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(*R*)- or (*S*)-Bi-2-naphthol assisted, L-proline catalyzed direct aldol reaction

Yan Zhou and Zixing Shan*

Department of Chemistry, Wuhan University, Wuhan 430072, China

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Abstract—Chiral Brønsted acids (*R*)- and (*S*)-BINOL were employed as additives in the classic L-proline catalyzed direct aldol reaction. Eighteen substrates were tested with 0.5 mol % (*R*)-BINOL loading and 1 mol % of (*S*)-BINOL loading, and the enantioselectivity was improved from 72% ee without additive to 98% ee. In the proposed transition state, the chiral Brønsted acid promoted the reaction through hydrogen bonding, which not only activated the carbonyl group but also stabilized the transition state.

1. Introduction

In catalytic asymmetric synthesis, the most challenging work is the development of efficient chiral catalysts. Low catalyst loading and high chiral induction continue to be the goals of synthetic chemists, and much effort has been devoted to this issue. For less active substrates, an activator is often needed, and chiral Brønsted acids are utilized to solve this problem.[1] In the early days, some inorganic compounds were employed as Brønsted acids;[2] now, with the concept of organocatalysis, small organic molecules are used in this role.[3] Recently, a lot of work has been done on organic chiral Brønsted acid catalyzed reactions. It is believed that these small molecules promote the reaction through hydrogen bonding with substrates via electrophilic activation[4] including C=N bond activation in Mannich-type reaction,[5] Diels–Alder reactions,[6] hydrophosphonylation reactions,[7] C=O bond activation in aza-Morita–Baylis–Hillman reactions,[8] and so on. In these reactions, most chiral Brønsted acids were self-derived chiral diols, and the diols themselves were also reported to serve directly as promoters or as ligands in reactions.[9] The aldol reaction was a research focus in recent years,[10] but chiral Brønsted acids assisted direct asymmetric aldol reaction has been seldom studied.[11]

Early studies revealed that L-proline could catalyze the direct aldol reaction, but in the case of aliphatic aldehydes, the enantioselectivity was better than that of aromatic aldehydes.[12] Attention was directed to the design of various functional catalysts for the aldol reaction, mainly L-proline derivatives.[13] It has been known that L-prolinamide was an efficient catalyst for the aldol reaction of ketones to aromatic aldehydes due to the formation of double hydrogen bonding.[14] Moreover, considering that chiral Brønsted acids like BINOL and TADDOL themselves could catalyze reactions through hydrogen bonding,[15] we assume that the stereoselectivity could be improved if this type of chiral Brønsted acid served as an additive in the L-proline catalyzed aldol reactions, due to a cooperative effect in the catalytic system (Fig. 1).[16]

In this paper, we report an improved L-proline catalyzed aldol reaction, where (*R*)- and (*S*)-1,1′-bi-2-naphthol are used as activators. Under the optimized conditions, the aldol products were afforded in up to 98% ee and 97% yield.

2. Results and discussion

2.1. Screening of the parameters of the reaction

The reaction of benzaldehyde with acetone was initially set as a template to investigate the influence of the catalyst and additive loadings on the reaction. Based on earlier studies, a mixture of acetone and DMSO was chosen as solvent, and all the reactions were sustained for 48 h. The result is listed in Table 1. It can be seen that the aldol products were

* Corresponding author. Tel.: +86 27 87219074; fax: +86 27 68754067; e-mail: zxshan@whu.edu.cn

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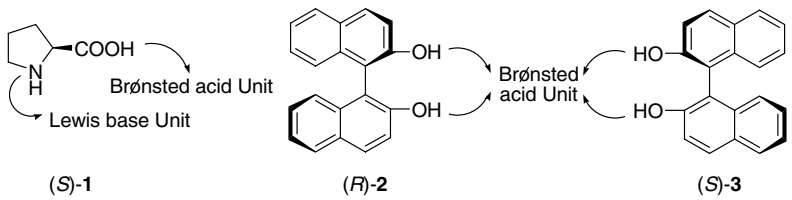


Figure 1. Concept of combined trifunctional organocatalyst.

