

# Catalytic Asymmetric Addition of Carbon Dioxide to Propylene Oxide with Unprecedented Enantioselectivity

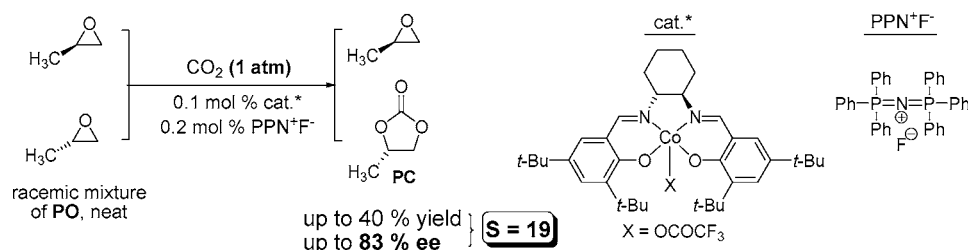
Albrecht Berkessel\* and Marc Brandenburg

Institut für Organische Chemie, Universität zu Köln, Greinstrasse 4,  
D-50939 Köln, Germany

berkessel@uni-koeln.de

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## ABSTRACT



New chiral catalyst systems were developed for the reaction of carbon dioxide with propylene oxide (PO) at atmospheric pressure to generate enantiomerically enriched propylene carbonate (PC). The best selectivity was achieved with a  $\text{Co}^{\text{III}}(\text{salen})$ -trifluoroacetyl complex and bis-(triphenylphosphoranylidene)ammonium fluoride ( $\text{PPN}^+\text{F}^-$ ) as catalysts, affording PC in 40% yield and 83% ee (selectivity factor = 19). In addition, PC was prepared for the first time by kinetic resolution of PO with tetrabutylammonium methyl carbonate (TBAMC,  $n\text{Bu}_4\text{N}^+\text{OOCOMe}$ ). With TBAMC as “activated  $\text{CO}_2$ ”, up to 71% ee was obtained.

Enantiopure epoxides are a particularly important class of chiral intermediates because of their versatile reactivity. In particular, stereospecific ring-opening reactions with nucleophiles have been exploited for the preparation of a wide variety of biologically and pharmaceutically important target compounds.<sup>1</sup>

Besides the enantioselective epoxidation of olefins,<sup>2</sup> the kinetic resolution of racemic epoxides by nucleophilic ring opening reactions is an efficient method for obtaining enantiopure epoxides.<sup>3</sup> The kinetic resolution of racemic epoxides, especially of propylene oxide (PO), with carbon

dioxide as reagent presents an attractive alternative, because it provides enantiopure epoxide and optically active cyclic carbonate. The latter are valuable building blocks for polymeric materials such as polycarbonates, masked 1,2-diols, and pharmaceutical/fine chemicals intermediates.<sup>4</sup> In most instances, enantiopure cyclic carbonates have been prepared by cyclization of chiral diols with triphosgene or by enzyme-mediated enantioselective hydrolysis of racemic cyclic carbonates.<sup>5</sup> However, the most attractive variant can be seen in the asymmetric catalytic addition of carbon dioxide to epoxides:  $\text{CO}_2$  represents a readily available nontoxic and nonflammable  $\text{C}_1$  feedstock.<sup>6</sup> Moreover, excess  $\text{CO}_2$  can be removed easily from the reaction system.<sup>7</sup>

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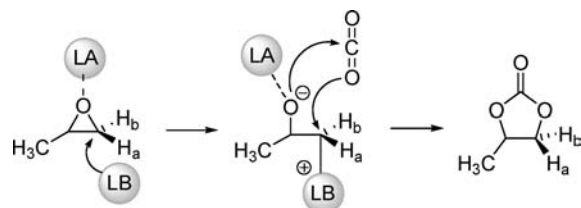
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The addition of carbon dioxide to epoxides was reported as early as 1956 by Lichtenwalter and Cooper.<sup>8</sup> As the result of extensive catalyst optimization, it was found that a combination of a Lewis acid catalyst and a nucleophilic cocatalyst (binary system) is most effective for this purpose.<sup>9</sup> This bifunctional mode of catalysis can be rationalized by the reaction mechanism shown in Scheme 1.<sup>10</sup>

