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Palladium-catalyzed cascade cyclization-coupling reactions of 2-bromo-1,6-enynes with organoboronic acids

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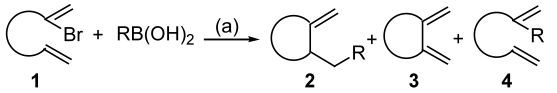
Abstract—2-Bromo-1,6-enynes **5** with a palladium catalyst would form the alkenylpalladium intermediates via an intramolecular Heck reaction, which were cross-coupled with various organoboronic acids **8** to give the cyclization–coupling products **6** in synthetically valuable yields. © 2002 Elsevier Science Ltd. All rights reserved.

The development of a new process forming several bonds in a single synthetic sequence represents an attractive and very active field of synthetic organic chemistry. Toward this end, there has been a growing interest in the application of transition metal-catalyzed processes, since they usually preceed under mild reaction conditions and are tolerant of many functional groups. A few studies trapping the transient alkylpalladium intermediates with hydrogen,[1] nitrogen,[2] or carbon species[3] have been reported.

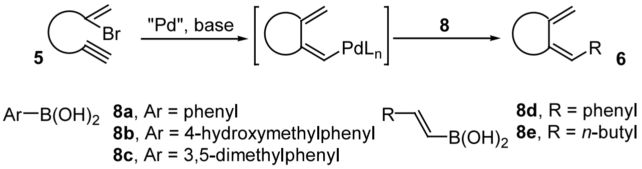
Weinreb reported intramolecular three-component condensation whereby vinyl halide, alkene, and nitrogen nucleophile were incorporated into a cyclization process to synthesize a diverse group of nitrogen heterocycles.[4] Delgado reported a similar tandem process utilizing nickel-promoted cyclization-quenching processes utilizing TMSCN, CO, $NaBH_4$, Et_3SiH and others.[5] Kibayashi reported that homoallylpalladium complexes, formed from treatment of enynes with a catalytic system of $Pd_2(dba)_3CHCl_3$ and AcOH, underwent in situ Stille coupling with various vinyltin reagents to give cyclized products bearing allyl appendages.[6] A process of palladium-catalyzed cyclization combined with Suzuki coupling was recently reported by Ahn wherein one of the *N*-sulfonyl oxygens of the substrates was thought to stabilize the alkylpalladium intermediate, thus preventing β-elimination.[7]

As a part of our ongoing research on palladium-catalyzed carbocyclization of enynes or dienes, we recently reported that the various 2-bromo-1,6-dienes and 2-bromo-1,7-dienes were cycloalkylated with organoboronic acids.[8] One major limitation can be of labile β-elimination of the alkylpalladium intermediates, unless they are trapped rapidly (Eq. (1)).



(a) 3 mol% $Pd(PPh_3)_4$, 2.0 eq. Cs_2CO_3, Ethanol (1)

We still need to search a way of successful cycloalkylation by diminishing two side reactions, β-elimination (**3**) and direct coupling (**4**). We thought to overcome the above problems by employing 2-bromo-1,6-enyne substrates **5** which would form the alkenylpalladium intermediates instead of the alkylpalladium intermediates in the catalytic cycle. Here we report the successful palladium-catalyzed one-pot cyclization-coupling of 2-bromo-1,6-enynes with various aryl- or alkenylboronic acids **8a**–**e** (Scheme 1).



Scheme 1.

We chose 2-propargyl-2-(2-bromo-allyl)-malonic acid diethyl ester (**5a**) as a representative substrate in order to optimize the reaction conditions by varying palladium catalysts and solvents as summarized in Table 1. Contrast to 2-bromo-1,*n*-dienes, 2-bromo-1,*n*-enynes

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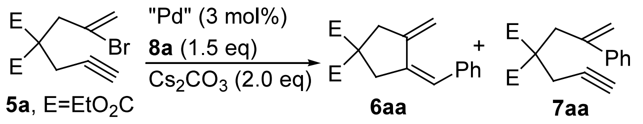
Table 1. Palladium-catalyzed cyclization-coupling reactions of 2-bromo-1,6-enyne **5a** with phenylboronic acid (**8a**)



