Asymmetric Hydrogenation

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Rh-Catalyzed Highly Enantioselective Synthesis of 3-Arylbutanoic Acids**

*Xianfeng Sun, Le Zhou, Chun-Jiang Wang, and Xumu Zhang**

Enantiomerically pure 3-arylbutanoic acids and their derivatives such as chiral 3-arylbutanols are important intermediates for the synthesis of aromatic sesquiterpenes of the bisabolane family[1] and useful building blocks in organic synthesis.[2,3a] A variety of asymmetric syntheses of the carboxylic acids have therefore been developed, such as 1,4-addition of organometallic reagents to chiral α,β-unsaturated esters and amides,[3] diastereoface-differentiating alkylation with a number of nucleophiles and chiral catalysts or promoters,[4] and the Mitsunobu reaction of chiral secondary benzylic alcohols.[5] However, low yields, moderate regioselectivities, and narrow substrate scopes limit the potential applications of these reactions. We envision that one of the most effective methods for the construction of these moieties will be asymmetric hydrogenation of the corresponding prostereogenic 3-aryl-3-butenoic acids. Although significant progress has been made in asymmetric hydrogenation of α-arylacrylic acids and other α,β-unsaturated acids with various ruthenium or rhodium complexes,[6] the asymmetric hydrogenation of β,γ-unsaturated carboxylic acids still remains a major challenge owing to moderate enantioselectivities (24–85% *ee*) and high catalyst loadings (1–2 mol%).[7] Herein we report a Rh-catalyzed highly enantioselective hydrogenation for the preparation of chiral 3-arylbutanoic acids which has several outstanding features: 1) Selectivities of up to 99% *ee* and turnover numbers (TONs) of up to 5000 can be achieved. 2) The combination of a highly rigid electron-donating P-chiral bisphospholane ligand with optimal solvent and additive effects is the key to efficient transformations. 3) The simplicity of obtaining substrates and highly enantioselective hydrogenation under mild conditions make this approach very attractive and practical.

A family of prostereogenic unsaturated carboxylic acids was prepared through a simple and versatile synthetic method developed by Itoh et al.[8] using $[Pd(PPh_3)_4]$ as a catalyst.[7b] As claimed in Itoh's report, two advantages make the preparation of substrates especially suitable for large-scale synthesis. First, reactions can be accomplished in one pot by a palladium(0)-catalyzed coupling reaction of diketene with an arylzinc chloride reagent, providing desired 3-aryl-3-butenoic acids in high yields. Second, pure products can be obtained easily by recrystallization or fractional distillation.[8,9]

A crucial point to achieving high enantioselectivities and activities for the asymmetric hydrogenation is finding effective catalysts.[10] We initiated our studies on the asymmetric hydrogenation of 3-phenyl-3-butenoic acid by briefly screening several chiral phosphorus ligands (Figure 1). Although the complexes [Rh(*S*,*S*,*R*,*R*)-TangPhos(cod)]BF_4 (**3a**; cod = cyclooctadiene)[11] and [Rh(*R*,*R*)-Et-DuPhos(cod)]BF_4 (**3b**)[12] were successful for the highly enantioselective hydrogenation of various substituted olefins, only low enantioselectivities were obtained at room temperature under low hydrogen pressure (Table 1, entries 1 and 2). Hydrogenation with [Rh(*S*)-Binapine(cod)]BF_4 (**3c**)[13] (Table 1, entry 3) resulted in 26% *ee* under analogous conditions, while the reaction with [Rh(*S*)-C_3-TunePhos(cod)]BF_4[14] offered poor enantioselectivity (Table 1, entry 4). To our delight, up to 80% *ee* and 100% conversion were achieved with the highly rigid electron-donating P-chiral bisphospholane complex

