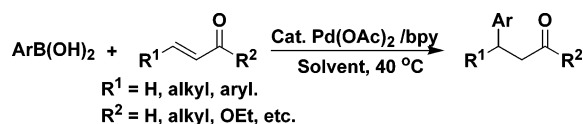## Pd(II)-Bipyridine Catalyzed Conjugate Addition of Arylboronic Acid to α,β-Unsaturated Carbonyl Compounds

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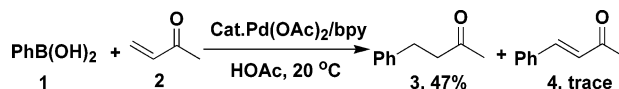
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A Pd(II)-catalyzed conjugate addition of arylboronic acid to α,β-unsaturated ketones, aldehydes, esters, etc. in the presence of 2,2′-bipyridine was developed. A mechanism involving transmetalation, insertion of the carbon−carbon double bond into the C−Pd bond, and protonolysis of the resulting C−Pd bond is proposed. The reaction conditions are mild and the yield is high. The presence of 2,2′-bipyridine is crucial for the reaction to inhibit β-hydride elimination.

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful tool for the construction of C−C bonds.[1] While the Rh(I)-catalyzed conjugate addition of organo-boron, silicon, and tin reagents to α,β-unsaturated carbonyl compounds has been well developed,[1d] the reports on Pd-catalyzed conjugate addition are rare. Different kinds of oganometallic reagents[2] have been surveyed in Pd-catalyzed conjugate addition. Most of them were troubled by the formation of the Heck-type coupling products. The reason might be that a palladium catalyst yields C-bound enolates in the insertion of enones into a C−Pd bond in contrast to the formation of O-bound enolates in the insertion of enones

SCHEME 1

into a C−Rh bond.[2h,3,4] β-Hydride elimination will easily occur in the former case, resulting in the formation of the Heck-type coupling products. Recently, Miyaura reported that the cationic Pd(II) complexes can catalyze the conjugate addition of arylboronic acids with enones, affording the addition products in excellent yields,[2h,i] and the detailed mechanism was also reported.[5]

From the reported Pd(II)-catalyzed conjugate addition of arylboronic acid to enones, it was known that the easily occurring β-hydride elimination represents the main drawback of the reaction.[2g,5] Thus, a method of suppressing β-hydride elimination is important in developing Pd(II)-catalyzed conjugate additions. In our ongoing studies in the Pd(II)-catalyzed nucleophile-alkene-α,β-unsaturated carbonyl coupling through nucleopalladation and conjugate addition, we found that the presence of halide ions (Cl⁻, Br⁻, and I⁻)[6] and bidentate nitrogen ligands (e.g., 2,2′-bipyridine and phenanthroline)[7] are crucial for inhibiting the β-hydride elimination. In all of these reactions, the carbon−palladium bonds are formed from the nucleopalladation (nucleophiles = halides, nitrogen, and oxygen) of the alkenes or alkynes, and it occurred to us whether the conjugate addition reaction could take place with the carbon−palladium bond formed from the transmetalation of arylboronic acid and Pd(II) species. Herein, we wish to report the Pd(II)-catalyzed conjugate addition of arylboronic acid to α,β-unsaturated ketones, aldehydes, esters, etc. in the presence of 2,2′-bipyridine.

First, we examined the reaction of phenylboronic acid **1** (1.0 mmol) and methylvinyl ketone **2** (2.0 mmol) in the presence of Pd(OAc)$_2$ (5 mol %) and 2,2′-bipyridine (bpy, 10 mol %) in acetic acid (1 mL) at 20 °C (Scheme 1). The reaction proceeded smoothly, yielding conjugate addition product **3** in 47% yield (based on PhB(OH)$_2$), together with a trace amount of Heck-type coupling product, 4-phenylbut-3-en-2-one (**4**). In the absence of bpy, 5% yield of **4** was isolated. When the reaction was performed in the absence of Pd(OAc)$_2$, no reaction occurred. The introduction of LiBr blocked the reaction.

