

Chiral Norbornadienes as Efficient Ligands for the Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Fumaric and Maleic Compounds

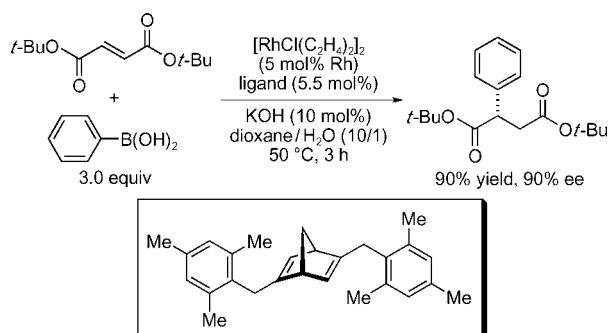
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ABSTRACT



A rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to fumaric and maleic compounds has been developed. While phosphorus-based chiral ligands fail to induce high stereoselectivity, chiral norbornadiene ligands have proved to be uniquely effective to achieve high enantioselectivity in these 1,4-addition reactions.

1,4-Addition to electron-deficient alkenes is a useful strategy for the construction of carbon–carbon bonds.¹ The development of its enantioselective variant by chiral catalysts has therefore been investigated extensively,² with α,β -unsaturated ketones (e.g., 2-cyclohexen-1-one) being the most commonly studied substrates. In contrast to these substrates, asymmetric 1,4-additions to fumaric or maleic compounds have met

much less success, despite the fact that 1,4-addition products of these compounds are synthetically useful 2-substituted 1,4-dicarbonyl compounds. In fact, to the best of our knowledge, there have been no successful reports on catalytic asymmetric 1,4-addition of organometallic reagents to fumaric or maleic substrates.^{3,4} In this paper, we demonstrate our significant progress toward this goal: specifically, a rhodium/chiral norbornadiene catalyst is highly effective for asymmetric 1,4-

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(2) For an overview, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 31.1. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Chapter 31.2. (c) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171.

(3) There are some reports on nonasymmetric rhodium-catalyzed 1,4-addition to these compounds. (a) 1,4-Addition of triphenylbismuth to diethyl maleate: Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, 42, 781. (b) 1,4-Addition of trimethylphenyllead to dimethyl fumarate and maleate: Ding, R.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Synlett* **2001**, 1470.

(4) For an example of diastereoselective 1,4-addition to fumarates with a chiral auxiliary, see: Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-x. *J. Org. Chem.* **2002**, 67, 1738.

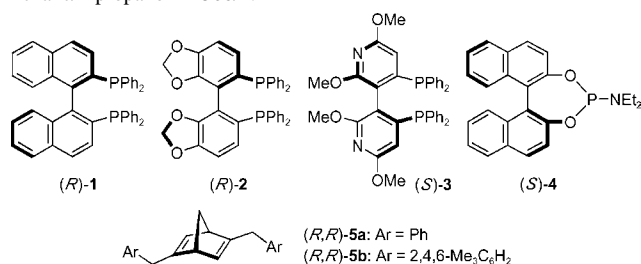
addition of arylboronic acids to fumaric acid diesters and maleimides.

In 1998, we described a rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids to α,β -unsaturated ketones in the presence of (*S*)-binap.⁵ Since then various chiral ligands have been used in this reaction, and bisphosphine ligands have proved to be particularly effective.⁶ Based on these precedents, we initially employed chiral bisphosphine ligands in the reaction of di-*tert*-butyl fumarate with PhB(OH)₂ in the presence of 5 mol % rhodium (Table 1).

Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Di-*tert*-butyl Fumarate

entry	Ar	ligand	product	yield ^a (%)	ee ^b (%)
1	Ph	(<i>R</i>)- 1	6a	96	21 (<i>R</i>)
2	Ph	(<i>R</i>)- 2	6a	99	3 (<i>R</i>)
3	Ph	(<i>S</i>)- 3	6a	94	13 (<i>S</i>)
4 ^c	Ph	(<i>S</i>)- 4	6a	50	32 (<i>S</i>)
5	Ph	(<i>R,R</i>)- 5a	6a	78	90 (<i>S</i>)
6	Ph	(<i>R,R</i>)- 5b	6a	90	90 (<i>S</i>)
7	4-MeOC ₆ H ₄	(<i>R,R</i>)- 5b	6b	78	86 (<i>S</i>) ^d
8	4-FC ₆ H ₄	(<i>R,R</i>)- 5b	6c	85	90 (<i>S</i>) ^d
9	2-naphthyl	(<i>R,R</i>)- 5b	6d	91	87 (<i>S</i>) ^d
10	2-MeC ₆ H ₄	(<i>R,R</i>)- 5b	6e	80	91 (<i>S</i>) ^{d,e}

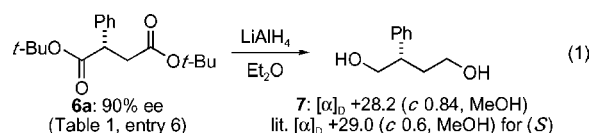
^a Isolated yield. ^b Determined by HPLC on a Chiralpak AD-H column with hexane/2-propanol = 95/5 unless otherwise noted. ^c 11 mol % of ligand was used. ^d The absolute configuration was assigned by analogy with entries 1–6. ^e ee was determined by HPLC on a Chiralcel OD-H column with hexane/2-propanol = 500/1.



