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Modulating Reactivity and Diverting Selectivity in Palladium-Catalyzed Heteroaromatic Direct Arylation Through the Use of a Chloride Activating/Blocking Group

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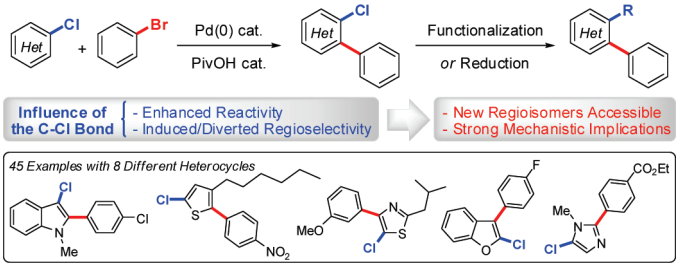

Through the introduction of an aryl chloride substituent, the selectivity of palladium-catalyzed direct arylation may be diverted to provide alternative regioisomeric products in high yields. In cases where low reactivity is typically observed, the presence of the carbon−chlorine bond can serve to enhance reactivity and provide superior outcomes. From a strategic perspective, the C−Cl bond is easily introduced and can be employed in a variety of subsequent transformations to provide a wealth of highly functionalized heterocycles with minimal substrate preactivation. The impact of the C−Cl functional group on direct arylation reactivity has also been evaluated mechanistically, and the observed reactivity profiles correlate very well with that predicted by a concerted metalation−deprotonation pathway.

Introduction

Direct arylation reactions[1−4] are finding increased application in the preparation of biaryl molecules since they can avoid the need for stoichiometric organometallic reagents along with any problems associated with their synthesis, stability, and/or functional group compatibility.[5] In many instances, high levels of regioselectivity occur to produce one biaryl regioisomer in good yield, such as with benzothiophenes and benzofurans that react at C2,[3q] indolizines that react at C3,[3c,q] as well as 1,2,3-triazoles[3g] and 2-substituted imidazoles,[3n] thiazoles,[3h,p,q] and oxazoles[3o] that react at C5

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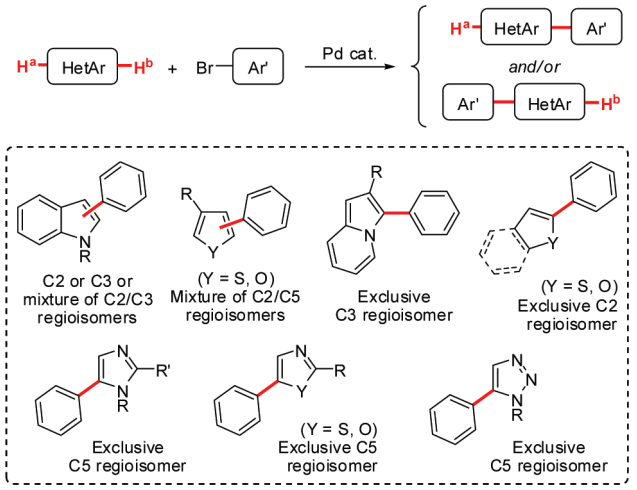
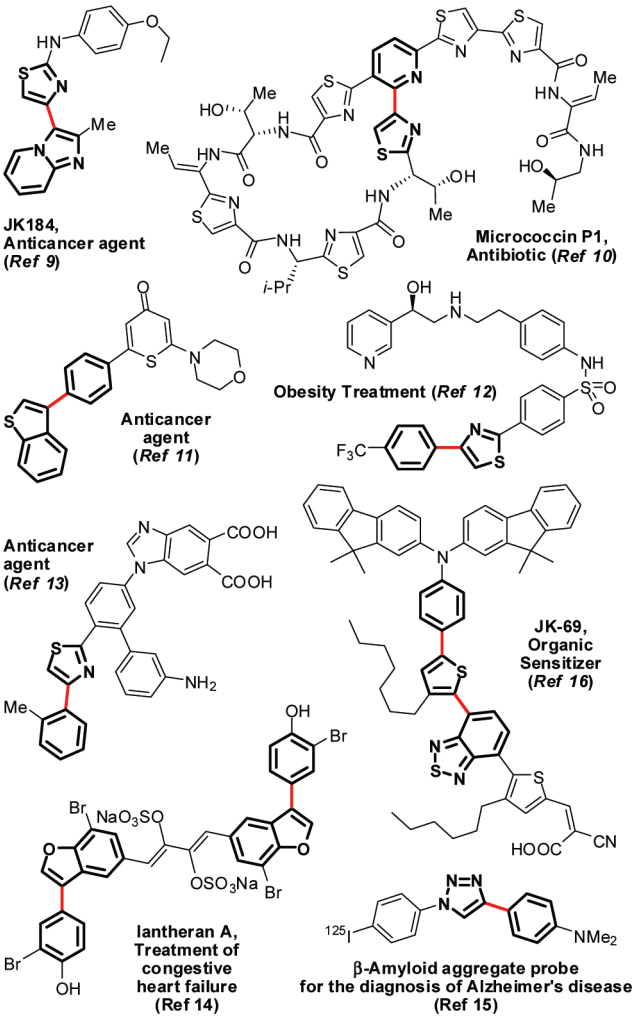
(Scheme 1). With other substrates, achieving acceptable regioselectivity can be problematic.[1p] For example, C3-substituted thiophenes and furans react to give mixtures of C2/C5 monoarylated products as well as a significant amount of C2,C5-diarylation.[6] Attaining uniformly high C2/C3 selectivity with indoles can also be challenging under direct arylation protocols employing readily available aryl halide coupling partners, prompting the establishment of clever alternatives.[2d,e,3e,f,j,k,m,x,4a,b,d,j,7,8]

SCHEME 1. Established Regioselectivity in Palladium(0)-Catalyzed Direct Arylation of Heteroaromatics



SCHEME 2. Heterobiaryl Compounds with Regiochemistry That Is Inaccessible via Established Direct Arylation Techniques



While the selective formation of only one regioisomer is desirable, it can also limit the applicability of direct arylation when the preparation of other isomeric compounds is called

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(6) In some rare examples, selectivity can be obtained through the use of ester or methoxy substituents at the C3 position; see: Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622−14623 and references cited therein. See also refs 3b and 4b.

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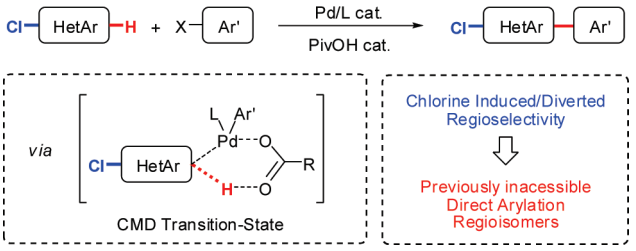
for (illustrative compounds are included in Scheme 2).[9−16] For example, while thiazole C5 direct arylation readily occurs, achieving direct arylation at the least reactive C4 position, even in the absence of C4/C5 regioselectivity issues,[3a,l,t] is exceedingly rare. In a similar fashion, the inherent bias for reaction of benzothiophenes and benzofurans at C2 makes this approach problematic when C3 arylation is desired.[17,18] For direct arylation to continue to grow as a synthetic tool in the preparation of biaryl molecules, strategies that overcome these limitations must be established.

Herein we describe a solution to several regiochemical limitations in palladium(0)-catalyzed direct arylation, with a wide range of heteroaromatic coupling partners, that should have broader implications as a general synthetic strategy. We have found that a chlorine atom on the heterocycle not only improves reactivity but also diverts typical direct arylation regioselectivity to obtain previously inaccessible direct arylation outcomes (Scheme 3).[19] In this way, the C−Cl bond becomes an invaluable handle for modulating reactivity, manipulating site selectivity, and greatly expanding the breadth of potential target compounds that may be accessible via this approach. From a synthetic perspective, the use of a chlorine substituent in this role is particularly useful since C−Cl bonds are typically very easily introduced on aromatic substrates and may be easily removed or transformed into a wide range of functional groups via well-established methods.[20] Of equal importance, this chemistry has strong mechanistic implications on the nature of the C−H bond cleavage step[21] in palladium-catalyzed direct arylation. The ability of a non-S_EAr,[22] concerted metalation−deprotonation (CMD) pathway[23−25] to accurately account for this reactivity and selectivity is supported by experimental and computational methods.

SCHEME 3. Palladium-Catalyzed Direct Arylation of Chlorine-Containing Heteroaromatics



Results and Discussion

1. Use of a Chlorine Substituent to Improve/Induce Regioselectivity. When palladium-catalyzed direct arylation is employed with substrates possessing two nonidentical reactive sites, low regioselectivities frequently occur. For example,

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(17) For selected methods developed for the synthesis of 3-arylbenzothiophenes, see: (a) Heynderickx, A.; Samat, A.; Guglielmetti, R. *Synthesis* **2002**, 213–216. (b) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5573–5576. (c) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529–5531. (d) Aoyama, T.; Orito, M.; Takido, T.; Kodomari, M. *Synthesis* **2008**, 2089–2099. (e) Kobayashi, K.; Horiuchi, M.; Fukamachi, S.; Konishi, H. *Tetrahedron* **2009**, *65*, 2430–2435.

