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Molybdenum-Catalyzed Diastereoselective *anti*-Dihydroxylation of Secondary Allylic Alcohols

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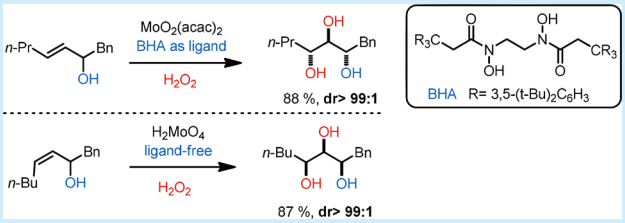
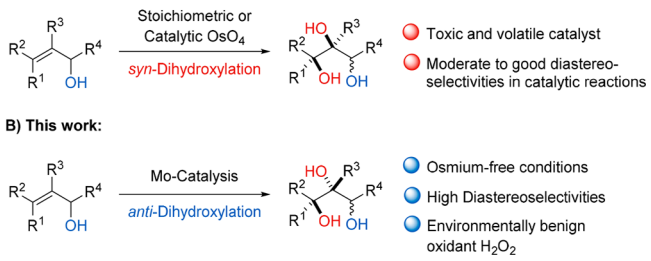
Supporting Information

ABSTRACT: In this protocol, we report a Mo-catalyzed *anti*-dihydroxylation of secondary allylic alcohols, providing a general method for the preparation of 1,2,3-triols bearing up to three continuous stereocenters with excellent diastereocontrol. The mechanistic studies reveal that this dihydroxylation reaction consists of two steps and up to excellent diastereomeric ratios of the final triol products can be achieved due to the high level of both diastereocontrol in the initial epoxidation and regiocontrol in the following hydrolysis in situ.



1,2,3-Triols are a characteristic structural motif contained in a large number of naturally occurring compounds ranging from sugars to polyketides.[1] Conventionally, 1,2,3-triols bearing three stereogenic centers are synthesized through diastereoselective addition of a carbon-centered nucleophile to a carbonyl moiety bearing two adjacent hydroxylated stereocenters.[2] On the other side, as a plethora of methods have been established for the synthesis of chiral secondary allylic alcohols in a highly enantioselective manner,[3] the diastereoselective dihydroxylation of enantioenriched secondary allylic alcohols also provides an alternative access to optically active 1,2,3-triols. Although Os-catalyzed *syn*-dihydroxylation of alkenes has proven to be very successful for a wide range of substrates,[4−6] only moderate to good diastereoselectivities could be obtained for dihydroxylation of secondary allylic alcohols.[7] Excellent results can be achieved only when an overstoichiometric amount of OsO_4 is employed in the presence of TMEDA as a ligand.[8] However, the toxicity, volatility, and high cost of OsO_4 limit the use of this method in the synthesis of 1,2,3-triols (Scheme 1A). Very recently, our group reported a Mo-catalyzed proximal selective direct *anti*-dihydroxylation of allylic alcohols bearing at least two olefinic units.[9,10] As a continuation of our interest in this area, we envisage that a diastereoselective *anti*-dihydroxylation of secondary allylic alcohols could also be achieved under the catalysis of molybdenum using environmentally benign hydrogen peroxide as the oxidant (Scheme 1B). The challenge of this reaction lies in not only the diastereocontrol 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 lead to low diastereomeric ratios of the final products.

Scheme 1. Os-Catalyzed Diastereoselective *syn*-Dihydroxylation of *sec* Allylic Alcohols (A) and Mo-Catalyzed *anti*-Dihydroxylation of *sec* Allylic Alcohols (B)



For optimization of the reaction conditions, we used racemic (*E*)-hept-3-en-2-ol [(±)-**1a**] as the standard substrate (Table 1), which is a very challenging substrate for achieving high diastereocontrol due to the weak steric effect of the small methyl group. Initially, we performed the reaction under the optimum conditions for dihydroxylation of simple primary allylic alcohols using $MoO_2(acac)_2$ as the catalyst and MeCN as the solvent (entry 1).[9] The desired triol was afforded as a mixture of *anti*/*anti*-isomer (±)-**2a** and *syn*/*anti*-isomer (±)-**2a′** after reductive workup with Ph_2S in an excellent yield, but the diastereoselectivity of this reaction was very low. Further screening of solvents and other Mo, V, and W salts as catalysts failed to deliver significantly improved results.[11] Relying on our previous discovery that bishydroxamic acids (BHA) can be employed as the ligand in Mo-catalyzed dihydroxylation,[9] we decided to explore the influence of BHA ligands on the outcome of the diastereoselectivity of the studied reaction. Next, several hydroxamic acids **L1**−**L6** were tested as ligands, and toluene was chosen as the solvent due to the high solubility of the BHA ligands in it (entries 2−7, respectively). In the case of monodentate *N*-hydroxy-*N*-phenylbenzamide (**L1**) as the ligand, only traces of the

