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L-Proline amide-catalyzed direct asymmetric aldol reaction of aldehydes with chloroacetone

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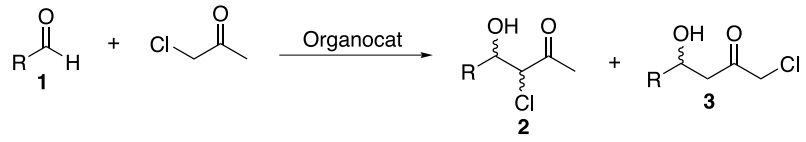
Abstract—L-Proline amides were evaluated for catalyzing the direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone. The presence of 30 mol% (*S*)-pyrrolidine-2-carboxylic acid (2,4,6-trimethyl-phenyl)-amide catalyzed the direct aldol reactions of a range of aldehydes with chloroacetone to give *anti*-α-chloro-β-hydroxyketones with high regio-, diastereo- and enantioselectivity.

1. Introduction

The aldol reaction has emerged as one of the most powerful carbon–carbon bond-forming reactions.[1] The asymmetric direct aldol reaction, because of its atom-economy,[2] has recently received great attention, and thus many chiral catalyst including biocatalysts,[3] transition metal complexes,[4–6] and organocatalysts[7–12] have been discovered for this transformation. The direct aldol reaction of an unsymmetric ketone with an aldehyde principally generates the β-hydroxyketone as a mixture of its regio-, diastereo-, and enantiomers. It is quite difficult to control the reaction to produce a single isomer. β-Hydroxyketones have been used as donors in the direct aldol reactions promoted by biocatalysts,[3] chiral transition metal complexes,[4b,5b] and organocatalysts.[7i–k,11] Both 1,2- and 1,4-diols with high enantioselectivities can be regioselectively approached under suitable reaction conditions. Very recently, Zhong and Barbas reported a L-prolinol catalyzed direct aldol reaction of fluoroacetone with aldehydes to regio- and diastereoselectively afford *anti*-α-fluoro-β-hydroxyaketones with good enantioselectivities (up to 87% ee).[13] However, the aldol reaction with chloroacetone as a donor has not yet been documented. Optically active α-chlorocarbonyl compounds are very useful in organic synthesis, the development of efficient method to access these molecules is therefore, of great importance. An important advance has been made on the asymmetric catalytic electronic α-chloronation of carbonyl compounds, which is considered a direct method to obtain optically active α-chloroketone or -esters.[14] The direct aldol reaction of chloroacetone with aldehydes provides an alternative to α-chloronation for preparing α-chloroketones (Scheme 1). Encouraged by our recent success in the L-proline amide catalyzed direct aldol reactions,[10] we herein extend the application of these organocatalysts (Fig. 1) to the direct aldol reaction of chloroacetone. As a result, high enanantioselectivities of up to 98% ee were provided for



Scheme 1. Aldol reactions of aldehydes with chloroacetone.

Keywords: Organocatalyst; L-proline amides; Direct aldol reaction; Asymmetric catalysis; Chloroacetone.
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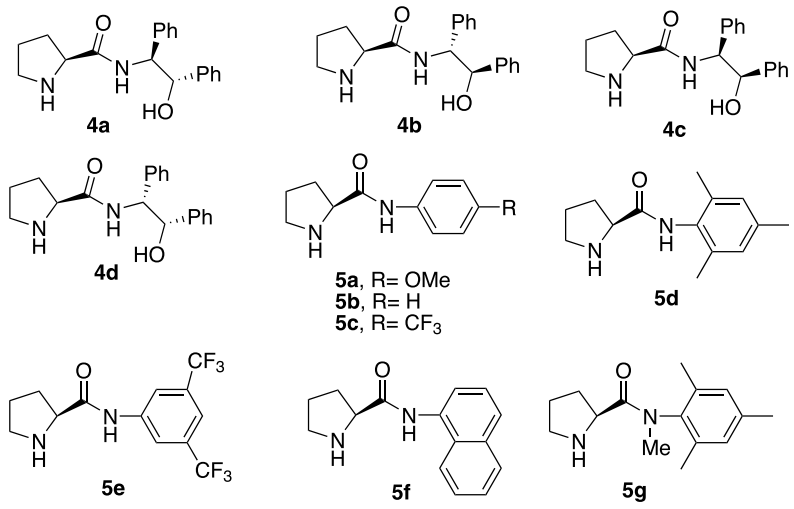


Figure 1. L-proline amides evaluated in this study.

anti-α-chloro-β-hydroxyketones by an optimal L-proline amide.

