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Diterpenoid Alkaloid Lappaconine Derivative Catalyzed Asymmetric α-Hydroxylation of β-Dicarbonyl Compounds with Hydrogen Peroxide

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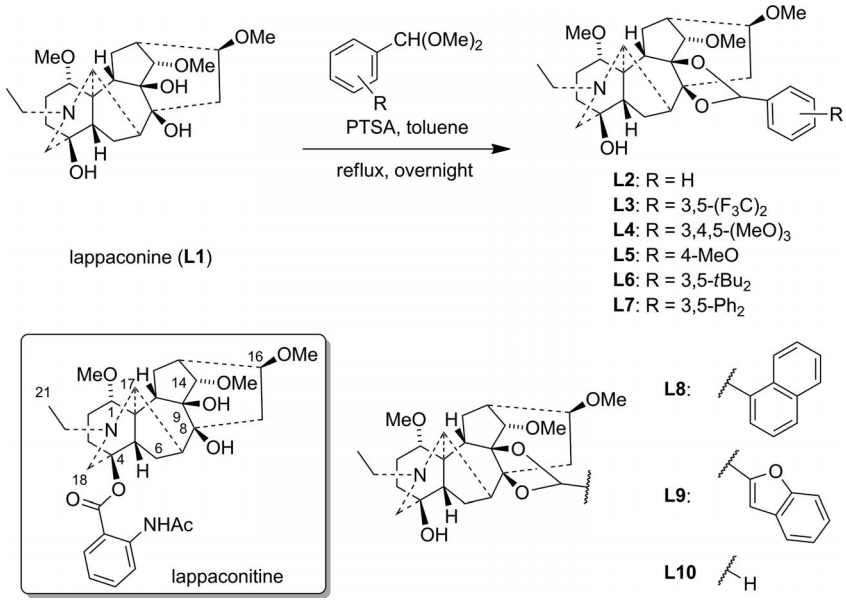
A new framework derived from the commercially available diterpenoid alkaloid lappaconitine was evaluated as a Brønsted base catalyst for the enantioselective α-hydroxylation of β-dicarbonyl compounds by using 30 % hydrogen peroxide as a green and highly practical source of oxygen. This protocol allows convenient access to the corresponding α-hydroxy-β-oxo esters, α-hydroxy-β-oxo amides and (–)-kjellmanianone with up to 98 % yield and 92 % *ee*.

Introduction

In the development of asymmetric organocatalysis with small chiral organic molecules as catalysts over the past decade, chiral natural compounds have played a significant role owing to their unique structures.[1] A number of natural compounds such as proline[2] and cinchona alkaloids[3] have been used as chiral auxiliaries and chiral catalysts in asymmetric organic synthesis. Alkaloids are important natural chiral compounds that contain basic nitrogen groups, including primary, secondary and tertiary amines, together with other functionalities, such as hydroxy and carbonyl groups, all of which can participate in hydrogen-bonding interactions, rendering them a class of potential organocatalysts. However, besides cinchona alkaloids, the use of other natural products as organocatalysts has rarely been reported. Thus, new asymmetric frameworks are urgently desired from natural chiral alkaloids to inspire wider catalyst applications.



Scheme 1. Diterpenoid alkaloid lappaconine and preparation of lappaconine derivatives.

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The α-hydroxy-β-oxo ester functionality is an important structural motif in a variety of agrochemicals, pharmaceuticals, and bioactive natural products, such as indoxacarb,[4] vindoline,[5] ginkgolide B,[6] and kjellmanianone.[7] The most convenient enantioselective synthesis of the α-hydroxy-β-dicarbonyl unit is through direct oxidation of β-oxo esters.[8,9] In the case of asymmetric organocatalysis toward α-hydroxylation of β-oxo esters, cinchona alkaloids,[9a,9d–9f] chiral phosphoric acids,[9b] chiral guanidines[9h] and the diterpenoid alkaloid lappaconitine[9c] (Scheme 1) have been reported as efficient catalysts with appropriate oxygenating agents, for example, cumyl hydroperoxide,[9a,9d,9f] *tert*-butyl hydroperoxide,[9c] oxaziridine,[9h] and molecular oxygen.[9e] To the best of our knowledge, there is no literature precedent with hydrogen peroxide as oxidant for this protocol.

