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Palladium-Catalyzed Direct Arylation of Azine and Azole *N*-Oxides: Reaction Development, Scope and Applications in Synthesis

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Abstract: Palladium-catalyzed direct arylation reactions are described with a broad range of azine and azole *N*-oxides. In addition to aspects of functional group compatibility, issues of regioselectivity have been explored when nonsymmetrical azine *N*-oxides are used. In these cases, both the choice of ligand and the nature of the azine substituents play important roles in determining the regioisomeric distribution. When azole *N*-oxides are employed, preferential reaction is observed for arylation at C2 which occurs under very mild conditions. Subsequent reactions are observed to occur at C5 followed by arylation at C4. The potential utility of this methodology is illustrated by its use in the synthesis of a potent sodium channel inhibitor **1** and a Tie2 Tyrosine Kinase inhibitor **2**.

Introduction

Heterobiaryl compounds are found in many medicinal compounds including Etoricoxib,[1] Rosuvistatin,[2] and Gleevec,[3] as well as molecules designed for other purposes including P,N ligands, such as QUINAP[4] (Figure 1).[5] Consequently, there has been significant effort in both academic and industrial laboratories directed at achieving efficient, high yielding, and highly selective functionalization of these types of molecules. Traditional cross-coupling methodologies (Suzuki, Stille, Kumada−Corriu, Negishi, and Hiyama) are highly versatile,[6] but several azine and azole substrates continue to pose challenges. For example, the instability of 2-pyridylboronic acids has limited their use in Suzuki cross-couplings, an issue that has only recently been addressed through the use of pyridylboronates.[7] In addition to the synthetic issues that may accompany the use of an organometallic cross-coupling partner, the need for dual substrate activation introduces additional waste to the overall process since both the organometallic and the aryl halide must be independently prepared prior to cross-coupling.

Recently, direct arylation reactions have emerged as increasingly viable alternatives to the use of stoichiometric organometallic reagents in standard cross-coupling reactions.[8−11] In addition to the improved efficiency that can arise when a simple arene is used in place of an arylorganometallic, this strategy becomes even more attractive when the organometallic species is difficult to prepare or is unstable under cross-coupling conditions. Given the difficulties associated with cross-couplings of 2-metalla-azines, we envisioned that the development of a

(1) Friesen, R. W.; et al. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2777.
(2) Quirk, J.; Thornton, M.; Kirkpatrick, P. *Nature* **2003**, *2*, 769.
(3) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nature* **2002**, *1*, 493.
(4) (a) For a review on P,N ligands with pyridyl donors see. Chelucci, G.; Orru, G.; Pinna, G. A. *Tetrahedron* **2003**, *59*, 9471. (b) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Asymmetry* **1993**, *4*, 743.
(5) (a) Carey, J. S.; Laffan, D.; Thomson, C; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (b) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéquiner, G. *Synlett* **2002**, *6*, 1008 Footnote 1.
(6) For reviews on this topic, see:(a) Diederich, F.; Stang, P. J. *Metal-catalyzed Cross-coupling Reactions*; Wiley-VCH: New York, 1998.
(7) (a) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695. (b) Yang, D. X.; Colletti, S. L.; Wu, K.; Song, M.; Li, G. Y.; Shen, H. C. *Org. Lett.* **2009**, *11*, 381.
(8) For selected direct arylation processes with Pd(0)/Pd(II) see:(a) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345. (c) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (d) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (e) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (f) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (g) Kawai, H.; Kobayashi, Y.; Oi, S.; Inoue, Y. *Chem. Commun.* **2008**, 1464. For selected analogous C−C bond forming processes initiated with Pd(II) see:(h) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (i) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (j) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (k) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (l) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (m) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (n) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. For oxidative cross-couplings in the absence of substrate pre-activation initiated with Pd(II), see:(o) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376. (p) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (q) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (r) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (s) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (t) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (u) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

10.1021/ja808332k CCC: $40.75

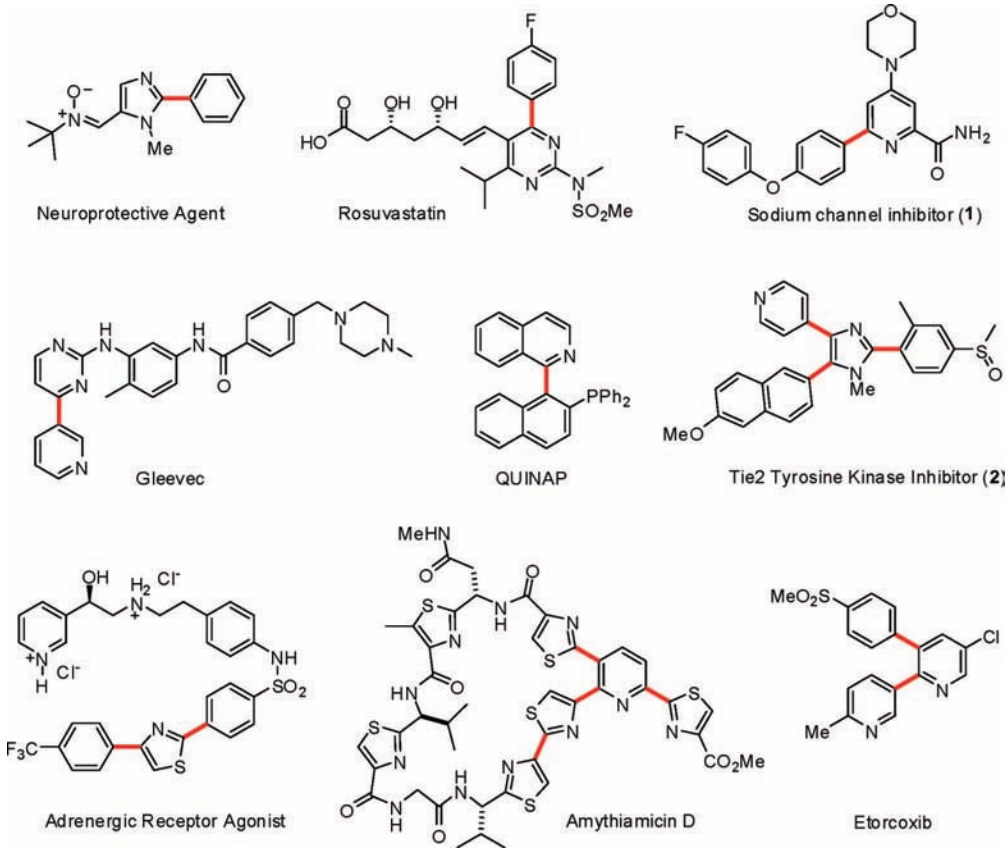
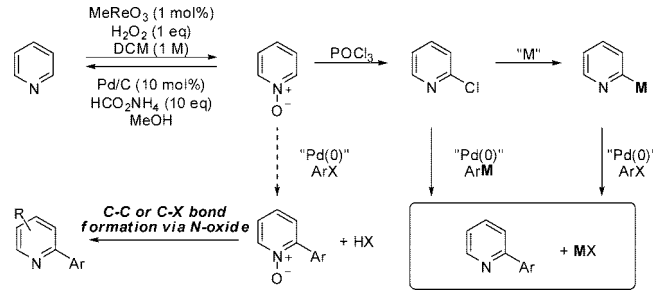


Figure 1. Azine and azole *N*-oxides found in bioactive compounds and chiral ligands.

generally applicable direct arylation alternative would be of particular value with these substrates.

While the use of π-deficient heterocycles is scarce in direct arylation, our attention was drawn to the potential applicability of azine *N*-oxides.[12,13] Such a strategy, though still requiring an activation step, would minimize the number of synthetic steps associated with this process. As illustrated in Scheme 1, the installation of both halide and organometallic functional groups adjacent to the nitrogen atom typically pass through an *N*-oxide species. Thus, improved efficiency would be obtained if the *N*-oxide could itself be employed in a cross-coupling process. Further to this, since the *N*-oxide moiety would not be consumed in the cross-coupling step, it could subsequently be used to introduce further functionality on the azine core following the formation of the biaryl carbon−carbon bond.

Scheme 1. General Strategy for *N*-Oxide Utility in Pyridine Arylation and Functionalization



We imagined that the presence of the *N*-oxide could both prevent nonproductive binding of the palladium catalyst to the

(9) For selected direct arylation processes with Rh, see:(a) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439. (b) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (c) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (d) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (e) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135. (f) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Alleyne, L. C. L.; Long, P. D.; Ceron, D. P.; Prashar, S. *Chem. Commun.* **2008**, 990. (g) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (h) Lewis, J. C.; Wu, J. Y.; Ellman, J. A.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (i) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (j) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131. (k) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202.

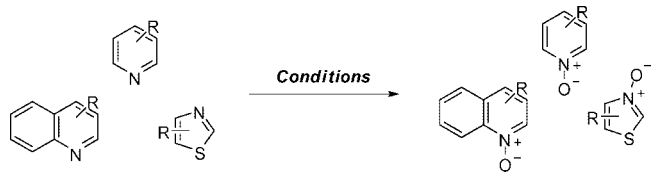
(10) For selected direct arylation processes with Ru, see:(a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (b) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156.

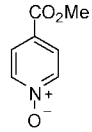
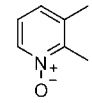
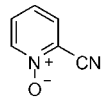
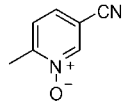
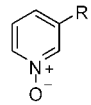
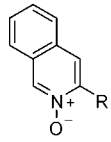
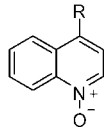
(11) For selected direct arylation processes with other metals see:(a) Fujita, K.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386. (e) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (f) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

(12) To our knowledge this constitutes the only example of direct arylation of an azine (without pre-activation) with an aryl halide under Pd catalysis:Mukhopadhyay, S.; Rothenberg, G.; Gitis, S.; Baidossi, M.; Ponde, D. E.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, *9*, 1809. For an important advance in regioselective azine direct arylation without substrate pre-activation catalyzed by Rh(I), see:Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

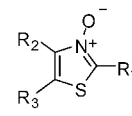
(13) For an example of metal-free, base-promoted biaryl formation between unactivated azine and diazines and aryl bromides and iodides, see:(a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.

