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Direct Arylation Reactions Catalyzed by $Pd(OH)_2/C$: Evidence for a Soluble Palladium Catalyst

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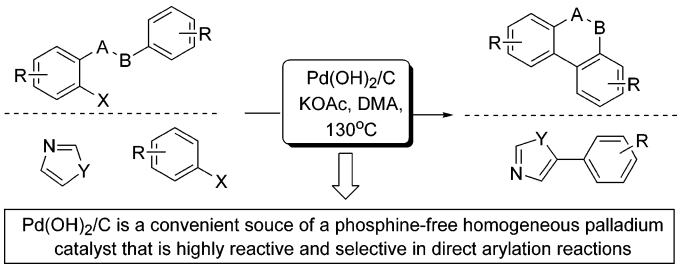
Received May 24, 2005



Palladium hydroxide on carbon (Pearlman's catalyst) effectively catalyzes direct arylation reactions of aryl iodides and bromides, providing excellent arylation-to-hydrodehalogenation ratios (>30:1) with broad scope for both intra- and intermolecular arylation processes. Studies aimed at determining the nature of the active catalyst indicate that an active homogeneous palladium species is produced under the reaction conditions.

Introduction

While direct arylation reactions have been known for 20 years,[1] their general application in organic synthesis has been slow to appear.[2] In recent years, these transformations have been successfully applied in intermolecular reactions with a variety of heterocyclic arenes,[3] arenes possessing a directing group,[4] and in intramolecular reactions for the formation of five- and six-membered rings.[5,6] In contrast to other more commonly employed cross-coupling reactions, very little knowledge has been gained with respect to the scope of potential catalysts, on the prerequisites for successful reaction, and on the variables involved in catalyst selection. Since these reactions have the potential in many cases to replace the use of organometallic reagents in the formation of biaryl molecules, this type of study is clearly warranted, particularly as it may contribute to the development and discovery of more highly reactive catalysts and conditions.

Solid-supported catalysts are attractive because the catalyst can frequently be removed at the end of the reaction by filtration allowing product isolation without transition metal and ligand impurities which can be challenging to remove. These attributes make such catalysts useful in reactions aimed at the preparation of pharmaceutical agents, where the fate of the metal catalyst and ancillary ligands is of particular importance.[7] The precise nature of the active catalyst when employing "heterogeneous" catalysts is often difficult to ascertain, however.[8] While reactions at the supported

(1) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.

(2) For recent reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(3) For example, see: (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. *Org. Lett.* **2003**, *5*, 301. (d) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(4) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330 and references therein. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2.

(5) For example, see: (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (c) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

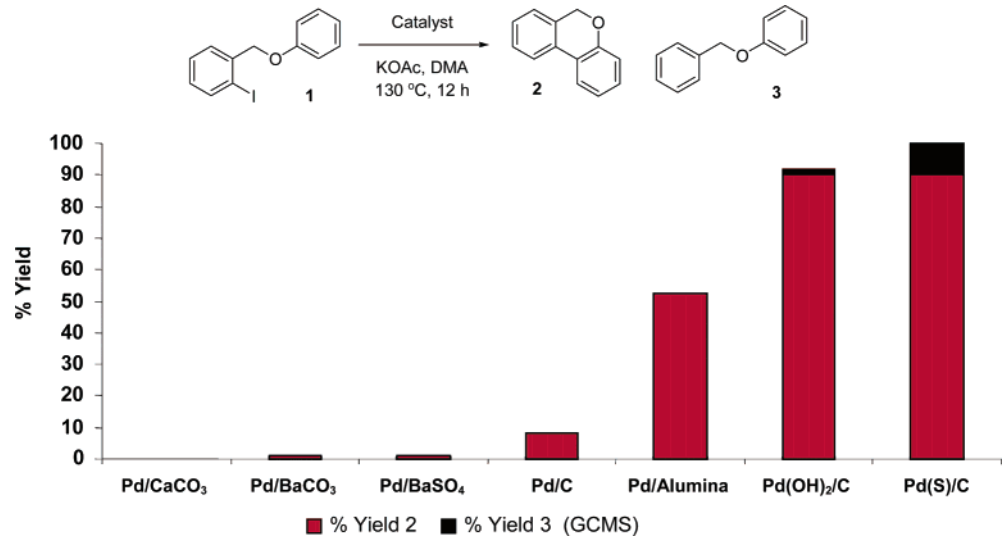
(6) For our own work in this area, see: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Commun.* **2004**, *24*, 2874. (c) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, 7, 1857.

(7) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(8) (a) Andrews, S. P.; Stephan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.* **2005**, *347*, 647. (b) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301. (c) Jaska, C. A.; Manners, I. *J. Am. Chem. Soc.* **2004**, *126*, 9776. For a review see: Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317.

