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Highly Regioselective Palladium-Catalyzed Direct Arylation of Oxazole at C-2 or C-5 with Aryl Bromides, Chlorides, and Triflates

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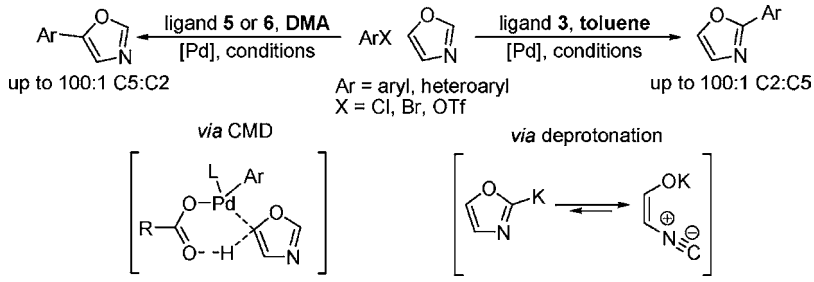
ABSTRACT



Complementary palladium-catalyzed methods for direct arylation of oxazole with high regioselectivity (>100:1) at both C-5 and C-2 have been developed for a wide range of aryl and heteroaryl bromides, chlorides, iodides, and triflates. C-5 arylation is preferred in polar solvents with phosphines 5 or 6, whereas C-2 arylation is preferred by nonpolar solvents and phosphine 3. This represents the first general method for C-5 selective arylation of oxazole and should see broad applicability in the synthesis of biologically active molecules. Additionally, potential mechanisms for these two competing arylation processes are proposed on the basis of mechanistic observations.

Oxazoles appear in numerous natural products and therapeutics, and these compounds exhibit biological activity over a wide range of targets.[1] For example, an oxazole ring is contained in the antibiotic ostreogrycin A (**1**)[2] as well as in the immunosuppressant merimepodib (VX-497)[3] (Figure 1). Despite the existence of numerous approaches to the construction and functionalization of oxazoles, there remains a need for more efficient methods that grant chemists facile access to this important class of compounds.

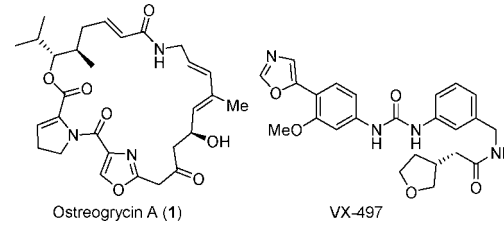


Figure 1. Examples of biologically active compounds containing oxazoles.

Recently, we disclosed methods for regioselective Suzuki couplings of dihaloazoles, including 2,4-diiodooxazole, with a variety of aryl and heteroaryl boronic acids.[4] To address certain

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(1) For review articles of oxazole-containing natural products, see: (a) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995–12042. (b) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584–605.

(2) Also known as virginiamycin M1: (a) Delpierre, G. R.; Eastwood, F. W.; Cream, G. E.; Kingston, D. G. I.; Sarin, P. S.; Todd, L.; Williams, D. H. *Tetrahedron Lett.* **1966**, *36*, 9–372. (b) Delpierre, G. R.; Eastwood, F. W.; Gream, G. E.; Kingston, D. G. I.; Sarin, P. S.; Todd, L.; Williams, D. H. *J. Chem. Soc. C* **1966**, *165*, 3–1669.

(3) Looker, A. R.; Littler, B. J.; Blythe, T. A.; Snoonian, J. R.; Ansell, G. K.; Jones, A. D.; Nyce, P.; Chen, M.; Neubert, B. J. *Org. Process Res. Dev.* **2008**, *12*, 666–673.

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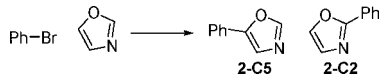
Table 1. Optimization of C-5- and C-2-Selective Direct Arylation of Oxazole with Bromobenzene



entry[a]	ligand	solvent	C5/C2 ratio
1	$Cy_3P–HBF_4$	toluene	1:4.5
2	t-$Bu_3P–HBF_4$	toluene	1:42
3	**3**	**toluene**	**1:100**
4[b]	**3**	toluene	1:100
5	**4**	toluene	1:23
6	**4**	DEE	1:1.6
7	**4**	DMA	21:1
8	**5**	**DMA**	**47:1**
9[b,c]	**5**	DMA	7.3:1
10[b]	**6**	**DMA**	**15:1**