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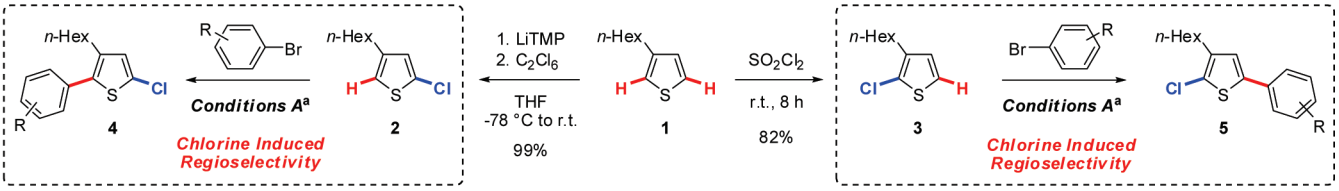
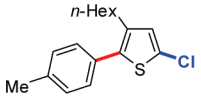
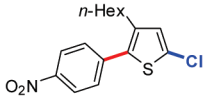
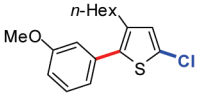
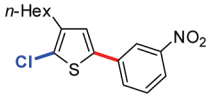
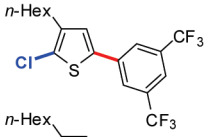
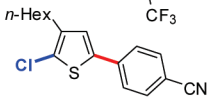
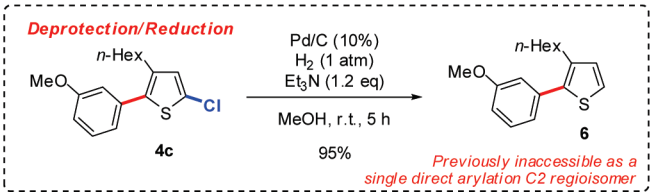
(25) One of the first instances where a CMD-type mechanism was proposed in a C−H bond cleaving event by a palladium species was reported by Ryabov and co-workers in the ortho-palladation of benzylamines. See: (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629–2638. However, concerted metalation−deprotonation events were also proposed with other metals in prior reports. For selected examples, see: (b) Winstein, S.; Traylor, T. G. *J. Am. Chem. Soc.* **1955**, *77*, 3747–3752. (c) De La Mare, P. B. D.; Hilton, I. C.; Varma, S. *J. Chem. Soc.* **1960**, 4044–4054. (d) Kresge, A. J.; Brenna, J. F. *J. Am. Chem. Soc.* **1967**, *32*, 752–755. (e) Deeming, A. J.; Rothwell, I. P. *Pure Appl. Chem.* **1980**, *52*, 649–655. For more recent mechanistic studies, see: (f) Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895–3908. (g) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755.

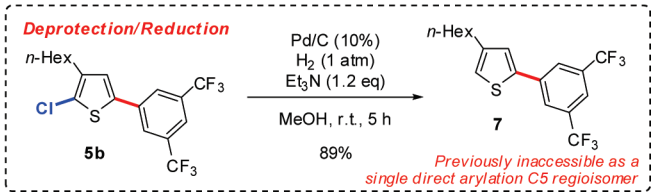
TABLE 1. Chlorine-Induced Regioselectivity. Direct Arylation of 2-Chloro-4-hexylthiophene 2 and 2-Chloro-3-hexylthiophene 3 (Conditions A)



Entry	Product		Time (h)	Yield (%)
1		**4a**	18	72
2		**4b**	13	85
3[b]		**4c**	16	13
4[b,c]		**4c**	13	66

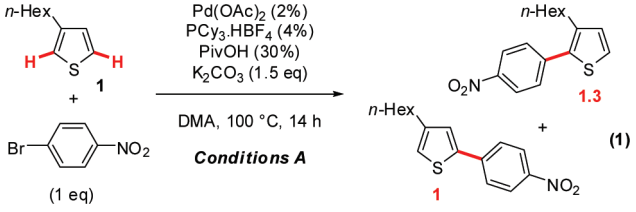
Entry	Product		Time (h)	Yield (%)
5		**5a**	14	88
6		**5b**	13	64
7		**5c**	14	81





[a]HetAr/ArBr 1:1. [b]HetAr/ArBr 1.5:1. [c]ArI was used instead of ArBr.

when employing general conditions for the direct arylation of heteroaromatics,[3q] reaction of 3-(*n*-hexyl)thiophene **1** with 1-bromo-4-nitrobenzene generates an inseparable mixture of isomers in a poor 1.3:1 ratio (eq 1).[26] In cases such as this, the use of an easily transformable blocking group could become a valuable tool to enable the regiocontrolled formation of either isomer at will.



Based on our previous work in direct arylation with aryl fluoride substrates,[23c,27,28] we reasoned that an aryl chloride functional group might also serve as an activating group for reactions at nearby C−H bonds. Less clear, however, was whether a chloride substituent might be able to transmit this activation over greater distances to enable a broad range of arenes to undergo selective direct arylation. In contrast to the synthetic difficulties associated with the preparation of aryl fluorides,[29] the aryl chloride functional group may be selectively formed under a variety of reaction conditions. For example, C3-substituted thiophene **1** may be easily and regioselectively chlorinated at either the C5 or C2 position, respectively, via deprotonation with the sterically encumbered base LiTMP[30] and trapping with C_2Cl_6 to give **2** in nearly quantitative yield, or by electrophilic chlorination by action of sulfuryl chloride[31] to give **3** in 82% yield (Table 1).

We were pleased to find that when subjected to direct arylation, both 2-chloro-4-hexylthiophene **2** and 2-chloro-3-hexylthiophene **3** react smoothly with various aryl halides to give products **4a**−**c** and **5a**−**c** as single regioisomers and in good yields (Table 1). For instance, when **2** is treated with 1 equiv of aryl halide in the presence of $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), PivOH (30 mol %), and K_2CO_3 (1.5 equiv) in DMA at 100 °C (conditions A),[3q] the exclusive site of direct arylation is adjacent to both the sulfur atom and the hexyl side chain. Illustrative examples include the use of 4-bromotoluene and 1-bromo-4-nitrobenzene which provided the corresponding thiophenes **4a** and **4b** in 72% and 85% isolated yields, respectively (entries 1 and 2). When 3-bromoanisole is used as the coupling partner, however, the desired aryl thiophene is isolated in only 13% yield (entry 3). Reasoning that with this more electron-rich aryl bromide competitive and undesired oxidative insertion of the

(26) The ratio of products was determined by ^{1}H NMR analysis of the crude reaction mixture; see the Supporting Information for details.

(27) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *22*, 5097–5100.

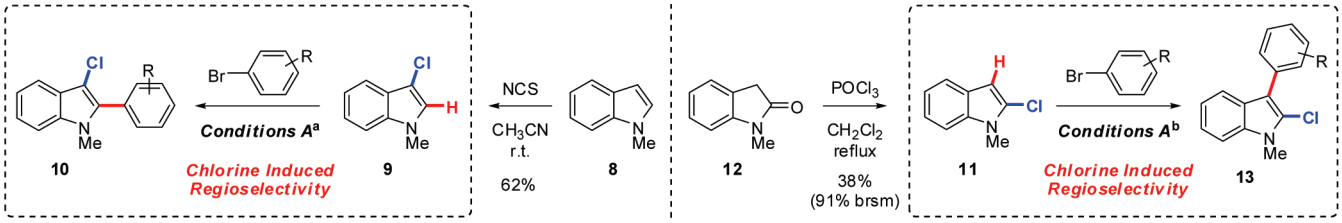
(28) For other related metal-catalyzed transformations involving polyfluorinated arenes, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (b) Johnson, S. A.; Huff, C. W.; Mustafa, F.; Saliba, M. *J. Am. Chem. Soc.* **2008**, *130*, 12278–12280. (c) Nakao, Y.; Kashihara, N.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 16170–16171. See also ref 4k.

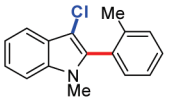
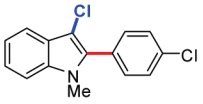
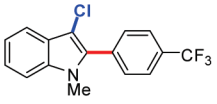
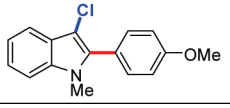
(29) (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664. (b) Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8610–8614.

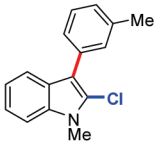
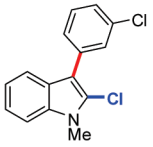
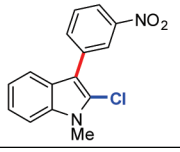
(30) TMP = 2,2,6,6-tetramethylpiperidine. See the Supporting Information for detailed preparation of **2**.

(31) Bidan, G.; De Nicola, A.; Enée, V.; Guillerez, S. *Chem. Mater.* **1998**, *10*, 1052–1058.

TABLE 2. Chlorine-Induced Regioselectivity. Direct Arylation of 3-Chloro-*N*-methylindole 9 and 2-Chloro-*N*-methylindole 11 (Conditions A)



Entry	Product		Time (h)	Yield (%)[d]
1		**10a**	16	73
2		**10b**	8	80
3		**10c**	16	89
4		**10d**	16	10
5[c]		**10d**	16	41

Entry	Product		Time (h)	Yield (%)
6		**13a**	16	79
7		**13b**	16	66
8		**13c**	16	80

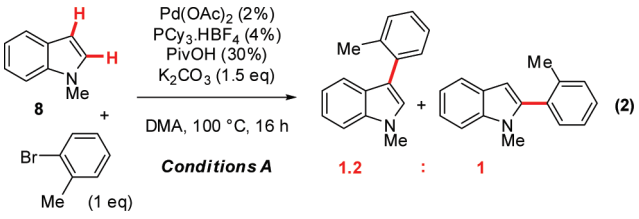
[a]HetAr/ArBr 1.5:1. [b]HetAr/ArBr 1:1. [c]ArI was used instead of ArBr.

palladium catalyst into the aryl chloride bond of **2** may occur, the reaction was instead performed with the corresponding aryl iodide, for which oxidative insertion should be favored. Indeed, substituting 3-bromoanisole for 3-iodoanisole led to the formation of thiophene **4c** in an improved 66% yield (entry 4).

