

Reverse Regioselectivity in Reductive Ring Opening of Epoxide Enabled by Zirconocene and Photoredox Catalysis

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ABSTRACT: A ring opening of epoxide with zirconocene and photoredox catalysis has been developed. Compared to the ring opening methods with titanocene, the present protocol exhibited reverse regioselectivity to afford more-substituted alcohols via putative less-stable radicals. The observed regioselectivity could be explained by shifting the transition states to more reactant-like structures by changing the metal center of the metallocene catalyst.

Epoxide is a common structural motif in bioactive compounds, naturally occurring feedstocks, and various synthetic intermediates. Due to their inherent ring strain, epoxides generally behave as an excellent electrophile. Contrastingly, homolysis of its C–O bond provides a nucleophilic carbon radical leading to a distinct product that is unavailable from polar mechanisms. For such transformations, titanocene (III) (Cp_2TiX) has been exclusively exploited over the past 30 years since its introduction by Nugent and RajanBabu.^{1,2} In general, an epoxide coordinates to titanocene (III) prepared by reduction of titanocene (IV) with a reducing metal, and the C–O bond cleavage proceeds via single electron transfer (Figure 1A). The resulting carbon radical reacts with a large array of trapping agents such as hydrogen atom donors or olefins to furnish alcohols. So far, considerable research efforts have been directed to broaden this transformation.^{3–7} This has enabled remarkable advances in functionalization of the radical generated via epoxide ring opening, even including cross-coupling.⁸ Mild reaction conditions have allowed this transformation to contribute to numerous natural product syntheses.^{9–11} Recent studies showed that the merger of titanocene and photoredox catalysis can circumvent the need for a stoichiometric reducing metal.^{12–14}

When an unsymmetrical epoxide is employed, regioselectivity issues must be addressed. The factors controlling the regioselectivity is a fascinating topic, and detailed studies have been carried out.^{15–17} In most cases, homolysis predominantly occurs at the C–O bond, which gives a more stable radical (Figure 1B). In particular, thermodynamically stable radicals in benzylic¹⁸, allylic¹⁹, and anomeric²⁰ positions are favorably generated, much like in many other radical reactions. For electronically unbiased epoxides, non-bonding interactions including steric hindrance are considered as a prevailing factor.^{15–17} However, the princi-

ples controlling the regioselectivity still remain to be elucidated, and only few examples exist where the product is derived from a putative less stable radical.^{15,21}

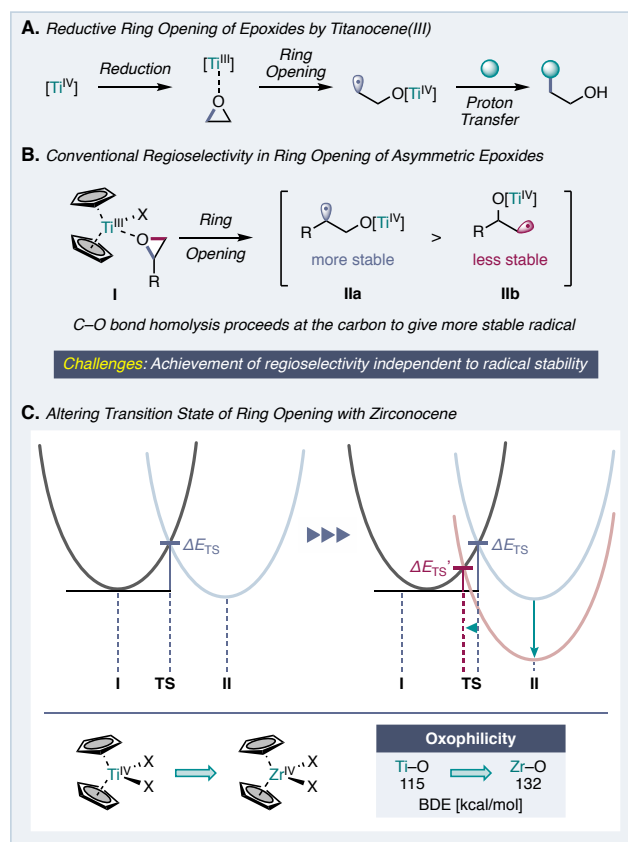
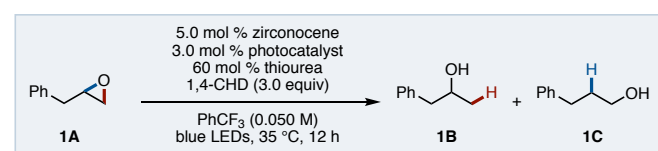


