Stereocontrolled, Divergent, Al(lll)-Catalyzed Coupling of Chiral N-Aryl Epoxy Amines and CO_2

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S *Supporting Information*

ABSTRACT: A divergent coupling reaction was achieved between N-aryl epoxy amines and CO_2. By using two different cocatalysts, tetrabutylammonium iodide (TBAI) or 4-dimethylaminopyridine (DMAP) together with an Al(III) Lewis acid, cyclic carbonates or oxazolidinones were selectively produced through two distinct reaction pathways, respectively. The proposed reaction mechanism was supported by the stereochemical determination of the products. A gram-scale production of Linezolid was successfully achieved.
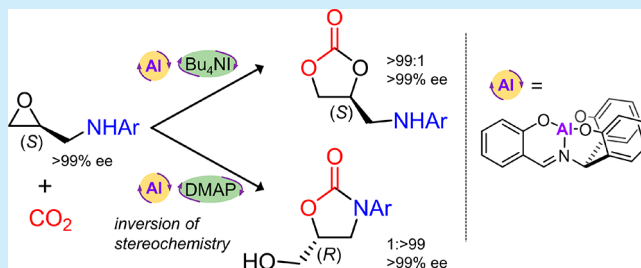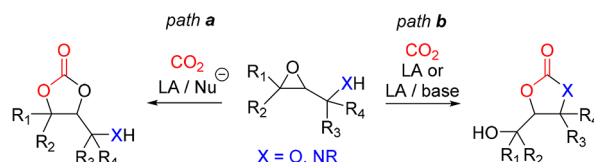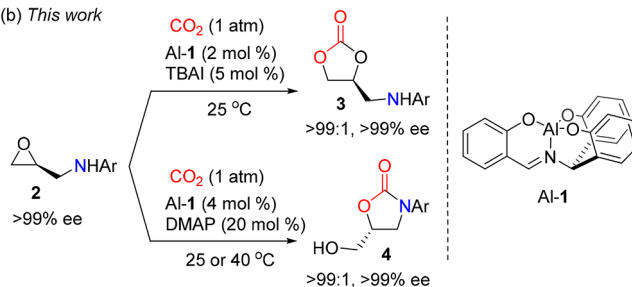
The conversion of carbon dioxide (CO_2), an abundant and renewable C_1 source, to commodity chemicals has received much recent attention as a sustainable solution for CO_2 recycling and reduction.[1] In particular, coupling of CO_2 and epoxides to synthesize polycarbonates[2] or cyclic carbonates[3] is one of the most promising industrial processes because these products are valuable materials, such as functional polymers, monomers for polycarbonate production, electrolytes, and polar solvents. The reported efficient catalysts mainly include metal catalysts and organocatalysts.[2,3] In the cases of metal catalysts, the choice of the metal center and the ligand design are reported to be crucial to control the reactivity and selectivity of the metal catalysts.[4] In general, reaction conditions for the formation of cyclic carbonates or polycarbonates, both a Lewis acid catalyst and nucleophilic cocatalyst are used (Scheme 1a, path a). This dual catalytic system is essential to activate the substrate epoxide via Lewis acid activation and epoxide ring opening.[5] In addition, Kleij and co-workers have recently reported a new catalytic combination of a Lewis acid and Brønsted base (Scheme 1a, path b).[6] The proposed reaction mechanism involves the formation of a carbonic acid monoester followed by intramolecular nucleophilic attack. With these two distinct mechanistic systems, they demonstrated product diversity by site-selective coupling reactions between CO_2 and epoxy alcohols or amines.