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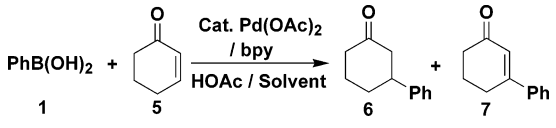
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(7) For the reactions of inhibiting β-hydride elimination in the presence of bidentate nitrogen ligands, see: (a) Zhao, L.; Lu, X. *Org. Lett.* **2002**, *4*, 3903. (b) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (c) Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059.

TABLE 1. Pd(II)-Bipyridine Catalyzed Conjugate Addition of Phenylboronic Acid to 2-Cyclohexenone[a]

PhB(OH)$_2$ + [5] $\xrightarrow[\text{HOAc / Solvent}]{\text{Cat. Pd(OAc)}_2 \text{ / bpy}}$ [6] + [7]

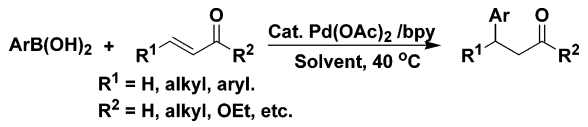| entry	1/5 molar ratio	bpy (mol %)	additive	6 yield (%)[b]
1[c]	1.5	10	none	0
2	1.5	10	none	58
3	3.0	10	none	73
4	3.0	20	none	78
5	3.0	20	KF·2H$_2$O[d]	96
6	3.0	20	H$_2$O[e]	94
7	3.0	0	H$_2$O[e]	6[f]

[a] Reaction conditions: 2-cyclohexenone (1.0 mmol), Pd(OAc)$_2$ (0.05 mmol) and bpy (0.20 mmol) in solvent (HOAc/THF = 1.0 mL/0.5 mL) at 40 °C. [b] Isolated yield. [c] Reaction temperature was 20 °C. [d] 3.0 mmol of KF·2H$_2$O. [e] 17.0 mmol of H$_2$O. [f] 10 mol % of Pd(OAc)$_2$ was loaded; 12% of biphenyl and 5% of 7 were formed with the precipitation of Pd black.

SCHEME 2

[8] [9] [10]
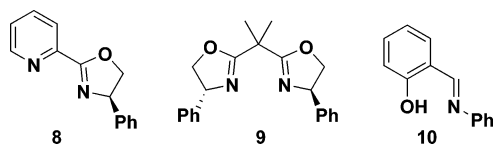
Then, 2-cyclohexenone (**5**) was used as the substrate to optimize the reaction conditions. The reaction can proceed at 40 °C, but no reaction occurred at 20 °C (Table 1, entries 1 and 2). Higher temperature led to the fast protonolysis of PhB(OH)$_2$. Through the survey of PhB-(OH)$_2$/enone/Pd(OAc)$_2$/bpy ratio and additives, we found that using 3 equiv of PhB(OH)$_2$ is the key for the complete conversion of the enone (Table 1, entry 3). In the absence of bpy, the addition product **6** (6%), together with biphenyl (12%) and 5% of the β-hydride elimination product, 3-phenylcyclohex-2-enone (**7**), was formed (Table 1, entry 7). The addition of 20 mol % of bpy can prevent the formation of biphenyl, the Heck-type coupling product, and the precipitation of palladium black. Conjugate addition product **6** was obtained without the detection of the β-hydride elimination product **7**. The addition of 3 equiv of KF·2H$_2$O improved the yield to 96% (Table 1, entry 5), and the parallel experiments showed that the addition of 17 equiv of water did the same job (Table 1, entry 6). To simplify the condition, PhB(OH)$_2$ (3 mmol), enone (1 mmol), Pd(OAc)$_2$ (5 mol %), and bpy (20 mol %) in HOAc (1 mL), THF (0.5 mL), and H$_2$O (0.3 mL) at 40 °C were chosen as the optimized conditions.

Other ligands such as pyridine, 1,10-phenanthroline, (*R*)-pymox-Ph (**8**), phenyl-substituted bisoxazoline (2,2′-isopropylidene-bis(4*R*)-phenyl-2-oxazolilne, **9**), and *N*-salicylideneaniline (**10**) (Scheme 2) were tried, but all afforded the product in poor yields.