**Scheme 1.** Proposed Mechanism for PO/CO<sub>2</sub> Coupling Catalyzed by a Binary System<sup>a</sup>



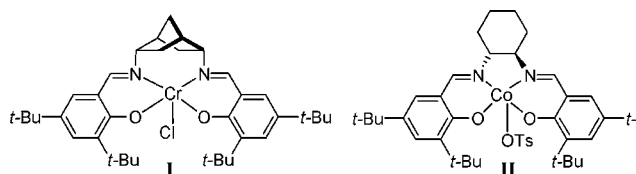
<sup>a</sup> LA: Lewis acid. LB: Lewis base.

Although the addition of CO<sub>2</sub> to epoxides has been known for quite some time, enantioselective versions are comparatively little studied. This is due to the fact that the enantioselectivity suffers from the harsh reaction conditions, such as elevated CO<sub>2</sub> pressures and high temperatures.<sup>10a</sup> One of the first and still best catalyst systems was reported by Lu and co-workers. It operates under mild reaction conditions (15 bar, 0 °C), providing a conversion of 40% with 70% ee for the *rac*-PO/CO<sub>2</sub> coupling.<sup>11</sup> This corresponds to a selectivity factor *s* of 9.0.<sup>12</sup>

In this paper, we report the addition of carbon dioxide to propylene oxide at low temperatures and at atmospheric pressure, in the presence of a catalytic amount of a chiral Lewis acid complex and a nucleophilic cocatalyst. As it turned out, the best selectivity factor obtained was 18.7 - unprecedented for this type of reaction.

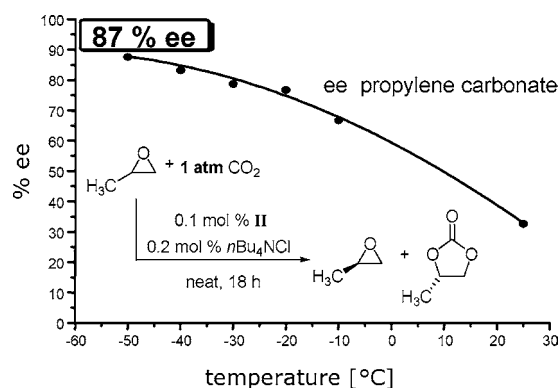
We first carried out experiments at 13 bar CO<sub>2</sub> pressure. The best catalyst system under these conditions was the Cr<sup>III</sup>-

DIANANE-salen-chlorid **I** (Figure 1) in combination with *n*Bu<sub>4</sub>NCl, which provides a selectivity factor of 5.3.<sup>13</sup>



**Figure 1.** Cr<sup>III</sup>-DIANANE-salen-chlorid **I** and Co<sup>III</sup>-DACH-salen-tosylate **II**.

Lu et al. reported that the addition of CO<sub>2</sub> to PO can also be conducted at atmospheric pressure, with the binary system Co<sup>III</sup>-DACH-salen-tosylate **II** (*n*Bu<sub>4</sub>NCl).<sup>14</sup> We found that the enantioselectivity (at atmospheric pressure) can be increased by carrying out the reaction at lower temperature. At -50 °C, the ee of propylene carbonate (PC) was found to be 87%, with *s* = 15.0 (Figure 2). At that point



**Figure 2.** Enantiomeric purity of PC versus temperature at atmospheric pressure.

in time, these values already constituted the best enantioselectivity and selectivity factor reported for the asymmetric addition of CO<sub>2</sub> to PO. To further increase the activity of the catalyst system, and to develop a more efficient kinetic resolution, we optimized the individual parts of the binary catalyst system, starting with the Lewis acidic metal center **M** (Figure 3).

