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In-Situ Monitoring of Enantiomeric Excess During a Catalytic Kinetic Resolution

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ABSTRACT: Vibrational Circular Dichroism combined with FTIR spectroscopy (VCD-IR) is demonstrated as a viable tool for the in-situ measurement of enantiomeric excess during asymmetric catalytic transformations. Employing the Jacobsen (salen)Co-catalyzed hydrolytic kinetic resolution of racemic epoxides as a proof-of-concept case study, methodology is developed to monitor the enantiomeric excess of the epoxide substrate as a function of conversion of the limiting reactant, water. Comparison of results for monomeric and oligomeric catalysts probes the molecularity of the catalyst by investigating nonlinear effects in catalyst enantiopurity. These results are in excellent agreement with previous mechanistic investigations of this reaction based on kinetic measurements and computational studies.

Keywords: enantiomeric excess, vibrational circular dichroism, kinetic resolution, nonlinear effects, reaction progress

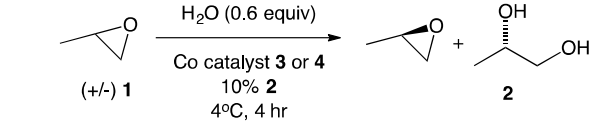
INTRODUCTION

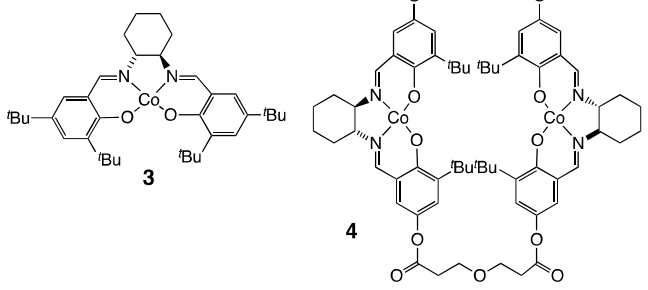
In-situ monitoring of reaction progress has become a standard tool in mechanistic analysis of catalytic reactions, particularly in the pharmaceutical industry. The ability to obtain a rapid scan of concentration profiles spanning the full conversion regime led to the development of Reaction Progress Kinetic Analysis (RPKA),[1] a streamlined methodology for determining concentration dependences to formulate a reaction rate law as well as for probing process robustness. Using RPKA, extensive information content is accessible from fewer separate experiments than is typical in classical kinetic analysis. This information may then be used to develop a mechanism, to optimize a reaction in batch, or to design an efficient flow process.

In a similar vein, one might envision the development of in-situ means of measuring reaction variables other than concentration dependences, for example temperature, as in adiabatic reaction calorimetry[2] or temperature-scanning reaction protocols.[3] One variable that has so far eluded general development of a non-invasive in-situ monitoring methodology is enantiomeric excess in asymmetric catalytic transformations.[4] A number of compelling cases exist for monitoring *ee* as a function of time. For example, temporal erosion in *ee* is a common indication of catalyst degradation, where in-situ monitoring of *ee* could serve as an early alert and be useful in modeling this behavior. Other important cases where *ee* changes with time include racemization or epimerization and kinetic resolution. In a kinetic resolution, the two enantiomers of a substrate react at different rates typically characterized by the selectivity factor, k_{rel}, described in terms of conversion (c) and *ee* for the case of initially racemic substrate (eq 1). In-situ temporal monitoring of *ee* with reaction progress could present a more accurate means of measuring k_{rel}, provide valuable mechanistic insights and allow process improvements.

$$R \xrightarrow{k_R} P^R \qquad S \xrightarrow{k_S} P^S \qquad k_{rel} = \frac{k_R}{k_S} = \frac{\ln\left[\left(1-c\right)\left(1-ee\right)\right]}{\ln\left[\left(1-c\right)\left(1+ee\right)\right]} \tag{1}$$

We report the development of vibrational circular dichroism (VCD-IR) as a tool for temporal monitoring of *ee*. We chose the Jacobsen (salen)Co-catalyzed hydrolytic kinetic resolution of racemic epoxides[5] (Scheme 1) as a test case for proof-of-concept because of its practical importance and its well-studied mechanism. The VCD-IR technique successfully monitors both ee and conversion over the course of this reaction, as validated by sampling and GC analysis. We were also able to confirm mechanistic insights into catalyst speciation for monomeric and oligomeric catalysts by probing for nonlinear effects of catalyst enantiopurity[6] on differential kinetic enantiomeric enhancement (DKEE).[7] These results are in good agreement with previous experimental rate measurements, kinetic modeling, and DFT calculations.[8] This work supports the general use of VCD-IR as an in-situ tool for temporal monitoring of enantiomeric excess.





