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Nickel-Catalyzed [2+2+2] Cycloaddition of Diynes and Cyanamides

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Abstract

A variety of bicyclic *N,N*-disubstituted 2-aminopyridines have been prepared from diynes and cyanamides by nickel-catalyzed [2+2+2] cycloaddition reactions. The reactions proceeded at room temperature with low catalyst loading to afford 2-aminopyridines in good to excellent yields. The method is amenable to both internal and terminal diynes and proceeds in a regioselective manner. A number of cyanamides with diverse functional group tolerance were used. The intermolecular version employing 3-hexyne and *N*-cyanopyrrolidine also afforded the desired *N,N*-disubstituted 2-aminopyridine in good yield.

Keywords

Nickel; Cycloaddition; Cyanamides; Alkynes; Carbenes

Introduction

2-Aminopyridines are attractive synthetic targets due to their use in many fields of chemistry as organometallic ligands,[1–4] chromophores,[5–7] and intermediates in biologically active molecules.[8–14] A variety of methods for the synthesis of 2-aminopyridines exist, namely the amination of pyridines from sodium amide (the Chichibabin reaction),[15,16] Buchwald–Hartwig amination reactions,[17–20] the substitution of halopyridines,[21–24] multi-component condensations,[25,26] hetero-Diels–Alder reactions,[27] and Ullman-type aminations.[28,29] To complement existing methods, an easily envisioned route is the [2+2+2] cycloaddition of alkynes and cyanamides.

The metal-catalyzed [2+2+2] cycloaddition of alkynes and nitriles using a variety transition metals has a rich and extensive history and continues to be a highly studied field.[30,31] Although studies of cycloadditions of alkynes and nitriles are expansive, independent studies of analogous cyanamides are few. The seminal work of Bönnemann et al.

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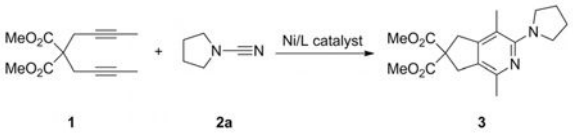
Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all compounds, as well as (^{1}H,^{13}C) HMBC and (^{1}H,^{13}C) HMQC spectra for compound **23**. HRMS and IR data available upon request from the authors.

demonstrated the cycloaddition of acetylene and cyanamide using a unique (η^6-boranato)cobalt catalyst at high temperature and pressure.[32] Heller et al. accomplished a [CpCo(cod)]-catalyzed cycloaddition of dimethylcyanamide and acetylene as a single example, which afforded a moderate 46% yield.[33] Maryanoff and co-workers performed a more focused study demonstrating the effectiveness of the cycloaddition of diynes with cyanamides using [CpCo-$(CO)_2$] as a catalyst.[34–36] More recently, Tanaka et al. developed a cationic [Rh(cod)]/BINAP cycloaddition catalyst that facilitated the [2+2+2] cycloaddition of a malonate-derived diyne and *N*-cyanomorpholine as a single example in 47% yield.[37] Heller and co-workers used a chiral cobalt catalyst to synthesize a variety of chiral 1-aryl-5,6,7,8-tetra-hydroquinolines from aryl-substituted diynes and nitriles. This system was also amenable to the cycloaddition of aryl-substituted diynes and piperidine-1-carbonitrile as a single example in an excellent yield.[38] Owing to our recent success in the mild and efficient nickel-catalyzed [2+2+2] cycloaddition of alkynes and nitriles to generate pyridines,[39] we believed that the use of cyanamides as coupling partners would be a practical extension of this methodology. Herein we report the nickel-catalyzed [2+2+2] cycloaddition of alkynes and cyanamides at room temperature with low catalyst loadings.

Results and Discussion

Reaction Optimization

Diyne **1** and *N*-cyanopyrrolidine (**2a**) were chosen as model substrates due to our familiarity and simplicity of **1** as well as the simplicity, ease of handling, and commercial availability of **2a** [Equation (1)]. Initial investigations focused on catalyst screening with [Ni$(cod)_2$] (cod = 1,5-cyclooctadiene) as an Ni^0 source in combination with a variety of ligands: Phosphanes, phosphites, amines, and N-heterocyclic carbenes (NHCs; Table 1). The resultant catalysts were then added to a 1:1 solution of diyne **1** and **2a** in toluene. The reactions were stirred at room temperature for 3 h and analyzed by gas chromatography (GC). The product **3** was detected with most of the ligands tested (Entries 1–5), which is significantly different to the results of Ni-catalyzed cycloaddition reactions of simple nitriles for which only select NHC ligands (i.e., no phosphanes) afforded appreciable amounts of pyridine products.[39] The highest yields were obtained when either IMes or SIPr was employed as the ligand. The effectiveness of the [Ni$(cod)_2$]/IMes catalyst is particularly surprising as this catalyst system typically produces significant amounts of a dimerized diyne as a side-product.[35–39] Brief optimization showed that increasing the concentration of the cyanamide retarded the reaction and that a 1:1 diyne/cyanamide ratio was ideal. In addition, catalyst loading could be reduced to 5 mol-% [Ni$(cod)_2$] and 10 mol-% IMes or SIPr without loss of yield.



1 2a 3

(1)

Upon addition of a solution of [Ni(cod)$_2$]/IMes to the reaction mixture, an instant and dramatic color change occurred, possibly an indication of a rapid reaction. As such, the reaction times of the [Ni(cod)$_2$]/IMes and [Ni(cod)$_2$]/SIPr systems were explored (Table 2). Two reaction mixtures, both consisting of equimolar amounts of diyne **1** and **2a** in toluene, were treated with either [Ni(cod)$_2$]/IMes or [Ni(cod)$_2$]/SIPr. Although the reactions with both SIPr and IMes as ligands each generated excellent yields of 2-aminopyridine **3**, we found that reactions run with IMes produced **3** in only 15 min, whereas the analogous reaction run with SIPr required 60 min to achieve the same yield (Entry 3 vs. 4).

