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Synthesis of Unsymmetrically Substituted Bipyridines by Palladium-Catalyzed Direct C–H Arylation of Pyridine *N*-Oxides

Sasa Duric and C. Christoph Tzschucke*

Freie Universität Berlin, Institut für Chemie und Biochemie, Takustrasse 3, 14195 Berlin, Germany

tzschucke@chemie.fu-berlin.de

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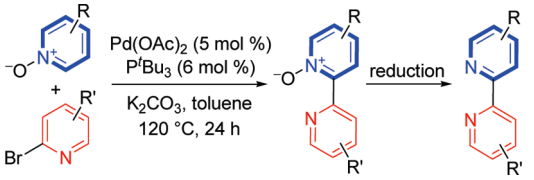
ABSTRACT



Substituted bipyridines were efficiently prepared by direct coupling between pyridine *N*-oxides and halopyridines using a palladium catalyst. Pyridine *N*-oxides with electron-withdrawing substitutents gave the best yields. This method allows the convenient preparation of 2,2′-, 2,3′-, and 2,4′-bipyridines which are useful as functionalized ligands for metal complexes or as building blocks for supramolecular architectures.

Bipyridines constitute an important class of heterocycles with numerous applications. Particularly, 2,2′-bipyridines have found widespread use as chelating ligands for a wide range of different metal ions,[1] and their complexes have been employed as catalysts,[2] as photosensitizers,[3] in light-emitting diodes,[4] as fluorescent dyes,[5] and as building blocks for supramolecular architectures.[6] Bipyridine motifs are also present in natural products with antibiotic and cytotoxic activities.[7] Due to their importance, numerous different synthetic approaches to bipyridines have been described.[8] Among these, transition-metal-catalyzed cross-coupling reactions between halopyridines and pyridyl organometallics are the most general and flexible ones.[9] However, pyridyl organometallics usually need

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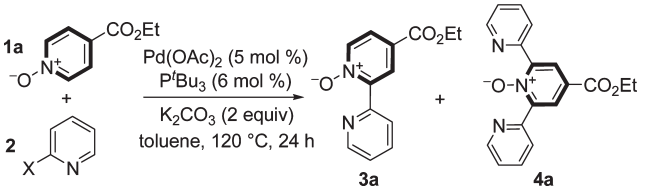
Table 1. Effect of the Substrate Ratio and of the Halopyridine



entry	*N*-oxide **1a**	**2** X=	bipyridine **3a**[a]	terpyridine **4a**[a]
1	1.0 mmol	Br	52%	24%
2	1.5 mmol	Br	60%	21%
3	1.5 mmol	Cl	57%	17%
4	1.5 mmol	I	14%	–
5	1.5 mmol	triflate	18%	–
6	1.5 mmol	nonaflate	39%	10%
7	1.5 mmol	tosylate	5%	–
8[b]	1.5 mmol	Br	41%	10%
9	2.0 mmol	Br	67%	13%
10	3.0 mmol	Br	72%	10%
11	4.0 mmol	Br	71%	6%
12[c]	1.0 mmol	Br (2.5 mmol)	50%	20%
13[c]	1.0 mmol	Br (4.0 mmol)	50%	27%
14[c,d]	1.0 mmol	Br (2.5 mmol)	39%	34%

[a] Isolated yields after column chromatography based on **2** (1.0 mmol). [b] PivOH (0.3 mmol) added. [c] Yield and catalyst loading based on **1a**. [d] 12.5 mol % $Pd(OAc)_2$, 15 mol % P^tBu_3.

to be prepared by multistep procedures and are frequently unstable.[10] Methods that obviate the need for functionalization at the site of the C–C coupling can greatly reduce the number of synthetic steps. Recently, an increasing number of methods for the direct arylation of arenes and heteroarenes based on transition-metal-catalyzed C–H activation has been developed.[11] Pyridine *N*-oxides have been introduced as easily available and bench-stable substrates for cross-coupling with aryl halides.[12]

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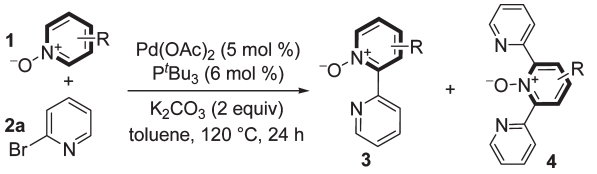
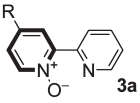
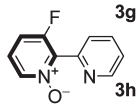
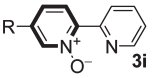
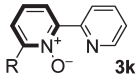
(11) For reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Chen, X.; Engle, K.-M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (f) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (g) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (h) Hartwig, J. F.; Scott, M. E.; Alberico, D.; Lautens, M., Direct Arylation. In Hartwig, J. F. *Organotransition Metal Chemistry*; University Science Books: Sausalito, CA, USA, 2010; p 938. (i) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (j) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (k) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. Selected recent examples:(l) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (m) Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem.* **2011**, *76*, 882. (n) Tredwell, M. J.; Gulias, M.; Gaunt-Bremeyer, N.; Johansson, C. C. C.; Collins, B. S. L.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1076. (o) Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109.

