organocatalytic reaction allows for the enantioselective formation of oxiranes from a wide array of electronically and sterically diverse α,β-unsaturated aldehydes. Fundamental to these studies has been the recognition that hypervalent iodine reagents are suitable oxidants for organocatalytic Weitz–Scheffer epoxidations using imidazolidinone catalyst **1**. Optimal levels of reaction efficiency and enantiocontrol have been accomplished using an 'internal syringe pump' protocol wherein the controlled release of monomeric iodosobenzene from an in situ iminoiodinane source is accomplished using a mild acid. NMR studies (^{15}N) have revealed that this slow, in situ production of monomeric iodosobenzene from NsNIPh is central to alleviating losses in catalytic efficiency arising from a variety of imidazolidinone oxidation pathways.

3. Experimental

3.1. General

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[27] Iodosobenzene reagents were synthesized and iodometrically titrated for purity prior to use.[28] All non-aqueous solvents were purified according to the method of Grubbs[29] and were transferred

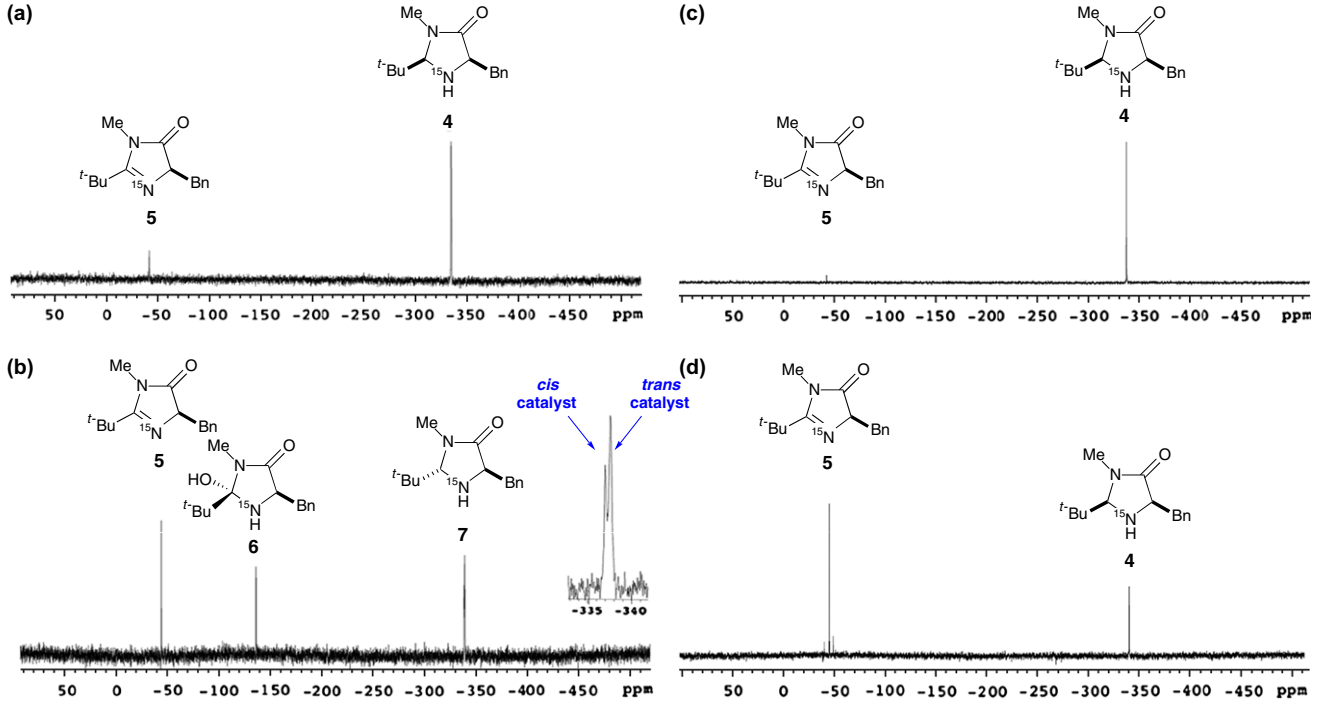


Figure 7. Catalyst degradation products during epoxidations mediated by iodosobenzene (a, c) and NsNIPh (b, d), as observed by ^{15}N NMR.

under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath for volatile compounds. Chromatographic purification of products was accomplished using force-flow chromatography on ICN 60 32–64 mesh silica gel 63 according to the method of Still[30] and where noted, Iatrobeads 6RS-8060 was used in place of silica gel. Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching, anisaldehyde, $KMnO_4$ or ninhydrin stain. ^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz or 75 MHz) or an Inova 500 (500 MHz and 125 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (hertz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. ^{15}N NMR spectra were externally referenced to 7 M nitromethane in deuterated chloroform and are reported in terms of chemical shift. IR spectra were recorded on a Perkin–Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett–Packard 6850 and 6890 Series gas chromatographs equipped with split-mode capillary injection system and flame ionization detectors using Bodman Chiraldex Γ-TA and Varian Chirasil-Dex-CB (30 m×0.25 mm) columns. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a variable-wavelength UV detector using a Chiralpak AD-H column (25 cm) and AD guard (5 cm).

