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PII:	S0040-4039(20)30724-3
DOI:	https://doi.org/10.1016/j.tetlet.2020.152257
Reference:	TETL 152257
To appear in:	Tetrahedron Letters
Received Date:	14 April 2020
Revised Date:	10 July 2020
Accepted Date:	14 July 2020



Please cite this article as: Shimizu, M., Yamamoto, T., 9-(Diphenylphosphino)anthracene-based phosphapalladacycle catalyzed conjugate addition of arylboronic acids to electron-deficient alkenes, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152257

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9-(Diphenylphosphino)anthracene-Based Phosphapalladacycle Catalyzed Conjugate Addition of Arylboronic acids to Electron-Deficient Alkenes

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ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: Palladacycle Pd catalyst 1,4-addition Arylboronic acid

Introduction

Transition-metal-catalyzed conjugate addition of arylboron compounds to electron-deficient alkenes is one of the useful carbon-carbon bond formation reaction in organic synthesis [1]. Although various transition metal catalysts such as Rh [2], Cu [3], Ru [4], Co [5] and Ni [6] are applied for the conjugate addition, palladium catalysts is more notably inexpensive and tractable than the other catalyst and have been developed vigorously since Ohe and Uemura' pioneering research [7-12]. Apart from Ohe and Uemura's Pd(OAc)₂/SbCl₃ catalyst, there are currently four kinds of the possible Pd(II) catalysts in this conjugate addition: bidentate diphosphine ligated cationic Pd(II) complexes [8], bidentate nitrogen contained diheterocycle ligated Pd(II) complexes [9], bidentate NHC ligated Pd(II) complexes [10] and phosphine organopalladium(II) complexes ligated [11]. The addition diphosphine/palladium-catalyzed conjugate has proceeded with lower catalyst loading and achieved high enantioselectivity, but the other three kind of Pd(II) catalysts often require large amount of catalyst loading for the conjugate addition. Since we found that organopalladium species generated from the combination of Pd(0)/PPh₃/CHCl₃ acts the catalyst for conjugate addition reactions in 2006 [11a], we have been concentrating on phosphapalladacycle as more active organopalladium catalysts for the reaction [11b,c]. We and other research groups independently reported the five-membered palladacycle-catalyzed conjugate addition so far, but none of them has achieved to reduce the catalytic amount much [11d-f]. Because the general palladacycles decompose quickly to zero-valent Pd species through the

9-(Diphenylphosphino)anthlacene-based phosphapalladacycle catalyzed conjugate addition of arylboronic acids to electron-deficient alkenes such as α,β -unsaturated ketones, esters, nitrile and nitroalkenes gave corresponding β -arylated alkanes in good yields and achieved TON up to 700.

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transmetalation with arylboronic acid under a basic condition, the conjugate addition required a large amount of catalyst. Recently, Pullarkat and co-workers reported that the naphthalene-based palladacycle has a slightly higher catalytic activity than benzene-based palladacycles [11h]. Therefore, we focused on the effect of extended π -conjugated aromatic rings for palladacycle catalysis. Herein, we report the synthesis of anthracene-based phosphapalladacycles and their catalysis for the conjugate addition of arylboronic acids to electron-deficient alkenes.

Result and discussion

At first, we examined the conjugate addition of phenylboronic acid 1a to calcone 2a using the combination of $Pd(OAc)_2$ and diphenylphosphinoarenes as a catalyst (Scheme 1). Although PPh₃ was not effective for this reaction as previously reports, the with the use reaction proceeded smoothly of 1-(diphenylphosphino)naphthalene 4a and 9-(diphenylphosphino)anthlacene 4b, which are generatable the five-membered palladacycle via C-H bond cleavage orthopalladation in situ. Pd(OAc)₂/4b catalyst provided the desired product in 95% yield with 1 mol% catalyst loading at low temperature, but the catalysis decreased with increasing reaction temperature. From the results, we thought that it was difficult to control two competitive reactions of a reduction of Pd(OAc)₂ to zero-valent Pd and a generation of a palladacycle under in situ conditions. Therefore, we expected that isolated palladacycles would act more active catalyst and examined the synthesis and the isolation of diphenylphosphinoarene 4-based palladacycles.

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Scheme 1. Pd(OAc)₂/Phosphine catalyzed conjugate addition.

After μ -chloro-bridged phosphapalladacycles were synthesized from K₂PdCl₄ and phosphines **4** [13] using Goldberg and coworkers reported method [14], the palladium dimer complexes reacted with P(OMe)₃ and P(OEt)₃ to give the monomeric palladacycles **5** [15] (**Scheme 2**). Palladacycle **5b** was obtained as a single isomer, whereas the sterically smaller P(OMe)₃ coordinated complex **5a** was obtained as a mixture of cis/trans isomers. The cis/trans ratio was ca.93:7 and was determined by ¹H NMR.



Scheme 2. Synthesis of monomeric palladacycles 5

Table 1 shows the results of palladacycles **5**-catalyzed conjugate addition of phenylboronic acid **2a** to chalcone **1a**. Predictably, isolated palladacycles exhibited the similar catalytic activity compared to be *in situ* generated catalysts (entries 1–4). Two kinds of trialkyl phosphites have a great influence on the catalytic activity in the reaction, with $P(OEt)_3$ gave better results than $P(OMe)_3$ (entries 1 and 2). Furthermore, palladacycle **5b** showed good catalytic activity even with 0.1 mol% catalyst loading (entry 3). The catalytic reaction occurred smoothly under argon atmosphere, but the catalytic activity was declined under air atmosphere. (entry 5).