Table 2. Influence of Substitution of the Pyridine *N*-Oxide



entry	product		**3** yield[a]	recovered **1**
1		**3a** R= CO_2Et	67% (**4a** 13%)	1.11 mmol
2		**3b** R= NO_2	41%	1.10 mmol
3		**3c** R= CN	56% (**4c** 15%)	1.20 mmol
4		**3d** R= CF_3	65% (**4d** 18%)	0.99 mmol
5		**3e** R= Cl	35% (**4e** 8%)	1.00 mmol
6		**3f** R= H	23% (12%[b], 11%[c])	1.51 mmol
7		**3g** R= ^{t}Bu	16% (9%[d])	1.58 mmol
8		**3h**	51%	1.13 mmol
9		**3i** R= CN	12% (**2i** 11%)	0.83 mmol
10		**3j** R= CO_2Me	25%	0.68 mmol
11		**3k** R= CO_2Et	10%	0.37 mmol
12		**3l** R= CN	58%	1.31 mmol

[a] 1.0 mmol **2a** and 2.0 mmol **1** were used. Isolated yields after column chromatography were based on **2a**. [b] 2,3′-Bipyridine *N*-oxide. [c] *N*-(2-Pyridyl)-2-pyridone. [d] *N*-(4-*tert*-Butylpyridine-2-yl)-2-pyridone.

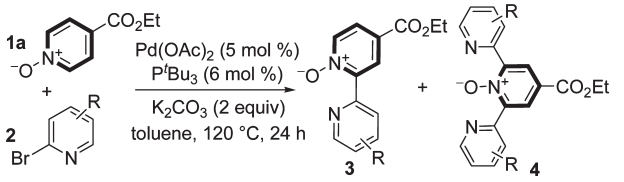
Coupling with pyridyl halides, however, has not been described in this context.

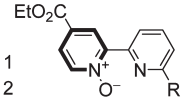
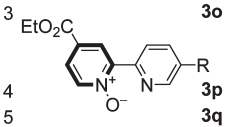
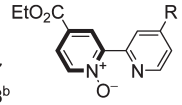
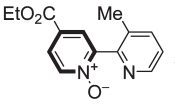
Herein, we report a convenient synthesis of substituted bipyridines based on the palladium-catalyzed direct coupling between halopyridines and pyridine *N*-oxides, many of which are commercially available or readily prepared in excellent yields. The resulting bipyridine *N*-oxides were efficiently reduced to the final products.

Our initial attempts to couple equimolar amounts of 2-bromopyridine and 4-alkylpyridine *N*-oxides under the published conditions[12a] failed to give detectable amounts of coupling product. When we switched to ester substituted *N*-oxide **1a** as a starting material, we could isolate the desired coupling product **3a** in 52% yield as well as 24% yield of terpyridine *N*-oxide **4a** resulting from double arylation (Table 1, entry 1). First, we examined the influence of the substrate ratio and of the leaving group (Table 1).

As expected, the ratio of monoarylated **3a** to bis-arylated product **4a** was dependent on the ratio of *N*-oxide **1a** to **2a** (entries 1, 2, 9–14). Thus, using an excess of *N*-oxide **1a** improved the yield of **3a** to 72%, whereas a 2.5-fold excess of bromide **2a** gave terpyridine *N*-oxide **4a** in 20% yield, which could be increased to 34% yield by raising the catalyst loading.[13] Since employing a large excess of

Table 3. Influence of Substitution of the 2-Bromopyridine



entry	product		3 yield[a]	recovered 1
1		**3m** R= Me	51% (**4m** 11%)	1.20 mmol
2		**3n** R= OMe	57% (**4n** 9%)	1.14 mmol
3		**3o** R= CF_3	56% (**4o** 12%)	1.13 mmol
4		**3p** R= Me	59%	1.07 mmol
5		**3q** R= OMe	57%	0.95 mmol
6		**3r** R= CF_3	14%	0.81 mmol
7		**3s** R= Me	35%	1.29 mmol
8[b]		**3t** R= OMe	39%	1.38 mmol
9		**3u**	40%	1.16 mmol

[a] 1.0 mmol **2** and 2.0 mmol **1a** were used. Isolated yields after column chromatography were based on **2**. [b] 2-Chloro-4-methoxypyridine was used instead of the bromopyridine.

