

Communication

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## Catalytic Asymmetric Epoxidation of Cyclic Enones

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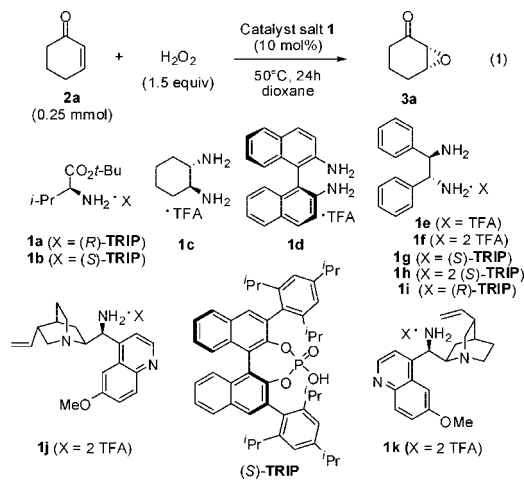
Enantioselective catalytic epoxidations of olefins provide chiral epoxides of central importance to various branches of chemistry.<sup>1</sup> While there are powerful solutions for several different classes of olefins,<sup>2</sup> a highly enantioselective epoxidation of simple cyclic enones has to our knowledge not been described. Here we report a practical solution to this important problem. We found that cyclic enones are readily epoxidized with excellent enantioselectivity upon treatment with hydrogen peroxide and a catalytic amount of a chiral primary amine salt.

Previously reported asymmetric epoxidations of cyclic  $\alpha,\beta$ -unsaturated ketones using cinchona alkaloid-derived quaternary ammonium salt catalysts,<sup>3</sup> poly(amino acid) catalysts,<sup>4</sup> or stoichiometric chiral hydroperoxides<sup>5</sup> gave only poor or moderate enantioselectivities with most cyclic enones. Recently, secondary amine catalysts and their salts have been used in enantioselective Weitz–Scheffer-type epoxidations of  $\alpha,\beta$ -unsaturated aldehydes via iminium catalysis.<sup>6</sup> An extension to  $\alpha,\beta$ -unsaturated ketones appeared attractive to us, and we were particularly encouraged by recent applications of primary amine salts in the iminium catalysis of enone substrates.<sup>7</sup> For example, we have developed a highly enantioselective conjugate reduction of enones with Hantzsch ester catalyzed by an  $\alpha$ -amino acid ester/chiral phosphate salt.<sup>8</sup>

Inspired by these studies, we investigated our previously used valine salts **1a** and **1b** for the epoxidation of cyclohexenone (**2a**) with 1.5 equiv of hydrogen peroxide (50% w/w in H<sub>2</sub>O) (eq 1 in Table 1). The epoxidation reaction to **3a** proceeded smoothly, but the enantioselectivity was only moderate (Table 1, entries 1 and 2). We next shifted our attention to diamine salts, expecting such bifunctional catalysts to possibly activate both the enone substrate via iminium ion formation and hydrogen peroxide via general base catalysis. Indeed, C<sub>2</sub>-symmetric TFA salts **1c** and **1d** gave promising results (entries 3 and 4). Gratifyingly, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (DPEN) salts **1e–i** proved to be both active and highly enantioselective catalysts. The best result in this series was achieved with DPEN-mono-TRIP salt **1g** (entry 7) although even TFA salt **1e** (entry 5) gave high yield and enantioselectivity. 9-Amino cinchona alkaloid<sup>9</sup> salts **1j** and **1k**, which have recently been used in primary iminium catalysis,<sup>7</sup> have also been investigated and gave excellent results. Especially, 9-amino-9-deoxyepiquinine salt **1j** proved to be both highly active and enantioselective (entry 10).

Having identified two useful catalysts (**1g** and **1j**) for the epoxidation of cyclohexenone (**2a**), scope and limitations of our new epoxidation reaction were investigated next (for a detailed comparison of catalysts **1e**, **1g**, and **1j** with different substrates, see Supporting Information). Indeed, treating different cyclic enones **2** with aqueous hydrogen peroxide (1.5 equiv) in the presence of the catalytic amine salts (10 mol %) at 30–50 °C in dioxane for 20–48 h gave the corresponding  $\alpha,\beta$ -epoxyketones **3** in good yields and excellent enantioselectivities in almost all cases studied (Table 2). In addition to cyclohexenone itself, a number of different substituted cyclohexenones could be converted with excellent results, including the natural product isophorone (entry 5) and a cyclohexenedione (entry 13).

