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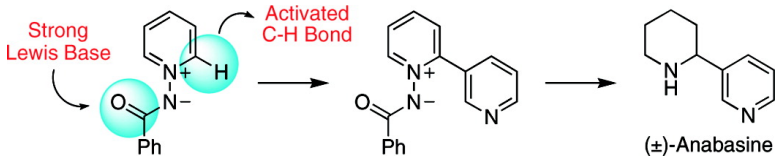
J. Am. Chem. Soc., **2008**, 130 (1), 52-54 • DOI: 10.1021/ja710073n



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Palladium-Catalyzed Direct C−H Arylation of *N*-Iminopyridinium Ylides: Application to the Synthesis of (±)-Anabasine

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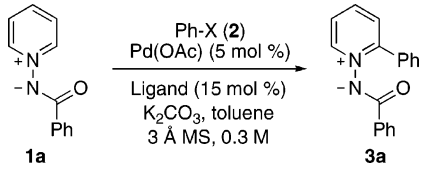
Pyridine and piperidine motifs are important pharmacophores that can be found in many natural products and bioactive molecules.[1] Our group has been interested in using activated pyridinium imidates and pyridinium ylides as starting materials to generate substituted piperidines via stereoselective Grignard additions[2,3] and catalytic asymmetric hydrogenation reactions.[4] This approach enables the preparation of highly substituted enantioenriched piperidines in a few steps from commercially available pyridine derivatives.

While pyridine is readily available, 2-aryl- and 2-heteroarylpyridine substrates are less common and significantly more expensive. These substrates are typically synthesized by cross-coupling reactions between 2-halopyridines and aryl organometallic derivatives[5] or by Grignard addition to the pyridine *N*-oxide.[6] More recently, considerable attention has been given to direct arylation reactions as a more efficient approach for aryl−aryl bond formation.[7] The benefit of this approach is that it avoids the utilization of stoichiometric amounts of organometallic reagents. While many direct arylation reactions of heteroaryl compounds have been reported, few exist for the direct arylation or heteroarylation of pyridine derivatives.[8] Furthermore, the chemoselective functionalization of one heterocycle in the presence of others is often difficult. Herein, we disclose a novel reactivity of *N*-iminopyridinium ylides[9] and a procedure that allows their direct arylation coupling with a variety of functionalized aryl and heteroaryl bromides. We also demonstrate that it is possible to further selectively functionalize the pyridinium ylide ring in the presence of a pyridine ring.

We initially examined the direct arylation of *N*-benzoyliminopyridinium ylides, which are easily prepared by the amination of pyridine.[10] A small portion of the optimization studies involving ylide **1a** is shown in Table 1. Treatment of **1a** (1.5 equiv) with bromobenzene in the presence of *t*-Bu_3P/$Pd(OAc)_2$ afforded the 2-arylated product in excellent yield (entry 1). Among the mono- and bidentate phosphines that were tested, tri-*t*-butylphosphine was found to be the most effective. Both the phosphine oxide (entry 2) and the protonated *t*-Bu_3P (entry 3) were less effective. The preformed $Pd(Pt\text{-}Bu_3)_2$ complex was as effective as the in situ prepared catalyst (entry 4). Lowering the temperature (entry 5), the amount of ylide (entries 6 and 7) or the reaction concentration (entries 8 and 9) resulted in lower yields. Although all reactions were run in the presence of molecular sieves, only slightly lower yields were observed without them (entry 10) or in the presence of H_2O (entry 11). While iodobenzene gave a slightly improved yield (entry 12), chlorobenzene resulted in a significantly lower yield (entry13).