10.1021/jo051039v CCC: $30.25
Published on Web 08/12/2005

SCHEME 1. Evaluation of Various Solid-Supported Palladium Catalysts



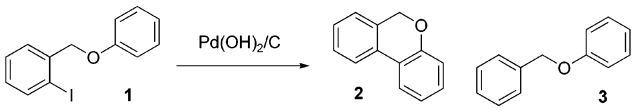
metal can occur, leaching of the metal into solution can also take place that may or may not be catalytically active.[9] Additionally, "release and capture" of a soluble metal species may occur, which further complicates analysis.[10] In contrast to application in more "traditional" cross-coupling reactions, solid-supported metal complexes have received scant attention in direct arylation processes. Herein, we demonstrate that $Pd(OH)_2$ on carbon is a very effective catalyst in intra- and intermolecular reactions exhibiting excellent selectivity for arylation over hydrodehalogenation. We also provide evidence for a soluble palladium species acting as an active catalyst for these reactions.

Results and Discussion

Recently, we reported that $Pd(OAc)_2$ in conjunction with 2-(diphenylphosphino)-2′-(*N,N*-dimethylamino)biphenyl is an excellent catalyst for intramolecular direct arylation reactions of simple arenes.[6a] While conducting catalyst screens, we noted that some successful reactions became black in the early stages of substrate conversion. This observation led us to wonder whether palladium colloids or nanoparticles generated under the reaction conditions could behave as a catalyst.[8c,11] Aware of the fact that reactions employing "heterogeneous" solid supported catalysts can actually occur via leaching of a homogeneous catalyst species such as soluble metal colloids, we assayed several commercially available heterogeneous palladium sources in the intramolecular direct arylation of iodo arene **1**.

In the initial screens, iodoarene **1** was treated with 10 mol % palladium catalyst and 2 equiv of potassium acetate in *N,N*-dimethylacetamide (DMA) at 130 °C for 12 h (Scheme 1). Palladium supported on calcium carbonate, barium carbonate, and barium sulfate gave trace amounts of product formation. The commonly used palladium on carbon also gave poor reactivity. Changing the support to alumina gave improved outcomes, reaching 53% yield. On the other hand, much better results were obtained with palladium hydroxide on carbon (Pearlman's catalyst) and sulfide palladium on carbon, both of which generated **2** in 89% yield. Since $Pd(OH)_2/C$ gave the optimal ratio of **2**:**3** (45:1), this catalyst was selected for further optimization.

SCHEME 2. Optimization[a]



Entry	Solvent	Base	T (°C)	% Yield (Ratio 1 / 2)[b]
1	DMF	KOAc	130	98% (19/1)
2	DMA	KOAc	130	92% (45/1)
3	DMA	K_2CO_3	130	62% (30/1)
4	DMA	KOAc	145	100% (45/1)

[a] Conditions: $Pd(OH)_2/C$ (10 mol %), base (2 equiv), and **1** dissolved in DMF or DMA and heated to the indicated temperature for 12 h. [b]Determined by GCMS analysis.

With $Pd(OH)_2/C$, the effects of base, solvent, and temperature were investigated, of which selected results are included in Scheme 2. Changing the solvent to *N,N*-dimethylformamide (DMF) resulted in an erosion of selectivity of cyclization to dehalogenation. Other solvents such as toluene, dioxanes, and acetonitrile resulted in no product formation. In DMA, use of potassium carbonate, which was an excellent base in our initial studies with homogeneous catalysts, gave only 62% conversion. By increasing the temperature of a reaction in DMA with potassium acetate as the base to 145 °C, 100% conversion was obtained with 45:1 selectivity for the desired product **2**. Use of lower reaction temperatures lead to inferior results. Less than 10 mol % catalyst can be used in some cases, but irreproducible outcomes were frequently ob-

(9) For a review, see: Bhanage, B. M.; Arai, M. *Catal. Rev.* **2001**, *43*, 315. For example, see: (a) Shieh, W.-C.; Shekhar, R.; Blacklock, T.; Todesco, A. *Synth. Commun.* **2002**, *32*, 1059. (b) Augustine, R. L.; O'Leary, S. T. *J. Mol. Catal.* **1992**, *72*, 229. (c) Iyer, S.; Thakur, V. V. *J. Mol. Catal. A: Chem.* **2000**, *157*, 275.

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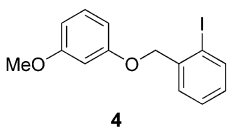
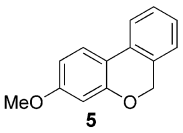
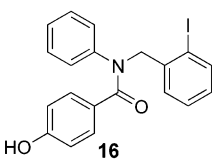
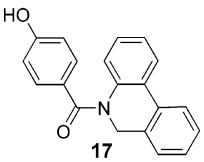
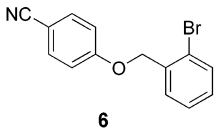
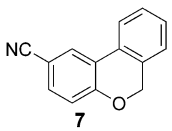
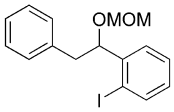
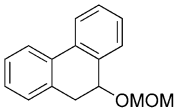
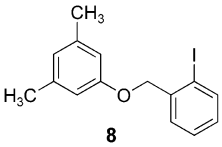
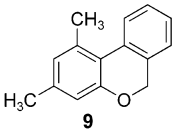
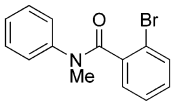
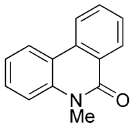
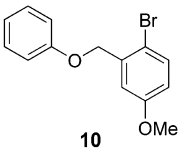
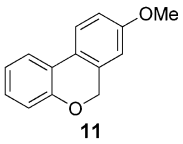
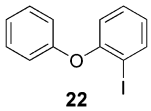
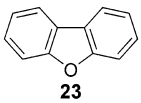
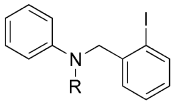
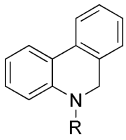
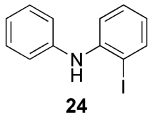
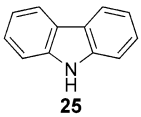
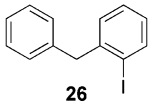
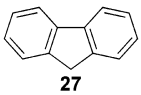
(11) For examples of in situ generation of Pd nanoparticles from $Pd(OAc)_2$, see: (a) Reetz, M. T.; Westerman, E. *Angew. Chem. Int. Ed.* **2000**, *39*, 165. (b) Moreno-Manas, M.; Pleixats, R. *Acc. Chem. Res.* **2003**, *36*, 638.

