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Stereoselective Synthesis of Optically Active Hydrobenzoins via Asymmetric Hydrogenation of Benzils with Ru(OTf)(TsDPEN)(η^6-cymene) as the Pre-catalyst

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Optically active hydrobenzoins are very important building blocks for further derivation of biologically active complexes, natural products, and pharmaceutical compounds. In this paper, A practical approach has been developed for asymmetric hydrogenation of benzils with Ru(OTf)(TsDPEN)(η^6-cymene) as a pre-catalyst in methanol. Therefore, a series of chiral hydrobenzoins was synthesized in good yields with good to moderate diastereoselectivities and good to excellent enantioselectivities.

Keywords asymmetric catalysis, benzil, ruthenium, hydrogenation, hydrobenzoin

Introduction

Optically active 1,2-diols, particularly, hydrobenzoins are versatile intermediates for the synthesis of biologically active compounds and also are related to the research area of asymmetric synthesis as ligands[1] and auxiliaries.[2] Chiral hydrobenzoins have been commonly prepared by asymmetric dihydroxylation (AD) reactions,[3] pinacol couplings of aldehydes or ketones,[4] resolutions of racemic hydrobenzoins[5] and asymmetric reductions.[6] Among various methods, asymmetric hydrogenation of benzils and benzoins represent one of the most direct and atom-economic approaches. To the best of our knowledge, limited literatures have been explored for this purpose so far, although asymmetric hydrogenation of simple ketones has been extensively studied.[7] The first asymmetric hydrogenation of 1,2-diketones was reported by Noyori and coworkers in the presence of (*R*)-BINAP-Ru(II) complexes. The hydrogenation of diacetyl furnishes a 26∶74 mixture of enantiomerically pure (*R*,*R*)-2,3-butanediol and the meso-diol. Unsatisfactorily, (*R*)-BINAP-Ru catalyzed hydrogenation of the benzil offers the meso-hydrobenzoin in 100% yield.[8] Mechanistically, it is explained in the way that the substrate control in the second hydrogenation step of the hydroxy ketone intermediate favored meso-diol formation. Subsequently, the asymmetric transfer hydrogenation (ATH) of benzils was reported by Ikariya *et al.* using chiral arene-*N*-tosyl-ethylenediamine-Ru(II) (Ru-TsDPEN) as a catalyst and the HCOOH/Et_3N＝5∶2 as a hydrogen source in DMF, which yielded hydrobenzoins of high diastereomeric and enantiomeric purities (Scheme 1).[9]

In the past several years, Noyori and Ohkuma have discovered that Ru(OTf)(cymene)(TsDPEN) and Cp*Ir(OTf)(MSDPEN) complexes, well-known catalysts for asymmetric transfer hydrogenation (ATH),[10] could be employed to catalyze the asymmetric hydrogenation of simple ketones through a slightly functional modification of the catalyst and by changing the reaction conditions.[11] Later on, Fan *et al.* and Xiao's group have respectively reported that the complexes of the same ligand system with various metal centers (Rh, Ir and Ru) and different counteranions were highly effective catalysts for the asymmetric hydrogenation of quinoline derivatives and prochiral imine compounds with excellent enantiomeric excess.[12] As a good example of phosphine-free catalyst, Ru-TsDPEN has deserved more studies on its catalytic activity, especially in the field where phosphine complexes have not performed well (Scheme 1).[8] In search for an efficient way to synthesize 1,2-diols via hydrogenation, herein, we reported our preliminary results on the asymmetric hydrogenation reactions of benzils catalyzed by an η^6-arene/*N*-tosyl-ethylenediamine-ruthenium(II) catalyst, by which a series of hydrobenzoins were provided in good yields with good to excellent enantioselectivities as well as moderate to good diastereoselectivities (Scheme 1).