The scope of the reaction was then investigated using various aryl bromide derivatives (Table 2). Under the optimized reaction conditions [**1** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $P(t\text{Bu})_3$ (15 mol %), K_2CO_3 (3 equiv), 3 Å mol. sieves, toluene 125 °C] using

Table 1. Palladium-Catalyzed Arylation of *N*-Iminopyridinium Ylide with Aryl Halide Derivatives



entry	ligand	X	equiv of ylide	temp (°C)	yield (%)[a]
1	*t*Bu_3P	Br	1.5	125	87
2	*t*$Bu_3P(O)$	Br	1.5	125	0
3	*t*$Bu_3P{\cdot}HBF_4$	Br	1.5	125	55
4	$Pd(t\text{Bu}_3P)_2$[b]	Br	1.5	125	90
5	*t*Bu_3P	Br	1.5	110	66
6	*t*Bu_3P	Br	1.0	125	36
7	*t*Bu_3P	Br	1.3	125	64
8[c]	*t*Bu_3P	Br	1.5	125	82
9[d]	*t*Bu_3P	Br	1.5	125	73
10[e]	*t*Bu_3P	Br	1.5	125	81
11[f]	*t*Bu_3P	Br	1.5	125	83
12	*t*Bu_3P	I	1.5	125	95
13	*t*Bu_3P	Cl	1.5	125	42

[a] Yields are measured by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b] Reaction run using 5 mol % of $Pd(Pt\text{-}Bu)_3$ instead of $Pd(OAc)_2$/ligand. [c] Run at 0.1 M. [d] Run at 0.05 M. [e] Run without 3 Å molecular sieves. [f] Run without 3 Å molecular sieves and in the presence of 5 equiv of H_2O.

bromobenzene (1 equiv), the 2-phenyl-*N*-iminopyridinium ylide was obtained in an 80% isolated yield. Both electron-rich (entries 2 and 3) and electron-poor (entries 4−8) aryl bromides are compatible under the reaction conditions, although 2.5 equiv of the ylide are necessary for the latter.

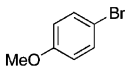
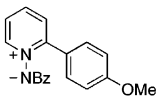
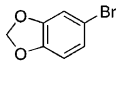
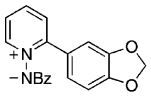
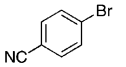
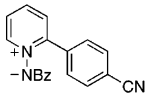
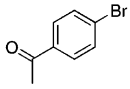
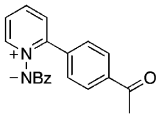
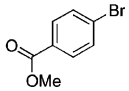
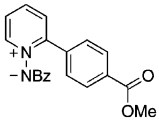
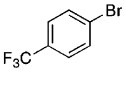
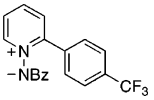
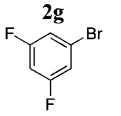
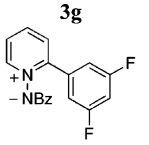
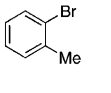
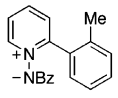
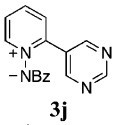
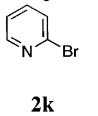
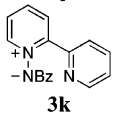
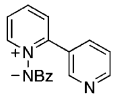
2-Bromotoluene (**2i**) gave a good yield of arylated product showing that sterically hindered bromides are compatible. These conditions were also successful for the coupling of heteroaryl bromide derivatives resulting in the formation of highly valuable bis(heteroaryl) substrates (entries 10−12).

Encouraged by these results, we explored the scope of the *N*-iminopyridinium ylide coupling partner **1** (Table 3). Generally, substituted *N*-iminopyridinium ylides resulted in lower yields and required an excess of the aryl bromide. *N*-Iminoquinolinium (**1b**) and *N*-iminoisoquinolinium ylides (**1c**) gave moderate and good yields of arylated products, respectively. Various 2- and 3-alkyl substituted *N*-iminopyridinium ylides also gave moderate yields of products. Notably, 3-methyl-*N*-iminopyridinium ylide (**1d**) resulted in a 10:1 regioselectivity, favoring the 2,5-disubstituted adduct **3o**.

