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

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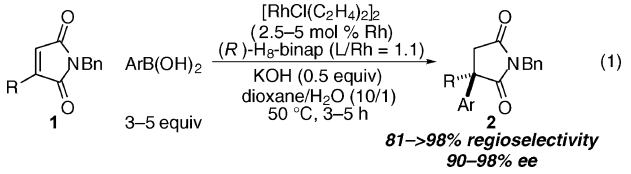
Enantioselective construction of quaternary carbon stereocenters is an important, but challenging, objective in organic chemistry.[1] 1,4-Addition of carbon nucleophiles to β,β-disubstituted α,β-unsaturated compounds is potentially a useful strategy for efficient assembly of this type of molecular skeleton. 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 reagents[3] 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 diene[7−9] (*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*)-H_8-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]

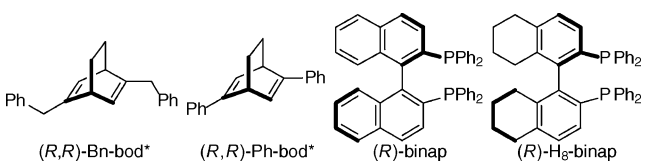
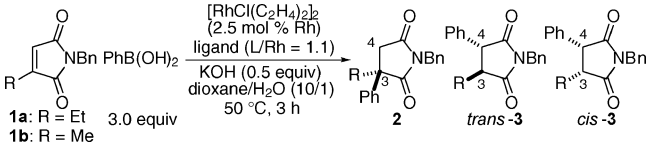


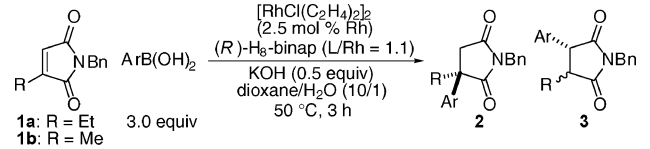
Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to Substituted Maleimides **1**: Ligand Effect



entry	**1**	ligand	yield (%)[a]	**2**/**3**[b] (*trans*/*cis*)[b]	ee of **2** (%)	ee of **3** (%) (*trans*, *cis*)
1	**1a**	(*R*,*R*)-Bn-bod*	93	22/**78** (1.6/1)	73	**82**, **97**
2	**1a**	(*R*,*R*)-Ph-bod*	94	15/**85** (1/2.3)	97	**83**, >**99**
3	**1a**	(*R*)-binap	99	**85**/15 (2.0/1)	**96**	68, 96
4	**1a**	(*R*)-H_8-binap	98	**87**/13 (2.3/1)	**97**	−19, 96
5	**1b**	(*R*,*R*)-Bn-bod*	94	20/**80** (2.1/1)	84	**82**, **93**
6	**1b**	(*R*,*R*)-Ph-bod*	94	11/**89** (1/1.4)	93	**79**, **99**
7	**1b**	(*R*)-binap	98	**75**/25 (2.1/1)	**95**	0, 96
8	**1b**	(*R*)-H_8-binap	98	**81**/19 (2.8/1)	**96**	−10, 94

[a] Combined yield of **2** and **3**. [b] Determined by ^{1}H 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_6H_4	95	92/8	97
3	**1a**	2-naphthyl	90	86/14	96
4	**1a**	2-MeC_6H_4	82	>98/2	90
5	**1b**	Ph	98	81/19	96
6	**1b**	4-$MeOC_6H_4$	95	84/16	90
7	**1b**	4-FC_6H_4	95	86/14	96
8[c]	**1c**	Ph	90	97/3	98
9[c]	**1c**	4-MeC_6H_4	85	97/3	98

[a] Combined yield of **2** and **3**. [b] Determined by ^{1}H 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*)-H_8-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

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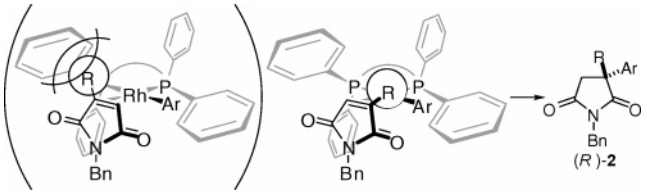


Figure 1. Proposed stereochemical pathway for the asymmetric 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(*R*)-H_8-binap.

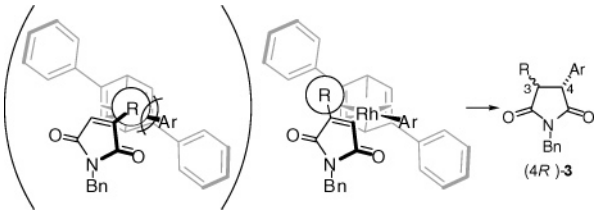
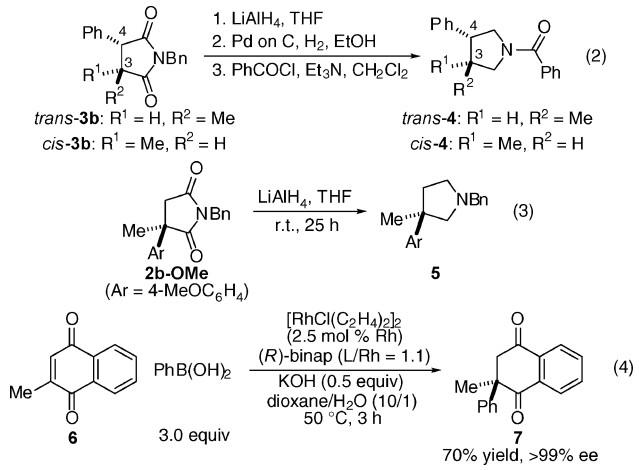


Figure 2. Proposed stereochemical pathway for the asymmetric 1,4-addition to a 3-substituted maleimide catalyzed by Rh/(*R*,*R*)-Ph-bod*.

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*)-H_8-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*)-H_8-binap provides (*R*)-isomers and Rh/(*R*,*R*)-Ph-bod* provides (4*R*)-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*)-H_8-binap.

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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**.

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