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Design of a New Bimetallic Catalyst for Asymmetric Epoxidation and Sulfoxidation

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Supporting Information

ABSTRACT: A new chiral tethered 8-quinolinol-based ligand class is developed. The binuclear titanium complex of the ligand operates through a novel mechanism allowing for the regio- and stereoselective epoxidation of primary and tertiary homoallylic alcohols (up to 98% ee), as well as first examples of 2-allylic phenols (up to 92% ee). The new catalyst system also promotes the asymmetric oxidation of γ-hydroxypropyl sulfides giving an important class of chiral sulfoxides that have been inaccessible to date (up to 95% ee).

The classical asymmetric transformations proceed in a substrate-controlled fashion, in which a new stereogenic center is created under the influence of the preexisting stereogenic centers in the molecule. Thus, the regio- and stereochemical outcomes are mostly dependent on the substrates and/or reagents.[1] In sharp contrast, multifunctional active sites of enzymes play an important role for achieving amazingly perfect regio- and stereoslectivites of biological transformations.[2] In this paper, we are pleased to describe the design and application of a novel binuclear catalyst with two independent metal centers—one metal center binds the substrate in the close proximity to the second metal center, which accelerates reactivity and facilitates the enantioselective process.[3]

The catalytic asymmetric epoxidation of olefinic alcohols is an important synthetic transformation.[4] After the pioneering discovery by Sharpless, various systems have been developed by our research group for the asymmetric epoxidation of allylic, homoallylic, and bis-homoallylic alcohols using V-, Zr-, Hf-, and W-based catalysts.[5,6] Despite the many successes of these reported catalysts, various classes of alkenols remain that cannot be epoxidized in high yields and enantioselectivities. We envisioned that the asymmetric epoxidation of a longer chain alkenol could be accomplished via the designing of a chiral binuclear metal catalyst, in which, if the two metal centers reside at an appropriate distance, one metal center would bind with the hydroxy function of the alkenol substrate, while the other metal center supplies the oxidant to the reactive olefin site (Figure 1). Thus, both the metal centers would act as a Lewis acid for the hydroxy-substrate as well as for the electrophilic oxidant.[7]

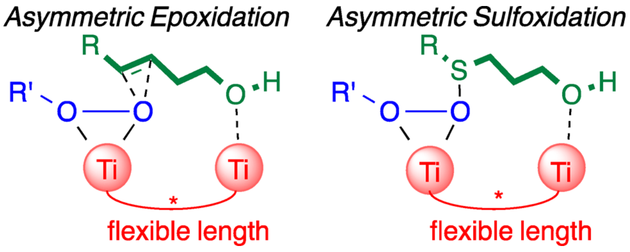
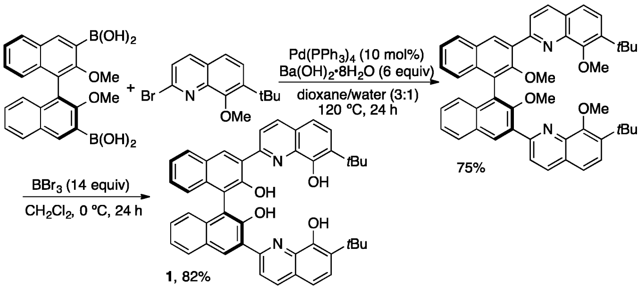


Figure 1. Working hypotheses of the new approach.

Herein, we report a new binuclear titanium catalyst that enables highly regio- and stereoselective oxidation processes, including epoxidation of homoallylic alcohols and 2-allylic phenols and sulfoxidation of γ-hydroxypropyl sulfides. The new method gives a convenient entry to some important classes of optically active compounds that were otherwise inaccessible, including by our previously reported V-, Zr-, Hf-, and W-based protocols (for a comparison see Supporting Information (SI)).

The required ligand[8] 3,3′-bis(7-*tert*-butyl-8-hydroxyquinolinyl)-2,2′-binaphthol (**1**) was simply prepared in two steps via Suzuki cross-coupling of (*S*)-2,2′-dimethoxy-1,1′-binaphthyl-3,3′-diyldiboronic acid with 2-bromo-7-*tert*-butyl-8-methoxyquinoline and subsequent demethylation of the resultant methoxy-compound (Scheme 1).

