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Bis(μ-oxo)−Dititanium(IV)−Chiral Binaphthyldisulfonate Complexes for Highly Enantioselective Intramolecular Hydroalkoxylation of Nonactivated Alkenes

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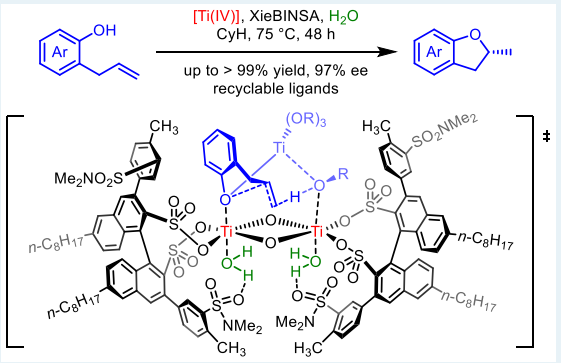
ABSTRACT: A series of chiral 1,1′-binaphthyl-2,2′-disulfonic acids was designed, synthesized, and applied in a highly enantioselective Ti-catalyzed intramolecular hydroalkoxylation of nonactivated alkenes. The catalyst is probably a complex between two chiral binaphthyldisulfonate ligands and a bis(μ-oxo)−dititanium(IV) core structure. The sulfonamide groups of the ligands and water are necessary for the catalysis, as they may stabilize the catalytically active complex through hydrogen bonding. Various 2-methylcoumarans were obtained in up to greater than 99% yields and up to 97% enantiomeric excess under mild conditions.



KEYWORDS: *asymmetric catalysis, hydroalkoxylation, alkene, binaphthyldisulfonic acid, titanium*

The asymmetric hydroalkoxylation of alkenes is an attractive method to construct chiral ethers, as it is simple and intrinsically atom-economical.[1] Strong Lewis and Brønsted acids enable a very efficient hydroalkoxylation of alkenes,[2−5] but an enantioselective hydroalkoxylation catalyzed by chiral Lewis acids has suffered from harsh reaction conditions and hampered enantioselectivity in comparison to that by chiral Brønsted acids (Scheme 1a−d).[6−14] An intriguing question would be whether the activity of strong Lewis acids and a high selectivity of chiral ligands can be combined in a single catalyst. The prevalence of triflate Lewis acids suggests that chiral binaphthyldisulfonic acids would be suitable candidates that preserve the Lewis acidity of the central metals. For example, chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA),[15−19] which itself is a strong chiral Brønsted acid, has been proven to be a promising chiral ligand for a metal-mediated enantioselective catalysis.[20−24] Here we report our design of a new type of chiral sulfonic acids and their applications in a highly enantioselective intramolecular hydroalkoxylation under mild conditions (Scheme 1e).

The new ligands, XieBINSAs, all contain a SO_2NMe_2 or SO_2NEt_2 moiety at the substituted aryl groups. The keys to synthesizing XieBINSAs are multiple cross-coupling reactions, Newman−Kwart rearrangement (NKR),[25] and oxidation of *S*-thiocarbamoyl compounds. The electron-withdrawing property of the sulfonamide groups made the synthesis easier in comparison to that for other existing sulfonic acids.[17] All ligands can be obtained with up to 37% total yield in 11 steps (see Figures S1−S3 in the Supporting Information for details).

We initially examined the reaction of 2-allylphenol (**1a**) using the $(CF_3)_2$Ph-substituted BINSA **L1** along with metals.[16,26] While **L1** itself enabled a complete conversion of the substrate without any asymmetric induction (Table 1, entry 1), the metal/ligand (M/L = 1:1) complex between Ti(O-*i*-Pr)$_4$ and **L1** gave a greater than 99% yield with 39% enatiomeric excess (ee) in dry toluene at 90 °C (Table 1, entry 2; see Table S1 in the Supporting Information for a detailed study of **L1**). Unfortunately, BINSAs with or without fluoroalkyl groups all afforded poor results (Table 1, entries 3−6).[15,27] A significant improvement in ee value was observed when using XieBINSA **L6** as the ligand, especially when the metal was applied in excess (entries 7−9). In addition, the reaction temperature could be reduced to 75 °C, producing 74% ee, albeit with more time (entry 11). More surprisingly, titanium alkoxides with bulkier alkyl groups gave higher ee values, among which Ti(EHO)$_4$ (tetrakis(2-ethylhexyoxy)-titanium) was the best (entries 11−13). Other metal alkoxides, such as those of Hf, Zr, La, and Pd, did not have as high an