TABLE 1. Scope of Intramolecular Direct Arylation Reactions

Entry	Substrate	Product	Yield[b]	Entry	Substrate	Product	Yield[b]
1	 **4**	 **5**	95	7	 **16**	 **17**	83
2	 **6**	 **7**	92	8	 **18**	 **19**	86
3	 **8**	 **9**	92	9	 **20**	 **21**	80
4	 **10**	 **11**	69[c]	10	 **22**	 **23**	92
				11	 **24**	 **25**	84
5	R = COPh **12**	R = COPh **13**	81	12	 **26**	 **27**	84
6	R = CO^{t}Bu **14**	R = CO^{t}Bu **15**	98				

[a] Conditions: substrate, KOAc (2 equiv), $Pd(OH)_2/C$ (10 mol %) added to a screw cap vial followed by DMA (0.2 M) and heating to 140 °C for 12−24 h. [b] Isolated yields. [c] 20% of the hydrodebrominated product was also obtained.

tained even at 5 mol %. For this reason, 10 mol % $Pd(OH)_2/C$ was employed as our standard conditions.

The use of Pearlman's catalyst in intramolecular arylation reactions exhibits broad scope for both aryl iodide and bromide substrates (Table 1). Electron-withdrawing groups are tolerated on the arene ring (entry 2), and more sterically encumbered substrates can be arylated in high yield (entry 3). When a nitrogen atom is located within the tether, an amide protecting group may be employed to give the arylated products in high yield (entries 5 and 6). An unprotected phenol group is also compatible with these reactions (entry 7). Substitution along the carbon tether is possible which demonstrates that protected alcohols are tolerated (entry 8). Aryl bromides are also compatible (entries 2, 4, and 9), but longer reaction times and lower yields are obtained when deactivated aryl bromides are employed (entry 4). Five membered heterocycles can be formed in good yield (entries 10 and 11) as can carbocyclic analogues (entry 12). High regioselectivity can also be observed in cases where direct arylation can occur at two chemically different arene positions as illustrated in entry 1. In this case, arylation occurs at the more sterically accessible position in a 13.5:1 ratio as determined by ^1H NMR analysis.

Pearlman's catalyst can also achieve intermolecular direct arylation of aryl iodides and bromides with heteroarenes (Table 2). Imidazo[1,2-*a*]pyrimidines are arylated selectively at the three position in good yields (entries 1−3).[12] Arylation of thiazole is selective at the five position (entries 4−6).[13] Coupling of 2-furaldehyde with phenyl bromide can also be achieved with a 12:1 mixture of 2,5- versus 2,3-disubstituted products (entry 7).[14] Other heterocycles such as imidazole, *N*-methylimidazole, and benzothiazole gave inferior results, providing the direct arylation products in less than 10% yield. It is also known that the addition of catalytic copper salts to reactions with some heterocycles can lead to a change in arylation regioselectivity, leading to reaction occurring at the more acidic C−H bond. In the present case, we determined that the addition of 20 mol % of CuBr to a reaction with thiazole and bromobenzene gave no change in yield or regioselectiviy to provide **31**.

With an active catalyst in hand, we were interested in determining if this was a true heterogeneous catalyst or if palladium was leaching off of the carbon support to produce an active homogeneous species. Two different approaches were taken to answer this question based on the three-phase test concept.[15] In the first case, the aryl

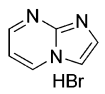
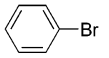
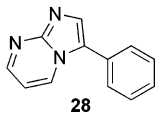
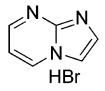
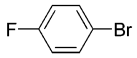
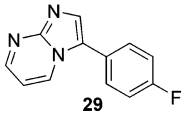
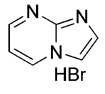
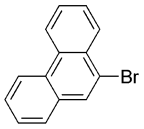
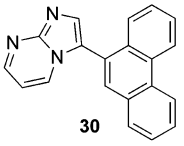
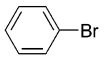
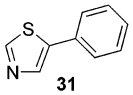
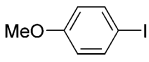
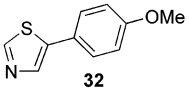
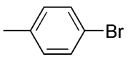
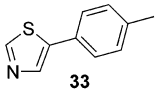
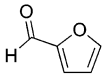
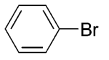
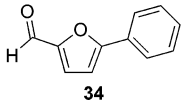
(12) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835.

