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Palladium-Catalyzed Cycloalkylations of 2-Bromo-1,*n*-dienes with Organoboronic Acids

Chang Ho Oh,*[,†] Hye Rhyan Sung,[†] Su Jin Park,[†] and Kyo Han Ahn[‡]

Department of Chemistry, Hanyang University, Sungdong-Gu, Seoul 133-791, Korea, and Department of Chemistry, Pohang University of Science and Technology, Pohang, Kyungbook 790-784, Korea

changho@hanyang.ac.kr

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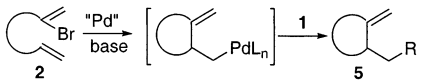
Abstract: Cascade palladium-catalyzed cycloalkylations of 2-bromo-1,*n*-dienes were accomplished in good to excellent yields, where the alkylpalladium intermediates, formed via an intramolecular Heck reaction of 2-bromo-1,*n*-dienes (*n* = 6 or 7), were successfully cross-coupled with various organoboronic acids. The optimal yields were achieved by the use of cesium carbonate in ethanol with $Pd(PPh_3)_4$ as catalyst, with 2-bromo-1,*n*-dienes and organoboronic acids at concentrations of 0.2 and 0.3 M (1.5 equiv), respectively.

The development of a new process forming several bonds in a single synthetic sequence represents an attractive and active field of synthetic organic chemistry.[11] Toward this end, there has been a growing interest in the application of palladium-catalyzed processes, since they usually proceed under mild reaction conditions and are tolerant of many functional groups. One severe limitation can be the facile β-elimination of the transient alkylpalladium intermediates, unless they are trapped rapidly. A few studies suppressing β-eliminations of alkylpalladium intermediates by trapping with hydrogen,[2] nitrogen,[3] or carbon species[4] have been reported. The reduction of alkylpalladium intermediates by trialkylsilanes is well-known.[5] Recently, we found that alkylpalladium intermediates, formed from enediynes, could be reduced with a stoichiometric amount of formic acid.[6] Weinreb reported an intramolecular three-component condensation whereby vinyl halide, alkene, and a nitrogen nucleophile were incorporated into a cyclization process to synthesize a diverse group of nitrogen heterocycles.[7] Delgado reported a similar tandem process utilizing nickel-promoted cyclization-quenching processes.[8] 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.[9] A process of palladium-catalyzed cyclization combined with Suzuki coupling was recently reported by one of us wherein one of the *N*-sulfonyl oxygens of the substrates is thought to stabilize the alkylpalladium intermediate, thus preventing β-elimination.[10] As a part of our ongoing research focused on palladium-catalyzed carbocyclizations of enynes or dienes, we have continued to search for a way of trapping alkylpalladium intermediates, formed from 2-bromo-1,*n*-dienes,[11] by external carbon nucleophiles leading to cycloalkylated products. Herein we report the successful palladium-catalyzed one-pot cycloalkylation of 2-bromo-1,*n*-dienes with various aryl- or alkenylboronic acids **1a**−**f**, as shown in Scheme 1.

SCHEME 1



R−B(OH)$_2$ **1a**, R = C_6H_5-
1b, R = 4-$HOCH_2C_6H_4$-
1c, R = 3,5-$(CH_3)_2C_6H_3$-
1d, R = C_6H_5CH=CH-
1e, R = *n*-C_4H_9CH=CH-
1f, R = *t*-C_4H_9CH=CH-

Initially, we chose 2-allyl-2-(2-bromoallyl)malonic acid diethyl ester (**2a**) as a representative substrate in order to optimize reaction conditions by varying palladium catalysts and solvents (Table 1). This reaction was expected to give the cyclized (but uncoupled) product **3aa** and its isomer **6aa**, the (uncyclized) coupled product **4aa**, and the desired product **5aa** and its isomer **7aa**.

When we subjected **2a** to Ahn's conditions[10] (6:1) (entry 1), the cyclized but uncoupled product **6aa** was isolated

[†] Hanyang University.
[‡] Pohang University of Science and Technology.