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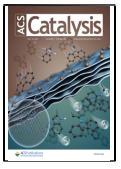
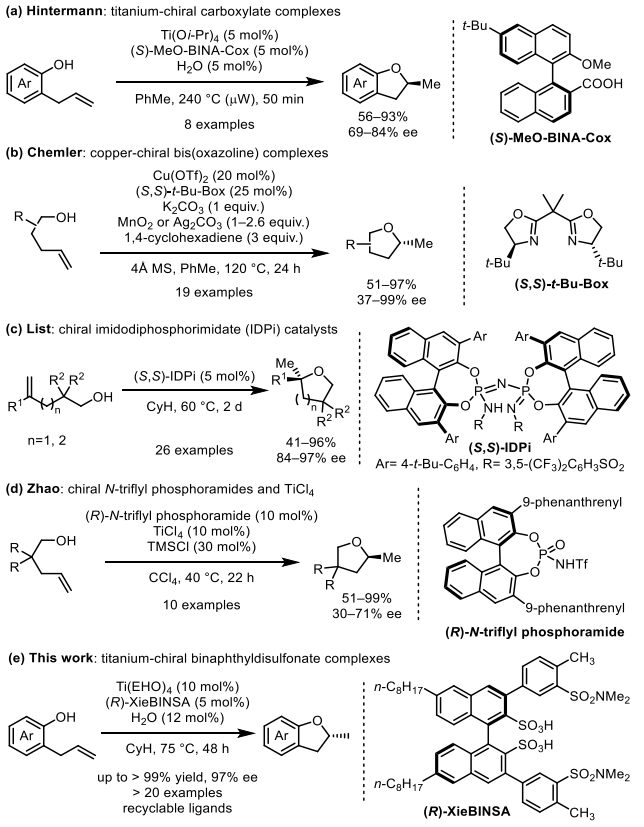


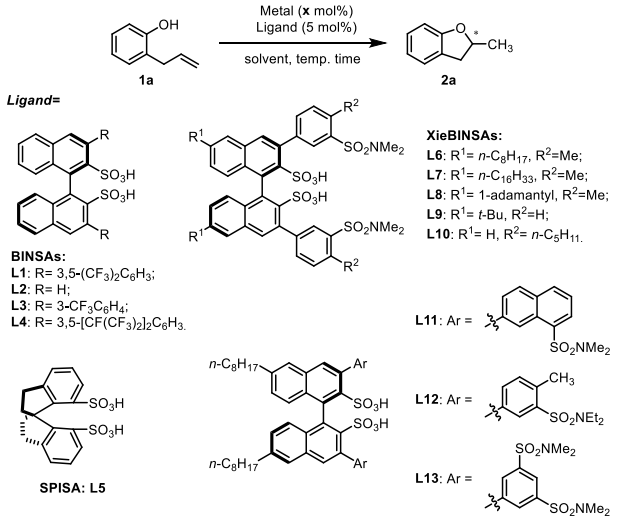
Scheme 1. Acid-Catalyzed Asymmetric Intramolecular Hydroalkoxylation of Nonactivated Alkenes



activity or enantioselectivity (Table S2). Subsequently, several XieBINSAs were used as the chiral ligands in an M/L ratio of 2:1 at 75 °C (entries 14−20). Although **L7**−**L13** did not provide as high an enantioselectivity as **L6**, their structural diversity demonstrated that, in the ligand design, the sulfonamide group and the 6,6′-alkyl groups are necessary. Finally, the reaction produced 97% ee with a greater than 99% yield in cyclohexane (CyH) at 75 °C (Table 1, entry 21; see Table S2 in the Supporting Information for additional data). Note that, because of their high water solubility, all XieBINSAs can be recycled by extraction into alkaline methanol followed by acidification with ion exchange resins.