In a similar vein, when the isomeric chlorothiophene starting material **3** was employed, arylation can be induced to occur exclusively at a position remote to the hexyl group. By employing conditions A and the corresponding aryl bromide coupling partner, products **5a**, **5b**, and **5c** were formed in 88%, 64%, and 81% isolated yields, respectively (entries 5−7).

Importantly (and in addition to several other uses of the Ar−Cl bond in substrate diversification), the chlorine atom can simply be removed by treatment with catalytic Pd/C under a hydrogen atmosphere[32] to provide the C2 and C5 monoarylated 3-hexylthiophenes **6** and **7** in very good yields (Table 1). In this way, the preparation and use of stoichiometric organoboron, tin, and other organometallic reagents can be avoided in the cross-coupling step while preserving the aryl chloride functionality for use in other valuable diversity-introducing transformations (vide infra).[20]

Indole direct arylation can also be used to illustrate the utility of the chloride functional group in cases where problematic regioselectivity may occur. While a wide range of indole direct arylation reactions have been established,[7] some substrate combinations remain problematic, particularly with the palladium(0)-catalyzed processes employing inexpensive and readily available aryl bromide coupling partners. For example, when *N*-methylindole **8** is reacted with sterically encumbered aryl halides, such as 2-bromotoluene, a mixture of C3 and C2 isomers is produced in a poor 1.2:1 ratio (eq 2).[26,33]



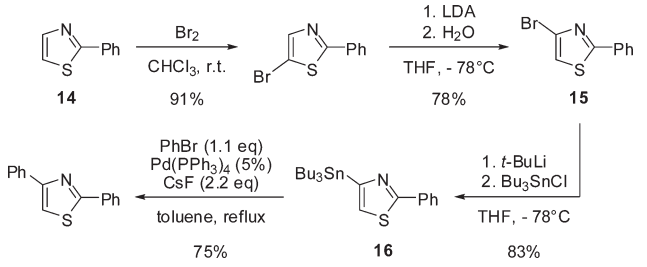
By employing a strategy similar to that described for 3-substituted thiophenes, an aryl chloride substituent may be introduced to enforce the desired regiochemical outcome. For example, 2-bromotoluene reacts efficiently with 3-chloro-*N*-methylindole **9**, prepared via electrophilic chlorination of **8**, to provide the C2 arylation product **10a** in 73% yield as a single regioisomer (Table 2, entry 1). 1-Bromo-4-chlorobenzene and 4-bromobenzotrifluoride may also be employed to provide indoles **10b** and **10c** in 80% and 89% yield, respectively (entries 2 and 3). As previously found, when an electron-rich aryl bromide is employed, in this case 4-bromoanisole, lower yields of the C2 arylated indole **10d** are obtained. Again, by changing to the corresponding aryl iodide, improved outcomes are observed (entries 4 and 5).

In an analogous manner, 2-chloro-*N*-methylindole **11**, prepared from commercially available (or easily prepared) *N*-methyloxindole **12** and $POCl_3$ in 38% yield (91% brsm), can also be employed to induce arylation at C3 with a range

(32) Monguchi, Y.; Kume, A.; Hattori, K.; Maegawa, T.; Sajiki, H. *Tetrahedron* **2006**, *62*, 7926–7933.

(33) It has also been previously reported that ratios can be strongly affected by steric hindrance of the aryl halide. See ref 3e.

SCHEME 4. Typical Metal-Catalyzed Synthesis of 4-Aryl-5*H*-thiazole Derivatives[36h]



of aryl bromide coupling partners (Table 2). For example, 3-bromotoluene, 1-bromo-3-chlorobenzene, and 1-bromo-3-nitrobenzene may be employed as direct arylation coupling partners with **11** to provide the C3 arylated indoles **13a**−**c** in yields of 79%, 66%, and 80%, respectively (entries 6−8). Given the prevalence of the indole core in materials and medicinal chemistry, the frequent need to introduce functionality in a site selective manner at both the C2 and C3 positions,[7] and the ease with which the aryl chloride functional group may be modified, these transformations should find wide application when the selective functionalization of both of these positions is called for.

2. Use of a Chlorine Substituent to Divert Direct Arylation away from Normal Site Selectivity. Despite the advances in direct arylation, regiocontrolled carbon−carbon bond formation at some positions of heteroaromatic compounds remains a challenging goal. This limitation can be illustrated by the reactivity of thiazoles. While useful reactivity has been achieved at C2[3a,l,r,t,34] and C5,[3a,h,l,p,t,34a,35] direct arylation at C4,[3a,l,t] even in the absence of C4/C5 regioselectivity issues, is extremely rare. Even with conventional metal-catalyzed cross-coupling processes, forming a C4 biaryl bond is an inefficient task due to the circuitous routes required to install a C4 activating group in the presence of a C5 C−H bond.[36] For example, electrophilic bromination of 2-phenylthiazole **14** at C5 can be followed by a C5 to C4 migration under a "halogen dance" process (Scheme 4).[36h,37] If an organometallic is required at this position to enable cross-coupling with another aryl halide, the resulting 4-bromothiazole **15** is most commonly transformed into an arylstannane **16** due to the greater stability of these reagents.[5,38] Considering a direct arylation solution to this problem, we also recognized that a similar reactivity profile disfavoring reaction at C4 is present. In this instance, we sought to evaluate the ability of a chloride functional group to not only block reaction at C5 but also to enhance reactivity at C4 toward direct arylation.

To determine whether a C5 chloride functionality could divert the site of direct arylation to C4, 5-chloro-2-phenylthiazole **17** was employed as a model substrate. While the use of conditions A failed to induce useful yields of C4 arylation product, we found that under modified conditions, i.e., $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me\cdot HBF_4$ (10 mol %), PivOH (30 mol %), and Cs_2CO_3 (2 equiv) in mesitylene at 140 °C (conditions B, see the Supporting Information for an optimization table), good yields of C4 arylation could be achieved for the first time with a diverse set of coupling partners (Table 3). For example, 5-chlorothiazole substrates **17**−**19** (prepared by deprotonation/electrophilic chlorination in good yields, see the Supporting Information), bearing either an aryl (**17**−**18**) or an isobutyl group (**19**) at the C2 position, underwent direct arylation at C4 with various electron-rich and electron-poor aryl bromides to provide the corresponding products **20**−**22**, in good yields ranging from 61% to 75% (entries 1−6). 5-Chloro-2-phenyloxazole **23** also participated well in these transformations to provide the C4-arylated oxazoles **24a** and **24b** in 58% and 56% yield, respectively (entries 7 and 8). To illustrate how this method might be applied to the preparation of functionalized 5*H*-thiazoles, hydrodechlorination[32] of **21b** was performed to provide **25** in an excellent yield (Table 3).

The direct arylation of benzothiophenes can also be used to illustrate the utility of the chloride functional group in diverted site selectivity. Benzothiophenes are excellent substrates in palladium-catalyzed direct arylation, providing C2 regioselectivity in high yields.[3q] By installing a C2 chlorine atom via deprotonation and electrophilic trapping (compound **26**, 91% yield), this methodology may also be used to access the C3 direct arylation regioisomers in good yields. Both electron-poor and electron-rich aryl bromides may be employed under these conditions to generate 3-aryl-2-chlorobenzothiophenes **27a**−**c** in 56−77% yields (conditions B, Table 4, entries 1−3). Likewise, 3-arylbenzofuran derivatives, usually prepared via elaborate routes,[18] can also be accessed from 2-chlorobenzofuran **28** in moderate to good yields (compounds **29a**,**b**, entries 4 and 5). As previously described, the products may be easily deprotected,[32] as illustrated by the reaction of **27a** which gave 3-(4-tolyl)-benzothiophene **30** in 98% yield.

3. Additional Examples Where the C−Cl Bond May Improve Reactivity. Even in cases where a deviation in site selectivity is not imparted by the presence of a chlorine functional group, performing direct arylation reaction in its presence may still be beneficial. Commercially available 2-chlorothiophene **31**, for instance, can be employed in these transformations with various electron-neutral and electron-poor 4-substituted aryl bromides to give the corresponding coupling products **32a**−**d** in good yields (conditions A, Table 5, entries 1−4). Sterically encumbered substrates provided

(34) For additional examples of palladium(0)-catalyzed C2 direct arylation of thiazoles, see: (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701. (b) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008**, *10*, 2909–2912.

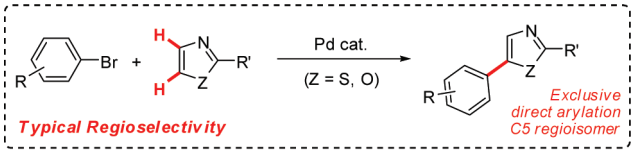
(35) For additional examples of palladium(0)-catalyzed C5 direct arylation of thiazoles, see: (a) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584. (b) Gottumukkala, A. L.; Doucet, H. *Eur. J. Inorg. Chem.* **2007**, 3629–3632. (c) Požgan, F.; Roger, J.; Doucet, H. *ChemSusChem* **2008**, *1*, 404–407. (d) Primas, N.; Bouillon, A.; Lancelot, J.-C.; El-Kashef, H.; Rault, S. *Tetrahedron* **2009**, *65*, 5739–5746.

