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Chiral Macrocyclic Organocatalysts for Kinetic Resolution of Disubstituted Epoxides with Carbon Dioxide

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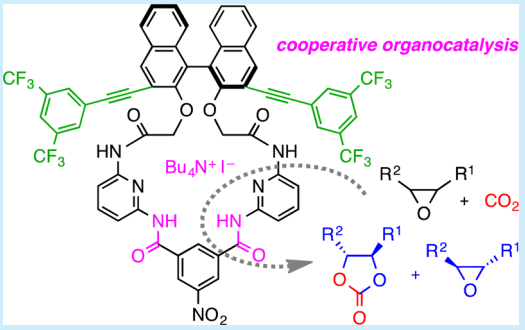
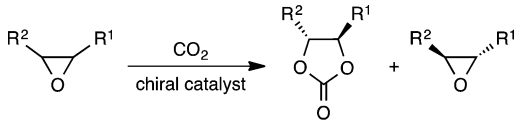
Supporting Information

ABSTRACT: Among chiral macrocycles **1** synthesized, **1m** with the 3,5-bis(trifluoromethyl)phenylethynyl group was the best organocatalyst for the enantioselective synthesis of cyclic carbonates from disubstituted or monosubstituted epoxides and CO_2. The X-ray crystal structure of **1m** revealed a well-defined chiral cavity with multiple hydrogen-bonding sites that is suitable for the enantioselective activation of epoxides. A catalytic cycle proposed was supported by DFT calculations.



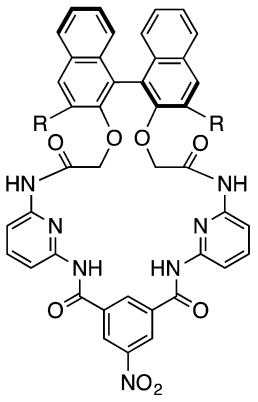
Carbon dioxide (CO_2) is a sustainable feedstock that can be used for various chemical transformations.[1] Among them, the formation of cyclic carbonates from epoxides and CO_2 is a useful reaction with high atom efficiency, where a catalyst plays a pivotal role.[2,3] Quite a number of achiral catalysts have been developed,[2] including bifunctional metalloporphyrins showing very high catalytic activity.[3] In contrast, there are only a limited number of examples of the kinetic resolution of epoxides with CO_2 (Scheme 1),[4] most of which are catalyzed by metal salen

Scheme 1. Kinetic Resolution of Epoxides with CO_2



complexes. The enantiomers of epoxides and cyclic carbonates are useful chiral building blocks.[5] Although optically active natural products such as amino acids,[6a,b] cellulose,[6c] and β-cyclodextrin[6d] can work as an organocatalyst for the production of cyclic carbonates from epoxides and CO_2, none of them is reported to show enantioselectivity. Only recently, an enantioselective organocatalytic reaction of epoxides with CO_2 has been reported (*s* value of up to 1.5).[4j] It should be noted that only *monosubstituted* epoxides have been resolved by chiral catalysts including metal complexes and organocatalysts,[4] while the kinetic resolution of *disubstituted* epoxides with CO_2 is not known at all. The enantioselective reaction of disubstituted epoxides is a challenging subject because the reactivity of epoxides remarkably decreases with an increase in the number of the substituent.[3d]

Asymmetric organocatalysis is a rapidly growing research area, where many excellent organocatalysts have been developed.[7] Despite the structural diversity of macrocycles,[8] macrocyclic organocatalysts are in the minority partly owing to laborious synthesis.[9] There is, however, much room for the development of macrocyclic organocatalysts because catalytic groups can be well arranged on a macrocyclic scaffold. We have developed a chiral macrocycle called Chirabite-AR (**1a**) (Figure 1) and its congeners.[10] They can be used for chiral discrimination in NMR, enantiomer resolution in HPLC, gas-phase recognition in ESI-FT-ICR MS, and fluorescence-detected anion sensing. Because the lower amide NH groups of **1a** act as a hydrogen-bond donor to bind a variety of guests



