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Organocatalyzed Asymmetric Aldol Reactions of Ketones and β,γ-Unsaturated α-Ketoesters and Phenylglyoxal Hydrates

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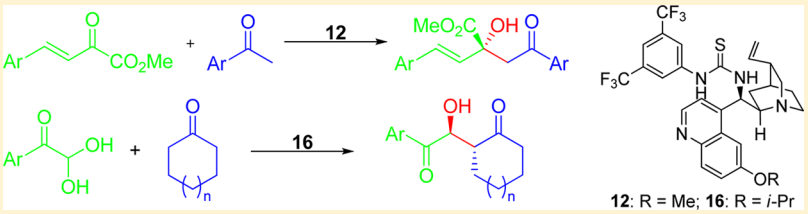
Supporting Information



ABSTRACT: Enantioselective aldol reactions of acetophenone with β,γ-unsaturated α-ketoesters and cyclic ketones with phenylglyoxal hydrates were realized with cinchona alkaloid-derived thiourea catalysts. The corresponding aldol products were obtained in high yields and good to excellent diastereoselectivities and enantioselectivities (up to 95% ee).

INTRODUCTION

The aldol reaction is a very powerful method for the formation of a carbon−carbon bond in organic chemistry.[1] Because of the importance of the aldol reaction products, chiral β-hydroxy carbonyl compounds, as synthetic intermediates in organic synthesis, many asymmetric variants have been developed in the past.[1] Since List et al. introduced the first example of a proline-catalyzed direct cross-aldol reaction in 2000,[2] great progresses have been made in the organocatalyzed asymmetric aldol reactions using primary or secondary amine-based organocatalysts via the enamine intermediate in the past decade.[3] Despite the success of this method, it still has some limitations. For example, it cannot be applied to carbonyl substrates that cannot form an enamine intermediate with the amine catalyst.

Recently, there has been considerable interest in applying β,γ-unsaturated-α-ketoesters in organocatalytic reactions due to the unique reactivities of the α,β-unsaturated system and the activated ketone group.[4−6] In this regard, several organocatalytic asymmetric aldol reactions of β,γ-unsaturated-α-ketoesters have been reported.[5] In 2007, Tang and co-workers reported a single example of the aldol reaction between acetone and ethyl (*E*)-2-oxo-4-phenylbut-3-enoate using *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide as the catalyst, although a poor ee value of 14% was obtained for the aldol product.[5a] Cyclic ketones yield the tandem Michael-aldol products instead.[5a] Zhao and co-workers later studied the aldol reaction of cyclic ketones with (*E*)-4-aryl-2-oxobut-3-enoates using 4-(*tert*-butyldiphenylsilyloxy)-pyrrolidine-2-carboxylic acid as the catalyst in water and obtained the desired aldol products in high dr and ee values.[5b] Nonetheless, a much lower ee value was obtained for the aldol product of acetone.[5b] Using a cinchonine-derived primary amine as the catalyst, Chan and co-workers obtained good to high ee values for the corresponding aldol products of cyclic and acyclic ketones, including acetone.[5c,d] This catalyst was also used by Lu and co-workers to achieve the cross-aldol reaction of hydroxyacetone derivatives.[5e] High enantioselectivities were also achieved for the acetone aldol products by Wang and co-workers using a primary−tertiary diamine catalyst.[5f] Likewise, Cheng and co-workers obtained good results in the cross-aldol reaction of cyclic ketones using a primary amine-imine catalyst.[5g] Most recently, the cross-aldol reaction with aldehydes was also realized by Yuan and co-workers.[5h] Despite these successes, acetophenone appears to be a tough substrate for the enamine-mediated cross-aldol reaction with β,γ-unsaturated-α-ketoesters. For example, Chan and co-workers briefly studied this substrate, but no yield of the desired aldol was obtained,[5d] probably due to the low electrophilicity of the keto group in acetophenone.

In contrast, although phenylglyoxal also has a highly electrophilic formyl group, this substrate has only been sporadically studied in the amine-catalyzed cross-aldol reactions.[7] Maruoka and co-workers reported a single example of a highly *syn*-selective cross-aldol reaction of phenylglyoxal hydrate and hexanal using an axially chiral amino sulfonamide as the catalyst.[7a,b] Most recently, Quignard and co-workers reported the cross-aldol of phenylglyoxal and cyclohexanone using chitosan as the catalyst, although the desired aldol product was obtained in only mediocre stereoselectivities.[7c]

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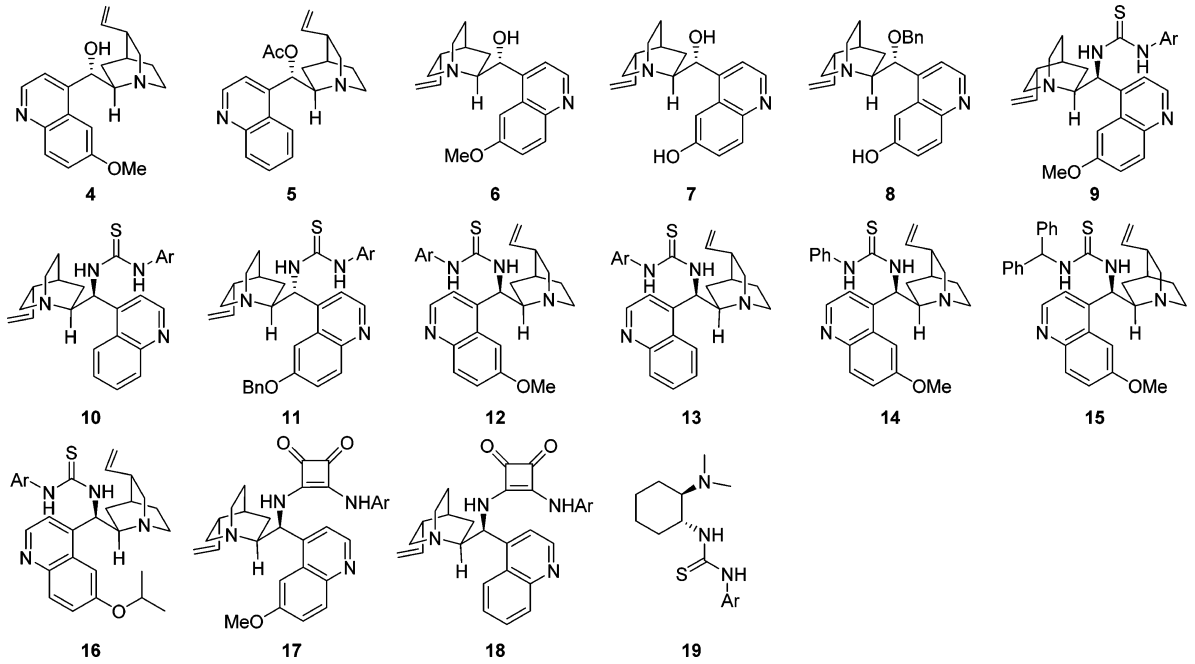


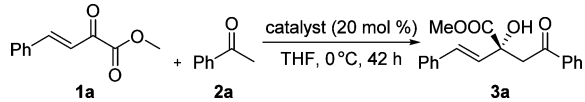
Figure 1. Catalysts screened in this study [Ar = 3,5-$(CF_3)_2C_6H_3$−].

Our group reported a quinidine thiourea-catalyzed cross-aldol reaction of unfunctionalized ketones and isatins that involved an enolate intermediate most recently.[8a] Phenylglyoxal hydrate was also briefly evaluated in this reaction.[8a] Since the formation of an enamine intermediate is not involved in this tertiary amine-catalyzed aldol reaction,[8−10] the success of this reaction does not rely on the electrophilicity of the keto group, but the acidity of the α-protons in the unfunctionalized ketones. Thus, acetophenone, which is a poor substrate for the enamine mechanism, should be a good substrate in the enolate-mediated cross-aldol reactions.[8a] Herein, we report enantioselective aldol reactions of β,γ-unsaturated α-ketoesters with acetophenone and a detailed study of the aldol reaction of phenylglyoxal hydrates with cyclic ketones, using cinchona alkaloid derivatives as the catalyst. These reactions yield aldol products with multiple functional groups, which should be very useful in organic synthesis. For example, the first aldol reaction yielded tertiary alcohols containing a quaternary stereogenic center[11] and multiple functional groups in excellent yields (up to 98%) and high enantioselectivities (up to 91% ee). Such a motif may be found in a variety of natural products and biologically active compounds.[12] Thus, these compounds should be useful synthetic building blocks in organic synthesis.[13] The second aldol reaction yields 2-hydroxy-1,4-diones with two stereogenic centers in high yields (up to 98%) and stereoselectivities (up to 88:12 dr and 95% ee), which should also be very useful in organic synthesis.