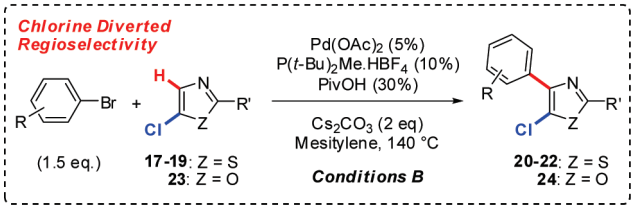
(36) For the preparation of 4-metallathia(oxa)zoles, see: (a) Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N. P.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 84–87. (b) Smith, A. B. III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834–4836. (c) Smith, A. B. III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *J. Org. Chem.* **2008**, *73*, 1201–1208. (d) Araki, H.; Katoh, T.; Inoue, M. *Synlett* **2006**, 555–558. (f) Nakashima, T.; Atsumi, K.; Kawai, S.; Nakagawa, T.; Hasegawa, Y.; Kawai, T. *Eur. J. Org. Chem.* **2007**, 3212–3218. (g) Hämmerle, J.; Schnürch, M.; Stanetty, P. *Synlett* **2007**, 2975–2978. (h) Hämmerle, J.; Spina, M.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Synthesis* **2008**, 3099–3107. (i) Martin, T.; Laguerre, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2009**, *11*, 3690–3693.

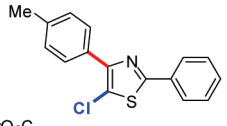
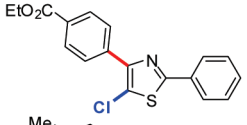
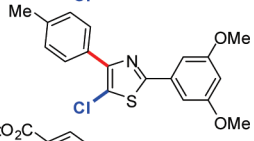
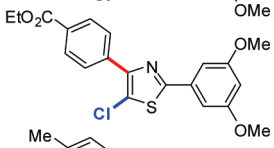
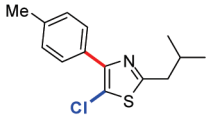
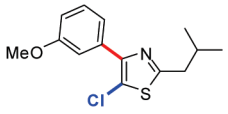
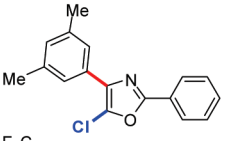
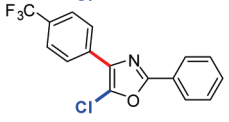
(37) For a review on "halogen dance" reactions, see: Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046–1057.

(38) For selected reviews on the Stille cross-coupling, see: (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508–524. (b) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704–4734.

TABLE 3. Chlorine-Diverted Regioselectivity. Direct Arylation of 2-Substituted 5-Chlorothiazoles 17−19 and 5-Chlorooxazole 23 (Conditions B)





Entry	Product		Time (h)	Yield (%)
1		**20a**	22	62
2		**20b**	22	75
3		**21a**	24	65
4		**21b**	24	62
5		**22a**	24	65
6		**22b**	24	61
7		**24a**	20	58
8		**24b**	20	56

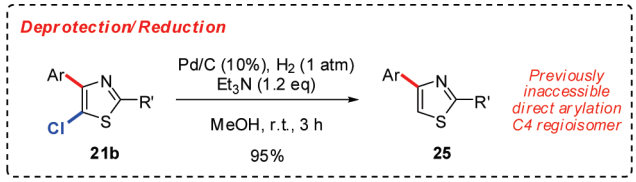
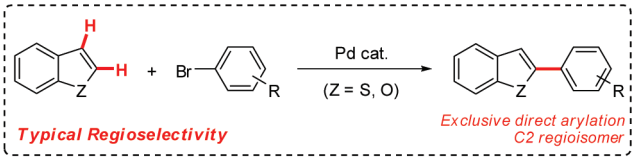
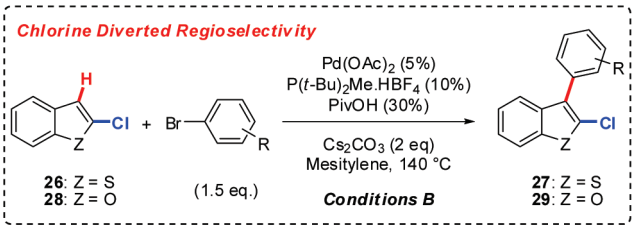
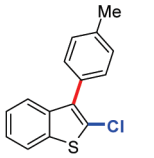
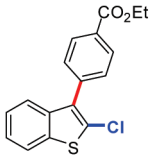
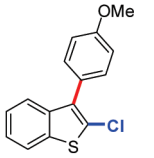
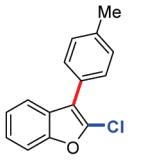
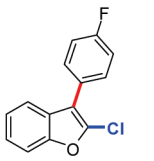
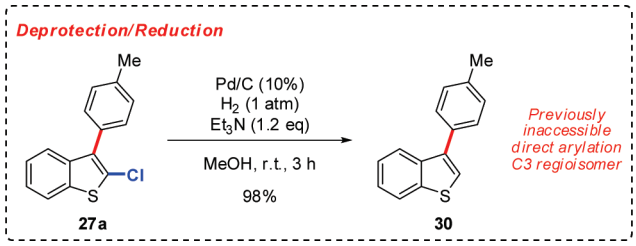


TABLE 4. Chlorine Diverted Regioselectivity. Direct Arylation of 2-Chlorobenzothiophene 26 and 2-Chlorobenzofuran 28 (Conditions B)





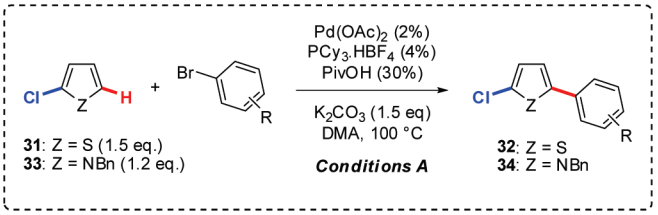
Entry	Product		Time (h)	Yield (%)
1		**27a**	26	77
2		**27b**	25	56
3		**27c**	35	56
4		**29a**	24	61
5		**29b**	24	40

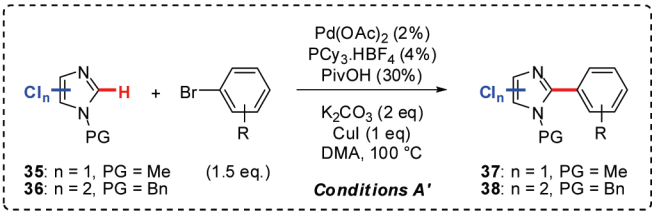


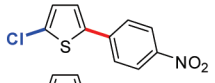
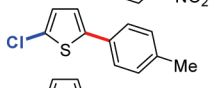
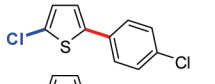
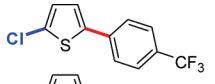
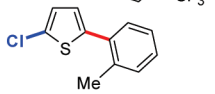
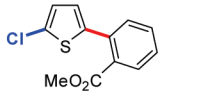
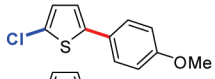
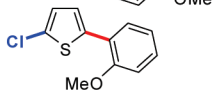
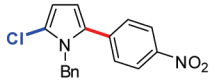
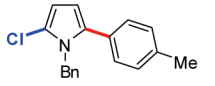
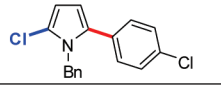
compounds **32e**−**f** without loss of reactivity (entries 5 and 6). In cases where unactivated electron-rich aryl halides were employed, the use of more reactive aryl iodides was found to result in improved yields for compounds **32g** (58% vs 13%) and **32h** (59% vs 37%) (entries 7−10). Analogous reactivity was also observed with *N*-benzyl-2-chloropyrrole **33**, easily prepared by electrophilic chlorination,[39] providing exclusive regioisomers **34a**−**c** in good

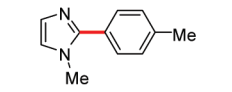
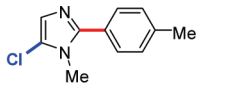
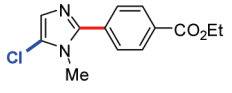
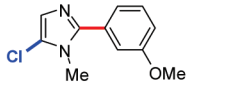
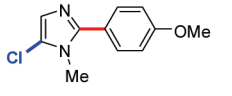
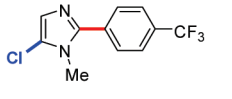
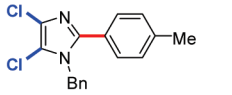
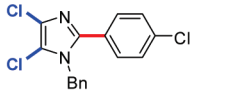
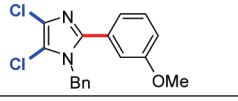
(39) Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161–3169.

TABLE 5. C5 Direct Arylation of 2-Chlorothiophene 31, *N*-Benzyl-2-chloropyrrole 33 (Conditions A), and C2 Direct Arylation of *N*-Methyl-5-chloroimidazole 35 and *N*-Benzyl-4,5-dichloroimidazole 36, in the Presence of a Copper Additive (Conditions A′)





Entry	Product		Time (h)	Yield (%)
1		**32a**	8	87
2		**32b**	8	72
3		**32c**	8	68
4		**32d**	16	56
5		**32e**	8	72
6		**32f**	14	74
7		**32g**	14	13
8[a]		**32g**	14	58
9		**32h**	14	37
10[a]		**32h**	14	59
11		**34a**	16	60
12		**34b**	16	74
13		**34c**	16	63

Entry	Product		Time (h)	Yield (%)
14[b]		*I*	24	0
15		**37a**	11	73
16		**37b**	14	71
17		**37c**	14	64
18		**37d**	19	55
19		**37e**	19	70
20		**38a**	43	54
21		**38b**	24	55
22		**38c**	24	34

[a]ArI was used instead of ArBr. [b]Chlorine-free *N*-methylimidazole was used as starting material.