Scheme 1. Hydrolytic Kinetic Resolution of Propylene Epoxide Catalyzed by (Salen)Co Complexes.

BACKGROUND

Vibrational circular dichroism (VCD)[9,10] extends the well-established method of electronic circular dichroism (ECD) from the UV/Vis to the IR region of the electromagnetic spectrum. One of the biggest advantages of expanding the probe to this region is the ability to detect a wider range of molecules, most notably including those without aromatic groups. While ECD has been employed for ee measurement during high throughput screening,[11-13] that approach is not compatible with the goal of unperturbed in-situ kinetic monitoring. VCD-IR spectra are highly sensitive to both the chirality and the conformation of the species being detected. The two enantiomers of a compound yield identical IR spectra, and their VCD spectra will be equal in intensity but opposite in sign, as shown in Figure 1a for the model system α-pinene. The experimentally observed VCD spectrum is the sum of the spectra from all different conformers, weighted by their relative distribution. This allows conformational information to be extracted from VCD spectra in addition to sense of chirality. VCD-IR has been used with great success over the past several decades for the determination of absolute configuration (AC),[14] made possible by improvements in the availability of high quality *ab initio* density functional theory calculations of VCD spectra. VCD spectroscopy has been used in a wide range of physical organic chemistry studies of small molecules as well as to probe supermolecular chirality.[15]

VCD spectra can provide a quantitative measurement of *ee* when coupled with vibrational spectra in the infrared region. The VCD signal intensity is proportional to the *difference* in concentration of the two enantiomers in the sample, while the IR signal is proportional to the *sum* of the two, as shown in Figure 1b and 1c. The enantiomeric excess may be calculated by combining the data from VCD and FTIR spectra as shown in eq 2.

$$ee = \frac{[R]-[S]}{[R]+[S]} \quad \begin{matrix}(\text{from VCD}) \\ (\text{from FTIR})\end{matrix} \qquad (2)$$

A number of early studies used offline VCD analysis of gas phase samples to monitor chiral reactions.[16] Continuous measurement of *ee* in a dynamic system, analogous to the use of traditional IR spectroscopy to monitor concentration continuously over a reaction time course, has only been explored to date in a small number of simple systems. Nafie and coworkers followed the pseudo-racemization of 2,2-dimethyl-1,3-dioxolane-4-methanol in a range of solvents by VCD-IR.[17] The extended reaction times allowed for excellent signal in this system containing only one chiral reactant or product. Grinberg and coworkers monitored the kinetics of racemization of an imidazoline, a class of molecules that are valuable building blocks for chiral ligands and for pharmaceuticals.[18] VCD-IR coupled with DFT calculations provided a detailed mechanistic picture of the reaction and demonstrated the role of aromatic substituents in the racemization process. Lüdeke and coworkers monitored the hydrolysis of a Ni sparteine complex using a custom VCD system employing a quantum cascade laser.[19]

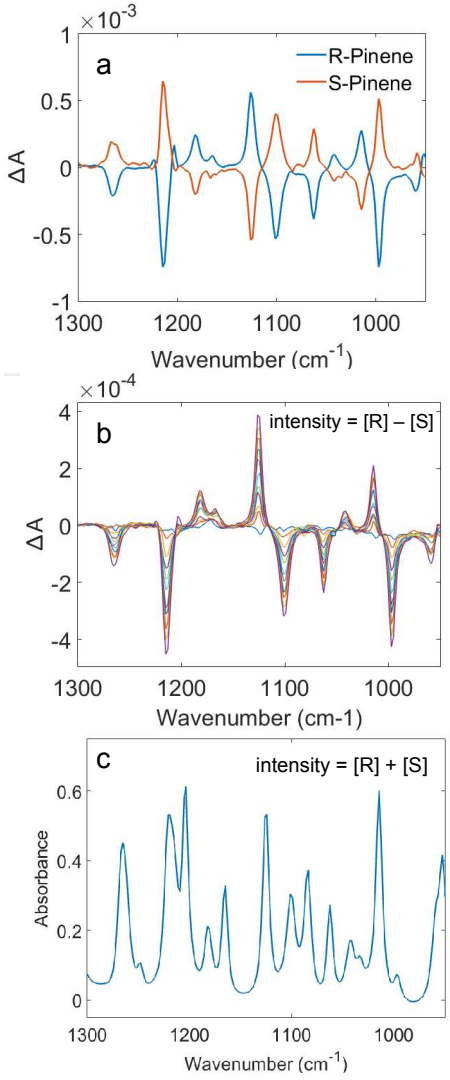
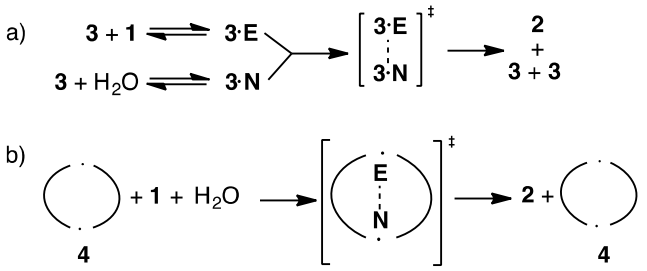


