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Cationic Pd(II)/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to *β*,*β*-Disubstituted Enones: Construction of Quaternary Carbon Centers

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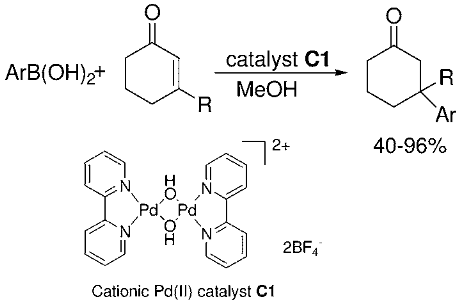
ABSTRACT



Cationic Pd(II)-catalyzed addition of arylboronic acids to *β*,*β*-disubstituted enones in high yields was developed. This method provided an efficient method for the construction of quaternary carbon centers, and only 0.5 mol % of Pd(II) catalyst was needed.

Transition metal catalysis provides mild and efficient methods for C−C bond formation,[1] but it is still not easy for quaternary carbon construction.[2] Copper-catalyzed conjugate addition of Grignard reagents to trisubstituted α,*β*-unsaturated carbonyl compounds is well-known,[3,4] but the reactions involve air and moisture sensitive organometallic reagents and some functional groups cannot be tolerated. In the past decade, organoboron reagents attracted many organic chemists' interest for their tolerance of a broad range of functional groups, low toxicity, and stability to water and air.[5] In the well-documented Rh(I)-catalyzed conjugate addition reaction of boronic acids,[6] Hayashi reported the use of sodium tetraarylborates as effective nucleophiles in rhodium/diene-catalyzed 1,4-addition to *β*,*β*-disubstituted α,*β*-unsaturated

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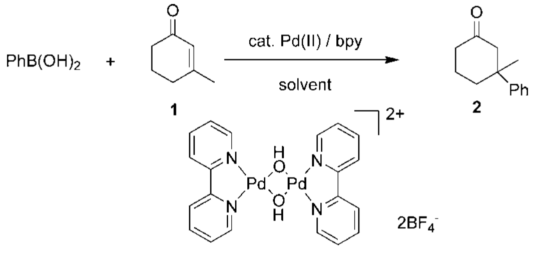
ketones.[7] In the palladium-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds, to the best of our knowledge, only a few examples were reported.[8] Recently, Miyaura reported the addition of arylboronic acids to enones catalyzed by cationic palladium(II)/phosphine complexes with successful results.[9]

We developed the Pd(OAc)$_2$/bipyridine-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds[10a] with high yields and its application in aqueous media.[10b] Also it was found that cationic Pd(II) complexes with bipyridine (bpy) as ligands catalyzed the addition of arylboronic acids to nitriles[10c,d] and aldehydes[10e] efficiently. This may be due to the high Lewis acidity and the vacant coordination site, making the cationic Pd(II) catalysts more active than neutral Pd(II) species in transmetalation, coordination with carbon−carbon multiple bonds or carbon−heteroatom multiple bonds, and the insertion steps.[9b] Herein, we report the cationic Pd(II)/bipyridine-catalyzed highly efficient conjugate addition of arylboronic acids to β,β-disubstituted enones for the construction of quarternary carbon centers.

In our initial study, we tried the addition of phenylboronic acid to 3-methylcyclohex-2-enone under neutral Pd(OAc)$_2$/bpy catalyst conditions. The reaction can hardly proceed in acetic acid at 50 °C, and only a trace of the desired product was detected (Table 1, entry 1). Then it was found that in dioxane/H$_2$O the reaction afforded a moderate yield of conjugate addition product (Table 1, entry 2). Alcoholic solvents demonstrated an important effect in this reaction and a 94% yield of the product was isolated in MeOH at 80 °C in a sealed tube (Table 1, entry 3). But in EtOH, the yield dropped sharply (Table 1, entry 4), and the reactions also gave poor yields in *n*-PrOH or *n*-BuOH (Table 1, entries 5 and 6). At the same time, palladium black was observed in these three solvents. However, *t*-BuOH showed similar result as MeOH (Table 1, entry 7).

Table 1. Pd(II)/bpy-Catalyzed Conjugate Addition of Phenylboronic Acid to 3-Methylcyclohex-2-enone[a]



Cationic Pd(II) catalyst **C1**

entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	Pd(OAc)$_2$/bpy	HOAc	50	12	trace
2	Pd(OAc)$_2$/bpy	dioxane/ H$_2$O	80	12	70
3	Pd(OAc)$_2$/bpy	MeOH	80	12	94
4	Pd(OAc)$_2$/bpy	EtOH	80	12	20
5	Pd(OAc)$_2$/bpy	*n*-PrOH	80	12	21
6	Pd(OAc)$_2$/bpy	*n*-BuOH	80	12	17
7	Pd(OAc)$_2$/bpy	*t*-BuOH	80	12	91
8	[Pd(dppe)(CH$_3$CN)$_2$]$^{2+}$ 2BF$_4^-$	MeOH	80	12	0[c]
9	**C1**	MeOH	25	4	96[d]
10	**C1**	MeOH	25	12	96[e]

