# A Serendipitous Discovery: Nickel Catalyst for the Cycloaddition of Diynes with Unactivated Nitriles**

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A variety of transition-metal complexes (i.e., Co, Ru, Rh, Ni, and Fe) catalyze the cycloaddition of alkynes and nitriles to form pyridines.[1–7] Most of the catalysts generate pyridines through a mechanism that involves initial oxidative coupling of the alkynes and then subsequent insertion of the nitrile (i.e., formation of **A**, Scheme 1).[4d, 8] In contrast, nickel-
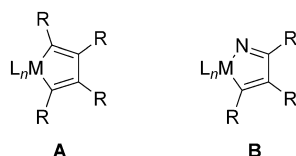
Scheme 1. Transition-metal intermediates in the cycloaddition of alkynes and nitriles.

mediated cycloadditions are thought to undergo hetero-oxidative coupling between a single alkyne and the hetero-atom-containing substrate, such as a nitrile, before insertion of the second alkyne (i.e., formation of **B**, Scheme 1).[9] Thus, a Ni/L_n-based system (especially where L_n = phosphine) that provided pyridines remained absent, because of the difficulty associated with forming the required azametallacyclopenta-diene intermediate, until two notable solutions were developed. Takahashi et al. accessed the azametallacyclopenta-diene intermediate *stoichiometrically* through transmetallation between [Ni(PPh$_3$)$_2$Cl$_2$] and an azazirconacyclopenta-diene complex.[9] Alternatively, catalytic pyridine formation was achieved at 100 °C between activated alkynes such as benzyne with Ni/dppe (dppe = 1,2-bis(diphenylphosphino)-ethane) as the catalyst.[10]

We successfully developed an efficient nickel catalyst for cycloaddition by replacing the phosphines with N-heterocylic carbene (NHC) ligands.[6] Thus, enhancing the nucleophilicity of the nickel center appeared to be the key for promoting oxidative coupling of the alkyne and nitrile. Recently, we reported a nickel-catalyzed cycloaddition of diynes and

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ketenes.[11] In our efforts to expand this chemistry to ketenimines, we serendipitously discovered that the combination of Ni^0 and Xantphos (Xantphos = 4,5-bis(diphenyl-phosphino)-9,9-dimethylxanthene) serves as a general catalyst system for the cycloaddition of diynes and nitriles. Furthermore, these cycloadditions proceed, in many cases, more effectively than the current state-of-the-art catalytic methods.

Upon investigating reaction conditions to promote the cycloaddition between the diyne **1a** and methyl 2-methyl-3-(phenylimino)acrylate, we found that pyridine **1$_{ket}$** (rather than the expected carbocycle) was obtained in moderate yield when Xantphos was used as the ligand [Eq. (1), cod = 1,5-
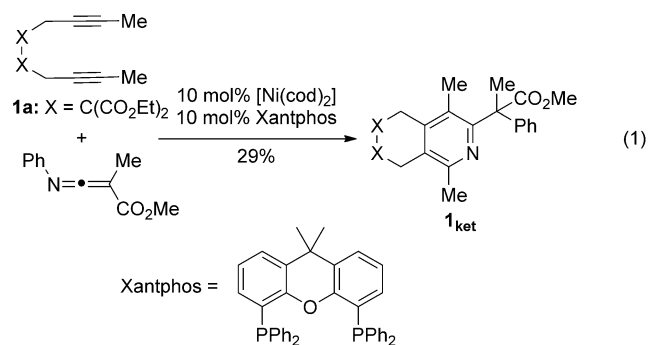
cyclooctadiene].[11–13] Surprised by this result, particularly in light of previous diffculties associated with pyridine formation using Ni/PR$_3$ catalysts (see above), we evaluated a variety of monodentate and bidentate phosphines as potential ligands in the nickel-catalyzed cycloaddition of diyne **1a** and the simple, unactivated benzonitrile **2a** at 100 °C (Table 1). As expected, in most cases, little to no pyridine product was observed despite good conversion of the diyne.[14] From the pool of monodentate phosphines screened (entries 1–5), only moderate catalytic activity was observed in reactions run with PPh$_3$ (θ = 145°) and PCy$_3$ (θ = 170°). Even worse catalytic activity was observed when the slightly larger monodentate phosphine P(o-tol)$_3$ (θ = 194°) was used.[15]

In general, bidentate phosphines did not fare any better. Dppe (β = 85°) was ineffective towards pyridine formation (Table 1, entry 6). Although pyridine was observed when bidentate ligands with larger bite angles such as binap (β = 92°) or dppf (β = 96°) were employed (entries 7 and 8), yields were still marginal. Surprisingly, a dramatic increase in pyridine formation occurred when Xantphos (β = 111°), a bidentate ligand with a large bite angle, was evaluated (entry 9).[15–16] Further optimization (entries 10–12) led to a

