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PRACTICAL APPROACH FOR HYDROHETEROARYLATION OF ALKYNES USING BENCH-STABLE CATALYST

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Abstract - A simple and convenient method for hydroheteroarylation of alkynes using air- stable catalyst precursors is described. The addition of a solution of AlMe_3 in hexane to $\text{Ni}(\text{acac})_2$ and tri(cyclopentyl)phosphonium tetrafluoroborate ($[\text{Cyp}_3\text{PH}]\text{BF}_4$) rapidly generates an active $\text{Ni}(0)/\text{Cyp}_3\text{P}$ catalyst for *cis*-hydroheteroarylation of alkynes under mild conditions. The catalytic reaction is applicable to a wide range of heteroarenes to give heteroaryl-substituted ethenes in excellent stereo- and regioselectivities.

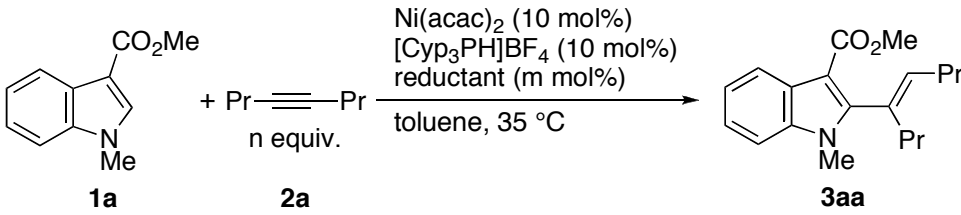
Recently, we reported a hydroheteroarylation reaction of alkynes under mild conditions in the presence of a catalyst prepared in situ from $\text{Ni}(\text{cod})_2$ and a tri(cyclopentyl)phosphine (Cyp_3P) ligand.¹ The reaction allows us to prepare a wide variety of heteroaryl-substituted ethenes in highly atom economical, regioselective, and stereoselective manners. However, the use of oxygen- and moisture-sensitive precursors for the catalysis requires a glove box technique to set up the reaction, and thus, has limited the application of this chemistry to practice. To increase the convenience and applicability of this methodology, we have explored the use of air-stable and readily available $\text{Ni}(0)$ precursors that generate the active $\text{Ni}(0)/\text{Cyp}_3\text{P}$ catalyst in situ as reported herein.

Using methyl 1-methylindole-3-carboxylate (**1a**) and 4-octyne (**2a**) as substrates, we first examined a suitable organometallic reagent which acts as a reductant and a base at the same time to convert air-stable $\text{Ni}(\text{acac})_2$ and $[\text{Cyp}_3\text{PH}]\text{BF}_4$ to a $\text{Ni}(0)$ species and Cyp_3P , respectively (Table 1).^{2,3} Whereas the Louie's protocol,^{4a} namely, a combination of $\text{Ni}(\text{acac})_2$, $[\text{Cyp}_3\text{PH}]\text{BF}_4$ and *n*-BuLi resulted in poor conversion of **1a** and poor yield of the corresponding hydroheteroarylation product **3aa** (entry 1), the use of AlMe_3 and DIBAL-H instead of *n*-BuLi led to considerably fair conversion of **1a**, and **3aa** was produced in 55% and 64% yield as estimated by GC (entries 2 and 3).⁴ Further optimization revealed that at least 1.5 equivalents of **2a** was necessary to achieve excellent conversion of **1a** (entries 4 and 5).

This paper is dedicated to Professor Yoshito Kishi of Harvard University on the occasion of his 70th birthday.

Although the need of excess alkyne is not clear, it may stabilize a Ni(0) species produced in situ.⁵ The amount of DIBAL-H could be reduced to 30 mol% (entry 6), whereas a small excess of AlMe₃ was required to achieve sufficient conversion of **1a** (entry 7). Importantly, the new protocol developed herein works well with a standard Schlenck technique.

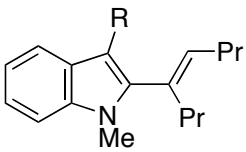
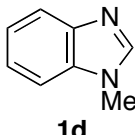
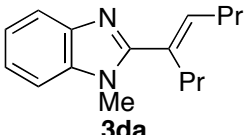
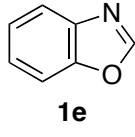
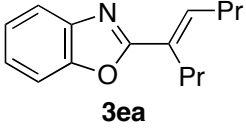
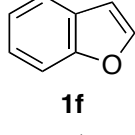
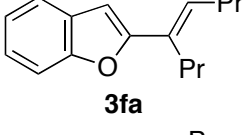
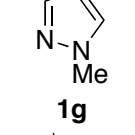
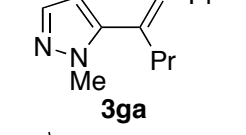
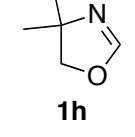
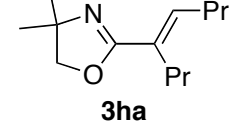
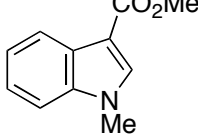
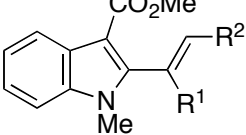
Table 1. Optimization of reductants for nickel-catalyzed hydroheteroarylation of 4-octyne (**2a**) with methyl 1-methylindole-3-carboxylate (**1a**).

					
entry	reductant (m)	n	time (h)	conv. of 1a (%) ^a	yield of 3aa (%) ^a
1	BuLi (40)	1.0	30	20	14
2	AlMe ₃ (30)	1.0	30	70	55
3	DIBAL-H (40)	1.0	30	60	64
4	DIBAL-H (40)	1.5	18	89	82
5	DIBAL-H (40)	2.0	18	94	89
6	DIBAL-H (30)	2.0	18	88	92 (91) ^b
7	AlMe ₃ (40)	1.5	12	91	92 (89) ^b

^a Estimated by GC using C₁₂H₂₆ as an internal standard. ^b Isolated yields based on **1a**.

