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Molybdenum-catalyzed asymmetric *anti*-dihydroxylation of allylic alcohols

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Asymmetric dihydroxylation of alkenes is one of the fundamental reactions in organic synthesis, but the *anti*-dihydroxylation is much less developed than its *syn*-variant. Here we report a highly enantio- and diastereoselective *anti*-dihydroxylation of allylic alcohols by using a chiral molybdenum-bishydroxamic acid complex as catalyst and environmentally benign hydrogen peroxide as oxidant. This reaction enables the construction of the 1,2,3-triol structural unit in high enantio- and diastereocontrol starting from simple allylic alcohol precursors. Our reaction complements the Sharpless dihydroxylation not only in its diastereoselectivity, but also in regiocontrol. The mechanistic studies indicate that this dihydroxylation reaction consists of an initial enantioselective epoxidation and the following in situ regioselective ring opening, both of which are promoted by the molybdenum-catalyst.

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Asymmetric dihydroxylation of alkenes is one of the cornerstone reactions in organic synthesis, as it provides a direct entry to optically active vicinal diols, which are a subunit in a large number of naturally occurring compounds and also important building blocks in many syntheses[1,2]. The classic Os-catalyzed asymmetric *syn*-dihydroxylation, known as Sharpless dihydroxylation, demonstrates high efficiency and enantiocontrol for a broad range of substrates, and thus finds widespread applications in the total synthesis of natural products[1,3–10]. However, the toxicity, volatility, and high cost of OsO_4 urge organic chemists to establish alternative catalytic systems for asymmetric dihydroxylation utilizing inexpensive and less toxic catalysts. In the past two decades, a number of Os-free asymmetric *syn*-dihydroxylations have been developed[11], including the examples using chiral Mn- [12,13] or Fe- [14,15] complexes, bimetallic nanoclusters[16] and organic phase transfers as catalysts[17,18]. In the field of *anti*-dihydroxylation, highly enantioselective variants are scarce. Jørgensen et al. reported a formal asymmetric *anti*-dihydroxylation of α,β-unsaturated aldehydes by merging amine-catalyzed enantioselective epoxidation and strong base-mediated methanolysis in a one-pot procedure (Fig. 1a)[19]. Moreover, Li and his co-workers applied successfully the combination of monooxygenase and epoxide hydrolase in the enzyme-catalyzed asymmetric *anti*-dihydroxylations (Fig. 1b)[20–23]. On the other side, molybdenum catalysis finds wide applications in oxidation reactions[24,25]. Recently, our group discovered that $MoO_2(acac)_2$ is

