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On-Demand Generation of an Efficient Catalyst for Pyridine Formation from Unactivated Nitriles and α,*ω*-Diynes Using $CoCl_2$-$6H_2O$, dppe, and Zn

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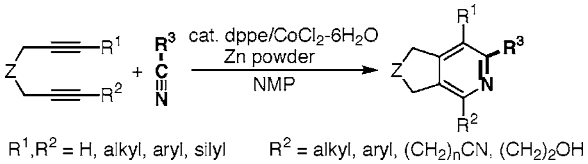
ABSTRACT



A highly practical, general method for catalytic formation of substituted pyridines from a variety of *unactivated* nitriles and α,*ω*-diynes is given. The reactions which were catalyzed by 5 mol % of dppe/$CoCl_2$–$6H_2O$ in the presence of Zn powder (10 mol %) could proceed at rt to ∼50 °C with high functional compatibility and regioselectivity.

The distribution of a pyridine structure in natural and synthetic biologically active compounds and the importance of the heterocycle as a reagent in organic and organometallic reactions have been driving forces for developing their synthetic methods. Besides traditional heterocyclic synthesis, the metal-catalyzed cycloaddition of nitriles and alkynes is particularly a straightforward method, which has been developed with use of Co, Fe, Ni, Rh, and Ru complexes.[1,2] Although harsher conditions (elevated temperature, photolytic conditions, or high catalyst loadings) are employed for Fe-, Rh-, and Co-catalyzed reactions in general,[2] among them Co-catalyzed reactions have been most widely utilized by using $CpCoL_2$ (Cp = cyclopentadienyl, L = ligand),[3] including commercially available $CpCo(CO)_2$. The relatively mild conditions could be applied for Ru- and Ni-catalysis:[4,5] Cp*RuCl(cod) forms pyridine from α,*ω*-diynes and nitriles at ambient temperature; however, the method requires activated nitriles such as those having an electron-withdrawing or a coordinative group.[4] Meanwhile, the Ni(0)/*N*-heterocyclic carbene catalyst enables the cycloaddition of unactivated nitriles, while the reactions reported have been

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[1] Reviews for the transition metal catalyzed [2 + 2 + 2] cycloaddition reactions: Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, p 741. Schore, N. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, UK, 1991; Vol. 5, p 1129. Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis*: *Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol. 1, pp 439−530. Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.

[2] Reviews for pyridine formation by the transition metal catalyzed [2 + 2 + 2] cycloaddition reactions: Bönnenmann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248. Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

[3] CpCo(cod) and its derivatives, preparation of which needs to be conducted under an inert atmosphere, could catalyze such a reaction under milder conditions. Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **1999**, *1*, 2141. Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131. Bonaga, L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2000**, 2394. Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795.

[4] Ru-catalyzed reaction: Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189. Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595. Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618.

[5] Ni-catalyzed reaction: (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030. (b) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834.

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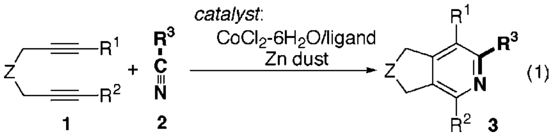
restricted to use of diynes that consist of less-hindered internal alkyne moieties.[5,6] Accordingly, development of a new route to pyridine from a wider range of nitrile and alkyne substrates under mild conditions has strongly been desired.[7−9]

The catalyst disclosed here enables pyridine formation from *unactivated* nitriles and α,ω-diynes including those with a terminal alkyne(s), at room temperature, where an active catalyst was generated in situ from inexpensive, stable materials on demand (eq 1). Such *instant* protocol for catalyst generation is user-friendly and highly practical since the difficulty and waste associated with preparation and isolation of catalyst can be avoided.[10]



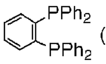
(1)

