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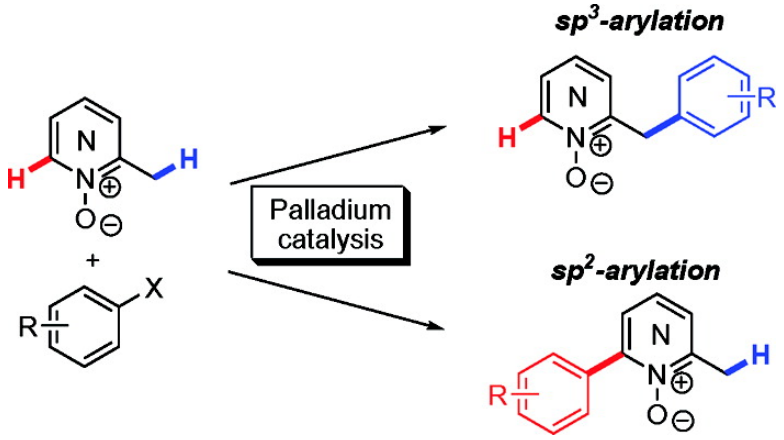

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Site-Selective sp^2 and Benzylic sp^3 Palladium-Catalyzed Direct Arylation

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Metal-catalyzed transformations at C−H bonds are emerging as valuable tools in organic synthesis.[1] A particularly appealing aspect of this chemistry is the potential to introduce multiple new functional groups at precise locations. Current practices, however, are usually limited to single site reactivity, ascribable to the challenges associated with achieving a high yielding reaction at even just one position. Toward the goal of multisite selectivity, important seminal advances have been made with heteroaromatic substrates at sp^2 positions.[2] As a greater appreciation of the reaction possibilities for C−H bond cleavage/functionalization is gained, particularly for reactions exhibiting orthogonal reactivity, the goal of site selective direct functionalization should increasingly become within reach.

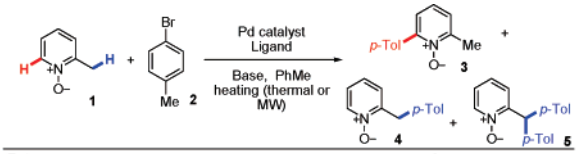
Herein, we describe site selective arylation reactions of both sp^2 and benzylic sp^3 sites[3,4] on azine and diazine *N*-oxide substrates and illustrate that this reactivity can be performed both divergently and sequentially. The products have demonstrated importance in medicinal chemistry and the new reactivity represents an attractive alternative to other routes to this class of molecule.[5] To realize this goal, the need to properly establish the metal to ligand ratio was uncovered in sp^2 arylation, and a complete reinvestigation of all reaction parameters was required for sp^3 arylation. From these studies, the choice of base emerged as a pivotal component for site selectivity, pointing to its intimate involvement in the mechanism of direct arylation.

We have described the use of *N*-oxides in direct arylation reactions as a means of avoiding the use of problematic organometallics in the formation of biaryl molecules.[6] Ongoing studies revealed that lower yields were encountered with substrates bearing methyl substituents adjacent to the *N*-oxide moiety. This prompted a re-evaluation of the sp^2 arylation conditions during which superior yields and selectivities were observed when using a 1:1 $Pd(OAc)_2$ to P^tBu_3 stoichiometry compared to a 1:3 ratio (Table 1, entries 1 and 2). Pertinent to the chemistry that follows, the selection of the base is crucial, with carbonates providing the optimal outcomes. Under these conditions, no other products are detected in ^1H NMR analysis of the crude reaction mixture. High yields of the azine/diazine biaryl compounds can also be achieved as illustrated by entries 1 to 4 of Table 2.

The challenges associated with these substrates lead us to question whether competing palladacycle formation (such as **6**) might be responsible for the challenging reactivity.[7] A corollary to this hypothesis is that intermediates such as **6** might also enable sp^3 arylation under appropriate conditions.[8] Toward this goal, every aspect of the reaction was reinvestigated. A promising lead involved the combination of **2** with 1.5 equiv of **1**, 2.5 mol % $Pd_2(dba)_3$, 6 mol % S-Phos, and 1.05 equiv of NaO^tBu in toluene at 70 °C, which provides 31% conversion to a 4.3:1 mixture of **4** and **5** (Table 1, entry 3).

