Direct Catalytic Asymmetric Aldol Reaction

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Abstract: The direct catalytic asymmetric aldol reaction using aldehydes and unmodified ketones is described for the first time herein. This reaction was first found to be promoted by 20 mol % of anhydrous (*R*)-LLB (L = lanthanum, L = lithium, B = (*R*)-binaphthol moiety) at −20 °C, giving a variety of aldol products in ee's ranging from 44 to 94%. This asymmetric reaction has been greatly improved by developing a new heteropolymetallic asymmetric catalyst [(*R*)-LLB, KOH, and H_2O]. Using 3−8 mol % of this catalyst, a variety of direct catalytic asymmetric aldol reactions were again found to proceed smoothly, affording aldol products in ee's ranging from 30 to 93% and in good to excellent yields. Interestingly, the use of this new heteropolymetallic asymmetric catalyst has realized a diastereoselective and enantioselective aldol reaction using cyclopentanone for the first time. It is also noteworthy that a variety of aldehydes, including hexanal, can be utilized for the current direct catalytic asymmetric aldol reaction. Chiral aldehydes containing α-hydrogen including (*S*)-hydrocinnamaldehyde-α-*d* have been found to produce the corresponding aldol products with negligible racemization (0−4%) at the α-position. One of the aldol products has been successfully converted to the key synthetic intermediates of epothilone A and bryostatin 7. The possible structure of the heteropolymetallic catalyst is also discussed. Finally, mechanistic studies have revealed a characteristic reaction pathway, namely that the reaction is kinetically controlled and the rate-determining step is the deprotonation of the ketone. This is consistent with the fact that the reaction rate is independent of the concentration of the aldehyde.

Introduction

The aldol reaction is generally regarded as one of the most powerful of the carbon−carbon bond-forming reactions. An extensive number of enantioselective aldol reactions[1] of B,[2] Ti,[3] Si[4] and other enolates[5] using stoichiometric amounts of chiral sources have been reported. Furthermore, the development of a range of catalytic asymmetric aldol-type reactions has proven to be a valuable contribution to asymmetric synthesis.[6] In all of these catalytic asymmetric aldol-type reactions, however, preconversion of the ketone moiety to a more reactive species such as an enol silyl ether, enol methyl ether, or ketene silyl acetal is an unavoidable necessity (Scheme 1). Development of a direct catalytic asymmetric aldol reaction, starting from aldehydes and *unmodified* ketones is thus a noteworthy endeavor.[7] Such reactions are known in enzyme chemistry,[8] with the fructose-1,6-bisphosphate and/or DHAP aldolases being characteristic examples. The mechanism of these enzyme-catalyzed aldol reactions is thought to involve cocatalysis by a Zn^{2+} cation and a basic functional group in the enzyme's active site, with the latter abstracting a proton from a carbonyl

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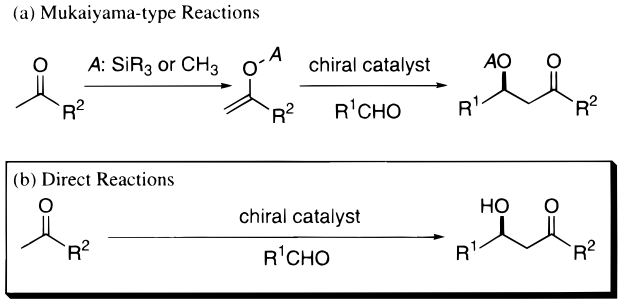
Scheme 1. Several Types of Catalytic Asymmetric Aldol Reactions



compound while the former functions as a Lewis acid to activate the other carbonyl component. These aldolases can thus be thought of as multifunctional catalysts displaying both Lewis acidity and Brønsted basicity, and thus making possible efficient catalytic asymmetric aldol reactions under typically mild in vivo conditions. An analogous cooperative mode of action can be seen in reactions mediated by any of several heterobimetallic asymmetric catalysts, having both Lewis acidity and Brønsted basicity, which have been developed by our research group.[9,10]

We speculated that it might be possible to develop a direct catalytic asymmetric aldol reaction of aldehydes and unmodified ketones by employing such catalysts in the manner shown in Scheme 2. Brønsted base functionality (OM) in the heterobimetallic asymmetric catalyst **I** could deprotonate an α-proton of a ketone to generate the metal enolate **II**, while at the same time Lewis acid functionality (LA) could activate an aldehyde to give **III**. The latter would then react with the metal enolate in a chelation-controlled asymmetric environment to afford a *β*-keto metal alkoxide **IV**. Proton exchange between the metal alkoxide moiety and an aromatic hydroxy proton or an α-proton of a ketone could then lead to the generation of an optically active aldol adduct and regeneration of the catalyst **I**. We now wish to report the first successful example of such a reaction,[11] *in which we have obtained optically active aldol adducts in up to 94% ee.*

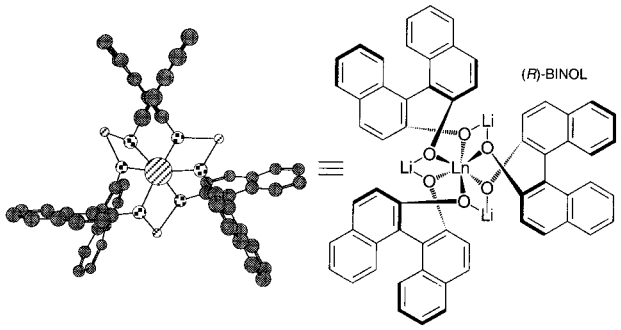
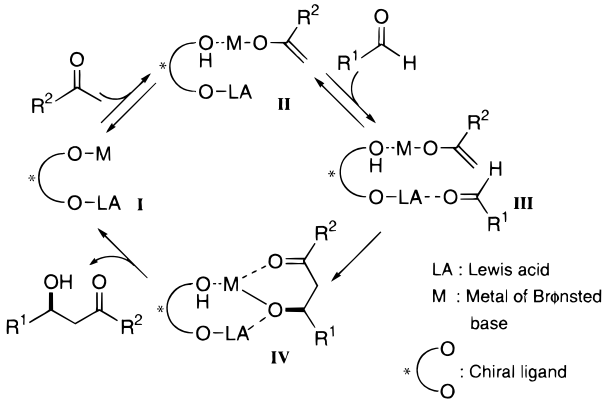


Figure 1. Structure of $LnLi_3$tris((*R*)-binaphthoxide) ((*R*)-LnLB).[9k]

Scheme 2. Catalytic Cycle of Direct Catalytic Asymmetric Aldol Reactions



Results and Discussion

Direct Catalytic Asymmetric Aldol Reactions of Aldehydes with Unmodified Ketones Promoted by Heterobimetallic Asymmetric Catalysts. Although we speculated that the development of a direct catalytic asymmetric aldol reaction might be feasible, our initial concerns were dominated by the possibility that our heterobimetallic asymmetric catalysts would be ineffective at promoting aldol reactions due to their rather low Brønsted basicity. We were thus pleased to find that aldol reactions of the desired type proceeded smoothly using $LaLi_3$-tris(binaphthoxide) (LLB)[9e] as catalyst (Figure 1). As shown in Table 1, when the direct catalytic asymmetric aldol reaction of pivalaldehyde (**1a**) with 5.0 equiv of acetophenone (**2a**) was carried out in the presence of 20 mol % of (*R*)-LLB, with 1.0 mol equiv of H_2O with respect to LLB in THF at −20 °C for

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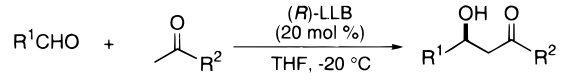
(10) For an excellent review, see: Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2339−2342.

(11) A partially successful attempt to develop a direct catalytic asymmetric aldol reaction has been reported; however, only one reactive aldehyde and acetone were used, and the ee of the corresponding product was not determined. See: Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391−394.

Table 1. Direct Catalytic Asymmetric Aldol Reactions Promoted by (*R*)-LLB (20 mol%)



1a: R^1 = *t*-Bu
1b: R^1 = $PhCH_2C(CH_3)_2$
1c: R^1 = cyclohexyl
1d: R^1 = *i*-Pr
1e: R^1 = $Ph(CH_2)_2$

2a: R^2 = Ph
2b: R^2 = 1-naphthyl
2c: R^2 = CH_3
2d: R^2 = Et

3a: R^1 = *t*-Bu, R^2 = Ph
3b: R^1 = *t*-Bu, R^2 = 1-naphthyl
3c: R^1 = $PhCH_2C(CH_3)_2$, R^2 = Ph
3d: R^1 = cyclohexyl, R^2 = Ph
3e: R^1 = *i*-Pr, R^2 = Ph
3f: R^1 = $Ph(CH_2)_2$, R^2 = Ph
3g: R^1 = $PhCH_2C(CH_3)_2$, R^2 = CH_3
3h: R^1 = *t*-Bu, R^2 = CH_3
3i: R^1 = $PhCH_2C(CH_3)_2$, R^2 = Et

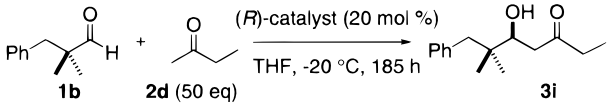
entry	aldehyde	ketone (equiv)	product	time (h)	yield (%)	ee (%)
1[a]	**1a**	**2a** (5)	**3a**	88	43	89
2	**1a**	**2a** (5)	**3a**	88	76	88
3	**1a**	**2a** (1.5)	**3a**	135	43	87
4	**1a**	**2a** (10)	**3a**	91	81	91
5	**1a**	**2b** (8)	**3b**	253	55	76
6	**1b**	**2a** (7.4)	**3c**	87	90	69
7	**1c**	**2a** (8)	**3d**	169	72	44
8[b]	**1d**	**2a** (8)	**3e**	277	59	54
9	**1e**	**2a** (10)	**3f**	72	28	52
10	**1b**	**2c** (10)	**3g**	185	82	74
11	**1a**	**2c** (10)	**3h**	100	53	73
12	**1b**	**2d** (50)	**3i**	185	71	94

[a] (*R*)-LLB and addition of 1 equiv of H_2O to LLB; see ref 13. [b] The reaction was carried out at −30 °C.