We also demonstrated the synthetic potential of this methodology by chemoselectively functionalizing the pyridinium ylide ring in the presence of a pyridine (Scheme 1). A substituent can be easily

10.1021/ja710073n CCC: $40.75

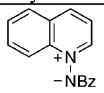
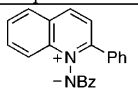
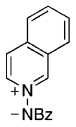
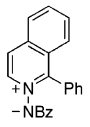
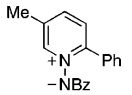
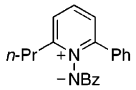
Table 2. Palladium-Catalyzed Arylation of *N*-Iminopyridinium Ylide with Aryl and Heteroaryl Bromide Derivatives[a]

entry	ylide	aryl bromide	product	yield (%)[b,c]
1				80 (80)
	1a	**2a**	**3a**	
2	**1a**			77
		2b	**3b**	
3	**1a**			69 (86)
		2c	**3c**	
4	**1a**			76[d]
		2d	**3d**	
5	**1a**			65[d]
		2e	**3e**	
6	**1a**			76[d]
		2f	**3f**	
7	**1a**			56[d]
		2g	**3g**	
8	**1a**			53[d]
		2h	**3h**	
9	**1a**			72
		2i	**3i**	
10	**1a**			50[d]
		2j	**3j**	
11	**1a**			50[d]
		2k	**3k**	
12	**1a**			83
		2l	**3l**	

[a] Reaction conditions: **1a** (1.5 equiv), **2** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), P(*t*Bu)$_3$ (15 mol %), K_2CO_3 (3 equiv), M.S. 3 Å, toluene 125 °C (0.3 M), 16−20 h. [b] Yield of isolated product. [c] Yield in parentheses is that of the 2-substituted pyridine obtained after cleavage of the *N*−*N* bond using MeI, acetone, 75 °C then Zn (dust), AcOH, room temp. [d] Run using 2.5 equiv of **1a** instead of 1.5 equiv.

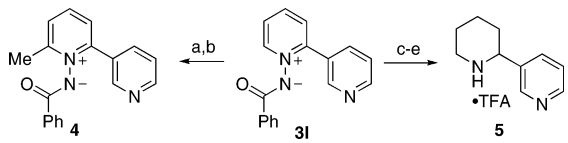
introduced at the 6-position by treatment of **3l** with a Grignard reagent followed by rearomatization (resulting in **4**). Alternatively,

Table 3. Arylation of Other *N*-Imino Ilides[a]

entry	ylide	aryl bromide	product	yield (%)[b,c]
1		**2a**		50
	1b		**3m**	
2		**2a**		78[d] (80)
	1c		**3n**	
3		**2a**		54 (84)
	1d		**3o**	
4		**2a**		57
	1e		**3p**	

[a] Reaction conditions: **1** (1.0 equiv), **2a** (2.5 equiv), $Pd(OAc)_2$ (5 mol %), P(*t*Bu)$_3$ (15 mol %), K_2CO_3 (3 equiv), M.S. 3 Å, toluene 125 °C (1.0 M), 16−20 h. [b] Yield of isolated product. [c] Yield in parentheses is that of the pyridine or isoquinoline obtained after cleavage of the *N*−*N* bond using MeI, acetone, 75 °C then Zn (dust), AcOH, room temp. [d] Run using 1.5 equiv of **1c**, 1.0 equiv of **2a** and 0.3 M concentration.

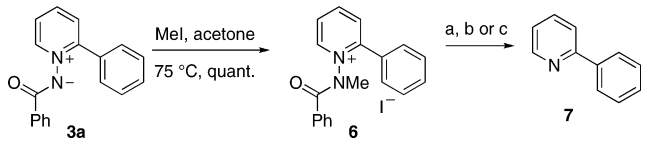
Scheme 1. Functionalization of 2-Heteroarylsubstituted Pyridinium Ylides and the Synthesis of (±)-Anabasine·TFA[a]



4 **3l** **5**

[a] Reagents and conditions: (a) MeMgBr, CH_2Cl_2; (b) O_2, TFA, CH_2Cl_2 (45%, two steps); (c) H_2, 300 psi, PtO_2 (9 mol %), MeOH (87%); (d) SmI_2, HMPA, THF, 0 °C; $(Boc)_2O$, NaOH, room temp (84%); (e) TFA, CH_2Cl_2 (quantitative).