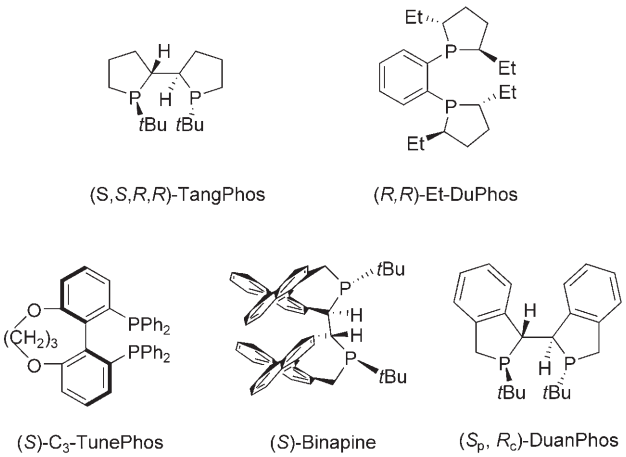

Figure 1. Structures of ligands for asymmetric hydrogenation.

[*] X. Sun, Prof. L. Zhou, Prof. X. Zhang
Department of Chemistry
The Pennsylvania State University
104 Chemistry Building, University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu
Prof. L. Zhou
College of Science
Northwest A&F University
Yangling, Shaanxi, 712100 (P.R. China)
Prof. C.-J. Wang
Green Catalysis Institute
Wuhan University
Hubei, 430072 (P.R. China)

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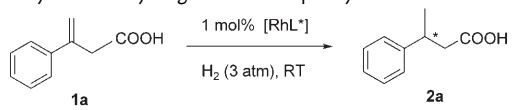
Table 1: Asymmetric hydrogenation of 3-phenyl-3-butenoic acid.[a]



Entry	Cat.[b]	Solvent	Et_3N [mol%]	*ee* [%][c]	Config.[d]
1	**3a**	MeOH	0	30	*S* (+)
2	**3b**	MeOH	0	7	(+)
3	**3c**	MeOH	0	26	(+)
4	**3d**	MeOH	0	17	(+)
5	**3e**	MeOH	0	80	(+)
6	**3e**	*i*PrOH	0	70	(+)
7	**3e**	CH_2Cl_2	0	50	(+)
8	**3e**	toluene	0	56	(+)
9	**3e**	THF	0	14	(+)
10	**3e**	MeOH	5	89	(+)
11	**3e**	EtOH	5	87	(+)
12	**3e**	*i*PrOH	5	87	(+)
13	**3e**	CH_2Cl_2	5	86	(+)
14	**3e**	EtOAc	5	82	(+)
15	**3e**	THF	5	85	(+)
16	**3e**	MeOH/H_2O (3:1)	5	92	(+)
17	**3e**	MeOH/H_2O (1:1)	5	97	(+)
18	**3e**	MeOH/H_2O (1:3)	5	nd[e]	nd

[a] Reactions were carried out with 0.2 mmol of substrate in 2 mL of solvent in the presence of 1 mol% of Rh catalyst for 12 h under an initial hydrogen pressure of 3 atm. In all cases ^{1}H NMR spectroscopy indicated complete conversion. [b] **3a**: [Rh(*S*,*S*,*R*,*R*)-TangPhos(cod)]BF_4; **3b**: [Rh(*R*,*R*)-Et-DuPhos(cod)]BF_4; **3c**: [Rh(*S*)-Binapine(cod)]BF_4; **3d**: [Rh(*S*)-C_3-TunePhos(cod)]BF_4; **3e**: [Rh(S_p,R_c)-DuanPhos(nbd)]SbF_6. [c] Determined by chiral GC. [d] Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data. [e] Not determined because of low reactivity.

[Rh(S_p,R_c)-DuanPhos(nbd)]SbF_6 (**3e**; nbd = 2,5-norbornadiene)[15] (Table 1, entry 5).

Subsequently, the effect of solvents was investigated in an effort to attain higher enantioselectivities. Strong solvent dependency was observed in the reaction. As shown in Table 1, complex **3e** performed well in alcohols to give good to high enantioselectivities (Table 1, entries 5 and 6), while reaction in aprotic solvents such as dichloromethane, THF, and toluene led to lower enantiomeric excesses (Table 1, entries 7–9).

