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Lewis Base Catalyzed Enantioselective Allylic Hydroxylation of Morita–Baylis–Hillman Carbonates with Water

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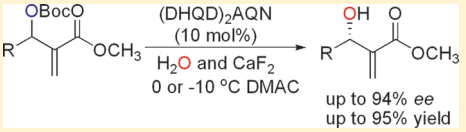
Supporting Information

ABSTRACT: A Lewis base catalyzed allylic hydroxylation of Morita–Baylis–Hillman (MBH) carbonates has been developed. Various chiral MBH alcohols can be synthesized in high yields (up to 99%) and excellent enantioselectivities (up to 94% ee). This is the first report using water as a nucleophile in asymmetric organocatalysis. The nucleophilic role of water has been verified using ^{18}O-labeling experiments.



MBH alcohols, containing condensed functional groups, are valuable intermediates for organic synthesis.[1,2] Many important biologically active compounds and natural products have been reported to be prepared from MBH alcohols.[3] The most efficient and direct protocol of preparing chiral MBH alcohols is via the well-known asymmetric Morita–Baylis–Hillman (MBH) reaction between activated terminal alkenes and aldehydes.[1−4] Other processes have also been developed, such as Nozaki–Hiyama–Kishi reaction from the addition of organochromium(III) vinylation reagents to carbonyl compounds,[5−7] carbonyl reduction of α-methylene ketones,[8−11] aldol oxidative deselenization cascade reaction,[12] acylative kinetic resolution of racemic MBH alcohols,[13] and a two-step protocol of allylic alkylation of MBH carbonates with oxa donors.[14−17] In 2002, Kim et al. presented an asymmetric hydroxylation of MBH acetates with moderate to excellent enantioselectivities in the presence of a Lewis base catalyst. This is a kinetic resolution route from the hydrolysis with $NaHCO_3$ and using water as a surrogate.[18] Despite the low reaction rate and low yield (of less than 50%), this methodology presents a significant improvement for the synthesis of MBH alcohols. Considering the reaction mechanisms of Kim's[18] and allylic alkylations of MBH adducts,[19−32] we postulate that, in the presence of a Lewis base catalyst, *tert*-butoxide is derived from the expulsion of MBH carbonate, which then generates hydroxide from water (pathway A, Scheme 1). Subsequently, under suitable reaction conditions, the hydroxide anion would act as a nucleophile and attack the intermediate to give the desired MBH alcohol (pathway A, Scheme 1). At the same time, the formation of hydrogen carbonate ion which acts as a water surrogate also cannot be excluded (pathway B, Scheme 1).[18,33]

Preliminary studies with the model substrate MBH carbonate **1a** were carried out. In the presence of 10 mol % of PPh_3, imidazole, DBU, DMAP, or TMG, no desired product, MBH alcohol **2a**, was obtained. However, when 10 mol % of DABCO was used, the reaction completed with good yield in 16 h (Table 1, entry 1). Further optimization with DMF allowed the reaction to achieve 96% yield within 6 h (Table 1, entry 2). However, no product was formed when protic solvent methanol was used (Table 1, entry 3). A plausible reason could be that the nucleophile's reactivity is diminished due to intermolecular hydrogen bonding between the nucleophile and methanol. When the concentration of water (Table 1, entries 5–9) was varied, the optimal condition was found be 2 equiv (Table 1, entry 6). However, no reaction was observed when the concentration of water is significantly increased to the ratio of 1:1 DMF/H_2O (Table 1, entry 9).

Scheme 1. Postulated Mechanisms for the Synthesis of MBH Alcohols from MBH Carbonates and Water

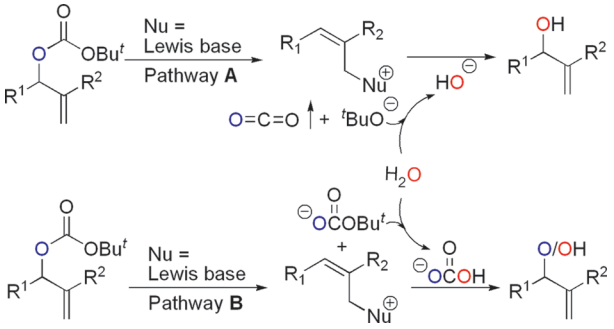


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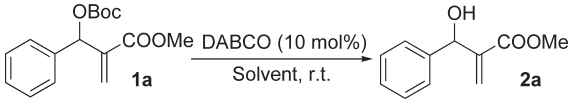
Table 1. Investigating Reactivity with Various Solvents[a]



entry	solvent[b]	additive	time (h)	yield (%)[c]
1	acetonitrile		16	91
2	DMF		6	96
3	methanol		24	NR[d]
4	DMF		0.25	36[e]
5	DMF	H_2O/1.0 equiv	0.25	74[e]
6	DMF	H_2O/2.0 equiv	0.25	96[e,f]
7	DMF	H_2O/5.0 equiv	0.25	78[e]
8	DMF	H_2O/10 equiv	0.25	66[e]
9	DMF	H_2O[g]	24	NR[d,e]

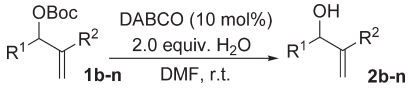
[a] Reactions were performed with 0.05 mmol of **1a** and 0.005 mmol of DABCO in 0.5 mL of solvent. [b] Dried and distilled before used. [c] Isolated yields. [d] NR = no reaction. [e] Conversion, determined by HPLC analysis. [f] Isolated yield = 99%, after 1 h, 1 mmol scale. [g] DMF (0.25 mL) and H_2O (0.25 mL) were used as solvent.