Changing the metal to Al<sup>III</sup> (**3**) or Cr<sup>III</sup> (**4**), or using Co<sup>II</sup>-salen (**2**) is detrimental for the catalyst activity at atmospheric CO<sub>2</sub> pressure (Table 1, entries 1–3). We therefore maintained the Co<sup>III</sup> ion and investigated the influence of the counterion X, and that of the cocatalyst.

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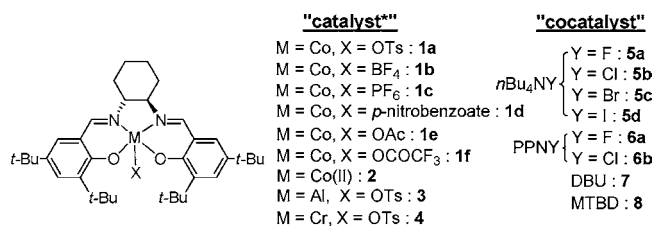
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(12) The selectivity factor, *s*, is determined by using the conversion, *C*, and ee of the propylene carbonate product in the following equation:  $s = \ln[1 - C(1 + ee)] / \ln[1 - C(1 - ee)]$ .



**Figure 3.** Binary catalyst systems.

It is interesting to note that the choice of the counterion X appears to be crucial for activity, but not for enantioselectivity. Changing to weakly coordinating BF<sub>4</sub><sup>-</sup> (**1b**) and PF<sub>6</sub><sup>-</sup> (**1c**), respectively, led to diminished activity (entries 4 and 5). Good activity was obtained with carboxylates such as *p*-nitrobenzoate (**1d**) (entry 6). In contrast, the cocatalyst's counterion was found to influence both the activity and enantioselectivity of the PC formation. We first examined various counterions for the tetrabutylammonium cation. From iodide to fluoride (**5d-5a**), the enantioselectivity was increased from 14% ee to 77% ee (entries 11, 10, 7, and 9). Unfortunately, this increase in ee is accompanied by decreasing activity (23% to 7% yield of PC after 18 h). Increasing

**Table 1.** Enantiospecific Addition of Carbon Dioxide to PO<sup>a</sup>

entry	cat.*	cocat.	mol %	yield of PC [%] <sup>b</sup>	ee of PC [%] <sup>b,c</sup>
1	<b>2</b>	<b>5b</b>	0.2	traces	—
2 <sup>d</sup>	<b>3</b>	<b>5b</b>	0.2	4	31
3 <sup>d</sup>	<b>4</b>	<b>5b</b>	0.2	8	41
4 <sup>d</sup>	<b>1b</b>	<b>5b</b>	0.2	4	62
5 <sup>d</sup>	<b>1c</b>	<b>5b</b>	0.2	8	59
6	<b>1d</b>	<b>5b</b>	0.2	22	67
7	<b>1a</b>	<b>5b</b>	0.2	15	73
8	<b>1a</b>	<b>5b</b>	0.5	36	65
9	<b>1a</b>	<b>5a</b>	0.2	7	77
10	<b>1a</b>	<b>5c</b>	0.2	18	49
11	<b>1a</b>	<b>5d</b>	0.2	23	14
12	<b>1a</b>	<b>6b</b>	0.2	20	73
13	<b>1e</b>	<b>6b</b>	0.2	29	70
14	<b>1f</b>	<b>6b</b>	0.2	35	70
15	<b>1f</b>	<b>6a</b>	0.2	39	75
16 <sup>e</sup>	<b>1f</b>	<b>6a</b>	0.2	40	83
17	<b>1f</b>	<b>7</b>	0.2	22	75
18	<b>1f</b>	<b>8</b>	0.2	23	72

<sup>a</sup> The reaction was carried out in 4.38 mL (62.5 mmol) of neat *rac*-propylene oxide, cat. 0.0625 mmol in a double-walled Schlenk flask. <sup>b</sup> Yields and ee values were determined by GC on chiral stationary phase, using diphenyl ether as internal standard. <sup>c</sup> Enantiomeric excess was in favor of the (*S*)-enantiomer of PC. Absolute configuration was determined by comparison of the retention times with enantiopure propylene carbonate. <sup>d</sup> -10 °C. <sup>e</sup> -40 °C, 5 d.

the amount of cocatalyst (**5b**) (0.5 mol % instead of 0.2 mol %) leads to higher activity, but lower ee (entries 7 and 8).

