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COMMUNICATIONS

Published on Web 06/07/2006

Hydroheteroarylation of Alkynes under Mild Nickel Catalysis

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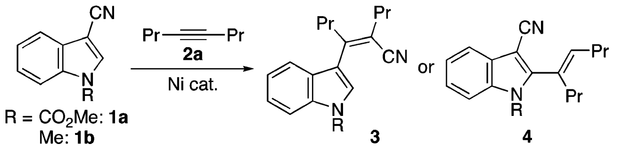
We report herein nickel-catalyzed activation of an Ar−H bond[1] of N-protected 3-cyanoindoles followed by addition reaction across alkynes to give **4** (eq 1), demonstrating divergent nickel catalysis[2] directed by a ligand and/or an N-protecting group. The observed catalysis has been extended to a wide range of heteroarenes and alkynes to give various heteroaryl-substituted ethenes highly chemo-, stereo-, and regioselectively under mild conditions.



(1)

As we have recently disclosed,[2a,b] the reaction of 3-cyano-1-methoxycarbonylindole (**1a**) with 4-octyne (**2a**) in the presence of Ni/PMe$_3$ catalyst in toluene at 100 °C gave the arylcyanation product **3aa** in 68% yield after 18 h (entry 1 of Table 1). We also isolated a small amount (6%) of (*E*)-3-cyano-1-methoxycarbonyl-2-(4-octen-4-yl)indole (**4aa**), which should be derived from the insertion of the alkyne into the Ar−H bond at the C-2 position of **1a**. On the other hand, the identical reaction but with tricyclopentylphosphine (PCyp$_3$) as a ligand instead of PMe$_3$ gave **4aa** in 16% yield together with 3% of **3aa**, the activation of the Ar−CN bond being preceded by that of the Ar−H bond (entry 2). With 3-cyano-1-methylindole (**1b**), the corresponding hydroarylation product **4ba** became dominant even under the Ni/PMe$_3$ catalysis (entry 3),[3] and the catalysis was found to be effective even at 35 °C by using PCyp$_3$ as a ligand to afford **4ba** in 95% yield.[4] It is worth noting that *the bond to be activated is controllable by choosing a ligand and/or an N-protecting group to induce a different catalysis of nickel*. Use of 1 mol % of the catalyst still worked well to give **4ba** in 88% yield, although the reaction took 96 h for completion (entry 5).

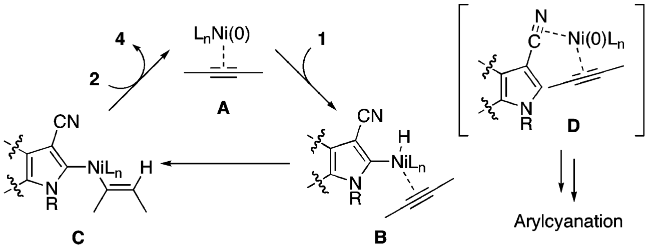
A catalytic cycle in Scheme 1 may be suggested that starts with alkyne-coordinating Ni(0) species **A**,[5] which subsequently undergoes oxidative addition of an Ar−H bond at the C-2 position to give alkyne-coordinating Ar−Ni(II)−H intermediate **B**, since the reaction proceeds best with heteroarenes having a rather acidic C−H bond (vide infra) adjacent to a heteroatom and an electron-rich nickel species as a catalyst.[6,7] Hydronickelation[8] would give aryl−Ni(II)−alkenyl intermediate **C**, which then would undergo reductive elimination to afford a *cis*-hydroarylation product **4** and regenerate Ni(0) species.[9] A bulky tri(*sec*-alkyl)phosphine ligand may retard requisite η^2-coordination of a cyano group[10] and/or the subsequent oxidative addition of the Ar−CN bond in cyano- and alkyne-coordinating Ni(0) species **D** due to a steric reason. Electron-donating substituents on the nitrogen atom would also slow the rate of the oxidative addition of the Ar−CN bond, making the hydroarylation catalysis a predominant pathway.[2a,b,10b]