With a set of optimized reaction conditions on hand (10 mol % of DABCO as catalyst, 2.0 equiv of H_2O as additive, in DMF at room temperature), we then investigated the scope of the achiral reaction. Different MBH alcohols **2b**−**2l** could be efficiently synthesized from MBH carbonates **1b**−**1l** derived from aromatic aldehydes and alkyl acrylates (Table 2, entries 1−11). In general, the reactions were complete in 7 h with good to excellent yields with the exception of **1k**. Electronic effect and its influence on reactivity are tuned in favor for electron-withdrawing MBH carbonates **1b**−**1f** (Table 2, entries 1−5). Less reactive MBH carbonates (**1m**,**1n**) with acrylonitrile and diethyl vinylphosphonate moieties instead of esters were also investigated, and the desired MBH alcohols **2m**,**2n** could be achieved with moderate yields (Table 2, entries 12 and 13). Aliphatic MBH carbonate **1o** was also under investigation. The reaction was finished within 0.5 h at room temperature. However, the yield of aliphatic MBH alcohol **2o** was less than 30%; an unknown compound was detected as the major product. Finally, 60% yield of **2o** was obtained after 12 h when the reaction was conducted at −10 °C (Table 2, entry 14).

Another important class of MBH carbonates **3a**−**c**, in which the alkenes are activated by cyclic ketones, was also investigated. The corresponding MBH alcohols **4a**−**c** were prepared (Scheme 2). Unfortunately, no product was formed under our established reaction conditions. It was found, after some attempts, that using 20 mol % of DMAP in the place of DABCO, gave moderate yields.

Next, we endeavored to prepare enantiopure MBH alcohols with our established protocol. Carbonate **1a** was subjected to allylic hydroxylation with 2 equiv of H_2O in DMF via screening with a series of *Cinchona* alkaloids as Lewis base organocatalysts (Table 3, entries 1−5).[34−40] The best enantioselectivity with 85% ee was achieved for $(DHQD)_2AQN$ with adduct **5a** (Table 3, entry 5). The ee was improved from 85 to 87% by replacing DMF with *N*,*N*-dimethylacetamide (DMAC) for the similar substrate (Table 3, entry 6). Next, several additives (Table 3, entries 7−14) were screened and it was found that the addition of pyridine decreased ee to 36% despite making the

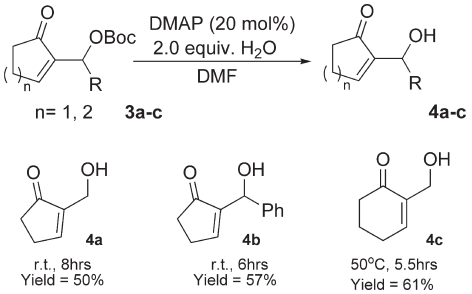
Table 2. Synthesis of MBH Alcohols from the Reactions between MBH Carbonates 1b−n and Water Catalyzed by DABCO[a]



entry	R^1	1	R^2	2	time (h)	yield (%)[b]
1	*p*-NO_2Ph	**1b**	COOMe	**2b**	0.5	99
2	*m*-NO_2Ph	**1c**	COOMe	**2c**	0.5	99
3	*p*-FPh	**1d**	COOMe	**2d**	0.4	99
4	*p*-BrPh	**1e**	COOMe	**2e**	0.4	99
5	*o*-ClPh	**1f**	COOMe	**2f**	0.6	94
6	*p*-CH_3Ph	**1g**	COOMe	**2g**	1.5	99
7	2-naphthyl	**1h**	COOMe	**2h**	1.0	99
8	*p*-CH_3OPh	**1i**	COOMe	**2i**	6.0	82
9	3-thienyl	**1j**	COOMe	**2j**	7.0	90
10	2-furyl	**1k**	COOMe	**2k**	6.0	60
11	Ph	**1l**	COO*t*Bu	**2l**	4.0	80
12	Ph	**1m**	CN	**2m**	5.0	67
13	Ph	**1n**	$PO(OEt)_2$	**2n**	7.5	76
14	Et	**1o**	COOMe	**2o**	12	60[c]

[a] At 0.1 mmol scale in 1.0 mL of DMF. [b] Isolated yields. [c] The reaction was conducted at −10 °C.