Using the optimized conditions, results of the conjugate addition of phenylboronic acid to different α,β-unsaturated carbonyl compounds are summarized in Table 2. Enals are also good Michael acceptors. For cinnamaldehyde, 93% yield of the conjugate addition product was isolated as the only product (Table 2, entry 4). To our delight, 96% yield of 3,3-diphenylpropanoate (**14**) was

TABLE 2. Pd(II)-Bipyridine Catalyzed Conjugate Addition of Arylboronic Acid to α,β-Unsaturated Carbonyl Compounds[a]

ArB(OH)$_2$ + R^1—CH=CH—COR^2 $\xrightarrow[\text{Solvent, 40 °C}]{\text{Cat. Pd(OAc)}_2 \text{ /bpy}}$ product

R^1 = H, alkyl, aryl.
R^2 = H, alkyl, OEt, etc.

entry	Ar	alkene	product	yield[b] (%)
1	C$_6$H$_5$	CH$_2$=CHCOCH$_3$	**3**	75
2	C$_6$H$_5$	2-cyclohexenone	**6**	94
3	C$_6$H$_5$	2-cyclopentenone	**11**	90
4	C$_6$H$_5$	(*E*)-PhCH=CHCHO	**12**	93
5	C$_6$H$_5$	(*E*)-CH$_3$CH=CHCHO	**13**	84
6	C$_6$H$_5$	(*E*)-PhCH=CHCO$_2$Et	**14**	96
7	C$_6$H$_5$	(*E*)-CH$_3$CH=CHCO$_2$Et	**15**	64
8	C$_6$H$_5$	CH$_2$=CHCONH$_2$	**16**	42
9	C$_6$H$_5$	(*E*)-PhCH=CHNO$_2$	**17**	53[c]
10	*p*-MeOC$_6$H$_4$	2-cyclohexenone	**18**	11
11	*p*-MeOC$_6$H$_4$	(*E*)-PhCH=CHCO$_2$Et	**19**	21
12	*m*-MeOC$_6$H$_4$	2-cyclohexenone	**20**	99
13	*m*-MeOC$_6$H$_4$	(*E*)-PhCH=CHCO$_2$Et	**21**	99
14	*p*-MeC$_6$H$_4$	2-cyclohexenone	**22**	81
15	*p*-MeC$_6$H$_4$	(*E*)-PhCH=CHCO$_2$Et	**23**	94
16	*p*-ClC$_6$H$_4$	2-cyclohexenone	**24**	90
17	*p*-ClC$_6$H$_4$	(*E*)-PhCH=CHCO$_2$Et	**25**	94
18	*p*-FC$_6$H$_4$	2-cyclohexenone	**26**	89
19	*p*-FC$_6$H$_4$	(*E*)-PhCH=CHCO$_2$Et	**27**	98
20	2-naphthyl	2-cyclohexenone	**28**	95
21	2-naphthyl	(*E*)-PhCH=CHCO$_2$Et	**29**	92

[a] Reaction conditions: arylboronic acid (3.0 mmol), alkene (1.0 mmol), Pd(OAc)$_2$ (0.05 mmol), and bpy (0.20 mmol) in solvent (HOAc/THF/H$_2$O = 1.0 mL/0.5 mL/0.3 mL) at 40 °C. [b] Isolated yield. [c] Solvent is THF/H$_2$O = 1.0 mL/0.3 mL.

isolated as the only product under optimized conditions from ethyl cinnamate (Table 2, entry 6). In the previous reports on Pd-catalyzed conjugate addition reactions, Heck-type reactions occurred almost exclusively for α,β-unsaturated esters,[2d,5] but in our optimized reaction conditions, high-yielding conjugate addition occurred without the formation of Heck-type products. In the absence of Pd(OAc)$_2$ or bpy, no conjugate addition product was detected for α,β-unsaturated esters. Acrylamide also reacted with PhB(OH)$_2$ but with lower yield (Table 2, entry 8). When 2-nitrostyrene was performed under the optimized conditions, a little addition product was observed after a week, but under neutral condition, 53% yield of addition product was isolated (Table 2, entry 9).

