

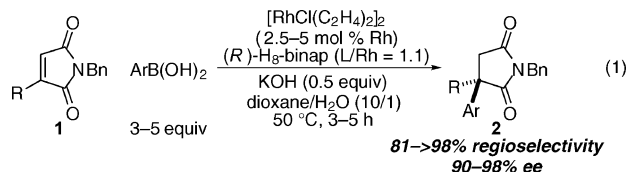
Rhodium-Catalyzed Asymmetric Construction of Quaternary Carbon Stereocenters: Ligand-Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides

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Enantioselective construction of quaternary carbon stereocenters is an important, but challenging, objective in organic chemistry.¹ 1,4-Addition of carbon nucleophiles to β,β -disubstituted α,β -unsaturated compounds is potentially a useful strategy for efficient assembly of this type of molecular skeleton. It is, therefore, of high value to achieve such a transformation in a catalytic asymmetric fashion.² Some successful examples in this regard have begun to appear in the copper-catalyzed asymmetric 1,4-addition of dialkylzinc reagents³ and trialkylaluminum reagents,⁴ and Carretero recently reported a rhodium-catalyzed 1,4-addition of alkenylboronic acids to α,β -unsaturated pyridyl sulfones for the construction of quaternary carbon stereocenters.⁵ In this communication, we describe the development of a rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to 3-substituted maleimides (**1**),⁶ furnishing 3,3-disubstituted succinimides (**2**) in high regio- and enantioselectivity (eq 1).



We initially conducted a reaction of 1-benzyl-3-ethylmaleimide (**1a**) with PhB(OH)₂ in the presence of 2.5 mol % rhodium catalyst bearing chiral diene⁷⁻⁹ (*R,R*)-Bn-bod*,^{7,8} obtaining 1-benzyl-3-ethyl-4-phenylsuccinimide (**3a**) as the major product along with its regioisomer **2a** (**2a/3a** = 22/78; Table 1, entry 1). Although the *trans/cis* ratio of **3a** was not very good (1.6/1), the enantioselectivity was high in both diastereomers (*trans*, 82% ee; *cis*, 97% ee). The employment of (*R,R*)-Ph-bod*⁷ as a ligand gave higher regioselectivity toward **3a** (**2a/3a** = 15/85; entry 2) with somewhat better enantioselectivity (*trans*, 83% ee; *cis*, >99% ee). In contrast, the use of bisphosphine ligands reversed the regioselectivity of 1,4-addition, preferentially forming compound **2a**.¹⁰ Thus, in the presence of (*R*)-binap,^{11,12} the products were obtained in 99% combined yield with **2a/3a** = 85/15, and the enantioselectivity of **2a** was as high as 96% ee (entry 3). By changing the ligand to (*R*)-H₈-binap,¹³ the regioselectivity toward **2a** was further enhanced with maintaining the high enantiomeric excess (87/13, 97% ee; entry 4). A similar trend was observed with substrate **1b** (R = Me; entries 5–8), and the absolute configurations of *trans*-**3b** and *cis*-**3b** in entry 5 were determined to be (4*R*) by converting them to *trans*-**4** and *cis*-**4**, respectively (eq 2).¹⁴

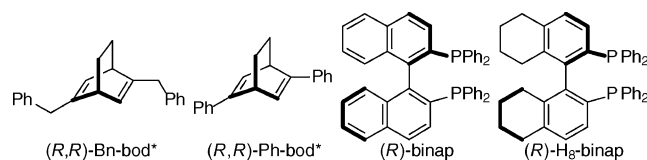


Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to Substituted Maleimides **1**: Ligand Effect

entry	1	ligand	yield (%) ^a	2/3 ^b (<i>trans/cis</i>) ^b	ee of 2 (%)	ee of 3 (%) (<i>trans, cis</i>)
1	1a	(<i>R,R</i>)-Bn-bod*	93	22/78 (1.6/1)	73	82, 97
2	1a	(<i>R,R</i>)-Ph-bod*	94	15/85 (1/2.3)	97	83, >99
3	1a	(<i>R</i>)-binap	99	85/15 (2.0/1)	96	68, 96
4	1a	(<i>R</i>)-H ₈ -binap	98	87/13 (2.3/1)	97	–19, 96
5	1b	(<i>R,R</i>)-Bn-bod*	94	20/80 (2.1/1)	84	82, 93
6	1b	(<i>R,R</i>)-Ph-bod*	94	11/89 (1/4)	93	79, 99
7	1b	(<i>R</i>)-binap	98	75/25 (2.1/1)	95	0, 96
8	1b	(<i>R</i>)-H ₈ -binap	98	81/19 (2.8/1)	96	–10, 94

^a Combined yield of **2** and **3**. ^b Determined by ¹H NMR of the crude material.

Table 2. Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Substituted Maleimides **1**: Scope

entry	1	Ar	yield (%) ^a	2/3 ratio ^b	ee of 2 (%)
1	1a	Ph	98	87/13	97
2	1a	3-ClC ₆ H ₄	95	92/8	97
3	1a	2-naphthyl	90	86/14	96
4	1a	2-MeC ₆ H ₄	82	>98/2	90
5	1b	Ph	98	81/19	96
6	1b	4-MeOC ₆ H ₄	95	84/16	90
7	1b	4-FC ₆ H ₄	95	86/14	96
8 ^c	1c	Ph	90	97/3	98
9 ^c	1c	4-MeC ₆ H ₄	85	97/3	98

^a Combined yield of **2** and **3**. ^b Determined by ¹H NMR of the crude material. ^c The reaction was conducted for 5 h with 5 mol % of catalyst and 5.0 equiv of ArB(OH)₂.