3.2. General epoxidation procedures

3.2.1. General epoxidation procedure A (using PhIO). A solution of the trifluoromethanesulfonic acid salt of (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 equiv) in dichloromethane (0.075 M) was prepared in a scintillation vial equipped with a magnetic stir bar at −50 or −40 °C (as noted) and stirred for 10 min. The aldehyde (3.0 equiv) and iodosobenzene (1.0 equiv) were then added to form a light yellow suspension and the reaction mixture was stirred at constant temperature for 10–15 h until no further conversion was observed as determined by TLC analysis. The cold solution was then filtered through Celite, washed with ether, and concentrated in vacuo. The resulting residue was purified by column chromatography (solvents noted) to provide the title compounds.

3.2.2. General epoxidation procedure B (using NsNIPh). A scintillation vial equipped with a magnetic stir bar was charged with perchloric acid (70 wt %, 0.2 equiv), dichloromethane, and 20 vol % of 1 M AcOH (0.15 M), and (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (0.2 equiv) and allowed to stir for 10 min at −30 °C. The aldehyde (1.0 equiv) and [(nosylimino)iodo]benzene (1.5 equiv) were then added to form a light yellow suspension in an icy solution, which was stirred at constant temperature for 6–16 h until complete consumption of the starting material was observed. The resulting solution was then treated with pH 7 buffer, filtered through Celite, and extracted with Et_2O (2×4 mL). The organic layer was then dried over Na_2SO_4 and concentrated in vacuo and the resulting residue was purified by column chromatography (solvents noted) to provide the title compounds.

3.3. Synthesis and characterization

3.3.1. ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (4). To a three-necked 100 mL round-bottom flask equipped with a reflux condenser and magnetic stirrer were added L-phenylalanine (98% ^{15}N-labeled, 3.0 g, 18.05 mmol) and methanol (36 mL) under an Ar atmosphere. Thionyl chloride (3.3 mL, 45.1 mmol) was then added dropwise at which time the reaction mixture became homogenous with exotherm and evolution of gas. The resulting solution was then refluxed for 12 h and then cooled to room temperature and partitioned with aqueous $NaHCO_3$ (30 mL) and EtOAc (2×30 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified on a short plug of silica gel and washed with EtOAc (20 mL) to yield ^{15}N-labeled (*R*)-methyl 2-amino-3-phenylpropanoate as a clear oil (3.22 g, quantitative yield).

To the resulting methyl ester (3.22 g, 18.05 mmol) was added methylamine (8 M in EtOH, 10 mL) and the resulting solution was stirred at room temperature for 12 h under an Ar atmosphere. The reaction was then diluted with 0.5 M aqueous HCl (20 mL) and partitioned by EtOAc (2× 20 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give ^{15}N-labeled (*R*)-2-amino-*N*-methyl-3-phenylpropanamide as a clear oil (3.22 g, quantitative yield).

To a dry, three-necked 100 mL round-bottom flask equipped with a reflux condenser, Dean–Stark trap, and magnetic stir bar was added $FeCl_3$ (586 mg, 3.61 mmol) under an N_2 atmosphere. A solution of the amide (3.22 g, 18.05 mmol) and pivaldehyde (2.10 mL, 18.05 mmol) in toluene (36 mL) was added by cannula addition to the flask containing $FeCl_3$. The reaction was refluxed for 12 h under an Ar atmosphere and cooled to room temperature before diluting with brine (50 mL) and partitioning with EtOAc (2×30 mL). The separated organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give a brown oil. ^1H NMR shows a cis:trans ratio of 1.2:1.0. The desired *cis*-isomer was purified from the *trans*-isomer by flash chromatography (silica gel, 50% EtOAc in hexanes) to yield the title compound as a yellow crystalline solid (2.13 g, 48% yield). IR (film) 3338, 2958, 1700, 1395, 1101, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H, aryl *H*), 4.07 (s, 1H, *N*,*N*-acetal *H*), 3.72–3.71 (br m, 1H, α-amino *H*), 3.17 (dt, 1H, *J*=3.8, 13.5 Hz, benzyl *H*), 2.95 (ddd, 1H, *J*=2.5, 8.0, 13.5 Hz, benzyl *H*), 2.30 (s, 3H, *N*-CH_3), 1.76 (br s, 1H, N*H*), 0.85 (s, 3H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.46, 142.90, 138.06, 129.78, 128.76, 126.82, 82.65 (d, $J_{^{15}N-C}$=3.02 Hz), 59.58 (d, $J_{^{15}N-C}$=3.64 Hz), 38.43 (d, $J_{^{15}N-C}$=2.39 Hz), 35.19 (d, $J_{^{15}N-C}$=1.76 Hz), 25.51 (d, $J_{^{15}N-C}$=1.13 Hz); ^{15}N NMR (50 MHz, $CDCl_3$) δ −337.08; ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOH) for the $HClO_4$ salt of the title compound, δ −336.35; HRMS (FAB$^+$) exact mass calculated for [M]$^+$ ($C_{15}H_{22}N^{15}NO$) requires *m*/*z*

247.1703, found *m/z* 247.1726; $[\alpha]_D$ −46.4 (*c* 1.10, $CHCl_3$).