Inspired by this seminal work, we became interested in determining the stereochemistry of two isomers synthesized by two catalytic systems. The stereochemical determination of the divergent coupling reaction is important because it can support the proposed reaction mechanism. Moreover, given the availability of chiral epoxides prepared from asymmetric epoxidation or chiral resolution,[7] it is also important to synthesize chiral products cyclic carbonates, or oxazolidinones, in a stereocontrolled enantiopure form because these products can be used for preparing bioactive compounds. In this work, we report a divergent conversion of N-aryl epoxy amines (2) to

Scheme 1. (a) Concept of Divergent Coupling of CO_2 and Epoxides and (b) Stereocontrolled Reaction of Epoxy Amines

cyclic carbonates (3) or oxazolidinones (4) with high selectivity (>99:1) at room temperature and atmospheric pressure of CO_2 catalyzed by Al-1 (Scheme 1b). Moreover, the reaction mechanism involving intermolecular or intramolecular substitution reactions was clearly verified by confirming the stereospecific nature of the reactions. A gram-scale production of Linezolid,[8] a chiral oxazolidinone antibiotic drug, was also demonstrated.

In the cases of epoxy alcohols, a highly selective (>99%) conversion to cyclic carbonates was reported.[6,9] However, N-aryl epoxy amine **2a** gave a somewhat reduced selectivity

(81%) for the formation of cyclic carbonates **3a** or oxazolidinone **4a** in the previous study.[6] To improve the selectivity, we began to optimize the selective coupling of *N*-aryl epoxy amine **2a** and CO_2 to synthesize cyclic carbonate **3a** or oxazolidinone **4a** (Table 1). We used our new N_1O_3 ligand

Table 1. Optimization of the Divergent Coupling between Epoxy Amine 2a and CO₂ To Prepare Cyclic Carbonate 3a or Oxazolidinone 4a[a]
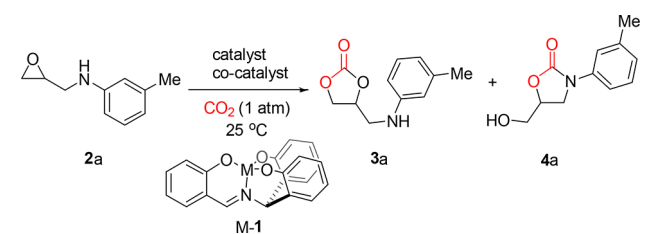
entry	catalyst (mol %)	cocatalyst (mol %)	solvent	time (h)	conv (%)[b]	3a:4a[b]
1	Al-**1** (2)	TBAB (2)	MEK	6	25	>99:1
2	Al-**1** (2)	TBAI (2)	MEK	6	32	>99:1
3	Al-**1** (2)	TBAI (2)	MEK	30	87	16:1
4	Al-**1** (2)	TBAI (5)	MEK	30	>99 (97)	>99:1
5	Fe-**1** (2)	TBAI (2)	MEK	6	29	>99:1
6	Fe-**1** (2)	TBAI (5)	MEK	30	>99	18:1
7	–	TBAI (2)	MEK	6	0	–
8	Al-**1** (2)	DIPEA (5)	CH₂Cl₂	6	0	–
9	Al-**1** (2)	KOAc (5)	CH₂Cl₂	6	0	–
10	Al-**1** (2)	K₂CO₃ (5)	CH₂Cl₂	6	0	–
11	Al-**1** (2)	DMAP (5)	CH₂Cl₂	6	14	<1:99
12	Al-**1** (4)	DMAP (20)	CH₂Cl₂	24	82 (79)	<1:99
13	–	DMAP (5)	CH₂Cl₂	6	0	–