The use of (*R*)-binap **1**,⁷ however, produced the 1,4-adduct **6a** only in 21% ee (entry 1), and other ligands, such as (*R*)-sephos **2**⁸ and (*S*)-P-phos **3**,⁹ turned out to be ineffective as well (3–13% ee; entries 2 and 3). In addition, phosphoramidite ligand (*S*)-**4**, which is also known to be effective in

asymmetric 1,4-addition to α,β -enones,¹⁰ did not provide a satisfactory result either (32% ee; entry 4).

Last year, we initiated a program directed toward the development of chiral dienes as conceptually novel ligands for asymmetric catalysis, and we described the synthesis of chiral norbornadiene (*R,R*)-**5a** and its application to the rhodium-catalyzed asymmetric 1,4-addition reactions.¹¹ In contrast to the phosphorus-based chiral ligands, the use of ligand **5a** in the 1,4-addition to di-*tert*-butyl fumarate significantly improved the enantioselectivity to 90% ee, with a slight decrease in reactivity (78% yield; entry 5). A modification of substituents in **5a** to bulkier mesitylmethyl groups (**5b**)¹² kept the same level of stereoselection with an increased reactivity (90% yield, 90% ee (*S*); entry 6).¹³ The absolute configuration of the 1,4-adduct **6a** was determined by comparison of the optical rotation of its reduction derivative **7** with the literature value as shown in eq 1.¹⁴ Under these conditions with (*R,R*)-**5b**, not only electron-rich or electron-deficient aromatic (entries 7 and 8) but also sterically hindered aromatic (entries 9 and 10) groups can be installed in high enantioselectivity (**6b–e**, 86–91% ee).



High enantioselectivity with the chiral norbornadiene ligand was also observed in the asymmetric 1,4-additions to maleimides, which are substrates of particular interest because the 1,4-adducts are synthetically and biologically important α -substituted succinimides.¹⁵ The reaction of *N*-methylmaleimide with PhB(OH)₂ in the presence of bisphosphine ligands produced the 1,4-adduct **8a** in moderate ee of 28–51% (Table 2, entries 1–3), and the use of phosphoramidite ligand (*S*)-**4** did not improve the enantioselectivity (45% ee; entry 4). Conversely, the use of chiral norbornadiene ligand (*R,R*)-**5a** gave **8a** in much higher ee of 70% (entry 5), and the newly developed analogue (*R,R*)-**5b** further enhanced the enantioselectivity up to 85% ee (entry 6). Other *N*-substituents on maleimide, such as

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(11) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, 125, 11508. Chiral bicyclo[2.2.2]octadienes have recently been reported: Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, 126, 1628.

(12) (*R,R*)-**5b** was synthesized following the procedure for (*R,R*)-**5a** (ref 11) using mesitylmethylmagnesium chloride in place of benzylmagnesium bromide: [α]_D²⁰ –77.3 (*c* 1.00, CHCl₃).

(13) Notes: (a) Smaller ester groups (e.g., dimethyl or diisopropyl fumarate) lead to the decrease in enantioselectivity. A similar trend has been observed in the asymmetric 1,4-additions to (*E*)-2-hexenoates: Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, 10, 4047. See also: Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, 65, 5951. (b) Fumaric acid diesters provide better stereoselection than the corresponding maleic acid diesters.

(14) Agami, C.; Couty, F.; Evano, G. *Eur. J. Org. Chem.* **2002**, 29.

(15) For some biological studies of α -substituted succinimides, see: (a) Jacyno, J. M.; Lin, N.-H.; Holladay, M. W.; Sullivan, J. P. *Curr. Top. Plant Physiol.* **1995**, 15, 294. (b) Ahmed, S. *Drug Des. Discovery* **1996**, 14, 77. (c) Curtin, M. L.; Garland, R. B.; Heyman, H. R.; Frey, R. R.; Michaelides, M. R.; Li, J.; Pease, L. J.; Glaser, K. B.; Marcotte, P. A.; Davidsen, S. K. *Bioorg. Med. Chem. Lett.* **2002**, 12, 2919.

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(6) For reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, 103, 2829. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, 103, 169.

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(8) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, 343, 264.

(9) Shi, Q.; Xu, L.; Li, X.; Jia, X.; Wang, R.; Au–Yeung, T. T.-L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. *Tetrahedron Lett.* **2003**, 44, 6505.

