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Catalytic C–H Arylation of SEM-Protected Azoles with Palladium Complexes of NHCs and Phosphines

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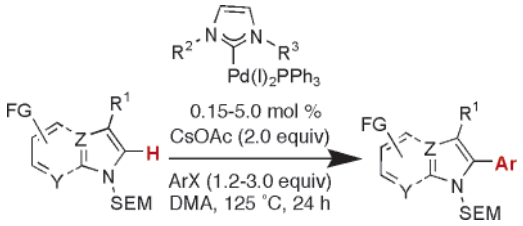
ABSTRACT



The synthesis and catalytic evaluation of palladium complexes containing imidazolyl carbene ligand of varying steric and electronic properties is reported. These complexes catalyze the efficient C–H arylation of SEM-protected azole heteroarenes and thus provide a good method for preparation of a wide range of arylated free (NH)-azoles including pyrroles, indoles, imidazoles, and imidazo[1,2-*a*]pyridines. The reaction is operationally simple; the complexes are insensitive to moisture.

Azoles are ubiquitous features of natural products, pharmaceuticals, and fluorescent dyes, as well as many other synthetics. This broad range of uses of azoles and related heteroarenes warrants the development of efficient and cost-effective methods for their elaboration. The recent advances in transition metal catalysis have unlocked many exciting opportunities in this arena. New synthetic strategies such as the direct functionalization of sp^2 C−H bonds are now emerging as viable alternatives to traditional cross-coupling reactions.[1] In these instances, the need for preactivating one of the reaction components as its halide, tin, silicon, or boron derivative is thus circumvented. The current repertoire includes catalytic systems for arylation of 1-alkyl/aryl azoles and binuclear azoles.[2,3] However, the direct arylation of free (NH)-azoles still remains a significant synthetic challenge. Currently, there are two approaches to this problem: (1) arylation of azole magnesium[4] and zinc salts[5] formed in situ and (2) direct rhodium-catalyzed arylation of free (NH)-pyrroles and indoles.[6] While the former method suffers from significant moisture sensitivity, the latter one is limited in scope, most notably it is not applicable to imidazoles and pyrrazoles.[6] A new method for C-2 arylation of benzimidazole and related systems has been reported.[7]

We have recently reported a practical palladium-catalyzed arylation of 1-alkyl indoles.[2] A major drawback of this procedure was the formation of biphenyl byproducts, which was marginalized by using low catalyst loading. Although satisfactory in the context of simple alkyl indoles, many attractive but less reactive substrates such as SEM-protected

(1) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241.
(2) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897−2900.
(3) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn* **1998**, *71*, 467−473. (b) Li, W. J.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, 4835−4837. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162. (d) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2005**, *70*, 3997−4005.
(4) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.
(5) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981−3983.
(6) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996−4997.
(7) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35−38.

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azoles were ineffective. SEM (2-(trimethylsilyl)ethoxymethyl) represents a versatile and robust protecting group for azoles that can readily be removed under a variety of reaction conditions.[8] Herein, we disclose a catalytic system that allowed the efficient arylation of SEM-protected azoles, which in turn enables rapid preparation of a wide range of arylated free (NH)-azoles.

Design of new catalyst precursors was founded on the premise that one robust ligand (permanent ligand) should be attached to the palladium center to improve its stability, modulate its reactivity, and disfavor biphenyl formation. Also, a labile ligand (i.e., Ph_3P) should improve the stability of the entire complex while in the reaction mixture it would be readily displaced by the substrate.