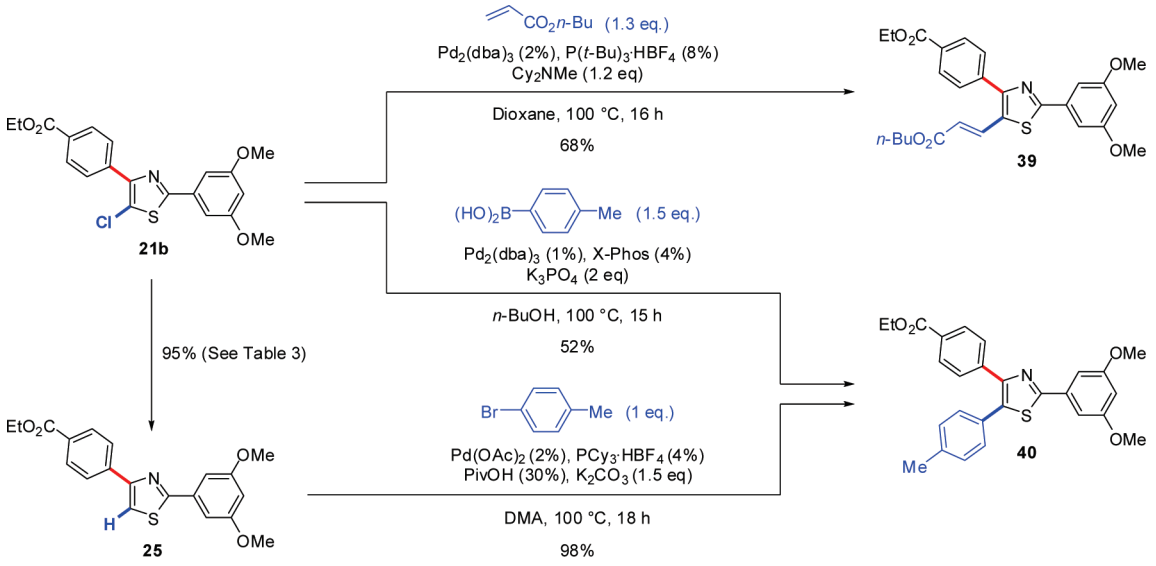
yields (entries 11−13). With imidazole substrates (entries 15−22), synthetically useful yields of C2 arylation products can be obtained in the presence of C5-chloride or C4,C5-dichloride substituents (compounds **35** and **36**, respectively). In these instances, superior outcomes were observed when the reactions were performed in the presence of one equivalent of CuI (conditions A′, Table 5).[40] When these same reactions were conducted on *N*-methylimidazole lacking chlorine substituents, no reaction was observed (entry 14), illustrating the activating effect of the remote chlorine substituent for such transformations.

4. Subsequent Transformations. A key benefit associated with the use of a C−Cl bond to divert direct arylation reactivity is not only its ease of installation but also its capacity to be employed in a wide range of subsequent transformations.[20] To demonstrate the utility of this strategy, 2,4-diarylated 5-chlorothiazole **21b** was subjected to various palladium-catalyzed transformations (Scheme 5), including a Heck reaction with butyl acrylate following Fu's conditions[41] providing alkene **39** in 68% yield,[42] and a Suzuki coupling with *p*-tolylboronic acid in the presence of $Pd_2(dba)_3$ and phosphine ligand X-Phos[43] to give tris-arylated thiazole

(40) The role of copper additives in palladium-catalyzed direct arylation of heteroaromatics has not been definitively elucidated. For selected examples, see: (a) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781–7786. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543–8546. (c) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125–6137. (d) Besselièvre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278–3280. (e) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *J. Org. Chem.* **2008**, *73*, 9048–9054. (f) Čerňová, M.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2009**, 3698–3701. See also refs 3a, 3l, and 3t.

(41) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
(42) Reaction conditions not optimized.
(43) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.

SCHEME 5. Subsequent Transformations of Thiazoles 21b and 25



40 in 52% yield.[42] Deprotected thiazole **25** (see Table 3) may also be subjected to a C5 direct arylation reaction (conditions A) to give compound **40** in 98% yield. This final approach may be an attractive alternative for the synthesis of such polyarylated azoles in cases where the requisite boronic acid coupling partners are expensive or not readily accessible.

5. Mechanistic Studies: Competition Experiments. To investigate the influence of a chlorine substituent in palladium-catalyzed direct arylation, competition experiments were performed and the results compared to the outcomes of S_EAr-type processes (Schemes 6 and 7). For example, when an equimolar mixture of 2-methylthiophene **41** and 2-chlorothiophene **31** was subjected to a direct arylation competition reaction with 0.2 equivalents of 2-bromotoluene (conditions A, Scheme 6), preferential reaction occurred at the more electron-deficient chlorothiophene **31** in an 11:1 ratio. A similar but less pronounced effect was observed for experiments performed with pyrroles **45** and **33**, where the chlorinated substrate **33** reacted preferentially in a 1.2:1 ratio. In stark contrast, when Vilsmeier−Haack formylation (known to proceed *via* an electrophilic aromatic substitution pathway)[44] competition experiments were performed with the same substrate combinations, the more electron-rich nonchlorinated heterocycles **41** and **45** reacted preferentially in 17:1 and 19:1 ratios, respectively.

The influence of the chlorine substituent in direct arylation and S_EAr reactions was also evaluated with indole substrates where the reaction occurs at both typical and atypical sites (Scheme 7). For instance, when *N*-methylindole **8** and 3-chloro-*N*-methylindole **9** were subjected to direct arylation reaction conditions, natural C2-arylation occurred preferentially at the chlorinated indole **9** in a 9:1 ratio. Under Vilsmeier−Haack formylation conditions where the natural site for electrophilic attack at C3 is blocked, reaction took place almost exclusively at the nonchlorinated indole **8**.

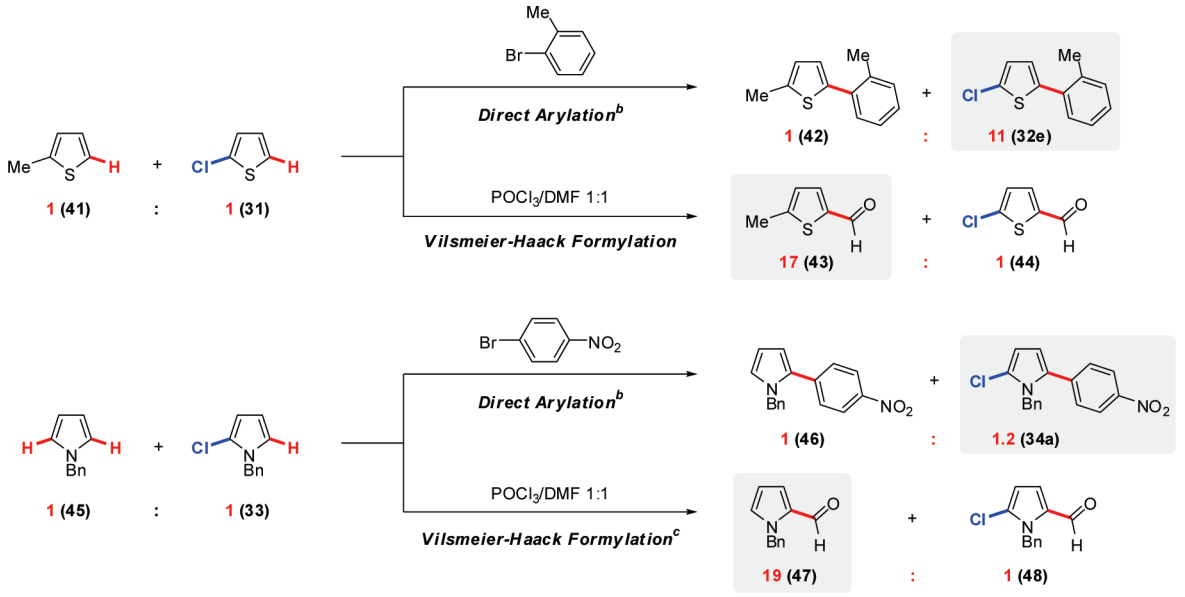
Competition experiments were also performed with **8** and 2-chloro-*N*-methylindole **11**. Despite the fact that the site of arylation is diverted from C2 to C3, chlorinated indole **11** still reacts preferentially in a 1.6:1 ratio over the nonchlorinated indole **8** (that undergoes arylation at C2). Under Friedel−Crafts acylation conditions, both substrates may undergo reaction at the natural C3 position. In this case, a less pronounced preference is observed for reaction at nonchlorinated substrate **8** (in a 2.3:1 ratio), in accord with electrophilic aromatic substitution chemistry. These experiments underline the different reactivity profiles observed for palladium-catalyzed direct arylation compared to electrophilic aromatic substitution. These results also provide a valuable experimental reference point against which computational work may be calibrated.

6. Mechanistic Studies: Computational Results. Density functional theory (DFT) calculations have been performed using the Gaussian 03 program.[45] In all calculations, the spin-restricted method was employed. Wave function stability calculations were carried out to confirm that the calculated wave functions corresponded to the electronic ground

(44) (a) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119–122. (b) Linda, P.; Marino, G.; Santini, S. *Tetrahedron Lett.* **1970**, *48*, 4223–4224. (c) Alunni, S.; Linda, P.; Marino, G.; Santini, S.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2070–2073. (d) Linda, P.; Lucarelli, A.; Marino, G.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1610–1612. (e) Mayr, H.; Ofial, A. R. *Tetrahedron Lett.* **1997**, *38*, 3503–3506. (f) Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1–330.

