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RESEARCH ARTICLE

Chiral ruthenium-SDPs/diamine complexes-catalyzed enantioselective hydrogenation of α-alkyl arylacetones via dynamic kinetic resolution

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The asymmetric hydrogenation of the conformationally flexible racemic α-substituted acyclic dialkyl ketones via dynamic kinetic resolution (DKR) has been developed by using Ru-SDPs/diamine catalysts. Chiral alcohols were produced in high yields with good to excellent enantioselectivities (85%–97% ee) and diastereoselectivities (up to 97:3). This hydrogenation reaction provided a new approach to the synthesis of the key intermediate of J-104118.

Keywords asymmetric hydrogenation, arylacetones, catalysis, diphosphine, diamine, ruthenium

1 Introduction

Enantiomerically pure α-alkyl arylpropan-2-ols are very important building blocks for the preparation of chiral drugs. For example, the potent inhibitor of the squalene synthase J-104118 [1,2] and the orally bio-available cannabinoid-1 receptor (CB-1R) inverse agonist MK-0346 [3] and MK-9470 [4] could be synthesized from corresponding (2*R*,3*S*)-3,4-diarylbutan-2-ol (Scheme 1). However, there is no practical method for the synthesis of this type of chiral alcohols with two adjacent stereogenic centers. The preparation of (2*R*,3*S*)-3,4-diarylbutan-2-ol in literature, which is based on the ring-opening of (2*R*,3*R*)-1-aryl-2-methyl-oxirane with benzylic Grignard reagents, is tedious. The (2*R*,3*R*)-1-aryl-2-methyl-oxirane is, however, obtained from Sharpless dihydroxylation of 1-arylprop-1-ene [1,2]. An efficient method is desirable for the preparation of this type of chiral alcohols, especially for the synthesis of enantiomerically pure 3,4-diarylbutan-2-ol.

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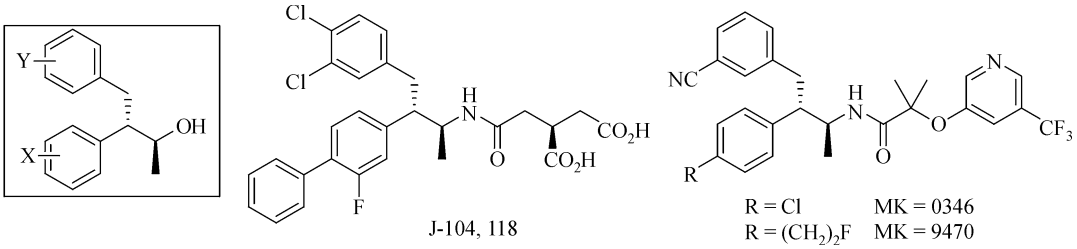
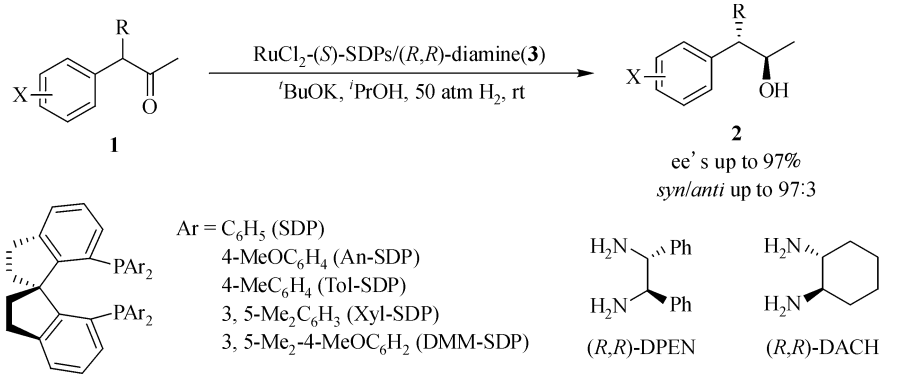
Initiated by Noyori and co-workers [5,6], the Ru-diphosphine/diamine complexes-catalyzed asymmetric hydrogenation of α-substituted ketones via dynamic kinetic resolution (DKR) [7–11] has been a very efficient method for the preparation of chiral alcohols with two stereogenic centers in a single chemical operation. In 1996, Noyori and co-workers realized the asymmetric hydrogenation of racemic α-alkylcyclohexanones via DKR by using [$RuCl_2$-(*S*)-BINAP/(*R*,*R*)-DPEN] (BINAP = 2,2′-bis- (diphenylphosphino)-1,1′-binaphthyl; DPEN = 1,2-diphenyl-ethylenediamine) as a catalyst [12]. Since then, the asymmetric hydrogenation of the conformationally anchored racemic α-substituted cycloalkanones has received intensive attention; excellent enantioselectivities and diastereoselectivities have been achieved [13–19]. High enantioselectivities and diastereoselectivities have also been obtained in the asymmetric hydrogenation of racemic α-substituted arylketones with $RuCl_2$-diphosphine/diamine catalysts [20,21]. However, the asymmetric hydrogenation of conformationally flexible racemic α-substituted acyclic dialkyl ketones is far from success. For example, in the asymmetric hydrogenation of racemic 3-(3-bromo-phenyl)-4-(4-chlorophenyl)butan-2-one, Chen et al. [22] gained the corresponding alcohol in high enantioselectivity (95% ee) but with low diastereoselectivity (dr = 8:1) by using [$RuCl_2$((*S*)-Xyl-BINAP)((*S*)-DAIPEN)] (Xyl-BINAP = 2,2′-bis[di-(3.5-dimethylphenyl)phosphino]-1,1′-binaphthyl; DAIPEN = 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) as a catalyst. A higher diastereoselectivity (dr = 23:1), but with lower enantioselectivity (88% ee), could be achieved by using [$RuCl_2$((*S*)-Xyl-PhanePhos)((*S*, *S*)-DPEN)] (Xyl- PhanePhos = 4,12-bis (diphenylphosphino)[2.2]-paracyclophane) as a catalyst. Thus, the asymmetric hydrogenation of conformationally flexible racemic α-substituted acyclic dialkyl ketones is still a challenge for chemists.