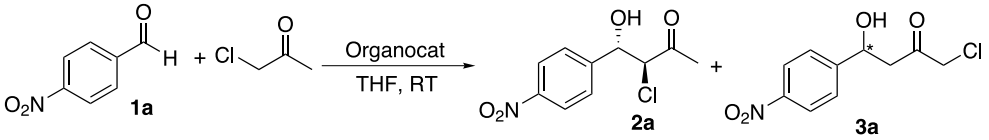
2. Results and discussion

2.1. The direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone catalyzed by L-proline amides 4 and 5: catalyst screening

The catalytic efficiency of L-proline amides **4** and **5** was evaluated by the direct aldol reaction of 4-nitrobenzaldehyde with chloroacetone at room temperature in THF. The results are summarized in Table 1.

All the L-proline amides catalyzed the reaction to give *anti*-3-chloro-4-hydroxy -4-(4′-nitro-phenyl)-butan-2-one (**2a**) as a favored product, however, low to moderate yields for **2a** were obtained probably due to low reactivity of chloroacetone relative to hydroxyacetone[7i–k,11] and fluoroacetone.[13] The L-proline amides **4a** and **4c**, which exhibited higher enantioselectivity than their diastereomers **4b** and **4d** at catalyzing the direct aldol reaction of aldehydes with acetone, however, catalyzed the reaction of 4-nitrobenzaldehyde with chloroacetone in lower yields and enantioselectivities (entries 1–4). We previously reported that simple L-proline amides such as **5a**–**g** catalyzed the direct aldol reaction of 4-nitrobenzaldehyde with acetone with very low enantioselectivity (up to 45% ee). Surprisingly, most of them showed higher enantioselectivities than **4a**–**d**, of which **5a**–**d** mediated the reaction with higher than 90% ees (entries 5–8). Results from organocatalysts **5a**–**c** demonstrated that the electron-nature of the substituent on the phenyl group of L-proline amide does not affect the enantiochemical outcome dramatically (entries 5–7). The sterical bulkiness of the aryl group in the organocatalyst trends to be an important factor to influence the reaction selectivity, for example, **5d** enabled the best result in the

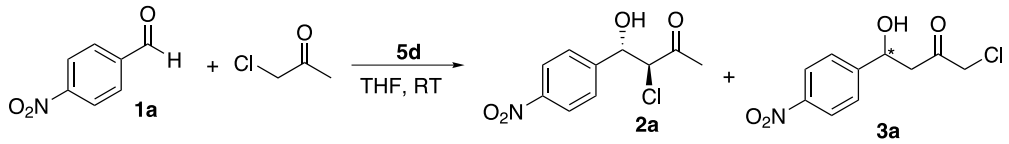
Table 1. Screening organocatalysts **4** and **5**[a]



Entry	Catalyst	Yield (%)[b]	Regioselectivity (**2a**/**3a**)[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	**4a**	23	4:1	3:1	82
2	**4b**	37	5:1	9:2	89
3	**4c**	19	8:1	3:1	78
4	**4d**	36	4:1	9:2	88
5	**5a**	25	4:1	6:1	92
6	**5b**	24	4:1	9:1	90
7	**5c**	29	3:1	9:1	92
8	**5d**	42	7:1	12:1	94
9	**5e**	33	5:1	9:2	87
10	**5f**	28	>20:1	12:1	86
11	**5g**	Trace	—	—	—
12	L-proline	8	—	—	74

[a] Unless indicated otherwise, the reaction of aldehyde (0.5 mmol) with chloroacetone (l.0 mL) in THF (1.0 mL) in the presence of 20 mol% organocatalyst.
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

Table 2. Effect of catalyst loading on the reaction[a]



Entry	Amount of **5d** (mol%)	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	20	42	7:1	12:1	94
2	30	57	7:1	7:1	91
3	40	56	7:1	5:1	89
4	45	55	7:1	5:1	88
5	50	53	6:1	4:1	86

[a] The reaction of aldehyde (0.5 mmol) with chloroacetone (l mL) was performed in THF (1.0 mL).
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

model reaction (entry 8). The proton on the amide function of the organocatalyst determines the catalytic efficacy. Thus, small organic molecule **5g**, which was derived from **5d** by a methylation, failed to catalyze the reaction (entry 11). However, the reaction proceeded incompletely in the presence of 20 mol% L-proline to give **2a** in only 8% yield with 74% ee (entry 12).