Led by the above criteria, $L^1L^2PdX_2$ palladium complexes wherein L^1 = *N*-heterocyclic carbene (NHCs) and L^2 = phosphine[9] were identified as promising leads. Accordingly, we initiated the synthesis of a series of these catalysts with particular emphasis on the steric and electronic properties of the carbene ligand. The requirement for sufficient steric demand of the carbene ligand became rapidly apparent, which led to selection of four complexes **1a**−**d** for further examination (Figure 1).[10] With the exception of **1c**,[11] these

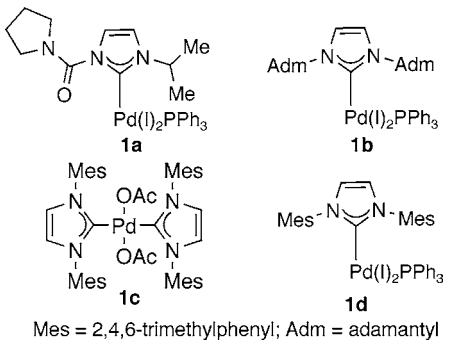


Figure 1. Structure of palladium complexes (catalyst precursors) investigated in this study.

catalysts may be purified by silica gel chromatography. In addition, they are characterized by a high tolerance to air and moisture.

The initial results revealed that the direct arylation of 1-SEM-azoles was feasible, suggesting the superior performance of **1a** in comparison to our previous system.[2] As expected, the less reactive substrates **2c**−**e** failed (Figure 2), which is consistent with the electrophilic metalation hypothesis proposed for these reactions.[3,4]

(8) (a) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203−205. (b) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891−1894.

(9) (a) Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K.; Grosche, M.; Reisinger, C.-P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617*−*618*, 616−628. (b) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411−1414.

(10) A detailed report on the chemistry of these carbenes will be given in due course.

(11) Konnick, M. M.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212−10213..

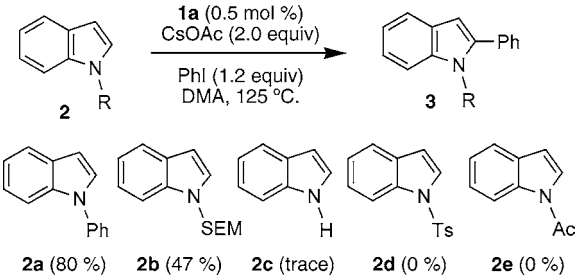


Figure 2. Relative reactivity of (NR)-indoles.

We next compared **1a** to the other catalysts using 1-SEM-indole (**2b**) as the model substrate. All four complexes catalyzed the arylation of **2b**, albeit with different efficiency (Figure 3).

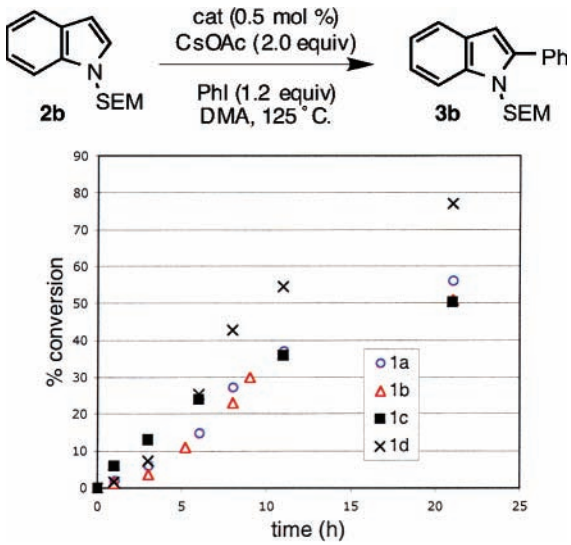


Figure 3. Direct comparison of catalysts **1a**−**d**, conversion established by HPLC or GC analysis with benzoic acid and dodecane, respectively, as internal standards (average of 2−3 runs).

Interestingly, the activity of the bulky and more electron-rich complex **1b** mirrored that of the electron-deficient analogue **1a**, implying the predominant role for sterics. Related systems **1c** and **1d**, containing the popular IMes ligand, also performed well. **1d** was clearly superior in terms of both rate and conversion.

As our objective was to develop an operationally simple arylation procedure, we chose **1a** for the exploration of the substrate scope, reserving the use of **1d** for difficult cases. The synthesis of **1d** is currently low yielding. In contrast, *N*-carbamoyl-substituted carbene ligand is readily available from the common reagent CDI (carbonyldiimidazole) and complex **1a** can be obtained in good yield on a benchtop (Supporting Information).

