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Facile Synthesis of Substituted Alkynes by Cyclopalladated Ferrocenylimine Catalyzed Cross-Coupling of Arylboronic Acids/Esters with Terminal Alkynes

Fan Yang[a] and Yangjie Wu*[a]

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A highly efficient and convenient catalytic system for the cross-coupling reaction of arylboronic reagents with terminal alkynes was described by using cyclopalladated ferrocenylimine (**I**)/silver oxide as the catalyst at room temperature. This method provides the first examples of a palladacycle-catalyzed cross-coupling reaction of arylboronic acids/esters with terminal alkynes under mild conditions, and also a facile route for the synthesis of substituted alkynes with a low Pd loading of 1 mol-%. The substrates could be extended to electron-poor alkynes, for which the traditional Sonogashira reaction does not proceed.

Introduction

Alkyne moieties are valuable intermediates for the synthesis of numerous natural products and bioactive compounds.[1–2] Of the various synthetic approaches available for aryl alkynes, the Sonogashira cross-coupling reaction is the most commonly used one.[3] However, it does not proceed well for electron-poor alkynes and harsh reaction conditions must be employed (usually temperatures >70 °C).[4] So, an easy and convenient approach for the synthesis of substituted alkynes under mild conditions should be developed. Up to now, there has been only one report on the cross-coupling reaction of boronic acids with terminal alkynes to afford aryl alkynes.[5] This catalytic system was quite efficient for electron-poor alkynes, but employed a high loading of the catalyst (5 mol-% of Pd) and did not work well for the cross-coupling of phenylboronic acid with phenylacetylene (30% yield). In this case, homocoupling of phenylacetylene occurred to give biphenylbutadiyne (60%) as the byproduct.

Palladacycles have emerged as promising catalysts in C–C and C–heteroatom bond-forming reactions during the past few years.[6] They are often stable and easy to handle and can be used as important alternatives to palladium(0) complexes, but there are no reported examples about the use of palladacycles as catalysts for the cross-coupling reaction of arylboronic acids with terminal alkynes up to now. In 2001, we found that a novel kind of palladacyclic catalysts: cyclopalladated ferrocenylimines could be used as efficient catalysts for Heck arylation.[7] Subsequently, we discovered their wide applications in catalytic reactions such as Heck reactions both in organic solvent and neat water, the dimerization of ArHgCl and Suzuki reactions.[7–9] Silver(I) oxide is known not only to be capable of activating the C–B bond to form alkyn-1-yl silver with alkynes in situ, but also to oxidize palladium(0) to palladium(II) species.[10] Here we would like to report a general and efficient protocol for the synthesis of substituted alkynes by the cyclopalladated ferrocenylimine catalyzed cross-coupling reaction of arylboronic acids/esters with terminal alkynes in the presence of Ag_2O as the additive at room temperature.

Results and Discussion

To evaluate the catalytic activity of the cyclopalladated ferrocenylimine/Ag_2O system, the reaction conditions were optimized by using phenylboronic acid (**1a**) with phenylacetylene (**2a**) as the substrates. The results are summarized in Table 1 (Figure 1). After various bases such as K_3PO_4, Cs_2CO_3, K_2CO_3, $KF{\cdot}2H_2O$, and KOAc were examined, KOAc gave the best result (Table 1, Entries 1–5). The oxidative silver salt played a key role in the successful cross-coupling reactions (Table 1, Entries 5–7). When TBAB was employed as the additive, it showed no activity for the reaction (Table 1, Entry 6). If the loading of oxidative silver was reduced to 10 mol-%, only a yield of 50% was obtained (Table 1, Entry 7). The cross-coupling reaction proceeded smoothly under air and gave a yield of 90% (Table 1, Entry 5). However, the homocoupling product (10%) was obtained as the byproduct. It is notable that when the reaction

[a] Chemistry Department, the Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, the Key and Open Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University,
Zhengzhou 450052, P. R. China
Fax: +86-371-67766667
E-mail: wyj@zzu.edu.cn

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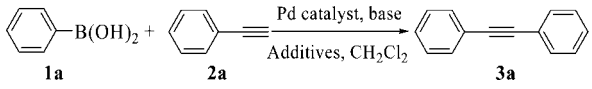
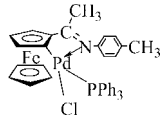
was performed under a nitrogen atmosphere, an excellent yield (95%) was obtained and no 1,3-butadiyne was detectable (Table 1, Entry 8). However, only a relatively lower yield (38%) was obtained with the lower catalytic loading of 0.1 mol-% (Table 1, Entry 9).