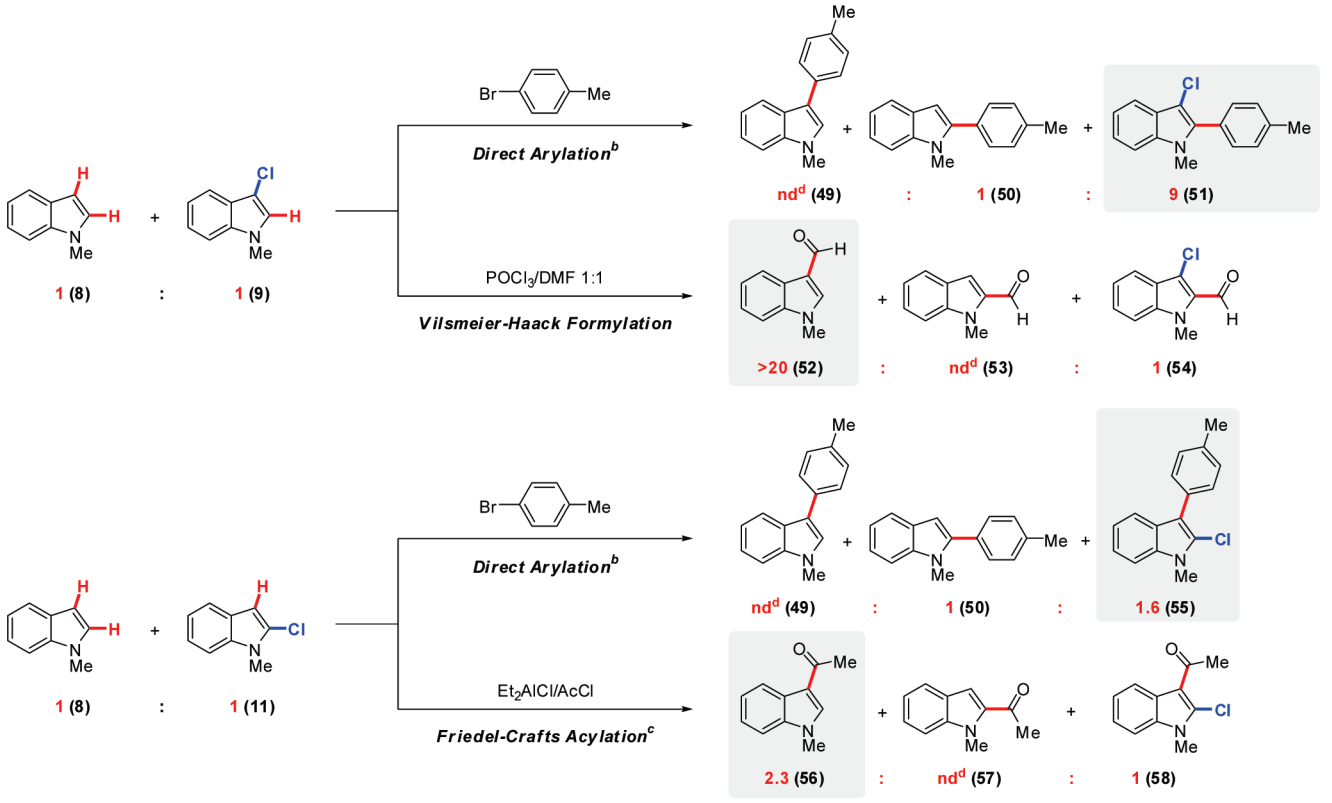
(45) *Gaussian 03, Revision C.02*: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

SCHEME 6. "Direct Arylation" and "Vilsmeier−Haack Formylation" Competition Experiments between Non-Chlorinated and Chlorinated Thiophenes 41 and 31 and Pyrroles 45 and 33[a]



[a]Ratios of products (red numbers) determined by ^{1}H NMR analysis of the crude reaction mixture (see the Supporting Information for detailed reaction conditions and NMR spectra).[b]Conditions A were used, with 0.2 equiv of the aryl bromide.[c]A small amount of product arising from formylation at the C3 position of **45** was also detected.

SCHEME 7. "Direct Arylation", "Vilsmeier−Haack Formylation", and "Friedel−Crafts Acylation" Competition Experiments between Non-Chlorinated and Chlorinated Indoles 8 and 9 and 8 and 11[a]



[a]Ratios of products (in red) determined by ^{1}H NMR analysis of the crude reaction mixture (see the Supporting Information for detailed reaction conditions and NMR spectra).[b]Conditions A were used, with 0.2 equiv of the aryl bromide.[c]A small amount of product arising from an intermolecular reaction between **8** and **11** was also detected.[d]Not detected.

state. The structures of all species were optimized using the B3LYP exchange-correlation functional[46] with the mixed basis set (DZVP[47] on Pd and TZVP[48] on all other atoms). The Pd catalyst was modeled with PMe_3 ligands and an acetate base. Tight SCF convergence criteria (10^{-8} au) were used for all calculations. Harmonic frequency calculations with the analytic evaluation of force gradients (OPT = CalcAll) were used to determine the nature of the stationary points. Intrinsic reaction coordinate (IRC)[49] calculations were used to confirm the reaction pathways through the CMD transition states (TSs). Free energies of species were evaluated at 298 K and 1 atm. Mayer bond orders[50] were calculated using the AOMix program.[51]

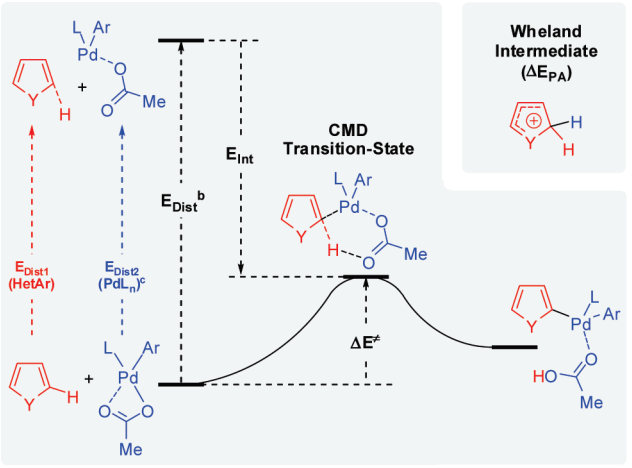
Gibbs Free Energy of Activation $\Delta G^{\ddagger}$. The reaction pathways for both direct arylation and S_EAr reactions were evaluated with nonchlorinated and chlorinated thiophenes **41** and **31** and indoles **8**, **9**, and **11**. By first considering a concerted metalation−deprotonation (CMD) pathway for the direct arylation reactions, the Gibbs free energy of activation $\Delta G^{\ddagger}$ was determined (Table 6). In accord with experimental outcomes, the $\Delta G^{\ddagger}$ for the CMD pathway was found to be significantly lower for substrates bearing a chlorine atom, with gaps of 1.4 kcal mol^{-1} for thiophenes **41** and **31** (entries 1 and 2) and 2.3 kcal mol^{-1} for indoles **8** and **9** (entries 3 vs 4) and **8** and **11** (entries 5 vs 6).

Proton Affinity. To evaluate the impact of the chlorine functional group on electrophilic aromatic substitution (S_EAr) pathways, the proton affinity (ΔE_{PA}) of the reactive sites was calculated. In accord with known S_EAr reactivity and experimental observations, the relative proton affinities correlate well with experimental S_EAr outcomes (Schemes 6 and 7) and follow an opposite trend to the CMD pathway calculated for direct arylation reactions. With thiophenes for example, values of 212.5 and 205.2 kcal mol^{-1} were determined for 2-methylthiophene **41** and 2-chlorothiophene **31**, respectively (entries 1 and 2). On the other hand, the addition of a chlorine atom at C2 appears to have little impact on the C3-nucleophilicity of indole **11**, with a decrease of ΔE_{PA} of only 1.2 kcal mol^{-1} when compared to indole **8** (226.8 vs 225.6 kcal mol^{-1}, entries 5 vs 6), in agreement with the low experimental ratio observed for the Friedel−Crafts acylation competition experiment (Scheme 7).

Distortion and Interaction Energies E_{Dist} and E_{Int}. To further evaluate and begin to explain the impact of the C−Cl bond on direct arylation reactivity, the elementary contributions to free energy of activation $\Delta G^{\ddagger}$ were calculated using the charge and energy decomposition analyses. In this approach, the distortion energy E_{Dist}, associated with distortion of both the heteroarene (HetAr) and the catalyst (PdL_n), and the electronic interaction energy E_{Int}, between PdL_n and the substrate in the CMD transition state, were evaluated (Table 6).[23i] Clear trends emerged from these studies. In each case, the presence of a chlorine substituent results in a decrease in E_{Dist}(HetAr) by 2.8 kcal mol^{-1} for thiophenes **41** and **31** (entries 1 vs 2) and 5.3 and 2.7 kcal mol^{-1} for indoles **8** and **9** (entries 3 vs 4) and **8** and **11** (entries 5 vs 6), respectively. On the other hand, $E_{Dist}(PdL_n)$ showed much less variation for reactions of substrates with and without chlorine substituents (between 0.4 and 0.8 kcal mol^{-1}), indicating that the presence of the C−Cl bond does not affect the structure of the PdL_n fragment in the CMD TS.