Figure 1. Reductive ring opening of epoxides (A) General scheme of titanocene(III)-catalyzed ring opening (B) Conventional regioselectivity in ring opening of asymmetric epoxides (C) Altering transition state of ring opening with zirconocene

tional regioselectivity. (C) Shifting transition state using zirconocene.

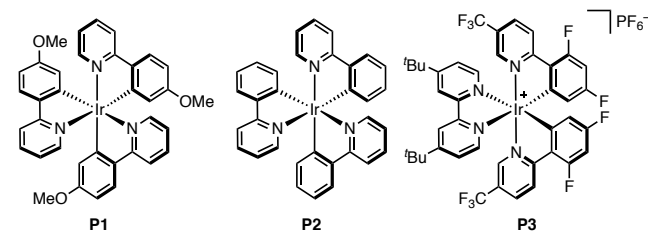
Considering the Bell–Evans–Polanyi principle,^{22,23} activation energy (ΔE_{TS}) decreases if epoxide opening becomes more exothermic (Figure 1C). Likewise, the transition state would shift earlier and become more similar to the starting material. In an earlier transition state, the contribution of stability of the resulting radicals in regioselectivity would diminish according to the Hammond postulate.²⁴ Inspired by the difference in bond dissociation energy (BDE) between Ti–O (115 kcal/mol)²⁵ and Zr–O (132 kcal/mol),²⁵ we became interested in using zirconocene instead of titanocene for the epoxide opening. Its stronger oxophilicity should render the ring opening dramatically exothermic. On this basis, we envisioned that a zirconocene-catalyzed ring opening of epoxide would reverse the conventional regioselectivity expected from relative radical stability.

Table 1. Reaction Optimization

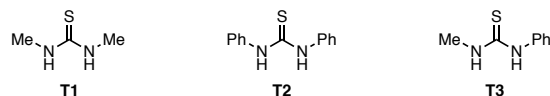


entry	Cp ₂ ZrX ₂	photocatalyst	thiourea	1B/1C (%) ^a
1	Cp ₂ ZrCl ₂	P1	none	0/0
2	Cp ₂ Zr(OTf) ₂ ·THF	P1	none	0/0
3	Cp ₂ Zr(OTf) ₂ ·THF	P1	T1	34/7
4	Cp ₂ Zr(OTf) ₂ ·THF	P1	T2	63/5
5	Cp ₂ Zr(OTf) ₂ ·THF	P1	T3	79/3
6 ^b	Cp ₂ Zr(OTf) ₂ ·THF	P1	T3	37/2
7 ^c	Cp ₂ Zr(OTf) ₂ ·THF	P1	T3	47/26
8	Cp ₂ Zr(OTf) ₂ ·THF	P2	T3	77/7
9	Cp ₂ Zr(OTf) ₂ ·THF	P3	T3	58/2
10	Cp ₂ ZrCl ₂	P1	T3	69/7
11	Cp ₂ Zr(OTs) ₂	P1	T3	53/47
12 ^d	Cp ₂ Zr(OTf) ₂ ·THF	P1	T3	80/3
13 ^d	none	P1	T3	0/0
14 ^d	Cp ₂ Zr(OTf) ₂ ·THF	none	T3	0/0
15 ^{d,e}	Cp ₂ Zr(OTf) ₂ ·THF	P1	T3	0/0

