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Palladium-Catalyzed Enantioselective Conjugate Addition of Arylboronic Acids

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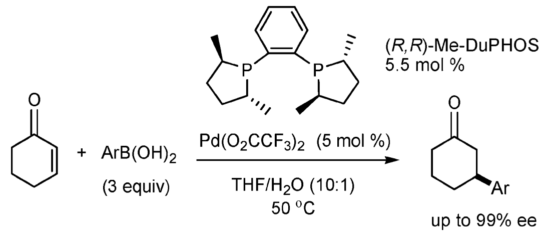
ABSTRACT



The first asymmetric palladium-catalyzed conjugate addition of arylboronic acids to α,*β*-unsaturated aldehydes, ketones, and esters is described. For cyclic substrates, excellent chemo-, regio-, and enantioselectivities are achieved when a Pd(O_2CCF_3)$_2$/DuPHOS catalyst is applied.

Carbon−carbon bond formation by catalytic asymmetric conjugate addition of organometallic reagents is one of the important reactions in organic synthesis.[1] In the past decade, considerable progress has been made in the transition-metal-catalyzed transfer of alkyl and aryl groups.[2] The asymmetric conjugate addition of dialkylzinc reagents catalyzed by copper complexes is now well established,[3] and recently, also the enantioselective addition of alkyl Grignard reagents to a range of substrates was achieved.[4]

For the enantioselective conjugate addition of aryl groups, the rhodium-catalyzed arylboronic acid addition developed by Miyaura[5] and Hayashi[6] is the method of choice at present. The stability and commercial availability of arylboronic acids have contributed to the popularity of this method. High enantioselectivities have been reported for the addition to a large variety of α,*β*-unsaturated compounds.[7] Next to BINAP, also monodentate phosphonites[8] amidophosphines,[9] and phosphoramidites[10] are used as chiral ligands. Very recently, chiral dienes have been introduced that can be applied as versatile ligands in this reaction type.[11]

Cationic palladium(II) complexes show relatively fast rates for transmetalation of organoboron and -silicon compounds,

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a process that is generally slow for transition metals.[12] This has stimulated research toward their use in conjugate addition reactions where the transmetalation is a critical step. Denmark and Amishiro and also Miyaura et al. have studied the addition of arylsiloxanes to α,β-unsaturated compounds,[13,14] whereas Miyaura et al. reported catalyst systems that are able to transfer arylboronic acids.[15] Recently, the palladium catalyzed asymmetric conjugate addition of triarylbismuth reagents[16] and aryltrifluoroborates[17] was reported by the same group. The asymmetric conjugate addition of the parent arylboronic acids, however, has been elusive until now.[18]

Herein, we report the first enantioselective palladium catalyzed conjugate addition of arylboronic acids to a variety of α,β-unsaturated compounds.

Initial experiments were carried out using the addition of phenylboronic acid **2a** to 2-cyclohexenone **1a** as the benchmark reaction. It has been shown previously that cationic palladium enolates are much more susceptible to hydrolytic Pd−C bond cleavage than neutral palladium species.[19] Fast Pd−C cleavage is essential to avoid competing β-hydride elimination leading to Heck-type products.[20] To create an electrophilic Pd(II) complex with weakly coordinating anions, $Pd(OAc)_2$ was used in combination with triflic acid (TfOH).

Of the bidentate ligands tested (Figure 1), Josiphos $\mathbf{L^*_1}$ and its analogue $\mathbf{L^*_2}$ did not show any activity over 48 h at 50 °C. In contrast, Me-DuPHOS $\mathbf{L^*_3}$ gave full conversion to the desired product in 12 h with an excellent 98% ee. The reaction afforded exclusively the desired conjugate addition product without traces either of the 1,2-addition product or the Heck coupling product.

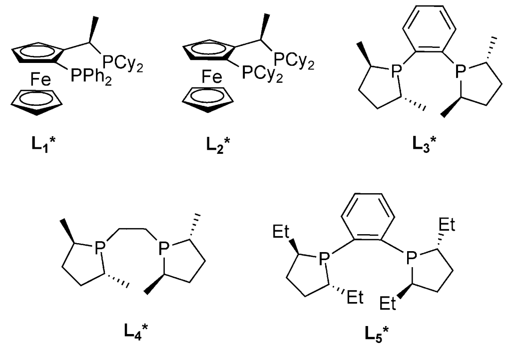
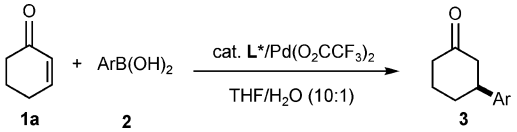


Figure 1. Chiral bidentate phosphines used in this study.

