N-Oxide Arylation

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Palladium-Catalyzed Cross-Coupling Reactions of Diazine *N*-Oxides with Aryl Chlorides, Bromides, and Iodides**

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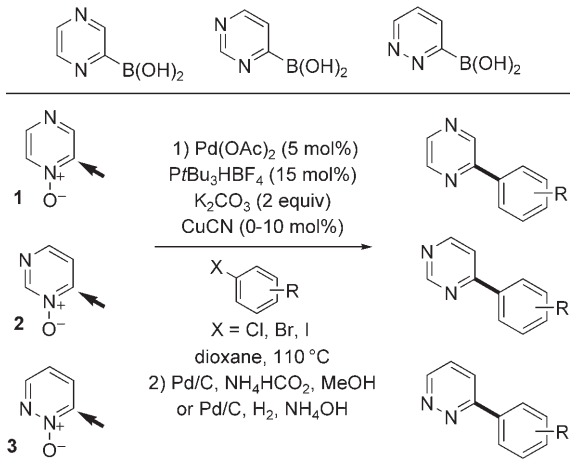
The use of palladium-catalyzed cross-coupling reactions in biaryl synthesis[1] is linked to, and limited by, the synthetic and commercial availability of organometallic reagents such as aryl boronic acids. Not only are most of these compounds expensive, important classes of aryl organometallic are very challenging prepare and/or use in cross-coupling reactions, including electron-deficient nitrogen heterocycles. The importance of these building blocks in medicinal chemistry and materials sciences[2] has prompted continued methodological efforts, and two very recent reports highlight the importance of this goal.[3,4] Absent from these and the predominance of reports are some of the most problematic organometallic reagents—azines bearing the metal adjacent to a nitrogen atom. The problem is even more severe with diazines (Scheme 1). These organometallic compounds are unstable, can rarely be isolated, and commonly decompose under cross-coupling reaction conditions. While some are commercially available, the price reflects both their value and the challenge associated with their preparation.[5]

Recently, the potential of direct arylation as an efficient alternative to standard cross-couplings is becoming recognized,[6] and we have been studying the use of *N*-oxides as replacements for unstable/unreactive organometallics.[7] In the context of this strategy, diazine *N*-oxides are more challenging than simple pyridine *N*-oxides since they possess a free nitrogen atom that could bind and poison the catalyst.[8] They are also more π-electron-deficient and less nucleophilic than pyridine *N*-oxides.

Herein we describe the establishment of reaction conditions that enable the use of readily available,[9] bench-stable[10] diazine *N*-oxides as cheap, high-yielding reagents in palladium-catalyzed cross-coupling reactions (Scheme 1). To overcome catalyst poisoning associated with some *N*-oxide substrates, a benefical effect of copper(I) salts was uncovered,



Scheme 1. Direct arylation in aryl diazine synthesis. Pyrazine, pyrimidine, and pyridazine boronic acids are unstable, difficult to prepare, and unsuited for cross-coupling reactions. Their *N*-oxides are readily prepared, bench-stable replacements for the organometallic reagent in biaryl synthesis.

and we demonstrate that the *N*-oxide functionality can be removed easily after cross-coupling or transformed into a wide range of other functional groups. These new reactions can be performed with aryl iodides, bromides, and chlorides and include the first examples of *N*-oxide arylation with equimolar ratios of the two coupling partners. Furthermore, the relative reactivities and regioselectivities point to C–H acidity as a critical factor in reactivity, encouraging consideration of this property in the design of other novel direct arylation processes.

Initial reaction screens with *N*-oxides **1**–**3** under previously described conditions led to disappointing results. Noting that the *N*-oxides were only sparingly soluble in toluene, we reinvestigated the reaction conditions. We found that changing the solvent from toluene to dioxane provides superior conversions with *N*-oxides **1** and **3**, giving the cross-coupled products **4** and **5** in yields of 75% and 72%, respectively (Table 1, entries 1 and 2). These two substrates are actually more reactive than pyridine *N*-oxide, as demonstrated by a competition experiment between **1** and pyridine *N*-oxide, which resulted in exclusive arylation of **1** (Table 1, entry 4). In contrast to the excellent results obtained with **1** and **3**, the reaction of pyrimidine *N*-oxide (**2**) proceeds in very low yield (Table 1, entry 3).

