Asymmetric Hydrogenation

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Rhodium(I)-Catalyzed Enantioselective Hydrogenation of Substituted Acrylic Acids with Sterically Similar β,β-Diaryls**

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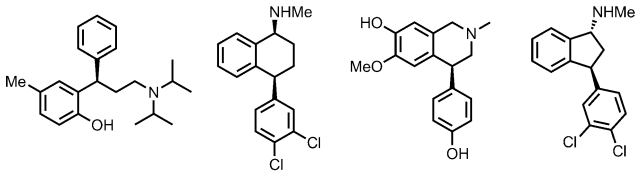
Dedicated to Professor Guo-Qiang Lin on the occasion of his 70th birthday

Optically active β,β-diarylpropionic acids are a class of important building blocks for the asymmetric synthesis of chiral diarylmethine compounds,[1] which are structural moieties that are found in many pharmaceuticals and bioactive compounds, including the therapeutically important molecules tolterodine,[1a–b] sertraline,[1c] indatraline,[1d] and natural products, such as cherylline.[1e]



(*R*)-tolterodine sertraline cherylline (+)-indatraline

Thus far, methods for the asymmetric synthesis of chiral β,β-diarylpropionic acids often involve a multistep sequence and/or stoichiometric transformation using chiral auxiliaries,[2] only a few examples of catalytic asymmetric methods, including Rh^{I}- or Cu^{II}-catalyzed reduction of β,β-diaryl unsaturated acrylates[3,4] or nitriles[5] using either polymethylhydrosiloxanes or diethoxymethylsilane as the reductants, and Rh^{I}-catalyzed 1,4-addition of organoboron reagents to arylidene Meldrum's acids,[6] have been reported to provide the corresponding β,β-diaryl propanoates or propanenitriles with good to high enantioselectivities. In terms of atom economy and environmental concerns, asymmetric hydrogenation of β,β-diarylacrylates with molecular H_2 is more advantageous. In this respect, Ir^{I}- or Rh^{I}-catalyzed asymmetric hydrogenation of trisubstituted olefins for the formation of diarylmethine stereogenic centers seems feasible.[7] However, reactions involving 3,3-diarylacrylates (especially free acids) proved to be challenging, as only moderate enantioselectivities were obtained, in most cases under high pressure (100 bar). Herein, we present the results of the development of an efficient asymmetric hydrogenation of β,β-diarylacrylic acids in the presence of a Rh complex based on the heterocombination of a chiral monodentate secondary phosphine oxide (SPO) preligand and an achiral monodentate phosphine ligand as the catalyst to afford a wide variety of the corresponding β,β-diarylpropionic acids with biological importance in excellent optical purities.

The most challenging issue associated with the control of stereochemistry in the asymmetric hydrogenation of β,β-diarylacrylic acids is the differentiation of a stereogenic center with two sterically similar aryl groups at the β-position of acrylic acids.[3–8] Very recently, we disclosed that Rh^{I} catalysts generated in situ by interaction with SPO preligands demonstrated excellent performance in the asymmetric hydrogenation of α-substituted ethenylphosphonic acids.[9] The salient features of SPO ligands, including ready accessibility, good air and moisture stability, and the potentially H-bonding OH group in the ligand,[9,10] prompted us to explore the catalytic potential of Rh^{I}/SPO systems in the asymmetric hydrogenation of challenging β,β-diarylacrylic acid substrates. As shown in Table 1, chiral monodentate SPO preligands **L1**–**L7** were evaluated in the rhodium-catalyzed asymmetric hydrogenation of (*E*)-3-phenyl-3-(*p*-tolyl) acrylic acid ((*E*)-**1a**). However, an initial screening of the catalysts generated in situ by mixing $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) and **L1**–**L7** in a 1:2 molar ratio resulted in only poor conversions under the conditions tested (entries 1–9), which indicates that the Rh complexes of **L1**–**L7** alone are not active enough for catalysis. Inspired by the fact that mixtures of chiral monodentate ligands (or chiral and achiral) can often improve the enantioselectivity and reactivity in many transition-metal-catalyzed reactions,[11] as evidenced by the elegant studies of several groups,[12–17] we moved to employ this mixed-ligand strategy in the present reaction. Gratifyingly, use of **L3** in combination with achiral triphenylphosphine indeed resulted in a dramatic enhancement in the conversion (from 15% to >99%) and *ee* values (from 38% to 95%) under otherwise identical conditions (entries 10 vs. 3). Notably, further modification of the Rh^{I} catalyst system by varying the relative amounts of **L3** and PPh_3 was found to have a profound influence on the reaction (entries 11 and 13–15). For example, reducing the molar ratio of Rh/**L3**/PPh_3 to 1:1:1 resulted in a slight decrease in the product *ee* value (from 95% to 92%; entries 10 and 11), presumably as a result of the background reaction catalyzed by the achiral Rh/PPh_3 species (entry 12). On the other hand, changing the Rh/**L3**/PPh_3 ratio from 1:2:1 to 1:1:2 or 1:3:1 also led to a substantial change in the

