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Chiral spiroborate esters catalyzed highly enantioselective direct aldol reaction☆

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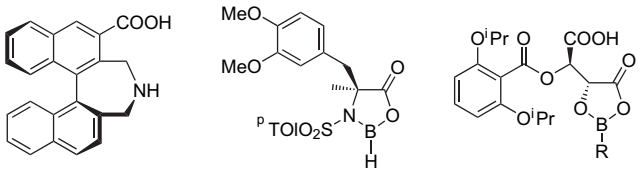
Abstract—Asymmetric catalysis of chiral spiroborate esters with an O_3BN framework toward the direct aldol reaction of acetone and aromatic aldehydes was examined, and a new, efficient chiral catalyst was discovered. In the presence of the novel catalyst, acetone was allowed to react with aromatic aldehydes at 0 °C for 50 h to afford chiral β-hydroxyketone in up to >99% ee and 92% yield. The catalyst, which is readily synthesized, is highly stable to hydrolysis, thermolysis, oxidation, and racemization, can be conveniently recovered.

1. Introduction

The asymmetric aldol reaction is considered to be one of the most powerful tools for the carbon–carbon bond formation.[1] Traditionally, catalytic asymmetric aldol reactions require pre-conversion of the carbonyl pro-nucleophile to a corresponding more active enolate or enol ether with the aid of stoichiometric Lewis acid[2] or Lewis base,[3] which plays a role in controlling stereochemistry of the aldol reaction. However, a more convenient method is direct addition of unmodified ketone to aldehyde in the presence of chiral catalyst. This is a protocol with high atom-economy.[4] The synthetic importance has continually stimulated chemists to search for highly enantioselective chiral catalysts. In the past decade, much work has been done in the direct aldol reaction, and numerous efficient catalysts have been developed. Shibasaki,[5] Evans,[6] and Trost[7] designed their own metallic chiral catalysts, and high ee was obtained. It was not until the work by List and Barbas that L-proline could act as an efficient catalyst in intermolecular direct aldol addition,[8] small organic molecules began to receive increasing attention. Now, non-metal small molecular organocatalyst has become a new focus in asymmetric synthesis.[9] Recent studies by Gong[10] demonstrated that L-prolinamide derivatives could catalyze the direct aldol reaction and the enantioselectivity was improved significantly for the aromatic aldehydes with 20 mol % catalyst loading. Several other proline derivatives have also been applied to highly enantioselective direct aldol reaction.[11] However, the preparation of those catalysts is not so easy.

The motivation for this investigation came from our recent study on borane reduction of prochiral ketones,[12] imines,[13] and oxime ethers catalyzed by tetra-coordinated chiral spiroborate esters with an O_3BN framework, which were synthesized conveniently from diol, boric acid, and L-proline,[14] and found that some α-amino acid and β-amino alcohol derivatives of 1,1′-bi-2-naphtholboric acid were high efficient chiral catalyst. We believe that the binaphthyl backbone in these chiral catalysts played an important role in the asymmetric induction.[12b] Later on, Maruoka[15a] designed a γ-amino acid based on binaphthyl backbone (*S*)-**1** (Fig. 1), which also showed high enantioselectivity in direct aldol reaction.[15] On the other hand, it was previously reported that tri-coordinated, moisture-sensitive chiral oxazaborolidinones (*S*)-**2**[16] and chiral 1,3,2-dioxaborole derivatives (*R*)-**3**[17] were employed as catalysts for the aldol addition of enol silyl ether and aldehyde. We suppose that chiral spiroborate esters (Fig. 2) could also show high asymmetric catalytic activity toward aldol reaction because the chiral spiroborate ester not only contains 1,1′-bi-2-naphthyl and (*S*)-proline moiety but also includes a boron atom and a nitrogen atom, which can act as an acidic center and a basic center under suitable conditions, respectively. If this hypothesis is



(*S*)-**1** (*S*)-**2** (*R*)-**3**

Figure 1. Tri-coordinated boron catalyst and binaphthyl backbone containing catalyst.

