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Catalyst-Controlled Regioselective Suzuki Couplings at Both Positions of Dihaloimidazoles, Dihalooxazoles, and Dihalothiazoles

Neil A. Strotman,*[,†] Harry R. Chobanian,*[,‡] Jiafang He,[‡] Yan Guo,[‡] Peter G. Dormer,[†] Christina M. Jones,[†] and Janelle E. Steves[‡]

[†]*Department of Process Chemistry and* [‡]*Department of Basic Research (Medicinal Chemistry), Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065*

neil_strotman@merck.com: harry_chobanian@merck.com

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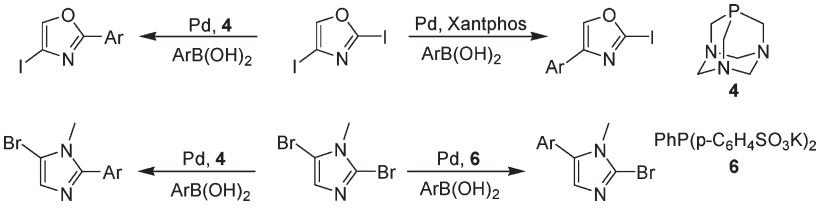

Various dihaloazoles can be monoarylated at a single C−X bond with high selectivity via Suzuki coupling. By changing the palladium catalyst employed, the selectivity can be switched for some dihaloazoles, allowing for Suzuki coupling at the other, traditionally less reactive C−X bond. These conditions are applicable to coupling of a wide variety of aryl-, heteroaryl-, cyclopropyl-, and vinylboronic acids with high selectivities and enable the rapid construction of diverse arrays of diarylazoles in a modular fashion.

Introduction

Oxazoles, imidazoles, and thiazoles are components of numerous biologically active natural products as well as pharmaceutical molecules (Figure 1).[1−3] While diarylazoles are common structural motifs in both natural products[4] and drug candidates,[5] they are not straightforward to synthesize in a modular fashion. For example, diaryloxazoles are generally prepared through the Fischer oxazole synthesis[6] or Robinson−Gabriel synthesis,[7] where the oxazole ring is constructed in the process. An elegant example of the preparation of 2-aryl-substituted-4-trifloyl oxazoles was showcased by Panek using a modified Hantzsch oxazole synthesis that was both high-yielding and efficient.[8] Greaney further demonstrated the utility of these 2-aryl-substituted-4-trifloyl oxazoles by performing Suzuki couplings to generate 2,4-diaryloxazoles.[9] The major drawback of this method is the lack of ability to vary the C-2 position without having to prepare each triflate independently.[10] More recently, Greaney made use of 2,4-diiodooxazole as a bifunctional linchpin to prepare linked oxazoles through sequential lithium−halogen exchange, protection, and direct arylation.[11] Direct C−H bond arylation of oxazole proceeds in a stepwise manner based on pK_a values (C2 > C5 > C4) making selective C4 arylation challenging.[12] We decided that 2,4-diiodooxazole and other dihaloazoles were ripe for attempting selective Suzuki couplings at either C−X bond.[13]

(1) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381.
(2) Wiglenda, T; Gust, R. *J. Med. Chem.* **2007**, *50*, 1475.
(3) Reader, J. C.; Ellard, J. M.; Boffey, H.; Taylor, S.; Carr, A. D.; Cherry, M.; Wilson, M.; Owoare, R. B. *PCT Int. Appl.* **2008**, WO 2008139161.
(4) Smith, A. B.; Liu, Z; Hogan, A. L.; Dalisay, D. S.; Molinski, T. F. *Org. Lett.* **2009**, *11*, 3766.
(5) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644.
(6) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1949**, 1028.
(7) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D.; Brenzovich, W. E.; Giuseppone, N.; O′Brate, A.; Giannakakou, P. *J. Am. Chem. Soc.* **2004**, *126*, 12897.
(8) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2485–2488.
(9) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2006**, *8*, 2495.
(10) For an earlier methodology involving selective iodination of oxazoles at C4 via lithiation see: Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011.
(11) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717.
(12) (a) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241–1243. (b) Hichiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740.
(13) Selective Suzuki couplings of 2,3-dibromo-5-formylpyrroles and dibromopyridines have been reported: (a) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537–1539. (b) Handy, S. T.; Wilson, T.; Muth, A. *J. Org. Chem.* **2007**, *72*, 8496–8500.