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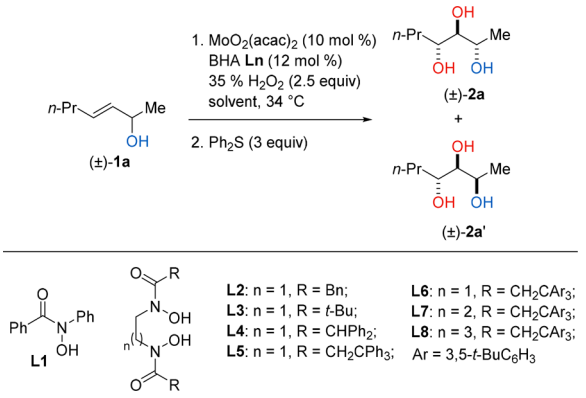
Table 1. Ligands, Solvents, and Temperature Screening for the Mo-Catalyzed *anti*-Dihydroxylation of (*E*)-Hept-3-en-2-ol[a]



entry	ligand	solvent	*t* (h)	yield (%)[b]	(±)-2a:(±)-2a′[c]
1	–	MeCN	14	90	33:67
2	**L1**	toluene	14	trace	nd[d]
3	**L2**	toluene	14	trace	nd[d]
4	**L3**	toluene	14	trace	nd[d]
5	**L4**	toluene	14	17	40:60
6	**L5**	toluene	14	trace	nd[d]
7	**L6**	toluene	14	85	91:9
8	**L7**	toluene	14	53	88:12
9	**L8**	toluene	14	29	82:18
10	**L6**	DCE	14	76	88:12
11	**L6**	EtOAc	14	45	75:25
12	**L6**	*t*BuOH	14	27	45:55
13	**L6**	CyH	14	75	90:10
14	**L6**	MeCN	14	39	40:60
15[e]	**L6**	toluene	96	90	86:14
16[f]	**L6**	toluene	**12**	**88**	**92:8**
17[g]	**L6**	toluene	4	92	86:14
18	–	toluene	12	0	–

[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of allylic alcohol (±)-**1a** using 2.5 equiv of 35% aqueous H_2O_2, 10 mol % $MoO_2(acac)_2$, and 12 mol % ligand in 1.0 mL of toluene at 34 °C for 14 h. [b]Yields of the isolated product after column chromatography. [c]Determined by ^1H NMR spectroscopy after flash chromatography. [d]Not determined. [e]Reaction temperature of 0 °C. [f]Reaction temperature of 38 °C. [g]Reaction temperature of 50 °C.

product were obtained (entry 2). When bidentate BHA **L2**–**L6** deriving from ethylenediamine were utilized, in the most cases the reactions also provided the product in very low yields (entries 3–7, respectively). An exception was observed in the reaction using BHA **L6** as the ligand, and in this case, the product (±)-**2a** was furnished in high yield and diastereoselectivity (entry 7), which was notably the inverse of the result obtained under ligand-free conditions. The high efficiency of this reaction might be attributed to the extreme bulkiness of **L6**, which could prevent the coordination of a second **L6** to the Mo center rendering a free site for activation of the substrate. Furthermore, we performed the reactions using BHA **L7** and **L8** as ligands, and the results revealed that both efficiencies and stereoselectivities diminished with an increase in distance between two hydroxamic moieties of the ligands (entries 8 and 9, respectively). Subsequently, a brief solvent screening was carried out, and no better result was obtained (entries 10–14). In MeCN and *t*BuOH, the *syn*/*anti*-isomer was formed as the major product (entries 12 and 14, respectively). Due to the low solubility of the BHA ligand **L6** in these two solvents, the inverse diastereoselectivity could be attributed to the background reaction catalyzed by $MoO_2(acac)_2$. Moreover, the impact of temperature on the outcome of this reaction was investigated (entries 15–17). Decreasing the temperature to 0 °C gave rise to a longer reaction time to achieve the full consumption of the substrate (±)-**1a** and decreased diastereoselectivity (entry 15). An improved result in terms of both efficiency and stereoselectivity was achieved when the reaction was carried out at 38 °C (entry 16). Further increasing the reaction temperature to 50 °C resulted in a lower diastereomeric ratio (entry 17). In the absence of the BHA ligand **L6**, no desired reaction occurred in toluene (entry 18).