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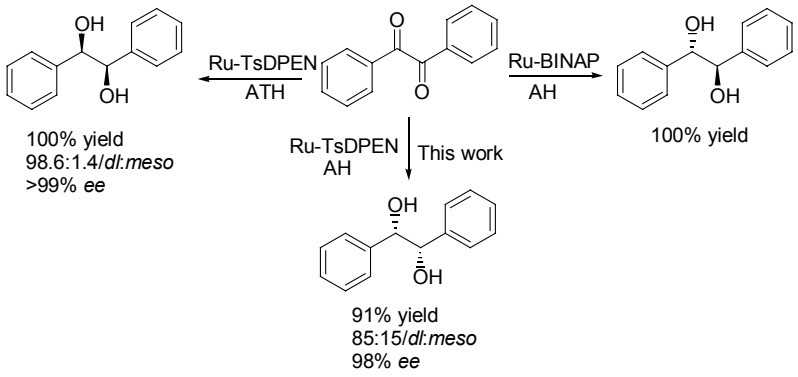
Scheme 1 Asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) of the benzil



Experimental

General procedure for asymmetric hydrogenation of benzils

Benzils (0.2 mmol), (*R*,*R*)-**1a** (3 mg, 4 μmol), and degassed MeOH (2 mL) were added to a glass tube under nitrogen. The tube was then placed into a stainless steel autoclave, which was purged with hydrogen gas for three times before pressurized with H_2 to 30 atm. Subsequently, the mixture was stirred under this H_2 pressure at r.t. for 24 h. After careful release of the hydrogen, organic layer was concentrated to afford the crude product. Purification was performed with a silica gel column eluted with petroleum ether/ethyl acetate (4∶1, *V*/*V*) to give the pure product.

Spectral data of 3a—4o

1,2-Diphenyl-ethane-1,2-diol (3a) 91% yield, 98% *ee*, *d.r.*=85∶15. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.8 mL/min; λ=210 nm: t_{major}=17.3 min, t_{minor}=19.3 min, t_{meso}=23.6 min. $[\alpha]_D^{28}$ =−68.1 (*c* 0.99 in C_2H_5OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 2H, *meso*), 3.1 (s, 2H, *dl*), 4.65 (s, 2H, *dl*), 4.79 (s, 2H, *meso*), 7.09 (s, 4H) , 7.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 79.0, 126.9, 127.1, 127.8, 128.1, 139.8. ESI-HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{14}H_{14}NaO_2$: 237.0886; found 237.0892.

1,2-Bis-(4-fluoro-phenyl)-ethane-1,2-diol (3b) 92% yield, 83% *ee*, *d.r.*=57∶43. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.8 mL/min; λ=210 nm: t_{minor}=16.7 min, t_{major}=18.9 min, t_{meso}=21.9 min. $[\alpha]_D^{28}$ =−26 (*c* 0.51 in C_2H_5OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 2H, *meso*), 3.02 (s, 2H, *dl*), 4.60 (s, 2H, *dl*), 4.81 (s, 2H, *meso*), 6.94 (t, *J*=8.4 Hz, 3H), 7.03 (s, 3H), 7.14(s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.9, 115.1, 115.4, 128.9, 135.6. ESI-HRMS *m*/*z*: $[M+Na]^+$calcd for $C_{14}H_{12}F_2NaO_2$: 273.0698; found 273.0700.

1,2-Bis-(4-chloro-phenyl)-ethane-1,2-diol (3c) 95% yield, 86% *ee*, *d.r.*=60∶40. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.3 mL/min; λ=210 nm: t_{minor}=47.3 min, t_{major}=48.8 min, t_{meso}=55.9 min. $[\alpha]_D^{28}$ =−43 (*c* 1.76 in C_2H_5OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.71 (s, 2H, *meso*), 3.12 (s, 2H, *dl*), 4.53 (s, 2H, *dl*), 4.76 (s, 2H, *meso*), 6.98 (dd, *J*=8.1 Hz, 4H), 7.20 (dd, *J*=9.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.7, 128.5, 128.6, 134.1, 137.9, 138.1. ESI-HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_2NaO_2$: 305.0107; found 305.0107.

