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Heteroarylation of Azine *N*-Oxides

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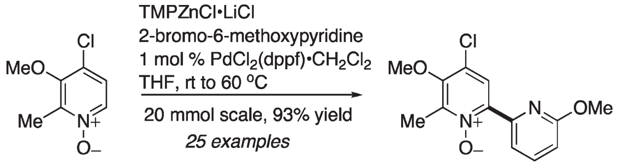
ABSTRACT



Azine *N*-oxides undergo highly regioselective metalation with TMPZnCl·LiCl under mild conditions. A palladium-catalyzed Negishi cross-coupling reaction of the resulting organozinc species with heteroaromatic bromides provides heterobiaryls specifically oxidized at one nitrogen position in up to 95% yield.

Heterobiaryls containing azines are important structural components of pharmaceutically relevant small-molecules and catalysts.[1,2] In the context of a research program in our laboratories, we required access to a number of heterobiaryl motifs where one of the azine nitrogens was specifically oxidized (Figure 1). The lack of stability of 2-pyridyl organometallics combined with the requirement for a challenging late-stage site-selective nitrogen oxidation prompted us to examine the metalation/heteroarylation of azine *N*-oxides. This approach would provide a stable organometallic species and would enable complete control over the site of nitrogen oxidation. The regioselective arylation of azines has been achieved through Pd-catalyzed direct arylation of the corresponding *N*-oxides and *N*-iminopyridinium-ylides.[3] Although attractive, direct arylation methods based on azine *N*-oxides have been reported to provide unsatisfactory yields of coupling products with heteroaryl halides.[3a] Furthermore, reactions performed on substituted azine *N*-oxides can result in diminished yields of desired arylation products.[3b,4] Alternative approaches involving halogen-metal exchange of 2-bromo-pyridine *N*-oxides under cryogenic conditions followed by Pd-catalyzed cross-coupling have also been reported.[5–8] Inspired by the recent work of Knochel and co-workers, we envisioned that tetramethylpiperidinylzinc chloride lithium chloride (TMPZnCl·LiCl, TMP = 2,2,6,6-tetramethylpiperidide) could perform selective metalation of azine *N*-oxides under mild conditions.[9–11] We report herein the regioselective metalation/heteroarylation of both simple and highly substituted azine

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[†] Small Molecule Process Chemistry.

[‡] Discovery Chemistry.

(1) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nature* **2002**, *1*, 493–502.

(2) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674–3677.

(3) For direct arylation of azine *N*-oxides, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020–18021. (b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306. (c) Campeau L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130* 3266–3267. (d) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164. For direct arylation of *N*-iminopyridinium ylides, see: (e) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52–54. Reviewed in: (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

(4) Direct arylation of pyridine *N*-oxides with bromopyridines proceeds in modest yields, see: Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310–2313.

(5) Duan, X.-F.; Ma, Z.-Q.; Zhang, F.; Zhang, Z.-B. *J. Org. Chem.* **2009**, *74*, 939–942.

(6) Lack of selectivity in lithiation of substituted azine *N*-oxides has been noted, see: (a) García-Flores, F.; Flores-Michel, L. S.; Juaristi, E. *Tetrahedron Lett.* **2006**, *47*, 8235–8238. (b) Abramovitch, R. A.; Smith, E. M.; Knaus, E. E.; Saha, M. *J. Org. Chem.* **1972**, *37*, 1690–1696.

(7) For an alternative approach involving ring-opening organometallic addition on pyridine *N*-oxides followed by ring-closure, see: Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335–1337.

(8) For addition of organomagnesium reagents to nitropyridine *N*-oxides, see: Zhang, F.; Duan, X.-F. *Org. Lett.* **2011**, *13*, 6102–6105.

(9) For metalation of pyridine *N*-oxide using Zn(TMP)$_2$ see: (a) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105–4108. Cross-coupling of the resulting diarylzinc species with PhBr was reported, albeit without isolated yield. For metalation with LiTMP under cryogenic conditions, see: (b) Denmark, S. E.; Fan, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 687–707.

(10) (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837–1840. (b) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686–4695. (c) Bresser, T.; Monzon, G.; Mosrin, M.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299–1303.

10.1021/ol203388j

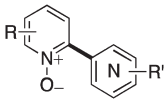
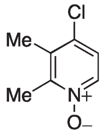
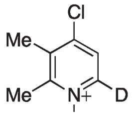
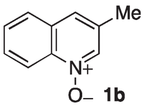
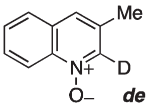


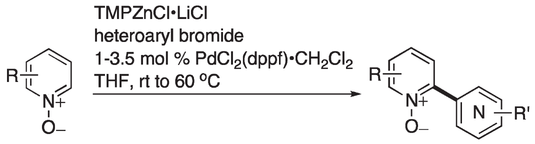
Figure 1. Target heterobiaryl motifs.