3.3.2. ^{15}N-labeled (2*S*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one (8). The title compound was prepared and isolated from the procedure for ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one as a yellow crystalline solid (1.57 g, 35% yield). IR (film) 3306, 2953, 1684, 1394, 1096, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H, aryl *H*), 3.85–3.83 (br m, 1H, α-amino *H*), 3.81 (t, 1H, *J*=1.5 Hz, *N*,*N*-acetal *H*), 3.11 (dt, 1H, *J*=3.6, 14.1 Hz, benzyl *H*), 2.89 (ddd, 1H, *J*=2.7, 6.9, 14.1 Hz, benzyl *H*), 2.89 (s, 3H, *N*-CH_3), 1.86 (br s, 1H, N*H*), 0.90 (s, 3H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.53, 137.68, 129.70, 128.74, 126.89, 83.62 (d, $J_{^{15}N-C}$=3.02 Hz), 59.71 (d, $J_{^{15}N-C}$=4.08 Hz), 38.77, 37.93, 31.54, 25.57; ^{15}N NMR (50 MHz, $CDCl_3$) δ −337.68; HRMS (FAB$^+$) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N^{15}NO$) requires *m/z* 248.1781, found *m/z* 247.1790; $[\alpha]_D$ −60.0 (*c* 1.13, $CHCl_3$).

3.3.3. (*R*)-2-*tert*-Butyl-4-benzyl-1-methyl-1*H*-imidazol-5(4*H*)-one (6). A scintillation vial equipped with a stir bar was charged with dichloromethane (5 mL), iodobenzene diacetate (403 mg, 1.25 mmol), and activated 3 Å molecular sieves (500 mg). After stirring for 10 min, (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one (61.6 mg, 0.25 mmol) was added to the vial and the reaction was stirred for 3 h at room temperature. The reaction was filtered through Celite, concentrated in vacuo, and purified by flash chromatography (Iatrobeads, 50% Et_2O in pentanes) to yield the title compound as a clear oil (51.9 mg, 85% yield). It should be noted that the crude reaction (as observed by NMR) initially produces the acetate addition product of the imine, which upon work-up and purification causes elimination of the acetate to yield the imine product. IR (film) 2961, 1706, 1636, 1495, 1425, 1395, 1366, 1232, 701, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H, aryl *H*), 4.73 (br s, 1H, α-imino *H*), 3.96 (dd, 1H, *J*=1.5, 14.4 Hz, benzyl *H*), 3.90 (d, 1H, *J*=14.7 Hz, benzyl *H*), 3.07 (s, 1H, *N*-CH_3), 0.97 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.12, 165.44, 135.72, 130.99, 129.58, 128.72, 126.98, 91.85, 36.76, 31.26, 26.34; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{15}H_{20}N_2O$) requires *m/z* 244.1576, found *m/z* 244.1586; $[\alpha]_D$ −76.3 (*c* 1.22, $CHCl_3$).

The title compound was also synthesized using ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one using the above procedure. ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOD) δ −42.2.

3.3.4. (5*R*)-2-*tert*-Butyl-5-benzyl-2-hydroxy-3-methyl-imidazolidin-4-one HCl salt (7). A scintillation vial equipped with a stir bar was charged with dichloromethane (5 mL) and 1 M AcOH (1 mL), iodosobenzene (161 mg, 0.5 mmol), and (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methyl-imidazolidin-4-one (61.6 mg, 0.25 mmol). The reaction was stirred for 2 h at room temperature before filtration and concentration in vacuo. Purification was by flash chromatography (silica gel, 40% EtOAc in hexanes) and the isolated residue was dissolved in HCl (2 M in diethyl ether, 125 mL) and dichloromethane (12.5 mL) and cooled to −70 °C to facilitate precipitation. The precipitate was filtered and washed with cold ether and dried under reduced pressure to yield the title compound as a white solid (18 mg, 24% yield). IR (KBr) 2961, 1780, 1657, 1495, 1253, 706 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H, aryl *H*), 4.79 (dd, 1H, *J*=3.0, 5.4 Hz, α-amino *H*), 4.00 (dd, 1H, *J*=5.4, 13.8 Hz, benzyl *H*), 3.35 (dd, 1H, *J*=3.0, 13.5 Hz, benzyl *H*), 3.09 (s, 3H, *N*-CH_3), 1.29 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.98, 175.16, 132.28, 130.27, 129.19, 128.59, 128.17, 61.05, 35.91, 35.86, 29.10, 28.54, 26.62; HRMS (FAB$^+$) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2O_2$) requires *m/z* 261.1603, found *m/z* 261.1605; $[\alpha]_D$ +4.2 (*c* 1.24, $CHCl_3$).

The title compound was also synthesized using ^{15}N-labeled (2*R*,5*R*)-2-*tert*-butyl-5-benzyl-3-methylimidazolidin-4-one using the above procedure. ^{15}N NMR (50 MHz, $CDCl_3$–1 M AcOD) δ −134.06.

3.3.5. (2*R*,3*S*)-3-Methyloxirane-2-carbaldehyde (2). Prepared according to general epoxidation procedure A using crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 at −50 °C with benzyl ether as an internal standard to establish NMR yield. After filtration through silica gel, the title compound was obtained in a 100% NMR yield and 93% ee.