2.2. Optimization of reaction conditions

L-proline amide **5d** was found to be the best for the reaction in terms of enantioselectivity among all the organocatalysts tested (Table 1), but it gave only moderate yield. In principle, variation of the catalyst loading will change the reaction conversion. We therefore, investigated the relationship between the amount of organocatalyst **5d** and reaction conversion, and hoped that the yield of the desired product **2a** would be improved by using increased amounts of **5d**.

The reaction of 4-nitrobenzaldehyde with chloroacetone was performed in THF at room temperature with various amounts of **5d**. The results are recorded in Table 2. The yield was increased to 57% by using 30 mol% **5d** (entry 2), however, the yield could not be further improved as the catalyst loading was increased (entries 3–5). In addition to that, both diastereo- and enantioselectivity dropped to some degree with the increase of the catalyst loading (entries 1–5). In terms of the yield and enantioselectivity, 30 mol% of **5d** can be considered an optimal catalyst loading.

Another possibility to enhance the conversion is variation of the amount of chloroacetone. In the presence of 30 mol% catalyst **5d**, the direct aldol reaction of 4-nitrobenzaldehyde with different amounts of chloroacetone was carried out. As shown in Table 3, the yield, diastereo- and enantioselectivity are independent on the amount of chloroacetone. However, regioselectivity gradually decreases as the amount of chloroacetone increases (entries 1–5). Study on the temperature effect revealed that the yield could be improved by performing the reaction at low temperature (entries 6–8). However, both diastereo- and enantioselectivity dropped as the decrease in the reaction temperature. For example, when the reaction was carried on at −10 °C, significantly high yield of 76% was isolated, but the dr of *anti*/*syn* was only 2:1 and enantioselectivity was decreased to 87% ee (entry 8).

In organocatalyzed direct aldol reactions, the solvent affects the reaction performance dramatically. Some common organic solvents were therefore, examined for the reaction of chloroacetone with 4-nitrobenzaldehyde. The related results are presented in Table 4. It was found that the use of THF, diethyl ether or 1-dioxane as a solvent gave better results in terms of both yield and enantioselectivity than the use of other organic solvents (entries 1–7). Performing the reaction in a polar solvent, for example, in either CH_3CN or DMSO, provided an excellent enantioselectivity, but a poor yield (entries 4 and 5). Neither chloroform nor toluene is a good solvent for the reaction. Although fair yields were

Table 3. Effects of the amount of chloroacetone and the reaction temperature[a]

Entry	Amount of chloroacetone (mL)	Temperature (°C)	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	0.4	25	56	17:1	6:1	89
2	0.6	25	56	10:1	7:1	89
3	0.8	25	56	7:1	7:1	89
4	1	25	57	7:1	7:1	91
5	2	25	50	8:1	6:1	89
6	1	10	58	5:1	5:1	89
7	1	0	68	5:1	3:1	88
8	1	−10	76	6:1	2:1	87

[a] The reaction was performed on a 0.5 mmol scale in THF (1.0 mL) in the presence of 30 mol% **5d**.
[b] Isolated yield of **2a**.
[c] The ratio of **2a**/**3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^{1}H NMR.
[e] Determined by HPLC.

Table 4. Solvent effect[a]

Entry	Solvent	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	THF	57	7:1	7:1	91
2	Et_2O	45	8:1	5:1	90
3	Dioxane	34	5:1	5:1	90
4	CH_3CN	23	4:1	4:1	90
5	DMSO	22	9:1	6:1	92
6	$CHCl_3$	33	5:1	3:1	74
7	Toluene	49	7:1	2:1	79

[a] The reaction of 4-nitrobenzaldehyde (0.5 mmol) with chloroacetone (1 mL) was performed in a solvent (1.0 mL) in the presence of 30 mol% **5d** at room temperature.
[b] Isolated yield of **2a**.
[c] The ratio of **2a/3a** is that of the diastereomers/regioisomer, and calculated on the basis of the isolated yields of **2a** and **3a**.
[d] Determined by ^1H NMR.
[e] Determined by HPLC.

observed when the reaction were carried out in chloroform and toluene, diastereo- and enantioselectivity were much lower than those with THF as the solvent (entries 6 and 7).