Scheme 2. Reductive Cleavage of the *N*−*N* Bond[a]



3a **6** **7**

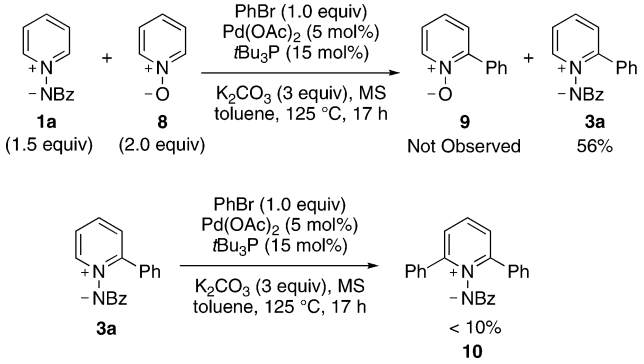
[a] Reagents and conditions: (a) Zn (dust), AcOH, room temp (80%); (b) HCO_2NH_4, Pt/C, MeOH, 80 °C (83%); (c) TMS_3SiH, AIBN, toluene, 80 °C (85%).

chemoselective hydrogenation of ylide **3l** followed by a one-pot SmI_2 reduction of the *N*−*N* bond and in situ Boc protection afforded *N*-protected anabasine in 61% yield over three steps. TFA treatment resulted in (±)-anabasine·TFA (**5**) in quantitative yield.[11]

It is also possible to reductively cleave the *N*−*N* bond to afford a 2-substituted *N*-heteroarene derivative (Scheme 2). The methylation of ylide **3a** afforded pyridinium salt **6** in quantitative yield.[12] Direct treatment of **6** either with zinc dust in acetic acid,[12] with ammonium formate in the presence of platinum on carbon[12] or with tris(trimethylsilyl)silane and AIBN[13] led to **7** in excellent yields. Some other representative cleavage yields are shown in Table 2 (entries 1 and 3) and Table 3 (entries 2 and 3).

To gain further insight about the mechanism of this reaction we directly compare the reactivity of the *N*-iminopyridinium ylide **1a** with that of the pyridinium *N*-oxide, a substrate that is also known

Scheme 3. Competition Experiments and Attempted Arylation of **3a**



to give efficient C−H arylation under palladium catalysis.[8b] In the latter case, however, 4 equiv of the *N*-oxide must be used to minimize the formation of the 2,6-diarylated product. We conducted a reaction with 2 equiv of pyridine *N*-oxide (**8**), 1.5 equiv of *N*-iminopyridinium ylide **1a**, and 1 equiv of bromobenzene (**2a**) (eq 1). Surprisingly, no *N*-oxide arylated product **9** could be detected and 2-phenyl-*N*-benzoyliminopyridinium ylide was obtained in 56% yield. We believe that the amide functionality of the pyridinium ylide acts as a strong Lewis base (stronger than the *N*-oxide) to direct the C−H insertion reaction at the 2-position. The minimal formation of the 2,6-diarylated product **10** when **1a** was used as starting material was also confirmed by the fact that the arylation of **3a** with bromobenzene proceeded very slowly under the standard reaction conditions (Scheme 3).

This observation is consistent with a decrease in the accessibility of the Lewis base for steric reasons in **3a** relative to **1a**. Upon the 2-substitution, the carbonyl group that is pointing above the pyridinium ring becomes significantly less accessible for complexation with palladium.

In conclusion, we have developed a new method for the functionalization of *N*-iminopyridinium ylides with various aryl and heteroaryl bromides. Furthermore, we have demonstrated that it is possible to chemoselectively functionalize the ylide heterocycle in the presence of pyridine. Further applications of this approach to the preparation of 2-substituted piperidines will be reported in due course.

Acknowledgment. This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), Merck Frosst Canada Ltd., Boehringer Ingelheim (Canada), Ltd., the Canada Research Chairs Program, the Canadian Foundation for Innovation, and the Université de Montréal. We thank Prof. Keith Fagnou (Univ. of Ottawa) for useful discussions.

Supporting Information Available: Experimental procedures, sample spectra and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA710073N