Scheme 2. Synthesis of MBH Alcohols Containing Cyclic Ketones (0.1 mmol Scale in 1.0 mL of DMF; Isolated Yield)



reaction faster (Table 3, entry 7).[27,41] Since inorganic fluorides were often used as additives to improve reactions,[42] we examined several fluorides as additives (Table 3, entries 8−12). The results show that alkaline earth fluorides, especially CaF_2 (Table 3, entry 10), are effective for enhancing the enantioselectivity. Finally, when 2.0 equiv of CaF_2 was used, the enantioselectivity improved to 91% (Table 3, entry 14).[43]

We expanded the reaction scope to synthesize other chiral MBH alcohols (Table 4). All of the reactions proceeded smoothly in good to excellent yields (up to 95%) and ee values (up to 94%). We found that the optimized condition for **1a** was not completely suitable for other MBH carbonates. The enantioselectivities were influenced by ratios of H_2O and CaF_2 as well as the reaction temperature. Five equivalents of H_2O and CaF_2 at −10 °C was required for the synthesis of **5b**−**g**, whereas 0 °C was essential to **5i**,**j** using the same amount of additives. Meanwhile, the MBH alcohols **5c**−**f** and **5h**−**j** with *meta*-substituted groups on the phenyl rings led to higher enantioselectivities. This synthetic protocol was also applicable to less

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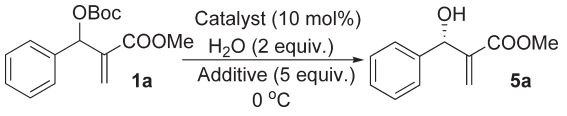
Table 3. Investigation of Reaction Conditions To Synthesize Chiral MBH Alcohol 5a from MBH Carbonate 1a and H_2O[a]



entry	catalyst	solvent	additive	time (h)	yield (%)[b]	ee (%)[c]
1	$(DHQD)_2PHAL$	DMF		60	45	81
2	$(DHQ)_2PYR$	DMF		60	60	−42
3	$(DHQ)_2AQN$	DMF		60	77	−44
4	$(DHQD)_2PYR$	DMF		60	56	77
5	$(DHQD)_2AQN$	DMF		48	94	85[d]
6	$(DHQD)_2AQN$	DMAC		72	88	87
7	$(DHQD)_2AQN$	DMAC	Py	24	63	36
8	$(DHQD)_2AQN$	DMAC	KF	72	55	87
9	$(DHQD)_2AQN$	DMAC	MgF_2	72	74	89
10	$(DHQD)_2AQN$	DMAC	CaF_2	72	88	90
11	$(DHQD)_2AQN$	DMAC	SrF_2	72	62	88
12	$(DHQD)_2AQN$	DMAC	BaF_2	72	80	89
13	$(DHQD)_2AQN$	DMAC	$CaCl_2$	72	40	87
14	$(DHQD)_2AQN$	DMAC	CaF_2	72	86	91[e]

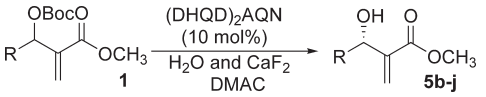
[a] At 0.05 mmol scale in 0.5 mL solvent. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC methods. [d] Enantiomeric excess was 85% when conducted at −20 °C with 57% yield after 48 h. [e] CaF_2 (2 equiv) was used and repeated at 0.1 mmol scale in 1.0 mL of solvent. $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether, $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether.

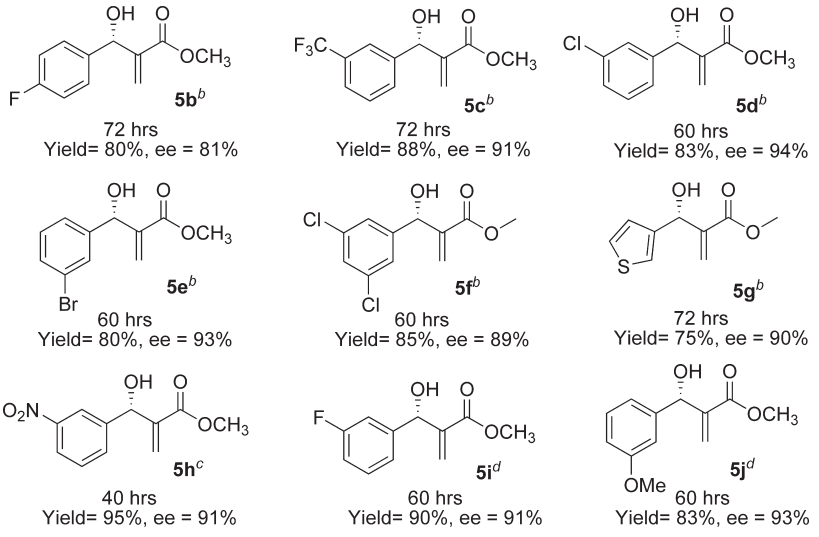
activated aldehydes (e.g., anisaldehydes) and deactivated Michael acceptors, for example, acrylonitrile,[44] which are generally poor partners from the viewpoint of efficiency to the established asymmetric MBH reactions.[1−4] Unfortunately, not all of the substituted aromatic chiral MBH alcohols could achieve excellent enantioselectivities under the established reaction conditions.[44] We believe that, with further investigations, satisfactory enantioselectivities of different MBH carbonates could be achieved.