RESULTS AND DISCUSSIONS

Aldol Reaction of β,γ-Unsaturated α-Ketoesters and Acetophenones. First, the cross-aldol reaction of acetophenone derivatives and β,γ-unsaturated-α-ketoesters was studied using methyl (*E*)-2-oxo-4-phenylbut-3-enoate (**1a**) and acetophenone (**2a**) as the model substrates. Various cinchona alkaloid derivatives (Figure 1) were screened as the catalyst to effect the desired aldol reaction. The results are summarized in Table 1.

Table 1. Catalyst Screening[a]



entry	catalyst	yield[b] (%)	ee[c] (%)
1	**4**	14	8
2	**6**	29	18[d]
3	**7**	15	52[d]
4	**8**	0	
5	**9**	75	79[d]
6	**10**	65	80[d]
7	**11**	28	42[d]
8	**12**	87	84
9	**13**	81	83
10	**14**	76	69
11	**15**	23	51
12	**16**	82	83
13	**17**	39	66[d]
14	**18**	46	64[d]
15	**19**	<5	nd[e]
16[f]	**12**	65	83

[a]Unless otherwise noted, the reaction was conducted with **1a** (0.10 mmol) and **2a** (2.0 mmol) in the presence of the catalyst (0.020 mmol, 20 mol %) in THF (0.1 mL) at 0 °C for 42 h. [b]Yield of isolated product **3a** after column chromatography. [c]Determined by chiral HPLC analysis on a ChiralPak AD-H column. [d]The opposite enantiomer was obtained as the major product. [e]Not determined. [f]The catalyst loading was 10 mol %.

As the results in Table 1 show, when quinidine (**4**) was used in THF at 0 °C, a very low yield and ee value were obtained for the desired product **3a** (entry 1). Similarly, poor results were obtained with quinine (**6**, entry 2), which yielded a low ee value for the opposite enantiomer. A better ee value of the product **3a** was obtained with cupreine (**7**), but the yield was still poor (entry 3). No formation of **3a** was observed when 9-*O*-benzylcupreine (**8**) was used (entry 4). A remarkable

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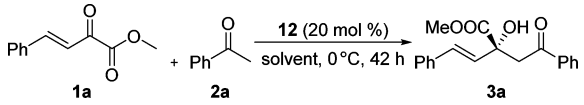
enhancement of the product yield (75%) and ee value (79%) was achieved when a quinine-derived thiourea catalyst **9** was applied (entry 5). Similar results were also obtained with the cinchonidine-derived thiourea **10** (entry 6). However, the epimerization of the thiourea moiety (as in catalyst **11**) resulted in a major loss in both the reactivity and the enantioselectivity of the catalyst (entry 7). These results indicate that both the thiourea moiety and its stereochemistry are crucial for the observed reactivity and stereoselectivity of the catalyst. When a quinidine-derived catalyst **12** was used, slightly better results were obtained (87% yield and 84% ee, entry 8). Similarly, good results were obtained with the cinchonine-derived thiourea **13** (entry 9). When the 3,5-bis(trifluoromethyl)phenyl group on the thiourea moiety of catalyst **12** was replaced by a phenyl or a diphenylmethyl group, as in catalysts **14** and **15**, respectively, much lower product ee values were obtained (entries 10 and 11). In addition, the yield also dropped significantly with catalyst **15** (entry 11). In comparison, catalyst **16**, which has an isopropoxy group instead of the methoxy group in the 6′-position, yielded similar results as catalyst **12** (entry 12). These results again hint that the enantioselectivity of this reaction is mainly controlled by the thiourea moiety of the catalyst. Interestingly, much lower yields and ee values were obtained for the cinchona alkaloid squaramide catalysts **17** and **18** (entries 13 and 14). On the other hand, the Takemoto thiourea **19** was not an effective catalyst for the desired aldol reaction (entry 15). In general, quinidine-based catalysts and quinine-based catalysts generate the opposite enantiomers. Thus, this screening identified the quinidine-derived thiourea catalysts **12** (entry 8) and **16** (entry 12) and the cinchonine-derived thiourea catalyst **13** (entry 9) as the best catalysts. The opposite enantiomer of **3a** may be obtained using the quinine thiourea **9** (entry 5) and cinchonidine thiourea **10** (entry 6) in a slightly lower ee value. When the catalyst loading of **12** was lowered to 10 mol %, the reaction became slower and produced a lower yield and a slightly lower product ee value (entry 16).

The effects of solvents, substrate concentration, reaction temperature, and the loading of **2a** were then studied with catalyst **12**, and the results are summarized in Table 2. As the data in Table 2 show, common organic solvents have only minimal effects on the enantioselectivities, but they do have some effects on the reactivities (entries 1−5). THF turned out to be the best solvent for this reaction in terms of both reactivity and stereoselectivity (entry 1). Interestingly, only a small amount of THF (0.1 mL) was needed. When the volume of THF was increased, the yield obtained was actually lower (data not shown). These results indicate that the substrate concentration is important for the reactivity. Nonetheless, when the reaction was carried out under neat conditions, a lower yield and ee value was obtained (entry 6). Thus, a small amount of THF is necessary for this reaction. When the reaction was carried out at rt or −10 °C, lower ee values and lower yields of **3a** were obtained (entries 7 and 8). On the other hand, when the loading of acetophenone was reduced to half, a much lower product yield was obtained (entry 9).

Once the reaction conditions were optimized, the substrate scope was evaluated. As the results summarized in Table 3 demonstrate, the ester group of the *β*,*γ*-unsaturated *α*-ketoesters has only a slight influence on the reactivity and enantioselectivity of this reaction (entries 1−3), with the methyl ester generating the highest yield and ee value for the desired aldol product (entry 1). Electron-withdrawing and electron-donating groups on the *para* position of the benzene ring of the *β*,*γ*-unsaturated-*α*-ketoester also have only small effects on the product ee values (entries 1, 4−8), with electron-donating groups generally yielding better ee values and slightly lower product yields (entries 7 and 8) than electron-withdrawing groups (entries 4−6). For reasons still unknown, a much lower product ee value (73%) was obtained for the 4-

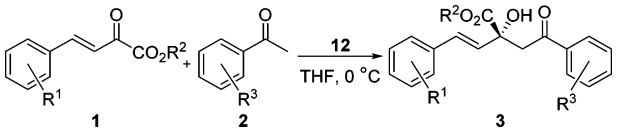
Table 2. Solvent and Temperature Study[a]



entry	solvent	yield[b] (%)	ee[c] (%)
1	THF	87	84
2	toluene	51	80
3	CH_2Cl_2	68	80
4	CH_3CN	69	86
5	Et_2O	68	79
6	neat	61	68
7[d]	THF	65	78
8[e]	THF	16	82
9[f]	THF	48	82

[a]Unless otherwise noted, the reaction was conducted with **1a** (0.10 mmol) and **2a** (2.0 mmol) in the presence of catalyst **12** (0.020 mmol, 20 mol %) in the specified solvent (0.1 mL) at 0 °C for 42 h. [b]Yield of the isolated product after column chromatography. [c]Determined by HPLC analysis of the purified product on a ChiralPak AD-H column. [d]The reaction was carried out at rt. [e]The reaction was carried out at −10 °C. [f]1.0 mmol of **2a** was used in this case.

Table 3. Substrate Scope Study[a]



entry	R^1	R^2	R^3	*t* (h)	3/yield[b] (%)	ee[c] (%)
1	H	Me	H	42	**3a**/87	84
2	H	Et	H	36	**3b**/82	80
3	H	*i*-Pr	H	38	**3c**/80	79
4	4-F	Me	H	24	**3d**/87	81
5	4-Cl	Me	H	36	**3e**/94	80
6	4-Br	Me	H	36	**3f**/99	73
7	4-Me	Me	H	36	**3g**/78	87
8	4-MeO	Me	H	30	**3h**/72	86
9	2-Cl	Me	H	36	**3i**/85	87
10	2-Br	Me	H	20	**3j**/78	91
11	3-Br	Me	H	24	**3k**76	81
12	H	Me	4-F	18	**3l**/86	82
13	H	Me	4-Cl	19	**3m**/88	83
14	H	Me	4-Br	42	**3n**/85	81
15	H	Me	4-NO_2	24	**3o**/76	75
16	H	Me	4-Me	36	**3p**/72	80
17	H	Me	4-MeO	48	**3q**/70	82
18	H	Me	2-Cl	36	**3r**/75	50
19	H	Me	3-Cl	28	**3s**/89	82

[a]All reactions were conducted with **1** (0.10 mmol) and **2** (2.0 mmol) in the presence of catalyst **12** (0.020 mol, 20 mol %) in THF (0.1 mL) at 0 °C. [b]Yield of isolated product **3** after column chromatography. [c]Determined by HPLC analysis of the purified product using a ChiralPak AD-H column.

