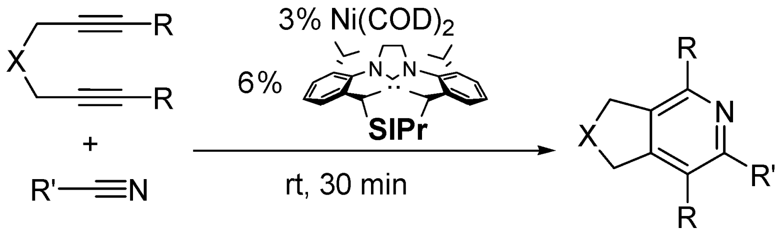
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

A Nickel-Catalyzed Route to Pyridines

Michael M. McCormick, Hung A. Duong, Gang Zuo, and Janis Louie

J. Am. Chem. Soc., **2005**, 127 (14), 5030-5031• DOI: 10.1021/ja0508931 • Publication Date (Web): 19 March 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

A Nickel-Catalyzed Route to Pyridines

Michael M. McCormick, Hung A. Duong, Gang Zuo, and Janis Louie*

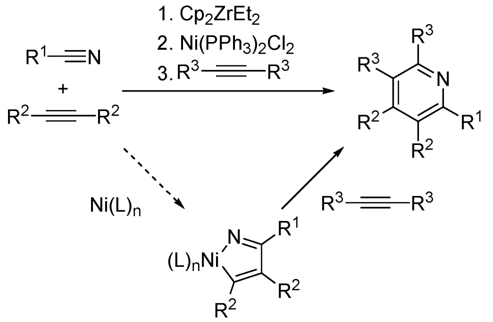
Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112-0850

Received February 11, 2005; E-mail: louie@chem.utah.edu

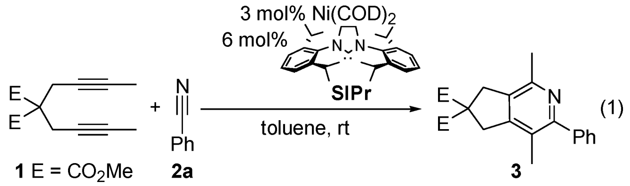
The ubiquity of pyridine rings in natural and synthetic pharmaceutical compounds has been a driving force for developing generalized methods for their synthesis. A particularly straightforward protocol is the transition metal mediated cycloaddition of alkynes and nitriles. Although a variety of stoichiometric methods have been described,[1,2] catalytic systems have been restricted to Fe, Rh, Co, and Ru complexes.[3] Unfortunately, both the Fe and Rh systems use elevated temperatures and afford more arene byproducts than the desired pyridine.[4] The versatility of Co catalysts makes an attractive approach to pyridines; however, elevated temperatures, photolytic conditions, and relatively high catalyst loadings are typically required.[5,6] In general, milder conditions are employed with Ru catalysts.[7] Nevertheless, substrates are currently limited to activated nitriles (e.g., dicyanides).

Ni complexes catalyze a variety of cycloaddition reactions,[8] yet a Ni-catalyzed route to pyridines remains elusive, which may be due to an inability to generate a nickelapyrrole intermediate through the oxidative coupling of alkynes and nitriles.[9] Interestingly, the requisite nickelacycle can be prepared via transmetalation between an azazirconapyrrole and $Ni(PPh_3)_2Cl_2$ (Scheme 1).[2] Subsequent addition of alkynes does ultimately afford asymmetrically substituted pyridines, albeit through the use of stoichiometric amounts of both Ni and Zr.

Scheme 1. Stoichiometric Protocol for Pyridine Synthesis via Nickelapyrrole Intermediate



We have recently developed a general Ni/NHC (NHC = N-heterocyclic carbene) based catalyst system for the cycloaddition of diynes and carbonyl substrates (CO_2,[10] isocyanates,[11] and aldehydes[12]). We surmised that this combination may be nucleophilic enough to promote oxidative coupling of an alkyne and nitrile such that products possessing a pyridine ring could be obtained catalytically. At the onset of this research, it was not clear whether cycloaddition or carbocyanation[13] of the alkyne would occur. Furthermore, it was possible that the active Ni/NHC catalyst would be incompatible with good donor ligands, such as nitriles[14] and pyridines.[15] We now report that the combination of Ni/SIPr effectively catalyzes the cycloaddition of diynes and nitriles *at ambient temperature* to afford pyridines in excellent yields.