To shed light on the role of water in allylic alkylation of MBH carbonates, isotope labeling experiments were conducted (Scheme 3). When $H_2{}^{18}O$ was used in the optimized achiral reaction conditions with MBH carbonate **1a**, it was observed that high yields of MBH alcohols [^{18}**O**]-**2a** were obtained with high ^{18}O incorporation level.[45] Next, ^{18}O-labeled MBH carbonate [^{18}**O**]-**1a**, which was prepared from [^{18}**O**]-**2a**, was subjected in the same reaction condition with 2 equiv of H_2O. MBH alcohol **2a** was obtained without the determination of [^{18}**O**]-**2a** (Scheme 3, eq 1). Thus, it is obvious that water acts as a nucleophile in this reaction, and the proposed pathway A is favored (Scheme 1, pathway A). The nucleophilic role of water in the asymmetric reaction was also confirmed (Scheme 3, eq 2).[46]

In conclusion, we have developed a practical allylic hydroxylation of MBH carbonates with H_2O in the presence of Lewis basic catalysts such as DABCO, DMAP, or *Cinchona* alkaloids. From this protocol, various synthetically valuable achiral MBH alcohols and chiral MBH alcohols were achieved directly in high yields and excellent enantioselectivities. This is the first report on organocatalytic asymmetric synthesis employing water as a nucleophile. We believe this work should serve to promote water as nucleophile in other C−O bond construction reactions. We also envisage opportunities to employ this chemistry for the facile, single-step synthesis of ^{18}O-labeled drugs or drug

Table 4. Synthesis of Chiral MBH Alcohols[a]





[a] At 0.05 mmol scale in 0.5 mL of DMAC. Enantiomeric excesses were determined by HPLC methods. Isolated yield. [b] At −10 °C, 5.0 equiv of H_2O and 5.0 equiv of CaF_2 were used. [c] At 0 °C, 2.0 equiv of H_2O and 2.0 equiv of CaF_2 were used. [d] At 0 °C, 5.0 equiv of H_2O and 5.0 equiv of CaF_2 were used.

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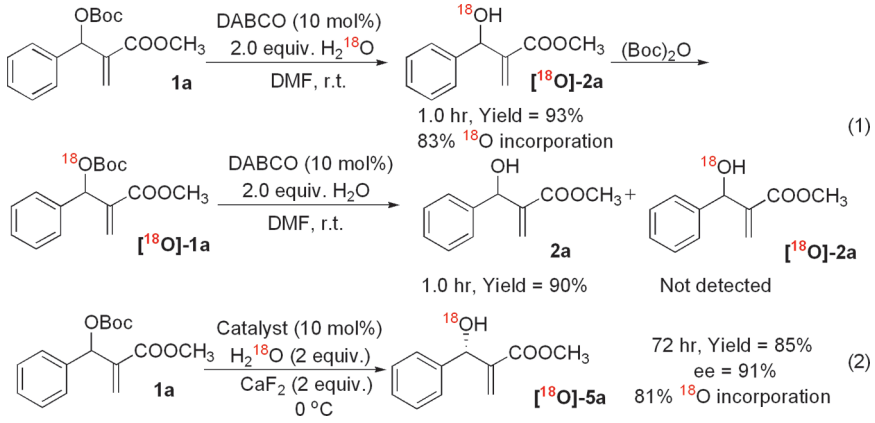
Scheme 3. ^{18}O-Labeling Experiments To Investigate the Reaction Mechanism



metabolites. Work is in progress to fully explore the substrate scope and will be reported in due course.

EXPERIMENTAL SECTION

Typical Experimental Procedure for the Reaction between MBH Carbonate 1a and H_2O Catalyzed by DABCO. **1a** (29.2 mg, 0.1 mmol, 1.0 equiv) and H_2O (4.0 μL, 0.2 mmol, 2.0 equiv) were dissolved in DMF (750 μL) and stirred at room temperature for 2.0 min, followed by DABCO (1.12 mg, 0.01 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After an hour and complete consumption of **1a**, the reaction mixture was directly loaded onto a short silica gel column, followed by gradient elution with petroleum ether/ethyl acetate mixture (100/1−5/1 ratio). Removal of the solvent in vacuo affords product **2a** (18.1 mg) as pale yellow oil in 96% yield.

Typical Experimental Procedure for the Reaction between MBH Carbonate 1a and H_2O Catalyzed by $(DHQD)_2AQN$. **1a** (29.2 mg, 0.1 mmol, 1.0 equiv), H_2O (4.0 μL, 0.2 mmol, 2.0 equiv), and CaF_2 (15.6 mg, 0.2 mmol, 2.0 equiv) were dissolved in DMF (1.5 mL) and stirred at 0 °C for 10.0 min, followed by $(DHQD)_2AQN$ (8.58 mg, 0.01 mmol, 0.1 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After 72 h and complete consumption of **1a**, the reaction mixture was directly loaded onto a short silica gel column, followed by gradient elution with petroleum ether/ethyl acetate mixture (100/1−5/1 ratio). Removal of the solvent in vacuo affords the product **5a** (16.6 mg) as pale yellow oil in 86% yield and 91% ee.