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bromo-substituted substrate (entry 6). In contrast, placing a chloro or bromo substituent at the *ortho* position improves the product ee values (entries 9–10). On the other hand, although a bromo substituent at the *meta* position of the phenyl ring does not show a similar extent of improvement in the ee value (entry 11), the product ee value is still better than that of the 4-bromo-substituted substrate (entry 6). Similarly, electron-withdrawing and electron-donating groups on the *para* position of the benzene ring of the acetophenone also have minimal effects on the product ee values (entries 12–17), except that a slightly lower ee value was obtained for the 4′-nitro substrate (entry 15). Slightly lower yields were also obtained for the 4′-nitro- (entry 15), 4′-methyl- (entry 16), and 4′-methoxy-substituted (entry 17) acetophenones. In contrast, a chloro substituent at the *ortho* position of the benzene ring greatly reduces the product ee value (to 50% ee) and slightly diminishes the reactivity, most likely due to steric effects (entry 18 vs entry 13). As expected, when the substituent is moved to the *meta* position of the benzene ring, the reactivity and the enantioselectivity are restored (entry 19 vs entries 13 and 18).

The absolute stereochemistry of the aldol product **3** was determined by the X-ray crystallographic analysis of the crystals of compound **3f**. According to the X-ray crystallographic data, compound **3f** is *R*-configured (Figure 2).[14] Thus, the major enantiomers obtained in this aldol reaction were assigned the *R* configuration on the basis of a similar reaction mechanism.

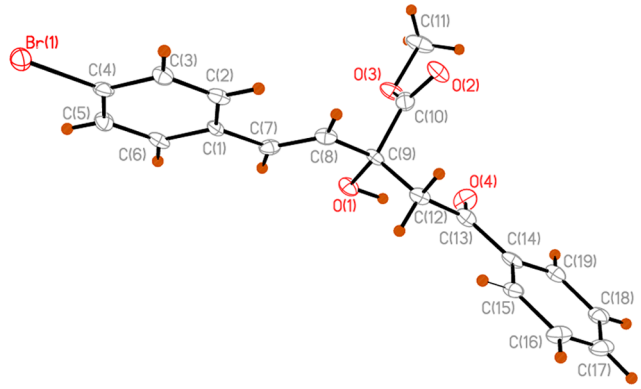
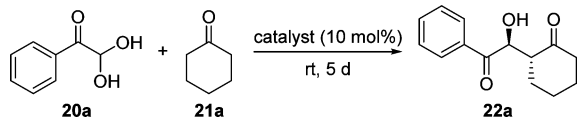


Figure 2. ORTEP drawing of compound **3f**.

Aldol Reaction of Phenylglyoxal Hydrates and Cyclic Ketones. The aldol reaction of phenylglyoxal hydrates and cyclic ketones generates 2-hydroxy-1,4-diones with two stereogenic centers, which should be very useful in organic synthesis. The reaction was briefly studied using quinidine thiourea (**12**) as the catalyst in our previous communication (a single example was reported).[8a] To further investigate this reaction, we screened more cinchona alkaloid derivatives (Figure 1) in order to find the optimal catalyst for this reaction, using phenylglyoxal hydrate (**20a**) and cyclohexanone (**21a**) as the model substrates. The results are summarized in Table 4.

According to our previous findings,[8a] the reactions were conducted at rt using the excessive cyclohexanone as the solvent. When quinidine (**4**) was used as the catalyst, the desired aldol product was obtained in an excellent yield (98%). Unfortunately, the stereoselectivities (both dr and ee values) were poor (entry 1). Protecting the 9-hydroxy group of **4** with an acetyl group was not helpful at all (entry 2). These two catalysts also yield the *syn*-diastereomer as the major product

Table 4. Catalyst Screening for the Aldol Reaction of Phenylglyoxal Hydrate[a]



20a **21a** **22a**

entry	catalyst	yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	**4**	98	40:60	32[e]
2	**5**	96	40:60	2
3	**9**	99	85:15	93[e]
4	**10**	98	84:16	92[e]
5	**11**	89	56:44	47[e]
6	**12**	99	85:15	93
7	**13**	98	85:15	92
8	**14**	96	78:22	85
9	**15**	88	54:46	28
10	**16**	98	88:12	94
11	**17**	76	81:19	90[e]
12	**18**	81	79:21	89[e]
13	**19**	93	40:60	30

[a]All reactions were conducted with phenylglyoxal monohydrate (**20a**, 0.20 mmol), the catalyst (0.020 mmol, 10 mol %), and cyclohexanone (**21a**, 2.0 mmol) at rt for 5 days. [b]Yield of isolated product **22a** after column chromatography. [c]Determined by ^{1}HNMR analysis of the crude reaction product. [d]Value of the antidiastereomer as determined by HPLC analysis of the purified product using a ChiralCel AS column. [e]The opposite enantiomer was obtained as the major product.

(entries 1–2). In contrast, when quinine thiourea (**9**) was used as the catalyst, the dr and the ee values of the *anti*-aldol product **22a** improved dramatically to 85:15 and 93% ee, respectively (entry 3). Similar results were obtained with cinchonidine thiourea (**10**, entry 4). Similar to the results of the aldol reaction of the α-ketoester (Table 1, entry 7), catalyst **11** with an inverted stereochemistry at the C9 position led to poor stereoselectivities of the aldol product (entry 5). Quinidine thiourea (**12**) produced **22a** in 99% yield, 85:15 dr, and 93% ee (entry 6). As expected, cinchonine thiourea (**13**) yielded results similar to those of **12** (entry 7). These results hint that the thiourea moiety and its stereochemistry are crucial for the observed high stereoselectivities. When the 3,5-bis(trifluoromethyl)phenyl group on the thiourea moiety of the catalyst was replaced by a phenyl or a diphenylmethyl group, as in catalysts **14** and **15**, respectively, the dr and ee values of the product dropped significantly (entries 8 and 9). Thus, the hydrogen-bonding capacity of the thiourea moiety is partially responsible for the observed stereoselectivities. Slightly improved dr and ee values of the product were achieved when 6′-isopropyl-substituted quinidine-based thiourea **16** was employed as the catalyst (entry 10). However, slightly lower stereoselectivities were obtained from the squaramide catalysts **17** and **18** (entries 11 and 12). In contrast, poor results were obtained with the Takemoto thiourea **19** (entry 13). It should be pointed out that catalysts **4**, **9**, **10**, and **11** produce the major enantiomer opposite to that of the rest of the catalysts. Thus, this screening identified catalyst **16** as the best catalyst for this aldol reaction, whereas catalysts **12** and **13** are also very good catalysts. The opposite enantiomer of the major *anti*-diastereomer may be obtained by using catalysts **9** and **10**. From the data presented in Tables 1 and 4, it is also evident that these two reactions follow a very similar trend in terms of stereoselectivity when the same catalysts are used.

