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Chiral amidomonophosphine-rhodium(I) catalyst for asymmetric 1,4-addition of arylboronic acids to cycloalkenones

Masami Kuriyama and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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Abstract—The asymmetric 1,4-addition reaction of arylboronic acids with cycloalkenones was catalyzed by 1 mol% of an amidomonophosphine-rhodium(I) catalyst in a 10:1 mixture of dioxane and water at 100°C, affording 3-arylcycloalkanones in reasonably high enantioselectivity (up to 96% ee) and high yields (up to 99%). The reaction efficacy of phenylboronic acid with cyclohex-2-enone was significantly dependent on the initiation procedure when BINAP was used as a phosphine.

The discovery and development of new and efficient chiral catalysts are of fundamental importance for efficient and clean organic synthesis.[1,2] In particular, an asymmetric carbon–carbon bond forming process is a recent focus for advanced materials and pharmaceuticals. We have been engaged in the asymmetric conjugate addition reactions[3] of organometallic reagents with enones and enoates, which are mediated or catalyzed by chiral ligands such as diethers,[4] amino ethers,[5] and phosphines.[6] Of particular interest is that a chiral amidomonophosphine **1**[7]-copper(I) catalyzes a conjugate addition of alkylzinc and alkyl Grignard reagents to enones, resulting in the production of the corresponding adducts in reasonably high enantioselectivity.[8] However, the addition reaction suffers from unsatisfactory poor efficacy with the addition of aryl groups.[9,10] In 1997, Miyaura and coworkers discovered a phosphine–rhodium(I) complex catalyst for 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones, giving the corresponding β-substituted ketones in high yield[11] (Fig. 1). In 1998, based on this finding, Hayashi and Miyaura developed a rhodium(I)-catalyzed asymmetric 1,4-addition reaction of organoboron reagents with enones, enoates and alkenylphosphonates.[12] They achieved high enantioselectivity and high yields, particularly when using (*S*)-BINAP **2**[13] as a chiral phosphine ligand for rhodium(I). However, the catalysis performance was critically dependent on the structural features of the phosphine ligands. Some other bisphosphines, (*S*,*S*)-diop and (*S*,*S*)-chiraphos, a monodentate phosphine, (*R*)-meo-mop, and phosphines containing nitrogen functionality, (*S*)-ip-phox and (*S*)-(*R*)-bppfa conveyed poor enantioselectivity and poor yields.[14] Here we describe that a highly efficient asymmetric 1,4-addition reaction of arylboronic acids with cycloalkenones was catalyzed by rhodium(I) using amidophosphine **1,** which is a characteristic monophosphine ligand effective in the copper-catalyzed conjugate addition of alkyllithium and alkyl Grignard reagents.[7] The efficacy of catalysis was dependent on the initiation procedure, particularly when BINAP **2** was used as a phosphine ligand.

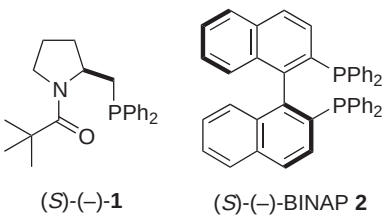
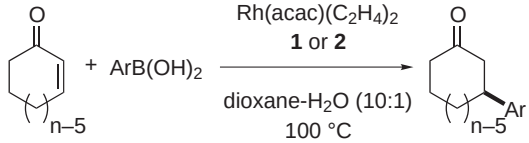


Figure 1. Chiral phosphine ligands **1** and **2**.

We were very pleased to find that amidomonophosphine **1** provided excellent catalysis performance, achieving reasonably high ee and yield. A representa-



Scheme 1. Asymmetric 1,4-addition of arylboronic acids to cycloalkenones controlled by chiral phosphines **1** and **2**.

* Corresponding author. E-mail: tomioka@pharm.kyoto-u.ac.jp

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tive procedure is given here for the reaction of phenylboronic acid (Ar=Ph) with cyclohex-2-enone ($n=6$) catalyzed by amidomonophosphine **1**-rhodium(I) (Scheme 1). Under argon atmosphere, a reaction flask was charged with $Rh(acac)(C_2H_4)_2$[15] (2.6 mg, 0.01 mmol), **1** (4.6 mg, 0.013 mmol), and $PhB(OH)_2$ (610 mg, 5.0 mmol). To the flask were added successively 1,4-dioxane (2.5 ml), water (0.25 ml), and cyclohex-2-enone (96 mg, 1.0 mmol). The mixture was allowed to warm from room temperature to 100°C over a period of 10 min (method B) and then stirred at 100°C for a further 1 h. After dilution with AcOEt, the mixture was washed with 10% NaOH and then dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 5/1) gave (*S*)-3-phenylcyclohexanone ($n=6$, Ar=Ph: 173 mg, 99% yield) as a colorless oil (Table 1, entry 2). The enantiomeric purity was determined to be 95% ee by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD, hexane/2-propanol = 50/1). The absolute configuration was determined to be *S* by comparison of the specific rotation ($[\alpha]_D^{20}$ −20.0 (*c* 1.13, $CHCl_3$)).[16] The chiral amidophosphine **1** was recovered quantitatively as an oxide that is reducible[17] to **1** for re-use in further catalytic addition reaction.