Nevertheless, despite the consistently high ee, the rate of the reaction varied considerably from run to run. This inconsistency could be avoided by using $Pd(O_2CCF_3)_2$ instead of $Pd(OAc)_2$/TfOH, suggesting it had its origin in the acetate/triflate exchange reaction. This led to reproducible and shorter reaction times without effecting the ee (Table 1, entry 1). The catalyst loading could be decreased, and on 1 mmol scale, 85% yield, 98% ee was obtained with 1 mol % of catalyst in 30 h (entry 2).

Table 1. Asymmetric 1,4-Addition of Boronic Acid **2** to 2-Cyclohexenone[a]



1a **2** **3**

entry	ligand	$ArBX_2$ **2**	time (h)	yield[b] (%) of **3**	ee[c] (%)
1	$\mathbf{L_3}$	**2a**	6	80 (**3a**)	98 (*R*)
2[d]	$\mathbf{L_3}$	**2a**	30	85 (**3a**)	98 (*R*)
3	$\mathbf{L_4}$	**2a**	24	nd	98 (*R*)
4	$\mathbf{L_5}$	**2a**	6	80 (**3a**)	98 (*R*)
5	$\mathbf{L_3}$	**2b**	18	80 (**3b**)	99 (*R*)
6	$\mathbf{L_3}$	**2c**	18	>99 (**3c**)	99 (*R*)
7	$\mathbf{L_3}$	**2d**	18	>99 (**3d**)	97 (+)
8	$\mathbf{L_3}$	**2e**	18	98 (**3e**)	98 (+)
9	$\mathbf{L_3}$	**2f**	18	90 (**3f**)	97
10	$\mathbf{L_3}$	**2g**	24	0 (**3g**)	
11	$\mathbf{L_3}$	**2h**	24	40 (**3h**)[e]	98

[a] Reactions were carried out in THF/H_2O (10/1) in the presence of 5 mol % of $Pd(O_2CCF_3)_2$ and 5.5 mol % of ligand at 50 °C unless stated otherwise. All reactions gave full conversion (TLC and NMR) unless stated otherwise. [b] Isolated yields after column chromatography. [c] Absolute configuration shown in parentheses. [d] Reaction performed with 1 mol % of catalyst. [e] 60% conversion.

With these reaction conditions established, the performance of the related ligands $\mathbf{L^*_4}$ and $\mathbf{L^*_5}$ was studied (Figure 1). The application of Me-BPE $\mathbf{L^*_4}$ resulted in a much slower reaction: after 24 h only 25% conversion was observed (98% ee). Et-DuPHOS $\mathbf{L^*_5}$, on the other hand, showed the same activity and excellent selectivity as Me-DuPHOS $\mathbf{L^*_3}$ (Table 1, entry 4).[21]

In the next stage, the scope of this new method for various boronic acids was examined, applying $\mathbf{L^*_3}$ as the ligand and **1a** as the substrate (Table 1). High yields and excellent ee's were obtained in the addition of *o*-, *m*-, and *p*-tolylboronic

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(12) (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317. For a comprehensive overview of palladium chemistry, see: (b) *Handbook of Organopalladium Chemistry for Organic synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

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(15) (a) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768. (b) For the coupling of arylboronic acids to alkynes, see: Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259 and references therein.

(16) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822.

(17) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2005**, *34*, 720.

(18) It should be noted that the palladium(II)-catalyzed addition of arylboronic acids to bicyclic alkenes has been reported; see: Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695. The asymmetric version using Tol-BINAP afforded ee's up to 71%.

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(20) The oxidative Heck-arylation using arylboronic acids and Pd/phenanthroline complexes has recently been reported, see: (a) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218. (b) Andappan, M. M. S.; Nilsson, P.; Von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212.