The $RuCl_2$-SDPs/diamine (SDPs = 7,7′-bis(arylphosphino)-1,1′-spirobiindanes) catalysts, developed by us [23], have been demonstrated to be highly efficient for the asymmetric hydrogenation of racemic α-substituted cycloalkanones [13,14], racemic α-alkyl arylaldehydes [24] via DKR, yielding the corresponding chiral alcohols with good to excellent enantioselectivities. These encouraging results spurred us to investigate the potential of the $RuCl_2$-SDPs/diamine catalysts for application in the asymmetric hydrogenation of racemic α-alkyl arylacetones. In this article, we wish to describe our results of the study on the asymmetric hydrogenation of racemic α-alkyl arylacetones, providing the corresponding chiral alcohols in high yields with high enantioselectivities (up to 97% ee) and good *syn*/*anti* stereoselectivities (up to 97:3) (Scheme 2).



Scheme 1 Chiral drugs with (2*R*,3*S*)-3,4-diarylbutan-2-ol unite.



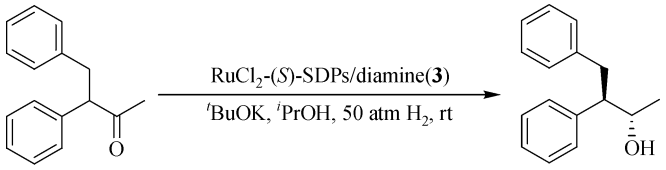
Scheme 2 Asymmetric hydrogenation of α-alkyl arylacetones.

2 Results and discussion

The enantioselective hydrogenation of racemic 3,4-diphenylbutan-2-one **1a** was initially performed under standard reaction conditions (50 atm H_2, S/C = 1000, 0.2 mol/L of substrate, and 0.04 mol/L of ^{t}BuOK in ^{i}PrOH at room temperature). From the data in Table 1, we can see that the substituents on *P*-phenyl rings of the SDP ligand imposed obvious effects on both the enantioselectivity and *syn*/*anti* stereoselectivity of the reaction. The ligand Xyl-SDP, with 3,5-dimethyl groups on *P*-phenyl rings, yielded the best results (*syn*/*anti* = 90∶10, 95% ee for *syn*-isomer) (Table 1, entry 4). When diamine (*R*,*R*)-DPEN, instead of (*R*,*R*)-DACH (DACH = 1,2-diaminocyclohexane), was used, the *syn*/*anti* stereoselectivity became slightly lower, and the enantioselectivity of the *syn*-isomer was dramatically decreased to 19% ee (Table 1, entry 6). Similar diminishment in *syn*/*anti* stereoselectivity and enantioselectivity was observed in the reaction using diamine (*S*,*S*)-DACH (Table 1, entry 7). These results showed that (*S*,*RR*)-**3d** is a catalyst of choice in terms of *syn*/*anti* stereoselectivity and enantioselectivity. The concentration of base ^{t}BuOK also has a manifest effect on the enantioselectivity of the reaction. Both the increase and decrease of the concentration of ^{t}BuOK reduced the enantioselectivity of the *syn*-isomer of the product (entries 8 and 9 vs 4). A higher concentration of the substrate gave lower enantioselectivity of the reaction (entries 10 and 11 vs 4). However, hydrogen pressure has little influence on the selectivities. When the hydrogenation was performed at 30 atm, the enantiomeric excess remained unchanged (entries 12 vs 4).

