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Practical Method for Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds Utilizing an In Situ Prepared Rhodium Catalyst

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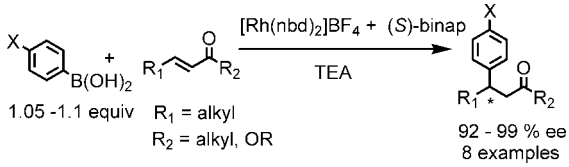
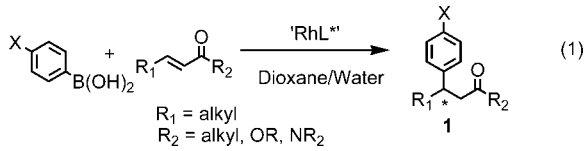


A new practical method for the asymmetric Michael addition of arylboronic acids to α,β-unsaturated carbonyl compounds utilizing in situ generated chiral rhodium-binap-based catalyst has been developed to address the unavailability of the preformed catalysts. While maintaining high levels of enantioselectivity reported for the preformed catalysts, the new method provides a convenient access to either enantiomeric form of the product and allows for a substantial reductions in both the boronic acid and the catalyst loads.

Rhodium-catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated carbonyl compounds, which was originally developed by Hayashi[1] and Miyaura,[2] has become an important synthetic method for the preparation of chiral β-aryl-substituted ketones and esters **1** (eq 1). High levels of asymmetric induction



(1)

observed in these reactions make this approach particularly valuable.[3] However, when considering applications of this methodology for large-scale preparations, the catalysts' availability becomes a substantial obstacle. The standard reaction protocol requires relatively high loads of the catalysts (typically 3 mol %);[1−3] however, only the *S*-form of the desirable second generation Hayashi catalyst (**2**) could be obtained commercially in gram quantities, while Miyaura catalyst (**3**) is not available at all. The older, first generation Hayashi catalyst (**4**) could be conveniently prepared in situ from the available starting materials, but its practical applications are limited due to insufficient reactivity.

{Rh[(*S*)-binap]OH}$_2$ (**2**) {Rh(nbd)[(*R*)-binap]}BF_4 (**3**)

Rh(acac)[(*S*)-binap] (**4**)

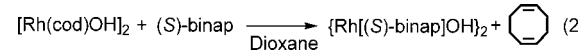
Alternative "in house" preparation of large quantities of catalysts **2** or **3** was deemed not feasible due to their particular air sensitivity requiring specialized equipment. Although a number of newer, more efficient catalysts have been introduced in recent years, these new entities typically employ "designer" ligands, which need to be independently synthesized, thus further limiting their utility.[4]

Another undesirable characteristic of the reaction outlined in eq 1 is the requirement to use 1.5−3 equiv of the corresponding arylboronic acid, which is needed to compensate for the protodeborylation (hydrolysis) side reaction.[3] The excess reagent and the side product formation complicate the product isolation and reduce the overall cost efficiency of the process.

In this note, we describe a new practical method for the asymmetric Michael addition of arylboronic acids to α,β-unsaturated carbonyl compounds, which utilizes in situ prepared Miyaura type catalyst **3**. This methodology provides convenient access to either enantiomer, utilizing commercially available starting materials, while maintaining the high enantioselectivity reported for the preformed catalysts. Additionally, our conditions allow reduction of the catalyst load from 3 to 1.5 mol % while decreasing the required excess of arylboronic acids from 1.5−3 to just 1.05−1.1 equiv.[5a]

To address the catalyst availability issue, we thought that its in situ generation from commercially available precursors could be a valuable solution. Additional advantages of this approach include the elimination of the special handling requirements for the highly air-sensitive active catalyst and convenient access to either desired enantiomer of the product by simply switching to a ligand with the opposite stereochemistry.

Unfortunately, we soon learned that in situ preparation of the most widely used Hayashi catalyst **2** was a difficult problem. Although, combining the available [Rh(cod)OH]$_2$ starting material with (*S*)-binap ligand liberates cyclooctadiene while providing the desired highly reactive binap complex (eq 2), the reactions utilizing the resulting catalyst displayed only modest asymmetric inductions.



(2)

For example, the addition of bromophenylboronic acid **5** to cyclopentenone (eq 3) gave product **6** with 55% ee (vs 96% ee observed for the preformed catalyst **2**). It was reported in the literature that achiral rhodium−cyclooctadiene complexes were highly active catalysts for the Michael-type addition of arylboronic acids.[2] We suggested that small amounts of such complexes could be presented in the reaction mixture and were

(1) (a) The first generation catalyst: Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) The second generation catalyst: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(2) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

(3) For reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Hayashi, T. *Synlett* **2001**, 879.