With the optimum reaction conditions in hand, we started to evaluate the substrate scope of this Mo-catalyzed *anti*-dihydroxylation (Scheme 2). First, various disubstituted (*E*)-allylic alcohols (±)-**1a**–**q** were employed as precursors affording products (±)-**2a**, *meso*-**2b**, and (±)-**2c**–**q**, respectively, in moderate to high yields. As expected, complete diastereoselectivities were achieved in the most cases, when the substitution at the C1 position is larger than a methyl group. It is noteworthy that a series of functional groups were tolerated, including alkyne [(±)-**1h**], chloride [(±)-**1l**], ester [(±)-**1m**], terminal olefin [(±)-**1k**], alcohol [(±)-**1n**], and ketone [(±)-**1s**]. Surprisingly, a complete loss of diastereocontrol was observed in the case of disubstituted (*Z*)-allylic alcohols (±)-**1t** and (±)-**1u** as substrates. In contrast, the reactions using terminal and trisubstituted allylic alcohols provided the products (±)-**2v**–**aa** in moderate to complete diastereoselectivities. Remarkably, the *anti*-products (±)-**2y** and (±)-**2z** were formed predominantly in the case of monosubstituted and 1,2,2-trisubstituted olefins, whereas the generation of *syn*-products (±)-**2v**–**x** and (±)-**2aa** was favored for the reactions employing 1,1-disubstituted and 1,1,2-trisubstituted alkenes as starting materials. These results demonstrate that a bulky geminal substitution R^3 (lager than H) gives rise to the preference of formation of the *syn*-products. Furthermore, cyclic allylic alcohols (±)-**1ab**–**ae** were also investigated as precursors for this Mo–BHA-catalyzed reaction. In the case of cyclohexenols **1ab**–**ad**, the *cis*/*trans*-diastereomers **2ab**–**ad**, respectively, were furnished as the only products. The reaction using cyclohept-2-en-1-ol [(±)-**1ae**] as the substrate yielded a triol (±)-**2ae** only in a moderately good diastereomeric ratio. Moreover, a 5 mmol scale reaction using alcohol (±)-**1b** was conducted providing the product *meso*-**2b** in a similar yield.

To demonstrate the crucial effect of the BHA ligand on the diastereocontrol, we chose a panel of representative allylic alcohols bearing different substitution patterns of the olefinic unit and used them as precursors in the BHA-free $MoO_2(acac)_2$-catalyzed dihydroxylation (Scheme 2, results shown in brackets). In the case of *E*-disubstituted, terminal, and trisubstituted olefins, all of the BHA-free reactions delivered the corresponding products (±)-**2b**, (±)-**2w**, (±)-**2z**, and *meso*-**2aa** with inverse diastereoselectivities. In contrast, the reaction utilizing cyclic allylic alcohol (±)-**1ab** furnished product (±)-**2ab** with the same preference of stereochemistry as the reaction involving a BHA ligand, albeit with a lower selectivity. Interestingly, a good diastereomeric ratio (dr of 91:9) was achieved under the BHA ligand-free conditions for (*Z*)-allylic alcohol (±)-**1t**, which turned out to be an unsuccessful substrate in the Mo–BHA catalytic system. Encouraged by this result, we decided to optimize the reaction

