C-O Versus C-C Bond Cleavage: Selectivity Control in Lewis Acid Catalyzed Chemodivergent Cycloadditions of Aryl Oxiranyldicarboxylates with Aldehydes, and Theoretical Rationalizations of Reaction Pathways

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Oxiranes have attracted significant attention mainly as a result of being useful as building blocks for the synthesis of organic structures, their ease of preparation, and their propensity for strain-induced ring-opening reactions. The dominant chemistry of oxiranes is ring opening reactions by C-O bond cleavage,^[1,2] with C-C bond cleavage as a notable exception.[3,4]

Due to their unique catalytic activity, selectivity, and reactivity under mild conditions, Lewis acids have been developed as an essential tool for synthetic transformations, and have been widely used in the synthesis of natural products and medicinal compounds.^[5] Each Lewis acid has characteristic features, thus a systematic screening of different Lewis acids is often unavoidable. To optimize this time-consuming screening process, a fundamental understanding and classification of Lewis acids is expected to help address this issue. Herein, we report the chemodivergent 1,3-dipoplar cycloaddition of aryl oxiranyldicarboxylates with aldehydes, in which the C-C or C-O bond cleavage of oxirane can be controlled by the appropriate choice of Lewis acid. Divergent synthesis from the same starting material(s) is an interesting, but challenging task that has attracted many chemists in past years.^[6] The mechanism of these transformations have also been computationally studied and, furthermore, these findings may be applied to the classification of Lewis acid into subgroups based on their catalytic activity, chemoselectivity, and stereoselectivity.

During the course of our research into developing new oxirane chemistry,^[4,7] we hypothesized that oxiranyldicarboxylates 1 might undergo two different reaction pathways

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in the presence of different Lewis acids (LAs). In mode I, the oxiranyldicarboxylate 1 could be activated by coordination of the sp³-O of oxirane and one of the carboxylate oxygen atoms (sp²-O) to a Lewis acid. Alternatively, in mode II another Lewis acid may activate the oxiranyldicarboxylates by association with two carboxylate oxygen atoms (sp³-O). These two coordination modes may result in two different ring opening pathways of the epoxide motif, that is, C-O or C-C bond breakage, respectively, that are then trapped by an aldehyde, leading to two chemodivergent cycloadducts, 3 and 4 (Scheme 1).



Scheme 1. Proposed routes for the oxirane bond cleavage reactions.

To test our hypothesis, dimethyl-3-para-tolyloxirane-2,2dicarboxylate (1a) and benzaldehyde 2a were subjected to a solution of Y(OTf)₃ (5 mol%) in CH₂Cl₂ with 4 Å molecular sieves at room temperature, yielding cycloadduct 3a (through C-O bond cleavage of oxirane) and cycloadduct 4a (through C–C bond cleavage of oxirane) in 26 and 66% yield, respectively (see the Supporting Information, Table S1, entry 1). After many attempts, the best reaction conditions for C-O bond cleavage were found to be the use of Sn(OTf)₂ (5 mol %) as the catalyst in CH₂Cl₂ at RT (conditions A; Table S1, entry 36). In sharp contrast, C-C bond cleavage to give oxirane product 4a occurred exclusively in excellent yield and diastereoselectivity when the reactions were performed in the presence of Ni(ClO₄)₂•6H₂O (Table S1, entries 37-39), and toluene was found to be the best solvent for this case (conditions B; Table S1, entry 39).

Based on the results shown in Table S1 (see the Supporting Information), these Lewis acids can be classified into several groups based on their efficiency as follows: A, active (yield \geq 50%); B or C, weak (10% \leq yield \leq 50%) or inac-