*Methyl-3-hydroxy-2-methylene-3-phenyl Propanoate (**2a**):* Colorless oil, 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40−7.26 (m, 5H), 6.34 (s, 1H), 5.83 (s, 1H), 5.57 (d, J = 5.7 Hz, 1H), 3.73 (s, 3H), 3.00 (d, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 141.8, 141.2, 128.4, 127.8, 126.5, 126.1, 73.1, 51.9; LRMS (ESI) m/z 214.9 (M + Na^+); HRMS (ESI) m/z 215.0684 (M + Na^+), calcd for $C_{11}H_{12}O_3Na$ 215.0679.

*Methyl-3-hydroxy-2-methylene-3-(4-nitrophenyl) Propanoate (**2b**):* Colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 6.39 (s, 1H), 5.87 (s, 1H), 5.63 (d, J = 6.0 Hz, 1H), 3.74 (s, 3H), 3.33 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 148.6, 147.3, 140.9, 127.3, 127.2, 123.5, 72.5, 52.1; LRMS (ESI) m/z 236.0 (M − H^+); HRMS (ESI) m/z 236.0560 (M − H^+), calcd for $C_{11}H_{10}O_5N$ 236.0564.

*Methyl-3-hydroxy-2-methylene-3-(3-nitrophenyl) Propanoate (**2c**):* Colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (t, J = 1.7 Hz, 1H), 8.15−8.13 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 6.41 (s, 1H), 5.90 (s, 1H), 5.63 (d, J = 6.1 Hz, 1H), 3.74 (s, 3H), 3.34 (d, J = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 148.1, 143.6, 140.9, 132.7, 129.2, 127.0, 122.6, 121.4, 72.2, 52.1; LRMS (ESI) m/z 236.1 (M − H^+); HRMS (ESI) m/z 236.0565 (M − H^+), calcd for $C_{11}H_{10}O_5N$ 236.0564.

*Methyl-3-hydroxy-2-methylene-3-(4-fluorophenyl) Propanoate (**2d**):* Colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36−7.32 (m, 2H), 7.04−7.00 (m, 2H), 6.33 (s, 1H), 5.83 (s, 1H), 5.54 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 163.6, 161.1, 141.9, 137.1 (two peaks), 128.4, 128.3, 126.1, 115.4, 115.2, 72.6, 52.0; LRMS (ESI) m/z 209.0 (M − H^+); HRMS (ESI) m/z 209.0623 (M − H^+), calcd for $C_{11}H_{10}O_3F$ 209.0619.

*Methyl-3-hydroxy-2-methylene-3-(4-bromophenyl) Propanoate (**2e**):* Pale yellow oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.47 (d, J = 9.6 Hz, 2H), 7.25 (d, J = 9.6 Hz, 2H), 6.34 (s, 1H), 5.82 (s, 1H), 5.51 (d, J = 5.4 Hz, 1H), 3.73 (s, 3H), 3.09 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 141.5, 140.3, 131.6, 128.3, 126.5, 126.4, 121.8, 72.8, 52.1; LRMS (ESI) m/z 293.0 (M + Na^+); HRMS (ESI) m/z 292.9770 (M + Na^+), calcd for $C_{11}H_{11}O_3BrNa$ 292.9784.

*Methyl-3-hydroxy-2-methylene-3-(2-chlorophenyl) Propanoate (**2f**):* Colorless oil; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.56 (dd, J = 7.6, 1.7 Hz, 1H), 7.36−7.22 (m, 3H), 6.33 (s, 1H), 5.98 (d, J = 4.7 Hz, 1H), 5.58 (s, 1H), 3.77 (s, 3H), 3.30 (d, J = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 140.6, 138.3, 132.6, 129.2, 128.8, 128.0, 126.8, 126.7, 68.8, 51.9; LRMS (ESI) m/z 248.9 (M + Na^+); HRMS (ESI) m/z 249.0289 (M + Na^+), calcd for $C_{11}H_{11}O_3ClNa$ 249.0289.

*Methyl-3-hydroxy-2-methylene-3-(4-methylphenyl) Propanoate (**2g**):* Colorless oil; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.32 (s, 1H), 5.86 (s, 1H), 5.53 (d, J = 3.7 Hz, 1H), 3.71 (s, 3H), 3.04 (d, J = 3.7 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 142.0, 138.3, 137.5, 129.1, 126.5, 125.8, 73.0, 51.9, 21.1; LRMS (EI) m/z 206.1 (M); HRMS (EI) m/z 206.0946 (M), calcd for $C_{12}H_{14}O_3$ 206.0943.