Scheme 1. Synthesis of the Ligand



To probe the viability of the hypothesis, we initially examined the asymmetric epoxidation of (*E*)-4-phenylbut-3-en-1-ol (**2a**) as the model substrate in CH_2Cl_2 in the presence of **1** and Ti(O-*i*Pr)$_4$ using anhydrous *tert*-butylhydroperoxide (TBHP) as the oxidant (for details see SI). The use of Ti(O-*i*Pr)$_4$ proved to be particularly effective in terms of yield and enantioselectivities compared to the other group 4 and 5 metal sources (Table 1, entry 1). The use of 70% aqueous solution of

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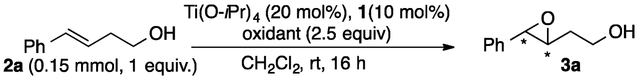
Table 1. Optimization of the Reaction Conditions[a]



no.	oxidant	yield (%)[a]	ee (%)[b]	no.	oxidant	yield (%)[a]	ee (%)[b]
1	TBHP	67	82	4	70% aq TBHP	87	93
2	CHP	81	80	5[c]	70% aq TBHP	56	78
3	30% aq H_2O_2	50	30	6[d]	70% aq TBHP	28	21

[a]Isolated yield. [b]Determined by chiral HPLC. [c]With 10 mol % Ti(O-*i*Pr)$_4$ and 5 mol % **1**. [d]With 10 mol % Ti(O-*i*Pr)$_4$ and 10 mol % **1**.

TBHP (entry 4) gave the best result.[9] This finding is in contrast to Sharpless epoxidation, which demands absolutely anhydrous TBHP to achieve a higher enantiomeric excess.[10] We observed that a 2:1 ratio of metal-to-ligand was crucial; the use of a 1:1 metal-to-ligand ratio gave poor results (entry 6). The formation of the 2:1 Ti−ligand complex in solution was also supported by HRMS analysis.[11] The two *tert*-butyl groups in the ligand were the key to achieving excellent enantioselectivity, as in its absence a virtually racemic product was obtained.

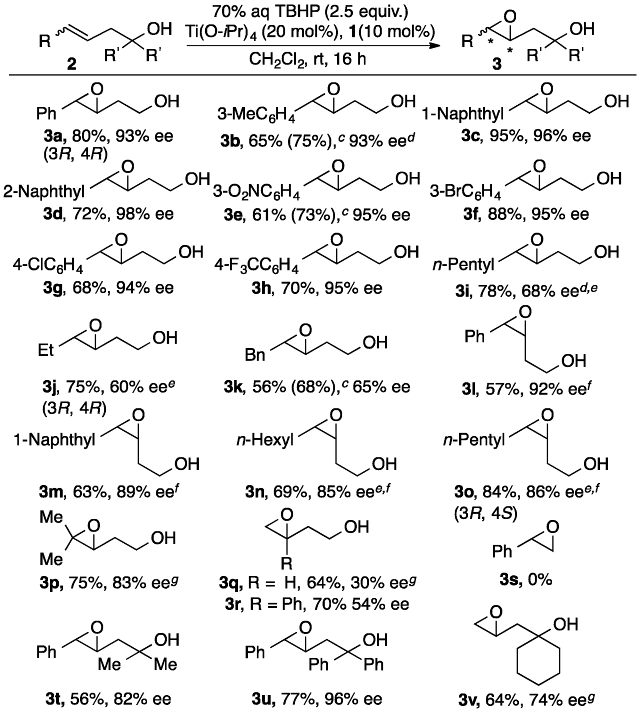
Cinnamyl alcohol reacts under the optimized conditions in a much slower rate with moderate stereoselectivity (40% yield, 55% ee) compared to **2a**, whereas the epoxidation of bis-homocinnamyl alcohol does not proceed. This suggests that the transition state of the reaction significantly differs from that previously proposed for single metal or cooperative dual metal catalysts,[12] as in such cases epoxidation only with allylic alcohols would give high stereoselectivities.