Photocatalysts



Thioureas



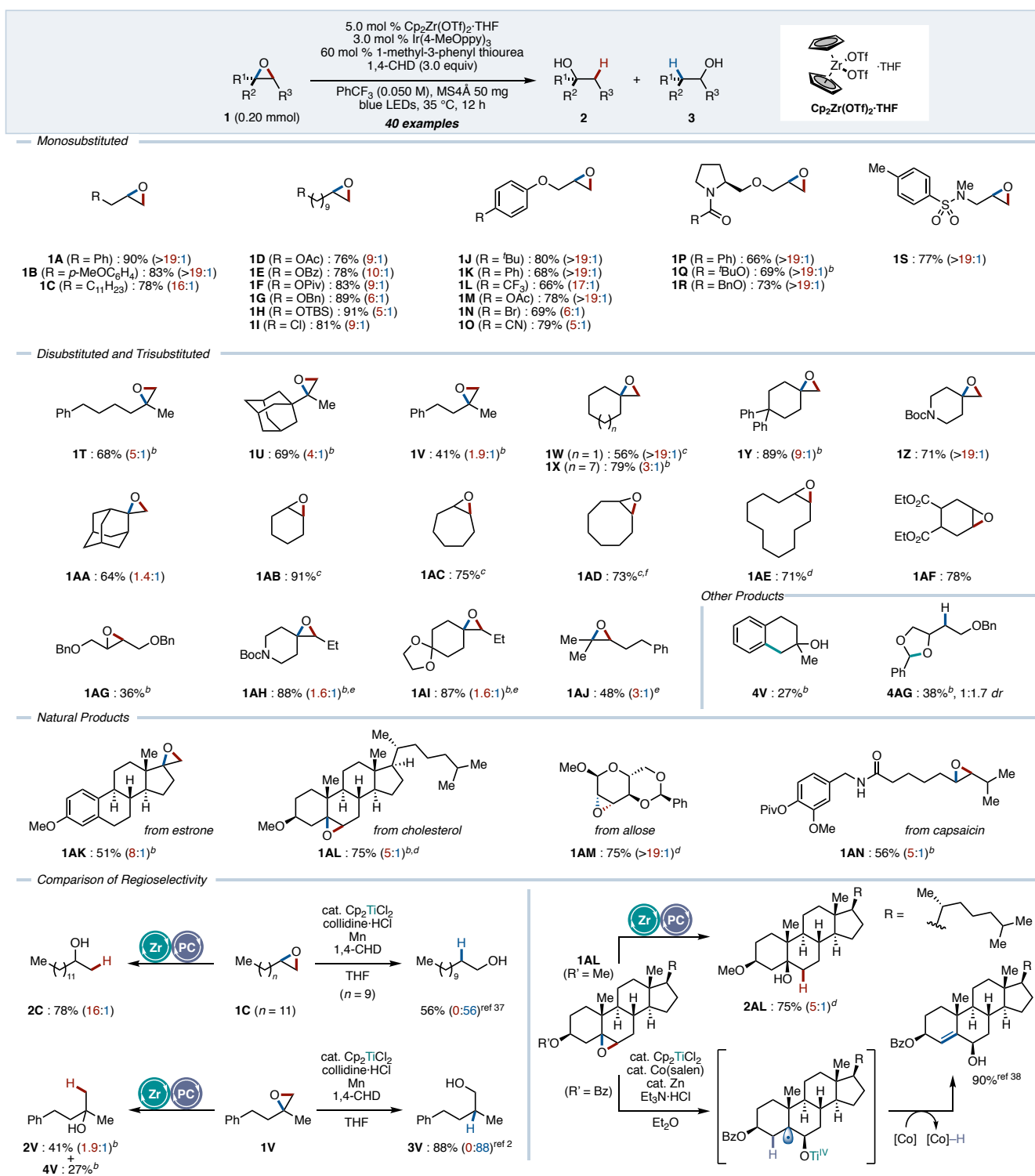
^aConditions: **1A** (0.10 mmol), zirconocene (5.0 mol %), photocatalyst (3.0 mol %), thiourea (60 mol %), 1,4-CHD (3.0 equiv),

PhCF₃ (2.0 mL), 35 °C, 12 h. NMR Yield. ^b In toluene. ^c In THF. ^d With MS4Å (50 mg). ^e Without irradiation.