A variety of racemic α-alkyl arylacetones **1a-n** can be hydrogenated under the optimized reaction conditions. From the results listed in Table 2, we can see that the alkyl group at the α-position of the arylacetones **1** imposed a crucial effect on *syn*/*anti*-selectivity. When the α-alkyl group was methyl (**1b**), the hydrogenated product (**2b**) was slightly dominated by the *anti*-isomer (*syn*/*anti*: 34/66) with good enantioselectivity (84% ee) (Table 2, entry 2). This result is different from that obtained with α-benzylic substrate **1a**, which generated the *syn*-isomer as the major product (entry 1). Similar results have been obtained in the reactions of the substrates with α-ethyl (**1c**) and α-isopropyl (**1d**) (entries 3 and 4). It is very interesting that only the substrate with α-benzyl generated the desired *syn*-isomer of the hydrogenated product with higher diastereoselectivity (*syn*/*anti*: 90:10) and enantioselectivity (95% ee, entry 1). Considering that the diastereoslectivity of the hydrogenation is dependent not only on the catalyst but also on the rate of the racemization of the ketone under basic conditions, the electronic nature of the substituents on the 3-phenyl of substrate **1** may play an important role in the reaction. A series of racemic α-benzyl arylacetones **1e-n** with

Table 1 Asymmetric hydrogenation. Condition optimization.[a)]



1a **2a**

entry	Cat.	SDPs	diamine	*syn*/*anti* [b)]	ee (%) [c)]
1	(*S*,*RR*)-**3a**	(*S*)-SDP	(*R*,*R*)-DACH	67:33	62,69
2	(*S*,*RR*)-**3b**	(*S*)-An-SDP	(*R*,*R*)-DACH	70:30	62,59
3	(*S*,*RR*)-**3c**	(*S*)-Tol-SDP	(*R*,*R*)-DACH	65:35	63,52
4	(*S*,*RR*)-**3d**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	90:10	95,59
5	(*S*,*RR*)-**3e**	(*S*)-DMM-SDP	(*R*,*R*)-DACH	88:12	79,45
6	(*S*,*RR*)-**3f**	(*S*)-Xyl-SDP	(*R*,*R*)-DPEN	81:19	19,77
7	(*S*,*SS*)-**3g**	(*S*)-Xyl-SDP	(*S*,*S*)-DACH	76:24	13,30
8 [d)]	(*S*,*RR*)-**3c**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	89:11	93,53
9 [e)]	(*S*,*RR*)-**3c**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	87:13	89,52
10 [f)]	(*S*,*RR*)-**3c**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	86:14	89,50
11 [g)]	(*S*,*RR*)-**3c**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	86:14	89,48
12 [h)]	(*S*,*RR*)-**3c**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	86:14	94,46

a) The reactions were performed at S/C = 1000 using $RuCl_2$-(*S*)-SDPs/diamine complex **3** as the catalyst, 0.2 mol/L of **1a**, and 0.04 mol/L of ^{t}BuOK, at 50 atm of H_2 and room temperature (25–30°C) for 10 h unless otherwise stated. The conversion is 100%, determined by GC or HPLC.
b) Determined by GC or HPLC.
c) The ee values were determined by HPLC; the former for *syn*-isomer and the latter for *anti*-isomer.
d) [^{t}BuOK] = 0.02 mol/L.
e) [*t*BuOK] = 0.06 mol/L.
f) 0.4 mol/L of **1a**.
g) 0.6 mol/L of **1a**.
h) 30 atm.

different substituents have been synthesized and evaluated. When the substituent was at the *para*-position, the electronic property of the substituent imposed a manifest effect on neither the diastereoselectivity nor the enantioselectivity. Compared with unsubstituted substrate **1a**, (entries 5-8), all *para*-substituted substrates yielded slightly lower *syn*/*anti* stereoselectivities and enantioselectivities of the *syn*-isomer. Higher *syn*-selectivity and enantioselectivity of the *syn*-isomer were obtained using the substrates with an *ortho*-substituent (entries 11-13). The substrate **1j**, which has a 2-MeO group, gave the highest *syn*-selectivity (97∶3) but with a slightly lower enantioselectivity of the *syn*-isomer (92% ee) (entry 10). These results showed that the substituent on the *ortho*-position of the 3-phenyl ring of the substrates is beneficial for the catalyst to discriminate the enantiotopic faces of the ketones and therefore increase the enatioselectivity of the products.

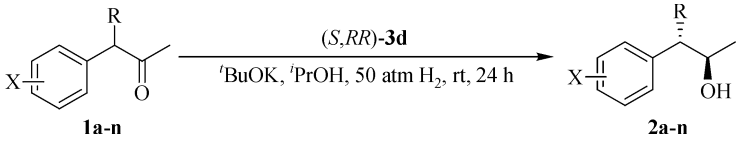
The (2*R*,3*S*)-4-(3,4-dichlorophenyl)-3-(2-fluoro-4- biphenylyl) butan-2-ol ((2*R*,3*S*)-**5**), which was a key intermediate for the squalene synthase inhibitor J-104,118 [1,2], could be synthesized using this protocol (Scheme 3). The asymmetric hydrogenation of the racemic ketone **4** was performed smoothly under the optimized reaction conditions by using the catalyst (*S*,*RR*)-**3d**. The product (2*R*,3*S*)-**5** was obtained in high yield (96%) with good enantioselectivity (90% ee) and *syn*-selectivity (*syn*/*anti* = 86:14).