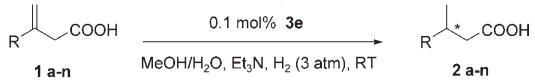
It has been reported that catalytic additives play a crucial role in improving the reactivity and enantioselectivity in the asymmetric hydrogenation of certain ketones, imines, and simple olefins.[16] Moreover, it was discovered that asymmetric hydrogenation of acids with the Rh–Diop catalyst system could be improved remarkably by the addition of tertiary amines.[7b] Accordingly, we tested a number of additives in our reaction, such as nBu_3N, iPr_2EtN, phthalimide, and benzylamine. The addition of Et_3N had a striking effect on the asymmetric induction (Table 1, entries 10–15), which was consistent with Yamamoto's report.[7b] Up to 89% *ee* was obtained when 5 mol% of Et_3N was present. A reasonable explanation raised by Yamamoto et al. is that the olefinic carboxylate anion formed with the addition of tertiary amine is more strongly chelated to the transition-metal center than the acid itself, resulting in higher enantioselectivity.[7b] Interestingly, when 5 mol% of Et_3N was added to the reaction mixture, the solvent effect was diminished dramatically. All reactions in different solvents provided comparable enantioselectivities (82–89% *ee*, Table 1, entries 10–15). In addition, the polarity of the solvent was further examined by using aqueous methanol as the solvent. The polarity of the mixed solvent was found to be significant for achieving high enantiomeric excess (Table 1, entries 16 and 17). The best result, 97% *ee*, was achieved when MeOH/H_2O (1:1, v/v) was employed (Table 1, entry 17). It could be rationalized that the generation of the cationic rhodium(I) species, as a RhL_2^+ fragment, was facilitated to coordinate with substrates in polar solvents, which could play an important role in determining the critical step for highly enantioselective hydrogenation of **1a**. The enhancement of *ee* might also be attributed to the stabilization of the olefinic carboxylate anion in polar solvents. However, much lower enantioselectivity and reactivity were observed in 25% aqueous methanol owing to the poor solubility of the substrate in the solvent (Table 1, entry 18).

To demonstrate the flexibility of this methodology, the hydrogenation of a series of β,γ-unsaturated carboxylic acids was studied with Rh complex **3e** under the optimized conditions (Table 1, entry 17). As shown for 3-aryl-3-butenoic acids (Table 2, entries 1–13), the hydrogenations proceeded to completion and afforded the corresponding 3-arylbutanoic acids in high yields (90–97%) with excellent enantioselectivities (94–99% *ee*). Outstanding selectivities of over 99% *ee* were achieved in the hydrogenation of 3-(3-fluorophenyl)- and 3-(4-chlorophenyl)-3-butenoic acids (Table 2, entries 7 and 9). These results indicated that the reaction system has a high tolerance to the pattern and electronic properties of the substituent on the phenyl ring of substrates. It is worth noting that the Rh-DuanPhos-catalyzed hydrogenations of aliphatic acids **1n** and **1o** were also conducted smoothly with good enantioselectivities (74% and 70% *ee*, respectively) to produce 3-methyl-4-phenylbutanoic acid (**2n**) and 3-methylheptanoic acid (**2o**), respectively, which are important intermediates in the synthesis of immunoregulatory agents (or their precursors).[17] To the best of our knowledge, these results represent the highest enantioselectivities in direct asymmetric hydrogenation for the preparation of optically active 3-arylbutanoic acids using chiral rhodium catalyst systems.

To address the potential of Rh-DuanPhos-catalyzed asymmetric hydrogenation as a practical means for the enantioselective synthesis of 3-arylbutanoic acids, substrate 3-(2-naphthyl)-3-butenoic acid (**1m**) was examined with a low catalyst loading. Impressively, complex **3e** displayed sufficient catalytic activity under mild conditions. Under an initial hydrogen pressure of 3 atm and at room temperature (substrate/catalyst (S/C) = 5000, 5 mol% Et_3N), **1m** was hydrogenated with full conversion within 24 h, resulting in 3-(2-naphthyl)butanoic acid without any loss of optical purity.