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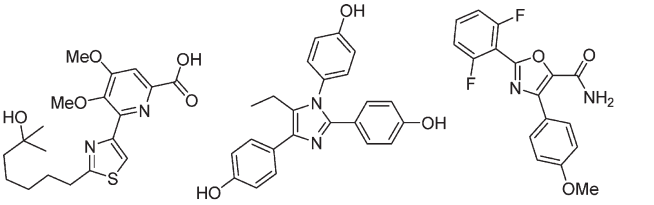
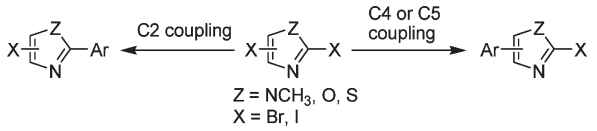


FIGURE 1. Pharmaceutically relevant azoles.

SCHEME 1. Selective Arylation of Dihaloazoles



Here we describe a general method for highly selective monoarylation of several dihaloazoles.[14] Our hypothesis was that these Suzuki couplings would show selectivity for arylation at C2, allowing for further functionalization at the typically less reactive C4 or C5 positions (Scheme 1).[15,16] This modular approach would allow for rapid introduction of diversity into oxazole, imidazole, and thiazole structures, which should be highly valuable for medicinal chemistry structure activity relationship (SAR) studies. Additionally, we describe catalyst systems capable of selective arylation at the traditionally *less reactive* C4 or C5 positions of azoles, over the C2 position, giving greater flexibility for SAR.

Results

Inspired by the work of Greaney et al, we initially investigated the Suzuki coupling of 2,4-diiodooxazole[11] with phenylboronic acid in the hopes of finding conditions for regioselective coupling. We were surprised to find that the preferred site of reaction using palladium and PPh_3 was C4 and not C2 as expected.[17] In addition to showing ^{13}C NMR shifts consistent with C4 phenylation, a 1D NOESY experiment on **1-C4** showed a 0.2% NOE from the *o*-phenyl protons to the proton at C5 of the oxazole (Figure 2). No NOE was observed in isomer **1-C2**.

Disappointingly, almost all ligands tested offered poor selectivity, giving large amounts of the bis-phenylation product (**1-bis**) and only a moderate C4:C2 preference as determined by LC-MS.[18] For example, three common, structurally diverse phosphine ligands, PPh_3, X-Phos, and DPPF, all gave almost identical levels of C4:C2 selectivity

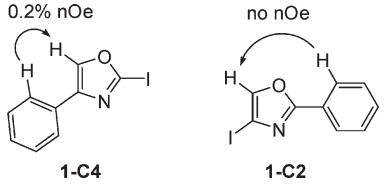
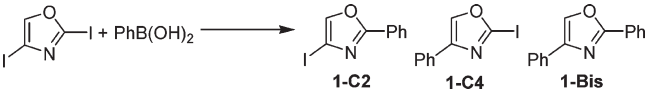


FIGURE 2. Nuclear Overhauser effects observed with C4 arylation of 2,4-diiodooxazole.

TABLE 1. Effects of Ligand on Phenylation of 2,4-Diiodooxazole



entry[a]	ligand	C4:C2 phenylation[b]	mono:bis phenylation[b]
1	PPh_3	1.9:1	1.3:1
2	X-Phos	1.7:1	0.5:1
3	DPPF	1.9:1	2.8:1
4	**2**	**13:1**	**7.3:1**
5	tBu_3P-HBF_4	0.47:1	1.7:1
6	**3**	0.59:1	2.3:1
7	**4**	1.0:1	4.5:1
8[c]	**4**	**0.077:1**	**14:1**

[a]All reactions were run with 5% $Pd(OAc)_2$, 1:1 ligand/Pd ratio for bidentate ligands and 2:1 ligand/Pd ratio for monodentate ligands, 3 equiv of K_3PO_4, with 1.1 equiv of phenyl boronic acid, 0.2 M 2,4-diiodooxazole in THF, at 60 °C for 16 h. [b]Ratio determined from the crude reaction mixture by LC-MS prior to purification. [c]ACN was used instead of THF.