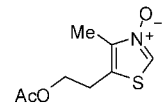
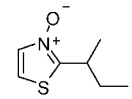
Table 1. Oxidation Methods for Azines and Thiazole[a]



Entry	Conditions	Product		Entry	Conditions	Product	
1	MTO		95%	12	MTO		85%
2	MTO		99%				
3	MTO		93%				
4	MTO		R=CO_2Me 83%				
5	MTO		R=CN 85%				
6	DMDO		R=H 68%				
7	MTO		R=H 95%				
8	MTO		R=Me 90%				
9	DMDO		R=H 96%				
10	MTO		R=H 99%				
11	*m*-CPBA		R=CO_2Me 68%				

		R_1	R_2	R_3	
13	*m*-CPBA	H	H	H	50%
14	*m*-CPBA	H	Me	Me	74%
15	*m*-CPBA	H	Me	H	72%
16	*m*-CPBA	H	H	Me	67%
17	*m*-CPBA	Ph	H	H	54%



18	*m*-CPBA		61%
19	*m*-CPBA		64%

[a] Conditions: MTO: azine (1 equiv), methyl trioxorhenium (1−4 mol %), H2O2 (50 wt % in water, 2 equiv), in DCM (2.5 M), room temperature, 12−24 h. DMDO: azine (1 equiv), acetone (2.5 M), phosphate buffer (0.25 M), oxone (2.4 equiv), room temperature, 3 h. *m*-CPBA: azine (1 equiv), *m*-chloroperoxybenzoic acid (1.2 equiv), DCM (0.5 M), room temperature, 16 h.

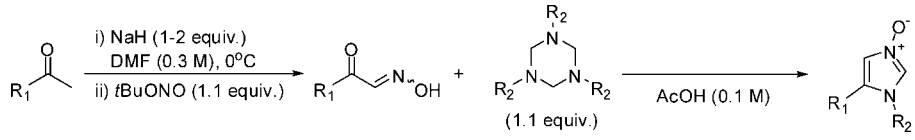
nitrogen lone pair and favor π-binding interactions leading to pyridine metalation. Furthermore, the *N*-oxide moiety increases the electron-density of the electron-deficient pyridine ring system,[14] and enhances the Brönsted acidity of the adjacent pyridyl C−H bonds.[15] While these properties have been capitalized on in other processes,[16] to our knowledge azine *N*-oxides had not been investigated in the context of metal catalyzed cross-coupling reactions. In 2005 and 2006 we showed that pyridine and diazine *N*-oxides undergo ortho direct arylation in synthetically useful yields.[17] In 2007 we extended this strategy to include thiazole *N*-oxides.[18] In this article, we disclose (1) a broad evaluation of the scope and functional group compatibilities for substituted pyridine and quinoline *N*-oxides, (2) conditions for the regioselective arylation of isoquinoline and 3-substituted pyridine *N*-oxides, (3) the establishment of a multigram scale protocol for the direct arylation of pyridine *N*-oxide, (4) an evaluation of the scope for the regioselective direct arylation of both thiazole and imidazole *N*-oxides, including conditions for challenging or hindered aryl halides, and (5) the application of this methodology in the synthesis of sodium channel inhibitor **1** (Scheme 2) and Tie2 tyrosine kinase inhibitor **2** (Scheme 3).

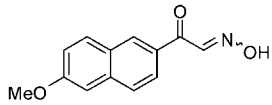
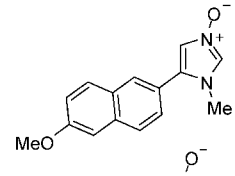
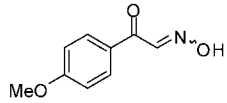
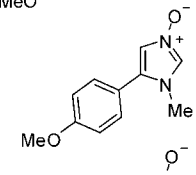
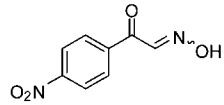
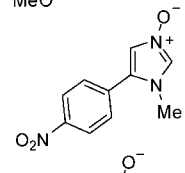
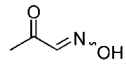
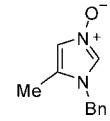
Results and Discussion

Azine and Thiazole *N*-Oxidation. Many azine *N*-oxides are increasingly commercially available. In other cases we have employed three different methods for their preparation. Each method offers its own advantages that can be selected depending on the substrate being oxidized. The methyltrioxorhenium (MTO)/H_2O_2 oxidation system, originally described by Sharpless, is our preferred method for azine oxidation.[19] The advantages of this protocol are that reactions can be run at very low catalyst loadings (<1 mol %), and high concentration (2.5 M). Alternatively, oxidation by

(14) For a review on pyridine *N*-oxides and their reactivity see:(a) Youssif, S. *ARKIVOC* **2001**, 242.
(15) (a) Kreuger, S. A.; Paudler, W. W. *J. Org. Chem.* **1972**, *37*, 4188. (b) Paudler, W. W.; Humphrey, S. A. *J. Org. Chem.* **1970**, *35*, 3467.
(16) See ref 14. Also, see (a) Choshi, T.; Matsuya, Y.; Okita, M.; Inada, K.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1998**, *39*, 2341. (b) Van Galen, P. J. M.; Nissen, P.; Van Wijngaarden, I.; Ijzerman, A. P.; Soudijn, W. *J. Med. Chem.* **1991**, *34*, 1202.
(17) (a) For azine and diazine *N*-oxides see:Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781.
(18) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277.
(19) Coperet, C.; Adolfsson, H.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.

Table 2. Preparation of Imidazole *N*-Oxide Substrates[a]



Entry	α-Ketooxime	Yield	R_2 group	*N*-oxide	Yield
1		61%	Me		83%
2		76%	Me		61%
3		21%	Me		84%
4		65%	Bn		67%

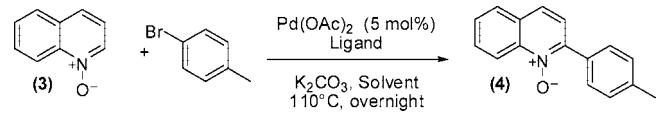
[a] Conditons: ketooxime formation; entries 1−3: acetophenone (1 equiv), NaH (2 equiv), DMF (0.3 M), *t*-butylnitrite (1.1 equiv), 0 °C to room temperature; entry 4: hydroxylamine hydrochloride (1 equiv), methylglyoxal (40% in water, 1 equiv), THF, room temperature. *N*-oxide: α-ketooxime (1 equiv), 1,3,5-trialkyl-1,3,5-triazinane (1.1 equiv), AcOH, room temperature.

peracids, such as *m*-CPBA, affords the azine *N*-oxide in high crude yield. However, the formation of *meta*-chlorobenzoic acid as a byproduct of the reaction can complicate isolation, and in many cases reduced yields are obtained—particularly when the scale of the reaction is increased. In situ generation of dimethyl dioxirane (DMDO) as an oxidant is also an efficient method for the oxidation of azines to azine *N*-oxides.[20] However, since this reaction is typically conducted in aqueous media, azines having low water solubility or azine *N*-oxides having high water solubility suffer from low isolated yields. Azine *N*-oxides that are moderately water soluble, such as quinoline *N*-oxide, can be prepared in high yield (>85%) on gram scale (>8 g) and isolated from the reaction via extraction with dichloromethane in analytically pure form without the need for additional purification. Thiazoles are readily oxidized by *m*-CPBA and MTO/H_2O_2, but the water solubility of many of the azole *N*-oxide products makes them incompatible with the DMDO protocol. Illustrative examples employing each of these methods are shown in Table 1.

In contrast to the oxidations of azine and thiazole substrates, all attempts to oxidize imidazole compounds resulted in decomposition or extremely slow reaction giving complex mixtures of products. Consequently, alternative pathways to imidazole *N*-oxides were employed. For example, the imidazole ring may be prepared with the *N*-oxide already in place by reaction of an α-ketooxime with 1,3,5-trimethyl-1,3,5-triazinane. Yields for each of the two steps (α-ketooxime preparation and subsequent azole formation)[21] are outlined in Table 2 for a variety of C5-substituted *N*′-alkyl imidazole *N*-oxides.

(20) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

Table 3. Influential Factors on the Outcome of the Arylation of Quinoline *N*-Oxide[a]

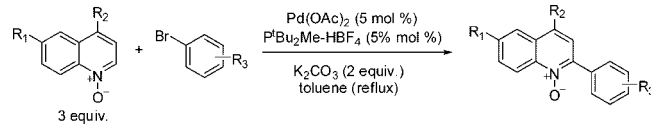


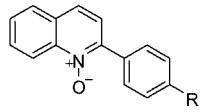
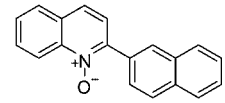
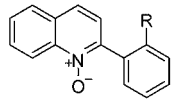
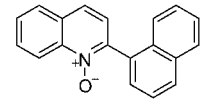
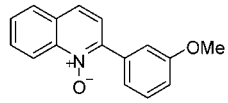
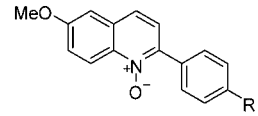
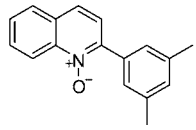
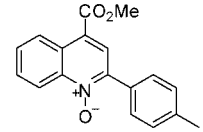
entry	equiv of *N*-oxide	ligand	ligand/Pd ratio	solvent	yield (%)[b]
1	3	P^tBu_3-HBF_4	3:1	PhMe	34
2	3	P^tBu_3-HBF_4	3:1	mesitylene	65
3	3	P^tBu_3-HBF_4	2:1	mesitylene	88
4	3	P^tBu_3-HBF_4	1:1	mesitylene	91
5	3	P^tBu_3-HBF_4	1:1	PhMe	77
6	3	PCy_3-HBF_4	1:1	PhMe	50
7	3	P^tBu_2Me-HBF_4	1:1	PhMe	96 (96)
8	2	P^tBu_2Me-HBF_4	1:1	PhMe	86 (85)
9	1.1	P^tBu_2Me-HBF_4	1:1	PhMe	(67)
10	3	P^tBu_2Me-HBF_4	1:1	dioxane	82
11	3	P^tBu_2Me-HBF_4	1:1	MeCN	75

[a] Conditions: 4-bromotoluene (1 equiv), quinoline *N*-oxide (3 equiv), $Pd(OAc)_2$ (5 mol %), ligand (5−15 mol %), K_2CO_3 (2 equiv), toluene (0.3 M), 110 °C, 16 h. [b] ^1H NMR yield, isolated yield in parentheses.