(13) (a) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2003**, *59*, 5685. (b) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111.

(14) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677.

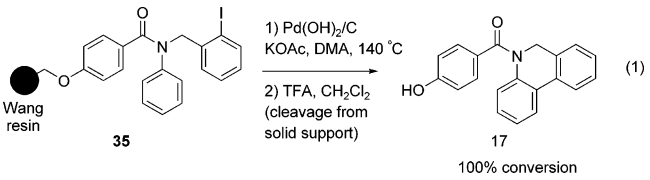
(15) (a) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139. (b) Rebek, J.; Gavina, F. *J. Am. Chem. Soc.* **1974**, *96*, 7112. (c) Rebek, J.; Brown, D.; Zimmerman, S. *J. Am. Chem. Soc.* **1975**, *97*, 454. (d) Rebek, J. *Tetrahedron* **1979**, *35*, 723.

TABLE 2. Scope of Intermolecular Direct Arylation Reactions

Entry	Arene	Aryl halide	Product	Yield[b]
1			 **28**	75
2			 **29**	76
3			 **30**	81
4			 **31**	82
5			 **32**	73
6			 **33**	71
7			 **34**	75[c]

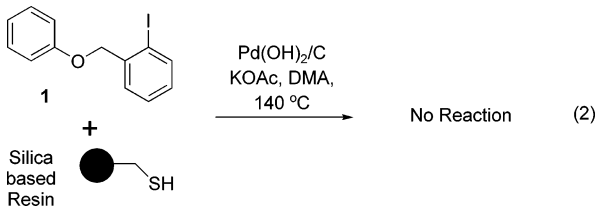
[a] Conditions: substrate, KOAc (2 equiv), Pd(OH)2/C (10 mol %) added to a screw cap vial followed by DMA (0.2 M) and heating to 140 °C for 12 to 24 h. [b] Isolated yields. [c] Isolated as a 12: 1 mixture of the 2, 5: 2, 3 isomers.

halide was anchored to a Wang resin via an amide linker.[16] If the true catalyst in these processes was purely heterogeneous, then interaction between the supported substrate and the matrix bound catalyst should not be possible, thus preventing reaction. In contrast, if palladium leaching occurs, and if this soluble palladium species is catalytically active, then direct arylation should be observed. When supported **35** was treated with Pearlman's catalyst under standard conditions for 4.5 h followed by cleavage from the resin via treatment with trifluoroacetic acid in dichloromethane,[17] 100% conversion to **17** was observed (eq 1). This lends strong support for the notion that a homogeneous active catalyst is generated under the reaction condition via leaching from the carbon support.



(1)

To determine if an active heterogeneous catalyst species was also contributing to the direct arylation reaction, another three-phase test was conducted. In this experiment, **1** was reacted under standard conditions in the presence of a silica-supported thiol-based scavenger resin. Since thiols are known to have a very high affinity for palladium, the presence of this heterogeneous metal scavenger should sequester the homogeneous catalyst as it is produced. On the other hand, a heterogeneous palladium species that is catalytically active should not be poisoned by the presence of the heterogeneous metal scavenger. After 16 h, less than 5% of the desired product had been formed, while an identical reaction run in parallel without the scavenger resin reached 100% conversion (eq 2). This indicates that the heterogeneous palladium is not catalytically active on the time scale examined and that the observed reactivity arises from the in situ generation of a homogeneous catalyst.



(2)

The observation that a homogeneous catalyst is produced by leaching from the solid support may account for the high catalyst loadings required in these reactions compared to our previously reported homogeneous catalyst system[6a] and for the irreproducible results achieved when the catalyst loading was decreased to 5 mol %. These observations may also, in part, explain the differing reactivity of the different matrix-supported palladium sources used in this study (Scheme 1). If leaching is inefficient under the reaction conditions, the active homogeneous species may not form, resulting in little or no reaction.[18]

Conclusion

We have demonstrated that palladium hydroxide on carbon (Pearlman's catalyst) efficiently catalyzes intra- and intermolecular direct arylation reaction of aryl iodides and bromides. These reactions occur in high yields and with excellent direct arylation-to-hydrodehalogentation ratios. Furthermore, we have obtained evidence that strongly indicates that a homogeneous catalyst species is generated under the reaction conditions and that this species is responsible for the observed catalysis.

Experimental Information

General Methods. All experiments were carried out under an atmosphere of nitrogen or argon. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ or DMSO-d_6 solutions with Me_4Si as an internal standard. HPLC grade THF, Et_2O, benzene, toluene, and CH_2Cl_2 were dried and purified prior to use Triethylamine was freshly distilled from NaOH before every use. *N*,*N*-Dimethylacetamide (DMA) (HPLC grade) was degassed with N_2 before every use. All other reagents and solvents were used without further purification from commercial sources.

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(18) We thank a reviewer for bringing the possibility of this to our attention.

Starting Materials. Compounds **4**[19] (95%), **6**[20] (93%), **20**[21] (94%), **24**[22] (89%), and **26**[23] (78%) were prepared according to the literature procedure and exhibited spectral data identical to those reported in the literature.