Table 2. Rhodium-Catalyzed 1,4-Addition of Arylboronic Acids to Maleimides

entry	ligand	R	Ar	product	yield ^a (%)	ee ^b (%)
1	(<i>R</i>)- 1	Me	Ph	8a	(100)	51
2	(<i>R</i>)- 2	Me	Ph	8a	(100)	47
3	(<i>S</i>)- 3	Me	Ph	8a	(98)	28
4 ^c	(<i>S</i>)- 4	Me	Ph	8a	(100)	45
5	(<i>R,R</i>)- 5a	Me	Ph	8a	(89)	70
6	(<i>R,R</i>)- 5b	Me	Ph	8a	(88)	85
7	(<i>R,R</i>)- 5b	Cy	Ph	8b	85	87
8 ^d	(<i>R,R</i>)- 5b	Bn	Ph	8c	88	69 (<i>R</i>)
9	(<i>R,R</i>)- 5b	Cy	4-MeOC ₆ H ₄	8d	77	84
10	(<i>R,R</i>)- 5b	Cy	4-FC ₆ H ₄	8e	88	85
11	(<i>R,R</i>)- 5b	Cy	3-ClC ₆ H ₄	8f	92	82
12	(<i>R,R</i>)- 5b	Cy	2-naphthyl	8g	93	84
13	(<i>R,R</i>)- 5b	Cy	2-MeC ₆ H ₄	8h	95	92

^a Isolated yield. Numbers in parentheses are conversions (%) determined by ¹H NMR of the crude mixture. ^b Determined by HPLC on a Chiralpak AD-H column (entries 1–6, 10–13) or a Chiralcel OD-H column (entries 7–9) with hexane/2-propanol = 90/10. ^c 11 mol % of ligand was used. ^d The absolute configuration was determined by comparison of the optical rotation with the literature value (see ref 16).

cyclohexyl group, are also suitable, leading to the 1,4-adduct **8b** with high enantiomeric excess in the presence of a Rh/(*R,R*)-**5b** catalyst (87% ee; entry 7). To determine the absolute configuration, *N*-benzylmaleimide was employed, whose 1,4-adduct **8c** was assigned to be (*R*)-enriched based on the sign of the optical rotation ($[\alpha]^{20}_D -33.7$ (*c* 1.20, CHCl₃); entry 8).¹⁶ With this catalyst system, the reaction tolerates a wide range of arylboronic acids, providing uniformly high yield and ee (**8d–h**, 77–95% yield, 82–92% ee; entries 9–13).

An X-ray crystal structure of [RhCl((*R,R*)-**5a**)]₂ shows that the steric difference between a bulky arylmethyl group and a small hydrogen on the ligand is effectively dissecting the space in a *C*₂-fashion, thereby creating a very good chiral environment around the rhodium (Figure 1). This steric differentiation is much more effective in the present asymmetric reactions than other systems such as Rh/(*R*)-binap, whose origin of stereocontrol comes from the face-and-edge difference of the phenyl groups on phosphorus atoms of (*R*)-binap.^{17,18} Based on the crystal structure of Rh/(*R,R*)-**5a**, a stereochemical course of the asymmetric 1,4-addition to

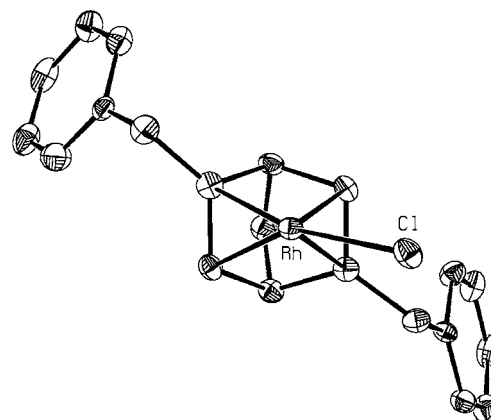


Figure 1. ORTEP illustration of [RhCl((*R,R*)-**5a**)]₂ with thermal ellipsoids drawn at the 50% probability level (shown as a monomer for clarity).

fumaric and maleic compounds can be proposed as depicted in Figure 2, leading to the observed stereochemical outcome in both cases.

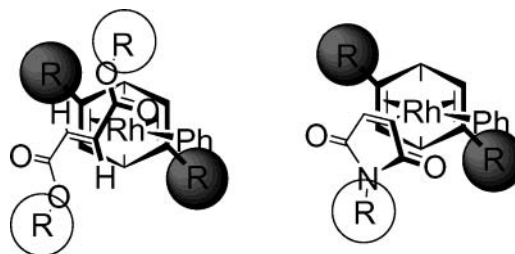


Figure 2. Proposed stereochemical pathways for the asymmetric 1,4-addition to a fumaric acid diester (left) and a maleimide (right) catalyzed by rhodium/chiral norbornadiene.

In summary, we have developed a rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to fumaric acid diesters and maleimides. By employing a chiral norbornadiene as ligand, we have efficiently coupled a range of arylboronic acids with these substrates in very good enantiomeric excess. The origin of stereocontrol in these reactions can be rationalized by the crystal structure of a rhodium/chiral norbornadiene complex.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) $[\alpha]^{20}_D +38$ (CHCl₃) for (*S*): Bettoni, G.; Franchini, C.; Morlacchi, F.; Tangari, N.; Tortorella, V. *J. Org. Chem.* **1976**, *41*, 2780.

(17) For an example of the X-ray crystal structure of a Rh/(*R*)-binap complex, see: Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(18) For discussion on the origin of stereocontrol in the 1,4-addition reactions catalyzed by Rh/binap, see refs 5 and 6.