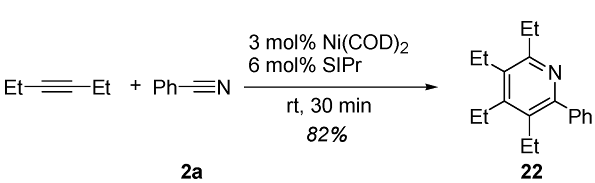


(1)

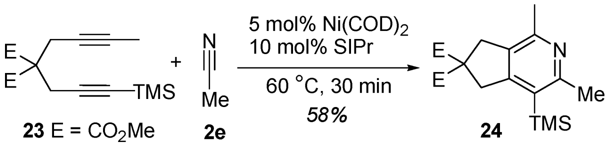
A variety of conditions were evaluated using diyne **1** and benzonitrile (**2a**) as model substrates for the cycloaddition reaction (eq 1). Ultimately, a protocol similar to the one found effective for our previous cycloadditions afforded pyridine **3**.[10−12] Excellent yields (as determined using gas chromatography) were obtained using 3% of $Ni(COD)_2$, 6% of SIPr,[16] and diyne and nitrile concentrations of 0.1 M in toluene at ambient temperature (eq 1).

With the optimized cycloaddition conditions at hand, we examined pyridine formation with a range of diyne and nitrile substrates (Table 1). In general, both aryl- and alkylnitriles were readily converted to the respective pyridine, although alkylnitriles gave slightly diminished yields. Both arylnitriles bearing either an electron-withdrawing group (*p*-CF_3, **2c**) or an electron-donating group (*p*-OMe, **2b**) readily cyclized (entries 2 and 3, respectively).[17] Notably, sterically hindered nitriles [such as *o*-tolunitrile (**2d**), *tert*-butyl nitrile (**2g**), and naphthalene-1-carbonitrile (**2h**)] delivered the desired pyridines (entries 4, 7, and 8, respectively). Pyridine yield was unaffected when degassed, but not dried, acetonitrile was employed (entry 5). Diynes devoid of internal substitution, such as 3,9-dodecadiyne (**12**) and diynes containing either an internal amino group (**15**) or the analogous ether (**17**), also coupled with nitriles to give pyridines (entries 10−14). Importantly, heteroarylnitriles are readily converted to pyridines in high yields (entry 9).[18] In addition, the reaction of 2,9-undecadiyne (**20**) afforded fused seven-membered ring pyridine **21** after cycloaddition (entry 15).

We also investigated pyridine synthesis from the cycloaddition of an untethered alkyne. Subjecting 3-hexyne (2 equiv) and benzonitrile (**2a**) to the optimized conditions described above (3% of catalyst, rt) afforded pyridine **22** in 82% yield (eq 2).[19]



(2)

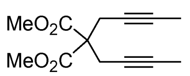
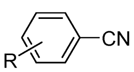
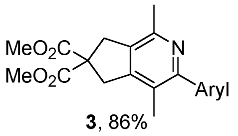
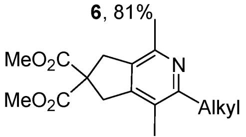
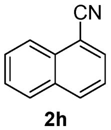
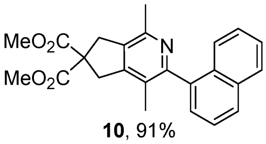
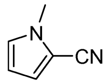
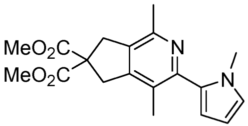
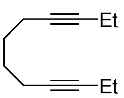
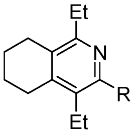
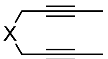
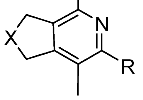
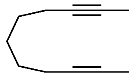
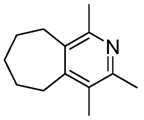


(3)

Previously, when asymmetrically substituted diynes were used in our Ni/NHC-catalyzed cycloaddition reaction, complete regioselectivity was observed when the size difference between terminal substituents was large.[10b] In accordance with these observations, the coupling of diyne **23** and benzonitrile (**2a**) afforded pyridine

10.1021/ja0508931 CCC: $30.25 © 2005 American Chemical Society

Table 1. Ni-Catalyzed Cycloaddition of Diynes and Nitriles[a]

Entry	Diyne	Nitrile	Product, % Yield[b]
			
1	**1**	**2a** R = H	**3**, 86%
2		**2b** R = *p*-MeO	**4**, 64%
3		**2c** R = *p*-CF$_3$	**5**, 94%
4		**2d** R = *o*-Me	**6**, 81%
			
