# **Enantioselective Organocatalytic Epoxidation Driven by Electrochemically Generated Percarbonate and Persulfate**

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Dedicated to Prof Andreas Pfaltz on the occasion of his 60th birthday

Abstract: An organocatalytic asymmetric epoxida-<br/>tion reaction using iminium salt catalysts is de-<br/>scribed, in which the stoichiometric persulfate oxi-<br/>dant is generated electrochemically. This system<br/>offers comparable *ees* to the use of commercially<br/>available persulfate. Electrochemically generatedpercarbonate ion is also a successful and novel oxi-<br/>dant system for use with iminium salts.Keywords:<br/>Oxone; percarbonates; persulfatesKeywords:<br/>catalysis; electrochemistry; epoxidation;<br/>Oxone; percarbonates; persulfates

### Introduction

We have developed a highly enantioselective organocatalytic asymmetric epoxidation process.<sup>[1]</sup> In this system, an iminium salt catalyst, for example 1 or 2 (Figure 1), is oxidized to the corresponding oxaziridinium salt, which is active in the transfer of oxygen to olefins. We have observed ees of up to 97%.<sup>[2]</sup> The use of iminium salts as pre-catalysts for asymmetric epoxidation reactions was first observed in 1987,<sup>[3]</sup> and has subsequently been reported by several groups.<sup>[4]</sup> As with other catalytic epoxidations, this system of course requires the presence of a stoichiometric, terminal oxidant, usually the water-soluble triple salt Oxone. We have demonstrated that tetraphenylphosphonium monoperoxysulfate (TPPP), which can be prepared from Oxone and is soluble in organic solvents,<sup>[5]</sup> is also a compatible terminal oxidant,<sup>[6]</sup> and use of this oxidant has allowed us to investigate the



nature of the reaction intermediates by NMR spectroscopy.<sup>[7]</sup>

Use of such a stoichiometric oxidizing reagent, with the concomitant production of inorganic by-products, necessarily brings inherent environmental disadvantages and other hazards, and we were therefore interested in seeking a 'green' variant of this reaction, in which the requirement for addition of an inorganic or organic stoichiometric oxidant would be eliminated. We conjectured that this aim might be achievable if the iminium salt-catalysed asymmetric epoxidation process could be driven by an electrochemical means, with water as the source of the epoxide oxygen atom. Electrochemically driven catalytic epoxidations were first reported in 1986;<sup>[8]</sup> in two independent reports, metalloporphyrins were used to mediate oxygen transfer to unfunctionalized olefins. Since these reports, there have been several further instances of catalytic electroepoxidations,<sup>[9]</sup> but in nearly all cases the oxygen transfer step has been reliant on a metal atom, and very few have been enantioselective.<sup>[9b,d]</sup> The formulation of an enantioselective organocatalytic variant of this reaction appears to be an attractive proposition. Herein we report such an approach, aided by the recently developed boron-doped diamond (BDD) electrode-based direct conversion of water into reactive peroxo intermediates.<sup>[10]</sup>

Figure 1. Iminium salt catalysts.

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#### **Results and Discussion**

Inorganic peracids such as peroxysulfates have previously been prepared electrochemically at both conventional and boron-doped diamond electrodes.<sup>[11]</sup> We reasoned that electrosynthetic monoperoxysulfate, the active oxidizing constituent of Oxone, could be a direct analogue of our successful Oxone system. The electrosynthetic process, however, is effective only at very low pH,<sup>[10a]</sup> which we deemed unsuitable for practical epoxidation reactions, and we therefore sought an alternative oxidant.