Table 1. Nickel-Catalyzed Reactions of 3-Cyanoindoles with 4-Octyne (**2a**)[a]

entry	1	ligand	time (h)	conv. of 1 (%)[b]	yield of 3 (%)[c]	yield of 4 (%)[c]
1	**1a**	PMe$_3$	18	86	68 (**3aa**)	6 (**4aa**)
2	**1a**	PCyp$_3$	18	57	3 (**3aa**)	16 (**4aa**)[d]
3	**1b**	PMe$_3$	30	69	<3 (**3ba**)	35 (**4ba**)
4[e]	**1b**	PCyp$_3$	18	>95	<3 (**3ba**)	95 (**4ba**)
5[e,f]	**1b**	PCyp$_3$	96	>95	<3 (**3ba**)	88 (**4ba**)

[a] Reactions were carried out using **1** (1.0 mmol), **2a** (1.0 mmol), Ni(cod)$_2$ (0.10 mmol), and a ligand (PMe$_3$, 0.20 mmol; PCyp$_3$, 0.10 mmol) in toluene (2.5 mL) at 100 °C. [b] Based on recovered **1**. [c] Isolated yields. [d] *E*:*Z* = 91:9. [e] The reaction was carried out at 35 °C. [f] Ni(cod)$_2$ (0.010 mmol) and PCyp$_3$ (0.010 mmol) were used.

Scheme 1. Plausible Mechanism

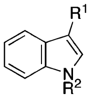
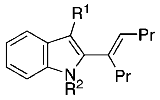
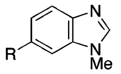
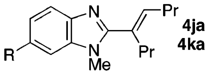
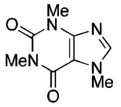
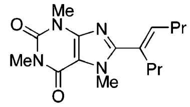
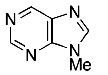
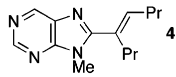
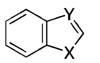
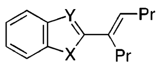
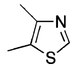
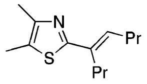
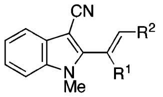


The catalysis is found to be effective for a wide range of heteroarenes (Table 2).[11] Methyl indole-3-carboxylates (**1c**−**1e**) reacted with **2a** in modest to good yields, irrespective of a substituent on nitrogen (entries 1−3). Indoles (**1f**−**1h**) having an electron-withdrawing functional group at the C-3 position all gave the corresponding hydroarylation products at 35 °C (entries 4−6), whereas 1-methyl-3-phenylindole (**1i**) required 100 °C to react with **2a** (entry 7). *The exclusive reaction of the Ar−H bond over the formyl C−H bond of **1g** is remarkable* in view of the fact that the latter is also activated to undergo addition across an alkyne under Ni/PBu$_3$ catalysis.[1b] Substituted imidazoles (entries 8−11) reacted exclusively at the C-2 position as well as benzofuran (**1n**) and benzothiophene (**1o**) (entries 12 and 13) *even in the presence of an Ar−Cl bond (entry 9) or other acidic C−H bonds (entry 11)*. Benzoxazole (**1p**) and 4,5-dimethylthiazole (**1q**) also participated in the reaction (entries 14 and 15). Unsymmetrical internal alkynes, 4-methyl-2-pentyne (**2b**), and silylacetylenes **2c** and **2d** all reacted with **1b** in excellent regioselectivities to give the adducts having a larger substituent *trans* to the aryl group (entries 16−18).[12,13]

In conclusion, we have demonstrated a divergent nickel catalysis on Ar−H versus Ar−CN activation and extended the catalysis to hydroheteroarylation[14] of alkynes under mild conditions. The present hydroheteroarylation is applicable to a diverse range of heteroarenes and alkynes to give various heteroaryl-substituted ethenes, versatile synthetic intermediates and/or targets of pharmaceuticals, natural products, and materials, highly chemo-, regio-, and stereoselectively, and thus would be complementary to well-established intermolecular hydroarylation reactions catalyzed by other transition metals.[7,9,15] Studies on the detailed mechanism and potential nickel catalysis on other C−H functionalizations[16,17] will be the subject of our future work.