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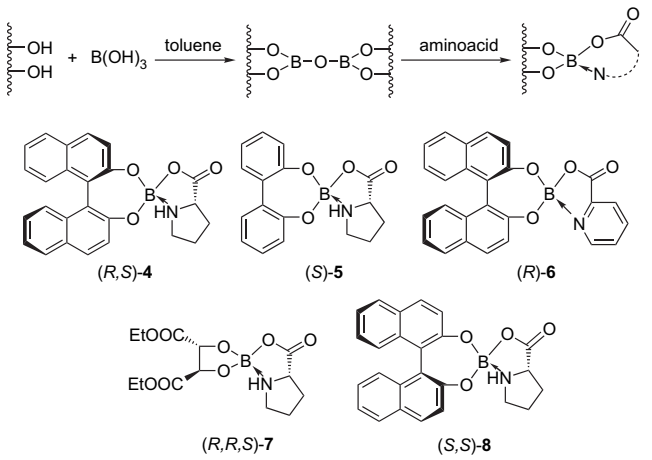


Figure 2. Chiral spiroborate esters evaluated in the aldol reaction.

validated, there will be greater merit than moisture-sensitive tri-coordinated boron compound due to their easy preparation and high stability to hydrolysis, thermolysis, oxidation, and racemization resulted from N→B coordination.[14b] Direct aldol reaction was examined under the catalysis of some chiral spiroborate esters and up to 90% ee was observed. In this paper, we will report the result of asymmetric reaction of acetone to aromatic aldehydes in the presence of some chiral borate esters with an O_3BN framework.

2. Results and discussion

2.1. Screening of chiral catalyst and optimization of the reaction condition

To explore the possibility of the catalysis, five chiral spiroborate esters (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8** were synthesized (Fig. 2) according to the literature procedure.[14] As a model experiment, we explored the direct addition of acetone to benzaldehyde in the presence of the above spiroborate esters, respectively, the influence of the catalyst loading, solvent, temperature, and reaction time on the stereoselectivity of the reaction were also examined.

Benzaldehyde was allowed to react with excess acetone at 0 °C for 50 h in the presence of chiral spiroborate esters (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8**, respectively. The reaction mixture was treated with saturated aqueous ammonium chloride, and followed by extraction with ethyl acetate. After the combined organic phase was dried and concentrated, the catalyst was recovered from the residue upon standing. The desired product was afforded after purified on column chromatography. The results were summarized in Table 1.

It was showed that the catalytic activity and the stereoselectivity were in close relationship with the composition and the loadings of the chiral spiroborate ester. The catalyst (*S*)-**5**, (*R*)-**6** showed little asymmetric induction to the aldol reaction with (*R*,*S*)-**4** an exception, which resulted in high enantioselectivity. It seemed that the stereoselectivity was influenced not only by the diol moiety (entries 2, 4) but also by the chiral carboxyl group and the secondary amine

Table 1. Exploration of various chiral spiroborates as catalyst of the direct asymmetric aldol addition of acetone to benzaldehyde

Entry	Cat.	Catalyst loading (%)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	(*R*,*S*)-**4**	20	0	50	12	81	*R*
2	(*R*,*S*)-**4**	30	0	50	44	96	*R*
3	(*R*,*S*)-**4**	40	0	50	19	89	*R*
4	(*S*)-**5**	30	0	50	18	7.4	*S*
5	(*R*)-**6**	30	0	50	48	4.4	*S*
6	(*R*,*R*,*S*)-**7**	30	0	50	Trace	—	—
7	(*S*,*S*)-**8**	30	0	50	Trace	—	—

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.

in the nitrogen containing moiety (entries 2, 5). In terms of catalytic activity, the diol moiety matters a lot. Almost no catalytic activity was observed when (*R*,*R*,*S*)-**7** or (*S*,*S*)-**8** was used. Specifically, it was quite unexpected that (*S*,*S*)-**8**, possessing the same composition as (*R*,*S*)-**4** almost did not show catalytic activity to the addition. Perhaps, this was originated from the chiral dismatching of the two chiral centers in (*S*,*S*)-**8**, which was disfavored for the catalysis. Moreover, the absolute configuration relied much on the composition of the catalyst. Little difference in the structure led to the opposite configuration (entries 4, 5).

The reaction in acetone (Table 1: entries 1–3) showed that 0.3 equiv of (*R*,*S*)-**4** was suitable for the reaction. To explore better solvent for the reaction, we examined the reaction of benzaldehyde with acetone in various solvent and at different temperatures in the presence of 0.3 equiv of (*R*,*S*)-**4**. The results were summarized in Table 2.