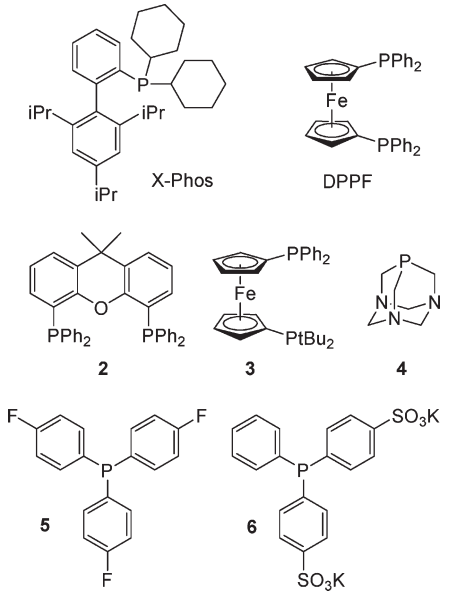


FIGURE 3. A selection of phosphine ligands employed in this study.

(Table 1, entries 1−3). However, we found that Xantphos (**2**) (Figure 3) was uniquely capable of mediating highly selective coupling at C4 to give **1-C4**, as well as demonstrating high selectivity for monophenylation (Table 1, entry 4).

We found it particularly surprising that a small number of ligands gave the opposite regiochemistry from PPh_3, showing a preference for coupling at C2 over C4 to give **1-C2** (Table 1, entries 5 and 6). An exhaustive survey of our

(14) For a review of the extensive work on cross-coupling reactions of monohaloazoles see: Schnurch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283–3307.

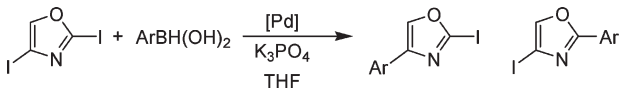
(15) The preferred site of lithium halogen exchange in 2,4-diiodooxazole[11] and 2,4-dibromothiazole is C2: Martin, T.; Laguerre, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2009**, *11*, 3690–3693.

(16) The preferred site of S_NAr on 2,4-dibromothiazoles with thiols is C2: Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K.-H.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3515–3520.

(17) Handy's method for predicting the site of coupling in dihaloheteroaromatics using the ^1H NMR shifts of the parent non-halogenated compound incorrectly predicts reaction at C2 of 2,4-diiodooxazole and 2,5-dibromo-1-methylimidazole: Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299–301.

(18) All LC-MS ratios were estimated by using the LC area percentage at either 210 or 254 nm.

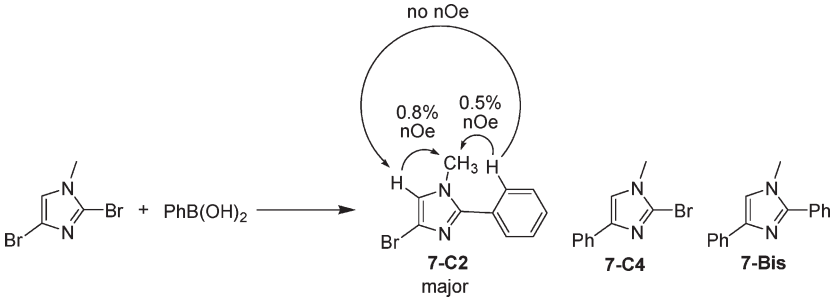
TABLE 2. Regioselective Suzuki Cross-Coupling of 2,4-Diiodooxazole with Various Arylboronic Acids



Entry[a]	dihaloazole	major product	ligand	Pd (mol%), temp (°C), time (hr)	Isolated yield of major (%)	major:minor regioisomer ratio[b]	mono:bis ratio[b]
1			**4**	5, 80, 5	55	14:1	14:1
2[c]			**2**	2.5, 60, 8	64	11:1	8.4:1
3[d]			**4**	10, 80, 5	53	22:1	26:1
4			**2**	5, 60, 6	54	11:1	5.7:1
5			**4**	5, 80, 3	60	6.7:1	25:1
6			**2**	2.5, 60, 5	44	13:1	5.1:1
7[e]			**2**	5, 60, 16	62	3.2:1	4.5:1
8			**2**	5, 60, 16	51	8.6:1	8.5:1
9[f,g]			**2**	5, 60, 16	47	5.8:1	13:1
10[h]			**2**	5, 60, 16	54	4.4:1	3.5:1
11[i]			**2**	5, 60, 16	58	11:1	3.9:1