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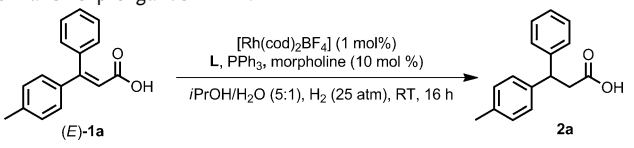
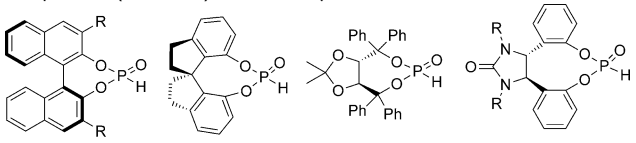
Table 1: Dramatic synergistic effect of achiral triphenylphosphine on the Rh^{I}-catalyzed enantioselective hydrogenation of (*E*)-**1a** in the presence of chiral SPO preligands **L1**–**L7**.[a]



Entry	L (mol%)	PPh_3 [mol%]	Conv. [%][b]	*ee* [%][c]
1	**L1** (2)	none	10	82
2	**L2** (2)	none	16	65
3	**L3** (2)	none	15	38
4	**L4** (2)	none	< 5	–
5	**L5** (2)	none	< 5	–
6	**L6** (2)	none	< 5	–
7	**L7** (2)	none	< 5	–
8[d]	**L3** (2)	none	3	–
9[e]	**L3** (2)	none	2	–
10	**L3** (2)	1	> 99	95
11	**L3** (1)	1	> 99	92
12	none	2	35	*rac*
13	**L3** (1)	2	18	77
14	**L3** (3)	1	90	95
15	**L3** (2)	2	trace	–

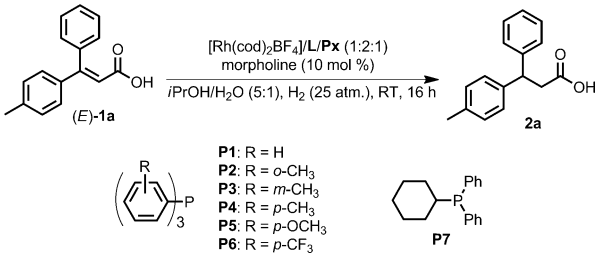
[a] Reaction conditions: $[Rh(cod)_2]BF_4$ (1 mol%), substrate (0.083 M), morpholine (10 mol%). [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase after the acids were transformed into their corresponding methyl esters with CH_2N_2. [d] CH_2Cl_2 solvent, morpholine (50 mol%). [e] THF solvent, morpholine (50 mol%). cod = 1,5-cyclooctadiene.



conversion and/or *ee* values (entries 13 and 14), which suggests that subtle equilibria exist among the $Rh(\mathbf{L3})_x(PPh_3)_y$ species in the system. Finally, the system with a Rh/**L3**/PPh_3 ratio of 1:2:2 was found to be virtually inactive (entry 15), probably owing to catalyst inhibition caused by coordinative saturation of the Rh centers by excessive P ligands. Further optimization of the reaction conditions (see the Supporting Information) revealed that the hydrogenation of (*E*)-**1a** catalyzed by Rh/**L3**/PPh_3 (1:2:1) was best performed in isopropanol/water (5:1) solvent with morpholine as the base.