We next investigated the scope of asymmetric epoxidation with primary and tertiary homoallylic alcohols (Scheme 2). Gratifyingly, both *trans*- and *cis*-substituted epoxides were achieved with good to high enantioselectivities and satisfactory yields. The absolute configurations of **3a** and **3j** were determined as (3*R*,4*R*) and that of **3o** as (3*R*,4*S*) by comparison of their optical rotation values with those in the literature.[13] However, the epoxidation does not proceed with terminal alkene **3s**, confirming that the hydroxy-group of the alkenol acts as an anchor to the Ti-catalyst.[14]

Encouraged by these promising results, we subsequently studied the regio- and enantioselective monoepoxidation of conjugated homoallylic alcohols at the proximal double bond. The resultant epoxy-alkenols and their chemically or enzymatically derived triols are the key subunits in numerous bioactive compounds.[15] It soon turned out that the catalyst system was equally effective for a range of conjugated homoallylic alcohols with diverse substitution patterns (Scheme 3). To the best of our knowledge, no existing catalyst system has allowed for monoepoxidation of homoallylic alcohols in high enantioselectivities to date.

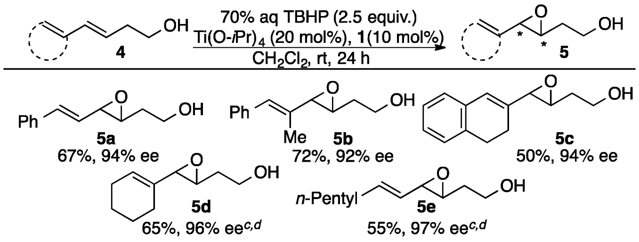
With the success of the asymmetric epoxidation, we applied this approach to the kinetic resolution of secondary homoallylic alcohols (Scheme 4). Both the starting homoallylic alcohol **6** and the epoxy alcohol **7** were obtained in high enantiopurity.

Scheme 2. Scope of the Asymmetric Epoxidation of Homoallylic Alcohols[a,b]



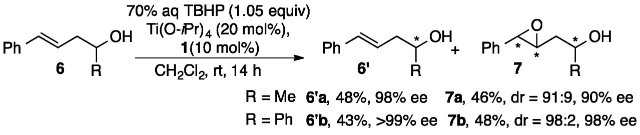
[a]Reaction conditions: 0.15 mmol of **2** (1 equiv), 2.5 equiv of 70% aq TBHP, 20 mol % Ti(O-*i*Pr)$_4$, 10 mol % **1**, in 3 mL of CH_2Cl_2 at room temperature for 16 h; isolated yields. [b]Ee was determined by chiral HPLC. [c]NMR yield of crude product. [d]At 0 °C. [e]Ee of the benzoyl derivative. [f]With 3.5 equiv of 70% aq TBHP, and for 48 h. [g]Ee was determined by chiral GC.

Scheme 3. Asymmetric Proximal-Selective Monoepoxidation of Conjugated Homoallylic Alcohols[a,b]



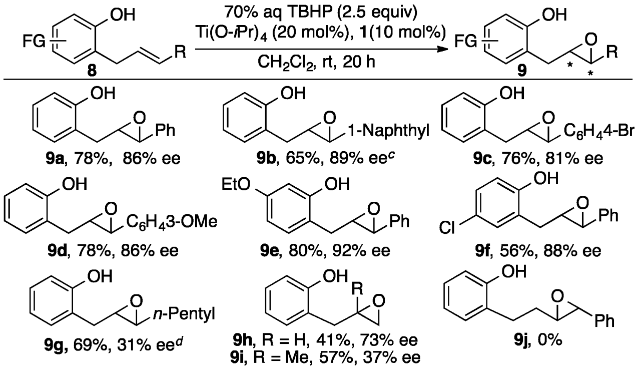
[a]Isolated yield. [b]Ee was determined by chiral HPLC. [c]Ee was determined by chiral GC. [d]At 0 °C.