Figure 1. a) VCD spectra of neat enantiopure *R* and *S* α-pinene; b) VCD spectra of mixtures of *R*-α-pinene with increasing amounts of *S*-α-pinene; c) FTIR spectrum of neat α-pinene.

These studies were carried out in less complex chiral environments than many asymmetric reactions, and these results inspired us to develop VCD-IR as a mechanistic tool to probe complex multi-step asymmetric catalytic reactions such as the hydrolytic kinetic resolution (HKR) of epoxides shown in Scheme 1. The HKR has been demonstrated to be bimolecular in catalyst, with the rate-determining step found to be reaction between one catalyst molecule bound to the epoxide (**3**·**E**) and a second catalyst molecule bound to the nucleophile, water (**3**·**N**), yielding a bimolecular transition state (Scheme 2a) and a second order dependence on catalyst concentration. Jacobsen and coworkers showed that reaction rates could be greatly accelerated by linking two catalyst molecules at an optimal distance from one another, as in **4**, creating a high effective molarity for the rate-determining step (Scheme 2b), which is first order in the dimeric catalyst **4**.

The involvement of two chiral catalyst molecules in a single step for the monomeric catalyst **3** raises the possibility of nonlinear effects in catalyst enantiopurity, which has been extensively studied by the Jacobsen group.[7] While epoxide and water substrates bind identically to either hand of the catalyst, only the "matched" interaction between epoxide- and water-bound catalyst molecules of like chirality are productive in the reaction. For monomeric catalyst **3**, this self-selection results in a nonlinear effect where the observed selectivity in the kinetic resolution is not proportional to enantiomeric excess of the monomeric catalyst. For the dimeric catalyst **4**, where each dimer contains two catalyst molecules of the same chirality, the reaction selectivity remains proportional to the enantiomeric excess of **4**. These mechanistic insights have been obtained through kinetic and computational studies and discrete measurements of enantiomeric excess. The aim of our study is to determine whether temporal probing of enantiomeric excess in the reaction of Scheme 1 by VCD-IR bears out this mechanistic picture, thus providing a proof-of-concept for its use as an in-situ mechanistic probe.



Scheme 2. Elementary steps and transition states in the HKR of Scheme 1 catalyzed by a) momeric catalyst 3 and b) dimeric catalyst 4.

Experimental

Both the reactant and the product of the kinetic resolution of Scheme 1 are chiral, as is the catalyst; we carried out preliminary studies of a number of different racemic epoxides that have been shown to undergo the HKR before choosing the propylene oxide system. Features of the molecule including its rigidity and number of conformers affet the VCD signal. The chosen system shows both a strong VCD signal for the epoxide reactant **1** as well as a nearly silent VCD spectrum for the product diol **2**.[20] Catalyst loadings were chosen to provide similar temporal progress curves for the monomeric catalyst **3** (5.7 mM) and the dimeric catalyst **4** (1.1 mM) to catalyze the reaction of 10.8 M *rac*-**1** 0.1 equiv. product propylene glycol and 0.6 equiv H_2O. A small amount (0.05 equiv.) of enantiopure epoxide was added to rac-**1** in order to improve the VCD signal of low *ee* data at the beginning of the reaction.[20] The HKR reaction is carried out in a recycling batch reactor in which the reaction solution is circulated through a flow cell mounted within the VCD spectrometer. Simultaneous collection of both IR and VCD spectra is possible using the ChiralIR-2X instrumental platform developed by BioTools, Inc. Spectra are acquired and co-added over blocks of five-minute duration that optimizes the balance between spectral and temporal resolution. These data are exported into MATLAB for analysis. Chemometric interrogation of the VCD and IR spectra using a Multivariate Curve Resolution (MCR) decomposition provides trends for individual reaction components and the *ee* of propylene oxide, which was validated by comparison to chiral chromatographic analysis of sample aliquots.[15] Once the method is validated in this way, further reactions may be carried out under different conditions with a single aliquot taken at the end of spectral data collection serving to normalize the traces to the conversion and ee value of the reaction endpoint.