[a]All reactions were run on a 1.0 mmol scale, ligand/Pd ratios of 2:1 for monodentate ligands and 1:1 for bidentate ligands, 3 equiv of K_3PO_4, and 1.1−1.3 equiv of phenyl boronic acid, with 0.2 M [dihaloazole] in THF. [b]Ratio determined from the crude reaction mixture by LC-MS prior to purification. [c]15% 4-iodooxazole present. [d]22% starting material recovered. [e]5:1 mono:bis. [f]27% starting material recovered. [g]Pinacolatoboronate ester with 15 vol % water in THF was used. [h]6:1 C4:C2 ratio. [i]5.2:1 C4:C2 ratio.

SCHEME 2. Selective Phenylation of 2,4-Dibromo-1-methylimidazole

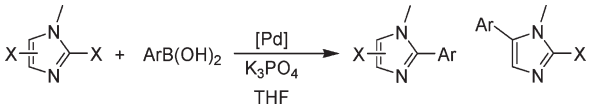


collection of ~200 achiral phosphine ligands revealed that 1,3,5-triaza-7-phosphaadamantane (**4**), when reacted in acetonitrile, was capable of high selectivity for the C2 position, and showed high selectivity toward monophenylation (Table 1, entries 7 and 8).

With these two sets of complementary conditions in hand (ligands **2** and **4**), we began to investigate the scope of this Suzuki coupling reaction (Table 2). We found that 2,4-diiodooxazole could be cross-coupled selectively at either C4 or C2 with a variety of electron-rich or electron-poor arylboronic acids (Table 2, entries 1−8).[19] In addition, these conditions were applicable to vinylboronic acids and heteroarylboronic acids such as 2-(*N*-Boc-pyrrole)- and 3-thienylboronic acid (entries 9−11). In some cases the isolated yields were low, due to poor mono:bis or poor isomer ratios. For example, entry 4 shows 54% isolated yield out of only 78%

(19) In the absence of added base, phenylzinc bromide could be coupled with 2,4-diiodoxazole with use of ligand **2** and under otherwise identical conditions, giving similar selectivities to those obtained with phenylboronic acid.

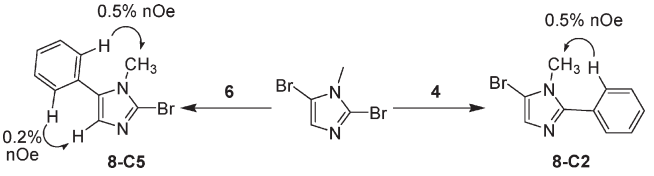
TABLE 3. Regioselective Suzuki Cross-Coupling of Dihaloimidazoles with Various Arylboronic Acids



Entry[a]	dihaloazole	major product	ligand	Pd (mol%), temp (°C), time (hr)	Isolated yield of major (%)	major:minor regioisomer ratio[b]	mono:bis ratio[b]
1			**5**	5, 80, 16	87	69:1	18:1
2			**5**	5, 80, 16	73	53:1	24:1
3			**5**	5, 80, 16	76	84:1	14:1
4[c]			**5**	5, 80, 16	42	31:1	70:1
5			**5**	5, 80, 16	65	25:1	28:1
6			**5**	5, 80, 16	98	18:1	>100:1
7[d]			**5**	20, 80, 16	39	36:1	49:1
8			**4**	10, 80, 16	64	11:1	12:1
9[e]			**6**	5, 80, 16	45	16:1	4.2:1
10			**4**	10, 80, 16	47	6.1:1	24:1
11[f]			**6**	5, 80, 16	52	9.5:1	6.9:1
12			**4**	10, 80, 16	75	42:1	9.1:1
13			**6**	5, 80, 16	51	7.1:1	4.9:1
14			**6**	5, 80, 16	78	39:1	37:1
15			**2**	5, 60, 16	48	16:1	19:1

[a]All reactions were run on a 1.0 mmol scale, ligand/Pd ratios of 2:1 for monodentate ligands and 1:1 for bidentate ligands, 3 equiv of K_3PO_4, and 1.1 equiv of phenyl boronic acid, with 0.2 M [dihaloazole] in THF. [b]Ratio determined from the crude reaction mixture by LC-MS prior to purification. [c]42% starting material recovered. [d]Employed 10% Pd_2dba_3 instead of $Pd(OAc)_2$ and 1.4 equiv of boronic acid. 30% starting material recovered. [e]29% starting material recovered. [f]19% starting material recovered.