Further investigations revealed that the poor outcomes associated with **2** do not result from low reactivity alone. For example, the addition of pyrimidine *N*-oxide (**2**) to a reaction with pyrazine *N*-oxide (**1**) results in the exclusive formation of **4** but in a significantly lower yield (9%) than when the reaction was performed in the absence of **2** (75% yield; Table 1, entries 5 and 1). The reason for catalyst inhibition with **2** and not with **1** or **3** is a focus of ongoing study.[11,12] We note that neither pyridine *N*-oxide nor pyridine poison the reaction of **1** (Table 1, entries 4 and 6), indicating that these deleterious effects are specific to pyrimidine *N*-oxide.[12]

To overcome catalyst inhibition, a variety of additives were investigated including phosphines, halides, and metals.

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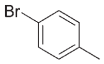
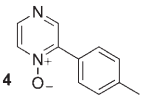
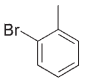
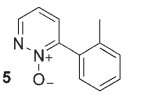
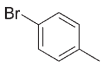
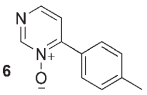
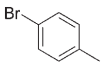
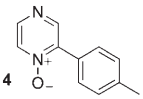
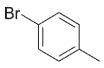
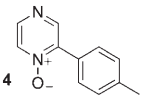
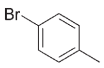
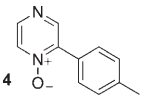
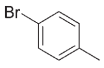
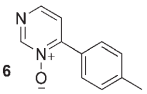
Table 1: Cross-coupling reactions of *N*-oxides **1**–**3** with aryl bromides.[a]

Entry	*N*-Oxide	Aryl bromide	Additive	Product	Yield [%][b]
1	 **1**		none	 **4**	75
2	 **3**		none	 **5**	72
3	 **2**		none	 **6**	17
4	 **1**			 **4**	70
5	 **1**		 **2**	 **4**	9
6	 **1**			 **4**	69
7	 **2**		CuCN (10 mol%)	 **6**	61[c]
8			CuBr (10 mol%)		54[c]

[a] Reaction conditions: The *N*-oxide (2 equiv), aryl halide, $Pd(OAc)_2$ (5 mol%), $PtBu_3$–HBF_4 (15 mol%), K_2CO_3 (2 equiv), and the additive (if indicated, 2 equiv) were added to a round-bottomed flask. Dioxane was added, and the reaction mixture was heated to 110°C. [b] Yield of isolated product. [c] 3 equivalents of **2** employed.

From these efforts, copper(I) salts such as CuCl, CuBr, and CuCN emerged as promising leads. CuCN and CuBr were selected for further optimization, and we found that when 10 mol% CuCN or CuBr was added under the new arylation conditions, biaryl **6** was obtained in 61 and 54% yield, respectively, as one regioisomer (Table 1, entries 7 and 8).[13] The yields observed with CuCN as the additive were typically higher than those with CuBr.

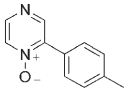
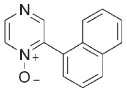
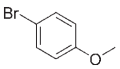
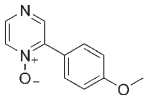
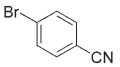
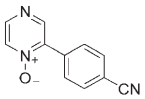
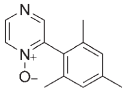
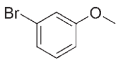
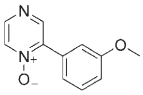
The scope of these transformations with respect to the aryl halide was evaluated with pyrazine *N*-oxide (**1**) (Table 2). High- yielding arylations are possible not only with aryl bromides but also with aryl iodides (Table 2, entries 17 and 18) and even with aryl chlorides (entries 13–16). With aryl iodides, Ag_2CO_3 must be employed as an additive. A variety of substituents are tolerated on the aryl halide including electron-donating (Table 2, entries 3, 6, and 7) and electron-withdrawing groups (entries 4, 8–10 and 16). More sterically encumbered aryl halides may also be employed (Table 2, entries 2, 5, 9, 10, 13, and 14). If an excess of aryl halide is used relative to the pyrazine *N*-oxide, the product of double direct arylation can be obtained in 50% yield (Table 2, entry 11).

