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Anionic Four Electron Donor-Based Palladacycles as Catalysts for Addition Reactions of Arylboronic Acids with α,β -Unsaturated Ketones, Aldehydes and α -Ketoesters

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Abstract

Anionic four electron donor-based palladacycle-catalyzed 1,4-additions of arylboronic acids with α,β -unsaturated ketones and 1,2-additions of arylboronic acids with aldehydes and α -ketoesters are described. Our study demonstrated that palladacycles were highly efficient, practical catalysts for these addition reactions. The work described here not only opened a new paradigm for the application of palladacycles, but may also pave the road for other metalacycles as practically useful catalysts for such addition reactions including asymmetric ones.

Anionic four electron donor-based palladacycles, one of the two general types of palladacycles (Figure 1), are readily accessible and air/moisture stable.^{1,2} They have been demonstrated as efficient catalyst systems for a number of bond forming reactions including cross-coupling reactions.^{1,3} Mechanistic studies suggested that in cross-coupling reactions such as the Suzuki couplings, palladacycles served as the sources of catalytically active species by undergoing transmetalation with organometallic reagents to form transmetalated intermediates such as **A** followed by reductive elimination (Scheme 1). As it has been established that the Pd(II) center in palladacycles could act as a Lewis acid,¹ we reasoned that when carbonyl moieties were present in the reaction system, in addition to undergoing reductive elimination to form Pd(0) species (Path A), **A** might coordinate with a carbonyl moiety to form complexes **B** (Path B) (Scheme 1). On the basis that elevated temperature, typically higher than 100 °C, was required for palladacycles to generate catalytically active species for cross-coupling reactions,¹ we surmised that the reductive elimination of **A** should be slow, especially at lower temperature. We further envisioned that at lower reaction temperature, such as room temperature, **B** might undergo aryl transfer to form addition products much faster than reductive elimination to form cross-coupling products (Scheme 1), and Type **I** palladacycles could thus catalyze addition reactions of arylboronic acids to carbonyl group-containing compounds,^{4, 5, 6} a field that is currently dominated by Rh(I) catalysis chemistry.^{7, 8, 9, 10, 11, 12} The exploration of such palladacycle-catalyzed addition reactions would create a new paradigm for palladacycle catalysis chemistry and may provide powerful catalyst systems for organic synthesis. In this communication, we established that Type **I** palladacycles could indeed act as efficient catalysts

for such addition reactions, specifically, the 1,4-addition of arylboronic acids with α,β -unsaturated ketones and the 1,2-additions of arylboronic acids with aldehydes and α -ketoesters.

We began our study by testing reported palladacycles **1**–**3** for the room temperature 1,4-addition of phenylboronic acid with chalcone, and our results are listed in Table 1. We found although palladacycle **1**¹³ showed no catalytic activity (Table 1, entry 1), palladacycles **2**¹⁴ and **3**¹⁵ gave encouraging results: 35% conversion was observed for **2** and 55% conversion for **3** (Table 1, entries 2, 3). It has been established that $\text{ArPd(II)R(L}_n\text{)}$ complexes with more electron-rich organic groups and/or with less sterically hindered ligands were more reluctant to undergo reductive elimination.^{16,17} We reasoned that increasing the electron-richness of Pd-bonded aromatic part of palladacycles and reducing the size of their ligand part could minimize the reductive elimination and thus might provide more efficient catalysts. We thus prepared ferrocenyl-containing palladacycle **4**.¹⁸ We were pleased to find that **4** was indeed an excellent catalyst for the addition reaction (Table 1, entry 4). We have further employed **4** for the optimization of the reaction condition and our results are also listed in Table 1. We found toluene was the best solvent among the solvents we screened, and K_3PO_4 and KF were the best bases.

With palladacycle **4** as the catalyst, toluene as the solvent and K_3PO_4 as the base, a number of arylboronic acids and α,β -unsaturated ketones were examined, and our results are listed in Table 2. We found **4** was a robust, general catalyst for the room temperature 1,4-addition of arylboronic acids with α,β -unsaturated ketones including cyclic and acyclic ones (Table 2). The reaction, like other Pd(II)-catalyzed 1,4-addition of arylboronic acids with α,β -unsaturated ketones, most likely involved Pd(II)-enolates as the intermediates, which could undergo reductive elimination to form Heck type cross-coupling products or protonation to generate the 1,4-addition products.⁴ The fact that the Heck coupling products, which are sometimes seen in other Pd(II) catalyst systems,⁴ were not detected in ^1H NMR suggested that the reductive elimination process of the Pd(II)-enolate intermediates occurred much slower than that of their protonation process.¹⁹

We have also employed **4** as the catalyst for the addition reaction of arylboronic acids with aldehydes.^{5, 6, 7, 9,12} We were pleased to find that **4** efficiently catalyzed such addition reactions at room temperature (Table 3). Complete conversions and high yields were obtained not only for aromatic aldehydes (Table 3, entries 1–12), but more impressively also for aliphatic aldehydes (Table 3, entries 13, 14). Since only low yields ($\leq 35\%$) were observed for room temperature Rh(I)-catalyzed additions of aliphatic aldehydes,^{9b} our results suggested that **4** might possess higher catalytic efficiency than reported Rh(I) catalysts.