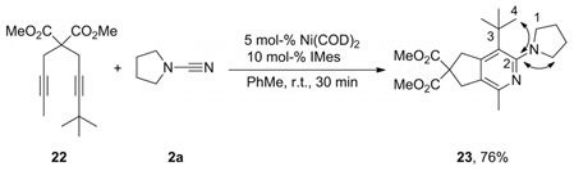
A variety of solvents were screened for the [Ni(cod)$_2$]/IMes-catalyzed cycloaddition of diyne **1** and cyanamide **2a** (Table 3). Excellent yields were obtained in pentane, 1,4-dioxane, and toluene. Toluene was chosen for use in further cycloaddition reactions, because the yields were higher in toluene than in dioxane and also because many substrates are only moderately soluble in pentane.

Substrate Scope

With the optimized conditions in hand, we examined the reactions of a range of diyne and cyanamide substrates with varying electronic and steric properties (Table 4). In addition to the model cyanamide **2a**, other dialkylcyanamides readily underwent cyclization, affording excellent yields. The yields appear to decrease with increasing steric bulk: Me (**4**) > Et (**5**) > Pr (**6**; Entries 2–4). This is further highlighted by the complete inactivity of diisopropylcyanamide (**2e**, see below) towards cycloaddition. The heterocyclic cyanamide *N*-cyanomorpholine (Entry 5) was an excellent substrate, affording product **7** in 97% yield. In addition to alkyl substituents, a variety of amine-protected cyanamides were evaluated, these include methyl PMB cyanamide (PMB = *p*-methoxybenzyl; **2g**), dibenzylcyanamide (**2h**), as well as carbonyl-protected cyanamides such as *N*-(*tert*-butoxycarbonyl)-*N*-butylcyanamide (**2i**) and *N*-butyl-*N*-cyanoacetamide (**2j**; Entries 6–9). Notable unreactive protected cyanamides are *N*-tosylated butylcyanamide (**2k**) and diallylcyanamide (**2l**; Figure 1). Note, *N*-tosylamines have been, for the most part, troublesome in many of our previous cycloaddition reactions.[39–43] It is unclear in this case whether the steric bulk or the reactivity of the *N*-tosyl moiety deactivates the catalyst. Diallylcyanamide was also employed but was also found to deactivate the catalyst. Free amine is incompatible with our catalyst system as seen by the lack of reaction of free cyanamide and *N*-butylcyanamide. Cyanamides containing pendant functional groups [methyl 2-(*N*-butylcyanamido)acetate (**2m**), *N*-butyl-*N*-(3-chloropropyl)cyanamide (**2n**), and *N*-butyl-*N*-(3-chloroethyl)cyanamide (**2o**)] were also evaluated and gave mixed results. Both chlorinated cyanamides **2n** and **2o** readily deactivated the catalyst as no conversion was observed in these reactions (Figure 1). Cyanamide **2m** afforded aminopyridine **12** in 81% yield as a light-sensitive aminopyridine that required purification by chromatography to be performed in a darkened room (Entry 10). Arylcyanamides are also good substrates with cyanamide **2p** affording aminopyridine **13** in excellent yield (Entry 11). Various diynes were subjected to the reaction conditions with model cyanamide **2a** and afforded excellent yields. For example, internal *N*-protected amines (**14**) and ethers (**16**) as well as linear diyne **18** all reacted well under our conditions (Entries 12–14, respectively). Notably, diyne **20** readily reacted to afford an aminopyridine

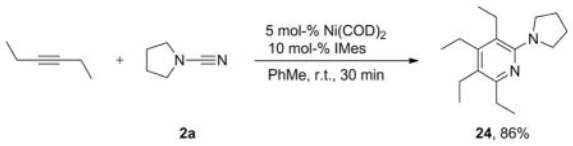
appended to a seven-membered ring in 76% yield despite the lack of Thorpe–Ingold assistance in the substrate (Entry 15).

The regioselectivity of the reaction was investigated by treating diyne **22** and cyanamide **2a** under the optimized reaction conditions; aminopyridine **23** was obtained as a single regioisomer in 76% yield [Equation (2)].[44] The structure was assigned through complementary HMQC and HMBC NMR experiments, with the regiochemistry being determined by exclusive correlations between C-2 and protons located on C-4 and C-1.



(2)

We also investigated the synthesis of *N,N*-disubstituted 2-aminopyridines by the cycloaddition of an untethered alkyne [Equation (3)]. Subjecting 3-hexyne (2 equiv.) and *N*-cyanopyrrolidine (**2a**) to the optimized conditions described above (5 mol-% of catalyst, room temp.) afforded 2-aminopyridine **24** in 86% yield.



(3)

Terminal diynes, a challenging substrate for the parent Ni-catalyzed nitrile cycloaddition reaction,[39] were also evaluated as potential substrates (Table 5). Initially, the [Ni(cod)$_2$]/IMes-catalyzed reaction between diyne **25** and cyanamide **2a** only yielded trace amounts of the desired product in an otherwise unidentifiable reaction mixture. However, when IMes was substituted for SIPr, the reaction was effective and generated aminopyridine **26** in 80% yield. Extended reaction times were required for the [Ni(cod)$_2$]/SIPr-catalyzed reactions. Interestingly, unlike internal diynes, the cycloaddition of terminal diynes and cyanamides using [Ni(cod)$_2$]/SIPr did not occur in 1,4-dioxane. The use of dioxane did lead to full conversion; however, no identifiable products were formed nor were any byproducts isolated from the complex reaction mixture. Thus, cycloaddition reactions using [Ni(cod)$_2$]/SIPr were carried out exclusively in toluene.