The influence on the reaction of the substituents on arylboronic acids was also studied. For *p*-tolyl-, *p*-chlorophenyl-, *p*-fluorophenyl-, and 2-naphthylboronic acids, excellent yields were observed with no influence of the electronic properties of the substituent group (Table 2, entries 14−21). When 4-methoxyphenylboronic acid was used, the yield decreased sharply (Table 2, entries 10 and 11). Gas chromatography studies revealed that most of the 4-methoxyphenylborbonic acid was hydrolyzed to anisole under the standard reaction condition. As a comparison, 3-methoxyphenylboronic acid worked quite well, affording the normal product in nearly quantitative yield (Table 2, entries 12 and 13). This result implies that strong electron-donating substituents in the *para*-position diminish the efficiency of aryl transfer. The transmetalation of *p*-methoxyphenylboronic acid occurred in decreased yield, whereas *m*-methoxyphenylboronic acid still reacted in high yield.

SCHEME 3
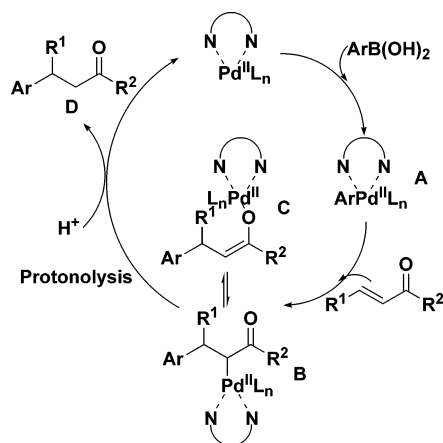
The possible mechanism for this divalent palladium-catalyzed reaction was proposed as shown in Scheme 3. First, transmetalation generates the arylpalladium species **A** from arylboronic acid and palladium acetate, which was followed by insertion of the alkene into the carbon−palladium bond to give palladium enolate **B** or **C**. The presence of bpy inhibits the β-hydride elimination of the C−Pd bond in **B**. Protonolysis of **B** or **C** gives the corresponding conjugate addition products **D** in a protonic medium with the regeneration of the divalent palladium species. The protonic medium will also lead to the protonolysis of arylpalladium species **A**, which may be stabilized by the coordination of bpy.[7]

In conclusion, we developed a Pd(II)-bipyridine catalyzed conjugate addition of arylboronic acids to α,β-unsaturated ketones, aldehydes, and esters to yield the addition products with excellent yields without the formation of β-hydride elimination products. The use of 2,2′-bipyridine as the ligand here is crucial for the high selectivity of the reaction. The development of asymmetric version of the reaction is on the way in our laboratory.

Experimental Section

Typical Procedure for Conjugate Addition of Phenylboronic Acid to 2-Cyclohexenone. To a Schlenk tube were added phenylboronic acid (366 mg, 3.0 mmol), 2-cyclohexenone (96 mg, 1.0 mmol), Pd(OAc)$_2$ (11.2 mg, 0.050 mmol), bpy (31.2 mg, 0.20 mmol), HOAc (1 mL), THF (0.5 mL), and H$_2$O (0.3 mL) under argon. The mixture was stirred and heated at 40 °C for 3 days until the substrate disappeared as monitored by TLC. The reaction mixture was neutralized with saturated NaHCO$_3$ and then extracted with Et$_2$O. The combined ether solution was washed with saturated NaCl, dried (MgSO$_4$), and concentrated. The residue was purified by flash chromatography (EtOAc/petroleum ether 1:20) to give the product **6** with 94% yield as a colorless oil.[2m] ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.39−7.19 (m, 5H), 3.07−2.94 (m, 1H), 2.30−2.64 (m, 4H), 2.02−2.22 (m, 2H), 1.93−1.71 (m, 2H). IR (KBr): ν 2939, 1710, 1452, 1224, 756, 700 cm^{-1}. MS (70 eV, EI) m/z (%): 175 (M$^+$ + 1), 174 (M$^+$), 131, 117 (100), 104, 91, 42.

Supporting Information Available: Typical experimental procedure, characterization data of all products, and copies of the ^{1}H NMR spectra for compounds **3**, **4**, **6**, **7**, and **11**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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