*Methyl-3-hydroxy-2-methylene-3-(2-naphthyl) Propanoate (**2h**):* White solid, mp 97.0−97.3 °C; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86−7.82 (m, 4H), 7.49−7.46 (m, 3H), 6.38 (s, 1H), 5.88 (s, 1H), 5.75 (d, J = 5.6 Hz, 1H), 3.73 (s, 3H), 3.14 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 141.8, 138.5, 133.2, 133.0, 128.2, 128.1, 127.6, 126.4, 126.1, 126.0, 125.5, 124.5, 73.3, 52.0; LRMS (ESI) m/z 265.0 (M + Na^+); HRMS (ESI) m/z 265.0838 (M + Na^+), calcd for $C_{15}H_{14}O_3Na$ 265.0835.

*Methyl-3-hydroxy-2-methylene-3-(4-methoxyphenyl) Propanoate (**2i**):* Colorless oil; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29−7.28 (d, J = 8.6 Hz, 2H), 6.87−6.85 (d, J = 8.6 Hz, 2H), 6.31 (s, 1H),

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5.85 (t, J = 1.2 Hz, 1H), 5.52 (s,1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.98 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 159.2, 142.1, 133.4, 127.8, 125.6, 113.8, 72.7, 55.2, 51.9; LRMS (ESI) m/z 244.9 ($M + Na^+$); HRMS (ESI) m/z 245.0794 ($M + Na^+$), calcd for $C_{12}H_{14}O_4Na$ 245.0784.

*Methyl-3-hydroxy-2-methylene-3-(3-thienyl) Propanoate (**2j**):* Pale yellow oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27 (dd, J = 5.0, 2.9 Hz, 1H), 7.21 (d, J = 2.9 Hz, 1H), 7.02 (dd, J = 5.0, 1.0 Hz, 1H), 5.83 (s,1H), 5.61 (d, J = 5.9 Hz, 1H), 3.73 (s, 3H), 3.30−3.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 142.8, 141.5, 126.1, 126.0, 121.8, 69.8, 52.0; LRMS (ESI) m/z 220.9 ($M + Na^+$); HRMS (ESI) m/z 221.0241 ($M + Na^+$), calcd for $C_9H_{10}O_3SNa$ 221.0243.

*Methyl-3-hydroxy-2-methylene-3-(2-furyl) Propanoate (**2k**):* Colorless oil; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 (t, J = 0.8 Hz, 1H), 6.36 (s, 1H), 6.30 (dd, J = 3.2, 2.0 Hz, 1H), 6.23 (d, J = 3.2 Hz, 1H), 5.94 (s, 1H), 5.56 (s, 1H), 3.72 (s, 3H), 3.38 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 154.1, 142.4, 139.4, 126.8, 110.4, 107.2, 67.4, 52.0; LRMS (ESI) m/z 204.6 ($M + Na^+$); HRMS (ESI) m/z 205.0474 ($M + Na^+$), calcd for $C_9H_{10}O_4Na$ 205.0471.

*tert-Butyl-3-hydroxy-2-methylene-3-phenyl Propanoate (**2l**):* Colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38−7.27 (m, 5H), 6.25 (s, 1H), 5.72 (t, J = 1.2 Hz, 1H), 5.50 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.7, 143.5, 141.7, 128.3, 127.7, 126.6, 125.1, 81.6, 73.4, 28.0; LRMS (ESI) m/z 256.9 ($M + Na^+$); HRMS (ESI) m/z 257.1150 ($M + Na^+$), calcd for $C_{14}H_{18}O_3Na$ 257.1148.

*3-Hydroxy-2-methylene-3-phenyl Propanenitrile (**2m**):* Colorless oil; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42−7.36 (m, 5H), 6.10 (s, 1H), 6.02 (s, 1H), 5.28 (d, J = 2.2 Hz, 1H), 2.68−2.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 139.0, 129.9, 128.5, 128.4, 126.3, 125.9, 116.8, 73.5; LRMS (ESI) m/z 158.1 ($M - H^+$); HRMS (ESI) m/z 158.0617 ($M - H^+$), calcd for $C_{10}H_8ON$ 158.0611.

*P-[1-(Hydroxyphenyl)ethenyl]phosphonic Acid, Diethyl Ester (**2n**):* Yellow oil; 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40−7.28 (m, 5H), 6.08 (d, J = 21.9 Hz, 1H), 6.01 (dt, J = 45.7, 1.2 Hz, 1H), 5.48 (dd, J = 13.2, 5.2 Hz, 1H), 4.11−3.95 (m, 2H), 3.95−3.85 (m, 1H), 3.79−3.69 (m, 1H), 3.53 (d, J = 5.5 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.6, 140.9, 140.8, 129.8, 129.7, 128.2, 127.7, 126.7, 74.2, 74.0, 62.2, 62.1 (two peaks), 62.0, 16.2, 16.1, 16.0, 15.9; ^{31}P (161.9755 MHz, $CDCl_3$, ppm) δ 17.4; LRMS (ESI) m/z 293.0 ($M + Na^+$); HRMS (ESI) m/z 293.0925 ($M + Na^+$), calcd for $C_{13}H_{19}O_4P$ 293.0913.