Under these revised conditions, terminal diynes were amenable to cycloaddition with most of the previously tested cyanamides (Table 5). Alkyl substituents work well with cyanamides **2a** and **2f** affording products **26** and **27** in 80 and 86% yields, respectively

(Entries 1 and 2). Terminal diynes were also compatible with *N*-Boc- (**2i**) and *N*-acyl-protected (**2j**) cyanamides, with yields comparable to internal diynes (Entries 3 and 4). However, no reaction was observed with diyne **25** and either PMB-protected cyanamide **2g** or ester-functionalized cyanamide **2m** (Entries 5 and 6). In addition to the alkylcyanamides, phenyl-substituted cyanamides (**2p**) are excellent substrates affording **32** in good yield (Entry 7).

In Situ Catalyst Generation

Previously, we developed a method that generates the active Ni^0/NHC catalyst in situ from air-stable, readily available precursors.[45] The method employed [$Ni(acac)_2$] as a nickel source, an appropriate NHC·HCl or HBF_4 salt, and *n*BuLi as a simultaneous reductant and base. We found this in situ method was also effective for the [2+2+2] cycloaddition reactions of diynes and cyanamides. When diyne **1** and cyanamide **2a** were treated with a stirred solution of [$Ni(acac)_2$], IMes·HCl, and *n*BuLi, aminopyridine **3** was obtained in 80% yield. Furthermore, a variety of aminopyridines were obtained in this fashion with yields comparable to the yields obtained in the initial substrate scope experiments (Table 6, Entries 1–5). In situ cycloaddition using terminal diyne **25** and cyanamide **2a** was also successful when IMes·HCl was replaced by SIPr·HBF_4. Further cyanamides were tested with diyne **25** with mixed results. The reactions with both cyanamides **2a** and **2p** went to completion and gave good yields, whereas the Boc (**2i**) and acyl (**2j**) cyanamides gave modest yields of 50 and 30% with 20 and 32% recovered starting material, respectively (Entries 6–9).

Conclusions

We have demonstrated that diynes undergo [2+2+2] cycloaddition reactions with cyanamides in the presence of an Ni–carbene catalyst to generate *N,N*-disubstituted 2-amino-pyridines. The method is effective for the cycloaddition of internal as well as terminal diynes with a variety of cyanamides, affording good to excellent yields. *N,N*-Disubstituted 2-aminopyridines were also obtained when using an in situ generated Ni–carbene catalyst prepared from air-stable, commercially available sources.

Experimental Section

General

Ligands 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr), 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidine (SIPr), and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine (IMes) were prepared according to literature procedures.[46,47] The diynes dimethyl 2,2-bis(but-2-ynyl)malonate (**1**),[48] dimethyl 2,2-bis(prop-2-yn-1-yl)malonate (**25**),[48] *N,N*-bis(but-2-ynyl)-*p*-toluene-sulfonamide (**14**),[49] 1-(but-2-ynyloxy)but-2-yne (**16**),[50] and di-methyl 2-(but-2-ynyl)-2-(4,4-dimethylpent-2-ynyl)malonate (**22**)[44] were also prepared according to literature procedures. *N*-Butylcyanamide was also prepared by literature procedures.[51] The diynes 3,9-dodecadiyne (**18**) and 2,9-undecadiyne (**20**) were purchased from GFS and Lancaster chemical companies, respectively, and distilled from CaH_2 before use. Bis(1,5-cyclooctadiene)nickel(0), [$Ni(cod)_2$], was purchased from the Strem chemical company and

used without further purification. All other reagents were purchased from commercial sources and used without further purification. All liquid reagents were degassed prior to use by the freeze-pump-thaw method. All reactions were preformed in a nitrogen-filled glove box or under nitrogen using standard Schlenk techniques unless otherwise noted.

***N*,*N*-Dipropylcyanamide (2d)—**Dipropylamine (3 mL, 21.9 mmol, 1.0 equiv.) was added dropwise to a stirred solution of Et_2O/THF (1:1) (50 mL) and BrCN (1.4 g, 13.3 mmol, 0.6 equiv.) over 10 min. The reaction mixture was stirred at ambient temperature for 3 h, after which time hexane (10 mL) was added followed by an additional 10 min of stirring. The mixture was then filtered through a pad of Celite and washed with H_2O (3 × 50 mL) and brine (2 × 50 mL). The organic phase was then dried with anhydrous Na_2SO_4 and concentrated to yield 1.35 g of **2d** as a colorless oil; yield 98%. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.5 Hz, 3 H), 1.59 (dt, J_1 = 5, J_2 = 10 Hz, 2 H), 2.87 (t, J = 5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.92, 20.9, 53.1, 117.8 ppm. IR (neat): $\tilde{\nu}$ = 2968, 2878, 2208, 1462, 1090 cm^{-1}. HRMS (ESI): calcd. for $C_7H_{15}N_2$ $[M + H]^+$ 127.1230; found 127.1230.

N*-(*tert*-Butoxycarbonyl)-*N*-butylcyanamide (2i)—N*-Butylcyanamide (740 mg, 7.6 mmol, 1 equiv.) in Et_2O (5 mL) was added to a suspension of NaH (217 mg, 9.1 mmol, 1.2 equiv.) in THF (75 mL) at 0 °C. The mixture was warmed to room temperature, after which Boc_2O (1.9 mL, 8.3 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 1 h, quenched with H_2O (1 mL), and Et_2O (10 mL) was added. The crude reaction mixture was poured into brine/water (1:1), extracted with Et_2O (3 × 15 mL), and concentrated. The residue was purified by column chromatography using CH_2Cl_2 to afford 1.41 g of the title compound as a colorless oil; yield 95%. ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.5 Hz, 3 H), 1.38 (m, 2 H), 1.51 (s, 9 H), 1.66 (dt, 2 H), 3.46 (t, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.7, 19.5, 27.9, 29.9, 47.6, 85.4, 109.8, 151.2 ppm. IR (neat): $\tilde{\nu}$ = 2966, 2361, 2241, 1748, 1461, 1152 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{19}N_2O_2$ $[M + H]^+$ 199.1441; found 199.1441.

