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Palladium-Catalyzed Benzylation of Heterocyclic Aromatic Compounds

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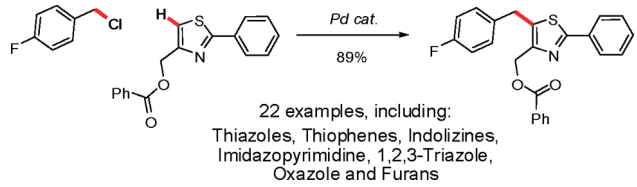
ABSTRACT



Broadly applicable palladium-catalyzed heteroarene benzylation reactions are described with a focus on the most challenging heterocyclic classes under traditional benzylation techniques such as sulfur-containing heterocycles and those bearing functional groups that would be incompatible with reactions requiring Lewis acids and/or strong bases.

While Friedel−Crafts or S_EAr arene alkylation is a front line technique in the formation of new arene−alkane C−C bonds,[1] application of this method to many heterocyclic aromatic compounds can be problematic, particularly when resonance electron-withdrawing groups are present or when there are functional groups that are sensitive to strong Lewis/Bronsted acids. These challenges are further exacerbated with sulfur-containing heterocycles, which are less nucleophilic than the corresponding oxa- and aza-homologues.[2] In these instances, arene deprotonation with strong bases (such as BuLi) followed by electrophilic trapping is the most common alternative.[3] While valuable, this approach necessitates the protection of all electrophilic and acidic functional groups, adding chemical steps, waste, and cost.[4]

Recently, metal-catalyzed cross-couplings of benzyl halides with aryl organometallics have emerged as alternatives to the use of strong acids or bases.[5] Our interest in the use of simple arenes as replacements of stoichiometric organometallic reagents[6] in cross-coupling reactions led us to question whether similar reactivity may also be possible with aliphatic electrophiles. In contrast to the rapid growth in

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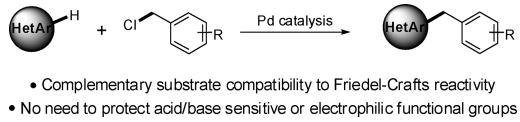
direct arylation with aryl halide electrophiles,[6] the use of aliphatic electrophiles is rare. Very recently, Yu described palladium(II)-catalyzed benzoic acid alkylation reactions,[7] and Ackermann has reported a directed arene alkylation employing a ruthenium catalyst where the catalytic cycle likely involves arene metalation prior to interaction with the alkyl halide.[8] Palladium(0)-catalyzed arene alkylations employing norbornene have also been described by Catellani[9] and Lautens,[10] enabling the preparation of a wide range of alkyl-substituted aromatic compounds.[11]

With a standard palladium(0) catalytic cycle employing aliphatic halides, important first steps have been made establishing intramolecular reactivity. For example, Buchwald and Henessy described the cyclization of α-chloroacetanilides in the formation of oxindoles,[12] and Cheng reported a cyclization of benzylic halides with a pendent pyrrole to close a six-membered ring.[13] An interesting tandem process has also been described by Wong involving closure of a six-membered ring between a benzyl bromide and a furan.[14] On the other hand, the reaction of oxazole with alkyl halides reported by Hoarau constitutes the only example of intermolecular arene alkylation under this reaction paradigm.[15]

In this letter, we describe the establishment of broadly applicable palladium-catalyzed heteroarene benzylation reactions (Figure 1). A particular focus is accorded to the most



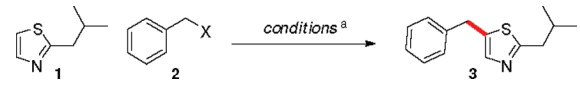
• Complementary substrate compatibility to Friedel-Crafts reactivity
• No need to protect acid/base sensitive or electrophilic functional groups

Figure 1. Palladium-catalyzed heteroarene benzylation.

challenging heterocycles of traditional benzylation techniques, such as sulfur-containing heterocycles and those bearing functional groups that would be incompatible with Lewis acids and/or strong bases. The reactions are highly regioselective and form industrially important diarylmethane compounds.[16] Furthermore, the establishment of generally applicable Csp^2-Csp^3 direct benzylation reactions provides compelling evidence that the wealth of reactivity uncovered with palladium catalysis in reactions at unactivated C−H bonds with sp^2 carbon halides[6] should also be accessible with sp^3 carbon electrophiles.