We furthermore employed the bis(triphenylphosphoranylidene)ammonium cation (PPN<sup>+</sup>) instead of *n*Bu<sub>4</sub><sup>+</sup>, because PPNCl (**6b**) is known to catalyze the addition of CO<sub>2</sub> at 100 °C and 5 bar.<sup>15</sup> To our surprise, the cation of the organic salt also significantly affected the CO<sub>2</sub> addition: In comparison to *n*Bu<sub>4</sub>NCl (**5b**), and under similar conditions, PPNCl (**6b**) showed enhanced activity at constant enantioselectivity (entry 12). Encouraged by this result, we examined a series of further catalyst systems and found that the reaction is indeed catalyzed by Co<sup>III</sup>salen acetate (**1e**)/PPNCl (entry 13) and most efficiently by Co<sup>III</sup>salen trifluoroacetate (**1f**)/PPNCl (entry 14). The best result was achieved with PPNF (**6a**) as cocatalyst (entries 15 and 16).<sup>16</sup> At -40 °C and with the Co<sup>III</sup>salen(OCOCF<sub>3</sub>)/PPNF system, PC was obtained in 40% yield and 83% ee (entry 16). To the best of our knowledge, this result corresponds to the highest selectivity factor (18.7) achieved to date for this reaction.

We furthermore found that the ionic nature of the cocatalyst is not essential for high reactivity. Strong and sterically hindered bases such as DBU (**7**) or the related 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **8**) can be applied as well, and afford good enantioselectivities (entries 17 and 18).

Please note that, at low temperatures, polypropylene carbonate (PPC) is temporarily formed as the major product.<sup>17</sup> The formation of the monomeric cyclic carbonate product results from complete degradation of the polycarbonate at room temperature within 4 h (mass balance PO + PC ≈ 1.0).

In addition to CO<sub>2</sub> itself, monoalkyl carbonates can be used as an alternative CO<sub>2</sub> source for the preparation of cyclic carbonates. In 2005, Bartoli, Melchiorre, et al. reported a method for the synthesis of enantiopure 5-methyloxazolidin-2-one from racemic propylene oxide by Co<sup>III</sup>salen-catalyzed kinetic resolution, using a urethane as the nucleophilic reagent.<sup>18</sup> As 5-methyloxazolidin-2-one is an N-analogue of propylene carbonate, we reasoned that PC can be obtained by reaction of a methyl carbonate (MC) with racemic PO.

In contrast to the direct CO<sub>2</sub> addition (Scheme 1), the addition of an *anionic* carbonate is expected to proceed via the mechanism shown in Scheme 2. The chiral Lewis acid catalyst (LA\*) can selectively complex and activate one enantiomer of racemic propylene oxide. Subsequent backside attack of methyl carbonate can be expected to occur at the less substituted carbon atom. Overall, enantioselective ring opening results. C–C-bond rotation and intramolecular displacement of methanolate afford the chiral cyclic carbonate.

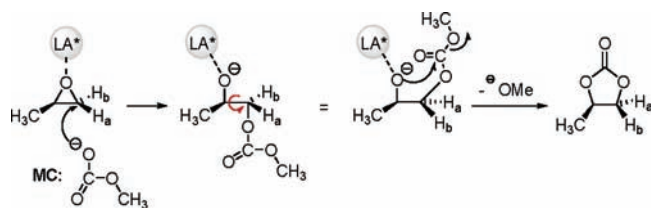
Sodium methyl carbonate (NaMC) is insoluble in most organic solvents and thus less suitable for our purposes.<sup>19</sup>

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(16) PPNF was synthesized from PPNCl by anion exchange (see the Supporting Information).