To this end, we set out to investigate a catalytic protocol for the ring opening of epoxides using zirconocene with photocatalysts even though Zr (III) has been scarcely utilized in organic synthesis.^{26–32} Since the reduction of zirconocene typically requires high reducing power ($-E_{1/2}$ (Cp₂ZrCl₂) = -1.85 V vs SCE)³³, we commenced with strongly reducing photocatalyst Ir[(4-MeO)ppy]₃ (**P1**, $E_{1/2}$ Ir(IV)/Ir(III)* = -1.95 V vs SCE in MeCN).³⁴ Visible light irradiation of **1A** in the presence of zirconocene dichloride, **P1**, and 1,4-cyclohexadiene (CHD) resulted in no product formation (Table 1, entry 1). A change to Cp₂Zr(OTf)₂·THF did not furnish either of the alcohols (Table 2, entry 2). Gratifyingly, we found that addition of dimethylthiourea (**T1**) furnished the desired alcohol **1B** in 34% yield along with the isomeric alcohol **1C** in 7% yield (Table 1, entry 3). Further screening revealed that the combination of 1-methyl-3-phenyl thiourea (**T3**) and PhCF₃ facilitates the reaction with a suppressed amount of **1C** (Table 1, entries 4–7). Applying Ir(ppy)₃ (**P2**, $E_{1/2}$ Ir(IV)/Ir(III)* = -1.88 V vs SCE in MeCN)³⁴ or Ir[(dFCF₃ppy)₂(dtbbpy)]PF₆ (**P3**, $E_{1/2}$ Ir(IV)/Ir(III)* = -1.21 V vs SCE in MeCN)³⁵ diminished the yield of **1B** (Table 1, entries 8 and 9). Although other zirconocenes were not effective, the addition of molecular sieves slightly increased the yield (Table 1, entries 10–12). Control experiments excluding zirconocene, photocatalyst, and light provided essentially no product (Table 1, entries 13–15).

With the optimized conditions in hand, we next evaluated the substrate scope of this protocol (Scheme 1). First, we examined terminal epoxides with a variety of functional groups. In addition to phenyl (**1A**), *p*-methoxyphenyl (**1B**), alkyl (**1C**), ester (**1D–1F**), benzyl and silyl ether (**1G** and **1H**), and chloride (**1I**) were accommodated to afford the corresponding secondary alcohols with high yield and regioselectivity. Electronically diverse substituents on aromatic rings (**1J–1O**) were all tolerated. Protected prolinol derivatives (**1P–1R**), as well as sulfonamide (**1S**), were found to be suitable substrates. We next evaluated di- and trisubstituted epoxides. The present protocol converted 1,1-disubstituted epoxides **1T** and **1U** to more-substituted alcohols with retained regioselectivity, whereas ring opening of epoxide **1V** afforded 41 % yield of **2V** and **3V** in total with considerable amount of cyclic product **4V** suggesting the addition of a primary radical to the aromatic ring. Spiro epoxides (**1W–1Z**) uniformly furnished the desired alcohol, although incorporation of bulky adamantane (**1AA**) considerably reduced regioselectivity. 1,2-Disubstituted epoxides with a variety of ring sizes were well-tolerated (**1AB–1AF**). Interestingly, ring opening of dibenzyl ether **1AG** produced alcohol **2AG** along with benzylidene acetal **4AG** obtained in the previous titanocene-mediated ring opening via 1,5-hydrogen atom transfer (HAT).³⁶ In addition to trisubstituted epoxides (**1AH–1AJ**), natural product-derived epoxides (**1AK–1AN**) could also be readily opened in good yields.