[a]Reaction condition: **2a** (0.5 mmol), CO_2 (1 atm), catalyst (2 or 4 mol %), cocatalyst (2–20 mol %), solvent (0.5 mL), 25 °C, 6–30 h. [b]The conversions and product ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures; 1,3,5-trimethoxybenzene was used as the internal standard, and the isolated yields are shown in the parentheses.
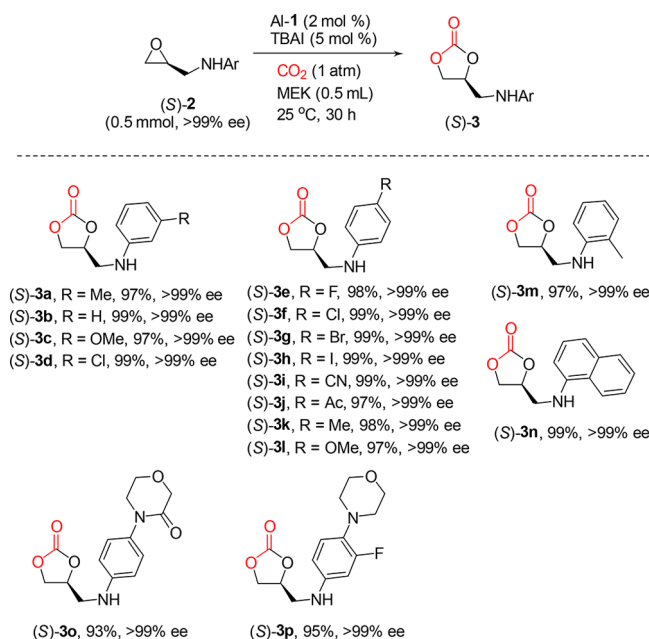
1 to prepare the Lewis acid catalyst. We have reported that the Fe-**1** complex efficiently catalyzes the selective conversion of internal epoxides with CO_2 to cyclic carbonates.[10] When the Al-**1** complex (2 mol %) and tetrabutylammonium bromide (TBAB, 2 mol %) were used at 25 °C in methyl ethyl ketone (MEK), the epoxy amine **2a** was reacted with CO_2 to form cyclic carbonate **3a** at 25% conversion after 6 h with an excellent selectivity of >99:1 (Table 1, entry 1). In the reaction mixtures, the isomer **4a** was not detected to any observable extent in the ^{1}H NMR spectra. It was also found that tetrabutylammonium iodide (TBAI) showed better reactivity than TBAB (Table 1, entry 2). While equimolecular (2 mol %) Al-**1** and TBAI showed a somewhat reduced reactivity (87%) and selectivity (16:1) after the reaction mixture was stirred for 30 h, an increased amount of TBAI (5 mol %) improved both the reactivity (>99%) and selectivity (>99:1) (Table 1, entries 3 and 4). The Fe-**1** complex was found to be less reactive and selective compared with the Al-**1** complex (Table 1, entries 5 and 6). The reaction did not proceed at all without Al-**1** (Table 1, entry 7).

As a divergent synthetic approach, Lewis acid and base catalyzed coupling reactions of epoxy amine **2a** and CO_2 were then investigated. When Al-**1** (2 mol %) was combined with

bases (5 mol %), such as diisopropyl ethylamine (DIPEA), KOAc, and K_2CO_3 in CH_2Cl_2 at 25 °C, the coupling reaction of **2a** and CO_2 gave no product (Table 1, entries 8–10). Remarkably, 4-dimethylaminopyridine (DMAP) was found to be an effective cocatalyst to provide the oxazolidinone **4a** selectively. An increased amount (20 mol %) of DMAP and a reaction time of 24 h were optimal to provide oxazolidinone **4a** with high yields (79%) and selectivity (>99:1) (Table 1, entries 11 and 12). In the absence of Al-**1**, the reaction did not proceed. Thus, we successfully optimized the coupling reaction between epoxy amine **2a** and CO_2 to cyclic carbonate **3a** by using a Lewis acid catalyst (Al-**1**) and a nucleophilic cocatalyst (TBAI), as well as the same coupling reaction to oxazolidinone **4a** by using a Lewis acid catalyst (Al-**1**) and a base (DMAP).