The scope of diazine *N*-oxide substrates was also evaluated (Table 3). Quinoxaline *N*-oxide (**7**) is an excellent substrate in these reactions, and an equimolar ratio of the *N*-oxide and aryl halide could be used for the first time (Table 3, entries 1–7). More sterically encumbered alkyl-substituted pyrazine *N*-oxides may also be coupled in synthetically useful yields (Table 3, entries 8–11). Different aryl halides were also examined in reactions with both pyridazine *N*-oxide (**3**) (Table 3, entries 12–15) and pyridimine *N*- oxide (**2**) (Table 3, entries 16–22). With **2**, 10 mol% CuCN or CuBr must be added to the reaction to achieve cross-coupling. In each case useful yields of the cross-coupled product are obtained.

If desired, the direct-arylation products can be easily deoxygenated (Table 4). Treatment of pyrazine *N*-oxides with ammonium formate and palladium/carbon in methanol at room temperature gives the corresponding free base in excellent yields (Table 4, entries 1–5, method A). This protocol is incompatible with pyridazine *N*-oxides, however (Table 4, entry 6). An extensive survey of methods for the reduction of *N*-oxides led to the discovery that high yields can be obtained with catalytic Pd/C in ammonium hydroxide under a hydrogen atmosphere (Table 4, entries 7–9, method B). Products from the direct arylation of pyrimidine *N*-oxide may also be deoxygenated by this second protocol in high yield (Table 4, entry 10).

N-Oxides are key intermediates in many processes that introduce functionality adjacent to the nitrogen atom. For example, for the pyrazine derivative shown in Scheme 2, a new carbon–oxygen bond adjacent to the nitrogen atom may be formed by reaction with acetic anhydride and heating to give **8**.[14] A second direct arylation can add a second aromatic group as in the formation of **9**. Alternatively, the *N*-oxide may be converted to chloropyrazine **10** by reaction with $POCl_3$[15] and subsequently used in a wide range of palladium catalyzed-cross coupling reactions. To illustrate this possibility, a Buchwald–Hartwig amination was performed, giving **11** in 70% yield.[16] Chloride **10** may also be treated with alkoxides

Table 2: Scope of the direct arylation of pyrazine *N*-oxide (**1**).[a]

Entry	**1** [equiv]	ArX	Product	Yield [%][b]
1	2			75
2	2			89
3	2			82
4	2			53
5	2			70
6	2			72
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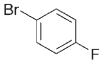
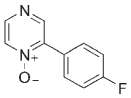
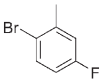
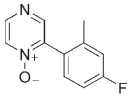
8	2			70
9	2			50
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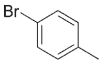
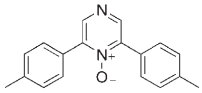
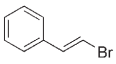
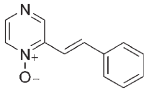
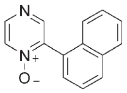
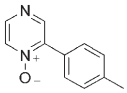
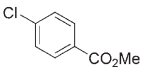
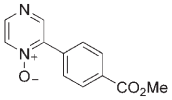
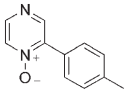
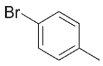
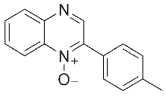
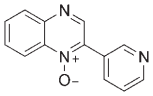
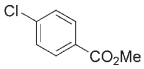
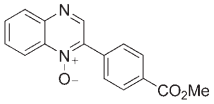
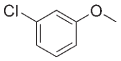
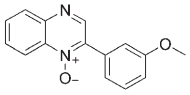
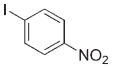
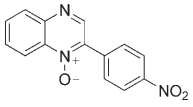
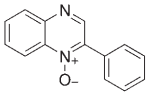
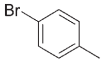
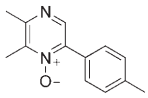
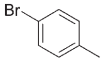
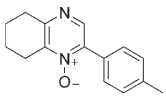
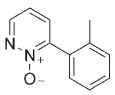
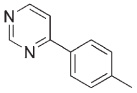
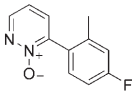
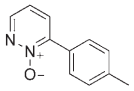
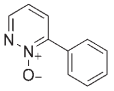
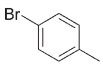
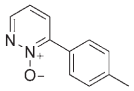
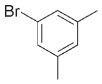
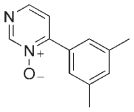
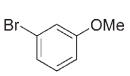
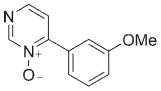
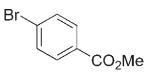
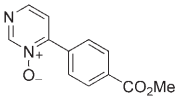
11	0.3			50
12	3			40
13	2			60
14	3			68
15	2			75
16	2			82
17	2			17
18	2[c]			77

[a] Reaction conditions: **1**, aryl halide, $Pd(OAc)_2$ (5 mol%), $PtBu_3$–HBF_4 (15 mol%), and K_2CO_3 (2 equiv) were added to a round-bottomed flask. Dioxane was added, and the reaction mixture was heated to 110°C. [b] Yield of isolated product. [c] Ag_2CO_3 (0.5 equiv) added.

to give compounds such as **12** in good yield. The diazine *N*-oxide ring may also be reduced to give arylpiperazine **13** in 68% yield by treatment with Pt_2O and H_2.