Also prepared according to general epoxidation procedure B with crotonaldehyde (296 μL, 3.57 mmol) in CD_2Cl_2 and mesitylene as an internal standard to establish NMR yield. After filtration through silica gel, the title compound was obtained in an 88% NMR yield and 93% ee. Material for characterization was obtained by flash chromatography (Iatrobeads, 20% Et_2O in pentanes). IR (film) 3416, 2965, 2929, 1443, 1380, 1124, 871 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, 1H, *J*=6.0 Hz, C*H*O), 3.30 (qd, 1H, *J*=2.1, 5.1 Hz, C*H* oxirane), 3.08 (dd, 1H, *J*=2.1, 6.3 Hz, C*H* oxirane), 1.42 (d, 3H, *J*=5.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.59, 60.23, 53.06, 17.06; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_4H_6O_2$) requires *m/z* 86.03678, found *m/z* 86.03649; $[\alpha]_D$ +47.9 (*c* 2.7, $CHCl_3$). The enantiomeric purity was determined on the alcohol product, which was prepared by an $NaBH_4$ reduction, and analyzed by GLC analysis using a Bodman Γ-TA column (40 °C isotherm, 12 psi); (2*R*,3*S*) isomer t_R=57.1 min, (2*R*,3*S*) isomer t_R=58.7 min.

3.3.6. (2*R*,3*S*)-3-Propyloxirane-2-carbaldehyde (Table 5, entry 2 and Table 7, entry 2). Prepared according to general epoxidation procedure A using (*E*)-hex-2-enal (591 μL, 5.09 mmol) at −50 °C. After stirring for 15 h, this reaction was filtered through silica, washed with dichloromethane (30 mL), and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3×30 mL) and concentrated in vacuo at 0 °C, before purifying by flash chromatography (silica gel, 50% Et_2O in pentanes) to afford the title compound as a clear, colorless oil in 93% yield (182 mg, 1.57 mmol), 88% ee.

Also prepared according to general epoxidation procedure B using (*E*)-hex-2-enal (234 mL, 2.0 mmol) to afford the title

compound as a clear, colorless oil (162 mg, 72% yield, 88% ee) after silica gel chromatography (silica gel, 30–70% Et_2O in pentanes, linear gradient). IR (film) 2962, 2935, 2875, 1731, 1671, 1534, 1458, 1378, 1350, 1125, 1092, 1044, 915.1, 737.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, 1H, J=6.3 Hz, C*H*O), 3.23 (td, 1H, J=2.1, 5.1, 7.8 Hz, C*H* oxirane), 3.13 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 1.69–1.50 (m, 4H, CH_2CH_2), 0.98 (t, 3H, J=7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 59.34, 56.83, 33.39, 19.39, 13.98; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_6H_9O_2$) requires m/z 113.0603, found m/z 113.0602; $[\alpha]_D$ +11.4 (c 2.38, $CHCl_3$). The enantiomeric purity was determined by GLC using a Bodman Γ-TA column (70 °C isotherm, 15 psi, flow=1.3 mL/min); (2*R*,3*S*) isomer t_R=8.87 min, (2*S*,3*R*) isomer t_R=9.79 min.

These data correlated with literature ^1H and ^{13}C NMR spectroscopic values for (2*S*, 3*R*)-3-propyloxirane-2-carbaldehyde.[31]

3.3.7. ((2*R*,3*S*)-3-Isopropyloxiran-2-yl)methanol (Table 5, entry 3). Prepared according to general epoxidation procedure A using (*E*)-4-methylpent-2-enal (592 μL, 5.09 mmol) and iodosobenzene (1.52 g, 6.92 mmol) in dichloromethane (18.3 mL) at −40 °C. After stirring for 15 h, this reaction was filtered through silica gel, washed with dichloromethane (50 mL), and cooled to 0 °C. Reduction to the alcohol was performed on the crude reaction solution by adding ethanol (1 mL) and $NaBH_4$ (770 mg, 20.4 mmol). The reaction was quenched with a saturated solution of Rochelle's salt (30 mL) on completion as judged by TLC. The alcohol product was extracted with dichloromethane (3×30 mL) and concentrated in vacuo at 0 °C, before purifying by flash chromatography (silica gel, 30–50% Et_2O in pentanes, linear gradient) to afford the title compound as a clear, colorless oil in 86% yield (505 mg, 4.35 mmol), 80% ee. IR (film) 2963, 2930, 1459, 1067, 895.1, 669.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (ddd, 1H, J=2.4, 5.7, 12.3 Hz, C*H*OH), 3.70 (ddd, 1H, J=4.20, 7.20, 12.3 Hz, C*H*OH), 3.02 (dt, 1H, J=3.00, 3.90 Hz, C*H* oxirane), 2.81 (dd, 1H, J=2.40, 6.90 Hz, C*H* oxirane), 1.70–1.59 (m, 1H, C*H*Me_2), 1.08 (d, 3H, J=6.60 Hz, CH_3), 1.02 (d, 3H, J=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.86, 61.14, 57.36, 30.07, 19.02, 18.37; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_6H_{11}O_2$) requires m/z 115.0759, found m/z 115.0702; $[\alpha]_D$ −14.0 (c 0.74, $CHCl_3$). The enantiomeric purity was determined by GLC analysis of the crude aldehyde product (60 °C isotherm, 12 psi); (2*R*,3*S*) isomer t_R=12.8, (2*S*, 3*R*) isomer t_R=16.2 min.

