JOC Article
pubs.acs.org/joc

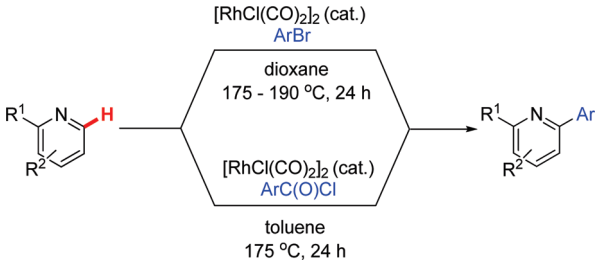
Rh(I)-Catalyzed Direct Arylation of Azines

Ashley M. Berman,[†] Robert G. Bergman,*[,†] and Jonathan A. Ellman*[,‡]

[†]*Department of Chemistry, University of California, and Division of Chemical Sciences, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States, and* [‡]*Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States*

jonathan.ellman@yale.edu; rbergman@berkeley.edu

Received September 15, 2010



The Rh(I)-catalyzed direct arylation of azines has been developed. Quinolines and 2-substituted pyridines couple with aryl bromides to efficiently afford ortho-arylated azine products using the commercially available and air-stable catalyst $[RhCl(CO)_2]_2$. Electron-deficient and electron-rich aromatic bromides couple in good yields, and hydroxyl, chloro, fluoro, trifluoromethyl, ether, and ketone functionalities are compatible with the reaction conditions. Aroyl chlorides also serve as effective azine coupling partners to give ortho-arylation products via a decarbonylation pathway.

Introduction

Methodology for the regioselective arylation of azines is dominated by strategies relying on initial stoichiometric pre-functionalization of the heterocycle, either as the halo or organometallic intermediate, prior to a subsequent arylation step.[1] While catalytic direct arylation protocols have been extensively developed for electron-rich heterocycle and arene classes,[2] the direct arylation of azines has met with considerably less success despite the enormous importance of azines in drugs.[3] Recently, conditions for the catalytic direct arylation of azine *N*-oxides,[4] *N*-iminopyridinium ylides,[5] and *N*-phenacylpyridinium bromides[6] with aryl halides have been developed. These methods represent a major improvement, obviating the need to handle costly and in many instances unstable organometallic azine intermediates; however, they do require preactivation of the azine as well as additional synthetic manipulations to obtain the final arylated azine products. The most direct route to this useful compound class would proceed by catalytic direct arylation of an unactivated azine with readily available electrophilic coupling partners.[7,8] In an

(1) The use of 2-pyridyl organometallics is particularly troublesome; for leading references on recent advances, see: (a) Metzger, A.; Bernhardt, S.; Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4665. (b) Kim, S.-H.; Rieke, R. D. *Tetrahedron* **2010**, *66*, 3135. (c) Ackermann, L.; Potukuchi, H. K.; Kapdi, A. R.; Schulzke, C. *Chem.—Eur. J.* **2010**, *16*, 3300. (d) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961. (e) Deng, J. Z.; Paone, D. V.; Ginnetti, A. T.; Kurihara, H.; Dreher, S. D.; Weissman, S. A.; Stauffer, S. R.; Burgey, C. S. *Org. Lett.* **2009**, *11*, 345. (f) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695.

(2) For recent reviews on direct arylation of heteroarenes, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (b) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(3) For an analysis of heterocycles used in the preparation of drug candidates, see: Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(4) (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (b) Campeau, L. S.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(5) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.

(6) Xu, J.; Cheng, G.; Su, D.; Liu, Y.; Wang, X.; Hu, Y. *Chem.—Eur. J.* **2009**, *15*, 13105.

(7) (a) For a recent example employing organozincs as a nucleophilic arylating reagent for the catalytic direct arylation of azines, see: Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (b) For a non-regioselective direct arylation of azines with aryl iodides promoted by KO*t*-Bu, see: Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (c) For the direct ortho-arylation of amides of nicotinic and isonicotinic acid, see: Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (d) For the Cu-catalyzed direct arylation of pyrimidine and pyridazine with phenyl iodide, see: Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

DOI: 10.1021/jo101793r Published on Web 10/29/2010

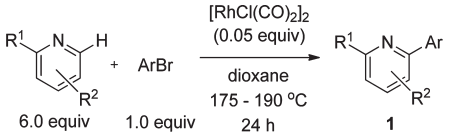
initial communication, we documented our efforts in this vein, culminating in a Rh(I)-catalyzed direct arylation of pyridines and quinolines with aryl bromides.[9] We now wish to report our studies further exploring the scope of this method, including the discovery that aroyl chlorides are competent electrophilic coupling partners in this direct arylation strategy.[10]