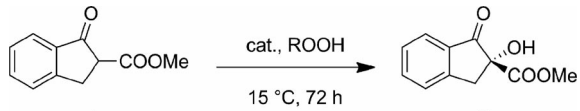
Results and Discussion

Inspired by our previous work,[9c] lappaconitine could promote an asymmetric hydroxylation of β-oxo esters, we expanded our investigation to some analogues of lappaconitine. Fortunately, we have found that the diterpenoid alkaloid lappaconine (**L1**) can be used for α-hydroxylation of β-oxo esters. Lappaconine was obtained from the alkaline hydrolysis of lappaconitine and later isolated from *Aconitum septentrionale* Koelle.[10] Lappaconine is a complex molecule that contains three stereogenic hydroxy groups (C4, C8 and C9), three stereogenic methoxy groups (C1, C14 and C16) and a basic tertiary amine (Scheme 1), which are sufficient structural features to suggest that it has potential as an organocatalyst. In this paper we report the asymmetric catalytic activity of lappaconine and lappaconine-derived analogues in the enantioselective α-hydroxylation of β-oxo esters by using commercially available hydrogen peroxide as an oxidant. Lappaconine analogues were synthesized by protecting the 8- and 9-hydroxy groups of **L1** as benzaldehyde dimethyl acetals. The compounds we synthesized for evaluation as catalysts are shown in Scheme 1.

Initial screening was performed for the α-hydroxylation of β-oxo ester **1a** with various diterpenoid alkaloid derivatives **L1**–**L10**, different oxidants and reaction conditions as outlined in Table 1.

We first attempted the enantioselective α-hydroxylation of β-oxo ester **1a** with catalyst **L1** (10 mol-%) and commercially available *tert*-butyl hydroperoxide (TBHP) as the oxidant in $CHCl_3$. To our delight, lappaconine (**L1**) afforded **2a** in 83% yield and 72% *ee* (Table 1, Entry 1). Next, we aimed to reduce the number of chiral hydroxy groups to make the structure more similar to the widely used cinchona alkaloids, which have a basic tertiary amine and only one stereogenic hydroxy group. To this end, we synthesized 8,9-*O*-benzylidenelappaconine (**L2**) by protecting the 8- and 9-hydroxy groups of **L1** with benzaldehyde dimethyl acetal. We found that **L2** was more effective than **L1**, affording **2a** in 86% yield and 80% *ee* (Table 1, Entry 2). Inspired by the initially surprising activity of **L2**, catalysts **L3**–**L6**, which bear different substituents on the aromatic ring, were evaluated. When catalyst **L3**, which bears a 3,5-$(CF_3)_2$-benzylidene acetal, was used the yield increased to 89%, and the *ee* value increased to 82% (Table 1, Entry 3). Remarkably, when we introduced three electron-donating OMe groups to the 3-, 4-, and 5-positions of the aromatic ring, the resulting catalyst **L4** promoted the formation of the corresponding product **2a** with a slightly decreased yield, but a significantly increased enantioselectivity (89% *ee*; Table 1, Entry 4). We also tested catalyst **L5**, which contains one electron-donating group at the *para* position of the aromatic ring, but this catalyst afforded **2a** in a lower yield and enantioselectivity (Table 1, Entry 5). Catalyst **L6**, which contains bulky *tert*-butyl groups at the 3- and 5-positions of the aromatic ring, and **L7**, which contains phenyl groups at the same positions, were also examined, and we found that they had comparable catalytic activity to **L3**, with 82 and 80% yield, respectively, and 84% *ee* (Table 1, Entries 6 and 7). Then we synthetized catalysts **L8**–**10** by changing the phenyl group of **L2** into 1-naphthyl, 2-benzofuranyl or hydrogen, but all of them afforded **2a** with reduced enantio-

Table 1. Screening of catalysts, peroxides, and reaction conditions for the organocatalytic α-hydroxylation of β-oxo ester **1a**.[a]