It was revealed that DMSO was a more appropriate solvent when the reaction was performed at 20 °C (entry 4); however, the reaction carried out in acetone at 0 °C for 50 h furnished the desired product in the highest ee and better yield (entry 5), and the enantioselectivity declines with the prolongation of reaction time (entries 9, 8, 10). It was suitable that the reaction was performed at 0 °C for 50 h in the presence of 0.3 equiv of (*R*,*S*)-**4** for the direct addition of acetone to aromatic aldehydes.

Table 2. Screening of the conditions on the direct addition of acetone to benzaldehyde in the presence of the catalyst (*R*,*S*)-**4**

Entry	Solvent	Catalyst loading (%)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Config.[c]
1	Acetone	30	20	50	11	70	*R*
2	THF	30	20	50	8	79	*R*
3	DMF	30	20	50	17	86	*R*
4	DMSO	30	20	50	48	87	*R*
5	Acetone	30	0	50	44	96	*R*
6	THF	30	0	50	23	92	*R*
7	DMF	30	0	50	35	96	*R*
8	Acetone	30	−15	50	64	83	*R*
9	Acetone	30	0	36	36	98	*R*
10	Acetone	30	0	72	44	76	*R*

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.

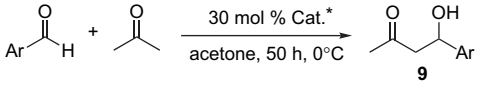
2.2. Asymmetric direct aldol addition of acetone to aromatic aldehydes catalyzed by (*R*,*S*)-4

Having established the optimal reaction conditions, the direct asymmetric aldol reaction of representative aldehydes with acetone was evaluated, and the results were summarized in Table 3.

Most of the reactions furnished good and better enantioselectivities under the experiment conditions. The addition of acetone to benzaldehyde, *p*-chlorobenzaldehyde, *m*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, and 1-naphthaldehyde gave enantioselectivity in over 90% ee; while the reactions of acetone with aromatic aldehydes bearing a methoxyl group in benzene ring exhibited only moderate stereoselectivity. That is to say, the aromatic aldehydes bearing an electron-withdrawing group in the benzene ring generally can offer the desired products of higher ee than those bearing an electron-donating group. So the electronic effect is a major factor, the existence of electron-withdrawing group in the benzene ring increases positive charge at the carbonylic carbon atom of the aldehyde, which is favorable for the attack of the α-carbon of ketone, while the existence of electron-donating group in the benzene ring does not. However, 4-nitrobenzaldehyde and 3,5-dichlorobenzaldehyde gave β-hydroxyketones of lower ee (entries 5, 7), meaning that the enantioselectivity of the aldol additions is in close relationship with the position and the number of the electron-withdrawing group in the aromatic ring. It appears that the steric and electronic effect of the substituted groups in the aromatic aldehydes considerably influence the enantioselectivity of the direct aldol addition.

Our catalyst (*R*,*S*)-**4** showed much stronger chiral inductive ability than (*S*)-proline in asymmetric catalysis toward direct aldol addition. It was assumed that (*R*,*S*)-**4** was a tetra-coordinated, polycyclic structural boron compound, in which all the atoms are in cycles except hydrogen atoms. This strong conformational rigidity and special configuration can provide a suitable quadrant and space for the attack of reactant, in other words, the attack of the reactant molecules have to occur in a limited small space due to the small size of the boron atom and steric bulk of the polycycle and 1,1′-bi-2-naphthyl moiety; as a result, the number of reaction transition states is reduced. Moreover, the catalyst can be conveniently recovered in high yield.

Table 3. Direct aldol reaction of aromatic aldehydes with acetone catalyzed by (*R*,*S*)-**1**



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Entry	Ar	Product	Yield[a] (%)	ee[b] (%)	Config.[c]
1	1-$C_{10}H_9$[d]	**9a**	34	96	*R*
2	Ph	**9b**	44	96	*R*
3	2-$NO_2C_6H_4$	**9c**	65	96	*R*
4	3-$NO_2C_6H_4$	**9d**	92	>99	*R*
5	4-$NO_2C_6H_4$	**9e**	65	75	*R*
6	4-ClC_6H_4	**9f**	55	90	*R*
7	3,5-$Cl_2C_6H_3$	**9g**	23	74	*R*
8	2-$MeOC_6H_4$	**9h**	26	nd	*R*[e]
9	3-$MeOC_6H_4$	**9i**	39	nd	*R*[e]
10	4-$MeOC_6H_4$	**9j**	42	67	*R*

[a] Isolated yield after column chromatography.
[b] Determined by HPLC.
[c] Assigned on the basis of the sign of the optical rotation reported in the literature.
[d] 1-Naphthyl.
[e] Assigned by analogy.