Table 1: Ligand screening for nickel-catalyzed cycloaddition of a diyne and a nitrile.[a,b]

1a: X = C(CO₂Et)₂   2a → 3aa

Entry	Ligand (L_n)	Catalyst loading [mol%]	T [°C]	Yield [%][c]
1	PCy₃	10	100	27
2	PBu₃	10	100	–
3	PPh₃	10	100	23
4	P(o-tol)₃	10	100	11
5	P(O-iPr)₃	10	100	–
6	dppe	10	100	–
7	dppf	10	100	21
8	rac-binap	10	100	7
9	Xantphos	10	100	>99 (86)[d]
10	Xantphos	5	100	>99
11	Xantphos	3	100	>99
12	**Xantphos**	**3**	**RT**	**>99 (98)[d,e]**

[a] For entries 1–5, 20 mol% L_n was used. For entries 6–9, 10 mol% L_n was used. For entry 10, 5 mol% L_n was used. For entries 11–12, 3 mol% L_n was used. [b] The reactions from entries 1–11 were analyzed after 24 h and >99% diyne conversion was observed for all the entries.
[c] Analyzed by GC analysis using naphthalene as an internal standard.
[d] Yields of isolated products in parentheses. [e] The reaction was complete in 3 h. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

system that provided pyridine **3aa** in excellent yields under mild reaction conditions (3 mol% Ni catalyst at RT for 3 h). Thus, in contrast to our previous hypothesis,[6a] sterics may play an equally or more important role than electronics in promoting both the challenging oxidative coupling and reductive elimination of C−N bond.[15]

The reaction has a broad substrate scope and tolerates a variety of functional groups (Table 2). Yields obtained using the Ni/NHC catalyst system are provided in parentheses for direct comparison.[6a] Diyne **1a** reacted with benzonitrile **2a** to afford **3aa** in excellent yields (entry 1). Electron-withdrawing groups (4-CF₃, 3,5-F₂; entries 4 and 5) on the arylnitrile afforded the cycloadduct in higher yields than arylnitriles bearing electron-donating groups (2-Me, 4-OMe; entries 2 and 3). 2-Napthylnitrile (**2f**) also afforded the pyridine product **3af** in excellent yield (entry 6). Interestingly, diyne **1b** reacted with a variety of nitriles to provide 5,6-membered fused-ring systems in higher yields than those obtained with the Ni/SIPr catalyst system (entries 7–10, 13, 14). In addition, similar trends in the yields of the pyridine products derived from diyne **1b** were observed when the electronics on the arylnitrile were modified (i.e., electron-withdrawing substituents gave higher yields than substrates bearing electron-donating substituents). However, these effects were not as pronounced as they were with the original Ni/NHC system (yields in parentheses; entry 9 versus entry 10). Nitrile **2g** bearing an activated olefin successfully reacted with **1b** to afford **3bg** (entry 12) in excellent yield, although an elevated temperature was required. Notably, no

Table 2: Nickel-catalyzed cycloaddition of diynes and nitriles.[a,b]

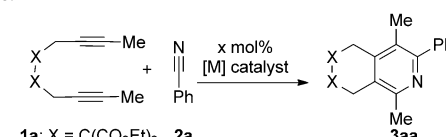| Entry	Diyne	Nitrile	Product	Yield [%][c]
1	**1a** [X = C(CO₂Et)₂]	**2a** (Ar = Ph)	**3aa**	98
2	**1a**	**2b** (Ar = 2-MeC₆H₄)	**3ab**	87
3	**1a**	**2c** (Ar = 4-OMeC₆H₄)	**3ac**	90
4	**1a**	**2d** (Ar = 4-CF₃C₆H₄)	**3ad**	99
5	**1a**	**2e** (Ar = 3,5-F₂C₆H₃)	**3ae**	>99
6	**1a**	**2f** (Ar = 2-naphtyl)	**3af**	96
7	**1b**	**2a**	**3ba**	92 (86)[d]
8	**1b** [X = C(CO₂Me)₂]	**2b**	**3bb**	85 (81)[d]
9	**1b**	**2c**	**3bc**	89 (64)[d]
10	**1b**	**2d**	**3bd**	98 (94)[d]
11	**1b**	**2e**	**3be**	>99
12	**1b**	**2g**	**3bg**	>99[e]
13	**1b**	**2h** (R = Me)	**3bh**	94 (69)[d]
14	**1b**	**2i** (R = iPr)	**3bi**	90 (72)[d]
15	**1c**	**2a**	**3ca**	73 (78)[d]
16	**1d**	**2a**	**3da**	80 (93)[d]
17	**1e**	**2a**	**3ea**	93