Table 1. Palladacycle-catalyzed cross-coupling of phenylboronic acid with phenylacetylene.[a]



Entry	Base	Additive	Yield[b]
1	K_3PO_4	Ag_2O	14
2	Cs_2CO_3	Ag_2O	7
3	K_2CO_3	Ag_2O	Trace
4	$KF·2H_2O$	Ag_2O	20
5[c]	KOAc	Ag_2O	90
6	KOAc	TBAB	Trace
7[d]	KOAc	Ag_2O	50
8[e]	KOAc	Ag_2O	95
9[f]	KOAc	Ag_2O	38

[a] Reaction conditions: $PhB(OH)_2$ (0.5 mmol), phenylacetylene (0.6 mmol), base (0.75 mmol), additive (0.5 mmol), and palladacycle **I** (1 mol-%) in CH_2Cl_2 (3 mL) for 24 h under air and at room temperature. [b] Isolated yield. [c] Biphenylbutadiyne (10%) was obtained as a byproduct. [d] When Ag_2O (0.05 mmol) was used, biphenylbutadiyne (25%) and biphenyl (25%) were obtained as byproducts. [e] Under a nitrogen atmosphere. [f] Palladacycle (0.1 mol-%) and under a nitrogen atmosphere.

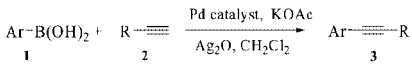


I

Figure 1. Palladacycle **I**.

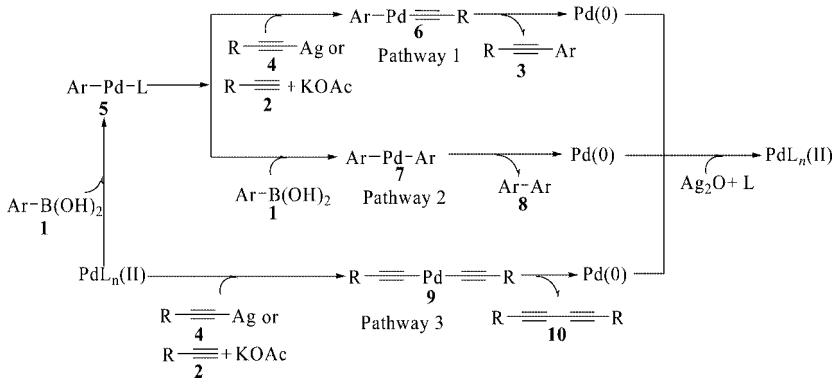
Under these optimized conditions, the results for investigating the scope of the substrates are summarized in Table 2. For arylboronic acids or esters, it can be seen that electron-donating (OCH_3 and CH_3), electron-withdrawing (CF_3), or heterocyclic aromatic groups had little effect on the cross-coupling reaction and moderate-to-good yields were obtained. However, for naphthylboronic acids with a large vicinal steric group (**1h**), the cross-coupling reaction did not proceed (Table 2, Entry 10). The cross-coupling of electron-rich aromatic alkyne **2b** proceeded smoothly and gave a good yield of 88% (Table 2, Entry 1). It is notable that the electron-poor aromatic alkyne 3-ethynylpyridine (**2c**) and ethyl propiolate (**2d**) also gave moderate yields (71, 75, and 80%, Table 2, Entries 2, 4, and 11, respectively), whereas the traditional Sonogashira reaction does not work for electron-poor alkynes. Aliphatic alkynes **2e**–**g** showed a similar reaction activity, affording moderate-to-good yields (Table 2, Entries 12–18). However, for hydroxy containing alkyne **2h**, the cross-coupling reaction proceeded slowly and a lower yield was obtained (Table 2, Entry 19).

Table 2. Palladacycle-catalyzed cross-coupling of arylboronic reagents with alkynes.[a]



Entry	Aryl boronic reagent	Alkyne	Product	Yield [%][b]
1	B(OH)$_2$ (**1a**)	n-C_5H_{11} (**2b**)	**3b**	88
2	B(OH)$_2$ (**1a**)	(**2c**)	**3c**	71
3	B(OH)$_2$ (**1b**)	(**2a**)	**3d**	86
4	B(OH)$_2$ (**1b**)	(**2c**)	**3e**	75
5	B(OH)$_2$ (**1c**)	(**2a**)	**3f**	85
6	(**1d**)	(**2a**)	**3c**	79
7	B(OH)$_2$ (**1e**)	(**2a**)	**3g**	81
8	H_3CO–B(OH)$_2$ (**1f**)	(**2a**)	**3h**	81
9	B(OH)$_2$ (**1g**)	(**2a**)	**3i**	61
10	(**1h**)	(**2a**)	–	–
11	B(OH)$_2$ (**1a**)	$CH_3CH_2OOCC{\equiv}CH$ (**2d**)	**3j**	80
12	B(OH)$_2$ (**1a**)	$CH_3(CH_2)_4C{\equiv}CH$ (**2e**)	**3k**	90
13	B(OH)$_2$ (**1a**)	$CH_3(CH_2)_5C{\equiv}CH$ (**2f**)	**3l**	83
14	B(OH)$_2$ (**1a**)	$CH_3(CH_2)_7C{\equiv}CH$ (**2g**)	**3m**	63
15	B(OH)$_2$ (**1b**)	$CH_3(CH_2)_4C{\equiv}CH$ (**2e**)	**3n**	81
16	B(OH)$_2$ (**1b**)	$CH_3(CH_2)_5C{\equiv}CH$ (**2f**)	**3o**	79
17	B(OH)$_2$ (**1b**)	$CH_3(CH_2)_7C{\equiv}CH$ (**2g**)	**3p**	67
18	B(OH)$_2$ (**1c**)	$CH_3(CH_2)_4C{\equiv}CH$ (**2e**)	**3q**	73
19[c]	B(OH)$_2$ (**1b**)	HO (**2h**)	**3r**	20