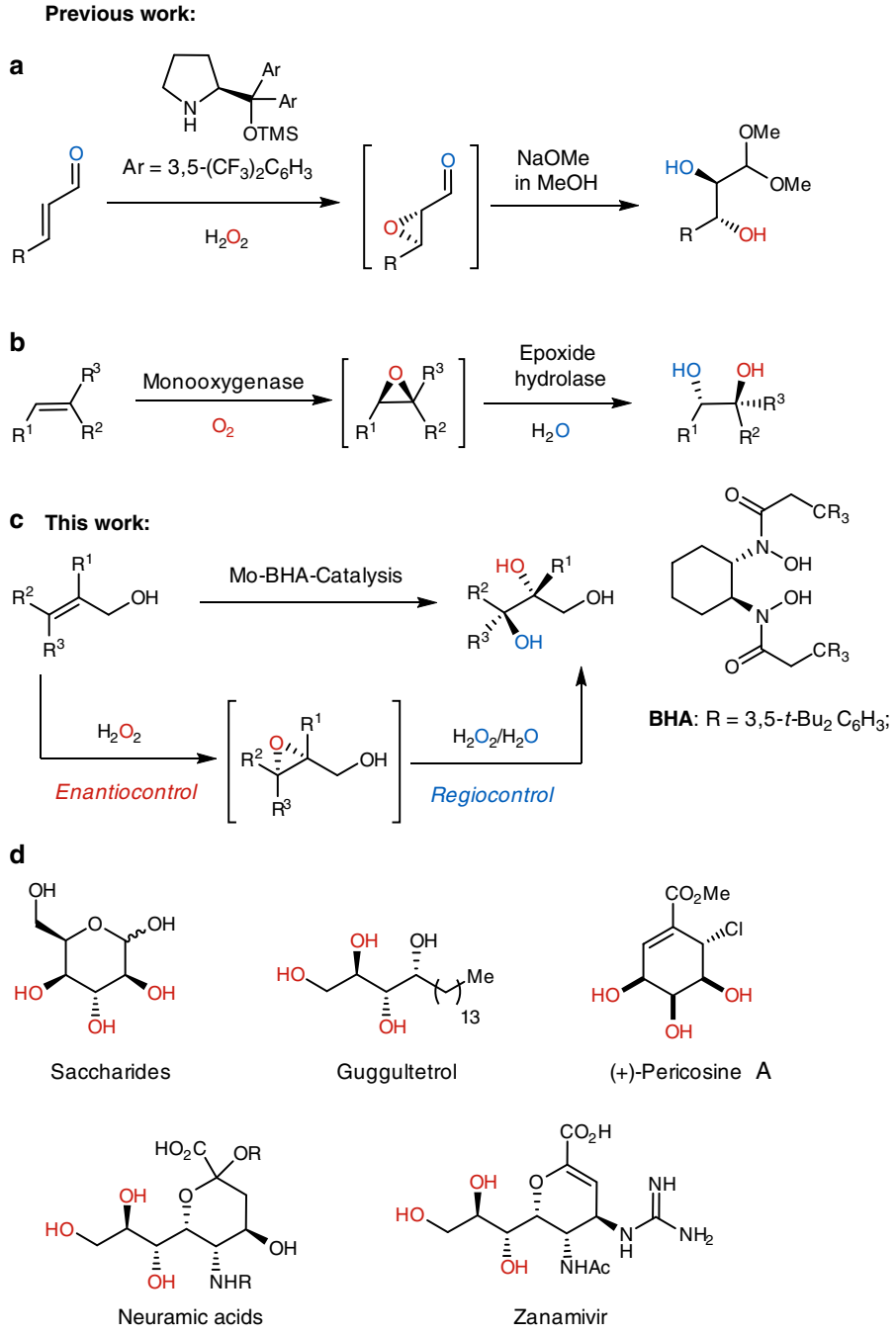


Fig. 1 *Anti*-dihydroxylation of alkenes. **a** Amine-catalyzed asymmetric formal *anti*-dihydroxylation. **b** Enzyme-catalyzed asymmetric *anti*-dihydroxylation. **c** This work: molybdenum-bishydroxamic acid-catalyzed asymmetric *anti*-dihydroxylation. **d** Examples of natural products and synthetic biologically active compounds containg a 1,2,3-triol unit

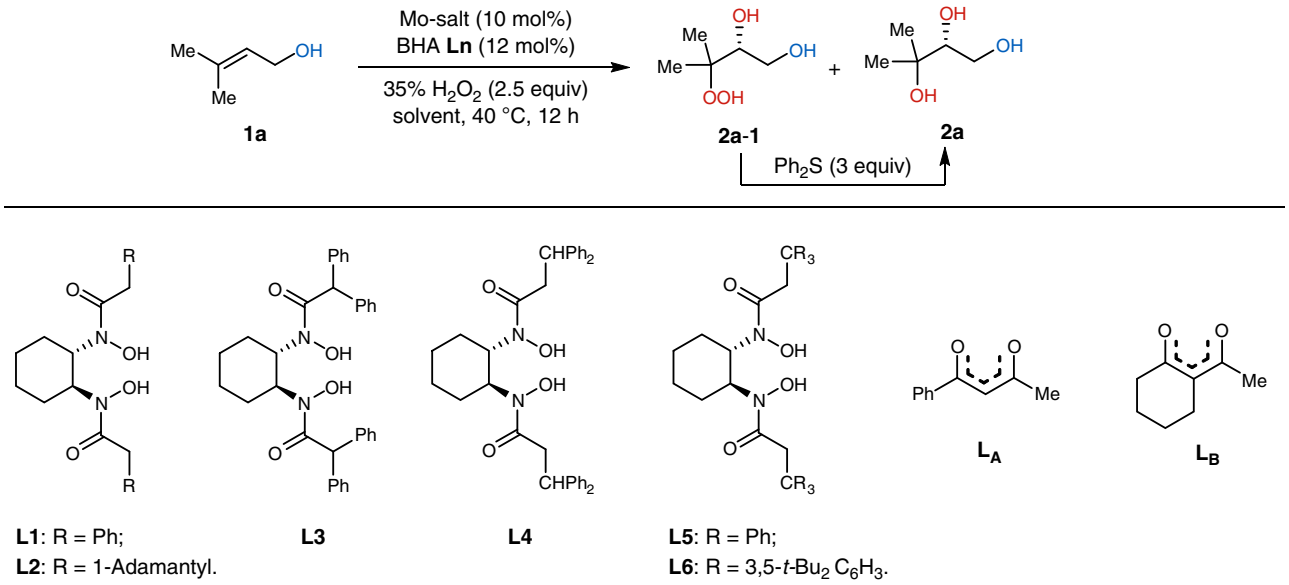


Fig. 2 Model system used for optimization of the reaction conditions. Full conditions are reported in Table 1