Table 1 summarizes the results of the reaction of 1,6-diynes **1a**,**b** with nitriles **2a** and **2b** with $CoCl_2-6H_2O$/Zn in the presence of a phosphine ligand.[11] As shown in entries 2−7, in the presence of a phosphine ligand, except for dppm, the catalyst could catalyze the reaction of diyne **1a** having two terminal alkynes in a solvent amount of **2a** to afford the corresponding pyridine **3aa** at room temperature. Among them, 1,4-diphosphines such as dppe and dppPh were the most effective (entries 4 and 7). With tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), or *N*-methylpyrrolid-2-one (NMP) as a solvent, the dppe/$CoCl_2-6H_2O$/Zn-catalyzed reaction of **1a** with a reduced amount of **2a** (5 equiv) provided **3aa**, but benzene derivatives (a dimer and a trimer of **1**) were coproduced (entries 8−10). Among the solvents, NMP was better for selective pyridine formation. In NMP, an increase of the amount of **2a** to 20 equiv was enough to improve selectivity for pyridine formation (entry 11). In contrast, disubstituted diyne **1b** reacted with 5 equiv of **2a** or essentially 1 equiv of **2b** in NMP selectively to yield pyridines **3ba** and **3bb**, respectively (entries 12 and 13), owing to no competition with formation of benzene derivative(s).[5] For the reaction with relatively more hindered diyne **1c**, use of 20 equiv of **2a** was better for completion of the reaction within reasonable time (entries 14 and 15).

Table 1. Reaction with Phosphine Ligand

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{Zn dust (10 mol \%)}\ \text{rt}]{\text{CoCl}_2\text{-6H}_2\text{O (5 mol \%)}\ \text{ligand (6 mol \%)}} \mathbf{3}$$

1a: $R^1 = R^2 = H$ **2a**: $R^3 = Me$
1b: $R^1 = R^2 = Me$ **2b**: $R^3 = Ph$
1c: $R^1 = R^2 = n$-Bu
[Z = $C(CO_2Et)_2$]

entry	**1**	**2** (equiv)	ligand	solvent	yield, %[a] (time)
1	**1a**	**2a** (80)	no	—	0 (24 h)
2			2 PPh_3		17 (24 h)
3			$Ph_2PCH_2PPh_2$ (dppm)		0 (24 h)
4			$Ph_2P(CH_2)_2PPh_2$ (dppe)		quant (1 h)
5			$Ph_2P(CH_2)_3PPh_2$ (dppp)		71 (12 h)
6			$Ph_2P(CH_2)_4PPh_2$ (dppb)		4 (12 h)
7		**2a** (80)	 (dppPh)	—	quant (12 h)
8		**2a** (5)	dppe	THF	19 (12 h)[b]
9				DMF	41 (12 h)[b]
10		**2a** (5)		NMP	52 (12 h)[b]
11	**1a**	**2a** (20)			96 (1 h)
12	**1b**[c]	**2a** (5)			74[d] (1 h)
13	**1b**[c]	**2b** (1.5)			60[d] (12 h)
14	**1c**	**2a** (20)			90 (3 h)
15	**1c**	**2a** (5)	dppe	NMP	54 (4 h)

[a] ^1H NMR yield. [b] Benzene derivatives were coproduced. For their structures, see Scheme 2. [c] Z = $C(CO_2Me)_2$. [d] Isolated yield.

With the $CoCl_2-6H_2O$/dppe/Zn reagent thus found, the reactions of representative diynes **1** and nitriles **2** (R^3CN) were carried out under appropriate reaction conditions. The results are summarized in Figure 1, where the structure of the product **3** and its isolated yield (equivalents of nitrile **2** used and reaction time are shown in parentheses) are indicated. Thus, to a mixture of diyne **1** (1.0 equiv), nitrile **2** (1.5−20 equiv), and Zn powder (10 mol %) in NMP was added a 1 M solution of $CoCl_2-6H_2O$ (5 mol %) and dppe (6 mol %) in NMP. The mixure was stirred at ~25 °C for the indicated period. An NMP solution of dppe and $CoCl_2-6H_2O$ thus used could be stored over at least 1 month. Several cases used nitrile **2** as a solvent (ca. 80 equiv).