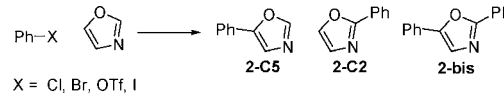
[a] Conditions: 1.5 equiv of oxazole, 0.1 M PhBr, 10% $Pd(OAc)_2$, 20% ligand, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. DEE = 1,2-diethoxyethane. [b] Used PhCl instead of PhBr. [c] <5% conversion.

limitations to this method, we investigated direct arylation of oxazole, which provides several advantages. Oxazole is readily available and inexpensive compared to dihaloazoles. Additionally, direct arylation allows the installation of a vast array of aryl and heteroaryl halides, which are far more numerous than boronic acid coupling partners. Most importantly, direct arylation would be expected to couple at both C-2 and C-5, which would be complementary to the 2,4-substitution pattern accessible with our Suzuki chemistry.

Among all of the direct arylations of oxazoles, there is but one report of selectivity at C-5 over C-2, and this was limited to a chloropyrazine substrate.[5,6] While C-5 and even C-4 can be arylated if C-2 is blocked, there is currently no method to couple selectively at either of these positions if C-2 is not substituted, due to preferential C-2 arylation.[7−10] This communication describes our efforts to develop general complementary conditions for direct arylation at C-5 of oxazole as well as at C-2 with aryl electrophiles, including inexpensive and readily available aryl chlorides.

We initiated this study by examining the direct arylation of oxazole using highly active ligands known to undergo facile oxidative addition into aryl bromides, chlorides, and triflates and looked for C-5 or C-2 selectivity. Arylation of oxazole with bromobenzene was mediated by Pd and Cy_3P to give moderate C-2 selectivity (Table 2, entry 1). Changing the ligand to t-Bu_3P still led to preferential arylation at C-2, but with higher selectivity (entry 2). Using RuPhos (**3**) (Figure 2) as the ligand, selectivities of >100:1 could be obtained for C-2 arylation (entry 3). These same conditions could be applied to arylation with chlorobenzene while still maintaining this high level of C-2 selectivity (entry 4). While the reaction with X-Phos (**4**) was C-2 selective in toluene (entry 5), we were pleasantly surprised to find that the regiochemical outcome switched to unselective in 1,2-diethoxyethane (DEE) (entry 6) and to highly C-5 selective in DMA (entry 7).[11] Subsequent optimization gave 47:1 C-5/C-2 selectivity using 3,4,5,6-tetramethyl-t-Bu-X-Phos (**5**) in DMA (entry 8). Disappointingly, **5** gave only moderate

Table 2. Direct Arylation of Oxazole with Phenyl Electrophiles at C-5 and C-2



entry	PhX (X =)	method[a]	major product	C5:C2	mono/bis	yield[b] (%)
1	Cl	A	**2-C5**	15:1	12:1	56
2	Br	B	**2-C5**	58:1	30:1	83
3	OTf	B	**2-C5**	31:1	49:1	64
4	I	B	**2-C5**	29:1	43:1	73
5	Cl	C	**2-C2**	1:100	25:1	77
6	Br	C	**2-C2**	1:100	18:1	75
7	OTf	C	**2-C2**	1:27	24:1	76
8[c]	I	C	**2-C2**	1:14	17:1	82

[a] Method A: 2.0 equiv of oxazole, 0.2 M ArX in DMA, 5% $Pd(OAc)_2$, 10% ligand **6**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. Method B: 2.0 equiv of oxazole, 0.2 M ArX in DMA, 5% $Pd(OAc)_2$, 10% ligand **5**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. Method C: 2.0 equiv of oxazole, 0.2 M ArX in toluene, 5% $Pd(OAc)_2$, 10% ligand **3**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. [b] Isolated yield of single isomer. [c] Used 3 equiv of Cs_2CO_3 instead of K_2CO_3.

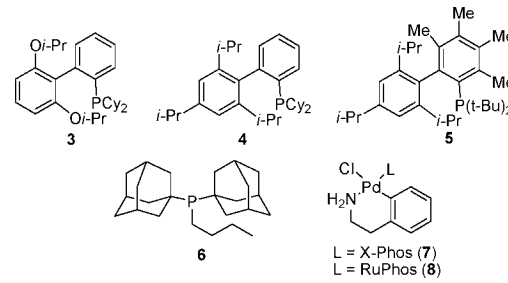


Figure 2. Ligands and precatalysts employed in this study.