(21) Although all reactions were performed in THF/water 10:1 as solvent, reactions can be performed as well in pure THF. Reaction rates are somewhat decreased but ee's are unaffected.

acid (Figure 2, Table 1). Also, the electron-rich *o*- and *m*-anisylboronic acids afforded the expected products in high yield and excellent ee. In contrast, *m*-nitrophenylboronic acid refused to react, whereas *m*-chlorophenylboronic acid gave incomplete conversion (Table 1, entry 11). This parallels the observations by Larhed et al. in the corresponding oxidative Heck arylation where they observed a lack of reactivity in the use of electron poor arylboronic acids that can be due to their slow insertion into Pd(II) complexes.[22]

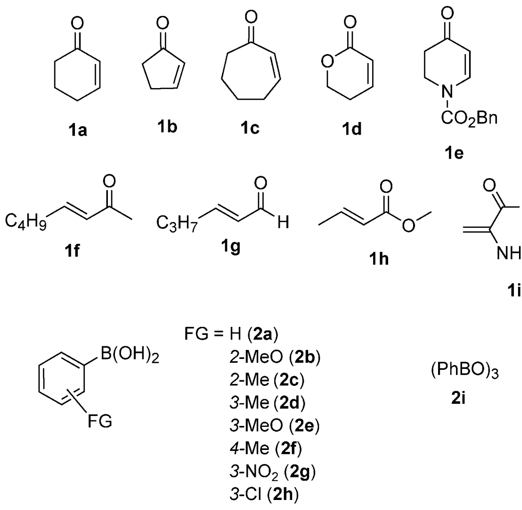


Figure 2. Substrates and boronic acids used in this study.

Using 2-cyclopentenone as substrate (Table 2), a somewhat lower (but still useful) 82% ee was obtained. As full conversion was reached at 50 °C in less than 4 h, the reaction was carried out at room temperature in order to increase the yield of the volatile product **3i**. A comparable ee was obtained in the addition to 2-cycloheptenone (86% ee) leading to **3j**. The use of **L*$_5$** led to virtually the same results.

Table 2. Asymmetric 1,4-Addition of Boronic Acid **2** to α,*β*-Unsaturated Compounds[a]

entry	substrate **1**	ArBX$_2$ **2**	time (h)	yield[b] (%) of **3**	ee[c] (%)
1[d]	**1b**	**2a**	6	75 (**3i**)	82 (*R*)
2[e]	**1c**	**2a**	18	55 (**3j**)	86 (*R*)
3	**1d**	**2i**[f]	5	75 (**3k**)	94 (*S*)
4[g]	**1e**	**2a**	22	60 (**3l**)	>99 (*R*)
5	**1f**	**2i**[f]	18	45 (**3m**)[h]	82
6	**1g**	**2i**[f]	24	30 (**3n**)[i]	49
7	**1h**	**2a**	22	nd (**3o**)[j]	8[k]
8	**1i**	**2a**	22	0 (**3p**)	

[a] Reactions were carried out in THF/H$_2$O (10/1) in the presence of 5 mol % of Pd(O$_2$CCF$_3$)$_2$ and 5.5 mol % of (*R*,*R*)-Me-DuPHOS at 50 °C unless stated otherwise. All reactions gave full conversion (TLC and NMR) unless stated otherwise. [b] Isolated yields after column chromatography. [c] Absolute configuration is shown in parentheses. [d] Reaction performed at room temperature. [e] **1c** was purchased with 80% purity. [f] A solution of 20 vol % of water in THF was added at 0.1 mL/h by means of a syringe pump over the reaction time (see the Supporting Information). [g] Reaction performed at 70 °C. [h] 60% conversion. [i] 42% conversion. [j] The crude reaction mixture consisted of 27% of **3o** and 73% of Heck coupling product **4**. [k] ee of the 1,4-product.

To study whether the substrate scope could be extended beyond enones, lactone **1d** was subjected to the same reaction conditions. Full conversion and a high 94% ee was obtained. Again, no 1,2-addition or Heck-type products could be detected.

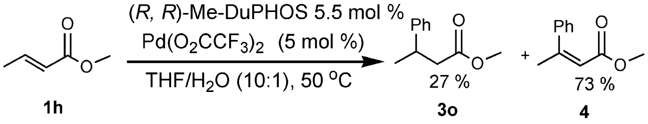
Dihydropyridone **1e** is an important substrate in the synthesis of alkaloids. It has proven to be a challenging substrate in the rhodium-catalyzed boronic acid addition due to its low reactivity.[10a,23] By applying the Pd(O$_2$CCF$_3$)$_2$/Me-DuPHOS catalyst at 70 °C, however, the reaction went to full completion and afforded the product with essentially complete enantioselectivity (>99% ee).

