

Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols

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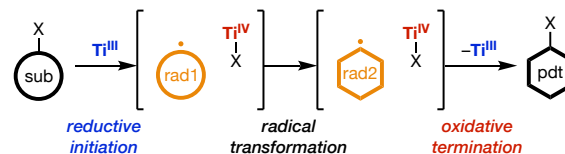
ABSTRACT: Organic radicals are generally short-lived intermediates with exceptionally high reactivity. Strategically, achieving synthetically useful transformations mediated by organic radicals requires both efficient initiation and selective termination events. Here, we report a new catalytic strategy, namely bimetallic radical redox-relay, in the regio- and stereoselective rearrangement of epoxides to allylic alcohols. This approach exploits the rich redox chemistry of Ti and Co complexes and merges reductive epoxide ring opening (initiation) with hydrogen atom transfer (termination). Critically, upon effecting key bond-forming and -breaking events, Ti and Co catalysts undergo proton-transfer/electron-transfer with one another to achieve turnover, thus constituting a truly synergistic dual catalytic system.

Epoxides are among the most important synthons in organic chemistry.¹ From canonical nucleophilic substitution² to transition-metal catalyzed cross coupling,³ a myriad of powerful transformations has been discovered that exploit the rich reactivity of these strained electrophiles. Among the reactions of epoxides, their rearrangement into allylic alcohols represents an attractive transformation, as it grants access to a class of highly useful synthetic intermediates in an efficient and atom-economical fashion. This transformation can be carried out under base-mediated conditions (e.g., with LiNR_2).⁴ The requirement for a strong base inevitably subjects the substrate to various side reactions (e.g., nucleophilic ring opening and reactions from α -deprotonation⁵) as well as narrowing functional group compatibility. Furthermore, methods for the synthesis of chiral allylic alcohols from epoxides are limited.⁶ Against this backdrop, we disclose a radical redox-relay strategy for the isomerization of epoxides to allylic alcohols under mild conditions using Ti and Co dual catalysis.

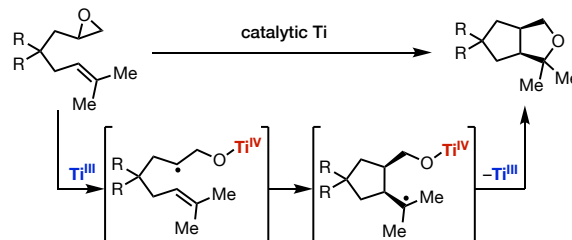
The rearrangement of epoxides to form allylic alcohols is a net redox-neutral transformation. To circumvent the use of a base promoter, we envision that this reaction could be achieved by combining a pair of single-electron oxidation and reduction events in the same catalytic cycle. This strategy, which we named radical redox-relay (Scheme 1A), has been demonstrated in the [3+2] cycloaddition of epoxides (Scheme 1B),⁷ *N*-acylaziridines,⁸ or cyclopropyl ketones⁹ with alkenes. In these reactions, a Ti^{III} catalyst reductively activates a functional group in the substrate to form a transient organic radical. Upon subsequent radical transformations to cleave and construct desired chemical bonds, Ti^{IV} oxidatively terminates the resultant radical in a way akin to atom transfer and completes the catalytic cycle.

Scheme 1. Radical redox-relay applied to allylic alcohol synthesis

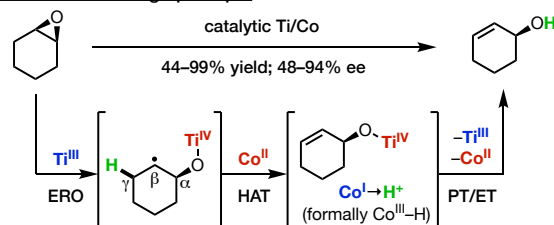
A. General principle of radical redox-relay catalysis