*Methyl 3-Hydroxy-2-methylidenepentanoate (**2o**):* Colorless oil; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.22 (s, 1H), 5.78 (s, 1H), 4.34−4.29 (m, 1H), 3.76 (s, 3H), 2.62 (d, J = 6.6 Hz, 1H), 1.71−1.58 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 142.1, 125.1, 73.0, 51.8, 29.0, 10.0; LRMS (EI) m/z 144.1 (M^+); HRMS (EI) m/z 144.0784 (M^+), calcd for $C_7H_{12}O_3$ 144.0786.

*2-(Hydroxymethyl)-2-cyclopenten-1-one (**4a**):* White solid, mp 55.0−56.7 °C; 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.54 - 7.52 (m, 1H), 4.39 - 4.38 (m, 2H), 2.67−2.63 (m, 2H), 2.47−2.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 209.9, 159.0, 144.9, 57.5, 35.0, 26.8; LRMS (EI) m/z 112.1 (M^+); HRMS (EI) m/z 112.0527 (M^+), calcd for $C_6H_8O_2$ 112.0524.

*2-(Hydroxyphenylmethyl)-2-cyclopenten-1-one (**4b**):* Pale yellow oil; 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36−7.23 (m, 6H), 5.50 (s, 1H), 3.85 (br, 1H), 2.54 (d, J = 1.6 Hz, 2H), 2.40−2.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 209.5, 159.5, 147.7, 141.3, 128.3, 127.6, 126.2, 69.4, 35.1, 26.5; LRMS (ESI) m/z 211.0 ($M + Na^+$); HRMS (ESI) m/z 211.0726 ($M + Na^+$), calcd for $C_{12}H_{12}O_2Na$ 211.0730.

*2-(Hydroxymethyl)-2-cyclohexen-1-one (**4c**):* Colorless oil; 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.02−6.91 (m, 1H), 4.20−4.18 (m, 2H), 2.40−2.32 (m, 4H), 1.99−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 200.7, 147.0, 138.2, 62.2, 38.2, 25.6, 22.7; LRMS (ESI) m/z 149.0 ($M + Na^+$); HRMS (ESI) m/z 149.0566 ($M + Na^+$), calcd for $C_7H_{10}O_2Na$ 149.0573.

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-phenyl Propanoate (**5a**):* Pale yellow oil, 86% yield; 91% ee; $[\alpha]^{10}_D$ +76.4 (c 0.14, MeOH) {lit: $[\alpha]^{22}_D$ +85.5 (c 1.11 MeOH), 84% ee, absolute configuration is determined as S}.[23] The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 9.7 min (major) and 15.8 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(4-fluorophenyl) Propanoate (**5b**):* Colorless oil; 80% yield; 81% ee; $[\alpha]^{21}_D$ +70.4 (c 0.50, MeOH). The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 8.3 min (major) and 10.6 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(4-trifluoromethylphenyl) Propanoate (**5c**):* Pale yellow oil; 88% yield; 91% ee; $[\alpha]^{22}_D$ +59.2 (c 0.25, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (s, 1H), 7.53 (t, J = 6.3 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 6.35 (s, 1H), 5.84 (s, 1H), 5.57 (s, 1H), 3.70 (s, 3H), 3.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.5, 142.3, 141.4, 130.8, 130.5, 130.0, 128.8, 126.6, 125.4, 124.6, 124.5 (two peaks), 123.4, 123.3 (three peaks), 122.6, 72.5, 52.0; LRMS (ESI) m/z 258.9 ($M - H^+$); HRMS (ESI) m/z 259.0584 ($M - H^+$), calcd for $C_{12}H_{10}O_3F_3$ 259.0588. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 5.6 min (major) and 6.7 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-chlorophenyl) Propanoate (**5d**):* Colorless oil; 83% yield; 94% ee; $[\alpha]^{22}_D$ +57.1 (c 0.53, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 (br, 1H), 7.25−7.21 (m, 3H), 6.32 (s, 1H), 5.84 (s, 1H), 5.47 (s, 1H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 143.3, 141.3, 134.2, 129.6, 127.8, 126.6, 126.5, 124.7, 72.4, 52.0; LRMS (EI) m/z 226.0 (M); HRMS (EI) m/z 226.0392 (M), calcd for $C_{11}H_{11}O_3Cl$ 226.0397. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 7.8 min (major) and 9.6 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-bromophenyl) Propanoate (**5e**):* Colorless oil; 80% yield; 93% ee; $[\alpha]^{21}_D$ +46.7 (c 0.41, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.53 (s, 1H), 7.42−7.40 (m, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.36 (s, 1H), 5.84 (s, 1H), 5.51 (d, J = 5.4 Hz,1H), 3.73 (s, 3H), 3.19 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.5, 143.6, 141.3, 130.9, 129.9, 129.6, 126.7, 125.2, 122.5, 72.7, 52.1; LRMS (ESI) m/z 293.0 ($M + Na^+$); HRMS (ESI) m/z 292.9770 ($M + Na^+$), calcd for $C_{11}H_{11}O_3BrNa$ 292.9784. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 8.2 min (major) and 10.1 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3,5-dichlorophenyl) Propanoate (**5f**):* Colorless oil; 85% yield; 89% ee; $[\alpha]^{22}_D$ +58.5 (c 0.35, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (s, 3H), 6.40 (s, 1H), 5.89 (s, 1H), 5.48 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 144.8, 140.7, 134.9, 127.8, 127.2, 125.0, 72.3, 52.2; LRMS (ESI) m/z 258.7 ($M - H^+$); HRMS (ESI) m/z 258.9942 ($M - H^+$), calcd for $C_{11}H_9O_3Cl_2$ 258.9934. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; retention time = 5.9 min (major) and 6.7 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-thienyl) Propanoate (**5g**):* Pale yellow oil; 75% yield; 90% ee; $[\alpha]^{21}_D$ +31.1 (c 0.45, MeOH); HRMS (ESI) m/z 221.0246 ($M + Na^+$), calcd for $C_9H_{10}O_3SNa$ 221.0243. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 10.1 min (major) and 14.6 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-nitrophenyl) Propanoate (**5h**):* Colorless oil; 95% yield; 91% ee; $[\alpha]^{22}_D$ +55.6 (c 0.42, MeOH); HRMS (EI) m/z 237.0647 (M^+), calcd for $C_{11}H_{11}O_5N$ 237.0637. The ee

