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Palladium-Catalyzed Benzylic C–H Insertion of 2-Substituted *N*-Iminopyridinium Ylides

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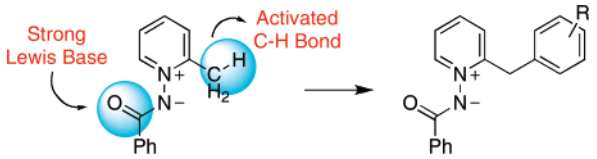
ABSTRACT



Palladium-catalyzed direct benzylic C–H arylation of 2-alkyl substituted *N*-iminopyridinium ylides is described. The insertion can be conducted with several electron-poor and electron-rich aryl chlorides in good yields. This work adds to the few examples of sp^3 C–H insertions that have been reported so far.

Pyridine derivatives are found in many bioactive molecules,[1] pharmaceuticals,[2] organic materials,[3] and ligands[4] used in various catalytic chemical transformations. In addition, our group has shown that pyridines can be readily converted into polysubstituted and enantioenriched piperidines,[5,6] which also exhibit important biological properties.[7] This was achieved by converting pyridine to a pyridinium ylide (via amination of pyridine, Figure 1, A) and subjecting these activated substrates to various reaction conditions (Figure 1, C).[5,6] Although this is an effective method for generating piperidines, the reaction is limited by the unavailability of more substituted pyridine starting materials. Recently, we have addressed this issue by exploiting the Lewis basic *N*-iminobenzoyl moiety of the ylide by using it as a directing group[8] for the direct arylation at the 2-position of the pyridinium substrate (Figure 1, B).[9] This gave access to a wide range of substituted pyridinium ylides, which can be easily converted into the corresponding pyridines (Figure 1, E)[9] or into highly functionalized piperidines (Figure 1, D).[10]

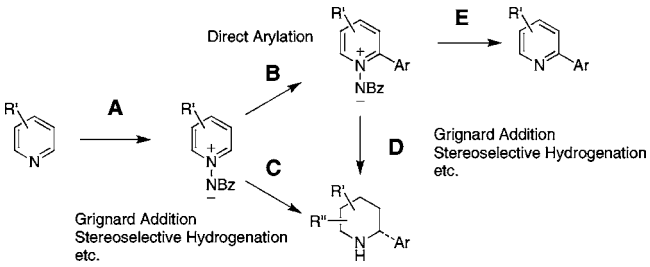


Figure 1. Scope of reactivity of pyridinium substrates.

(1) Borivoj, J.; Elving, P. J. *Chem. Rev.* **1968**, *68*, 295.
(2) (a) Laird, T. *Org. Process Res. Dev.* **2006**, *10*, 851. (b) Yurovskaya, M. A.; Karchava, A. V. *Chem. Heterocycl. Compd.* **1994**, *30*, 1331.
(3) (a) Baxter, P. N. W.; Lehn, J.-M.; Fischer, J.; Youinou, M.-T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2284. (b) Lehn, J.-M. *Science* **2002**, *295*, 2400.
(4) (a) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119. (b) Gibson, V. C.; Redshaw, C.; Solen, G. A. *Chem. Rev.* **2007**, *107*, 1745.
(5) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360.
(6) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966.
(7) For recent reviews on the stereoselective synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Felpin, F.−X.; Lebreton, J. M. *Eur. J. Org. Chem.* **2003**, 3693. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953.
(8) For an example of palladation of pyridinium ylides, see: Dias, S. A.; Downs, A. W.; McWhinnie, W. R. *J. Chem. Soc., Dalton Trans.* **1975**, 162.
(9) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.
(10) This approach has been used in the total synthesis of (±)-anabasine. See ref 9 for details.