With the optimized reaction conditions, we then explored the stereochemistry for the divergent reactions of chiral epoxy amines. Several (*S*)-epoxy amines (**2a**–**p**) in enantiopure form were prepared by the reaction of anilines and enantiopure epichlorohydrin resolved by the Co(III)-salen catalyzed kinetic resolution.[11] When Al-**1** (2 mol %) and TBAI (5 mol %) were mixed with (*S*)-epoxy amines (**2a**–**p**) at 25 °C in MEK under atmospheric pressure of CO_2, all reactions proceeded well to provide cyclic carbonates in excellent isolated yields (Scheme 2). *N*-Aryl substituents with electron-donating or electron-
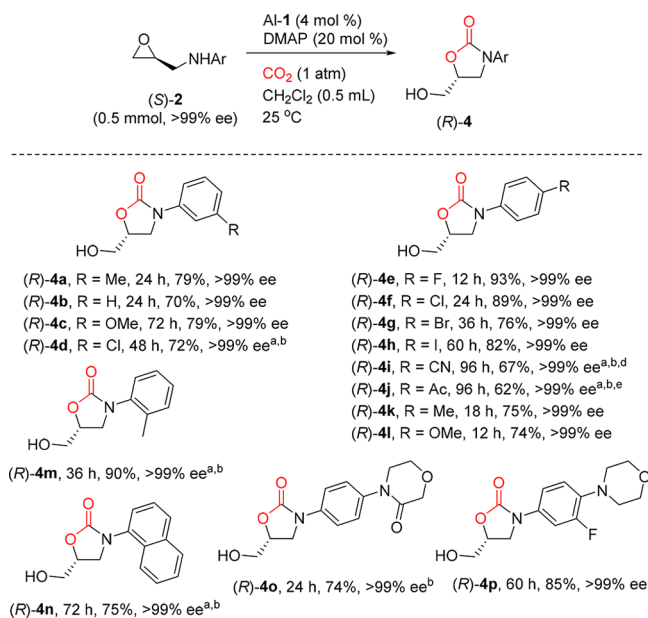
Scheme 2. Stereoselective Synthesis of Cyclic Carbonates

(*S*)-**3a**, R = Me, 97%, >99% ee
(*S*)-**3b**, R = H, 99%, >99% ee
(*S*)-**3c**, R = OMe, 97%, >99% ee
(*S*)-**3d**, R = Cl, 99%, >99% ee

(*S*)-**3e**, R = F, 98%, >99% ee
(*S*)-**3f**, R = Cl, 99%, >99% ee
(*S*)-**3g**, R = Br, 99%, >99% ee
(*S*)-**3h**, R = I, 99%, >99% ee
(*S*)-**3i**, R = CN, 99%, >99% ee
(*S*)-**3j**, R = Ac, 97%, >99% ee
(*S*)-**3k**, R = Me, 98%, >99% ee
(*S*)-**3l**, R = OMe, 97%, >99% ee

(*S*)-**3m**, 97%, >99% ee

(*S*)-**3n**, 99%, >99% ee

(*S*)-**3o**, 93%, >99% ee

(*S*)-**3p**, 95%, >99% ee

withdrawing groups at different positions were well tolerated. The substrates with *N*-heterocycles such as 3-morpholinone and morpholine also gave the products **3o** and **3p** with high yields. It appears that the reactivity for the formation of cyclic carbonate is not affected by the *N*-aryl substituent of the epoxy amines. Our stereochemical determination by using chiral-phase HPLC analysis indicated that all the (*S*)-epoxy amines were converted to (*S*)-cyclic carbonates without loss of enantiopurity (see the Supporting Information).

In Scheme 3, (*S*)-epoxy amines (**2a**–**p**) were used for the Al-**1**/DMAP catalyzed coupling reactions with CO_2 to form oxazolidinones. Unlike the previous cyclic carbonate formation, these reaction conditions may induce the racemization reaction because the proton at the chiral carbon center can be

Scheme 3. Stereoselective Synthesis of Oxazolidinone

(R)-4a, R = Me, 24 h, 79%, >99% ee
(R)-4b, R = H, 24 h, 70%, >99% ee
(R)-4c, R = OMe, 72 h, 79%, >99% ee
(R)-4d, R = Cl, 48 h, 72%, >99% ee[a,b]