Results and Discussion

The kinetic resolution of Scheme 1 was monitored by VCD-IR using both the monomeric catalyst **3** and the dimeric catalyst **4** at varying values of enantiomeric excess. Validation of the methodology for determining *ee* is shown in Figure 2 by comparison to *ee* determined by chiral HPLC of discrete samples. Temporal ee profiles are shown in Figure 3 for reactions carried out with the two catalysts at a range of catalyst *ee* values. As shown by the slopes of these curves, the rate of change of *ee* in racemic substrate **1** in the kinetic resolution of Scheme 1 decreases with decreasing catalyst *ee* for both the monomeric catalyst **3** and the dimeric catalyst **4**.

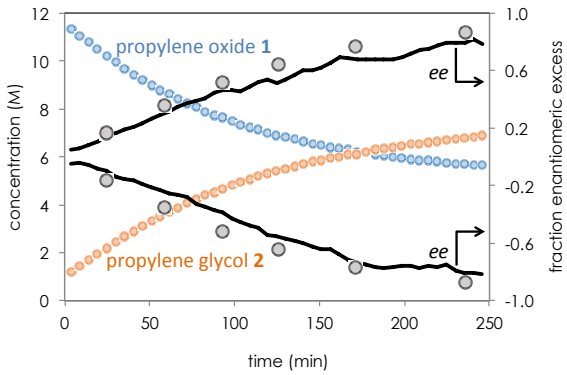


Figure 2. Temporal profiles from the reaction of Scheme 1 using catalyst **3**. Racemic reactant **1** (blue symbols) and product **2** (orange symbols) from FTIR spectra of the reaction using (*R,R*)-**3**. Enantiomeric excess (*ee*) of **1** from VCD-IR (black lines) compared with *ee* from analytical sampling from aliquots (gray symbols) using (*R,R*)-**3** (top) and (*S,S*)-**3** (bottom), validating the technique for in-situ *ee* measurement in the reaction of Scheme 1.[20]

The selectivity factor for a kinetic resolution given in eq 1 may be written in general terms as the ratio of the rate constant for the major pathway to that of the minor pathway, as in eq 3. Solving for the rate of change of the enantiomer of **1** on the major pathway compared to that of the enantiomer of **1** on the minor pathway gives the classic expression for kinetic resolution of eq 4. Combining VCD and IR data allows us to calculate the selectivity factor for this reaction. By fitting the major and minor epoxide concentration profiles for both catalysts **3** and **4** gives $k_{rel} = 32$ for enantiopure catalysts in the reaction of Scheme 1 under the conditions employed in these studies.[20]

$$k_{rel} = \frac{k_{major}}{k_{minor}} \tag{3}$$

$$\left(\frac{[\mathbf{1}]_{major}}{[\mathbf{1}]_{major,0}}\right) = \left(\frac{[\mathbf{1}]_{minor}}{[\mathbf{1}]_{minor,0}}\right)^{\frac{k_{major}}{k_{minor}}}$$

(4)

Values for k_{rel} may also be calculated for each scalemic run for both catalyst **3** and catalyst **4**. We employ the Singleton treatment where a variable termed differential kinetic enantiomeric enhancement, DKEE, has been defined (eq 5).

$$DKEE = \frac{k_{major} - k_{minor}}{k_{major} + k_{minor}} = \frac{k_{rel} - 1}{k_{rel} + 1} \quad (5)$$