N*-Butyl-*N*-cyanoacetamide (2j)—N*-Butylcyanamide (770 mg, 7.9 mmol, 1 equiv.) in Et_2O (5 mL) was added to a suspension of NaH (230 mg, 9.4 mmol, 1.2 equiv.) in THF (25 mL) at 0 °C. The mixture was warmed to room temperature, after which acetyl chloride (0.617 mL, 8.6 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 1 h, quenched with H_2O (1 mL), and Et_2O was added (10 mL). The crude reaction mixture was poured into brine/water (1:1), extracted with Et_2O (3 × 15 mL), and concentrated. The residue was purified by column chromatography using CH_2Cl_2 to afford 1.07 g of the title compound as a colorless volatile oil; yield 98%. ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.5 Hz, 3 H), 1.35 (m, 2 H), 1.64 (dt, 2 H), 2.38 (s, 3 H), 3.54 (t, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 19.6, 22.3, 29.7, 45.9, 111.1, 169.4 ppm. IR (neat): $\tilde{\nu}$ = 2963, 2875, 2361, 2233, 1730, 1373, 1244 cm^{-1}. HRMS (ESI): calcd. for $C_7H_{13}N_2O$ $[M + H]^+$ 141.1022; found 141.1023.

N*-Butyl-*N*-cyano-4-methylbenzenesulfonamide (2k)—N*-Butylcyanamide (1.21 g, 12.3 mmol, 1 equiv.) in Et_2O (5 mL) was added to a suspension of NaH (356 mg, 14.8 mmol, 1.2 equiv.) in THF (50 mL) at 0 °C. The mixture was warmed to room temperature, after which *p*-toluene sulfonyl chloride (2.9 g, 14.8 mmol, 1.2 equiv.) in THF (5 mL) was added. The reaction mixture was stirred for 4 h, quenched with H_2O (1 mL), and Et_2O (10

mL) was added. The crude reaction mixture was poured into brine/water (1:1), extracted with Et_2O (3 × 15 mL), and concentrated. The residue was purified by column chromatography using CH_2Cl_2 to afford 1.3 g of the title compound as a viscous colorless oil; yield 97%. ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, J = 7.5 Hz, 3 H), 1.29 (m, 2 H), 1.59 (m, 2 H), 2.44 (s, 3 H), 3.33 (m, 2 H), 7.38 (d, 2 H), 7.78 (d, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.3, 19.1, 21.7, 29.6, 49.8, 108.5, 127.7, 130.4, 133.5, 146.5 ppm. IR (neat): $\tilde{\nu}$ = 2963, 2875, 2230, 1380, 1173 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{17}N_2O_2S$ $[M + H]^+$ 253.1005; found 253.1006.

Methyl 2-(*N*-Butylcyanamido)acetate (2m)—*N*-Butylcyanamide (1.01 g, 10.3 mmol, 1 equiv.) in Et_2O (5 mL) was added to a suspension of NaH (295 mg, 12.3 mmol, 1.2 equiv.) in THF (50 mL) at 0 °C. The mixture was warmed to room temperature, after which methyl 2-bromoacetate (1.0 mL, 11 mmol, 1.1 equiv.) was added. The reaction mixture was stirred for 3 h, quenched with H_2O (1 mL), and Et_2O (10 mL) was added. The crude reaction mixture was poured into brine/water (1:1), extracted with Et_2O (3 × 15 mL), and concentrated. The residue was purified by column chromatography using CH_2Cl_2 to afford 1.53 g of the title compound as a pale-yellow oil; yield 88%. ^{1}H NMR (C_6D_6): δ = 0.59 (t, J = 7.5 Hz, 3 H), 0.98 (m, 2 H), 1.21 (dt, 2 H), 2.52 (t, 2 H), 3.19 (s, 2 H), 3.23 (s, 3 H) ppm. ^{13}C NMR (C_6D_6): δ = 13.9, 20.1, 30.1, 52.1, 52.2, 52.6, 117.0, 168.9 ppm. IR (neat): $\tilde{\nu}$ = 2960, 2875, 2360, 2216, 1752, 1217 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{15}N_2O_2$ $[M + H]^+$ 171.1128; found 171.1128.

N*-Butyl-*N*-(3-chloropropyl)cyanamide (2n)—N*-Butylcyanamide (805 mg, 8.2 mmol, 1 equiv.) in Et_2O (5 mL) was added to a suspension of NaH (250 mg, 9.9 mmol, 1.2 equiv.) in THF (50 mL) at 0 °C. The mixture was warmed to room temperature, after which 1-bromo-3-chloropropane (2.45 mL, 24.7 mmol, 3 equiv.) was added. The mixture was heated to reflux and stirred overnight. The reaction mixture was then quenched with H_2O (1 mL), and Et_2O (10 mL) was added. The crude reaction mixture was poured into brine/water (1:1), extracted with Et_2O (3 × 15 mL), and concentrated. The residue was purified by column chromatography using CH_2Cl_2 to afford 1.3 g of the title compound as a colorless oil; yield 91%. ^{1}H NMR (C_6D_6): δ = 0.59 (t, J = 7.5 Hz, 3 H), 0.93 (m, 2 H), 1.15 (dt, 2 H), 1.48 (m, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 2.46 (t, J = 7.5 Hz, 2 H), 3.04 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.99, 20.1, 30.1, 30.8, 41.9, 48.7, 51.9, 117.0 ppm. IR (neat): $\tilde{\nu}$ = 2961, 2874, 2361, 2208, 1459 cm^{-1}. HRMS (ESI): calcd. for $C_8H_{16}ClN_2$ $[M + H]^+$ 175.0997; found 175.0997.

