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Palladium-Catalyzed Arylation and Alkylation of 3,5-Diphenylisoxazole with Boronic Acids via C−H Activation

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*Summary: A method for stoichiometric C−H activation of 3,5-diphenylisoxazole (**1**) using $Pd(OAc)_2$ as a reagent in acetic acid leading to the isoxazole palladacycle **I** was described. Ortho aryl- and alkyl-substituted 3,5-diphenylisoxazoles **3a−f** and **5a−i** were synthesized by the reaction of **I** with various boronic acids **2a−f** and **4a−i**, respectively. p-Benzoquinone was found to be the best oxidant and 1,4-dioxane the best solvent for the transmetalation−reductive-elimination step of **I** with boronic acids.*

Isoxazole-containing molecules have received considerable attention, because they are excellent precursors in transforming to a variety of bifunctional compounds[1] and show diverse biological activities.[2] Recently, functionalizations of aryl C−H bonds using organometallic reagents,[3] olefins,[4] peroxides,[5] or diethyl azodicarboxylate[6] catalyzed by transition metals have been investigated intensively.[7] In order to achieve the ortho-selective C−H bond functionalization, a functional-group-containing heteroatom, such as a pyridyl, imine, acetyl, or acetoamino group, is required to form a stable metal complex. According to these observations, we anticipate that isoxazole could provide a good anchor for ortho metalation of aromatic rings and would allow us to prepare a variety of multiply substituted isoxazoles. We herein report the ortho arylation and

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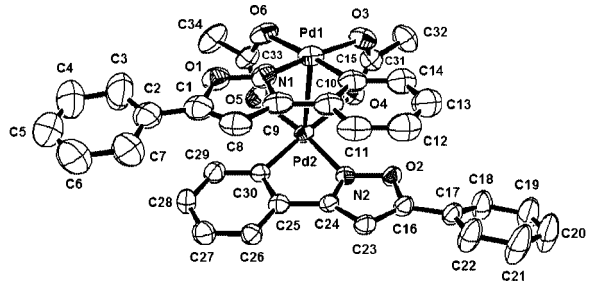


Figure 1. ORTEP drawing of the isoxazole palladacycle **I**. Selected bond lengths (Å): Pd1−Pd2 = 2.8370(7); Pd1−N1 = 1.990(5); Pd1−C15 = 1.995(6); Pd1−O3 = 2.042(4); Pd1−O6 = 2.176(4); Pd2−N2 = 1.978(7); Pd2−C30 = 2.004(8); Pd2−O4 = 2.137(6); Pd2−O5 = 2.034(5).

Table 1. Reaction of the Isoxazole Palladacycle I with Phenylboronic Acid (2a) in the Presence of Various Oxidants[a]

entry	oxidant[b]	product	yield (%)[c]
1	none	**3a**	0
2	*p*-benzoquinone	**3a**	66
3	Ag_2CO_3	**3a**	22
4	Ag_2O	**3a**	19
5	AgOAc	**3a**	11
6	$Cu(OAc)_2$	**3a**	11
7	$Cu(OTf)_2$	**3a**	0
8	$Hg(OAc)_2$	**3a**	0

[a] Conditions: isoxazole palladacycle **I** (15.0 mg, 0.02 mmol), phenylboronic acid (**2a**; 5.90 mg, 0.05 mmol), and 1,4-dioxane (2 mL) at reflux temperature for 1 h. [b] Two equivalents was used. [c] All yields were determined by ^{1}H NMR using dichloromethane (5 μL) as the internal standard.

Table 2. Reaction of the Isoxazole Palladacycle I with Phenylboronic Acid (2a) using *p*-Benzoquinone as the Oxidant in Various Solvents[a]

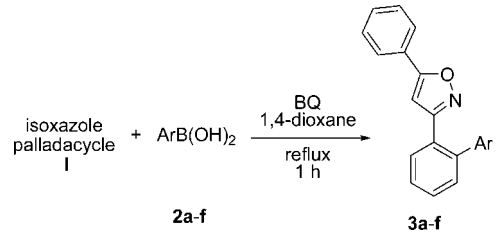
entry	solvent[b]	product	yield (%)[c]
1	1,4-dioxane	**3a**	66
2	dichloromethane	**3a**	50
3	*tert*-amyl alcohol	**3a**	47
4	acetonitrile	**3a**	45
5	acetic acid	**3a**	11