SCHEME 3. Selective Phenylation of 2,5-Dibromo-1-methylimidazole

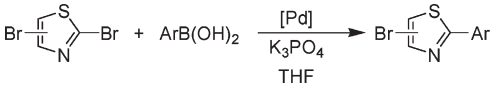


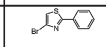
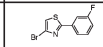
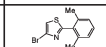
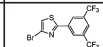
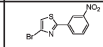
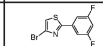
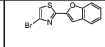
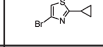
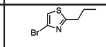
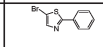
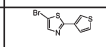
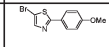
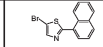
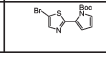
possible yield based on the mono:bis and isomer ratios, and assuming full conversion.[20] Unfortunately, pyridyl, pyrimidinyl, and quinolyl boronic acids showed no more than a trace (< 3%) of product with these catalysts due to negligible conversion. At elevated temperatures or longer reaction times necessary to cross couple 3-pyridyl boronic acids with **2** or **4**, other processes such as dehalogenation and homocoupling became competitive.

We next attempted to apply these conditions developed for 2,4-diiodooxazole to other commercially available dihaloazoles. We expected that 2,4-dibromo-1-methylimidazole would have similar ligand-dependent reactivity to 2,4-diiodoxazole. However, we were surprised to find that the major site of reaction for ligand **4**, as well as for **2**, was C2 to give **7-C2** almost exclusively (Scheme 2). Further experiments revealed that no ligand in our collection provided any appreciable reaction at C4, which was the more reactive position observed for 2,4-diiodoxazole. While ligand **4**, and surprisingly **2**, were among the best in terms of mono:bis ratio (~6:1), one ligand (tri(4-fluorophenyl)phosphine (**5**), Figure 3) was found to yield superior results of 18:1 mono:bis. Again, 1D NOESY experiments were employed to

(20) The maximum yield in this reaction is equal to (major isomer/(major isomer + minor isomer)) multiplied by (mono/(mono + bis) = (5.7/6.7) × (11/12) = 0.78. This yield can be further reduced by incomplete conversion of dihaloazole, caused by consumption of $ArB(OH)_2$ to form the bis compound.

TABLE 4. Regioselective Suzuki Cross-Coupling of Dibromothiazoles with Various Boronic Acids



entry[a]	dihaloazole	major product	ligand	Pd (mol%), temp (°C), time (hr)	Isolated yield of major (%)	major:minor regioisomer ratio[b]	mono:bis ratio[b]
1			**2**	2.5, 80, 16	73	>100:1	20:1
2			**2**	2.5, 80, 16	72	>100:1	37:1
3			**2**	2.5, 80, 16	60	>100:1	28:1
4			**2**	2.5, 80, 16	82	>100:1	>100:1
5			**2**	2.5, 80, 16	86	>100:1	84:1
6			**2**	2.5, 80, 16	62	>100:1	23:1
7			**2**	2.5, 80, 16	71	>100:1	>100:1
8			**2**	5, 80, 16	83	>100:1	>100:1
9[c]			**2**	5, 80, 16	89	>100:1	>100:1
10			**2**	2.5, 80, 16	59	>100:1	5.4:1
11			**2**	2.5, 80, 16	65	>100:1	18:1
12			**2**	2.5, 80, 16	74	>100:1	10:1
13			**2**	2.5, 80, 16	68	>100:1	8.5:1
14			**2**	2.5, 80, 16	76	>100:1	30:1

[a]All reactions were run on a 0.5−2.0 mmol scale, with ligand/Pd ratio 1:1, 3 equiv of K_3PO_4, and 1.1 equiv of phenyl boronic acid, with 0.2 M dihaloazole in THF. [b]Ratio determined from the crude reaction mixture by LC-MS prior to purification. [c]1.1 equiv of *n*-propylzinc bromide and no base was used.