N*-Butyl-*N*-(2-chloroethyl)cyanamide (2o)—N*-Butylcyanamide (1.1 g, 11.2 mmol, 1.0 equiv.) in THF (5 mL) was added dropwise to a stirring suspension of NaH (400 mg, 16.8 mmol, 1.5 equiv.) in THF/DCE (1,2-dichloroethane) (1:1) (20 mL). The reaction mixture was stirred at ambient temperature for 15 min, then heated at reflux for 8 h. The mixture was cooled to room temperature, quenched with MeOH (5 mL), and then poured into H_2O (100 mL). The suspension was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated, and purified by column chromatography eluting with CH_2Cl_2 to afford 1.38 g of **2o** as a pale-yellow oil; yield 77%. ^{1}H NMR (C_6D_6): δ = 0.68 (t, J = 7.5 Hz, 3 H), 0.97 (m, 2 H), 1.18 (dt, 2 H), 2.28 (t, J = 7.5 Hz, 2 H), 2.42 (t, J

= 7.5 Hz, 3 H), 2.92 (t, J = 5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.6, 19.5, 29.8, 40.9, 51.7, 53.1, 116.8 ppm. IR (neat): $\tilde{\nu}$ = 2962, 2874, 2210, 1461, 1106 cm^{-1}. HRMS (ESI): calcd. for $C_7H_{13}N_2$ $[M + H]^+$ 161.0840; found 161.0841.

N*-Methyl-*N*-phenylcyanamide (2p)—N*-Methylaniline (1.7 mL, 15.6 mmol, 1 equiv.) was added to a solution of cyanogen bromide (1 g, 9.4 mmol, 0.6 equiv.) in Et_2O/THF (1:1) (25 mL) at room temperature. The reaction mixture was then stirred overnight, after which time hexane (5 mL) was added, and the mixture was stirred for an additional 10 min. It was then filtered through a pad of Celite, and the filtrate was washed with H_2O (4 × 25 mL) and brine (2 × 25 mL). The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using ethyl acetate/hexane (1:1) to afford 2.19 g of the title compound as a colorless solid: yield 82%. M.p. 28–30 °C. ^{1}H NMR (C_6D_6): δ = 2.21 (s, 3 H), 6.96 (m, 2 H), 6.76 (m, 1 H), 6.7 (m, 2 H) ppm. ^{13}C NMR (C_6D_6): δ = 36.2, 115.1, 123.3, 129.9, 141.4 ppm. IR (neat): $\tilde{\nu}$ = 2361, 2223, 1600, 1114 cm^{-1}. HRMS (ESI): calcd. for $C_8H_9N_2$ $[M + H]^+$ 133.0760; found 133.0760.

General Co-Cycloaddition Procedure for Terminally Substituted Diynes (A)

In a nitrogen-filled glove-box, $[Ni(cod)_2]$ (1 equiv.) and IMes (2 equiv.) were diluted to 0.036 M in toluene or dioxane and stirred for at least 4 h. A solution of diyne (100 mg) and cyanamide (1 equiv.) in toluene or dioxane was placed in an oven-dried vial equipped with a stirring bar. The $[Ni(cod)_2$/IMes solution was added to this stirred solution with a total reaction concentration of 0.1 M in the diyne. The reaction mixture was stirred at ambient temperature for 30 min, taken out of the glove-box, concentrated, and then purified by flash column chromatography to afford the aminopyridine product.

General Co-Cycloaddition Procedure for Terminal Diynes (B)

In a nitrogen-filled glove box, $[Ni(cod)_2]$ (1 equiv.) and SIPr (2 equiv.) were diluted to 0.036 M in toluene and stirred for at least 4 h. A solution of diyne (100 mg) and cyanamide (1 equiv.) in toluene was placed in an oven-dried vial equipped with a stirring bar. The $[Ni(cod)_2]$/SIPr solution was added to this stirred solution with a total reaction concentration of 0.1 M in the diyne. The reaction mixture was stirred at ambient temperature for 1 h, taken out of the glove box, concentrated, and then purified by flash column chromatography to afford the aminopyridine product.

In Situ Cycloaddition Procedure

In a nitrogen-filled glove box, $[Ni\text{-}(acac)_2]$ (5.3 mg, 0.02 mmol) and either IMes·HCl (14.1 mg, 0.04 mmol) or SIPr·HBF_4 (19.8 mg, 0.04 mmol) were suspended in pentane (1.5 mL). To this was added a 2.5 M solution of *n*BuLi in hexanes (45 mL, 0.103 mmol). The resultant suspension was stirred at room temperature for 10 min. Concurrently, the appropriate diyne (0.41 mmol) and cyanamide (0.41 mmol) were placed in an oven-dried vial equipped with a stirring bar and dissolved in toluene (3 mL). The catalyst solution was then added to the toluene solution and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of MeOH (5 drops). The reaction solution was then concentrated and purified by column chromatography.

Dimethyl 1,4-Dimethyl-3-(pyrrolidin-1-yl)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2a** (42.7 mL, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 130.7 mg of the title compound as a white solid; yield 93%. M.p. 85–87 °C. ^{1}H NMR ($CDCl_3$): δ = 1.885 (m, 4 H), 2.162 (s, 3 H), 2.30 (s, 3 H), 3.440 (m, 4 H), 3.475 (s, 2 H), 3.483 (s, 2 H), 3.763 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.9, 21.9, 25.7, 38.7, 40.2, 50.3, 53.2, 60.0, 113.5, 124.7, 147.5, 150.3, 159.1, 172.4 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2870, 2211, 1738, 1600, 1430 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1809; found 333.1808.