The presence of a chorine substituent was also found to influence the interaction energy E_{Int} (Table 6). Here, substrates bearing a chlorine substituent exhibit decreased E_{Int} values, with gaps of 1.9 kcal mol^{-1} for thiophenes **41** and **31**

TABLE 6. Reaction Pathway Analysis for Direct Arylation and Electrophilic Aromatic Substitution of Non-Chlorinated and Chlorinated Heteroaromatics[a]

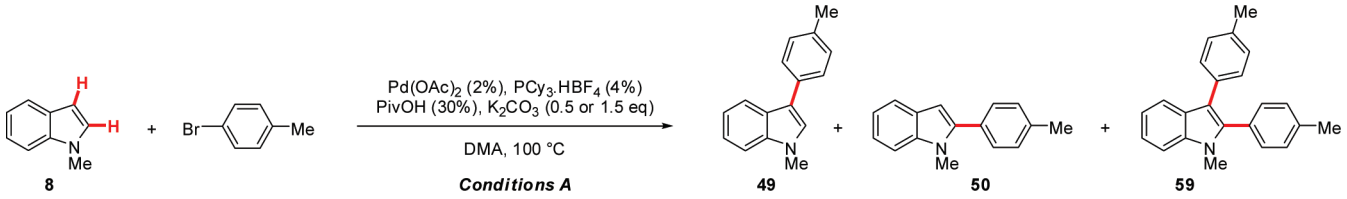


Entry	HetAr	CMD Transition-State E_{Dist1}	E_{Dist2}	E_{Int}	$\Delta E^{\neq}$	$\Delta G^{\neq}$	$B_{Pd\text{-}C}$[d]	ΔE_{PA}[e]
1	**41**	40.7	17.8	-42.9	15.6	25.8	0.537	**212.5**
2	**31**	**37.9**	17.4	-41.0	14.3	**24.4**	0.499	205.2
3	**8**	43.3	18.5	-44.3	17.5	28.2	0.559	218.0
4	**9**	**38.0**	17.7	-41.0	14.7	**25.9**	0.493	217.9
5	**8**	46.1	18.9	-47.7	17.3	28.0	0.569	**226.8**
6	**11**	**43.4**	18.1	-46.0	15.5	**25.7**	0.535	**225.6**

[a]Energies expressed in kcal mol^{-1}. [b]E_{Dist} = E_{Dist}(HetAr) + E_{Dist}-(PdL_n). [c]PdL_n = Pd(Ph)(PMe_3)(OAc). [d]Pd−C bond order. [e]Electronic component of proton affinity at the corresponding carbon site.

(46) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
(47) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560–571.
(48) Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829–5835.
(49) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
(50) Mayer, I. *Chem. Phys. Lett.* **1983**, *97*, 270–274.
(51) (a) Gorelsky, S. I.; Basumallick, L.; Vura-Weis, J.; Sarangi, R.; Hedman, B.; Hodgson, K. O.; Fujisawa, K.; Solomon, E. I. *Inorg. Chem.* **2005**, *44*, 4947–4960. (b) Gorelsky, S. I.; Version 6.43 ed.; University of Ottawa: Ottawa, Canada, 2009; http://www.sg-chem.net.

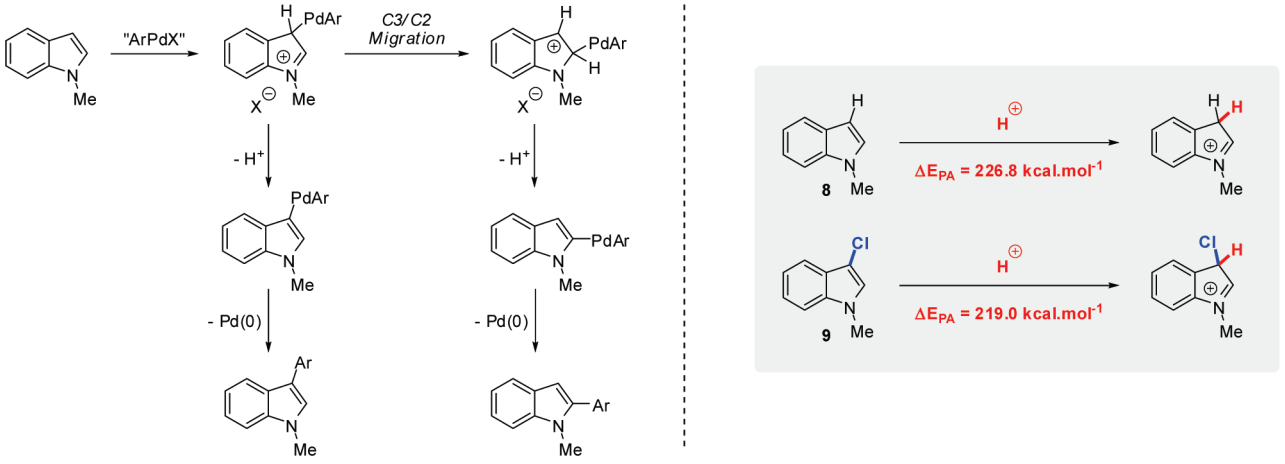
TABLE 7. C3/C2 Regioselectivity in the Palladium-Catalyzed Direct Arylation of *N*-Methylindole 8 with 4-Bromotoluene



entry	ArBr (equiv)	K_2CO_3 (equiv)	time (h)	ratio of products[a]		
1	1.0	1.5	14	1	5.5	0.9
2	0.2	0.5	4	1	2.6	nd[b]

[a]Ratios of products determined by ^{1}H NMR analysis of the crude reaction mixture (see Supporting Information for detailed reaction conditions and NMR spectra). [b]Not detected.

SCHEME 8. C3/C2 Migration Pathway for C3/C2 Selectivity in the Direct Arylation of Indoles According to the S_EAr Pathway (Neutral Atom Donor Ligands on Palladium Are Omitted for Clarity) and Calculated C3 Proton Affinity Values for Indoles 8 and 9



(entries 1 vs 2) and 3.3 and 1.7 kcal mol^{-1} for indoles **8** and **9** (entries 3 vs 4) and **8** and **11** (entries 5 vs 6), respectively. An electronic structure analysis of the covalent interactions in the CMD TSs indicates that the Pd−C bond order decreases with the presence of a chlorine substituent by 0.038 for thiophenes **41** and **31** (entries 1 vs 2) and by 0.066 and 0.034 for indoles **8** and **9** (entries 3 vs 4) and **8** and **11** (entries 5 vs 6), respectively.

These studies begin to paint a more accurate picture of the underlying factors governing palladium(0)-catalyzed direct arylation. *Since the positive influence of the chlorine substituent on the magnitude of E_{Dist}(HetAr) is larger than its negative influence on E_{Int}, the improved reactivity associated with these substrates is predominantly a consequence of this effect*. Ongoing efforts are directed at using this knowledge in the establishment of a set of guidelines that may be employed to predict and understand this type of reactivity with the broadest set of aromatic coupling partners possible.

Indole C3/C2 Selectivity. A more detailed discussion on the C3/C2 selectivity of *N*-alkylindole arylation is warranted.[52] According to the CMD pathway, the calculated values of the Gibbs free energies of activation $\Delta G^{\ddagger}$ for C2- and C3-arylation of indole **8** are strikingly similar (28.2 and 28.0 kcal mol^{-1}, respectively). To establish an experimental reference point, reactions employing *N*-methylindole **8** with 4-bromotoluene were carried out (Table 7). Under conditions A, a mixture of three products was obtained, C3-arylindole **49**, C2-arylindole **50**, and C2,C3-diarylindole **59**, in a 1:5.5:0.9 ratio and a combined yield of 65% (entry 1). To better establish the inherent C3/C2 selectivity, the same reaction was performed with only 0.2 equiv of 4-bromotoluene, thereby minimizing the potential for diarylation. In this case, a 1:2.6 ratio of **49** and **50** was obtained (entry 2). Given the ease with which C3/C2 selectivity can be influenced experimentally by changing the reaction parameters and aryl halide substitution patterns (see also eq 2),[3e,53] reaction pathways leading to both outcomes must be energetically accessible. In this light, the similarity of the calculated values of the Gibbs free energies of activation $\Delta G^{\ddagger}$ (Table 6, entries 3 and 5) should be anticipated. With

(52) It is important to distinguish between reactions involving *N*-alkyl and *N*-H indoles that may become deprotonated under the basic reaction conditions employed for palladium(0)-catalyzed direct arylation. Such anionic species should exhibit different reactivity and behave much more like typical nucleophiles in palladium-catalyzed cross-coupling processes. See: (a) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett*. **2007**, *48*, 2415–2419. (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem*. **2007**, *72*, 1476–1479. (c) Cusati, G.; Djakovitch, L. *Tetrahedron Lett*. **2008**, *49*, 2499–2502. See also refs 2d and 3m, 3x.

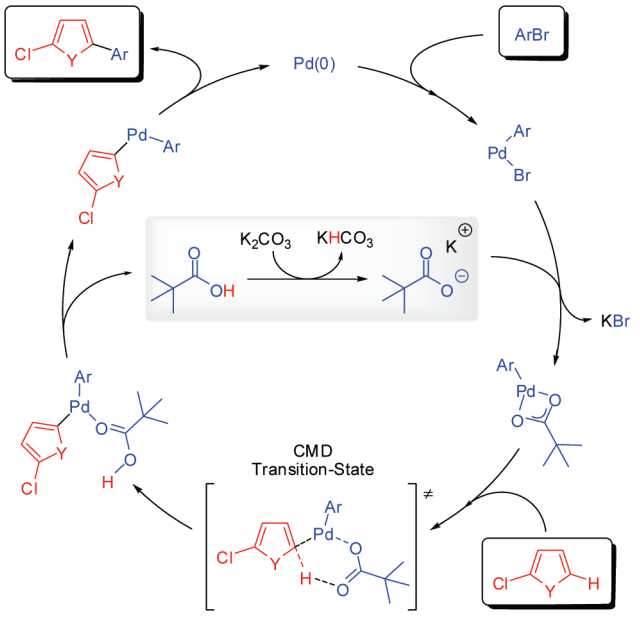
(53) The influence of the nature of the halide substituent on regioselectivity has previously been noticed. See: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 581–590. (b) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett*. **2008**, *10*, 4533–4536.

continued refinement and additional advances in our understanding of the important reaction variables that influence this type of reactivity, the precision of this mechanistic rationale will continue to grow.

