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Nickel-Catalyzed Reaction of Arylzinc Reagents with N-Aromatic Heterocycles: A Straightforward Approach to C−H Bond Arylation of Electron-Deficient Heteroaromatic Compounds

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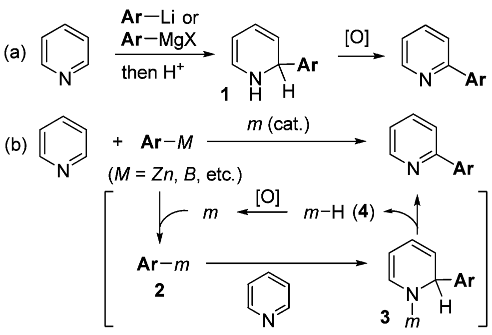
The catalytic direct arylation of aromatic C−H bonds has emerged as an atom-efficient alternative to conventional cross-coupling between halides and organometallics for the synthesis of (hetero)biaryls.[1] Despite significant advancement in this method, C−H bonds in electron-deficient heteroaromatics, such as pyridines and quinolines, are often not directly applicable.[2−5] This serious limitation of the C−H bond arylation reactions stems from the fact that the vast majority of them depend on either electrophilic substitution or concerted metalation/deprotonation mechanisms,[6] which inherently restricts the substrates to electron-rich or acidic C−H bonds, respectively. We report herein an alternate approach to catalytic C−H bond arylation that is suitable for electron-deficient heteroaromatics.

It has long been known that aryllithium and -magnesium reagents add to pyridines in a 1,2 fashion to afford dihydropyridines **1** after aqueous workup (Scheme 1a). Oxidation of **1** finally furnishes 2-arylpyridines in low to moderate yields.[7] This dearomatizing 1,2-addition/oxidation approach would be a potentially useful complement to the direct arylation methods if the reaction could meet the following criteria: (1) the use of a milder arylating agent, such as arylzinc or boron compounds and (2) a one-pot operation without the need for the isolation of the unstable dyhydropyridines **1**. We envisioned a simplified working catalytic cycle that addresses the above issues (Scheme 1b). The arylmetal species **2** is initially generated via transmetalation from mild arylating agents. The 1,2-addition of **2** across a pyridine affords dihydropyridine intermediate **3**, which aromatizes to provide the 2-arylpyridine via β-hydrogen elimination. The resultant metal hydride **4** is finally oxidized to regenerate the catalyst.

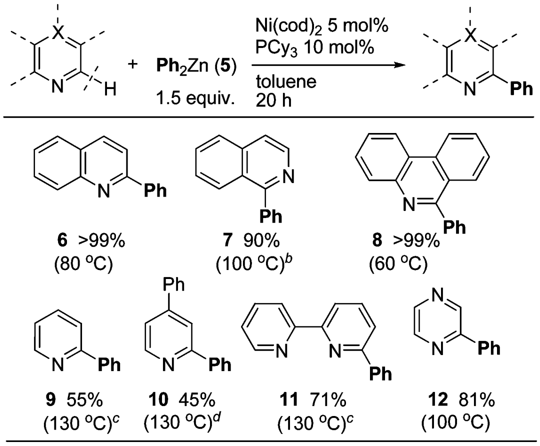
Scheme 1. Dearomatizing 1,2-Addition/Oxidation Strategy for Arylation of Electron-Deficient Heteroaromatics



The key to establishing the catalytic process shown in Scheme 1b is the identification of two elements: (1) a catalyst that promotes the unprecedented 1,2-addition of mild arylating agents toward pyridines and (2) an oxidant that accommodates the hydride derived from **3** without inducing undesired reactions, such as oxidative dimerization of the arylating agent.[8]

We initiated our study by investigating the reaction of quinoline with several arylating agents in the presence of an array of catalysts and oxidants. As a result, we discovered that the use of diphenylzinc (**5**) as an aryl donor furnished the desired 2-arylated product **6** in the absence of an additional oxidant. Although several transition-metal complexes exhibited catalytic activity, $Ni(cod)_2/PCy_3$ proved to be an optimal catalyst to afford **6** quantitatively (Table 1).[9]

Table 1. Ni-Catalyzed Arylation of N-Aromatic Heterocycles with **5**[a]



[a] Reaction conditions: N-aromatic heterocycle (0.25 mmol), **5** (0.375 mmol), $Ni(cod)_2$ (0.0125 mmol), and PCy_3 (0.025 mmol) in toluene (1.0 mL) for 20 h. Isolated yields based on the N-heterocycles are shown. [b] Using 0.50 mmol of **5**. [c] Using 0.75 mmol of **5**. [d] Using PPh_3 instead of PCy_3.