3 Experimental

3.1 Preparation of α-alkyl arylacetones

General procedure [25] The mixture of aryl acetone (25 mmol), potassium hydroxide (50 mmol), and tetrabutylammonium iodide (0.25 mmol) in 10 mL anhydrous ether was stirred at room temperature for 1 h. The appropriate alkyl halide (25 mmol) was added slowly, and the mixture was stirred for several hours for the reaction to complete (monitored by thin layer chromatography). The reaction mixture was filtrated through diatomite and washed with ether, and evaporated to yield the residue. The residue was purified by chromatography on a silica gel column or by distillation to provide the pure products.

Table 2 Asymmetric hydrogenation of racemic α-alkylarylacetones using catalyst (*S*,*RR*)-**3d**.[a)]



1a-n **2a-n**

Entry	R	X	**2**	*syn*/*anti* [b)]	ee (%) [b)]
1	Bn	H	**2a**	90:10	95,59
2	Me	H	**2b**	34:66	56,84 [c)]
3	Et	H	**2c**	37:63	74,89 [c)]
4	^{i}Pr	H	**2d**	42:58	92,92
5	Bn	4-MeO	**2e**	86:14	88,63
6	Bn	4-Me	**2f**	83:17	87,70
7	Bn	4-Br	**2g**	83:17	85,74
8	Bn	4-Cl	**2h**	85:15	90,74
9	Bn	3-MeO	**2i**	84:16	92,86
10	Bn	2-MeO	**2j**	97:3	92,–
11	Bn	2-Br	**2k**	90:10	97,70
12	Bn	2-Cl_2	**2l**	92:8	96,49
13	Bn	2,4-Cl	**2m**	91:9	95,42
14	Bn	-$(CH)_4$-	**2n**	80:20	97,60

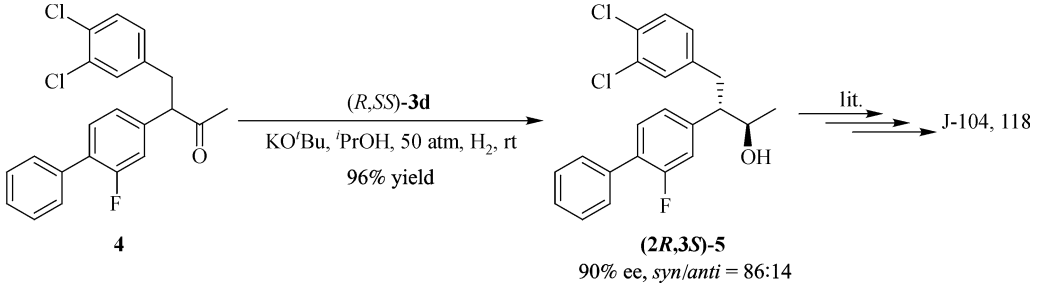
a) Reactions were performed at 25–30°C under 50 atm of H_2 pressure using a 0.4 mmol/mL solution of **1** in ^{i}POH containing (*S*,*RR*)-**3c** (S/C = 1000) and ^{t}BuOK ([^{t}BuOK] = 0.04 mmol/mL). The conversions were 100%, determined by GC or HPLC.
b) Determined by GC or HPLC, the former for *syn*-isomer and the latter for *anti*-isomer.
c) (2*R*,3*S*) for *syn*-isomer and (2*S*,3*S*) for *anti*-isomer.

3-(4-methylphenyl)-4-phenylbutan-2-one (1f): Colorless liquid, 79% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01 (s, 3H), 2.32 (s, 3H), 2.88 (dd, *J* = 13.6 and 7.2 Hz, 1H), 3.41 (dd, *J* = 13.6 and 7.2 Hz, 1H), 3.89 (t, *J* = 7.2 Hz, 1H), 7.04–7.22 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.7, 140.2, 137.2, 135.9, 130.0, 129.4, 128.6, 126.4, 61.3, 38.7, 29.6, 21.4. Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.72; H, 7.8. MS (EI) m/z 238 (M^+).

3-(4-bromophenyl)-4-phenylbutan-2-one (1g): White solid, 60% yield, mp 67–68.5°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 3H), 2.86 (dd, *J* = 13.6 and 7.6 Hz, 1H), 3.38 (dd, *J* = 14.0 and 7.2 Hz, 1H), 3.88 (t, *J* = 7.6 Hz, 1H), 7.00–7.43 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.3, 139.4, 137.6, 132.3, 130.3, 129.2, 128.6, 126.6, 121.7, 61.0, 38.6, 29.9. Anal. Calcd. for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Found: C, 63.44; H, 5.14. MS (EI) m/z 302 (M^+).