3.3.8. (2*R*,3*R*)-Methyl 3-formyloxirane-2-carboxylate (Table 5, entry 5). Prepared according to general epoxidation procedure A using 1 equiv of (*E*)-methyl 3-formylacrylate (250 mg, 2.19 mol) in dichloromethane (0.25 M) at −50 °C. The title compound was isolated as a clear, colorless oil (128 mg, 45% yield, 85% ee) after flash chromatography (silica gel, 30% ether in pentanes). IR (film) 3447, 1744, 1441, 1212 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, 1H, J=6.3 Hz, C*H*O), 3.62 (dd, 1H, J=1.5, 6.3 Hz, oxirane C*H*), 3.76 (d, 1H, J=1.8 Hz, oxirane C*H*), 3.83 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.03, 57.68, 53.37, 50.92; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_4H_5O_3$) requires m/z 101.0239, found m/z 101.0240; $[\alpha]_D$ +4.1 (c 0.75, $CHCl_3$). The enantiomeric purity was determined by SFC using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 80 °C oven, flow=4.0 mL/min); (2*S*,3*S*) isomer t_R=23.9 min, (2*R*,3*R*) isomer t_R=27.0 min.

3.3.9. (2*R*,3*S*)-3-Cyclohexyloxirane-2-carbaldehyde (Table 7, entry 3). Prepared according to general epoxidation procedure B using 3-cyclohexylacrylaldehyde[32] (147 mg, 1.06 mmol) to afford the title compound as a clear, colorless oil (124 mg, 77% yield, 92% ee) after flash chromatography (silica gel, 20% Et_2O in pentanes with 1% Et_3N). IR (film) 2928, 2853, 1730, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, 1H, J=6.0 Hz, C*H*O), 3.17 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 3.02 (dd, 1H, J=2.1, 6.6 Hz, C*H* oxirane), 1.85–1.66 (m, 5H), 1.41–1.30 (m, 1H), 1.26–1.05 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_9H_{13}O_2$) requires m/z 153.0916, found m/z 153.0910; $[\alpha]_D$ +75.6 (c 1.02, $CHCl_3$). The enantiomeric purity was determined by GLC using a Varian Chirasil-Dex-CB column (80 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=42.07 min, (2*R*,3*S*) isomer t_R=46.87 min.

This data correlated with literature ^1H and ^{13}C NMR spectroscopic values.[31]

3.3.10. (2*R*,3*S*)-3-(Pent-4-enyl)oxirane-2-carbaldehyde (Table 7, entry 4). Prepared according to general epoxidation procedure B using 3-(*E*)-octa-2,7-dienal[33] (270 mg, 2.18 mol) to afford the title compound as a clear, colorless oil (292 mg, 95% yield, 92% ee) after flash chromatography (silica gel, 20% Et_2O in pentanes). IR (film) 1729, 1440, 1148, 993.1, 914.4, 849.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, 1H, J=6.3 Hz, C*H*O), 5.82–5.69 (m, 1H, C*H*=CH_2), 5.04–4.94 (m, 2H, CH=CH_2), 3.11 (dd, 1H, J=1.8, 6.3 Hz, C*H* oxirane), 3.23–3.19 (m, 1H, C*H* oxirane), 2.10 (q, 2H, J=6.9 Hz, CH_2), 1.71–1.52 (m, 4H, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 61.05, 58.28, 39.51, 29.72, 28.91, 26.24, 25.68, 25.60; HRMS (EI^+) exact mass calculated for $[M-H]^+$ ($C_8H_{11}O_2$) requires m/z 139.0760, found m/z 139.0759; $[\alpha]_D$ +48.8 (c 1.10, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (80 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=21.75 min, (2*R*,3*S*) isomer t_R=22.27 min.

3.3.11. ((2*R*,3*S*)-3-Formyloxiran-2-yl)methyl benzoate (Table 7, entry 5). Prepared according to general epoxidation procedure A using (*E*)-3-formylallyl benzoate[34] (104 mg, 0.55 mol) to afford the title compound as a clear, colorless oil (101 mg, 89% yield, 85% ee) after flash chromatography (silica gel, 20% EtOAc in hexanes). IR (film) 3447, 1723, 1273, 1111, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, 1H, J=6.3 Hz, C*H*O), 8.08–8.04 (m, 2H, aryl *H*), 7.63–7.57 (m, 1H, aryl *H*), 7.49–7.44 (m, 2H, aryl *H*), 4.75 (dd, 1H, J=3.0, 12.6 Hz, CH_2), 4.34 (dd, 1H, J=5.4, 12.6 Hz, CH_2), 3.68 (m, 1H, C*H* oxirane), 3.44 (dd, 1H, J=2.1, 6.3 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.01, 166.15, 133.72, 129.97, 129.35, 128.73, 63.13, 56.73, 54.0; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_{11}H_{10}O_4$) requires m/z 206.0579, found m/z

206.0581; $[\alpha]_D$ +16.0 (*c* 1.12, $CHCl_3$). The enantiomeric purity was determined by SFC using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 35 °C oven, flow=4.0 mL/min); (2*S*,3*R*) isomer t_R=4.19 min, (2*R*,3*S*) isomer t_R=4.96 min.