(4) Strotman, N. A.; Chobanian, H. R.; He, J.; Guo, Y.; Dormer, P. G.; Jones, C. M.; Steves, J. E. *J. Org. Chem.* **2010**, *75*, 1733–1739.

(5) For recent examples of benzoxazole arylation with Cu, Ni, and Pd, respectively, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740. (c) Ackerman, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724–726.

(6) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, K. T.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257–272.

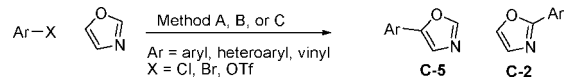
(7) C-5 arylation when C-2 is substituted: (a) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, *124*, 1–1243. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.

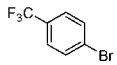
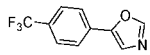
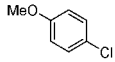
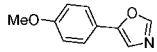
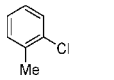
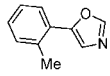
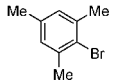
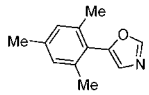
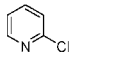
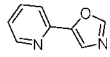
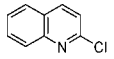
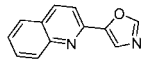
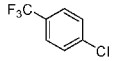
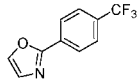
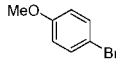
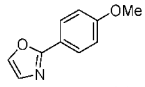
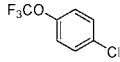
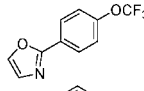
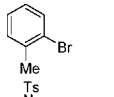
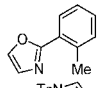
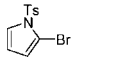
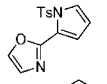
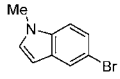
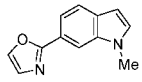
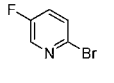
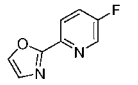
(8) C-4 arylation when both C-2 and C-5 are substituted: Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834.

(9) There are several examples of selective C-2 arylation of oxazoles even when C-5 is not substituted, for example: (a) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717–2720. (b) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383–7386. (c) Derridj, F.; Djebbar, S.; Benali-Baitich, O.; Doucet, H. *J. Organomet. Chem.* **2008**, *693*, 135–144. (d) Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005**, *46*, 8573–8577.

(10) For a general review of direct arylation including C-2/C-5 selective arylation of thiazole and *N*-alkylimidazoles, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310.

Table 3. Direct Arylation of Oxazole with Various Aryl and Heteroaryl Halides



entry	PhX	method[a]	major product	C5:C2	yield (%)[b]
1		B		100:1	85
2		A		12:1	74
3		A		100:1	79
4		A		50:1	82
5		A		12:1	58
6		A		17:1	69
7		C		1:100	69
8		C		1:100	74
9		C		1:100	77
10		C		1:100	78
11[c]		C		1:100	74
12		C		1:88	78
13[d]		C		1:26	34

[a] Method A: 2.0 equiv of oxazole, 0.2 M ArX in DMA, 5% $Pd(OAc)_2$, 10% ligand **6**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. Method B: 2.0 equiv of oxazole, 0.2 M ArX in DMA, 5% $Pd(OAc)_2$, 10% ligand **5**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. Method C: 2.0 equiv of oxazole, 0.2 M ArX in toluene, 5% $Pd(OAc)_2$, 10% ligand **3**, 3 equiv of K_2CO_3, 0.4 equiv of pivalic acid, 110 °C, 16 h. [b] Isolated yield of single isomer. [c] Required 10% Pd and 20% ligand. [d] Used 3 equiv of Cs_2CO_3 instead of K_2CO_3.

C-5 selectivity for arylation with chlorobenzene (entry 9), although high selectivity could again be obtained by employing CataCXium A (**6**) (entry 10).[12] These trends where more polar solvents led to greater C-5 arylation and where the use of aryl chlorides instead of bromides led to greater C-2 arylation were observed across all of the ligands we investigated.

(11) For related solvent effects with a 3-carboalkoxy furan and thiophene, see: Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301–304.

(12) Except for CataCXium A, every other ligand that we examined showed much lower C-5/C-2 selectivity when arylated with chlorobenzene rather than with bromobenzene.