Azine *N*-Oxides. Development and Scope of Palladium-Catalyzed Direct Arylation of Substituted Quinoline and Pyridine *N*-Oxides. Following the development of our original conditions for the arylation of pyridine *N*-oxide,[17a] we sought to further improve the reactivity and undertook a secondary reaction optimization with quinoline *N*-oxide **3**, a substrate which gave lower yields under the initially described conditions (Table 3, entry 1). This work was performed under slightly modified conditions to facilitate a rapid evaluation of the important reaction parameters: in sealed vials heated

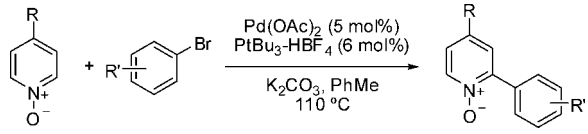
Table 4. Scope in the Direct Arylation of Quinoline *N*-Oxide[a]

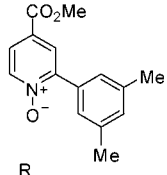
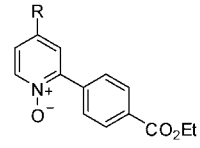
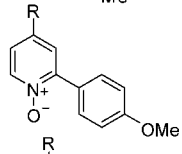
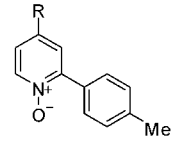
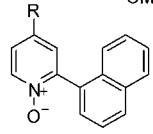


Entry	Product	Yield[b]	Entry	Product	Yield[b]
1		R=H 89	9		73
2		R=^{t}Bu 94			
3		R=OMe 88			
4		R=CO_2Et 61			
5[c]		R=Me 80	10[c]		83
6[c]		R=Cl 70			
7		87	11		R=H 72
			12		R=Me 85
			13		R=OMe 77
			14		R=Cl 55
8		92	15		91

[a] Conditions: Quinoline *N*-oxide (3 equiv), bromoarene (1 equiv, 0.3 M), $Pd(OAc)_2$ (5 mol %), P^tBu_2Me-HBF_4 (5 mol %), K_2CO_3 (2 equiv), toluene, reflux, 16 h. [b] Isolated yield. [c] Addition of Ag_2CO_3 (0.5 equiv).

Table 5. Scope in the Direct Arylation of 4-Substituted Pyridine *N*-Oxides[a]

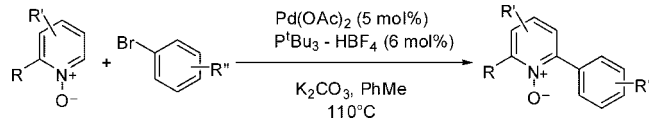


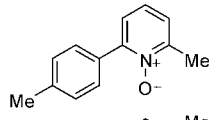
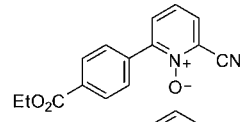
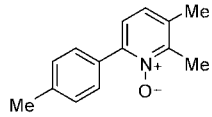
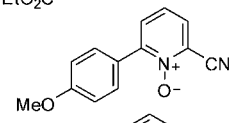
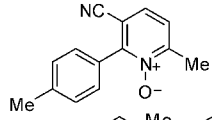
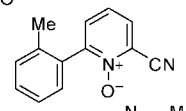
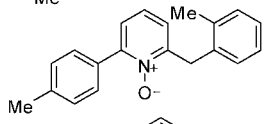
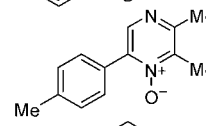
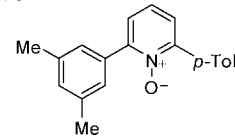
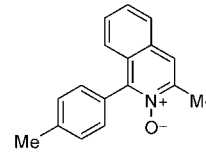
Entry	Product	Yield[b]	Entry	Product	Yield[b]
1		97	6		R = Me 76
			7		R = Ph 90
2		R = CO_2Me 88	8		R = NO_2 78
3		R = Me 95	9		R = OMe 80
4		R = Me 85			
5		R = OMe 54			

[a] Conditions: Aryl halide (1 equiv), pyridine *N*-oxide (4 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv) and P^tBu_3-HBF_4 (0.15 eq.) in toluene (0.3M) at 110 °C overnight. [b] Isolated Yields.

in an aluminum block with mesitylene as the solvent in place of toluene to reduce solvent volatility at elevated temperature. Under these conditions, it was determined that reducing the ligand/Pd ratio from 3:1 to 1:1 results in an increase in yield of the 2-arylquinoline *N*-oxide **4** from 65% to 91% (Table 3, entries 2−4). Upon returning to a more traditional reaction setup (round-bottom flask with a reflux condenser heated in an oil bath with toluene as the solvent) a slight decrease in the yield to 77% was noted, though this still represents a marked increase from the initially reported conditions (Table 3, entries 1 and 5). A scan of other trialkyl phospine ligands revealed that the yield could be improved from 77% to 96% by replacing the more sterically encumbered tri-*t*-butylphosphonium tetrafluoroborate as the preligand with di-*t*-butylmethylphosphonium tetrafluoroborate in a 1:1 ligand/Pd ratio (Table 3, entries 5−7).

Table 6. Scope in the Direct Arylation of 2-Substituted Pyridine *N*-Oxides[a]



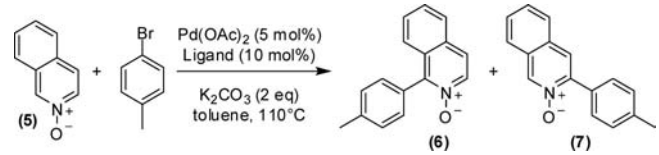
Entry	Product	Yield[b]	Entry	Product	Yield[b]
1		56	6		81[c]
2		34	7		81[c]
3		74	8		68[c]
4		59	9		89
5		74	10		90[d]

[a] Conditions: Aryl halide (1 equiv), pyridine *N*-oxide (2−3 equiv), K_2CO_3 (2 equiv), $Pd(OAc)_2$ (0.05 equiv) and P^tBu_3-HBF_4 (0.06 equiv) in toluene (0.15 M) at 110 °C overnight. [b] Isolated Yields. [c] With 4 equiv of *N*-oxide and 15 mol % P^tBu_3-HBF_4. [d] With 1.1 equiv of *N*-oxide.

Under these conditions, the amount of *N*-oxide **3** can also be reduced while maintaining synthetically useful isolated yields. For example, the use of 2 equiv of *N*-oxide **3** results in an 85% isolated yield of **4**, while the use of a slight excess of the *N*-oxide (1.1 equiv) provides 67% isolated yield (Table 3, entries 8 and 9). Other solvents, such as dioxane and acetonitrile, can also be employed at refluxing temperatures to provide the 2-arylquinoline *N*-oxide in good yield (Table 3, entries 10 and 11).

Additional examples of quinoline *N*-oxide are included in Table 4. The reaction is compatible with a range of functional groups and substitution patterns on the aryl bromide, and both electron-donating and electron-withdrawing groups are tolerated on the quinoline *N*-oxide. Alkyl substitution in the para, ortho, and meta positions is tolerated on the arylbromide (Table 4, entries 2, 5, 8). Activated and unactivated aryl bromides are also compatible in the reaction (Table 4, entries 3, 4, 7). If the arene bears both a chloride and a bromide substituent, the reaction takes place selectively at the aryl bromide (Table 4, entry 6). Naphthyl bromides also react cleanly providing the 2-(1-naphthyl)quinoline *N*-oxide or 2-(2-naphthyl)quinoline *N*-oxides in good yield (Table 4, entries 9 and 10). 5-Methoxy-substituted quinoline *N*-oxide also participates in these reactions with a range of aryl bromides (Table 4, entries 11−14) as does an electron-deficient *N*-oxide (Table 4, entry 15).

Table 7. Ligand Effects on the Regioselectivity in the Arylation of Isoquinoline *N*-Oxide[a]



entry	ligand	6:7[b]	conversion (%)[c]
1	P^tBu_3-HBF_4	1.7:1	>99
2	PCy_3-HBF_4	7.5:1	90
3	PMe^tBu_2-HBF_4	12.8:1	>99

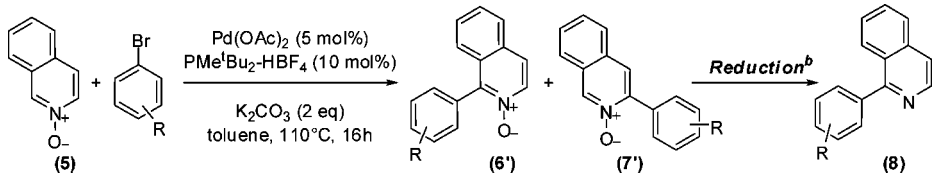
[a] Conditions: 4-Bromotoluene (1 equiv), *N*-oxide (3 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_2CO_3 (2 equiv), toluene (0.3 M), 110 °C, 16 h. [b] Isomeric ratio determined by ^1H NMR. [c] Conversion determined by integration against an internal standard (trimethoxybenzene) in the ^1H NMR spectrum.

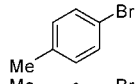
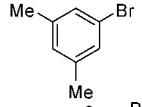
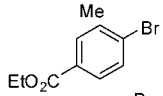
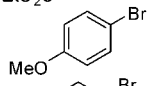
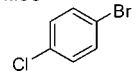
These reactions were also evaluated with a range of substituted pyridine *N*-oxides (Tables 5 and 6). A diverse set of functional groups may be present, including ester, alkyl, and aryl groups affording the products in high yield with both electron-rich and electron-poor aryl halides. Notably, both electron-donating alkoxy and electron-withdrawing nitro groups are tolerated on the *N*-oxide, leading to good yields of the aryl pyridine products (Table 5, entries 8 and 9). 2-Alkyl pyridines such as picoline *N*-oxide and 2,3-lutidine *N*-oxide are less reactive under these conditions affording the corresponding products in poor to modest yields (Table 6, entries 1 and 2).