B. An example of Ti-catalyzed radical redox-relay (ref 7)



C. This work: Ti/Co bimetallic radical redox-relay for epoxide isomerization – design principle



We envision that this radical redox-relay strategy could be extended to the synthesis of allylic alcohols with the introduction of a Co co-catalyst. In the proposed reaction, we exploit the well-established reactivity of Ti^{III} to induce homolytic epoxide ring opening (ERO; Scheme 1C).¹⁰ The developing radical character at the β -C induces significant weakening of the C–H bond at the γ -position,^{11,12} and this enables hydrogen atom transfer (HAT) with a Co^{II} catalyst to furnish the desired alkene functionality. The resultant $\text{Co}^{\text{III}}\text{-H}$, depending on the ligand, can be acidic ($\text{p}K_{\text{a}} 10\text{--}15$)¹³ and may be viewed as Co^{I} coordinated to H^+ . This catalytic intermediate could then undergo proton-transfer/electron-transfer (PT/ET)¹⁴ with the Ti^{IV} -alkoxide to deliver the desired allylic alcohol and regenerate both Ti^{III} and Co^{II} catalysts. Implementation of this proposed reaction thus relies on identifying catalysts that would accommodate the thermodynamics and kinetics of the key ERO, HAT, and PT/ET steps in the same catalytic cycle.

We note that our reaction design was constructed with immense inspiration from prior art on the redox reactions of Ti^{III} ^{10,15,16} and Co^{II} ^{12,17,18} complexes in methodologically related contexts. In particular, recent reports have detailed Ti-catalyzed epoxide isomerization mediated by Ti–

H intermediates.¹⁹ The scope of this reaction, however, is generally restricted to α -methyl epoxides and precludes the formation of *endo*-olefins (*vide infra*). Moreover, a super-stoichiometric metal reductant (Mn or Zn, >6 equiv with respect to epoxide) is necessary to achieve high yields. Recently, Weix disclosed an elegant Ti^{III}/Ni⁰ dual catalysis for the arylation of epoxides.^{3b,c} In this setting, both catalytic species crucial for reactivity were regenerated using stoichiometric Mn reductant. Therefore, these precedent systems are net reductive and mechanistically distinct from our reaction design.

We set out to evaluate various combinations of Ti and Co catalysts, which led to the discovery that Cp₂TiCl₂ (10 mol%) and [Co] **4** (5 mol%) in the presence of Zn (20 mol%) and Et₃N·HCl (2 equiv) promoted the conversion of epoxide **1a** to the desired product **2a** in 65% yield (Table 1, entry 1). However, 11% byproduct **3a** was also formed concurrently, which arose from reductive ring opening of **1a**. The allylic alcohol product was *in situ* protected with benzoyl chloride to minimize the loss of volatile products and facilitate product analysis. Notably, Ti alone without Co—conditions synonymous to related previously reports^{19c}—led only to byproduct **3a** (entry 2). This undesired side reaction could be mitigated at the expense of increased Co loading (entries 3, 4). Alternatively, elaboration of the electronic profile of Co(salen) to include electron-withdrawing CF₃ groups ([Co] **5**) furnished **2a** in quantitative yield and complete chemoselectivity (entry 5). This more reactive HAT agent allowed us to decrease catalyst loading to 1 mol% while maintaining synthetically useful yield and selectivity (entry 6). Decreasing the equivalents of Et₃N·HCl, however, proved detrimental (entries 7, 8). Importantly, Co(salen) alone could not affect the isomerization (entry 9).¹⁸ Finally, control experiments demonstrated that catalytic Zn, which is proposed to reduce Ti^{IV} precatalyst to Ti^{III} to kick start the catalytic cycle, was vital to the formation of **2a** (entry 10). We note that the regioselectivity of the HAT process is practically exclusive and cyclohexanone, which would arise from H-atom abstraction α -to the –OTi^{IV} motif, was not observed. We hypothesize that this selectivity stems from both electronic and steric reasons: the α -H is both hydridic²⁰ (polarity mismatched with electron-rich Co^{II}) and sterically encumbered by the pendant Ti catalyst.

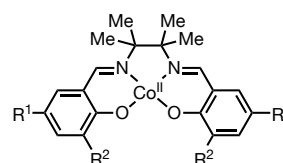
Under optimal conditions, a variety of epoxides underwent the isomerization reaction to furnish desired allylic alcohols in good to excellent efficiency (Scheme 2A). Trisubstituted epoxide **1k** gave varying ratios of regioisomeric alkenes with [Co] **4** favoring the *endo* product (71:29) and [Co] **5** favoring the *exo* (39:61). Although the *endo/exo* selectivity remains moderate at this stage, the capability of steric/electronic tuning of reaction regioselectivity is intriguing. Notably, enantioenriched epoxides **1s** and **1t** were converted to the corresponding alcohols with complete retention of configuration. In the case of **2t**, only one regioisomer was observed presumably because the β -H adjacent to the OBz group in **1t** is hydridic and polarity-mismatched with Co^{II}. Reaction of **1w** gave a mixture of **2w** and bicyclic **2w'** in 53% and 31% yield, respectively; **2w** was readily converted to **2w'** under acidic conditions.