The Ni(0)/Cyp₃P catalyst prepared in situ was found effective for hydroheteroarylation of alkynes using a variety of heteroarenes (Table 2). Indoles having an electron-withdrawing functional group at C-3 position gave the respective hydroheteroarylation products in excellent yields (entries 1 and 2). 1-Methyl-substituted benzimidazole (**1d**), benzoxazole (**1e**), and benzofuran (**1f**) also participated in the reaction nicely to give the corresponding products in excellent chemo- and stereoselectivities (entries 3–5). The scope of heteroarenes was further extended to 5-membered derivatives. 1-Methylpyrazole (**1g**) and 4,4-dimethyl-2-oxazoline (**1h**) participate in the reaction smoothly to give their respective adducts in 96% and 75% yield (entries 6 and 7). Hydroheteroarylation of unsymmetrical internal alkynes led to *cis*-adducts having a larger substituent *trans* to the aryl group. Thus, 4-methyl-2-pentyne (**2b**), 4,4-dimethyl-2-pentyne (**2c**) and trimethyl(phenylethynyl)silane (**2d**) all reacted with **1a** in excellent regioselectivity to afford the corresponding *cis*-adducts in good yields (entries 8–10). We believe that steric factors are responsible for the regioselectivity observed for unsymmetrical internal alkynes as discussed previously.¹

Table 2. Hydroheteroarylation of alkynes with Ni(0)/Cyp₃P catalyst generated in situ.^a

$\text{hetAr-H} + \text{R}^1\text{—}\equiv\text{—R}^2 \xrightarrow[\text{toluene, 35 } ^\circ\text{C}]{\begin{array}{l} \text{Ni(acac)}_2 \text{ (10 mol\%)} \\ [\text{Cyp}_3\text{PH}]\text{BF}_4 \text{ (10 mol\%)} \\ \text{AlMe}_3 \text{ (40 mol\%)} \end{array}} \text{hetAr}-\text{C}(\text{R}^1)=\text{CH-R}^2$					
entry	hetAr-H	alkyne	time (h)	product	yield (%) ^b
					
1	R = COMe: 1b	2a	12	R = COMe: 3ba	84 (89) ^c
2	CN: 1c	2a	12	CN: 3ca	84
3		2a	12		87
4		2a	12		86
5		2a	8		92
6		2a	12		96
7		2a	12		75
		$\text{R}^1\text{—}\equiv\text{—R}^2$			
8	1a	R ¹ , R ² = Me, <i>i</i> -Pr: 2b	14	R ¹ , R ² = Me, <i>i</i> -Pr: 3ab	93
9	1a	Me, <i>t</i> -Bu: 2c	18	Me, <i>t</i> -Bu: 3ac	82
10 ^d	1a	Ph, SiMe ₃ : 2d	36	Ph, SiMe ₃ : 3ad	85

^a Reaction conditions: heteroarene (1.0 mmol), alkyne (1.5 mmol), Ni(acac)₂ (0.10 mmol), [Cyp₃PH]BF₄ (0.10 mmol), AlMe₃ (1.03 M solution in hexane, 0.4 mmol), and toluene (2.5 mL) at 35 °C. ^b Isolated yield based on the heteroarene. ^c DIBAL-H (30 mol%) and **2a** (2.0 mmol) were used. ^d The reaction was carried out using 3.0 mmol of **2d** at 100 °C.

In conclusion, we have demonstrated a simple and convenient protocol for hydroheteroarylation of alkynes using air-stable and commercially available $\text{Ni}(\text{acac})_2$ and $[\text{Cyp}_3\text{PH}]\text{BF}_4$ as catalyst precursors. Highly chemo-, stereo- and regioselective preparation of a diverse range of heteroaryl-substituted ethenes with an operationally feasible standard Schlenk technique would find many applications of this chemistry to synthesis of biologically active substances and materials.

EXPERIMENTAL

Nickel-catalyzed hydroheteroarylation of alkynes. A general procedure. $\text{Ni}(\text{acac})_2$ (26 mg, 0.10 mmol), $[\text{Cyp}_3\text{PH}]\text{BF}_4$ (33 mg, 0.10 mmol) and toluene (2.5 mL) were put in a 20 mL Schlenk tube. To the suspension was added a 1.03 M solution of AlMe_3 in hexane (0.39 mL, 0.40 mmol) dropwise, and then the resulting black suspension was stirred for an additional 5 min. Heteroarene (1.0 mmol) and alkyne (1.5 mmol) were added sequentially, and the mixture was stirred at 35 °C. After completion of the reaction (monitored by GC), the mixture was filtered through a silica gel pad. The filtrate was concentrated in vacuo, and the residue was purified on flash column chromatography on silica gel to afford the corresponding hydroheteroarylation products.

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