Hemisquaramide Tweezers as Organocatalysts: Synthesis of Cyclic Carbonates from Epoxides and CO₂

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(5) Supporting Information

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ABSTRACT: Hemisquaramide tweezers, a new family of H-bond donor organocatalysts, are reported. The catalysts could be synthesized within two steps. Among them, H₈-binaphthyl-linked hemisquaramide 7 markedly accelerated the synthesis of cyclic carbonates from epoxides and CO_2 . The reactions proceeded well under mild and solvent-free conditions. Kinetic resolution was also achieved at -20 °C (s = 3.0). The adjustable bite angle and orientation of the two NH groups of the catalysts are important for the high activity.



ydrogen-bond organocatalysis is widely used in organic \mathbf{L} synthesis.¹ Squaramide² and thiourea³ structures with two hydrogen-bond-donating NH groups were recently adopted as catalysts in various reactions. Some of these catalysts were used for carbon dioxide (CO₂) fixation.^{2a,3e} CO₂ is a useful C1-building block and is expected to provide an alternative to petroleum-based chemicals. The development of CO₂ fixation catalysts presents a major challenge in chemistry.⁴ The synthesis of cyclic carbonates 2 from CO₂ and epoxides 1 has received much attention because of the high atom economy, and cyclic carbonates are useful as raw materials for polycarbonates and polyurethanes and as intermediates for various important materials (Scheme 1).5 Various organocatalysts have been developed, including squaramides,^{2a} thioureas,^{3e} aliphatic alcohols,⁶ aromatic alcohols,⁷ and carboxylic acids.8 We have recently reported macrocyclic amides⁹ and calixpyrroles¹⁰ as organocatalysts. D'Elia and coworkers have recently reported that phenol acts as a catalyst

Scheme 1. Synthesis of Cyclic Carbonates from Epoxides and CO_2



under mild conditions.^{6d} Organocatalysts, however, occasionally require high CO_2 pressure and/or high-temperature conditions. A new family of organocatalysts capable of acting under mild conditions is required, and its development presents significant challenges.

In the present work, we first designed and synthesized binaphthyl-linked squaramides 3 and 4 with four NH groups, on the grounds that a greater number of NH groups would provide better activity (Figure 1). We also prepared binaphthyl-linked hemisquaramide 6 as a synthetic intermediate of 3 and biphenyl analogue 5 and H₈-binaphthyl analogue 7 as control catalysts. To our surprise, hemisquaramides 5-7, especially 7, exhibited much higher catalytic activities than those of the related catalysts 3-4 (Figure 1) and thiourea or selenourea organocatalysts 12-16 (Scheme S1), although each of the hemisquaramide tweezer catalysts has only two NH groups. Herein, we report the synthesis, catalytic activity toward CO₂ fixation, and a plausible catalytic mechanism. This is the first example of hemisquaramide tweezers acting as an organocatalyst.¹¹

Hemisquaramides 5–7 were synthesized in only one or two steps (Scheme 2). They were prepared by the $Zn(OTf)_2$ catalyzed reaction¹² of diaminobiaryls (2,2'-diaminobiphenyl (8), BINAM (9), or H₈-BINAM (10)) with an excess amount of diethyl squarate (11). Compounds 8, 9, and 11 are

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Figure 1. Structures of squaramides **3** and **4** and hemisquaramides **5**–7.



commercially available, and 10 could be easily obtained by reducing 9.¹³ Squaramide 3 was synthesized from 6 and 3,5-bis(trifluoromethyl)aniline, and 4 was prepared from 2,2'-bis(aminomethyl)-1,1'-binaphthyl¹⁴ and 11 (Scheme S2).

The catalytic activities of 3-7 were examined for styrene oxide (1a) in the presence of 5.0 mol % catalyst and nucleophilic cocatalyst, tetrabutylammonium iodide (TBAI), a CO₂ atmosphere (1 atm, balloon), and no solvent at 30 °C for 24 h (Table 1, entries 1-5). Hemisquaramides 5-7, especially 7, gave 2a in high yields (60-99%, entries 3-5). The high activity of 5-7, which were originally regarded as simple synthetic intermediates or control catalysts for squaramides, was totally unexpected. The activities of several related thioureas¹⁵ and selenoureas¹⁶ were also explored, but the yields were much lower than that of 7 (Scheme S1). The reaction using 7 alone or TBAI alone did not progress significantly (entries 8 and 9), suggesting that 7 and TBAI acted cooperatively. The reactions conducted with tetrabutylammonium bromide (TBAB) or tetrabutylammonium chloride (TBAC) instead of TBAI exhibited lower yields (30-84%, entries 6 and 7). The smaller halides may be entrapped by forming hydrogen bonds with the two NH groups of the catalyst, which reduces the nucleophilicity of the halide anion.¹⁷ In fact, DFT calculations of the complexation energies for 7, after applying the BSSE correction, were -23.9 kcal/mol for TBAC, -19.5 kcal/mol for TBAB, and -15.0 kcal/mol for TBAI (Figure S1).¹⁸ Even at room temperature (ca. 20 °C), 7 maintained a high activity (>99%, entry 10). The catalyst loading could be decreased to 2.0 mol %, which gave over a 90% yield of 2a (entry 11). The catalyst 7 is an unprecedented hemisquaramide tweezer catalyst showing a high organocatalytic activity.