Table 1 Ligands, solvents and Mo-precatalyst screening for the Mo-catalyzed asymmetric *anti*-dihydroxylation of 3-methylbut-2-en-1-ol[a]

entry	ligands	Mo-precatalyst	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	$MoO_2(acac)_2$	EtOAc	89	−11
2	**L2**	$MoO_2(acac)_2$	EtOAc	81	−16
3[d]	**L3**	$MoO_2(acac)_2$	EtOAc	96	−10
4	**L4**	$MoO_2(acac)_2$	EtOAc	60	12
5	**L5**	$MoO_2(acac)_2$	EtOAc	88	28
6	**L6**	$MoO_2(acac)_2$	EtOAc	85	93
7	**L6**	$MoO_2(acac)_2$	MeCN	54	71
8	**L6**	$MoO_2(acac)_2$	1,4-dioxane	88	86
9	**L6**	$MoO_2(acac)_2$	DCM	48	89
10	**L6**	$MoO_2(acac)_2$	HFIP	47	76
11	**L6**	$MoO_2(acac)_2$	nitromethane	trace	n.d.[e]
12	**L6**	$MoO_2(acac)_2$	acetone	49	90
13	**L6**	MoO_2Cl_2	EtOAc	82	82
14	**L6**	MoO_3	EtOAc	87	91
15	**L6**	$MoCl_5$	EtOAc	53	70
16	**L6**	H_2MO_4	EtOAc	78	88
17	**L6**	$Mo_2(OAc)_4$	EtOAc	98	91
18	**L6**	$MoO_2(\mathbf{L_A})_2$	EtOAc	87	91
19	**L6**	$MoO_2(\mathbf{L_B})_2$	EtOAc	82	92
20[f]	**L6**	$MoO_2(acac)_2$	EtOAc	72	93
21[f,g]	**L6**	**$MoO_2(acac)_2$**	**EtOAc**	**90**	**94**

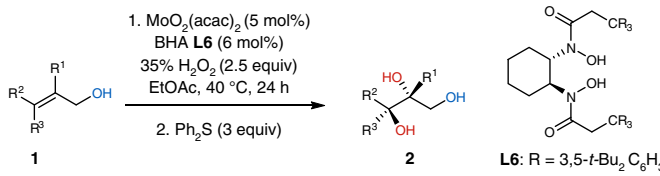
[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the allylic alcohol **1a** using 2.5 equiv 35% aqueous H_2O_2, 10 mol % Mo-precatalyst and 12 mol% ligand in 1.0 mL solvent at 40 °C for 12 h
[b]Yields of the isolated product after column chromatography
[c]Determined by HPLC-analysis on chiral stationary phase
[d]Reaction time: 40 h
[e]Not determined
[f]Reaction was performed with 5 mol% $MoO_2(acac)_2$, 6 mol% **L6**
[g]Reaction performed in 2 mL EtOAc for 24 h

able to catalyze direct *anti*-dihydroxylation of allylic alcohols with hydrogen peroxide as oxidant, providing diverse racemic 1,2,3-triols as products[26,27]. The challenge of realizing the highly enantioselective version of this reaction lies in not only the enantiocontrol of the initial epoxidation but also the regiocontrol of the following ring opening reaction. The lack of control in either of these two elementary steps will result in low level of asymmetric induction of the final products. Furthermore, the ligand-mismatch effect in the potential kinetic resolution in the ring opening process can also erode the high enantioselectivity obtained for the epoxides intermediates. Herein, we report a chiral molydenum-bishydroxamic acid-catalyzed asymmetric *anti*-dihydroxylation of allylic alcohols, providing an efficient entry to a variety of 1,2,3-triols in high enantioselectivities (Fig. 1c). Notably, the 1,2,3-triol moeity is contained as a structural motif in numerous natural products and synthetic biologically active compounds (Fig. 1d).