During the conditions study, inconsistent results were sometimes obtained. In particular, the reaction did not proceed at all in the presence of activated 4 Å molecular sieves (Table S2). This indicates that water may be involved in the catalyst formation process, which is not uncommon for titanium complexes.[7,28−30] The effect of water was then evaluated by adding different amounts of water to a preformed anhydrous mixture of **L6** and $Ti(EHO)_4$. The catalysis results indeed confirmed that the yields and enantioselectivities are both correlated to the amount of water by showing a volcano plot (Figure 1a; see Table S3 in the Supporting Information for details).[7] Moreover, the relative ratio between water and $Ti(EHO)_4$ also seriously affects the reaction rate and enantioselectivity (see Table S4 in the Supporting Information). When the optimal 10−12 mol % water was added, (*R*)-**2a** was obtained in a greater than 99% yield with 97% ee in only 24 h, which is much faster than in any previous investigations.

Table 1. Optimization of Catalytic Asymmetric Hydroalkoxylation of 2-Allylphenol



entry[a]	metal (*x*)	ligand	temp, °C	yield,[b] %	ee,[c] %
1		**L1**	90	>99	0
2	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L1**	90	>99	−39
3	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L2**	90	>99	−1
4	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L3**	90	96	−33
5	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L4**	90	11	−2
6	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L5**	90	15	−5
7	$Ti(O\text{-}i\text{-}Pr)_4$ (5)	**L6**	90	51	46
8	$Ti(O\text{-}i\text{-}Pr)_4$ (7.5)	**L6**	90	89	57
9	$Ti(O\text{-}i\text{-}Pr)_4$ (10)	**L6**	90	98	63
10	$Ti(O\text{-}i\text{-}Pr)_4$ (15)	**L6**	90	36	36
11	$Ti(O\text{-}i\text{-}Pr)_4$ (10)	**L6**	75	95	74
12	$Ti(O\text{-}i\text{-}Bu)_4$ (10)	**L6**	75	98	86
13	$Ti(EHO)_4$ (10)	**L6**	75	>99	89
14	$Ti(EHO)_4$ (10)	**L7**	75	70	70
15	$Ti(EHO)_4$ (10)	**L8**	75	56	69
16	$Ti(EHO)_4$ (10)	**L9**	75	14	33
17	$Ti(EHO)_4$ (10)	**L10**	75	43	8
18	$Ti(EHO)_4$ (10)	**L11**	75	72	40
19	$Ti(EHO)_4$ (10)	**L12**	75	>99	76
20	$Ti(EHO)_4$ (10)	**L13**	75	65	−30
21[d]	$Ti(EHO)_4$ (10)	**L6**	75	>99	97

[a]Reaction conditions: after a mixture of the ligand (5 mol %) and metal alkoxides (*x* mol %) in PhMe (0.5 mL) was stirred at 60 °C for a catalyst formation process of 0.5 h, **1a** (0.1 mmol) was added. Entries 1−10, 90 °C, 36 h; entries 11−21, 75 °C, 48 h. See Tables S1 and S2 in the Supporting Information for details. [b]Determined by ^1H NMR using CH_2Ph_2 as an internal standard. [c]Determined by chiral SFC analysis. Positive values represent the enrichment of (*R*)-**2a**. [d]CyH as solvent.

A matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) analysis showed the predominance of the formula $Ti_2O_2(XieBINSA)_2$, consistent with a polynuclear bis(μ-oxo)−dimetal Ti_2O_2−chiral binaphthyldisulfonate complex,[7,28−34] from the samples prepared from a mixture of $Ti(EHO)_4$, water, and XieBINSAs (**L6**, **L8**, **L9**, and **L13**) in CyH. As a comparison, similarly prepared samples of conventional BINSAs (such as **L1** and **L3**), which showed no catalytic activity (Table S4), did not show signals of such complexes (Figures S4−S6). The SO_2NMe_2 moiety is probably necessary for the formation of the active metal complex. 2-Ethylhexanol (EHOH) generated during the metal complex

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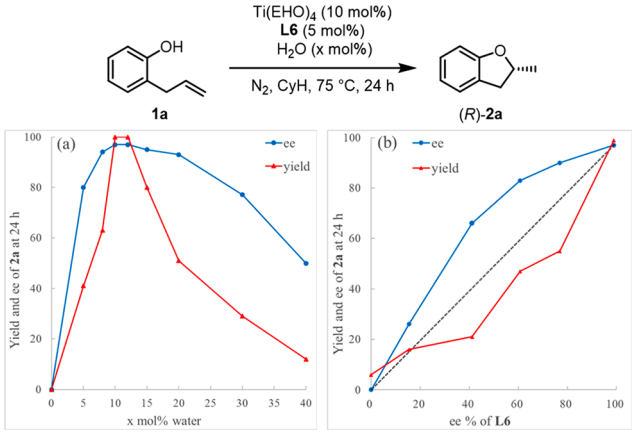


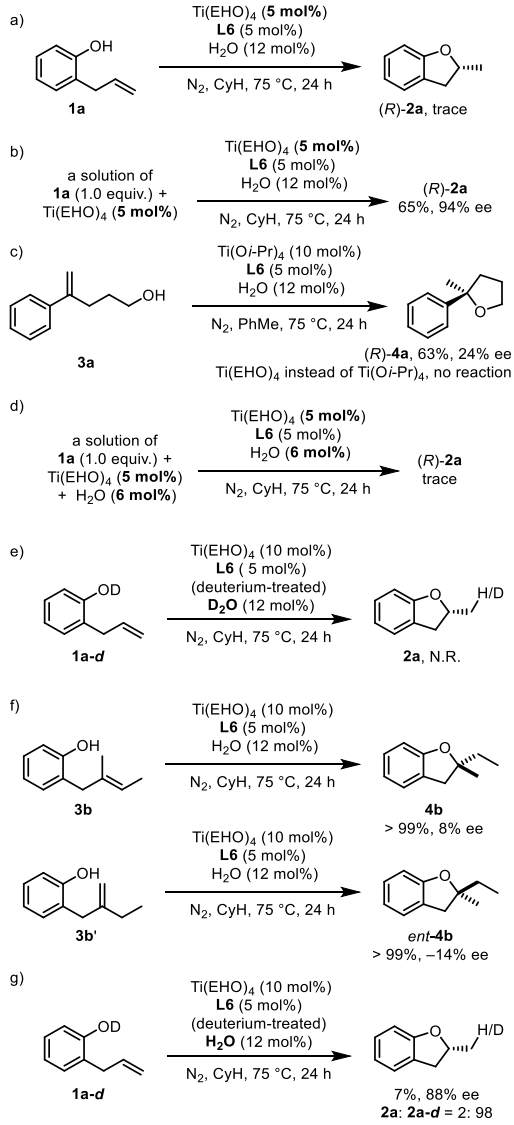
Figure 1. Water effects on yield and enantioselectivity (a) and NLE between (*R*)-**2a** and (*R*)-**L6** (b, $x = 12$).

formation seemed to promote the solubility of the catalyst. Using Ti(O-*i*-Pr)$_4$ as the metal source resulted in a cloudy mixture and poor results (see Figure S7). In addition, a positive nonlinear effect (NLE) was observed by using **L6** with different ee values (Figure 1b; see Table S5 in the Supporting Information for details), indicating the active catalyst is likely not monomeric in the chiral ligand.