Table 1. Screening of influence of the loading of catalyst and additive **2** and **3** on the aldol reaction[a]

Entry	Additive	Sub.:cat.:additive	Time/h	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
1	**2**	10:3:3	48	79	38	90
2	**2**	10:3:2	48	93	52	91
3	**2**	10:3:1	48	87	52	85
4	**2**	10:3:0.5	48	80	60	97
5	**2**	10:3:0.1	48	87	60	96
6	**2**	10:3:0.05	48	66	59	97
7	**2**	10:2.5:0.05	48	76	59	93
8	**2**	10:1.5:0.05	48	77	60	93
9	**2**	10:1:0.05	48	68	60	94
10	**2**	10:0.5:0.05	48	66	66	87
11	**3**	10:3:2	48	76	52	94
12	**3**	10:3:0.5	48	64	59	89
13	**3**	10:3:0.1	48	79	56	98
14	**3**	10:3:0.05	48	68	63	85
15	No additive	10:3:0	48	60	43	72

[a] The reaction was carried out in acetone/DMSO (3:1) at 0 °C for 48 h.
[b] Based on the aldehyde recovery after column chromatography.
[c] Isolated yield after column chromatography.
[d] Determined by HPLC and the configuration was assigned as *R*.

afforded in better ee in the cases of 5–0.5 mol % additive loading and 30 mol % catalyst loading (entries 4–6) than in the cases without additive loading (entry 15). Taking all aspects into consideration, the more practical strategy was to use 30 mol % catalyst loading and 0.5 mol % (*R*)-BINOL loading (entry 6) or 1 mol % (*S*)-BINOL loading (entry 13).

Influence of reaction time and temperature on the reaction was further explored (Table 2). Table 2 shows that the enantioselectivity only fluctuated in a small range within 8–48 h, but that the conversion and yield increased with the extension of reaction time (entries 1–5). As far as the reaction temperature was concerned, it was unfavorable for higher or lower temperature than 0 °C for the reaction (entries 6–8).

Taking the above factors into consideration, the reaction condition was optimized at 0 °C for 48 h with 0.3 equiv of L-proline and 0.005 equiv of (*R*)-**2** or 0.01 equiv of (*S*)-**3**.

2.2. Enantiopure BINOL assisted direct aldol reaction catalyzed by L-proline

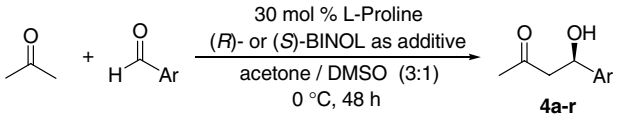
To widen the scope of the application, different aromatic aldehydes were evaluated under the above optimized condition, and the results are listed in Table 3.

Table 2. Optimization of the parameters of the aldol reaction[a]

Entry	Additive	Sub.:cat.:additive	Time/h	Temperature (°C)	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
1	**2**	10:3:2	48	0	93	52	91
2	**2**	10:3:2	36	0	76	40	91
3	**2**	10:3:2	24	0	77	39	91
4	**2**	10:3:2	12	0	77	23	92
5	**2**	10:3:2	8	0	74	19	95
6	**2**	10:3:0.05	48	−20	55	24	96
7	**2**	10:3:0.05	48	0	66	59	97
8	**2**	10:3:0.05	48	20	62	49	80

[a] The reaction was carried out in acetone/DMSO (3:1).
[b] Based on the aldehyde recovery after column chromatography.
[c] Isolated yield after column chromatography.
[d] Determined by HPLC and the configuration was assigned as *R*.