Linear substrates turned out to be considerably less reactive. Enone **1f** showed 60% conversion (45% yield) in 18 h using a combination of phenylboroxine **2i** and slow addition of water. No Heck-type products were observed, and a reasonable 82% ee was obtained, comparable with the results obtained by Miyaura et al. in the palladium/Chira-PHOS/Cu(BF$_4$)$_2$ catalyzed asymmetric addition of arylbismuth compounds.[16]

The asymmetric rhodium-catalyzed arylboronic acid addition to unsaturated aldehydes has been troublesome, partly because of competing 1,2-addition. Very recently the group of Carreira reported excellent results in the conjugate addition to aryl-substituted enals.[24] The sole paper on the use of aliphatic enals as substrates reported moderate yields but high enantioselectivities.[25] In the corresponding palladium-catalyzed conjugate addition of boronic acids using an achiral ligand (dppe),[15a] good yields were obtained. Interestingly, using Pd(O$_2$CCF$_3$)$_2$/Me-DuPHOS as the catalyst, 2-*E*-hexenal underwent selective conjugate addition, without formation of the 1,2-addition product. The conversion was only 42%, however, and a moderate 49% ee was obtained, which comes close to the results reported with triphenylbismuth.[26]

In sharp contrast with the reaction of **1f** and **1g**, the addition to methyl-*E*-crotonate took a different course (Scheme 1). In this reaction, the Heck coupling product dominates, together with 27% of racemic conjugate addition product.[27] This parallels the results in the Pd(dppe)(PhCN)$_2$-

Scheme 1



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[22] See ref 20a: in that study, boronic acids with electronwithdrawing groups at the meta position gave only moderate yield and para substituents refused to react.

[23] Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.

[24] (a) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. For examples using achiral catalysts, see: (b) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450.

[25] Itooka, R.; Igushi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

$(SbF_6)_2$-catalyzed addition of phenylboronic acid to ethyl acrylate.[28] The attempt to use methyl 2-acetamido acrylate **1i** as substrate[29] only resulted in recovery of starting material.

In conclusion, we have shown that the palladium-catalyzed asymmetric conjugate addition of boronic acids is feasible. Catalysts based on palladium trifluoroacetate and Me-DuPHOS or Et-DuPHOS afford excellent results for several substrates, comparable to the best rhodium-based systems. For linear substrates results are unsatisfactory as yet. In particular, the complete absence of Heck-type products, except in case of **1h**, is remarkable and encouraging. The method is readily applicable: the catalyst is formed in situ at room temperature and both the ligand **L*₃** and $Pd(O_2CCF_3)_2$ are commercially available. A significant advantage over existing palladium-catalyzed conjugate additions is the application of arylboronic acids instead of the less readily available aryltrifluoroborates and triarylbismuths. Reaction conditions are mild, and the scope seems to be broad, although further study is required to improve the performance with noncyclic substrates.

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Supporting Information Available: Experimental procedures, NMR spectra, and chromatographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The palladium/ChiraPHOS/$Cu(BF_4)_2$-catalyzed addition of triphenylbismuth to 2-hexenal afforded the conjugate addition product in 55% yield, 68% ee; see ref 16.

(27) The composition of the reaction mixture was determined by GC−MS and ^1H NMR analysis. The enantioselectivity of **3o** in the mixture was determined by chiral GC. Compound **4** was synthesized for comparison according to a literature procedure (See Supporting Information).

(28) (a) Reference 15a. The rhodium-catalyzed enantioselective addition of arylboronic acids to substituted cinnamic esters has recently been reported; see: (b) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett*. **2005**, *7*, 3821. The rhodium-catalyzed enantioselective addition to aliphatic esters has been reported in: (c) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem*. **2000**, *65*, 5951. (e) Navarre, L.; Pucheault, M.; Darses, S.; Genet, J.-P. *Tetrahedron Lett*. **2005**, *46*, 4247.

(29) Substrate **1i** has been used successfully in the corresponding rhodium-catalyzed reaction; see: Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719 and references therein.