1a **2a**

Entry	Catalyst	Solvent	Peroxide	Yield [%][b]	*ee* [%][c]
1	**L1**	$CHCl_3$	TBHP	83	72
2	**L2**	$CHCl_3$	TBHP	86	80
3	**L3**	$CHCl_3$	TBHP	89	82
4	**L4**	$CHCl_3$	TBHP	85	89
5	**L5**	$CHCl_3$	TBHP	65	79
6	**L6**	$CHCl_3$	TBHP	82	84
7	**L7**	$CHCl_3$	TBHP	80	84
8	**L8**	$CHCl_3$	TBHP	81	77
9	**L9**	$CHCl_3$	TBHP	84	75
10	**L10**	$CHCl_3$	TBHP	83	72
11	**L4**	CH_2Cl_2	TBHP	82	83
12	**L4**	$ClCH_2CH_2Cl$	TBHP	79	79
13	**L4**	toluene	TBHP	74	78
14	**L4**	toluene/$CHCl_3$ (9:1)	TBHP	87	84
15	**L4**	$CHCl_3$	CHP[d]	30	86
16	**L4**	$CHCl_3$	*m*CPBA[e]	98	24
17	**L4**	$CHCl_3$	Oxone[f]	42	62
18	**L4**	$CHCl_3$	30% H_2O_2	90	84
19	**L4**	$CHCl_3$/MeOH (9:1)[g]	30% H_2O_2	96	85
20[h]	**L4**	$CHCl_3$/MeOH (9:1)	30% H_2O_2	88	86
21[i]	**L4**	$CHCl_3$/MeOH (9:1)	30% H_2O_2	99	82
22[j]	**L4**	$CHCl_3$/MeOH (9:1)	30% H_2O_2	89	85

[a] Unless otherwise specified, reactions were run with β-oxo ester **1a** (0.1 mmol), oxidant (0.5 mmol), the specified amount of catalyst, and solvent (2 mL) at 15 °C for 72 h. [b] Isolated yields after column chromatography. [c] The enantiomeric excess was determined by HPLC analysis of the product by using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (90:10) as the eluent. [d] CHP = cumyl hydroperoxide. [e] *m*CPBA = *m*-chloroperoxybenzoic acid. [f] Oxone monopersulfate. [g] Reaction time was 37 h. [h] Reaction conducted at 0 °C. [i] Reaction conducted at 25 °C. [j] Catalyst 5 mol-%.

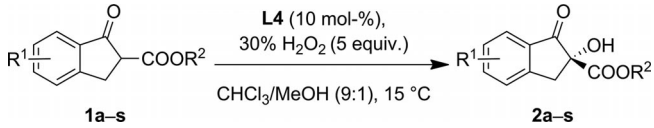
selectivity (Table 1, Entries 8–10). These results indicate that *meta*-substituted derivatives of **L1** are quite effective in this asymmetric induction; *meta* substitution, regardless of whether the *meta* substituent was an electron-withdrawing CF_3, an electron-donating OMe or a sterically hindered *t*Bu, led to increased reactivities and selectivities relative to the analogous *para*-substituted catalysts. Although the role of the substituent group in the *meta* position of the phenyl ring of **L3**–**L7** is not clear at present, **L4** was the most effective organocatalyst in our study thus far.

To establish the optimal reaction conditions for organocatalyst **L4**, we first screened for the optimal reaction solvent. The results obtained in various solvents, including CH_2Cl_2, $ClCH_2CH_2Cl$, toluene and toluene/$CHCl_3$, are summarized in Table 1, Entries 11–14. Although the reaction proceeded smoothly to afford the desired product in all of the tested solvents, chloroform was the only solvent that generally gave high chemical and optical yields (85% yield and 89% *ee*). The effect of commercially available oxidants on both the enantioselectivity and catalytic activity was then investigated (Table 1, Entries 15–18). The use of CHP and Oxone resulted in more sluggish reactions, whereas *m*CPBA raised the yield to 98% but reduced the enantioselectivity. To our delight, 30% H_2O_2 proved a good choice of oxidant and afforded **2a** in 90% yield and 84% *ee* (Table 1, Entry 18). To the best of our knowledge, there is no report with hydrogen peroxide as oxidant on this α-hydroxylation. Taking availability, yield, and enantioselectivity into account, commercially available 30% H_2O_2 was chosen as the optimal oxidant. To increase the solubility of 30% H_2O_2 in $CHCl_3$, a small quantity of MeOH was added. By using a mixed solvent of $CHCl_3$/MeOH (9:1), the reaction time was reduced to 37 h, but had no deleterious effect on the enantioselectivity (Table 1, Entry 19). A slightly increased level of enantioselectivity was obtained when the reaction temperature was decreased to 0 °C, but the yield dropped considerably to 88% (Table 1, Entry 20). Elevating the reaction temperature to 25 °C caused an increase in the yield with a decreased *ee* value of 82% (Table 1, Entry 21). Finally, 15 °C was selected as the optimal reaction temperature. Decreasing the catalyst loading to 5 mol-% reduced the yield (Table 1, Entry 22). Therefore, the optimized reaction conditions were as follows: $CHCl_3$/MeOH (9:1) as the solvent, with 10 mol-% **L4** as the organocatalyst, and 30% H_2O_2 as the oxidant at 15 °C.

