Diastereo- and Enantioselective Direct Catalytic Aldol Reaction of 2-Hydroxyacetophenones with Aldehydes Promoted by a Heteropolymetallic Complex: Catalytic Asymmetric Synthesis of *anti*-1,2-Diols

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Received October 31, 2001

An *anti*-selective direct catalytic asymmetric aldol reaction of 2-hydroxyacetophenones with aldehydes is described. The reaction is catalyzed by a heteropolymetallic complex to afford *anti*-α,*β*-dihydroxy ketones as the major diastereomer with excellent enantioselectivity. The use of 2-hydroxyacetophenones bearing electron-donating groups at the phenyl moiety enabled efficient transformation of the aldol products (α,*β*-dihydroxy ketones) into the corresponding α,*β*-dihydroxy ester derivatives via Baeyer−Villiger oxidation. A plausible reaction mechanism is also discussed based on the stereochemistry of the products.

Introduction

A wide range of important compounds in organic chemistry comprise the optically active 1,2-diol unit. This unit occurs in many natural products as represented by sugars and also has an important role as a chiral ligand in asymmetric catalysis, attracting a great deal of attention from chemists. Accordingly, extensive efforts have been made to develop a general synthetic tool to stereoselectively produce 1,2-diols. Among the many methods reported to date, the catalytic asymmetric dihydroxylation (AD) of olefins, which was developed by Sharpless et al., is widely accepted as reliable, with high levels of diastereo- and enantioselectivity. Whereas a variety of *syn*-diols are prepared in a highly enantioselective manner from *trans*-olefins,[1] *anti*-diols are less accessible due to the moderate selectivity obtained in the dihydroxylation of *cis*-olefins.[2] The development of a general method for the catalytic asymmetric synthesis of *anti*-diols, therefore, requires a different approach.[3,4]

The aldol reaction of α-hydroxy ketones with aldehydes might enable an efficient synthesis of 1,2-diols, because this process constructs vicinal hydroxyl groups by controlling the two stereogenic centers to form a C−C bond simultaneously. In practice, aldolases catalyze aldol reactions in vivo between dihydroxyacetone phosphate (DHAP) and aldehydes[3] to produce 1,2-diols, which are transformed into a series of carbohydrates. In artificial catalysis by a small molecule, Kobayashi et al. utilized chiral tin(II) Lewis acids for diastereo- and enantioselective Mukaiyama-type aldol reactions of ketene silyl acetals derived from *O*-protected α-hydroxy esters to obtain *syn*-α,*β*-dihydroxy ester derivatives in a highly stereoselective manner.[5] Some drawbacks remain, however, when using this method, such as the necessity for protection of the α-hydroxyl group and preparation of the ketene silyl acetals from esters.

In 1997, we reported a successful example of a direct catalytic asymmetric aldol reaction of unmodified ketones, for which the preformation of enol ethers was no longer needed.[6] Since that time, we[7−10] and others[11−15] have reported several new types of catalytic asymmetric

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(2) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568−7570.
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(11) Aldolase catalytic antibodies were reported. See: (a) Sinha, S. C.; Sun, J.; Miller, G.; Barbas, C. F., III; Lerner, R. A. *Org. Lett.* **1999**, *1*, 1623−1626. (b) Zhong, G.; Lerner, R. A.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **1999**, *38*, 3738−3741 and references therein.
(12) For direct aldol reactions promoted by Zn catalysts, see: (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (b) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497−2500.
(13) For amino acids catalyzed direct aldol reactions, see: (a) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267 and references therein.
(14) For direct aldol reactions promoted by diamine−protonic acid catalysts, see: Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245−1248.
(15) Catalytic asymmetric cyclocondensations between acyl halide and aldehyde have been reported. See: (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. Another group has reported a rhodium-catalyzed enantioselective reductive aldol reaction. See: (b) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528−4529.

10.1021/jo0162538 CCC: $22.00
Published on Web 03/19/2002

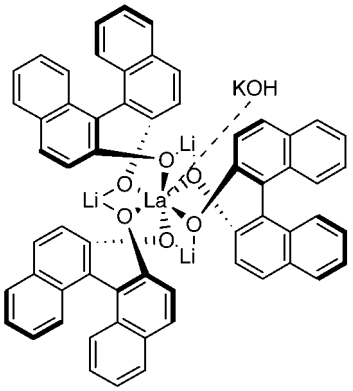
aldol reactions. List et al. recently reported that (*S*)-proline is an effective catalyst for the asymmetric direct aldol reaction of hydroxyacetone,[16] affording the corresponding *anti*-α,*β*-dihydroxy ketones in moderate yield with excellent enantioselectivity. Although this system was applicable to α-substituted aldehydes, only one example had been reported for an α-unsubstituted aldehyde. At the same time, we attempted to extend the direct enantioselective aldol reaction of methyl ketones to a diastereoselective variant using ethyl ketones[9] and hydroxy ketones as a substrate.[17−19] Consequently, our investigations resulted in the development of diastereoselective direct asymmetric aldol reactions of 2-hydroxyacetophenone with aldehydes,[17,18] where either *anti*- or *syn*-1,2-diols were obtained by choosing the appropriate catalyst. Whereas a heteropolymetallic catalyst[8] that is based on La, Li, and K afforded *anti*-1,2-diols,[17] a Zn−Zn-linked-BINOL complex afforded 1,2-diols in a highly *syn*-selective manner,[17,18] with excellent enantioselectivity. In the present article, the use of the heteropolymetallic catalyst for *anti*-selective direct aldol reactions of 2-hydroxyacetophenones is described. We examined a series of 2-hydroxyacetophenones bearing substituent(s) on the phenyl group as a substrate for the aldol reaction and found a consistent relationship between the reaction rate and the electron density of the aryl group in 2-hydroxyacetophenones. Moreover, the determination of the absolute and relative configuration of the aldol products provided a clue to the reaction mechanism.

Results and Discussion

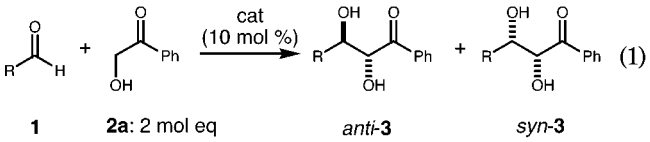
Optimization of Reaction Conditions. In 1999, we reported a direct enantioselective aldol reaction of methyl ketones that was catalyzed by a complex prepared from LLB ($LaLi_3$tris(binaphthoxide)),[20,21] KHMDS (potassium bis(trimethylsilyl)amide), and H_2O, and the catalyst was referred to as a "heteropolymetallic catalyst" (Chart 1).[8] We also reported that α,α-disubstituted aldehydes are the most suitable substrates.

We first examined the reaction of aldehydes with 2-hydroxyacetophenone (**2a**) using 10 mol % of the heteropolymetallic catalyst (eq 1). In contrast to the previous case, the reaction of α,α-disubstituted or α-monosubstituted aldehydes with **2a** afforded the aldol products with poor yield and poor enantiomeric excess. α-Unsubstituted aldehydes, however, which gave less satisfactory results in the previous system, reacted rapidly with **2a**

Chart 1



to afford the products in good yield with good enantiomeric excess. For example, the reaction of hexanal (**1b**) with **2a** at −20 °C gave the *anti*- and *syn*-aldol products (*anti*-**3b** and *syn*-**3b**) in 79% combined yield with a diastereomeric ratio of 1 to 1 after 18 h. The enantiomeric excess of the *anti*-isomer (*anti*-**3b**) was determined to be 79%, and that of the *syn*-isomer (*syn*-**3b**) to be 56% by HPLC analysis. The formation of the desirable *anti*-diastereomer (*anti*-**3b**) was dominant (74:26) when the reaction was performed at a lower temperature (−50 °C), and the enantioselectivity also improved to 93% ee (*anti*).

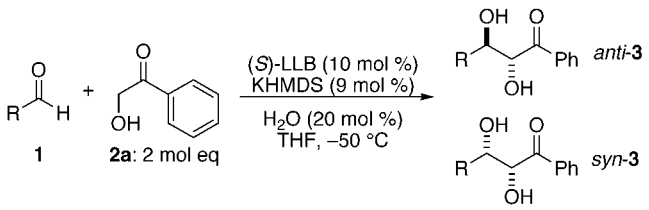


Because the *anti*-isomer (*anti*-**3b**) slightly decomposed during purification by silica gel column chromatography, the crude mixture of the aldol products (crude **3b**) was treated with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid to form the corresponding acetonides (**4b**) before isolation of the products. The diastereomeric acetonides were separable by silica gel column chromatography. The conditions for aldol reactions were eventually optimized to afford the acetonides (**4b**) in 84% overall yield (based on the aldehyde used) with 94% ee (*anti*) and 84% ee (*syn*) (*anti*:*syn* = 74:26, entry 3 in Table 1).[22] The relative and absolute configuration of *syn*-isomers (*syn*-**3**) was revealed by conversion to the acetonides (*syn*-**4**) and comparison with authentic samples obtained after Sharpless AD followed by acetonide formation.[23] Determination of the relative and absolute configuration of the *anti*-isomers was performed after epimerization of the acetonides (*anti*-**4**) obtained from the *anti*-aldol products (*anti*-**3**).[23]

The Aldol Reactions of 2-Hydroxyacetophenone (2a) with Aldehydes 1a−e. According to the optimized procedure, the aldol reactions of several α-unsubstituted aldehydes (**1a**−**e**) with 2-hydroxyacetophenone (**2a**) were examined using 10 mol % of the heteropolymetallic catalyst at −50 °C (Table 1). All the substrates tested afforded the corresponding *anti*-α,*β*-dihydroxy ketones (*anti*-**3**) as the major diastereomer in a highly enantioselective manner. Aldehyde **1a** reacted with **2a** to produce a better diastereomeric ratio (*anti*:*syn* = 84:16),

(16) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387.
(17) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467.
(18) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539−1542.
(19) Trost et al. have independently reported the direct aldol reaction of hydroxy ketones with various aldehydes using a chiral semi-crown Zn complex, and *syn*-1,2-diols were accessible by means of this reaction. See: Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368.
(20) For reviews of heterobimetallic multifunctional catalysts developed in our group, see: (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Shibasaki, M.; Sasai, H.; Arai, T.; Iida, T. *Pure Appl. Chem.* **1998**, *70*, 1027−1034. (c) Shibasaki, M.; Iida, T.; Yamada, Y. M. A. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 344−356. (d) Shibasaki, M. *Chemtracts-Org. Chem.* **1999**, *12*, 979−998. (e) Shibasaki, M. *Enantiomer* **1999**, *4*, 513−527. (f) Shibasaki, M.; Yamada, K.-i.; Yoshikawa, N. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2, Chapter 20.
(21) LLB is now commercially available as a solution in THF from Fluka.
(22) The diastereomeric ratio was determined by ^{1}H NMR of the crude mixture of the diols.