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**Scheme 2.** Proposed Mechanism for *rac*-PO/MC Coupling

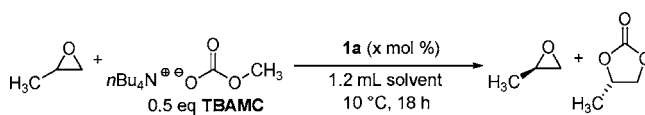
In contrast, the tetrabutylammonium salt (TBAMC) is highly soluble.<sup>20</sup> We were delighted to find that chiral Co<sup>III</sup>salen complexes (**1a** and **1f**) alone can effect the addition of TBAMC to *rac*-PO with more than 70% ee. Presumably, TBAMC takes the role of the nucleophilic cocatalyst. To the best of our knowledge, this is the first time that propylene carbonate has been produced via this route. In contrast to the “direct” CO<sub>2</sub> addition, a solvent is necessary when ionic monocarbonate is used (Table 2, entry 1). Therefore, various solvents were examined and chloroform was found as the optimal one (entries 2–5). The kinetic resolution was optimized independently in terms of catalyst loading, conversion, and selectivity. Our current best result (18% yield and 71% ee) was achieved by using 2 mol % of Co<sup>III</sup>salen(OCOCF<sub>3</sub>) as catalyst (entry 6). In the absence of a Lewis acidic catalyst, no reaction took place (entry 7). As may be expected, lowering of the catalyst loading resulted in a decrease of reaction rate, but not of product enantiopurity (entries 8 and 9). Increasing the catalyst concentration gave rise to better conversion (25%, entry 10), but at the same time to somewhat lower product ee (61%).

Although the methanolate formed as byproduct can in principle participate in epoxide opening, no such reaction was observed, as evidenced by the mass balance ( $\approx 1.0$ ). No PPC formation was detected during this reaction.

In conclusion, we have found that the combination of Co<sup>III</sup>salen(OCOCF<sub>3</sub>) and PPNF is a very active and enantioselective catalyst system for the addition of carbon dioxide to propylene oxide (40% yield and 83% ee of propylene carbonate). It is particularly noteworthy that the reaction

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**Table 2.** Enantiospecific Reaction of TBAMC with PO<sup>a</sup>

entry	solvent	catalyst loading [mol %]	yield of PC [%] <sup>b</sup>	ee of PC [%] <sup>b,c</sup>
1	none	2.0	0	–
2	MTBE	2.0	traces	n.d.
3	THF	2.0	11	72
4	CH <sub>2</sub> Cl <sub>2</sub>	2.0	18	57
5	CHCl <sub>3</sub>	2.0	16	70
6 <sup>d</sup>	CHCl <sub>3</sub>	2.0	18	71
7	CHCl <sub>3</sub>	none	0	–
8	CHCl <sub>3</sub>	0.5	9	72
9	CHCl <sub>3</sub>	1.0	11	70
10	CHCl <sub>3</sub>	3.0	25	61

<sup>a</sup> The reaction was carried out with 1 equiv of *rac*-propylene oxide and 0.5 equiv of TBAMC in 1.2 mL of solvent at 10 °C for 18 h. <sup>b</sup> Yields and ee values were determined by GC on chiral stationary phase, using diphenyl ether as internal standard. <sup>c</sup> Enantiomeric excess was in favor of the (*S*)-enantiomer of PC. Absolute configuration was determined by comparison of the retention times with enantiopure propylene carbonate. <sup>d</sup> **1f** was used as catalyst.

proceeds at atmospheric pressure and that no solvent is needed. Furthermore, propylene carbonate was prepared from propylene oxide and tetrabutylammonium methyl carbonate for the first time with good enantioselectivity (71% ee). Future work will aim at exploring the full substrate scope. Furthermore, kinetic and mechanistic studies on the Co<sup>III</sup>salen(OCOCF<sub>3</sub>)/PPNF catalyst system are currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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