With the optimized reaction conditions established, a series of β-oxo esters **1a**–**1s** with various substituents on the ester group and aromatic scaffold were used to investigate the scope of the reaction. The results are summarized in Table 2.

To the best of our knowledge, numerous studies indicate that a bulky *tert*-butyl ester group was crucial for obtaining good yields and enantioselectivities in phase-transfer catalysis[9d–9f] with β-dicarbonyl substrates, whereas small ester groups, such as methyl and ethyl, were necessary for homogeneous reactions when peroxides were used as oxygen sources.[9a,9c,9g] With these conflicting observations in mind, we initially investigated the steric influence of the ester

Table 2. **L4**-catalyzed asymmetric hydroxylation of β-oxo esters by using 30% H_2O_2 as the oxidant.[a]



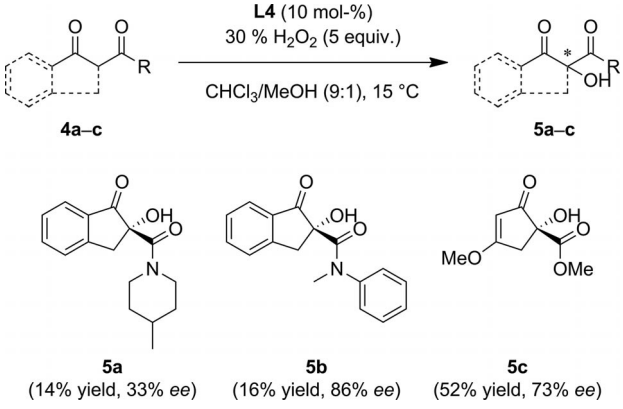
1a–s **2a–s**

Entry	**2**	R^1	R^2	Time [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	H	Me	37	96	85
2	**2b**	H	Et	45	93	82
3	**2c**	H	*i*Pr	42	96	87
4	**2d**	H	*t*Bu	8	98	84
5	**2e**	H	^{1}Ad	6	91	77
6	**2f**	H	CEt_3	21	97	87
7	**2g**	5-Cl	Me	42	92	83
8	**2h**	5-Cl	CEt_3	23	93	87
9	**2i**	6-F	Me	24	94	81
10	**2j**	6-Br	Me	48	87	84
11	**2k**	5-Br	Me	30	96	84
12	**2l**	4-Br	Me	19	94	84
13	**2m**	6-Me	Me	24	92	85
14	**2n**	6-Me	CEt_3	22	93	91
15	**2o**	4-MeO	Me	47	96	84
16	**2p**	4-MeO	CEt_3	22	93	89
17	**2q**	6-MeO	Me	47	98	86
18	**2r**	5,6-$(MeO)_2$	Me	23	98	89
19	**2s**	5,6-$(MeO)_2$	CEt_3	48	73	92

[a] Unless otherwise noted, reactions were conducted with β-oxo ester **1** (0.1 mmol), catalyst (0.01 mmol, 10 mol-%), and 30% H_2O_2 (0.5 mmol, 50 μL) in $CHCl_3$/MeOH (9:1, 2 mL) at 15 °C. [b] Isolated yields after column chromatography. [c] The enantiomeric excess was determined by HPLC analysis of the product by using a chiral column.