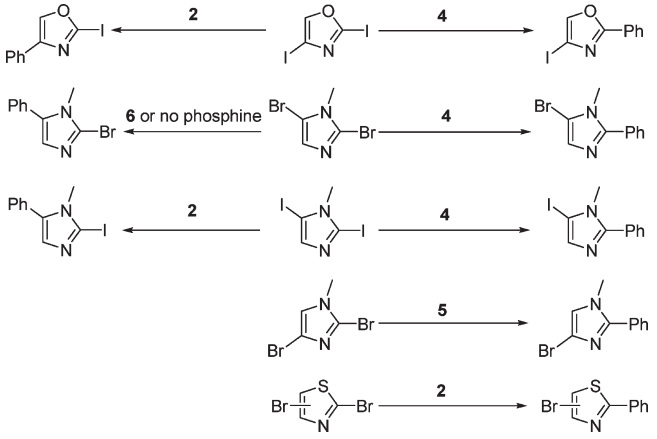


FIGURE 4. Ligand-Dependent Reactivity of Dihaloazoles toward Pd-Catalyzed Suzuki Coupling.

establish the regiochemistry of the major product as **7-C2** (Scheme 2).

We next investigated how 2,5-dibromo-1-methylimidazole compares to the 2,4-isomer and observed dichotomous behavior. The 2,5-dibromo-1-methylimidazole showed reactivity analogous to 2,4-diiodooxazole, rather than to 2,4-dibromo-1-methylimidazole. C2 was quite unreactive in 2,5-dibromo-1-methylthiazole, and the only ligand that promoted selective cross-coupling at this position was **4** (33:1 C2/C5), also the most selective ligand for coupling at C2 of 2,4-diiodooxazole (Scheme 3). Position C5, on the other hand, was far more reactive and was favored by every ligand in our collection other than **4**. While **2** gave only low selectivity for C5 of 2,5-dibromo-1-methylimidazole (1.9:1 C5/C2), it was found that several ligands[21] displayed superior performance, with bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt (**6**) giving the best balance of reactivity, C2:C5 selectivity (23:1), and mono: bis selectivity (4.3:1). The assignments of 5-bromo-2-phenyl-1-methylimidazole (**8-C2**) and 2-bromo-5-phenyl-1-methylimidazole (**8-C5**), resulting from cross coupling with ligands

(21) Several diverse ligands showed high C5 selectivity for this particular dibromide including 3,4,5,6-tetramethyl-*t*Bu-XPhos, dppb monoxide, 1-diisopropylphoshino-2-dimethylaminoindene, and SiPr-HBF_4. It was discovered in subsequent experiments that phosphine-free palladium gave comparable results to palladium with **6**.

4 and **6**, respectively, were established by 1D NOESY experiments (Scheme 3).

We investigated the scope of selective Suzuki couplings of dibromo-1-methylimidazoles with a variety of boronic acids. 2,4-Dibromo-1-methylimidazole could be coupled with electron-rich or electron-poor arylboronic acids, as well as with heteroaryl- and vinylboronic acids with high yields and regioselectivites (Table 3, entries 1−6). It could also be coupled with 3-quinolineboronic acid in moderate yield by switching to $Pd_2(dba)_3$ from $Pd(OAc)_2$ and increasing the catalyst loading (entry 7). By employing either ligand **4** or **6**, 2,5-dibromo-1-methylimidazole could be selectively coupled at either C2 or C5 with electron-rich or electron-poor arylboronic acids (Table 3, entries 8−14).

We compared 2,5-diiodo-1-methylimidazole to the corresponding dibromide and observed very similar reactivity. As with 2,5-dibromo-1-methylimidazole, C5 was the major site of reaction of 2,5-diiodooxazole (as confirmed by 1D NOESY), although ligand **6** gave slow conversion and poor C5:C2 and mono:bis selectivities. However, faster conversion and high selectivities were obtained by employing ligand **2** (Table 3, entry 15). Additionally, ligand **4** provided highly selective cross-coupling (21:1 C2:C4, >100:1 mono/bis) at C2 of 2,5-diiodo-1-methylimidazole, as it had with the 2,5-dibromo analogue.[22]

