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Unprecedentedly mild direct Pd-catalyzed arylation of oxazolo[4,5-*b*]pyridine

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Abstract—Pd-catalyzed C-2 arylation of oxazolo[4,5-*b*]pyridine proceeds efficiently at 30 °C and tolerates a variety of aryl halides, including derivatized amino acids for which no racemization was observed during the reaction. Experimental evidence for facile deprotonation of oxazolo[4,5-*b*]pyridine under the reaction conditions is presented and the nature of the anionic intermediates is computationally examined.

Inhibition of fatty acid amide hydrolaze (FAAH) is emerging as a promising therapeutic strategy for pain intervention, anxiety management, and treatment of sleep disorders.[1] Several new classes of reversible FAAH inhibitors based on azole heterocycles have been recently disclosed.[2,3] Among those, oxazolo[4,5-*b*]pyridines functionalized at C-2 showed exceptionally high levels of potency and selectivity. The introduction of carbon-based substituents at the C-2 position of azoles, however, remains a demanding task often requiring fully stoichiometric pre-functionalization, such as metalation. This significantly limits functional group compatibility and increases the length of the reaction sequence. The development of a mild and general methodology allowing for direct catalytic carbon–carbon functionalization of azoles is, therefore, of great importance. In recent years, significant progress has been made toward the development of direct arylation of a wide variety of substrates, including oxazoles,[4,5] thiazoles,[4–7] imidazoles,[4,6,8,9] indoles,[9–13] pyrroles,[9,12] indolizines,[14] imidazo[1,2-*a*]pyrimidines,[7,15] imidazo[1,2-*b*][1,2,4]triazines,[16] and purine.[9] The majority of these reactions use palladium catalysis although some success was also reported with cobalt[5] and rhodium-based[12] catalytic systems. All these examples, however, require forcing reaction conditions with temperatures typically in the range of 100–140 °C. Extended reaction times are often necessary for achieving good yields. This letter reports the first example of the Pd-catalyzed arylation of oxazolo[4,5-*b*]pyridine, which readily proceeds at ambient temperature and accommodates a variety of aryl halides including those with sensitive functionalities.

Initial attempts to effect the arylation of oxazolo[4,5-*b*]pyridine with phenyl iodide under conditions most frequently found in the literature ($Pd(OAc)_2/PPh_3/Cs_2CO_3$, DMF, 140 °C) indicated rapid consumption of the starting material and the formation of 2-phenyloxazolo[4,5-*b*]pyridine, also prepared independently.[17] Optimization of the reaction temperature revealed that ambient temperatures were adequate for efficient arylation: at 30 °C the product was obtained in 68% isolated yield (Table 1, entry 1). Using this reaction as a platform for further screening, the choice of solvent and base was addressed. In accordance with previous reports polar solvents performed well; acetone, in particular, was found to have an advantage over DMF in terms of yields and ease of work-up. Cesium carbonate proved to be the base of choice as other common inorganic bases, including potassium carbonate failed to give any product. Two equivalents of base were needed since the yield dropped to 32% with 1 equiv of Cs_2CO_3.

Next, the effect of ligand and Pd source was examined. As expected, the combination $Pd(OAc)_2/PPh_3$ worked well giving a 72% yield. A 4:1 molar ratio of $PPh_3/Pd(OAc)_2$ was found to be important for maintaining catalytic efficiency as lowering the amount of triphenylphosphine from 20 to 10 mol % decreased the reaction

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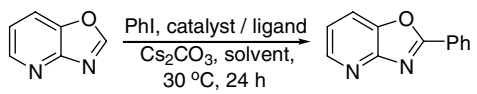
Table 1. Screening studies