88 h, we obtained the desired adduct **3a** in 43% yield and with 89% ee (entry 1).[12] The use of anhydrous LLB instead of hydrated LLB was found to be more effective, affording **3a** in 88% ee and in 76% yield after 88 h (entry 2).[13] Furthermore, the use of 1.5 equiv of **2a** gave **3a** with 87% ee, albeit in only 43% yield (entry 3), and the use of 10 equiv of **2a** afforded **3a** in 91% ee and in 81% yield after 91 h (entry 4).[14]

With these results in hand we then turned our attention to broadening the range of substrates. The reaction of **1a** with **2b** proceeded satisfactorily at −20 °C to give **3b** in 76% ee and in 55% yield (entry 5), together with the reaction of **1b** with **2a (**at −20 °C) which gave the aldol adduct **3c** in 69% ee and in 90% yield (entry 6). The achievement of developing an efficient catalytic asymmetric aldol reaction using aldehydes with α-hydrogens clearly represents a much greater challenge than for cases such as those above, since self-aldol products can easily be formed. However, we found that the reaction of cyclohexanecarboxaldehyde (**1c**) with **2a** proceeded smoothly *without significant formation of the self-aldol product of **1c***. Thus, after several experiments, the reaction of **1c** with 8.0 equiv of **2a**, in the presence of 20 mol % of LLB, was found to give **3d** in 44% ee and in 72% yield. No self-condensation products were detected (entry 7).[15,16] The reaction of isobutyraldehyde (**1d**) also proceeded smoothly at −30 °C, giving **3e** in 54% ee and in 59% yield (entry 8). However, the reaction between hydrocinnamaldehyde (**1e**), which possesses two α-hydrogens, and **2a** proved more difficult. Although **3f** was obtained in 52% ee, the yield was low (28%) due to the formation of self-condensation byproducts (entry 9).[17]

Table 2. Effects of Other Heterobimetallic Complexes



entry	catalyst	yield (%)	ee (%)
1	LLB	71	94
2	LSB	trace	nd
3	LPB	trace	nd
4	ALB	trace	nd
5	GaLB	trace	nd

Aldol reactions which utilize acetone (**2c**) as a starting material are generally difficult to control. However, in this case the reaction between aldehyde (**1b**) and 10 equiv of acetone (**2c**), with LLB, gave **3g** in 74% ee and in 82% yield (entry 10). The reaction of **1a** with 10 equiv of **2c**, at −20 °C, gave **3h** in 73% ee and in 53% yield (entry 11), and the reaction of **1b** with 50 equiv of 2-butanone (**2d**) at −20 °C, afforded the adduct **3i** in excellent ee (94%) and in 71% yield (entry 12).[18,19] Acetone and 2-butanone are widely used as solvents and are much cheaper than the corresponding enol silyl ethers and methyl enol ethers, which are used as substrates in the catalytic asymmetric Mukaiyama-aldol reaction.[4,6] The use of large excesses of ketone can thus be justified in this particular case.

The effects of other heterobimetallic complexes were also examined in the reaction of **1b** with 50 equiv of **2d** at −20 °C (Table 2). We have already succeeded in developing a variety of heterobimetallic catalysts[9] for other enantioselective reactions, with the best choice of catalyst being strongly dependent on the type of reaction. For example, $LaNa_3$tris(binaphthoxide) (LSB)[9g] and AlLibis(binaphthoxide) (ALB)[9h] are efficient catalysts for asymmetric Michael reactions, and GaLibis(binaphthoxide) (GaLB) is suitable for the asymmetric ring-opening reaction of epoxides,[9i] whereas LaK_3tris(binaphthoxide) (LPB)[9d,j] promotes the asymmetric hydrophosphonylation of imines, most effective among our heterobimetallic complexes. These four complexes, however, all afforded only a trace amount of the aldol product (**3i**) (Table 2, entry 2−5). Consequently, the LLB complex in THF proved to be the best catalyst system for direct catalytic asymmetric aldol reactions.

Improved Direct Catalytic Asymmetric Aldol Reactions Using the Heteropolymetallic Asymmetric Catalyst. As described above, we have achieved success in carrying out direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones for the first time, utilizing *heterobimetallic* catalyst $LaLi_3$tris(binaphthoxide) (LLB).[20a,b] However, to attain a syn-

(12) The enantiomeric excesses of all of the aldol adducts were determined by HPLC analysis using DAICEL CHIRALPAK AS, AD, CHIRALCEL OJ or OD. The absolute configurations of **3k**, **3m**, and **3o** were determined to be (*S*)-form and that of **3l** to be (*R*)-form by the Mosher's method. See: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. The absolute configuration of **3n** was determined to be (*R*)-form by relation to **3m**. For other adducts, see refs 20a, c and references therein.

(13) To (*R*)-LLB in THF was added 1.0 mol equiv of H_2O in THF (1.0 M) to give hydrated (*R*)-LLB. This had been found to be a more effective catalyst for previously reported catalytic asymmetric nitroaldol reactions. See ref 9c.

(14) Results using 5 or 10 mol % of (*R*)-LLB: 42% yield, 77% ee; 52% yield, 88% ee, respectively.

(15) Results using 20 mol % of other catalysts at −20 °C: LLB in toluene (25%, 31% ee), LLB in CH_2Cl_2 (33%, 15% ee), LnLB where Ln = Pr, Sm, Gd, Dy, or Yb in THF (low ee's), LLB* in THF (B* = 6,6′-bis-((triethylsilyl)ethynyl)(binaphthoxide) (low ee), 6,6′-dibromo(binaphthoxide) (low ee), 6,6′-dimethoxy(binaphthoxide) (low ee)).

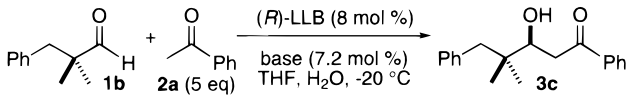
(16) The moderate yield is mainly due to the low reactivity of LLB. A small amount of dehydrated product was detected.

(17) The self-condensation of the aldehyde can be suppressed at low temperature (−40 °C) using 3′-nitroacetophenone (see Table 4, entry 11).

(18) A trace amount of 4-hydroxy-3,5,5-trimethyl-6-phenyl-2-hexanone was detected.

(19) The reaction of benzaldehyde and 8 equiv of **2a** in the presence of 20 mol % of (*R*)-LLB for 198 h gave the desired aldol adduct with only 3% ee (*S*) and 41% yield. However, when (*R*)-LLB was replaced with $YbLi_3$-tris((*R*)-binaphthoxide) ((*R*)-YbLB), the same reaction conditions gave the aldol product with 36% ee (*R*) and 47% yield.

Table 3. Direct Catalytic Asymmetric Aldol Reactions of **1b** with **2a** under Various Conditions



entry	base	H_2O (mol %)	time (h)	yield (%)	ee (%)
1	(LLB itself)		18	trace	
2	KHMDS	0	18	83	58
3	KHMDS	8	18	89	79
4	KHMDS	16	18	83	85
5[a]	KHMDS	16	33	71	85
6	KHMDS	32	18	67	89
7	LHMDS	16	5	22	80
8	NHMDS	16	5	28	86
9	KHMDS	16	5	74	84

[a] 3 mol % of catalyst was used.

thetically useful level for this methodology, the challenge remains to reduce the amounts of ketones and catalysts used, shorten reaction times, and increase enantioselectivities. In this section we report our efforts in this direction utilizing a novel concept in *heteropolymetallic* catalysis for direct catalytic asymmetric aldol reactions, leading to a synthetically valuable method, and we outline mechanistic studies of these reactions.

Previously we observed for a different reaction (asymmetric nitroaldol reaction) that the LLB·LiOH tight complex enhanced the catalytic activity of LLB.[9c] Encouraged by this result, development of a new strategy to activate LLB for the direct catalytic asymmetric aldol reaction was attempted. As a result the catalyst generated from LLB, KHMDS (0.9 equiv to LLB), and H_2O (1 equiv to LLB), which presumably forms a *heteropolymetallic* complex, was found to be a superior catalyst for the direct catalytic asymmetric aldol reaction, giving **3c** in 89% yield and 79% ee [using 8 mol % of LLB (Table 3, entry 3)]. We employed this method to generate KOH in situ because of its insolubility in THF. The use of KO-*t*-Bu instead of KHMDS gave a similar result, indicating that HMDS does not play a key role. Interestingly, further addition of H_2O (1 equiv with respect to LLB) resulted in the formation of **3c** in 83% yield and higher ee (entry 4), different from LLB catalysis (Table 1, entry 1). The powder obtained from the catalyst solution by evaporation of the solvent showed a similar result. This powder can be easily handled without the need of an inert atmosphere. In addition, we were pleased to find that *as little as 3 mol % of the catalyst promoted the reaction efficiently* to give **3c** in 71% yield and 85% ee (entry 5). However, in the absence of base, 8 mol % of LLB afforded only a trace amount of **3c** under similar reaction conditions (entry 1). Moreover, in contrast to catalytic asymmetric nitroaldol reactions, the generation of LiOH or other bases was found to give less satisfactory results (entry 7 and 8). The results are summarized in Table 3.

This newly developed *heteropolymetallic* catalyst system was applied to a variety of direct catalytic asymmetric aldol reactions, giving aldol products **3a**−**3o** in modest to good ee's as shown in Table 4. It is evident from the table that aldehydes **1a**, **1b**, and **1f** (tertiary aldehydes) react with the ketones **2a**, **2c**, and **2d** as described in Table 4 to give the corresponding aldol products in good to excellent yields (62−91%) and ee's (76−93%) (entries 1−6). The reaction of secondary aldehyde **1d** with **2a** produces **3e** in 90% yield but in rather low ee (33%) (entry 7), whereas the same aldehyde with **2e** yields **3k** in 68% yield and 70% ee (entry 8). Substrate **1g**, another secondary aldehyde, is also found to form the aldol product **3l** with **2e** highly selectively (yield 60%, 80% ee, entry 9). The higher ee's observed in the products derived from **2e** than those derived from **2a** can be understood by considering that lower reactive enolate from **2e** reacts only with an activated aldehyde.

It is noteworthy that even **3m** can be produced from hexanal (**1h**), which has two acidic protons at the α-position, in 55% yield and 42% ee without the formation of the corresponding self-aldol product (entry 10). This result can be understood by considering that, in general, aldehyde enolates are not generated by the catalyst at low temperature. To ensure this assumption, the reaction of chiral aldehyde **1i**[21] with acetophenone (**2a**) was carried out (Scheme 3). The corresponding aldol product (*anti*-**3p**) was obtained in 73% yield and 99% ee (*syn*-**3p**: y. 12%, 93% ee). From this result, the racemization of aldehyde **1i** during the reaction has been found to be less than 1%.[22] Moreover, a primary aldehyde **1j**,[23] which possesses a chiral center with a deuterium at α-position, was treated with 3′-nitroacetophenone (**2e**) in the presence of heteropolymetallic catalyst to determine the extent of the racemization of the aldehyde. Consequently, the corresponding aldol products *syn*-**3q** and *anti*-**3q** were obtained in more than 95 and 78% ee respectively (Scheme 3), indicating that the racemization of the aldehyde should be less than 4%.[24]

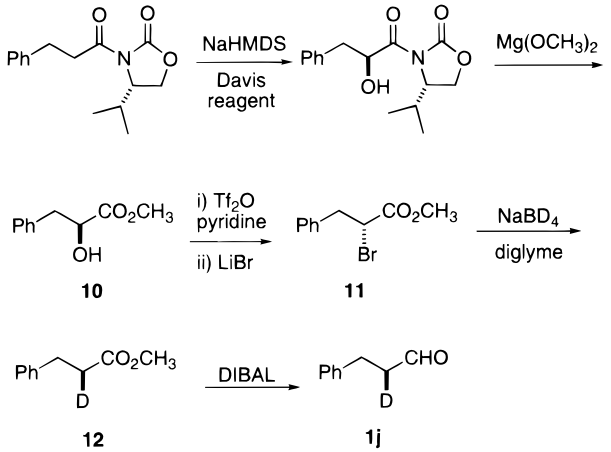
The direct catalytic asymmetric aldol reaction between **1b** and cyclopentanone (**2f**) also proceeded smoothly to afford **3o** in 95% yield (*syn*/*anti* = 93/7, *syn* = 76% ee, *anti* = 88% ee) (Table 4, entry 12).[25] To the best of our knowledge, this is the first example of a diastereoselective catalytic asymmetric aldol reaction using an unmodified ketone.