Saha demonstrated that solutions containing sodium percarbonate (i.e.,  $Na_2CO_4$ ), in equilibrium with a mixture of hydrogen peroxide in carbonate electrolyte, could be readily generated electrochemically from solutions of the corresponding carbonate<sup>[12]</sup> when boron-doped diamond was used as the working electrode. This process was selected as a suitable starting point as it more closely matched the pH range at which our epoxidation system had been developed. Percarbonate for epoxidation reactions has also been generated from hydrogen peroxide prepared electrochemically in ionic liquids.<sup>[9g]</sup>

Electrolyses of solutions of 1M aqueous Na<sub>2</sub>CO<sub>3</sub> were performed with vigorous stirring in a two-electrode undivided cell, using a BDD working electrode (area  $3 \text{ cm}^2$ ) and a small Pt wire counter electrode (area  $0.2 \text{ cm}^2$ ), with an applied potential of 10.0 V, producing an anodic current density of  $100 \text{ mA cm}^{-2}$ . In this process, the small counter electrode causes high current density hydrogen evolution, and diffusion-controlled peroxide losses are minimized. Electrolysis and chemical reactions were carried out in an ice bath to dissipate heat. The presence of peroxy intermediate was subsequently confirmed by quantitative hydrodynamic voltammetric determination (see Experimental Section) at the Pt electrode using a commercial percarbonate standard. Following a 1 hour electrolysis, the peroxide concentration reached 30-40 mM (approx. 30% current efficiency), a similar concentration to that used in our reactions with stoichiometric oxidants.

When an acetonitrile solution of catalyst **1** and 1phenylcyclohexene was emulsified with this percarbonate solution (approx. 2–4 equiv.) using vigorous stirring, complete conversion into the epoxide was observed within one hour. The results of these experiments are presented in Table 1.

It can be seen that the concentration and precise nature of the percarbonate precursor are crucial to the success of the reaction. Carbonate concentrations less than 1.0M appear to be too low for successful epoxidation (entries a and b). While the nature of the metal cation appears to have no effect on the success of the system (entries c, f, g), the use of a bicarbonate anion clearly prevents the reaction from proceeding

 
 Table 1. Percarbonate-mediated epoxidation of 1-phenylcyclohexene.



			(Isolated yield [%])
a	0.1 M Na <sub>2</sub> CO <sub>3</sub>	MeCN	<5
b	$0.5 \text{ M} \text{ Na}_2 \text{CO}_3$	MeCN	<5
с	$1.0 \text{ M} \text{ Na}_2 \text{CO}_3$	MeCN	100 (99)
d	1.0 M NaHCO <sub>3</sub>	MeCN	<5
e	1.0 M KHCO <sub>3</sub>	MeCN	<5
f	$1.0 \text{ M K}_2 \text{CO}_3$	MeCN	100 (95)
g	$1.0 \text{ M Cs}_2 \text{CO}_3$	MeCN	99 (83)
h	$1.0 \text{ M} \text{ Na}_2 \text{CO}_3$	DCM	<5
i	$1.0 \text{ M} \text{ Na}_2 \text{CO}_3$	MeOH	<5
j	$1.0 \text{ M} \text{ Na}_2 \text{CO}_3$	Acetone	<5
k	$1.0 \text{ M} (\text{NH}_4) \text{HCO}_3$	MeCN	10

<sup>[a]</sup> Conversions were determined by <sup>1</sup>H NMR spectroscopy, by integration of alkene and epoxide signals.

(entries d and e); use of the more basic ammonium bicarbonate was also unsuccessful (entry k). Quantitative voltammetric determination at the Pt electrode using 1M aqueous sodium bicarbonate indicated that percarbonate is not generated by the electrolysis process at this pH. Changing the reaction solvent completely impeded the reaction: No epoxide was detected when the reaction was conducted in dichloromethane, methanol, or acetone (entries h–j).

Having proven the potential of the electrochemically generated percarbonate system for epoxidation reactions, we were eager to investigate the potential asymmetric induction of this process. Analyses of the *ees* of epoxides prepared using catalyst **1** showed near-racemic material in most cases (Table 2). This is puzzling when it is considered that under both our original Oxone- and TPPP-mediated conditions this conversion proceeds with *ees* of between 17 and 49% for these substrates.<sup>[13]</sup> As a further test, catalyst **2** was also evaluated. In this instance, low to moderate *ees* were observed.