A salient advantage of using the mixed-ligand approach is that it allows for rapid generation of a chiral catalyst library with substantial diversity, thus obviating the need for tedious synthesis of a chiral bidentate ligand.[11–17] The synergistic effect of ligand mixtures has also been observed in a variety of catalytic asymmetric reactions.[18] With these in mind, we shifted our attention to the screening of a combinatorial library of Rh catalysts for hydrogenation of the model substrate (*E*)-**1a**. The catalyst library was generated in situ by combining $[Rh(cod)_2]BF_4$, an SPO preligand (**L1**–**L7**), and an achiral tertiary phosphine (**P1**–**P7**) in a molar ratio of 1:2:1. The reactions were conducted under the above optimized conditions, and the results are shown in Table 2. Remarkably, in most cases the heterocombinations resulted in a considerable improvement in both conversion and enantioselectivity, as compared to the cases using the corresponding chiral SPO alone (**P1** and **P3**–**P7** vs. None). These results demonstrated that the heterocomplexes were generally more reactive and steroselective than the homocomplexes, which suggests that the use of different P donors with distinct electronic features (a σ-donating phosphine and a π-accepting phosphorous acid diester ligand) is favorable for the reaction. An exception was found in cases using **P2**, wherein the substrate conversions remain similar to those obtained using the chiral ligands alone, probably owing to the steric bulk of tri(*o*-tolyl)phosphine (**P2**), which prevents the effective formation of the corresponding heterocomplexes or blocks substrate approach to the catalyst. It was also found that catalysts with phosphines bearing electron-donating *para* substituents on the aryl groups (**P4** and **P5**) usually afforded better results than those with electron-withdrawing *para* substituents (**P6**), but the correlation between reactivity and the electronic properties of the tertiary phosphines is still elusive in the case of **P7**. The combinatorial search revealed that several SPO/P heterocombination ligand systems, for example, **L2**/**P1**, **L2**/**P4**, **L3**/**P1**, **L3**/**P5**, are optimal for Rh^{I}-catalyzed hydrogena-

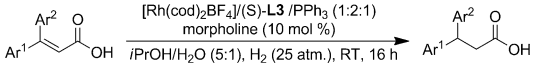
Table 2: Screening of catalyst libraries of $[Rh(cod)_2]BF_4$/**L**/**Px** in the asymmetric hydrogenation of (*E*)-**1a**.[a]



L/P	None[b,c]	**P1**[b]	**P2**[b]	**P3**[b]	**P4**[b]	**P5**[b]	**P6**[b]	**P7**[b]
L1	10 (82)	86 (79)	14 (80)	80 (71)	62 (74)	75 (80)	56 (54)	88 (82)
L2	16 (65)	> 99 (95)	22 (68)	> 99 (91)	> 99 (95)	> 99 (94)	95 (80)	> 99 (85)
L3	15 (38)	> 99 (95)	22 (31)	19 (38)	> 99 (94)	> 99 (95)	75 (93)	27 (56)
L4	< 5[d]	44 (93)	< 5[d]	38 (79)	35 (82)	62 (81)	88 (90)	80 (83)
L5	< 5[d]	92 (17)	< 5[d]	98 (21)	96 (18)	92 (10)	40 (30)	90 (26)
L6	< 5[d]	> 99 (80)	8 (86)	93 (81)	86 (67)	59 (62)	83 (38)	83 (72)
L7	< 5[d]	> 99 (81)	15 (75)	> 99 (82)	> 99 (75)	> 99 (73)	98 (56)	96 (68)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$/**L**/**Px** (1:2:1, 1 mol%), morpholine (10 mol%), (*E*)-**1a** (0.25 mmol), *i*PrOH/H_2O (3 mL, 5:1). [b] Data shown is for conversions [%]. Data in parentheses are *ee* values [%]. Conversion was determined by ^1H NMR spectroscopy, and the *ee* value of **2a** was determined by HPLC analysis on a chiral stationary phase after esterification with CH_2N_2. [c] No phosphine was used. [d] The *ee* values were not determined.