While increasing the amount of *N*-oxide improves selectivity (entry 4), we also found that use of 3 equiv of NaOtBu also

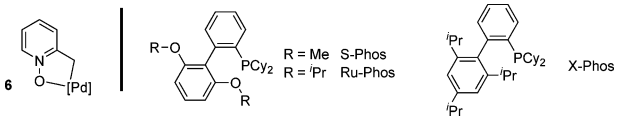
Table 1. Optimization of Picoline *N*-Oxide sp^3-Arylation[a]



Entry	Pd Source	Ligand (L:Pd)	Base (equiv.)	Equiv. 1	Temp (°C)	Ratio 3:4:5	Yield
1	$Pd(OAc)_2$	$^tBu_3PHBF_4$ (3:1)	K_2CO_3 (1.05)	2	110	1:0:0	21%
2	$Pd(OAc)_2$	$^tBu_3PHBF_4$ (1:1)	K_2CO_3 (1.05)	2	110	1:0:0	56%
3	$Pd_2(dba)_3$	S-Phos (1:1)	NaO^tBu (1.05)	1.5	70	0:4.3:1	31%
4	$Pd_2(dba)_3$	S-Phos (1:1)	NaO^tBu (1.05)	4	70	0:20:1	48%
5	$Pd_2(dba)_3$	S-Phos (1:1)	NaO^tBu (3)	2	70	0:6.7:1	77%[b]
6	$Pd_2(dba)_3$	X-Phos (1:1)	NaO^tBu (3)	2	70	0:20:1	41%
7	$Pd_2(dba)_3$	Ru-Phos (1:1)	NaO^tBu (3)	2	70	0:8:1	78%
8	$Pd_2(dba)_3$	X-Phos (1:1)	NaO^tBu (3)	1.5	110 (mw)	0:20:1	89%[b]
9	$Pd_2(dba)_3$	X-Phos (1:1)	NaO^tBu (3)	1.5	110 (mw)	0:20:1	84%[b,c]

[a] Conditions: substrates, Pd, ligand and base dissolved in PhMe and heated in an oil bath or microwave reactor. ^1H NMR yield of the major product. [b] Isolated yield of the major product. [c] Using 1 mol % Pd.

increased conversion and selectivity for **4** with 2 equiv of *N*-oxide (entry 5). A survey of other ligands revealed that X-Phos provides **4** exclusively, albeit with only 41% conversion (entry 6). We were



gratified to find that employing X-Phos and microwave heating at 110 °C provides an 89% isolated yield of **4** with no drop in selectivity (entry 8). With these conditions, 1 mol % palladium and 1.5 equiv of **1** can be used to provide **4** in 84% isolated yield (entry 9). Importantly, *no products arising from arylation at the sp^2 position are detected by ^1H NMR analysis of the crude reaction mixture, indicating that a complete inversion in catalyst selectivity can be achieved*. These results underline the eminent tunability of palladium in organic chemistry and its excellent responsiveness to changing reaction conditions.

A variety of substitution patterns, including *ortho*, *meta*, and *para*, can be employed (Table 2). Although di-*ortho* substitution is tolerated, we found that replacing X-Phos with S-Phos led to