As revealed from Figure 1, the method is reasonably general: Tri-, tetra-, and pentasubstituted pyridines were effectively synthesized. As a nitrile, primary, secondary, and tertiary alkyl and aryl nitriles could be used, although the reaction with a tertiary nitrile resulted in moderate yield due to its steric hindrance (**3ae**). Functional groups such as ester, hydroxy (**3af**), ketone (**3da**), amide (**3ea**), urea (**3ea**), silyl (**3la**−**3oa**), and amine (**3fb**) moieties tolerated the reaction conditions. Pyridines having five- and six-membered carbocyclic annulating structures as well as *N*- and *O*-heterocyclic ones (**3fb** and **3ha**) could be synthesized. The reactions with malononitrile and succinonitrile were much faster than other alkyl and aryl nitriles and proceeded effectively under the

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(6) The reports involve the results of the reaction with Me- or Et-substituted diynes, except for an example of Me_3Si-substitued diyne, but do not include the reaction with diynes having a terminal alkyne group(s) such as **1a** or sterically demanding substituents.

(7) Co-catalyzed reactions: Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 708. Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **1997**, *62*, 4189. Moretto, A. F.; Zhang, H.-C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157. Varela, J. A.; Castedo, L.; Maestro, M.; Mahía, J.; Saá, C. *Chem. Eur. J.* **2001**, *7*, 5203. Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852. Fe-, Rh-catalyzed reactions: Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291. Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U.; Floch, P. L.; Mathey, F. *Organometallics* **1996**, *15*, 2713.

(8) For the stoichiometric reactions, see: Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, F. *J. Am. Chem. Soc.* **2005**, *127*, 7774 and references cited therein. See also ref 2.

(9) Recently, formation of pyridine from activated nitriles with diynes catalyzed by cationic rhodium(I)/BINAP at room temperature has been reported. Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917.

(10) Fully intermolecular pyridine formation from alkynes catalyzed by $CoCl_2-6H_2O$ and $NaBH_4$ in acetonitrile has been reported: (a) Boennemann, H.; Brinkmann, R.; Schenkluhn, H. *Synthesis* **1974**, 575. Our efforts for benzene formation: (b) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129. (c) Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, *8*, 1439. (d) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065.

(11) Examples for phosphine(s)/CoX_n (n = 1 or 2) reagents for cycloaddition of alkynes to benzenes: Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, *690*, 5170. Slowinski, F.; Aubert, C.; Malacria, M. *Adv. Synth. Catal.* **2001**, *343*, 64. See also ref 10c.