Table 3. Direct aldol reaction in the presence of L-proline and additives[a]



Entry	Ar	Product	Config.[b]	No additives			Assisted by additives[c]		
				Conv.[d] (%)	Yield[e] (%)	ee[f] (%)	Conv.[d] (%)	Yield[e] (%)	ee[f] (%)
1	Ph	**4a**	*R*	60	43	72	66(79)	59(56)	97(98)
2	1-Naphthyl	**4b**	*R*	55	30	57	67(71)	62(64)	71(79)
3	9-Anthryl	**4c**	*R*[g]	14	10	Nd	31(30)	23(23)	86(87)
4	4-BrC_6H_4	**4d**	*R*	88	82	75	89(90)	74(76)	97(97)
5	3-BrC_6H_4	**4e**	*R*	92	89	75	90(89)	87(86)	91(95)
6	2-BrC_6H_4	**4f**	*R*[g]	85	74	72	97(97)	97(96)	68(71)
7	2,6-$Cl_2C_6H_3$	**4g**	*R*	94	80	89	94(95)	89(90)	96(96)
8	2,4-$Cl_2C_6H_3$	**4h**	*R*[g]	89	76	57	94(95)	88(91)	56(61)
9	4-ClC_6H_4	**4i**	*R*	82	76	75	93(94)	78(79)	83(83)
10	3-ClC_6H_4	**4j**	*R*[g]	79	75	Nd	87(87)	85(87)	Nd
11	2-ClC_6H_4	**4k**	*R*	78	71	66	99(99)	96(95)	73(73)
12	4-$NO_2C_6H_4$	**4l**	*R*	67	49	72	97(96)	66(63)	71(79)
13	3-$NO_2C_6H_4$	**4m**	*R*	46	35	Nd	95(96)	81(75)	77(75)
14	2-$NO_2C_6H_4$	**4n**	*R*	56	49	80	99(99)	82(84)	75(75)
15	4-MeC_6H_4	**4o**	*R*	35	23	74	49(61)	41(43)	73(73)
16	4-$MeOC_6H_4$	**4p**	*R*	23	17	75	44(47)	27(25)	68(62)
17	3-$MeOC_6H_4$	**4q**	*R*	36	34	77	63(65)	61(63)	77(76)
18	2-$MeOC_6H_4$	**4r**	*R*[g]	26	18	Nd	41(44)	21(21)	Nd

[a] The reaction was carried out in acetone/DMSO (3:1) at 0 °C for 48 h.
[b] Assigned by comparison of the retention time with the reported data.[13e,14b]
[c] Results assisted by 0.5 mol % (*R*)-**2** and data in the brackets indicate the result assisted by 1 mol % (*S*)-**3**.
[d] Based on the aldehyde recovery after column chromatography.
[e] Isolated yield after column chromatography.
[f] Determined by HPLC.
[g] Assigned by analogy.

From Table 3, it can be seen that the conversion and yield were always much higher in the case of aromatic aldehydes bearing an electron-withdrawing group (entry 4–14). As to the aromatic aldehydes with the same substituent on the benzene ring, the results were influenced considerably by the location of the substituent. When the electron-withdrawing group was located at the *para*-position, the yield and conversion were relatively poor, while the enantioselectivity was the best; and the yield and conversion were better when located at the *meta*- and *ortho*-position, while the enantioselectivity was lowered. The fused ring of the aromatic aldehydes is also important. The reaction of 1-naphthaldehyde afforded higher conversion and yield than 9-anthraldehyde due to the bulky 9-anthryl group, which is unfavorable for nucleophilic attack due to steric hindrance.

Compared with the results catalyzed by L-proline without additives, the yield and enantioselectivity were considerably improved. We attributed this to the hydrogen bonding interaction between the chiral diol and the substrate. We examined the ^1H NMR of the phenolic protons of BINOL in the reaction mixture, and it revealed that they shifted downfield by ca. 0.1 ppm. Based on this and the early proposed transition state (TS-1) for the proline catalyzed aldol reaction without additive,[12a] the possible transition states (TS-2 and TS-3) are suggested for (*R*)-BINOL and (*S*)-BINOL as additives, respectively (Fig. 2). It can be seen

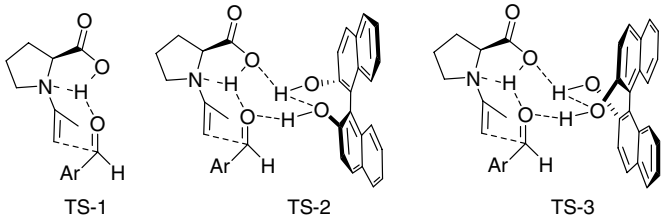


Figure 2. Transition state of chiral Brønsted acid assisted activation of carbonyl group.

that the chiral Brønsted acids promoted the reaction through hydrogen bonding interaction, which not only activated the carbonyl group of the aldehyde, but also stabilized the transition state. This cooperative effect of a Brønsted acid/Lewis base provided a new strategy for the design of multifunctional catalysts.