(20) The result was reported previously, see: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (b) *C&EN News* **1997**, *September 8*, 30. We have also succeeded in developing the direct asymmetric aldol reaction utilizing the first asymmetric barium catalyst. See: (c) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561−5564.

(21) Aldehyde **1i** was synthesized as follows:

(22) (*R*)-Catalyst has also been found to promote the aldol reaction with negligible racemization of aldehyde **1i** as well.

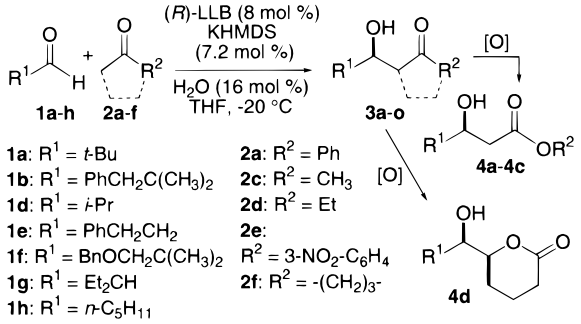
(23) Aldehyde **1j** was synthesized as follows: (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346−4348. (b) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259−2267.



(24) The purity of starting aldehyde (**1j**) was calculated to be less than 98% by considering the D atom purity of $NaBD_4$. Furthermore, the ee of this aldehyde was determined to be more than 92% on the basis of analyses of the corresponding aldol products.

(25) The diastereomeric ratio was determined by ^1H NMR analysis of the crude product. The relative configuration of *syn* -**3o** was determined by X-ray crystallographic analysis.

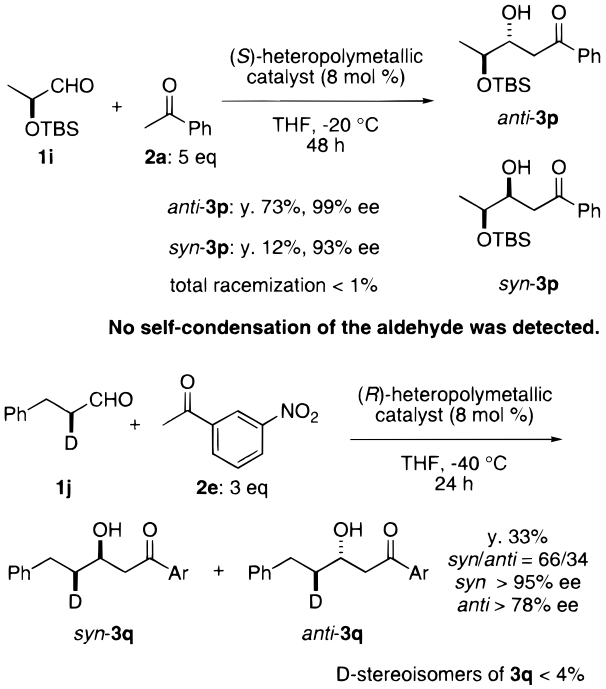
Table 4. Direct Catalytic Asymmetric Aldol Reactions Promoted by Heteropolymetallic Asymmetric Catalyst and Following Baeyer−Villiger Oxidations



entry	aldehyde (R^1)	ketone[a] (R^2) (equiv)	aldol	time (h)	yield (%)	ee (%)	yield of ester[b]
1	**1a**	**2a** (5)	**3a**	15	75	88	
2	**1b**	**2a** (5)	**3c**	28	85	89	**4a**: 80%[c]
3	**1b**	**2c** (10)	**3g**	20	62	76	
4[d]	**1b**	**2d** (15)	**3i**	95	72	88	
5	**1f**	**2a** (5)	**3j**	36	91	90	
6[e]	**1f**	**2a** (5)	**3j**	24	70	93	**4b**: 73%[f]
7[g]	**1d**	**2a** (5)	**3e**	15	90	33	
8[h]	**1d**	**2e** (3)	**3k**	70	68	70	**4c**: 80%[i]
9[j]	**1g**	**2e** (3)	**3l**	96	60	80	
10[h,k]	**1h**	**2e** (5)	**3m**	96	55	42	
11[l]	**1e**	**2e** (3)	**3n**	31	50	30	
12	**1b**	**2f** (5)	**3o**	99 (*syn*/*anti* = 93/7)	95	76/88 (*syn*/*anti*)	**4d**: 85%[c]

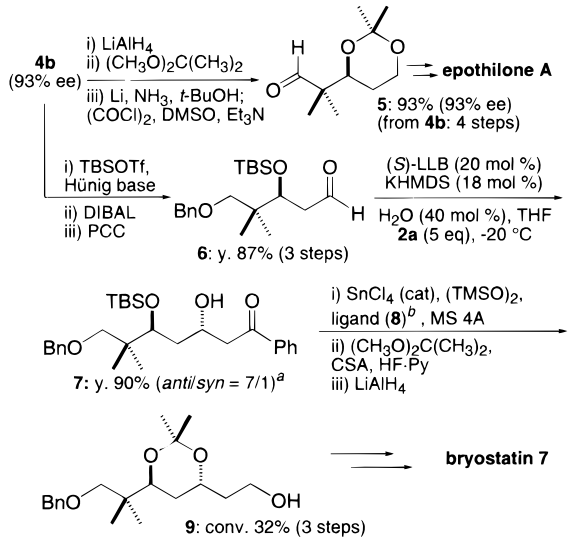
[a] Excess of ketone was recovered after reaction. [b] The yield from aldol product **3**. See ref 28. [c] Conditions: $SnCl_4$ (cat.), $(TMSO)_2$, ligand **8** (cat.), MS 4 Å, CH_2Cl_2. [d] 8 mol % of H_2O was used. [e] The reaction was carried out in 5.7 mmol (**1f**) scale. [f] Conditions: *m*CPBA, NaH_2PO_4, DCE. [g] The reaction was carried out at −30 °C. [h] The reaction was carried out at −50 °C. [i] Conditions: (i) PtO_2, H_2, MeOH; (ii) ZCl, Na_2CO_3, MeOH−H_2O; (iii) $SnCl_4$ (cat.), $(TMSO)_2$, ligand **8** (cat.), MS 4 Å, CH_2Cl_2. R^2 (**4c**) = 3-ZNH-C_6H_4. [j] Conditions: (*R*)-LLB (15 mol %), KHMDS (13.5 mol %), H_2O (30 mol %), −45 °C. [k] Conditions: (*R*)-LLB (30 mol %), KHMDS (27 mol %), H_2O (60 mol %). [l] The reaction was carried out at −40 °C.

Scheme 3. Aldol Reactions of Aldehydes Possessing a Chiral Center at α-Position



Applications to the Syntheses of Natural Products. Several of the aldol products obtained were readily converted to their corresponding esters by Baeyer−Villiger oxidation (Table 4). Ester **4b** was further transformed into key epothilone A intermediate **5**,[26] by a four-step sequence of reactions (Scheme 4), and also into aldehyde **6** which upon treatment with acetophenone (**2a**) in the presence of (*S*)-heteropolymetallic catalyst, produced the *anti*-adduct **7** in high yield (90%, *anti*/*syn* = 7/1). This reaction was found to be catalyst-controlled, giving *anti*-**7** (95% ee) and *syn*-**7** (61% ee), respectively. This diastereoselective aldol reaction was also examined using achiral base. For

Scheme 4. Synthesis of the Key Intermediates *en route* to Natural Products



[a] The ee of *anti*-**7** was 95%; that of *syn*-**7** was 61%. [b] *trans*-*N*,*N*′-Bis(*p*-toluenesulfonyl)cyclohexane-1,2-diamine (see ref 28).

(26) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523−524.

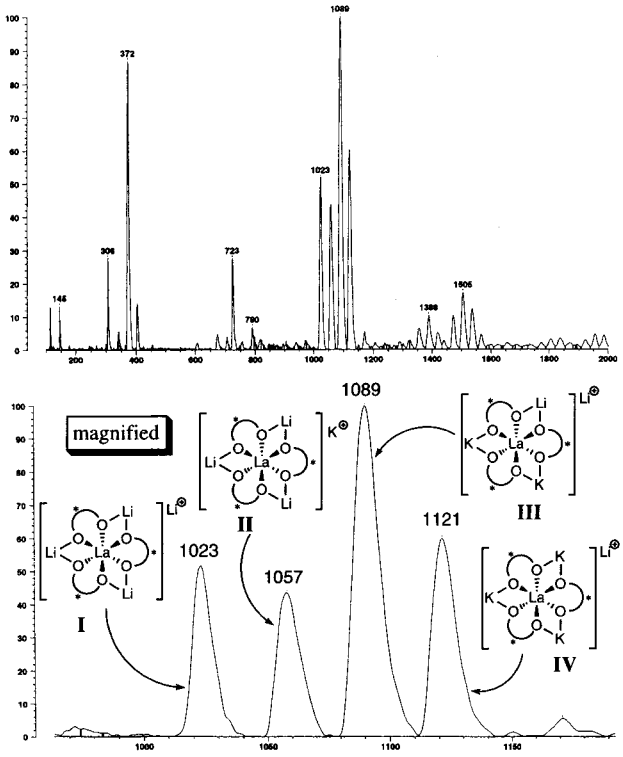


Figure 2. The LDI-TOF(+)MS of the heteropolymetallic asymmetric catalyst.