While it was satisfying to observe reasonable asymmetric induction with catalyst **2**, the *ees* obtained are lower than we had expected, based on our previous results using commercial Oxone (up to  $60\% \ ee$ ).<sup>[13]</sup> As percarbonate is a novel oxidant for this catalyst system, the possibility exists that significant background epoxidation is occurring, which would be expected to reduce the observed *ees* significantly. Entry i shows that this is unlikely: a control experiment run in the absence of iminium salt showed only a 1.9% conversion into epoxide in the same time period,

Table 2. Percarbonate-mediated asymmetric epoxidation.



Entry	Substrate	Catalyst	Conversion <sup>[a]</sup> [%]	Isolated yield [%]	Absolute configuration <sup>[f]</sup>	ee [%]
a	1-Phenylcyclohexene	1	100	98		3 <sup>[b]</sup>
b	Styrene	1	100	100		9 <sup>[b]</sup>
c	1,2-Dihydronaphthalene	1	91	79		$< 1^{[c]}$
d	1-Phenyl-3,4-dihydronaphthalene	1	96	28		8 <sup>[b]</sup>
e	trans-a-Methylstilbene	2	43	21	(-)-(1S,2S)	14 <sup>[b]</sup>
f	1-Phenyl-3,4-dihydronaphthalene	2	97	60		3 <sup>[c]</sup>
g	1,2-Dihydronaphthalene	2	100	89	(-)-(1S,2R)	35 <sup>[b,c]</sup>
ĥ	1-Phenylcyclohexene	2	100	91	(-) - (1S, 2S)	32 <sup>[b,c]</sup>
i	1-Phenylcyclohexene <sup>[d]</sup>	2	1.9	0		-
j	1-Phenylcyclohexene <sup>[e]</sup>	2	96	84	(-)-(1S,2S)	32 <sup>[c]</sup>

<sup>[a]</sup> Conversions were determined by <sup>1</sup>H NMR spectroscopy, by integration of alkene and epoxide signals.

<sup>[b]</sup> Determined by chiral shift reagent <sup>1</sup>H NMR spectroscopy.

<sup>[c]</sup> Determined by chiral stationary phase gas chromatography using a Chiralcel OD column.

<sup>[d]</sup> Experiment performed in the absence of catalyst.

<sup>[e]</sup> Experiment performed with commercially available sodium percarbonate.

<sup>[f]</sup> Established by comparison with literature data.

demonstrating that the background epoxidation process does not make a significant contribution to the observed conversions, and ruling out the significant involvement of peroxyimidic acid derived from the acetonitrile solvent. Indeed, we were unable to detect any benzamide, the by-product of oxidation by peroxyimidic acid, in the reaction mixture when benzonitrile was used as the reaction solvent.

A further control experiment was performed using a commercially available sample of sodium percarbonate (Aldrich).<sup>[14]</sup> Significantly, in this instance (entry j), the conversion and *ee* were essentially identical to those obtained using the electrochemical system (entry h). These data support the suggestion that the *ees* obtained using the electrochemically driven system are a direct consequence of percarbonate-driven, iminium ion-mediated epoxidation.

This interesting difference in the *ee*s obtained by two distinct oxidant systems, monoperoxysulfate from Oxone, and commercial percarbonate, could be interpreted as evidence that iminium ion-mediated epoxidation with percarbonate as the terminal oxidant proceeds through a different mechanism from the reaction in which monoperoxysulfate is the oxidant. In order to investigate this hypothesis further, we felt it to be desirable to run organocatalytic electroepoxidations using a monoperoxysulfate system, to allow a direct comparison with the original oxone and percarbonate systems. As indicated above, this is problematic because, unlike percarbonate generation, electrochemical generation of peroxymonosulfuric acid occurs only at very low pH.<sup>[10a]</sup> Serrano reported the presence in low concentration of monoperoxysulfuric acid ( $H_2SO_5$ ) as a side product in the electrosynthesis of peroxydisulfuric acid ( $H_2S_2O_8$ ) from solutions of concentrated sulfuric acid.<sup>[10a]</sup> Monoperoxysulfuric acid is thought to stem from the hydrolysis of peroxydisulfuric acid, which ultimately leads to hydrogen peroxide. Under electrosynthesis reaction conditions, however, both monoperoxysulfuric acid and hydrogen peroxide are believed to decompose rapidly, giving oxygen. It appears that the rate of oxidation of the monoperoxysulfuric acid is higher than its rate of formation under the electrochemical reaction conditions, which would explain the low concentration.<sup>[11b]</sup>