3. Conclusion

In summary, chiral Brønsted acids (*R*)-BINOL and (*S*)-BINOL were explored as additives in the L-proline catalyzed aldol reaction, and in certain cases, the results were considerably improved compared to those without additives. This improvement could be attributed to a hydrogen bonding

interaction among the chiral diol, the aldehyde and L-proline, which activated the substrate and stabilized the transition state.

4. Experimental

4.1. General

IR spectra were recorded on a Testscan Shimadzu FTIR 8000 or a Nicolet 170 SX FT-IR spectrophotometer in KBr. The ^{1}H 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. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS-H and OJ-H were purchased from Daicel Chemical Industries (Hong Kong, China). 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

Commercially available starting materials were used without further purification if not specified. Acetone was dried over anhydrous K_2CO_3 and redistilled from $KMnO_4$. L-Proline was dried prior to use.

4.3. General procedure for direct aldol reaction

In a test tube fitted with a magnetic bar, L-proline and an additive were charged, and followed by injection of acetone (3 ml) and DMSO (1 ml), after stirring for 15 min in an ice bath, the aromatic aldehyde (5 mmol) was added and stirred continuously at 0 °C for 48 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (10 ml × 3). The combined organic phase was dried over anhydrous Na_2SO_4, worked up and purified through flash column chromatography on a silica gel (200–300 mesh, eluent: petroether/acetate 2:1) to give the desired product.

4.4. (4*R*)-Hydroxy-4-phenyl-butan-2-one 4a

Yield: 59%; $[\alpha]_D^{20} = +59.7$ (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.33–7.25 (m, 5H, Ph–H), 5.14–5.11 (d, $J = 6.7$ Hz, 1H, CH), 3.57 (s, 1H, OH), 2.92–2.74 (m, 2H, CH_2), 2.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.2, 143.0, 128.7, 127.9, 125.8, 70.1, 52.3, 31.1; IR (KBr): *v* 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, major: t_R 8.1 min and minor: t_R 9.0 min.

4.5. (4*R*)-Hydroxy-4-(1′-naphthyl)-butan-2-one 4b

Yield: 62%; mp: 99–101 °C; $[\alpha]_D^{25} = +72.7$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.97–7.43 (m, 7H, Naph–H), 5.93 (s, 1H, CH), 3.42 (t, $J = 1.7$ Hz, 1H, OH), 2.99–2.97 (m, 2H, CH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.6, 138.1, 133.8, 129.9, 129.1, 128.1, 126.3, 125.6, 123.1, 122.8, 67.3, 52.0, 31.7; IR (KBr): *v* 3358 (s, OH), 3065 (w, Ar–H), 2903 (w, CH), 1689 (vs, C=O). Enantiomeric excess: 71%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 280 nm, flow rate: 1 ml/min, major: t_R 9.8 min and minor: t_R 9.4 min.

4.6. (4*R*)-Hydroxy-4-(1′-anthranyl)-butan-2-one 4c

Yield: 23%; mp: 107–109 °C; $[\alpha]_D^{25} = -53.9$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.63–7.42 (m, 9H, anth–H), 6.79 (d, $J = 11.3$, 1H, CH), 3.46 (s, 1H, OH), 3.78–3.68 (m, 1H, CH_2), 2.93–2.87 (m, 1H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.1, 133.2, 132.3, 130.1, 129.9, 129.1, 126.6, 125.6, 67.6, 51.7, 32.3; IR (KBr): *v* 3421 (s, OH), 3051 (w, Ar–H), 2928 (w, CH), 1700 (vs, C=O). Enantiomeric excess: 86%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 3:97), UV 260 nm, flow rate: 1 ml/min, major: t_R 38.7 min and minor: t_R 42.4 min.