3.3.12. *tert*-Butyl 4-(((2*R*,3*S*)-3-formyloxiran-2-yl)-methyl)piperidine-1-carboxylate (Table 7, entry 6). A solution of *tert*-butyl 4-((*E*)-3-(methoxycarbonyl)allyl)piperidine-1-carboxylate[35] (1.8 g, 6.68 mmol) in ether (60 mL) in a 100 mL round-bottom flask was equipped with a magnetic stir bar and was cooled to −78 °C. DIBAL (1 M in hexanes, 13.4 mL) was added dropwise to the flask and the reaction was stirred at constant temperature for 15 min before warming to 0 °C. After 3 h, the reaction was quenched by the addition of a saturated solution of Rochelle's salt (30 mL) and was stirred at room temperature until the biphasic solution no longer effervesces and both layers became clear. The organic layer was extracted, dried, and concentrated in vacuo. The resulting oil was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to yield *tert*-butyl 4-((*E*)-3-hydroxybut-2-enyl)piperidine-1-carboxylate as a clear oil (1.1 g, 61% yield). IR (film) 3436, 2915, 1669, 1429, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.62 (m, 2H, C*H*=C*H*), 4.08 (t, 2H, α-hydroxy CH_2), 4.03 (br s, 1H, O*H*), 3.20 (br t, 2H, *J*=12.0 Hz, piperidine CH_2), 1.98 (t, 2H, *J*=6.0 Hz, CH=CH–CH_2), 1.65 (br s, 1H, piperidine CH_2), 1.60 (br s, 1H, piperidine CH_2), 1.40 (s, 9H, C(CH_3)$_3$), 1.27 (m, 1H, piperidine CH_2), 1.07 (ddd, 2H, *J*=4.2, 12.0, 24.6 Hz, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.10, 130.99, 130.69, 79.45, 63.80, 39.42, 36.31, 32.09, 43.92, 39.42, 36.31, 32.09, 31.14, 28.67; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{25}NO_3$) requires *m*/*z* 255.1834, found *m*/*z* 255.1837.

In a scintillation vial equipped with a magnetic stir bar was a solution of *tert*-butyl 4-((*E*)-3-hydroxybut-2-enyl)piperidine-1-carboxylate (198 mg, 0.78 mmol), *N*-methylmorpholine *N*-oxide (96 mg, 0.82 mmol), and activated 3 Å molecular sieves (150 mg) in dichloromethane (4 mL) at room temperature. After 5 min, tetrapropylammonium perruthenate (14 mg, 0.04 mmol) was added in one portion. The reaction was complete after 30 min and was filtered through a pad of Celite and concentrated in vacuo and purified by flash chromatography (silica gel, 20% acetone in pentanes) to yield *tert*-butyl 4-((*E*)-3-formylallyl)piperidine-1-carboxylate as a light yellow oil (160 mg, 80% yield). IR (film) 2929, 1691, 1417, 1365, 1240, 1163, 976, 866, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, 1H, *J*=8.1 Hz, C*H*O), 6.78 (dt, 1H, *J*=7.2, 15.9 Hz, CH=C*H*), 6.01 (ddd, 1H, *J*=1.2, 2.7, 9.0 Hz, CHO–C*H*=CH), 3.20 (br d, 2H, *J*=11.1 Hz, piperidine CH_2), 2.66 (br t, 2H, *J*=12.0 Hz, piperidine CH_2), 2.24 (t, 2H, *J*=7.5 Hz, piperidine CH_2), 1.67 (br s, 1H, piperidine CH_2), 1.64 (br s, 1H, piperidine CH_2), 1.39 (s, 9H, C(CH_3)$_3$), 1.07 (ddd, 2H, *J*=3.0, 13.8, 25.8 Hz, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.90, 156.20, 154.95, 134.64, 79.62, 43.92, 39.76, 35.73, 32.08, 28.62; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_3$) requires *m*/*z* 253.1678, found *m*/*z* 253.1671.

The title compound was prepared according to general epoxidation procedure B using *tert*-butyl 4-((*E*)-3-formylallyl)-piperidine-1-carboxylate (156 mg, 0.62 mmol) to afford the title compound as a clear, yellow oil (134 mg, 86% yield, 87% ee) after flash chromatography (silica gel, 25% EtOAc in hexanes). IR (film) 3436, 2915, 2361, 1678, 1413, 1164, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, 1H, *J*=18.0 Hz, C*H*O), 4.08 (br d, 2H, *J*=10.5 Hz, piperidine CH_2), 3.26–3.21 (m, 1H, C*H* oxirane), 3.09 (dd, 1H, *J*=1.8, 6.3 Hz, C*H* oxirane), 3.72–3.63 (m, 2H, piperidine CH_2), 1.72–1.61 (m, 3H, piperidine CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 1.21–1.15 (m, 2H, piperidine CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.36, 151.03, 79.63, 59.29, 55.27, 43.92, 38.31, 34.44, 32.38, 32.03, 28.64; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_{14}H_{23}NO_4$) requires *m*/*z* 269.1627, found *m*/*z* 269.1628; $[\alpha]_D$ +30.9 (*c* 0.95, $CHCl_3$). The enantiomeric purity was determined by SFC analysis using a Chiralpak AD-H column (5–50% EtOH, linear gradient, 100 bar, 35 °C oven, flow=4.0 mL/min); (2*S*, 3*R*) isomer t_R=6.97 min, (2*R*, 3*S*) isomer t_R=7.74 min.