[a] Reaction conditions: 3 mol% [Ni(cod)₂], 3 mol% Xantphos, diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), toluene, RT, 3 h. [b] Nitriles were neither distilled nor degassed. Nitriles were used as received. [c] Yields of isolated products. [d] Yields reported for the Ni/NHC catalyst; Ref. [6a]. [e] The reaction was run at 100°C. Ts = 4-toluenesulfonyl.

product arising from incorporation of the olefin was observed.[17] The challenging alkyl nitriles (**2h** and **2i**) also

afforded the desired pyridines in excellent yields (entries 13 and 14). Similarly, sulfonamide diyne **1c** and diyne ether **1d** reacted with benzonitrile **2a** to yield products in good yields (entries 15 and 16). The Thorpe–Ingold effect was not a necessity of this reaction as diyne **1e** reacted to afford the cycloadduct **3ea** in excellent yield (entry 17). It is important to note that all nitriles evaluated were not purified prior to use; instead, they were used as received from commercial suppliers.

The efficacy of the Ni/Xantphos cycloaddition catalyst system was compared to other, state-of-the-art transition-metal catalysts based on Co, Ru, Rh, and Ni (Table 3, entries 1–5 versus 6). Specifically, diyne **1a** and benzonitrile **2a** were subjected to a variety of catalytic conditions and monitored for pyridine formation. Even after 24 hours in the presence of a large excess of nitrile (20 equiv), full conversion of the diyne was not reached with 5 mol% [Co] catalyst (Table 3, entry 1). Also, the desired cycloadduct was formed in only 70% yield.[18]

**Table 3:** Comparison of metal catalysts in the cycloaddition of diynes and nitrile.

Entry	[M] (x mol%)	2a [equiv]	T [°C]	t [h]	1a Conv. [%][a]	Yield [%][a]
1	[Co][c] (5 mol%)	20	RT	24	86	70
2	[Rh][d] (3 mol%)	1.5	60	3	>99	>99
3	[Rh][e] (3 mol%)	1.5	RT	3	32	15
4	[Ru][f] (10 mol%)	1.5	60	24	6[g]	–
5	[Ni/SIPr][h] (3 mol%)	1.5	RT	3	>99	80
6	[Ni/Xant][i] (3 mol%)	1.5	RT	3	>99	>99 (98)[b]

[a] Analyzed by GC using naphthalene as an internal standard. [b] Yield of isolated product given within parentheses. [c] 5 mol% CoCl₂, 6 mol% dppe, excess Zn, diyne (1 equiv, 1 M), nitrile (20 equiv), NMP, RT. [d] 3 mol% [Rh(cod)]BF₄, 3 mol% Segphos, diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), 1,2-DCE, 60°C. [e] Same conditions as in [d], but the reaction was run at RT. [f] 10 mol% [Cp*Ru(cod)Cl], diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), 1,2-DCE, 60°C, 24 h. [g] Analyzed by NMR spectroscopy. [h] 3 mol% [Ni(cod)₂], 3 mol% SIPr, diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), THF, RT. [i] 3 mol% [Ni(cod)₂], 3 mol% Xantphos, diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), toluene, RT. Cp* = C₅Me₅, 1,2-DCE = 1,2-dichloroethane, NMP = N-methylpyrrolidone, Segphos = (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphine), SIPr = N,N-bis(2,6-di-isopropylphenyl)dihydroimidazol-2-ylidene, THF = tetrahydrofuran.

A Rh/binap catalyst[5a] developed by Tanaka et al. is known for exhibiting excellent catalytic activity for activated nitriles (an approach complementary to the Ru-catalyzed cycloaddition developed independently by the groups of Yamamoto and Saà).[4] However, replacement of binap with Segphos was required when simple nitriles, such as acetonitrile or benzonitrile, were employed. Although excellent yield and conversion were observed at 60°C, the reaction afforded the pyridine in lower yield at room temperature with the Rh/

Segphos catalyst (Table 3, entries 2 and 3 versus entry 6). The [Ru] catalyst[4a] was found to be completely ineffective towards pyridine product formation (entry 4). Although excellent conversion of the diyne **1a** was observed with the Ni/SIPr catalyst, **3aa** was produced in lower yields than with the Ni/Xantphos system (entry 5 versus entry 6). Thus, lower catalyst loadings, milder reaction conditions, and equimolar substrate stoichiometry make Ni/Xantphos a more efficient catalyst for coupling of diynes and unactivated nitriles.