The dimeric complex became a bigger puzzle in deciphering the true catalyst, because it can only account for a 2:2:2 metal/ligand/water (M/L/W) ratio composition, while the optimal M/L/W ratio is 4:2:4. The excess Ti(EHO)$_4$ may act as an essential substrate transporter to the catalytic center by forming a mixed alkoxide salt with the substrate, and a few experiments support this hypothesis. First, a composition of 2:2:4 M/L/W could not catalyze the reaction (Scheme 2a), but when the excess portion of Ti(EHO)$_4$ was added separately into the reaction system after the catalyst formation process, the reaction proceeded as usual (Scheme 2b, see eq S3 in the Supporting Information for details). These experiments suggest that the excess Ti(EHO)$_4$ did not serve as the metal source of the chiral metal complex. Second, the primary alcohol substrate **3a** underwent a cyclization using Ti(O-*i*-Pr)$_4$ as the metal source but not Ti(EHO)$_4$ (Scheme 2c; see Table S6 in the Supporting Information for details), suggesting that the ligand exchange product, Ti(EHO)$_m$(OR^{Sub})$_{4-m}$, in which R^{Sub}OH represents the substrate, is essential and that the higher pK_a of **3a** in comparison to phenol substrates prevented its reaction with Ti(EHO)$_4$. Third, too much Ti(EHO)$_4$ inhibited the reaction, which could be attributed to the increase in m of Ti(EHO)$_m$(OR^{Sub})$_{4-m}$ that may reduce the transportation efficiency of R^{Sub}O to the catalyst (Figure S8). Thus, Ti(EHO)$_m$(OR^{Sub})$_{4-m}$ could be the key intermediate that transports the substrate to the dimeric catalyst.

The excess water is believed to be involved in the catalyst formation process, because separate additions of excess water and Ti(EHO)$_4$ into a 2:2:2 M/L/W mixture did not give any product (Scheme 2d; see eq S4 in the Supporting Information for details). Since an MALDI-TOF analysis did not reveal the incorporation of additional water into the dimeric complex, we believe the excess water most likely interacts with the complex through hydrogen bonding. As a further demonstration, the reaction did not work if H_2O was replaced with D_2O (Scheme 2e), in which a formula of one less oxygen [Ti$_2$O-(XieBINSA)$_2$] was detected as the major component in the MALDI-TOF analysis (Figure S9). This could be attributed to

Scheme 2. Mechanistic Studies and Control Reactions



a shorter D−O hydrogen bond in comparison an H−O hydrogen bond, which might disrupt the formation of the delicate catalytically active metal complex.[35]

With the information on the possible catalyst and intermediates in hand, we were able to propose a tentative catalytic cycle of the asymmetric hydroalkoxylation (Scheme 3). First, the complex [(μ-O)Ti(XieBINSA)]$_2$ was generated in situ from Ti(EHO)$_4$, **L6**, and H_2O in a 4:2:4 ratio. The excess water most likely bridges one SO_2NMe_2 group of one XieBINSA and one Ti(IV) of the Ti_2O_2 cluster through hydrogen bonding. The dimeric complex may thus adopt *cis*- or *trans*-diaqua configurations (Figure S11). The *cis*-diaqua configuration seems to be the favored structure for catalysis, since its two open coordination sites are facing the same side and constitute a wide chiral pocket. The excess Ti(EHO)$_4$ may coordinate with the free SO_2Me_2 (Figure S11) before forming the substrate-transporting complex titanium phenoxide **A** with **1a** and releasing EHOH, which was clearly observed in an NMR spectrum (Figure S8). Then, the substrate RO was transported to the titanium metal center of the active *cis*-diaqua-[(μ-O)Ti(XieBINSA)]$_2$ as intermediate **B** by a ligand exchange. Subsequently, the reaction underwent a concerted