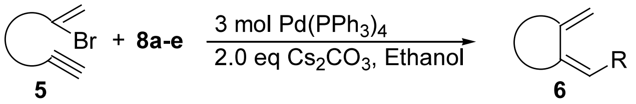
	Pd compounds (mol%)	Solvent	Temp. (°C)/time (h)	% Yield of **6aa**
1	Pd(OAc)$_2$	Toluene	rt/20	Trace
2	Pd(OAc)$_2$	CHCl$_3$	rt/20	Trace
3	Pd(OAc)$_2$	1,4-Dioxane	rt/5	33
4	Pd(OAc)$_2$	DMF	rt/20	15
5	Pd(OAc)$_2$	IPA	rt/2	34
6	Pd(OAc)$_2$	Ethanol	rt/2	61
7	Pd(OAc)$_2$	Ethanol	60/1	53
8	Pd(OAc)$_2$/PPh$_3$	Ethanol	rt/2	51
9	**Pd$_2$(dba)$_3$**	**Ethanol**	**rt/20**	**78**
10	Pd(PPh$_3$)$_2$Cl$_2$	Ethanol	rt/20	42
11	Pd(PPh$_3$)$_4$	Ethanol	rt/20	60
12	**Pd(PPh$_3$)$_4$**	**Ethanol**	**60/1**	**80**

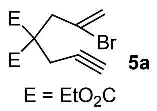
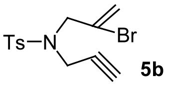
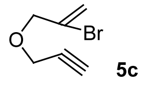
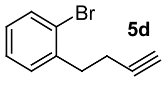
like **5a** was expected to give only the cyclized product **6aa** and/or the direct-coupling product **7aa**.

The presence of a mineral base seems to be fundamental for the success of the Suzuki-type cross-coupling, although its role is under debate.[9] One explanation is that a base RO$^-$ is introduced in the coordination sphere of Pd, which makes reductive elimination of the Pd intermediates to the products and B(OH)$_2$OR possible. Another explanation has been suggested that the transmetallation step occurs on a [Ar′B(OH)$_3$]$^-$ species rather than on the arylboronic acid.[10] We chose cesium carbonate and palladium acetate as a base and a catalyst, and the reaction was screened in various solvents, where ethanol gave the best result (entries 6 and 7). The nature of a palladium catalyst was surveyed to Pd(PPh$_3$)$_4$, Pd(OAc)$_2$, Pd(OAc)$_2$–PPh$_3$, Pd$_2$(dba)$_3$, and Pd(PPh$_3$)$_2$Cl$_2$. Although Pd(dba)$_2$ was shown to be the equally efficient catalysts to Pd(PPh$_3$)$_4$ in terms of the product yields, much longer reaction time at room temperature (entry 9) and many side reactions at elevated temperature (60°C) were observed. It should be noted that the cross-coupling product **7aa** was not isolated in all cases. Based on these experiments, the optimal yield (80%) was achieved by the use of cesium carbonate (2.0 equiv.) in ethanol with 3.0 mol% of Pd(PPh$_3$)$_4$ as catalyst, phenylboronic acid **8a** (1.5 equiv.) with respect to the substrate **5a** (entry 12). Using these conditions, we have tested Palladium-catalyzed cycloalkylations of a series of 2-bromo-1,6-enynes **5a**–**d** with organoboronic acids **8a**–**e** and our results are summarized in Table 2.[11] 2-Bromo-1,6-enyne substrate **5a** smoothly underwent cycloalkylation with arylboronic acids (**8a**–**c**) and alkenylboronic acids (**8d**–**e**) to the expected products **6aa**–**6ae** in 64–82% yields. The reaction was extended to the *N*-containing substrate **5b**, where cyclic products **6ba**–**6ce** in 70–85% yields. An *O*-containing substrate **5c** was also cycloalkylated to give the products **6ca**–**6ce** under the same conditions. 2-Bromo-(3-butynyl)benzene **5d** was prepared as a structurally equivalent to 2-bromo-1,6-enynes **5a**–**c**. The **5d** underwent cycloalkylation to 5-membered ring product **6da**–**de** in 70–85% yields.

The present reaction would be of good synthetic potential, since the initially formed alkenylpalladium intermediates would undergo only cyclization to give the new alkenylpalladium intermediates which were cou-

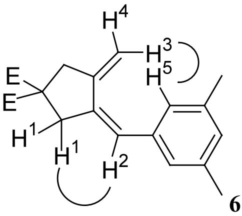
Table 2. Palladium-catalyzed cyclization-coupling reactions of 2-bromo-1,6-enyne and organoboronic acid



Bromoenynes	RB(OH)$_2$	Temp (℃) /Time (h)	Products	% Yield
 **5a** E = EtO$_2$C	**8a**	60/1	**6aa**	80
	8b	60/2	**6ab**	75
	8c	60/2	**6ac**	64
	8d	60/1	**6ad**	80
	8e	60/1	**6ae**	82
 **5b**	**8a**	60/1	**6ba**	70
	8b	70/4	**6bb**	75
	8c	60/4	**6bc**	73
	8d	60/3	**6bd**	73
	8e	60/1	**6be**	85
 **5c**	**8a**	60/2	**6ca**	75
	8b	60/2	**6cb**	63
	8c	60/2	**6cc**	62
	8d	60/2	**6cd**	60
	8e	60/2	**6ce**	70
 **5d**	**8a**	80/1	**6da**	70
	8b	80/6	**6db**	72
	8c	80/2	**6dc**	85
	8d	80/1	**6dd**	77
	8e	60/2	**6de**	80

pled with the organoboronic acids. The direct coupling of the bromoenynes with the organoboronic acids was not observed in any case.