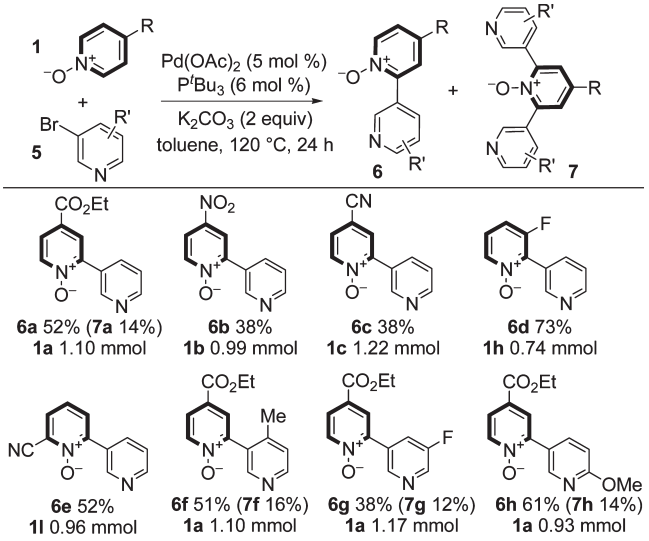
one reagent is obviously undesirable, we used 1.5 or 2.0 equiv of *N*-oxide for further experiments. While 2-chloropyridine was only slightly less reactive than **2a** (entry 3), the yield dropped markedly with 2-iodopyridine or pyridylsulfonates as substrates (entries 4–7). For the related arylation of azaindole *N*-oxides, Fagnou reported that the addition of pivalic acid led to increased yields.[12f] In the present reaction, however, the addition of 0.3 equiv of pivalic acid decreased the yield of **3a** to 41% (entry 8).

We next explored the substrate scope with regard to pyridine *N*-oxide (Table 2). Pyridine *N*-oxides with electron-withdrawing substituents in the 4-position gave moderate to good yields of bipyridine *N*-oxide products (entries 1–5). While unsubstituted pyridine *N*-oxide gave only a 23% yield of 2,2′-bipyridine *N*-oxide **3f**, remarkably a 12% yield of 2,3′-bipyridine *N*-oxide, where the C–H-arylation had taken place in the 3-position of the starting pyridine *N*-oxide, was isolated (entry 6). Additionally, an 11% yield of *N*-(2-pyridyl)-2-pyridone was obtained.[14] With 3-fluoropyridine *N*-oxide, coupling took place selectively in the 2-position, which is activated by both the fluoro-substituent and the *N*-oxide (entry 8). Such preferential reaction at the most polarized C–H bond has been previously observed in similar arylation reactions.[12i]

The influence of the substitution pattern of the bromopyridine on the arylation of *N*-oxide **1a** is exemplified by the results in Table 3. While in the 6-position of the bromopyridine an electron-donating or -withdrawing group was each well tolerated (entries 1–3), a more pronounced influence of the substituent's electronic properties was observed for 5-substituted bromopyridines. While with a methyl or methoxy substituent good yields were achieved (entries 4, 5), a trifluoromethyl group led to a low yield of coupling product (entry 6).

Our results are consistent with previous reports that pyridine *N*-oxides bearing electron-withdrawing substituents are significantly more reactive in the direct arylation reaction than *N*-oxides with electron-donating substituents.[12a] This has been explained in terms of a concerted metalation–deprotonation (CMD) mechanism for the C–H activation step.[12h,i] So far the influence of the aryl halide on the reactivity has not been evaluated in detail. The present work shows that electron-poor aryl halides, such as bromopyridines, significantly decrease the reactivity, probably by slowing down the rate-limiting metalation of the *N*-oxide.