(21) For α-ketooxime preparation passing through the enol, please see:(a) Rüedi, G.; Oberli, M. A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett.* **2004**, *13*, 2315. (b) Mohammed, A. H. A.; Nagendrappa, G. *Tetrahedron Lett.* **2003**, *44*, 2753. For α-ketooxime preparation passing through the enolate, please see:(c) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Shabunina, O. V.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2005**, *46*, 1791. (ca) For preparation of the imidazole *N*-oxide please see:(d) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311. (e) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Sainz, Y. F.; Piro, O. E. *Synthesis* **2004**, *16*, 2678.

(22) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.

Table 8. Regioselectivity and Scope in the Direct Arylation of Isoquinoline *N*-Oxide[a]



Entry	Aryl Bromide	Yield[c] of 6' + 7'	Ratio[d] of 6' : 7'	Yield[c] of 8
1		98%	13.5 : 1	80%
2		91%[e]	14.4 : 1	—
3		71%[f]	39.6 : 1	—
4		92%	12.4 : 1	73%
5		95%	15.8 : 1	83%
6		96%	13.5 : 1	83%
7		63%	14.1 : 1	85%

[a] Conditions: Aryl bromide (1 equiv), isoquinoline *N*-oxide (3 equiv), $Pd(OAc)_2$ (5 mol %), P^tBu_2Me-HBF_4 (10 mol %), K_2CO_3 (2 equiv), toluene (0.3 M), 110 °C, 16 h. [b] Entries 1, 4−6: Mixture of **6′** and **7′** (1 equiv), ammonium formate (14 equiv), 10% wt Pd/C (0.1 equiv of Pd), MeOH (0.1 M), 40 °C, 2−5 h. Entry 5: Mixture of **6′** and **7′** (1 equiv), zinc dust (10 equiv), $THF/NH_4Cl_{(aq,sat)}$ (1:1 vol/vol, 0.033 M), rt, 1 h. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy. [e] 2 equiv of isoquinoline *N*-oxide was used. [f] 1.1 equiv of isoquinoline *N*-oxide was used.

These lower yields may be due to a competitive palladacycle formation with the ortho alkyl group, resulting in a sequestering of the catalyst—a hypothesis that lead to the development of a palladium-catalyzed α-arylation protocol of picoline *N*-oxide and its derivatives.[22] Benzyl, as well as aryl, substitution on the pyridine *N*-oxide is also tolerated under the reaction conditions (Table 6, entries 4 and 5). 2-Cyanopyridine *N*-oxide may also be employed (Table 6, entries 6−8) and 3-methyl isoquinoline *N*-oxide can be used even with only 1.1 equiv of the *N*-oxide (Table 6, entry 10).

Regioselectivity in the Direct Arylation of Unsymmetrical Azine *N*-Oxides. Use of the *N*-oxide cross-coupling strategy can also offer advantages to the use of traditional cross-coupling techniques when nonsymmetrical substrates bearing two potential sites for reaction are employed. Traditional techniques rely on the availability of regioisomerically pure haloazines or azine organometallics that may be difficult to prepare. To ascertain whether the *N*-oxide cross-coupling strategy could provide a solution in some of these cases, isoquinoline *N*-oxide **5** was employed as a test substrate. Under our previously reported reaction conditions[17a] the arylation of **5** provides a regioisomeric product ratio of 1.7:1 (**6**:**7**, Table 7). Our previous work in regioselective intramolecular direct arylation of simple arenes prompted us to consider a ligand effect.[23] We were pleased to find that, on changing the ligand from tri-*tert*-butylphosphine to tricyclohexylphsphine to di-*tert*-butylmethylphosphine the yield remained high and the regioselectivity could be improved from 1.7:1 to 7.5:1 to 12.8:1, respectively. In these cases, contrary to reactions employing *N*-oxides that do not possess two different regioisomeric sites for reaction, we found that the use of a ligand to metal ratio of 2:1 provided the most reproducible results.

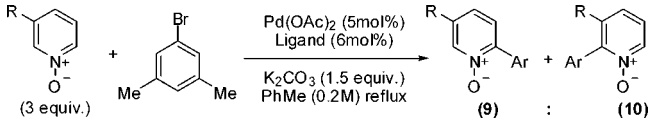
Aspects of regioselectivity were investigated with isoquinoline *N*-oxide and a number of different aryl bromides with various functional groups and substitution patterns (Table 8). During the course of these studies it was determined that the *N*-oxide regioisomeric products were often inseparable by silica gel flash chromatography. For this reason, the *N*-oxide products were isolated as a mixture and subjected to deoxygenation reaction conditions. Conveniently, the free bases exhibit sufficient chromatographic separation to permit facile isomer separation. While 3 equiv of the *N*-oxide are regularly employed and give excellent yields of the major regioisomer (Table 8, entry 1), good to excellent yields are still obtained with 1.1 and 2 equiv of isoquinoline *N*-oxide (Table 8, entries 2 and 3). Meta substitution, as well as activated and unactivated aryl bromides, may be employed providing products in excellent yield and regioselectivities ranging from 16:1 to 12:1 for the 1-arylisoquinoline *N*-oxide (Table 8, enties 4−6). A chloride substituent may also be present on the aryl bromide and the product can be obtained in good yield with high regioselectivity (Table 8, entry 7). In this case, the use of zinc powder in an aqueous THF ammonium chloride solution is employed instead of Pd/C in the presence of ammonium formate to minimize undesired reduction of the aryl chloride moiety.[24]

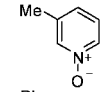
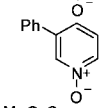
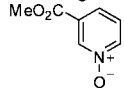
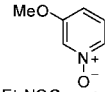
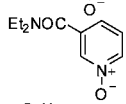
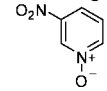
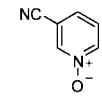
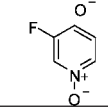
Similar studies were also performed with a variety of 3-substituted pyridine *N*-oxides. With these substrates the regioselectivity is dramatically influenced by the nature of the azine substituents. In some cases, the presence of a C3 substituent induces reaction at the more sterically accessible azine para position. This is the case with 3-methylpyridine *N*-oxide which reacts with low regioselectivity (3:1, Table 9, entry 1). Slightly improved para selectivity (10:1) is observed

(23) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

(24) For reduction with Pd/C/ammonium formate see:Balicki, R. *Synthesis* **1989**, 645. For reduction with Zn/ammonium chloride see:Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.

Table 9. Regioselectivity and Scope in the Direct Arylation of 3-Substituted Pyridine *N*-Oxides[a]



Entry	Pyridine *N*-Oxide	Ligand	Yield (%)[b]	Ratio **9**:**10**[c]
1		P^tBu_3-HBF_4	78 (59)	3.3 : 1
2		P^tBu_3-HBF_4	94 (80)	10 : 1
3		P^tBu_3-HBF_4	86 (74)	6.7 : 1
4		P^tBu_3-HBF_4	88	1.1 : 1
5		P^tBu_2Me-HBF_4	96 (79)	1 : 5.2
6		P^tBu_3-HBF_4	99 (50)	1.1 : 1
7		P^tBu_2Me-HBF_4	83	1 : 1.4
8		P^tBu_3-HBF_4	89 (67)	1 : 3.7
9		P^tBu_2Me-HBF_4	86	1 : 6.3
10		P^tBu_3-HBF_4	98 (88)	1 : 9.5
11		P^tBu_2Me-HBF_4	88	1 : 15
12		P^tBu_3-HBF_4	83 (78)[d]	>1 : 25

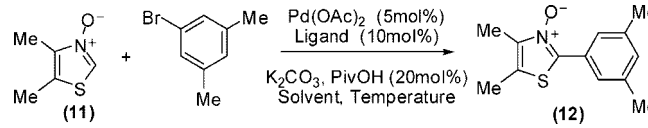
[a] Conditions: Aryl bromide (1 equiv), *N*-oxide (3 equiv), K_2CO_3 (1.5 equiv), $Pd(OAc)_2$ (5 mol %), ligand (6 mol %), toluene (0.15 M), 110 °C, 16 h. [b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as a standard. Yield in parentheses are isolated yield of major isomer. [c] Determined by ^1H NMR spectroscopy. [d] Using 1.1 equiv of *N*-oxide.

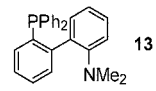
in a reaction with 3-phenylpyridine *N*-oxide (Table 9, entry 2). In contrast, other substituents favor arylation at the ortho position. For example, 3-nitro-, 3-cyano-, and 3-fluoropyridine *N*-oxide all react to give the major product of direct arylation at the site adjacent to the substituent (entries 8−12). This bias is particularly striking with a fluorine substituent, which results in greater than 25:1 regioselectivity (entry 12). Such reactivity has previously been observed in reactions with similarly substituted benzene substrates and may indicate that a similar mode of reaction is occurring here as well.[25] Other substrates were found to give more variable selectivity depending on the other factors at play including the choice of ligand (vide infra). For example, the presence of a methoxy or an amide substituent at C3 results in a nearly completely unselective arylation at both positions next to the *N*-oxide group.

As with isoquinoline substrates, the choice of ligand influences the regioselectivity of these transformations. This is illustrated in reactions with methoxy, nitro, and nitrile substituents at C3. In each of these cases, by changing to the smaller di-*tert*-butylmethylphosphine ligand, enhanced regioselectivity for arylation at the more sterically encumbered site is observed. In each case, the major isomer could be separated and purified via silica gel chromatography and the isolated yield is reported in Table 9. In each case, synthetically useful yields can be obtained.

(25) This will be discussed in detail in a separate full account outlining experimental and computational mechanistic studies for direct arylation reactions of these substrates.

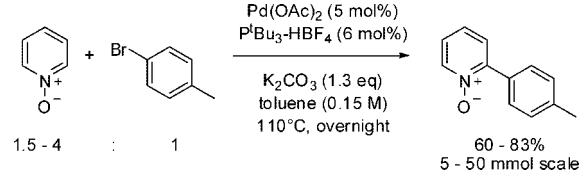
Table 10. Optimization for the C2 Arylation of Thiazole *N*-Oxide[a]



Entry	Ligand	Solvent	Temperature	Yield[b]
1	P^tBu_3-HBF_4	Toluene	110°C	79%[c]
2	P^tBu_3-HBF_4	Toluene	25°C	5%
3	PPh_3	MeCN	25°C	3%
4	dppf	MeCN	25°C	4%[d]
5	 **13**	MeCN	25°C	40%
6	**13**	Dioxane	25°C	89%
7	**13**	DMSO	25°C	88%
8	**13**	^{i}PrOAc	25°C	91%
9	**13**	Toluene	25°C	98%
10	DavePhos	Toluene	25°C	97%

[a] Conditions: *m*-Bromomesitylene (1 equiv), 4,5-dimethylthiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_2CO_3 (1.5 equiv), PivOH (20 mol %), solvent (0.2 M), temperature, 16 h. [b] Yields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield without pivalic acid. [d] 5 mol % of dppf was used.