Table 1 Comparison of reaction activity 5a vs. 5b



Entry	Catalyst	Yield ^a
1	0.2 mol% 5a	63
2	0.2 mol% 5b	95(92) ^b
3	0.1 mol% 5b	70
4 ^c	1.0 mol% 5b	92
5 ^d	0.2 mol% 5b	56

^a: Yields were determined by ¹H-NMR using triphenylmethane as an internal standard, ^b: Isolated yield, ^c: Reaction was carried out at 30 °C. ^d: Reaction was carried out under air.

Further optimization of reaction conditions of **5b**-catalyzed addition of phenylboronic acid **2a** to chalcone **1a** is summarized in **Table 2**. The yield by the use of K_2CO_3 or CsF instead of KF provided virtually the same yields, while K_3PO_4 and Cs_2CO_3 were unsuitable for this reaction (entries 1–4). Triethylamine was less effective than inorganic bases for this addition (entry 5). The

toluene, but the yields were declined in polar solvents such as THF, 1,4-dioxane, acetonitrile, DMF and ethanol (**Table 1**, entry 2 *vs.* **Table 2**, entries 6-10).

Table 2 Optimization of reaction conditions of 5b-catalyzedconjugate addition of phenylboronic acid 1a to calcone 2a

1a 0.5 mmc	+ B(OH) ₂ -	atalyst 5b (0.2 mol%) Base 1 equiv. Solvent 1 mL 60°C, 18 h	
Entry	Solvent	Base	Yield(%)
1	Toluene	K ₂ CO ₃	83 ^a
2	Toluene	K ₃ PO ₄	68 ^a
3	Toluene	Cs ₂ CO ₃	55 ^a
4	Toluene	CsF	89 ^a
5	Toluene	Triethylamine	10 ^b
6	THF	KF	7 ^b
7	1,4-Dioxane	KF	10 ^b
8	Acetonitrile	KF	24 ^b
9	DMF	KF	43 ^b
10	Ethanol	KF	61 ^b

^a: Isolated Yields. ^b: Yields were determined by ¹H-NMR using triphenylmethane as an internal standard.

The scope and limitation of arylboronic acids in the **5b**catalyzed arylation of chalcone **1a** are summarized in **Table 3**. Not only phenyl, 2-naphtyl, 4-biphenyl and electron-rich arylboronic acids such as 4-methoxy and 4-methylphenyl, but also electronpoor arylboronic acids such as 4-fluoro, 3-nitro, 4-acetyl and 4methoxycarbonylphenyl were converted to the corresponding adducts in excellent yields (entries 1, 2 and 4–9), although a sterically hindered arylboronic acid such as 2-methylphenyl and a highly coordinating functional group substituted arylboronic acid like 3-cyanophenyl required 1 mol% of catalyst (entries 3 and 10).

Next, we examined the conjugate addition to various electrondeficient alkenes such as α,β -unsaturated ketones, esters, nitrile and nitroalkenes using 4-biphenylboronic acid **2e** and the results have shown in **Table 4**. The conjugate addition of 4biphenylboronic acid proceeded smoothly to various cyclic and acyclic α,β -unsaturated ketones and esters in excellent yields (**Table 4**, entries 1–5). The catalytic activity of complex **5b** declined notably in the presence of nitrile compounds, so cinnamonitrile **1g** needed 1 mol% catalyst in this reaction and afforded the desired product in moderate yield (entry 6). While β nitrostyrene **1h** reacted in moderate yield under 3 mol% catalyst loading, a sterically hindered nitroalkene like **1i** was not suitable for this reaction (entries 7 and 8).

Conclusion

In conclusion, we developed the anthlacene-based phosphapalladacycle that catalyzed conjugate addition of arylboronic acids to various electron-deficient alkenes. The monomeric phosphapalladacycle catalyst which readily synthesized from K_2PdCl_4 , 9-(diphenylphosphino)anthlacene and trialkyl phosphites exhibited high turnover numbers in this addition. Further examinations of asymmetric catalytic reaction using chiral phosphine-based palladacycle complexes are underway in our laboratory.

as

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acid to electron-deficient alkenes

calcone

KF 1 equiv. Toluene 1 mL 60°C, 18 h 2 1.2 equiv 1a 0.5 mmol Entry Arylboronic acid 2 Product 3 Yield(%)^a QΜe B(OH)₂ 1 96 MeC 2b 3b .B(OH)₂ 2 95 2c 3c B(OH)₂ 3^b 57 2d 3d B(OH)₂ 95 4 Ph 2e 3e B(OH)₂ 5 85 2f 3f B(OH)₂ 6 78 F 2g 3g NO₂ B(OH)₂ O_2N 7 77 2h 3h B(OH)₂ 8 86 č 2i 3i 0 .OMe B(OH)₂ 9 89 MeC ő 2j 3j CN NC B(OH)₂ 10^{b} 68 2k 3k

B(OH)₂

catalyst 5b (0.5 mol%





^a: Isolated yields. ^b: 1 mol% catalyst loading. ^c: 3 mol% catalyst loading.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We thank Prof. Mino, Chiba University, for the HRMS measurements. This work was supported in part by the Research Institute for Science and Technology, Tokyo Denki University Grant Number Q19E-06.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.XXXX.XXXXX.

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