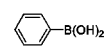
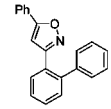
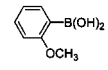
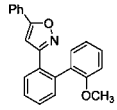
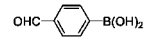
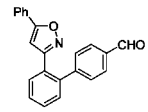
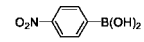
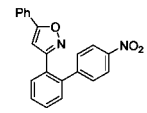
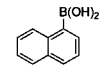
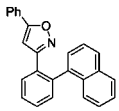
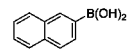
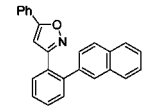
[a] Conditions: isoxazole palladacycle **I** (15.0 mg, 0.02 mmol), phenylboronic acid (**2a**; 5.90 mg, 0.05 mmol), *p*-benzoquinone (4.10 mg, 0.04 mmol) at reflux temperature for 1 h. [b] Two milliliters was used. [c] All yields were determined by ^{1}H NMR using dichloromethane (5 μL) as the internal standard.

alkylation of 3,5-diphenylisoxazole (**1**) with organoboronic acids using palladium as a catalyst.

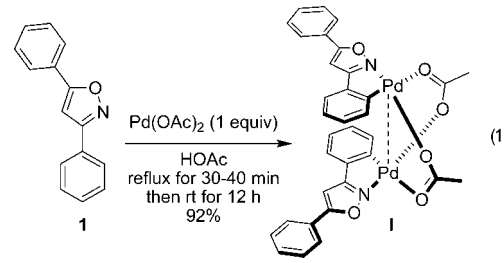
3,5-Diphenylisoxazole (**1**) was prepared by the method of *Click chemistry*.[8] To confirm our hypothesis that isoxazole could provide a good anchor for ortho metalation of aromatic rings, compound **1** was treated with a stoichiometric amount of palladium acetate in acetic acid to give the isoxazole palladacycle **I** in 92% yield (eq 1). Other solvents, such as dichloromethane, 1,2-dichloroethane, acetonitrile, *tert*-amyl alcohol, and 1,4-dioxane, did not give the complex **I**. The structure of complex **I** was unambiguously determined by a single-crystal X-ray crystallography analysis, as shown in Figure 1. Two interesting phenomena were found in the structure of isoxazole palladacycle **I**: (a) the phenyl and isoxazole rings on the metal center of **I** are parallel in space and located in opposite directions in a head-to-tail structure and (b) the $\pi-\pi$ interactions between these two aromatic rings appear to play a critical role in reducing the Pd−Pd distance (2.837 Å).[9]

Table 3. Arylation of the Isoxazole Palladacycle I with Boronic Acids[a]



Entry	$ArB(OH)_2$	Product	Yield (%)[b]
1	 **2a**	 **3a**	65
2	 **2b**	 **3b**	65
3	 **2c**	 **3c**	92
4	 **2d**	 **3d**	90
5	 **2e**	 **3e**	55
6	 **2f**	 **3f**	60

[a] Conditions: $ArB(OH)_2$ (2.5 equiv), *p*-benzoquinone (2 equiv), 1,4-dioxane, reflux for 1 h. [b] The isolated yield was determined by three runs.



The palladium-catalyzed Suzuki-type cross-coupling reaction is a powerful method for carbon−carbon bond formation.[10] To test the C−C bond formation reaction, the isoxazole palladacycle **I** was treated with 2.5 equiv of phenylboronic acid (**2a**) in the

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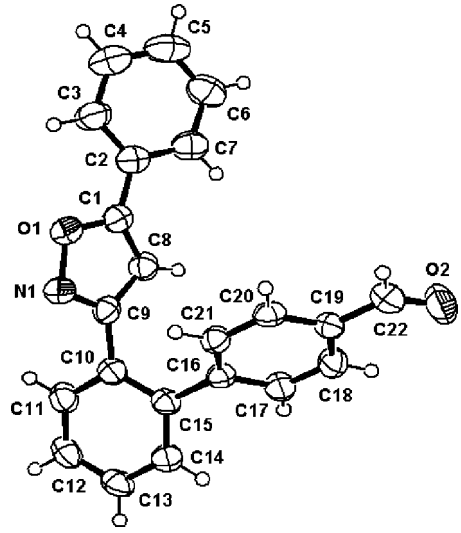