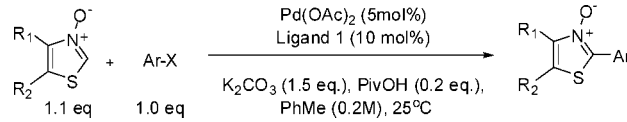
Optimization of a Multigram Process. Reaction optimization was performed on a slightly larger scale (0.5 mmol) with a focus on minimizing the need for excess reagents whenever possible. The optimal conditions emerged as follows. Pyridine *N*-oxide (1.5 equiv), aryl bromide (1 equiv, 0.15 M), $Pd(OAc)_2$ (5 mol %), P^tBu_3-HBF_4 (6 mol %), K_2CO_3 (1.3 equiv), toluene (reflux), overnight. Under these conditions, yields between 65% and 75% can be obtained on 0.5 mmol scale in a Radley's Greenhouse Reactor. Scaling up the reaction to 5−6 mmol in conventional glassware resulted in slightly diminished yields (60−69%); however, by increasing the amount of pyridine *N*-oxide to 2 equiv results in yields between 70−72% and the use of 4 equiv improves the yield to 78−83% even on 50 mmol scale. Thus, it is possible to employ fewer equivalents of the *N*-oxide component if this material is precious due to cost or preparation. In these cases, slightly lower yields are observed, but they remain synthetically useful, above 60%.

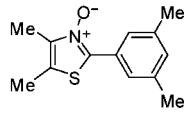
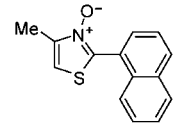
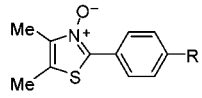
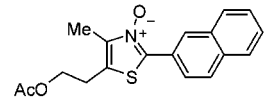
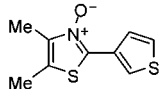
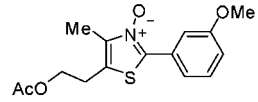
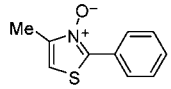
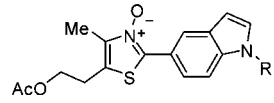
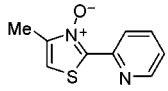
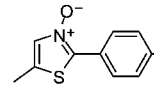
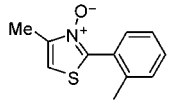
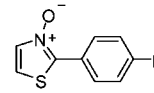
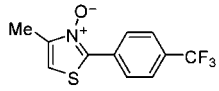
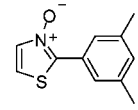


(1)

Azole *N*-Oxides. Comprehensive Scope of Thiazole *N*-Oxide Direct Arylation. Azoles will participate in direct arylation without *N*-oxide activation, but these reactions are typically characterized by the need for elevated temperatures.[26] With simple thiazoles, reaction is predominantly observed at C5,[26] adjacent to the sulfur atom, although this is typically associated with the production of C5/C2 double arylation side products.[27] Selective C2 arylation has also been described if

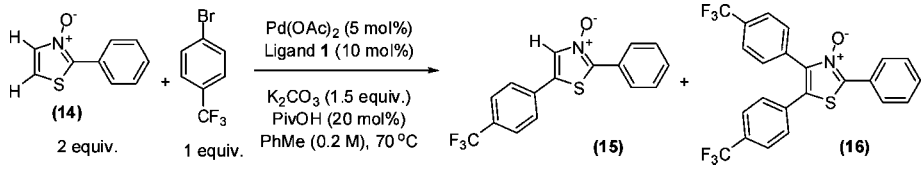
Table 11. C2 Direct Arylation of Thiazole *N*-Oxides[a,b]



Entry	Product	Yield	Entry	Product	Yield
1		84[c]	9		67[f,m]
2		R=Me 88[c], 79[d,g]	10		86[c]
3		R=CO_2Me 80[c], 79[e,h]			
4		83[c]	11		85[c,j]
5		65[c], 86[f,m]	12		R=Bz 77[c,j]
			13		R=H 64[c,j]
6		86[c,i]	14		R=Me 92[d,k]
			15		R=OMe 88[d,k]
7		78[c,n]	16		R=CO_2Me 84[d,k]
			17		R=NO_2 67[c,l]
			18		R=H 84[d,k]
			19		R=OMe 69[d,k]
8		76[f,m]	20		76[d,k]

[a] Conditions: Arylhalide (1 equiv), thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), Ligand 1 (2-(diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl) (10 mol %), K_2CO_3 (1.5 equiv), PivOH (20 mol %), in toluene (0.2 M) at 25 °C. [b] Isolated yields are reported above. [c] X = Br. [d] X = I. [e] X = Cl. [f] X = OTf. [g] Cs_2CO_3 (1.5 equiv) was used as base. [h] DavePhos (10 mol %) was used as the ligand and the reaction was heated to 70 °C for 48 h. [i] JohnPhos (10 mol %) was used as the ligand and the reaction was heated to 70 °C. [j] DavePhos (10 mol %) was used as the ligand. [k] Cs_2CO_3 (1.5 equiv) was used as the base and CuBr (10 mol %) as an additive. [l] CuBr (10 mol %) was used as an additive. [m] DavePhos (10 mol %) used as the ligand and heated at 70 °C overnight. [n] Heated to 70 °C.

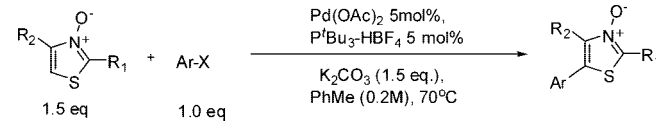
Table 12. Optimization for the C5 Arylation of Thiazole *N*-Oxide[a]

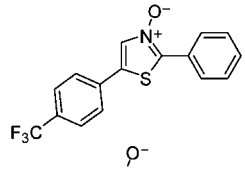
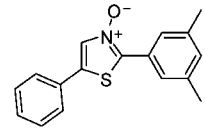
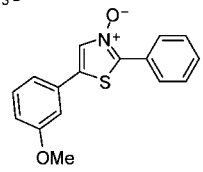
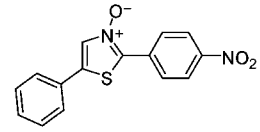
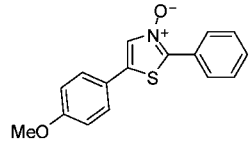
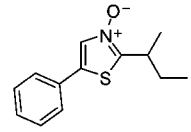
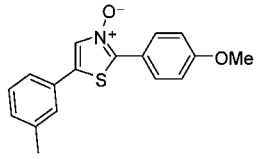
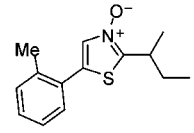
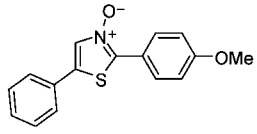
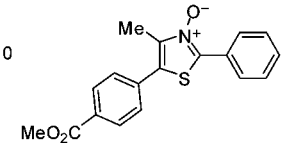


entry	equiv of thiazole	ligand	Pd/ligand	additive	^{1}H NMR yield of **15** (%)[b]	^{1}H NMR yield of **16** (%)[b]
1	2.0	**13**	1:2	PivOH	40	35
2	2.0	**13**	1:2	PivOH/CuBr	50	30
3	2.0	**13**	1:2	none	50	0
4	2.0	DavePhos	1:2	none	76	0
5	2.0	PPh_3	1:2	none	60	15
6	2.0	$P^tBu_3 \cdot HBF_4$	1:2	none	92	0
7	2.0	$P^tBu_3 \cdot HBF_4$	1:1	none	100	0
8	1.5	$P^tBu_3 \cdot HBF_4$	1:1	none	80	0
9	1.1	$P^tBu_3 \cdot HBF_4$	1:1	none	53	0

[a] Conditions: 4-Bromo-α,α,α-trifluorotoluene (1 equiv), 2-phenylthiazole *N*-oxide (1.1−2 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_2CO_3 (1.5 mol %), PivOH (20 mol %), toluene (0.2 M), 70 °C, 16−24 h. [b] ^{1}H NMR yields are relative to an internal standard (1,3,5-trimethoxybenzene).

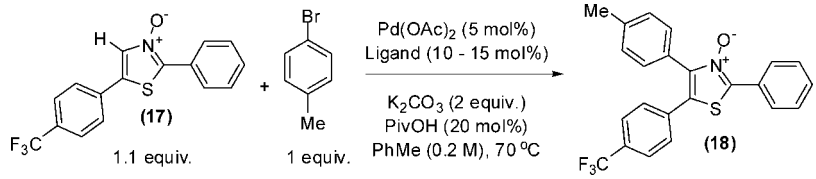
Table 13. C5 Direct Arylation of Thiazole *N*-Oxides[a,b]



Entry	Product	Yield	Entry	Product	Yield
1		79	6		85
2		82	7		62
3		86	8		X = Br 80, X = I 65 X = OTf 55[c]
4		67	9		72
5		80	10		99[d]

[a] Conditions: ArX (1 equiv), thiazole *N*-oxide (1.5 equiv), $Pd(OAc)_2$ (5 mol %), P^tBu_3-HBF_4 (5 mol %), K_2CO_3 (1.5 equiv), in toluene (0.2 M) at 70 °C. [b] Isolated yields are reported above. [c] DavePhos (15 mol %) was used as the ligand. [d] 2 equiv of thiazole *N*-oxides used.