was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 15.8 min (major) and 17.7 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-fluorophenyl) Propanoate (**5i**):* Pale yellow oil; 90% yield; 91% ee; $[\alpha]^{21}_{D}$ +59.2 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32−7.28 (m, 1H), 7.14−7.07 (m, 2H), 6.98−6.93 (m, 1H), 6.34 (s, 1H), 5.83 (s, 1H), 5.52 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 164.0, 161.6, 143.9, 143.8, 141.4, 129.9, 129.8, 126.6, 122.1 (two peaks), 114.7, 114.5, 113.6,113.3, 72.6 (two peaks), 52.0; LRMS (ESI) *m*/*z* 209.0 (M − H^+); HRMS (ESI) *m*/*z* 209.0623 (M − H^+), calcd for $C_{11}H_{10}O_3F$ 209.0619. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 210 nm; retention time = 7.5 min (major) and 9.4 min (minor).

*(S)-(+)-Methyl-3-hydroxy-2-methylene-3-(3-methoxyphenyl) Propanoate (**5j**):* Colorless oil; 83% yield; 93% ee; $[\alpha]^{21}_{D}$ +73.3 (*c* 0.12, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.16−7.12 (t, *J* = 8.2 Hz, 1H), 6.83−6.82 (t, *J* = 2.4 Hz, 2H), 6.72−6.70 (m, 1H), 6.22 (s,1H), 5.73 (s, 1H), 5.41−5.40 (d, *J* = 5.3 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.16−3.14 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 159.7, 142.9, 141.7, 129.4, 126.3, 118.8, 113.3, 112.0, 73.2, 55.2, 52.0; LRMS (ESI) *m*/*z* 245.0 (M + Na^+); HRMS (ESI) *m*/*z* 245.0785 (M + Na^+), calcd for $C_{12}H_{14}O_4Na$ 245.0784. The ee was determined by HPLC analysis. LUX Cellulose-2 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 230 nm; retention time = 16.4 min (major) and 24.2 min (minor).

*Methyl-3-hydroxy^{18}-2-methylene-3-phenyl Propanoate (**[^{18}O]-2a**):* Colorless oil, 90% yield; LRMS (ESI) *m*/*z* 217.1 (M + Na^+); HRMS (ESI) *m*/*z* 217.0723 (M + Na^+), calcd for $C_{11}H_{12}O_2{}^{18}ONa$ 217.0727. The ^{18}O incorporation of [^{18}O]-**2a** was 83% as determined by MS analysis ($H_2{}^{18}O$ is 90% atom of ^{18}O).

*(S)-(+)-Methyl-3-hydroxy^{18}-2-methylene-3-phenyl Propanoate (**[^{18}O]-5a**):* Colorless oil, 85% yield. The ^{18}O incorporation of [^{18}O]-**5a** was 81% as determined by MS analysis ($H_2{}^{18}O$ is 90% atom of ^{18}O).

■ ASSOCIATED CONTENT

Supporting Information. General information, HPLC spectra of chiral products, and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) In the presence of 10 mol % of $(DHQD)_2AQN$ at 0 °C, the reaction between **1a** and 2.0 equiv of H_2O was conducted in DMF with 2.0 equiv of CaF_2 as additive. The desired product **5a** was achieved with 81% yield and 83% ee after 72 h.
(44) See the Supporting Information for details.
(45) The ^{18}O incorporation of [^{18}**O**]-**2a** was 83% as determined by MS analysis ($H_2{}^{18}O$ is 90% atom of ^{18}O).
(46) The ^{18}O incorporation of [^{18}**O**]-**5a** was 81% as determined by MS analysis ($H_2{}^{18}O$ is 90% atom of ^{18}O).