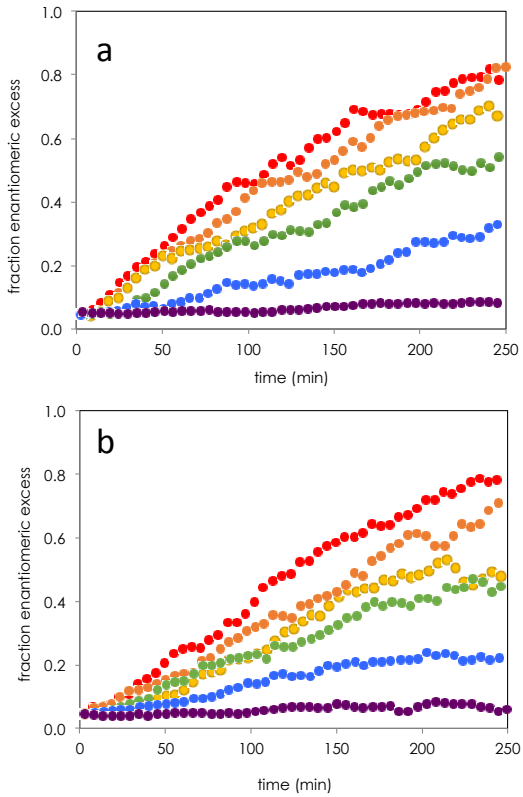


Figure 3. Fraction enantiomeric excess from VCD-IR measurements for the reaction of Scheme 1 carried out using a) (*R,R*)-**3** and b) (*R,R*)-**4** at varying *ee* values: red = 100% *ee*; orange: 79% *ee* **3**, 75% *ee* **4**; yellow: 59% *ee* **3**, 50% *ee* **4**; green: 39% *ee* **3**, 38% *ee* **4**; blue: 20% *ee* **3**, 19% *ee* **4**; indigo: 0% *ee* **3**, 1% *ee* **4**.[20]

The relationship between DKEE and catalyst ee affords a means to analyze nonlinear effects of catalyst enantiopurity in kinetic resolution in a similar graphical treatment as that developed by Kagan for asymmetric catalysis. When the k_{rel} values for catalysts **3** and **4** are determined for the reactions at different catalyst ee values and plotted as DKEE vs. catalyst ee, the relationships shown in Figure 4 are revealed.[17] The dimeric catalyst exhibits linear behavior in DKEE with respect to catalyst ee, as shown by the fit of the points to the dashed line. By contrast, the monomeric catalyst exhibits a positive nonlinear effect. Fitting these data fit to the Kagan ML_2 model with the parameters K=4 and g = 0 gives the blue line shown in Figure 4.

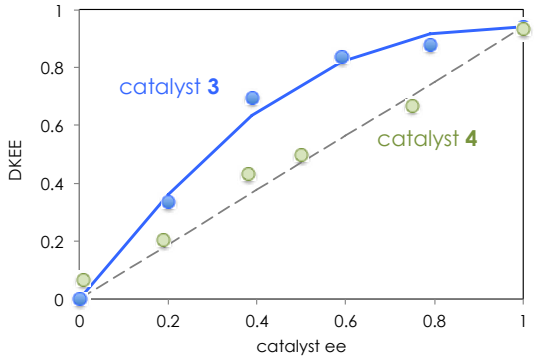


Figure 4. DKEE (eq 5) plotted as a function of catalyst *ee* in the reaction of Scheme 1 catalyzed by **3** (blue circles) and **4** (green circles). Dashed line shows the linear relationship. Solid blue line is the fit to the Kagan ML_2 model with K=4 and g=0.[20]

The parameters of the Kagan ML_2 model have been reinterpreted in the context of the mechanism of the reaction of Scheme 1.[7] That model was developed for the case of dimeric catalysts, where two chiral ligands L bind to one or two metal centers M. When both hands of the ligand, L_R and L_S, are present, the possibility exists for both homochiral (ML_RL_R and ML_SL_S) and heterochiral (ML_RL_S) catalytic species to be formed. The parameter K represents the equilibrium composition of these species. While the homochiral species will act as catalysts to give identical rates and opposite product *ee* values, the heterochiral species as catalyst may exhibit a different relative rate, characterized by the parameter g, and will produce racemic product. The case of K = 4, g = 0 in the standard ML_2 model describes the stochastic formation of species (i.e., no preference between forming heterochiral or homochiral species) where the heterochiral species is inactive as a catalyst. In the case of the reaction of Scheme 1 catalyzed by monomeric **3**, rather than considering bimetallic intermediate species, the model describes the potential for homochiral or heterochiral transition states rather than stable species. In this context, K = 4 implies that matched and mismatched **3**·**E** and **3**·**N** species may encounter each other with equal preference, while g = 0 implies that only the matched encounters result in a productive reaction. The results of Figure 4 are in excellent agreement with the findings of the Jacobsen group.