We recently reported that Ni/NHC catalyzes the cyclo-addition of diynes and cyanamides to access 2-aminopyridines.[19] These cycloadditions possessed an expanded substrate scope as terminal diynes were successfully converted into pyridine products. However, SIPr was required as a ligand rather than the standard IMes ligand employed for the coupling of internal diynes and cyanamides. The Ni/Xantphos system was evaluated and proved effective for the coupling of particularly challenging substrates (Scheme 2). Specifically, 2,7-diynes (i.e., **1a** and tetraethyl octa-1,7-diyne-4,4,5,5-
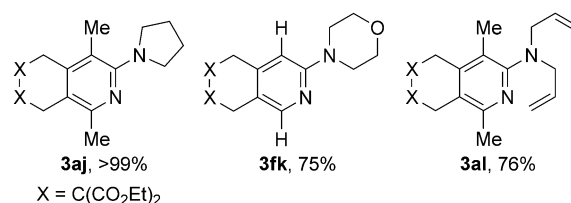
**Scheme 2.** Nickel-catalyzed cycloaddition of diynes and cyanamides.

tetracarboxylate (**1f**)) were successfully reacted with either pyrrolidine-1-carbonitrile (**2j**), morpholine-4-carbonitrile (**2k**), or N,N-diallylcyanamide (**2l**) to give 6,6-fused bicyclic products (**3aj**, **3fk**, **3al**). In addition, the same Ni/Xantphos system could be used for both internal and terminal diynes. Importantly, diallyl cyanamide, a cyanamide that is unreactive with the Ni/IMes catalyst, gave **3al** in good yield.

Treatment of the unsymmetrical diyne **1g** with benzonitrile **2a** led to the regioselective formation of the cycloadduct **3ga** (Scheme 3). Despite the higher reactivity of terminal diynes, the regioselectivity is governed by the insertion of a less-sterically hindered alkyne (bearing H on the terminal carbon atom) in the azametallacycle formed by initial oxidative coupling of the internal alkyne (bearing Me on the terminal carbon atom) and **2a**. Analogous to the reaction of the diyne **1g** and **2a**, N,N-dimethylcyanamide (**2m**) was also regioselectively coupled with **1g** to afford the 2-amino-pyridine **3gm** (Scheme 3).
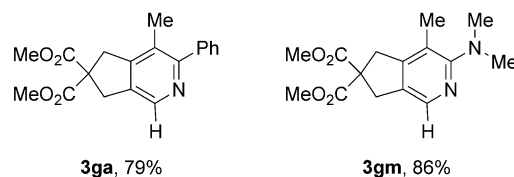
Scheme 3. Regioselectivity in the nickel-catalyzed cycloaddition of diynes and nitriles.

The combination of high yields, mild reaction conditions, and, importantly, efficient stoichiometry led us to investigate the use of this system to rapidly click together a diyne with a complex nitrile. Specifically, equimolar amounts of both the diyne **1b** and δ-tocopherol-derived nitrile **2n** were subjected to the Ni/Xantphos catalyst at room temperature. After only 3 hours, pyridine **3bn** was obtained in 94% yield [Eq. (2)]. Thus, excess nitrile is not required to obtain high yields of potential pyridine bioconjugates.
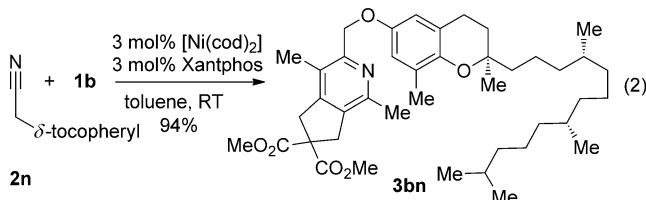
In summary, we discovered a Ni/phosphine system that promotes both oxidative coupling between an alkyne and a nitrile as well as C−N bond-forming reductive elimination. The combination of catalytic amounts of Xantphos and Ni^0 produced a variety of pyridines from unactivated nitriles and diynes under mild and efficient reaction conditions. Studies focused on understanding the mechanism of this reaction and the application of this methodology toward the synthesis of bioconjugates are ongoing.

Experimental Section

Representative procedure: In a nitrogen-filled glove box, diyne (1 equiv, 0.1M) and nitrile (1.5 equiv) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In a separate vial [Ni(cod)$_2$] and Xantphos were weighed out (in 1:1 molar ratio) and dissolved in toluene. The catalyst (3 mol%) solution was added to the reaction mixture. The vial was sealed and brought out of the glove box. The reaction was stirred at RT for 3 h. The resulting reaction mixture was concentrated and purified by flash column chromatography on silica gel using first 15%, 30%, and finally 50% EtOAc/hexanes.

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