group on the yield and enantioselectivity of the asymmetric α-hydroxylation reaction (Table 2, Entries 1–6). Substrates that bare methyl or ethyl groups afforded products in high enantioselectivities of 85 and 82% *ee*, respectively (Table 2, Entries 1 and 2). To our delight, the sterically more hindered *i*Pr or *t*Bu derivatives also provided similar reactivities and selectivities with 87 and 84% *ee*, respectively (Table 2, Entries 3 and 4), but ^{1}Ad (1-adamantoyl) led to a reduction in both of yield and enantioselectivity (Table 2, Entry 5). Remarkably, the substrate containing the sterically even more hindered triethylmethyl group afforded 87% *ee* (Table 2, Entry 6). Even more noteworthy was that all of the β-oxo esters could afford the corresponding α-hydroxylation products in high yields of 91–98%. There appears to be no substantial steric effect of the ester moiety with this new catalyst. Next, the influence of substituents on the benzene ring of the β-oxo ester was investigated. Halogenated substrates (Cl, F and Br) gave the desired products in high yield and enantioselectivity (Table 2, Entries 7–12). Remarkably, electron-donating substituents, for example methyl and methoxy, at the phenyl ring afforded a mild increase in enantioselectivity (Table 2, Entries 13–19), especially **1s** that provided **2s** in 92% *ee* (Table 2, Entry 19). This was the highest enantioselectivity we obtained with the use of 30% H_2O_2 as oxidant. To the best of our knowledge, this is the first efficient asymmetric α-hydroxylation of β-oxo esters with 30% H_2O_2 as the oxidant.

To investigate possible extensions of this reaction to other kinds of β-dicarbonyl compounds, the oxidation of β-oxo amides **4a**, **4b** and cyclopentenone ester **4c** were tested (Scheme 2). The substrates with an amide group underwent hydroxylation reaction slowly with lowered yields, and the amido group in the β-oxo amide played an important role in the enantioselectivity. When **4a** was used, which bears a 4-methylpiperidine amide portion, gave just 33% *ee*, whereas **4b**, which contains an *N*-methylaniline group, afforded 86% *ee*. To our delight, cyclopentenone ester **4c** afforded cyclopentenoid (–)-kjellmanianone (**5c**) in 52% yield and 73% *ee* when 30% H_2O_2 was used as oxidant. To the best of our knowledge, there is no literature precedent with asymmetric organocatalysis on this direct α-hydroxylation.

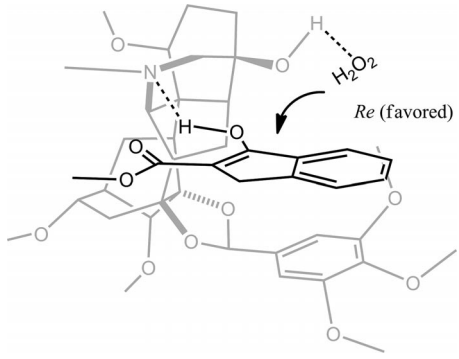


Scheme 2. Substrate scope of the α-hydroxylation process.

To test the scale-up potential of our asymmetric oxidation methodology, **1a** and **4c** were treated with 30% H_2O_2 (5.0 equiv.) on a gram-scale under the same conditions of 10 mol-% catalyst loading at 15 °C for 36 h. Hydroxylation products **2a** and **5c** were obtained in 93 and 53% yield, and 84 and 71% *ee*, respectively. In addition, the *ee* value of **5c** was improved to 99% after a single recrystallization from ethyl acetate.

As far as we are aware, these conditions for the hydroxylation of β-oxo esters afford higher enantioselectivities than other reported procedures when peroxide is used as the oxidant. The absolute configurations of **2a**–**2h**, **2j**–**2k**, **2m**, **2o**–**2s** and **5c** were tentatively determined to be (*R*) by comparison of their optical rotations with literature data,[7a,9c–9h] and the stereochemistries of the other α-hydroxy-β-dicarbonyl compounds were tentatively assigned by analogy.

Although the real stereochemical pathway has not yet been fully understood, a postulated transition state, based on experiments and previous reports[8b,8d,9c,9d,10,11] for the origin of the stereoselectivity in this reaction, is outlined in Scheme 3. The nitrogen atom of the lappaconine moiety could coordinate with the hydroxy group in the enolate form of the β-oxo ester by hydrogen-bonding interaction. The trimethoxyphenyl moiety of **L4** can block one side of the substrate by π–π stacking so that the *Re* face lacks steric congestion. Concurrently, hydrogen peroxide has a hydrogen-bonding interaction with the hydroxy group at C-4 of the catalyst. Therefore, hydrogen peroxide attacks the enolate from the least-hindered *Re* face to afford the (*R*) product.