3-(2-methoxyphenyl)-4-phenylbutan-2-one (1j): Light yellow liquid, 85 % yield, bp 158°C/1 mmHg. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90 (s, 3H), 2.89 (dd, *J* = 13.6 and 7.2 Hz, 1H), 3.47 (dd, *J* = 13.6 and 7.2 Hz, 1H), 3.61 (s, 3H), 4.38 (t, *J* = 7.0 Hz, 1H), 6.77–7.18 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.5, 157.2, 140.6, 129.4, 129.1, 128.7, 128.3, 127.7, 126.2, 121.2, 111.3, 55.6, 54.3, 37.3, 29.4. Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.72; H, 7.62. MS (EI) m/z 254 (M^+).

3-(2-bromophenyl)-4-phenylbutan-2-one (1k): Light yellow



4 **(2*R*,3*S*)-5**
90% ee, *syn*/*anti* = 86:14

Scheme 3 Asymmetric synthesis of 3,4-diarylbutan-2-ol (2*R*,3*S*)-5.

liquid, 86% yield, bp 163–164°C/1 mmHg. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.99 (s, 3H), 2.87 (dd, J = 13.8 and 6.6 Hz, 1H), 3.39 (dd, J = 13.8 and 8.1 Hz, 1H), 4.58 (t, J = 7.2 Hz, 1H), 7.07–7.55 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.6, 139.4, 138.3, 133.4, 129.2, 129.2, 129.0, 128.4, 128.2, 126.4, 125.5, 59.3, 37.9, 29.8. Anal. Calcd. for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Found: C, 63.31; H, 4.90. MS (EI) m/z 302 (M^+).

3-(2,4-dichlorophenyl)-4-phenylbutan-2-one (1m): White solid, 85% yield, mp 86–88°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.03 (s, 3H), 2.88 (dd, J = 13.8 and 7.0 Hz, 1H), 3.39 (dd, J = 13.6 and 7.6 Hz, 1H), 4.52 (t, J = 7.2 Hz, 1H), 7.08–7.39 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6, 139.0, 135.2, 135.1, 134.0, 130.1, 129.9, 129.2, 128.6, 127.9, 126.6, 56.4, 37.8, 30.2. Anal. Calcd. for $C_{16}H_{14}Cl_2O$: C, 65.55; H, 4.81. Found: C, 65.34; H, 5.00. MS (EI) m/z 292 (M^+).

3-(naphthalen-1-yl)-4-phenylbutan-2-one (1n): Light yellow liquid, 81 % yield, bp 193–194°C/1 mmHg. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.94 (s, 3H), 3.00 (dd, J = 14.0 and 6.2 Hz, 1H), 3.65 (dd, J = 13.8 and 7.8 Hz, 1H), 4.61 (t, J = 6.9 Hz, 1H), 7.07–8.04 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.2, 140.5, 135.5, 134.6, 132.0, 129.5, 129.3, 128.6, 128.3, 126.9, 126.4, 126.4, 126.1, 125.9, 123.4, 57.6, 38.3, 29.1. HRMS (ESI) m/z Calcd. for $C_{20}H_{18}O$ ([M + Na]$^+$): 297.1250. Found: 297.1252.

3.2 Asymmetric hydrogenation of racemic α-alkyl arylacetones

General procedure The catalyst (0.002 mmol) was placed in a 30 mL hydrogenation vessel. Anhydrous ^{i}PrOH (8.0 mL) was introduced using a syringe, and the vessel was purged with hydrogen and pressurized to 30 atm. After releasing the pressure, α-alkyl arylacetones (2 mmol) and a solution of ^{t}BuOK in ^{i}PrOH (0.2 mmol/mL, 2.0 mL, 0.4 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirring at room temperature for 8–20 h, the reaction was stopped. The diastereoselectivities and enantioselectivities of the corresponding alcohols were determined by GC or HPLC analyses after flash chromatography on a silica gel column.

3,4-diphenylbutan-2-ol (2a): White solid, 96% yield, *syn*/*anti* = 90:10. *syn*-isomer, mp 34–36.5°C, 95% ee, $[\alpha]_D^{20}$ + 105.7 (c 1.03, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.4 Hz, 3H), 1.27 (d, J = 4.8 Hz, 1H), 2.83 (dd, J = 14.4 and 6.0 Hz, 1H), 2.92 (dd, J = 13.2 and 8.8 Hz, 1H), 3.18 (dd, J = 13.2 and 6.0 Hz, 1H), 3.99 (m, 1H), 7.06–7.31 (m, 10H). The ee value of **2a** was determined by HPLC analysis using a Chiralcel OD column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 9.49 min; t_R (major) = 12.26 min].