(R)-4e, R = F, 12 h, 93%, >99% ee
(R)-4f, R = Cl, 24 h, 89%, >99% ee
(R)-4g, R = Br, 36 h, 76%, >99% ee
(R)-4h, R = I, 60 h, 82%, >99% ee
(R)-4i, R = CN, 96 h, 67%, >99% ee[a,b,d]
(R)-4j, R = Ac, 96 h, 62%, >99% ee[a,b,e]
(R)-4k, R = Me, 18 h, 75%, >99% ee
(R)-4l, R = OMe, 12 h, 74%, >99% ee

(R)-4m, 36 h, 90%, >99% ee[a,b]

(R)-4o, 24 h, 74%, >99% ee[b]

(R)-4p, 60 h, 85%, >99% ee

(R)-4n, 72 h, 75%, >99% ee[a,b]

[a]Reaction was carried out at 40 °C. [b]1,2-Dichloroethane was used as the solvent. [c]1:1 Mixture of CH_2Cl_2 and 1,4-dioxane was used as the solvent. [d]3i:4i = 1:3.3. [e]3j:4j = 1:24.

deprotonated by the base. Indeed, in the cases of epoxy alcohols, a somewhat reduced diastereoselectivity (97:3) was observed, possibly due to epimerization, as previously reported.[6] To our satisfaction, all (S)-epoxy amines (2a−p) were successfully converted to (R)-oxazolidinones (4a−p) without loss of enantiopurity. The chiral analysis by HPLC indicated the inversion of stereochemistry for the reaction. Because N-aryl groups participate in the formation of oxazolidinones, the reactivity is highly dependent on the N-aryl substituents. The N-aryl substituents with electron-donating groups promoted the reaction better than those with electron-withdrawing groups. The reaction was also retarded by the ortho substituents of the N-aryl groups due to a steric effect. Thus, the substrates with chloro, cyano, and acetyl groups as well as those with N-aryl groups of 2-tolyl and 1-naphthyl required an elevated temperature (40 °C) or longer reaction time (48−96 h) for the reaction to proceed. Moreover, the reduced selectivities of 1:3.3 and 1:24 were observed for the formation of 4i and 4j, respectively. The exact structures of the products, cyclic carbonate and oxazolidinone, were confirmed by the X-ray crystal structure analysis of (S)-3f and (R)-4f (CCDC 1849495 and 1849496) (Figure 1).
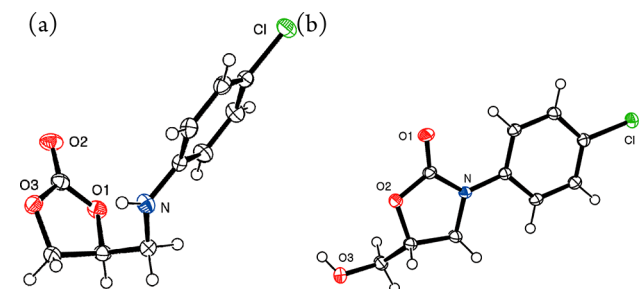

Figure 1. Crystal structures of (a) (S)-3f and (b) (R)-4f (thermal ellipsoids at the 50% probability).

Based on the stereochemical analysis of the divergent conversion, the involvement of the stereospecific substitution reactions is fully supported. Moreover, we have shown the crucial role of Lewis acid Al-1 that activates the epoxide functional groups (Table 1, entries 7 and 13). In the synthesis route for the cyclic carbonates (Figure 2, left), the nucleophile
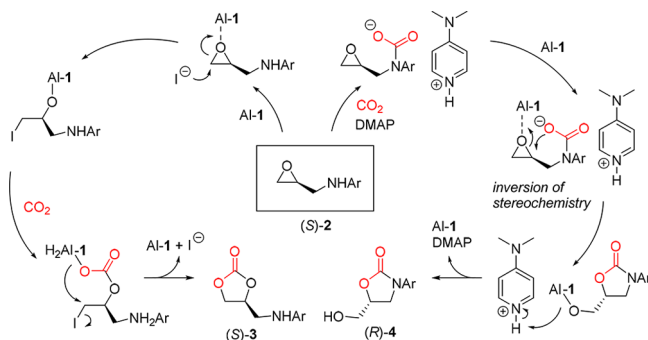