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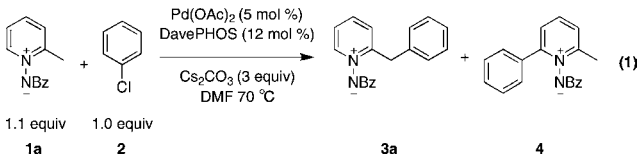
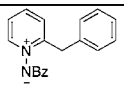
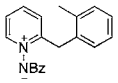
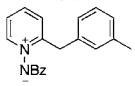
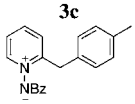
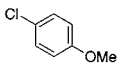
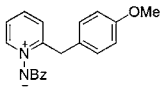
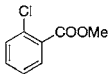
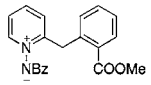
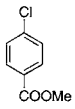
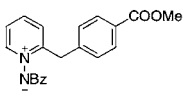
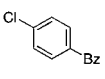
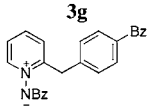
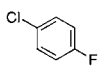
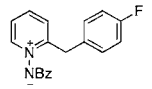
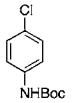
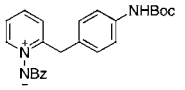
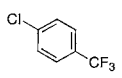
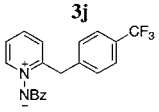
During the course of our work on the direct arylation reactions of these pyridinium ylides,[9] we discovered that a methyl group at the 2-position led to a marked decrease in the yield for the formation of the expected product **4**. Interestingly, we observed arylation on the benzylic methyl group as the major product, in a 2.7:1 ratio with the sp^2 arylation product (**3a**:**4**). Although direct arylation reactions on sp^2 centers are relatively well-known,[11] little has been reported about the direct arylation of sp^3 centers. The functionalization of sp^3 C−H bonds remains a challenge in organic synthesis.[12] Herein, we report the optimization and scope of the selective arylation of the benzylic carbon of 2-alkyl substituted *N*-iminopyridinium ylides, underlining another novel reactivity of these ylides giving more functionalized pyridines.



Several phosphine ligands were screened and DavePHOS proved to be the most effective.[13] Dimethylformamide (DMF) was the optimal solvent. It was found, as with sp^2 arylation, that carbonate bases were required and subsequently Cs_2CO_3 gave the best yields. At 125 °C, the reaction was found to work equally well with aryl bromides and aryl chlorides, whereas aryl iodides gave slightly poorer results. The reaction temperature using aryl chlorides could be lowered to 70 °C without a significant effect on the yield. Indeed, it was found that at 70 °C the results with aryl iodides were improved, although aryl chlorides remained the best substrates. In addition, under the optimized conditions no sp^2 arylation was observed via NMR.

The scope of the reaction was next investigated using various aryl chlorides (Table 1). Under the optimized reaction conditions [**1a** (1.1 equiv), $Pd(OAc)_2$ (5 mol %), DavePHOS (12 mol %), Cs_2CO_3 (3 equiv), DMF, 70 °C] chlorobenzene (1 equiv), afforded the 2-benzyl-*N*-iminopyridinium ylide **1a** in 86% isolated yield. Both electron-rich (entries 2−5) and most electron-poor (entries 6−11) substrates are compatible under the reaction conditions. 2-Chlorotoluene (**2b**) gave a good yield of the arylated product showing that sterically hindered aryl chlorides do not inhibit the reaction. However, lower yields are observed with an electron-withdrawing substituent ortho to the halide (entry 6). The lower yields are attributed to unreacted starting material and not side

Table 1. Palladium-Catalyzed sp^3 Arylation of *N*-Iminopyridinium Ylide with Aryl Chloride Derivatives[a]

entry	ylide	aryl chloride	product	yield (%)[a,b]
1	 **1a**	 **2a**	 **3a**	86
2	**1a**	 **2b**	 **3b**	93
3	**1a**	 **2c**	 **3c**	76
4	**1a**	 **2d**	 **3d**	72
5	**1a**	 **2e**	 **3e**	69
6	**1a**	 **2f**	 **3f**	43
7	**1a**	 **2g**	 **3g**	72
8	**1a**	 **2h**	 **3h**	71
9	**1a**	 **2i**	 **3i**	94
10	**1a**	 **2j**	 **3j**	48
11	**1a**	 **2k**	 **3k**	64

[a] Reaction conditions: **1a** (1.1 equiv), **2** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), DavePHOS (12 mol %), Cs_2CO_3 (3 equiv), DMF (0.8 M), 70 °C, 16 h. [b] Yield of isolated product.