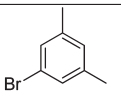
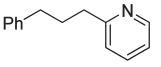
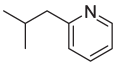
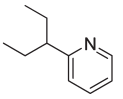
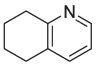
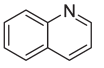
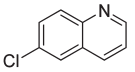
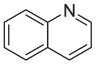
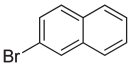
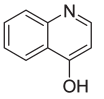
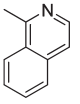
Results and Discussion

Catalytic Direct Arylation of Azines with Aryl Bromides. We previously developed a Rh(I)-catalyzed direct arylation of pyridines and quinolines allowing for the efficient arylation of this azine class without prefunctionalization of the heterocycle component.[9] The optimized conditions employ the electron-poor catalyst $[RhCl(CO)_2]_2$, an aryl bromide as the limiting reagent,[11] the appropriate heterocycle starting material (3−6 equiv), and heating in dioxane for 24 h. A more extensive evaluation of heterocycle scope has now established that a variety of substituted pyridines, and to some extent other heterocycles, are effective substrates under these reaction conditions (Table 1). Straight chain (entries 1 and 2), α-branched (entry 3), and *β*-branched (entry 4) aliphatic substituted pyridines at the C-2 position all undergo efficient cross-coupling with 3,5-dimethylbromobenzene. Tetrahydroquinoline also provides the arylated product in good yield (entry 5), as does the more highly substituted 2,4-dimethylpyridine (entry 6). In contrast, when a substituent at the C-2 position is absent, arylation does not occur, as observed for the attempted direct arylation of pyridine (entry 7). Consistent with the requirement for C-2 substitution, quinoline also participates in regioselective direct arylation (entry 8), as do chloro- and hydroxy-substituted derivatives (entries 9 and 11, respectively). An appropriately substituted isoquinoline can be regioselectively arylated, albeit in lower yields (entry 12). Further studies exploring the scope in heterocycle identified 2,3-dimethylpyrazine and 4,6-dimethylpyrimidine as competent diazenes for this direct arylation reaction (entries 13 and 14, respectively). We surveyed the use of a variety of 2-heteroatom-substituted pyridines (including 2-chloropyridine, 2-aminopyridine, and several 2-hydroxypyridine derivatives). In all cases, no arylation product was detected.

The substrate scope in aryl bromide was also evaluated with quinoline as the coupling partner (Table 2). Electron-rich and electron-poor aryl bromides are accommodated with equal efficiency (compare, for example, entries 4 and 11). A variety of useful functional groups are tolerated, including aryl and alkyl ethers (entries 3 and 4), chloride (entry 8), fluoride (entry 9), and ketone functionality (entry 10).

TABLE 1. Investigation of Scope in Heterocycle



entry	azine	ArBr	product	yield (%)[a]
1			**1a**	53
2		”	**1b**	51
3		”	**1c**	78
4		”	**1d**	70
5		”	**1e**	76
6		”	**1f**	67
7		”	**1g**	0
8		”	**1h**	86[b]
9		”	**1i**	65[b]
10			**1j**	73[b]
11		”	**1k**	49[c]
12		”	**1l**	24[b]
13		”	**1m**	26[b]
14		”	**1n**	33[b]

[a]Isolated yield of analytically pure product; 0.4 mmol scale in ArBr; 0.8 M absolute concentration in ArBr. [b]Reaction run at 175 °C and 0.3 M absolute concentration in ArBr. [c]Reaction run at 165 °C and 0.3 M absolute concentration in ArBr.

While cross-coupling proceeds smoothly with meta substitution on the aryl bromide ring (see, for example, entry 1), attempted cross-coupling with 2-bromotoluene failed to afford product (entry 13), with only unreacted

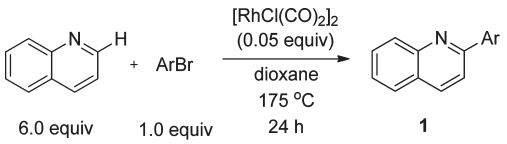
(8) For the direct alkylation or alkenylation of pyridines, see: (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (b) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170. (c) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (d) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (e) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2978. (f) Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277. (g) Nakao, Y.; Yamada, Y.; Ksahihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666.