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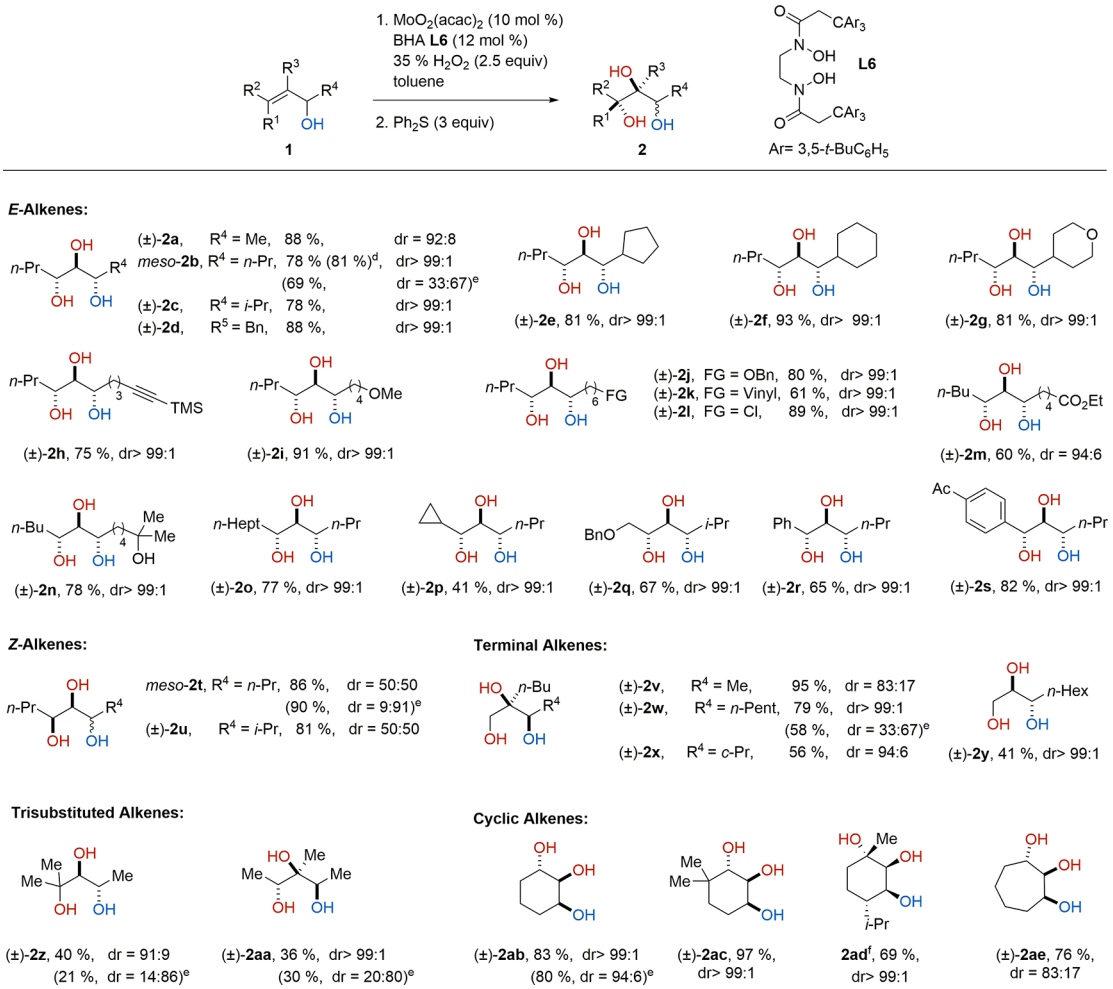
Scheme 2. Evaluation of the Substrate Scope of the Mo−BHA-Catalyzed *anti*-Dihydroxylation of Secondary Allylic Alcohols[12],[a−c]



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of allylic alcohols **1** using 2.5 equiv of 35% aqueous H_2O_2, 10 mol % $MoO_2(acac)_2$, and 12 mol % **L6** in 1.0 mL of toluene. Reaction temperatures of 34 °C for **2v**, **2z**, and **2ab**; 38 °C for **2a**, **2b**, **2t**, **2aa**, and **2ac−ae**; and 40 °C for **2c−s**, **2u**, and **2w−y**. Reaction times of 6 h for **2k**; 12 h for **2a**, **2f**, and **2h**; 14 h for **2b**, **2c**, **2i**, **2l**, **2m**, **2q**, **2t−v**, **2x−z**, and **2ab−ae**; 16 h for **2w** and **2aa**; and 18 h for **2d**, **2e**, **2g**, **2j**, **2o**, **2p**, and **2r**. [b]Yields of the isolated products after column chromatography. [c]The diastereomeric ratios were determined by ^{1}H NMR spectroscopy after flash chromatography. [d]The reaction was performed on a 5 mmol scale of racemic allylic alcohol (±)-**1b**. [e]Reactions were performed under ligand-free conditions: 10 mol % $MoO_2(acac)_2$ as the catalyst in 1 mL of MeCN at 34 °C for 14 h. [f]Enantiopure precursor **1ad** was employed.