Scheme 1. sp^2/sp^3 Arylation in Heterocycle Functionalization

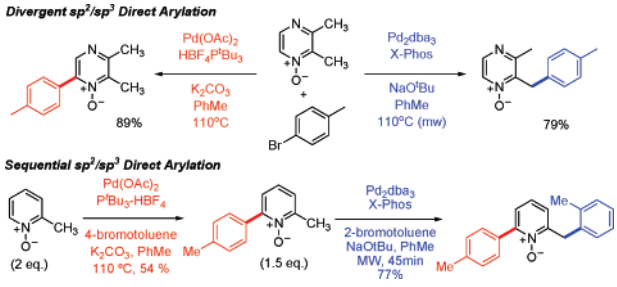


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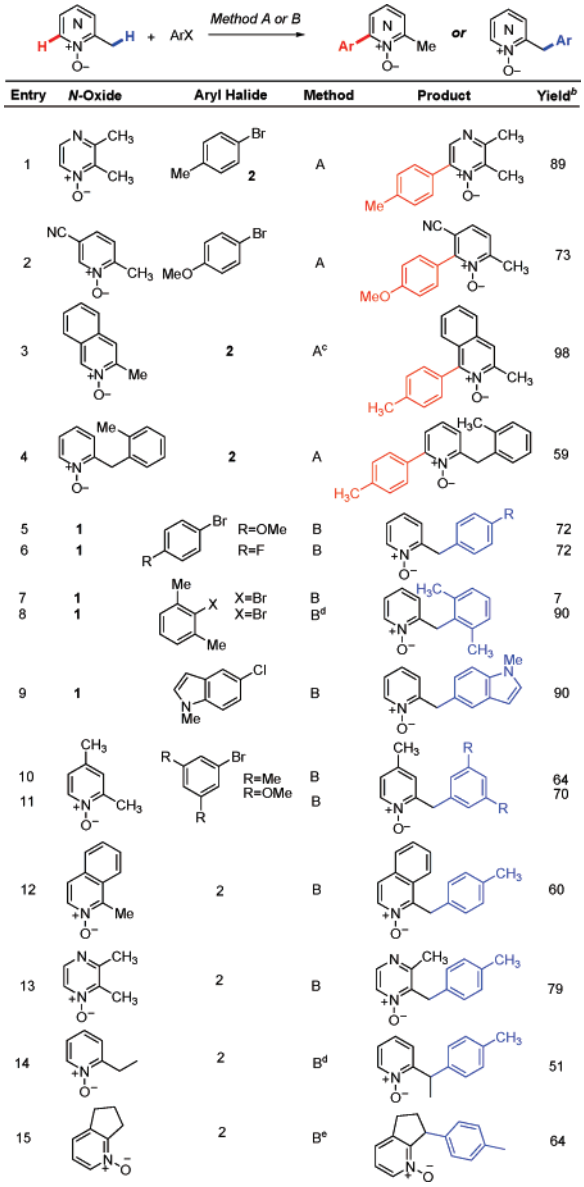
Table 2. Scope of Picoline *N*-Oxide sp^2/sp^3-Arylation[a]



[a] Conditions A: *N*-oxide (2 equiv), aryl halide (1 equiv), $Pd(OAc)_2$ (5 mol %), $P^tBu_3HBF_4$ (5 mol %), K_2CO_3 (1.5 equiv) dissolved in toluene and heated to 110 °C. Conditions B: *N*-oxide (1.5 equiv), aryl halide (1 equiv), Pd_2dba_3 (2.5 mol %), X-Phos (5 mol %) and NaO^tBu (3 equiv) dissolved in PhMe and heated in a microwave reactor at 110 °C for 45 min. [b] Isolated yield. [c] Using 1.1 equiv of *N*-oxide. [d] Using Ru-Phos (10 mol %). [e] Using S-Phos (10 mol %) and 3 equiv of the *N*-oxide.

superior yields (entries 7, 8). Other alkyl groups can also be arylated where use of the corresponding alkyl organometallic may be problematic due to β-hydride elimination at the alkylpalladium intermediate (entries 14, 15).

This methodology has been validated in both divergent sp^2/sp^3 arylation and in sequential sp^2/sp^3 arylation which should be useful for the rapid derivatization of heterocyclic compounds (Scheme 1). Furthermore, the *N*-oxide moiety can be used to introduce a wide range of other functional groups or easily de-oxygenated under mild conditions if desired.[9,10] Consequently, these reactions should be useful for the derivatization of heterocyclic compounds in medicinal chemistry. Finally, the ability of palladium to selectively react at both sp^2 and sp^3 centers under different reaction conditions should prompt its evaluation for similar selectivity switches with other substrates and reaction classes.

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

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(9) For example, see ref 6a,b and references therein.

(10) See Supporting Information for examples of product deoxygenation.

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