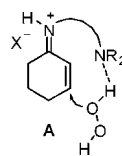
Table 1. Catalyst Investigation



entry	cat	conv (%) <sup>a</sup>	er <sup>b</sup>	entry	cat	conv (%) <sup>a</sup>	er <sup>b</sup>
1	<b>1a</b>	73	62:38	6	<b>1f</b>	92	94:6
2	<b>1b</b>	92	44:56	7	<b>1g</b>	98	96:4 <sup>c</sup>
3	<b>1c</b>	93	82:18	8	<b>1h</b>	91	92:8
4	<b>1d</b>	71	38:62	9	<b>1i</b>	49	90:10
5	<b>1e</b>	95	95:5 <sup>c</sup>	10	<b>1j</b>	82	4:96 <sup>c</sup>

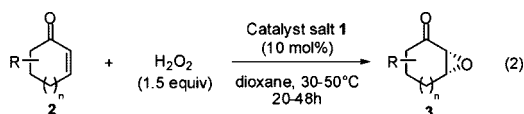
<sup>a</sup> Determined by GC with external standard. <sup>b</sup> Determined by chiral GC. <sup>c</sup> Absolute configuration [2*R*,3*R*] of **3a** with catalysts **1g** was determined from its optical rotation.<sup>3a</sup>

In the case of  $\beta$ -substituted cyclohexenones, quinine-derived catalyst **1j** proved to be particularly suitable (entries 6–11). As expected, quinidine-derived catalyst **1k** gave the opposite enantiomer with equally high enantioselectivities (entry 12). 2-Cycloheptenones turned out to be excellent substrates, furnishing high yields of essentially enantiopure epoxides (entries 14–16). In contrast, 2-cyclopentenone exhibited lower reactivity to give epoxide **3o**, which to our knowledge for the first time was obtained in good enantioselectivity (entry 17).  $\alpha$ -Substituted enones were unreactive under the reaction conditions. Consistent with this and the fact that the corresponding nonprotonated amines **1** as well as quinine itself are much less active and enantioselective (see Supporting Information), we propose the reaction to proceed via iminium ion **A**. The second basic amine



site of the catalyst may organize the transition state by directing the attack of hydrogen peroxide toward one enantioface of the double bond.

Pretransition state assembly **A** resembles structures proposed by Yamaguchi et al. and by Taguchi et al. in their pioneering studies on asymmetric iminium catalysis with proline-derived

**Table 2.** Preliminary Scope of the Epoxidation of Enones<sup>a</sup>

entry	epoxide	cat	yield <sup>b</sup> (%)	e <sup>c</sup>
1		<b>3a</b>	<b>1g</b> 68(96)	96.4
2		<b>3a</b>	<b>1j</b> 58(91)	3:97
3		<b>3b</b>	<b>1g</b> 80	97.3
4		<b>3c</b>	<b>1g</b> 76	98.2
5		<b>3d</b>	<b>1g</b> 63	96.4
6		<b>3e</b>	<b>1j</b> 70	98.2
7		<b>3f</b>	<b>1j</b> 73	98.5:1.5
8		<b>3g</b>	<b>1j</b> 79	99.1
9		<b>3h</b>	<b>1j</b> 73	98.2
10		<b>3i</b>	<b>1j</b> 84	98.5:1.5
11		<b>3j</b>	<b>1j</b> 78	99.1
12		<b>3j</b>	<b>1k</b> 77	98.5:1.5
13		<b>3k<sup>d</sup></b>	<b>1j</b> 49	96.4
14		<b>3l</b>	<b>1g</b> 82	99.1
15		<b>3m</b>	<b>1j</b> 82	>99.5:0.5
16		<b>3n</b>	<b>1j</b> 85	>99.5:0.5
17		<b>3o</b>	<b>1g</b> (33)	89:11

<sup>a</sup> Reactions with catalyst **1j** and **1k** (**1g**) were performed on a 1.0 (0.5) mmol scale. <sup>b</sup> Isolated yield. GC yields of highly volatile products are in parentheses. <sup>c</sup> Determined by chiral GC or HPLC. <sup>d</sup> 20 mol% catalyst loading.

secondary amine catalysts.<sup>10</sup> Our current studies focus on expanding the scope of this catalytic asymmetric epoxidation

of  $\alpha,\beta$ -unsaturated ketones as well as the development of even more efficient catalysts and a more detailed mechanistic understanding. Our work adds to a growing number of conceptually interesting reactions that are catalyzed by primary amine salts, combining iminium and Brønsted acid catalysis.<sup>7,11</sup>

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**Supporting Information Available:** Experimental procedures, compound characterization, NMR spectra, and GC and HPLC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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