Dimethyl 3-(Dimethylamino)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (4)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2b** (34.2 mL, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 129.5 mg of the title compound as a white solid; yield 99%. M.p. 63–64 °C. ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H), 2.34 (s, 3 H), 2.30 (s, 3 H), 2.78 (s, 6 H), 3.49 (s, 2 H), 3.50 (s, 2 H), 3.77 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.0, 21.8, 38.8, 40.1, 42.5, 53.3, 59.9, 117.2, 127.3, 147.9, 150.4, 172.3 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2360, 1735, 1588, 1442, 1277 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{23}N_2O_4$ $[M + H]^+$ 307.1652; found 307.1652.

Dimethyl 3-(Diethylamino)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (5)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2c** (42.7 mL, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 135.8 mg of the title compound as a colorless oil; yield 93%. ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, J = 8 Hz, 6 H), 2.11 (s, 3 H), 2.30 (s, 3 H), 3.09 (m, 4 H), 3.48 (s, 2 H), 3.49 (s, 2 H), 3.74 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4, 14.6, 21.7, 38.8, 40.1, 45.7, 53.0, 59.7, 119.3, 127.3, 147.8, 149.9, 160.3, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 2967, 2361, 1738, 1588, 1433, 1264 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{27}N_2O_4$ $[M + H]^+$ 335.1965; found 335.1968.

Dimethyl 3-(Dipropylamino)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (6)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2d** (53.5 mg, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 136.4 mg of the title compound as a colorless oil; yield 89%. ^{1}H NMR ($CDCl_3$): δ = 0.839 (t, J = 8 Hz, 6 H), 1.24 (m, 4 H), 2.13 (s, 3 H), 2.32 (s, 3 H), 3.02 (m, 4 H), 3.49 (s, 2 H), 3.50 (s, 2 H), 3.77 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.9, 14.7, 21.4, 21.9, 38.9, 40.2, 53.3, 53.9, 59.8, 119.2, 127.3, 147.9, 150.1, 160.8, 172.4 ppm. IR (neat): $\tilde{\nu}$ = 2956, 2872, 1739, 1589, 1433, 1267 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{31}N_2O_4$ $[M + H]^+$ 363.2278; found 363.2279.

Dimethyl 1,4-Dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6-(7*H*)-dicarboxylate (7)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2f** (42.8 mL, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 142.9

mg of the title compound as a white solid; yield 97%. M.p. 82–83 °C. ^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 3 H), 2.34 (s, 3 H), 3.08 (m, 4 H), 3.49 (s, 2 H), 3.51 (s, 2 H), 3.77 (s, 6 H), 3.84 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 21.8, 38.8, 40.1, 50.8, 53.3, 59.9, 67.5, 117.9, 128.4, 148.6, 150.5, 160.3, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2848, 2361, 1737, 1588, 1431, 1259 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_5$ $[M + H]^+$ 349.1758; found 349.1757.

Dimethyl 3-[(4-Methoxybenzyl)(methyl)amino]-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (8)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2g** (74.6 mg, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 151.9 mg of the title compound as a viscous colorless oil; yield 87%. ^{1}H NMR ($CDCl_3$): δ = 2.26 (s, 3 H), 2.41 (s, 3 H), 2.71 (s, 3 H), 3.57 (s, 2 H), 3.58 (s, 2 H), 3.82 (s, 6 H), 3.84 (s, 3 H), 6.92 (d, J = 8 Hz, 2 H), 7.37 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 21.7, 38.7, 39.6, 40.0, 53.1, 55.3, 57.7, 59.8, 113.7, 117.8, 127.6, 129.3, 131.9, 148.0, 150.3, 172.1 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2838, 1737, 1588, 1512, 1436, 1246 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_5$ $[M + H]^+$ 413.2071; found 413.2069.

Dimethyl 3-(Dibenzylamino)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (9)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2h** (94.1 mg, 0.42 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 170.8 mg of the title compound as a viscous colorless oil; yield 88%. ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3 H), 2.36 (s, 3 H), 3.55 (s, 2 H), 3.55 (s, 2 H), 3.82 (s, 6 H), 4.31 (s, 3 H), 7.24 (m, 2 H), 7.32 (m, 4 H), 7.38 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 21.7, 38.8, 40.1, 53.2, 55.4, 59.8, 118.9, 126.8, 128.2, 128.3, 128.6, 139.9, 148.2, 150.5, 159.9, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 3029, 2952, 2360, 1737, 1591, 1434, 1267 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{31}N_2O_4$ $[M + H]^+$ 459.2278; found 459.2282.

Dimethyl 3-[(*tert*-Butoxycarbonyl)(butyl)amino]-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (10)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2i** (87.2 mg, 0.44 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 149.7 mg of the title compound as a colorless solid; yield 82%. M.p. 64–66 °C. ^{1}H NMR ($C_6D_5CD_3$, 60 °C): δ = 0.85 (t, J = 8 Hz, 3 H), 1.28 (m, 2 H), 1.38 (s, 9 H), 2.11 (s, 3 H), 2.21 (s, 3 H), 3.37 (s, 6 H), 3.45 (s, 2 H), 3.51 (s, 2 H), 3.88 (br. s, 2 H) ppm. ^{13}C NMR ($C_6D_5CD_3$, 60 °C): δ = 14.1, 14.8, 20.4, 21.5, 30.4, 38.6, 40.0, 51.4, 52.0, 52.7, 53.1, 59.8, 116.6, 127.2, 147.4, 150.6, 159.1, 172.1, 172.7 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2361, 1738, 1595, 1434, 1271 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{35}N_2O_6$ $[M + H]^+$ 435.2490; found 435.2497.