General Procedure for the Synthesis of Arenes 1, 6, 8, and 10. To a mixture of potassium carbonate (3 equiv) and the appropriate phenol (2 equiv) was added acetone (0.5 M) in a round-bottom flask equipped with a mechanical stir bar. To the stirring mixture was added the required benzyl bromide (1 equiv) followed by heating to 50 °C overnight. The reaction mixture was then cooled to room temperature, poured into a solution of NaOH (2 N), and extracted three times with ether. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was done by flash chromatography using ethyl acetate/hexanes mixtures to afford the halo ethers.

1-Iodo-2-phenoxymethyl-benzene (1). The substrate was prepared following the general procedure (92%): mp 50−52 °C; IR (ν_{max}/cm^{-1}) 3064, 2945, 2884, 1373, 1232, 759, 751; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 5.04 (2H, s), 6.99 (4H, m), 7.33 (3H, m), 7.51 (1H dd, J = 0.75, 7.8 Hz), 7.86 (1H, dd, J = 1.2, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 73.5, 97.1, 112.5, 122.9, 128.2, 128.5, 129.2, 139.0, 139.0, 139.2, 158.4; HRMS calcd for $C_{13}H_{11}IO$ (M^+) 309.9855, found 309.9847

1-((3,5-Dimethylphenoxy)methyl)-2-iodobenzene (8). The substrate was prepared following the general procedure (94%): mp 42−43 °C; IR (ν_{max}/cm^{-1}) 2917, 2865, 1295, 828, 748; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 2.30 (6H, s), 5.00 (2H, s), 6.62 (3H, m), 7.01 (1H, td, J = 1.5, 7.8 Hz), 7.36 (1H, td, J = 1.2, 7.8 Hz), 7.51 (1H, dd, J = 0.75, 7.8 Hz), 7.85 (1H, dd, J = 0.9, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 21.5, 73.7, 97.2, 112.6, 123.0, 128.3, 128.6, 129.4, 139.2, 139.3, 139.4, 158.4; HRMS calcd for $C_{15}H_{15}IO$ (M^+) 338.0168, found 338.0172

1-(2-Bromo-5-methoxybenzyloxy)benzene (10). The substrate was prepared following the general procedure (91%): IR (ν_{max}/cm^{-1}) 3062, 3006, 2935, 1585, 1472, 1295, 1230, 1054, 753; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 3.78 (3H, s), 5.09 (2H, s), 6.74 (1H, dd, J = 3.1, 8.7 Hz), 6.98 (3H, m), 7.13 (1H, d, J = 2.4 Hz), 7.29 (1H, d, J = 6.7 Hz), 7.32 (1H, d, J = 7.6 Hz), 7.46 (1H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 55.4, 69.2, 112.2, 114.3, 114.8, 114.8, 121.2, 129.5, 133.1, 137.3, 158.3, 159.1; HRMS calcd for $C_{14}H_{14}INO$ (M^+) 292.0099, found 292.0088

***N*-(2-Iodobenzyl)aniline.** To a mixture of aniline (1 equiv) and 2-iodobenzaldehyde (1 equiv) was added 1,2-dichloroethane in a round-bottom flask equipped with a mechanical stir bar. To the stirring mixture were added acetic acid (1.05 equiv) and sodium triacetoxyborohydride (1.3 equiv). The mixture was stirred overnight. The reaction mixture was quenched with 1 N HCl. The solution was brought to pH 7.5 using NaOH. The reaction was extracted with dichloromethane and water. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification was done by flash chromatography using 5% ethyl acetate in hexanes (82%): mp 66−68 °C; IR (ν_{max}/cm^{-1}) 3419, 3051, 3017, 1602, 1506, 1324, 1011, 747; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 4.18 (1H, s), 4.31 (2H, s), 6.59 (2H, m), 6.71 (1H, t, J = 7.5 Hz), 6.96 (1H, td, J = 1.8, 7.5 Hz), 7.16 (2H, m), 7.28 (1H, td, J = 1.3, 7.5 Hz), 7.37 (1H, dd, J = 2.1, 7.3 Hz), 7.84 (1H, dd, J = 1.3, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 53.2, 98.5, 112.9, 117.7, 128.4, 128.7, 128.9, 129.2, 139.4, 140.9, 147.6; HRMS calcd for $C_{13}H_{12}IN$ (M^+) 309.0014, found 309.0032

***N*-(2-Iodobenzyl)-*N*-phenylbenzamide (12).** To a solution of benzoyl chloride (1 equiv) in dichloromethane (0.25 M) at 0 °C was first added triethylamine (2 equiv) dropwise followed by *N*-2-iodobenzylaniline (0.9 equiv) in one portion. The mixture was allowed to warm to room temperature and stirred overnight. An aqueous $NaHCO_3$ solution was then added, and the mixture was extracted with dichloromethane. The organic phase was dried using $MgSO_4$ and filtered, and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 30% ethyl acetate in hexanes (87%): mp 122−125 °C; IR (ν_{max}/cm^{-1}) 3064, 3031, 2851, 1648, 1376, 1247, 759, 736; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 5.19 (2H, s), 6.92 (3H, m), 7.06−7.45 (10H, m), 7.79 (1H, d, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 58.4, 98.6, 126.7, 127.3, 127.8, 128.4, 128.5, 128.8, 128.9, 129.0, 129.8, 135.6, 139.2, 139.5, 143.2, 170.6; HRMS calcd for $C_{20}H_{16}INO$ (M^+ $C_{20}H_{16}NO$) 286.1232, found 286.1229