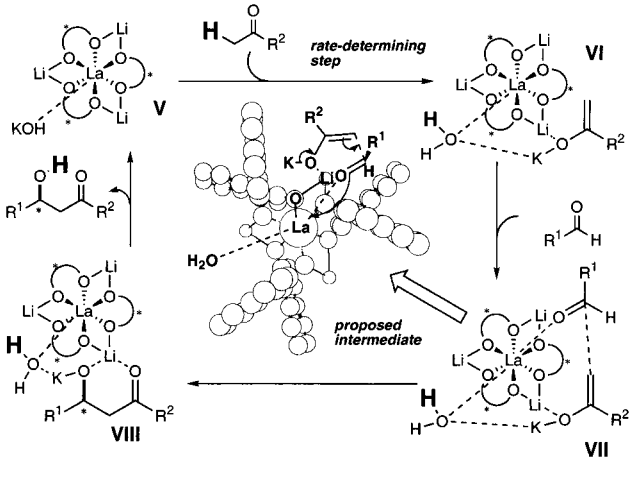
example the enolate, generated from acetophenone (**2a**) and LDA, was reacted with aldehyde **6** to afford aldol product **7** in a lower diastereomeric ratio (*anti/syn* = 3/1). Alcohol **9**, which is a key synthetic intermediate for bryostatin 7, was successfully synthesized from **7** in three steps (Scheme 4).[27]

Mechanistic Studies. What is the mechanism of the present direct catalytic asymmetric aldol reactions using a heteropolymetallic asymmetric catalyst? It is obvious that the self-assembly of LLB and KOH (generated from KHMDS and H_2O) takes place because of the formation of a variety of aldol products in high ee's and yields. The ^{13}C NMR spectrum of LLB·LiOH clearly shows 10 peaks, whereas the spectrum of LLB·KOH does not indicate any significant peak corresponding to binaphthol moiety. This result appears to suggest that there is a rapid exchange between Li^+ and K^+. Indeed, the LDI-TOF(+)MS spectrum of LLB·KOH shows four peaks corresponding to [LLB + Li]$^+$ (**I**, $m/z = 1023$), [LLB + K]$^+$ (**II**, $m/z = 1057$), [$LaLiK_2$-tris(binaphthoxide) + Li]$^+$ (**III**, $m/z = 1089$) and [LaK_3tris-(binaphthoxide) (LPB) + Li]$^+$ (**IV**, $m/z = 1121$) (Figure 2). We have already found that LPB itself is not a useful catalyst for aldol reactions and that the complexes LPB·KOH or LPB·LiOH, where the three lithium of LLB are substituted by potassium, give rise to much less satisfactory results. Consequently, we believe that the BINOL core of the active complex is essentially LLB. Therefore, the heteropolymetallic complex of LLB and KOH, with KOH axially coordinated to La (see Scheme 5), among other possible complexes (eg., **I**, **III**, etc.), would be the most effective catalyst for the present reaction.

As outlined above in these reactions the lanthanum atom is believed to function as a Lewis acid, and potassium hydroxide (KOH) to act as a Brønsted base. To clarify the reaction mechanism, we carried out kinetic studies. As a result, significant isotope effects ($k_H/k_D \approx 5$) were observed (Figure 3), and the

(27) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407−7408.

Scheme 5. Working Model for Direct Catalytic Asymmetric Aldol Reactions Promoted by the Heteropolymetallic Asymmetric Catalyst



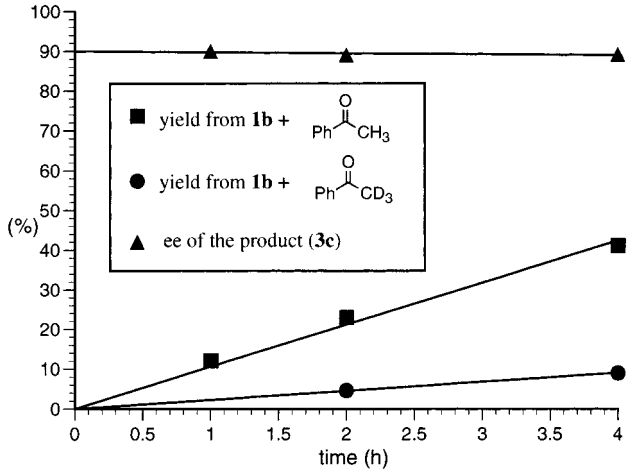


Figure 3. Isotope Effects of aceto-d_3-phenone on the aldol reaction of **1b** with **2a**.

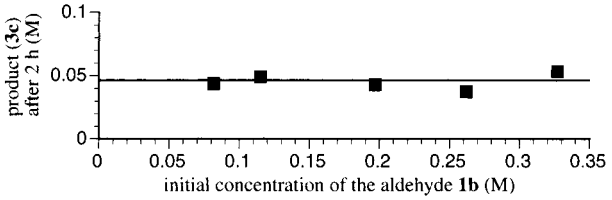


Figure 4. Dependence of the reaction (**1b** + **2a**) rate on the concentration of the aldehyde.

reaction rate has been found to be independent of the concentration of the aldehyde (Figure 4).[29] Both of these results indicate that the rate-determining step is the deprotonation of the ketone, and they also suggest that the catalyst readily forms a relatively tight complex with the aldehyde, thus activating it.

The nature of the coordination of the aldehyde appears to be important since the accompanying activation makes possible the smooth reaction of the postulated LLB-enolate (**VII** in Scheme 5). On the basis of pK_a values this enolate can be

(28) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973.

(29) In usual aldol reactions, the rate is known to be proportional to the concentration of the aldehyde. See: (a) Coombs, E.; Evans, D. P. *J. Chem. Soc.* **1940**, 1295−1300. (b) Noyce, D. S.; Pryor, W. A. *J. Am. Chem. Soc.* **1955**, *77*, 1397−1401. (c) Noyce, D. S.; Pryor, W. A.; Bottini, A. H. *J. Am. Chem. Soc.* **1955**, *77*, 1402−1405.

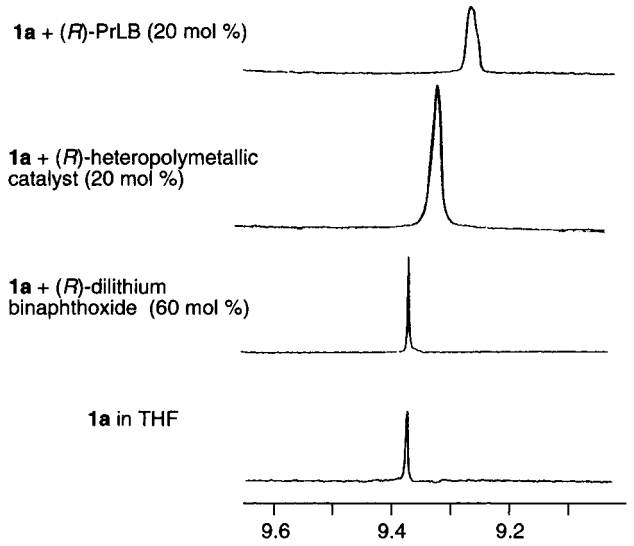


Figure 5. Chemical shift of formyl hydrogen in **1a**.

expected to be present in only low concentrations, thus enabling control of the orientation of the aldehyde and therefore facilitating an enantioselective reaction. To determine the extent of coordination between aldehydes and the lanthanum cation, we carried out a ^{1}H NMR study using a mixture of $PrLi_3$tris(binaphthoxide) (PrLB)[9e] and **1a** (Figure 5).[9b] The PrLB catalyst was chosen because the propensity of Pr complexes to induce upfield shifts is known[30] and also because Pr-containing catalysts show comparable chemical reactivity to La-containing catalysts as seen by the reaction of **1a** with **2a** [(*R*)-PrLB gives **3a** in 79% ee, whereas (*R*)-LLB gives **3a** in 88% ee]. In the relevant ^{1}H NMR spectra the chemical shift of the formyl hydrogen of **1a** in THF is $\delta = 9.37$. However, when 20 mol % of PrLB, or a heteropolymetallic catalyst containing Pr, was added, an upfield shift of this signal was observed ($\delta = 9.27$ and 9.33, respectively). In contrast, the addition of 60 mol % of the dilithium salt of (*R*)-BINOL alone gave no detectable chemical shift of **1a**, and moreover, the reaction of **1a** with **2a** catalyzed by this salt gave *rac*-**3a**. These results clearly indicate that coordination of the aldehyde to Pr is occurring, thus allowing activation and stereocontrol to occur as proposed.[31]

Although the precise role of H_2O is not clear at present, we have suggested a working model of the catalytic cycle and a possible reaction intermediate which allows us to explain the observed absolute configurations of the products (Scheme 5). The stereoselectivities appear to be kinetically controlled. In fact, the ee of **3c** was constant during the course of the reaction (Figure 3).

Conclusion

In conclusion, we have succeeded in carrying out the first catalytic asymmetric aldol reaction between aldehydes and unmodified ketones by using heterobimetallic multifunctional catalysts. Furthermore, we have succeeded in developing a novel *heteropolymetallic* asymmetric catalysis system for the much improved direct catalytic asymmetric aldol reaction. Several reactions are already synthetically useful especially in the case of tertiary aldehyde, leading to the catalytic asymmetric synthesis of key intermediates en route to natural products. The results of secondary aldehydes are also encouraging. However, further fine-tuning of the catalyst is needed to overcome the difficulties associated with primary aldehydes (i.e., low yield and selectivity). We have also succeeded in demonstrating the first example of a direct diastereoselective catalytic asymmetric aldol reaction. In addition, mechanistic studies have revealed a characteristic reaction pathway. Further studies are currently underway.

(30) For a review, see: Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553−588 and references therein.

(31) It is unlikely, even if the aldehyde coordinates to a Li-atom of the Pr complex, that either the proximity to the Pr or alternatively the positioning of the formyl C−H in the shielding region of the naphthyl ring could produce a shift of such magnitude, since no such chemical shift is observed in the presence of LLB.

Experimental Section

General. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ and C_6D_6 were reported on the δ scale relative to $CHCl_3$ (7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR) or C_6H_6 (7.15 ppm for ^{1}H NMR and 128.00 ppm for ^{13}C NMR), respectively, as an internal reference. THF was used as solvent for the NMR investigations of the catalysts. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were measured on JEOL JMS-DX303 or JMS−BU20 GCmate. LDI-TOF mass spectra were measured on Shimadzu MALDI IV. Column chromatography was performed with silica gel Merck 60 (230−400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, DAICEL CHIRALPAK AS, AD, DAICEL CHIRALCEL OD or OJ; mobile phase, hexane−2-propanol; flow rate, 0.30−1.0 mL/min. Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. La(O-*i*-Pr)$_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax, ++(81)-492-84-1351). Other reagents were purified by the usual methods.

General Procedure for the Direct Catalytic Asymmetric Aldol Reactions of Aldehydes 1 Using (*R*)-LLB (GP1). To a stirred solution of (*R*)-LLB (0.1 mmol) in THF (1.67 mL) at −20 °C, was added 2-butanone (**2d**, 25 mmol). After 30 min, 2,2-dimethyl-3-phenylpropanal (**1b**, 0.5 mmol) was added, and the solution was stirred at −20 °C for 185 h. The reaction mixture was then quenched by addition of 2 mL of 1 N HCl and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, Et_2O/hexane 1/12) to give (*S*)-**3i** in 94% ee and in 71% yield.

Procedure for the Preparation of (*R*)-LLB Complex (Which Was Used for (*R*)-Heteropolymetallic Asymmetric Catalyst). To a stirred solution of (*R*)-binaphthol (3.50 g, 12.2 mmol), in THF (39.7 mL) at 0 °C, was added a solution of La(O-*i*-Pr)$_3$ (20.4 mL, 4.07 mmol, 0.2 M in THF, freshly prepared from the powder of La(O-*i*-Pr)$_3$ and dry THF). The solution was stirred for 30 min at room temperature, and then the solvent was evaporated under reduced pressure. The resulting residue was dried for 1 h under reduced pressure (ca. 5 mmHg) and dissolved in THF (60.5 mL). The solution was cooled to 0 °C, and *n*-BuLi (7.45 mL, 12.2 mmol, 1.64 M in hexane) was added. The mixture was stirred for 12 h at room temperature to give a 0.06 M (*R*)-LLB solution, which was used for the preparation of (*R*)-heteropolymetallic asymmetric catalyst. This catalyst solution can be stored for several months under an atmosphere of argon. (CAUTION: The powder of La(O-*i*-Pr)$_3$ should be used immediately after opening the ampule).