Subsequently, the scope of the system was explored with emphasis on SEM-protected azoles that cannot be currently

arylated in the free (NH)-form.[4−6] Tables 1−3 present a wide array of substrates, demonstrating a good functional group tolerance. The arylation of 1-SEM-indole proceeded with complete conversion and good isolated yield with relatively low catalyst loading (1.5 mol %). Bromobenzene can also be used in this process; however, it affords only modest yield of the product and low regioselectivity. It is worth noting that both nitro and cyano functionalities are tolerated on the benzene ring of indole. The reactions with iodo donors predominantly yielded the 2-arylation products, a regioselectivity that is only significantly altered by the use of ortho-substituted aryl halides (Table 1, entry 5).

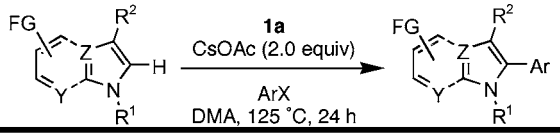
The direct arylation of 2- or 3-substituted indoles to generate 2,3-disubstituted products still remains a major challenge. We were pleased that the prototype substrate 3-methylindole (Table 1, entry 6) was efficiently arylated. However, electronically deactivated analogues as illustrated by methyl indole-3-carboxylate only afforded low yields of the corresponding products (Table 1, entry 7). Nonetheless, this example demonstrates the feasibility of accessing such attractive products in a single synthetic operation. The current methodology also addressed the problematic direct arylation of electron-deficient pyrroles. 2-Cyanopyrrole was arylated selectively at the 5-position in moderate yield (entries 8 and 9). In contrast, the arylation of 3-acetylpyrrole afforded a mixture of products with modest preference for the 5-position (Table 1, entry 10).

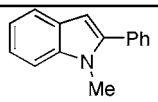
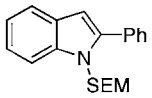
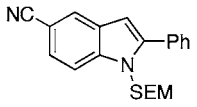
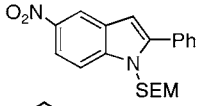
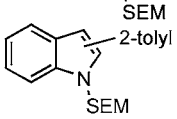
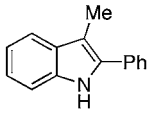
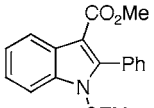
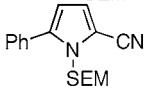
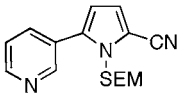
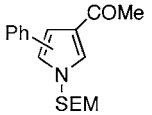
Heteroarenes bearing a basic nitrogen were also arylated with good efficiency (Table 2). The arylation of SEM-imidazole afforded the 5-phenyl product in moderate yield along with 3−5% of C-2, and C2/5 phenylated byproducts, a significant improvement over the previously reported 2.3:1 ratio for 1-methylimidazole.[3a] Cesium acetate performed poorly in the arylation of 2-phenyl-1-SEM-imidazole; silver carbonate was a superior base in this instance (Table 2, entry 3).

Next, we tested complex **1a** against imidazo[1,2-*a*]-pyridines. As shown in Table 3, both bromo- and iodo-arene donors can be used in this transformation, and electron-draining substituents were tolerated.

The results presented above outline the applicability and limits of catalyst **1a**. It was of interest to compare the

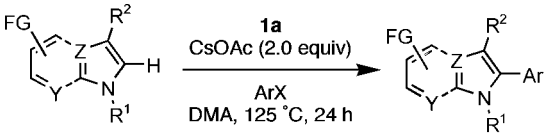
Table 1. Substrate Scope of the Reaction[a,b]