1,2-Bis-(4-bromo-phenyl)-ethane-1,2-diol (3d) 96% yield, 81% *ee*, *d.r.*=53∶47. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.3 mL/min; λ=210 nm: t_{minor}=53.9 min., t_{major}=57.4 min., t_{meso}=63.5 min. $[\alpha]_D^{28}$ =−35 (*c* 1.95 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.68 (s, 2H, *meso*), 3.24 (s, 2H, *dl*), 4.51 (s, 2H, *dl*), 4.74 (s, 2H, *meso*), 6.94 (dd, *J*=7.2 Hz, 4H), 7.36 (t, *J*=7.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.4, 122.0, 128.6, 131.2, 131.3, 138.2, 138.4. ESI-HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{14}H_{12}Br_2NaO_2$: 394.9078, 396.9058; found 394.9078, 396.9058.

1,2-Di-*p*-tolyl-ethane-1,2-diol (3e) 79% yield, 98% *ee*, *d.r.*=84∶16. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.5 mL/min; λ=210 nm; t_{major}=29.4 min, t_{minor}=30.8 min, t_{meso}=35.7 min. $[\alpha]_D^{28}$ =−58.4 (*c* 1.27 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 6H), 2.35 (s, 2H, *meso*), 2.98 (s, 2H, *dl*), 4.62 (s, 2H, *dl*), 4.71 (s, 2H, *meso*), 7.01—7.14 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1, 78.7, 126.8, 127.0, 128.8, 128.9, 136.9, 137.4; ESI-HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{16}H_{18}NaO_2$: 265.1199; found 265.1207.

1,2-Bis-(4-isopropyl-phenyl)-ethane-1,2-diol (3f) 74% yield, 98% *ee*, *d.r.*=87∶13. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.5 mL/min; λ=210 nm: t_{major}=23.0 min, t_{minor}=24.2 min, t_{meso}=26.1 min. $[\alpha]_D^{28}$ =−96 (*c* 1.49 in C_2H_5OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.19 (dd, *J*=1.8, 6.9 Hz, 12H), 2.76—2.90 (m, 4H), 4.66 (s, 2H), 7.07—7.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.2, 34.0, 78.7,

126.4, 126.7, 127.0, 127.4, 137.8, 148.7. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{26}NaO_2$: 321.1825; found 321.1829.

1,2-Bis(4-methoxyphenyl)ethane-1,2-diol (3g) 26% yield, >99% *ee*, *d.r.*=87∶13. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (80∶20) as the eluent. Flow: 1 mL/min; λ=210 nm: t_{major}=23.8 min, t_{minor}=25.2 min, t_{meso}=29. 4 min. $[\alpha]_D^{15}=-65$ (*c* 0.13 in C_2H_5OH) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.27 (s, 2 H), 3.76 (s, 6H, *dl*), 3.80 (s, 6H, *meso*), 4.64 (s, 2H, *dl*), 4.74 (s, 2H, *meso*), 6.76 (d, *J*=8.8 Hz, 4H, *dl*), 6.86 (d, *J*=8.8 Hz, 4H, *meso*), 7.04 (d, *J*=8.4 Hz, 4H, *dl*), 7.21 (d, *J*=8.4 Hz, 4H, *meso*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.1, 78.8 , 113.5, 128.2, 128.3, 132.1. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{18}NaO_4$: 297.1097; found 297.1103.

1,2-Bis-(3-chloro-phenyl)-ethane-1,2-diol (3h) 97% yield, 88% *ee*, *d.r.*=59∶41. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.3 mL/min; λ=210 nm: t_{minor}=40.6 min, t_{major}=44.9 min, t_{meso} = 48.4 min. $[\alpha]_D^{28}=-24.6$ (*c* 2.10 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.66 (s, 2H, *meso*), 3.22 (s, 2H, *dl*), 4.57 (s, 2H, *dl*), 4.75 (s, 2H, *meso*), 6.87 (d, *J*=7.5 Hz, 1H), 7.00 (d, *J*=7.8 Hz, 1H), 7.14 (t, *J*=7.8 Hz, 3H), 7.19—7.22 (m, 3H), 7.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.5, 125.4, 127.1, 127.4, 128.5, 129.6, 141.6, 141.8. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_2NaO_2$: 305.0107; found 305.0116.