General Procedure for the Direct Catalytic Asymmetric Aldol Reactions of Aldehydes 1 Using Heteropolymetallic Asymmetric Catalyst (GP2). To a stirred solution of potassium bis(trimethylsilyl)-amide (KHMDS, 43.2 μL, 0.0216 mmol, 0.5 M in toluene) at 0 °C, was added a solution of water (48.0 μL, 0.048 mmol, 1.0 M in THF).

The solution was sitirred for 20 min at 0 °C and then (*R*)-LLB [prepared by the procedure described above (400 μL, 0.024 mmol, 0.06 M in THF)] was added and the mixture was stirred at 0 °C for 30 min. The resulting pale yellow solution was then cooled to −20 °C, and acetophenone (**2a**) (175 μL, 1.5 mmol) was added. The solution was stirred for 20 min at this temperature and then 2,2-dimethyl-3-phenylpropanal (**1b**) (49.9 μL, 0.3 mmol) was added and the reaction mixture was stirred for 28 h at −20 °C. The mixture was quenched by addition of 1 N HCl (1 mL), and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, ether/hexane 1/12) to give **3c** (72 mg, 85%, 89% ee).

Synthesis of the Aldol Products 3a−3o Using (*R*)-Heteropolymetallic Asymmetric Catalyst. The aldol products **3a−3o** were prepared according to the general procedure (GP2). The compounds **3b**, **3c**, **3g**, **3i**, and **3j** were reported in ref 20a or 20c. For the compounds **3a**, **3d−3f**, and **3h**, see: Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, 1399−1402; Ramachandran, P. V.; Xu, W.-C.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4911−4914.

(*S*)-3-Hydroxy-4-methyl-1-(3-nitrophenyl)-1-pentanone (3k): IR (neat) ν 3541, 1688, 1535, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.77 (m, 1H), 8.44−8.42 (m, 1H), 8.31−8.29 (m, 1H), 7.69 (m, 1H), 4.04 (m, 1H), 3.14 (d, J = 7.0 Hz, 1H), 3.13 (d, J = 5.0 Hz, 1H), 2.85 (d, J = 3.5 Hz, 1H), 1.82 (m, 1H), 1.02 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 198.7, 148.5, 138.2, 133.6, 129.9, 127.6, 123.0, 72.3, 42.6, 33.2, 18.5, 17.7; MS *m*/*z* 237 (M^+), 194 ($M^+ - CH_3$), 165 (M^+ − *i*-PrCHO), 150 (ArC≡O^+, base peak); $[\alpha]^{28}_D$ −40.8 (*c* 0.56, $CHCl_3$) (70% ee); HPLC (DAICEL CHIRALPAK AS, 2-propanol/hexane 1/9, flow 1.0) t_R 16.1 and 18.4 min; Anal. Calcd for $C_{12}H_{15}NO_4$ C, 60.75; H, 6.37; N, 5.90. Found C, 60.49; H, 6.51; N, 5.71.

(*S*)-4-Ethyl-3-hydroxy-1-(3-nitrophenyl)-1-hexanone (3l): IR (neat) ν 3545, 2963, 1686, 1534 cm^{-1}; ^1H NMR (C_6D_6) δ 8.45−8.44 (m, 1H), 7.79−7.77 (m, 1H), 7.66−7.64 (m, 1H), 6.65−6.62 (m, 1H), 4.16 (m, 1H), 2.69 (dd, J = 17.1, 9.8 Hz, 1H), 2.45 (brs, 1H), 2.44 (dd, J = 17.1, 2.1 Hz, 1H), 1.52−1.31 (m, 3H), 1.22−1.13 (m, 2H), 0.89 (t, J = 7.6 Hz, 6H); ^{13}C NMR (C_6D_6) δ 198.3, 138.2, 133.0, 129.3, 127.1, 123.0, 68.9, 46.6, 42.6, 22.3, 21.7, 11.9, 11.9; MS *m*/*z* 266 ($M^+ + 1$), 248 (M^+ − OH); $[\alpha]^{28}_D$ −47.5 (*c* 0.42, $CHCl_3$) (80% ee); HPLC (DAICEL CHIRALPAK AS, 2-propanol/hexane 1/9, flow 1.0) t_R 12.0 and 13.6 min; HRMS (M^+ − OH) Calcd for $C_{14}H_{18}NO_3$ 248.1287. Found 248.1294.

(*R*)-3-Hydroxy-1-(3-nitrophenyl)-1-octanone (3m): IR (neat) ν 3432, 2929, 1688, 1532, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (m, 1H), 8.38−8.35 (m, 1H), 8.23−8.21 (m, 1H), 7.64−7.61 (m, 1H), 4.22−4.16 (m, 1H), 3.12−3.04 (m, 2H), 1.60−1.24 (m, 8H), 0.85−0.83 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 198.4, 148.5, 138.1, 133.6, 130.0, 127.6, 123.0, 67.7, 45.5, 36.6, 31.7, 25.2, 22.6, 14.0; MS *m*/*z* 266 ($M^+ + 1$), 248 (M^+ − OH), 150 (ArC≡O^+, base peak); $[\alpha]^{28}_D$ −29.5 (*c* 0.3, $CHCl_3$) (42% ee); HPLC (DAICEL CHIRALPAK AS, 2-propanol/hexane 1/9, flow 1.0) t_R 12.6 and 15.3 min; HRMS ($M^+ + 1$) Calcd for $C_{14}H_{20}NO_4$ 266.1392. Found 266.1393.

(*R*)-3-Hydroxy-1-(3-nitrophenyl)-5-phenyl-1-pentanone (3n): IR (neat) ν 3543, 2926, 1688, 1530, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.74−8.73 (m, 1H), 8.44−8.41 (m, 1H), 8.27−8.25 (m, 1H), 7.70−7.67 (m, 1H), 7.31−7.18 (m, 5H), 4.31−4.25 (m, 1H), 3.16 (d, J = 5.7 Hz, 1H), 3.08 (d, J = 3.3 Hz, 1H), 2.92−2.86 (m, 1H), 2.80−2.73 (m, 1H), 2.01−1.93 (m, 1H), 1.89−1.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 198.3, 148.4, 141.6, 137.9, 133.5, 130.0, 128.4, 127.7, 125.9, 122.9, 66.8, 45.5, 38.0, 31.7; MS *m*/*z* 299 (M^+), 281 ($M^+ - H_2O$), 150 (ArC≡O^+); $[\alpha]^{24}_D$ −10.7 (*c* 0.825, $CHCl_3$) (30% ee); HPLC (DAICEL CHIRALCEL OJ, 2-propanol/hexane 1/9, flow 1.0) t_R 54.8 and 70.0 min; HRMS (M^+) Calcd for $C_{17}H_{17}NO_4$ 299.1157. Found 299.1161.

(2*S*)-2-[(1*S*)-1-Hydroxy-2,2-dimethyl-3-phenylpropyl]cyclopentanone (*syn*-3o): IR (KBr) ν 3437, 1730 cm^{-1}; ^1H NMR (C_6D_6) δ 7.19−7.05 (m, 5H), 4.02 (d, J = 5.5 Hz, 1H), 2.52 (d, J = 12.4 Hz, 1H), 2.41 (d, J = 12.4 Hz, 1H), 1.99−1.86 (m, 2H). 1.76−1.67 (m, 2H), 1.57−1.51 (m, 1H), 1.28 (d, J = 5.5 Hz, 1H), 1.22−1.10 (m, 1H), 0.77 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (C_6D_6) δ 220.2, 139.2, 131.1, 126.3, 75.9, 51.4, 45.6, 39.2, 38.0, 24.3, 23.6, 23.1, 21.0; MS *m*/*z* 246 (M^+), 228 ($M^+ - H_2O$); $[\alpha]^{29}_D$ −100.0 (*c* 0.89, $CHCl_3$) (75% ee); HPLC (DAICEL CHIRALPAK AS, 2-propanol/hexane 1/9, flow 1.0) t_R 8.0 and 10.6 min; Anal. Calcd for $C_{16}H_{22}O_2$ C, 78.01; H, 9.00. Found C, 77.84; H, 9.24.

(2*R*)-2-[(1*S*)-1-Hydroxy-2,2-dimethyl-3-phenylpropyl]cyclopentanone (*anti*-3o): IR (KBr) ν 3456, 1717 cm^{-1}; ^1H NMR (C_6D_6) δ 7.33−7.31 (m, 2H), 7.22−7.18 (m, 2H), 7.13−7.09 (m, 1H), 5.16 (d, J = 2.3 Hz, 1H), 3.32 (dd, J = 7.8, 2.3 Hz, 1H), 3.19 (d, J = 12.4 Hz, 1H), 2.38 (d, J = 12.4 Hz, 1H), 1.83−1.74 (m, 2H), 1.60−1.54 (m, 1H), 1.52−1.43 (m, 1H), 1.26−1.21 (m, 1H), 0.94 (s, 3H), 0.95−0.84 (m, 2H), 0.77 (s, 3H); ^{13}C NMR (C_6D_6) δ 223.8, 139.4, 131.4, 126.2, 77.6, 50.8, 45.5, 39.3, 37.7, 29.4, 24.2, 22.9, 20.6; MS *m*/*z* 246(M^+), 228 ($M^+ - H_2O$); $[\alpha]^{27}_D$ +95.1 (*c* 0.54, CH_2Cl_2) (88% ee); HRMS ($M^+ - H_2O$) Calcd for $C_{16}H_{20}O$ 228.1514. Found 228.1508.

The Aldol Reaction of Aldehyde 1i with Acetophenone (2a). The aldol reaction was carried out according to the general procedure (GP2). Diastereomers of the aldol product (**3p**) were separated from each other by flash chromatography (SiO_2, hexane/ether 12/1) to afford *anti*-**3p** and *syn*-**3p**. Both diastereomers were analyzed by chiral HPLC (DAICEL CHIRALCEL OD) to determine the enantiomeric excesses.

(3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-phenyl-1-pentanone (*anti*-3p): IR (neat) ν 3490, 2929, 2857, 1682, 1256, 1088 cm^{-1}; ^1H NMR (C_6D_6) δ 7.86−7.84 (m, 2H), 7.11−7.07 (m, 1H), 7.03−7.00 (m, 2H), 4.08−4.04 (m, 1H), 3.89−3.84 (m, 1H), 3.23 (brs, 1H), 3.08−2.98 (m, 2H), 1.13 (d, J = 6.0 Hz, 3H), 0.93 (s, 9H), 0.062 (s, 3H), 0.058 (s, 3H); ^{13}C NMR (C_6D_6) δ 200.2, 137.6, 133.1, 128.6, 128.3, 72.8, 71.5, 40.6, 26.0, 19.7, 18.2, −4.4, −4.6; MS *m*/*z* 309 ($M^+ + 1$), 251 (M^+ − *t*-Bu), 105 (PhC≡O^+, base peak); $[\alpha]^{20}_D$ +45.2 (*c* 1.13, CH_2Cl_2) (99% ee); HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane 5/95, flow 0.3) t_R 16.4 and 18.3 min; Anal. Calcd for $C_{17}H_{28}O_3S$ C, 66.19; H, 9.15. Found C, 66.48; H, 9.14.