conditions for the (*Z*)-allylic alcohols.[11] After systematic screening of catalysts, solvents, and temperatures, the best outcome concerning diastereoselectivity was achieved for the catalysis of molybdic acid with acetonitrile as the solvent at 30 °C. Under these conditions, a variety of (*Z*)-allylic alcohols (±)-**1t**, (±)-**1u**, and (±)-**1af−ai** were subjected to the *anti*-dihydroxylation reaction, furnishing the triols with the *syn*/*syn*-configuration, mostly in high to complete diastereoselectivities (Scheme 3). The relatively low diastereoselectivity of (±)-**2af** could be attributed to the OH moiety in the homoallylic position undermining the orienting effect of the allylic alcohol.

By employing our Mo-catalyzed diastereoselective *anti*-dihydroxylation as a key step, we completed a five-step synthesis of benzyl-protected 2-deoxy allonic acid **2aj** in excellent stereoselectivity (dr of >99:1, 96% ee) starting from commercially available (*Z*)-but-2-en-1,4-diol and ethyl acetate (Scheme 4).[13] Notably, a high enantiospecificity was achieved in this Mo-catalyzed dihydroxylation. In addition, during the progress of dihydroxylation, the hydrolysis of the ester moiety occurred, which is possibly directed by the *β*-hydroxyl group, because no hydrolyzed product was formed in the case of (±)-**2m**.

Subsequently, several control experiments were conducted for mechanistic purposes (Scheme 5). First, the crucial directing effect of the allylic hydroxyl group was confirmed, because protecting it with methyl led to the complete shutdown of the dihydroxylation reaction (Scheme 5A). Furthermore, we noticed the formation of a certain amount of epoxides in the beginning phase of the Mo-catalyzed dihydroxylation, indicating this reaction might consist of two stages, which are the initial epoxidation and the subsequent hydrolysis. To verify this, we quenched the Mo−BHA-catalyzed reaction employing (*E*)-allylic alcohol (±)-**1b** after 2 h, providing both triol *meso*-**2b** and *anti*-epoxide (±)-**2b-1** in diastereomerically pure form (Scheme 5B). Next, isolated *anti*-epoxide (±)-**2b-1** was subjected to the standard reaction conditions yielding triol *meso*-**2b** in a diastereomeric ratio of >99:1 (Scheme 5C). Notably, in the absence of the Mo salt, no

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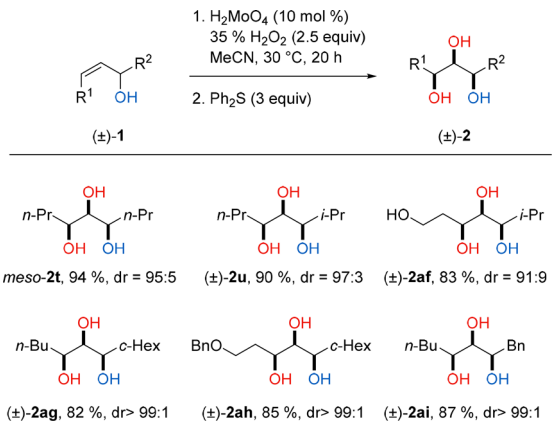
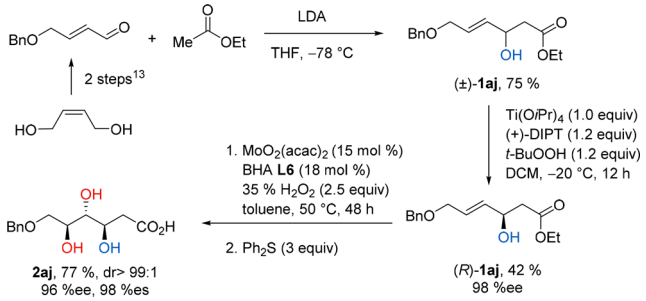
Scheme 3. Evaluation of the Substrate Scope of the $HMoO_4$-Catalyzed *anti*-Dihydroxylation of Secondary (*Z*)-Allylic Alcohols[12,a−c]



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of allylic alcohols **1** using 2.5 equiv of 35% aqueous H_2O_2 and 10 mol % H_2MoO_4 in 1.0 mL of MeCN. [b]Yields of the isolated products after column chromatography. [c]The diastereomeric ratios were determined by ^1H NMR spectroscopy after flash chromatography.