The Ti/Co dual catalytic system was also successfully applied to the kinetic resolution of diastereomeric mixtures of several epoxides (Scheme 2B). For example, 1,2-epoxycyclododecane (**1x**, *cis/trans* = 69:31) delivered **2x** in 78% yield with 17% recovered *trans*-**1x**, indicating that *cis*-**1x** reacts at a faster rate. Limonene oxide (**1y**) reacted to furnish **2y** in 44% yield alongside recovered *trans*-**1y** (40% yield). Reactions with epoxy-cholesterol (**1z**) with varying ratios of α - and β -anomers were also diastereoselective. For this substrate, [Co] **5** gave substantial amounts of reduced byproducts (**3z**) presumably due to the poor steric accessibility of the β -H in this complex substrate. Thus, [Co] **8** (R¹ = Cl, R² = Me) with a smaller size and similar electronic property was employed. α -Predominant mixture of **1z** (α/β 72:28) gave 28% **2z** (α/β 6:94) with full recovery of α -**1z** whereas β -predominant mixture (α/β 5:95) produced β -**2z** as a single diastereomer.²¹ This reaction thus

offers access to these synthetically useful epoxides in diastereomerically pure form, which are challenging via direct olefin epoxidation.

Table 1. Reaction optimization

Entry	mol% Ti	[Co]	mol% Zn	2a (%)	3a (%)
1	10	4 (5 mol%)	20	65	11
2	10	None	40	—	(25)
3	10	4 (10 mol%)	20	82	7
4	10	4 (15 mol%)	20	82	—
5	10	5 (5 mol%)	20	99	—
6	10	5 (1 mol%)	20	71	4
7 ^b	10	5 (5 mol%)	20	—	—
8 ^c	10	5 (5 mol%)	20	(40)	—
9	0	5 (5 mol%)	40 or 200	—	—
10	10	5 (5 mol%)	0	—	—



- 4**, R¹ = R² = Me
5, R¹ = CF₃, R² = ^tBu
6, R¹ = CF₃, R² = H
7, R¹ = CF₃, R² = Me
8, R¹ = Cl, R² = Me
9, R¹ = Br, R² = Me
10, R¹ = Cl, R² = Cl

^aIsolated yields are reported; yields in parentheses are determined by ¹H NMR using mesitylene as internal standard. ^bNo Et₃N·HCl. ^cWith 0.5 equiv Et₃N·HCl.