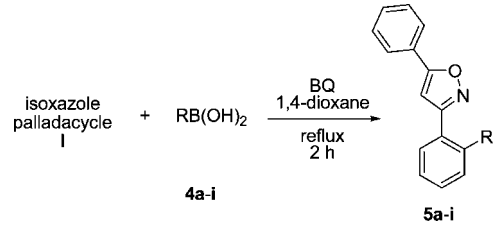
Figure 2. ORTEP drawing of compound **3c**.

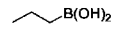
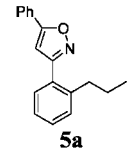
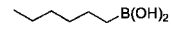
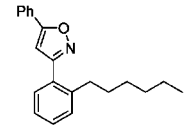
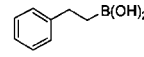
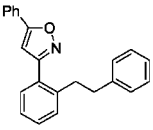
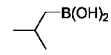
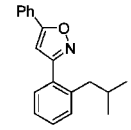
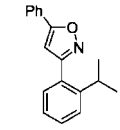
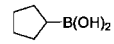
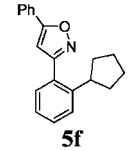
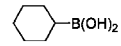
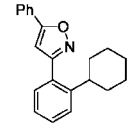
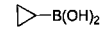
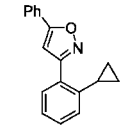
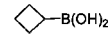
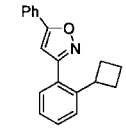
presence of 2 equiv of *p*-benzoquinone in various solvents for 1 h. The relative yields of **3a** by different solvents were determined by proton NMR using dichloromethane as the internal standard. The results are summarized in Table 1. 1,4-Dioxane appears to be the best solvent in this C−C bond formation reaction. In addition to *p*-benzoquinone, various oxidants were also employed in this study. The results are shown in Table 2, which indicated that *p*-benzoquinone is the best oxidant for the reaction of **I** with phenylboronic acids.[11]

According to the test results, the isoxazole palladacycle **I** was then reacted with 2.5 equiv of phenylboronic acid in the presence of 2 equiv of *p*-benzoquinone in refluxing 1,4-dioxane for 1 h and the product **3a** was isolated after column chromatography in 65% yield. Other arylboronic acids bearing electron-donating or -withdrawing groups at the phenyl ring were used in this study. The coupling adducts **3b**−**f** were obtained in 55−92% yields (Table 3). The structure of the product **3c** was further confirmed by a single-crystal X-ray crystallography analysis, as shown in Figure 2. The results show that the boronic acids having electron-withdrawing subsituents on the phenyl ring gave better yields than those with electron-donating groups.

In the alkylation reactions of isoxazole palladacycle **I**, we found that reaction of **I** with the primary alkylboronic acids **4a**−**d** in refluxing 1,4-dioxane for 2 h gave the alkylating adducts **5a**−**d** in 45−65% yields. When secondary alkylboronic acids such as isopropyl-, cyclopentyl-, and cyclohexylboronic acids (**4e**−**g**) were employed under the described reaction conditions, no desired alkylating adduct was obtained. However, reactions of **I** with cyclopropyl- and cyclobutylboronic acids (**4h**,**i**) gave the alkylating adducts **5h**,**i** in 40% and 30% yields,

Table 4. Alkylation of the Isoxazole Palladacycle I with Alkylboronic Acids[a]



Entry	$RB(OH)_2$	Product	Yield (%)[b]
1	 **4a**	 **5a**	65
2	 **4b**	 **5b**	65
3	 **4c**	 **5c**	55
4	 **4d**	 **5d**	45
5	 **4e**	 **5e**	trace[c]
6	 **4f**	 **5f**	trace[c]
7	 **4g**	 **5g**	trace[c]
8	 **4h**	 **5h**	40
9	 **4i**	 **5i**	30

[a] Conditions: $RB(OH)_2$ (2.5 equiv), *p*-benzoquinone (2 equiv), 1,4-dioxane, reflux for 2 h. [b] Isolated yield was determined by three runs. [c] Analyzed by GC-MS spectroscopy.