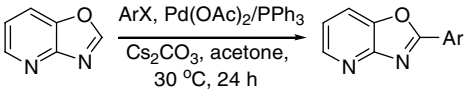
Entry	Solvent	Catalyst[a]/ligand[b]	Yield (%)
1	DMF	$Pd(OAc)_2/PPh_3$	68
2	Acetone	$Pd(OAc)_2/PPh_3$	72
3	Acetone	$Pd(OAc)_2$/10 mol % PPh_3	42
4	Acetone	$Pd(PPh_3)_4$	76
5	Acetone	$Pd(OAc)_2/P(2\text{-furyl})_3$	71
6	Acetone	$Pd(OAc)_2$/dppf	52
7	Acetone	$Pd(OAc)_2/P(o\text{-Tol})_3$ or $P(Cy)_3$	—[c]
8	DMF	Pd(0) EnCat NP30[d]	—
9	DMF	$Pd(OAc)_2/PPh_3$/CuI[e]	35[f]

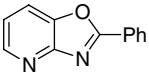
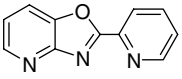
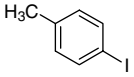
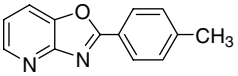
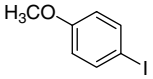
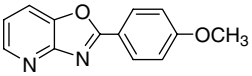
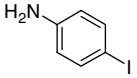
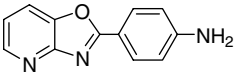
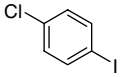
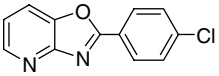
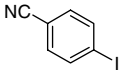
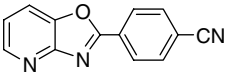
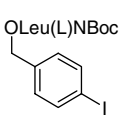
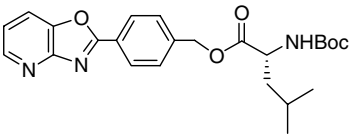
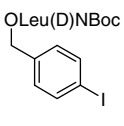
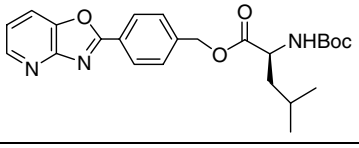
[a] 5 mol %.
[b] 20 mol %.
[c] Below TLC detection limit (<0.5%).
[d] Available from Aldrich.
[e] 25 mol %.
[f] 45% in acetone.

yield (entry 3). Further investigations into the effect of ligand indicated that steric factors appeared to be one of the essential control elements. Tri-2-furylphosphine[18] was found to be as efficient as the marginally larger PPh_3 (cone angles 133° and 145°). Spatially constrained dppf led to a lower yield (entry 6) while the use of $P(Cy)_3$ and $P(o\text{-Tol})_3$ (cone angles 170° and 194°, respectively) gave no reaction. A recent report[7] on direct arylation of π-excessive aromatics catalyzed by palladium leached from the solid support led to an attempt to use palladium nanoparticles encapsulated in polyurea matrix as an alternative source of Pd(0). This gave no arylated product (entry 8). A number of inorganic additives were also tested. Among these, CuI was reported to promote direct arylation of thiazole and thiophene derivatives.[4] In the present case, addition of CuI had a deleterious effect on the reaction yield (entry 9). Neither $Pd(OAc)_2$ nor CuI alone were able to catalyze direct arylation.

The optimized conditions were applied to investigate the scope of arylation (Table 2). Phenyl iodide proved to be

Table 2. Reaction scope



Entry	Aryl halide	Product[a]	Yield (%)
1			52
2			33
3			52
4			67
5			74
6			39
7			61
8[b]			41
9[c]			48

[a] Conditions: 2 equiv aryl halide, 1 equiv heterocycle, 5 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2 equiv Cs_2CO_3.
[b] 1 equiv aryl halide, heterocycle.
[c] 1 equiv aryl halide, 2 equiv heterocycle.

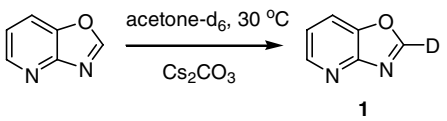
a better coupling partner then phenyl bromide (entry 1), which in turn was superior to 2-chloropyridine. Both electron-rich (entries 3–5) and electron poor aryl halides (entries 6 and 7) were similarly reactive giving moderate to good yields of arylated products.