Table 3: Rh-catalyzed asymmetric hydrogenation of β,β-diarylacrylic acids **1a–v**.[a]



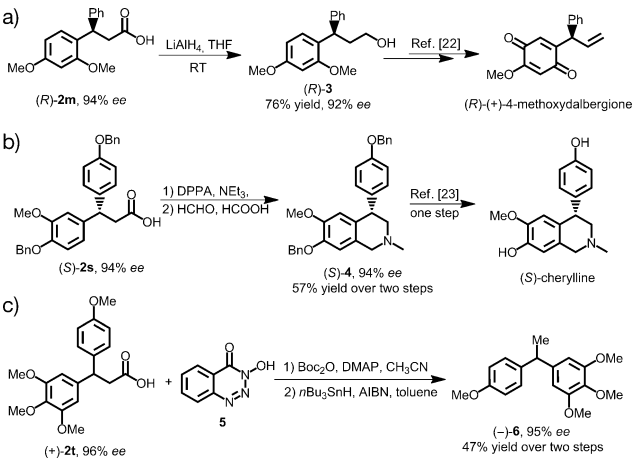
Entry	Substrate	Ar^1	Ar^2	Product	*ee* [%]
1	(*E*)-**1a**	4-MeC_6H_4	Ph	**2a**	95 (+)
2	(*E*)-**1b**	4-$MeOC_6H_4$	Ph	**2b**	96 (+)
3	(*E*)-**1c**	4-OHC_6H_4	Ph	**2c**	94 (+)
4	(*E*)-**1d**	4-FC_6H_4	Ph	**2d**	94 (+)
5	(*E*)-**1e**	4-ClC_6H_4	Ph	**2e**	94 (+)
6	(*E*)-**1f**	4-BrC_6H_4	Ph	**2f**	94 (*R*)
7	(*E*)-**1g**	4-$CF_3C_6H_4$	Ph	**2g**	94 (+)
8	(*E*)-**1h**	3-FC_6H_4	Ph	**2h**	94 (+)
9[b]	(*E*)-**1i**	2-FC_6H_4	Ph	**2i**	91 (*R*)
10[b]	(*E*)-**1j**	2-ClC_6H_4	Ph	**2j**	85 (*R*)
11[b]	(*E*)-**1k**	2-$MeOC_6H_4$	Ph	**2k**	92 (*R*)
12[c]	(*E*)-**1l**	2-$BnOC_6H_4$	Ph	**2l**	95 (+)
13[b]	(*E*)-**1m**	2,4-$(MeO)_2C_6H_3$	Ph	**2m**	94 (*R*)
14[b]	(*E*)-**1n**	2-MeO-5-MeC_6H_4	Ph	**2n**	93 (+)
15[d]	(*E*)-**1o**	3,4-$(OCH_2O)C_6H_3$	Ph	**2o**	96 (+)
16	(*E*)-**1p**	3,4-$Cl_2C_6H_3$	Ph	**2p**	93 (*R*)
17	(*E*)-**1q**	3,5-$F_2C_6H_3$	Ph	**2q**	92 (+)
18[d]	(*E*)-**1r**	2-naphthyl	Ph	**2r**	95 (−)
19[c]	(*Z*)-**1s**	4-$BnOC_6H_4$	3-MeO-4-$BnOC_6H_3$	**2s**	94 (+)
20[e]	(*Z*)-**1t**	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	**2t**	96 (+)
21	(*Z*)-**1u**	Ph	2-furyl	**2u**	92 (+)
22	(*E*)-**1v**	Ph	Me	**2v**	91 (*S*)
23	(*Z*)-**1a**	Ph	4-MeC_6H_4	**2a**	95 (−)
24[b]	(*Z*)-**1i**	Ph	2-FC_6H_4	**2i**	96 (*S*)
25[b]	(*Z*)-**1j**	Ph	2-ClC_6H_4	**2j**	96 (*S*)
26[f]	(*E*)-**1p**	3,4-$Cl_2C_6H_3$	Ph	**2p**	93 (*R*)