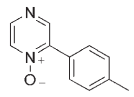
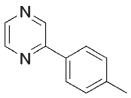
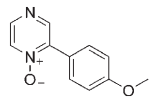
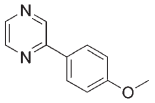
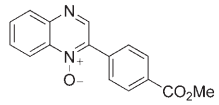
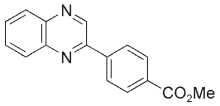
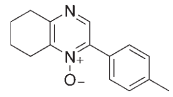
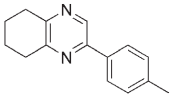
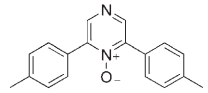
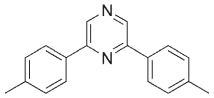
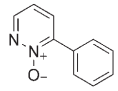
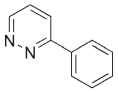
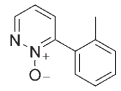
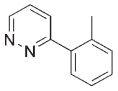
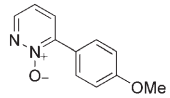
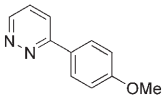
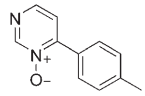
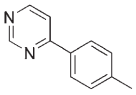
The relative reactivities of diazine *N*-oxides **1**–**3** as well as the regioselectivity of the reaction with **2** provide insight into the reaction mechanism. In competition studies[17] **1** is approximately twice as reactive as **3**. While significant catalyst inhibition is observed in competition experiments of **1** with **2**, exclusive reaction of **1** is observed. In each case, the reaction is completely selective for reaction at the carbon adjacent to the N–O functionality.[18] Furthermore, with pyrimidine *N*-oxide (**2**), direct arylation occurs exclusively at the position *para* to the free nitrogen atom.[18] All of these outcomes parallel the relative acidities of the different C–H bonds of the *N*-oxide substrates.[19] We observed a similar dependence on pK_a in reactions with perfluoroarenes which were deter-

Table 3: Scope of the direct arylation of diazine *N*-oxides.[a]

Entry	*N*-Oxide	*N*-Oxide [equiv]	Aryl halide	Product	Yield [%][b]
1	 **7**	1			68
2	**7**	1			50
3		2			80
4	**7**	1			84
5	**7**	1			57
6	**7**	1			70[c]
7	**7**	1			84[c]
8		2			48
9		3			56
10		2			52
11		3			56
12		2			76
13	**3**	2			74
14	**3**	2			73
15	**3**	2			92[c,d]
16		3 (CuCN[e])			61
17		3 (CuBr[e])			54
18	**2**	3 (CuCN[e])			55
19	**2**	3 (CuCN[e])			62
20	**2**	3 (CuBr[e])			45
21	**2**	3 (CuCN[e])			50
22	**2**	3 (CuBr[e])			41

[a] Reaction conditions: Diazine *N*-oxide, aryl halide, $Pd(OAc)_2$ (5 mol%), $P\mathit{t}Bu_3$–HBF_4 (15 mol%), and K_2CO_3 (2 equiv) were added to a round-bottomed flask. followed by the addition of dioxane and heating to 110°C. Dioxane was added, and the reaction mixture was heated to 110°C. [b] Yield of isolated product. [c] Ag_2CO_3 (0.5 equiv) added. [d] Performed on a 1-g scale. [e] 10 mol% Cu salt as additive.

Table 4: Deoxygenation of the direct-arylation products.

Entry	*N*-Oxide	Method[a]	Product	Yield [%][b]
1		A		86
2		A		82
3		A		98
4		A		84
5		A		76
6		A		0[c]
7		B		87
8		B		70
9		B		70
10		B		81

[a] Reaction conditions: Method A: Pd/C (10 mol%), NH_4HCO_2, MeOH; Method B: Pd/C, H_2, NH_4OH. [b] Yield of isolated product. [c] Decomposition.