3-phenylbutan-2-ol (2b) [26]**:** Colorless liquid, 95% yield, *syn*/*anti* = 34:66. *anti*-isomer, 84 % ee (2*S*,3*S*), $[\alpha]_D^{20}$ + 0.8 (c 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, J = 6.3 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H), 1.38(d, J = 4.8 Hz, 1H), 2.69–2.79 (m, 1H), 3.83–3.93 (m, 1H), 7.19–7.34 (m, 5H). *syn*-isomer, 56 % ee (2*R*,3*S*), $[\alpha]_D^{20}$ – 12.4 (c 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 7.2 Hz,3H), 1.36 (d, J = 3.6 Hz, 1H), 2.63–2.73 (m, 1H), 3.82–3.88 (m, 1H), 7.21–7.37 (m, 5H). The ee value of *anti*-**2b** and *syn*-**2b** were determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; *anti*-**2b**: ^{i}PrOH /*n*-Hex = 1:99, 1.0 mL/min, 254 nm; t_R (2*S*,3*S*) = 9.78 min; t_R (2*R*,3*R*) = 10.54 min; *syn*-**2b**: ^{i}PrOH /^{n}Hex = 1:99, 1.0 mL/min, 254 nm; t_R(2*S*,3*R*) = 8.98 min; t_R (2*R*,3*S*) = 9.23 min].

3-phenylpentan-2-ol (2c): Colorless liquid, 97% yield, *syn*/*anti* = 37:63. *anti*-isomer, 89% ee (2*S*,3*S*), $[\alpha]_D^{20}$ + 27.5 (c 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.76 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H), 1.41 (d, J = 6.0 Hz, 1H), 1.56–1.69 (m, 1H), 1.94–2.03 (m, 1H), 2.43–2.50 (m, 1H), 3.87–3.93 (m, 1H), 7.14–7.33 (m, 5H). *syn*-isomer, 74% ee (2*R*,3*S*), $[\alpha]_D^{20}$ + 9.8 (c 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.76 (t, J = 7.4 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 4.2 Hz, 1H), 1.63–1.69 (m, 1H), 1.73–1.85 (m, 1H), 2.37–2.47 (m, 1H), 3.87–3.98 (m, 1H), 7.13–7.38 (m, 5H). The ee value of *anti*-**2c** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (2*S*,3*S*) = 6.15 min; t_R (2*R*,3*R*) = 6.86 min]. The ee value of *syn*-**2c** was determined by HPLC analysis using a Chiralcel OJ column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 2:98, 1.0 mL/min, 254 nm; t_R(2*S*,3*R*) = 9.43 min; t_R(2*R*,3*S*) = 12.76 min].

4-methyl-3-phenylpentan-2-ol (2d): 96% yield, *syn*/*anti* = 42:58. *anti*-isomer, white solid, mp 58–60.5°C. 92% ee, $[\alpha]_D^{20}$ + 4.51 (c 1.02, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 5.4 Hz, 1H), 2.13–2.29 (m, 1H), 2.48 (t, J = 7.5 Hz, 1H), 4.15–4.26 (m, 1H), 7.11–7.33 (m, 5H). *syn*-isomer, colorless liquid, 92% ee, $[\alpha]_D^{20}$ + 19.7 (c 1.02, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.73 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.0 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 5.1 Hz, 1H), 2.11–2.22 (m, 2H), 4.26–4.30 (m, 1H), 7.19–7.34(m, 5H). The ee value of *anti*-**2d** was determined by HPLC analysis using a Chiralcel OJ column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 2:98, 1.0 mL/min, 209.8 nm; t_R (minor) = 9.56 min; t_R (major) = 11.30 min]. The ee value of *syn*-**2d** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 1:99, 1.0 mL/min, 254 nm; t_R (minor) = 7.00 min; t_R (major) = 7.37 min].

3-(4-methoxyphenyl)-4-phenylbutan-2-ol (2e): Colorless liquid, 96% yield, *syn*/*anti* = 86:14. *syn*-isomer, 88% ee, $[\alpha]_D^{20}$ + 104.7 (*c* 1.02, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 5.1 Hz, 1H), 2.74–2.92 (m, 2H), 3.13 (q, 1H), 3.78 (s, 3H), 3.9–4.02 (m, 1H), 6.76–7.25 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 140.7, 132.6, 130.1, 129.2, 128.2, 125.9, 113.8, 69.6, 55.2, 54.4, 38.7, 21.6. Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.10; H, 7.43. MS (EI) m/z 256 (M^+). The ee value of *syn*-**2b** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 10.17 min; t_R (major) = 14.32 min].