Scheme 1. Substrate Scope^a



^aConditions: **1** (0.20 mmol), Cp₂Zr(OTf)₂·THF (5.0 mol %), Ir(4-MeOppy)₃ (3.0 mol %), **T3** (60 mol %), 1,4-CHD (3.0 equiv), PhCF₃ (4.0 mL), 35 °C, 12 h. All data are the average of two experiments. Unless otherwise noted, yields are for purified material of inseparable alcohols and isomeric ratios are determined by ¹H NMR analysis of crude reaction mixture. ^bIsomeric ratios are for isolated material. ^cYields and isomeric ratios were determined by GC analysis due to volatility. ^d10.0 mol % of Cp₂Zr(OTf)₂·THF was used. ^e4,4-Dimethyl-2-imidazolidinethione was used instead of **T3**. ^fReactions were performed for 24 h. See the SI for details.

Comparisons to the analogous precedents performed by titanocene highlighted the reverse reactivity in ring opening. As mentioned above, ring opening of **1C** provided **2C** with high regioselectivity, which was contrasting to the

previous study with titanocene.³⁷ Similarly, the ring opening of **1V** afforded tertiary and primary alcohols along with **4V** in our conditions, whereas primary alcohol **3V** is preferably obtained with titanocene.² While our protocol con-

verted **1AL** to **2AL**, ring opening of a similar cholesterol ($R' = \text{Bz}$) with titanocene furnished a tertiary radical, and the adjacent hydrogen was abstracted by a cobalt catalyst leading to an allylic alcohol.³⁸ These contrasting results demonstrated that our catalytic protocol is complementary to conventional methods with titanocene.

To gain insights into the reaction mechanism, ring opening of cyclopropyl-bearing epoxide **1AO** was conducted (Figure 2A). Treatment of this probe with the optimized conditions afforded the allylic alcohol **5AO**, suggesting a C–C bond cleavage via a cyclopropylcarbinyl radical. The same product was obtained in Oshima's conditions where Zr(III) was prepared from $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$.²⁹ Furthermore, intramolecular radical addition could be achieved with an epoxy ester (**1AP**; Figure 2B). These observations, as well as formation of **4V** and **4AG**, are in agreement with the C–O bond cleavage proceeding via a radical pathway.

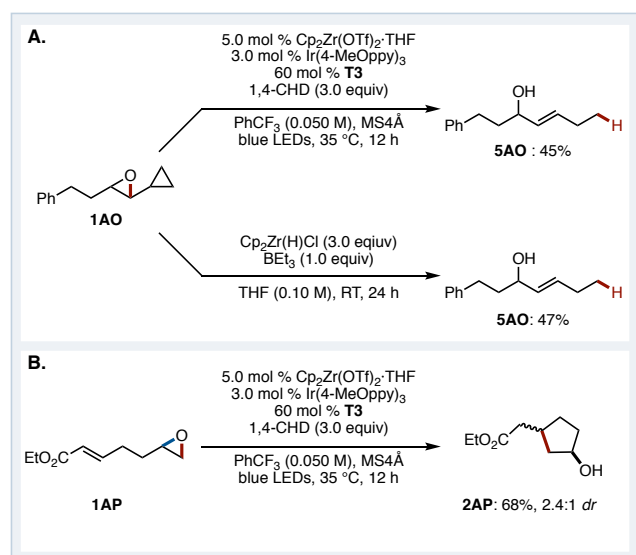


Figure 2 (A) Radical clock experiment. (B) Intramolecular radical addition.