| Ph O 1a (1.0 mmol) | CO ₂ (cat. (5 co-cat. (no s 30 ° | balloon) .0 mol %) 5.0 mol %) solvent C, 24 h | Ph O O 2a |
|-----------------------------|---|---|------------------------|
| entry | cat. | cocat. | yield (%) ^a |
| 1 (. | R)- 3 | TBAI | 68 |
| 2 (R | ,R)- 4 | TBAI | 22 |
| 3 | 5 | TBAI | 60 |
| 4 (. | R)- 6 | TBAI | 94 |
| 5 (. | R)-7 | TBAI | >99 |
| 6 (. | R)-7 | TBAB | 84 |
| 7 (. | R)-7 | TBAC | 30 |
| 8 (. | R)-7 | - | 0 |
| 9 | - | TBAI | 7 |
| 10 ^b (1 | R)-7 | TBAI | >99 |
| 11 ^c (. | R)-7 | TBAI | 92 |

^{*a*}Determined by ¹H NMR using mesitylene as an internal standard. ^{*b*}Room temperature (ca. 20 °C). ^{*c*}(R)-7 (2.0 mol %) was used.

Next, the reactions of several epoxides **1b**–i were conducted with the best catalyst 7 and TBAI at 30 °C or a little higher temperature than the melting point of substrates and/or products (Scheme 3). Styrene oxides, alkene oxides, glycidyl

Scheme 3. Substrate Scope^a

| R | CO ₂ (ball (<i>R</i>)- 7 (5.0 r TBAI (5.0 r | oon) nol %) nol %) | R | |
|---|---|--|--------------------------|--|
| \checkmark | no solve | ent | | |
| 1b–i | 30 °C, 2 | 4 h | U O | |
| (1.0 mmol) | | | 2b—i | |
| b : R = 4-CI-C ₆ | H ₄ (75%) | f : R = CH | l ₂ OEt (99%) | |
| c : $R = 4 - NO_2 - C_6 H_4 (81\%)^b$ | | g : R = CH ₂ CI (81%) | | |
| d : R = n-Bu (>99%) | | h : R = CH ₂ NPh ₂ (97%) ^b | | |
| e : R = n-C ₁₂ H ₂ | ₂₅ (95%) ^b | i: R = CH | ₂ OPh (75%) | |
| solated vield. $^{b}80^{\circ}$ | C. | | | |

ethers, and other epoxides were converted to the corresponding cyclic carbonates (75–99%), indicating that the catalyst possessed a broad substrate scope.

The natural population analysis (NPA) reveals that the charges of NH protons of 5-7 (0.359-0.361) are less positive than those of 3-4 (0.402-0.431) and thioureas (Table S1). Therefore, the high activities of the hemisquaramides could not be explained by the acidity (and number) of the NH groups. The activity arose from the distance and angle between the two NH groups, which adapted to the substrate by rotation of the biaryl axis like tweezers. Moreover, the substrate could approach the NH groups without restriction due to the acyclic structures of 5-7 without bulky substituents around the catalytic sites. The activity of 5-7 may be modulated by the dihedral angle of the biaryl axis. The biphenyl of 5 can freely rotate, whereas the binaphthyl of 6 is somewhat restricted, and the H₈-binaphthyl of 7 is highly restricted due to the bulky cyclohexene rings.¹⁹ DFT calculations suggested that the angular range (within 2.7 kcal/mol from the most stable conformation) were 45-135° for 5, 60-120° for 6, and 70 115° for 7 (Figure S2).²⁰ The appropriately preorganized catalyst 7 can bind to the substrate with the least entropy loss.

A plausible catalytic cycle for a model reaction, the 7/TBAIcatalyzed reaction of ethylene oxide (EO) with CO_2 , is shown in Scheme 4, which was supported by DFT calculations.^{9,10,21}





^aTBA cation omitted for clarity.