Dimethyl 3-(*N*-Butylacetamido)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (11)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2j** (63.1 mg, 0.45 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using 5 % MeOH/CH_2CH_2 to afford 137.5 mg of the title compound as a colorless yellow viscous oil; yield 87%. ^{1}H NMR ($C_6D_5CD_3$, 60

°C): δ = 0.81 (m, 3 H), 2.11 (br. s, 2 H), 1.59 (br. s, 2 H), 1.66 (s, 3 H), 1.87 (s, 3 H), 2.20 (s, 3 H), 3.35 (s, 6 H), 3.44 (s, 4 H), 4.03 (br. s, 1 H) ppm. ^{13}C NMR ($C_6D_5CD_3$, 60 °C): δ = 13.4, 13.9, 20.5, 21.4, 22.0, 30.4, 38.9, 39.9, 47.4, 52.7, 59.7, 123.9, 133.8, 137.4, 150.9, 151.5, 153.5, 168.9, 171.3 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2361, 1738, 1595, 1434, 1271 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_5$ $[M + H]^+$ 377.2071; found 377.2072.

Dimethyl 3-[(Butyl)(2-methoxy-2-oxoethyl)amino]-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (12)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2m** (73 mg, 0.43 mmol) in toluene (3.6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 138.3 mg of the title compound as a viscous colorless oil; yield 81%. (Note: The title compound is light-sensitive, and chromatography was performed in a dimly lit room. The green degradation products were not isolated.) ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 7.5 Hz, 3 H), 1.27 (dt, J_1 = 5, J_2 = 10 Hz, 3 H), 1.55 (m, 2 H), 2.15 (s, 3 H), 2.23 (s, 3 H), 3.15 (m, 2 H), 3.45 (s, 2 H), 3.46 (s, 2 H), 3.65 (s, 3 H), 3.73 (s, 6 H), 3.91 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 14.8, 20.4, 21.5, 30.4, 38.6, 40.0, 51.4, 52.0, 52.7, 53.1, 59.8, 116.6, 127.2, 147.4, 150.6, 159.1, 172.1, 172.7 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2361, 1738, 1595, 1434, 1271 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_6$ $[M + H]^+$ 407.2177; found 407.2186.

Dimethyl 1,4-Dimethyl-3-[(methyl)(phenyl)amino]-5*H*-cyclopenta-[*c*]pyridine-6,6(7*H*)-dicarboxylate (13)—General Procedure A was used with diyne **1** (100 mg, 0.42 mmol) and cyanamide **2p** (55.5 mg, 0.42 mmol) in toluene (3.0 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 139 mg of the title compound as a colorless waxy oil; yield 90%. ^{1}H NMR ($C_6D_5CD_3$): δ = 1.77 (s, 3 H), 2.29 (s, 3 H), 3.33 (s, 3 H), 3.34 (s, 6 H), 3.46 (s, 2 H), 3.53 (s, 2 H), 6.68 (d, J = 10 Hz, 2 H), 6.74 (t, J = 7.5 Hz, 1 H), 7.03 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 21.6, 38.9, 39.8, 39.8, 39.9, 52.4, 59.9, 117.9, 119.9, 120.9, 129.2, 129.9, 137.4, 149.8, 149.9, 150.7, 157.1, 171.6 ppm. IR (neat): $\tilde{\nu}$ = 2956, 1737, 1592, 1436, 1265 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{25}N_2O_4$ $[M + H]^+$ 369.1809; found 369.1810.

4,7-Dimethyl-6-(pyrrolidin-1-yl)-2-tosyl-2,3-dihydro-1*H*-pyrrolo-[3,4-*c*]pyridine (15)—General Procedure A was used with diyne **14** (100 mg, 0.36 mmol) and cyanamide **2a** (36.6 mL, 0.36 mmol) in toluene (3.0 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (2:1) to afford 113.3 mg of the title compound as a white solid; yield 84%. M.p. 110–112 °C (dec.). ^{1}H NMR ($CDCl_3$): δ = 1.88 (m, 4 H), 2.09 (s, 3 H), 2.23 (s, 3 H), 2.42 (s, 3 H), 3.44 (m, 4 H), 4.50 (s, 4 H), 7.33 (d, J = 9 Hz, 2 H), 7.79 (d, J = 9 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.9, 21.7, 21.8, 25.8, 50.3, 52.6, 53.6, 111.4, 120.8, 127.7, 130.1, 134.1, 143.9, 146.5, 146.7, 159.2 ppm. IR (neat): $\tilde{\nu}$ = 2963, 2875, 2230, 1380, 1173 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{26}N_3O_2S$ $[M + H]^+$ 372.1740; found 372.1749.

4,7-Dimethyl-6-(pyrrolidin-1-yl)-1,3-dihydrofuro[3,4-*c*]pyridine (17)—General Procedure A was used with diyne **16** (103.4 mg, 0.85 mmol) and cyanamide **2a** (85.3 mL, 0.85 mmol) in toluene (7.2 mL). The remaining residue was purified by flash column

chromatography using hexanes/ethyl acetate (2:1) to afford 174.3 mg of the title compound as a colorless oil; yield 94%. ^{1}H NMR ($CDCl_3$): δ = 1.91 (m, 4 H), 2.13 (s, 1 H), 2.27 (s, 3 H), 3.49 (m, 4 H), 4.99(s, 2 H), 5.02 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.1, 21.9, 25.7, 50.2, 72.8, 73.2, 110.3, 123.7, 145.1, 149.9, 159.1 ppm. IR (neat): $\tilde{\nu}$ = 2960, 2865, 2361, 1591, 1430.5, 1345, 1060 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{19}N_2O$ $[M + H]^+$ 219.1492; found 219.1493.