2.3. Scope and limitations

Under the optimal conditions, a range of aldehydes including aromatic and aliphatic ones were examined to react with chloroacetone. As demonstrated in Table 5, the organocatalyst **5d** exhibited generally excellent enantioselectivities ranging from 91–98% ee for most of aldehydes tested, with exception of the case involving 2-chlorobenzaldehyde, in which 86% ee was provided (entry 5). The *ortho*-substituted benzaldehydes reacted much more diastereoselectively than *para*- and *meta*-substituted benzaldehydes with chloroacetone (entries 1–8). Diastereomeric ratios of *anti*/*syn* from 10:1 to 30:1 were obtained for benzaldehyde derivatives bearing an *ortho*-substituent (entries 2, 5, 7, and 8). On the contrary, much lower drs of *anti*/*syn* from 5:1 to 7:1 were given for *para*- and *meta*-substituted benzaldehydes (entries 1, 3, 4, and 6). The aliphatic aldehyde is less reactive than aromatic aldehydes toward chloroacetone. Low yield of 18% was therefore, observed for cyclohexylformaldehyde, but a very high enantioselectivity of 98% ee was induced (entry 9).

3. Conclusion

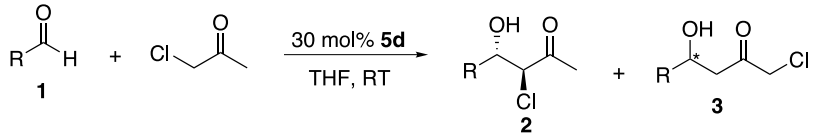
A series of L-prolinamides, derived from L-proline and optically pure 1,2-diphenyl-2-aminoethanols, simple aliphatic, and aromatic amines, were evaluated for catalyzing the direct aldol reaction of chloroacetone and 4-nitrobenzaldehyde. The proton of the amide function in the organocatalyst determined its catalytic efficacy. An L-proline amide **5d**, which was prepared from L-proline and 2,4,6-trimethyl-phenylamine, was found to be the best catalyst. Under the optimal conditions, the direct adol reactions of chloroacetone with aldehydes catalyzed by 30 mol% **5d** gave rise to *anti*-α-chloro-β-hydroxyketones with high diastereo- and enantioselectivity.

4. Experimental

4.1. General

Chemicals were purchased from Acros and organic solvents were distilled before use. NMR spectra were recorded on a Bruker-300 MHz spectrometer. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectromter. HPLC analysis was performed

Table 5. Study on the scope and limitation of aldehydes[a]



Entry	Product	R	Yield (%)[b]	Regioselectivity[c]	dr (*anti*/*syn*)[d]	ee (%)[e]
1	**2a**	4-$NO_2C_6H_4$	57	7:1	7:1	91
2	**2b**	2-$NO_2C_6H_4$	35	4:1	30:1	93
3	**2c**	3-$NO_2C_6H_4$	37	>20:1	5:1	94
4	**2d**	4-CNC_6H_4	31	>20:1	7:1	91
5	**2e**	2-ClC_6H_4	52	>20:1	19:1	86
6	**2f**	4-$MeO_2CC_6H_4$	40	>20:1	6:1	91[f]
7	**2g**	2-FC_6H_4	28	5:1	10:1	97[f]
8	**2h**	2-BrC_6H_4	43	5:1	29:1	91[f]
9	**2i**	*c*-C_6H_{11}	18	>20:1	31:1	98[f]

[a] Unless indicated otherwise, the reaction of aldehyde (0.5 mmol) with chloroacetone (l mL) was performed in THF (1.0 mL).
[b] Overall yield of *anti*-**2** and *syn*-**2**.
[c] The ratios of **2/3** were calculated on the basis of the isolated yields of **2** and **3**, and the enantioselectivities of **3** were not determined.
[d] Determined by ^1H NMR.
[e] Determined by HPLC.
[f] The reaction was performed at 0 °C.

on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, AD columns were purchased from Daicel Chemical Industries, LTD. Chiral GC analysis was performed on VARIAN CP-3380 with a CP CHIPASIL-DEX column.

4.2. General procedure for the direct aldol reaction of chloracetone with aldehydes

To a solution of an aldehyde (0.5 mmol) and chloroacetone (1.0 mL) in anhydrous THF (1.0 mL) was added L-prolinamide **5d** (34.8 mg, 0.15 mmol). After being stirred at room temperature for 96 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (3×10 mL) and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified through a flash column chromatography on silica gel to give desired aldol products **2**.