The stereochemistry of **6ac** was determined by 2-D NOESY NMR experiments. The ^{1}H NMR spectrum shows that H^1, H^2, H^3, H^4 and H^5 appear at 3.12, 6.42, 5.17, 4.89, 6.94 ppm, respectively. A significant positive NOE effect was observed between H^1 and H^2, H^3 and H^5; no NOE effect was observed between H^1 and H^5, H^2 and H^3. It showed the stereodefined coupling of the alkenylpalladium intermediates with organoboronic acids (Fig. 1).

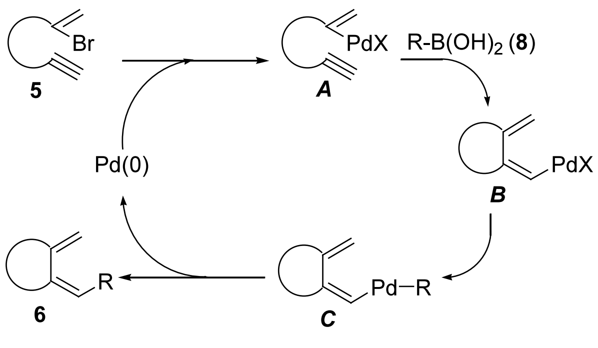


6ac

Figure 1. Relative stereochemistry of the product **6ac**.

The widely accepted catalytic cycle in Heck reaction is initiated by the oxidative addition of the organic halide to the Pd(0) species enyne to form the intermediate ***A*** (Scheme 2).[12] The alkenylpalladium intermediate ***A*** was carbopalladated with the pendant triple bonds to form the methylenepalladium intermediate ***B***, a Heck intermediate. Then, the R-group of organoboronic acid **8** can transfer to the palladium to generate an intermediate ***C***. It has been well-documented that the high oxophilicity of the boron center and the electron richness of palladium(0) complexes would induce transmetallation, whereby organic groups on the boron atom readily transfer to $Pd(OAc)_2$, $[\eta^3\text{-}C_3H_5PdOAc]_2$, $\eta^3\text{-}C_3H_5Pd(acac)$, $Pd(OR)L_2$ (R = H, Me, Ac), and $[Pt(OR)(S)L_2]$ = (R = H, Me) under neutral conditions.[13] Reductive elimination from this intermediate ***C*** produces the cross-coupling product **6**.

In conclusion, we have accomplished a cascade cycloalkylation reactions of 2-bromo-1,6-enynes with various organoboronic acids, where the alkenylpalladium intermediates, formed via an intramolecular Heck reaction of 2-bromo-1,6-bromoenynes, were cross-coupled with various organoboronic acids to give the products **6** in synthetically valuable yields.



Scheme 2.

Acknowledgements

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11. All new products **6aa**–**6de** were characterized by ^{1}H, ^{13}C NMR, IR, and high-resolution mass spectroscopy. A typical procedure is as follows. To a mixture of phenylboronic acids (**8a**, 35.0 mg, 0.29 mmol) and cesium

carbonate (123 mg, 0.38 mmol) in dry ethanol (1.0 mL) was added a solution of 2-bromo-1,6-enynes **5a** (60.0 mg, 0.2 mmol) and Pd(PPh_3)$_4$ (6.6 mg, 0.03 mmol) in dry ethanol (1 ml) under argon atmosphere. The reaction mixture was stirred for 2 h at 70°C, then cooled down to 0°C, quenched with water, extracted with diethylether, and separated by flash chromatography (eluent: hexane:ethyl acetate = 10:1) to give the desired products **6aa** (50.3 mg, 80% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.15 (m, 5H), 6.47 (s, 1H), 5.11 (s, 1H), 4.89 (s, 1H), 4.20 (q, J = 6.8 Hz, 4H), 3.14 (s, 2H), 3.05 (s, 2H), 1.26 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 142.31, 137.39, 136.88, 128.28, 128.12, 126.65, 124.79, 110.89, 57.15, 43.06, 42.89, 14.17; FT-IR (neat, cm^{-1}): 2986, 1733, 1600, 1494, 1249, 1189; HRMS calcd for $C_{19}H_{22}O_4$ (M^+) 314.1518, found 314.1527.

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