3-(4-methylphenyl)-4-phenylbutan-2-ol (2f): White solid, 96% yield, *syn*/*anti* = 83:17. *syn*-isomer, mp 64–67°C, 87% ee, $[\alpha]_D^{20}$ + 102.6 (*c* 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (d, *J* = 6.3 Hz, 3H), 1.30 (d, *J* = 5.4 Hz, 1H), 2.30 (s, 3H), 2.75–2.94 (m, 2H), 3.14 (q, 1H), 3.90–4.00 (m, 1H), 7.05–7.24 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.8, 137.6, 136.5, 129.3, 129.2, 128.4, 126.1, 69.7, 55.0, 38.8, 21.9, 21.3. Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.29; H, 8.92. MS (EI) m/z 240 (M^+). The ee value of *syn*-**2f** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 5.85 min; t_R (major) = 7.58 min].

3-(4-bromophenyl)-4-phenylbutan-2-ol (2g): White solid, 96% yield, *syn*/*anti* = 83:17. *syn*-isomer, mp 62–63.5°C, 85% ee, $[\alpha]_D^{20}$ + 101.3 (*c* 1.01, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, *J* = 6.3 Hz, 3H), 1.28 (d, *J* = 4.8 Hz, 1H), 2.76–2.93 (m, 2H), 3.14 (q, 1H), 3.93–4.03 (m, 1H), 7.03–7.41 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.1, 139.9, 131.4, 131.0, 129.1, 128.3, 126.1, 120.6, 69.3, 54.6, 38.6, 21.8. Anal. Calcd. for $C_{16}H_{17}BrO$: C, 62.96; H, 5.61. Found: C, 62.97; H, 5.67. MS (EI) m/z 304 (M^+). The ee value of *syn*-**2g** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 7.58 min; t_R (major) = 9.25 min].

3-(4-chlorophenyl)-4-phenylbutan-2-ol (2h): White solid, 96% yield, *syn*/*anti* = 85:15. *syn*-isomer, mp 73–76°C, 90% ee, $[\alpha]_D^{20}$ + 117.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.13 (d, *J* = 6.3 Hz, 3H), 1.34 (d, *J* = 5.1 Hz, 1H), 2.76–2.92 (m, 2H), 3.14 (q, 1H), 3.92–4.02 (m, 1H), 7.03–7.25 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.3, 139.6, 132.7 130.9, 129.4, 128.7, 128.6, 126.3, 69.6, 54.7, 38.9, 22.0. Anal. Calcd. for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57. Found: C, 73.63; H, 6.41. MS (EI) m/z 260 (M^+). The ee value of *syn*-**2h** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 7.87 min; t_R (major) = 9.37 min].

3-(3-methoxyphenyl)-4-phenylbutan-2-ol (2i): Colorless liquid, 95% yield, *syn*/*anti* = 84:16. *syn*-isomer, 92% ee, $[\alpha]_D^{20}$ + 94.9 (*c* 1.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.34 (d, *J* = 5.1 Hz, 1H), 2.78–2.95 (m, 2H), 3.14 (q, 1H), 3.76 (s, 3H), 3.95–4.0 (m, 1H), 6.74–7.22 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 142.7, 140.7, 129.5, 129.4, 128.4, 126.1, 121.8, 115.4, 112.1, 69.7, 55.5, 54.4, 38.7, 21.8. Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.80; H, 7.95. MS (EI) m/z 256 (M^+). The ee value of *syn*-**2i** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 5.67 min; t_R (major) = 6.53 min].

3-(2-methoxyphenyl)-4-phenylbutan-2-ol (2j): Colorless liquid, 95% yield, *syn*/*anti* = 97:3. *syn*-isomer, 92% ee, $[\alpha]_D^{20}$ +55.3 (*c* 1.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (d, *J* = 6.4 Hz, 3H), 2.32 (s, 1H), 3.04–3.31 (m, 2H), 3.57 (q, 1H), 3.76 (s, 3H), 4.14–4.17 (m, 1H), 6.88–7.37 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0, 141.3, 130.1, 129.5, 128.4, 127.9, 126.0, 121.0, 111.2, 71.1, 69.4, 55.7, 37.8, 21.8. Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.95; H, 8.00. MS (EI) m/z 256 (M^+). The ee value of *syn*-**2j** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 7.06 min; t_R (major) = 7.71 min].

3-(2-bromophenyl)-4-phenylbutan-2-ol (2k): Colorless liquid, 95% yield, *syn*/*anti* = 90:10. *syn*-isomer, 97% ee, $[\alpha]_D^{20}$ + 23.9 (*c* 1.04, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.37 (d, *J* = 5.6 Hz, 1H), 2.92–3.2 (m, 2H), 3.65 (q, 1H), 4.03 (m, 1H), 7.04–7.54 (m, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.5, 139.9, 132.9, 129.7, 129.2, 128.3, 128.0, 127.4, 126.7, 126.1, 69.3, 51.6, 38.3, 21.3. Anal. Calcd. for $C_{16}H_{17}BrO$: C, 62.96; H, 5.61. Found: C, 63.07; H, 5.72. MS (EI) m/z 304 (M^+). The ee value of *syn*-**2k** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 6.17 min; t_R (major) = 7.29 min].