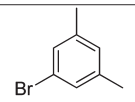
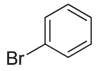
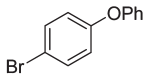
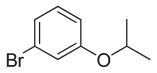
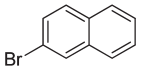
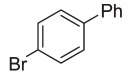
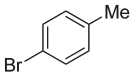
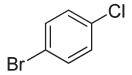
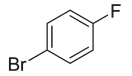
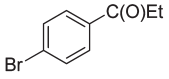
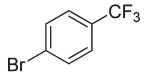
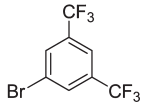
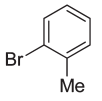
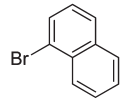
(9) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926.

(10) For the use of acid chlorides and acid anhydrides as electrophilic arylating reagents in Rh(I)-catalyzed direct arylation of arenes, see: (a) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (b) Jin, W.; Yu, Z.; He, W.; Ye, W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 1317.

(11) For a complete list of optimization parameters examined, refer to ref 9.

TABLE 2. Investigation of Scope in Aryl Bromide

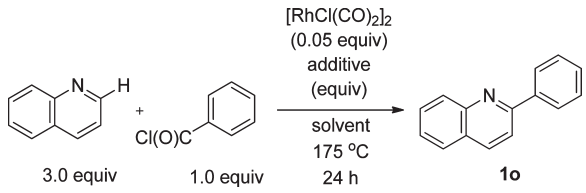


entry	ArBr	product	yield (%)[a]
1		**1h**	86
2		**1o**	74
3		**1p**	62
4		**1q**	70
5		**1j**	73
6		**1r**	77
7		**1s**	69
8		**1t**	68
9		**1u**	69
10		**1v**	70
11		**1w**	65
12		**1x**	45
13		**1y**	0
14		**1z**	9

[a]Isolated yield of analytically pure product; 0.4 mmol scale in ArBr; 0.3 M absolute concentration in ArBr.

starting material recovered. In the case of 1-bromonaphthalene, the arylated product was obtained in only 9% yield (entry 14).

TABLE 3. Direct Arylation of Quinoline with Benzoyl Chloride



entry	additive (equiv)	solvent	concn (M)[a]	yield (%)[b]
1	none	dioxane	0.3	32
2	none	dichlorobenzene	0.3	45
3	none	trifluorotoluene	0.3	56
4	none	mesitylene	0.3	58
5	none	toluene	0.3	56
6	Na_2CO_3 (3.0)	toluene	0.3	10
7	K_3PO_4 (3.0)	toluene	0.3	0
8	none	toluene	0.15	29
9	none	toluene	0.6	64
10[c]	none	toluene	0.3	60
11[d]	none	toluene	0.3	75

[a]Refers to the absolute concentration in benzoyl chloride. [b]Determined by GC analysis with hexamethylbenzene as an internal standard. [c]Reaction run at 190 °C. [d]With 6.0 equiv of quinoline employed.

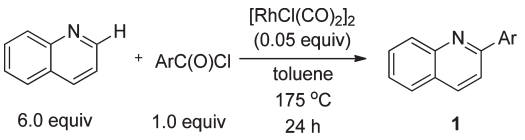
Catalytic Direct Arylation of Azines with Aroyl Chlorides. Recent work has documented the use of aroyl chlorides in Rh(I)-catalyzed decarbonylative direct arylation of arenes.[10] Owing to the similarity in reaction conditions employed in these systems to our own, we envisioned that this manifold may be amenable to our present system. As such, with the optimized conditions for the direct arylation of quinoline with aryl bromides as a starting point, we evaluated the use of benzoyl chloride as an electrophilic coupling partner (Table 3).[12] Under these conditions, an encouraging 32% yield of 2-phenylquinoline was obtained (entry 1). Importantly, we did not observe any formation of ketone, consistent with a decarbonylative manifold for the present reaction. Switching from dioxane to a variety of aromatic solvents proved fruitful, with yields improving under otherwise identical conditions with dichlorobenzene, trifluorotoluene, mesitylene, or toluene as solvent (entries 2−5). We next evaluated the inclusion of inorganic base additives, but consistent with our previous observations for the direct arylation with aryl bromides,[9] these additives also proved deleterious when benzoyl chloride is used as the electrophile (entries 6 and 7). The choice of absolute concentration proved important, with the best results being obtained at relatively high concentrations in benzoyl chloride (compare entries 8 and 9). The reactions were typically run at 175 °C but could be heated to 190 °C with equal efficiency (entry 10). Lastly, the product was obtained in modestly higher yield upon using 6 equiv of quinoline under otherwise identical conditions (compare entries 5 and 11).[13]