Scheme 1. Direct Arylation with 3-Bromopyridines[a]



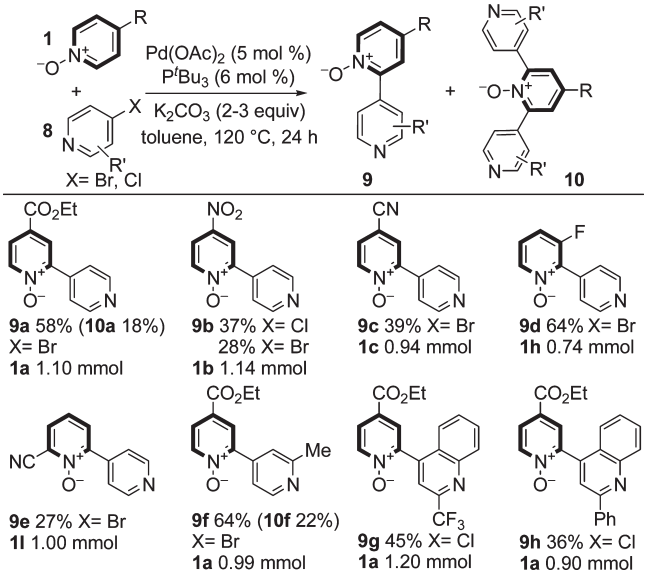
[a] 1.0 mmol **5** and 2.0 mmol **1** were used. Isolated yields after column chromatography were based on **5**.

(12) (a) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (d) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. (e) 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. (f) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357. (g) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749. For mechanistic studies:(h) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (i) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180. Arylation of *N*-iminopyridinium ylides: (j) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2007**, *130*, 52. Arylation of *N*-phenacylpyridium bromides: (k) Xu, J.; Cheng, G.; Su, D.; Liu, Y.; Wang, X.; Hu, Y. *Chem.—Eur. J.* **2009**, *15*, 13105.

(13) The ratio of **3a** to **4a** in all cases is close to the expected ratio for sequential formation of **4a** from **3a**, taking into account that **3a** has only one potential coupling site whereas **1a** has two. From this it can be concluded that **1a** and **3a** have the same reactivity toward C–H activation and no product inhibition is taking place.

To extend the scope of the reaction further, we also investigated the arylation of pyridine *N*-oxides with 3-bromopyridines (Scheme 1) and 4-bromo- or 4-chloropyridines (Scheme 2). The reactivity followed the same general trends observed for the 2-bromopyridines, and the coupling products were isolated in moderate to good yields.

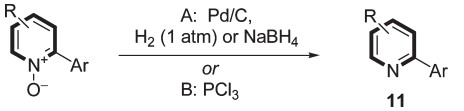
Scheme 2. Direct Arylation with 4-Halopyridines[a]



[a] 1.0 mmol **8** and 2.0 mmol **1** were used. Isolated yields after column chromatography were based on **8**.

The final deoxygenation of the bipyridine *N*-oxides to the desired bipyridines is a well-precedented high yielding transformation and can be achieved by several different convenient methods.[12e,15] In most cases reduction with hydrogen or sodium borohydride using palladium on charcoal as a catalyst gave very good to near quantitative yields (Table 4). Under these conditions the nitro group of **3b** was reduced to an amino function (entry 2). In the case of **3c** a competing reduction of the nitrile to an aminomethyl group could be completely prevented using phosphorus trichloride as a reducing agent (entry 3).[15a] Likewise, we employed phosphorus trichloride in the reduction of **3e** to prevent possible dehalogenation (entry 5).

Table 4. Deoxygenation of Bipyridine *N*-Oxides



entry	product		yield(cond.)[a]
1	**11a**	R= CO_2Et	96% (A)
2[b]	**11b**	R= NH_2	86% (A)
3	**11c**	R= CN	98% (B), 61% (A)
4	**11d**	R= CF_3	86% (A)
5	**11e**	R= Cl	93% (B)
6	**11f**		81% (A)
7	**11g**		96% (A)
8	**11h**		89% (A)
9	**11i**		80% (A)
10	**11j**		96% (A)

[a] Isolated yields. [b] Starting material **3b** R = NO_2.

In conclusion, we describe the palladium-catalyzed direct coupling between pyridine *N*-oxides and halopyridines as the key step of an efficient and versatile preparation of substituted bipyridines from readily available starting materials. This method significantly reduces the number of steps in comparison to conventional synthetic approaches.

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Supporting Information Available. Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The pyridone probably derives from nucleophilic attack of the pyridine *N*-oxide on the bromopyridine and subsequent rearrangement; *cf.* Ramirez, F.; von Ostwalden, P. W. *J. Am. Chem. Soc.* **1959**, *81*, 156. Depending on the conditions, the pyridone was formed as the main product (65% from pyridine *N*-oxide, 89% from 4-*tert*-butylpyridine *N*-oxide). For details see Supporting Information.

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