3-(2-chlorophenyl)-4-phenylbutan-2-ol (2l): Colorless liquid, 95% yield, *syn*/*anti* = 92:8. *syn*-isomer, 96% ee, $[\alpha]_D^{20}$ +38.4 (*c* 1.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (d, *J* = 6.4 Hz, 3H), 1.94 (s, 1H), 3.04–3.3 (m, 2H), 3.76 (q, 1H), 4.13 (m, 1H), 7.15–7.61 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.2, 138.9, 135.6, 129.7, 129.8, 129.4, 128.6, 127.9, 127.0, 126.3, 69.4, 49.0, 38.3, 21.6. Anal. Calcd. for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57. Found: C, 73.68; H, 6.55. MS (EI) m/z 260 (M^+). The ee value of *syn*-**2l** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 6.42 min; t_R (major) = 7.92 min].

3-(2,4-dichlorophenyl)-4-phenylbutan-2-ol (2m): Colorless liquid, 95% yield, *syn*/*anti* = 91:9. *syn*-isomer, 95% ee, $[\alpha]_D^{20}$ + 59.6 (*c* 1.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (d, *J* = 6.0 Hz, 3H), 2.24 (s, 1H), 3.00–3.29 (m, 2H), 3.73 (q, 1H), 4.12 (m, 1H), 7.24–7.58 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.9, 137.7, 136.1, 132.9, 131.0, 129.5, 129.4, 128.7, 127.3, 126.5, 69.2, 48.6, 38.4, 21.6. Anal. Calcd. for $C_{16}H_{16}Cl_2O$: C, 65.10; H, 5.46. Found: C, 65.12; H, 5.41. MS (EI) m/z 294 (M^+). The ee value of *syn*-**2m** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 6.74 min; t_R (major) = 7.56 min].

3-(2-naphthyl)-4-phenylbutan-2-ol (2n): Colorless liquid, 95% yield, *syn*/*anti* = 80:20. *syn*-isomer, 97% ee, $[\alpha]_D^{20}$ – 33.6 (*c* 1.15, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (d, *J* = 5.2 Hz, 3H), 1.47 (d, *J* = 5.2 Hz, 1H), 3.07–3.39 (m, 2H), 3.95 (q, 1H), 4.18 (m, 1H), 7.09–8.08 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6, 137.5, 134.2, 133.3, 129.3, 129.1, 128.4, 127.4, 126.1, 125.6, 125.2, 123.5, 70.0, 47.5, 38.5, 21.7. HRMS (ESI) m/z Calcd. for $C_{20}H_{20}O$ ($[M + Na]^+$): 299.1406. Found: 299.1408. The ee value of *syn*-**2n** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH/^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (minor) = 8.95 min; t_R (major) = 11.46 min].

(2*R*,3*S*)-4-(3,4-dichlorophenyl)-3-(2-fluoro-4-biphenylyl) butan-2-ol (5): Colorless liquid, 96% yield, *syn*/*anti* = 86:14. *syn*-isomer, 90% ee, $[\alpha]_D^{20}$ + 134 (*c* 1.0, $CHCl_3$) [Lit.[1b] $[\alpha]_D^{20}$ + 148 (*c* 1.0, $CHCl_3$)]. The ee value of **5** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm × 0.46 cm ID; ^{i}PrOH /^{n}Hex = 8:92, 1.0 mL/min, 254 nm; t_R (2*R*,3*S*) = 8.84 min; t_R (2*S*,3*R*) = 9.90 min].

4 Conclusion

Chiral complex [$RuCl_2$-(*S*)-Xyl-SDP/(*R*,*R*)-DPEN] ((*S*,*RR*)-**3d**) was demonstrated to be an effective catalyst for the asymmetric hydrogenation of *racemic* α-alkyl arylacetones **1a-n** via dynamic kinetic resolution. In the asymmetric hydrogenation of *α*-methyl, ethyl, or isopropyl substituted arylacetones, the corresponding products were dominated by *anti*-isomers with lower diastereoselectivies and good to high enantioselectivities (84%–92% ee), while the asymmetric hydrogenation of *α*-benzylic substrates provided products dominated by *syn*-isomers with high diastereoselectivities (*syn*/*anti*: 80:20 to 97:3) and high enantioselectivtes (85%–97% ee). The catalytic asymmetric hydrogenation of the *α*-benzylic arylacetones is a useful method for the synthesis of optically active *α*-benzylic alcohols, such as (2*R*,3*S*)-4-(3,4-dichlorophenyl)-3-(2-fluoro-4-biphenylyl)butan-2-ol, the key intermediate for the synthesis of the squalene synthase inhibitor, J-104118.

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