Table 14. Optimization of C4 Arylation of Thiazole *N*-Oxides[a]



entry	temp (°C)	ligand	Pd/ligand	additive	^{1}H NMR yield (%)[b]
1	70	**13**	1:2	PivOH	29
2	70	**13**	1:2	PivOH/CuBr	22
3	110	**13**	1:2	PivOH	48
4	110	PPh_3	1:2	PivOH	35
5	110	PPh_3	1:3	PivOH	71
6	110	PPh_3	1:3	none	76

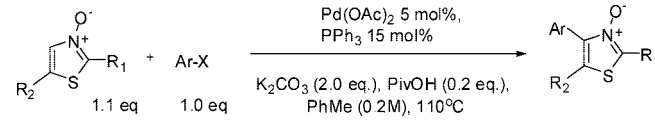
[a] Conditions: 4-Bromotoluene (1 equiv), **17** (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10−15 mol %), K_2CO_3 (2 equiv), additive (see Table 14), toluene (0.2 M), 70 °C, 16−24 h. [b] ^{1}H NMR yields are relative to an internal standard (1,3,5-trimethoxybenzene).

the reaction is performed in the presence of a copper additive.[28] The use of imidazole substrates has not been as intensively studied as the thiazoles, nonetheless, C5 and C2 arylations have been described under forcing conditions.[27a,b] While rarely employed in synthesis compared to the use of azine *N*-oxides, azole *N*-oxides were also evaluated in palladium-catalyzed direct arylation reactions.[18]

To evaluate the compatibility of thiazole *N*-oxides in these transformations, 4,5-dimethylthiazole *N*-oxide **11** was selected as a test substrate to eliminate any issues of regioselectivity. While the use of our standard conditions for azine *N*-oxide arylation provided the C2-arylated thiazole *N*-oxide in 79% isolated yield (Table 10, entry 1), we were pleased to find that

(26) For a recent advance under very mild conditions (60 °C) see:Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.

Table 15. C4 Direct Arylation of Thiazole *N*-Oxides[a–c]



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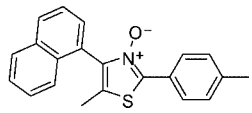
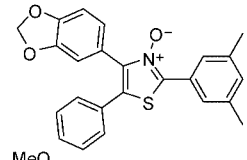
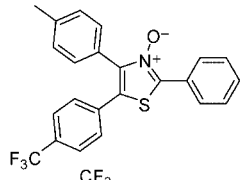
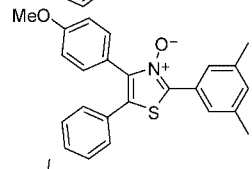
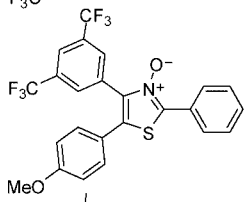
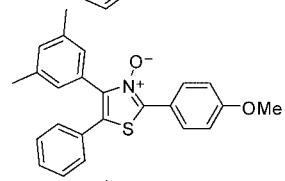
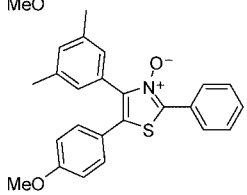
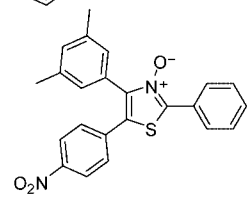
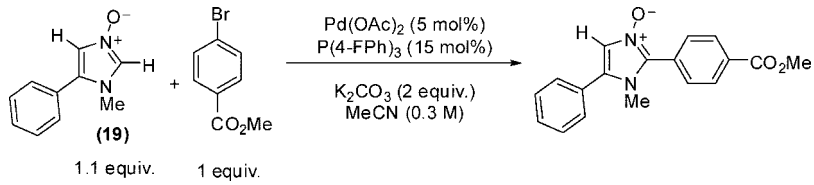
1		65	5		68
2		79	6		84
3		99	7		64
4		59	8		55

[a] Conditions: ArX (1 equiv), thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), K_2CO_3 (2.0 equiv), PivOH (20 mol %) in toluene (0.2 M) at 110 °C. [b] Isolated yields are reported above. [c] Cs_2CO_3 (2.0 equiv) used as the base.

Table 16. Optimization of a Mild C2 Arylation of Imidazole *N*-Oxides[a]

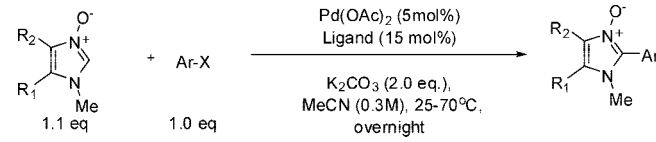


entry	ligand	additive (mol %)	temperature (°C)	^{1}H NMR yield (%)
1	$P(4\text{-}FPh)_3$	–	70	89
2	$P(4\text{-}FPh)_3$	PivOH (30)/CuBr (10)	25	68
3	Cy-John-Phos	PivOH (30)/CuBr (10)	25	1
4	Dave-Phos	PivOH (30)/CuBr (10)	25	83
5	**13**	PivOH (30)/CuBr (10)	25	92
6	**13**	PivOH (30)	25	75
7	**13**	CuBr (10)	25	15

[a] Conditions: Methyl-4-bromobenzoate (1 equiv), **19** (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (15 mol %), K_2CO_3 (2 equiv), additive (see Table 16), MeCN (0.3 M), temperature (see Table 16), 16−24 h. [b] ^{1}H NMR yields are relative to an internal standard (1,3,5-trimethoxybenzene).

thiazole *N*-oxides could be reacted under significantly milder conditions, even at 25 °C. At this temperature **13** was found to be the optimal ligand resulting in excellent yields in a variety of solvents. The C2 direct arylation of thiazole *N*-oxide is compatible with both activated and unactivated arylbromides (Table 11). If sterically encumbered arylbromides are used, superior yields may be obtained by changing the ligand from **13** to DavePhos. Arylchlorides may also be employed with DavePhos as the ligand if the reaction is performed at 70 °C. Aryl iodides are also compatible, however, in these cases, increased yield is observed if the base is changed from K_2CO_3 to Cs_2CO_3. When the C4 position is unsubstituted, the use of 10 mol % CuBr as an additive was found to enhance reactivity and provide greater reproducibility (Table 11, entries 14−21). While copper additives have been found to induce enhanced reactivity in reaction with other azole substrates,[28] its precise mechanism of action has not been definitively elucidated. Daugulis has shown that copper salts themselves may catalyze

Table 17. C2 Direct Arylation of Imidazole *N*-Oxide



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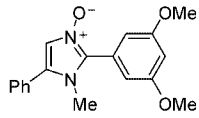
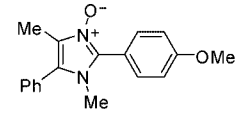
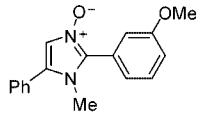
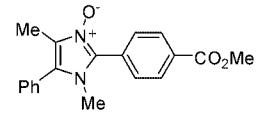
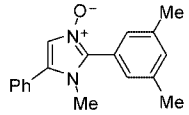
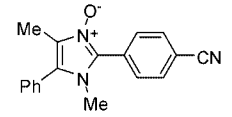
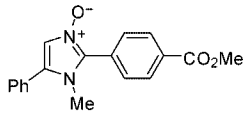
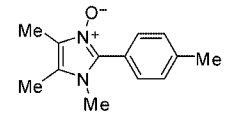
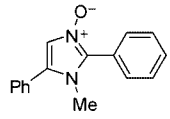
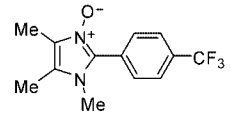
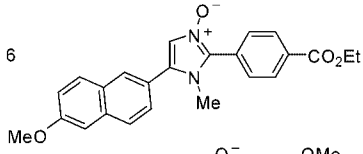
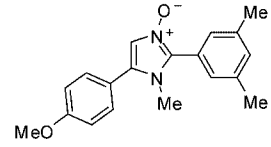
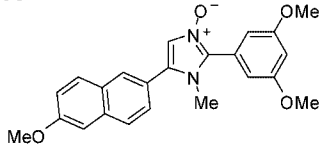
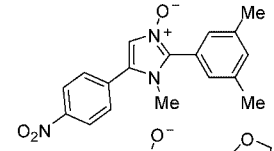
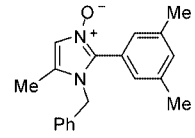
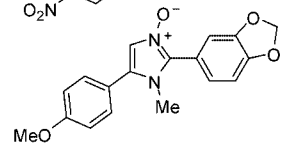
1		94[a]	9		70[a,c]
2		72[b]	10		96[a]
3		90[a], 61[b]	11		93[b]
4		95[a], 89[b]	12		70[a]
5		85[a], 73[b]	13		83[a,c]
6		93[a]	14		97[a]
7		79[a]	15		70[a]
8		91[a,c]	16		93[a,c]

[a] Conditiions: imidazole *N*-oxide (1.1 equiv), ArBr (1 equiv), $Pd(OAc)_2$ (5 mol %), *p*-FPh_3Ph (15 mol %), K_2CO_3 (2 equiv), MeCN (0.3 M), 70 °C, 20 h. [b] Conditions: imidazole *N*-oxide (1.1 equiv), ArBr (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand **13** (15 mol %), K_2CO_3 (2 equiv), PivOH (30 mol %), CuBr (10 mol %) MeCN (0.3 M), 25 °C, 20 h. [c] 30 mol % of PivOH was added.

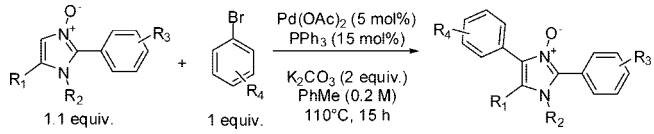
the cross-coupling of acidic arenes and aryl iodides via the intermediacy of an aryl copper intermediate.[11b,c,f] Given the mild nature of the reaction conditions and the lack of strong base to induce deprotonation, the mechanistic role for the copper in these copper-catalyzed processes and those involving the *N*-oxide substrates are plausibly dissimilar. A reaction with an aryltriflate was also performed (Table 11, entry 5) and a good yield was obtained when done at slightly higher temperature.