3.3.13. Methyl 3-((2*R*,3*S*)-3-formyloxiran-2-yl)propanoate (Table 7, entry 7). Prepared according to general epoxidation procedure B using (*E*)-methyl 5-formylpent-4-enoate[36] (142 mg, 1.0 mol) to afford the title compound as a clear, colorless oil (137 mg, 86% yield, 90% ee) after flash chromatography (silica gel, 40% Et_2O in pentanes). IR (film) 1731, 1438, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, 1H, *J*=6.3 Hz, C*H*O), 3.72 (s, 3H, CO_2CH_3), 3.38–3.34 (m, 1H, C*H* oxirane), 3.20 (dd, 1H, *J*=2.0, 6.0 Hz, C*H* oxirane), 2.52 (t, 2H, *J*=6.9 Hz, CH_2CO_2Me), 2.15–1.88 (m, 2H, C$H_2CH_2CO_2$Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.06, 151.08, 59.29, 55.81, 52.16, 30.11, 26.66; HRMS (EI$^+$) exact mass calculated for $[M-H]^+$ ($C_7H_9O_4$) requires *m*/*z* 157.0501, found *m*/*z* 157.0501; $[\alpha]_D$ +27.3 (*c* 1.25, $CHCl_3$). The enantiomeric purity was determined by GLC using a Chirasil-DEX CB column (90 °C isotherm, 15 psi, flow=1.0 mL/min); (2*R*,3*S*) isomer t_R=60.62 min, (2*S*,3*R*) isomer t_R=62.23 min.

3.3.14. (2*R*, 3*S*)-3-Phenyloxirane-2-carbaldehyde (3) (Table 7, entry 8). Prepared using general epoxidation procedure A using cinnamaldehyde (159 μL, 1.26 mmol) and iodosobenzene (378 mg, 1.72 mmol) in dichloromethane (5.04 mL) at −40 °C. Flash chromatography (silica gel, 30% Et_2O in pentanes) afforded the title compound as a clear, light yellow oil in a 71% yield (133 mg, 0.90 mmol), 78% ee.

Prepared according to general epoxidation procedure B using cinnamaldehyde (94.4 μL, 0.75 mmol), 1 M AcOH (0.75 mL), and chloroform (3.0 mL). Flash chromatography (silica gel, 30% Et_2O in pentanes) afforded the title compound as a clear, light yellow oil (101 mg, 92% yield, 92% ee). IR (film) 1726, 1460, 1137, 990.8, 754.3, 697.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.20 (d, 1H, *J*=6.0 Hz, C*H*O), 7.39–7.28 (m, 5H, aryl *H*), 4.17 (d, 1H, *J*=2.1 Hz, C*H* oxirane), 3.45 (dd, 1H, *J*=2.1, 6.0 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 129.4, 129.0, 125.9, 63.2, 56.9; HRMS (EI$^+$) exact mass calculated for $[M]^+$ ($C_9H_8O_2$) requires *m*/*z* 148.0524, found *m*/*z* 148.0522; $[\alpha]_D$ +35.8 (*c* 0.76, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Bodman Γ-TA column (90 °C isotherm, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R=29.9 min, (2*R*,3*S*) isomer t_R=33.1 min.

Absolute sense of rotation and spectroscopic data was in agreement with reported literature values.[37]

3.3.15. (2*R*,3*S*)-3-(4-Nitrophenyl)oxirane-2-carbaldehyde (Table 7, entry 9). Prepared according to general epoxidation procedure B using 4-nitrocinnamaldehyde (138 mg, 0.75 mmol) using 1 M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 40% Et_2O in hexanes with 2% NEt_3) afforded the title compound as a light yellow solid (154 mg, 89% yield, 97% ee). IR (film) 1727, 1605, 1520, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, 1H, J=6.0 Hz, C*H*O), 8.21 (dd, 2H, J=2.4, 9.1 Hz, aryl *H*), 7.46 (dd, 2H, J=2.4, 9.1 Hz, aryl *H*), 4.26 (d, 1H, J=1.8 Hz, C*H* oxirane), 3.41 (dd, 1H, J=1.8, 5.7 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 141.2, 126.3, 123.8, 62.5, 55.3; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_9H_7NO_4$) requires m/z 193.0375, found m/z 193.0374; $[\alpha]_D$ −13.0 (c 1.18, $CHCl_3$). The enantiomeric purity was determined by GLC analysis using a Chirasil-DEX CB column (120 °C ramp 5 °C/min to 145 °C, 15 psi, flow=1.0 mL/min); (2*S*,3*R*) isomer t_R= 74.8 min, (2*R*,3*S*) isomer t_R=75.9 min.

3.3.16. (2*R*,3*S*)-3-(4-Bromophenyl)oxirane-2-carbaldehyde (Table 7, entry 10). Prepared according to general epoxidation procedure B using 4-bromocinnamaldehyde (158 mg, 0.75 mmol) using 1 M AcOH (0.75 mL) and chloroform (3.0 mL). Flash chromatography (silica gel, 30% Et_2O in pentanes with 2% NEt_3) afforded the title compound as a clear oil (158 mg, 93% yield, 93% ee). IR (film) 1727, 1490, 1070, 1011, 824.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.16 (d, 1H, J=6.0 Hz, C*H*O), 7.48 (d, 2H, J=9.0 Hz, aryl *H*), 7.14 (d, 2H, J=9.0 Hz, aryl *H*), 4.11 (d, 1H, J=1.8 Hz, C*H* oxirane), 3.37 (dd, 1H, J=1.7, 6.2 Hz, C*H* oxirane); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 132.2, 127.5, 62.92, 56.28; HRMS (EI^+) exact mass calculated for $[M]^+$ ($C_9H_7O_2Br$) requires m/z 225.9629, found m/z 225.9626; $[\alpha]_D$ −10.5 (c 0.945, $CHCl_3$). The enantiomeric purity was determined by HPLC analysis of the alcohol using a Chiralpak AD column (5% EtOH/hexanes, flow= 1.0 mL/min); (2*R*,3*S*) isomer t_R=33.7 min, (2*S*,3*R*) isomer t_R=36.9 min.