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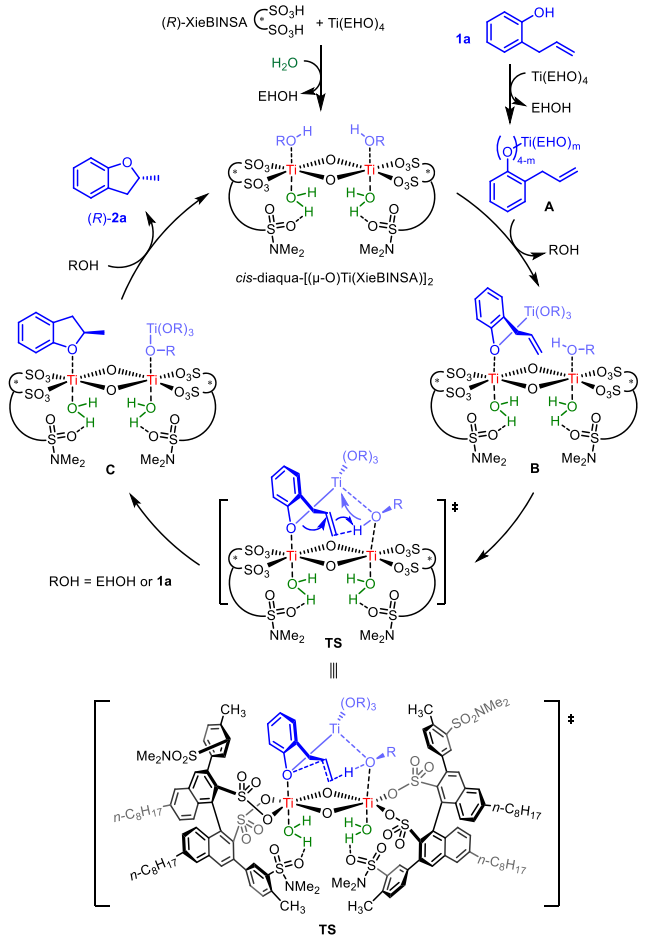
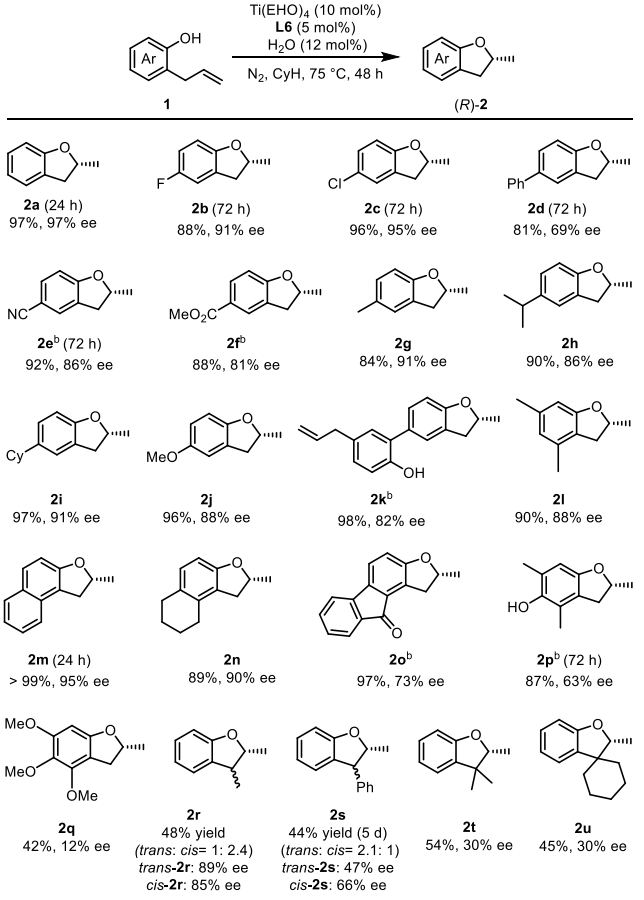
Scheme 3. Proposed Catalytic Cycle