Given their challenging use under Friedel−Crafts reaction conditions, sulfur-containing heterocycles[2] were selected for reaction development and optimization. From these studies, we determined that treatment of the heterocycle with a benzyl chloride (1.5 equiv) in the presence of $Pd(OPiv)_2$[17] (2 mol %), 2-Ph_2P-2′-(Me_2N)biphenyl[18] (4 mol %), PivOH (20 mol %), and Cs_2CO_3 (1.5 equiv) in toluene (0.5 M) at 110 °C were optimal conditions. Choice of the appropriate electrophile is crucial (Table 1). While reactions with bromide,

Table 1. Effect of the Benzylic Leaving Group on Reactivity



entry	X	% GC yield
1	Cl (**2a**)	81(78[b])
2	$OP(O)OEt_2$	51
3	Br	6
4	O_2CCF_3	11
5	OAc	0
6	OPiv	0
7	O_2COMe	0

[a] Conditions: benzyl chloride (0.75 mmol), heteroarene (0.50 mmol), $Pd(OPiv)_2$ (0.01 mmol), 2-Ph_2P-2′-(Me_2N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs_2CO_3 (0.75 mmol), toluene (1.0 mL), 110 °C, 16−20 h. [b] Isolated yield.

acetate, pivalate, trifluoroacetate, and carbonate electrophiles provide little (less than 10%) or none of the desired cross-coupling product, use of benzylic chloride or phosphonate substrates generates **3** in 81% and 51% GC yields, respectively (Table 1, entries 1 and 2). The importance of the leaving group is interesting and merits further consideration. From a convenience and cost effectiveness perspective, the fact that the inexpensive, readily available benzyl chlorides perform best is a desirable outcome. For this reason, we opted to evaluate the scope with this class of electrophile. It is important to note, however, that the use of the benzyl phosphonate electrophiles may have particular utility since they may be easily prepared form the corresponding benzyl alcohol.

Illustrative examples with a range of sulfur-containing heterocycles are included in Table 2. Thiazole substrates, which are problematic under S_EAr benzylation conditions or necessitate deprotonation with strong bases followed by electrophilic trapping,[19] are ideal substrates for palladium-

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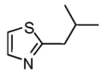
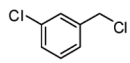
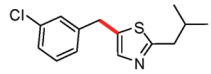
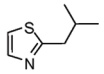
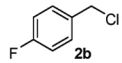
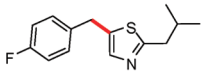
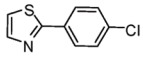
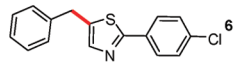
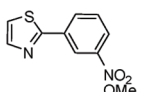
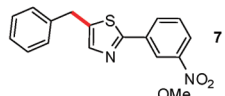
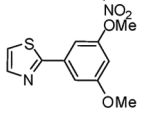
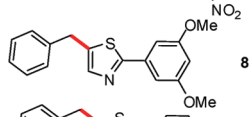
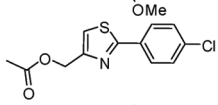
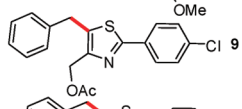
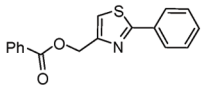
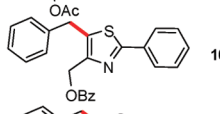
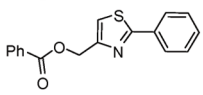
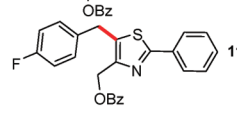
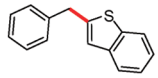
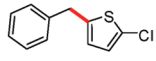
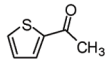
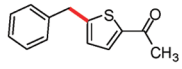
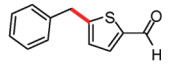
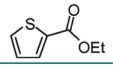
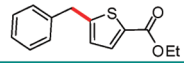
(18) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

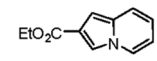
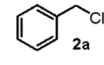
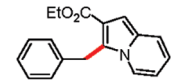
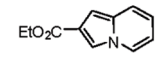
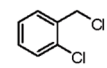
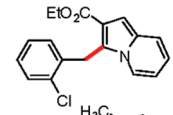
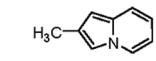
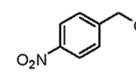
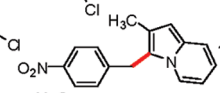
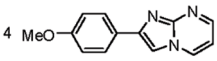
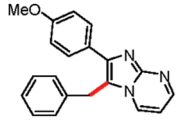
Table 2. Benzylation of Sulfur-Containing Heterocycles[a,b]

entry	arene	benzyl chloride	product	yield (%)
1				**4** 73
2		 **2b**		**5** 72
3		 **2a**		**6** 84
4		**2a**		**7** 75
5		**2a**		**8** 78
6		**2a**		**9** 78
7		**2a**		**10** 80
8		**2b**		**11** 89
9		**2a**		**12** 65 69[c]
10		**2a**		**13** 66[c]
11		**2a**		**14** 70[c]
12		**2a**		**15** 52 57[c]
13		**2a**		**16** 67