***N*-(2-Iodobenzyl)-*N*-phenylpivalamide (14).** The same procedure as for compound **12** was used (89%): mp 118−121 °C; IR (ν_{max}/cm^{-1}) 3062, 2958, 2873, 1638, 1493, 1290, 1187, 748; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 1.06 (9H, s), 4.92 (2H, s), 6.88 (1H, m), 7.04 (2H, m), 7.26 (5H, m), 7.72 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 29.5, 41.1, 60.2, 99.5, 128.0, 128.1, 128.7, 129.3, 129.7, 139.2, 139.6, 142.7, 177.7; HRMS calcd for $C_{18}H_{20}INO$ (M^+ $C_{18}H_{20}NO$) 266.1545, found 266.1564.

***N*-(2-Iodobenzyl)-4-hydroxy-*N*-phenylbenzamide (16).** 4-Hydroxybenzoic acid (1 equiv) was treated with oxalyl chloride (1.2 equiv) and 2 drops of DMF in dichloromethane (0.5 M). The reaction was allowed to stir at room temperature for 6 h, at which time the volatiles were evaporated under reduced pressure. The acid chloride was dissolved in dichloromethane (0.25 M) and placed in an ice bath. To the stirring mixture was first added triethylamine (2 equiv) dropwise followed by *N*-(2-iodobenzyl)aniline (0.9 equiv) in one portion. The mixture was allowed to warm to room temperature and stirred overnight. An aqueous $NaHCO_3$ solution was then added, and the mixture was extracted with dichloromethane. The organic phase was dried using $MgSO_4$ and filtered, and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 30% ethyl acetate in hexanes (78%): mp 155−158 °C; IR (ν_{max}/cm^{-1}) 3261, 1607, 1579, 1388, 1280, 1013, 759; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 5.14 (2H, s), 6.49 (2H, d, J = 8.2 Hz), 6.92 (3H, m), 7.08−7.20 (5H, m), 7.27 (1H, t, J = 7.3 Hz), 7.37 (1H, d, J = 7.3 Hz), 7.77 (1H, d, J = 7.3 Hz), 8.40 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 59.1, 98.5, 114.9, 125.8, 126.8, 127.1, 128.2, 128.4, 129.0, 129.0, 131.0, 138.9, 139.5, 143.4, 158.6, 171.4; HRMS calcd for $C_{20}H_{16}INO_2$ (M^+) 429.0226, found 429.0210

1-(2-Iodophenyl)-2-phenylethanol. Prepared according to literature procedure and exhibited spectral data identical to literature values (81%).[24]

1-Iodo-2-(1-(methoxymethoxy)-2-phenylethyl)benzene (18). Sodium hydride (1.2 equiv) was triturated with pentane in a flask equipped with a mechanical stir bar. After leftover pentane was removed using a flow of nitrogen, THF (0.1 M) was added. The reaction vessel was placed in an ice bath, and 1-(2-iodophenyl)-2-phenylethanol (1 equiv) was added. The reaction mixture was stirred for 2 h. Chloromethyl methyl ether (1.2 equiv) was then added at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride and extracted with ether. The organic phase was dried with $MgSO_4$ and filtered, and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 5% ethyl acetate/hexanes (83%): mp 44−46 °C; IR (ν_{max}/cm^{-1}) 3061, 2944, 2886, 1150, 1098, 1052, 1020, 756; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 2.75 (1H, dd, J = 9.9, 14.1 Hz),

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2.88 (3H, s), 3.07 (1H, dd, J = 3.0, 14.1 Hz), 4.37 (2H, s), 5.04 (1H, dd, J = 3.0, 9.9 Hz), 6.99 (1H, t, J = 7.5 Hz), 7.25 (6H, m), 7.49 (1H, d, J = 7.8 Hz), 7.82 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 43.8, 55.7, 82.5, 94.8, 98.8, 126.7, 127.8, 128.5, 128.9, 129.7, 130.0, 139.0, 139.7, 144.5; HRMS calcd for $C_{16}H_{17}IO_2$ (M^+ $C_{14}H_{12}I$) 306.9984, found 307.0012.

1-(2-Iodophenoxy)benzene (22). Prepared according to literature procedure (87%):[25] mp 53−54 °C; IR (ν_{max}/cm^{-1}) 3062, 2923, 1573, 1234, 748; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 6.87 (2H, m), 6.94 (2H, m), 7.11 (1H, td, J = 0.9, 7.5 Hz), 7.30 (3H, m), 7.86 (1H, dd, J = 1.5, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 88.9, 118.4, 119.4, 123.4, 125.3, 129.6, 129.7, 139.8, 156.4, 156.8; HRMS calcd for $C_{12}H_9IO$ (M^+) 295.9698, found 295.9690.

Products. General Procedure for Intramolecular Direct Arylation Reactions. To a mixture of potassium acetate (2 equiv), Pd(OH)$_2$/C (0.1 equiv), and substrate (1 equiv), under nitrogen atmosphere, was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °C. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then purified via silica gel column chromatography using ethyl acetate/hexanes mixtures.