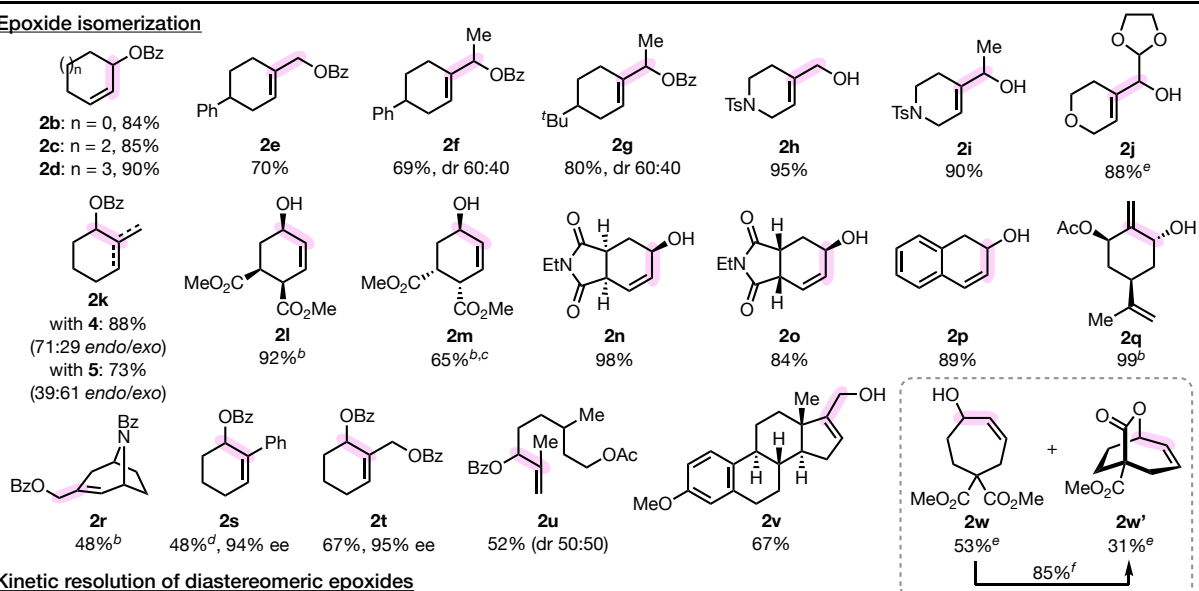
The intermediacy of organic radicals was confirmed using epoxides **1aa** and **1ab** (Scheme 2C). [Co] **4** gave a mixture of uncyclized **2aa** and cyclized **2aa'** in 57:43 ratio. [Co] **5** instead gave an 80:20 mixture of **2aa/2aa'**. These results are indicative of the HAT process occurring at a faster rate with the electron deficient [Co] **5** over [Co] **4** and is competitive with the transannular cyclization ($k_c \approx 3.3 \times 10^4 \text{ s}^{-1}$).²² Increasing the loading of [Co] **5** led to nearly complete suppression of cyclization, giving **2aa** in 75% yield. Pinene derivative **1ab** was converted to a 33:67 mixture of **2ab/2y** using [Co] **4** and a 64:36 mixture using [Co] **5**. These data again indicate a facile HAT process with both Co catalysts that is comparable to the radical-induced fragmentation of pinene.²³

Comparing with previous work on Ti-mediated epoxide isomerization,^{19b-d} our dual catalytic system exhibits complementary chemoselectivity with several substrates tested (Scheme 2D). For example, 1,2-epoxycyclododecane (**1x**), which was converted smoothly to allylic alcohol **2x** under Ti/Co co-catalysis, underwent deoxygenation to yield cyclododecene under solely Ti-mediated conditions (**2x'**).^{19b} In addition, the isomerization of epoxycyclohexane (**1a**) to **2a** was not observed using Ti only, with cyclohexanol (**3a'**) formed as the major product. Notably, farnesol-derived epoxide **1ac** underwent cascade cyclization to **2ac'** using Ti but was converted to linear allylic alcohol **2ac** quantitatively using Ti/Co.^{19d} Lastly, the desired rearrangement of carvone-derived **1ad** were observed using Ti/Co, producing **2ad** without observation of Ti-mediated acetate elimination (**2ad'**).^{19c}

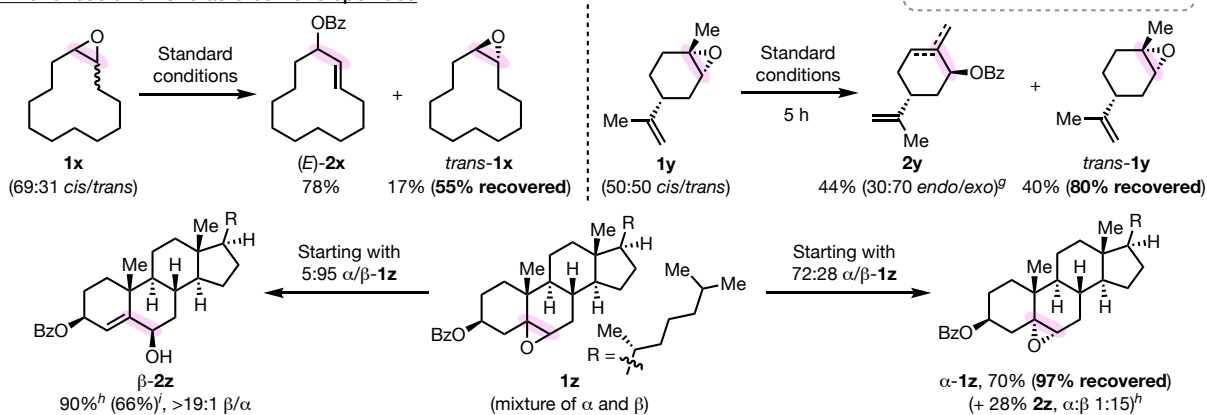
Finally, we developed an enantioselective protocol using chiral Ti complexes. Few methods are available for the synthesis of enantioenriched cyclic allylic alcohols. The Kharasch-Sosnovsky reaction enables the functionalization of allylic C–H bonds but often suffers from low enantioselectivity and functional-group tolerance.²⁴ Elegant base-mediated strategies require a strong base and a chiral amine catalyst;^{4,25} the former precludes base-sensitive substrates and the latter often requires multistep synthesis. The Corey-Bakshi-Shibata reduction also falls short when considering conjugated enones.²⁶