1,2-Dim-tolylethane-1,2-diol (3i) 76% yield, 98% *ee*, *d.r.*=83∶17. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (97∶3) as the eluent. Flow: 0.5 mL/min; λ=210 nm: t_{minor}=60.8 min, t_{major}=67.6 min, t_{meso}=95.5 min. $[\alpha]_D^{28}=-57$ (*c* 1.00 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.27 (s, 6H, *dl*), 2.32 (s, 6H, *meso*), 2.41 (s, 2H, *meso*), 3.19 (s, 2H, *dl*), 4.62 (s, 2H, *dl*), 4.71 (s, 2H, *meso*), 6.89 (d, *J*=7.2 Hz, 2H), 6.98 (s, 2H), 7.02 (d, *J*=7.8 Hz, 2H), 7.10 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.3, 78.7, 124.0, 127.5, 127.8, 128.4, 137.6, 140.0. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{18}NaO_2$: 265.1199; found 265.1197.

1,2-Bis(3-nitrophenyl)ethane-1,2-diol (3j) 97% yield, 22% *ee*, *d.r.*=48∶52. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 1 mL/min; λ=210 nm: t_{minor}=32.8 min, t_{major}=45.2 min, t_{meso}=35.6 min. $[\alpha]_D^{15}=+3$ (*c* 0.6 in C_2H_5OH); ^{1}H NMR (300 MHz, DMSO) δ: 4.66 (s, 1H), 4.86 (d, *J*=3.3 Hz, 1H), 5.72 (s, 1H), 5.75 (d, *J*=3.6 Hz, 1H) 7.54 (d, *J*=7.5 Hz, 1H), 7.62 (d, *J*=7.8 Hz, 1H), 7.94 (s, 1H), 7.99 (d, *J*=5.1 Hz, 1H), 8.04 (d, *J*=6.3 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ: 75.5, 76.1, 122.1, 122.2, 122.3, 122.4, 129.2, 129.4, 134.2, 134.6, 144.8, 145.6, 147.5, 147.7. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{12}N_2NaO_6$: 327.0588; found 327.0580.

1,2-Di(furan-2-yl)ethane-1,2-diol (3l) 94% yield, 95% *ee*, *d.r.*=67∶33. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 1 mL/min; λ=210 nm; t_{major}=17.2 min, t_{minor}=18.1 min, t_{meso}=19.4 min. $[\alpha]_D^{15}=-14$ (*c* 1.4 in C_2H_5OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.72 (br, 2H), 4.96 (s, 2H, *dr*), 5.01 (s, 2H, *meso*), 6.24 (d, *J*=3.2 Hz, 1H), 6.26—6.29 (m, 2H), 6.32—6.34 (m, 1H), 7.48 (d, *J*=0.8 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 70.0, 70.3, 108.2, 108.4, 110.5, 110.6, 142.6, 142.7. ESI-HRMS *m/z*: $[M+Na]^+$calcd for $C_{10}H_{10}NaO_4$: 217.0471; found 217.0479

1-(4-Chloro-phenyl)-2-phenyl-ethane-1,2-diol (3m) 72% yield, 97% *ee*, *d.r.*=85∶15. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (94∶6) as the eluent. Flow: 0.8 mL/min; λ=210 nm; major diastereoisomer t_{major}=32.1 min, t_{minor}=30.6 min; minor diastereoisomer t_{major}=40.4 min, t_{minor}=46.3 min. $[\alpha]_D^{28}=-66$ (*c* 1.07 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.57—3.2 (m, 2H), 4.58—4.78 (m, 2H), 6.98 (d, *J*=7.2 Hz, 2H), 7.07 (s, 2H), 7.16 (d, *J*=6.9 Hz, 2H), 7.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.7, 79.4, 127.2, 128.5, 128.6, 133.8, 138.5, 139.8. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{13}ClNaO_2$: 271.0496; found 271.0486.