3. Conclusion

A novel, efficient catalyst (*R*,*S*)-**4** for direct aldol addition of acetone to aromatic aldehydes was developed. In the presence of 0.3 equiv of (*R*,*S*)-**4**, acetone was allowed to react with aromatic aldehydes at 0 °C for 50 h to afford chiral 4-aryl-4-hydroxyl-2-butanone in >99% ee and 92% yield. In the catalytic addition, the aromatic aldehydes bearing an electron-withdrawing group in benzene ring generally offered the desired products in higher ee than those bearing an electron-donating group in the benzene ring. On the other hand, the position and the number of the electron-withdrawing groups in the aromatic ring influenced considerably the enantioselectivity of the direct aldol addition.

4. Experimental

4.1. General

IR spectra were recorded on a Testscan Shimadzu FTIR 8000 or a Nicolet 170 SX FTIR spectrophotometer in KBr. The ^1H and ^{13}C NMR spectra were performed on a Varian Mercury VX 300, and all chemical shifts were reported as δ values (ppm) relative to Me_4Si. Optical rotations were measured on a Perkin–Elmer 341 Mc polarimeter. Melting points were determined on a VEB Wagetechnik Rapio PHMK 05 instrument and were not corrected.

4.2. Materials

All reactions were carried out under an Ar atmosphere in freshly dried glassware. Commercially available starting materials were used without further purification if not specified. Acetone was treated successively with small portions of $KMnO_4$ under reflux, until the violet color persists, followed by distillation, and then stored over 4 Å molecular sieves. Benzaldehyde was washed successively with 10% Na_2CO_3 (until no more CO_2 is evolved), saturated Na_2SO_3 and H_2O, followed by drying with $MgSO_4$, and then distilled under Ar under reduced pressure. (*S*)-Proline and boric acid were dried prior to use.

4.2.1. General procedure for the synthesis of the catalysts.[14a] A mixture of a chiral or non-chiral diol and boric acid were allowed to dehydrate in toluene under azeotropic condition for 7–8 h, and then a chiral or non-chiral α-amino acid was added and continued to reflux for several hours to precipitate the desired optically active products (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, (*R*,*R*,*S*)-**7**, and (*S*,*S*)-**8** in high yield. The data of (*R*,*S*)-**4**, (*S*)-**5**, (*R*)-**6**, and (*S*,*S*)-**8** were identical with the literature.[14a] (*R*,*S*)-**4** and (*S*,*S*)-**8** can also be prepared from racemic BINOL via diastereomeric seperation.[14b]

(*R*,*R*,*S*)-**7**: yield, 82.8%; mp: 168–170 °C; $[\alpha]_D^{25}$ −12.78 (*c* 1.033, in CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz, TMS)

δ (ppm): 1.28–1.33 (m, 6H, CH_3), 1.89–1.97 (m, 2H, NCH_2CH_2), 2.20–2.28 (m, 2H, $CHCH_2$), 3.16–3.24 (m, 1H, NCHH), 3.90–3.92 (m, 1H, NCHH), 4.23 (d, J=8.0 Hz, 4H, CH_3CH_2), 4.54 (d, J=5.7 Hz, 2H, OCH), 4.68 (d, J=8.3 Hz, 1H, NCH), 6.55 (s, 1H, NH); IR (KBr): ν 3230 (s, NH), 2991 (s, CH), 1764, 1748 (COOR), 1371 (ms, B–O), 1211 (vs, N→B), 1233 (s, C–O), 1069 (vs, B–O).