Scheme 2. Reaction scope^a

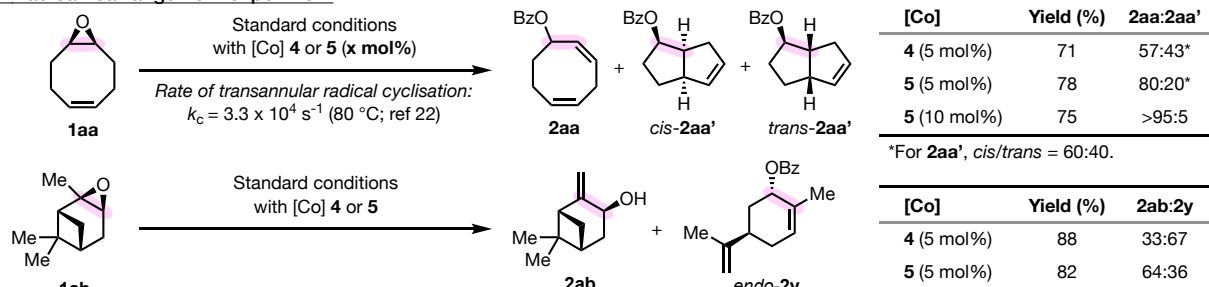
A. Epoxide isomerization



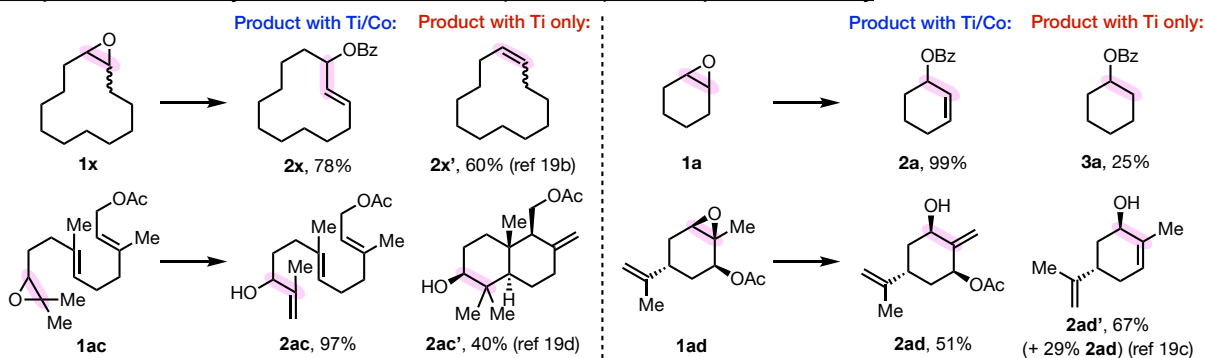
B. Kinetic resolution of diastereomeric epoxides



C. Radical rearrangement experiment



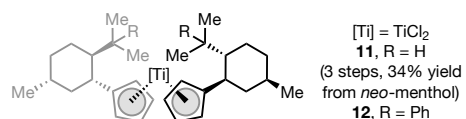
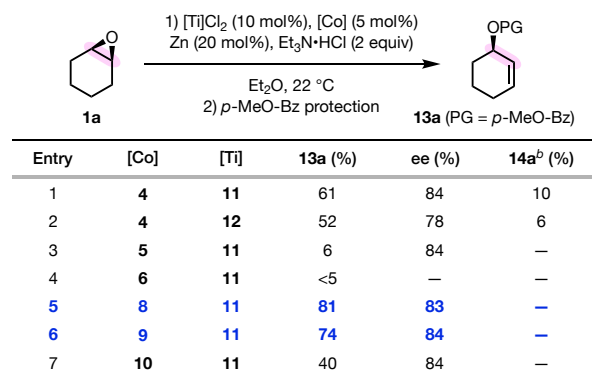
D. Comparison with Ti-catalyzed reductive isomerization (refs 19b–d): different product selectivity