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tive (yield $\leq 10\%$). According to their selectivity, Lewis acids in group A were further divided into A-1 (C-O bond cleavage selectivity, $3a/4a \ge 2:1$), A-2 (C-C bond cleavage selectivity, $4a/3a \ge 2:1$) and A-3 (neutral). Similarly, Lewis acids in group B were divided into B-1 (C-O bond cleavage selectivity, $3a/4a \ge 2:1$), B-2 (C-C bond cleavage selectivity, $4a/3a \ge 2:1$) and B-3 (neutral). The results listed in Table S1 in the Supporting Information show that most Lewis acids are classified into group A (active) (Table S1, entries 1-2, 4-5, 11, 13-26, and 28-32). Moreover, Fe(OTf)₃, Ga(OTf)₃, In(OTf)₃, Hg(OTf)₂, Sn-(OTf)₂, Bi(OTf)₃, Y(ClO₄)₃·6H₂O, Ce(ClO₄)₃·6H₂O, Gd- $(ClO_4)_3 \cdot 6H_2O$, $Yb(ClO_4)_3 \cdot 6H_2O$, $La(ClO_4)_3 \cdot 6H_2O$, Fe-(ClO₄)₃•xH₂O, Hg(ClO₄)₂•6H₂O, Zn(ClO₄)₂•6H₂O, and In-(ClO₄)₃•8H₂O are classified into group A-1; Y(OTf)₃, Gd-(OTf)₃, Yb(OTf)₃, Ni(ClO₄)₂·6H₂O, and Cu(ClO₄)₂·6H₂O are classified into group A-2. Group A-3 Lewis acids include Sc(OTf)₃, Al(OTf)₃, Mg(ClO₄)₂•6H₂O, and Al- $(ClO_4)_3$ ·9H₂O. None of the Lewis acids are classified into group B-1; Ce(OTf)₃ (Table S1, entry 3) is classified into group B-2; and Zn(OTf)₂ and Cu(OTf)₂ (Table S1, entries 10 and 12) are classified into group B-3. The reaction proceeded slowly when La(OTf)3, Mg(OTf)2, Ni-(OTf)₂, AgOTf, or AgClO₄·H₂O was used as the catalyst, and these catalysts are classified into group C (Table S1, entries 6-9, 33).

Interestingly, the group 3 metal triflates $(Sc(OTf)_3 \text{ and } Y(OTf)_3)$ are both active, whereas the lanthanide triflates show different activities and selectivities. With the increase in metal atomic number, the lanthanide triflates have a tendency to bind to the carbonyl sp²-O of the oxirane **1a**, leading to C–C bond cleavage as the predomi-

nant reaction pathway (Table S1, entries 3–5). On the other hand, the Group 13–15 metal triflates are all active (Table S1, entries 13–15, 17, and18), and Lewis acids such as Al-(OTf)₃, Ga(OTf)₃, and In(OTf)₃ have a tendency to selectively bind to the ether sp³-O of the oxirane **1a**, leading to C–O bond cleavage. In some cases, metal perchlorates are much more active than metal triflates (Table S1, entry 6 vs. entry 24; entry 7 vs. entry 19; entry 8 vs. entry 26), indicating that the anion also plays an important role in the activity of the Lewis acid.

With optimal reaction conditions in hand, the oxirane substrate scope was examined for this Lewis acid catalyzed, selective, 1,3-dipolar cycloaddition (Table 1). In general, the C–O bond cleavage products **3** are obtained exclusively in high yields with moderate diastereoselectivities from catalysis with Sn(OTf)₂; whereas C–C bond cleavage products **4** are obtained with high to excellent yields in the presence of Ni(ClO₄)₂ (5 mol%). However, the Ni^{II}-catalyzed reaction is much slower than the corresponding Sn^{II}-catalyzed reaction. Introduction of an electron-donating group on the phenyl ring of the oxirane accelerates the reaction rate. For example, the reaction of oxirane **1c** containing a weakly electronwithdrawing chloride group required 3 days for full conversion under reaction conditions B (Table 1, entry 6). In contrast, the reaction of oxirane **1d** with an electron-donating







 $\begin{array}{ll} \textbf{1a} \ (R^{1} = 4 - \text{MeC}_{6}\text{H}_{4}, \ R^{2} = \text{Me}) \ \textbf{1d} \ (R^{1} = 4 - \text{MeOC}_{6}\text{H}_{4}, \ R^{2} = \text{Me}) \ \textbf{1g} \ (R^{1} = 4 - \text{MeC}_{6}\text{H}_{4}, \ R^{2} = \text{Et}) \\ \textbf{1b} \ (R^{1} = \text{Ph}, \ R^{2} = \text{Me}) \ \textbf{1e} \ (R^{1} = 2 - \text{MeOC}_{6}\text{H}_{4}, \ R^{2} = \text{Me}) \ \textbf{1h} \ (R^{1} = 4 - \text{MeC}_{6}\text{H}_{4}, \ R^{2} = \text{allyl}) \\ \textbf{1c} \ (R^{1} = 4 - \text{ClC}_{6}\text{H}_{4}, \ R^{2} = \text{Me}) \ \textbf{1f} \ (R^{1} = 3 - \text{MeC}_{6}\text{H}_{4}, \ R^{2} = \text{Me}) \end{array}$