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(9) (a) Kibayashi, C.; Yamada, H.; Aoyagi, S. *Tetrahedron Lett.* **1997**, *38*, 3027−3030. (b) Kibayashi, C.; Yamada, H.; Aoyagi, S. *Tetrahedron Lett.* **1996**, *37*, 8787−8790.
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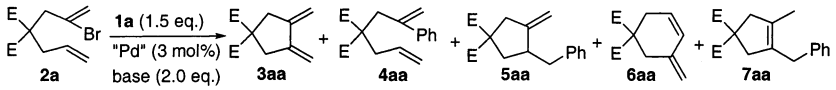
TABLE 1. Pd-Catalyzed Cycloalkylations of 2-Bromo-1,6-diene 2a with Phenylboronic Acid (1a)



	Pd catalysts	base	solvent	temp (°C)/ time (h)	products (ratio)	% yield
1	$Pd(PPh_3)_4$	K_2CO_3	THF(aq)	60/3	**6aa**	59
2	$Pd(PPh_3)_4$	K_2CO_3	DMF	60/10	**7aa**	41
3	$Pd(PPh_3)_4$	K_2CO_3	ethanol	60/4	**3aa, 5aa** (1:2)	54
4	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	60/4	**7aa**	75
5	$Pd(PPh_3)_4$	Cs_2CO_3	ethanol	60/2	**5aa**	85
6	$Pd(OAc)_2/PPh_3$ (1:2)	Cs_2CO_3	ethanol	60/4	**5aa**	80
7	$Pd(OAc)_2$	Cs_2CO_3	ethanol	60/4	**5aa**	79
8	$Pd_2(dba)_3/PPh_3$ (1:4)	Cs_2CO_3	ethanol	60/4	**5aa**	69
9	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	ethanol	60/4	**5aa**	48

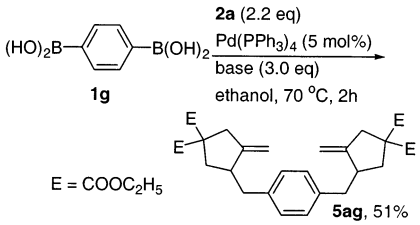
as the predominant product. When the reaction was carried out in DMF (entry 2), the isomer of the desired product **7aa** was obtained in 41% yield, suggesting that the reaction solvent might play a crucial role. Among protic solvents, ethanol gave the best result, where the desired product **5aa** was isolated along with cyclized diene **3aa** in a ratio of 1:2 (entry 3). Cesium carbonate as a base gave much better results than potassium carbonate (entries 4 and 5). The nature of the palladium catalyst was also surveyed, and $Pd(PPh_3)_4$ and $Pd(OAc)_2$ were shown to be optimal. On the basis of these experiments, the optimal yield was achieved by the use of cesium carbonate in ethanol with $Pd(PPh_3)_4$ as catalyst, with the substrate **2a** and phenylboronic acid **1a** at concentrations of 0.2 and 0.3 M (1.5 equiv), respectively.

Using these conditions, we have tested the scope of this method with a series of bromodienes **2a**−**f** and organoboronic acids and our results are summarized in Table 2. We have tested cycloalkylations of a series of 1,6-, 1,7-, and 1,8-bromodiene with organoboronic acids. The 2-bromo-1,6-diene substrate **2a** smoothly underwent cycloalkylations to the expected products **5aa**−**af** in 58 to 85% yields. Compared to the 2-bromo-1,6-diene **2a**, 2-bromo-1,7-diene **2b** was cycloalkylated with arylboronic acids **1a**−**c** to give the expected products **5ba**−**bc**, but with alkenylboronic acids **1d**−**f** to give the Suzuki-type products **4bd**−**bf** as major products. 2-Bromo-1,8-diene **2c** under similar conditions gave only the Suzuki-type products **4** with both arylboronic acid and alkenylboronic acid. The more substituted 2-bromo-1,6-diene **2d** underwent such cycloalkylation less readily. While cycloalkylation of **2d** with arylboronic acid **1a** gave the product **5da** exclusively, cycloalkylation of **2d** with alkenylboronic acid **1d** gave a mixture of **4dd** and **5dd**.