Table 1. Aldol Reaction of 2-Hydroxyacetophenone (2a) with Aldehydes 1a−e Promoted by 10 mol % of a Heteropolymetallic Catalyst



entry	aldehyde (R)	diol	time (h)	yield[a] (%)	dr[b] (*anti*:*syn*)	ee[c] (*anti*/*syn*)
1	$C_6H_5(CH_2)_3$ (**1a**)	**3a**	24	84	84:16	95/74
2[d]	**1a**	**3a**	40	78	78:22	92/70
3	*n*-C_5H_{11} (**1b**)	**3b**	24	84	74:26	94/84
4	(*E*)-$CH_3(CH_2)_4CH{=}CH(CH_2)_2$ (**1c**)	**3c**	28	90	72:28	94/83
5	*i*-Bu (**1d**)	**3d**	24	86	65:35	90/83
6	$C_6H_5(CH_2)_2$ (**1e**)	**3e**	24	89	69:31	95/87

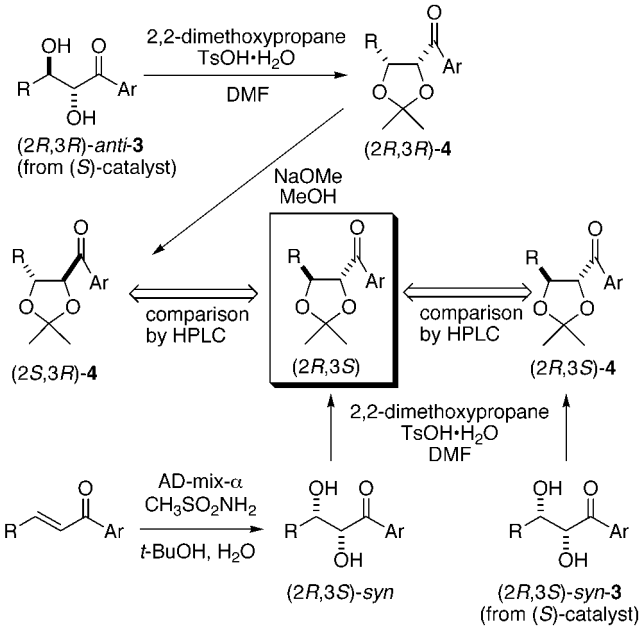
[a] Isolated yield of acetonides **4** (see the main text). [b] Determined by ^{1}H NMR of the crude mixture of aldol products (diols). [c] Ee of acetonide **4** (see the main text). [d] Catalyst (5 mol %), −40 °C.

with an enantiomeric excess of the major diastereomer of 95% (entry 1). The *anti*-adduct was obtained in 92% ee even with a reduced amount of the catalyst (5 mol %) (entry 2). Aldehyde **1c**, which bears a C−C double bond, was also a suitable substrate for this system to afford the products in 90% yield (*anti*:*syn* = 72:28) with 94% ee (*anti*) (entry 4). This result indicates that the present catalytic system tolerates substrates bearing C−C double bonds, which is a functional group that can be used as a scaffold for further manipulation of the aldol products, whereas this is not the case in the Sharpless AD. Although a substitution at the β- or γ-position of the aldehydes produced lower diastereoselectivity, the enantioselectivity was maintained at high levels (>90%; *anti*) (entries 5 and 6).

Transformations of Aldol Products 3. To demonstrate the synthetic utility of the present aldol reaction, we attempted to convert the aldol products (α,β-dihydroxy ketones **3**) into synthetically more versatile compounds. The conversion of the ketone moiety in the aldol products to an ester moiety by Baeyer−Villiger oxidation would fulfill this purpose. As a preliminary experiment, we treated acetonide **4b** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of phosphate buffer, and the reaction proceeded with a rapid, regioselective rearrangement of the alkyl group to produce benzoate ester **6** in 91% yield. We next attempted to obtain a phenyl ester, instead of the benzoate, by changing the regioselectivity in the Baeyer−Villiger oxidation. To achieve the rearrangement of the phenyl moiety, another protecting group for the diol moiety was pursued, and carbonate **5b**[18] was synthesized from diol *anti*-**3b** and subjected to Baeyer−Villiger oxidation using *m*-CPBA. The reaction was, however, very sluggish and messy. The use of another oxidant such as bis(trimethylsilyl) peroxide (BTSP)[24] was also ineffective.

The disappointing results prompted us to modify the phenyl moiety in 2-hydroxyacetophenone as a substrate for the aldol reaction, because an electron-rich aryl group might undergo a facile rearrangement during Baeyer−Villiger oxidation. Thus, a series of substituted 2-hydroxyacetophenones were prepared, and the effects of the electron density of the aryl group were investigated in aldol reactions at −40 °C (Table 2). The use of ketones possessing a methoxy group on the phenyl group (**2b**−**d**) decelerated the aldol reaction (entries 1−3), and much slower reaction rates were observed when 2-hydroxy-2′,5′-dimethoxyacetophenone (**2e**) was used. In contrast, the aldol reaction of 2-hydroxy-2′-methylacetophenone (**2f**) proceeded at a reasonable rate to afford the diols (**3k**) in 90% yield, albeit with lower selectivity (*anti*:*syn* = 77:23, *anti* = 84% ee) (Table 2, entry 6). On the other hand, excellent enantioselectivity was obtained in the reaction of 2-hydroxy-4′-methylacetophenone (**2g**) with aldehyde **1a** (yield 90%, *anti*:*syn* = 83:17, *anti* = 97% ee) (entry 7). The reaction is essentially completed within a shorter time (13 h), as shown in entry 8. These results illustrate the dependency of the reaction rate on the electron density of the aryl group of the ketone (**2**). The decreased reaction rates observed for methoxy-substituted hydroxyacetophenones **2b**−**e** are probably due to the resulting lower acidity of the α-proton of the ketone.

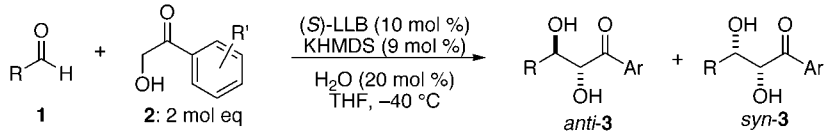
(23) The relative and absolute configuration of the aldol products was determined according to the following procedures:



For **3c** and **3i**, see Supporting Information.

(24) (a) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973. (b) Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902. (c) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029. See also 8.

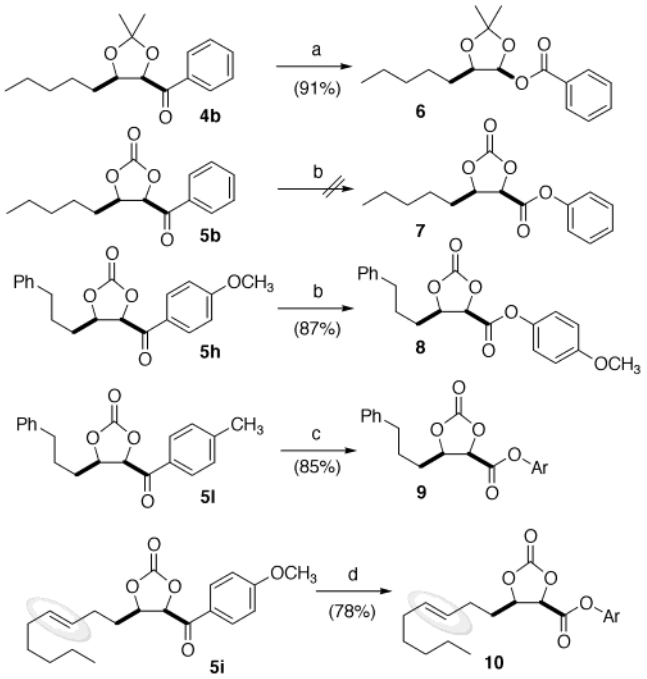
Table 2. Aldol Reaction of Substituted 2-Hydroxyacetophenones (2b−g) Promoted by 10 mol % of a Heteropolymetallic Catalyst



entry	aldehyde (R)	ketone (R′)	diol	time (h)	yield[a] (%)	dr[a] (*anti*:*syn*)	ee[b] (*anti*/*syn*)
1	$C_6H_5(CH_2)_3$ (**1a**)	2-MeO (**2b**)	**3f**	35	69	76:24	95/74
2	**1a**	3-MeO (**2c**)	**3g**	35	82	77:23	95/83
3	**1a**	4-MeO (**2d**)	**3h**	35	50	81:19	98/79
4[c]	(*E*)-$CH_3(CH_2)_4CH{=}CH(CH_2)_2$ (**1c**)	**2d**	**3i**	13	76[d]	67:33[e]	93/91[f]
5	$C_6H_5(CH_2)_3$ (**1a**)	2,5-$(MeO)_2$ (**2e**)	**3j**	35	42[g]	74:26	80/41
6	**1a**	2-Me (**2f**)	**3k**	35	90	77:23	84/57
7	**1a**	4-Me (**2g**)	**3l**	35	90	83:17	97/85
8	**1a**	**2g**	**3l**	13	96	82:18	96/83
9	*n*-C_5H_{11} (**1b**)	**2g**	**3m**	12	96	75:25	96/89

[a] Determined by ^{1}H NMR of the crude mixture of aldol products (diols). [b] Ee of acetonide **4** (see the main text). [c] The reaction was carried out at −30 °C. [d] Isolated yield of diols. [e] The ratio calculated based on isolated diols. [f] The ee of *anti*-**3i** was determined at the stage of the diol. [g] Isolated yield of acetonides **4** (see the main text).