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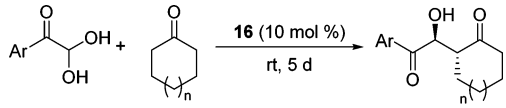
With the best catalyst identified, we then explored the scope of this novel aldol reaction with catalyst **16**. The results are summarized in Table 5. As shown in Table 5, besides

Table 5. Substrate Scope Study[a]



20 **21** **22**

entry	Ar	*n*	**22**/yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	Ph	1	**22a**/98	88:12	94
2	4-FC_6H_4	1	**22b**/93	88:12	95
3	4-ClC_6H_4	1	**22c**/96	82:18	92
4	4-BrC_6H_4	1	**22d**/95	85:15	93
5	4-MeC_6H_4	1	**22e**/97	88:12	94
6	4-$MeOC_6H_4$	1	**22f**/93	88:12	94
7	3-ClC_6H_4	1	**22g**/94	80:20	94
8	2-ClC_6H_4	1	trace		
9	2-naphthyl	1	**22h**/96	88:12	95
10	Ph	0	**22i**/93	85:15	59
11	Ph	2	**22j**/87	85:15	90
12	Ph	3	**22k**/85	80:20	71

[a]All reactions were conducted with arylglyoxal monohydrate (**20**, 0.20 mmol), catalyst **16** (0.020 mmol, 10 mol %), and the ketone (**21**, 2.0 mmol) at rt for 5 days. [b]Yield of isolated product **22** after column chromatography. [c]Determined by ^{1}HNMR analysis of the crude reaction product. [d]Value of the major *anti*-diastereomer as determined by HPLC analysis of the purified product.

phenylglyoxal monohydrate, substituted phenylglyoxal monohydrates are also good substrates for this reaction. The electronic nature of the substituent at the *para* position of the benzene ring has almost no influence on the reactivity, the diastereoselectivity, or the enantioselectivity of this reaction when they are reacted with cyclohexanone (entries 2−6). A slightly lower diastereoselectivity was observed when 3-cholrophenylglyoxal monohydrate was applied (entry 7), but the product ee value was not affected. In contrast, 2-chlorophenylglyoxal monohydrate does not participate in this reaction at all (entry 8), most likely due to steric reasons. On the other hand, 2-naphthylglyoxal monohydrate reacts readily under the above conditions and generates the desired aldol product in a high yield, a good dr, and a high ee value (entry 9). Besides cyclohexanone, some common cyclic ketones were also studied, and it was found that the stereoselectivity of this reaction was highly dependent on the ring size of the ketone component. For examples, when cyclopentanone was applied, the reaction gave the desired product in a high yield and a good dr, but the ee value of the major diastereomer is much lower (59% ee, entry 10) as compared to that of the cyclohexanone product (94% ee, entry 1). Nonetheless, when cycloheptanone was employed, a high ee value (90% ee) was obtained for the aldol product (entry 11). In contrast, a slightly lower dr (80:20) and a much lower ee value (71% ee) were obtained when cyclooctanone was applied (entry 12).

In our previous communication, the absolute stereochemistry of the aldol product **22a** was tentatively assigned *S* and *R* for the C2 and the hydroxy-substituted stereogenic centers, respectively.[8a] Now, with compound **22d**, we were able to obtain crystals that were suitable for the X-ray analysis. According to the X-ray crystallographic data of compound **22d** (Figure 3),[15] the major enantiomer obtained in this aldol

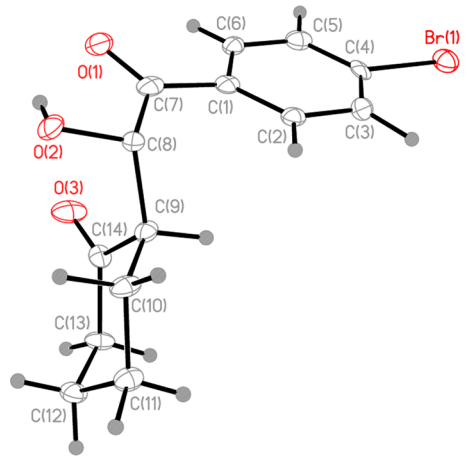


Figure 3. ORTEP drawing of compound **22d**.

reaction actually has *R* and *S* stereochemistry for the C2 and the hydroxy-substituted stereogenic centers, respectively, which is opposite to the original assignment.[8a] Thus, the original absolute stereochemistry assignment for compound **22a** has to be revised.

These two reactions are very similar in terms of the catalyst selectivity and stereochemistry of the major products when the same catalyst is applied. These results hint that the transition states of these reactions are most likely also similar. On the basis of the stereochemical outcomes of these two reactions, unified plausible transition state models are proposed to account for the formation of major stereoisomers (Scheme 1). As shown in Scheme 1, after enolization, the enolate of the ketone [acetophenone (R^3 = H, R^4 = Ph) or cyclohexanone (R^3,R^4 = $-(CH_2)_4-$)] is closely associated with the quinuclidinium backbone of the quinidine thiourea catalyst through ionic interactions and potential hydrogen bonding between the ammonium and the enolate. In the meantime, the electrophilic substrate [α-ketoester (R^1 = *trans*-2-phenylvinyl, R^2 = OMe) or glyoxalal (R^1 = H, R^2 = Ph)] is hydrogen-bonded to the thiourea moiety of the catalyst. In the favored transition state, the enolate is attacking the *Si* face of the electrophilic substrate using its *Si* face. Such an *Si*-*Si* attack (Scheme 1, upper equation) is favored over the *Re*-*Re* attack (Scheme 1, bottom equation) because the enolate and the reactive carbonyl group of the electrophilic substrate are in proximity, which is expected to lead to faster reaction. The *Si*-*Si* attack leads to the formation of the observed major stereoisomer for the aldol products of β,γ-unsaturated α-ketoester and phenylglyoxal (Scheme 1).

■ CONCLUSIONS

In summary, we have developed an enantioselective aldol reaction of acetophenone with β,γ-unsaturated α-ketoesters as the organocatalyst and a highly stereoselective aldol reaction of arylglyoxal monohydrates with cyclic ketones using quinidine-derived thioureas. The desired aldol products may be obtained in excellent yields (up to >99%), and good to high enantioselectivities (up to 95% ee) and diastereoselectivities (up to 88:12 dr).

■ EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out in oven-dried glass vials. Solvents were dried using standard protocols. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz,

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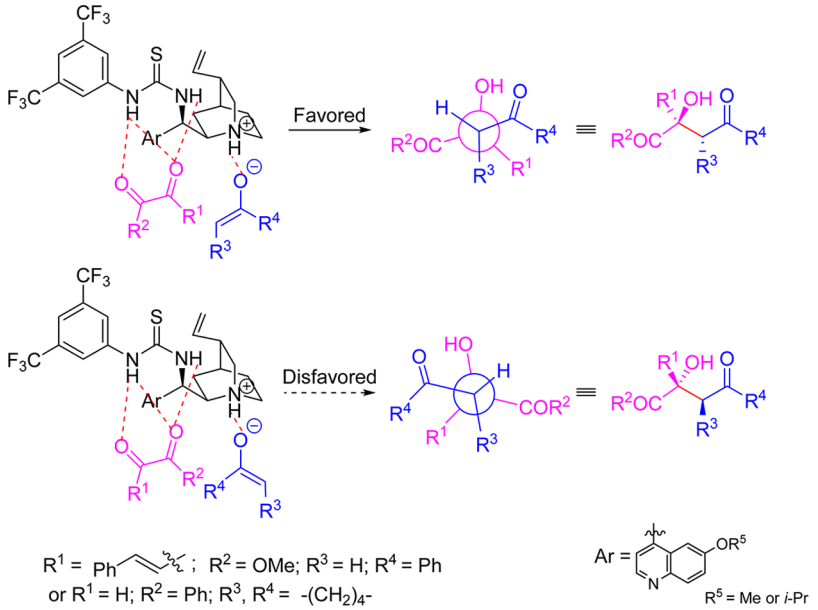
Scheme 1. Proposed Transition States



respectively) spectra were recorded at 25 °C using $CDCl_3$ as solvent. Catalysts used in this study are either purchased from commercial resources or synthesized according to the reported procedures.[16] The known compound **22a** was characterized by comparing its NMR spectra with the literature data.[7c,8a] High-resolution mass spectrum (HRMS) was recorded using the electrospray ionization (ESI) technique with a TOF analyzer. HPLC were conducted with a ChiralPak AD-H, a ChiralCel AS, or a ChiralPak IC column using a mixture of hexanes/*i*-PrOH as the eluent. The detailed conditions are given at the characterization part of the products.

Typical Procedure for the Aldol Reaction of Acetophenone and *β,γ*-Unsaturated-*α*-ketoester. To a mixture of acetophenone (**2a**, 0.2 mL) and quinidine thiourea (**12**, 11.9 mg, 0.020 mmol) was added methyl (*E*)-2-oxo-4-phenylbut-3-enoate (**1a**, 19.0 mg, 0.10 mmol) in THF (0.1 mL) at 0 °C. After the reaction mixture was stirred for 42 h at this temperature (monitored by TLC), the reaction mixture was directly transferred to a prepacked silica gel column and purified by column chromatography (EtOAc/hexane 1:5 to 1:3) to give the product **3a** (26.9 mg, 87% yield).