Table 1. Regioselective Metalation of Azine *N*-Oxides[a]

entry	substrate	product	selectivity
1	 **1a**	 ***deuterio*-1a**	>95:5
2	 **1b**	 ***deuterio*-1b**	>95:5

[a] Conditions: TMPZnCl·LiCl (100 mol %), THF, rt then quench with 35 wt % DCl in D_2O.

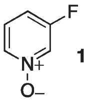
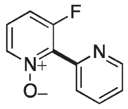
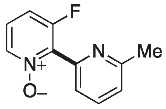
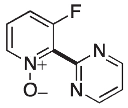
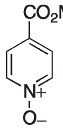
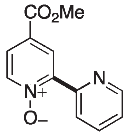
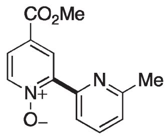
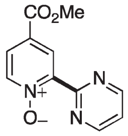
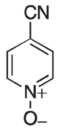
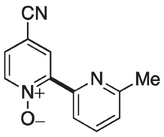
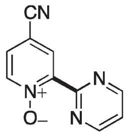
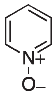
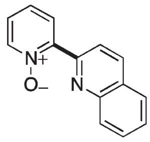
Scheme 1. Metalation/Negishi Cross-coupling



N-oxides that affords heterobiaryl motifs under mild conditions with complete control over the site of nitrogen oxidation.

Metalation of representative azine *N*-oxides **1a** and **1b** using commercially available TMPZnCl·LiCl (100–150 mol %) proceeded cleanly at rt. The resulting organozinc species were quenched with deuterium chloride in D_2O and ^1H NMR analysis of the crude products indicated the formation of *deuterio*-**1a/1b** with >95:5 selectivity for the aromatic C–H vs benzylic C–H (Table 1).[12] Even upon extended contact (18–24 h) with excess TMPZnCl·LiCl, we found no detectable metalation at the benzylic position in *deuterio*-**1a**.

Table 2. Cross-coupling of Pyridine *N*-Oxides[a]

entry	substrate	product		% yield[b]
1	 **1c**		**2**	59
2	**1c**		**3**	83
3	**1c**		**4**	67
4	 **1d**		**5**	47
5	**1d**		**6**	52
6	**1d**		**7**	31
7	 **1e**		**8**	53
8	**1e**		**9**	30
9	 **1f**		**10a**	70[c]

[a] Conditions: (a) Azine *N*-oxide (150 mol %), TMPZnCl·LiCl (150 mol %, heteroaryl bromide (100 mol %), 3.5 mol % PdCl$_2$(dppf)·CH$_2$Cl$_2$, THF, rt to 60 °C, 18 h. (b) Isolated yields. (c) The corresponding 2,6-diarylation product **10b** was also isolated in 15% yield (see Supporting Information).

A Negishi cross-coupling reaction of the organozinc species proceeded smoothly under mild conditions with PdCl$_2$(dppf)[13] as catalyst in THF at 60 °C (Scheme 1, Tables 2–5).[14] The compatibility of TMPZnCl·LiCl with the reaction components is remarkable since we found no

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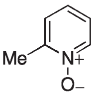
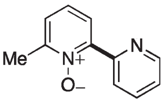
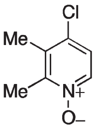
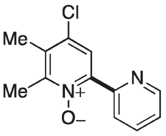
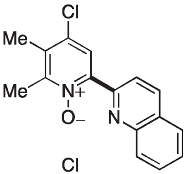
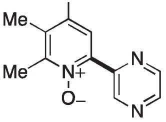
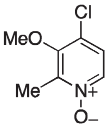
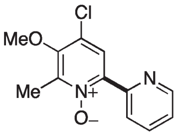
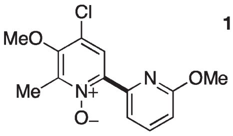
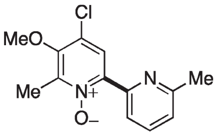
(11) Metalations using hindered metal amide bases are reviewed in: Haag, B; Mosrin, M.; Hiriyakkanavar Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794–9825.

(12) In our hands, iodination (0.5 M I_2 in THF) of the resulting organozinc species led to erratic results as ascertained by HPLC analysis.

(13) dppf = 1,1′-bis(diphenylphosphino)ferrocene.