1-(4-Bromo-phenyl)-2-phenyl-ethane-1,2-diol (3n) 84% yield, 91% *ee*, *d.r.*=67∶33. The enantiomeric excess was determined by HPLC on Daicel Chiralpak AD-H with hexane/*i*-PrOH (90∶10) as the eluent. Flow: 0.5 mL/min; λ=210 nm; major diastereoisomer t_{major}=33.1 min, t_{minor}=35.1 min; minor diastereoisomer t_{major}=36.9 min, t_{minor}=43.1 min. $[\alpha]_D^{28}=-49$ (*c* 1.68 in C_2H_5OH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.66—3.34 (m, 2H), 4.51—4.74 (m, 2H), 6.89 (d, *J*=8.1 Hz, 2H) 7.01 (t, *J*=8.7 Hz, 2H), 7.13 (s, 1H), 7.25 (t, *J*=8.7 Hz, 3H), 7.31—7.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 78.4, 79.0, 121.7, 121.9, 128.1, 128.2, 131.1, 138.7, 139.4. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{13}BrNaO_2$: 314.9991, 316.9991; found 314.9969, 316.9950

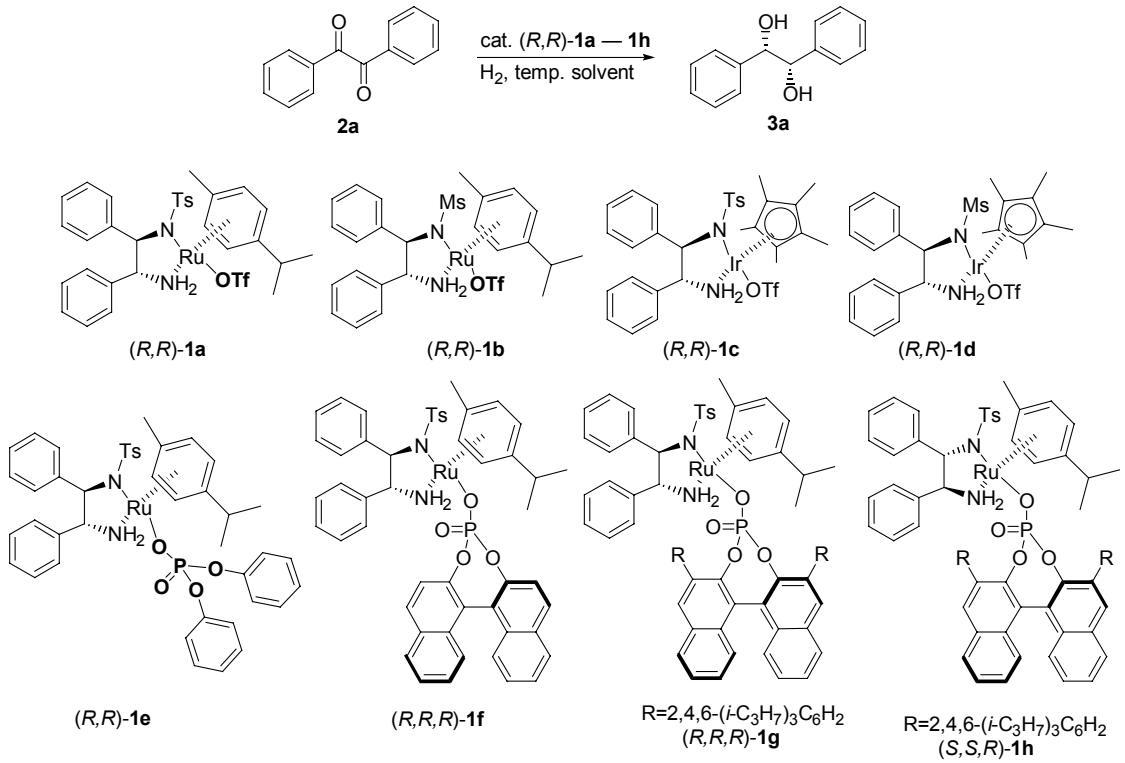
Phenyl-2-*p*-tolyl-ethane-1,2-diol (3o) 69% yield, >99% *ee*, *d.r.*=85∶15. The enantiomeric excess was determined by HPLC on Daicel Chiralpak OJ-H with hexane/*i*-PrOH (97∶3) as the eluent. Flow: 1 mL/min; λ=210 nm: major diastereoisomer t_{major}=42.3 min, t_{minor}=40.6 min; minor diastereoisomer t_{major}=59.6 min, t_{minor}=66.2 min. $[\alpha]_D^{28}=-73$ (*c* 1.02 in C_2H_5OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.31—2.99 (m, 2H), 4.66—4.76 (m, 2H), 6.87 (d, *J*=5.4 Hz, 1H), 6.96 (s, 1H), 7.04 (s, 1H), 7.10—7.12 (m, 3H), 7.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 79.2, 79.2, 124.3, 127.2, 127.8, 128.1, 128.2, 128.3, 128.9, 138.0, 140.1, 140.2. ESI-HRMS *m/z*: $[M+Na]^+$ calcd for $C_{15}H_{16}NaO_2$: 251.1048; found 251.1049.