Scheme 1. Baeyer−Villiger Oxidations[a]



[a] Reagents and conditions: (a) *m*-CPBA (2 mol equiv), NaH_2PO_4 (2.5 mol equiv), 1,2-dichloroethane, rt, 3.5 h; (b) *m*-CPBA (4 mol equiv), NaH_2PO_4 (6 mol equiv), 1,2-dichloroethane, 50 °C, 5 h; (c) *m*-CPBA (8 mol equiv), NaH_2PO_4 (10 mol equiv), 1,2-dichloroethane, 40 °C, 2.5 h; (d) $SnCl_4$ (1 mol equiv), *N*,*N*-bis(*p*-toluenesulfonyl)cyclohexane-1,2-diamine (1 mol equiv), bis(trimethylsilyl) peroxide (4 mol equiv), CH_2Cl_2, MS 4A, −20 °C, 50 min.

The aldol products (*anti*-**3h**, *anti*-**3i**, and *anti*-**3l**) with electron-donating substituents on the aryl group were transformed into the corresponding cyclic carbonates (**5h**, **5i**, and **5l)** in 86 to 91% yield by treatment with triphosgene. Baeyer−Villiger oxidation of carbonate **5h** proceeded with a smooth, clean rearrangement of the aryl group (Scheme 1), as we expected. In addition, the same type of reaction with carbonate **5l**, derived from *anti*-**3l**, cleanly produced the corresponding aryl ester (**9**) in 85% yield (Scheme 1). Furthermore, carbonate **5i**, which has a C−C double bond, also underwent a chemoselective rearrangement of the aryl group by utilizing BTSP as an oxidant to afford ester **10** in 78% yield.

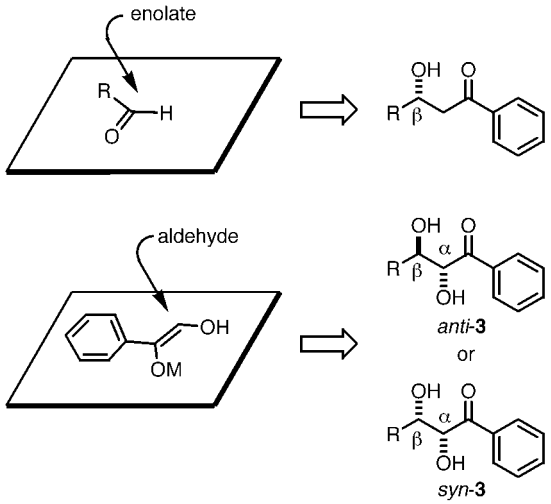


Figure 1. Stereochemical course of the direct aldol reaction of methyl ketones (top) and hydroxy ketones (bottom).

Reaction Mechanism. Examination of the stereochemistry of the aldol products (**3**) revealed that the configuration at the *β*-position of the major diastereomer (*anti*-**3**, bottom of Figure 1) is opposite to that of previously reported aldol products from acetophenone (top of Figure 1).[25] Moreover, an identical configuration (*R*) was expressed at the α-position both of *anti*- and of *syn*-products for all direct aldol reactions examined (eq 1 or bottom of Figure 1), suggesting that the aldehyde attacks the *Re*-face of the (*Z*)-enolate for the formation of both diastereomers.

The enantio- and diastereoselectivity can be rationalized by considering models depicted in Figure 2. Because the majority (97.5% for **3l**) of the product bears (α*R*)-hydroxyl group, the shielding of the *Si*-face of the enolate by the catalyst should be almost perfect. The configuration of the *β*-position, meanwhile, would depend on a direction in which the enolate−LLB complex approaches the aldehyde, namely the differentiation of the enantioface of the *aldehyde* (**a** vs **b** in Figure 2).

(25) Note that the aldol products in ref 8 were obtained using (*R*)-catalyst, whereas the catalyst described in this article possesses the (*S*)-configuration. We extrapolated in this article the absolute configuration of the product for (*S*)-LLB for consistency.

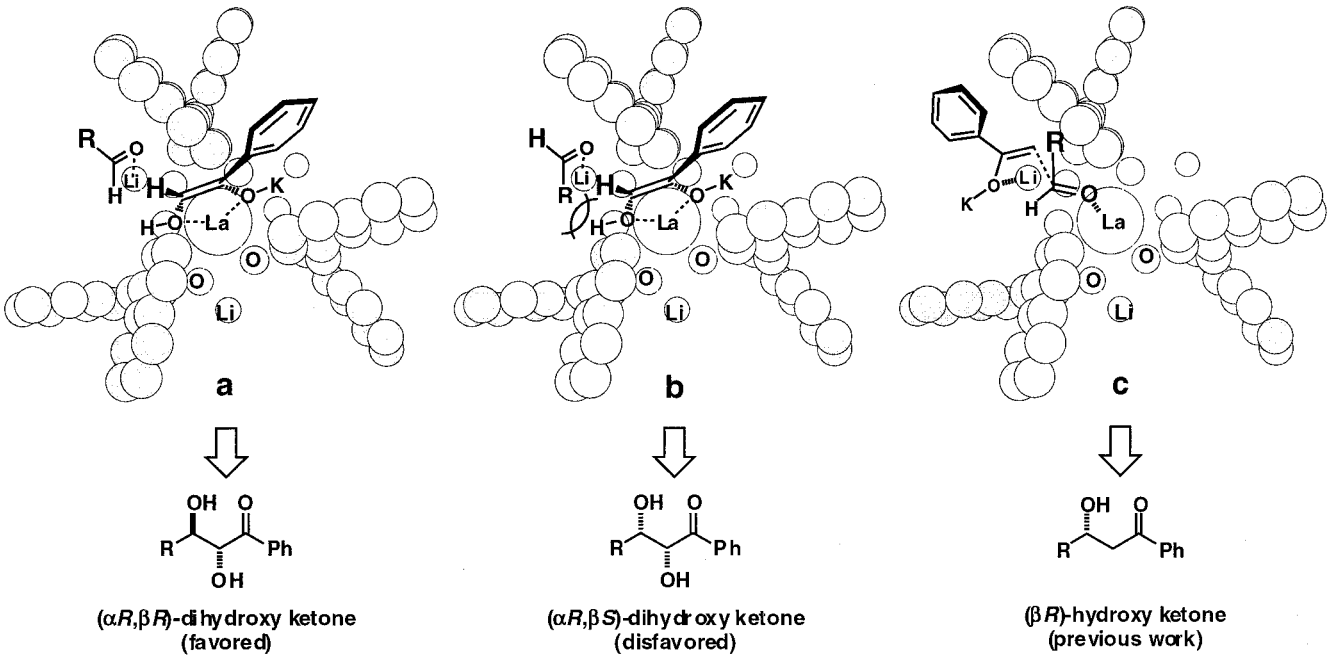
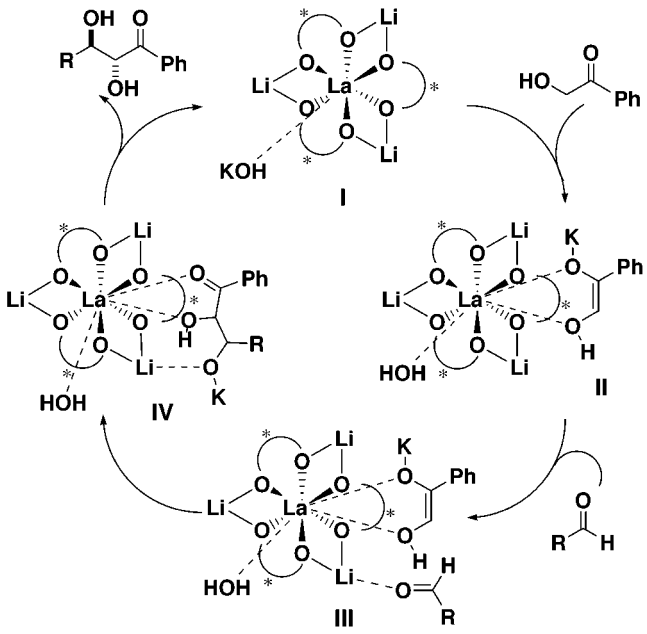


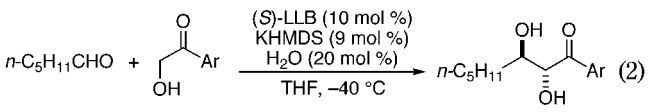
Figure 2. Postulated intermediates for the formation of *anti*-diol (**a**), *syn*-diol (**b**), and *β*-hydroxy ketone (**c**).

Scheme 2. Postulated Catalytic Cycle



Previously, some kinetic studies and other experimental results led us to propose that the direct aldol reaction of acetophenone is promoted by the synergistic functions of the heteropolymetallic catalyst, wherein the lanthanum ion acts as a Lewis acid to activate the aldehyde, and the KOH functions as a Brønsted base to generate an enolate from the ketone.[8] On the basis of the previously proposed mechanism and the above-described stereochemistry of the products (**3**), we postulated the following catalytic cycle (Scheme 2) for the present system. First, 2-hydroxyacetophenone coordinates to the lanthanum metal of the catalyst (**I**) in a bidentate fashion and is deprotonated by KOH at the α-position. The resulting potassium enolate then forms a chelate complex (**II**) with the lanthanum metal of LLB. The priority of the ketone for the coordination to the lanthanide center metal over that of the aldehyde can be explained by the possible capability of the ketone to form a stable complex with Lewis acids such as a lanthanum ion. Avoiding the resulting sterically crowded lanthanide center, the aldehyde subsequently coordinates to the lithium metal and is then attacked by the enolate, affording an alkoxide−LLB complex (**IV**) via intermediate **III** (see also Figure 2). In this intermediate (**III**), proper orientation of the enolate in the cavity of the catalyst permits the *Re*-face of the enolate to be selectively exposed to the electrophilic attack of the aldehyde coordinating to the lithium. The resulting alkoxide−LLB complex (**IV** in Scheme 2) is then protonated by H_2O to produce the dihydroxy ketone, and the catalyst (**I**) is regenerated.

All the steps should be reversible in principle so that prolonged reaction time may decrease the enantiomeric or diastereomeric excess of the product through a retro-aldol reaction or epimerization at the α-position.[26] Nevertheless, the time-course of the present aldol reaction indicates that either the enantiomeric or diastereomeric ratio of the aldol product was maintained almost constant during at least 49 h (eq 2). Hence, the stereochemistry of the products is likely to be kinetically controlled under the reaction conditions.