4.7. (4*R*)-Hydroxy-4-(4′-bromophenyl)-butan-2-one 4d

Yield: 74%; mp: 58–60 °C; $[\alpha]_D^{27} = +48.3$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.38–7.11 (m, 4H, Ar–H), 5.01 (q, $J = 8.7$ Hz, 1H, CH), 3.36 (s, 1H, OH), 2.74–2.71 (m, 2H, CH_2), 2.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.3, 141.6, 131.6, 127.4, 121.5, 69.7, 52.4, 31.7; IR (KBr): *v* 3450 (s, OH), 3056 (w, Ar–H), 2900 (w, CH), 1709 (vs, C=O). Enantiomeric excess: 97%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 262 nm, flow rate: 1 ml/min, major: t_R 10.6 min and minor: t_R 13.3 min.

4.8. (4*R*)-Hydroxy-4-(3′-bromophenyl)-butan-2-one 4e

Yield: 87%; $[\alpha]_D^{20} = +48.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.48–7.17 (m, 4H, Ar–H), 5.07 (q, $J = 6.7$ Hz, 1H, CH), 3.73 (d, $J = 3.3$ Hz, 1H, OH), 2.82–2.78 (m, 2H, CH_2), 2.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.1, 145.1, 130.6, 130.2, 128.8, 124.4, 122.7, 69.6, 52.5, 31.7; IR (KBr): *v* 3424 (s, OH), 3063 (w, Ar–H), 2901 (w, CH), 1710 (vs, C=O). Enantiomeric excess: 91%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 254 nm, flow rate: 1 ml/min, major: t_R 14.1 min and minor: t_R 17.8 min.

4.9. (4*R*)-Hydroxy-4-(2′-bromophenyl)-butan-2-one 4f

Yield: 97%; $[\alpha]_D^{20} = +81.8$ (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.58–7.06 (m, 4H, Ar–H), 5.44–5.40 (m, 1H, CH), 3.77–3.73 (m, 1H, OH), 2.98–2.58 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.4, 141.7, 132.6, 129.0, 127.9, 127.4, 121.3, 69.3, 50.9, 31.4; IR (KBr): *v* 3427 (s, OH), 3064 (w, Ar–H), 2914 (w, CH), 1709 (vs, C=O). Enantiomeric excess: 68%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 20:80), UV 220 nm, flow rate: 1 ml/min, major: t_R 7.7 min and minor: t_R 6.3 min.

4.10. (4*R*)-Hydroxy-4-(2′,6′-dichlorophenyl)-butan-2-one 4g

Yield: 89%; mp: 67–70 °C; $[\alpha]_D^{20} = -51.1$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.33–7.13 (m, 3H, Ar–H), 6.03–5.96 (m, 1H, CH), 3.53–3.44, 2.79–2.73 (m, 2H, CH_2), 3.22 (d, $J = 7.3$ Hz, 1H, OH), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 206.9, 136.1, 134.5, 129.5, 129.3, 67.7, 48.5, 31.3; IR (KBr): *v* 3415 (s, OH), 3076 (w, Ar–H), 2919 (w, CH), 1710 (vs, C=O). Enantiomeric excess: 96%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 220 nm, flow rate: 1 ml/min, major: t_R 5.7 min and minor: t_R 5.1 min.

4.11. (4*R*)-Hydroxy-4-(2′,4′-dichlorophenyl)-butan-2-one 4h

Yield: 88%; mp: 53–54 °C; $[\alpha]_D^{20} = +66.2$ (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.57–7.27 (m, 3H, Ar–H), 5.45–5.42 (d, $J = 10.3$ Hz, 1H, CH), 3.68 (m, 1H, OH), 2.99–2.59 (m, 2H, CH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.2, 138.9, 133.8, 131.8, 129.2, 128.3, 127.7, 66.5, 50.1, 31.0; IR (KBr): *v* 3346 (s, OH), 3001 (w, Ar–H), 2917 (w, CH), 1710 (vs, C=O), 1645 (w, Ar–H). Enantiomeric excess: 55%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 220 nm, flow rate: 1 ml/min, major: t_R 5.2 min and minor: t_R 4.8 min.