The substrates were reacted under the general procedure for intramolecular direct arylation reactions. Compounds **2**[1] (91%), **5**[19] (95%), **21**[26] (80%), **23**[27] (92%), **25**[28] (84%), and **27**[29] (84%) exhibited spectral data identical to those reported in the literature.

6*H*-Benzo[*c*]chromene-2-carbonitrile (7). The substrate was treated under the general procedure for intramolecular direct arylation reactions (92%): mp 85−87 °C; IR (ν_{max}/cm^{-1}) 2224, 1609, 1493, 1248, 1011, 824; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 5.16 (2H, s), 6.98 (1H, d, J = 7.8 Hz), 7.13 (1H, d, J = 7.3 Hz), 7.35 (2H, m), 7.45 (1H, dd, J = 8.2, 1.9 Hz), 7.61 (1H, d, J = 7.3 Hz), 7.94 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 68.6, 105.5, 118.5, 119.1, 122.1, 123.7, 124.9, 127.6, 127.8, 128.9, 129.0, 130.6, 133.1, 158.1; HRMS calcd for $C_{14}H_9NO$ (M^+) 207.0684, found 207.0697.

1,3-Dimethyl-6*H*-benzo[*c*]chromene (9). The substrate was treated under the general procedure for intramolecular direct arylation reactions (92%): mp 76−77 °C; IR (υ_{max}/cm^{-1}) 2855, 1453, 1065, 747; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 2.30 (3H, s), 2.63 (3H, s), 4.91 (2H, s), 6.74 (2H, d, J = 6.6 Hz), 7.21 (2H, m), 7.35 (1H, td, J = 1.2, 7.5 Hz), 7.72 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 21.1, 22.5, 69.0, 115.4, 124.7, 125.9, 126.4, 126.6, 126.7, 127.7, 130.8, 133.4, 135.2, 138.6, 156.3; HRMS calcd for $C_{15}H_{14}O$ (M^+) 210.1045, found 210.1056.

8-Methoxy-6*H*-benzo[*c*]chromene (11). The substrate was treated under the general procedure for intramolecular direct arylation reactions (69%): mp 71−73 °C; IR (ν_{max}/cm^{-1}) 3066, 2936, 2836, 1605, 1408, 1321, 1277, 1168, 846, 748; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 3.81 (3H, s), 5.07 (2H, s), 6.66 (1H, d, J = 2.5 Hz), 6.88 (1H, dd, J = 2.6, 8.5 Hz), 6.99 (2H, m), 7.17 (1H, td, J = 1.5, 7.7 Hz), 7.63 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 55.3, 68.4, 110.0, 113.9, 117.2, 122.1, 122.6, 122.9, 122.9, 123.4, 128.4, 133.0, 153.9, 159.3; HRMS calcd for $C_{14}H_{12}O_2$ (M^+) 212.0837, found 212.0842.

***N*-Benzoyl-(6*H*)-phenanthridine (13).** The substrate was treated under the general procedure for intramolecular direct arylation reactions (81%): mp 115−117 °C; IR (ν_{max}/cm^{-1}) 3064, 2851, 1650, 1374, 1350, 761, 736; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 5.02 (2H, s), 6.72 (1H, s), 6.97 (1H, t, J = 8.2 Hz), 7.11−7.48 (9H, m), 7.78 (1H, d, J = 7.5 Hz), 7.84 (1H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 46.8, 123.3, 124.2, 125.5, 126.4, 127.3, 128.0, 128.1, 128.2, 128.5, 129.0, 130.1, 131.7, 134.3, 135.1, 138.2, 169.1; HRMS calcd for $C_{20}H_{15}NO$ (M^+) 285.1154, found 285.1162.

***N*-(2,2-Dimethylpropanoyl)-(6*H*)-phenanthridine (15).** The substrate was treated under the general procedure for intramolecular direct arylation reactions (98%): mp 114−116 °C; IR (ν_{max}/cm^{-1}) 3068, 2973, 1650, 1358, 1168, 764, 738; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 1.34 (9H, s), 4.82 (2H, s), 7.28 (4H, m), 7.39 (1H, t, J = 7.4 Hz), 7.55 (1H, d, J = 7.5 Hz), 7.76 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 28.9, 39.8, 49.1, 123.5, 124.0, 125.3, 125.8, 126.3, 127.3, 127.7, 128.3, 132.5, 134.4, 138.9, 177.4; HRMS calcd for $C_{18}H_{19}NO$ (M^+) 265.1467, found 265.1451.

***N*-(4-Hydroxybenzoyl)-(6*H*)-phenanthridine (17).** The substrate was treated under the general procedure for intramolecular direct arylation reactions (83%): mp 142−144 °C; IR (ν_{max}/cm^{-1}) 3259, 2926, 1608, 1495, 1390, 1230, 757; ^{1}H NMR (300 MHz, DMSO, 293 K) δ 4.90 (2H, s), 6.66 (2H, d, J = 8.3 Hz), 6.77 (1H, d, J = 8.3 Hz), 7.10 (3H, m), 7.21 (1H, t, J = 7.4 Hz), 7.30−7.48 (3H, m), 7.91 (1H, d, J = 7.7 Hz), 7.97 (1H, d, J = 5.4 Hz), 10.00 (1H, s); ^{13}C NMR (75 MHz, DMSO, 293 K) δ 46.6, 114.8, 123.3, 124.3, 125.1, 125.1, 125.2, 126.1, 127.3, 127.7, 128.0, 128.2, 130.8, 131.2, 134.1, 138.4 159.5, 168.1; HRMS calcd for $C_{20}H_{15}NO_2$ (M^+) 301.1103, found 301.1095.