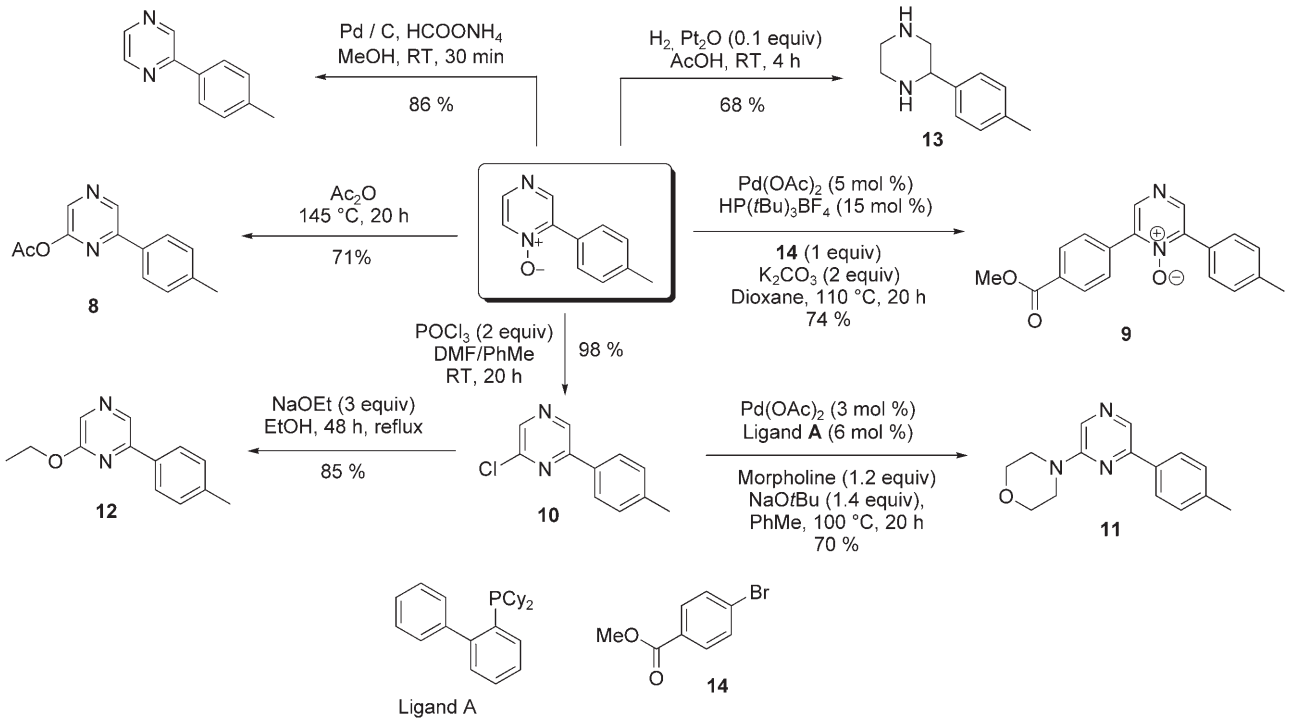
mined to occur by a concerted palladation–deprotonation pathway.[20] A similar reaction mechanism may be operable here and is under investigation.

In conclusion, diazine *N*-oxides are convenient, inexpensive, and readily available replacements for problematic diazine organometallic substates in palladium-catalyzed cross-coupling reactions. In some cases the necessary reactivity could be achieved by the addition of copper salts, and the products can be easily converted into a wide range of substituted nitrogen heterocycles by taking advantage of the *N*-oxide functionality. This chemistry should be of considerable use in the synthesis of these medicinally important compounds.

Experimental Section

Caution: Some aromatic *N*-oxides can undergo thermally induced exothermic decomposition at elevated temperatures.[21] The diazine *N*-oxide starting materials and representative examples of direct arylation products were analyzed by differential scanning calorimetry up to 250 °C. In no instance was there indication of exothermic decomposition.[22] Regardless, we recommend that controlled heating be employed and calorimetry data be obtained if the reactions are to be conducted on large scale.

