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C2, C5, and C4 Azole *N*-Oxide Direct Arylation Including Room-Temperature Reactions

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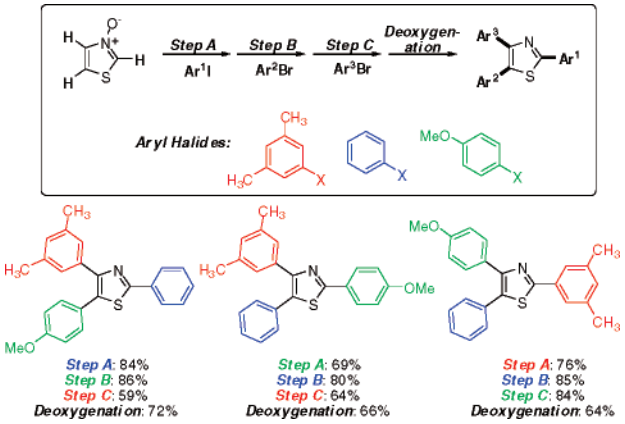
Because of their importance in medicinal chemistry and in materials science[1] methods for the derivatization of heterocyclic aromatics such as palladium-catalyzed cross-coupling reactions find broad academic and industrial use.[2,3] Recently, processes capable of forming similar products while avoiding the use of stoichiometric organometallic reagents, such as direct arylation, are emerging as attractive alternatives.[4]

An underlying challenge associated with direct arylation is that, in the absence of preactivating groups, the reactivity is governed by the inherent properties of the heterocycle itself. In nonideal cases, this can complicate regioselectivity and/or necessitate the use of very forcing reaction conditions. Methods to manipulate the reactivity of heterocyclic substrates are thus invaluable, especially if new or improved reactivity/regiocontrol can be achieved. Azole direct arylation reactions, which are believed to be facilitated by azole π-nucleophilicity at C5 and C−H acidity at C2, are illustrative. In most cases, arylation at C5 is preferred,[5] although the formation of C5/C2 double arylation side products is commonplace.[6] C2 arylation has been achieved through the use of copper additives with palladium catalysis,[7] but a broadly applicable process remains to be identified. Typically, very high reaction temperatures are required, and a high yielding C4 arylation has not been described.

We have been investigating the use of azine and diazine *N*-oxide substrates as alternatives to problematic organometallic reagents in biaryl synthesis.[8] These substrates have proven useful in other nickel[9] and copper[10] catalyzed processes as well. Herein, we demonstrate that the *N*-oxide group not only imparts a dramatic increase in reactivity in direct arylation at all positions of the azole ring but also changes the weak azole bias for C5 > C2 arylation to a reliable C2 > C5 > C4 reactivity profile (Scheme 1). This permits high yielding, regioselective, and room temperature arylation at C2, high yielding arylation at C5, and the first examples of arylation at C4—providing a unique opportunity for exhaustive functionalization of the azole core. A correlation of reactivity with relative HOMO populations at the different carbon atoms is observed and discussed (Scheme 2).

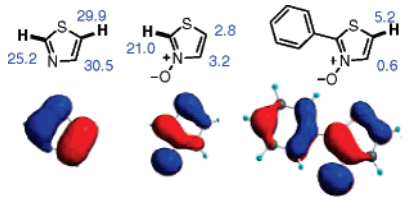
The thiazole *N*-oxides were easily prepared by treatment with *m*CPBA or with H_2O_2 in the presence of catalytic $MeReO_3$.[11] Preliminary investigations on the direct arylation of thiazole *N*-oxide revealed a strong bias for reaction at C2. Further optimizations lead to the establishment of high yielding C2 direct arylations under very mild conditions (Scheme 3). For example, treatment of an aryl halide with 1.1 equiv of a thiazole *N*-oxide in the presence of $Pd(OAc)_2$ (5 mol %), 2-(diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl **1** (10 mol %), acid[12] (20 mol %), and K_2CO_3 (1.5 equiv) in toluene at 25 °C results in C2 arylation as the exclusive product (Schemes 1 and 3).[13] These are rare examples of direct arylation occurring under such mild conditions.[14] If the C2 position is blocked, the thiazole *N*-oxide can then undergo a highly selective

Scheme 1. Stepwise C2-C5-C4 Thiazole Arylation[a]



[a] **Conditions: Step A:** ArI, thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand **1** (10 mol %), Cs_2CO_3 (1.5 equiv), PivOH (20 mol %), CuBr (10 mol %), PhMe (0.2 M), 25 °C; **Step B:** ArBr, thiazole *N*-oxide (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $^tBu_3PHBF_4$ (5 mol %), K_2CO_3 (1.5 equiv), PhMe (0.2 M), 70 °C; **Step C:** ArBr, thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), K_2CO_3 (2 equiv), PhMe, (0.2 M), 110 °C; **Deoxygenation:** thiazole *N*-oxide, zinc powder, $NH_4Cl_{(aq)}$, THF. Reported yields are isolated.

Scheme 2. HOMO for Thiazole and Thiazole *N*-Oxide Substrates[a]



[a] Numbers represent % atomic contributions to the HOMO. C-H bonds are drawn at the site of direct arylation.

C5 arylation when reacted with $Pd(OAc)_2$ (5 mol %), $^tBu_3PHBF_4$ (5 mol %), and K_2CO_3 (1.5 equiv) in toluene at 70 °C. Interestingly, the addition of pivalic acid to C5 arylation reactions reduces the C5:C4 selectivity compared to a reaction performed in its absence. We were also pleased to find that the *N*-oxide moiety will also enable C4 arylation, the first time that such reactivity has been obtained. Optimal conditions for C4 arylation were determined to involve the use of $Pd(OAc)_2$ (5 mol %) in the presence of PPh_3 (15 mol %) and 2 equiv of K_2CO_3 in toluene at 110 °C. The breadth of products that are readily accessible are illustrated in Scheme 3.