5	**1**	**2e** MeCN	**7**, 69% (69%)[c]
6	**1**	**2f** *i*-BuCN	**8**, 72%
7	**1**	**2g** *t*-BuCN	**9**, 56%
8	**1**	 **2h**	 **10**, 91%
9	**1**	 **2i**	 **11**, 97%
			
10	**12**	**2a**	**13** R = Ph, 92%
11	**12**	**2e**	**14** R = Me, 46%
			
12	**15** X = NTs	**2a**	**16** R = Ph, 78%
13	**17** X = O	**2a**	**18** R = Ph, 93%
14	**17** X = O	**2e**	**19** R = Me, 37%
15	 **20**	**2e**	 **21**, 29%

[a] Reaction conditions: 0.1 M diyne, 0.1 M nitrile, 3% of Ni(COD)$_2$, 6% of SIPr, rt. [b] Isolated yields (average of two runs). [c] Isolated yield of reaction with MeCN that was degassed, but not dried.

24 as a single regioisomer in 58% yield (eq 3). Initial oxidative coupling of the TMS-terminated alkyne and nitrile followed by insertion of the methyl-terminated alkyne explains the observed regioselectivity.

In conclusion, we have developed a mild and efficient method for preparing a wide range of pyridines from alkynes and nitriles. Both intramolecular and intermolecular reactions were catalyzed by a combination of a Ni(0) precursor and an imidazolylidene ligand. Furthermore, cycloaddition of an asymmetrical diyne afforded a single pyridine regioisomer.

Acknowledgment. We gratefully acknowledge the University of Utah, ACS (PRF Type G), and the NSF (Career Award) for support of this research.

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

References

(1) (a) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518. (b) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett.* **1995**, 851. (c) Hill, J. E.; Balaich, G.; Fanwich, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911. (d) Smith, D. P.; Strickler, J. R.; Gray, S. D.; Bruck, M. A.; Holmes, R. S.; Wigley, D. E. *Organometallics*, **1992**, *11*, 1275. (e) Bianchini, C.; Meli, A.; Peruzzini, M.; Vacca, A.; Vizza, F. *Organometallics* **1991**, *10*, 645.

(2) (a) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

(3) (a) Bönnenmann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248. (b) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(4) (a) Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291. (b) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U.; Floch, P. L.; Mathey, F. *Organometallics* **1996**, *15*, 2713.

(5) (a) Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 708. (b) Vollhardt, K. P. C. *Angew. Chem.* **1984**, *96*, 525.

(6) Milder reaction conditions can be employed with modified Co catalysts; however, these catalysts are not readily available. For example, the preparation involves purification by column chromatography under an inert atmosphere: Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131.

(7) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189.

(8) (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

(9) Eisch, J. J.; Ma, X.; Han, K. I.; Gitua, J. N.; Krüger, C. *Eur. J. Inorg. Chem.* **2001**, 77.

(10) (a) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. (b) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431.

(11) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438.

(12) Tekavec, T. N.; Louie, J. Unpublished results.

(13) Ni complexes readily undergo oxidative addition of both alkyl− and aryl−CN bonds. For example, Ni complexes catalyze the carbocyanation of alkynes: (a) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997. (b) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (c) Wilting, J.; Müller, C.; Hewat, A. C.; Ellis, D. D.; Tooke, D. M.; Spek, A. L.; Vogt, D. *Organometallics* **2005**, *24*, 13.

(14) Ni complexes are known to cause homodimerization of nitriles (see ref 9).

(15) Both SIPr and IPr ligands readily dissociate from Ni(0), even upon the addition of COD (see ref 10a).

(16) Unsaturated analogue IPr gave slightly lower conversion under identical reaction conditions (99% versus 66% for SIPr and IPr, respectively) (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene).

(17) This is in contrast to the Ni/NHC-catalyzed route to pyridones where electron-deficient isocyanates required elevated temperatures for complete cycloaddition (see ref 11).

(18) (a) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (b) Sarkar, T. K.; Basak, S.; Wainer, I.; Moaddel, R.; Yamaguchi, R.; Jozwiak, K.; Chen, H.-T.; Lin, C.-C. *J. Med. Chem.* **2004**, *47*, 6691.

(19) Cycloaddition with acetonitrile (**2e**) afforded 2,3,4,5-tetraethyl-6-methylpyridine (**25**) in 25% yield. See Supporting Information.

JA0508931