*Methyl (R,E)-2-Hydroxy-2-(2-oxo-2-phenylethyl)-4-phenyl-but-3-enoate (**3a**).* Colorless solid, 26.9 mg (87% yield); mp 88−91 °C; $[\alpha]_D^{25}$ = +135.5 (*c* = 0.5 in $CHCl_3$, 84% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.90 (d, *J* = 8.0 Hz, 2H), 7.55−7.21 (m, 8H), 6.87 (d, *J* = 15.6 Hz, 1H), 6.21 (d, *J* = 15.6 Hz, 1H), 4.14 (s, 1H), 3.76 (s, 3H), 3.70 (d, *J* = 18.7 Hz, 1H), 3.48 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 198.0, 174.0, 144.9, 136.1, 133.9, 131.0, 129.6, 128.8, 128.7, 128.5, 128.2, 126.9, 75.8, 53.5, 47.7. ν_{max} (neat): 3547, 2952, 2849, 1725, 1664, 1595, 1284 cm^{-1}. HRMS calcd. for $C_{19}H_{18}NaO_4$ [M + Na]$^+$: 333.1097; Found: 333.1097. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer: t_R = 28.4 min, minor enantiomer: t_R = 42.7 min.

*Ethyl (R,E)-2-Hydroxy-2-(2-oxo-2-phenylethyl)-4-phenyl-but-3-enoate (**3b**).* Colorless oil, 27.7 mg (82% yield); $[\alpha]_D^{25}$ = +92.7 (*c* = 0.8 in $CHCl_3$, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 8.0 Hz, 2H), 7.62−7.24 (m, 8H), 6.93 (d, *J* = 15.6 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 4.30 (dd, *J* = 6.9, 15.1 Hz, 2H), 4.17 (s, 1H), 3.76 (d, *J* = 18.7 Hz, 1H), 3.48 (d, *J* = 17.6 Hz, 1H), 1.30 (t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.9, 174.0, 136.5, 136.3, 133.9, 131.0, 128.9, 128.8, 128.3, 128.2, 126.9, 75.6, 62.6, 47.8, 14.5. ν_{max} (neat): 3514, 3058, 2978, 2931, 1725, 1681, 1596, 1494, 1357, 1286 cm^{-1}. HRMS calcd. for $C_{20}H_{20}NaO_4$ [M + Na]$^+$: 347.1254; Found: 347.1257. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer: t_R = 25.3 min, minor enantiomer: t_R = 42.4 min.

*Isopropyl (R,E)-2-Hydroxy-2-(2-oxo-2-phenylethyl)-4-phenyl-but-3-enoate (**3c**).* Colorless oil, 27.0 mg (80% yield); $[\alpha]_D^{25}$ = +90.8 (*c* = 0.5 in $CHCl_3$, 79% ee.). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.59−7.25 (m, 8H), 6.93 (d, *J* = 15.6 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.18−5.10 (m, 1H), 4.17 (s, 1H), 3.70 (d, *J* = 18.7 Hz, 1H), 3.48 (d, *J* = 17.6 Hz, 1H), 1.30 (d, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.7, 173.5, 136.6, 136.3, 130.9, 128.9, 128.8, 128.3, 128.2, 126.9, 75.6, 70.3, 47.8, 22.1, 21.9. ν_{max} (neat): 3514, 2978, 2849, 1725, 1681, 1596, 1494, 1357,1286 cm^{-1}. HRMS calcd. for $C_{21}H_{22}NaO_4$ [M + Na]$^+$: 361.1410; Found: 361.1424. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer: t_R = 20.9 min, minor enantiomer: t_R = 38.2 min.

*Methyl (R,E)-4-(4-Fluorophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3d**).* Colorless solid, 28.5 mg (87% yield); mp 98−100 °C; $[\alpha]_D^{25}$ = −63.3 (*c* = 0.58 in $CHCl_3$, 81% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.61−7.03 (m, 7H), 6.96 (d, *J* = 15.6 Hz, 1H), 6.21 (d, *J* = 15.6 Hz, 1H), 4.20 (s, 1H), 3.79 (d, *J* = 18.7 Hz, 1H), 3.76 (s, 3H), 3.50 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 198.0, 174.5, 164.3, 161.0, 136.3, 134.0, 132.3 (d, J_{C-F} = 3.3 Hz), 129.9, 128.9, 128.6, 128.4 (d, J_{C-F} = 8.0 Hz), 115.9, 115.6, 75.6, 53.5, 47.8. ν_{max} (neat): 3547, 2951, 2922, 2851, 1729, 1663, 1595, 1284, 1255 cm^{-1}. HRMS calcd. for $C_{19}H_{17}FNaO_4$ [M + Na]$^+$: 351.1003; Found: 351.1010. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 33.1 min, minor enantiomer t_R = 43.7 min.

*Methyl (R,E)-4-(4-Chlorophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3e**).* Colorless solid, 32.3 mg (94% yield); mp 116−118 °C; $[\alpha]_D^{25}$ = +136.4 (*c* = 0.5 in $CHCl_3$, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.96 (d, *J* = 8.3 Hz, 2H), 7.58−7.30 (m, 7 H), 6.91 (d, *J* = 15.6 Hz, 1H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.20 (s, 1H), 3.79 (d, *J* = 18.7 Hz, 1H), 3.76 (s, 3H), 3.50 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.9, 174.3, 136.3, 134.6, 134.0, 129.9, 129.2, 128.9, 128.4, 128.1, 75.6, 53.6, 47.7. ν_{max} (neat): 3517, 2956, 1745, 1658, 1597, 1494, 1343, 1249, 1268 cm^{-1}. HRMS calcd. for $C_{19}H_{17}ClNaO_4$ [M + Na]$^+$: 367.0708; Found: 367.0726. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 33.7 min, minor enantiomer t_R = 44.7 min.

*Methyl (R,E)-4-(4-Bromophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3f**).* Colorless solid, 38.5 mg (99% yield); mp

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124−125 °C; $[\alpha]_D^{25}$ = +84.8 (*c* = 1.0 in $CHCl_3$, 73% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.60−7.43 (m, 5H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 15.6 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.20 (s, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 17.5 Hz, 1H), 3.50 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.9, 174.3, 135.1, 134.0, 131.9, 130.0, 129.3, 128.9, 128.5, 128.4, 122.1, 75.7, 53.6, 47.7. ν_{max} (neat): 3543, 2948, 1729, 1680, 1579, 1487,1360, 1280, 1257 cm^{-1}. HRMS calcd. for $C_{19}H_{17}BrNaO_4$ $[M + Na]^+$: 411.0202; Found: 411.0230. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 36.7 min, minor enantiomer t_R = 49.0 min.

*Methyl (R,E)-2-Hydroxy-4-(4-methylphenyl)-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3g**).* Colorless solid, 25.2 mg (78% yield); mp 82−84 °C; $[\alpha]_D^{25}$ = +90.2 (*c* = 0.5 in $CHCl_3$, 87% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 8.5 Hz, 2H), 7.59−7.12 (m, 7H), 6.94 (d, *J* = 15.7 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.24 (s, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 17.5 Hz, 1H), 3.50 (d, *J* = 17.4 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 198.1, 174.6, 138.1, 136.4, 133.9, 133.3, 131.0, 129.5, 128.9, 128.4, 127.5, 126.9, 75.7, 53.5. 47.7, 30.1, 21.6. ν_{max} (neat): 3515, 3025, 2956, 2914, 2852, 2019, 1720, 1675, 1573, 1490, 1350, 1285, 1258 cm^{-1}. HRMS calcd. for $C_{20}H_{20}NaO_4$ $[M + Na]^+$: 347.1254; Found: 347.1262. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (75:25 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 10.5 min, minor enantiomer t_R = 15.5 min.

*Methyl (R,E)-2-Hydroxy-4-(4-methoxyphenyl)-2-(2-oxo-2-phenylethyl)but-3-enoate (**3h**).* Colorless solid, 24.4 mg (72% yield); mp 94−96 °C; $[\alpha]_D^{25}$ = +57.0 (*c* = 0.5 in $CHCl_3$, 86% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 6.9 Hz, 2H), 6.95−6.82 (m, 3H), 6.17 (d, *J* = 15.7 Hz, 1H), 4.17 (s, 1H), 3.82 (s, 6H), 3.76 (d, *J* = 16.9 Hz, 1H), 3.53 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 198.2, 174.7, 159.6, 136.4, 133.9, 130.4, 128.9, 128.4, 128.2, 126.3, 114.2, 75.7, 55.6, 53.5, 47.9. ν_{max} (neat): 3511, 2958, 2921, 2850, 1726, 1685, 1578, 1447, 1341, 1287, 1239 cm^{-1}. HRMS calcd. for $C_{20}H_{20}NaO_5$ $[M + Na]^+$: 363.1203; Found: 363.1216. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (75:25 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 15.2 min, minor enantiomer t_R = 22.5 min.