1a: R = H
1b: R = Ph
1c: R = C≡C–Ph
1d: R = C≡C–(4-Me-C_6H_4)
1e: R = C≡C–(4-OMe-C_6H_4)
1f: R = C≡C–(4-NMe_2-C_6H_4)
1g: R = C≡C–(4-*t*-Bu-C_6H_4)
1h: R = C≡C–(4-Cl-C_6H_4)
1i: R = C≡C–(4-NO_2-C_6H_4)
1j: R = C≡C–(4-CN-C_6H_4)
1k: R = C≡C–(4-CF_3-C_6H_4)
1l: R = C≡C–(3,5-$(OMe)_2$-C_6H_3)
1m: R = C≡C–(3,5-$(CF_3)_2$-C_6H_3)
1n: R = C≡C–(3,5-(*t*-Bu)$_2$-C_6H_3)
1o: R = C≡C–(3,4,5-F_3-C_6H_2)
1p: R = C≡C–(2,4,6-Me_3-C_6H_2)
1q: R = C≡C–C_6F_5
2: R = I

Figure 1. Structures of macrocycles **1** and **2**.

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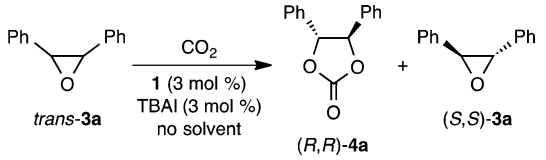
including epoxides,[10a,b] we envisioned that they might work as a Brønsted acid catalyst to accelerate an organic reaction. Here, we synthesized and used a series of **1** as a chiral organocatalyst for the kinetic resolution of epoxides with CO_2 (Scheme 1). As a result, they exhibited catalytic activity and enantioselectivity at atmospheric CO_2 pressure (balloon) under solvent-free conditions. Even disubstituted epoxides could be transformed enantioselectively. To the best of our knowledge, this is the first example of the kinetic resolution of disubstituted epoxides with CO_2.

The 3,3′-positions of the binaphthyl moiety of **1** are the "hot spots" to adjust the size and shape of the chiral cavity (Figure 1). The Suzuki–Miyaura and Sonogashira reactions successfully introduced the aryl and arylethynyl substituents, respectively, into the hot spots of diiodide **2** in good to high yields. A variety of **1** could be prepared rapidly from a single precursor **2**. The kinetic resolution of *trans*-stilbene oxide (**3a**) with catalyst **1** (3 mol %) and co-catalyst (3 mol %) was performed at 75 °C for 72 h at atmospheric CO_2 pressure (balloon) under solvent-free conditions. After separation of **3a** and **4a** by silica gel column chromatography, the enantiomeric purities (% ee) were determined by chiral HPLC, and the degree of enantioselectivity was evaluated by the *s* value.[11] The results are summarized in Table 1.

When both catalyst **1a** and co-catalyst, tetrabutylammonium iodide (TBAI), were used together, the reaction proceeded enantioselectively (*s* = 1.7) (entry 1). In contrast, no reaction proceeded in the presence of either **1a** alone or TBAI alone (not shown). It is likely that the lower amide NH groups of **1a** and the I^- anion of TBAI act cooperatively as a Brønsted acid and a nucleophile, respectively. When either tetrabutylammonium bromide or tetrabutylammonium chloride was used as a co-catalyst, the reaction mixture was solidified, leading to a very slow reaction (not shown). Macrocycles **1** were screened using the best co-catalyst, TBAI. Catalyst **1b** with the phenyl group resulted in a much lower conversion (6%) with comparable enantioselectivity (*s* = 1.5) (entry 2), while **1c** with the phenylethynyl group yielded a comparable conversion (17%) with improved enantioselectivity (*s* = 2.7) (entry 3). In view of these results, we modified the arylethynyl group. Table 1 indicates that the electronic effect is more important for catalytic activity and enantioselectivity than the steric effect. For example, **1d–g** with the electron-donating group gave modest *s* values of 2.4–3.4 (entries 4–7), whereas the electron-withdrawing group had a better influence on catalytic activity and enantioselectivity (*s* = 4.7–6.5) (entries 8–11). A clearer difference can be seen for the catalysts with two substituents in the arylethynyl group (entries 12–14). Compound **1m** with the 3,5-bis(trifluoromethyl)phenylethynyl group achieved a high conversion (41%) with the highest enantioselectivity (*s* = 10) (entry 13), whereas **1l** and **1n** with two electron-donating groups at the 3,5-positions of the phenylethynyl group exhibited lower conversions (14–29%) with poor enantioselectivity (*s* = 2.7–3.8) (entries 12, 14). Comparison of **1o** and **1q** reveals that the substituents at the 2,6-positions of the phenylethynyl group hinder the reaction (entries 15, 17). Indeed, **1p** with the mesitylethynyl group showed poor performance (entry 16).