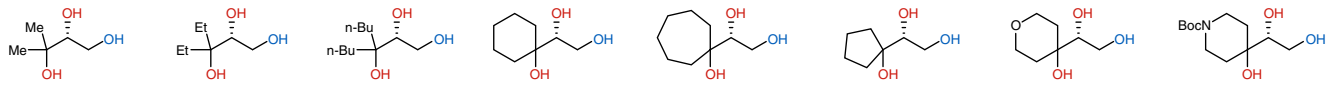
Results

Optimization. For optimization of the reaction conditions, we used commercially available 3-methylbut-2-en-1-ol (**1a**) as the standard substrate (Fig. 2). Initially, a series of chiral bishydroxamic acids (BHA) **L1**-**6** bearing *trans*-cyclohexane diamine scaffold were investigated as ligands in the reaction using $MoO_2(acac)_2$ as catalyst in EtOAc at 40 °C (Table 1, entries 1–6). In all these cases mentioned above, the reactions afforded a mixture of the desired product **2a** and a hydroperoxide **2a**-**1**, and after reductive work-up with diphenyl sulfide the triol **2a** was obtained in good to excellent yields. However, in the most cases the enantiocontrol was low (entries 1–5). Only in the case of the ligand **L6**, the reaction furnished the product in an excellent enantiomeric excess (entry 6). Notably, opposite enantioselectivities were achieved even for the reactions using the ligands with the same absolute configuration. Next, a brief solvent and Mo-precatalysts screenings were undertaken (entries 7–19), providing no better outcome in terms of enantioselectivity. Reducing the catalyst loading to 5 mol% resulted in a diminished yield (entry 20). Finally, excellent result with respect to both efficiency and selectivity was obtained, when the reaction was conducted in lower concentration with extended reaction time (entry 21).

Substrate scope. With the optimal reaction conditions in hand, we started to evaluate the substrate scope of this Mo-catalyzed asymmetric *anti*-dihydroxylation of allylic alcohols (Fig. 3). First, various symmetric β,β-disubstituted allylic alcohols **1a**-**g** were employed as substrates, affording the products **2a**-**g** in high to excellent yields and enantioselectivities. When the substituents on the β-position are not identical, both *E*- and *Z*-alkenes turned out to be suitable precursors for this Mo-catalyzed reaction,

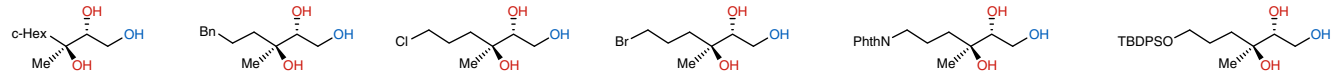


1,2,2-Trisubstituted olefins:

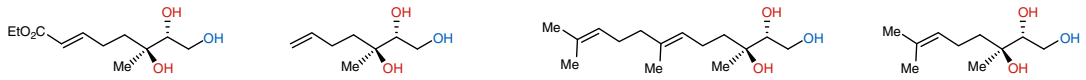


2a, 96%, 94%*ee* **2b**, 89%, 96%*ee* **2c**, 85%, 92%*ee* **2d**, 95%, 96%*ee* **2e**, 92%, 96%*ee* **2f**, 90%, 95%*ee* **2g**, 97%, 91%*ee* **2h**, 90%, 87%*ee*

(*E*)-1,2,2-Trisubstituted olefins:

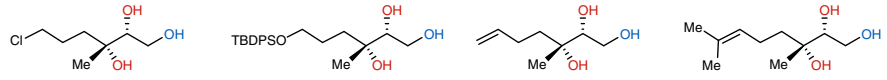


2i, 85%, 94%*ee* **2j**, 93%, 95%*ee* **2k**, 89%, 96%*ee* **2l**, 82%, 95%*ee* **2m**, 91%, 96%*ee* **2n**, 78%, 96%*ee*[d]



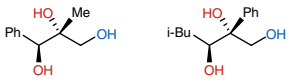
2o, 82%, 94%*ee*[iv,v] (78%, 95%*ee*)[iv,v,vi] (77%, 95%*ee*)[iv,v,vi,vii] **2p**, 94%, 93%*ee*[iv,v] **2q**, 61%, 96%*ee*[v,viii] **2r**, 71%, 96%*ee*[v,viii]

(*Z*)-1,2,2-Trisubstituted olefins:



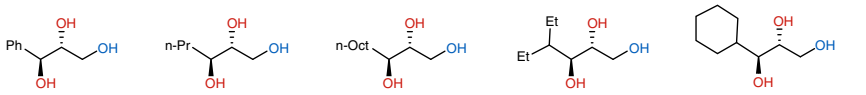
2s, 81%, 96%*ee* **2t**, 72%, 96%*ee* **2u**, 90%, 93%*ee*[iv,v] **2v**, 65%, 96%*ee*[v,viii]

(*E*)-1,1,2-Trisubstituted olefins:



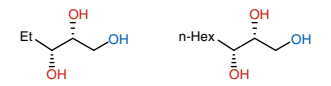
2w, 54%, 59%*ee*[ix] **2x**, 90%, 80%*ee*[ix]

(*E*)-Disubstituted olefins:



2y, 76%, 96%*ee*[ix,x] **2z**, 92%, 85%*ee*[ix,x] **2aa**, 98%, 83%*ee*[ix,x] **2ab**, 72%, 80%*ee*[ix,x] **2ac**, 79%, 90%*ee*[ix,x]

(*Z*)-Disubstituted olefins:



2ad, 89%, 52%*ee*[ix,x] **2ae**, 78%, 42%*ee*[ix,x]

Fig. 3 Evaluation of the substrate scope of the Mo-BHA-catalyzed asymmetric *anti*-dihydroxylation of allylic alcohols. [i–iii] [(i)] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the allylic alcohols **1** using 2.5 equiv 35% aqueous H_2O_2, 5 mol % $MoO_2(acac)_2$ and 6 mol% **L6** in 2.0 mL EtOAc at 40 °C. [ii] Yields of the isolated products after column chromatography. [iii] The enantiomeric excesses were determined by HPLC-analysis on chiral stationary phase. [iv] Reaction time: 4 h. [v] Reaction temperature: 30 °C. [vi] Reaction was performed on a 5 mmol scale of the allylic alcohol **1o**. [vii] Reaction performed with the recycled BHA **L6**. [viii] Reaction time: 1.5 h. [ix] Catalyst loading: 10 mol% $MoO_2(acac)_2$ and 12 mol% **L6**. [x] Reaction performed in 1,4-dioxane

furnishing the products **2h**-**u** with high efficiency and excellent enantiocontrol. It was observed that a series of functional groups were tolerated including carbamate (**2h**), halide (**2k**, **2l**, and **2s**), imide (**2m**), silyl ether (**2n** and **2t**), and ester (**2o**). Moreover, a complete proximal selective dihydroxylation was achieved, when the allylic alcohols bearing at least one distal olefinic unit (**2o**-**r**, **2u** and **2v**) were used as substrates. Remarkably, the oxidation of the distal C-C double bond of these substrates is favored in the case of Sharpless dihydroxylation[6], indicating that our method is complementary to the Os-catalyzed *syn*-dihydroxylation concerning both diastereo- and regioselectivity. Furthermore, 1,1,2-trisubstituted and disubstituted alkenes turned out to be less reactive and thus required higher catalyst loading (10 mol%). Under the modified conditions, the reactions proceeded smoothly, affording the products **2w**-**ae** in good to high yields. Good to excellent asymmetric induction was achieved for the *erythro*-triols **2y**-**ac** starting from disubstituted *E*-olefins. Notably, only low to moderate enantioselectivities (<74% *ee*) can be obtained for the synthesis of *erythro*-triols using asymmetric Os-catalyzed *syn*-dihydroxylation of *Z*-allylic alcohols[5]. One limitation of our method was observed in the case of 1,1,2-trisubstituted and disubstituted *Z*-olefins, as relatively low enantiomeric excesses were obtained. Of note is that the reactions involving the alkenes **1i**-**ae** delivered all the corresponding products in high diastereoselectivities (dr > 95:5, determined by ^{1}H-spectroscopy). Moreover, a 5-mmol-scale reaction using the alcohol **1o** was conducted, providing the product **2o** in a similar yield and enantioselectivity. In this case we discovered that the Mo-BHA-catalyst decomposed completely on silica gel, releasing the chiral BHA-ligand, which was isolated in an excellent recovered yield (95%) through column chromatography and determined to be analytically pure. The reaction using the recycled ligand and $MoO_2(acac)_2$ afforded a similar result with no decrease of the enantiomeric excess.

Some derivatizations based on the conversion of the alcohol moiety were carried out (Fig. 4). First, selective tosylation of the primary alcohol group of the triol **2r** followed by S_N2 nucleophilic substitution by benzyl amine provided an amino alcohol **3** in a