Entry	1	Conditions	<i>t</i> [h]	Yield [%] ^[b]	cis/trans ^[c]
1	1a	А	1	3a (83)	4:1
2		В	6	4a (91)	47:1
3 ^[d,e]	1b	А	7	3b (72)	3.3:1
4		В	40	4b (93)	50:1
5 ^[d,e]	1c	А	12	3c (59)	2:1
6 ^[e,f]		В	72	4c (84)	25:1
7	1 d	А	1	3d (83)	3.3:1
8 ^[e,g]		В	7	4d (90)	10:1
9 ^[e]	1e	А	1	3e (68)	2.7:1
10 ^[h]		В	23	4e (80)	5:1
11	1 f	А	3	3 f (64)	2.7:1
12		В	27	4 f (87)	>99:1
13	1g	А	1	3g (86)	1.6:1
14		В	11	4g (95)	33:1
15	1h	А	1	3h (81)	3:1
16		В	16	4h (90)	20:1

[a] **1** (0.5 mmol), **2a** (0.55 mmol), catalyst (5 mol%) and activated 4 Å molecular sieves (100 mg) in solvent (5 mL) at room temperature. Conditions A: Sn(OTf)₂, CH₂Cl₂; Conditions B: Ni(ClO₄)₂·6H₂O, toluene. [b] Isolated yield. [c] Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. [d] 10 mol% of Sn(OTf)₂. [e] 2.0 equivalents of **2a**. [f] The reaction was conducted at 50°C and 20 mol% Ni-(ClO₄)₂·6H₂O was used. [g] The reaction was conducted at -10° C. [h] Trace amounts of **3e** were obtained.

methoxy group was complete within 7 h (Table 1, entry 8). The *ortho* methoxy substitutent significantly decreases the diastereoselectivity for the Ni^{II}-catalyzed transformation, which is not the case for the Sn^{II}-catalyzed reaction (Table 1, entries 9 and 10). Gratifyingly, the dicarboxylates can be switched to ethyl or allyl esters to give the desired products in high yields (Table 1, entries 13–16).

We next studied the scope of this reaction by variation of the aldehyde component (Table 2). The data in Table 2 shows that the reaction of an aldehyde 2 that contains an electron-donating or electron-withdrawing group at the para position of the phenyl ring proceeded smoothly to provide the corresponding cycloadducts in 82-95% yield (Table 2, entries 1-6). Furthermore, polysubstituted benzaldehyde 2e and the heterocyclic aldehyde furfural (2 f) were also compatible, giving the desired products in 70-96% yield (Table 2, entries 7-10). Finally, the reactions of aliphatic aldehydes 2g-2i produced the corresponding cycloadducts in 73-95% yield with moderate to good diastereoselectivities (Table 2, entries 11-18). The structure and the relative stereochemistry of the products were established by X-ray crystallographic analysis of the cis isomers of **3a** and **4j** (see the Supporting Information, Figure S1).^[8]

Synthetic applications of 1,3-dioxolane **4** have been showcased by the selective transformations of the representative Table 2. The reaction of 1a and various aldehydes 2

MeO ₂ C O R ³ ~ O	CO ₂ Me	R ³ CHO condition Me-p	2 R ³ C s A condi 1a	HO 2 tions B <i>p</i> -MeC ₆ H		
3 : C-0	C cleavage	Э		4:	C-C cleavage	
2b (R ³	³ = 4-MeO	C ₆ H ₄) 2e (2e (R ³ = 3,4,5-(MeO)C ₆ H ₂)		2h (R ³ = pentyl)	
2c (R ³	$3 = 4 - CIC_{6}$	H ₄) 2f (F	2f (R ³ = 2-furyl)		2i (R ³ = cyclohexyl)	
2d (R ³	$^{3} = 4 - NO_{2}$	C ₆ H ₄) 2g (2g (R ³ = ethyl)		2j (R ³ = cinnamyl)	
Entry	2	Conditions	s t [h]	Yield [%] ^[a]	cis/trans ^[b]	
1	2b	А	1	3i (84)	4.5:1	
2		В	10	4i (95)	> 99:1	
3	2 c	А	1	3j (82)	1:1.1	
4		В	22	4j (86)	25:1	
5	2 d	А	1	3k (82)	1:1.7	
6 ^[c]		В	60	4k (85)	10:1	
7	2 e	А	1	31 (74)	3.8:1	
8		В	18	41 (96)	>99:1	
9	2 f	А	1	3m (70)	1:1	
10		В	22	4m (88)	2:1	
11	2 g	А	1	3n (83)	1:1.6	
12		В	26	4n (95)	8.3:1	
13	2 h	А	1	30 (81)	1:1.5	
14		В	11	4o (73)	8.3:1	
15	2i	А	1	3p (80)	1:1	
16		В	16	4p (79)	16:1	
17	2j	А	1	3q (78)	2.3:1	
18	-	В	72	4q (77)	6.2:1	