To a dried flask was added the diazine *N*-oxide (1.0–3.0 equiv), K_2CO_3 (2.0 equiv), $Pd(OAc)_2$ (5 mol%), and $HP(tBu)_3BF_4$ (15 mol%). If the aryl halide is a solid, it was added at this point (1.0 equiv). The flask and its contents were then purged under nitrogen for 10 min. If the aryl halide is a liquid, it was added by syringe after purging, and then degassed dioxane was added (to produce a reaction concentration of 0.3 M). The reaction mixture was then heated at 110 °C for 8–16 h (overnight), after which the



Scheme 2. Further reactions of a pyrazine derivative for the preparation of substituted nitrogen heterocycles.

volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography.

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Keywords: arylation · biaryls · nitrogen heterocycles · *N*-oxides · palladium

[1] For reviews on this topic, see: a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**; b) J. Hassan, M. Sévignon, C. Gozzi, E. Shulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; c) O. Beudoin, *Eur. J. Org. Chem.* **2005**, 4223.

[2] A. F. Pozharski, A. T. Soldartenko, A. Katritsky, *Heterocycles in Life and Society*, Wiley, New York, **1997**.

[3] N. Kudo, M. Perseghini, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1304; *Angew. Chem. Int. Ed.* **2006**, *45*, 1282.

[4] K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 3564; *Angew. Chem. Int. Ed.* **2006**, *45*, 3484.

[5] For example, a number of pinacol boronic esters of the type illustrated in Scheme 1 are commercially available from Combiphos Catalysts, Inc. for approximately 1000 USD per gram (http://www.combiphos.com).

[6] For recent reviews, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; c) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211; d) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; e) L.-C. Campeau, K. Fagnou, *Chem. Commun.* **2005**, 1253.

[7] L. C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc.* **2005**, *127*, 18020.

[8] During preliminary studies with pyridine *N*-oxides, we found that pyridine was an effective poison for the palladium catalyst, completely inhibiting direct arylation. L. C. Campeau, K. Fagnou, unpublished results. See also Table 1, entry 6 herein.

[9] High-yielding oxidation of the corresponding free diazine could be achieved by reaction with *m*CPBA.

[10] The *N*-oxides used in this study are bench stable and show no signs of decomposition after storage in vials at room temperature for several months.

[11] It is noteworthy that resonance contributions for **2** induce properties different from those of **1** and **3**. For example, distribution of the positive charge within the ring places a positive charge on the free nitrogen of **1** and **3** but not **2**. This may result in a diminished capacity to bind to palladium and explain the experimental observations. On the other hand, mesomeric resonance forms where electrons are pushed from the oxyanion into the ring put negative charges on the free nitrogen of **1** and **3** but not **2**. This should produce a trend opposite to that predicted above and to that obtained experimentally.

[12] Other poisoning studies, in which the positions adjacent to the *N*-oxide functional group of pyrimidine *N*-oxide were blocked with aryl groups, also resulted in catalyst inhibition. This indicates that an interaction with either of these positions is not responsible for the poor reaction of **2**. See the Supporting Information for details.

[13] Use of CuCN may result in the in situ formation of a more nucleophilic heteroarylcopper species or reversibly bind the free nitrogen atom.

[14] Adapted from T. Choshi, Y. Matsuya, M. Okita, K. Inada, E. Sugino, S. Hibino, *Tetrahedron Lett.* **1998**, *39*, 2341.

[15] P. J. M. van Galen, et al., *J. Med. Chem.* **1991**, *34*, 1202.

[16] J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2005**, *70*, 1158.

[17] See the Supporting Information for details.

[18] Arylation regioselectivity was proven by X-ray crystal analysis for pyridazine *N*-oxide and pyrimidine *N*-oxide. Regioselectivity for pyriazine *N*-oxide was proven by treatment with $POCl_3$ to give a known compound. See the Supporting Information for details.

[19] a) S. A. Kreuger, W. W. Paudler, *J. Org. Chem.* **1972**, *37*, 4188; b) W. W. Paudler, S. A. Humphrey, *J. Org. Chem.* **1970**, *35*, 3467.

[20] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754.

[21] Examples of exothermic onset temperatures (T_o): Pyridine *N*-oxide: 288 °C; 2,6-lutidine *N*-oxide: 288 °C; nicotinic acid *N*-oxide: 302 °C; γ-picoline *N*-oxide: 285 °C; picolinic acid *N*-oxide: 307 °C; from: T. Ando, Y. Fujimoto, S. Morisaki, *J. Hazard. Mater.* **1991**, *28*, 251.

[22] See the Supporting Information for details.