We have determined that the scope of this asymmetric construction of quaternary carbon stereocenters catalyzed by Rh/(*R*)-H₈-binap is fairly broad (Table 2). Both substrates **1a** and **1b** can react with various arylboronic acids with high regioselectivity (81/19–92/8; entries 1–3 and 5–7), furnishing desired 1,4-adducts **2** with excellent enantioselectivity (90–97% ee). It is worth noting that an *o*-tolyl group can be installed in **1a** with almost perfect regioselectivity (>98/2, 90% ee; entry 4). Furthermore, substrate **1c** (R = *i*-Pr) undergoes the 1,4-addition with very high regio- and

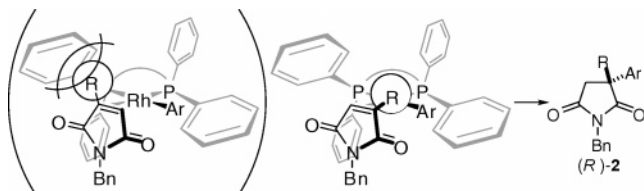


Figure 1. Proposed stereochemical pathway for the asymmetric 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(R)-H₈-binap.

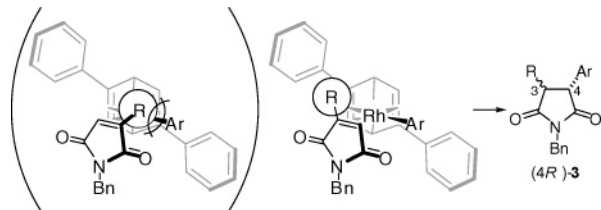
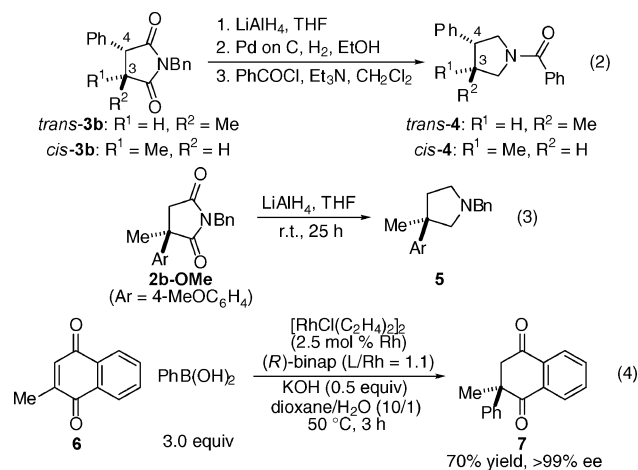


Figure 2. Proposed stereochemical pathway for the asymmetric 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(R,R)-Ph-bod*.

enantioselectivity (97/3, 98% ee; entries 8 and 9). The absolute configuration of 1,4-adduct **2b-OMe** in entry 6 was determined to be (*R*) by reducing it to pyrrolidine **5** (eq 3).¹⁴

We have also examined the reaction with quinone-based substrates. For example, 2-methyl-1,4-naphthoquinone (**6**) undergoes the 1,4-addition of PhB(OH)₂ in the presence of 2.5 mol % of Rh/(*R*)-binap, furnishing product **7** in 70% yield with >99% ee (eq 4).



The observed regioselectivity in these 1,4-additions to 3-substituted maleimides can be explained as follows. In the presence of a rhodium catalyst bearing (*R*)-H₈-binap (Figure 1), due to the severe steric repulsion between the substituent *R* on maleimide and the phenyl group sticking out from the phosphorus atom of the ligand, maleimide preferentially coordinates to rhodium, keeping its *R* group away from the ligand phenyl group, leading to the selective formation of **2**.

In contrast, in the presence of (*R,R*)-Ph-bod* (Figure 2), the upward orientation of the phenyl substituent on the diene ligand significantly reduces the steric repulsion with the *R* group on maleimide. As a result, the steric hindrance between an aryl group on the rhodium and the *R* group on maleimide becomes the dominant factor, leading to selective insertion of maleimide toward the formation of **3**.

With regard to the absolute configurations, to avoid the unfavorable steric interaction between the imide moiety of maleimide and

the phenyl group on the ligand, Rh/(*R*)-H₈-binap provides (*R*)-isomers and Rh/(*R,R*)-Ph-bod* provides (*4R*)-isomers, respectively.¹⁵

In summary, we have developed a rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to 3-substituted maleimides. The regioselectivity has been controlled by the choice of ligand (dienes or bisphosphines), and 1,4-adducts with a quaternary stereocenter can be obtained with high regio- and enantioselectivity by the use of (*R*)-H₈-binap.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

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

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- (15) Currently, we do not fully understand the exact factors that determine the ratio of *trans* and *cis* in the formation of 1,4-adducts **3**.

JA061430D