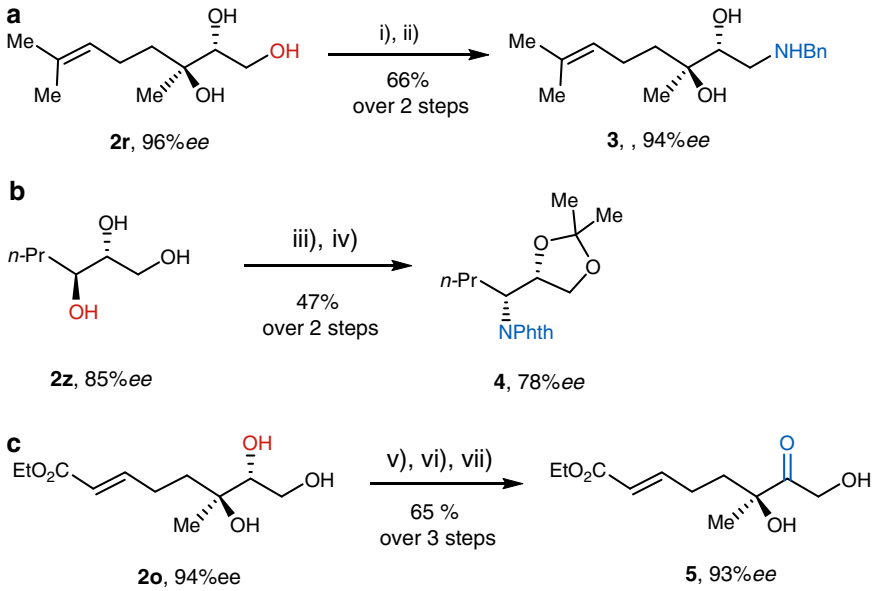


Fig. 4 Derivatizations of the dihydroxylation products. **a** Conversion of the primary hydroxyl to amine. **b** Conversion of the secondary hydroxyl to imide. **c** Oxidation of the secondary hydroxyl to ketone. (i) TsCl (1.1 equiv), NEt_3 (1.2 equiv), DMAP (5 mol%), DCM, 0 °C, 3 h; (ii) $BnNH_2$ (5 equiv), NEt_3 (2.5 equiv), MeOH, 80 °C, overnight; (iii) $CH(OMe)_2$ (3.0 equiv), *p*-TsOH (10 mol%), acetone, r.t., 2 h; (iv) PhthNH (1.2 equiv), PPh_3 (3 equiv), DIAD (3.0 equiv), THF, 0 °C—r.t., 12 h; (v) TBDPSCl (1.05 equiv), NEt_3 (2.0 equiv), DMAP (5 mol%), DCM, 0 °C-r.t., 12 h; (vi) SO_3•Py (5.0 equiv), NEt_3 (7.0 equiv), DMSO, DCM, 0 °C—r.t., 24 h; (vii) TBAF (1.5 equiv), HOAc (20 mol%), THF, 0 °C—r.t., 6 h

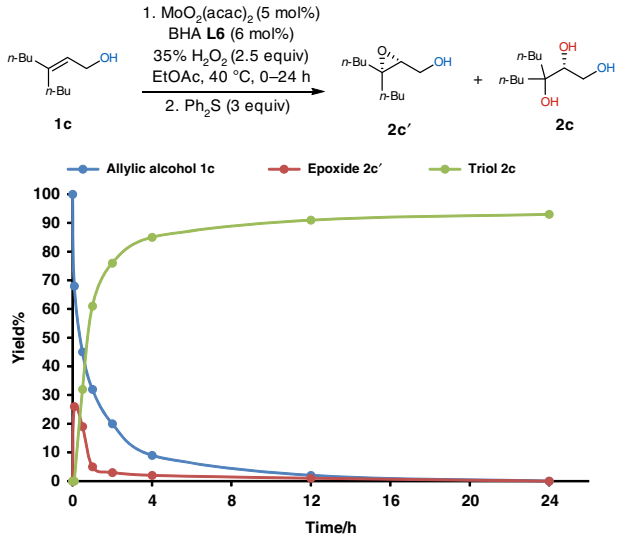


Fig. 5 Kinetic study. Reaction kinetic progress study of the Mo-BHA-catalyzed asymmetric *anti*-dihydroxylation

good yield over two steps (Fig. 4a). Moreover, the conversion of the hydroxyl group on C-3 position of the triol **2z** into an imide was accomplished via Mitsunobu reaction after protecting 1,2-diol with the formation of ketal (Fig. 4b). In addition, a chiral α-hydroxyl ketone **5** was synthesized in highly enantioselective manner starting from the triol **2o** by means of Silyl ether-protective group manipulation and Parikh-Doering oxidation (Fig. 4c).

Mechanistic studies. Subsequently, some mechanistic investigations were carried out for this Mo-catalyzed *anti*-dihydroxylation. First, we chose the reaction using the allylic alcohol **1c** as the standard reaction for the reaction progress kinetic analysis. The yields of the recovered allylic alcohol **1c**, the epoxide intermediate **2c′** and the product **2c** were determined after reduction with diphneyl sulfide over the reaction time using ^{1}H-NMR spectroscopy (Fig. 5). We noticed the formation of a certain amount of epoxide in the beginning of the reaction, indicating the dihydroxylation reaction consists of a cascade of epoxidation and the following ring opening.