This chemistry has also been validated in a stepwise, exhaustive arylation of the thiazole core which is highly divergent and may find application in a diversity oriented evaluation of the biological and physical properties of these types of molecule (Scheme 1). An initial evaluation with imidazole *N*-oxides has also been performed

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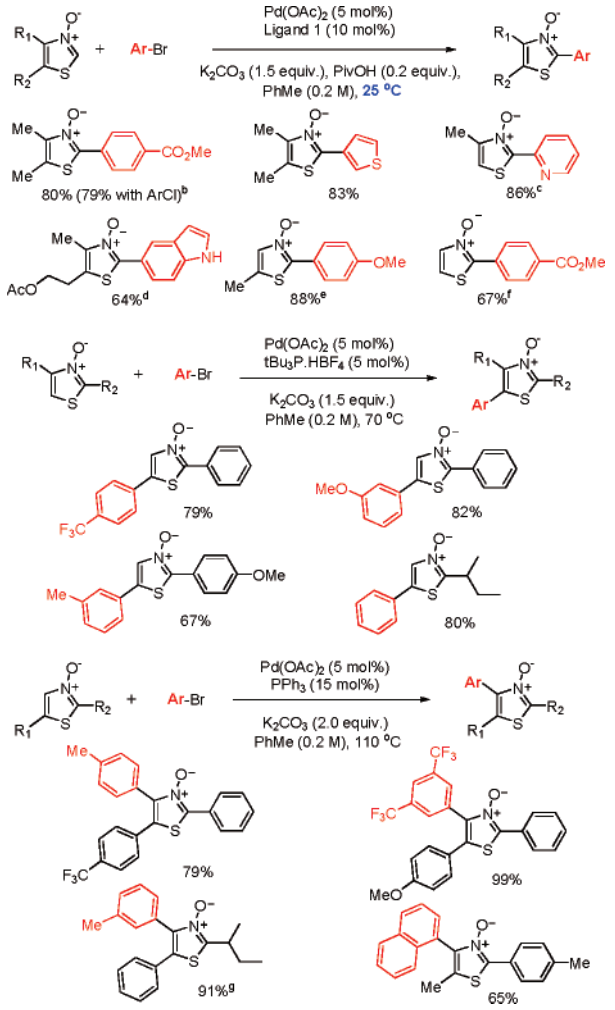
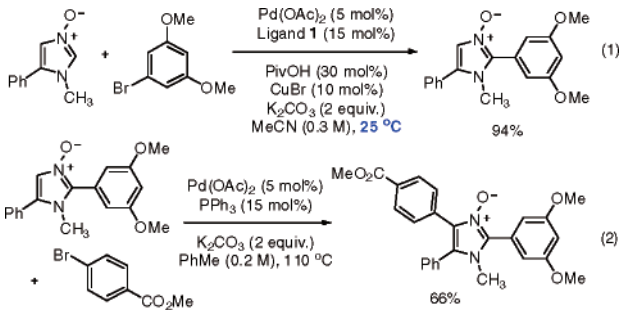
Scheme 3. Direct Arylation of Thiazole *N*-Oxides[a]



[a] **Conditions**: **C2 arylation:** ArBr, (1 equiv), thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand **1** (10 mol %), K_2CO_3 (1.5 equiv), PivOH (20 mol %) in PhMe (0.2 M) at 25 °C; **C5 arylation:** ArBr, (1 equiv), thiazole *N*-oxide (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $^tBu_3PHBF_4$ (5 mol %), K_2CO_3 (1.5 equiv) in PhMe (0.2 M) at 70 °C; **C4 arylation:** ArBr, (1 equiv), thiazole *N*-oxide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (15 mol %), K_2CO_3 (2 equiv) in PhMe (0.2 M) at 110 °C. [b]Using DavePhos (10 mol %) at 70 °C. [c]Using 2-(dicyclohexyl-phosphino)biphenyl (10 mol %). [d]Using DavePhos (10 mol %). [e]Using the aryl iodide (1 equiv), Cs_2CO_3 (1.5 equiv) as base, and CuBr additive (10 mol %). [f]Using CuBr as an additive (10 mol %). [g]Using the aryl iodide (1 equiv) and Cs_2CO_3 (2 equiv).



(eqs 1 and 2). Once arylation has been achieved, the *N*-oxide moiety may be easily deoxygenated (Scheme 1 and the Supporting Information).

The influence of the *N*-oxide fragment on the reactivity of the thiazole core was evaluated by molecular orbital analysis (Scheme 2).[15] Since π-nucleophilicity may contribute to reactivity and site selectivity, the relative contribution of each carbon atom to the HOMO is informative. The nearly equal distribution at all three carbons of thiazole (25.2, 29.9, 30.5%) correlates well with the challenges associated with C5/C2 regioselectivity for that substrate. In stark contrast, the HOMO of thiazole *N*-oxide is localized at C2 and has very small density at C4 and C5 (~3% contribution at each). This maps well onto the high C2 selectivity and the mild reaction conditions. Furthermore, the larger density at C5 of 2-phenylthiazole *N*-oxide corresponds well to the subsequent preference for reaction at C5. This reactivity should have a broader impact not only in direct arylation but also in the growing number of metal-catalyzed heterocycle transformations that could make use of the *N*-oxide activation strategy in the rapid functionalization of these substrates.

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

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