[a] Isolated yield. [b] Determined by 1 H NMR spectroscopic analysis of the crude reaction mixture. [c] Two equivalents of **2d** were used.



Scheme 2. Examples of synthetic applications of the bond cleavage reaction by using a 1,3-dioxolane, 4.

compound **41** (Scheme 2). This 1,3-dioxolane (**41**) underwent a highly selective Krapcho decarboxylation^[9] to afford trisubstituted 1,3-dioxolane **5** in 56% yield as a single isomer. This compound then underwent further reduction upon treatment with NaBH₄ in methanol, yielding a trisubstituted 1,3-dioxolane **6** in 76% yield. Gratifyingly, the sterically less hindered ester of **41** can be selectively reduced by treatment with NaBH₄ in methanol, affording a 1,3-dioxolane **7** in 82% yield as a single isomer.

To gain some insight into the mechanistic issues raised during this study, we carried out density functional theory COMMUNICATION

(DFT) studies by using oxirane 1a and benzaldehyde 2a as the model substrates, with $Sn(OTf)_2$ and $Ni(ClO_4)_2$ as the respective catalysts (see the Supporting Information for all details).^[10-12] Both Sn(OTf)₂- and Ni(ClO₄)₂-catalyzed C-O bond cleavages favor S_N2 stepwise pathways through an anti attack. Figure 1 shows that the metal anions are coordinated to the sp³-oxygen of the oxirane and one of the carbonyl groups, forming the intermediate IM_1 on the C–O cleavage pathway. The interaction between the anion and the sp³-O weakens the C-O bond of the oxirane, and nucleophilic attack on the oxirane from the back of this C-O bond occurs via transition state TS₁. Subsequently the C-C bond of the IM₂ oxirane, which has a gauche conformation, rotates by 120° to form IM₃. The newly formed C-O bond then rotates to allow ring closure into a heterocyclic intermediate, IM_4 . From IM_2 to IM_3 there are two possible rotation directions with a similar energy barrier (8 kcal mol^{-1}). The different rotation directions from IM₃ to IM₄ lead to the cis- and trans-isomers.^[13] Finally, the catalyst is released and the product is formed. The rate-determining step is the $S_N 2$ step from IM₁-2a to TS₁, in which the old C–O bond is cleaved and the new C-O bond is going to be formed. The single bond rotations, including the steps from IM_2 to TS_2 and IM₃ to TS₃, are important for controlling the stereoselectivity of the reactions (see Figure 2).

In contrast, on the C–C bond cleavage pathways the anions are coordinated to the two carbonyl groups of oxir-

ane 1a to form IM₅. The IM₅, which has a six-membered-ring structure, is energetically more favorable than the IM_1 . The variation of the natural bond orbital (NBO) charges (see the Supporting Information, Table S2 for details) of oxirane shows that the polarity of the C-C bond increases. The C-C bond is weakened and cleaved by thermal ring opening to generate a carbonyl ylide intermediate, IM_6 (the polar zwitterionic intermediate). This reacts with the aldehyde via a [3+2]cycloaddition pathway,^[14] stepping from IM_6 to IM_7 in Figure 1, and this step is pre-

dicted to be the rate-determining step and to determine the distereoselectivity of the reaction.^[15] Electron-rich aldehydes are expected to react faster if the key step is IM_6 to IM_7 (nucleophilic attack of the oxygen lone pair on the aldehyde on the complex IM_6), and this theoretical prediction has been corroborated by the experimental results [Eq. (1)].