4.2.2. General procedure for direct aldol reaction. In a Schlenk test tube fitted with a magnetic bar, catalyst (*R*,*S*)-**4** (0.61 g 1.5 mmol) was charged, and followed by injection of acetone (5 ml), after stirring for 15 min in ice bath, an aromatic aldehyde (5 mmol) was added and continued to stir at 0 °C for 50 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×10 ml). The combined organic phase was dried over anhydrous Na_2SO_4. After concentration, white solid isolated upon standing (recovered catalyst), filtered and the liquor was worked up through flash column chromatography on a silica gel (200–300 mesh, eluent: petroether/acetate 2:1) to give the desired product.

4.2.3. (4*R*)-Hydroxy-4-(1′-naphthyl)-butan-2-one (9a). Yield: 34%; $[\alpha]_D^{25}$ +56.30 (*c* 0.08, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.02–7.46 (m, 7H, Naph–H), 5.94 (m, 1H, CH), 3.38 (s, 1H, OH), 3.02–2.99 (m, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 207.8, 137.0, 132.5, 128.6, 127.8, 126.8, 125.0, 124.3, 121.7, 121.5, 65.5, 50.2, 29.7; IR (KBr): ν 3421 (s, OH), 3050 (w, Ph–H), 2923 (w, CH), 1687 (vs, C=O), 1614 (w, Ph–H). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=8.7 min and (*S*)-isomer, t_R=10.7 min.

4.2.4. (4*R*)-Hydroxy-4-phenyl-butan-2-one (9b). Yield: 44%; $[\alpha]_D^{20}$ +58.58 (*c* 0.39, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.34–7.26 (m, 5H, Ph–H), 5.15–5.11 (m, 1H, CH), 3.50 (s, 1H, OH), 2.92–2.75 (m, 2H, CH_2), 2.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.1, 143.0, 129.2, 128.7, 128.5, 127.9, 125.8, 70.1, 52.3, 31.1; IR (KBr): ν 3420 (s, OH), 3031 (w, Ph–H), 2902 (w, CH), 1708 (vs, C=O), 1602 (w, Ph–H). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=8.1 min and (*S*)-isomer, t_R=8.9 min.

4.2.5. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (9c). Yield: 65%; $[\alpha]_D^{27}$ −107.91 (*c* 1.11, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.95–7.39 (m, 4H, Ph–H), 5.66 (d, J=10.7 Hz, 1H, CH), 3.67 (s, 1H, OH), 3.13–2.68 (m, 2H, CH_2), 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.8, 147.2, 138.7, 134.0, 128.5, 128.4, 124.6, 65.9, 51.4, 30.8; IR (KBr): ν 3418 (s, OH), 3077 (w, Ph–H), 2920 (w, CH), 1712 (vs, C=O), 1609 (w, Ph–H), 1524, 1348 (s, NO_2). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=9.0 min and (*S*)-isomer, t_R=3.8 min.

4.2.6. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (9d). Yield: 92%; $[\alpha]_D^{27}$ +58.88 (*c* 0.45, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.24–7.50 (m, 4H, Ph–H), 5.26 (s, 1H, CH), 3.63 (d, J=3.3 Hz, 1H, OH), 2.89 (d, J=5.7 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.7, 148.6, 145.0, 132.0, 129.7, 122.8, 121.0, 69.1, 51.8, 31.0; IR (KBr): ν 3417 (s, OH), 3090 (w, Ph–H), 2917 (w, CH), 1709 (vs, C=O), 1618 (w, Ph–H), 1529, 1351 (s, NO_2). Enantiomeric excess: >99%, determined by HPLC (Daicel chiralpak OJ-H, *i*-PrOH/hexane 20:80), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=18.7 min and (*S*)-isomer, t_R=21.3 min.

4.2.7. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (9e). Yield: 65%; $[\alpha]_D^{16}$ +51.03 (*c* 0.28, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.23–7.53 (m, 4H, Ph–H), 5.27 (s, 1H, CH), 3.64 (s, 1H, OH), 2.86 (t, J=4.5 Hz, 2H, CH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.5, 150.2, 147.4, 129.0, 126.6, 124.4, 123.9, 69.2, 51.9, 31.1; IR (KBr): ν 3436 (s, OH), 3081 (w, Ph–H), 2902 (w, CH), 1707 (vs, C=O), 1602 (w, Ph–H), 1517, 1347 (s, NO_2). Enantiomeric excess: 75%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=10.5 min and (*S*)-isomer, t_R=13.5 min.