4.12. (4*R*)-Hydroxy-4-(4′-chlorophenyl)-butan-2-one 4i

Yield: 78%; mp: 46–47 °C; $[\alpha]_D^{27} = +53.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.30–7.24 (m, 4H, Ar–H), 5.10 (s, 1H, CH), 3.45 (s, 1H, OH), 2.82–2.80 (m, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.4, 141.2, 133.3, 128.7, 127.1, 69.7, 52.6, 31.7; IR (KBr): *v* 3430 (s, OH), 3051 (w, Ph–H), 2883 (w, CH), 1700 (vs, C=O), 1594 (w, Ar–H). Enantiomeric excess: 83%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 220 nm, flow rate: 1 ml/min, major: t_R 11.7 min and minor: t_R 14.4 min.

4.13. (4*R*)-Hydroxy-4-(3′-chlorophenyl)-butan-2-one 4j

Yield: 85%; $[\alpha]_D^{20} = +54.6$ (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.32–7.15 (m, 4H, Ar–H), 5.07 (t, $J = 4.7$ Hz, 1H, CH), 3.64 (d, $J = 3.3$ Hz, 1H, OH), 2.81–2.77 (m, 2H, CH_2), 2.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.2, 144.8, 134.3, 129.8, 127.7, 125.9, 123.9, 69.6, 52.5, 31.6; IR (KBr): *v* 3426 (s, OH), 3066 (w, Ar–H), 2902 (w, CH), 1710 (vs, C=O).

4.14. (4*R*)-Hydroxy-4-(2′-chlorophenyl)-butan-2-one 4k

Yield: 96%; $[\alpha]_D^{20} = +74.6$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.61–7.16 (m, 4H, Ar–H), 5.56–5.47 (m, 1H, CH), 3.74 (s, 1H, OH), 2.97–2.65 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.3, 140.4, 131.3, 129.5, 128.8, 127.4, 127.3, 66.8, 50.4, 30.9; IR (KBr): *v* 3422 (s, OH), 3068 (w, Ar–H), 2914 (w, CH), 1709 (vs, C=O), 1629 (w, Ph–H). Enantiomeric excess: 73%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 8:92), UV 220 nm, flow rate: 1 ml/min, major: t_R 12.2 min and minor: t_R 9.9 min.

4.15. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one 4l

Yield: 66%; mp: 53–55 °C; $[\alpha]_D^{16} = +49.9$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.20–7.51 (m, 4H, Ar–H), 5.25 (s, 1H, CH), 3.67 (s, 1H, OH), 2.85 (d, $J = 6.7$ Hz, 2H, CH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.6, 150.2, 147.4, 126.6, 123.9, 123.9, 69.2, 51.8, 31.1; IR (KBr): *v* 3443 (s, OH), 3086 (w, Ar–H), 2903 (w, CH), 1708 (vs, C=O), 1517, 1348 (s, NO_2). Enantiomeric excess: 71%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 254 nm, flow rate: 1 ml/min, major: t_R 11.8 min and minor: t_R 15.2 min.

4.16. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one 4m

Yield: 81%; mp: 50–52 °C; $[\alpha]_D^{27} = +58.7$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.23–7.49 (m, 4H, Ar–H), 5.25 (s, 1H, CH), 3.66 (s, 1H, OH), 2.88 (d, $J = 5.3$ Hz, 2H, CH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.7, 148.6, 145.0, 132.0, 129.7, 122.8, 120.9, 69.1, 51.8, 31.1; IR (KBr): *v* 3490 (s, OH), 3095 (w, Ar–H), 2917 (w, CH), 1701 (vs, C=O), 1620 (w, Ar–H), 1530, 1347 (s, NO_2). Enantiomeric excess: 77%, determined by HPLC (Daicel chiralpak OJ-H, *i*-PrOH/hexane 20:80), UV 260 nm, flow rate: 1 ml/min, major: t_R 14.5 min and minor: t_R 16.4 min.

