ORGANIC
LETTERS

2012
Vol. 14, No. 3
862–865

Heteroarylation of Azine *N*-Oxides

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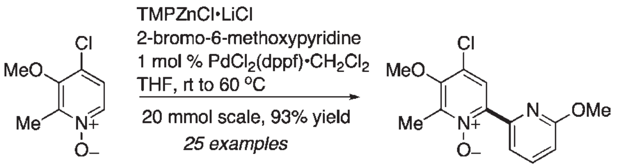
Received December 19, 2011

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

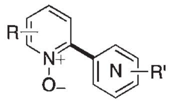
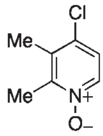
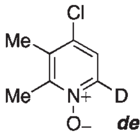
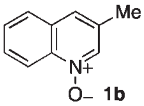
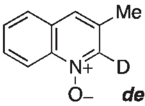


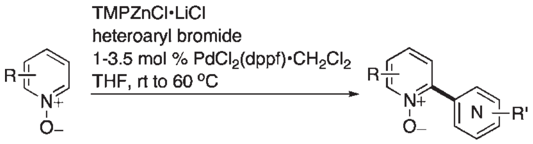
Figure 1. Target heterobiaryl motifs.

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

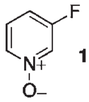
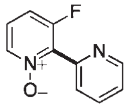
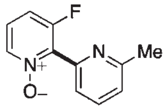
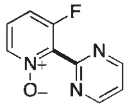
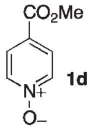
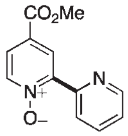
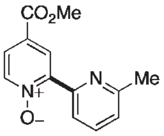
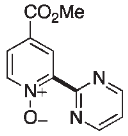
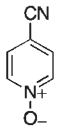
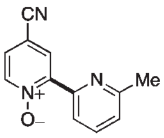
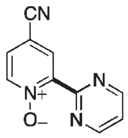
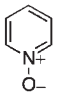
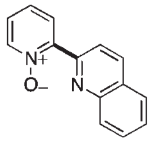


N-oxides that affords heterobiaryl motifs under mild conditions with complete control over the site of nitrogen oxidation.

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**.

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,

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_2Cl_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).

Tables 2–5).[14] The compatibility of TMPZnCl·LiCl with the reaction components is remarkable since we found no

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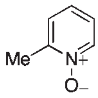
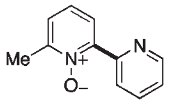
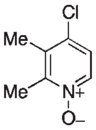
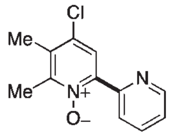
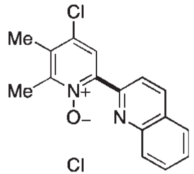
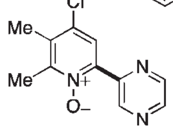
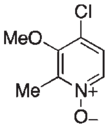
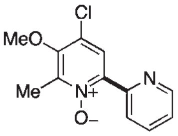
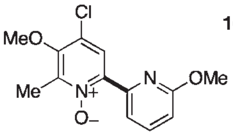
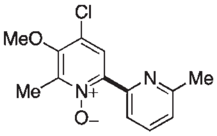
(11) Metalations using hindered metal amide bases are reviewed in: Haag, B; Mosrin, M.; Hiriyakkanavar Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794–9825.

(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.

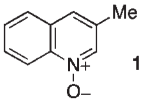
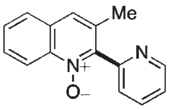
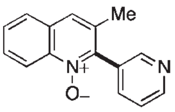
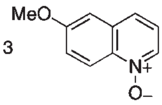
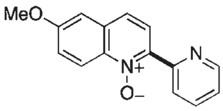
(14) (a) Negishi, E.-i. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: New York, 1998; chap. 1. (b) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298–3299. (c) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340–348.

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

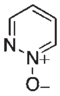
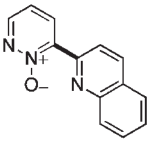
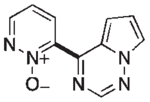
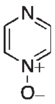
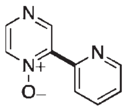
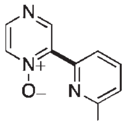
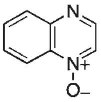
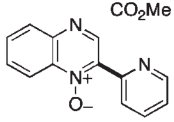
[a] Conditions: (a) Azine *N*-oxide (150 mol %), TMPZnCl·LiCl (150 mol %), heteroaryl bromide (100 mol %), 3.5 mol % PdCl$_2$(dppf)·CH$_2$Cl$_2$, THF, rt to 60 °C, 18 h. (b) Isolated yields.

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$_2$Cl$_2$, THF, rt to 60 °C, 18 h. (b) Isolated yields. (c) Pd(dba)$_2$ (5 mol %)/Cy$_3$P (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$_2$Cl$_2$, 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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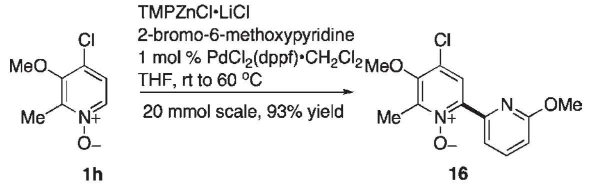
(15) Both TMPZnCl·LiCl and (TMP)$_2$Zn·LiCl metalated azine *N*-oxides but in our hands the subsequent Negishi cross-coupling was more sluggish with the diarylzinc species.

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.

Acknowledgment. We thank Dr. Alan Deese for help with NMR analysis, Dr. Christine Gu for HRMS analysis, and Dr. Sushant Malhotra and Dr. Chong Han (Genentech) for helpful discussions and careful review of the manuscript.

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$_2$Cl$_2$ (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$_4$Cl (100 mL) and diluted with 50% aqueous acetonitrile (50 mL). The solution was extracted with dichloromethane (2×100 mL), dried with Na$_2$SO$_4$ 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$_2$O$_3$ [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.