Furthermore, we quenched the reaction at 5 min and were able to obtain the epoxide **2c′** in 26% yield and 97%ee, which is slightly higher than the enantioselectivity of final triol product **2c** (Fig. 6a). The decrease of the optical purity can be reasoned by either the ligand-mismatch effect in the kinetic resolution of the epoxide via hydrolysis or the imperfect regiocontrol in the ring opening process. To verify this, we employed the racemic epoxide **2c′** as precursor under the standard reaction conditions (Fig. 6b). In the beginning we did observe the kinetic resolution of the epoxide **2c′** in favor of the ring opening of the minor enantiomer of the oxirane formed in the epoxidation step. However, the selectivity was very low, and after 30 min the enantiomeric excess of the triol product **2c** diminished to 2%. Performing this reaction in the absence of Mo-catalyst resulted in complete shutdown of the ring opening reaction, excluding the non-catalyzed background hydrolysis or perhydrolysis (Fig. 6c). Next, we conducted the ring opening reactions of the enantioenriched epoxide **2ac′** and its enantiomer employing the BHA ligand **L6**, both of which were prepared through W-catalyzed asymmetric epoxidation[28] (Fig. 6d). Within 1 h a full consumption of both epoxides was observed, providing the products in distinct enantiomeric excesses. Comparison of the absolute configuration of **2ac** and **2ac′** indicates a C3-selective ring opening as the major reaction pathway[29]. This result implies that the main reason for the erosion of the enantioselectivity is the competitive ring opening on the C-2 position, and the two enantiomers of the epoxides undergo the ring opening reaction with distinct regioselectivity under the catalysis of the same chiral Mo-catalyst. Moreover,