10.1021/ja0623459 CCC: $33.50 © 2006 American Chemical Society

Table 2. Nickel-Catalyzed Hydroheteroarylation of Alkynes[a]

entry	heteroarene	alkyne	time (h)	product		yield (%)[b]
	 R^1, R^2 =					
1	CO_2Me, Me (**1c**)	**2a**	15		**4ca**	85
2	CO_2Me,CH_2Ph (**1d**)		15		**4da**	57
3[c]	CO_2Me,CH_2OMe (**1e**)		120		**4ea**	84
4	C(O)Me, Me (**1f**)		30		**4fa**	70
5	CHO, Me (**1g**)		6		**4ga**	91
6	(*E*)-CH=CHCO$_2$Me, Me (**1h**)		10		**4ha**	88
7[d]	Ph, Me (**1i**)		35		**4ia**	67
	 R =					
8	H (**1j**)	**2a**	12		**4ja**	92
9	Cl (**1k**)		10		**4ka**	80
10	 **1l**	**2a**	10		**4la**	94
11	 **1m**	**2a**	6		**4ma**	94
	 X, Y =					
12	O, CH (**1n**)	**2a**	6		**4na**	94
13	S, CH (**1o**)		24		**4oa**	47
14	O, N (**1p**)		8		**4pa**	89
15	 **1q**	**2a**	15		**4qa**	89
		$R^1-\!\!\equiv\!\!-R^2$ R^1, R^2 =				
16	**1b**	Me, *i*-Pr (**2b**)	6		**4bb**	97
17[e]		Me, $SiMe_3$ (**2c**)	40		**4bc**	74
18[f]		Ph, $SiMe_3$ (**2d**)	35		**4bd**	67

[a] Unless otherwise noted, all reactions were carried out using a heteroarene (1.0 mmol), an alkyne (1.0 mmol), Ni(cod)$_2$ (0.10 mmol), and PCyp$_3$ (0.10 mmol) in toluene (2.5 mL) at 35 °C. [b] Isolated yields based on the heteroarene. [c] The reaction was carried out at 50 °C using 4.0 mmol of **2a**. [d] The reaction was carried out at 100 °C using 3.0 mmol of **2a**. [e] The reaction was carried out at 50 °C. [f] The reaction was carried out at 100 °C using 2.0 mmol of **2d**.

Acknowledgment. This work has been supported financially by a Grant-in-Aid for Creative Scientific Research, No. 16GS0209, and COE Research on "United Approach to New Material Science" from MEXT.

Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For rare examples of stoichiometric and catalytic C−H activation by nickel, see: (a) Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544. (b) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554. (c) Brunkan, N. M.; Brestensky, D. M.; Jones, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 3627. (d) Clement, N. D.; Cavell, K. J.; Jones, C.; Elsevier, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1277. (e) Clement, N. D.; Cavell, K. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3845. (f) Ogoshi, S.; Ueta, M.; Oka, M.; Kurosawa, H. *Chem. Commun.* **2004**, 2732. (g) Keen, A. L.; Johnson, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 1806.

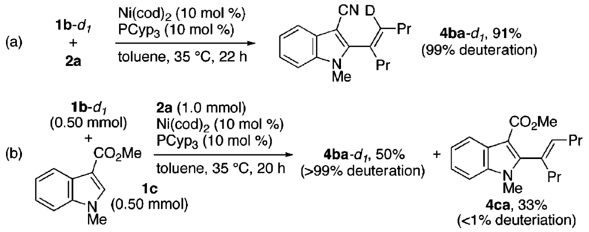
(2) For ligand-dependent divergent nickel catalysis on the reactions of benzonitrile with alkynes, see: (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904. (b) Nakao, Y.; Oda, S.; Yada, A.; Hiyama, T. *Tetrahedron*, in press. (c) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2004**, *127*, 13904.

(3) A stereochemically unidentified product derived from the insertion of two molecules of **2a** into the Ar−H bond at the C-2 position of **1b** was also obtained in 31% yield.

(4) Other bulky tri(*sec*-alkyl)phosphines, such as PCy$_3$ and P(*i*-Pr)$_3$, also gave comparable results (>90% yield estimated by GC), whereas P(*t*-Bu)$_3$ and PPh$_3$ were found totally ineffective for the present hydroarylation.