When we applied these direct arylation conditions to other phenyl electrophiles, we were pleased to find that phenyl triflate and iodobenzene reacted under the same conditions as bromobenzene to give both C-5 (method B (**5** in DMA)) and C-2 (method C (**3** in toluene)) products with high selectivity (Table 2, entries 3, 4, 7, and 8).[13,14] Arylation with chlorobenzene (method A (**6** in DMA) or C) and bromobenzene (method B or C) could be carried out with high C-5 or C-2 selectivity and high isolated yields (Table 2, entries 1, 2, 5, and 6).

With these three sets of optimized conditions (methods A−C) in hand, we began to look at direct arylation of oxazole with a variety of aryl and heteroaryl chlorides and bromides (Table 3). It was quickly found that method B was sufficiently reactive with bromobenzene or electron-deficient aryl bromides but that method A was superior for electron-rich or sterically hindered aryl bromides.[15] C-5 arylation of oxazole with aryl bromides, chlorides, and several heteroaryl chlorides was accomplished with high selectivity and in good yield using methods A or B (entries 1−6).

Method C was effective for the regioselective arylation of oxazole at C-2 for a variety of aryl and heteroaryl bromides and chlorides in high selectivities and good yields (entries 7−12). Although the C-2 selectivity was low for 2-bromo-5-fluoropyridine (and other 2-halopyridines) under our standard conditions (2.5:1 C-2/C-5), changing the base to Cs_2CO_3 led to high C-2 selectivity (entry 13).

Over the course of this study, we made several observations that suggest possible mechanisms for these competing arylation processes. Our initial assumption had been that both C-5 arylation and C-2 arylation occurred through concerted metalation-deprotonation (CMD) pathways, as proposed by Fagnou for direct arylation of other heterocycles (Figure 3,

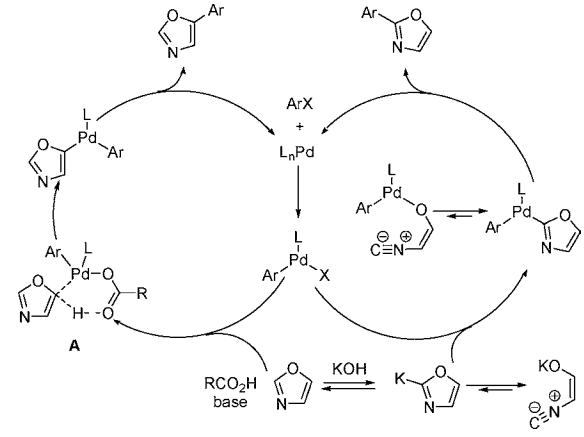


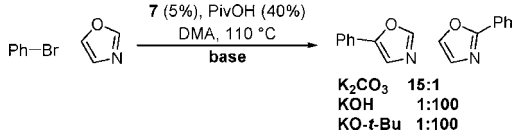
Figure 3. Proposed catalytic cycles for direct oxazole arylation through CMD and deprotonation pathways.

structure A).[10,16] However, the dependence of the selectivity on the nature of the base (Cs_2CO_3 vs K_2CO_3) and aryl halide (PhCl vs PhBr) seemed inconsistent with solely a CMD pathway in which neither of these factors should be involved in the selectivity-determining step.

In several head-to-head experiments in DMA with a variety of catalysts, we demonstrated that the C-5/C-2 ratio increased with higher concentrations of PivOH. This supported the hypothesis that C-5 arylation was proceeding through a CMD pathway, which is thought to require the intermediacy of a Pd−carboxylate complex (Figure 3, structure A), and that C-2 arylation was occurring through a different pathway. The involvement of a CMD pathway for arylation at C-5 is consistent with experimental[10] and computational[17] results for thiazole and imidazoles. However, even with no PivOH, C-5 arylation, while considerably slower, was still dominant in some cases. We realized that our results were confounded by the use of $Pd(OAc)_2$, which could also facilitate a CMD pathway. Moreover, even the carbonate bases that we were employing could theoretically coordinate to Pd and mediate a CMD pathway.

Using X-Phos and RuPhos precatalysts (**7** and **8**, Figure 2), we examined direct arylation of oxazole with bromobenzene using a variety of bases, with or without PivOH. We were surprised to find that with strong bases like KOH or KO-*t*-Bu, reactions gave >100:1 C-2/C-5 selectivity regardless of the catalyst, solvent, or presence of PivOH. The 100:1 ratios favoring C-2 obtained with KOH or KO-*t*-Bu and **7** in DMA are in stark contrast to the 15:1 ratio favoring C-5 obtained under otherwise identical conditions with K_2CO_3 as the base (Scheme 1). The use of these stronger bases resulted in a 1500 fold increase in the relative rate of C-2 arylation vs C-5 arylation.