[a] Reaction conditions: $[Rh(cod)_2]BF_4$/**L**/**Px** (1:2:1, 1 mol%), morpholine (10 mol%), (*E*)-**1a** (0.25 mmol), *i*PrOH/H_2O (3 mL, 5:1). The conversion was >99% for all substrates. The *ee* values of the products were determined by HPLC analysis on a chiral stationary phase after esterification with CH_2N_2. [b] Morpholine (20 mol%). [c] An additional THF (2.5 mL), catalyst (2 mol%), and morpholine (100 mol%) and H_2 (50 atm) were added. [d] An additional THF (0.5 mL) and morpholine (100 mol%) were added. [e] An additional THF (0.5 mL), morpholine (100 mol%), and H_2 (50 atm) were added. [f] Conditions: (*E*)-**1p** (0.17 M, 0.2 mol%), H_2 (50 atm), 24 h. **2p** was isolated in 98% yield. Bn = benzyl.

tion of (*E*)-**1a** in terms of reactivity and enantioselectivity. As **L3** was found to be more resistant to water hydrolysis than **L2**, the hetercombination of **L3** and **P1** was chosen as the ligand system for the further study.

With these results in hand, the hydrogenation of various β,β-diarylacrylic acids (**1a–1v**) was studied using $[Rh(cod)_2]BF_4$/**L3**/PPh_3 (1:2:1) as the catalyst and morpholine as the base (Table 3). The catalyst system proved to be quite versatile; the reactions of all substrates, irrespective of their configurations or the stereoelectronic nature of the 3,3-substituents, proceeded smoothly to afford full conversions of substrates, and the enantioselectivities were generally excellent (91–96% *ee*). The only exception was the reaction involving (*E*)-**1j**, wherein a slightly lower *ee* value (85%) was obtained (entry 10). Notably, substrate (*E*)-**1c**, with a free OH group in the *para* position of the aryl substituent, was also amenable to the method, smoothly giving **2c** with an *ee* value of 94% (entry 3). In some cases, extra THF and/or morpholine was used to increase the solubility of the substrates (entries 15 and 18). For the sterically more hindered substrates, including (*E*)-**1l**, (*Z*)-**1s**, and polysubstituted (*Z*)-**1t**, the reactions also ran smoothly to afford the corresponding hydrogenation products with high *ee* values (94–96%), albeit at an elevated catalyst loading (2 mol%) and/or higher hydrogen pressure (50 atm) for full conversion of substrates (entries 12, 19, and 20). The asymmetric hydrogenation of substrates with a heteroaryl (2-furyl, **1u**) or alkyl (methyl, **1v**) group were also successful, affording the corresponding products, **2u** and **2v**, respectively, with excellent *ee* values (entries 21 and 22). Under otherwise identical conditions, both *E* and *Z* substrates can be hydrogenated with full conversion. Importantly, the (*E*) and (*Z*) isomers of **1a**, **1i**, and **1j** give products with similar *ee* values, but enriched in opposite enantiomers (entries 1 vs. 23, 9 vs. 24, 10 vs. 25). It seems most likely that the substrate binds to the Rh center in a chelating fashion, so that the catalyst can differentiate the enantiotopic faces of the alkene on the basis of the orientation of the carboxylic group.[8] In this way, both enantiomers of the chiral β,β-diarylpropionic acids can be easily accessed in high optical purity by hydrogenating the *E* or *Z* substrates using the same catalyst. Finally, the asymmetric hydrogenation of (*E*)-**1p** proceeded smoothly at a reduced catalyst loading (0.2 mol% Rh) to afford the corresponding product **2p**, a key intermediate for the synthesis of bioactive (+)-indatraline,[19] in excellent yield (98%) with high enantioselectivity (93% *ee*) after 24 h (entry 26).

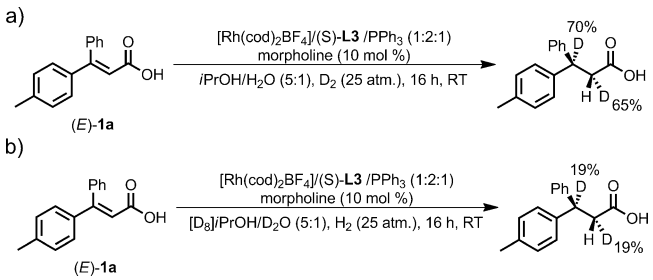
The synthetic utility of the present method was further demonstrated in the asymmetric synthesis of intermediates for the natural products (*R*)-(+)-4-methoxydalbergione[20] and (*S*)-cherylline,[1d] as well as an anti-viral (smallpox) agent (−)-**6**,[21] with the hydrogenation products (*R*)-**2m**, (*S*)-**2s**, and (+)-**2t**, respectively, as the starting materials (Scheme 1). Reduction of (*R*)-**2m** with $LiAlH_4$ at room