Another mechanistic hypothesis has also been proposed that does not involve direct C2 or C3 metalation and instead involves an initial C3 electrophilic palladation followed by a C3/C2 palladium migration (Scheme 8).[3e] This C3/C2 migration pathway, which has also been documented in the broader indole literature,[54] is supported experimentally by the detection of a secondary kinetic isotope effect (KIE) of 1.6 at C3 when arylation is occurring at C2 (under slightly different conditions than those described herein). A similar hypothesis has also been advanced for other palladium(II)- and copper(I/III)-catalyzed indole functionalization processes.[4d,55] To probe the compatibility of this hypothesis with the experimental outcomes from the competition experiments involving the chlorinated and nonchlorinated indoles, the C3 proton affinity ΔE_{PA} of 3-chloro-*N*-methylindole **9** was determined as a means of approximating the relative propensity of this indole to undergo electrophilic palladation at this site compared to the nonchlorinated indole **8** (Scheme 8). These calculations revealed a C3 proton affinity of 219.0 kcal mol^{-1} for **9** which is 7.8 kcal mol^{-1} lower than the corresponding value for indole **8**. This result indicates that unsubstituted indole **8** should exhibit enhanced reactivity compared to **9** under an S_EAr-like reaction profile, a trend that is not supported by the direct arylation competition experiment outcomes (that do correlate well with calculated CMD-type reactivity, Table 6). What is difficult to reconcile with the CMD pathway is the previously observed secondary KIE at C3 for a reaction occurring at C2.[3e] Our ability to evaluate this feature under the conditions employed herein is complicated by the formation of significant amounts of C3 monoarylation and C2/C3 diarylation products − processes that may exhibit significant primary kinetic isotope effects. More mechanistic work will be required before a more definitive statement can be made on the attributes of this particular substrate class, the first to be successfully employed in these reactions more than 20 years ago,[2e] and its responsiveness to subtle changes in reaction variables.

General Discussion and Implications in Reaction Development. Several mechanistic scenarios have been proposed to explain palladium(0)-catalyzed direct arylation outcomes including oxidative C−H insertion,[56] S_EAr,[22] Heck-like additions,[57,58] and CMD.[23,59] One hypothesis that may rationalize the breadth of palladium-catalyzed direct arylation reactivity and the seemingly divergent outcomes is the presence of flat direct arylation reaction energetics allowing for mechanistic promiscuity and the involvement of both S_EAr and CMD pathways (and potentially others) depending on subtle differences in the substrate combinations and reaction conditions.[1f,23i] The ability of the CMD pathway to accurately explain and predict reaction outcomes across a broad and chemically very diverse set of aromatic coupling partners leads us to favor a second hypothesis where a CMD pathway is operative in the majority of cases. This mode of reactivity in palladium(0)-catalyzed direct arylation has the power to explain reaction outcomes that might appear anomalous under a simple S_EAr paradigm. It can also explain the important base effects that have been documented in these transformations, such as the common use of acetate and carbonate bases,[2] the improvements due to the use of stoichiometric pivalate salts by the groups of Larock[60] and Sames[61] in palladium(0)- and rhodium(I)-catalyzed direct arylation, respectively, and later the use of catalytic

SCHEME 9. Proposed Catalytic Cycle for the Palladium-Catalyzed Direct Arylation of Heteroaromatics in the Presence of a Co-Catalytic Amount of Pivalic Acid (Neutral Atom Donor Ligands on Palladium Are Omitted for Clarity)



(54) For example, see: (a) Jackson, A. H.; Smith, P. *Chem. Commun.* **1967**, 264–266. (b) Jackson, A. H.; Smith, A. E. *Tetrahedron* **1968**, *24*, 403–413. (c) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119–6129. (d) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761. (e) Jackson, A. H.; Lynch, P. P. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1215–1219. (f) Biswas, K. M.; Jackson, A. H.; Kobaisya, M. M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 461–467. (g) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439–440.

(55) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125–3129.

(56) For reactions where an oxidative C−H insertion pathway has been proposed; see: Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507.

(57) For reactions where a Heck-like addition pathway has been proposed, see: (a) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293–4296. (b) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923–2926. See also ref 3b.

(58) For reactions where a Heck-like addition pathway seems to be less likely to occur, see: (a) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680. (b) Hughes, C. C.; Trauner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569–1572.

(59) Given the pronounced "non-electrophilic substitution"-like influences on these arylation reactions, description as an electrophilic process does not reflect reactivity. Furthermore, only placing emphasis on the deprotonation step does not reflect that in some instances there can be important electronic parameters that may contribute to the energetics of the transition state. Consequently, we prefer the use of "concerted metalation−deprotonation" since it underlines the fact that there are two key processes that occur simultaneously and that exert important influences on the overall reactivity.

(60) (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461. (b) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251–8257. (c) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1873–1875. (d) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288–5295.

(61) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997.

quantities of pivalate salts in conjunction with a stoichiometric and insoluble carbonate.[3l,q,t,u,23d,f,i,24a,53b,62] *In contrast to true S_EAr-like mechanisms, arene nucleophilicity is only one component of CMD reactivity and in many instances may not be the primary governing influence*.[23i] Importantly, this mindset is likely to inspire different lines of thought in reaction development and substrate selection.

6. Proposed Catalytic Cycle. In agreement with experimental and theoretical studies described above, the catalytic cycle can be depicted as previously proposed by our group and others (Scheme 9).[23] Initial oxidative addition of the palladium(0) species into the aryl halide bond is followed by a bromide/pivalate ligand exchange, the latter being generated in situ from the catalytic pivalic acid and the insoluble stoichiometric carbonate base. Approach of the heteroaromatic partner leads to a concerted metalation−deprotonation (CMD) transition state, enabled by the pivalate ligand. Subsequent reductive elimination produces the biaryl product and regenerates the active catalytic species.

Conclusion

In summary, we described the palladium-catalyzed direct arylation of chlorine-containing heteroaromatics with various aryl halides. The chlorine atom, which remains intact under the reaction conditions, not only enhances reactivity but also allows arylation to occur at usually unreactive positions. The resulting chlorine-containing biaryl products may also be used for further functionalization, a feature that should find application in the synthesis of more complex targets. These aspects as well as more detailed mechanistic studies are currently being investigated by our group and will be reported in due course.

Experimental Section

General Procedure for the Direct Arylation of Chlorine-Containing Heteroaromatics: Conditions A[3q]. $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), PivOH (30 mol %), and K_2CO_3 (1.5 equiv) were weighed to air and placed in a 2 mL screw-cap vial equipped with a magnetic stir bar. The heterocycle (0.5−1 mmol) and the aryl bromide (1 equiv, unless otherwise specified) were added at this point if solids. The vial was purged with argon, and DMA (0.3 M) was added. The heterocycle and the aryl bromide were added at this point if liquids. The reaction was then vigorously stirred at 100 °C for the indicated time. The solution was then cooled to rt, diluted with EtOAc, washed with H_2O, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford the desired product. 2-Chloro-4-(*n*-hexyl)-5-(*p*-tolyl)thiophene (**4a**): yellow oil; R_f 0.6 (petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.77 (s, 1H), 2.54 (m, 2H), 2.38 (s, 3H), 1.54 (m, 2H), 1.31−1.20 (m, 6H), 0.85 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.5, 136.5, 130.8, 129.3, 129.2, 128.3, 127.5, 31.6, 30.8, 29.0, 28.7, 22.6, 21.2, 14.0; IR (ν_{max}) 2957, 2929, 2859, 1510, 811 cm^{-1}; HRMS calcd for $C_{17}H_{21}ClS$ (M^+) 292.1052, found 292.1045.

General Procedure for the Direct Arylation of Chlorine-Containing Heteroaromatics: Conditions B (See the Supporting Information for Optimization). $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me \cdot HBF_4$ (10 mol %), PivOH (30 mol %), and Cs_2CO_3 (2 equiv) were weighed to air and placed in a 2 mL screw-cap vial equipped with a magnetic stir bar. The heterocycle (0.5−1 mmol) and the aryl bromide (1.5 equiv, unless otherwise specified) were added at this point if solids. The vial was purged with argon, and mesitylene (0.3 M) was added. The heterocycle and the aryl bromide were added at this point if liquids. The reaction was then vigorously stirred at 140 °C over the indicated time. The solution was then cooled to rt, diluted with EtOAc, washed with H_2O, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford the corresponding product. 5-Chloro-2-phenyl-4-(*p*-tolyl)thiazole (**20a**): white solid; mp 72−74 °C; R_f 0.25 (petroleum ether/toluene 80/20); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, $J = 8.0$ Hz, 2H), 7.93−7.89 (m, 2H), 7.47−7.41 (m, 3H), 7.28 (d, $J = 8.0$ Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.5, 138.4, 133.2, 130.4, 130.2, 129.1, 129.0, 128.2, 126.2, 119.6, 21.4; IR (ν_{max}) 928, 831, 746, 724 cm^{-1}; HRMS calcd for $C_{16}H_{12}ClNS$ (M^+) 285.0379, found 285.0364.

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Supporting Information Available: General considerations; optimization table (conditions B); competition experiments details; synthesis, characterization, and NMR spectra of all new starting materials and all coupling products; optimized geometries of substrates and the corresponding CMD transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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