Results and Discussion

Initially, several common catalysts were examined for the enantioselective hydrogenation of benzil **2a** un-

der a catalyst loading of 1.0 mol% in methanol under 50 atm of H_2 at room temperature for 24 h. (*R*,*R*)-**1a** was proved to be the potent catalyst, which afforded the hydrobenzoin with high enantiomeric and diastereomeric purities (>99% *ee* and 91∶9 *dr*), although the yield was moderate (39%) (Table 1, Entry 1). Subsequently, different complexes (*R*,*R*)-**1b**—**1d** were examined under identical conditions, and the results were summarized in Table1. (*R*,*R*)-**1b** and (*R*,*R*)-**1d** could catalyze the reaction to furnish the desired products in less than 21% yields albeit with the *dr*s and *ee*s maintained (Table 1, Entries 2 and 4). (*R*,*R*)-**1c** was found to

Table 1 Asymmetric hydrogenation of benzyl



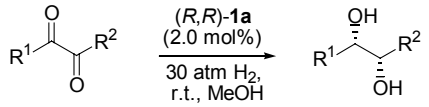
Entry	Cat.	Solvent	Temp/℃	Yield[b]/%	*dl*∶*meso*[d]	*ee*[c]/%
1	**1a**	MeOH	r.t.	39	91∶9	>99
2	**1b**	MeOH	r.t.	10	92∶8	99
3	**1c**	MeOH	r.t.	<5	nd	nd
4	**1d**	MeOH	r.t.	21	97∶3	99.9
5	**1e**	MeOH	r.t.	22	76∶24	5
6	**1f**	MeOH	r.t.	14	84∶16	93
7	**1g**	MeOH	r.t.	49.2	74∶26	85
8	**1h**	MeOH	r.t.	44.4	80∶20	−74
9[f]	**1a**	CH_2Cl_2	60	41	3∶97	84
10[f]	**1a**	toluene	60	<5	nd	nd
11[e]	**1a**	MeOH	r.t.	43	90∶10	>99
12[e]	**1a**	MeOH/H_2O=90∶10	r.t.	67	84∶16	>99
13	**1a**	MeOH	r.t.	90	79∶21	96
14	**1a**	MeOH	50	75	84∶16	97
15	**1a**	MeOH	65	64	85∶15	97
16[f]	**1a**	MeOH	r.t.	88	81∶19	98
17[g]	**1a**	MeOH	r.t.	91	85∶15	98
18[h]	**1a**	MeOH	r.t.	79	88∶12	99

[a] Reaction conditions: 0.2 mmol **2a** in 2 mL solvent, 1.0 mol% catalyst for Entries 1—8, 2.0 mol% catalyst for Entries 9—18, 50 atm of H_2. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral column. [d] Determined by HPLC with a chiral column or ^{1}H NMR. [e] For 46 h. [f] 40 atm pressure of H_2. [g] 30 atm pressure of H_2. [h] 20 atm pressure of H_2.