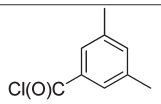
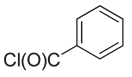
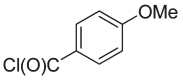
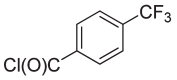
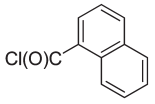
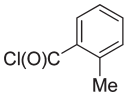
Having identified optimal conditions for the direct arylation of quinoline with benzoyl chloride, we next evaluated the generality of this new protocol with a variety of aroyl chlorides (Table 4). Both benzoyl chloride and 3,5-dimethylbenzoyl chloride provided high isolated yields of the 2-arylquinolines **1h** and **1o** (entries 1 and 2, respectively). Electron-rich aroyl chlorides coupled efficiently under these conditions, while the

(12) The use of benzoic acid anhydride was also evaluated; in this case, only trace cross-coupling product was detected.

(13) Other rhodium complexes served as competent precatalysts for this reaction. Under the conditions described in Table 3, entry 5, the following yields of **1o** were obtained with 5 mol % of catalyst: $[RhCl(COD)]_2$, 50%; $Rh(acac)(CO)_2$, 51%; $[RhCl(CH_2CH_2)]_2$, 37%.

TABLE 4. Investigation of Scope in Aroyl Chloride

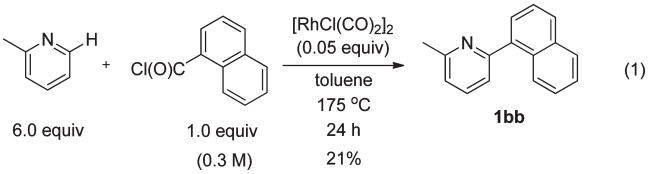


entry	ArC(O)Cl	product	yield (%)[a]
1		**1h**	76
2		**1o**	66
3		**1aa**	56
4		**1w**	24
5		**1z**	54
6		**1y**	52

[a]Isolated yield of analytically pure product; 0.4 mmol scale in ArC(O)Cl; 0.3 M absolute concentration in ArC(O)Cl.

use of electron-poor aroyl chlorides proved more challenging (compare entries 3 and 4). Importantly, sterically congested 1-naphthoyl and 1-methylbenzoyl chlorides proved to be competent coupling partners, providing access to the 2-arylquinolines **1z** and **1y** in good yields (entries 5 and 6, respectively). The successful coupling of 2-substituted aroyl chlorides expands the range of direct arylation products that can be obtained because coupling ortho-substituted aryl bromides was previously found to proceed in very low yields (see Table 2, entries 13 and 14).

The use of heterocycles other than quinoline was evaluated. For the case of 2-methylpyridine, a 21% yield of **1bb** was obtained upon reaction with 1-naphthoyl chloride, indicating that the efficiency of coupling aroyl chlorides is quite sensitive to azine structure (eq 1).[14]



(1)

Proposed Mechanism. A plausible mechanism for the Rh(I)-catalyzed direct arylation of azines with aryl bromides is presented in Figure 1. Initial nitrogen coordination of the 2-substituted pyridine to $[RhCl(CO)_2]_2$ provides adduct **2**. Subsequent *ortho*-C−H activation provides **3**, which may tautomerize to N-heterocyclic carbene (NHC) complex **4**. We have previously characterized NHC Rh complexes for a variety of nitrogen heterocycles,[15] and others have characterized pyridine- and quinoline-based Os, Ru, and Ir-NHC complexes also prepared via C−H activation.[16] Upon solvent or azine coordination and reductive elimination of HX to give **5**, oxidative addition of the aryl bromide would then provide **6**. Subsequent reductive elimination and exchange with the pyridine starting material would regenerate N-bound Rh complex **2**. This catalytic cyclic is also applicable to the direct arylation with aroyl chlorides whereby oxidative addition to **5** would be followed by decarbonylation to generate **6** (Br would be replaced with Cl). Alternative catalytic cycles are possible; for example, oxidative addition of the aryl bromide or aroyl chloride might occur prior to C−H bond activation.[17] Mechanistic study will clearly be necessary to discriminate between the different possible catalytic cycles.