4.2.8. (4*R*)-Hydroxy-4-(4′-chlorophenyl)-butan-2-one (9f). Yield: 55%; $[\alpha]_D^{27}$ +46.36 (*c* 0.48, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.33–7.26 (m, 4H, Ph–H), 5.11 (q, J=4.7 Hz, 1H, CH), 3.44 (s, 1H, OH), 2.83–2.79 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.0, 141.4, 133.5, 128.9, 127.2, 69.5, 52.1, 31.1; IR (KBr): ν 3426 (s, OH), 3001 (w, Ph–H), 2902 (w, CH), 1711 (vs, C=O), 1597 (w, Ph–H). Enantiomeric excess: 90%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=10.9 min and (*S*)-isomer, t_R=12.6 min.

4.2.9. (4*R*)-Hydroxy-4-(3′,5′-dichlorophenyl)-butan-2-one (9g). Yield: 23%; $[\alpha]_D^{16}$ +39.22 (*c* 0.26, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.25, 7.24 (s, 3H, Ph–H), 5.09 (s, 1H, CH), 3.58 (s, 1H, OH), 2.81 (d, J=6.7 Hz, 2H, CH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 208.6, 146.3, 135.3, 127.9, 124.4, 68.9, 51.8, 31.1; IR (KBr): ν 3430 (s, OH), 3078 (w, Ph–H), 2925 (w, CH), 1711 (vs, C=O), 1594 (w, Ph–H), 689 (s, C–Cl). Enantiomeric excess: 74%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=5.1 min and (*S*)-isomer, t_R=6.1 min.

4.2.10. (4*R*)-Hydroxy-4-(2′-methoxyphenyl)-butan-2-one (9h). Yield: 26%; $[\alpha]_D^{25}$ +61.02 (*c* 0.15, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.44–6.84 (m, 4H, Ph–H), 5.40 (t, J=10.3 Hz, 1H, CH), 3.83 (s, 1H, OCH_3), 3.43 (d, J=4.3 Hz, 1H, OH), 2.96–2.74 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.7, 156.0, 131.1, 128.6, 126.6, 121.1, 110.5, 65.8, 55.5, 50.6, 30.8; IR (KBr): ν 3442 (s, OH), 3003 (w, Ph–H), 2939 (w, CH), 1708 (vs, C=O), 1600 (w, Ph–H), 1240, 1068 (s, O–CH_3).

4.2.11. (4*R*)-Hydroxy-4-(3′-methoxyphenyl)-butan-2-one (9i). Yield: 39%; $[\alpha]_D^{25}$ +38.45 (*c* 0.53, in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.27–6.79 (m, 4H,

Ph–H), 5.11 (d, J=10.0 Hz, 1H, CH), 3.80 (s, 1H, OCH_3), 3.40 (s, 1H, OH), 2.86–2.80 (m, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.0, 159.9, 144.8, 129.7, 118.1, 113.4, 111.3, 70.0, 55.5, 52.4, 31.1; IR (KBr): ν 3434 (s, OH), 3000 (w, Ph–H), 2966 (w, CH), 1708 (vs, C=O), 1602 (w, Ph–H), 1161, 1042 (s, O–CH_3).

4.2.12. (4*R*)-Hydroxy-4-(4′-methoxyphenyl)-butan-2-one (9j). Yield: 42%; $[\alpha]_D^{16}$ +25.51 (c 0.24, in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.98–6.86 (m, 4H, Ph–H), 5.10–5.07 (m, 1H, CH), 3.80 (s, 1H, OCH_3), 3.25 (s, 1H, OH), 2.93–2.74 (m, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 209.2, 159.3, 152.9, 127.1, 124.1, 118.1, 114.1, 69.8, 70.0, 55.6, 52.3, 31.1; IR (KBr): ν 3414 (s, OH), 3059 (w, Ph–H), 2964 (w, CH), 1703 (vs, C=O), 1616 (w, Ph–H), 1248, 1032 (s, O–CH_3). Enantiomeric excess: 67%, determined by HPLC (Daicel chiralpak AD-H, *i*-PrOH/hexane 10:90), UV 254 nm, flow rate: 1 ml/min. (*R*)-Isomer, t_R=6.0 min and (*S*)-isomer, t_R=4.7 min.

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