To probe the generality of this catalytic arylation, we next examined the reaction of various N-aromatic heterocycles. Isoquinoline, which contains two possible sites for 1,2-addition, underwent arylation under our catalytic conditions to afford 1-phenylisoquinoline (**7**) in excellent yield and regioselectivity.[7b] The arylation of a N-heterocycle containing an extended π system proceeded even at a lower temperature to form **8**. As expected on the basis of the reactivity trend in the 1,2-addition of organolithium to N-aromatics,[7a] harsher reaction conditions were required to obtain 2-arylated products **9** and **10** from pyridines. Interestingly, 2,2′-bipyridine, which is a good chelating ligand for transition-metal complexes, did not interfere with the catalysis and efficiently and selectively afforded the monoarylated product **11** even in the presence of an excess amount of **5**.[7c] Pyrazine served as a suitable substrate for the catalytic arylation reaction to furnish monoarylated product **12**.

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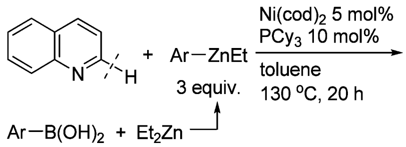
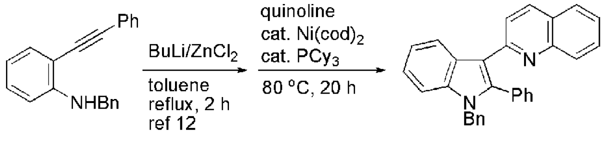
Table 2. Ni-Catalyzed Arylation of Quinoline with Various Arylzincs[a]



entry	Ar	yield (%)[b]	entry	Ar	yield (%)[b]
1	phenyl	73	4	4-(MeO)C_6H_4	97
2	3,5-$Me_2C_6H_3$	71	5	4-(Me_2N)C_6H_4	93
3	2-naphthyl	56	6	3-Cl-5-(MeO)C_6H_3	51

[a] Reaction conditions: ArB(OH)$_2$ (0.75 mmol) and ZnEt$_2$ (1.05 mmol) in dioxane (0.5 mL) at 60 °C for 12 h; quinoline (0.25 mmol), Ni(cod)$_2$ (0.0125 mmol), and PCy$_3$ (0.025 mmol) in toluene (1.0 mL) at 130 °C for 20 h. [b] Isolated yield based on quinoline.

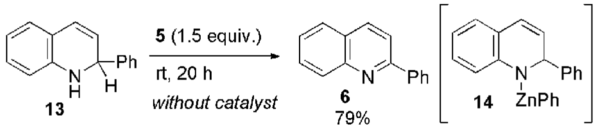
We next turned our attention to the scope of arylzinc reagents. After extensive studies,[10] arylzinc reagents prepared by treatment of readily available arylboronic acids with diethylzinc proved to be effective aryl donors in this Ni-catalyzed reaction (Table 2).[11] Although the reactions required higher temperatures than those using **5**, an array of aryl groups could be introduced through this procedure. Functional groups such as ethers (entry 4), amines (entry 5), and chlorides (entry 6) were tolerated under these conditions. Moreover, heteroarylzinc reagents prepared by Nakamura's procedure[12] could also be employed, further demonstrating the utility of this catalytic arylation (eq 1).