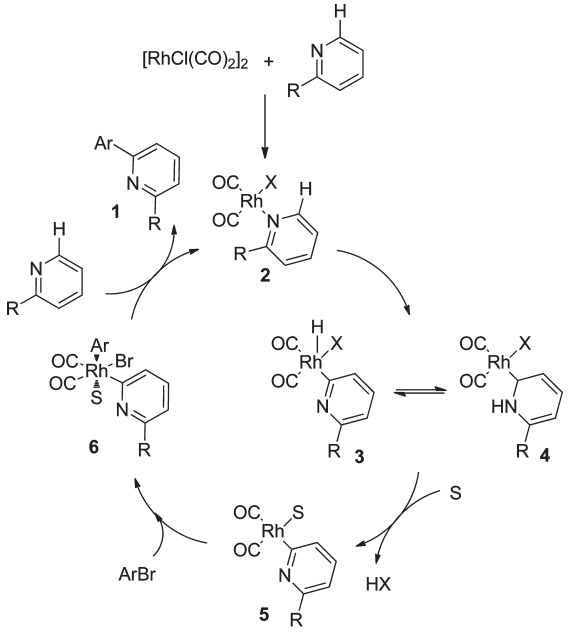


FIGURE 1. Proposed mechanism for the catalytic direct arylation of azines with aryl bromides.

The proposed mechanism can be used to rationalize the requirement that the pyridine be ortho-substituted in order to achieve successful arylation (see entry 7, Table 1). Presumably, unfavorable steric interactions in the N-bound complex of ortho-substituted pyridines increase the equilibrium ratio of the C2-bound rhodium complexes **3** or **4**

(14) Similar results were obtained with other substituted pyridines and diazenes; under identical conditions, the coupling of 2-(3-pentyl)pyridine with 3,5-dimethylbenzoyl chloride afforded a 16% yield of 2-(3,5-dimethylphenyl)-6-(3-pentyl)pyridine, while the coupling of 2,3-dimethylpyrazine with 3,5-dimethylbenzoyl chloride afforded a 31% assay yield of 2-(3,5-dimethylphenyl)-5,6-dimethylpyrazine.

(15) (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (b) Wiedemann, S. H.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 2452.

(16) (a) Alvarez, E.; Conejero, S.; Paneque, M.; Petronilho, A.; Poveda, M. L.; Serrano, O.; Carmona, E. *J. Am. Chem. Soc.* **2006**, *128*, 13060. (b) Esteruelas, M. A.; Fernandez-Alvarez, F. J.; Onate, E. *J. Am. Chem. Soc.* **2006**, *128*, 13044. (c) Buil, M. L.; Esteruelas, M. A.; Garcés, K.; Oliván, M.; Oñate, E. *J. Am. Chem. Soc.* **2007**, *129*, 10998.

(17) For the related Rh-catalyzed alkylation of azines with alkenes, C−H activation is followed by alkene insertion, suggesting the competence of C−H activation prior to ArBr or aroyl chloride activation. See ref 8a.

relative to the N-bound rhodium complex **2**. These results are consistent with reports on the preparation and characterization of (2-substituted)-pyridine- and quinoline-based Os and Ir-NHC complexes wherein ortho-substitution was necessary for obtaining the complexes.[16] The requirement for ortho-substitution is also consistent with our observations that the Rh-catalyzed intermolecular alkylation of pyridines with alkenes only occurs when the pyridine substrates are substituted at the ortho position.[8a]

Conclusion

In summary, we have developed a Rh(I)-catalyzed strategy for the direct arylation of azines. A variety of differentially substituted aryl bromides and aroyl chlorides can be used in this protocol, including chloro, fluoro, trifluoromethyl, ether, and ketone functionality. The heterocycle is used directly *without* requiring any prefunctionalization. This strategy represents an expeditious route to an important class of arylated azines and for appropriate substrates should be of broad utility.

Experimental Section

General Procedure for the Catalytic Direct Arylation of Azines with Aryl Bromides. To a 15 or 25 mL sealable flame- or oven-dried Schlenk tube (Kontes No. 218710-0015 or 218710-0025) containing a stir bar were added $[RhCl(CO)_2]_2$ (0.0078 g, 0.0200 mmol), the heterocycle (2.400 mmol), the aryl bromide (0.400 mmol), and 1,4-dioxane (reaction solution diluted to a total concentration of 0.30−0.80 M). The volume of the heterocycle is not negligible at the concentrations used and must therefore be included in the concentration calculation. The reaction vessel was sealed, removed from the glovebox, submerged to the neck in a silicone oil bath, heated at the indicated temperature with stirring for 24 h, and then cooled to room temperature. The reaction mixture was transferred to a 60 mL separatory funnel using 3 × 5.0 mL of CH_2Cl_2 and 2.5 mL of MeOH. The resulting solution was washed with saturated $NaHCO_3$ (1 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with saturated NaCl (1 × 20 mL), dried over Na_2SO_4, filtered through glass wool, and concentrated to dryness under reduced pressure. The crude product mixture was loaded onto a Biotage samplet using a minimal amount of CH_2Cl_2 (ca. 0.5 mL). This solvent was removed by placing the samplet under reduced pressure in a vacuum desiccator for ca. 15 min, and the samplet was loaded into a Biotage SP1 system. Eluting with an ethyl acetate/hexanes gradient calculated by the instrument from the R_f of the product in a specified ethyl acetate/hexanes mixture provided the desired product.