(5) Preliminary ^{31}P NMR studies show that PCyp$_3$ does not coordinate to the nickel center of Ni(cod)$_2$ in the absence of an alkyne; see also ref 1f.

(6) The following experiments could suggest that an electrophilic metalation pathway as a C−H activating step[7] would be unlikely. (a) The reaction of 3-cyano-2-deuterio-1-methylindole (**1b**-*d*$_1$) with **2a** gave the corresponding deuterated adduct **4ba**-*d*$_1$. (b) The reaction of an equimolar (0.50 mmol) mixture of **1b**-*d*$_1$ and methyl 1-methylindole-3-carboxylate (**1c**) with **2a** (1.0 mmol) under the identical conditions did not cause intermolecular deuterium crossover. (c) Nickel(II) complexes, such as Ni(acac)$_2$ and NiCl$_2$, failed to catalyze the reaction in the presence or absence of external bases, such as Et$_3$N and Cs$_2$CO$_3$.



(7) For *trans*-selective hydroarylations of alkynes via electrophilic metalation, see: (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518. (c) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440.

(8) Similar regiochemistry was also reported for hydronickelation of unsymmetrical alkynes; see entries 16−18 of Table 2 and refs 1b and 1f.

(9) For representative examples of *cis*-hydroarylation of alkynes via oxidative addition of an Ar−H bond at high temperature or under irradiation, see: (a) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1979**, 339. (b) Tokunaga, Y.; Sakakura, T.; Tanaka, M. *J. Mol. Catal.* **1989**, *56*, 305. (c) Aulwurm, U. R.; Melchinger, J. U.; Kisch, H. *Organometallics* **1995**, *14*, 3385. (d) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. (e) Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 615. (f) Kakiuchi, F.; Sato, T.; Igi, K.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 386. (g) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (h) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. The mechanism of *cis*-hydroarylation of alkynes catalyzed by dinuclear palladium complexes is unclear. See: (i) Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12102.

(10) (a) García, J. J.; Jones, W. D. *Organometallics* **2000**, *19*, 5544. (b) García, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547.

(11) At present, the following (hetero)arenes have failed to participate in the reaction: 4-(trifluoromethyl)benzonitrile, methyl 4-(trifluoromethyl)benzoate, ethyl 1-methylindole-2-carboxylate, 1-methylpyrrole, 1-methyl imidazole. Unsubstituted indoles gave a mixture of 2- and 3-alkenylated products.

(12) A similar reaction of **1g** with **2c** in the presence of a Ru(H)$_2$(CO)(PPh$_3$)$_3$ catalyst at 115 °C has been reported to give the corresponding adduct as a mixture of stereoisomers in 42% yield; see ref 9f.

(13) Terminal alkynes failed to give the corresponding adducts due to rapid background oligomerization of alkynes.

(14) For selected examples of related hydroheteroarylations of unsaturated bonds, see: (a) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, 507. (b) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. (c) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493. (d) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (e) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (f) Pittard, K. A.; Lee, J. P.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *Organometallics* **2004**, *23*, 5514. (g) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720. (h) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (i) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (j) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700. (k) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329. (l) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (m) Tsukada, N.; Murata, K.; Inoue, Y. *Tetrahedron Lett.* **2005**, *46*, 7515.

(15) For hydroarylation of alkynes via the Friedel−Crafts alkenylations, see: (a) Yamaguchi, M.; Kido, Y.; Hayashi, A.; Hirama, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1313. (b) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573. (c) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (d) Shi, Z.; He, S. *J. Org. Chem.* **2004**, *69*, 3669.

(16) For selected recent work on intermolecular transition-metal-catalyzed C−C bond formation of indoles via C−H activation, see: (a) Sawada, T.; Fuerst, D. E.; Wood, J. L. *Tetrahedron Lett*. **2003**, *44*, 4919. (b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (d) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc*. **2006**, *128*, 4972.

(17) For selected recent work on intermolecular transition-metal-catalyzed C−C bond formation of other heteroarenes via C−H activation, see: (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 4667. (b) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (c) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607. (d) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 2300. (e) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2005**, *70*, 3997. (f) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc*. **2005**, *127*, 18020. (g) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 581. (h) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589.

JA0623459