1b **2g**: 2 mol eq **3m**

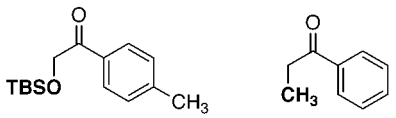
(Ar = 4-CH_3-C_6H_4)

4 h: y. 50%, *anti* : *syn* = 76:24, *anti* = 97% ee, *syn* = 90% ee
20 h: y. 90%, *anti* : *syn* = 77:23, *anti* = 98% ee, *syn* = 91% ee
49 h: y. 88%, *anti* : *syn* = 76:24, *anti* = 98% ee, *syn* = 90% ee

The use of other ketones as substrates was investigated to obtain supporting evidence for the bidentate interac-

(26) A deterioration in the enantiopurity of aldol adducts was observed in a direct aldol reaction promoted by a calcium-based catalyst. See ref 10.

tion between the 2-hydroxyacetophenones (**2**) and the catalyst. Ketones **11** and **12** are expected to be much less effective for generating a chelate complex, compared with 2-hydroxyacetophenones (**2**). The aldol reaction of either **11** or **12** with aldehyde **1a** under the optimized conditions (catalyst: 10 mol %, −40 °C) did not give aldol products even after a prolonged reaction time (66 h). On the basis of these results, the presence of the hydroxyl group in the ketones (**2**) seems to be essential for the present system.[27]



11 **12**

The formation of an enolate would be facilitated by a strong interaction between the ketone and the catalyst through a bidentate coordination with the hydroxyl and carbonyl group of **2**, and the chelate complex (vide supra) could be formed only from (*Z*)-enolate. The present catalytic system, therefore, seems to require the participation of the (*Z*)-enolates rather than the (*E*)-enolates.[28]

Conclusions. We achieved an *anti*- and enantioselective direct aldol reaction of α-unsubstituted aldehydes with 2-hydroxyacetophenones, which is promoted by a heteropolymetallic catalyst. The method allows for direct access to *anti*-α,*β*-dihydroxy ketones with excellent enantioselectivity from aldehydes and hydroxy ketones, which are commonly available materials in organic synthesis. Although the diastereoselectivity remains to be improved, the system described is one of the most effective methods of catalytic asymmetric synthesis of *anti*-1,2-diols so far reported.[2−4,16,17] Hence, synthesis of 1,2-diols by means of a direct aldol reaction is a new, efficient, and direct approach, together with the already-established *syn*-selective variants.[1,3,4,17−19] The direct aldol reaction of α-hydroxy esters instead of ketones, however, has not yet been achieved and is currently being investigated, because that process would preclude the necessity of using the Baeyer−Villiger oxidation step to obtain synthetically versatile compounds.

Experimental Section

Instruments and Materials. NMR spectra were recorded at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (= 0) or in the scale relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. Chemical shifts in C_6D_6 were reported in the scale relative to C_6H_6 (7.15 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm for ^{13}C NMR) or C_6H_6 (128.0 ppm for ^{13}C NMR) as an internal reference. Column chromatography was performed with silica gel Merck 60 (230−400 mesh ASTM). The HPLC analysis was performed using UV at 254 nm. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was dissolved in chloroform and then washed with phosphate buffer (pH 7.5) before recrystallization from chloroform, unless otherwise noted. (*S*)-BINOL was dried at 45 °C for 3 h under reduced pressure before use. Aldehydes were distilled before use. 2-Hydroxyacetophenones were recrystallized before use. Acetophenones as a starting material for the preparation of 2-hydroxyacetophenones were purchased and used without further purification.

General Procedure for Single-step Preparation of 2-Hydroxyacetophenones (2a−g) (Only Applicable to Small-Scale Synthesis).[29] A mixture of acetophenone or substituted acetophenone (8.32 mmol), trifluoroacetic acid (1.27 mL, 16.6 mmol), acetonitrile (42 mL), H_2O (8.3 mL), and (bis(trifluoroacetoxy)iodo)benzene (7.16 g, 16.6 mmol) was heated to reflux until the starting ketone was consumed (1−5 h) based on TLC. After cooling to room temperature, acetonitrile was evaporated, and CH_2Cl_2 and H_2O were added. The aqueous layer was separated and extracted with CH_2Cl_2 twice. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to afford the α-hydroxylated acetophenone in 30−50% yield, which was recrystallized before use.

2-Hydroxy-2′-methoxyacetophenone (2b). Colorless solid; mp 83 °C; IR (KBr) ν 3441, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (ddd, J = 8.2, 7.1, 1.8 Hz, 1H), 7.06 (ddd, J = 7.8, 7.1, 0.8 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 4.76 (d, J = 4.8 Hz, 2H), 3.94 (s, 3H), 3.74 (t, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 199.1, 160.2, 135.3, 131.0, 123.0, 120.9, 111.7, 70.0, 55.5; LRMS (EI) *m*/*z* 166 (M^+), 135 (ArC≡O^+, base peak). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.83; H, 6.05.

2-Hydroxy-3′-methoxyacetophenone (2c). Colorless solid; mp 50 °C; IR (KBr) ν 3501, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47−7.45 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.16 (ddd, J = 8.0, 2.6, 0.9 Hz, 1H), 4.85 (d, J = 4.6 Hz, 2H), 3.86 (s, 3H), 3.49 (t, J = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 198.3, 160.0, 134.7, 130.0, 120.7, 120.1, 112.1, 65.5, 55.5; LRMS (EI) *m*/*z* 166 (M^+), 135 (ArC≡O^+, base peak). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.91; H, 6.11.

2-Hydroxy-4′-methoxyacetophenone (2d). Pale yellow solid; mp 106−107 °C; IR (KBr) ν 3387, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91−7.89 (m, 2H), 6.98−6.96 (m, 2H), 4.82 (s, 2H), 3.88 (s, 3H), 3.52 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 196.7, 164.4, 130.0, 126.4, 114.2, 65.0, 55.5; LRMS (EI) *m*/*z* 166 (M^+), 135 (ArC≡O^+, base peak). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.90; H, 6.07.

2-Hydroxy-2′,5′-dimethoxyacetophenone (2e). Pale yellow solid; mp 100−101 °C; IR (KBr) ν 3492, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 3.2 Hz, 1H), 7.12 (dd, J = 8.9, 3.2 Hz, 1H), 6.94 (d, J = 8.9 Hz, 1H), 4.76 (d, J = 4.7 Hz, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.71 (t, J = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 198.9, 154.9, 153.7, 123.2, 122.6, 113.6, 70.0, 56.0; LRMS (EI) *m*/*z* 196 (M^+), 165 (ArC≡O^+, base peak). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.99; H, 6.35.

2-Hydroxy-2′-methylacetophenone (2f). Colorless solid; mp 32−33 °C; IR (KBr) ν 3449, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.45 (dt, J = 7.5, 0.9 Hz, 1H), 7.32−7.28 (m, 2H), 4.76 (d, J = 4.6 Hz, 2H), 3.60 (t, J = 4.6 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.9, 139.7, 133.0, 132.8, 132.4, 128.4, 126.0, 66.5, 21.6; LRMS (EI) *m*/*z* 150 (M^+), 119 (ArC≡O^+, base peak). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.83.

2-Hydroxy-4′-methylacetopheone (2g). Pale yellow solid; mp 83 °C; IR (KBr) ν 3434, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83−7.81 (m, 2H), 7.31−7.29 (m, 2H), 4.85 (s, 2H), 3.51 (brs,

(27) Evans et al. reported a Mukaiyama-type aldol reaction catalyzed by a copper complex, in which catalyst−substrate chelation proved to be essential. See: Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685.

(28) Analogous arguments appeared in the literature describing the diastereoselective aldol reactions of α-alkoxy esters. See: Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161−8174. See also ref 5.

(29) Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065−6068.

1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.9, 145.3, 130.9, 129.6, 127.8, 65.3, 21.8; LRMS (EI) *m*/*z* 150 (M^+), 119 ($ArC{\equiv}O^+$, base peak). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.83.

Representative Procedure for Large-Scale Preparation of 2-Hydroxyacetophenones. Several hydroxy ketones were prepared in large scale. Because the above-mentioned procedure requires a large amount of (bis(trifluoroacetoxy)-iodo)benzene, we recommend the following procedure for a large-scale preparation. To a stirred solution of diisopropylamine (25.1 mL, 0.179 mol) in THF (358 mL), a hexane solution of *n*-BuLi (101 mL, 0.158 mol, 1.56 M) was added over 10 min at 0 °C. The resulting solution was stirred for 30 min at 0 °C, and a solution of 4′-methylacetophenone (20 g, 0.149 mol) in THF (14.9 mL) was then added over 10 min at −78 °C. After stirring for 1 h, chlorotrimethylsilane (32.2 mL, 0.253 mol) was added via syringe over 5 min at −78 °C. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The mixture was poured into a stirred, ice-cooled mixture of saturated aqueous solution of $NaHCO_3$ (300 mL) and ether (300 mL), and the aqueous layer was separated and extracted with ether (200 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (200 mL), H_2O (200 mL), and brine (150 mL) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (700 mL). Solid $NaHCO_3$ (31.3 g, 0.373 mol) and *m*-CPBA (0.179 mol, >65%, commercial reagent was used as served) were added to the solution at −50 °C, and the resulting suspension was stirred at −50 °C for 3.5 h and then diluted with ethyl acetate (1.1 L). The mixture was washed with 10% aqueous solution of $Na_2S_2O_3$ (300 mL), saturated aqueous solution of $NaHCO_3$ (200 mL × 2), and brine and then dried over Na_2SO_4. The solvent and other volatile materials were removed under reduced pressure, and the resulting residue was dissolved in MeOH (500 mL). After aqueous solution of NH_4F (200 mL, 1 M) was added, the resulting mixture was stirred at room temperature for 15 min. Evaporation of MeOH was followed by the addition of ethyl acetate (1 L), and the mixture was washed with H_2O (twice) and brine and then dried over Na_2SO_4. After evaporation of the solvents, recrystallization (from ether/hexane) of the crude material yielded analytically pure 2-hydroxy-4′-methylacetophenone (8.0 g) as pale yellow crystals. The rest was recovered by concentration of the filtrate followed by column chromatography to afford 3.6 g of the desired hydroxy ketone (52% combined yield). Several 2-hydroxyacetophenones were prepared according to similar procedures in yields around 50%. Yields are not optimized.