For the dimeric catalyst **4**, since each catalyst molecule contains two sites with the same chirality, mismatched encounters cannot occur, and product *ee* remains proportional to catalyst *ee*. This difference between the two catalysts is also manifested by differences in selectivity and rates for scalemic catalysts, as highlighted in Figure 5. Selected *ee* data from Figure 3 for both catalysts are plotted together as a function of conversion in Figure 5a, while Figure 5b plots product formation vs time for both catalysts at 40% *ee*.

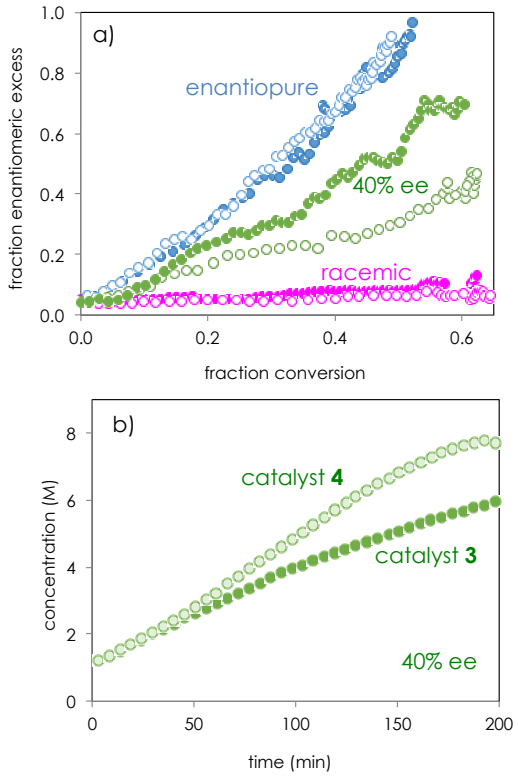


Figure 5. a) Fraction enantiomeric excess plotted as a function of conversion of substrate **1** in the reaction of Scheme 1 catalyzed by enantiopure (blue symbols), 40% *ee* (green symbols) and racemic (magenta symbols) **3** (filled circles) and **4** (open circles); b) product **2** concentration as a function of time for catalysts **3** and **4** at 40% *ee*.

Figure 5a reveals while both racemic and enantiopure catalysts **3** and **4** show similar trends for product *ee* as a function of conversion, the scalemic case shows a divergence between the two catalysts. A greater change in ee observed as conversion increases for the monomeric catalyst **3** than for the dimeric catalyst **4**. This difference may be understood in the context of the nonlinear effect observed for **3**, with the reaction employing the monomeric catalyst exhibiting higher *ee* at a given conversion compared to that for **4**. Figure 5b, showing that the dimeric catalyst **4** shows a higher rate of reaction compared to **3** as the reaction progresses, is also consistent with theoretical predictions of the ML_2 model.[6b] A positive nonlinear effect, or asymmetric amplification, comes at the expense of reaction rate as the unproductive mismatched interactions effectively decrease the active catalyst concentration.

CONCLUSIONS

VCD-IR spectroscopy has been demonstrated to provide a practical means of monitoring enantiomeric excess over the course of an asymmetric catalytic transformation. These studies successfully confirm complex mechanistic details of the Jacobsen hydrolytic kinetic resolution previously obtained through experimental kinetic studies and computational investigations. This work promises to add an important process analytical tool for mechanistic understanding and for reaction monitoring and process improvement in asymmetric catalytic transformations.

Supporting Information. Experimental details and details for analysis of VDC spectra. This information is available free of charge on the ACS Publications website.

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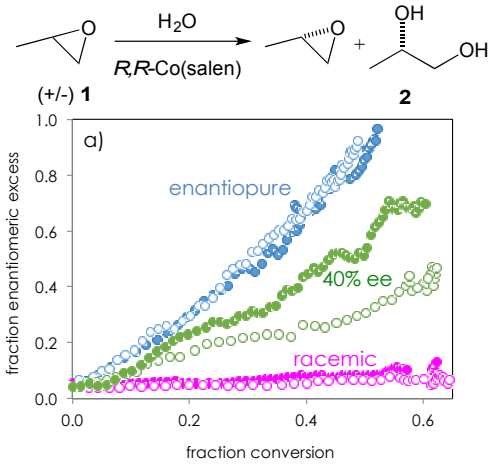
20 See Supporting Information.


H2O
R,R-Co(salen)
OH
OH
(+/-) 1
2
a)
enantiopure
40% ee
racemic
fraction enantiomeric excess
fraction conversion
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6