*Methyl (R,E)-4-(2-Chlorophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3i**).* Colorless solid, 29.2 mg, (85% yield); mp 129−130 °C; $[\alpha]_D^{25}$ = +128.8 (*c* = 0.5 in $CHCl_3$, 87% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.3 Hz, 2H), 7.58−7.30 (m, 7H), 6.91 (d, *J* = 15.6 Hz, 1H), 6.31 (d, *J* = 15.6 Hz, 1H), 4.22 (s, 1H), 3.87 (s, 3H), 3.79 (d, *J* = 18.7 Hz, 1H), 3.55 (d, *J* = 17.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.6, 174.4, 137.9, 136.0, 135.2, 133.8, 130.2, 128.8, 128.5, 128.4, 128.3, 126.9, 75.6, 53.6, 47.9. ν_{max} (neat): 3517, 2956, 1745, 1658, 1597, 1494, 1343, 1249, 1268 cm^{-1}. HRMS calcd. for $C_{19}H_{17}ClNaO_4$ $[M + Na]^+$: 367.0708, Found: 367.0712. The ee value was determined by chiral stationary phase HPLC using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 24.4 min, minor enantiomer t_R = 32.9 min.

*Methyl (R,E)-4-(2-Bromophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)-but-3-enoate (**3j**).* Colorless solid, 30.2 mg (78% yield); mp 134−135 °C; $[\alpha]_D^{25}$ = +120.0 (*c* = 0.5 in $CHCl_3$, 91% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.10 (d, *J* = 8.0 Hz, 2H), 7.78−7.75 (m, 3H), 7.44−7.26 (m, 5H), 6.36 (d, *J* = 15.6 Hz, 1H), 4.31 (s, 1H), 3.98 (s, 3H), 3.78 (d, *J* = 17.5 Hz, 1H), 3.66 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.8, 174.3, 138.3, 136.3, 134.0, 131.1, 130.1, 129.8, 129.6, 128.9, 128.4, 125.8, 122.9, 75.6, 53.6, 47.7. ν_{max} (neat): 3543, 2948, 1729, 1680, 1579, 1487,1360, 1280, 1257 cm^{-1}. HRMS calcd. for $C_{19}H_{17}BrNaO_4$ $[M + Na]^+$: 411.0202; Found: 411.0200. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 26.4 min, minor enantiomer t_R = 35.2 min.

*Methyl (R,E)-4-(3-Bromophenyl)-2-hydroxy-2-(2-oxo-2-phenylethyl)but-3-enoate (**3k**).* Colorless solid, 29.4 mg (76% yield); mp 128−130 °C; $[\alpha]_D^{25}$ = +120.6 (*c* = 0.5 in $CHCl_3$, 81% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.60−7.19 (m, 7H), 6.89 (d, *J* = 15.6 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.18 (s, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 17.5 Hz, 1H), 3.50 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.8, 174.3, 138.3, 136.3, 134.0, 131.1, 130.1, 129.8, 129.6, 128.9, 128.4, 125.8, 122.9, 75.6, 53.6, 47.7. ν_{max} (neat): 3543, 2948, 1729, 1680, 1579, 1487, 1360, 1280, 1257 cm^{-1}. HRMS calcd. for $C_{19}H_{17}BrNaO_4$ $[M + Na]^+$: 411.0208; Found: 411.0201. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 27.7 min, minor enantiomer t_R = 37.8 min.

*Methyl (R,E)-2-[2-(4-Fluorophenyl)-2-oxoethyl]-2-hydroxy-4-phenylbut-3-enoate (**3l**).* Colorless solid, 28.2 mg (86% yield); mp 92−93 °C; $[\alpha]_D^{25}$ = +104.2 (*c* = 0.5 in $CHCl_3$, 82% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.12−7.28 (m, 9H), 7.00 (d, *J* = 15.6 Hz, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 4.27 (s, 1H), 3.96 (s, 3H), 3.79 (d, *J* = 18.9 Hz, 1H), 3.60 (d, *J* = 17.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.4, 174.5, 167.9, 164.5, 136.0, 132.9, 131.2, 131.0, 128.8, 128.5 (d, J_{C-F} = 8.0 Hz), 126.9, 115.9 (d, J_{C-F} = 21.4 Hz), 75.7, 53.6, 47.7. ν_{max} (neat): 3547, 2951, 2922, 2851, 1729, 1663, 1595, 1284, 1255 cm^{-1}. HRMS calcd. for $C_{19}H_{17}FNaO_4$ $[M + Na]^+$: 351.1003, Found: 351.1020. The ee value was determined by chiral stationary phase HPLC using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 10.2 min, minor enantiomer t_R = 16.8 min.

*Methyl (R,E)-2-[2-(4-Chlorophenyl)-2-oxoethyl]-2-hydroxy-4-phenylbut-3-enoate (**3m**).* Colorless solid, 30.2 mg (88% yield); mp 102−104 °C; $[\alpha]_D^{25}$ = +136.4 (*c* = 0.5 in $CHCl_3$, 83% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.83 (d, *J* = 8.3 Hz, 2H), 7.40−7.20 (m, 7H), 6.88 (d, *J* = 15.7 Hz, 1H), 6.21 (d, *J* = 15.6 Hz, 1H), 4.05 (s, 1H), 3.76 (s, 3H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.42 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3): δ (ppm) 196.7, 174.4, 140.4, 136.0, 134.7, 131.2, 129.8, 129.2, 128.8, 128.4, 128.3, 126.9, 75.6, 53.6, 47.7. ν_{max} (neat): 3517, 2956, 1745, 1658, 1597, 1494, 1343, 1249, 1268 cm^{-1}. HRMS calcd. for $C_{19}H_{17}ClNaO_4$ $[M + Na]^+$: 367.0708; Found: 367.0720. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (70:30 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 12.8 min, minor enantiomer t_R = 19.9 min.

*Methyl (R,E)-2-[2-(4-Bromophenyl)-2-oxoethyl]-2-hydroxy-4-phenylbut-3-enoate (**3n**).* Colorless solid, 32.9 mg (85% yield); mp 112−113 °C; $[\alpha]_D^{25}$ = +88.4 (*c* = 1.0 in $CHCl_3$, 81% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.43−7.29 (m, 5H), Hz, 6.89 (d, *J* = 15.8 Hz, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 4.10 (s, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 17.5 Hz, 1H), 3.50 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.9, 174.4, 136.0, 135.1, 132.2, 129.9, 128.8, 128.4, 126.9, 75.6, 53.6, 47.7. ν_{max} (neat): 3543, 2948, 1729, 1680, 1579, 1487, 1360, 1280, 1257 cm^{-1}. HRMS calcd. for $C_{19}H_{17}BrNaO_4$ $[M + Na]^+$: 411.0202; Found: 411.0209. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 13.9 min, minor enantiomer t_R = 21.5 min.

*Methyl (R,E)-2-Hydroxy-2-[2-(4-nitrophenyl)-2-oxoethyl]-4-phenylbut-3-enoate (**3o**).* Colorless solid, 26.9 mg (76% yield); mp 150−151 °C; $[\alpha]_D^{25}$ = +80.6 (*c* = 0.5 in $CHCl_3$, 75% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.31 (d, *J* = 8.6 Hz, 2H), 8.10 (d, *J* = 8.6 Hz, 2H), 7.42−7.25 (m, 5H), 6.94 (d, *J* = 15.6 Hz, 1H), 6.28 (d, *J* = 15.6 Hz, 1H), 4.00 (s, 1H), 3.85 (s, 3H), 3.75 (d, *J* = 17.5 Hz, 1H), 3.58 (d, *J* = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.2, 174.3, 150.7, 140.8, 135.9, 131.4, 129.4, 128.8, 128.4, 128.2, 126.9, 124.1, 75.5, 53.7, 48.2. ν_{max} (neat): 3543, 2948, 1729, 1680, 1579,1487,1360, 1280, 1257 cm^{-1}. HRMS calcd. for $C_{19}H_{17}NNaO_6$ $[M + Na]^+$: 378.0948; Found: 378.0963. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (70:30 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 20.3 min, minor enantiomer t_R = 39.1 min.