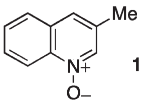
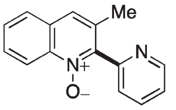
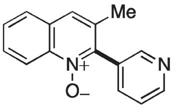
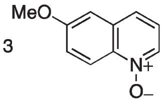
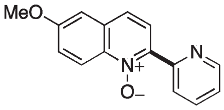
(14) (a) Negishi, E.-i. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; chap. 1. (b) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299. (c) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340–348.

Table 3. Cross-coupling of Picoline *N*-Oxides[a]

entry	substrate		product		% yield[b]
1		**1g**		**11**	88
2		**1a**		**12**	85
3		**1a**		**13**	86
4		**1a**		**14**	92
5		**1h**		**15**	85
6		**1h**		**16**	95
7		**1h**		**17**	81

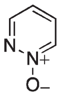
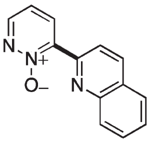
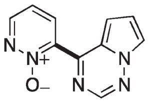
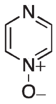
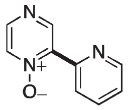
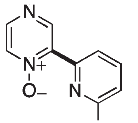
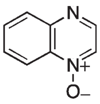
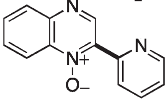
[a] Conditions: (a) Azine *N*-oxide (150 mol %), TMPZnCl·LiCl (150 mol %), heteroaryl bromide (100 mol %), 3.5 mol % $PdCl_2$(dppf)·CH_2Cl_2, THF, rt to 60 °C, 18 h. (b) Isolated yields.

Table 4. Cross-coupling of Quinoline *N*-Oxides[a]

entry	substrate		product		% yield[b]
1		**1b**		**18**	74
2		**1b**		**19**	73[c]
3		**1i**		**20**	49

[a] Conditions: (a) Azine *N*-oxide (150 mol %), TMPZnCl·LiCl (150 mol %), heteroaryl bromide (100 mol %), 3.5 mol % $PdCl_2$(dppf)·CH_2Cl_2, THF, rt to 60 °C, 18 h. (b) Isolated yields. (c) $Pd(dba)_2$ (5 mol %)/Cy_3P (10 mol %) as catalyst.

Table 5. Cross-coupling of Diazine *N*-Oxides[a]

entry	substrate		product		% yield[b]
1		**1j**		**21**	77
2		**1j**		**22**	66
3		**1k**		**23**	84[c,d]
4		**1k**		**24**	78[c,d]
5		**1l**		**25**	79[c]

[a] Conditions: (a) Azine *N*-oxide (150 mol %), TMPZnCl·LiCl (150 mol %), heteroaryl bromide (100 mol %), 3.5 mol % $PdCl_2$(dppf)·CH_2Cl_2, THF, rt to 60 °C, 18 h. (b) Isolated yields. (c) TMPZnCl·LiCl (110 mol %), THF:NMP (1:1). (d) Azine *N*-oxide (300 mol %) was used.

requirement for a separate metalation step prior to the cross-coupling.[15]

Reactions of 3-fluoropyridine *N*-oxide **1c** with 2-bromopyridines and 2-bromopyrimidine gave the cross-coupling products **2**–**4** in 59–83% isolated yield (Table 2, entries 1–3). In comparison, cross-coupling reactions with methyl nicotinate *N*-oxide **1d** and 4-cyanopyridine *N*-oxide **1e** proved more challenging and afforded products **5**–**9** in moderate yields ranging from 30 to 53%. Cross-coupling of pyridine *N*-oxide **1f** with 2-bromoquinoline afforded the desired heteroarylation product **10a** in 70% yield along with the corresponding 2,6-diarylation byproduct **10b** in 15% yield. We found that purification of these products was challenging because of their highly polar nature. In addition, competing diarylation often led to reduced yields of desired products for simple pyridine *N*-oxides.

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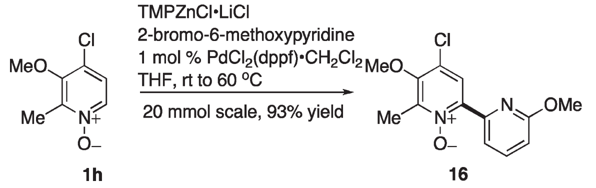
[15] Both TMPZnCl·LiCl and $(TMP)_2Zn$·LiCl metalated azine *N*-oxides but in our hands the subsequent Negishi cross-coupling was more sluggish with the diarylzinc species.