transition state **TS**,[26] in which protonation of the double bond and C−O bond formation occur simultaneously.[9,36] Finally, the product (*R*)-**2a** was obtained through a ligand exchange between the intermediate **C** and any ROH (such as EHOH or $\mathbf{R}^{Sub}$OH) in the system. The concerted **TS** is supported by the following experiments: if the reaction operates under a stepwise mechanism through any carbocation intermediate before the enantioselectivity-determining step, substrates **3b** and **3b′** should provide the same selectivity, since they generated the same carbocation. However, in reality they gave the opposite selectivity of **4b** under the same conditions (Scheme 2f). Second, a reaction kinetics study revealed the first-order kinetics of **1a** (Table S7), and the reaction of 2-allylphenol-*d* catalyzed by a catalyst made with H_2O resulted in a low yield (7%), unusually large kinetic isotope effect (KIE) = 66.7(±8.2), and reasonable ee (88%) (Scheme 2g; see Figure S10 in the Supporting Information for details). The rate-determining step likely involves the cleavage or formation of an X−H bond (X = O or C) in a linear transition state of a hydrogen transfer.[37] Note that, since the reaction system with all active protons replaced by deuterium did not give any conversion (Scheme 2e), the extra KIE could be the result of the generation of inactive Ti complexes in the presence of deuterium.

Under the optimized reaction conditions, the intramolecular hydroalkoxylation substrate scope was examined using 10 mol % of Ti(EHO)$_4$, 5 mol % of (*R*)-XieBINSA **L6**, and 12 mol % of H_2O as the standard catalyst. Various 2-allylphenols **1a**−**1u** underwent facile cyclization, giving the Markovnikov-type 2-methylcoumaran derivative addition products **2a**−**2u** in high yields and ee values (Scheme 4). The *para* substituents of the

Scheme 4. Catalytic Asymmetric Hydroalkoxylation of Non-Activated Alkenes[a]



[a]Isolated yields at 48 h. Chiral SFC analysis for ee. See Section 5 in the Supporting Information for details. Cy = cyclohexyl. [b]PhMe as solvent.

phenol did not affect the enantioselectivities, regardless of their electronic and steric properties (**2b**−**2k**). The *meta* substituents on either side of the OH group also allow good reaction results (**2l**−**2q**). Note that substrates such as **1e**, **1f**, **1k**, **1o**, and **1p** suffered from poor solubility in CyH, and their reactions had to be performed in toluene. The reaction tolerates a variety of functional groups: halogens (**1b**, **1c**), nitrile (**1e**), ester (**1f**), ether (**1j**, **1q**), phenol (**1k**, **1p**), isolated alkene (**1k**), and ketone (**1o**). Racemic 2-(but-3-en-2-yl)-phenol **1r** could cyclize into both diastereomers of **2r**, with 89% ee of *trans*-**2r** and 85% ee of *cis*-**2r** in a 1:2.4 diasteriomeric ratio (dr) at 48 h, while 26% ee of the remaining **1r** was left. However, reactions of 2-(1-phenylallyl)-phenol **1s**, *α*,*α*-dimethyl 2-allylphenol **1t**, and spirocyclic cycloalkyl derivative **1u** proceeded with low reaction rates and poor ee values, likely due to steric hindrance according to the mechanism, which also explains why the *ortho*-substituted 2-allyl-6-methylphenol **1v** did not react at all (Table S8). In the **TS**, the position *ortho* to the phenol OH is very close to the SO_2NMe_2-substituted aryl ring, while the benzyl position is

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close to the SO_2NMe_2 moiety. Any substituents on these positions greatly hampered the reactivity and selectivity.

In conclusion, we have developed a new type of chiral binaphthyldisulfonic acid ligands, XieBINSAs, and discovered that their complexes with a bis(μ-oxo)−dititanium core structure are able to catalyze asymmetric intramolecular hydroalkoxylation of 2-allylphenols to chiral 2-methylcoumarans in excellent yields and enantioselectivities under mild conditions. The reaction likely proceeds via a concerted mechanism of protonation−cyclization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01146.

Details of the preparation of ligands and starting materials, details of the optimization of the reactions, details of nonlinear effect data, details of the preparation and characterization of catalysts, details of the deuteration experiments and kinetic studies data, details of the experimental procedures, and characterization data (NMR, MS, SFC analysis) (PDF)

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Notes

The authors declare the following competing financial interest(s): Part of the results have been filed in a patent in which Z. L. and W.-B. X. are the inventors.

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