Scheme 3. Predicted stereochemical pathways in the transition state.

Conclusions

We have extended the use of the diterpenoid alkaloid lappaconine and its derivatives as organocatalysts for the enantioselective α-hydroxylation reaction of β-dicarbonyl compounds. The reaction proceeds in high yields to give the corresponding products in up to 92% *ee* with **L4** as catalyst, 30% hydrogen peroxide as oxidant and chloroform/methanol as solvent under mild conditions. This is the first efficient asymmetric α-hydroxylation of β-oxo esters by using 30% H_2O_2 as the oxidant. These results will allow us to continue our search for chiral alkaloids and other natural products that can catalyze asymmetric reactions. Additional investigations to clarify the reaction mechanism and the application of the aconitane series of alkaloids and other alkaloids in different enantioselective reactions are underway.

Experimental Section

Preparation of Lappaconine (L1): A solution of lappaconitine (20.00 g, 34.2 mmol), NaOH (4.10 g, 102.6 mmol), water (30 mL), and ethanol (300 mL) was heated to reflux with a condenser for 4 h and then cooled to room temperature. The solvent was subsequently removed in vacuo, and the crude mixture was dissolved in water (300 mL) and extracted with CH_2Cl_2 (3× 150 mL). The solution was washed with water (3× 50 mL), brine (3× 50 mL), dried with Na_2SO_4, and filtered. The solvent was removed in vacuo to give the crude product. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc/TEA, 70:30:2) to afford lappaconine (**L1**) as a hygroscopic white foam (13.02 g, 90%). $[\alpha]_D^{25}$ = 19.20 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (s, 1 H), 3.42 (m, 1 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 3.20–3.09 (m, 1 H), 2.93 (s, 1 H), 2.75 (d, *J* = 11.1 Hz, 1 H), 2.61–2.55 (m, 1 H), 2.55–2.48 (m, 1 H), 2.46 (s, 1 H), 2.41 (d, *J* = 8.6 Hz, 1 H), 2.38 (d, *J* = 5.6 Hz, 1 H), 2.36–2.32 (m, 2 H), 2.29 (s, 1 H), 2.25 (s, 1 H), 2.21 (m 1 H), 2.15 (m, 1 H), 2.12–2.06 (m, 1 H), 2.04 (m, 1 H), 2.01 (m, 1 H), 2.00–1.95 (m, 1 H), 1.85 (m, 1 H), 1.83 (m, 1 H), 1.59 (m, 1 H), 1.52 (m, 1 H), 1.46 (m, 1 H), 1.31 (s, 1 H), 1.08 (t, *J* = 7.0 Hz, 3 H) ppm.

General Procedure for the Synthesis of Catalysts L2–L10: A mixture of lappaconine (1.00 g, 34.2 mmol), benzaldehyde dimethyl acetal (3.0 equiv.), *p*-toluenesulfonic acid (PTSA; 2.0 equiv.) and toluene (50 mL) was heated to reflux in a 50 mL round-bottomed flask with a Dean–Stark apparatus overnight. The solvent was removed in vacuo, and the crude mixture was dissolved in CH_2Cl_2 (100 mL). The solution was washed with saturated Na_2CO_3 (3× 20 mL), water (3× 20 mL), brine (3× 20 mL) and dried with Na_2SO_4. The solvent was removed in vacuo to give the crude product. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc/TEA, 80:20:2 to 50:50:2) to give the corresponding catalyst.

General Procedure for Enantioselective Hydroxylation: β-Oxo ester **1** (0.1 mmol) and catalyst (10 mol-%) were added to a test tube equipped with a stirring bar and dissolved in $CHCl_3$/MeOH (9:1, 2 mL). 30% H_2O_2 (0.5 mmol, 50 μL) was added, and the resulting mixture was stirred at 15 °C. After completion of the reaction, the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography to give alcohols **2**. The *ee* of the product was determined by chiral HPLC.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization of the prepared compounds, copies of NMR spectra, and chiral HPLC data of the hydroxylation products.

Acknowledgments

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