4.2.1. 3-Chloro-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one (2a). Yield: 57%, as a 7:1 inseparable mixture of *anti*-**2a** and *syn*-**2a**. *Anti*-**2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.86 (d, J=4.2 Hz, 1H), 4.26 (d, J=8.1 Hz, 1H), 5.12 (dd, J=8.1, 4.2 Hz, 1H), 7.57 (d, J=8.7 Hz, 2H), 8.19 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 63.5, 73.8, 123.5, 127.3, 128.1, 145.9, 202.9; IR (neat): γ 3488, 2947, 1718, 1606, 1519, 1348, 1085, 857, 699 cm^{-1}. Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=18.498 min; t_{Rmajor}=23.248 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0294; found: 243.0314.

4.2.2. 3-Chloro-4-hydroxy-4-(2′-nitrophenyl)-butan-2-one (2b). Yield: 35%, as a 30:1 inseparable mixture of *anti*-**2b** and *syn*-**2b**. *Anti*-**2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (s, 3H), 2.82 (br s, 1H), 4.55 (d, J=7.0 Hz, 1H), 5.73 (d, J=7.0 Hz, 1H), 7.49–7.55 (m, 1H), 7.65–7.74 (m, 2H), 7.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.1, 63.3, 70.9, 124.8, 129.2, 129.4, 133.4, 133.8, 148.5, 202.9; IR (neat): γ 3485, 2925, 1718, 1525, 1344, 1097, 857, 789, 744, 703 cm^{-1}. Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=13.707 min; t_{Rmajor}=15.46 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0293; found: 243.0288.

4.2.3. 3-Chloro-4-hydroxy-4-(3′-nitrophenyl)-butan-2-one (2c). Yield: 37%, as a 5:1 inseparable mixture of *anti*-**2c** and *syn*-**2c**. *Anti*-**2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (d, J=2.5 Hz, 3H), 3.46 (d, J=3.2 Hz, 1H), 4.27 (d, J=8.3 Hz, 1H), 5.12 (dd, J=8.3, 3.2 Hz, 1H), 7.53 (m, 1H), 7.72 (d, J=7.7 Hz, 1H), 8.18–8.21 (m, 1H), 8.27–8.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 63.5, 73.7, 122.1, 123.5, 129.4, 133.4, 141.0, 148.1, 203.0; IR (neat): γ 3482, 2928, 1719, 1531, 1352, 1096, 737, 692 cm^{-1}. Enantiomeric excess: 94%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=15.024 min; t_{Rmajor}=16.960 min; HR-MS for $C_{10}H_{10}ClNO_4$: calcd 243.0293; found: 243.0305.

4.2.4. 3-Chloro-4-hydroxy-4-(4′-cyanophenyl)-butan-2-one (2d). Yield: 31%, as a 7:1 inseparable mixture of *anti*-**2d** and *syn*-**2d**. *Anti*-**2d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (d, J=3.6 Hz, 3H), 3.28 (d, J=4.2 Hz, 1H), 4.24 (d, J=8.1 Hz, 1H), 5.07 (dd, J=8.1, 4.2 Hz, 1H), 7.51 (d, J=8.3 Hz, 2H), 7.67 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 28.0, 63.6, 74.0, 112.4, 118.5, 127.9, 132.2, 143.9, 202.9; IR (KBr): γ 3438, 2921, 2230, 1718, 1360, 1052, 837, 795 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=21.30 min; t_{Rmajor}=25.27 min; HR-MS for $C_{11}H_{10}ClNO_2$: calcd 223.0395; found: 223.0399.

4.2.5. 3-Chloro-4-hydroxy-4-(2′-chlorophenyl)-butan-2-one (2e). Yield: 52%, as a 19:1 inseparable mixture of *anti*-**2e** and *syn*-**2e**. *Anti*-**2e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H), 3.36 (d, J=5.2 Hz, 1H), 4.54 (d, J=6.5 Hz, 1H), 5.48 (dd, J=6.5, 5.2 Hz, 1H), 7.25–7.35 (m, 2H), 7.37–7.40 (m, 1H), 7.48–7.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.1, 46.6, 63.2, 127.2, 128.1, 129.7, 129.7, 132.9, 136.2, 202.8; IR (neat): γ 3453, 2926, 1721, 1439, 1358, 1032, 756, 699 cm^{-1}. Enantiomeric excess: 86%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=6.726 min; t_{Rmajor}=8.411 min; HR-MS for $C_{10}H_{10}Cl_2O_2$: calcd 232.0052; found: 232.0062.