2-(3,5-Dimethylphenyl)quinoline (1h). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), 1-bromo-3,5-dimethylbenzene (0.0740 g, 0.400 mmol), and 1.0 mL of 1,4-dioxane at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0800 g, 86% yield of **1h** as a clear, colorless oil: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.34−8.12 (m, 2 H), 7.91−7.67 (m, 5 H), 7.49−7.45 (m, 1 H), 7.08 (br s, 1 H), 2.41 (s, 6 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 157.9, 148.4, 139.8, 138.5, 136.7, 131.2, 129.8, 129.7, 127.6, 127.3, 126.3, 125.6, 119.4, 21.6; HRMS-EI (m/z) calcd for $C_{17}H_{15}N$ 233.1205, observed 233.1203.

2-(2-Naphthyl)-4-hydroxyquinoline (1k). To a 15 mL sealable flame-dried Schlenk tube (Kontes No. 218710-0015) containing a stir bar were added $[RhCl(CO)_2]_2$ (0.0038 g, 0.0100 mmol), 4-hydroxyquinoline (0.0436 g, 0.300 mmol), 2-bromonaphthalene (0.0207 g, 0.100 mmol), and 0.33 mL of 1,4-dioxane. The reaction vessel was sealed, removed from the glovebox, submerged to the neck in a silicone oil bath, heated at 165 °C for 24 h, and then cooled to room temperature. The reaction mixture was transferred to a 60 mL separatory funnel using 3 × 5.0 mL of CH_2Cl_2 and -2.5 mL of MeOH. The resulting solution was washed with saturated $NaHCO_3$ (1 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with saturated NaCl (1 × 20 mL), dried over Na_2SO_4, filtered through glass wool, and concentrated to dryness under reduced pressure. The crude product mixture was loaded onto a Biotage samplet using a minimal amount of CH_2Cl_2 and MeOH (ca. 0.5 mL). This solvent was removed by placing the samplet under reduced pressure in a vacuum desiccator for ca. 15 min, and the samplet was loaded into a Biotage SP1 system. Eluting with a methanol/dichloromethane gradient calculated by the Biotage instrument provided 0.0133 g, 49% yield of **1k** as a pale yellow powder: R_f (5% methanol/dichloromethane) 0.45; mp 275 °C (decomp); ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 11.87 (br s, 1 H), 8.48 (s, 1 H), 8.14−8.10 (m, 3 H), 8.06−8.03 (m, 1 H), 7.96−7.94 (m, 1 H), 7.83−7.81 (m, 1 H), 7.73−7.64 (m, 3 H), 7.38−7.35 (m, 1 H), 6.50 (s, 1 H); ^{13}C {^{1}H} NMR (100.61 MHz, DMSO-d_6) δ 176.7, 150.3, 141.1, 134.0, 133.0, 132.3, 132.0, 129.1, 129.1, 128.2, 128.0, 127.6, 127.5, 125.4, 125.2, 125.0, 123.8, 119.2, 108.2; HRMS-EI (m/z) calcd for $C_{19}H_{14}NO$ 272.1070, observed 272.1072.

1-Methyl-3-(2-naphthyl)isoquinoline (1l). The reaction was conducted with 1-methylisoquinoline (0.3432 g, 2.400 mmol), 2-bromonaphthalene (0.0828 g, 0.400 mmol), and 1.00 mL of 1,4-dioxane at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0236 g, 22% yield of **1l** as a white powder: R_f (10% ethyl acetate/hexanes) 0.50; mp 128 − 130 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.33−8.30 (m, 1 H), 8.21−8.19 (m, 1 H), 8.12 (s, 1 H), 8.05−8.00 (m, 2 H), 7.95−7.92 (m, 2 H), 7.76−7.72 (m, 1 H), 7.66−7.61 (m, 1 H), 7.58−7.52 (m, 2 H), 3.14 (s, 3 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 158.7, 149.8, 137.1, 136.9, 133.7, 133.4, 130.1, 128.7, 128.4, 127.7, 127.7, 126.9, 126.7, 126.2, 126.2, 125.7, 124.8, 115.6, 22.8; HRMS-EI (m/z) calcd for $C_{20}H_{16}N$ 270.1277, observed 270.1286.