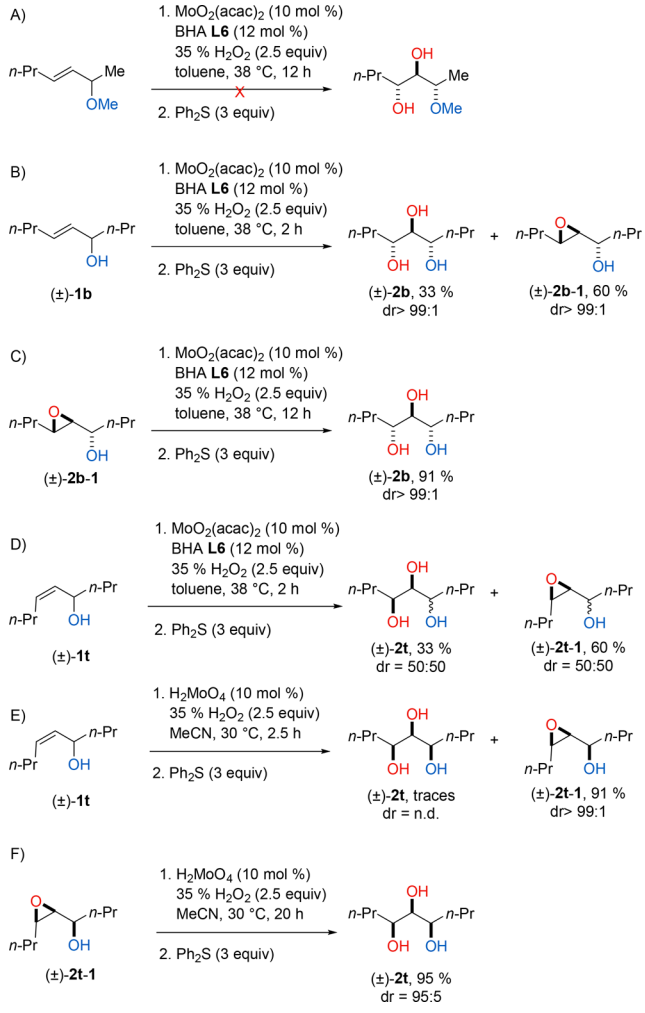
Scheme 4. Synthesis of Bn-Protected 2-Desoxy Alonic Acid Using Mo−BHA-Catalyzed *anti*-Dihydroxylation as a Key Step



ring opening reaction occurred, excluding the uncatalyzed background reaction. This result confirms a Mo-catalyzed C3 selective ring opening in the hydrolysis step with complete regioselectivity. In contrast, the reaction using (*Z*)-allylic alcohol (±)-**1t** afforded triol (±)-**2t** and epoxide (±)-**2t-1** both in a 1:1 diastereomeric mixture (Scheme 5D). In the case of the BHA-free reaction, *syn*-epoxide (±)-**2t-1** was formed as the single diastereomer (Scheme 5E). In the subsequent hydrolysis, the formation of a slight amount of the *anti*/*syn*-product was observed, which is attributed to the imperfect regioselectivity in this epoxide ring opening step (Scheme 5F). Again, no ring opening product was formed when the reaction was conducted without $MoO_2(acac)_2$.

In conclusion, we developed a Mo-catalyzed diastereoselective *anti*-dihydroxylation of secondary allylic alcohols, providing an efficient entry to 1,2,3-triols with up to three continuous stereogenic centers. The Mo−BHA catalytic system enables the highly diastereoselective dihydroxylation of *E*-disubstituted, terminal, and trisubstituted alkenes, while the ligand-free conditions using molybdic acid as the catalyst allow the synthesis of 1,2,3-triols with the *syn*/*syn*-configuration with high diastereoselectivities. This reaction is distinguished by a broad substrate scope, up to excellent

Scheme 5. Control Experiments for the Mo-Catalyzed *anti*-Dihydroxylation



diastereocontrol, a high level of enantiospecificity, and the use of environmentally benign hydrogen peroxide as the oxidant. The preliminary mechanistic investigations reveal that this *anti*-dihydroxylation consists of an initial epoxidation and the subsequent hydrolysis. Because of the high level of diastereo- and regiocontrol in the epoxidation and hydrolysis, respectively, the final triol products can be obtained in excellent diastereomeric ratios.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00735.

Representative experimental procedures and necessary characterization data for all new compounds (PDF)

Accession Codes

CCDC 1866250−1866251 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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