4.2.6. 4-(2-Chloro-1-hydroxy-3-oxo-butyl)-benzoic acid methyl ester (2f). Yield: 40%, as a 6:1 inseparable mixture of *anti*-**2f** and *syn*-**2f**. *Anti*-**2f**: ^{1}H NMR (300 MHz $CDCl_3$): δ 2.36 (s, 3H), 3.17 (d, J=4.2 Hz, 1H), 3.92 (s, 3H), 4.30 (d, J=7.9 Hz, 1H), 5.07 (dd, J=7.9, 4.2 Hz, 1H), 7.47 (d, J=8.2 Hz, 2H), 8.03 (d, J=8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 52.2, 63.9, 74.5, 127.1, 128.7, 129.7, 143.6, 166.7, 203.0; IR (neat): γ 3510, 2956, 1726, 1709, 1700, 1435, 1291, 1118, 1107, 1047, 767, 705 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min, t_{Rminor}=8.687 min; t_{Rmajor}=11.108 min; HR-MS for $C_{12}H_{13}ClO_4$: calcd 256.0497; found: 256.0488.

4.2.7. 3-Chloro-4-hydroxy-4-(2′-fluorophenyl)-butan-2-one (2g). Yield: 28%, as a 10:1 inseparable mixture of *anti*-**2g** and *syn*-**2g**. *Anti*-**2g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.27 (br s, 1H), 4.46 (d, J=7.7 Hz, 1H), 5.31 (d, J=7.7 Hz, 1H), 7.04–7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.8, 63.1, 69.7, 115.4 (d, J=21.7 Hz), 124.4 (d, J=2.9 Hz), 125.9 (d, J=12.8 Hz), 128.4 (d, J=3.5 Hz), 130.2 (d, J=8.3 Hz), 158.6 (d, J=245.4 Hz), 202.9; IR (neat): γ 3431, 2924, 1718, 1490, 1358, 1228, 1030, 757 cm^{-1}. Enantiomeric excess: 97%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=8.601 min; t_{Rmajor}=9.142 min; HR-MS for $C_{10}H_{10}ClFO_2$: calcd 216.0348; found:216.0341.

4.2.8. 3-Chloro-4-hydroxy-4-(2′-bromophenyl)-butan-2-one (2h). Yield: 43%, as a 29:1 inseparable mixture of *anti*-**2h** and *syn*-**2h**. *Anti*-**2h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.35 (br s, 1H), 4.56 (d, J=6.4 Hz, 1H), 5.46 (dd, J=6.4, 4.9 Hz, 1H), 7.18–7.26 (m, 1H), 7.34–7.39 (m, 1H), 7.46 (dd, J=7.8, 1.7 Hz, 1H), 7.56 (dd, J=8.0,

1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.2, 63.2, 74.1, 123.0, 127.8, 128.3, 130.0, 132.9, 137.8, 202.8; IR (neat): γ 3439, 2944, 1716, 1357, 1031, 762 cm^{-1}. Enantiomeric excess: 91%; determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane=15:85), UV 254 nm, flow rate 1.0 mL/min; t_{Rminor}=7.056 min; t_{Rmajor}=8.289 min; HR-MS for $C_{10}H_{10}ClBrO_2$: calcd 275.9547; found: 275.9554.

4.2.9. 4-Cyclohexyl-3-chloro-4-hydroxy-butan-2-one (2i). Yield: 18%, as a 31:1 inseparable mixture of *anti*-**2i** and *syn*-**2i**. *Anti*-**2i**: ^1H NMR (300 MHz $CDCl_3$): δ (ppm) 1.09–1.32 (m, 6H), 1.58–1.76 (m, 5H), 2.36 (s, 3H), 2.37–2.42 (m, 1H), 3.76 (m, 1H), 4.19 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.7, 25.9, 26.2, 27.6, 29.8, 38.9, 61.8, 76.1, 203.9; IR (neat): γ 3461, 2958, 2929, 1718, 1357, 1083, 789 cm^{-1}. Enantiomeric excess: 98%, determined by chiral GC analysis (CP CHIRASIL-DEX), inject temperature 240 °C, column temperature 145 °C, FID Oven temperature 260 °C, inlet pressure 10 psi, t_{Rminor}= 6.465 min, t_{Rmajor}=6.732 min; HR-MS for $C_{10}H_{17}ClO_2$, calcd 204.0911; found: 204.0908.

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