be ineffective for the reaction, affording only trace amount of the desired products (Table 1, Entry 3). Then **1e**—**1h** containing chiral or achiral phosphate anions were also investigated for the reaction. Unfortunately, these catalysts displayed unsatisfactory catalytic results in terms of both reactivity and stereoselectivity (Table 1, Entry 1 vs. Entries 5—8). With the best pre-catalyst (*R*,*R*)-**1a**, the other parameters were further optimized for the asymmetric hydrogenation of benzil **2a**, including reaction medium, catalyst loading, hydrogen pressure and reaction temperature. In aprotic solvents such as CH_2Cl_2 and toluene, the reactions showed either poor ratios of *dl* to *meso* or worse reactivity (Table 1, Entries 9 and 10). In an attempt to improve the chemical yield, the reaction time was prolonged to 46 h, which gave slightly higher yield (43%) while the stereoselectivity was maintained (Table 1, Entry 11). Interestingly, when the mixture of water and methnol (*V*/*V*= 1/9) was used as the reaction medium, higher yield (67%) was observed albeit the *dr* dropped to 84∶16 (Table 1, Entry 12), which implied that this catalytic system was stable in aqueous solution and exhibited its superiority to the phosphine catalysts. Improvement of the catalyst loading to 2.0 mol% resulted in a better yield (90%) within 24 h but slightly lower diastereoselectivity (79∶21 of *dl* to *meso*) (Table 1, Entry 13). The influences of the hydrogen pressure and temperature were investigated as well. At higher temperatures of 50 and 65 ℃, the yields dropped to 75% and 64%, respectively (Table 1, Entries 14 and 15), which indicates that the active catalysts may be decomposed at elevated temperatures. Furthermore, when the hydrogen pressure was decreased from 50 atm to 30 atm, the ratios of *dl* to *meso* increased and the enantioselectivities and yields maintained (Table 1, Entry 13 vs. Entries 16 and 17). When the hydrogen pressure was further decreased to 20 atm, the chemical yield obviously dropped (79%) (Table 1, Entry 18). Finally, we found that the optimal reaction conditions for this transformation involved the use of methanol as the reaction medium under 30 atm of H_2 at room temperature for 24 h in the presence of the catalyst (2.0 mol%). As the Ru-TsDPEN complexes are powerful catalysts for the asymmetric transfer hydrogenation (ATH) of aromatic ketones and methanol could be mediated as both hydrogen source and solvent, the control reaction without hydrogen gas was carried out under the optimal reaction conditions. However, no expected products were observed at all after 24 h in this case. This experiment unambiguously demonstrated the asymmetric hydrogenation (AH) nature of the catalytic systems.

Having established the optimal reaction conditions, the substrate scope of this reaction was subsequently studied and the results were summarized in Table 2. Some symmetrical benzils with either electron donating or withdrawing substituents at *ortho*-, *meta*- and *para*-positions on phenyl ring were firstly investigated. We found that substitutions on phenyl ring and their positions had a great impact on the catalytic results.

Table 2 Substrate scope for asymmetric hydrogenation of benzils



2a—2l **3a—3l**

Entry	Sub./R^1, R^2	Yield[b]/%	*dl*∶*meso*[d]	*ee*[c]/%
1	**2a**/R^1, R^2=C_6H_5	**3a**/91	85∶15	98
2	**2b**/R^1, R^2=*p*-FC_6H_4	**3b**/92	57∶43	83
3	**2c**/R^1, R^2=*p*-ClC_6H_4	**3c**/95	60∶40	86
4	**2d**/R^1, R^2=*p*-BrC_6H_4	**3d**/96	53∶47	81
5	**2e**/R^1, R^2=*p*-$CH_3C_6H_4$	**3e**/79	84∶16	98
6	**2f**/R^1, R^2=*p*-*i*-PrC_6H_4	**3f**/74	87∶13	98
7	**2g**/R^1, R^2=*p*-$CH_3OC_6H_4$	**3g**/26	87∶13	>99
8	**2h**/R^1, R^2=*m*-ClC_6H_4	**3h**/97	59∶41	88
9	**2i**/R^1, R^2=*m*-$CH_3C_6H_4$	**3i**/76	83∶17	98
10	**2j**/R^1, R^2=*m*-$NO_2C_6H_4$	**3j**/96	48∶52	22
11	**2k**/R^1, R^2=*o*-ClC_6H_4	**3k**/<5	—	—
12	**2l**/R^1, R^2=furan	**3l**/94	67∶33	95
13	**2m**/R^1=C_6H_5, R^2=*p*-ClC_6H_4	**3m**/72	85∶15	97
14	**2n**/R^1=C_6H_5, R^2=*p*-BrC_6H_4	**3n**/84	67∶33	91
15	**2o**/R^1=C_6H_5, R^2=*m*-$CH_3C_6H_4$	**3o**/69	85∶15	>99