We attempted the oxidation reaction of 1-phenylcyclohexene under our standard oxone-mediated conditions<sup>[15]</sup> using commercially available 'potassium persulfate' (peroxydisulfate,  $K_2S_2O_8$ ). This commercial material does not appear to activate iminium salts, and we were unable to isolate the corresponding epoxide. We were therefore pleased to find that a suitable oxidant could be conveniently prepared by the electrolysis of concentrated sulfuric acid solution, followed by subsequent addition of solid K<sub>2</sub>CO<sub>3</sub> until the cloudy suspension reached basic pH (pH 7-9). This technique is reminiscent of the reported procedure for the industrial preparation of the Oxone triple salt.<sup>[16]</sup> Agitating this suspension with an organic solvent containing an olefin and iminium salt catalyst 2 was found to promote acceptable conversion of 1phenylcyclohexene into the corresponding (-)-(1S,2S)-epoxide (Table 3). Quantitative voltammetric

#### Table 3. Persulfate-mediated asymmetric epoxidation of 1-phenylcyclohexene.



solvent. 0 °C

Entry	Cat. Loading [mol%]	Sulfate source	Co-solvent	Conversion <sup>[a]</sup> [%]	Isolated yield [%]	ee [%]
a	20	2.5 M H <sub>2</sub> SO <sub>4</sub>	MeCN	100	85	64 <sup>[b]</sup>
b	10	2.5 M KHSO <sub>4</sub>	MeCN	0		-
с	10	$0.6 \text{ M} \text{ Na}_2 \text{SO}_4$	MeCN	0		-
d	10	$2.5 \text{ M} (\text{NH}_4) \text{HSO}_4$	MeCN	13		-
e	10	$1.0 \text{ M} H_2 \text{SO}_4$	MeCN	16		
f	10	$2.0 \text{ M} \text{ H}_2 \text{SO}_4$	MeCN	31	31	
g	10	$2.5 \text{ M H}_2 \text{SO}_4$	MeCN	100	80	58 <sup>[b]</sup>
ĥ	10	$5.0 \text{ M} \text{ H}_2 \text{SO}_4$	MeCN	100	62	54 <sup>[c]</sup>
i	10	$2.5 \text{ M H}_2 \text{SO}_4$	MeCN <sup>[f]</sup>	81	54	53 <sup>[b]</sup>
i	5	$2.5 \text{ M H}_2 \text{SO}_4$	MeCN	95	93	59 <sup>[c]</sup>
k	$10^{[d]}$	$2.5 \text{ M H}_2^2 \text{SO}_4$	MeCN	47	44	33 <sup>[c]</sup>
1 <sup>[e]</sup>	10	$2.5 \text{ M H}_2^2 \text{SO}_4$	MeCN	11		-
m <sup>[e]</sup>	10	$5.0 \text{ M H}_2 \text{SO}_4$	MeCN	100	100	64 <sup>[c]</sup>
n	10	$5.0 \text{ M H}_2^2 \text{SO}_4$	DCM	100	86	34 <sup>[b]</sup>
0	10	$2.5 \text{ M H}_2^{-} \text{SO}_4^{-}$	MeOH	47	44	39 <sup>[c]</sup>

<sup>[a]</sup> Conversions were determined by <sup>1</sup>H NMR spectroscopy, by integration of alkene and epoxide signals.

<sup>[b]</sup> Determined by chiral shift reagent <sup>1</sup>H NMR spectroscopy.

<sup>[c]</sup> Determined by chiral stationary phase gas chromatography using a Chiralcel OD column.

<sup>[d]</sup> Catalyst **1** used.

<sup>[f]</sup> 100 mL used.

determination at the Pt electrode using 2.5M sulfuric acid indicated that the total peroxide concentration reached 60–70 mM following a one-hour electrolysis.