Preparation of $LaLi_3$tris((*S*)-binaphthoxide) ((*S*)-LLB). A 200 mL flask equipped with a three-way tap was charged with solid La(O-*i*-Pr)$_3$ (4.61 g, 14.57 mmol) in a glovebox. Addition of dry THF (72.8 mL) via syringe under argon atmosphere gave a 0.2 M solution of La(O-*i*-Pr)$_3$ (**NOTE**: we recommend that the solution is prepared immediately before use; otherwise it must be stored below −20 °C under argon atmosphere. The decomposition of La(O-*i*-Pr)$_3$ was sometimes observed at higher temperatures in THF). A separate 100 mL flask was charged with (*S*)-BINOL (6.78 g, 24 mmol), equipped with a three-way tap and a magnetic stirrer, and heated at 45 °C under reduced pressure for 2 h. After the BINOL was dissolved in dry THF (21 mL) under argon, the solution of La(O-*i*-Pr)$_3$ (40.0 mL, 8 mmol) was added at 0 °C, and the resulting pale yellow solution was stirred at room temperature for 30 min. The solvent was removed under reduced pressure at room temperature by using a vacuum pump, and the resulting residue was further dried at the same temperature under reduced pressure for 1 h. The residue was dissolved in dry THF (65.7 mL), and a solution of *n*-BuLi in hexanes (14.3 mL, 24 mmol, 1.68 M) was added at 0 °C. Stirring for another 12 h at room temperature gave a pale yellow solution of (*S*)-LLB (0.1 M), which can be stored at room temperature under argon atmosphere for at least 6 months without loss of activity. The flask containing the LLB was also shielded from light during storage.

General Procedure for Catalytic Asymmetric Aldol Reaction Promoted by (*S*)-Heteropolymetallic Complex (GP 1). To a stirred solution of potassium bis(trimethylsilyl)-amide (KHMDS) in toluene (0.027 mmol, 54 μL, 0.5 M) was added a solution of H_2O in THF (0.06 mmol, 60 μL, 1.0 M) at 0 °C. After stirring for 15 min a solution of $LaLi_3$tris((*S*)-binaphthoxide) ((*S*)-LLB) in THF (0.03 mmol, 300 μL, 0.1 M) was added, and the stirring was continued at 0 °C for 30 min. The resulting solution was cooled to temperature indicated in Table 1 or 2, and a solution of **2** (0.6 mmol) in THF (2 mL for **2a**; 3 mL for **2b**−**g**) and **1** (0.3 mmol) were added successively. The stirring was continued until the reaction was quenched by addition of 1 M HCl (2 mL). The mixture was extracted with ethyl acetate (×3), and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a crude mixture of the aldol products. The chemical yield and diastereomeric ratio of all aldol products except for *anti*-**3i** were determined by measuring the ^{1}H NMR of the crude material after addition of 0.3 mmol of anisole, 1,3-dimethoxybenzene, or *N*,*N*-dimethylformamide as an internal standard, unless otherwise stated. The products except for **3i** were converted into the corresponding acetonides (**4**) before isolation. Diols (*anti*- and *syn*-) **3i** were isolated by flash silica gel column chromatography.

General Procedure for the Conversion of the Aldol Products to the Corresponding Acetonides. The crude mixture of the aldol product obtained according to the general procedure (GP1; starting aldehyde: 0.3 mmol) was treated with *p*-toluenesulfonic acid monohydrate (10 mg) in *N*,*N*-dimethylformamide/2,2-dimethoxypropane (1.5 mL/1.5 mL) at room temperature for 2 h. Saturated aqueous solution of $NaHCO_3$ (2 mL), H_2O and ether were added to the mixture, and the aqueous layer was separated and extracted with ether (×2). The combined organic layers were washed with H_2O and brine (×2) and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography to afford the acetonides (**4**). The diastereomers were separated at this stage. The enantiomeric excess of the acetonides (**4a**−**g**) was determined by HPLC. Acetonides **4a**−**e** were reported in ref 17. HRMS data of **4a**−**e** are provided below.

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1,6-diphenyl-1-hexanone (*anti*-4a from *anti*-3a). HRMS (EI) calcd for $C_{21}H_{24}O_3$ (M^+) 324.1725, found 324.1708.

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1,6-diphenyl-1-hexanone (*syn*-4a from *syn*-3a). HRMS (EI) calcd for $C_{21}H_{24}O_3$ (M^+) 324.1725, found 324.1724.

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-phenyl-1-octanone (*anti*-4b from *anti*-3b). HRMS (EI) calcd for $C_{16}H_{21}O_3$ ($M^+ - CH_3$) 261.1491, found 261.1489.

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-phenyl-1-octanone (*syn*-4b from *syn*-3b). HRMS (EI) calcd for $C_{16}H_{21}O_3$ ($M^+ - CH_3$) 261.1491, found 261.1490.

(2*R*,3*R*,6*E*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-phenyl-6-dodecen-1-one (*anti*-4c from *anti*-3c). HRMS (EI) calcd for $C_{21}H_{30}O_3$ (M^+) 330.2195, found 330.2196.

(2*R*,3*S*,6*E*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-phenyl-6-dodecen-1-one (*syn*-4c from *syn*-3c). HRMS (EI) calcd for $C_{21}H_{30}O_3$ (M^+) 330.2195, found 330.2194.

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-5-methyl-1-phenyl-1-hexanone (*anti*-4d from *anti*-3d). HRMS (EI) calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1575.

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-5-methyl-1-phenyl-1-hexanone (*syn*-4d from *syn*-3d). HRMS (EI) calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1568.

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1,5-diphenyl-1-pentanone (*anti*-4e from *anti*-3e). HRMS (EI) calcd for $C_{20}H_{22}O_3$ (M^+) 310.1569, found 310.1583.

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1,5-diphenyl-1-pentanone (*syn*-4e from *syn*-3e). HRMS (EI) calcd for $C_{20}H_{22}O_3$ (M^+) 310.1569, found 310.1579.

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(2-methoxyphenyl)-6-phenyl-1-hexanone (*anti*-4f from *anti*-3f). 95% ee; colorless oil; IR (neat) ν 1682, 1089 cm^{-1}; $[\alpha]_D^{26}$ +60.2

(*c* 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.80 (dd, J = 7.5, 1.9 Hz, 1H), 7.50 (ddd, J = 8.1, 7.3, 1.9 Hz, 1H), 7.21−7.18 (m, 2H), 7.14−7.11 (m, 1H), 7.05−7.03 (m, 3H), 6.93 (d, J = 8.1 Hz, 1H), 5.57 (d, J = 6.9 Hz, 1H), 4.48 (ddd, J = 9.9, 6.9, 3.1 Hz, 1H), 3.82 (s, 3H), 2.53 (ddd, J = 13.5, 8.5, 6.4 Hz, 1H), 2.47 (ddd, J = 13.5, 8.4, 6.5 Hz, 1H), 1.87−1.78 (m, 1H), 1.62 (s, 3H), 1.59−1.50 (m, 1H), 1.46−1.38 (m, 1H), 1.42 (s, 3H), 1.34−1.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 197.2, 158.3, 142.0, 134.2, 131.0, 128.1, 126.6, 125.6, 121.1, 111.6, 109.4, 82.6, 77.8, 55.4, 35.3, 30.6, 28.1, 27.2, 25.6; LRMS (EI) *m*/*z* 354 (M^+), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1831; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 5.4 min (minor) and 17.8 min (major).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(2-methoxyphenyl)-6-phenyl-1-hexanone (*syn*-4f from *syn*-3f). 74% ee; colorless oil; IR (neat) ν 1686, 1246 cm^{-1}; $[\alpha]_D^{26}$ −15.3 (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.51 (dd, J = 7.4, 1.8 Hz, 1H), 7.45 (ddd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.27−7.24 (m, 2H), 7.19−7.12 (m, 3H), 7.00 (ddd, J = 7.4, 7.3, 0.8 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 4.91 (d, J = 6.7 Hz, 1H), 4.26−4.22 (m, 1H), 3.80 (s, 3H), 2.64−2.60 (m, 2H), 1.86−1.76 (m, 1H), 1.73−1.61 (m, 3H), 1.45 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.6, 157.9, 142.0, 133.4, 130.1, 128.4, 128.2, 127.5, 125.7, 120.8, 111.5, 110.2, 84.7, 78.3, 55.5, 35.6, 33.3, 27.5, 27.2, 26.1; LRMS (EI) *m*/*z* 354 (M^+), 339 ($M^+ - CH_3$), 296 (base peak), 91 (Bn^+); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1830; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 7.6 min (minor) and 10.4 min (major).

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(3-methoxyphenyl)-6-phenyl-1-hexanone (*anti*-4g from *anti*-3g). 95% ee; colorless solid; mp 62−64 °C; IR (KBr) ν 1695 cm^{-1}; $[\alpha]_D^{26}$ +30.8 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.46−7.45 (m, 2H), 7.39−7.35 (m, 1H), 7.21−7.17 (m, 2H), 7.15−7.11 (m, 2H), 7.03−7.01 (m, 2H), 5.47 (d, J = 7.0 Hz, 1H), 4.53 (ddd, J = 10.2, 6.9, 3.1 Hz, 1H), 3.84 (s, 3H), 2.48 (t, J = 7.6 Hz, 2H), 1.84−1.74 (m, 1H), 1.64 (s, 3H), 1.60−1.51 (m, 1H), 1.46−1.34 (m, 1H), 1.44 (s, 3H), 1.27−1.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 195.7, 159.9, 141.8, 137.4, 129.7, 128.2, 128.1, 125.6, 120.7, 119.9, 112.5, 109.8, 80.0, 77.9, 55.4, 35.3, 30.4, 27.8, 27.3, 25.6; LRMS (EI) *m*/*z* 354 (M^+), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1829; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 6.6 min (minor) and 16.7 min (major).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(3-methoxyphenyl)-6-phenyl-1-hexanone (*syn*-4g from *syn*-3g). 83% ee; colorless oil; IR (neat) ν 1686, 1256 cm^{-1}; $[\alpha]_D^{26}$ −30.2 (*c* 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.64−7.62 (m, 1H), 7.56−7.54 (m, 1H), 7.39−7.36 (m, 1H), 7.27−7.24 (m, 2H), 7.18−7.12 (m, 4H), 4.71 (d, J = 7.1 Hz, 1H), 4.48−4.44 (m, 1H), 3.86 (s, 3H), 2.67−2.64 (m, 2H), 1.87−1.79 (m, 1H), 1.76−1.67 (m, 3H), 1.50 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.1, 159.7, 142.0, 136.9, 129.5, 128.4, 128.3, 125.7, 122.0, 113.3, 110.4, 82.0, 77.7, 55.4, 35.7, 33.0, 27.5, 27.3, 26.1; LRMS (EI) *m*/*z* 354 (M^+, base paek), 339 ($M^+ - CH_3$); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1831; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 0.5 mL/min, t_R 10.8 min (major) and 12.0 min (minor).