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Figure 1. The Gibbs free energy profiles (ΔG_{298} in units of kcalmol⁻¹ at 298 K) of the reaction pathways for C–O and C–C bond cleavage catalyzed by a) Sn(OTf)₂ and b) Ni(ClO₄)₂ in CH₂Cl₂ solution (by using a PCM solvent model, $\varepsilon = 8.9$).

When Sn(OTf)₂ is used as the catalyst (Figure 1a), the activation energies of the C–O and C–C bond cleavages are 5.0 and 10.8 kcalmol⁻¹, respectively, and the energy barrier from **IM**₆ to **TS**₅ is 14.6 kcalmol⁻¹. This indicates that the C– O bond cleavage is a more favorable reaction pathway than the C–C bond cleavage, and is consistent with the experimental results (see the Supporting Information; Table S1, entry 17). In contrast, the energy barriers of the Ni(ClO₄)₂catalyzed C–O and C–C bond cleavages are 12.6 and 13.9 kcalmol⁻¹, respectively (Figure 1b). This seems to be a more kinetically favorable reaction pathway for the C–O cleavage than the C–C cleavage; however, the C–C cleavage pathway (Figure 1b, gray line) is much less endothermic

Figure 2. Geometries of the key transition states in the cleavage reaction.

overall than the C–O cleavage pathway (Figure 1b, black line). Thus, the C–C cleavage is favored when $Ni(ClO_4)_2$ is used as the catalyst. This is also in agreement with experimental results (see the Supporting Information; Table S1, entries 26 and 27).

In summary, we have developed a method for the Lewis acid catalyzed chemodivergent cycloaddition of aryl oxiranyldicarboxylates with aldehydes in which the C–C or C–O bond cleavage of oxiranes can be controlled by the use of a Ni(ClO₄)₂ or Sn(OTf)₂ catalyst, respectively. DFT calculations support the proposed mechanism of these two reaction pathways. These chemodivergent transformations may be used as a probe to classify the Lewis acids into subgroups, which will make a fundamental contribution to this field.

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- [11] The B3LYP functional was used for geometry optimizations, with the standard 6-31+G[d] basis sets for the light elements, and LANL2DZ basis sets containing the pseudo potential for metal atoms. The stabilities of the wavefunctions were tested and the compounds that contained Ni favoured triplet ground states, thus the unrestricted methods were employed. Frequency calculations were performed to test the obtained stationary points, intermediates (IM) and transition states (TS), and to find their thermochemical corrections. The solvent effects from dichloromethane ($\varepsilon = 8.9$) were investigated by using a polarized continuum model (PCM) at the optimized gas phase structures. The molecular cavities were built up using a UFF model. The Gibbs free energies in the solution were obtained by employing the following equation: $\Delta G_{sol} = \Delta G_{gas} +$ $(\Delta E_{\rm sol} - \Delta E_{\rm gas}).$
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- [13] By using Sn(OTf)₂, the energy barrier from IM₃ to the trans transition state is 3.9 kcalmol⁻¹, compared with 3.2 kcalmol⁻¹ for the *cis* transition state. The ratio of cis to trans product is 3.3:1, which is close to the experimental result.
- [14] Because the potential energy surface is quite flexible when the C1-O2 bond (see Figure 2) has recently formed, it is difficult to locate a minimum between TS5 and IM7. We propose that the cycloaddition is stepwise, as there is an obvious intermediate with one small imaginary frequency on the optimizing path from TS5 to IM7.
- [15] By using Ni(ClO₄)₂, the cycloaddition energy barriers for trans and cis products are 15.4 and 9.1 kcal mol⁻¹, respectively. This result indicates that there may be a small amount of trans product in the dichloromethane solution, which is consistent with the experimental results.

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CHEMISTRY

Cycloaddition Reactions -

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C-O Versus C-C Bond Cleavage: Selectivity Control in Lewis Acid Catalyzed Chemodivergent Cycloadditions of Aryl Oxiranyldicarboxylates with Aldehydes, and Theoretical Rationalizations of Reaction Pathways



A clean break: Lewis acid catalyzed chemodivergent [3+2] cycloadditions of aryl oxiranyldicarboxylates with aldehydes are revealed, in which the C-C or C-O bond cleavage of oxiranes can be controlled by the use of $Ni(ClO_4)_2$ or $Sn(OTf)_2$ catalysts (see scheme). Possible reaction pathways for these transformations are demonstrated by theoretical calculations.