[a] Reaction conditions: PhB(OH)$_2$ (0.50 mmol), 3-methylcyclohex-2-enone (0.25 mmol), Pd(OAc)$_2$ (0.0125 mmol, 5 mol %), and bpy (0.015 mmol, 6 mol %) in a sealed tube at 80 °C. [b] Isolated yield. [c] [Pd(dppe)(CH$_3$CN)$_2$]$^{2+}$•2BF$_4^-$ (0.0125 mmol, 5 mol %). [d] Catalyst **C1** (0.0062 mmol, 2.5 mol %). [e] PhB(OH)$_2$ (0.75 mmol), 3-methylcyclohex-2-enone (0.50 mmol), and catalyst **C1** (0.0025 mmol, 0.5 mol %).

Different catalysts showed different activities. When cationic palladium [Pd(dppe)(CH$_3$CN)$_2$]$^{2+}$•2BF$_4^-$ was used, no reaction occurred (Table 1, entry 8). But when the catalyst was changed to the cationic Pd(II) with bpy as the ligand (**C1**), the reaction proceeded smoothly at room temperature with excellent yield (Table 1, entry 9). The high yield was maintained even when the catalyst loading was decreased to 0.5 mol % (Table 1, entry 10).

With these results in hand, we began to survey the scope of the reaction with different β,β-disubstituted α,β-unsaturated carbonyl compounds. The results of the conjugate addition are summarized in Table 2.

Cationic Pd(II) catalyst **C1** showed high activity for the addition reaction of arylboronic acids to cyclic β,β-disubstituted enones. For 3-methylcyclopent-2-enone (**3**) and 3-butylcyclohex-2-enone (**5**), excellent yields of conjugate addition were obtained (Table 2, entries 2 and 3). For the substrates with bulky substituents (Table 2, entries 4 and 5), the reactions gave lower conversion with 0.5 mol % of cationic palladium catalyst. Increasing the catalyst loading to 2.5 mol % made higher yields, but higher temperature did not help further conversion. It is worth noting that β-phenyl-substituted enones (3-phenylcyclohex-2-enone (**11**)) showed no reactivity with either cationic or neutral palladium catalysts (Table 2, entry 6), which might be due to the steric hindrance or the conjugation with enones of the phenyl group. Interestingly, when cyclohex-1,3-dione (**12**) and 3-ethoxycyclohex-2-enone (**13**) were used as the substrates to react with phenylboronic acid, the reaction did not afford the normal conjugate addition products but gave 3-phenylcyclohex-2-enone (**11**) in moderate yields (Table 2, entries 7 and 8). When mesityl oxide (**14**) was performed in the optimized cationic palladium conditions, a trace of the product was detected, but 70% yield was afforded in neutral palladium conditions (Table 2, entry 9).

The influence of different arylboronic acids in this reaction was evaluated, and moderate to excellent yields were obtained (Table 2, entries 11−14). Even the bulky 2-naph-

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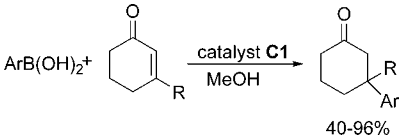
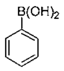
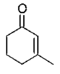
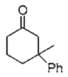
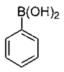
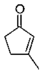
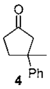
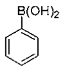
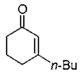
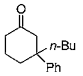
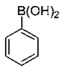
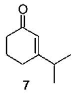
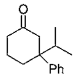
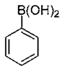
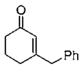
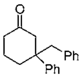
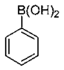
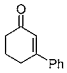
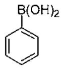
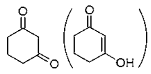
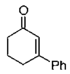
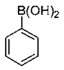
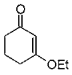
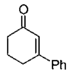
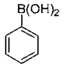
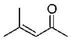
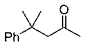
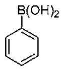
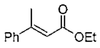
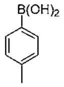
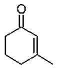
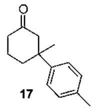
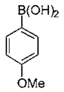
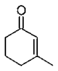
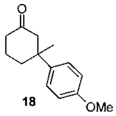
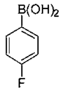
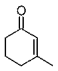
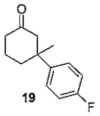
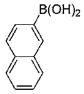
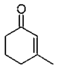
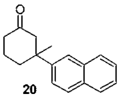
Table 2. Cationic Pd(II)/bpy-Catalyzed Conjugate Addition of Arylboronic Acids to β,β-Disubstituted α,β-Unsaturated Carbonyl Compounds[a]