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methoxyphenyl)-6-phenyl-1-hexanone (*anti*-4h from *anti*-3h). 98% ee; colorless solid; mp 58 °C; IR (neat) ν 1686 cm^{-1}; $[\alpha]_D^{27}$ +42.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.93−7.90 (m, 2H), 7.21−7.17 (m, 2H), 7.14−7.10 (m, 1H), 7.04−7.02 (m, 2H), 6.95−6.93 (m, 2H), 5.44 (d, J = 7.0 Hz, 1H), 4.52 (ddd, J = 10.2, 7.0, 3.1 Hz, 1H), 3.89 (s, 3H), 2.48 (t, J = 7.6 Hz, 2H), 1.83−1.74 (m, 1H), 1.64 (s, 3H), 1.59−1.50 (m, 1H), 1.45−1.37 (m, 1H), 1.44 (s, 3H), 1.26−1.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 194.1, 163.7, 141.9, 130.6, 129.1, 128.2, 128.1, 125.6, 113.9, 109.7, 79.9, 77.9, 55.5, 35.3, 30.5, 27.8, 27.4, 25.5; LRMS (EI) *m*/*z* 354 (M^+), 339 ($M^+ - CH_3$), 296 (base paek); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1846; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 0.5 mL/min, t_R 23.4 min (minor) and 25.5 min (major).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methoxyphenyl)-6-phenyl-1-hexanone (*syn*-4h from *syn*-3h). 79% ee; colorless oil; IR (neat) ν 1678, 1260 cm^{-1}; $[\alpha]_D^{26}$ −26.9 (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.06−8.04 (m, 2H), 7.27−7.24 (m, 3H), 7.18−7.15 (m, 3H), 6.95−6.93 (m, 2H), 4.67 (d, J = 7.2 Hz, 1H), 4.49−4.45 (m, 1H), 3.88 (s, 3H), 2.70−2.64 (m, 2H), 1.86−1.80 (m, 1H), 1.76−1.70 (m, 2H), 1.65−1.55 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.6, 163.9, 142.1, 131.7, 128.7, 128.4, 128.3, 125.7, 113.8, 110.2, 81.9, 77.7, 55.5, 35.7, 33.0, 27.5, 26.1; LRMS (EI) *m*/*z* 354 (M^+), 339 ($M^+ - CH_3$); HRMS (EI) calcd for $C_{22}H_{26}O_4$ (M^+) 354.1831, found 354.1834; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 9/1 (v/v), flow: 0.5 mL/min, t_R 10.7 min (minor) and 14.4 min (major).

(2*R*,3*R*,6*E*)-2,3-Dihydroxy-1-(4-methoxyphenyl)-6-dodecen-1-one (*anti*-3i). This diol was isolated from the crude mixture of the aldol reaction by flash silica gel column chromatography. The enantiomeric excess was determined to be 93% by HPLC. Colorless solid; mp 75−77 °C; IR (KBr) 3426, 3302, 1679, 1605 cm^{-1}; $[\alpha]_D^{26}$ +18.0 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.95−7.93 (m, 2H), 6.98−6.96 (m, 2H), 5.27 (dt, J = 14.5, 6.2 Hz, 1H), 5.19 (dt, J = 14.5, 6.1 Hz, 1H), 5.16 (t, J = 3.3 Hz, 1H), 3.95−3.90 (m, 2H), 3.88 (s, 3H), 2.41 (br-s, 1H), 2.12−2.06 (m, 1H), 1.96−1.88 (m, 1H), 1.86−1.81 (m, 2H), 1.49−1.42 (m, 1H), 1.28−1.11 (m, 7H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.0, 164.7, 131.6, 131.3, 129.1, 127.1, 114.4, 77.5, 73.2, 55.8, 32.6, 31.6, 30.9, 29.3, 28.6, 22.7, 14.2; LRMS (EI) *m*/*z* 320 (M^+), 135 (ArC≡O^+, base peak); HRMS (EI) calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1981; HPLC, column: DAICEL CHIRALPAK AD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 12.0 min (minor) and 13.7 min (major).

(2*R*,3*S*,6*E*)-2,3-Dihydroxy-1-(4-methoxyphenyl)-6-dodecen-1-one (*syn*-3i). This diol was isolated from the crude mixture of the aldol reaction by flash silica gel column chromatography. Colorless solid; mp 55−56 °C; IR (KBr) 3409, 1677, 1599, 1258 cm^{-1}; $[\alpha]_D^{26}$ −8.9 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.89−7.87 (m, 2H), 6.97−6.95 (m, 2H), 5.50 (dt, J = 14.8, 6.2 Hz, 1H), 5.43 (dt, J = 14.8, 6.2 Hz, 1H), 4.94 (br-s, 1H), 4.00 (d, J = 4.2 Hz, 1H), 3.96−3.93 (m, 1H), 3.88 (s, 3H), 2.25−2.12 (m, 2H), 2.03−1.86 (m, 1H), 1.98 (q, J = 6.8 Hz, 2H), 1.78 (q, J = 7.0 Hz, 2H), 1.36−1.22 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.3, 164.2, 131.6, 131.0, 129.1, 126.4, 114.1, 74.8, 72.6, 55.5, 34.4, 32.5, 31.4, 29.2, 28.8, 22.5, 14.0; LRMS (EI) *m*/*z* 320 (M^+), 135 (ArC≡O^+, base peak); HRMS (EI) calcd for $C_{19}H_{28}O_4$ (M^+) 320.1988, found 320.1979. The enantiomeric excess was determined to be 91% by HPLC after conversion to the corresponding acetonide; HPLC, column: DAICEL CHIRALPAK AD, eluent: hexane/2-propanol 98/2 (v/v), flow: 0.3 mL/min, t_R 21.8 min (major) and 24.5 min (minor).

(2*R*,3*R*)-1-(2,5-Dimethoxyphenyl)-2,3-dihydroxy-2,3-*O*-isopropylidene-6-phenyl-1-hexanone (*anti*-4j from *anti*-3j). 80% ee; colorless oil; IR (neat) ν 1683 cm^{-1}; $[\alpha]_D^{26}$ +33.6 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.37 (d, J = 3.1 Hz, 1H), 7.21−7.18 (m, 2H), 7.14−7.11 (m, 1H), 7.07 (dd, J = 8.9, 3.1 Hz, 1H), 7.05−7.03 (m, 3H), 6.87 (d, J = 8.9 Hz, 1H), 5.60 (d, J = 7.0 Hz, 1H), 4.48 (ddd, J = 9.9, 7.0, 3.2 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.53 (ddd, J = 13.5, 8.3, 6.4 Hz, 1H), 2.48 (ddd, J = 13.5, 8.4, 6.6 Hz, 1H), 1.87−1.78 (m, 1H), 1.62 (s, 3H), 1.60−1.50 (m, 1H), 1.43−1.27 (m, 2H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.8, 153.7, 153.0, 142.0, 128.3, 128.1, 126.7, 125.6, 121.3, 114.0, 113.2, 109.4, 82.6, 77.9, 55.9, 55.8, 35.4, 30.6, 28.2, 27.6, 25.6; LRMS (EI) *m*/*z* 384 (M^+), 165 (ArC≡O^+, base peak); HRMS (EI) calcd for $C_{23}H_{28}O_5$ (M^+) 384.1937, found 384.1918; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 9.5 min (minor) and 26.1 min (major).

(2*R*,3*S*)-1-(2,5-Dimethoxyphenyl)-2,3-Dihydroxy-2,3-*O*-isopropylidene-6-phenyl-1-hexanone (*syn*-4j from *syn*-3j). 41% ee; colorless oil; IR (neat) ν 1685, 1226 cm^{-1}; $[\alpha]_D^{26}$ −10.2 (*c* 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.27−7.24 (m, 2H), 7.18−

7.12 (m, 3H), 7.08 (d, J = 2.9 Hz, 1H), 7.01 (dd, J = 8.9, 2.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 4.96 (d, J = 6.5 Hz, 1H), 4.25−4.21 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.64−2.61 (m, 2H), 1.85−1.76 (m, 1H), 1.71−1.63 (m, 3H), 1.46 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.1, 153.6, 152.4, 142.1, 128.4, 127.7, 125.7, 119.8, 114.2, 113.1, 110.3, 84.7, 78.4, 56.1, 55.8, 35.6, 33.3, 27.5, 27.2, 26.2; LRMS (EI) m/z 384 (M^+), 165 (ArC≡O^+, base peak); HRMS (EI) calcd for $C_{23}H_{28}O_5$ (M^+) 384.1937, found 384.1932; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 8.1 min (minor) and 9.7 min (major).