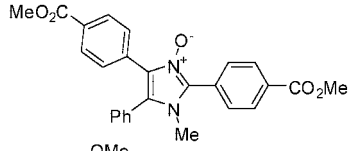
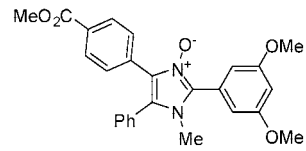
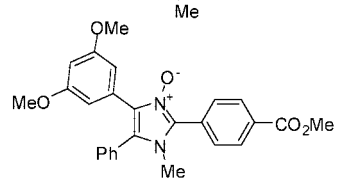
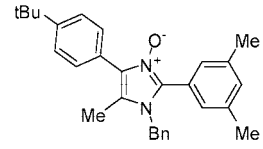
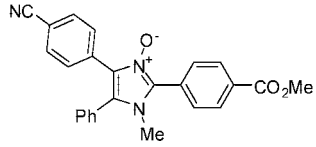
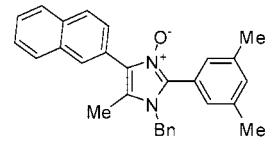
C2-substituted thiazole *N*-oxides have also been found to participate in these transformations at higher temperature, resulting in preferential arylation at C5 along with a mixture of C4- and C5/C4 double arylation under the C2 selective arylation protocol (Table 12, entries 1 and 2). Removal of the additives PivOH or PivOH/CuBr was found to improve selectivity for reaction at C5 arylation albeit with reduced conversion (Table 12, entry 3). A ligand screen revealed that P^tBu_3 in a ligand/Pd ratio of 1:1 not only maintained high C5 selectivtiy but also resulted in 100% conversion to the desired product (Table 12,

(27) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (b) Bellina, F.; Cauteruccio, S.; Mannina, L. *J. Org. Chem.* **2005**, *70*, 3997. (c) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. (d) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578. (e) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Tokunaga, K.; Gohma, K.; Komatsu, J.; Sekine, K.; Miyafuji, A.; Kunoh, J.; Honuma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257.

(28) (a) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379. (c) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, H.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (d) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111.

Table 18. C4 Direct Arylation of Imidazole *N*-Oxide[a]



Entry	Product	Yield[b]	Entry	Product	Yield[b]
1		73	4		66
2		77	5		63
3		87	6		59

[a] Conditions: Arylbromide (1 equiv), imidazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), K_2CO_3 (2 equiv), toluene (0.2 M), 110 °C, 15 h. [b] Isolated yields.

entries 6 and 7). Under these conditions, good yields could still be obtained when the stoichiometry of the thiazole *N*-oxide was reduced to 1.5 with respect to the aryl halide (entry 8). The C5 arylation of thiazoles is compatible with activated (Table 13, entries 1 and 11), unactivated (Table 13, entries 2 and 3), and sterically encumbered arylbromides (Table 13, entry 9). In addition, aryliodides and aryltriflates (when DavePhos is used as the ligand) also provide the C5 arylated thiazole *N*-oxide in synthetically useful yields (Table 13, entry 8).

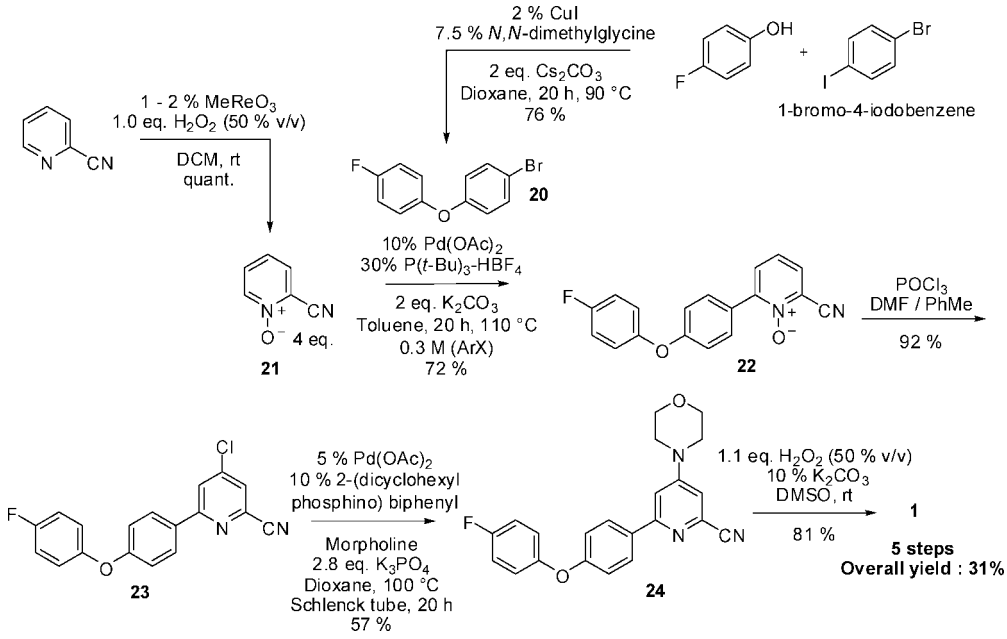
While precedent exists for arylation at C2 and C5 of the thiazole core, arylation at C4 has not previously been achieved. We were thus pleased to find that, under more forcing conditions, high-yielding C4 arylation could be achieved on thiazole *N*-oxide **17** possessing substituents at C2 and C5. Reaction optimization revealed that, at 110 °C, inexpensive triphenylphosphine provided the best results when used in a 3:1 ligand/Pd ratio and that no additional additives were required. Under these conditions a 76% yield of the triaryl thiazole *N*-oxide product **18** could be obtained (Table 14). Additional examples are included in Table 15. Aryl and alkyl groups are tolerated at C2 and C5, and activated, unactivated, and sterically encumbered arylbromides can be coupled in good to excellent yield (Table 15). Aryliodides were also found to be compatible if Cs_2CO_3 is used as the base.

Development of Conditions for the Direct Arylation of Imidazole *N*-Oxide. In conjunction with our studies on the arylation of thiazole *N*-oxides, attempts were made to extend these reactions to other azole substrates. These efforts lead to the discovery that imidazole *N*-oxides are also excellent substrates for direct arylation at C2 and C4. Optimization efforts focusing on C2 lead to the development of two sets of reaction conditions. The first set of conditions is operationally simple and does not require the use of pivalic acid or copper additives. It was determined that treatment of the aryl bromide with a slight excess of the imidazole *N*-oxide **19** in the presence of 5 mol % $Pd(OAc)_2$, 15 mol % tri(4-fluorophenyl)phosphine, and 2 equiv of K_2CO_3 in acetonitrile at 70 °C gives the C2-arylated product in 89% yield (Table 16, entry 1). With the goal of establishing a room temperature process, these conditions were reinvestigated and it was ultimately determined that by changing the ligand to **13** and adding 30 mol % pivalic acid along with 10 mol % CuBr, the same process can be induced to occur at 25 °C. We hypothesize that the pivalate generated by the combination of the pivalic acid and the carbonate base could serve in several roles in the catalytic cycle, including as a proton shuttle. Thus, it may be intimately involved in the C−H bond cleaving transition state and subsequently deliver the proton to the largely insoluble potassium carbonate stoichiometric base.[29] Regardless of the precise roles, both the pivalic acid and the copper act to enhance the yield of the reaction. For example, if either is removed from the reaction mixture, reduced yields are obtained (Table 16 entries 6 and 7). More mechanistic work will be required on this aspect of the chemistry before a more precise hypothesis can be advanced.

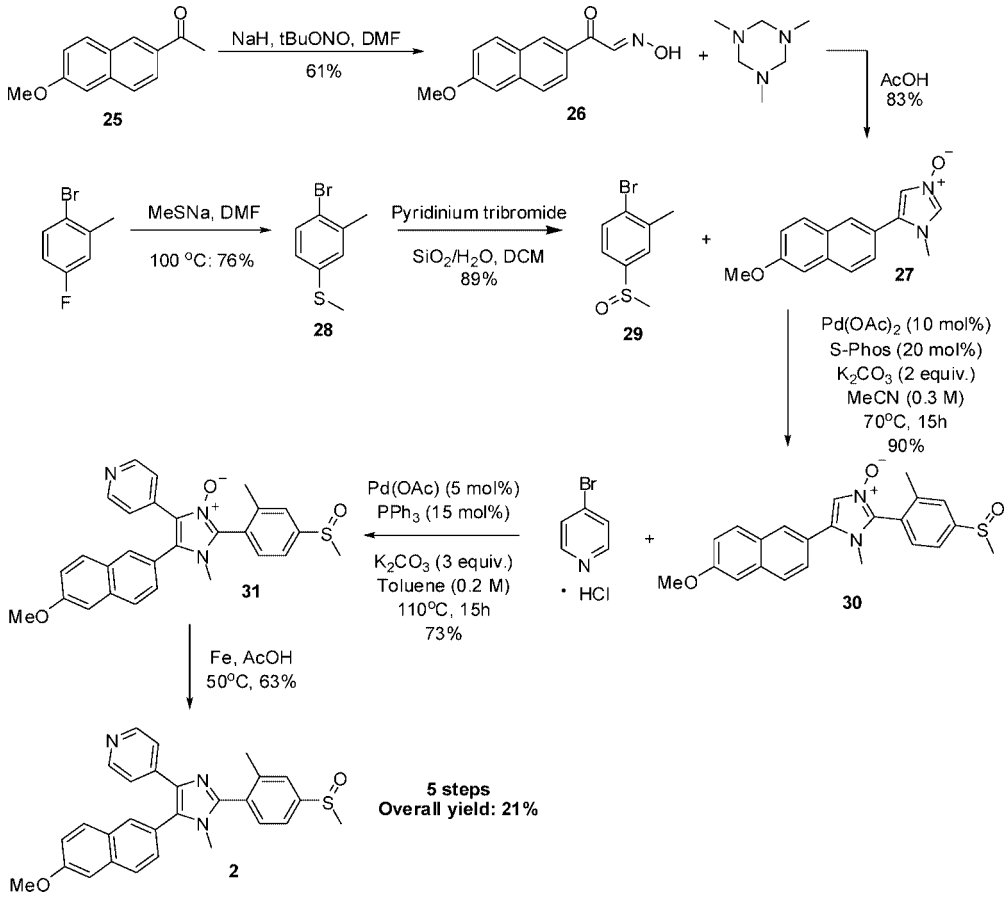
Additional examples of C2 arylation are illustrated in Table 17. Activated and unactivated aryl bromides react to give C2 arylation in good to excellent yields in the presence of alkyl or aryl substitution at the C4 or C5 positions (Table 17). In addition, when the *N*-oxide is unsubstituted at the C4 position a single regioisomer arylated at the C2 position can be obtained illustrating a strong preference for reaction of C2 over C4. (Table 17). As was determined with the thiazole *N*-oxide substrates, when both the C2 and C5 positions are substituted, arylation may also be achieved at C4 under identical conditions used for the thiazole *N*-oxide compounds (Table 18). Again, both aryl and alkyl substitution is tolerated at the C5 position. Also,