The kinetic resolution of disubstituted epoxides **3b–j** was conducted at 50 °C for 120 h with the best catalyst **1m** (3 mol %) and TBAI (3 mol %) (Table 2). The epoxides with the electron-donating or electron-withdrawing group were resolved with good *s* values of up to 13, and bulky epoxide **3j** with the 1-naphthyl group was also converted into the corresponding cyclic carbonate **4j** with a comparable *s* value. Table 2 indicates

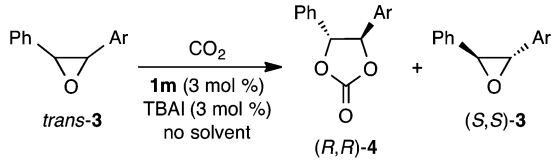
Table 1. Screening of Catalysts[a]



entry	1	c[b] (%)	% yield[c] (% ee)[d] (R,R)-4a	(S,S)-3a	s value[e]
1	**1a**	20	18 (24)	61 (6.1)	1.7
2	**1b**	6	10 (20)	77 (1.3)	1.5
3	**1c**	17	14 (42)	69 (8.7)	2.7
4	**1d**	19	19 (42)	75 (10)	2.7
5	**1e**	8	11 (53)	66 (4.8)	3.4
6	**1f**	14	14 (38)	65 (6.2)	2.4
7	**1g**	24	21 (47)	59 (15)	3.2
8	**1h**	32	32 (57)	57 (27)	4.7
9	**1i**	34	30 (65)	54 (34)	6.5
10	**1j**	36	35 (60)	39 (34)	5.5
11	**1k**	41	33 (57)	51 (40)	5.3
12	**1l**	14	14 (43)	77 (6.9)	2.7
13	**1m**	41	41 (72)	51 (50)	10
14	**1n**	29	17 (51)	64 (21)	3.8
15	**1o**	38	35 (66)	55 (40)	7.2
16	**1p**	16	12 (19)	70 (3.7)	1.5
17	**1q**	24	21 (52)	64 (16)	3.7

[a]Conditions: epoxide **3a** (1.0 mmol), cat. **1** (3 mol %), TBAI (3 mol %), CO_2 (1 atm, balloon), 75 °C, 72 h. [b]Conversion calculated from *c* = ee(**3a**)/(ee(**3a**) + ee(**4a**)). [c]Isolated yield. [d]Determined by HPLC analysis. [e]Calculated from $s = \ln[1 - c(1 + ee(\mathbf{4a}))]/\ln[1 - c(1 - ee(\mathbf{4a}))]$.

Table 2. Kinetic Resolution of Internal Epoxides 3[a]



b: Ar = 2-Cl-C_6H_4 **c**: Ar = 3-Cl-C_6H_4 **d**: Ar = 3-Br-C_6H_4 **e**: Ar = 2-Me-C_6H_4 **f**: Ar = 3-Me-C_6H_4 **g**: Ar = 4-Me-C_6H_4 **h**: Ar = 2-OMe-C_6H_4 **i**: Ar = 3-OMe-C_6H_4 **j**: Ar = 1-naphthyl

entry	3	c[b] (%)	% yield[c] (% ee)[d] (R,R)-4	(S,S)-3	s value[e]
1	**3b**	21	20 (83)	78 (22)	13
2	**3c**	37	34 (77)	61 (45)	12
3	**3d**	32	31 (75)	67 (35)	9.8
4	**3e**	35	30 (74)	61 (39)	9.8
5	**3f**	25	24 (82)	72 (28)	13
6[f]	**3g**	51	48 (71)	46 (73)	13
7	**3h**	34	31 (74)	62 (38)	9.7
8	**3i**	27	26 (78)	68 (29)	11
9	**3j**	21	20 (77)	79 (21)	9.4

[a]Conditions: epoxide **3** (1.0 mmol), cat. **1m** (3 mol %), TBAI (3 mol %), CO_2 (1 atm, balloon), 50 °C, 120 h. [b]Conversion calculated from *c* = ee(**3**)/(ee(**3**) + ee(**4**)). [c]Isolated yield. [d]Determined by HPLC analysis. [e]Calculated from $s = \ln[1 - c(1 + ee(\mathbf{4}))]/\ln[1 - c(1 - ee(\mathbf{4}))]$. [f]At 60 °C, 78 h.