Given the success of arylation with a set of conventional aryl halides, it was intriguing to see whether more complex and potentially biologically relevant substances such as terminally modified peptides could be successfully coupled. For these, potential epimerization of stereogenic centers becomes an additional concern. To test whether the stereochemical integrity is conserved during the reaction, the L and D enantiomers of *N*-Boc protected *p*-iodobenzylleucinate[19] were subjected to arylation with 1 and 2 equivalents of oxazolo[4,5-*b*]pyridine. Both experiments resulted in similar yields (entries 8 and 9) and gave enantiomerically pure compounds within the limits of NMR detection.[20]

The high reactivity of oxazolo[4,5-*b*]pyridine opens the question of whether the inherent electronic properties of the substrate are responsible for the unusually high rates of arylation or whether some other factors intervene.[21] A competition experiment, in which an equimolar mixture of oxazolo[4,5-*b*]pyridine and benzoxazole was reacted with two equivalents of phenyl iodide yielded exclusively 2-phenyloxazolo[4,5-*b*]pyridine.

The competition experiment has important mechanistic ramifications. Electrophilic pathways have been recurrently implicated in Pd-catalyzed arylation of azoles,[4,8,15,16] including benzoxazole.[4] Despite apparent structural similarities between benzoxazole and oxazolo[4,5-*b*]pyridine the electronics of the two are significantly different: the presence of an electron-withdrawing pyridine ring deactivates oxazolo[4,5-*b*]pyridine toward electrophilic processes. The combination of high reactivity and electron-deficiency might suggest that arylation of oxazolo[4,5-*b*]pyridine proceeds via a non-electrophilic pathway. The C–H acidity of benzoxazole was measured at <15.7 (THF);[22] oxazolo[4,5-*b*]pyridine is expected to be even more acidic. Thus, the involvement of an anionic reaction manifold appears to be a viable mechanistic alternative. Kinetic studies provided further support for this hypothesis. Running the arylation in deuteroacetone under otherwise standard conditions and monitoring the progress by ^{1}H NMR revealed a rapid disappearance of the oxazolo[4,5-*b*]pyridine C-2 proton signal. Importantly, neither the position nor the absolute intensity of the remaining protons on the pyridine ring of the starting material significantly changed. The rate of product formation substantially lagged behind the rate of deprotonation. These observations pointed to facile deuteration of the C-2 position of the heterocycle under the reaction conditions.

This was further examined by reacting 1 equiv of oxazolo[4,5-*b*]pyridine with 2 equiv of Cs_2CO_3 in acetone-d_6. ^{1}H NMR showed that within several hours the starting material was consumed and the product, characterized as 2-deutero-oxazolo[4,5-*b*]pyridine **1** was isolated in 42% yield (Scheme 1). Attempts to generate



1

Scheme 1. Deuterium exchange.

and characterize the deprotonated species in anhydrous solvents using a variety of bases, however, were frustrated by extensive decomposition.

To obtain further insight into the nature of the deprotonated species, calculations (B3LYP/6-31G*+) were performed.[23] Two minima on the potential energy surface were located (Fig. 1). 2-Isocyanopyridinolate **2** originates from the ring opening of the oxazolo[4,5-*b*]pyridinide **3** and is the more stable of the two. This is expected: previous experimental and computational studies demonstrated that Li oxazolyl anions strongly favor ring-opened structures.[24,25] Compared to the 20 kcal/mol that lithiated oxazole gains upon ring-opening, oxazolo[4,5-*b*]pyridinide is unusually stable being only 8.8 kcal/mol uphill in energy from **2**.