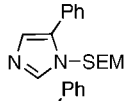
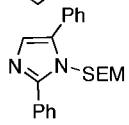


entry	ArX	**1a** (mol %)	product	yield (%)
1	PhI	0.15		91
	PhBr	5.0		58
2	PhI	1.5		77
	PhBr	5.0		47
3	PhI	1.5		82
4	PhI	2.0		68
5	2-I-Tol	3.5		52[c]
6	PhI	5.0		67[d]
7	PhI	5.0		22
8	PhI	5.0		59
9	3-I-pyr	5.0		49
10	PhI	5.0		51[e]

[a] All reactions were performed at 1.0−2.0 M concentration of substrate. Average of two isolated yields. [b] PhI afforded a better C2/C3 ratio of the product than PhBr (10−20:1 versus 3−4:1); small amounts of bisarylation products are also formed. [c] 3.5:1 ratio in favor of the 2-regioisomer. [d] Product characterized after deprotection (see the Supporting Information). [e] Mixture of isomers: 5-phenyl, 2,5-diphenyl, 2-phenyl in 4:2:1 ratio (see the Supporting Information).

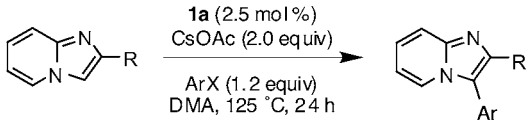
Table 2. Arylation of Heteroarenes Bearing Basic Nitrogens[a]

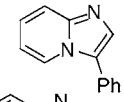
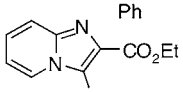
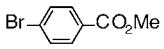
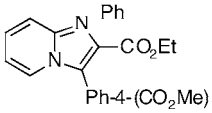


entry	ArX	**1a** (mol%)	product	yield (%)
1	PhI	1.5		81
2	PhI	5.0		57[b]
3	PhI	5.0		24 88[c]

[a] All reactions were performed at 1.0−2.0 M concentration of substrate. Average of two isolated yields. [b] 3−5% of 2-phenyl side products was also isolated. [c] With Ag_2CO_3 as base.

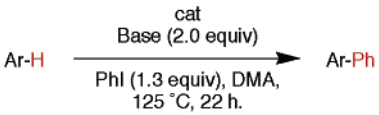
Table 3. Direct Arylation of Imidazo[1,2-*a*]pyridines[a]

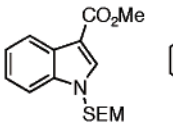
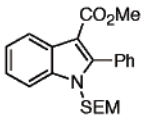
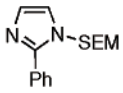
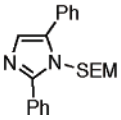


entry	ArX	product	yield (%)
1	PhI		93
2	PhI		98
3			51

[a] All reactions were performed at 1.0−2.0 M concentration of substrate. Average of two isolated yields.

Table 4. Direct Comparison of Azoles Arylation Conditions[a]



entry	substrate	product	conditions	yield (%)
1			A	22
			B	21
2			C	54
			D	34

[a] All reactions were performed at 0.5 M concentration of substrate: (A) **1a** (5.0 mol %), CsOAc; (B) **1d** (5.0 mol %), CsOAc; (C) **1a** (2.5 mol %), Ag_2CO_3; (D) **1d** (2.5 mol %), Ag_2CO_3. Entry 1: average of two isolated yields. Entry 2: ^{1}H NMR yield with *t*-BuOH as internal standard.

performance of this system with **1d** against some difficult arylation substrates (Table 4). With the indole substrate, the catalysts were comparable (Table 4, entry 1). In contrast, in the context of 1-SEM-2-phenylimidazole, complex **1a** outperformed **1d**. These results forecast that fine-tuning of the coordination sphere of the catalyst will be required for each azole ring type, especially with less reactive analogues. A notable example of unsuccessful substrates was methyl 1-SEM-pyrrole-2-carboxylate, which gave no arylation product.

In summary, we have reported a new catalytic system that provides a direct access to a wide range of SEM-protected azoles. Simple deprotection of these products lead to free (NH)-azoles, many of which cannot currently be accessed via direct arylation. Future investigations will focus on shedding light on the mechanism of these processes, including the subtle interplay between the steric and electronic properties of the ligand.

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

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