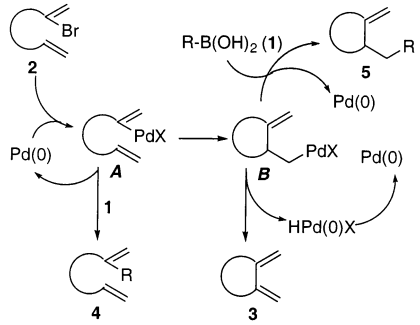
Next, heteroatom-linked bromodienes **2e** and **2f** were tested. A nitrogen-containing bromodiene **2e** was tested with aryl- and alkenylboronic acids for comparison with Ahn's results. The substrate **2e** was smoothly cycloalkylated with the arylboronic acids **1a**, **1b**, and **1c**, but less selectively with the alkenylboronic acid **1d**. An oxygen-containing bromodiene **2f** was also cycloalkylated with both arylboronic acids **1a**−**b** and an alkenylboronic acid **1e** to give the products **5fa**, **5fb**, and **5fe** in 78%, 72%, and 33% yields, respectively.

When this method was further extended to double-cycloalkylation by using 2-bromo-1,6-diene **2a** and phenyldiboronic acid **1g**, the product **5ag** was isolated in 51% yield (Scheme 2).

SCHEME 2



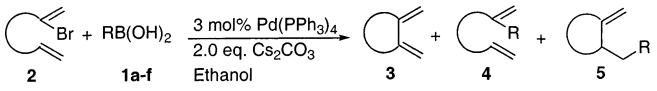
SCHEME 3



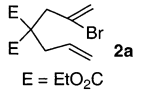
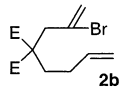
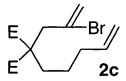
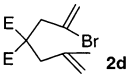
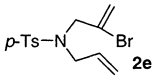
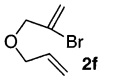
A plausible mechanism is depicted in Scheme 3, as suggested before.[10] First, a 2-bromo-1,*n*-diene oxidatively adds to Pd(0) to form intermediate ***A***. Intermediate ***A*** might couple with $RB(OH)_2$ to give **4** through a direct Suzuki coupling, or undergo intramolecular carbopalladation to form the Heck-type intermediate ***B***. Intermediate ***B*** could undergo β-elimination to form diene **3**, a Heck product, or further cross-coupling with $RB(OH)_2$ through a Suzuki-type reaction to form the product **5**. Consistent with the formation of ***A*** as the first intermediate, we observed that the higher concentration of organoboronic acid (**1**) gave the more Suzuki product **4** and lower concentration of organoboronic acid gave the more Heck product **3**.

In conclusion, we have established cascade cycloalkylation reactions of 2-bromo-1,*n*-dienes with various organoboronic acids, where the alkylpalladium intermediates, formed via an intramolecular Heck reaction of 2-bormo-1,*n*-dienes ($n = 6$ or 7), were successfully cross-coupled with various organoboronic acids to give the cycloalkylated products **5** in synthetically valuable yields.

TABLE 2. Pd-Catalyzed Cycloalkylations of 2-Bromo-1,*n*-dienes 2 with Organoboronic Acids