4.17. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one 4n

Yield: 82%; $[\alpha]_D^{27} = -108.2$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.95–7.39 (m, 4H, Ar–H), 5.66 (d, $J = 10.7$ Hz, 1H, CH), 3.78 (s, 1H, OH), 3.16–2.68 (m, 2H, CH_2), 2.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 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): *v* 3417 (s, OH), 3075 (w, Ar–H), 2921 (w, CH), 1710 (vs, C=O), 1525, 1349 (s, NO_2). Enantiomeric excess: 75%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 30:70), UV 260 nm, flow rate: 1 ml/min, major: t_R 9.1 min and minor: t_R 7.3 min.

4.18. (4*R*)-Hydroxy-4-(4′-methylphenyl)-butan-2-one 4o

Yield: 41%; $[\alpha]_D^{20} = +52.5$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.22–7.11 (m, 4H, Ar–H), 5.07–5.04 (m, 1H, CH), 3.62 (s, 1H, OH), 2.89–2.68 (m, 2H, CH_2), 2.32 (s, 3H, Ar–CH_3), 2.13 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 209.2, 140.2, 137.5, 129.4, 125.8, 70.0, 52.4, 31.1, 21.5; IR (KBr): *v* 3427 (s, OH), 3024 (w, Ph–H), 2922 (w, CH), 1708 (vs, C=O), 1610 (w, Ar–H). Enantiomeric excess: 73%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 15:85), UV 220 nm, flow rate: 1 ml/min, major: t_R 8.1 min and minor: t_R 9.8 min.

4.19. (4*R*)-Hydroxy-4-(4′-methoxyphenyl)-butan-2-one 4p

Yield: 27%; $[\alpha]_D^{16} = +46.3$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.21–6.79 (m, 4H, Ar–H),

5.17 (q, $J = 10.0$ Hz, 1H, CH), 3.73 (s, 1H, OCH_3), 3.49 (s, 1H, OH), 2.87–2.56 (m, 2H, CH_2), 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 208.4, 158.8, 135.1, 127.0, 114.0, 70.0, 55.9, 52.7, 31.6; IR (KBr): v 3426 (s, OH), 3001 (w, Ar–H), 2958 (w, CH), 1709 (vs, C=O), 1612 (w, Ar–H), 1248, 1032 (s, O–CH_3). Enantiomeric excess: 67%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 220 nm, flow rate: 1 ml/min, major: t_R 23.9 min and minor: t_R 28.0 min.

4.20. (4*R*)-Hydroxy-4-(3′-methoxyphenyl)-butan-2-one 4q

Yield: 61%; $[\alpha]_D^{25} = +48.5$ (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.27–6.79 (m, 4H, Ar–H), 5.11 (q, $J = 6.7$ 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 ($CDCl_3$, 75 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): v 3433 (s, OH), 3000 (w, Ar–H), 2941 (w, CH), 1710 (vs, C=O), 1602 (w, Ar–H), 1160, 1043 (s, O–CH_3). Enantiomeric excess: 77%, determined by HPLC (Daicel chiralpak AS-H, *i*-PrOH/hexane 10:90), UV 280 nm, flow rate: 1 ml/min, major: t_R 16.1 min and minor: t_R 19.2 min.

4.21. (4*R*)-Hydroxy-4-(2′-methoxyphenyl)-butan-2-one 4r

Yield: 21%; $[\alpha]_D^{25} = +61.0$ (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.44–6.85 (m, 4H, Ar–H), 5.40 (t, $J = 5.0$ 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 ($CDCl_3$, 75 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): v 3398 (s, OH), 3070 (w, Ar–H), 2937 (w, CH), 1705 (vs, C=O), 1602 (w, Ph–H), 1242, 1049 (s, O–CH_3).

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