When 5 M sulfuric acid is used during the electrolysis (see Experimental Section), it is convenient to remove by vacuum filtration the  $K_2SO_4$  that precipitates during basification, and to perform epoxidations by emulsifying an organic solvent with the resulting persulfate solution. The use of more dilute acid (2.5 M) also allows quantitative conversion into epoxides, but in this instance it was found that filtering the precipitated solids from the oxidant reduced the conversion (entry l vs. entry g); it is possible that monoperoxysulfate is co-precipitated under these conditions.

It is interesting to note that, unlike the carbonate system, when the sulfate system was used it was possible to observe good conversions in solvents other than acetonitrile. This is similar to the pattern of catalytic activity we have observed when our original Oxone system is used in these solvents. With the sulfate system, dichloromethane was successful when using the more active catalysts, for example **2**, particularly when using emulsification by Ultraturrax agitation. When the reaction was performed in dichloromethane, a 76% conversion was observed by <sup>1</sup>H NMR spectroscopy (entry n). Performing the reaction in methanol (entry o) allowed a moderate conversion to epoxide, although the observed *ee* was somewhat reduced. It is possible that transport of the oxidizing species across the aqueous/organic interface occurs following reaction of the inorganic oxidant with the iminium salt to give a neutral adduct incorporating a sulfate or carbonate residue; transport properties would be expected to be different for the two species. An alternative scenario is that the inorganic oxidant is transported across the aqueous/organic interface as an ion pair by the iminium salt acting as a phase-transfer agent; again, transport would be expected to be different for the percarbonate- and persulfate-derived species.

Gratifyingly, analyses of epoxides produced by this system using acetonitrile as the organic phase showed *ees* of a similar magnitude to those observed in our original Oxone-driven system.<sup>[13]</sup> This provides evidence that the active oxidant in this instance is indeed monoperoxysulfate. As described above, the percarbonate-driven system provides lower *ees*.

There are two distinct mechanistic steps that could conceivably contribute to the control of enantioselectivity in a subsequent epoxidation reaction. These are the transfer of active oxygen from the peroxy salt to

<sup>&</sup>lt;sup>[e]</sup> Suspension was filtered prior to addition of organics.

the iminium cation, generating an oxidizing species, and the subsequent oxygen transfer from this oxidizing species to the alkene substrate. The fact that the percarbonate-driven system provides lower *ees* than the persulfate-driven system suggests that one of these steps is less selective for percarbonate.

It is possible that the percarbonate and persulfate systems generate different concentrations of hydrogen peroxide in the respective equilibria, but, in the absence of carbonate or sulfate, hydrogen peroxide does not induce epoxidation in the presence of the iminium salt catalysts.

In each system, the active peroxy agent could add to either face of the iminium ion, producing a pair of diastereoisomeric oxidizing intermediates, which would each be expected to provide different enantioselectivities upon reaction with alkene substrates. The difference in ionic Gibbs free energy of transfer between percarbonate and persulfate could affect the transition state reactivity during oxygen transfer and therefore the ratio of oxaziridinium diastereoisomers. The additional role, if any, of the counter-ion of the oxaziridinium cation is unclear, but if, as we believe, the enantioselective oxidizing agent is in both percarbonate and persulfate systems the same pair of diastereoisomeric oxaziridinium species, and the inorganic components have no great effect on the epoxidation process, then the oxygen transfer step to the alkene substrate occurs from the same pair of diastereoisomeric oxidizing species in both systems. This points to a different diastereofacial selectivity between the percarbonate and persulfate systems in the reaction of the oxidant with the iminium cation, so generating a different ratio of the diastereoisomeric oxaziridinium intermediates, and consequently different ees in the epoxidation process (Figure 2).



**Figure 2.** Catalytic reaction scheme showing the duality of the overall enantioselection.

### Conclusions

In summary, we have further developed our organocatalytic asymmetric epoxidation reaction such that the terminal, stoicheiometric oxidant can now be separately generated electrochemically as required. The system generates persulfate on an as-required basis, and offers comparable ees to commercially available persulfate. Further to this, we have identified electrochemically generated percarbonate ion as a novel oxidant system for use with iminium salts, although at this stage it appears that, despite permitting good conversions to epoxides, this system is not able to provide high asymmetric induction.