9,10-Dihydro-9-(methoxymethoxy)phenanthrene (19). The substrate was treated under the general procedure for intramolecular direct arylation reactions (86%): IR (ν_{max}/cm^{-1}) 3067, 3033, 2941, 2887, 1327, 1147, 1096, 1041, 755, 740; ^{1}H NMR (300 MHz, $CDCl_3$, 293 K, TMS) δ 3.15 (2H, dd, J = 3.5, 4.6 Hz), 3.36 (3H, s), 4.65 (2H, dd, J = 7.0, 11.8 Hz), 4.82 (1H, t, J = 4.8 Hz), 7.22−7.33 (4H, m), 7.41 (2H, m), 7.80 (2H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K, TMS) δ 35.2, 55.3, 71.7, 94.1, 123.5, 124.1, 127.2, 127.4, 127.9, 128.3, 128.9, 129.2, 133.7, 133.7, 133.9, 134.9; HRMS calcd for $C_{16}H_{16}O_2$ (M^+) 240.1150, found 240.1150.

Procedure for the Intermolecular Direct Arylation of Imidazo[1,2-*a*]pyrimidine. To a mixture of potassium acetate (3 equiv), Pd(OH)$_2$/C (0.1 equiv), imidazo[1,2-*a*]pyrimidine (1 equiv), and the appropriate aryl halide (1.1 equiv), under nitrogen atmosphere, was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °C. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then purified via silica gel column chromatography using ethyl acetate/hexanes mixtures. Compounds **28**[12] (75%), **29**[12] (76%), and **30**[12] (81%) exhibited spectral data identical to that reported in the literature.

Procedure for the Intermolecular Direct Arylation of Thiazole. To a mixture of potassium acetate (3 equiv), Pd(OH)$_2$/C (0.1 equiv), thiazole (1 equiv), and the appropriate aryl halide (3 equiv), under nitrogen atmosphere, was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °C. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then purified via silica gel column chromatography using ethyl acetate/hexanes mixtures. Compounds **31**[30] (82%), **32**[31] (73%), and **33**[32] (71%) (81%) exhibited spectral data identical to those reported in the literature.

5-Phenyl-2-furaldehyde (34). To a mixture of potassium acetate (3 equiv), Pd(OH)$_2$/C (0.1 equiv), 2-furaldehyde (3 equiv), and phenyl bromide (1 equiv) under nitrogen atmo-

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sphere was added DMA (0.2 M) in a 2 mL screw cap vial equipped with a mechanical stir bar. The reaction mixture was then heated overnight at 145 °C. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then purified via silica gel column chromatography using 2.5% ethyl acetate/hexanes (75%). Compound **34** exhibited spectral data identical to those reported in the literature.[14]

Preparation of Resin (35). To a suspension of Wang resin (0.3 equiv) and triphenylphosphine (1 equiv) in dichloromethane (0.2 M) was added a solution of compound **16** (1 equiv) in dichloromethane (0.4 M). The mixture was purged with argon and cooled to 0 °C. A solution of diisopropyl azodicarboxylate (1 equiv) in dichloromethane (0.4 M) was added over 1 h via syringe pump. The reaction mixture was refluxed for 48 h. The reaction mixture was filtered and washed twice with each of the following solvents to afford compound **35** (0.5 mmol/g of resin): dichloromethane, DMF, water, methanol, dichloromethane (a second time), and ether. The unreacted hydroxyl functionalities of the Wang resin were then capped via treatment of a suspension of the resin **35** (1 equiv) in dichloromethane (0.1 M) with acetic anhydride (5 equiv), pyridine (6 equiv), and 4-(*N*,*N*-dimethylamino)pyridine (0.01 equiv). The reaction was stirred for 2 h at room temperature. The reaction mixture was filtered and washed twice with each of the following solvents to afford the capped resin **35**: dichloromethane, DMF, water, methanol, dichloromethane (a second time) and ether.

Intramolecular Direct Arylation and Cleavage of Compound (16) from Resin 35. After being submitted to the general procedure for intramolecular direct arylation reactions, the resin (1 equiv) was filtered and washed thoroughly before being stirred in a 1:1 mixture of trifluoroacetic acid and dichloromethane (0.5 M) for 2 h. The resulting mixture was filtered and washed twice with each of the following solvents: dichloromethane, DMF, water, methanol, dichloromethane (a second time), and ether. The volatiles were evaporated under reduced pressure, and the resulting mixture was extracted with water and ether. The organic phase was dried with $MgSO_4$ and filtered, and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using 30% ethyl acetate/hexanes to afford compound **16**.

Acknowledgment. We thank the National Science and Engineering Research Council of Canada, the Canada Foundation for Innovation, the Ontario Innovation Trust, the Ontario government (Premier's Research Excellence Award), and the University of Ottawa for valuable support.

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.

JO051039V