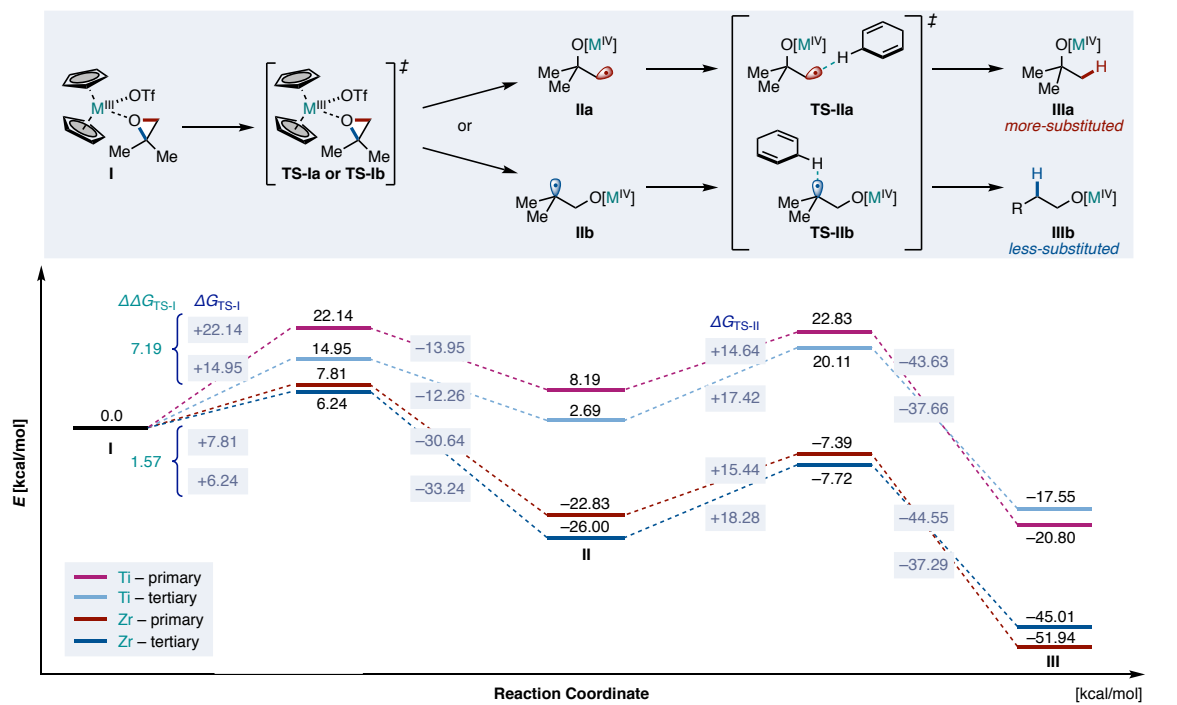
Next, we performed DFT calculations to reveal the energy profile of ring opening and HAT based on a model reaction of 1,1-dimethyl oxirane and metallocene triflates (**III**) ($M = \text{Ti}$ or Zr) (Figure 3A). The reaction proceeds from complex **I** via the respective transition state (**TS-Ia** and **TS-Ib**) to afford the corresponding ring-opened forms (**IIa** and **IIb**). The resulting radicals would then undergo HAT with CHD to be converted to alcohols (**IIIa** and **IIIb**). The energy profile with primary (purple) and tertiary (aqua) radical with titanocene, and primary (red) and tertiary (blue) radical with zirconocene are shown in Figure 3A. In accord with our design hypothesis, activation free energies of ring opening $\Delta G_{\text{TS-I}}$ with zirconocene (7.81 and 6.24 kcal/mol,

respectively) are remarkably lower than those of titanocene (22.14 and 14.95 kcal/mol, respectively).³⁹ Similarly, $\Delta\Delta G_{\text{TS-I}}$ with zirconocene (1.57 kcal/mol) is much smaller than that of titanocene (7.19 kcal/mol). This significant difference can be accounted for by the consequence of shifting the TS of ring opening earlier, which would reduce the influence of the thermodynamic stability between the resulting primary and tertiary radicals at the TS. Structures of **TS-1** provide further insight into shifting the TS of ring opening. The scissile C–O bonds in **Zr-TS-I** are shorter than that of **Ti-TS-I** by approximately 0.2 Å, suggesting that **Zr-TS-I** are more reactant-like. The spin density on the evolving carbon radical in **Zr-TS-Ia** (0.39) and **Zr-TS-Ib** (0.29) was smaller than that in **Ti-TS-Ia** (0.57) and **Ti-TS-Ib** (0.42). These structural features are consistent with more reactant-like **Zr-TS**.