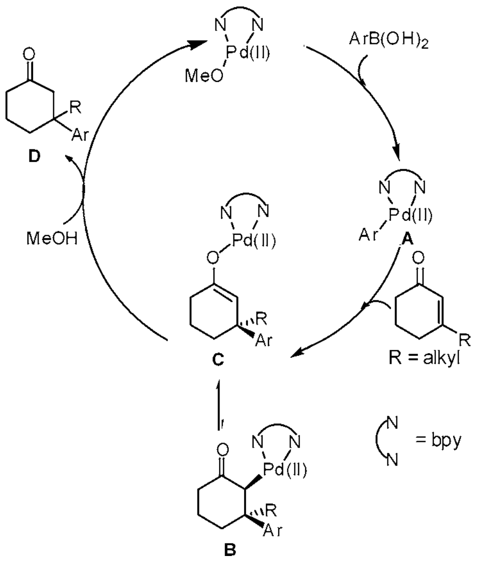
entry	arylboronic acid	enone	product	yield (%)[b]
1		 1	 2	96
2		 3	 4	94
3		 5	 6	92
4		 7	 8	88[c]
5		 9	 10	80[c]
6		 11	---	0[c]
7		 12	 11	45
8		 13	 11	38
9		 14	 15	70[d]
10		 16	---	0[c]
11		 1	 17	93
12		 1	 18	82
13		 1	 19	81
14		 1	 20	61

[a] Reaction conditions: $ArB(OH)_2$ (0.75 mmol), enone (0.50 mmol), catalyst **C1** (0.0025 mmol, 0.5 mol %), and MeOH (0.4 mL) at 25 °C. [b] Isolated yield. [c] Catalyst **C1** (2.5 mol %). [d] $Pd(OAc)_2$ (0.025 mmol, 5 mol %) and bpy (0.030 mmol, 6 mol %) in a sealed tube at 80 °C.

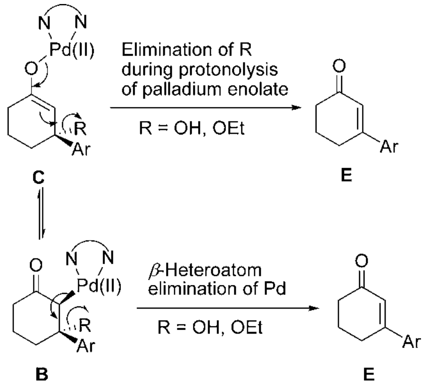
thylboronic acid gave 61% yield of conjugate addition product (Table 2, entry 14).

A plausible mechanism for the cationic palladium-catalyzed addition of arylboronic acids to β,β-disubstituted enones is shown in Scheme 1.[8a,9a] It involves transmetalation between arylboronic acid and cationic palladium yielding the arylpalladium species **A**. Then, the insertion of the double bond of enones into the carbon−palladium bond gives palladium enolate **B** or **C** with the construction of the quaternary carbon center. Protonolysis of the palladium enolate[11] yields the corresponding conjugate addition product **D** and regenerates the divalent palladium species to complete the catalytic cycle. In the case of cyclohex-1,3-dione (**12**) or 3-ethoxycyclohex-2-enone (**13**) (Table 2, entries 7 and 8), it might be possible to eliminate the potential leaving

Scheme 1. Plausible Mechanism for the Cationic Palladium-Catalyzed Addition of Arylboronic Acids to β,β-Disubstituted Enones



Scheme 2. Possible Pathways for the Elimination of Hydroxy or Methoxy Groups in **C** or **B**



groups (OH in **12** and OEt in **13**) simultaneously during the protonolysis of the palladium enolate especially in the presence of the boron compounds.[12] Of course, another pathway for the trans β-heteroatom elimination[13] of **B** to give 3-arylcyclohex-2-enone (**E**) as the product and divalent palladium species for regeneration of the catalyst cannot be excluded (Scheme 2).

It is worth noting that this reaction involved the protonolysis of the palladium enolate in alcoholic solvents (see Scheme 1), and an alkoxypalladium species was formed during the reaction. For the alkoxypalladium species with a β-hydrogen atom, β-hydride elimination will occur to generate Pd(0) species making the catalytic cycle impossible to occur and leading to poor yields. That the reaction gave better yields in MeOH may be due to the slower β-hydride elimination of methoxypalladium species compared with other alkoxypalladium species.[14] For the solvent with no β-hydrogen atom, like *t*-BuOH, the reaction preceeds with high yield.

In conclusion, we found that cationic Pd(II)/bpy species did catalyze the addition of arylboronic acids to β,β-disubstituted enones in high yields with only 0.5 mol % catalyst loading for the construction of a quaternary carbon center.

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Supporting Information Available: Typical experimental procedure and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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