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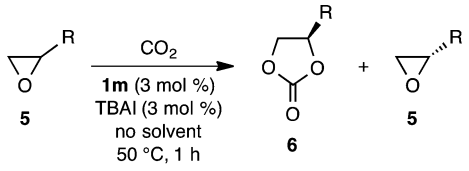
that **1m** is tolerant of the electronegativity, bulkiness, and position of the substituent in **3**. The substrate scope of **1m** for monosubstituted epoxides **5** was also investigated under the same conditions (Scheme 2). Because of 2 orders of magnitude higher reactivity of **5** relative to **3**, the reactions were stopped in only 1 or 0.5 h in most cases. The *s* values for **5** were 2.5−4.3.

Scheme 2. Kinetic Resolution of Terminal Epoxides 5



a: R = CH_2OPh — *s* = 4.1 (*c* = 54%)
b: R = CH_2O-(4-Cl-C_6H_4) — *s* = 4.3 (*c* = 33%)
c: R = CH_2O-(4-Br-C_6H_4) — *s* = 2.5 (*c* = 35%, 60 °C)
d: R = CH_2O-(4-OMe-C_6H_4) — *s* = 4.0 (*c* = 26%)
e: R = CH_2O-(2-OMe-C_6H_4) — *s* = 3.8 (*c* = 44%)
f: R = CH_2OBz — *s* = 2.5 (*c* = 51%)
g: R = CH_2NPh_2 — *s* = 3.4 (*c* = 52%, 5 h)
h: R = Ph — *s* = 3.3 (*c* = 42%, 0.5 h)
i: R = 4-Cl-C_6H_4 — *s* = 3.3 (*c* = 32%, 0.5 h)

The X-ray crystal structure indicates that **1m** has a well-defined chiral cavity (Figure 2). The cavity is not occluded by

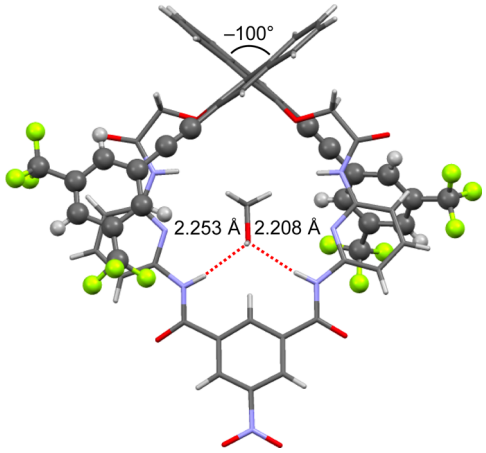
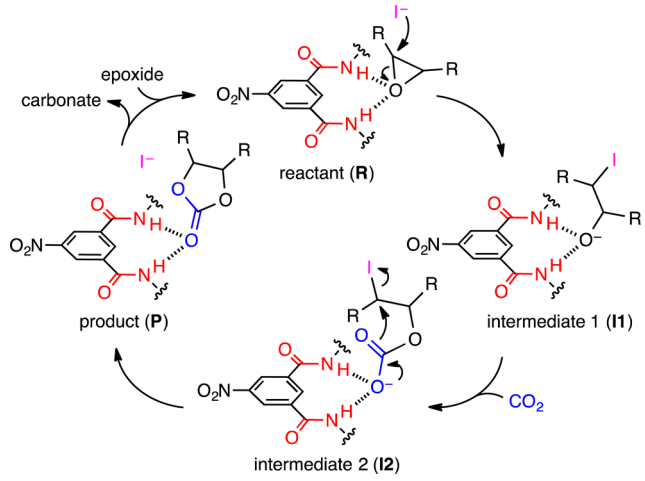


Figure 2. X-ray crystal structure of **1m** where the 3,3′-substituents are highlighted by a ball-and-stick representation. A MeOH molecule in the binding cavity is shown.

the 3,5-bis(trifluoromethyl)phenylethynyl group, and the lower amide NH groups of **1m** are hydrogen bonded with the O atom of a MeOH molecule with distances of 2.208 and 2.253 Å. ^{1}H NMR titrations exhibited a large downfield shift ($\Delta\delta$ = 0.83 ppm) of the amide NH signal of **1m** upon addition of styrene oxide (*R*)-**5h** or (*S*)-**5h**, which strongly suggests the activation of the epoxide by hydrogen bonding. The binding constants (K_a) of **1m** for (*R*)-**5h** and (*S*)-**5h** in $CDCl_3$ at 21 °C were determined to be 11.3 and 4.8 M^{-1}, respectively. We suppose that this chiral recognition leads to the differential ring-opening transition state in the kinetic resolution. NMR titrations also suggested the formation of a supramolecular assembly of **1m** and TBAI (K_a = 3.5 M^{-1} in $CDCl_3$ at 21 °C).