Scheme 1. Asymmetric syntheses of a) (*R*)-(+)-4-methoxydalbergione, b) (*S*)-cherylline, and c) anti-viral agent (−)-**6** starting from the hydrogenation products (*R*)-**2m**, (*S*)-**2s**, and (+)-**2t**. AIBN = azobisisobutyronitrile, Bn = benzyl, Boc = *tert*-butoxycarbonyl, DMAP = dimethylaminopyridine, DPPA = diphenylphosphoryl azide.

temperature gave (*R*)-**3** in 76% yield with 92% *ee*, which has been used as a key intermediate for the preparation of (*R*)-(+)-4-methoxydalbergione (Scheme 1a).[22] Treatment of (*S*)-**2s** with diphenylphosphoryl azide (DPPA) in the presence of triethylamine, followed by cyclization/reductive amination using aqueous formaldehyde and formic acid in one pot, afforded a good yield of highly enantioenriched (*S*)-**4**, which can be readily transformed into (*S*)-cherylline after debenzylation (Scheme 1b).[23] Finally, esterification of (+)-**2t** with benzotriazine **5** and subsequent decarboxylation with tributylstannane led to the formation of (−)-**6** in 47% overall yield without loss of optical purity (95% *ee*) (Scheme 1c).

To shed some light on the mechanism of the hydrogenation reaction, a deuterium-labeling study was performed for the $[Rh(cod)_2]BF_4$/**L3**/PPh_3 (1:2:1) catalyzed reaction of (*E*)-**1a**, using D_2 in *i*PrOH/H_2O (5:1) or H_2 in [D_8]isopropanol/D_2O (5:1) (Scheme 2a and b). In both



Scheme 2. Deuterium-labeling studies.

cases, deuterium atoms were found to be partially incorporated into both the α and β positions of the product in similar ratios, respectively, indicating the existence of H/D exchange between the Rh–H (Rh–D) species and the solvent, in which a heterolytic cleavage of the O–D bond of the solvent with the assistance of the OH group of the ligand might be involved.[24] Such a deuterium distribution pattern also strongly supports a hydrogenolysis mechanism instead of a protonlysis mechanism in the product-yielding step. Furthermore, preliminary ^{31}P NMR studies (Supporting Information, Figure S4) indicated the exclusive formation of a homo-ligand $[Rh(\mathbf{L3})_2]$ species ($\delta = 121.3$ ppm, $^1J_{Rh\text{-}P} = 253.6$ Hz) in the original Rh/**L3** (1:1 or 1:2) system that, upon the introduction of PPh_3 and water, partially evolved into a minor amount of hetero-ligand species $[Rh(\mathbf{L3})(PPh_3)]$, which might be responsible for the catalysis. Finally, a trial using a phosphite analogue of **L3** (methyl-capped OH group; Figure S5) for the hydrogenation of (*E*)-**1a** under the otherwise identical conditions as above yielded significantly inferior results (63% conversion and 44% *ee*), which suggests that the free OH group in the ligand should be favorable for the reaction.

In conclusion, we have developed a highly versatile and enantioselective Rh^I-catalyzed asymmetric hydrogenation of β,β-diarylacrylic acids with sterically similar diaryl groups at the stereogenic center using a mixed-ligand approach that affords a variety of enantioenriched β,β-diarylpropionic acids in high optical purities. Both enantiomers of the chiral β,β-diarylpropionic acids can be accessed in high enantiopurity using the same catalyst by simply switching the *E* and *Z* substrates for hydrogenation. This method has provided a facile approach for the concise synthesis of a variety of biologically important natural and non-natural products. Further studies to explore the mechanism of this asymmetric reaction, and extend the method to other catalytic reactions are undergoing in this lab.

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