We have also employed **4** as the catalyst for the addition reaction of arylboronic acids with α -ketoesters, a reaction that could yield useful α -hydroxy esters with an α -quaternary carbon center.²⁰ Gratifyingly, we found that **4** also efficiently catalyzed such addition reactions at room temperature (Table 4). To our knowledge, these are the first examples of the addition reaction of arylboronic acids with α -ketoesters.²¹

In summary, we have demonstrated that anionic four electron donor-based, air/moisture stable palladacycle **4** was a highly efficient, robust catalyst for the addition reactions of arylboronic acids with α,β -unsaturated ketones, aldehydes and α -ketoesters at room temperature. Our study suggested that other readily available and air/moisture stable metalacycles including palladacycles might also be highly efficient, practical catalysts for addition reactions.²² Our future work will be directed to determine the scope and limitation of metalacycle-including palladacycle-catalyzed addition reactions and to develop the asymmetric version of these processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
General Types of Palladacycles

Figure 2.
Tested Palladacycles

Scheme 1.
Cross-Couplings vs. Hypothetic Addition Reactions for Type I Palladacycles

Table 1

Reaction Optimization^a

$\text{Ph-B(OH)}_2 + \text{Ph}-\text{CH}=\text{CH}-\text{C(=O)-Ph} \xrightarrow[\text{solvent, base, rt, 0.5 h}]{5\% \text{ palladacycle}} \text{Ph}-\text{CH(Ph)}-\text{CH}_2-\text{C(=O)-Ph}$				
entry	palladacycle	solvent	base	conversion (%) ^b
1	1	Toluene	CS ₂ CO ₃	0 ^c
2	2	Toluene	CS ₂ CO ₃	35 ^c
3	3	Toluene	CS ₂ CO ₃	55 ^c
4	4	Toluene	CS ₂ CO ₃	95 ^c
5	4	ClCH ₂ CH ₂ Cl	K ₃ PO ₄	57
6	4	CH ₂ Cl ₂	K ₃ PO ₄	63
7	4	THF	K ₃ PO ₄	54
8	4	Dioxane	K ₃ PO ₄	72
9	4	Toluene	K ₃ PO ₄	99
10	4	Toluene	CS ₂ CO ₃	79
11	4	Toluene	KF	99
12	4	Toluene	K ₂ CO ₃	68
13	4	Toluene	Ag ₂ CO ₃	36

^a Reaction conditions: chalcone (1.0 equiv), phenylboronic acid (1.5 equiv), solvent (2 mL), base (1 equiv), room temperature.^b Based on ¹H NMR.^c Reaction time: 1 h.

Table 2Palladacycle **4**-Catalyzed Michael Addition of Arylboronic acids with α,β -Unsaturated Ketones ^a

$\text{Ar-B(OH)}_2 + \text{R} \begin{array}{c} \text{O} \\ \parallel \\ \text{CH=CH} \end{array} \text{R}' \xrightarrow[\text{rt, 1-4 h}]{5\% \text{ 4/K}_3\text{PO}_4/\text{Toluene}} \text{R} \begin{array}{c} \text{Ar} \\ \\ \text{CH}_2 \end{array} \begin{array}{c} \text{O} \\ \parallel \\ \text{CH} \end{array} \text{R}'$			
entry	ArB(OH) ₂	R $\begin{array}{c} \text{O} \\ \parallel \\ \text{CH=CH} \end{array}$ R'	yield(%) ^b
1			95
2			92
3			91
4			94
5			81
6			93
7			93
8			89
9			98
10			90 ^c
11			85 ^c

^aReaction conditions (not optimized): ketone (1.0 equiv), arylboronic acid (1.2–2.0 equiv), **4** (5%), K₃PO₄ (1 equiv), toluene (2 mL), room temperature.^bIsolated yields (average of two runs). c. Reaction time: 40 h.

Table 3Palladacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes^a

$\text{Ar-B(OH)}_2 + \text{RCHO} \xrightarrow[\text{rt, 24-48 h}]{5\% \text{ 4/K}_3\text{PO}_4/\text{Toluene}} \text{Ar-CH(OH)-R}$			
entry	Ar-B(OH) ₂	RCHO	yield (%) ^b
1			98
2			99
3			94
4			91
5			90
6			95
7			86
8			95
9			98
10			80
11			96
12			91
13			93
14			91
15			89

^aReaction conditions (not optimized): aldehyde (1.0 equiv), arylboronic acid (1.2–2.0 equiv), K₃PO₄ (1 equiv), toluene (2 mL), room temperature.^bIsolated yields (average of two runs).

Table 4Palladacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with α -Ketoesters^a

$\text{Ar-B(OH)}_2 + \text{R-C(=O)CO}_2\text{Et} \xrightarrow[\text{rt, 24-48 h}]{5\% \text{ 4/K}_3\text{PO}_4/\text{Toluene}} \text{R-C(OH)(Ar)CO}_2\text{Et}$			
entry	Ar-B(OH) ₂	R	yield (%) ^b
1		Ph	94
2		Ph	69
3		Ph	95
4		CH ₃	70
5		CH ₃	65

^a Reaction conditions (not optimized): α -ketoester (1.0 equiv), arylboronic acid (1.5–2.0 equiv), K₃PO₄ (1 equiv), toluene (2 mL), room temperature.^b Isolated yields (average of two runs).