2-(2-Naphthyl)-5,6-dimethylpyrazine (1m). The reaction was conducted with 2,3-dimethylpyrazine (0.2594 g, 2.400 mmol), 2-bromonaphthalene (0.0828 g, 0.400 mmol), and 1.10 mL of 1,4-dioxane at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0153 g, 16% yield of **1m** as a pale yellow powder: R_f (10% ethyl acetate/hexanes) 0.20; mp 111−112 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.90 (s, 1 H), 8.52 (s, 1 H), 8.18−8.16 (m, 1 H), 8.01−7.92 (m, 3 H), 7.57−7.56 (m, 2 H), 2.70 (s, 3 H), 2.65 (s, 3 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 151.9, 150.6, 149.3, 138.5, 134.2, 133.7, 133.5, 128.7 (2 carbons), 127.7, 126.7, 126.5, 126.1, 124.1, 22.3, 21.8; HRMS-EI (m/z) calcd for $C_{16}H_{15}N_2$ 235.1230, observed 235.1233.

2-(2-Naphthyl)-4,6-dimethylpyrimidine (1n). The reaction was conducted with 4,6-dimethylpyrimidine (0.2594 g, 2.400 mmol), 2-bromonaphthalene (0.0828 g, 0.400 mmol), and 1.10 mL of 1,4-dioxane at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0205 g, 22% yield of **1n** as a white powder: R_f (10% ethyl acetate/hexanes) 0.40; mp 116−117 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 8.61−8.59 (m, 1 H), 8.06−7.91 (m, 3 H), 7.57−7.54 (m, 2 H), 7.00 (s, 1 H), 2.63 (s, 6 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 166.9, 135.5, 134.6, 133.4, 129.2, 128.3, 128.1, 127.7, 126.9, 126.1, 125.4, 118.1, 24.3; HRMS-EI (m/z) calcd for $C_{16}H_{15}N_2$ 235.1230, observed 235.1234.

General Procedure for the Catalytic Direct Arylation of Azines with Aroyl Chlorides. To a 15 or 25 mL sealable flame- or oven-dried Schlenk tube (Kontes No. 218710-0015 or 218710-0025)

containing a stir bar were added $[RhCl(CO)_2]_2$ (0.0078 g, 0.0200 mmol), the heterocycle (2.400 mmol), the aroyl chloride (0.400 mmol), and toluene (reaction solution diluted to a total concentration of 0.30 M). The volume of the heterocycle is not negligible at the concentrations used and must therefore be included in the concentration calculation. The reaction vessel was sealed, removed from the glovebox, submerged to the neck in a silicone oil bath, heated at 175 °C with stirring for 24 h, and then cooled to room temperature. The reaction mixture was transferred to a 60 mL separatory funnel using 3 × 5.0 mL of CH_2Cl_2 and 2.5 mL of MeOH. The resulting solution was washed with saturated $NaHCO_3$ (1 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with saturated NaCl (1 × 20 mL), dried over Na_2SO_4, filtered through glass wool, and concentrated to dryness under reduced pressure. The crude product mixture was loaded onto a Biotage samplet using a minimal amount of CH_2Cl_2 (ca. 0.5 mL). This solvent was removed by placing the samplet under reduced pressure in a vacuum desiccator for ca. 15 min, and the samplet was loaded into a Biotage SP1 system. Eluting with an ethyl acetate/hexanes gradient calculated by the instrument from the R_f of the product in a specified ethyl acetate/hexanes mixture provided the desired product.