Finally, we studied selective Suzuki couplings of dibromothiazoles.[23] Ligand **2** proved very reactive and highly selective for C2 of 2,4- and 2,5-dibromothiazoles, requiring only 2.5% Pd and never producing any detectable minor isomer. This is in stark contrast to 2,4-diiodooxazole and 2,5-dibromo-1-methylimidazole, where **2** showed minimal reaction at C2, and high selectivity at C4 or C5, respectively. The selectivity of the dibromothiazoles mirrored that of 2,4-dibromo-1-methylimidazole, where C2 was the more reactive position and no ligand was identified to give selectivity for the less reactive position. ^{1}H NMR spectra of 4-bromo-2-phenylthiazole and 5-bromo-2-phenylthiazole were matched to literature spectra, confirming the assigned regiochemistry of these compounds.[24,25]

These conditions were used to cross-couple, with high yields, a wide variety of electron-rich, electron-poor, and sterically hindered arylboronic acids. This same set of conditions also proved useful for cross-coupling of heteroarylboronic acids and cyclopropylboronic acid (Table 4). Additionally, when K_3PO_4 was omitted, these conditions were suitable for a Negishi coupling of 1-propylzinc bromide with 2,4-dibromothiazole, giving the monoalkylated product in very high yield (entry 9).

Discussion

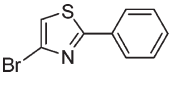
The dependence of the relative rates of C2 vs C4 or C5 coupling on the identity of the ligand is highly complex. In general, electron-deficient ligands (**2**, **5**, and **6**) or phosphine-free palladium, which undergo slow oxidative addition, only inserted at the most active positions of each electrophile (C2 for dibromothiazoles and 2,4-dibromo-1-methylimidazole, C4 for 2,4-diiodooxazole, C5 for 2,5-dibromo-1-methylimidazole) (Figure 4). However, we hypothesize that the trans binding mode of Xantphos (**2**) to Pd is also responsible in part for its unique reactivity. On the other hand, more active ligands such as mono-, di-, and trialkylphosphines were able to insert into the less active positions as well, leading to mixtures of regioisomers and large amounts of bis-arylated species. However, for reasons that are not yet understood, some highly electron-rich ligands (**4**, tBu$_3$P, **3**) tended to prefer oxidative addition at the less reactive C2 positions of 2,4-diiodooxazole and 2,5-dibromo-1-methylimidazole (Figure 4). However, there are numerous exceptions to this electronic trend. For example, 3,4,5,6-tetramethyl-tBu-XPhos and SiPr-HBF$_4$, both electron-rich ligands, offered high selectivity for the C5 position of 2,5-dibromo-1-methylimidazole.[26] Also, DPPF and DTBPF both prefer C4 oxidative insertion for 2,4-diiodooxazole, while **3**, a hybrid of these two ligands, anomalously prefers C2 insertion.[27] These findings suggest that the regiochemical preference imparted by different ligands is a complex mixture of steric and electronic effects which are not fully understood.

Conclusions

We have developed methods for highly selective Suzuki couplings of dihaloimidazoles, dihalooxazoles, and dihalothiazoles, providing efficient access to a wide array of valuable mono- or bis-functionalized azoles. These reactions exhibit a broad substrate scope, with numerous aryl and heteroaryl boronic acids being coupled. These methods should prove highly valuable to chemists wishing to prepare diverse arrays of imidazoles, oxazoles, or thiazoles in a modular fashion. Additionally, we discovered a ligand capable of selective cross couplings at C2 of 2,4-diiodooxazole and 2,5-dibromo-1-methylthiazole, giving access to both regioisomeric products. This will allow for selective arylation (or alkylation, vinylation) at the typically less reactive C−X bond, and further functionalization at C4 or C5 by metalation and subsequent reaction or cross-coupling. The ability to cross couple at either C−X bond of these azoles would allow for a specific aryl group to be installed at either position, and then for a wide variety of coupling partners to be added at the other C−X bond. Studies are underway to develop more selective catalysts and extend this methodology to different types of cross-coupling reactions.

Experimental Section

General Procedure for Suzuki Cross-Coupling Reactions. This will be demonstrated with the preparation of 4-bromo-2-phenylthiazole:



Under nitrogen $Pd(OAc)_2$ (8.4 mg, 0.038 mmol, 2.5%) was combined with Xantphos (**2**) (22 mg, 0.038 mmol, 2.5%) in

(22) The identity of 5-iodo-1-methyl-2-phenylimidazole was determined solely by LC-MS and showed a very different retention time than its isomer 2-iodo-1-methyl-5-phenylimidazole. This product readily decomposed upon attempted isolation.