(11) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Ellman, J. *Science* **2007**, *316*, 1131. (c) Seregin, I. Y.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) LeClerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (e) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (f) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (g) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625. (h) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (i) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (j) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.

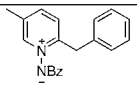
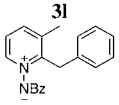
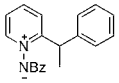
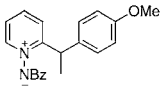
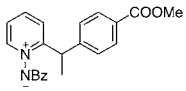
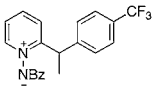
(12) For selected examples of sp^3 arylation, see: (a) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (b) Niwa, T.; Yorimitsu, H.; Oshiwa, K. *Org. Lett.* **2007**, *9*, 2373. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643. (e) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Sanders, L. B.; Yu, J.-Q. *J. Am Chem. Soc.* **2007**, *129*, 3510. (f) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (g) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (h) Chen, X.; Goodhue, G. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (i) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (j) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (k) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (l) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (m) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

(13) See Supporting Information for selected optimization.

products. In addition, no sp^2 arylation was observed in any case.

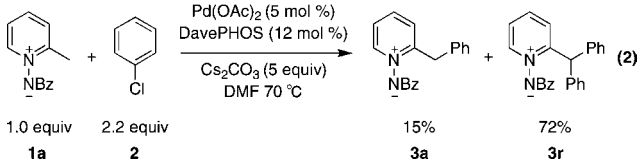
We next explored the scope of the 2-substituted *N*-iminopyridinium ylide coupling partner **1** (Table 2). Although the 2,3- and 2,5-dimethyl pyridines are electronically equivalent, the 2,3-dimethyl substrate resulted in significantly higher yield of product. This was surprising due to the extra steric encumbrance of the 2,3-dimethyl substrate. Furthermore, 2-ethyl pyridinium ylides were found to undergo selective arylation at the benzylic position in good yields, again with no noticeable arylation at the sp^2 center. This can be reasoned due to the higher relative acidity of these benzylic protons as well as the kinetic preference for the formation a 5-membered palladacycle intermediate involving the ylide nitrogen during the course of the reaction.

Table 2. Arylation of Other *N*-Iminopyridinium Ylides[a]

entry	ylide	aryl chloride	product	yield (%)[a,b]
1	 **1b**	**2a**	 **3l**	43
2	 **1c**	**2a**	 **3m**	92
3	 **1d**	**2a**	 **3n**	86
4	**1d**	**2e**	 **3o**	79
5	**1d**	**2g**	 **3p**	53
6	**1d**	**2l**	 **3q**	69

[a] Reaction conditions: **1a** (1.1 equiv), **2** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), DavePHOS (12 mol %), Cs_2CO_3 (3 equiv), DMF (0.8 M), 70 °C, 16 h. [b] Yield of isolated product.

It was also possible to arylate twice at the sp^3 center.[14] Upon the addition of 2.2 equiv of chlorobenzene the di-sp^3 arylated product was obtained in 72% yield.



In conclusion, we have developed a new method for the selective sp^3 arylation of 2-substituted-*N*-iminopyridinium ylides with various aryl chlorides. This further demonstrates the synthetic use of these pyridinium ylides. Applications and mechanistic insights to the novel sp^3 C−H insertion will be reported in due course.

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

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(14) The di-arylated product is formed as a side-product in some cases.