[a] Reaction conditions: 0.2 mmol substrate in 2.0 mL methanol, 2.0 mol% catalyst, 30 atm of H_2, stirred at room temperature for 24 h. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral column. [d] Determined by HPLC with a chiral column and ^{1}H NMR.

Among them, the substrates **2b**—**2d** bearing electron withdrawing substituents (F, Cl, Br) gave the desired products **3b**—**3d** in excellent yields (92%—96%) but with moderate to good enantioselectivities and diastereoselectivities (81%—86% *ee*s, 53∶47 to 60∶40 *dr*s) (Table 2, Entries 2—4). For the substrates bearing electron-donating substituents (Me, *i*-Pr, OCH_3) at the *para*-position on the phenyl ring, although the desired products **3e**—**3g** could be obtained with good diastereoselectivities and excellent enantioselectivities (98% *ee*s, 86—14 and 87—13 *dr*s), the chemical yields dramatically decreased (Table 2, Entries 5—7). Apparently, electron-withdrawing substituents on the phenyl ring of the benzils were favorable to the reactivities but had a negative effect on the stereoselectivities, whereas electron-donating substituents on the phenyl ring of the benzils were good at the stereoselectivities but harmful

for the reactivities. For substrates **2h**—**2j** respectively bearing Cl, Me and NO_2 at the *meta*-position on the phenyl ring, the same regulation was observed (Table 2, Entries 8—10). The substrate **2i** with Me substituent could provide the desired product **3i** in 76% yield along with 83∶17 *dr* and 98% *ee*. While **2j** bearing NO_2 group as substrate, the corresponding reaction was proceeded very well to produce the desired product **3j** in 96% yield, only with 48∶52 *dr* and 22% *ee* (Entry 10). Gratefully, the substrate **2l** containing furan ring was also proven to be suitable for this transformation, affording the corresponding product **3l** in 94% yield with 67∶33 *dr* and 95% *ee* (Entry 12). However, the substrate **2k** with Cl substituent at the *ortho*-position on the phenyl ring was found to be ineffective for the transformation, probably due to the effects of steric hindrance (Table 2, Entry 11). Furthermore, unsymmetrical substrates **2m**—**2o** were also tested under otherwise identical conditions, and the corresponding hydrobenzoins **3m**—**3o** were provided in 69%—84% yields with 91—>99% *ee*s and 67∶33 to 85∶15 *dr*s (Table 2, Entries 13—15). Generally, electronic effect on the catalytic reaction was obviously observed. Substrates bearing electron-donating substituents provided the expected products in much lower yields. The reason may be that the hyrobenzoin products could act as bidentate ligands and further poison the Ru-TsDPEN catalyst, and the hydrobenzoins with electron-donating substituents would enhance its coordination ability.

Conclusions

In summary, we have developed the asymmetric hydrogenation of benzils using the phosphine-free chiral Ru(OTf)(TsDPEN)(η^6-cymene) complex as the pre-catalyst. A series of chiral hydrobenzoins were synthesized in good yields, good to moderate diastereoselectivities and good to excellent enantioselectivities. Further research on new catalyst and expansion of the substrate scope of this transformation, as well as practical utilization of those enantiomerically entriched hydrobenzoins is in progress in our laboratory.

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