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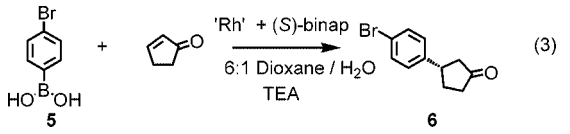
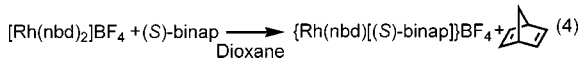
responsible for the observed background reaction. Indeed, attempted removal of cyclooctadiene from the in situ generated catalyst under vacuum resulted in the improvement of the product chiral purity to ~90% ee but was not practical due to its insufficient reproducibility.[5]



With these lessons learned, we thought that Miyaura catalyst **3** could be a better fit for the in situ preparation method because it could be synthesized from commercially available rhodium−norbornadiene complex (eq 4), which has been previously found poorly active in Michael additions of arylboronic acids.[2]

Indeed, we were pleased to find that the reaction outlined in eq 3 utilizing the catalyst prepared by combining bis(norbornadiene)rhodium tetrafluoroborate with (*S*)-binap (eq 4) in dioxane gave the desired compound **6** in 85% isolated yield and 97% ee purity versus 87% yield and 96.5% ee obtained with preformed catalyst **3**.



Further reaction optimization allowed us to develop a very robust protocol, where the catalyst was prepared in situ by combining the phosphine and rhodium components directly in a dioxane slurry of the desired boronic acid at room temperature (see Experimental Section for details). Upon the formation of the active catalyst, water cosolvent was added, followed by the addition of α,β-unsaturated carbonyl compound and triethylamine as a base. Under these optimized conditions, the reaction proceeded at room temperature and required only 1.5 mol % of the catalyst, versus previously reported 3%. Moreover, as we observed very little protodeborylation in the reaction mixture under these conditions, the possibility of reduction of the excess boronic acid below the standard 1.5 equiv was investigated. We found that only 1.05 equiv of the boronic acid was required to achieve complete consumption of the carbonyl component. The reduction in the arylboronic acid amount also allowed us to simplify the reaction workup. Thus common chromatographic isolation could be replaced with a simple extractive protocol, which gave the products suitable for further utilization.

To demonstrate the generality of this practical method, we conducted a series of asymmetric additions of arylboronic acids to α,β-unsaturated carbonyl compounds using the standard set of literature substrates **7**−**10**, affording the formation of compounds **6** and **11**−**14** (Figure 1). The results of these experiments are summarized in Table 1.

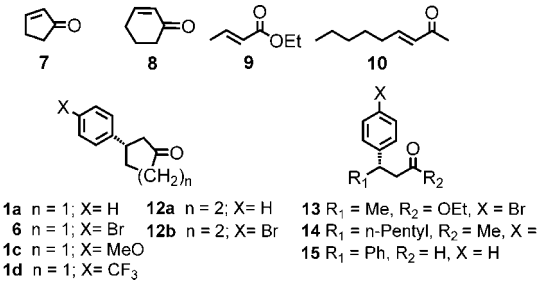


FIGURE 1. α,β-Unsaturated carbonyl components and products in asymmetric Michael additions of arylboronic acids.

TABLE 1. Asymmetric Additions of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds[a]

entry	product	reaction yield (%)[b]	isolated yield (%)[c]	chiral purity (% ee for *S*-series)
1	**6**	96	85	97.0
2	**11a**	90	78	95.1
3	**11c**[d]	93	75	95.7
4	**11d**	96	81	97.3
5	**12a**	94	80	98.6
6	**12b**	86	71	98.7
7	**13**	99	79	93.4
8	**14**[e]	92	75	91.6
9	**15**	0	0	N/A

[a] Reaction conditions: 1.05 equiv of arylboronic acid, 1.5 mol % of catalyst, 23−27 °C. [b] As determined by HPLC method. [c] After column chromatography. [d] 1.1 equiv of arylboronic acid was used. [e] In 12:1 dioxane/water.

We were pleased to find that the levels of asymmetric induction and the assayed reaction yields observed in these experiments matched the literature data.[6] The isolated yields of individual compounds in Table 1 have not been optimized and in some cases were slightly lower than those reported. Most of the reactions were also repeated with the *R*-form of binap ligand in order to achieve accurate assessment of the chiral purity of products.[7]

The following additional observations are noteworthy: (a) the water content in dioxane for the reactions listed in Table 1 could be reduced from typical 15 to 7%. Lower water content benefited the reaction involving compounds with larger lypophilic groups (entry 8), which resulted in better conversion and chiral purity; (b) 1.1 equiv of 4-(methoxyphenyl)boronic acid was used due to its faster hydrolysis under the reaction conditions (entry 3); (c) no addition to *trans*-cinnamaldehyde[8] was observed under the current conditions.