2-(3,5-Dimethylphenyl)quinoline (1h). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), 3,5-dimethylbenzoyl chloride (0.0674 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0706 g, 76% yield of **1h** as a clear, colorless oil. Analytical data consistent with that previously reported.[9]

2-Phenylquinoline (1o). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), benzoyl chloride (0.0562 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0538 g, 66% yield of **1o** as a white powder. Analytical data consistent with that previously reported.[9]

2-(4-(Trifluoromethyl)phenyl)quinoline (1w). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), 4-(trifluoromethyl)benzoyl chloride (0.0834 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0321 g, 29% yield of **1w** as a white powder. Analytical data consistent with that previously reported.[9]

2-(1-Methylphenyl)quinoline (1y). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), *o*-toluoyl chloride (0.0618 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0455 g, 52% yield of **1y** as a white powder: mp 71−72 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.27−8.25 (m, 1 H), 8.22−8.20 (m, 1 H), 7.92−7.90 (m, 1 H), 7.81−7.77 (m, 1 H), 7.63−7.54 (m, 3 H), 7.39−7.36 (m, 3 H), 2.47 (s, 3 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 160.3, 147.9, 140.7, 136.1, 136.0, 130.9, 129.7, 129.7, 129.6, 128.5, 127.5, 126.8, 126.4, 126.1, 122.4, 20.4; HRMS-EI (m/z) calcd for $C_{16}H_{14}N$ 220.1121, observed 220.1120.

2-(1-Naphthyl)quinoline (1z). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), 1-naphthoyl chloride (0.0764 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0553 g, 54% yield of **1z** as a pale yellow powder: R_f (10% ethyl acetate/hexanes) 0.30; mp 96−98 °C (lit.[18] 96−97 °C); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.35−8.33 (m, 1 H), 8.29−8.27 (m, 1 H), 8.19−8.17 (m, 1 H), 8.02−7.96 (m, 3 H), 7.85−7.81 (m, 1 H), 7.78−7.75 (m, 2 H), 7.67−7.63 (m, 2 H), 7.59−7.50 (m, 2 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 159.5, 148.2, 138.8, 136.3, 134.0, 131.3, 129.8, 129.8, 129.1, 128.4, 127.8, 127.6, 127.0, 126.6 (2 carbons), 126.0, 125.7, 125.4, 123.3; HRMS-EI (m/z) calcd for $C_{19}H_{14}N$ 256.1121, observed 256.1127.

2-(4-Methoxyphenyl)quinoline (1aa). The reaction was conducted with quinoline (0.3100 g, 2.400 mmol), 4-methoxybenzoyl chloride (0.0682 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0530 g, 56% yield of **1aa** as a white powder: R_f (10% ethyl acetate/hexanes) 0.45; mp 123−124 °C (lit.[19] 124−125 °C); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.23−8.18 (m, 4 H), 7.89−7.84 (m, 2 H), 7.78−7.73 (m, 1 H), 7.56−7.52 (m, 1 H), 7.11−7.09 (m, 2 H), 3.93 (s, 3 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 160.8, 156.9, 148.3, 136.7, 132.3, 129.6, 129.6, 128.9, 127.5, 126.9, 125.9, 118.6, 114.3, 55.4; HRMS-EI (m/z) calcd for $C_{16}H_{14}NO$ 236.1070, observed 236.1076.

2-(1-Naphthyl)-6-methylpyridine (1bb). The reaction was conducted with 2-methylpyridine (0.2234 g, 2.400 mmol), 1-naphthoyl chloride (0.0764 g, 0.400 mmol), and 1.00 mL of toluene at 175 °C for 24 h. The crude mixture was purified by flash chromatography using an ethyl acetate/hexanes gradient to provide 0.0183 g, 21% yield of **1bb** as a clear, colorless oil: R_f (10% ethyl acetate/hexanes) 0.25; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.10−8.08 (m, 1 H), 7.95−7.93 (m, 2 H), 7.77−7.74 (m, 1 H), 7.64−7.48 (m, 4 H), 7.42−7.40 (m, 1 H), 7.26−7.24 (m, 1 H), 2.72 (s, 3 H); ^{13}C {^{1}H} NMR (100.61 MHz, $CDCl_3$) δ 158.7, 158.3, 138.8, 136.6, 134.0, 131.3, 128.7, 128.3, 127.4, 126.3, 125.8, 125.8, 125.4, 122.1, 121.6, 24.8; HRMS-EI (m/z) calcd for $C_{16}H_{14}N$ 220.1121, observed 220.1122.

Acknowledgment. This work was supported by NIH Grant GM069559 to J.A.E. and the DOE, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC03-76SF00098 to R.G.B. A.M.B. was supported by a NRSA postdoctoral fellowship (GM082080).

Supporting Information Available: General experimental information and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Yang, C.-H.; Tai, C.-C.; Huang, Y.-T.; Sun, I. *Tetrahedron* **2005**, *61*, 4857.

(19) Korn, T. J.; Schade, M. A.; Cheemala, M. N.; Wirth, S.; Guevara, S. A.; Cahiez, G.; Knochel, P. *Synthesis* **2006**, *21*, 3547.