Scheme 4. Kinetic Resolution of Secondary Homoallylic Alcohols



Next, we tested the asymmetric epoxidation of 2-allylic phenols as a new substrate class in which the double bond is situated three carbons away from the hydroxyl group. Although the synthesis of racemic epoxides of such substrates was accomplished via *m*-CPBA-mediated[16] or V-catalyzed[17] protocols, the asymmetric version has never been documented in the literature. When 2-cinnamyl phenol **8a** was subjected to epoxidation under the optimized conditions, the desired epoxide **9a** was formed in good yield and with significant enantioselectivity. A variety of 2-allylic phenols underwent asymmetric epoxidation with good to high enantioselectivities (Scheme 5). The presence of functional groups, such as Cl, Br, OMe, OEt, etc., in both of the phenyl rings (**9c**−**9f**) does not

Scheme 5. Asymmetric Epoxidation of 2-Allylic Phenols[a,b]

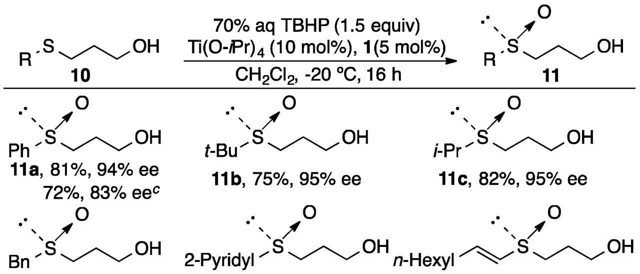


[a]Isolated yields. [b]Ee was determined by chiral HPLC. [c]For 24 h. [d]At 0 °C.

significantly alter the reaction rate or stereoselectivity. However, the enantioselectivity drops in the presence of an aliphatic substituent in the allylic side chain (**9g**), presumably due to the flexible aliphatic chain allowing the catalyst to oxidize from both faces of the alkene. 2-Allylic phenols with terminal double bonds were also epoxidized with considerable enantioselectivity (**9h** and **9i**). Unfortunately, 2-homocinnamyl phenol did not undergo epoxidation under the optimized conditions (**9j**).

In order to demonstrate the general synthetic applicability of the new approach, we further studied the asymmetric sulfoxidation of various hydroxy-containing sulfides.[18] It soon turned out that the presence of the hydroxy-directing group at the γ-position of the sulfide is crucial to achieving excellent enantioselectivity, as the sulfoxidation of simple propyl phenyl sulfide and β-hydroxyethyl phenyl sulfide proceeded with very poor yields and enantioselectivities.[19] Thus, a diverse range of γ-hydroxypropyl sulfides were subjected to sulfoxidation (**11a**–**11f**), giving high yields and excellent enantioselectivities (Scheme 6).

Scheme 6. Asymmetric Sulfoxidation of γ-Hydroxypropyl Sulfides[a,b]



[a]Isolated yield. [b]Ee was determined by chiral HPLC. [c]With 5 mol % $Ti(O\text{-}iPr)_4$ and 2.5 mol % ligand.

DFT calculations at the B3LYP/6-311G* level were also conducted to address the observed stereoselectivities. The most favorable transition state is in accord with our previously mentioned working hypothesis for the epoxidation reaction of **2a** catalyzed by (*S*)-**1** (Figure 2).[20]

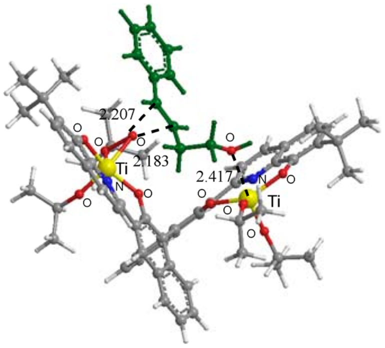


Figure 2. B3LYP/6-311G* optimized transition-state structure of the epoxidation of **2a**.

In conclusion, we have developed a new optically active ligand class that can accommodate two "independent" titanium centers in the active site. The binuclear Ti-complex allows for highly regio- and enantioselective processes, e.g., epoxidation of not only homoallylic alcohols but also 2-allylic phenols and sulfoxidation of γ-hydroxypropyl sulfides. The selective binding abilities of the ligand with metal ions in the bimetallic catalyst scaffold open up the new possibility of "catalyst-controlled chemical reactions". Hence, the ligand system offers numerous opportunities for variation in the future and is currently under further investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11429.

Experimental procedures (PDF)
Spectral data (PDF)
HPLC and GC chromatograms (PDF)
Computational details (PDF)

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Notes

The authors declare no competing financial interest.

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(20) DFT calculations for all the possible transition states are described in detail in the SI.