This stability can be rationalized by suggesting that the structure of the ring-closed form **3** can be better described as an anionic carbene (Fig. 1, structure on the right). In the anionic carbene structure, the negative charge can be delocalized onto both the pyridine and oxazole nitrogen atoms while retaining the aromaticity of the oxazolopyridine moiety. The NBO charge distribution supports this description: −0.71 at the oxazole N, −0.55 at the pyridine N, and 0.08 at C-2. The p-donation from the oxygen and nitrogen atoms into the carbene p orbital is an additional important stabilization factor. The deuterium quench will occur under Curtin–Hammett conditions, where the stronger but less stable base **3**, is deuterated either at C-2 or at the oxazole nitrogen by the solvent. In the latter case, the resulting neutral carbene will undergo a 1,2-deuterium shift giving **1**.

The results presented above invite speculation concerning the overall mechanism of the Pd-catalyzed arylation of oxazolo[4,5-*b*]pyridine. One can hypothesize that the transmetalation of $ArPd(PPh_3)_2I$ by ambidently nucleophilic **2** and **3** leads to intermediates **4** and **5**, which reductively eliminate to give the arylated product (Scheme 2). Under this scenario, the transmetalation step is expected to be rate determining and would rationalize the ligand steric requirements observed for this reaction (vide supra). Metalation of oxazole to oxazol-2ylzinc followed by Pd-catalyzed cross-coupling with

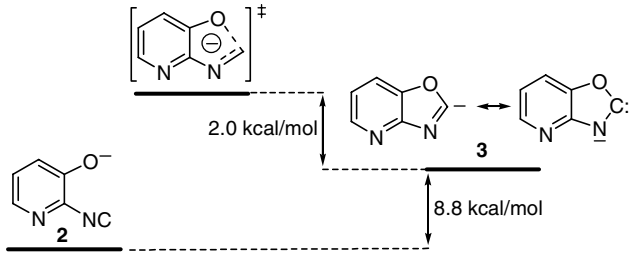
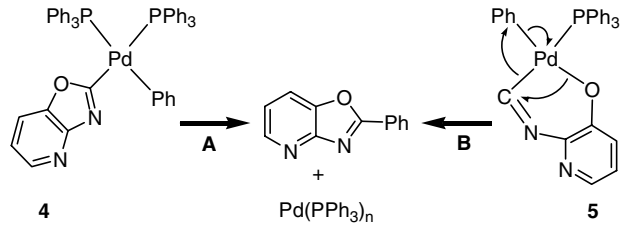


Figure 1. B3LYP/6-31G*+ (energy levels drawn not to scale).



Scheme 2. Suggested key intermediates in the catalytic cycle.

aryl halides and triflates was reported to give 2-aryloxazole at room temperature.[26,27] The documented proclivity of oxazol-2ylzinc to form ring closed structures[25] lends support for the suggested intermediate **4**. The suggested pathway B and the palladacycle **5** for which any experimental support is lacking appears to be both kinetically and thermodynamically competitive from the DFT calculations currently being studied.

In conclusion, the Pd-catalyzed C-2 arylation of oxazolo[4,5-*b*]pyridine is reported. The reaction efficiently proceeds at 30 °C and tolerates a variety of aryl halides, including D- and L-*p*-iodobenzylleucinates for which no racemization was observed. A facile deuteration of the C-2 position of oxazolo[4,5-*b*]pyridine is likely to occur via deprotonation. DFT calculations indicated that the resulting anionic intermediates exist as a rapidly equilibrating mixture of open and closed forms. Either one or both have been suggested to enter the catalytic cycle as key intermediates.

Acknowledgments

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Supplementary data

Experimental procedures and spectroscopic data for all new compounds and computational details are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.117.

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19. See Supplementary data.
20. Enantiomeric purity was determined using a lanthanide chiral shift reagent; see Supplementary data.
21. An alternative mechanistic scenario might include, for example, an in situ catalyst modification by potentially ligating oxazolo[4,5-*b*]pyridine.
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