In conclusion, high enantiomeric excesses were obtained in the asymmetric hydrogenation of various β,γ-unsaturated carboxylic acids catalyzed with a Rh complex containing a highly rigid electron-donating P-chiral bisphospholane ligand,

Table 2: Rh-catalyzed asymmetric hydrogenation of β,γ-unsaturated carboxylic acids **1**.[a]



Entry	1	R	Product	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**a**	phenyl	**2a**	93	97	*S* (+)
2	**b**	2-Me-C_6H_4	**2b**	91	98	(−)
3	**c**	3-Me-C_6H_4	**2c**	93	96	(+)
4	**d**	4-Me-C_6H_4	**2d**	94	97	(+)
5	**e**	3-OMe-C_6H_4	**2e**	95	97	(+)
6	**f**	4-OMe-C_6H_4	**2f**	92	94	*S* (+)
7	**g**	3-F-C_6H_4	**2g**	93	>99	(+)
8	**h**	4-F-C_6H_4	**2h**	90	95	(+)
9	**i**	4-Cl-C_6H_4	**2i**	93	>99	(+)
10	**j**	4-Br-C_6H_4	**2j**	91	98	(+)
11	**k**	4-CF_3-C_6H_4	**2k**	94	98	(+)
12	**l**	1-naphthyl	**2l**	93	98	*R* (−)
13	**m**	2-naphthyl	**2m**	97	97	*S* (+)
14	**n**	benzyl	**2n**	92	74	*R* (+)
15	**o**	*n*-butyl	**2o**	85	70	*R* (+)

[a] Reactions were carried out with 0.1 mol% of Rh-DuanPhos complex and 5 mol% Et_3N for 12 h under an initial hydrogen pressure of 3 atm in $MeOH/H_2O$ (1:1). In all cases ^1H NMR spectroscopy indicated complete conversion. [b] Yield of isolated product. [c] The enantiomeric excesses were determined by chiral HPLC or chiral GC (see the Supporting Information). [d] The absolute configurations of **2a**, **2f**, **2l**, **2m**, **2n**, and **2o** were assigned by comparison of the observed optical rotation with reported data.

DuanPhos. High turnover numbers for selected substrates were also achieved under mild conditions. This strategy establishes one of the most practical methods for the synthesis of enantiomerically pure 3-arylbutanoic acids and their derivatives, which are important pharmaceutical intermediates and chiral building blocks in organic synthesis. Further investigation of the substrate scope with this catalytic system will be reported in due course.

Experimental Section

General procedure: A suspension of (S_p,R_c)-DuanPhos (140 mg, 0.366 mmol) in THF (6 mL) was added to a solution of [Rh(nbd)$_2$]SbF_6 (182.6 mg, 0.35 mmol) in THF (2 mL) at −20 °C. The resulting red solution was allowed to warm to room temperature and stirred for an additional 15 min. The solution was concentrated to about 6 mL. Then Et_2O (25 mL) was added under vigorous stirring, during which an orange precipitate was formed. The precipitate was filtered off and washed with Et_2O (2 × 10 mL) to afford the orange solid complex (198 mg, 67%).[15] The complex was stored in a nitrogen-filled glovebox for further usage. The complex (16.3 mg, 0.02 mmol) was dissolved in degassed methanol (100 mL) in a glovebox. A 10-mL portion of the complex solution was divided equally among 10 vials. Et_3N (1.01 mg, 0.01 mmol) in 1 mL of degassed water was added to each of the vials, followed by β,γ-unsaturated acid substrate (0.2 mmol, S/C = 1000). The resulting solution was then transferred into an autoclave and charged with 3 atm of hydrogen. The hydrogenation was performed at room temperature for 12 h. The hydrogen was released carefully, and the solvent was removed by evaporation. The residue was dissolved in diethyl ether (20 mL) and extracted with 3 equivalents of aq. NaOH (2 × 30 mL). The alkaline solution was acidified with 6 equivalents of aq. HCl, and then extracted with diethyl ether (3 × 20 mL). The ether extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was subject to silica gel column chromatography using hexanes/ether (8:1) as eluent for further purification. Enantiomeric excesses were directly measured by chiral GC (Gamma Dex 225 and Beta Dex 325) or HPLC (Chiral OD and OJ-H).

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