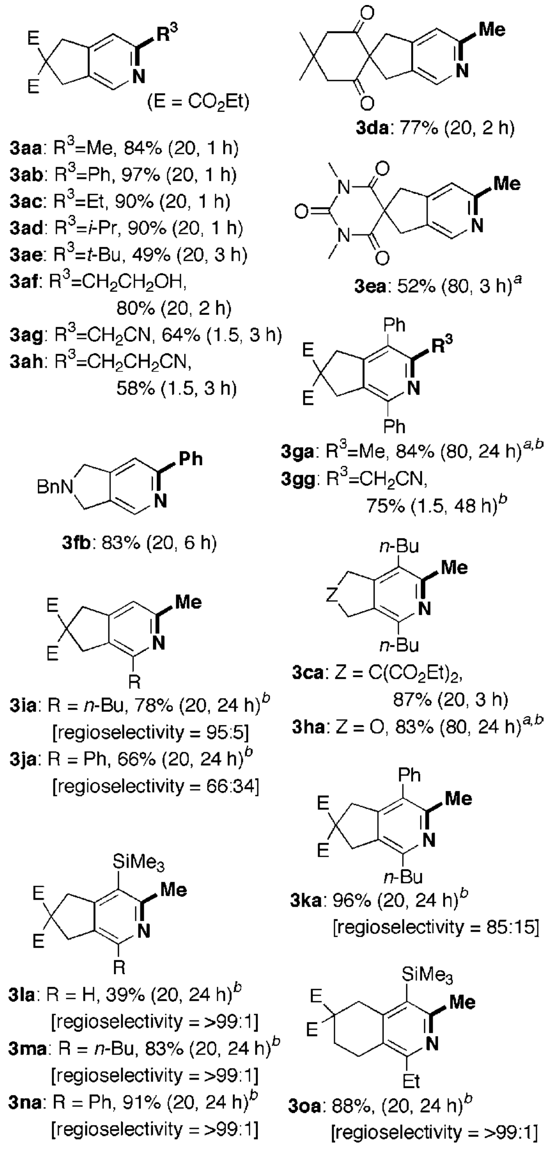


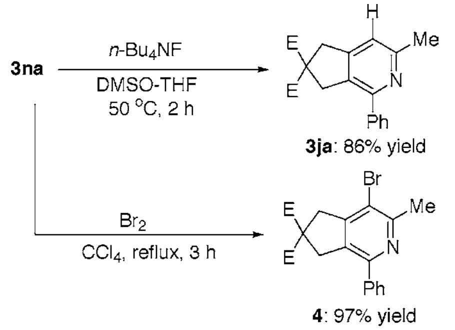
Figure 1. The yields (equiv of **2**, the reaction time) for representative examples of pyridine synthesis by a dppe/$CoCl_2$-$6H_2O$/Zn catalyst: footnote a, nitrile was used as a solvent; footnote b, the reaction was performed at 50 °C.

conditions with 1.5 equiv of the nitrile to provide the corresponding pyridines, **3ag**, **3ah**, and **3gg**, in good yields, due to the coordination effect of an additional cyano moiety.[4] Since the reaction of a cyano group present in these products with diyne did not compete, it was found that the pyridine moiety was not an effective coordination group.

The catalysis exhibited unique regioselectivity arising from use of unsymmetrical diynes: Diynes with terminal, alkyl- and aryl-substituted alkyne moieties reacted with acetonitrile (**2a**) to yield a mixture of regioisomers (**3ia**, **3ja**, and **3ka**). In contrast, the reaction of silyl-substituted diynes gave the corresponding pyridines (**3la**, **3ma**, **3na**, and **3oa**) as a single regioisomer, in all cases of which the silyl group located at the 3-position of the resulting pyridines, although explanation for the regiocontrol must await further study.[5] Formation of **3ia**, **3ja**, and **3la** resulted in somewhat low yield because dimerization of the corresponding diyne (formation of benzene derivatives) competed.

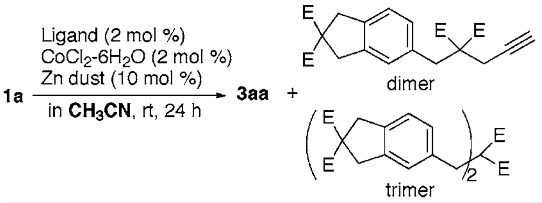
The silyl-substituted pyridines thus obtained are synthetically useful. Thus, as shown in eq 2, silylpyridine **3na** was smoothly protiodesilylated or halogenodesilylated to give regioisomerically pure **3ja** and bromopyridine **4**, respectively, in good yields.

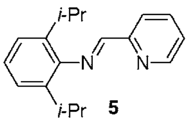
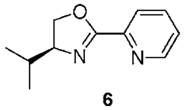
Scheme 1. Transformations of Silylated Pyridine **3na**



Although the reaction mechanism and explanation for extraordinary high regioselectivity for formation of silyl-substituted pyridines are unclear at this time and must await further study, an interesting ligand effect on selectivity of pyridine vs benzene formation was observed as illustrated in Scheme 2. Instead of dppe, the use of ligand **5**, which has been found to be an effective ligand for benzene formation in THF,[10c] for the reaction of diyne **1a** in acetonitrile afforded no pyridine **3aa** at all but a dimer and trimer derived from **1a** were obtained. In contrast, the reaction using ligand **6** was slow but selectively proceeded to provide **3aa** in 38% yield. These results may help further development of more selective catalyst to avoid the use of a large excess of nitriles in the dppe/$CoCl_2$−$6H_2O$/Zn-

Scheme 2. Reaction with Iminopyridine Ligand



ligand	3aa	dimer	trimer	recovered 1a
 5	trace	37%	43%	trace
 6	38%	7%	trace	55%

catalyzed reaction of diynes with terminal alkynes, which was required for selective pyridine formation against the competitive benzene formation. Investigation in this line is underway.

In summary, we have developed a highly practical, general method for catalytic formation of substituted pyridines from a variety of *unactivated* nitriles and α,ω-diynes. The reactions could proceed under mild conditions with high functional compatibility and regioselectivity.

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

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