In summary, we have developed a highly practical protocol for asymmetric additions of arylboronic acids to conjugated carbonyl compounds utilizing an in situ generated Miyaura-type catalyst. Due to commercial availability of the catalyst components, the overall simplicity, and convenient access to either of the desired enantiomers, this method represents a substantial improvement over the previously reported conditions. In the current form, the methodology could be applied for the

(4) (a) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. *J. Org. Chem.* **2003**, *68*, 9481. (b) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (c) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (d) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (e) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172.

(5) (a) A solvent switch from water to isopropyl alcohol was recently reported to reduce the boronic acid loss due to protodeborylation: Brock, S.; Hose, D. R. J.; Mosely, J. D.; Parker, A. J.; Patel, I.; Williams, A. J. *Org. Process Res. Dev.* **2008**, *12*, 496. (b) In situ generation of catalyst **2** from $[RhCl(S)\text{-binap})]_2$ and KOH has been reported (ref 1b). However, the precursor complex is not available commercially. Additionally, formation of a racemic product was reported when utilizing the catalyst prepared in this way (ref 2).

(6) Literature data for rhodium-catalyzed asymmetric additions of arylboronic acids to compounds **11**−**14**: **11a**, ref 1a; **11c**,**11d**, ref 1b; **12b**: Pucheault, M.; Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2002**, *21*, 3552. **12a**,**14**, ref 2.

(7) Experiments in *R*-series gave products with slightly lower chiral purities probably due to the lower chiral purity of the ligand used (99.3 vs 99.9% ee for *S*-series): **6**, 96.1% ee; **11c**, 93.2% ee; **11d**, 96.6% ee; **12a**, 98.8% ee; **12b**, 99.1% ee; **13**, 91.2% ee.

(8) α,β-Unsaturated aldehydes have been reported to give poor yields/chiral purities in rhodium-binap-catalyzed additions of arylboronic acids. See, for example, ref 4c.

robust and scalable preparations of β-aryl-substituted carbonyl compounds with high yields and enantiomeric purities.

Experimental Section

General Procedure for the Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds. Synthesis of 3-(*S*)-(4-Bromophenyl)cyclopentanone (6). Bis(norbornadiene)rhodium tetrafluoroborate (0.28 g, 0.75 mmol) and (*S*)-binap (0.5 g, 0.8 mmol) were added to a mixture of 4-bromophenylboronic acid (10 g, 50 mmol) in nitrogen sparged dioxane (65 mL) under nitrogen atmosphere. After 2 h of agitation at ambient temperature, water was added (10 mL) followed by 2-cyclopenten-1-one (3.9 g, 47.5 mmol) and triethylamine (4.8 g, 47.5 mmol). The agitation was continued for 15 h at 23−27 °C.[9] The mixture was then diluted with heptane (65 mL), MTBE (17.5 mL), and water (50 mL). The organic layer was separated and washed with water (50 mL). The aqueous layers were combined and extracted with MTBE/heptane (1:2, 50 mL). Combined organic layers were filtered through filtrol and concentrated in vacuo. The resulting solid was re-slurried in heptane, filtered, and dried in vacuo to give **6** (9.65 g, 85% yield, 97% ee chiral purity).

Ethyl (*S*)-3-(4-Bromophenyl)butenoate (13) was prepared according to a general procedure from ethyl crotonate (**9**, 0.51 g, 4.5 mmol) and 4-bromophenylboronic acid (0.95 g, 4.75 mmol). General isolation procedure followed by column chromatography gave compound **13** (1.01 g, 79% yield, 93% ee chiral purity).

Other compounds listed in Table 1 were prepared using the above procedure in the specified yields and chiral purities.[10] The reaction yields were determined by HPLC method using isolated reference material. The reference materials were obtained from the crude isolated products by column chromatography (silica; ethyl acetate−hexane).[11] Crude isolated products typically had >90% purity (as determined by HPLC and ^{1}H NMR) and were suitable for further chemical transformations.

Supporting Information Available: HPLC methods for chiral analysis and ^{1}H spectra of compounds **6** and **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction is exothermic with adiabatic heat of 40 °C. External cooling was used to maintain 23−27 °C temperature.

(10) Literature refs for the isolated compounds. **6**: Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hajdu, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G.-J.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quackenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. *J. Med. Chem.* **2005**, *48*, 6169. **11a**: Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858. **11c**,**11d**: Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. **12a**: Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821. **12b**: Zhang, Y.; Schuster, G. B. *J. Org. Chem.* **1994**, *59*, 1855. **13**: Marugesan, N.; Barrish, J. C.; Lloyd, J. Jpn. Kokai Tokkyo Koho; Patent JP 09124620 A 19970513, 1997. **14**: Ref 1a.

(11) No further enhancement in the chiral purity of products was observed during the isolation.