*Methyl (R,E)-2-Hydroxy-2-[2-oxo-2-(4-methylphenyl)ethyl]-4-phenylbut-3-enoate (**3p**).* Colorless solid, 23.3 mg (72% yield); mp 90−92 °C; $[\alpha]_D^{25}$ = +80.6 (*c* = 0.5 in $CHCl_3$, 80% ee). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.87 (d, *J* = 8.5 Hz, 2H), 7.43−7.26 (m, 7H),

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6.94 (d, J = 15.7 Hz, 1H), 6.28 (d, J = 15.7 Hz, 1H), 4.24 (s, 1H), 3.82 (s, 3H), 3.75 (d, J = 17.5 Hz, 1H), 3.50 (d, J = 17.5 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 197.7, 174.5, 144.9, 136.1, 133.9, 131.0, 129.6, 128.8, 128.5, 128.2, 126.9, 75.8, 53.5, 47.7. ν_{max} (neat): 3515, 3025, 2956, 2914, 2852, 2019, 1720, 1675, 1573, 1490, 1350, 1285, 1258 cm^{-1}. HRMS calcd. for $C_{20}H_{20}NaO_4$ [M + Na]$^+$: 347.1254; Found: 347.1261. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 40.6 min, minor enantiomer t_R = 46.7 min.

*Methyl (R,E)-2-Hydroxy-2-[2-(4-methoxyphenyl)-2-oxoethyl]-4-phenylbut-3-enoate (**3q**).* Colorless solid, 23.8 mg (70% yield); mp 102−103 °C; $[\alpha]_D^{25}$ = +90.8 (c = 0.5 in $CHCl_3$, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.93 (d, J = 8.8 Hz, 2H), 7.44−7.26 (m, 7H), 6.95 (d, J = 15.7 Hz, 1H), 6.30 (d, J = 15.7 Hz, 1H), 4.29 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.78 (d, J = 17.5 Hz, 1H), 3.46 (d, J = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 198.2, 174.7, 159.6, 136.4, 133.9, 130.4, 128.9, 128.2, 126.3, 114.2, 75.7, 55.6, 53.5, 47.9. ν_{max} (neat): 3511, 2958, 2921, 2850, 1726, 1685, 1578, 1447, 1341, 1287, 1239 cm^{-1}. HRMS calcd. for $C_{20}H_{20}NaO_5$ [M + Na]$^+$: 363.1203; Found: 363.1218. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (90:10 hexanes/*i*-PrOH at 0.7 mL/min): major enantiomer t_R = 21.3 min, minor enantiomer t_R = 25.9 min.

*Methyl (R,E)-2-[2-(2-Chlorophenyl)-2-oxoethyl]-2-hydroxy-4-phenylbut-3-enoate (**3r**).* Colorless solid, 25.8 mg (75% yield); mp 120−122 °C; $[\alpha]_D^{25}$ = +80.7 (c = 0.5 in $CHCl_3$, 50% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.58 (d, J = 7.1 Hz, 1H), 7.43−7.26 (m, 8H), 6.92 (d, J = 15.7 Hz, 1H), 6.25 (d, J = 15.7 Hz, 1H), 4.08 (s, 1H), 3.86 (s, 3H), 3.80 (d, J = 17.4 Hz, 1H), 3.50 (d, J = 17.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 200.4, 132.6, 131.1, 130.9, 129.8, 128.8, 128.4, 128.3, 127.2, 126.9, 75.9, 53.6, 51.8. ν_{max} (neat): 3517, 2956, 1745, 1658, 1597, 1494, 1343, 1249, 1268 cm^{-1}. HRMS calcd. for $C_{19}H_{17}ClNaO_4$ [M + Na]$^+$: 367.0708; Found: 367.0710. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (70:30 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 9.4 min, minor enantiomer t_R = 11.2 min.

*Methyl (R,E)-2-[2-(3-Chlorophenyl)-2-oxoethyl]-2-hydroxy-4-phenylbut-3-enoate (**3s**).* Colorless solid, 30.6 mg (89% yield). mp 116−117 °C; $[\alpha]_D^{25}$ = +75.8 (c = 0.5 in $CHCl_3$, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (m, 2H), 7.83 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.46−7.26 (m, 5H), 6.92 (d, J = 15.7 Hz, 1H), 6.28 (d, J = 15.6 Hz, 1H), 4.08 (s, 1H), 3.83 (s, 3H), 3.74 (d, J = 17.4 Hz, 1H), 3.48 (d, J = 17.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.6, 174.4, 137.9, 136.0, 135.2, 133.8, 131.2, 130.2, 128.8, 128.5, 128.4, 126.9, 126.5, 75.6, 53.6, 47.9. ν_{max} (neat): 3517, 2956, 1745, 1658, 1597, 1494, 1343, 1249, 1268 cm^{-1}. HRMS calcd. for $C_{19}H_{17}ClNaO_4$ [M + Na]$^+$: 367.0708; Found: 367.0712. The ee value was determined by HPLC analysis using a ChiralPak AD-H column (70:30 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer t_R = 8.8 min, minor enantiomer t_R = 12.7 min.

Typical Procedure for the Aldol Reaction of Cyclic Ketones and Phenylglyoxal Monohydrate. To a mixture of phenylglyoxal monohydrate (**20a**, 30.4 mg, 0.20 mmol) and the quinidine-derived catalyst **16** (12.6 mg, 0.020 mmol, 10 mol %) was added cyclohexanone (**21a**, 196.0 mg, 2.0 mmol) at rt. After the reaction mixture was stirred for 5 days at this temperature, it was directly transferred to a prepacked silica gel column and purified by column chromatography (EtOAc/hexane 1:5 to 1:3) to give the aldol product.

*(R)-2-[(S)-1-Hydroxy-2-oxo-2-phenylethyl]cyclohexanone (**22a**).*[7c,8a] Colorless oil, 45.5 mg (98% yield), dr: 88:12. $[\alpha]_D^{25}$ = +26.4 (c = 1.0, MeOH, 94% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56−1.68 (m, 2H), 1.92−2.03 (m, 3H), 2.15−2.37 (m, 3H), 2.97−3.05 (m, 1H), 4.06 (br s, 1H), 4.83 (s, 1H), 7.45−7.60 (m, 3H), 7.83−7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 26.8, 30.7, 42.1, 53.9, 63.5, 74.6, 128.5, 128.7, 133.2, 135.3, 200.3, 211.3. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 20.3 min; minor enantiomer: t_R = 42.3 min.

*(R)-2-[(S)-1-Hydroxy-2-(4-fluorophenyl)-2-oxoethyl]cyclohexanone (**22b**).* Colorless oil, 46.6 mg (93% yield), dr: 88:12. $[\alpha]_D^{25}$ = +22.5 (c = 0.90, MeOH, 95% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62−2.41 (m, 8H), 3.00−3.08 (m, 1H), 4.03 (br, 3H), 4.76 (d, J = 3.3 Hz, 1H), 7.12 (t, J = 8.7 Hz, 2H), 7.96 (dd, J = 5.4, 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 27.3, 31.1, 42.5, 54.1, 75.0, 115.9 (d, J_{C-F} = 21.8 Hz), 131.6 (d, J_{C-F} = 9.2 Hz), 164.1, 167.5, 198.7, 211.1. ν_{max} (neat): 3496, 2942, 2855, 1699, 1669, 1595, 1507, 1229, 1110 cm^{-1}. Anal. calcd. for $C_{14}H_{15}FO_3$: C, 67.19; H, 6.04; Found: C, 67.37; H, 6.11. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 19.5 min; minor enantiomer: t_R = 43.8 min.

*(R)-2-[(S)-1-Hydroxy-2-(4-chlorophenyl)-2-oxoethyl]cyclohexanone (**22c**).* Colorless oil, 51.2 mg (96% yield), dr: 82:18. $[\alpha]_D^{25}$ = +10.9 (c = 0.96, MeOH, 92% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61−2.40 (m, 8H), 2.99−3.07 (m, 1H), 4.01 (br, 1H), 4.73 (d, J = 3.6 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 27.0, 30.7, 42.1, 53.7, 74.8, 128.7, 129.2, 130.0, 139.3, 198.8, 211.5. ν_{max} (neat): 3475, 2937, 2856, 1698, 1664, 1589, 1397, 1287, 1095 cm^{-1}. Anal. calcd. for $C_{14}H_{15}ClO_3$: C, 63.04; H, 5.67; Found: C, 63.16; H, 5.54. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 16.7 min; minor enantiomer: t_R = 34.4 min.