2 1a-f 3 4 5

2-Bromo-1,n-diene (**2**)	$RB(OH)_2$ (**1**)	temp (°C) time (h)	products	% yield (ratio)
 **2a** $E = EtO_2C$	$C_6H_5B(OH)_2$ (**1a**)	60/2.0	**5aa**	85
	$(4\text{-}HOCH_2)C_6H_4B(OH)_2$ (**1b**)	60/2.0	**5ab**	82
	$3,5\text{-}(CH_3)_2C_6H_3B(OH)_2$ (**1c**)	60/2.0	**5ac**	76
	$C_6H_5CH{=}CHB(OH)_2$ (**1d**)	70/1.0	**5ad**	68
	$n\text{-}C_4H_9CH{=}CHB(OH)_2$ (**1e**)	50/1.0	**5ae**	72
	$t\text{-}C_4H_9CH{=}CHB(OH)_2$ (**1f**)	70/2.0	**3af, 5af**	35, 58
 **2b**	$C_6H_5B(OH)_2$ (**1a**)	60/0.5	**5ba**	87
	$(4\text{-}HOCH_2)C_6H_4B(OH)_2$ (**1b**)	60/1.0	**4bb, 5bb**	89 (1:4)
	$3,5\text{-}(CH_3)_2C_6H_3B(OH)_2$ (**1c**)	60/1.0	**5bc**	81
	$C_6H_5CH{=}CHB(OH)_2$ (**1d**)	80/0.5	**4bd, 5bd**	85 (2:1)
	$n\text{-}C_4H_9CH{=}CHB(OH)_2$ (**1e**)	60/0.5	**4be**	85
	$t\text{-}C_4H_9CH{=}CHB(OH)_2$ (**1f**)	60/0.5	**4bf**	89
 **2c**	$C_6H_5B(OH)_2$ (**1a**)	80/0.5	**4ca**	73
	$C_6H_5CH{=}CHB(OH)_2$ (**1d**)	60/2.0	**4cd**	83
 **2d**	$C_6H_5B(OH)_2$ (**1a**)	60/1.0	**5da**	76
	$C_6H_5CH{=}CHB(OH)_2$ (**1d**)	60/2.0	**4dd, 5dd**	60 (1:2)
 **2e**	$C_6H_5B(OH)_2$ (**1a**)	70/0.5	**5ea**	82
	$(4\text{-}HOCH_2)C_6H_4B(OH)_2$ (**1b**)	60/2.0	**5eb**	90
	$3,5\text{-}(CH_3)_2C_6H_3B(OH)_2$ (**1c**)	60/2.0	**5ec**	75
	$C_6H_5CH{=}CHB(OH)_2$ (**1d**)	70/2.0	**5ed**	51
 **2f**	$C_6H_5B(OH)_2$ (**1a**)	RT/22	**5fa**	78
	$(4\text{-}HOCH_2)C_6H_4B(OH)_2$ (**1b**)	RT/20	**5fb**	72
	$n\text{-}C_4H_9CH{=}CHB(OH)_2$ (**1e**)	50/2.0	**5fe**	33

Experimental Section

General Procedure. Cycloalkylation of 2-Bromo-1,6-diene 2a is a general procedure. Into a mixture of cesium carbonate (69.1 mg, 0.21 mmol) and phenylboronic acid **1a** (26.4 mg, 0.21 mmol) was added a solution of **2a** (45.1 mg, 0.14 mmol) in dry ethanol (0.7 mL) and then tetrakistriphenylphosphine palladium (4.9 mg, 0.0042 mmol) was added at 0 °C. The resulting mixture was stirred under argon atmosphere for 2 h in a preheated 60 °C oil bath. Then the reaction mixture was concentrated under reduced pressure, diluted with water (10 mL), and extracted with ether (2 × 20 mL). The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and purified by flash chromatography (*n*-hexane/ethyl acetate = 20:1) as an eluent to give the cyclized product **5aa** (39.0 mg, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.18 (m, 5H), 4.98 (q, J = 2.4 Hz, 1H), 4.87 (q, J = 2.4 Hz, 1H), 4.16 (m, 4H), 3.06−2.94 (m, 3H), 2.86 (m, 1H), 2.51 (dd, J = 13.6, 9.8 Hz, 1H), 2.37 (dd, J = 13.6, 7.6 Hz, 1H), 1.86 (dd, J = 13.2, 10.0 Hz, 1H), 1.23 (t, J = 6.8 Hz, 3H), 1.20 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 151.41, 140.20, 128.71, 128.19, 125.87, 106.49, 61.53, 61.45, 58.30, 43.81, 41.09, 40.37, 39.65, 14.15, 14.11; FT-IR (neat, cm^{-1}) 2983, 2935, 1731, 1656, 1495, 1453, 1366, 1253, 1182, 1070, 1019, 884, 744, 700; HRMS calcd for $C_{19}H_{24}O_4$ (M^+) 316.1675, found 316.1670.

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Supporting Information Available: Details on the spectral data for **5aa**−**ag**, **5ba**−**bd**, **5da**, **5dd**, **5ea**−**ed**, **5fa**, **5fb**, **5fe**, **4bd**, **4be**, **4bf**, **4ca**, and **4cd**. This material is available free of charge via the Internet at http://pubs.acs.org.

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