Scheme 3 shows a plausible catalytic cycle. The epoxide is hydrogen-bonded with the amide NH groups of the catalyst in the reactant complex (**R**), and the activated epoxide is ring-opened by the nucleophilic attack of the I^- anion to give

Scheme 3. Proposed Catalytic Cycle



intermediate 1 (**I1**). The subsequent CO_2 addition to the alkoxide intermediate generates a linear carbonate anion (**I2**), which is then cyclized by the intramolecular S_N2 reaction to give cyclic carbonate (**P**). This catalytic cycle was supported by DFT calculations on a model substrate, ethylene oxide (Supporting Information).[12] The transition-state structure for the initial ring opening, which is the rate-determining step, is shown in Figure 3. The breaking C−O bond (1.98 Å) and the

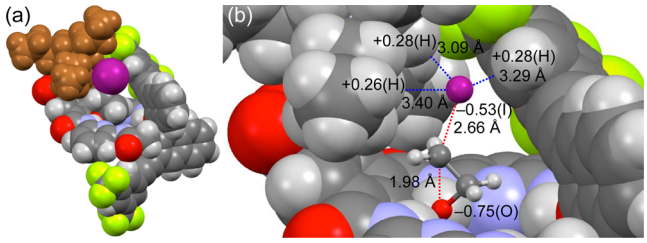


Figure 3. Transition-state structure for the initial ring opening step in the **1m**/TBAI-catalyzed reaction of ethylene oxide with CO_2. DFT calculations were performed at the B3LYP/6-31G(d) level for the H, C, N, O, and F atoms and at the B3LYP/LanL2DZ level for the I atom. (a) Space-filling model, where the tetrabutylammonium cation is shown in brown to clarify the supramolecular contacts. (b) Close-up view with bond lengths and atomic charges. The I atom and ethylene oxide are shown in ball-and-stick representation.

forming C−I bond (2.66 Å) are almost the same lengths as those (2.01 and 2.64 Å, respectively) calculated for a bifunctional Mg porphyrin catalyst with a quaternary ammonium iodide.[3b] The leaving O atom of the epoxide is hydrogen bonded with the two amide H atoms of **1m**, and both of the O···H distances are short (1.778 and 1.778 Å),[13] which suggests strong hydrogen bonding. This is due to the negative charge (natural atomic charge of −0.75) on the leaving O atom that is induced by the nucleophilic attack of I^-. The I^- anion is electrostatically stabilized by the H atom adjacent to the trifluoromethyl group of **1m** as well as the tetrabutylammonium cation with the positive charges on the H atoms, but not on the central N atom.[3b] The tetrabutylammonium cation also makes contacts with the F atom of the trifluoromethyl group and the O atoms of the nitro group of **1m** via hydrogen bonds, forming a supramolecular assembly. The relatively small energy barrier (16.7 kcal/mol) is consistent with the high catalytic activity of **1m**. All the subsequent anionic intermediates and transition

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states are stabilized by double hydrogen bonding in the cavity (Supporting Information).

In summary, the enantioselective reaction of epoxides with CO_2 was achieved by the synergistic action of chiral macrocyclic organocatalyst **1m** and TBAI. **1m** has a chiral cavity with multiple hydrogen-bonding sites that is suitable for the enantioselective activation of epoxides. To the best of our knowledge, this is the first example of the enantioselective synthesis of cyclic carbonates from disubstituted epoxides and CO_2. Further work is underway to explore the scope and limitations of the chiral macrocyclic organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01838.

Synthesis, NMR spectra, determination of binding constants, and computational details (PDF)
Crystallographic data for **1m** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The corresponding O···H distances in reactant complex **R** (Scheme 3) are 1.959 and 2.005 Å.

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