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References and notes

1. (a) Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, NY, 1993; pp 159–202; (b) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, NY, 1993; pp 103–158.
2. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
3. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
4. Irie, R.; Noda, K.; Ito, Y.; Masumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.
5. Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.
6. Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.
7. Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887.
8. Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621.
9. For a review of the epoxidation of electron-deficient olefins, see: Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215 and references therein.
10. Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 2327.
11. (a) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 1725; (b) Enders, D.; Zhu, J.; Kramps, L. *Liebigs Ann. Recl.* **1997**, 1101.
12. (a) Elson, C. L.; Jackson, R. F. W.; MacDonald, S. F. J.; Murray, P. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 410; (b) Jacques, O.; Richards, S. J.; Jackson, R. F. W. *Chem. Commun.* **2001**, 2712.
13. (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1237; (b) Bougauchi, M.; Wantabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329.
14. Dhanda, A.; Drauz, K.-H.; Geller, T. P.; Roberts, S. M. *Chirality* **2000**, *12*, 313.
15. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289.
16. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.
17. Marigo, M.; Poulsen, T. B.; Zhang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.
18. Antoniotti, S.; Dunach, E. *Synthesis-Stuttgart* **2003**, *18*, 2753.
19. (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240; (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; (c) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32; (d) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482; (e) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894; (g) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.
20. For a recent article that elegantly employs these oxidants in an enantioselective epoxidation using a different amine catalyst, see Ref. 17.
21. For excellent reviews on hypervalent iodine, see: (a) Stang, P. *Chem. Rev.* **1996**, *96*, 1123; (b) Wirth, T.; Ochiai, M.; Varvgolis, A.; Zhdankin, V. V.; Koser, G. F.; Tohma, H.; Kita, Y. *Topics in Current Chemistry: Hypervalent Iodine Chemistry -/- Modern Developments in Organic Synthesis*; Springer: Berlin, 2002; Vol. 224.
22. For an example of a 1,4-addition with iodosobenzene, see: (a) Pettus, L. P.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2001**, *3*, 905; For examples of nucleophilic attack by the oxygen of iodosobenzene, see: (b) Moriarty, R. M.; Gupta, S. C.; Hu, H.; Berenschot, D. R.; White, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 686; (c) Zefirov, N. S.; Kozhushkov, S. I.; Zhdankin, V. V.; Safronov, S. O. *Zh. Org. Khim.* **1989**, *25*, 1109.
23. Iminium content is observable by ^1H NMR.

24. (a) Sawaguchi, M.; Aruba, S.; Hara, S. *Synthesis* **2002**, *13*, 1802; (b) For a discussion of substituent effects on the phenyl ring of hypervalent iodides, see: Harden, G. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1883 and Gao, Y.; Jiao, X.; Fan, W.; Shen, J.-K.; Shiu, Q.; Basolo, F. *J. Coord. Chem.* **1993**, *29*, 349; (c) Note: other substituted iodosobenzenes (*p*-NO_2, *o*-Me, and *o*-Cl) were found to be much less efficient than unfunctionalized iodosobenzene.
25. For examples of non-metal mediated oxidations by iodosobenzene, see: (a) Huang, W.-J.; Singh, O. V.; Chen, C.-H.; Choiu, S.-Y.; Lee, S.-S. *Helv. Chim. Acta* **2002**, *85*, 1069; (b) Tohma, H.; Maegawa, T.; Takizawa; Kita, Y. *Adv. Synth. Catal.* **2002**, *344*, 328; (c) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424; (d) Sohmiya, H.; Kimura, T.; Fujita, M.; Ando, T. *Tetrahedron* **1998**, *54*, 13737.
26. Concentrations of iodosobenzene species were calculated relative to benzyl methyl ether (internal standard) and were determined after removal of oligomeric iodosobenzene by filtration through Celite.
27. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
28. (a) Saltzman, H.; Sharefkin, J. G. *Org. Synth.* **1973**, *5*, 658; (b) Simàndi, L. I.; Nèmeth, S.; Besenyei, G. *Tetrahedron Lett.* **1993**, *34*, 6105.
29. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
30. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.
31. Righi, G.; Chionne, A.; Bonini, C. *Eur. J. Org. Chem.* **2000**, 3127.
32. Martin, S. F.; Garrison, P. J. *Tetrahedron Lett.* **1977**, *44*, 3875.
33. Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067.
34. Guziec, F. S.; Luzzio, F. A. *J. Org. Chem.* **1982**, *47*, 1787.
35. Orlek, B. S. *Synlett* **1993**, 758.
36. Kukovinets, O. S.; Kasradze, V. G.; Chernukha, E. V.; Odinokov, V. N.; Dolidze, A. V.; Galin, F. Z.; Spirikhin, L. B.; Abdullin, M. I.; Tolstikov, G. A. *Russ. J. Org. Chem.* **1999**, *35*, 1156.
37. Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474.
38. *CRC Handbook of Chemistry and Physics*, 81st ed.; Lide, D. R., Ed.; CRC: Boca Raton, FL, 2000.