(1)

83% overall yield

Although a complete picture of the catalytic cycle remains elusive, several observations are worth noting. First, treatment of dihydroquinoline **13** with **5** afforded **6**, presumably via zinc amide **14**,[13] *even in the absence of a nickel catalyst at room temperature* (eq 2):



(2)

This finding suggests that the arylation is initiated by the nickel-catalyzed dearomatizing 1,2-addition of an arylnickel species,[14] as proposed in Scheme 1b. However, the subsequent aromatization event is more likely to occur via a zinc amide species similar to **14**, which can be formed under the catalytic conditions via transmetalation between nickel amide **3** (m = Ni) and **5** rather than β-hydrogen elimination of **3** (m = Ni). Alternatively, zinc amide **14** could also be generated by the reaction of **5** with an azanickelacyclopropane intermediate, which can be formed via coordination of the C=N bond in quinoline to a nickel center.[15] Second, a deuterium substituted at the 2-position of quinoline is finally incorporated into one of the phenyl groups in **5** to form deuteriobenzene, as was confirmed by ^{2}H NMR measurements of the arylation reaction of deuterated quinoline (see eq S1 in the Supporting Information). This observation indicates that **5** functions as both an aryl donor and an oxidant.[16]

In conclusion, we have developed a catalytic 1,2-addition-based approach to the arylation of electron-deficient heteroaryls, which are notoriously poor substrates in catalytic direct arylation reactions. Additional scope and mechanistic studies are ongoing.

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

References

(1) Reviews published after 2008: (a) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.*, in press.

(2) A notable exception: (a) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926. Intramolecular coupling: (b) Basolo, L.; Beccali, E. M.; Borsini, E.; Broggini, G. *Tetrahedron* **2009**, *65*, 3486.

(3) Several transformations other than arylation via catalytic C−H bond activation of pyridines have been reported. Carbonylation: (a) Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888. Alkenylation: (b) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720. (c) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. Alkylation: (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. Borylation: (e) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649. Dimerization: (f) Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* **2007**, *129*, 11006.

(4) The use of N-activated pyridines, such as *N*-oxides, provides a partial solution to this issue. For leading references, see: (a) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) 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.

(5) An approach based on the radical process has also been reported, although it is still in its infancy from the synthetic point of view. For leading examples, see: (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (b) Li, M.; Hua, R. *Tetrahedron Lett.* **2009**, *50*, 1478. (c) Kobayashi, O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009**, *11*, 2679.

(6) For a comprehensive discussion of these two mechanisms, see: (a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(7) (a) Boulton, A. J.; McKillop, A. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 2, pp 262−270. (b) Geissman, T. A.; Schlatter, M. J.; Webb, I. D.; Roberts, J. D. *J. Org. Chem.* **1946**, *11*, 741. (c) Pijper, P. J.; van der Goot, H.; Timmerman, H.; Nauta, W. T. *Eur. J. Med. Chem.* **1984**, *19*, 399. (d) Goldstein, S. W.; Dambek, P. *Synthesis* **1989**, 221.

(8) For example, see: (a) ArB(OH)$_2$: Yamamoto, Y. *Synlett* **2007**, 1913. (b) ArZnX: Hossain, K. M.; Kameyama, T.; Shibata, T.; Takagi, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2415.

(9) Yields with other metal complexes in place of Ni(cod)$_2$ in the reaction of quinoline with **5**: Pd(OAc)$_2$, 15%; Cu(OTf)$_2$, 16%; [RhCl(cod)]$_2$, 38%; none, 0%. See the Supporting Information for complete data from the screening of arylating agents, oxidants, catalysts, and ligands.

(10) The reaction is sensitive to the contaminated metal salts, as is often encountered in the reaction using organozinc reagents (see the Supporting Information).

(11) Among several protocols, the following one afforded the highest yields: Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645.

(12) (a) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944. (b) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803.

(13) Zinc amides formed by the reaction of diorganozinc and chelating diamines have been characterized: Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2005**, *24*, 4116.

(14) Although the exact structure of the arylnickel species remains to be clarified, one possibility is a nickelate complex. For a proposal of a similar nickelate complex, see: Terao, J.; Nii, S.; Chowdhury, F. A.; Nakamura, A.; Kambe, N. *Adv. Synth. Catal.* **2004**, *346*, 905.

(15) For a proposal of azanickelacyclopropanes from imines, see: Ohashi, M.; Kishizaki, O.; Ikeda, H.; Ogoshi, S. *J. Am. Chem. Soc.* **2009**, *131*, 9161.

(16) In the catalytic arylation reactions and the reaction shown in eq 2, metallic precipitates were observed upon completion of the reactions. The metallic precipitates dissolved with gas evolution upon addition of aqueous HCl. On the basis of these observations, we currently believe that **5** is finally reduced to metallic Zn(0).

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