#### **Experimental Section**

# Epoxidation using Commercially Available Sodium Percarbonate

Potassium carbonate (276 mg, 2 mmol) was dissolved in a water:acetonitrile mixture (2:1, 30 mL) and the solution was cooled to 0°C. Sodium percarbonate (314 mg, 2 mmol) was then added to the solution. Catalyst **2** (35 mg, 10 mol%) was dissolved in acetonitrile (1 mL) and added to the reaction mixture at 0°C. 1-Phenylcyclohexene (80  $\mu$ L, 0.5 mmol) was added, neat or in solution, and the reaction mixture stirred at 0°C for one hour. Diethyl ether (20 mL) was then added and the organic phase separated, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was then placed on a column of silica gel and eluted with ethyl acetate:petroleum ether (1:4) to afford the title compound as a yellow oil; yield: 73 mg (84%).

# Epoxidation using Electrosynthesis of a Solution of Sodium Carbonate

Aqueous sodium carbonate (1M, 100 mL) was placed in a two-electrode undivided cell fitted with a boron-doped diamond (Diafilm, Windsor Scientific, UK) electrode (3 cm<sup>2</sup>) as the working electrode and a small platinum wire electrode  $(0.2 \text{ cm}^2)$  as the counter electrode. The cell was placed in an ice bath. With vigorous stirring, a 10.0 V current at 0.3 A (Thurlby power source, anodic current density approx. 100 mA cm<sup>-2</sup>) was applied to the solution for one hour at 0°C. A flow of nitrogen ensured that hydrogen gas evolving at the cathode was removed and safely vented. The concentration of peroxide was monitored by hydrodynamic voltammetry at the 0.2 cm<sup>2</sup> platinum wire electrode in the stirred solution. Under these conditions, the anodic limiting current is mass transport controlled and directly proportional to the peroxide concentration. Catalyst 1 or 2 (10 mol%) was dissolved in the corresponding organic solvent (50 mL), and the solution cooled to 0°C and added to the solution of percarbonate. The alkene (1.25 mmol), neat or in solution, was added, and the reaction mixture stirred for one hour at 0°C. Diethyl ether (50 mL) was added, and the organic phase separated, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate:petroleum ether to yield the epoxide.

# Epoxidation using Electrosynthesis of a Solution of Sulfuric Acid

Aqueous sulfuric acid (2.5 M, 100 mL) was placed in a twoelectrode undivided cell fitted with a boron-doped diamond (Diafilm, Windsor Scientific, UK) electrode (3 cm<sup>2</sup>) as the working electrode and a small platinum wire electrode  $(0.2 \text{ cm}^2)$  as the counter electrode. The cell was placed in an ice bath. With vigorous stirring, a 5.0 V potential resulted in a 1.0 A current (anodic current density approx.  $330 \text{ mA cm}^{-2}$ ) applied to the solution for one hour at 0 °C. A flow of nitrogen ensured that hydrogen gas evolving at the cathode was removed and safely vented. The concentration of peroxide was monitored by hydrodynamic voltammetry at the  $0.2 \text{ cm}^2$  platinum wire electrode in the stirred solution. Under these conditions, the anodic limiting current is mass transport controlled and directly proportional to the peroxide concentration. The solution was basified using potassium carbonate until the pH of the mixture reached pH 7–9. Catalyst 1 or 2 (10 mol%) was dissolved in the corresponding organic solvent (50 mL), and the solution cooled to 0°C and added to the solution of peroxymonosulfate. 1-Phenylcyclohexene (1.25 mmol), neat or in solution, was added, and the reaction mixture stirred for one hour at 0°C. Diethyl ether (50 mL) was added, and the organic phase separated, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was placed on a column of silica gel and eluted with ethyl acetate:petroleum ether (1:4) to yield the epoxide.

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