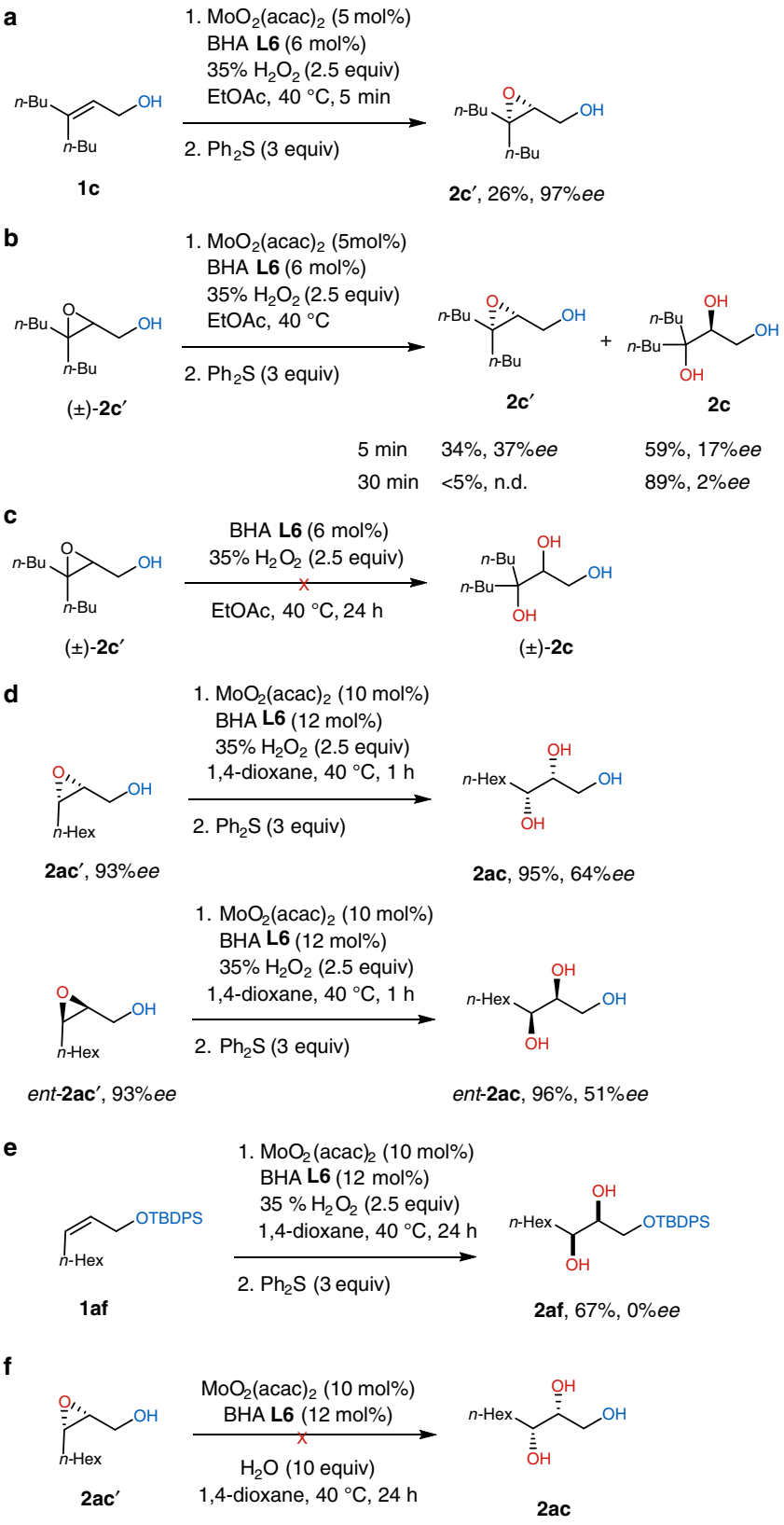


Fig. 6 Control experiments for the Mo-BHA-catalyzed asymmetric *anti*-dihydroxylation. **a** Dihydroxylation quenched at 5 min. **b** Ring opening of racemic epoxide under catalysis of chiral Mo-complex. **c** Ring opening reaction in the absence of chiral Mo-complex. **d** Ring opening of enantioenriched epoxides under the catalysis of chiral Mo-complex. **e** Dihydroxylation of TBDPS-protected allylic alcohol. **f** Ring opening with water as nucleophile

we employed TBS-protected allylic alcohol **1af** as substrate and the dihydroxylation reaction still occurred. However, the product **2af** was delivered in racemic form, confirming that the presence of hydroxyl moiety as anchoring group is crucial for obtaining successful result of this Mo-catalyzed *anti*-dihydroxylation (Fig. 6e). Finally, we conducted the ring opening reaction of the epoxide **2ac′** with water in the presence of both Mo-catalyst and the ligand **L6**. Surprisingly, no hydrolysis of the epoxide occurred in this case, indicating that H_2O_2 plays a key role in the ring opening of the epoxides intermediates (Fig. 6f).

Discussion

In conclusion, we developed a Mo-BHA-catalyzed asymmetric *anti*-dihydroxylation of allylic alcohols, providing an efficient entry to 1,2,3-triols in highly enantioselective manner. Being complementary to the Sharpless dihydroxylation in terms of both diastereo- and regioselectivity, our method is bestowed with the following advantages including the high level of diastereo- and enantiocontrol and the used of environmentally benign hydrogen peroxide as oxidant. The preliminary mechanistic investigations reveal that this *anti*-dihydroxylation consists of an initial enantioselective epoxidation and the following regio- and diastereoselective ring opening.

Methods

Synthesis and characterization. See Supplementary Methods (general information about chemicals and analytical methods, synthetic procedures, ^{1}H and ^{13}C NMR data and HPLC data), Supplementary Figs. 1–3 (synthetic procedures), Supplementary Figs. 10–50 (^{1}H and ^{13}C NMR spectra) and Supplementary Figs. 51–87 and Supplementary Table 1 (HPLC chromatograms).

General procedure. To a stirred solution of $MoO_2(acac)_2$ (5 mol%)[a] and **BHA L6** (6 mol%)[a] in EtOAc [b] (2 mL) at 40 °C[c] was added H_2O_2 (2.5 equiv, 35% w/w aq.). After stirring for 30 min, the alcohols **1** (0.2 mmol) were added to the suspension and stirred at the same temperature for 24 h[d]. Then the reaction was quenched with diphenyl sulfide (3.0 equiv). After stirring for 1 h at 50 °C, the solvent was removed under reduced pressure. The residue was purified through column chromatography (silica gel, petroleum ether/ethyl acetate) to afford the desired products **2**. [a] $MoO_2(acac)_2$ (10 mol%), BHA **L6** (12 mol%): **2w**-**2ae**; [b] 1,4-dioxane: **2y**-**2ae**; [c] 30 °C: **2o**-**r**, **2 u** and **2 v**; [d] 4 h: **2o**, **2p** and **2 u**, 1.5 h: **2q**, **2r** and **2 v**.

Synthetic transformations. Full procedures for synthetic transformations to prepare compounds **3**–**5** are available in the Supplementary Methods and Supplementary Figs. 4–6.

Determination of the absolute configuration. For determination of the absolute configuration of triol products **2r**, **2z** and **2ad**, see Supplementary Fig. 7 and 8. The stereochemistry of all the other products was assigned by assuming a common reaction pathway.

Proposed catalytic cycle. A plausible catalytic cycle is proposed in Supplementary Fig. 9.

Data availability

The data sets generated and analyzed during the current study are included in the Supplementary Information.

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Author contributions

C.W. designed the project and wrote the paper. P.F. carried out the experimental work. Both authors analyzed the data and discussed the results and commented on the paper.

Additional information

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