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(2-methylphenyl)-6-phenyl-1-hexanone (*anti*-4k from *anti*-3k). 84% ee; colorless oil; IR (neat) ν 1697 cm^{-1}; $[\alpha]_D^{22}$ +29.6 (c 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.59−7.57 (m, 1H), 7.42−7.38 (m, 1H), 7.28−7.20 (m, 4H), 7.16−7.13 (m, 1H), 7.06−7.04 (m, 2H), 5.31 (d, J = 6.9 Hz, 1H), 4.44 (ddd, J = 9.9, 6.9, 3.2 Hz, 1H), 2.53 (t, J = 7.3 Hz, 2H), 2.47 (s, 3H), 1.87−1.78 (m, 1H), 1.59−1.40 (m, 2H), 1.56 (s, 3H), 1.42 (s, 3H), 1.34−1.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 200.3, 141.8, 138.8, 136.4, 132.1, 131.6, 128.4, 128.3, 128.2, 125.7, 125.5, 109.8, 81.0, 78.2, 35.4, 30.2, 28.8, 27.1, 25.5, 21.0; LRMS (EI) m/z 338 (M^+), 323 ($M^+ - CH_3$), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1869; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 7.2 min (major) and 8.3 min (minor).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(2-methylphenyl)-6-phenyl-1-hexanone (*syn*-4k from *syn*-3k). 57% ee; colorless oil; IR (neat) ν 1686 cm^{-1}; $[\alpha]_D^{23}$ −16.7 (c 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.66−7.64 (m, 1H), 7.40−7.37 (m, 1H), 7.27−7.24 (m, 4H), 7.19−7.13 (m, 3H), 4.65 (d, J = 7.2 Hz, 1H), 4.33−4.29 (m, 1H), 2.65−2.61 (m, 2H), 2.45 (s, 3H), 1.86−1.76 (m, 1H), 1.72−1.65 (m, 3H), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.0, 142.0, 138.3, 136.4, 131.7, 131.5, 129.3, 128.4, 128.3, 125.8, 125.4, 110.4, 83.5, 78.1, 35.6, 33.2, 27.4, 27.2, 26.0, 20.8; LRMS (EI) m/z 338 (M^+), 323 ($M^+ - CH_3$), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1880; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 7.6 min (minor) and 9.4 min (major).

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methylphenyl)-6-phenyl-1-hexanone (*anti*-4l from *anti*-3l). 97% ee; colorless solid; mp 63−65 °C; IR (KBr) ν 1691, 1088 cm^{-1}; $[\alpha]_D^{24}$ +48.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83−7.81 (m, 2H), 7.28−7.26 (m, 2H), 7.21−7.17 (m, 2H), 7.14−7.11 (m, 1H), 7.03−7.01 (m, 2H), 5.47 (d, J = 6.9 Hz, 1H), 4.53 (ddd, J = 10.1, 6.9, 3.1 Hz, 1H), 2.48 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.83−1.73 (m, 1H), 1.64 (s, 3H), 1.59−1.50 (m, 1H), 1.45−1.37 (m, 1H), 1.44 (s, 3H), 1.26−1.19 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 195.3, 144.3, 141.9, 133.6, 129.4, 128.3, 128.2, 128.1, 125.6, 109.7, 79.9, 77.8, 35.3, 30.5, 27.8, 27.3, 25.5, 21.6; LRMS (EI) m/z 338 (M^+), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1878; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 9/1 (v/v), flow: 1.0 mL/min, t_R 6.2 min (minor) and 8.0 min (major).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methylphenyl)-6-phenyl-1-hexanone (*syn*-4l from *syn*-3l). 85% ee; colorless oil; IR (neat) ν 1684 cm^{-1}; $[\alpha]_D^{26}$ −31.5 (c 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.95−7.93 (m, 2H), 7.27−7.24 (m, 4H), 7.18−7.15 (m, 3H), 4.70 (d, J = 7.0 Hz, 1H), 4.48−4.44 (m, 1H), 2.67−2.63 (m, 2H), 2.42 (s, 3H), 1.89−1.79 (m, 1H), 1.76−1.67 (m, 3H), 1.49 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.9, 144.5, 142.0, 133.2, 129.4, 129.2, 128.4, 128.3, 125.7, 110.3, 82.0, 77.7, 35.7, 33.0, 27.5, 27.3, 26.1, 21.7; LRMS (EI) m/z 338 (M^+), 323 ($M^+ - CH_3$), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{22}H_{26}O_3$ (M^+) 338.1882, found 338.1879; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 98/2 (v/v), flow: 1.0 mL/min, t_R 5.4 min (minor) and 7.6 min (major).

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methylphenyl)-1-octanone (*anti*-4m from *anti*-3m). 96% ee; colorless oil; IR (neat) ν 2934, 1694, 1607 cm^{-1}; $[\alpha]_D^{24}$ +56.3 (c 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84−7.82 (m, 2H), 7.27−7.25 (m, 2H), 5.45 (d, J = 6.9 Hz, 1H), 4.51 (ddd, J = 10.2, 6.9, 3.1 Hz, 1H), 2.40 (s, 3H), 1.63 (s, 3H), 1.46−1.32 (m, 2H), 1.43 (s, 3H), 1.25−1.09 (m, 6H), 0.78 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 195.4, 144.3, 133.6, 129.4, 128.3, 109.6, 80.0, 78.1, 31.4, 30.9, 27.4, 25.8, 25.5, 22.4, 21.6, 13.8; LRMS (EI) m/z 290 (M^+), 275 ($M^+ - CH_3$), 171 (M^+ − ArC═O, base peak), 119 (ArC≡O^+); HRMS (EI) calcd for $C_{17}H_{23}O_3$ ($M^+ - CH_3$) 275.1647, found 275.1648; HPLC, column: DAICEL CHIRALCEL OD, eluent: hexane/2-propanol 98/2 (v/v), flow: 1.0 mL/min, t_R 6.1 min (minor) and 8.8 min (major).

(2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-1-(4-methylphenyl)-1-octanone (*syn*-4m from *syn*-3m). 89% ee; colorless oil; IR (neat) ν 2932, 1685, 1607 cm^{-1}; $[\alpha]_D^{24}$ −34.6 (c 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.96−7.95 (m, 2H), 7.28−7.26 (m, 2H), 4.72 (d, J = 7.0 Hz, 1H), 4.45−4.41 (m, 1H), 2.42 (s, 3H), 1.70−1.62 (m, 2H), 1.52−1.46 (m, 1H), 1.50 (s, 3H), 1.38−1.25 (m, 5H), 1.37 (s, 3H), 0.89−0.86 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 197.0, 144.6, 133.3, 129.4, 129.2, 110.2, 82.0, 78.0, 33.6, 31.8, 27.3, 26.1, 25.5, 22.5, 21.7, 14.0; LRMS (EI) m/z 290 (M^+), 275 ($M^+ - CH_3$), 171 (M^+ − ArC═O), 119 (ArC≡O^+, base peak); HRMS (EI) calcd for $C_{18}H_{27}O_3$ (M^+ + H) 291.1960, found 291.1963; HPLC, column: DAICEL CHIRALPAK AS, eluent: hexane/2-propanol 199/1 (v/v), flow: 0.3 mL/min, t_R 16.4 min (minor) and 20.0 min (major).

(4*S*,5*R*)-4-Benzoyl-2,2-dimethyl-5-pentyl-1,3-dioxolane (6). To a solution of acetonide **4b** (13.2 mg, 0.048 mmol) in 1,2-dichloroethane (0.5 mL) were added anhydrous NaH_2PO_4 (14.3 mg, 0.119 mmol) and *m*-CPBA (16.5 mg, 0.096 mmol). The mixture was stirred at room temperature for 4 h and poured into a mixture of ether and H_2O. The organic phase was separated, washed with an aqueous solution of $Na_2S_2O_3$, saturated aqueous solution of $NaHCO_3$, H_2O and brine, and dried over Na_2SO_4. After evaporation of solvent, the resulting residue was purified by flash silica gel column chromatography to afford ester **6** (12.7 mg, 91% yield) as a colorless oil; 94% ee; IR (neat) ν 1728 cm^{-1}; $[\alpha]_D^{27}$ −74.8 (c 0.49, CH_2Cl_2); ^{1}H NMR (C_6D_6) δ 8.18−8.16 (m, 2H), 7.09−7.05 (m, 1H), 7.02−6.99 (m, 2H), 6.62 (d, J = 3.1 Hz, 1H), 3.90 (ddd, J = 8.0, 5.1, 3.1 Hz, 1H), 1.85−1.78 (m, 1H), 1.61−1.54 (m, 1H), 1.53 (s, 3H), 1.45−1.35 (m, 1H), 1.30 (s, 3H), 1.26−1.09 (m, 5H), 0.78 (t, J = 6.9 Hz, 3H); ^{13}C NMR (C_6D_6) δ 165.5, 133.1, 130.8, 129.9, 128.7, 111.0, 95.4, 80.2, 32.0, 29.0, 28.7, 26.1, 25.9, 22.8, 14.1; LRMS (EI) m/z 277 ($M^+ - CH_3$), 171 ($M^+ - C_6H_5CO$), 105 ($ArCO^+$, base peak); HRMS (EI) calcd for $C_{16}H_{21}O_4$ ($M^+ - CH_3$) 277.1440, found 277.1439.

(2*R*,3*R*)-2,3-Carbonyldioxy-1-phenyl-1-octanone (5b). Colorless solid; IR (KBr) ν 1793, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.1 Hz, 1H), 7.54 (dd, J = 7.2, 7.1 Hz, 2H), 6.02 (d, J = 7.7 Hz, 1H), 5.03 (ddd, J = 10.2, 7.7, 2.6 Hz, 1H), 1.54−1.42 (m, 2H), 1.35−1.23 (m, 2H), 1.21−1.10 (m, 4H), 0.79 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 191.6, 153.8, 134.8, 134.6, 129.4, 128.2, 79.1, 77.9, 30.9, 30.3, 25.2, 22.2, 13.7; LRMS (EI) m/z 262 (M^+), 105 ($PhCO^+$, base peak); HRMS (EI) calcd for $C_{15}H_{18}O_4$ (M^+) 262.1205, found 262.1210.