At the same time, we examined the reaction of phenylboronic acid with cyclohex-2-enone using BINAP **2** under the reported conditions.[12a] Under initiation method B, the reaction was not completed, affording the adduct in only 24% yield after 5 h (entry 5). However, under alternative initiation conditions (method A), in which the reaction flask was immersed in an oil bath preheated at 100°C, the reaction gave the adduct in 99% yield after 3 h (entry 4). The ees were very high under both initiation conditions A and B. In contrast, the catalyst derived from amidophosphine **1** was not so sensitive to the initiation conditions, affording the adducts in almost the same yields and ees (entries 1 and 2). These differences in catalysis performance due to the nature of phosphine ligands **1** and **2** may be useful to the future study of catalytic processes. It is also important to note that the phosphine–rhodium(I) molar ratio is not critical, giving the similar levels of high enantioselectivity. For example, the 3:1 molar ratio of **1**/Rh(I) catalyst gave the adduct in 80% yield and 94% ee (entry 3). This indicates that **1** behaves like a bidentate ligand, probably using phosphorous and amide carbonyl oxygen as coordinating heteroatoms.[18,19]

The reactions of phenylboronic acid with cyclopent-2-enone ($n=5$) and cyclohept-2-enone ($n=7$) proceeded in a satisfactory manner, affording the corresponding adducts in reasonably high ees and yields (entries 6–8). Initiation method B seems to be slightly superior to method A, as shown by the compared reaction of cyclopent-2-enone giving 3-phenylcyclopentanone in 83% ee and 90% yield by method B (entries 6 and 7).

The **1**/Rh(I)-catalyzed asymmetric reaction was applicable to the addition reaction of substituted phenyl groups with cyclohex-2-enone. Phenyl groups bearing electron-donating 4-methyl and 3-methoxy substituents conveyed 92% and 93% ees and high yields (entries 9 and 10). An electron-withdrawing group does not disturb the reaction, affording 3-(3-chlorophenyl)-cyclohexanone (Ar=3-ClPh, $n=6$) in 91% ee and 90% yield (entry 11). Steric hindrance was not a disturbing factor, as shown in the reaction of 2-methylphenylboronic acid, affording the product in 91% ee and 99% yield after 1 h (entry 12).

In summary, we have found that a high level of catalysis performance for enantioselectivity and yield is attainable in the asymmetric 1,4-addition of a variety of arylboronic acids to cycloalkenones using an amidomonophosphine **1** as a phosphine ligand for rhodium(I). Further studies directed towards clarifying the structural features of the **1**-Rh(I) complex and its application to other catalytic reactions are in progress in our laboratory.

Table 1. Catalytic asymmetric 1,4-addition of arylboronic acids to cycloalkenones controlled by **1** and **2**

Entry	Ar	*n*	**1**/**2**	Rh (mol%)	Rh/lig[a]	A/B[b]	Time (h)	Yield (%)	ee (%)
1	Ph	6	**1**	1	1/1.3	A	1	99	96
2	Ph	6	**1**	1	1/1.3	B	1	99	95
3	Ph	6	**1**	1	1/3	B	1	80	94
4	Ph	6	**2**	3	1/1	A	3	99	97
5	Ph	6	**2**	3	1/1	B	5	24	98
6	Ph	5	**1**	1	1/1.3	A	6	83	73
7	Ph	5	**1**	1	1/1.3	B	6	90	83
8	Ph	7	**1**	1	1/1	B	24	95	91
9	4-MePh	6	**1**	1	1/1	A	1	99	92
10	3-MeOPh	6	**1**	1	1/1	A	1	99	93
11	3-ClPh	6	**1**	1	1/1	A	3	90	91
12	2-MePh	6	**1**	1	1/1	A	1	99	91

[a] Molar ratio between Rh(I) and **1** or **2**.

[b] Method A: Reaction flask was immersed in an oil bath preheated at 100°C. Method B: Reaction flask was allowed to warm from room temperature to 100°C over 10 min.

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