(3*S*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-1-phenyl-1-pentanone (*syn*-3p): IR (neat) ν 3484, 2929, 2857, 1683, 1255, 1093 cm^{-1}; ^1H NMR (C_6D_6) δ 7.88−7.85 (m, 2H), 7.11−7.08 (m, 1H), 7.04−7.01 (m, 2H), 4.24−4.20 (m, 1H), 3.92−3.87 (m, 1H), 3.02 (dd, J = 16.2, 3.8 Hz, 1H), 2.92 (dd, J = 16.2, 8.1 Hz, 1H), 2.88 (d, J = 5.0 Hz, 1H), 1.16 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (C_6D_6) δ 199.6, 137.6, 133.0, 128.6, 128.4, 71.9, 70.8, 40.9, 26.0, 19.0, 18.2, −4.4, −4.8; MS *m*/*z* 251 (M^+ − *t*-Bu), 105 (PhC≡O^+, base peak); $[\alpha]^{20}_D$ −26.5 (*c* 1.06, CH_2Cl_2) (99% ee); HPLC (DAICEL CHIRALCEL OD, 2-propanol/hexane 5/95, flow 0.3) t_R 17.0 and 20.9 min; Anal. Calcd for $C_{17}H_{28}O_3S$ C, 66.19, H, 9.15. Found C, 66.05, H, 9.00.

The Aldol Reaction of Aldehyde 1j with 3′-Nitroacetophenone (2e): The aldol reaction was carried out according to the general procedure (GP2). After purification by flash chromatography (SiO_2), (*R*)-OH-product and (*S*)-OH-product were separated by chiral HPLC (DAICEL CHIRALCEL OJ, 2-propanol/hexane 1/9, flow 1.0). Both stereoisomers were analyzed by ^1H NMR to determine diastereomeric ratios.

(3*S*,4*S*)-3-Hydroxy-1-(3-nitrophenyl)-5-phenyl(4-$^2H_1$)-1-pentanone (*syn*-3q). This material contains less than 6% of another diastereomer on the basis of ^1H NMR analysis. IR (neat) ν 3432, 2924, 1688, 1531, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.75−8.74 (m, 1H), 8.45−8.43 (m, 1H), 8.27−8.25 (m, 1H), 7.71−7.63 (m, 1H), 7.32−7.18 (m, 1H), 4.30−4.25 (m, 1H), 3.16 (d, J = 5.1 Hz, 1H), 3.15 (d, J = 6.2 Hz, 1H), 3.01 (d, J = 3.1 Hz, 1H), 2.88 (dd, J = 13.2, 9.1 Hz, 1H), 2.77 (dd, J = 13.2, 6.8 Hz, 1H), 1.84−1.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 198.3, 148.5, 141.6, 137.9, 133.5, 130.0, 128.5, 127.7, 126.0, 123.0, 66.8, 45.5, 37.8, 31.7; MS *m*/*z* 300 (M^+), 282 ($M^+ - H_2O$), 150 (ArC≡O^+), 91 (Bn^+, base peak); $[\alpha]^{14}_D$ −29.8 (*c* 0.42, $CHCl_3$) (> 99% ee); HRMS (M^+) Calcd for $C_{17}H_{16}{}^2HNO_4$ 300.1219. Found 300.1213.

(3*R*,4*S*)-3-Hydroxy-1-(3-nitrophenyl)-5-phenyl(4-$^2H_1$)-1-pentanone (*anti*-3q): This material contains less than 5% of another diastereomer on the basis of ^1H NMR analysis. IR (neat) ν 3426, 2924, 1688, 1496, 1352 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.75−8.74 (m, 1H), 8.45−8.43 (m, 1H), 8.28−8.25 (m, 1H), 7.71−7.67 (m, 1H), 7.32−7.18 (m, 5H), 4.30−4.25 (m, 1H), 3.16 (m, 2H), 3.01 (d, J = 3.5 Hz, 1H), 2.87 (dd, J = 13.1, 5.1 Hz, 1H), 2.77 (dd, J = 13.1, 8.8 Hz, 1H), 1.98−1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 198.3, 148.4, 141.6, 137.9, 133.5, 130.0, 128.5, 127.7, 126.0, 123.0, 66.8, 45.5, 31.7; MS *m*/*z* 300 (M^+), 282 ($M^+ - H_2O$), 150 (ArC≡O^+, base peak), 91 (Bn^+); $[\alpha]^{14}_D$ +32.7

(*c* 0.15, $CHCl_3$) (> 99% ee); HRMS (M^+) Calcd for $C_{17}H_{16}{}^2HNO_4$ 300.1219. Found 300.1206.

Phenyl (*S*)-3-Hydroxy-4,4-dimethyl-5-phenylpentanoate (4a): To a mixture of molecular sieves 4 Å (111 mg, dried at 180 °C under reduced pressure (ca. 5 mmHg) for 12 h) and racemic *trans*-*N*,*N*′-bis-(*p*-toluenesulfonyl)cyclohexane-1,2-diamine (**8**) (18.8 mg, 0.0446 mmol) was added bis(trimethylsilyl)peroxide (2.23 mL, 2.23 mmol, 1.0 M in CH_2Cl_2). $SnCl_4$ (44.6 μL, 0.0446 mmol, 1.0 M in CH_2Cl_2) was added at 0 °C, and the suspension was stirred for 10 min. A solution of aldol product **3c** (157.4 mg, 0.557 mmol, 89% ee) in 3 mL of CH_2Cl_2 was then added (1.2 mL rinse) at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. Saturated aqueous $NaHCO_3$ (1 mL) and sodium sulfite (330 mg) were added at 0 °C, and the reaction mixture was allowed to warm to room temperature (3 h) while being stirred. After filtration through a pad of Celite, the filtrate was washed with 1 N HCl and brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was dissolved in THF/H_2O (3.23 mL/0.87 mL), and acetic acid (1.47 mL) was added to the solution. The reaction mixture was stirred for 18 h and then washed twice with saturated aqueous $NaHCO_3$. The combined aqueous layers were extracted twice with ether, and the combined organic layers were washed with 1 N HCl and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, ether/hexane 1/10) to give the ester **4a** (133.2 mg, 80%) as a colorless oil: IR (neat) ν 3526, 1749, 1196 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.37 (m, 2H), 7.30−7.20 (m, 6H), 7.11−7.08 (m, 2H), 3.88 (ddd, J = 10.2, 3.7, 2.1 Hz, 1H), 2.89 (d, J = 3.7 Hz, 1H), 2.84 (d, J = 12.6 Hz, 1H), 2.81 (dd, J = 16.0, 2.1 Hz, 1H), 2.72 (dd, J = 16.0, 10.2 Hz, 1H), 2.56 (d, J = 12.6 Hz, 1H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 150.4, 138.4, 130.8, 129.5, 127.9, 126.1, 126.0, 121.5, 73.5, 44.6, 38.2, 36.6, 23.3, 22.1; MS *m*/*z* 298 (M^+), 94 (PhO^+H); $[\alpha]^{27}_D$ +2.43 (*c* 3.93, $CHCl_3$); HRMS (M^+) Calcd for $C_{19}H_{22}O_3$ 298.1569. Found 298.1583.

Phenyl (*S*)-5-Benzyloxy-3-hydroxy-4,4-dimethylpentanoate (4b): To a solution of **3j** (21.6 mg, 0.069 mmol, 93% ee) in 1,2-dichloroethane (1.0 mL) were added NaH_2PO_4 (49.7 mg, 0.41 mmol) and *m*-chloroperoxybenzoic acid (*m*CPBA, 85 mg, 0.35 mmol, >70%). The mixture was stirred for 50 h at 40 °C, and the resulting suspension was filtered through a pad of Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine (twice) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, ether/hexane 1/9) to give the starting ketone **3j** (2.3 mg, 11%) and the ester **4b** (16.5 mg, 73%) as a colorless oil: IR (neat) ν 3493, 2963, 2873, 2360, 1757, 1593 cm^{-1}; ^1H NMR (C_6D_6) δ 7.25−6.94 (m, 10H), 4.26 (brs, 1H), 4.24 (s, 2H), 3.37 (brs, 1H), 3.17 (d, J = 8.9 Hz, 1H), 3.10 (d, J = 8.9 Hz, 1H), 2.68−2.56 (m, 2H), 0.89 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (C_6D_6) δ 171.4, 151.5, 138.7, 130.0, 129.5, 125.7, 122.1, 78.2, 74.1, 73.5, 38.5, 37.9, 22.0, 20.0; MS *m*/*z* 328 (M^+ + 1); $[\alpha]^{25}_D$ −31.2 (*c* 0.35, $CHCl_3$); Anal. Calcd for $C_{20}H_{24}O_4$ C, 73.15; H, 7.32. Found C, 72.88; H, 7.47.

The Conversion of the Aldol Product 3k to the Ester 4c, (*S*)-1-(3-Aminophenyl)-4-methyl-3-hydroxy-1-pentanone (i). To a solution of **3k** (951 mg, 4.01 mmol, 70% ee) in MeOH (24 mL) was added PtO_2 (19.5 mg). This suspension was stirred under H_2 (1 atm) for 45 min at room temperature. The reaction mixture was filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, acetone/hexane 1/4) to give **i** (828 mg, quant) as a pale yellow oil: IR (neat) ν 3363, 1671 cm^{-1}; ^1H NMR (C_6D_6) δ 7.17−7.12 (m, 2H), 6.94 (m, 1H), 6.37−6.35 (m, 1H), 3.94 (m, 1H), 3.32 (brs, 1H), 2.97 (brs, 2H), 2.77 (dd, J = 16.7, 8.5 Hz, 1H), 2.73 (dd, J = 16.7, 2.8 Hz, 1H), 1.64 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (C_6D_6) δ 201.2, 147.5, 138.6, 129.4, 119.5, 118.3, 113.9, 72.4, 42.6, 33.6, 18.9, 17.8; MS *m*/*z* 207 (M^+), 120 ($ArC{\equiv}O^+$, base peak); $[\alpha]^{28}_D$ −53.8 (*c* 0.575, $CHCl_3$); Anal. Calcd for $C_{12}H_{17}NO_2$ C, 69.54; H, 8.27; N, 6.76. Found C, 69.63; H, 8.11; N, 6.50.