[a] Conditions: benzyl chloride (0.75 mmol), heteroarene (0.50 mmol), $Pd(OPiv)_2$ (0.01 mmol), 2-Ph_2P-2′-(Me_2N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs_2CO_3 (0.75 mmol), toluene (1.0 mL), 110 °C, 16−20 h. [b] Isolated yield. [c] Benzyl chloride (1.00 mmol), heteroarene (0.50 mmol), $Pd(OPiv)_2$ (0.025 mmol), 2-Ph_2P-2′-(Me_2N)biphenyl (0.05 mmol), PivOH (0.10 mmol), Cs_2CO_3 (0.75 mmol), toluene (1.0 mL), 110 °C, 16−20 h.

catalyzed benzylation. A variety of aliphatic and aromatic substituents are tolerated including chloride, ester, ketone, and nitro functional groups (Table 2, entries 1−8). Benzothiophene also undergoes clean C2 benzylation, which is complementary to standard S_EAr-type benzylation outcomes that produce the C3 isomer preferentially (Table 2, entry 9).[20] Similarly, electron-deficient thiophenes, which are particularly challenging under Friedel−Crafts reactivity,[21] undergo regioselective palladium-catalyzed benzylation adjacent to the sulfur atom (Table 2, entries 10−13). A variety of other heterocycles also undergo regioselective palladium-catalyzed benzylation, as illustrated in Table 3, including indolizines imidazopyrimidine, 1,2,3-triazoles, oxazoles, and electron-deficient furans. It is important to note that under these conditions the palladium selectively reacts at the benzylic C−Cl bond rather than the aryl−Cl bond (Table 2, entries 1, 3, 6, and 10 and Table 3, entry 2). In this way, substrates bearing useful functional groups may be employed that can subsequently be applied in other metal-catalyzed functionalization processes.[22]

Table 3. Additional Examples of Heterocycle Benzylation[a,b]

entry	arene	benzyl chloride	product	yield (%)
1		 **2a**		**17** 92
2				**18** 87
3				**19** 65
4		**2a**		**20** 97
5		**2a**		**21** 62 79[c]
6		**2a**		**22** 61
7		**2a**		**23** 72
8		**2a**		**24** 67[c]
9		**2b**		**25** 53[c]

[a] Conditions: benzyl chloride (0.75 mmol), heteroarene (0.50 mmol), $Pd(OPiv)_2$ (0.01 mmol), 2-Ph_2P-2′-(Me_2N)biphenyl (0.02 mmol), PivOH (0.10 mmol), Cs_2CO_3 (0.75 mmol), toluene (1.0 mL), 110 °C, 16−20 h. [b] Isolated yield. [c] Benzyl chloride (1.00 mmol), heteroarene (0.50 mmol), $Pd(OPiv)_2$ (0.025 mmol), 2-Ph_2P-2′-(Me_2N)biphenyl (0.05 mmol), PivOH (0.10 mmol), Cs_2CO_3 (0.75 mmol), toluene (1.0 mL), 110 °C, 16−20 h.

The utility of palladium-catalyzed arene benzylation compared to traditional techniques may be illustrated by the successful formation of **14** and **15** (Table 2, entries 11 and 12). In addition to low nucleophilicity that is problematic for S_EAr-like reactivity, the 2-acetylthiophene starting ma-

(19) For examples, see: (a) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1982**, 333. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87. (c) Deng, S.; Taunton, J. *Org. Lett.* **2005**, *7*, 291. (d) Teng, P.-F.; Tsang, C.-S.; Yeung, H.-L.; Wong, W.-L.; Kwong, H.-L.; Williams, I. D. *J. Organomet. Chem.* **2006**, *691*, 2237.

(20) Clark, P. D.; Mesher, S. I. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *105*, 157.

(21) Friedel−Crafts additions of electrophiles to thiophenes bearing EWG are exceedingly rare. For examples involving thiophene deprotonation using a strong base, see: (a) Slocum, D. W.; Gierer, P. L. *Chem. Commun.* **1971**, 305. (b) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442. See also ref.4a

(22) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

terial required in the formation of **14** would be incompatible with the strong alkyl-lithium bases required for arene deprotonation, due to the presence of more acidic protons on the acetyl moiety. This example highlights the inherent preference of the palladium catalyst to induce sp^2 C−H bond cleavage under the conditions described herein compared to similar reactions on the same substrate that result in ketone α-arylation when performed in the presence of a stronger base.[23,24] Similarly, the formation of **15** would be equally problematic under traditional techniques due to the presence of the resonance electron-withdrawing and electrophilic aldehyde group that would necessitate the use of additional protection/deprotection steps.[4]

These palladium-catalyzed heterocycle benzylation reactions should find application in the preparation of a wide range of diarylmethane compounds. Importantly, the ability to achieve useful reactivity with some of the most problematic cases of traditional techniques should be invaluable when the preparation of these types of molecules is called for. Finally, the establishment of broadly applicable intermolecular cross-couplings between simple heteroarenes (without organometallic preactivation) and aliphatic electrophiles should prompt a much wider examination of this chemistry.

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

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(23) This tendency was also observed with picoline *N*-oxide substrates. See: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

(24) For ketone α-arylation, see: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.