The H₈-binaphthyl has a tweezers shape. Initially, 7 and EO form the reactant complex **R** via two hydrogen bonds between NH groups of 7 and the oxygen atom of EO, and the epoxide is activated simultaneously. Next, the epoxide is attacked and ring-opened by a nucleophile, the I⁻ anion, to form a linear alkoxide, intermediate **I1**. Insertion of a CO₂ molecule gives a carbonate anion as intermediate **I2**. Finally, the intramolecular S_N^2 reaction affords the ring-closed product **P**. ¹H NMR titrations indicated that the NH group of 7 was downfield shifted upon addition of **1a** in CDCl₃ at 20 °C, which suggests activation of the epoxide by hydrogen bonding (Figure S5).

The energy profile for the reaction and the optimized transition-state structures are shown in Figure 2. The ratedetermining step is the ring-opening step via I1_TS with a ΔG^{\ddagger} of 24.0 kcal/mol. Both I1 TS and I2 TS are stabilized by two NH-O hydrogen bonds (1.69-1.82 Å). Interestingly, P TS included only one hydrogen bond between the NH hydrogen and the carbonate oxygen with an NH-O distance of 1.83 Å. One of the two hydrogen bonds is cleaved by the rotation of the N-aryl bond, which enhances the nucleophilicity of the carbonate anion. Throughout the reaction, the dihedral angle of the H₈-binaphthyl is changed in a range of $84.1-93.2^{\circ}$ (Figure S4). The catalyst can provide the optimum NH scaffold for stabilizing the substrate, the reaction intermediates, and the transition states by the rotation of the N-aryl bond and the biaryl axis, which is an ability specific to the hemisquaramide tweezers.

Finally, 1a was kinetically resolved by either (*R*)-6 or (*R*)-7 (Table 2). Interestingly, at 30 °C, (*R*)-6 and (*R*)-7 gave (*S*)-2a preferentially with *s* values (k_s/k_R) of 1.7 and 1.8, respectively. At -20 °C, the *s* values increased to 2.8 for (*R*)-6 and 3.0 for



Figure 2. (a) Theoretical Gibbs free energy profile for the 7/TBAI catalyzed reaction of ethylene oxide with CO₂. (b) Transition-state structures. DFT calculations were performed at the B3LYP/6-31G(d) level for the H, C, N, and O atoms and at the B3LYP/LanL2DZ level for the I atom. Distances are shown in Å.

| Table 2. | Kinetic | Resolution | of | Styrene | Oxide (| (1a) |) |
|----------|---------|------------|----|---------|---------|------|---|
|----------|---------|------------|----|---------|---------|------|---|

| | Ph c TI TI | CO ₂ (balloon) cat. (5.0 mol%) TBAI (5.0 mol%) no solvent | | → 0 (S)-2 | Ph 0 (<i>R</i>)-1a | |
|---------------|------------------|---|--------------------|--------------------------------|-------------------------------|----------------------|
| cat. | temp. (°C) | time (h) | c ^a (%) | % yield ^b (S)-2a | (% ee) ^c (R)-1a | s value ^d |
| (R)- 6 | 30 | 3 | 38 | 29 (21) | 58 (13) | 1.7 |
| (R)- 6 | -20 | 72 | 6 | 12 (46) | 52 (3) | 2.8 |
| (R)-7 | 30 | 3 | 56 | 57 (19) | 31 (24) | 1.8 |
| (R)-7 | -20 | 72 | 10 | 17 (47) | 56 (5) | 3.0 |
| | | | | | | |

^{*a*}Conversion calculated from c = ee(2a)/(ee(2a) + ee(1a)). ^{*b*}Isolated yield. ^{*c*}Determined by HPLC and GC analyses. ^{*d*}Calculated from s = ln[1 - c(1 + ee(2a))]/ln[1 - c(1-ee(2a))].

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(*R*)-7. The kinetic resolution of epoxides using organocatalysts is very rare, 9,22 and the *s* values of the hemisquaramides are high for organocatalysts. In contrast, (*R*)-3 and (*R*,*R*)-4 exhibited little or no enantioselectivity (not shown).

In summary, we developed a new family of hemisquaramide tweezers 5–7 as organocatalysts, which were synthesized within two steps. Among them, 7 with the H_8 -binaphthyl moiety exhibited the highest catalytic activity toward CO₂ fixation. Under mild and solvent-free conditions, the reaction proceeded well. DFT calculations indicated that the two adjustable NH groups of the catalyst were important for this activity. The kinetic resolution also proceeded with an *s* value of up to 3.0. We are currently investigating the other utility of this type of organocatalyst, expecting that hemisquaramide tweezers have a great potential in various organocatalytic reactions.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00117.

Synthesis, spectra, catalytic activities, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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