*(R)-2-[(S)-1-Hydroxy-2-(4-bromophenyl)-2-oxoethyl]cyclohexanone (**22d**).* Colorless solid, 59.1 mg (95% yield), dr: 85:15, mp 134 °C. $[\alpha]_D^{25}$ = +14.6 (c = 0.93, MeOH, 93% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57−2.37 (m, 8H), 2.97−3.04 (m, 1H), 4.00 (br, 1H), 4.70 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 26.9, 30.6, 42.1, 53.6, 74.7, 128.0, 130.1, 131.6, 133.8, 199.1, 211.4. ν_{max} (neat): 3467, 2944, 2860, 1699, 1659, 1604, 1395, 1268, 1111 cm^{-1}. Anal. calcd. for $C_{14}H_{15}BrO_3$: C, 54.04; H, 4.86; Found: C, 54.04; H, 4.91. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 17.6 min; minor enantiomer: t_R = 35.1 min.

*(R)-2-[(S)-1-Hydroxy-2-(4-methylphenyl)-2-oxoethyl]cyclohexanone (**22e**).* Colorless oil, 47.8 mg (97% yield), dr: 88:12. $[\alpha]_D^{25}$ = +30.2 (c = 0.87, MeOH, 94% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58−2.50 (m, 8H), 2.38 (s, 3H), 2.94−3.01 (m, 1H), 4.02 (br, 1H), 4.80 (d, J = 3.9 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 24.7, 26.8, 30.7, 42.1, 54.0, 74.2, 128.5, 129.1, 132.3, 143.8, 199.4, 210.8. ν_{max} (neat): 3462, 2936, 2857, 1697, 1660, 1585, 1395, 1287, 1111 cm^{-1}. Anal. calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 72.99; H, 7.31. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 18.6 min; minor enantiomer: t_R = 48.8 min.

*(R)-2-[(S)-1-Hydroxy-2-(4-methoxyphenyl)-2-oxoethyl]cyclohexanone (**22f**).* Colorless oil, 48.7 mg (93% yield), dr: 88:12. $[\alpha]_D^{25}$ = +37.6 (c = 0.95, MeOH, 94% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59−2.37 (m, 8H), 2.94−3.01 (m, 1H), 3.84 (s, 3H), 4.09 (br, 1H), 4.82 (d, J = 3.9 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 27.0, 30.9, 42.2, 54.1, 55.4, 74.0, 113.7, 127.7, 130.8, 163.4, 198.0, 211.2. ν_{max} (neat): 3445, 2940, 2859, 1699, 1652, 1596, 1253, 1173, 1110 cm^{-1}. Anal. calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92; Found: C, 68.73; H, 6.79. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 27.2 min; minor enantiomer: t_R = 91.6 min.

*(R)-2-[(S)-1-Hydroxy-2-(3-chlorophenyl)-2-oxoethyl]cyclohexanone (**22g**).* Colorless oil, 50.1 mg (94% yield), dr: 80:20. $[\alpha]_D^{25}$ = +16.9 (c = 1.0, MeOH, 94% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55−2.32 (m, 8H), 2.96−3.03 (m, 1H), 4.00 (br, 1H), 4.67 (s, 1H), 7.301−7.50 (m, 2H), 7.70 (dd, J = 0.9, 7.5 Hz, 1H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 26.7, 30.4, 41.9, 53.5, 74.7, 126.5, 128.4, 129.6, 132.6, 134.4, 136.6, 198.8, 211.3. ν_{max} (neat): 3468, 2937, 2863, 1684, 1570, 1422, 1211, 1127 cm^{-1}. Anal. calcd. for $C_{14}H_{15}ClO_3$: C, 63.04; H, 5.67; Found: C, 63.32; H, 5.81. The ee value was

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determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 19.2 min; minor enantiomer: t_R = 29.4 min.

*(R)-2-[(S)-1-Hydroxy-2-naphthalen-2-yl-2-oxoethyl]cyclohexanone (**22h**).* Colorless oil, 54.2 mg (96% yield), dr: 88:12. $[\alpha]_D^{25}$ = +10.3 (*c* = 1.0, MeOH, 95% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59−1.74 (m, 2H), 1.90−2.37 (m, 6H), 3.04−3.11 (m, 1H), 4.15 (br, 1H), 4.96 (d, *J* = 3.6 Hz, 1H), 7.51−7.62 (m, 2H), 7.84−7.96 (m, 4H), 8.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 6.9, 30.8, 42.1, 54.1, 74.5, 124.2, 126.7, 127.6, 128.4, 129.4, 130.0, 132.2, 132.4, 135.4, 200.0, 211.2. ν_{max} (neat): 3429, 2934, 2862, 1675, 1626, 1597, 1276, 1185, 1113 cm^{-1}. Anal. calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; Found: C, 76.77; H, 6.56. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 23.6 min; minor enantiomer: t_R = 65.4 min.

*(R)-2-[(S)-1-Hydroxy-2-oxo-2-phenylethyl]cyclopentanone (**22i**).* Colorless oil, 40.6 mg (93% yield), dr: 85:15. $[\alpha]_D^{25}$ = +29.4 (*c* = 1.0, MeOH, 59% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61−2.50 (m, 7H), 3.87 (d, *J* = 6.0 Hz, 1H), 5.65 (dd, *J* = 2.1, 6.0 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.92 (dd, *J* = 1.5, 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 21.4, 38.3, 52.3, 71.5, 128.3, 128.9, 132.8, 134.1, 200.3, 217.3. ν_{max} (neat): 3462, 2941, 2869, 1660, 1604, 1394, 1267, 1110 cm^{-1}. Anal. calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; Found: C, 71.32; H, 6.40. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 55.6 min; minor enantiomer: t_R = 80.2 min.

*(R)-2-[(S)-1-Hydroxy-2-oxo-2-phenylethyl]cycloheptanone (**22j**).* Colorless oil, 42.8 mg (87% yield), dr: 85:15. $[\alpha]_D^{25}$ = +19.6 (*c* = 0.8, MeOH, 90% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33−1.50 (m, 3H), 1.81−2.06 (m, 5H), 2.45−2.51 (m, 2H), 3.02−3.08 (m, 1H), 4.19 (d, *J* = 6.9 Hz, 1H), 4.96 (dd, *J* = 3.0, 6.6 Hz, 1H), 7.43−7.59 (m, 3H), 7.88 (d, *J* = 11.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 28.9, 29.0, 29.7, 44.3, 55.3, 77.1, 128.5, 133.2, 134.6, 200.0, 215.4. ν_{max} (neat): 3431, 2923, 2855, 1696, 1664, 1449, 1270, 1083 cm^{-1}. Anal. calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 72.98; H, 7.31. The ee value was determined by chiral stationary phase HPLC analysis using a ChiralCel AS column (91.5:8.5 hexanes/*i*-PrOH at 0.8 mL/min): major enantiomer: t_R = 22.3 min; minor enantiomer: t_R = 32.4 min.

*(R)-2-[(S)-1-Hydroxy-2-oxo-2-phenylethyl]cyclooctanone (**22k**).* Colorless oil, 44.3 mg (85% yield), dr: 80:20. $[\alpha]_D^{25}$ = +18.6 (*c* = 0.8, MeOH, 71% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16−2.11 (m, 9H), 2.37−2.47 (m, 2H), 2.68−2.76 (m, 1H), 3.17−3.24 (m, 1H), 4.55 (br, 1H), 5.03 (d, *J* = 3.0 Hz, 1H), 7.16−7.28 (m, 2H), 7.44−7.61 (m, 2H), 8.00 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 24.8, 25.3, 28.2, 31.8, 44.1, 50.2, 77.5, 128.4, 128.9, 133.4, 134.7, 199.7, 221.3. ν_{max} (neat): 3405, 2926, 1677, 1597, 1447, 1160, 1099 cm^{-1}. Anal. calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; Found: C, 73.51; H, 7.61. The ee value of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (90:10 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 26.8 min; minor enantiomer: t_R = 42.7 min.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystal data (including CIF) for compounds **3f** and **22d**. Copies of NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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