[a] Reaction conditions: arylboronic reagent (0.5 mmol), alkyne (0.6 mmol), KOAc (0.75 mmol), Ag_2O (0.5 mmol), and palladacycle **I** (1 mol-%) in CH_2Cl_2 (3 mL) for 24 h under a nitrogen atmosphere at room temperature. [b] Isolated yield. [c] Biaryl (60%) was obtained as a byproduct.



Scheme 1. Proposed mechanism for the palladium-catalyzed cross-coupling reaction of arylboronic acids with terminal alkynes.

Mechanism

As shown in Scheme 1, a reaction mechanism for the palladium-catalyzed cross-coupling reaction of arylboronic acids with terminal alkynes was proposed on the basis of the mechanism of previous reports and our results.[5,10] The replacement reaction of palladium(II) with arylboronic acids would occur to form palladium(II) intermediate **5**. Palladium(II) intermediate **5** could react with alkynylsilver(I) **4** to afford palladium(II) intermediate **6**. Reductive elimination of intermediate **6** could undergo to form desired product **3** and palladium(0). The palladium(0) species can be oxidized to regenerate palladium(II) by the silver(I) species to close the catalytic cycle (pathway 1).[10] Though mechanistic pathway 1 provides cross-coupling products, the homocoupling of arylboronic acids and alkynes occurred through pathways 2 and 3. Both pathway 1 and 2 started with oxidative addition of alkynylsilver(I) **4** or arylboronic acid **1** to palladium(II) intermediate **5**. Pathway 3 began with the replacement reaction of palladium(II) with alkynylsilver(I) **4**. Therefore, the three pathways should be competitive with each other. When the reaction activity of the alkyne was much lower than that of the arylboronic acid, the homocoupling product of boronic acid was obtained as the major product (Table 2, Entry 19).

It should be noted that without the aid of Ag_2O, a trace amount of desired product **3** was observed (Table 1, Entry 6). It is suggested that palladium(II) intermediate **6** or **9** could also be formed from the reaction of intermediate **5** or palladium(II) with alkynes **2** in the presence of KOAc, respectively. However, the rate of this reaction would be much lower than that of alkynylsilver(I) **4**.

Conclusions

In summary, we have developed an efficient and convenient protocol for the synthesis of substituted alkynes from the cross-coupling reaction of arylboronic acids/esters with terminal alkynes catalyzed by cyclopalladated ferrocenylimine **I** with a low loading of 1 mol-% in the presence of Ag_2O as the additive. This method provides the first examples of a palladacycle-catalyzed cross-coupling reaction of arylboronic acids/esters with terminal alkynes under mild conditions, and also a facile route for the synthesis of substituted alkynes. The substrate scope can include electron-poor alkynes, for which the traditional Sonogashira reaction does not proceed. Further studies and applications in organic synthesis are currently underway in our laboratory.

Experimental Section

Typical Procedure for the Cyclopalladated Ferrocenylimine Catalyzed Cross-Coupling Reaction of Arylboronic Reagents with Terminal Alkynes: Under a nitrogen atmosphere, a mixture of the arylboronic reagent (**1**) (0.5 mmol), alkyne (**2**) (0.6 mmol), palladacycle **I** (1 mol-%), Ag_2O (0.5 mmol), KOAc (0.75 mmol), and CH_2Cl_2 (3 mL) was stirred at room temperature, and the reaction was followed by TLC or GC. After the reaction was complete, the mixture was filtered. The solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane or hexane/ethyl acetate) to afford pure **3**.

Supporting Information (see footnote on the first page of this article): Selected characterization data for compounds **3**. The characterization of these compounds is identical to the literature.[11–23]

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