(*S*)-1-[3-(Benzyloxycarbonylamino)phenyl]-3-hydroxy-4-methyl-1-pentanone (ii). To a solution of **i** (103.5 mg, 0.499 mmol) in MeOH/H_2O (1.5 mL/2.0 mL) at 0 °C were added Na_2CO_3 (68.8 mg, 0.649 mmol) and benzyl chloroformate (92.7 μL, 0.649 mmol). The resulting mixture was stirred for 30 min at 0 °C and then allowed to warm to room temperature over 30 min. Water and ethyl acetate were added to the mixture, and the aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, acetone/hexane 1/8) to give **ii** (168.8 mg, 99%) as a colorless solid: IR (KBr) ν 3511, 3311, 1714, 1670, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.71−7.64 (m, 2H), 7.44−7.35 (m, 6H), 6.81 (brs, 1H), 5.23 (s, 2H), 4.00−3.96 (m, 1H), 3.14 (d, J = 17.0 Hz, 1H), 3.08 (d, J = 3.4 Hz, 1H), 3.03 (dd, J = 17.0, 9.3 Hz, 1H), 1.83−1.76 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.9, 153.4, 138.5, 137.6, 135.8, 129.3, 128.6, 128.4, 128.2, 123.5, 123.0, 118.0, 72.4, 67.1, 42.1, 33.1, 18.5, 17.8; MS *m*/*z* 341 (M^+), 323 ($M^+ - H_2O$); $[\alpha]^{29}_D$ −32.6 (*c* 0.71, $CHCl_3$); Anal. Calcd for $C_{20}H_{23}NO_4$ C, 70.36; H, 6.79; N, 4.10. Found C, 70.11; H, 6.89; N, 3.80.

3-(Benzyloxycabonylamino)phenyl (*S*)-3-hydroxy-4-methylpentanoate (4c). To a mixture of molecular sieves 4 Å (40 mg, dried at 180 °C under reduced pressure (ca. 5 mmHg) for 12 h), racemic trans-*N*,*N*′-bis(*p*-toluenesulfonyl)cyclohxane-1,2-diamine (**8**) (21.1 mg, 0.05 mmol) and ketone **ii** (68.3 mg, 0.2 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C were added bis(trimethylsilyl)peroxide (0.8 mL, 0.8 mmol, 1.0 M in CH_2Cl_2) and $SnCl_4$ (50.0 μL, 0.05 mmol, 1.0 M in CH_2Cl_2). The suspension was stirred for 3 h, and then saturated aqueous $NaHCO_3$ (1 mL) and sodium sulfite (120 mg) were added to the suspension. The mixture was stirred for 3 h and then filtered through a pad of Celite. The aqueous layer was separated and extracted with ether, and the combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was dissolved in THF/H_2O (2.0 mL/0.5 mL). Acetic acid (500 μL) was added, and the solution was stirred at room temperature for 1 h. The reaction mixture was then washed with saturated aqueous $NaHCO_3$, and the combined aqueous layers were extracted twice with ether. The combined organic layers were washed with 1 N HCl and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, acetone/hexane 1/6) to give the ester **4c** (57.1 mg, 80%) as a colorless oil: IR (neat) ν 3334, 1733, 1605, 1546, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.33 (m, 5H), 7.27−7.24 (m, 1H), 7.15−7.13 (m, 1H), 7.00 (brs, 1H), 6.80−6.78 (m, 1H), 5.19 (s, 2H), 3.91 (m, 1H), 2.81 (brs, 1H), 2.73 (dd, J = 15.9, 2.9 Hz, 1H), 2.66 (dd, J = 15.9, 9.3 Hz, 1H), 1.82−1.75 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.8, 153.1, 150.9, 139.0, 135.9, 129.6, 128.6, 128.3, 128.3, 116.3, 116.0, 72.7, 67.1, 38.8, 33.3, 18.4, 17.6; MS *m*/*z* 357 (M^+), 243 (ArO^+H); $[\alpha]^{30}_D$ −13.3 (*c* 2.52, $CHCl_3$); HRMS (M^+) Calcd for $C_{20}H_{23}NO_5$ 357.1576. Found 357.1565.

(6*S*)-6-[(1*R*)-1-Hydroxy-2,2-dimethyl-3-phenylpropyl]-2-pyrone (4d). To a mixture of molecular sieves 4 Å (60 mg, dried at 180 °C under reduced pressure (ca. 5 mmHg) for 12 h), racemic trans-*N*,*N*′-bis(*p*-toluenesulfonyl)cyclohxane-1,2-diamine (**8**) (10 mg, 0.024 mmol) and the aldol product *syn*-**3o** (73.9 mg, 0.3 mmol, 76% ee), in dry CH_2Cl_2 (1.5 mL) at 0 °C, were added bis(trimethylsilyl)peroxide (1.2 mL, 1.2 mmol, 1.0 M in CH_2Cl_2) and $SnCl_4$ (24.0 μL, 0.024 mmol, 1.0 M in CH_2Cl_2). The reaction mixture was stirred for 23 h at room temperature, and then saturated aqueous $NaHCO_3$ (600 μL) and sodium sulfite (180 mg) were added. The mixture was stirred for 3 h at room temperature and then filtered through a pad of Celite. The aqueous layer was separated, and the organic layer was washed with 1 N HCl and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in THF/AcOH (1.0 mL/50 μL). Tetrabutylammonium fluoride (TBAF, 300 μL, 1.0 M in THF) was added to the solution. After 2 h of stirring at room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, which was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO_2, acetone/hexane 1/15−1/8) to give the ester **4d** (66.9 mg, 85%) as a colorless solid: IR (KBr) ν 3424, 1708, 1254 cm^{-1}; ^1H NMR (C_6D_6) δ 7.20−7.08 (m, 5H), 3.94−3.89 (m, 1H), 3.38−3.35 (m, 1H), 2.69 (d, J = 13.0 Hz, 1H), 2.43 (d, J = 13.0 Hz, 1H), 2.06−1.91 (m, 2H), 1.82 (brs, 1H), 1.49−1.39 (m, 1H), 1.36−1.30

(m, 1H), 1.18−1.10 (m, 1H), 1.05−0.95 (m, 1H), 0.83 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (C_6D_6) δ 171.1, 138.9, 131.2, 128.3, 128.1, 126.4, 81.6, 77.9, 46.1, 38.0, 29.8, 23.7, 23.2, 23.0, 18.5; MS *m*/*z* 262 (M^+), 171 (M^+ − Bn); $[\alpha]^{28}_D$ +11.9 (*c* 0.665, $CHCl_3$); Anal. Calcd for $C_{16}H_{22}O_3$ C,73.25; H, 8.45. Found C, 72.96; H, 8.59.

Synthesis of the Key Epothilone A Intermediate, (*S*)-5-Benzyloxy-4,4-dimethyl-1,3-pentanediol (iii). To a solution of **4b** (255 mg, 0.777 mmol, 93% ee) in ether (9.0 mL) at 0 °C, was added $LiAlH_4$ (74 mg, 1.94 mmol). The suspension was stirred for 15 min at 0 °C and then allowed to warm to room temperature and stirred for a further 30 min. The reaction was quenched by adding Na_2SO_4·$10H_2O$ (300 mg) at 0 °C and stirred for an additional 1 h. The reaction mixture was filtered through a pad of Celite and then concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2, acetone/hexane 1/6) to give the diol **iii** (183 mg, 99%) as a colorless oil: IR (neat) ν 3398, 1073 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38−7.29 (m, 5H), 4.51 (s, 2H), 3.86−3.83 (m, 2H), 3.74−3.70 (m, 1H), 3.40 (d, J = 8.5 Hz, 1H), 3.32 (d, J = 8.5 Hz, 1H), 3.04 (brs, 2H), 1.68−1.62 (m, 2H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.6, 128.5, 127.8, 127.6, 80.1, 79.8, 73.7, 62.5, 38.2, 32.9, 22.6, 19.5; MS *m*/*z* 220 (M^+ − H_2O); $[\alpha]^{30}_D$ −15.6 (*c* 1.04, $CHCl_3$); HRMS (M^+ − H_2O) Calcd for $C_{14}H_{20}O_2$ 220.1463. Found 220.1467.

(*S*)-4-(2-Benzyloxy-1,1-dimethylethyl)-2,2-dimethyl-1,3-dioxane (iv). The diol **iii** (18.7 mg, 0.078 mmol) was dissolved in acetone/2,2-dimethoxypropane (200 μL/100 μL), and the solution was treated with *p*-toluenesufonic acid (TsOH·H_2O, 2.7 mg). The mixture was stirred at room temperature for 17 h, and then the mixture was washed twice with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography (SiO_2, ether/hexane 1/30) to give **iv** (21.8 mg, quant) as a colorless oil: IR (neat) ν 1098 cm^{-1}; ^{1}H NMR (C_6D_6) δ 7.30−7.28 (m, 2H), 7.20−7.14 (m, 2H), 7.11−7.07 (m, 1H), 4.33 (s, 2H), 3.78 (dd, J = 11.0, 2.3 Hz, 1H), 3.71−3.61 (m, 2H), 3.33 (d, J = 8.2 Hz, 1H), 3.10 (d, J = 8.2 Hz, 1H), 1.62−1.53 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 1.00 (s, 3H), 0.98−0.92 (m, 1H), 0.90 (s, 3H); ^{13}C NMR (C_6D_6) δ 139.5, 128.5, 127.6, 127.6, 98.3, 76.7, 73.5, 72.4, 60.2, 38.2, 30.3, 25.6, 21.2, 20.2, 19.4; MS *m*/*z* 263 (M^+ − CH_3), 115 (M^+ − $BnOCH_2C(CH_3)_2$); $[\alpha]^{29}_D$ +8.3 (*c* 1.62, $CHCl_3$); Anal. Calcd for $C_{17}H_{26}O_3$ C, 73.34; H, 9.41. Found: C, 73.13; H, 9.34.

(*S*)-2-(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methylpropionaldehyde (5). To a solution of the acetonide **iv** (26.3 mg, 0.094 mmol) in THF (260 μL) were added *t*-BuOH (36.0 μL) and liquid NH_3 (ca. 1 mL). The solution was cooled to −78 °C, and then lithium (25 mg) was added. The reaction mixture was stirred at −78 °C for 20 min. The mixture was diluted with ether (3.0 mL), and then NH_4Cl (200 mg) was added. The liquid ammonia was allowed to evaporate, and the suspension was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the corresponding crude alcohol.

DMSO (27.2 μL, 0.351 mmol) was added to a stirred solution of oxalyl chloride (17.3 μL, 0.198 mmol) in CH_2Cl_2 (100 μL) at −78 °C. The solution was stirred at −78 °C for 1 h, and then previously obtained crude alcohol dissolved in CH_2Cl_2 (150 μL) was added (the flask was rinsed with 50 μL of CH_2Cl_2). The reaction mixture was stirred for 30 min at −78 °C, and then Et_3N (62.0 μL, 0.445 mmol) was added at the same temperature. It was then allowed to warm to 0 °C and stirred for 3 h. After the reaction mixture was quenched with the addition of water (1 mL), the aqueous layer was separated, and the organic layer was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated to afford aldehyde **5** (16.5 mg, 94%) as a colorless oil, The analytical data of this product was found to be identical to the reported literature values. $[\alpha]^{20}_D$ (lit.) +10.7 (*c* 1.0, $CHCl_3$); $[\alpha]^{29}_D$ +10.2 (*c* 0.76, $CHCl_3$) (Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996**, *2*, 1477−1482).