Scheme 1. Effect of Base on Selectivity for Direct Arylation of Oxazole



Given the reasonable acidity of the C-2 proton of oxazole,[17] it seems plausible that reaction at this center may occur through formal deprotonation.[18] Either the potassium oxazole species or the dominant ring-opened enolate tautomer[19] could react with an ArPdX species. We propose the following catalytic cycle to account for the differences in regioselectivity that we observed with different bases,[20] with different halide leaving groups, and with or without PivOH (Figure 3). Both catalytic cycles begin with oxidative addition of the aryl halide to a Pd(0) complex.[21] In the presence of PivOH and weak bases, the ArPdX species would form an ArPd(OPiv) intermediate which could undergo CMD with oxazole at C-5. Reductive elimination of the ArPd(5-oxazoyl) intermediate would lead to the C-5 arylated product and regenerate Pd(0). Alternatively, when strong base is employed, a potassium oxazole species (or ring-opened tautomer) may directly attack ArPdX, forming an ArPd(2-oxazole) intermediate.[22] After reductive elimination, this would regenerate Pd(0) and form the C-2-arylated product.

We believe that the solvent effects that we observe may be related to greater stabilization of a polar CMD transtition state by DMA than toluene, leading to greater C-5 selectivity. Additionally, the rate at which poorly nucleophilic KOPiv displaces halide from the ArPdX intermediate should be substantially slower in less polar solvents, allowing for a more C-2 selective reaction. Moreover, the higher C-2 selectivity (lower C-5 selectivity) that we observe with PhCl vs PhBr could also be explained by slower displacement of the chloride from ArPdCl by KOPiv, allowing the deprotonation pathway to dominate.

In conclusion, we have developed general conditions for highly selective direct arylation of oxazole at both C-5 and C-2. These methods are applicable to a variety of aryl and heteroaryl electrophiles, including bromides, chlorides, and triflates. Additionally, this represents the first general method for C-5 selective direct arylation of oxazole, which is a common structural motif in natural products and pharmaceuticals. Moreover, these methods should be highly valuable to pharmaceutical chemists wishing to install one aryl group at either C2 or C5 and then build a library of analogues functionalized at the other position. Finally, we have proposed a catalytic cycle that rationalizes the complementary selectivities that we obtained under different reaction conditions.

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Supporting Information Available: Experimental details, characterization data, and NMR spectra of all coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Replacing K_2CO_3 with Cs_2CO_3 for arylation with PhI using C-5-selective method B led to low regioselectivity (1.5:1 C2/C5). On the other hand, C-2-selective method C gave poor reactivity and selectivity (28% conversion, 1.8:1 C2/C5) with PhI using K_2CO_3, but the rate and regioselectivity were improved by switching to Cs_2CO_3.

(14) Phenyl tosylate was very poorly reactive.

(15) 2-Bromotoluene, 2-bromomesitylene, and 4-bromoanisole all showed incomplete conversion with method B but full conversion with method A.

(16) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(17) H/D exchange of the C-2 proton of oxazole in 1.43 M NaOMe in MeOD proceeded at room temperature with a $t_{1/2}$ of 17 min: Brown, D. J.; Ghosh, P. B. *J. Chem. Soc. B* **1969**, 270–276.

(18) The formation of Cu−2-thiazoyl and Cu−2-*N*-arylimidazoyl intermediates has been implicated in the C-2-selective direct arylation of thiazole and imidazoles: (a) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693. (b) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700.

(19) It has been shown through trapping experiments and spectroscopically that 2-lithiooxazoles and 2-oxazole magnesiates exist predominantly in the ring-opened form: (a) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449–452. (b) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058–3063. (c) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, *70*, 5190–5196.

(20) Although Cs_2CO_3 is not an appreciably stronger base than K_2CO_3, it has a higher solubility in toluene, making the base concentration much higher when employing Cs_2CO_3 instead of K_2CO_3.

(21) It is worth noting that Pd(0) is probably generated from $Pd(OAc)_2$ through formation of a $Pd(oxazole)_2$ intermediate followed by reductive elimination. In reactions that are C-5 selective, we have isolated 5,5′-bis-oxazole.

(22) Formation of an ArPd(2-oxazole) intermediate may also involve coordination of oxazole to Pd through N or O and subsequent deprotonation.