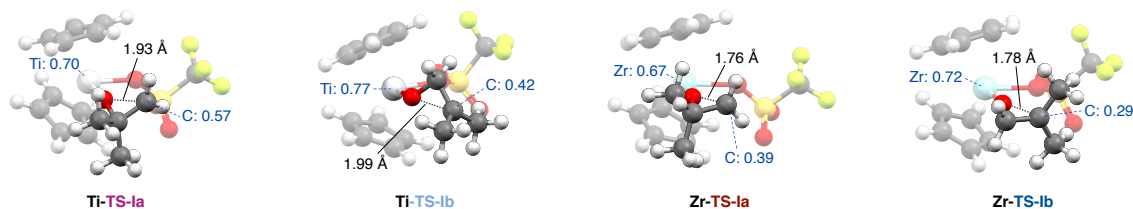
DFT calculations indicated that ring opening with titanocene was endothermic, which is consistent with a previous study.³⁶ Since titanocene-bounded tertiary radical **IIb** is more stable than the corresponding primary radical **IIa** by 6.82 kcal/mol, ring opening under thermodynamic control results in a large abundance of **IIb** which undergoes HAT to afford **IIIb** as a major product. In contrast, ring opening with zirconocene was found to be extremely exothermic and practically irreversible. By means of computational studies to provide a rough picture of the energy profile, **Zr-TS-Ia** was calculated to be less stable than **Zr-TS-Ib**. This discrepancy with our results prompted further investigation into the identity of the zirconocene complex.

In a possible scenario to explain the regioselectivity, ring opening proceeds via an epoxide–zirconocene–thiourea complex.^{40–42} In this case, $\Delta G_{\text{TS-Ia}}$ might be lower than $\Delta G_{\text{TS-Ib}}$, which is opposite to the calculated results with the zirconocene triflate complex. Diffusion-ordered NMR spectroscopy (DOSY) measurements evidently demonstrated that thiourea interacts with zirconocene (Figure 3B). In this experiment, tetramethylthiourea was used to facilitate NMR analysis. A 1:1 mixture of zirconocene and thiourea furnished several new signals in ^1H NMR. The diffusion coefficient for the newly generated signals ($D = 1.44 \times 10^{-9} \text{ m}^2/\text{s}$) was smaller than that of zirconocene ($D = 1.55 \times 10^{-9} \text{ m}^2/\text{s}$) and completely different from that of parent thiourea ($D = 3.45 \times 10^{-9} \text{ m}^2/\text{s}$), suggesting the interaction of zirconocene and thiourea. Thiourea probably interacts with not only Zr(IV) but also Zr(III) species since regioselectivity of the ring opening was influenced by the selected thiourea. Furthermore, Stern-Volmer analysis indicated that quenching of the excited photocatalyst by the zirconocene thiourea complex (see the SI for details)