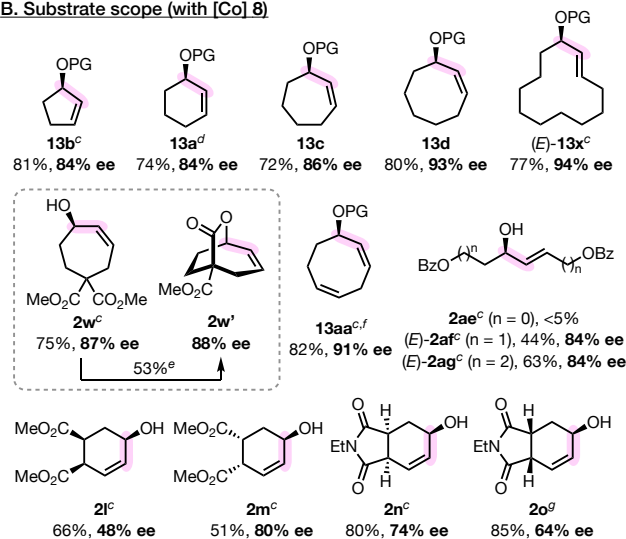
^aUsing Cp₂TiCl₂ (10 mol%), [Co] **5** (5 mol%), Zn (20 mol%), Et₃N·HCl (2 equiv) in Et₂O at 22 °C unless otherwise noted; depending on substrate, in situ Bz protection is carried out; isolated yields are reported. ^bWith [Co] **5** (10 mol%). ^c**2m/3m** = 78:22. ^dUsing enantioenriched epoxide (94% ee), with [Co] **5** (15 mol%). ^eWith Cp₂TiCl₂ (20 mol%), [Co] **5** (10 mol%). ^fTFA, CHCl₃, rt, 1 h. ^g*endo* product dr 50:50, *exo* product dr 75:25. ^h[Co] **8** (10 mol%). ⁱ1 mmol scale.

Scheme 3. Enantioselective epoxide isomerization

A. Optimization of enantioselective isomerization of *meso*-epoxide **1a**



B. Substrate scope (with [Co] **8**)



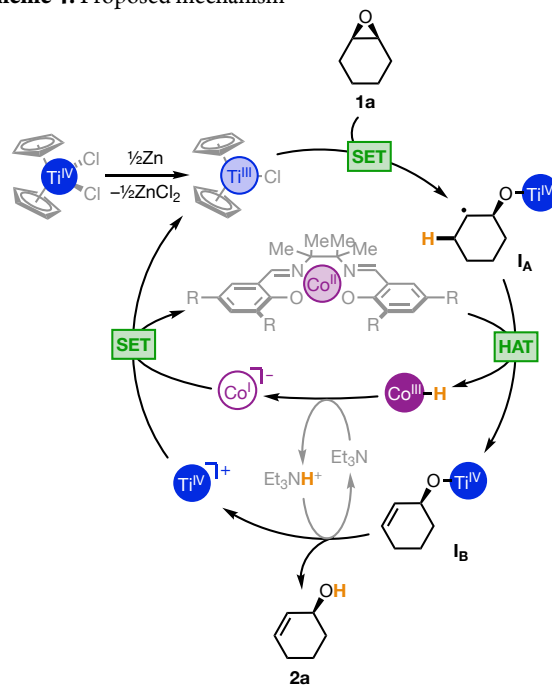
^aIsolated yields are reported. ^b14a = cyclohexyl *p*-methoxybenzoate, analogous to 3a. ^cWith **11** (20 mol%), [Co] **8** (10 mol%). ^dWith [Co] **9** (5 mol%). ^eTFA, CHCl₃, rt, 1h. ^f13aa/*cis*-13aa'/*trans*-13aa' = 85:6:9; *cis*/*trans*-13aa' are transannular cyclization products and are analogous to *cis*/*trans*-2aa. ^gWith [Co] **8** (10 mol%).