(2*R*,3*R*)-2,3-Carbonyldioxy-1-(4-methoxyphenyl)-6-phenyl-1-hexanone (5h). The crude mixture of aldol products (**3h**), which was obtained according to GP1, was dissolved in 0.9 mL of dry CH_2Cl_2, and the solution was cooled to −20 °C. Pyridine (97 μL, 1.2 mmol) and a solution of triphosgene (356 mg, 1.2 mmol) in CH_2Cl_2 (1.2 mL) were added, and the resulting mixture was stirred at the same temperature for 2 h. The reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ solution and ether, and the organic phase was washed with 1 M HCl and with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 8/1 → 4/1) to afford 65 mg of carbonate **5h** (86% yield from the diol) as a colorless solid. The yield is not optimized; mp 101−103 °C; IR (KBr) ν 1805, 1685 cm^{-1}; $[\alpha]_D^{27}$ +36.9 (c 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86−7.84 (m, 2H), 7.22−7.18 (m, 2H), 7.16−7.12 (m, 1H), 7.01−6.97 (m, 4H), 5.93 (d, J = 8.1 Hz, 1H), 4.98 (ddd, J = 10.0, 8.1, 3.0 Hz, 1H), 2.52 (ddd, J = 13.2, 8.3, 6.3 Hz, 1H), 2.47 (ddd, J = 13.2, 8.4, 6.3 Hz, 1H), 1.88−1.77 (m, 1H), 1.63−1.50 (m, 2H), 1.40−1.34 (m, 1H); ^{13}C

NMR ($CDCl_3$) δ 189.6, 164.8, 153.9, 141.0, 130.6, 128.3, 128.2, 127.5, 125.9, 114.6, 78.9, 77.6, 55.7, 34.9, 29.8, 27.2; LRMS (EI) *m*/*z* 340 (M^+), 135 ($ArC{\equiv}O^+$, base peak); HRMS (EI) calcd for $C_{20}H_{20}O_5$ (M^+) 340.1311, found 340.1311.

(2*R*,3*R*,6*E*)-2,3-Carbonyldioxy-1-(4-methoxyphenyl)-6-dodecen-1-one (5i). To a stirred solution of diol *anti*-**3i** (34 mg, 0.106 mmol) in CH_2Cl_2 (0.3 mL), were added pyridine (21.5 μL, 0.265 μL) and a solution of triphosgene (79 mg, 0.265 mmol) in CH_2Cl_2 (0.5 mL) at −20 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched by addition of saturated aqueous solution of $NaHCO_3$ and diluted with ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (×2), and the combined organic layers were washed with 1 M HCl and brine and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 4/1) to afford carbonate **5i** (33 mg, y. 90%) as a colorless oil; IR (neat) ν 1807, 1601, 1174 cm^{-1}; $[\alpha]_D^{28}$ +13.5 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.90−7.88 (m, 2H), 7.01−6.99 (m, 2H), 5.95 (d, J = 8.1 Hz, 1H), 5.40−5.34 (m, 1H), 5.21−5.15 (m, 1H), 5.01 (ddd, J = 10.8, 8.1, 2.8 Hz, 1H), 3.90 (s, 3H), 2.18−2.10 (m, 1H), 2.05−1.97 (m, 1H), 1.93−1.88 (m, 2H), 1.63−1.54 (m, 1H), 1.39−1.18 (m, 7H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 189.7, 164.8, 153.9, 133.0, 130.7, 127.5, 126.8, 114.6, 78.2, 77.5, 55.7, 32.4, 31.3, 30.1, 29.0, 28.3, 22.4, 14.0; LRMS (EI) *m*/*z* 346 (M^+), 135 ($ArC{\equiv}O^+$, base peak); HRMS (EI) calcd for $C_{20}H_{26}O_5$ (M^+) 346.1780, found 346.1777.

(2*R*,3*R*)-2,3-Carbonyldioxy-1-(4-methylphenyl)-6-phenyl-1-hexanone (5l). This compound was prepared according to a procedure similar to that for **5h**. Yield 91% (from diol); colorless solid; mp 137−139 °C; IR (KBr) ν 1802, 1690 cm^{-1}; $[\alpha]_D^{28}$ +43.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.77−7.75 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.21−7.18 (m, 2H), 7.16−7.12 (m, 1H), 4.98 (ddd, J = 9.7, 8.1, 3.0 Hz, 1H), 2.55−2.43 (m, 2H), 2.46 (s, 3H), 1.87−1.79 (m, 1H), 1.63−1.49 (m, 3H), 1.40−1.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 190.9, 153.7, 146.1, 140.9, 132.2, 130.0, 128.4, 128.3, 128.2, 126.0, 78.8, 77.8, 34.9, 29.8, 27.1, 21.8; LRMS (EI) *m*/*z* 324 (M^+), 91 (Bn^+, base peak); HRMS (EI) calcd for $C_{20}H_{20}O_4$ (M^+) 324.1362, found 324.1348.

4-Methoxyphenyl (2*R*,3*R*)-2,3-Carbonyldioxy-6-phenylhexanoate (8). To a stirred solution of ketone **5h** (23 mg, 0.0676 mmol) in 1,2-dichloroethane (0.5 mL), were added anhydrous NaH_2PO_4 (48.6 mg, 0.405 mmol) and *m*-CPBA (46.6 mg, 0.270 mmol). The resulting mixture was stirred vigorously at 50 °C for 5 h. After cooling to room temperature, the reaction mixture was diluted with ether, washed with saturated aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, H_2O, and brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography (hexane/ether 1/1) to afford ester **8** (21 mg, 87%) as a colorless solid; 98% ee; mp 92−93 °C; IR (KBr) ν 1826, 1774 cm^{-1}; $[\alpha]_D^{29}$ −20.6 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32−7.28 (m, 2H), 7.24−7.21 (m, 1H), 7.18−7.14 (m, 2H), 6.89 (s, 4H), 5.22 (d, J = 8.2 Hz, 1H), 4.93 (ddd, J = 9.3, 8.2, 3.9 Hz, 1H), 3.82 (s, 3H), 2.76−2.66 (m, 2H), 2.05−1.95 (m, 1H), 1.87−1.73 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.9, 157.9, 153.2, 142.9, 140.7, 128.6, 128.4, 126.2, 121.7, 114.7, 78.5, 75.9, 55.6, 35.1, 29.5, 27.0; LRMS (EI) *m*/*z* 356 (M^+), 124 ($HO^+C_6H_4OCH_3$, base peak); HRMS (EI) calcd for $C_{20}H_{20}O_6$ (M^+) 356.1260, found 356.1265.

4-Methylphenyl (2*R*,3*R*)-2,3-Carbonyldioxy-6-phenylhexanoate (9). To a stirred solution of ketone **5l** (22 mg, 0.068 mmol) in 1,2-dichloroethane (0.5 mL), were added anhydrous NaH_2PO_4 (81 mg, 0.68 mmol) and *m*-CPBA (94 mg, 0.54 mmol). The resulting mixture was stirred vigorously at 40 °C for 2.5 h. After cooling to room temperature, ethyl acetate and H_2O were added, and the organic layer was washed with saturated aqueous $Na_2S_2O_3$ solution. The combined aqueous layers were extracted with ethyl acetate (twice) and washed with saturated aqueous $NaHCO_3$ solution, 1 M HCl, H_2O, and brine. After the organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 3/1) to afford ester **9** (20 mg, 85%) as a colorless solid. 97% ee; mp 104−105 °C; IR (KBr) ν 1825, 1780 cm^{-1}; $[\alpha]_D^{29}$ −18.6 (*c* 0.64, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32−7.28 (m, 2H), 7.24−7.15 (m, 5H), 6.86−6.84 (m, 2H), 5.23 (d, J = 8.1 Hz, 1H), 4.95−4.91 (m, 1H), 2.76−2.66 (m, 2H), 2.37 (s, 3H), 2.05−1.95 (m, 1H), 1.87−1.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 153.2, 147.2, 140.7, 136.6, 130.2, 130.2, 128.6, 126.2, 120.5, 78.5, 75.9, 35.1, 29.5, 27.0, 20.9; LRMS (EI) *m*/*z* 340 (M^+), 108 ($HO^+C_6H_4OCH_3$); HRMS (EI) calcd for $C_{20}H_{20}O_5$ (M^+) 340.1311, found 340.1323.

4-Methoxyphenyl (2*R*,3*R*,6*E*)-2,3-Carbonyldioxy-6-dodecenoate (10). Molecular sieves 4A (80 mg) was placed in a test tube and heated at 180 °C under reduced pressure for 12 h. After cooling to room temperature, *trans*-*N*,*N*-bis(*p*-toluenesulfonyl)-1,2-cyclohexanediamine (35 mg, 0.0828 mmol) and CH_2Cl_2 (500 μL) were added under argon. After cooling to −20 °C, a solution of $SnCl_4$ (82.8 μL, 0.0828 mmol, 1 M in CH_2Cl_2) and bis(trimethylsilyl) peroxide (53 μL, 0.249 mmol) were added via syringe. After stirring for 5 min, ketone **5i** (28.7 mg, 0.0828 mmol) in CH_2Cl_2 (700 μL) was added, and the resulting mixture was stirred at −20 °C for 50 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and diluted with ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (twice), and the combined organic layers were washed with H_2O and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 6/1) to afford ester **10** (23.5 mg, yield 78%) as a colorless solid; mp 61−63 °C; IR (KBr) ν 2924, 1833, 1768, 1508, 1083 cm^{-1}; $[\alpha]_D^{24}$ −13.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.06−7.03 (m, 2H), 6.92−6.90 (m, 2H), 5.56−5.50 (m, 1H), 5.39−5.33 (m, 1H), 5.24 (d, J = 8.2 Hz, 1H), 4.97 (dt, J = 8.2, 4.8 Hz, 1H), 3.81 (s, 3H), 2.36−2.28 (m, 1H), 2.25−2.17 (m, 1H), 2.02−1.97 (m, 2H), 1.91−1.81 (m, 2H), 1.38−1.22 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 157.9, 153.2, 143.0, 133.5, 126.7, 121.7, 114.7, 77.8, 75.9, 55.6, 32.4, 31.4, 29.9, 29.0, 28.3, 22.5, 14.0; LRMS (EI) *m*/*z* 362 (M^+), 124 ($HO^+C_6H_4OCH_3$, base peak); HRMS (EI) calcd for $C_{20}H_{26}O_6$ (M^+) 362.1729, found 362.1719.

Acknowledgment. We thank Mr. Naoya Kumagai, Mr. Shigeki Matsunaga, and Dr. Takashi Ohshima for fruitful discussions and the generous gift of several substrates. This study was financially supported by CREST and RFTF. Naoki Yoshikawa thanks the Japan Society for the Promotion of Science (JSPS) for a research fellowship.

Supporting Information Available: Copies of ^1H and ^{13}C spectra for all new compounds. The procedure for the determination of the relative and absolute configuration of **3c** and **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0162538