(29) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

Scheme 2. Synthetic Route to **1** Employing Direct Arylation Methodology



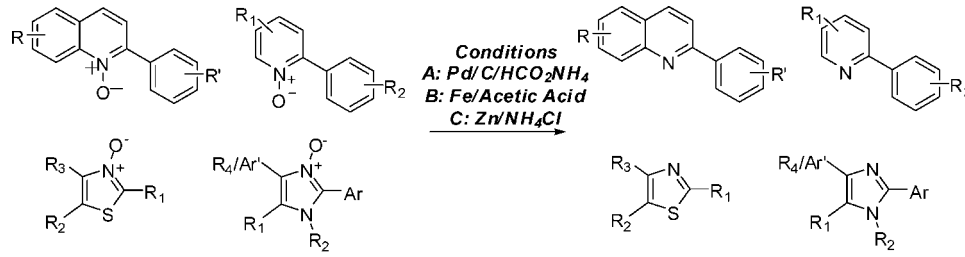
Scheme 3. Synthesis of a Tie2 Tyrosine Kinase Inhibitor

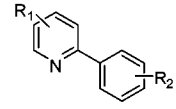
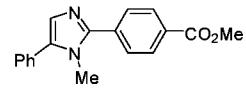
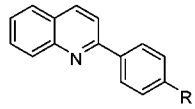
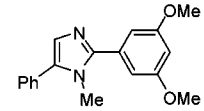
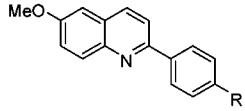
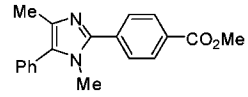
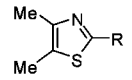
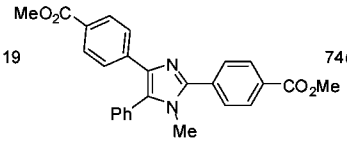
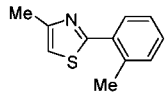
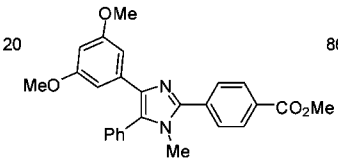
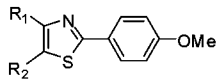
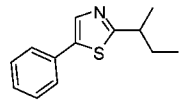
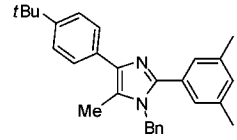


activated and unactivated arylbromides provide the completely functionalized imidazole *N*-oxide products in good yield (Table 18).

Azine, Azole *N*-Oxide Deoxygenation. The utility of the direct arylation methodology of azine and azole *N*-oxides relies on the ability either to employ the *N*-oxide moiety in other types of azine/azole functionalization[16] or to easily induce *N*-oxide deoxygenation under mild conditions subsequent to direct arylation.[30] Three different conditions were typically employed on the basis of the substrate undergoing reaction. Azine *N*-oxides can be readily reduced to the corresponding aryl azine by Pd/C with ammonium formate or under a hydrogen atmosphere. Reactions are run at room temperature, proceed in relatively short reaction times, and provide the products in good to

Table 19. Reduction of Azine and Azole *N*-Oxides[a]



Entry	Product	Yield(Cond.)[b]	Entry	Product	Yield(Cond.)[b]
1		R_1=H; R_2=4-Me 95(A)	16		94(B)
2		R_1=H; R_2=3-OMe 87(A)			
3		R_1=4-OMe; R_2=4-Me 84(A)			
4		R_1=H; R_2=4-CO_2Me 87(A)			
5		R=Me 94(A)	17		76(B)
6		R=OMe 93(A)			
7		R=CO_2Et 80(A)			
8		R=H 93(A)	18		94(B)
9		R=OMe 79(A)			
10		R=*m*-xylyl 83(B)	19		74(B)
11		R=tolyl 99(C)			
12		65(C)	20		86(B)
13		R_1=H; R_2=H 84(C)			
14		R_1=H; R_2=Ph 99(C)			
15		78(C)	21		70(B)

[a] Conditions: (**A**) *N*-oxide (1 equiv), 10% Pd/C (10 mol % Pd), ammonium formate (10 equiv), methanol (0.1 M), room temperature. (**B**) *N*-oxide (1 equiv), Fe (dust, 10 equiv), acetic acid (0.1 M), 50 °C, 20 h. (**C**) *N*-oxides (1 equiv), zinc dust (10 equiv), THF/$NH_4Cl_{(aq,sat)}$ (1:1 vol/vol, 0.033 M), rt, 1 h. [b] Isolated yields are reported.

excellent yield. This protocol is not compatible with some functional groups such as aryl halides, however. In these cases use of Zn dust in aqueous ammonium chloride/THF can selectively achieve deoxygenation without inducing hydrodechlorination (see Table 8, entry 7). In our hands, the deoxygenation of azole *N*-oxide compounds, proceeded most smoothly under the latter two sets of conditions (Fe/acetic acid or Zn/ammonium chloride). Illustrative examples are shown in Table 19.

Applications in Synthesis. With the goal of illustrating the utility of this methodology in the preparation of medicinal compounds, two targets were selected—the sodium channel inhibitor **1**[31] and the Tie2 Tyrosine Kinase inhibitor **2**[32] (Scheme 1). The synthesis of sodium channel inhibitor **1** has been previously described by Perdue Pharma in seven steps providing an overall yield of 7%.[31] We envisioned that the *N*-oxide cross-coupling strategy could not only employ the *N*-oxide to form the biaryl carbon−carbon bond, but also be used to form the C4 carbon−nitrogen bond. Thus, the diarylether fragment **20** was prepared by a copper-catalyzed cross-coupling of 4-fluorophenol and 1-bromo-4-iodobenzene.[33] Now commercially available, the 2-cyanopyridine *N*-oxide **21** was prepared quantitatively by treatment of 2-cyanopyridine with methyltrioxorhenium (MTO) and aqueous hydrogen peroxide in dichloromethane.[19] These two fragments were coupled under standard direct arylation conditions to afford the 2-aryl-6-cyanopyridine *N*-oxide **22** in 72% yield. With the 2- and 6-positions blocked,

(30) Please see ref 23 for reduction with Pd/C/ammonium formate and Zn/ammonium chloride. For reduction with Fe/acetic acid please see: Julemont, F.; de Leval, X.; Michaux, C.; Renard, J.-F.; Winum, J.-Y.; Montero, J.-L.; Damas, J.; Dogne, J.-M.; Pirotte, B. *J. Med. Chem.* **2004**, *47*, 6749.

(31) Shao, B.; Victory, S.; Ilyin, V. I.; Goehring, R. R.; Sun, Q.; Hogenkamp, D.; Hodges, D. D.; Islam, K.; Sha, D.; Zhang, C.; Nguyen, P.; Robledo, S.; Sakellaropoulos, G.; Carter, R. B. *J. Med. Chem.* **2004**, *47*, 4277.

(32) (a) Johnson, N. W.; Semones, M.; Adams, J. L.; Hansbury, M.; Winkler, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5514. (b) Semones, M.; Feng, Y.; Johnson, N.; Adams, J. L.; Winkler, J.; Handbury, M. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4756.

(33) Dawei, M.; Cai, Q. *Org. Lett.* **2003**, *21*, 3799.

treatment of **22** with $POCl_3$ results in deoxygenation and the formation of the C4 carbon−chlorine bond in **23** in 92% yield.[16b] The newly installed C4-chlorine was used in a Buchwald−Hartwig amination with morpholine to give **24**.[34] Finally the nitrile functional group was hydrolyzed to the corresponding amide by treatment with hydrogen peroxide[35] to provide **1** in five steps and an overall yield of 31%.

The medicinal chemistry synthesis of Tie2 Tyrosine Kinase inhibitor **2** builds the imidazole core with the requisite substitution at C2, C4, and C5 already installed.[32] We envisioned that the triaryl arrangement around the imidazole ring would lend itself well to an exhaustive direct arylation of the imidazole *N*-oxide core and that such an approach may also be amenable to analogue synthesis. To begin, ketone **25** was treated with NaH and *t*-butylnitrite to provide the α-ketooxime **26**.[21c] Reaction of α-ketooxime **26** with 1,3,5-trimethyl-1,3,5-triazinane provides imidazole *N*-oxide **27** in 51% yield over two steps.[21d,e] The bromoarylsulfoxide **29** was prepared via an S_NAr reaction of 4-fluoro-2-methylbromobenzene with sodium methanethiolate followed by oxidation to the sulfoxide in 68% yield over two steps. Use of the sterically encumbered **29** in the direct arylation of **27** resulted in lower yields under the standard C2 arylation conditions, ascribable to the increased steric bulk of the aryl halide coupling partner. A rapid reinvestigation of other ligands revealed that the use of S-Phos was superior to the use of tri-*p*-fluorophenylphosphine. Under these modified conditions, desired direct arylation was achieved to provide **30** in 90% isolated yield. A second direct arylation at C4 using 4-bromopyridine was achieved with no change to the standard C4 arylation conditions to generate the triarylimidazole *N*-oxide **31** in 73% isolated yield. Selective reduction of the *N*-oxide moiety leaving the sulfoxide intact was carried out with iron and acetic acid to yield **2** with the longest linear sequence of five steps and an overall yield of 21%.

(34) Wolfe, J. P.; Tomori, H.; Sadihgi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
(35) Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis* **1989**, *12*, 949.

Conclusion

Palladium-catalyzed direct arylation can be performed with a broad range of azine and azole *N*-oxides and should provide a valuable alternative to the use of traditional cross-coupling techniques when the synthesis of appropriate heterobiaryl compounds is required. In addition to functional group compatibility, issues of regioselectivity have been explored and the potential utility of these processes in the preparation of medicinal compounds has been evaluated. In addition to laying the groundwork for a broader application of this chemistry, the results described should provide useful benchmarks in the consideration of possible reaction mechanisms for the azine/azole C−H bond cleavage. These studies are underway and will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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