(23) A highly selective Negishi coupling at C2 of 2,4-dibromothiazole has been reported as part of a total synthesis: Bach, T.; Heuser, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3184–3185.

(24) Bach, T.; Heuser, S. *J. Org. Chem.* **2002**, *67*, 5789–5795. Vachal, P.; Toth, L. M. *Tetrahedron Lett.* **2004**, *45*, 7157–7161.

(25) Since one ^{1}H NMR resonance of 5-bromo-2-phenylthiazole did not match that reported in the literature, we compared it to an authentic commercial sample, which matched our cross-coupling product perfectly.

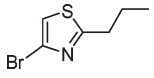
(26) We hypothesize that catalyst formation may be slow or problematic with these two ligands and **6**, allowing phosphine-free palladium to affect the majority of the oxidative addition at C5.

(27) On the basis of its reactivity, we postulate that **3** behaves as a bulky, electron-rich, monodentate phosphine (only binding through the (tBu)$_2$P phosphorus), similar to tBu$_3$P, rather than as a bidentate phosphine.

degassed THF (7.5 mL). After stirring for 5 min, this solution was transferred to a separate vessel under nitrogen containing 2,4-dibromothiazole (364 mg, 1.5 mmol), phenylboronic acid (196 mg, 1.6 mmol, 1.07 equiv), and K_3PO_4 (955 mg, 4.5 mmol, 3 equiv). The sealed vessel was heated at 60 °C for 18 h. Upon cooling to room temperature, LC-MS showed 100% conversion of starting material, 19.5:1 mono:bis product ratio, and >100:1 C2:C4 product isomer ratio. The reaction mixture was filtered and the solid was washed with DCM. The solvents were removed by rotary evaporation and the title compound was purified by column chromatography (silica gel, EtOAc/hexane) to give a white waxy solid (0.264 mg, 73%, mp 80 °C (lit.[28] mp 77−78 °C)).

^{1}H NMR (500 MHz, CD_3Cl_3) δ 7.23 (s, 1H), 7.46 (m, 3H), 7.95 (dd, J = 7.5, 2.5 Hz, 2H); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.54 (m, 3H), 7.68 (s, 1H), 7.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 116.6, 126.2, 126.5, 129.2, 130.9, 132.7, 169.2; LCMS $[M + H]^+$ calcd for $C_9H_6BrNS \cdot H^+$ 239.95, found 239.92; HRMS (ESI) $[M + H]^+$ calcd for $C_9H_6BrNS \cdot H^+$ 239.9482, found 239.9491.

Negishi Cross-Coupling To Prepare 4-Bromo-2-propylthiazole. Under nitrogen $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5%) was combined with Xantphos (**2**)



(29 mg, 0.05 mmol, 5%) in degassed THF (2.5 mL). After stirring for 5 min, this solution was transferred to a separate vessel under nitrogen containing 2,4-dibromothiazole (243 mg, 1.0 mmol) and propylzinc bromide (2.2 mL, 0.5 M solution in THF, 1.1 mmol, 1.1 equiv). The sealed vessel was heated at 80 °C for 18 h. Upon cooling to room temperature, LC-MS showed 100% conversion of starting material, >100:1 mono:bis product ratio, and >100:1 C2:C4 product isomer ratio. The reaction mixture was filtered and the solid was washed with DCM. The solvents were removed by rotary evaporation and the title compound was purified by column chromatography (silica gel, EtOAc/hexane) to give a white powder (0.184 mg, 89%, mp 98−100 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.0 Hz, 3H), 1.80 (sextet, J = 7.0 Hz, 2H), 2.96 (t, J = 7.5 Hz, 2H), 7.06 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 23.2, 35.4, 115.6, 124.0, 172.5; LCMS $[M + H]^+$ calcd for $C_6H_8BrNS \cdot H^+$ 205.9, found 205.9; HRMS (ESI) $[M + H]^+$ calcd for $C_6H_8BrNS \cdot H^+$ 205.9639, found 205.9639.

Acknowledgment. The authors gratefully acknowledge Ms. Huifang Yao, Dr. Vincent Tong, and Ms. Kate Rausted for help in obtaining HRMS data. The authors would also like to thank Dr. Thomas Weingarten, Dr. Wendy Cornell, and Dr. Gene Fluder for helpful computational discussions, and Dr. Jonathan Wilson for helpful chemistry discussions.

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

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