Using epoxycyclohexene (**1a**), Kagan's complex^{3c,27,28} **11** along with [Co] **4** promoted the reaction with high enantioselectivity albeit with the formation of byproduct **14a** in 10% (Scheme 3A, entry 1). Unexpectedly, [Co] **5**, a more reactive HAT catalyst, gave minimal conversion to desired **13a** likely due to steric interactions with encumbered **11** (entry 3). Removing the *t*Bu groups on [Co] **5** (i.e., [Co] **6**), low reactivity was observed due to low catalyst solubility (entry 4). Owing to the difficulty in synthesizing the (CF₃,Me)-substituted [Co] **7**, we prepared halogenated derivatives ([Co] **8–10**) with similar electronic properties to **5** (see SI for cyclic voltammograms) but a smaller steric profile. Indeed, [Co] **8** proved optimal, producing **13a** in 81% yield and 83% ee.

The scope of the enantioselective isomerization was expanded to various *meso*-epoxides (Scheme 3B). With simple cyclic systems, the products (**13a–d**, **x**) formed in excellent yields and high enantioselectivity. Epoxide **1w** was smoothly converted to **2w**, which was further converted to bicyclic **2w'** with two bridge-head stereocenters in 88% ee. Dienol **13aa** was obtained from **1aa** in 91% ee alongside traces of transannular cyclization products. While linear *meso*-epoxide **1ae** was not compatible with this transformation, **1af** and **1ag** led to desired products **2af** and **2ag** in high ee. Several polysubstituted cyclic epoxides were transformed

to the corresponding products with multiple new stereocenters (**2l–o**). Although the enantioselectivities in some of these cases are moderate, our methodology provides access to these interesting molecules that are challenging with base-mediated isomerization due to competing epimerization.²⁵ Given the synthetic accessibility of menthol derivatives, the optimization of these systems by ligand modification is promising.

Scheme 4. Proposed mechanism



We propose a synergistic dual catalytic cycle for the epoxide isomerization (Scheme 4). The formation of Cp₂Ti^{III}Cl (monomer or dimer)^{10d} via Zn reduction of Cp₂Ti^{IV}Cl₂ triggers 1e⁻ reduction of epoxide **1a** to Ti^{IV}-bound β-alkoxy radical **I_A**. Subsequently, **I_A** undergoes HAT with Co^{II}, giving Ti^{IV}-intermediate **I_B** and Co^{III}-H. Finally, **I_B** undergoes PT/ET with Co^{III}-H to regenerate Co^{II} and Ti^{III}. We propose this PT/ET process is mediated by Et₃N. Specifically, Et₃N·HCl protonates **I_B** to liberate product **2a** and Cp₂Ti^{IV}Cl₂. The resultant Et₃N (p*K*_a ~ 10) then deprotonates Co^{III}-H to furnish Co^I. This process is thermodynamically feasible given the acidity of Co^{III}-H.¹³ The incipient Co^I and Ti^{IV} will then undergo ET to close both catalytic cycles. This step is also favorable on thermodynamic grounds given the highly reducing character of Co^I [*E*_{p/2}(Co^{II/I}) = -1.65 V vs *E*_{p/2}(Ti^{IV/III}) = -1.06 V; see SI].

The proposed reaction mechanism does not account for the requirement for stoichiometric Et₃N·HCl. However, Et₃N·HCl has been postulated to also play critical roles in activating Zn dust and stabilizing Ti^{III} catalytic species.^{10d,29} In this reaction, the solely Ti-mediated pathway was not operative, as GC analysis of the reaction headspace did not show evidence of H₂ formation, which would be expected if Ti^{IV}-H intermediates are present.^{19e}

In summary, the redox-neutral epoxide isomerization was achieved using Ti/Co redox-relay catalysis. The optimized process showed the intricacy in balancing steric and electronic characteristics of the Co^{II} catalyst. The reaction scope includes a wide range of cyclic and acyclic epoxides using readily available catalysts. The resolution of diastereomeric epoxides and desymmetrization of *meso*-epoxides were also discovered. This work represents a rare example of Ti redox catalysis in the absence of stoichiometric reductants, where turnover was achieved through redox-relay with a Co co-catalyst. Further understanding the

thermodynamics and kinetics of each elementary step of the reaction and applications to new organic transformations are underway.

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Notes

The authors declare no competing financial interests.

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