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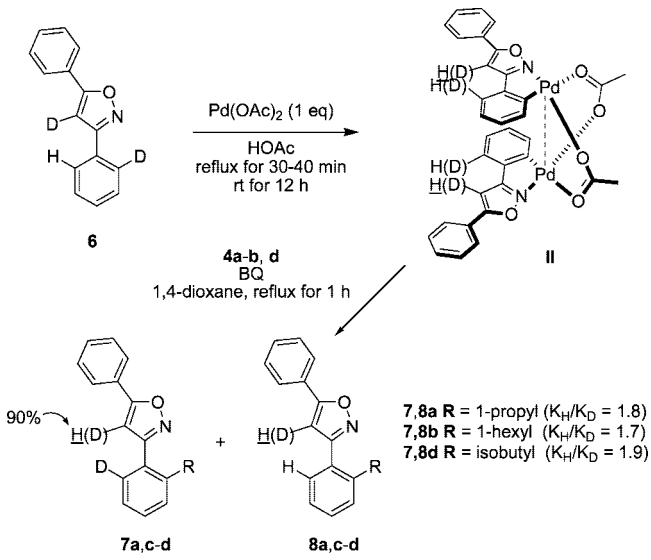
(11) The oxidant, *p*-benzoquione, was found to promote reductive elimination in metal-catalyzed coupling reactions; please see: (a) Albeniz, A. C.; Espinet, P.; Martin-Ruiz, B. *Chem. Eur. J.* **2001**, *7*, 2481–2489. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. (c) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971.

Scheme 1



respectively (Table 4). The failure to obtain the coupling adducts by isopropyl-, cyclopentyl-, and cyclohexylboronic acids could be due to the steric hindrance or poor stability of the secondary carbanion. However, cyclopropyl- and cyclobutylboronic acids, having significant sp^2 carbon character, would allow the reaction to take place smoothly.[12]

To determine the isotope effect of the C−H bond activation of 3,5-diphenylisoxazole (**1**) by palladium, dideuterio-3,5-diphenylisoxazole (**6**) was synthesized from 3-phenyl-5-(2-bromophenyl)isoxazole by treating it with *n*BuLi, followed by quenching with D_2O (see the Supporting Information).[13] Treatment of compound **6** with 1 equiv of palladium acetate in refluxing acetic acid gave the palladacycle **II**. The palladacycle **II** was then reacted with boronic acid **4a** to give the product as a mixture of **7a** and **8a**. The ratio of **7a** to **8a** was determined to be 1.8 using ^{1}H NMR analysis by measuring the integration of the numbers of hydrogen at the ortho position. Similar results were observed by the reaction of **II** with boronic acids **4b**,**d** (Scheme 1). This indicated that the value of K_H/K_D for the C−H bond activation averages 1.8.

We have also attempted to use a catalytic amount of palladium acetate to carry out the C−H activation and C−C bond formation of 3,5-diphenylisoxazole (**1**). Thus, compound **1** was treated with 2.5 equiv of (2-methoxyphenyl)boronic acid (**2b**) and 2.5 equiv of *p*-benzoquinone in the presence of 5 mol % of $Pd(OAc)_2$ in refluxing 1,4-dioxane; no desired product was obtained, and most of the starting materials were recovered.

In summary, we have developed a protocol for the arylation and alkylation of 3,5-diphenylisoxazole (**1**) through a stepwise C−H activation/C−C bond forming reaction pathway. Further mechanistic investigation and the development of catalytic reaction pathways are currently under investigation in our laboratory and will be reported in due course.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support.

Supporting Information Available: Text and figures giving experimental procedures and characterization data for all compounds and CIF files giving crystallographic data for compounds **I** and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800606C

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(13) Compound **6** was prepared according to the following reaction conditions: to a stirred solution of compound **12** (2.33 g, 7.75 mmol) in THF (50 mL) was added dropwise a solution of *n*-butyllithium (19.4 mL of 1.6 M in hexane, 31.0 mmol) at −40 °C. The resulting reaction mixture was stirred at this temperature for 1 h and quenched with D_2O (14 mL) to give the desired compound **6** (1.64 g, 7.35 mmol) in 95% yield.