Figure 2. Reaction mechanism.

iodide attacks the terminal position of the epoxide activated by Al-1. The alkoxy Al complex then reacts with CO_2 to form carbonate, which releases iodide through an intramolecular substitution reaction. In this process, the stereogenic carbon center is not affected. In the synthesis route for oxazolidinones (Figure 2, right), the first step is the formation of carbamate salts formed by the deprotonation of the NH group and the addition of CO_2. This carbamate salt then reacts with epoxide activated by Al-1. This intramolecular substitution reaction results in the inversion of the stereochemistry.

As shown in Scheme 4a, (S)-cyclic carbonate 3a and (R)-oxazolidinone 4a were hydrolyzed to give (S)- and (R)-3-(m-

Scheme 4. (a) Stereodivergent Synthesis of Chiral Diol 5 and (b) Synthesis of Linezolid
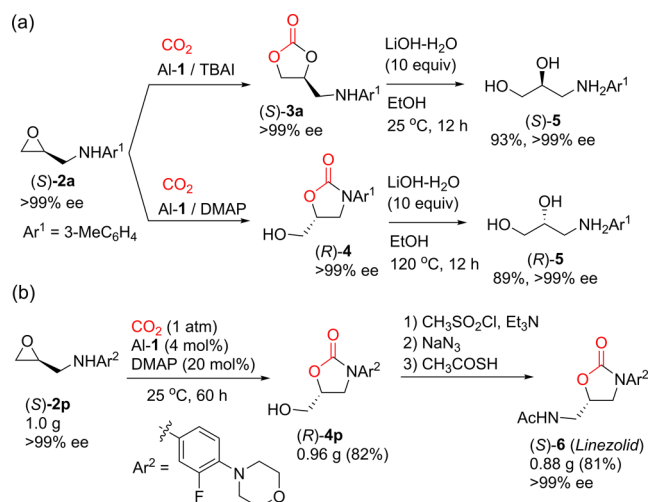
tolylamino)propane-1,2-diol 5, respectively. Because the inversion of the stereochemistry is involved in the formation of the oxazolidinones, this divergent reaction can be used to prepare both enantiomers from a single enantiopure epoxy amine. Moreover, N-aryl oxazolidinones are found in bioactive compounds. By utilizing the stereospecific conversion of epoxy amines to oxazolidinones, we demonstrated a short enantio-pure synthesis of Linezolid.[8] In a gram-scale reaction, the

oxazolidinone (*R*)-**4p** was prepared in 82% yield, which was subsequently converted to Linezolid in three steps.[12] From 1.0 g of epoxy amine (*S*)-**2p**, 0.88 g of Linezolid was prepared in an enantiomerically pure form.

In conclusion, we have demonstrated the divergent coupling of *N*-aryl epoxy amines and CO_2 to prepare two different products, cyclic carbonates and oxazolidinones. Our $Al-N_1O_3$ complex (Al-**1**) efficiently promoted the coupling reactions at 25–40 °C under atmospheric pressure of CO_2, and the choice of cocatalyst was crucial to control the product selectivity. In the coupling reactions, a Lewis acid catalyst (Al-**1**) and a nucleophilic cocatalyst (TBAI) provided cyclic carbonates, whereas a Lewis acid catalyst (Al-**1**) and a base (DMAP) provided oxazolidinones. Notably, stereospecific conversion was observed in both cases, which enables us to propose reliable mechanisms. Because chiral oxazolidinones or aminols show biological activities, this method will enable the use of CO_2 to produce important bioactive compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02186.

> Experimental procedures, spectroscopic, and crystallographic details (PDF)

Accession Codes

CCDC 1849495−1849496 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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