Next we investigated the metalation and cross-coupling of picoline *N*-oxides **1g**, **1a** and **1h** under the same reaction conditions (Table 3). Consistent with our deuteration experiments, we observed that metalation and arylation of the 2-methyl group of picolines was not a competing pathway under the reaction conditions.[16] 2-Picoline *N*-oxide **1g** underwent cross-coupling to furnish **11** in 88% yield. It is also noteworthy that, in contrast to Pd-catalyzed direct arylation, the present Negishi cross-coupling of highly substituted picoline *N*-oxides **1a** and **1h** proceeded in consistently high yields to afford highly functionalized heterobiaryls **12**–**17** in 81–95% yields.

Cross-coupling of quinoline *N*-oxide **1b** with both 2- and 3-bromopyridine gave the desired heterobiaryls **18**–**19** in 74 and 73% yield, respectively (Table 4, entries 1–2). Methoxyquinoline *N*-oxide **1i** afforded heterobiaryl **20** in 49% yield.

We also found that diazine *N*-oxides performed well in the reaction (Table 5). Pyridazine *N*-oxide **1j** underwent reaction with 2-bromoquinoline to give **21** in 77% yield. Cross-coupling with 4-bromopyrrolo-[1,2-f][1,2,4]-triazine gave **22** in 66% yield. Similarly, pyrazine *N*-oxide **1k** and quinoxaline *N*-oxide **1l** afforded the desired heterobiaryl products **23**–**25** in 78–84% yield.[17,18]

Scheme 2. Multi-gram Scale Reaction



Finally, as demonstrated in Scheme 2, this process is preparatively useful as the desired cross-coupling product **17** was isolated in 93% yield on multigram scale.[19]

In summary, we have developed a mild and practical protocol for the heteroarylation of azine *N*-oxides via a Pd-catalyzed Negishi cross-coupling using in situ generated organozinc intermediates. This approach also unambiguously positions the *N*-oxide group as a handle for further functionalization.[20] Further studies are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization of compounds **2**–**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Although it has been reported that picolines are metalated smoothly with TMPZnCl·LiCl at rt, the *N*-oxide group in the present system appears to direct the deprotonation at the aromatic C–H selectively. For metalation and benzylic cross-coupling of picolines under similar conditions, see: Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686–7690.

(17) At the present time cross-coupling with 5-membered heterocycles represents a limitation to this method. Cross-coupling of *N*-oxide **1h** with 4-bromothiazole and 2-bromothiophene gave the corresponding products in 30–35% yields (see Supporting Information).

(18) In contrast, pyrimidine *N*-oxide failed to provide any desired products and apparent ring-opening byproduct were observed under the reaction conditions.

(19) Multigram scale procedure: To a solution of 2-methyl-3-methoxy-4-chloropyridine *N*-oxide **1h** (5.21 g, 30 mmol, 150 mol %) and 2-bromo-6-methoxypyridine (2.46 mL, 3.76 g, 20 mmol) in THF (52 mL, 10 mL/g) was added TMPZnCl·LiCl (43 mL, 30 mmol, 150 mol %, 0.69 M in THF) over 2 min. The internal temperature increased from 23.4 to 30.0 °C during the addition. A thin slurry formed after 1–2 min. The slurry was sparged with N_2 bubbles for 5 min and solid dichloro-1,1′-[bis-(diphenylphosphino)ferrocene]palladium·CH_2Cl_2 (219 mg, 0.3 mmol, 1 mol %) was added. The resulting tan-orange slurry was then heated at 60 °C (internal temperature) for 18 h. LC-MS analysis showed complete conversion to **16**. The deep red reaction mixture was cooled to rt and quenched with saturated aqueous NH_4Cl (100 mL) and diluted with 50% aqueous acetonitrile (50 mL). The solution was extracted with dichloromethane (2 × 100 mL), dried with Na_2SO_4 and concentrated. The residue was chromatographed (0–100% EtOAc in hexanes) and the combined fractions were concentrated to afford the desired product 4-chloro-3-methoxy-6-(6-methoxypyridin-2-yl)-2-methylpyridine 1-oxide **17** as a free-flowing white solid (5.32 g, 93% yield): mp = 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 8.68 (d, 1H, J = 7.5 Hz), 8.22 (s, 1H), 7.68 (app t, 1H, J = 8.0 Hz), 6.79 (d, 1H, J = 8.0 Hz), 3.98 (s, 3H), 3.90 (s, 3H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.3, 151.5, 147.3, 145.7, 144.5, 139.3, 125.9, 124.6, 118.6, 112.4, 61.4, 53.5, 12.5; HRMS calcd for $C_{13}H_{14}ClN_2O_3$ [M + H] = 281.0687, found 281.0695.

(20) Recent examples of nucleophilic addition to pyridine *N*-oxides include: (a) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2011**, *13*, 1840–1843. (b) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554–4557.