Synthesis of the Key Bryostatin 7 Intermediate, (*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-4,4-dimethyl-1-pentanal (6). To a stirred solution of ester **4b** (330 mg, 1.01 mmol, 93% ee) in CH_2Cl_2 (2 mL) at 0 °C, was added diisopropylethylamine (350 mL, 2.01 mmol) at 0 °C followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 342 μL, 1.5 mmol). The reaction was quenched with water after 45 min and diluted with ether. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent and flash chromatography (SiO_2, ether/hexane 2/98) yielded a TBS−ether (435 mg). This substrate (425 mg) in CH_2Cl_2 (2 mL) at −78 °C, was reduced to the alcohol by the addition of diisobutylaluminum hydride (DIBAL, 2.12 mL, 1 M in CH_2Cl_2). The reaction mixture was stirred for 1 h at −78 °C, and then MeOH was added to quench the reaction. The mixture was allowed to warm to room temperature and then filtered through a pad of Celite to remove the solid precipitate. The filtrate was washed with 1 N HCl followed by aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and purification of the residue by flash chromatography (SiO_2, ether/hexane 1/9) afforded an alcohol (320 mg). A solution of this alcohol (300 mg) in CH_2Cl_2 (2 mL) was added to a stirred suspension of PCC (266 mg, 1.23 mmol) and Celite (530 mg) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 5 h and then ether (15 mL) was added and the mixture was passed through a florisil column, which was washed thoroughly with ether (25 mL). Evaporation of the solvent and purification by flash chromatography (ether/hexane 2/98) yielded the aldehyde **6** (270 mg, 87% from **4b**) as a colorless oil; IR (neat) ν 2956, 2856, 2700, 2361, 1727, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1H), 7.23 (m, 5H), 4.39 (d, J = 12.2 Hz, 1H), 4.30 (d, J = 12.2 Hz, 1H), 4.15 (t, J = 5.4 Hz, 1H), 3.17 (d, J = 8.9 Hz, 1H), 3.09 (d, J = 8.9 Hz, 1H), 2.64 (dd, J = 5.4, 1.8 Hz, 1H), 2.47 (dd, J = 5.4, 2.8 Hz, 1H), 0.90 (s, 3H), 0.85 (s ×2, 3H and 9H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.1, 138.5, 128.3, 127.5, 127.4, 76.6, 73.0, 71.5, 48.2, 40.0, 25.9, 21.4, 21.2, 18.1, −4.0, −4.8; MS *m*/*z* 350 (M^+); $[\alpha]^{29}_D$ +0.88 (*c* 1.14, $CHCl_3$); Anal. Calcd for $C_{20}H_{34}O_3Si$ C, 68.52; H, 9.77. Found C, 68.60; H, 9.67.

(3*S*,5*S*)-7-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-6,6-dimethyl-1-phenyl-1-heptanone (*anti*-7) and (3*R*,5*S*)-7-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-6,6-dimethyl-1-phenyl-1-heptanone (*syn*-7). A solution of water (230 μL, 0.23 mmol, 1 M in THF) was added to KHMDS (210 μL, 0.105 mmol, 0.5 M in toluene) in a 10-mL test tube at 0 °C, and the mixture was stirred at the same temperature for 0.5 h. (*S*)-LLB solution which was prepared by the procedure described above (1.90 mL, 1.14 mmol, 0.06 M in THF) was added, and the mixture was stirred at 0 °C for 0.5 h and then further cooled to −20 °C. Acetophenone (**2a**) (334 μL, 2.87 mmol) was added, and after the solution was stirred for 30 min, aldehyde **6** (200 mg, 0.57 mmol) in THF (300 μL) was added. The reaction mixture was stirred at −20 °C for 24 h and then quenched by addition of 1 N HCl (2 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (SiO_2) produced *anti*-**7** (212 mg, 78.9%) as a colorless oil: IR (neat) ν 3525, 2956, 2855, 1679, 1450 cm^{-1}; ^{1}H NMR (C_6D_6) δ 7.73−7.00 (m, 10H), 4.53 (m, 1H), 4.46 (d, J = 12.2 Hz, 1H), 4.29 (d, J = 12.2 Hz, 1H), 4.25 (m, 1H), 3.31 (d, J = 8.8 Hz, 1H), 3.29 (m, 3H), 3.27 (d, J = 8.8 Hz, 1H), 2.64 (m, 2H), 1.82 (m, 1H), 1.49 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 1.02 (s, 9H), 0.32 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_6D_6) δ 200.2, 139.4, 137.2, 133.12, 77.5, 73.8, 73.4, 64.5, 46.3, 40.0, 39.9, 26.6, 22.0, 21.6, 18.8, −3.5, −3.9; MS *m*/*z* 471 (M^+ + 1), 453 (M^+ − OH); $[\alpha]^{29}_D$ +1.58 (*c* 1.09, $CHCl_3$) (95% ee); HPLC (DAICEL CHIRALPAK AS, 2-propanol/hexane 1/9, flow 0.5) t_R 7.5 and 8.0 min; Anal. Calcd for $C_{28}H_{42}O_5Si$ C, 69.09; H, 8.70. Found C, 68.92; H, 8.74, and *syn*-**7** (30 mg, 11.2%) as a colorless oil: IR (neat) ν 3535, 2955, 2855, 1680, 1450 cm^{-1}; ^{1}H NMR (C_6D_6) δ 7.75−7.00 (m, 10H), 4.36 (d, J = 12.2 Hz, 1H; m, 1H), 4.29 (d, J = 12.2 Hz, 1H), 4.04 (m, 1H), 3.26 (d, J = 8.9 Hz, 1H), 3.21 (d, J = 8.9 Hz, 1H; m, 1H), 2.74 (s, 1H), 2.72 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.08 (s, 3H), 1.03 (s, 9H), 0.99 (s, 3H), 0.28 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_6D_6) δ 200.2, 139.4, 137.6, 133.3, 77.9, 74.1, 73.7, 66.9, 46.1, 41.8, 40.8, 26.6, 21.8, 21.3, 18.8, −3.3, −4.3; MS *m*/*z* 470 (M^+); $[\alpha]^{29}_D$ −19.7 (*c* 1.34, $CHCl_3$) (95% ee); Anal. Calcd for $C_{28}H_{42}O_4Si$ C, 71.44; H, 8.99. Found C, 71.21; H, 8.71. The relative configuration of *anti*-**7** was confirmed after conversion to known compound **9** and comparison of data with literature values.

2-[(4*R*,6*S*)-6-(2-Benzyloxy-1,1-dimethylethyl)-2,2-dimethyl-1,3-dioxan-4-yl]ethanol (9): To a mixture of molecular sieves 4 Å (85 mg, dried at 180 °C under reduced pressure (ca. 8 mmHg)) and racemic

trans-*N*,*N*′-bis(*p*-toluenesulfonyl)-cyclohexane-1,2-diamine (**8**) (45 mg, 0.106 mmol) in CH_2Cl_2 (200 μL) was added a solution of $SnCl_4$ (106 μL, 0.106 mmol, 1 M in CH_2Cl_2). The reaction mixture was cooled to 0 °C, and bis(trimethylsilyl)peroxide (424 μL, 0.424 mmol, 1 M in CH_2Cl_2) was added via syringe. Ketone *anti*-**7** (50 mg, 0.106 mmol) in CH_2Cl_2 (300 μL) was then added, and the reaction mixture was stirred at 0 °C for 6 h. Aqueous $NaHCO_3$ solution was added, and the mixture was diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were stirred with solid Na_2SO_3 for 3 h and filtered, and the solvent was evaporated under reduced pressure. Purification by flash chromatography (ether/hexane 1/9) gave the starting ketone *anti*-**7** (10 mg) and an ester (20.5 mg).

To a mixture of this ester (15 mg), 2,2-dimethoxypropane (15 μL, 0.12 mmol) and camphorsulfonic acid (CSA) (1 mg), in CH_2Cl_2 (200 μL) at 0 °C, was added 70% hydrogen fluoride−pyridine (HF·Py) solution (4 drops). The cooling bath was removed, and the reaction mixture was stirred for 0.5 h and then cooled to 0 °C and quenched by the addition of saturated aqueous $NaHCO_3$ solution. Ether (5 mL) was added to this solution, and organic layer was separated. The aqueous layer was extracted with ether (2 × 5 mL), and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography yielded an acetonide (9 mg).

To a stirred suspension of $LiAlH_4$, in THF (200 μL) at 0 °C, was added a solution of the preceding acetonide (9 mg) in THF (200 μL). The cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature. MeOH (200 μL) was added to quench the reaction, and the precipitate was filtered through a pad of Celite and washed thoroughly with ether. Concentration of the filtrate and purification of the resulting residue by flash chromatography afforded the alcohol **9** as a colorless oil. Analytical data of the product was identical with the reported data for the known compound in the literature (IR, ^{1}H NMR, ^{13}C NMR, MS): $[\alpha]^{24}_D$ (lit.) −28.4 (*c* 2.7, $CHCl_3$); $[\alpha]^{29}_D$ −28.4 (*c* 0.63, $CHCl_3$) (95% ee) (Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 2817−2825).

Observation of Isotope Effects of Aceto-d_3-phenone on the Direct Catalytic Asymmetric Aldol Reaction (Figure 3). To a stirred solution of KHMDS (28.8 μL, 0.0144 mmol, 0.5 M in toluene), at 0 °C, was added a solution of deuterium oxide (32.0 μL, 0.032 mmol, 1.0 M in THF). The mixture was stirred for 20 min at this temperature and then (*R*)-LLB (prepared by the procedure described above, 267 μL, 0.016 mmol, 0.06 M in THF) was added and the solution was stirred for 30 min at 0 °C. The resulting pale yellow solution was cooled to −20 °C, and aceto-d_3-phenone (234 μL, 2 mmol, 10 eq to the aldehyde) was added. The solution was stirred for 20 min and then 2,2-dimethyl-3-phenylpropanal (**1b**) (33.3 μL, 0.2 mmol) was added and the mixture was stirred at −20 °C. The reaction was quenched by addition of 1 N HCl (1 mL) and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was analyzed by HPLC (DAICEL CHIRALPAK AD, 2-propanol/hexane 1/9, flow 1.0).

Kinetic Study to Find Out the Dependence of the Reaction Rate on the Concentration of the Aldehyde (1b) (Figure 4). The reactions were carried out under the following conditions: [(*R*)-LLB] = 0.0196 M; KHMDS (0.9 equiv to LLB); H_2O (2 equiv to LLB); [acetophenone (**2a**)] = 3.27 M; THF; −20 °C; 2 h. The reactions were worked up according to the procedure (GP2). The crude product was analyzed by HPLC (DAICEL CHIRALPAK AD, 2-propanol/hexane 1/9, flow 1.0).

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of products, synthesis of aldehydes **1i** and **1j** and X-ray structual information on *syn*-**3o** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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