

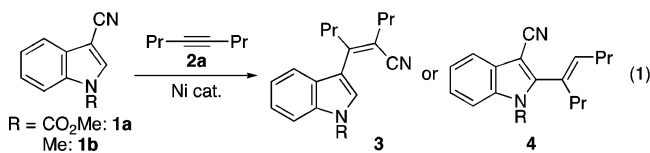
Hydroheteroarylation of Alkynes under Mild Nickel Catalysis

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We report herein nickel-catalyzed activation of an Ar–H bond¹ of N-protected 3-cyanoindoles followed by addition reaction across alkynes to give **4** (eq 1), demonstrating divergent nickel catalysis² 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.



As we have recently disclosed,^{2a,b} the reaction of 3-cyano-1-methoxycarbonylindole (**1a**) with 4-octyne (**2a**) in the presence of Ni/PMe₃ catalyst in toluene at 100 °C gave the arylation 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 (PCyp₃) as a ligand instead of PMe₃ 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/PMe₃ catalysis (entry 3),³ and the catalysis was found to be effective even at 35 °C by using PCyp₃ 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} Hydronickelation⁸ 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 η²-coordination of a cyano group¹⁰ 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}

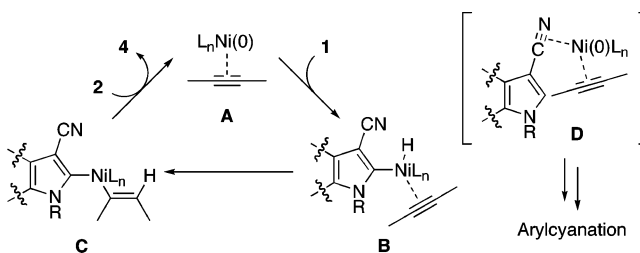
The catalysis is found to be effective for a wide range of heteroarenes (Table 2).¹¹ Methyl indole-3-carboxylates (**1c**–**1e**) reacted with **2a** in modest to good yields, irrespective of a

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 (PMe₃, 0.20 mmol; PCyp₃, 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 PCyp₃ (0.010 mmol) were used.

Scheme 1. Plausible Mechanism



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/PBu₃ 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 hydroheteroarylation¹⁴ 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.

Table 2. Nickel-Catalyzed Hydroheteroarylation of Alkynes^a

entry	heteroarene	alkyne	time (h)	product	yield (%) ^b	
1		R ¹ , R ² =				
2		CO ₂ Me, Me (1c)	2a	15		85
1		CO ₂ Me, CH ₂ Ph (1d)	2a	15		57
3 ^c		CO ₂ Me, CH ₂ OMe (1e)	2a	120		84
4		C(O)Me, Me (1f)	2a	30		70
5		CHO, Me (1g)	2a	6		91
6		(E)-CH=CHCO ₂ Me, Me (1h)	2a	10		88
7 ^d	Ph, Me (1i)	2a	35		67	
8		R =				
9		H (1j)	2a	12		92
		Cl (1k)	2a	10		80
10		2a	10		94	
11		2a	6		94	
12		X, Y =				
13		O, CH (1n)	2a	6		94
14		S, CH (1o)	2a	24		47
		O, N (1p)	8		89	
15		2a	15		89	
16		R ¹ ≡R ²				
17 ^e		Me, <i>i</i> -Pr (2b)	2a	6		97
18 ^f		Me, SiMe ₃ (2c)	2a	40		74
	Ph, SiMe ₃ (2d)	2a	35		67	

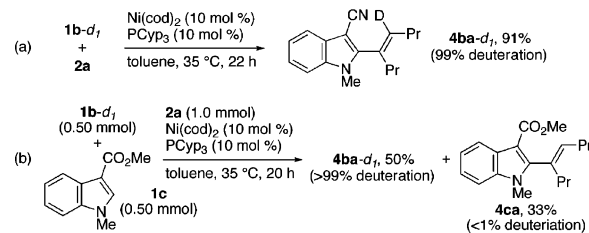
^a Unless otherwise noted, all reactions were carried out using a heteroarene (1.0 mmol), an alkyne (1.0 mmol), Ni(cod)₂ (0.10 mmol), and PCy₃ (0.10 mmol) in toluene (2.5 mL) at 35 °C. ^b Isolated yields based on the heteroarene. ^c The reaction was carried out at 50 °C using 4.0 mmol of **2a**. ^d The 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**.

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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>.

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- 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.
- Other bulky tri(*sec*-alkyl)phosphines, such as PCy₃ and P(*i*-Pr)₃, also gave comparable results (>90% yield estimated by GC), whereas P(*t*-Bu)₃ and PPh₃ were found totally ineffective for the present hydroarylation.
- Preliminary ³¹P NMR studies show that PCy₃ does not coordinate to the nickel center of Ni(cod)₂ in the absence of an alkyne; see also ref 1f.
- The following experiments could suggest that an electrophilic metalation pathway as a C–H activating step⁷ 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 NiCl₂, failed to catalyze the reaction in the presence or absence of external bases, such as Et₃N and Cs₂CO₃.



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- 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-methylimidazole. Unsubstituted indoles gave a mixture of 2- and 3-alkenylated products.
- A similar reaction of **1g** with **2c** in the presence of a Ru(H)₂(CO)(PPh₃)₃ catalyst at 115 °C has been reported to give the corresponding adduct as a mixture of stereoisomers in 42% yield; see ref 9f.
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