A. Energy Diagram of Epoxide Ring Opening and Hydrogen Atom Abstraction with Metallocene(III)



Structures of TS-I



B. Interaction of Zirconocene and Thiourea

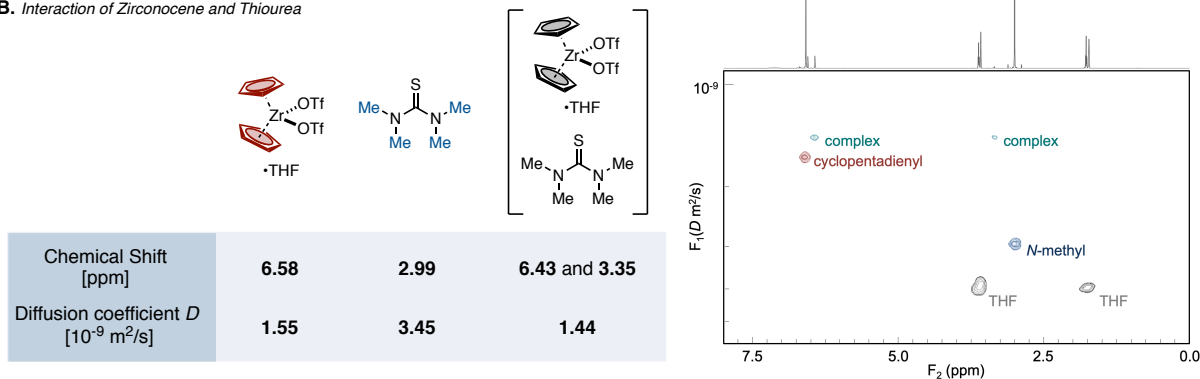


Figure 3. Mechanistic studies. (A) DFT calculations for the ring opening and HAT of asymmetric epoxide with metallocene triflate (II). Potential energies of transition states (TS) and intermediates (I, II, and III) in ring opening and HAT (B3LYP/6-31+G(d,p)//B3LYP/def2SVP) are shown. Each ΔG value between two structures is shown in the light blue box. All energies are given in kcal/mol. (B) A DOSY spectrum for a 1:1 mixture of Cp₂Zr(OTf)₂·THF and tetramethylthiourea in THF-*d*₈ at 25 °C. Chemical shifts and diffusion coefficients of zirconocene, thiourea, and the mixture are shown respectively.

Given these experimental results, a possible mechanism is depicted in Figure 4. The reaction could be initiated by reduction of zirconocene by an excited photocatalyst to furnish Zr(III) and triflate. Coordination between Zr(III) and epoxide could result in C–O bond homolysis to afford a carbon radical, which abstracts hydrogen from 1,4-CHD. The cyclohexadienyl radical undergo oxidation by Ir^{IV} catalyst ($E_{1/2}$ Ir(IV)/Ir(III) = +0.70 V vs SCE in MeCN).³⁴ The resulting cation and triflate would work as a Brønsted acid

to protonate zirconocene alkoxide to complete the catalytic cycle, with release of the desired alcohol and benzene.¹⁷

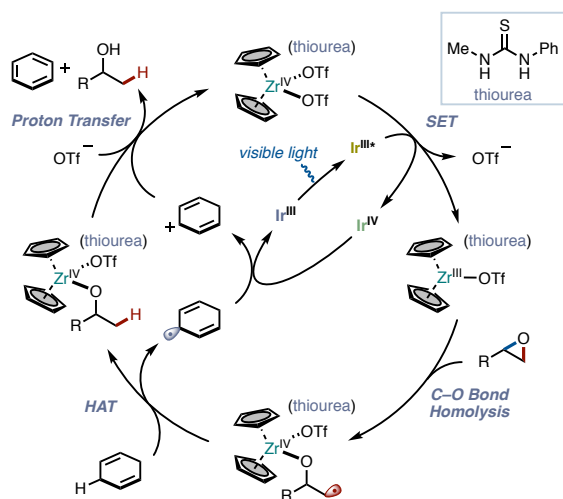


Figure 4. Proposed catalytic cycle.

In summary, we succeeded in the development of a zirconocene-photoredox cooperative catalysis for the ring opening of epoxide, exhibiting reverse regioselectivity compared to titanocene-mediated reactions. To our knowledge, this is the first example that harnesses a radical intermediate generated by C–O homolysis of epoxide using zirconocene.^{43–45} Exploring transformations with this new cooperative catalysis and further mechanistic studies are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, additional experimental results, computational study, and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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