1,4-Diethyl-3-(pyrrolidin-1-yl)-5,6,7,8-tetrahydroisoquinoline (19)—General Procedure A was used with diyne **18** (107 mg, 0.66 mmol) and cyanamide **2a** (66.5 mL, 0.66 mmol) in toluene (5.2 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 156.6 mg of the title compound as a colorless viscous oil; yield 92%. ^{1}H NMR ($CDCl_3$): δ = 1.21 (t, J = 7.5 Hz, 3 H), 1.31 (t, J = 7.5 Hz, 3 H), 1.81 (m, 4 H), 1.95 (m, 4 H), 2.69 (m, 8 H), 3.47 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.3, 13.8, 20.5, 23.0, 23.1, 25.6, 25.8, 26.9, 27.6, 51.1, 122.2, 123.1, 145.5, 155.4, 157.2 ppm. IR (neat): $\tilde{\nu}$ = 2931, 2866, 2361, 1739, 1563, 1416 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{27}N_2$ $[M + H]^+$ 259.2169; found 259. 2170.

1,4-Dimethyl-3-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta-[*c*]pyridine (21)—General Procedure A was used with diyne **20** (104 mg, 0.70 mmol) and cyanamide **2a** (71 mL, 0.70 mmol) in toluene (6 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 130.3 mg of the title compound as a colorless viscous oil; yield 76%. ^{1}H NMR ($CDCl_3$): δ = 1.59 (m, 4 H), 1.81 (m, 2 H), 1.89 (m, 4 H), 2.17 (s, 3 H), 2.42 (s, 3 H), 2.75 (m, 4 H), 3.38 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.7, 23.1, 25.5, 26.8, 27.6, 29.2, 30.1, 32.2, 50.4, 116.1, 128.5, 148.9, 152.3, 158.2 ppm. IR (neat): $\tilde{\nu}$ = 2920, 2853, 1570, 1420 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{25}N_2$ $[M + H]^+$ 245.2012; found 245.2014.

Dimethyl 4-*tert*-Butyl-1-methyl-3-(pyrrolidin-1-yl)-5*H*-cyclopenta-[*c*]pyridine-6,6(7*H*)-dicarboxylate (23)—General Procedure A was used with diyne **22** (70 mg, 0.30 mmol) and cyanamide **2a** (31.0 mL, 0.30 mmol) in toluene (3.0 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 85.4 mg of the title compound as a colorless viscous oil; yield 76%. ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 1.88 (m, 4 H), 2.18 (s, 3 H), 3.42 (s, 2 H), 3.48 (m, 4 H), 3.68 (s, 2 H), 3.75 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.7, 25.7, 29.34, 29.55, 38.4, 39.2, 40.5, 50.2, 53.2, 60.5, 112.6, 122.3, 151.5, 157.2, 157.8, 172.3 ppm. IR (neat): $\tilde{\nu}$ = 2959, 1739, 1704, 1612, 1569, 1480, 1389, 1275, 1141 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_4$ $[M + H]^+$ 375.2278; found 375.2284.

2,3,4,5-Tetraethyl-6-(pyrrolidin-1-yl)pyridine (24)—General Procedure A was used with 3-hexyne (75 mL, 0.66 mmol) and cyanamide **2a** (33.3 mL, 0.33 mmol) in toluene (7.0 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 74 mg of the title compound as a waxy colorless oil; yield 86%. ^{1}H NMR ($CDCl_3$): δ = 1.17 (m, 9 H), 1.31 (t, J = 7.5 Hz, 3 H), 1.91 (m, 4 H), 2.67 (m, 8 H), 3.45 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.5, 14.7, 15.58, 15.61, 20.9, 21.1, 22.0,

25.7, 27.9, 50.8, 122.8, 126.5, 150.3, 155.3, 157.5 ppm. IR (neat): $\tilde{\nu}$ = 2966, 2871, 1562, 1416 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{29}N_2$ $[M + H]^+$ 261.2325; found 261.2328.

Dimethyl 3-(Pyrrolidin-1-yl)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (26)—General Procedure B was used with diyne **25** (100 mg, 0.48 mmol) and cyanamide **2a** (48.4 mL, 0.48 mmol) in toluene (4.1 mL). The remaining residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) to afford 116.8 mg of the title compound as a light-yellow solid; yield 80%. M.p. 98–99 °C. ^{1}H NMR ($CDCl_3$): δ = 1.95 (m, 4 H), 3.38 (m, 4 H), 3.45 (s, 4 H), 3.71 (s, 6 H), 6.20 (s, 1 H), 7.92 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.6, 37.5, 40.5, 46.9, 53.1, 60.7, 101.8, 123.2, 143.1, 151.0, 157.0, 171.9 ppm. The melting point and spectra match known values.[32]

Dimethyl 3-Morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (27)—General Procedure B was used with diyne **25** (100 mg, 0.48 mmol) and cyanamide **2f** (48.5 mL, 0.48 mmol) in toluene (4.1 mL). The remaining residue was purified by flash column chromatography using dichloromethane to afford 132.2 mg of the title compound as a light-yellow wax; yield 86%. ^{1}H NMR ($CDCl_3$): δ = 3.43 (m, 4 H), 3.49 (s, 4 H), 3.74 (s, 6 H), 3.79 (m, 4 H), 6.51 (s, 1 H), 8.01 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.6, 40.6, 46.3, 53.2, 60.7, 66.9, 102.8, 126.32, 143.1, 151.7, 159.5, 171.8 ppm. The spectra match known values.[32]

Dimethyl 3-[(*tert*-Butoxycarbonyl)(butyl)amino]-5*H*-cyclopenta-[*c*]pyridine-6,6(7*H*)-dicarboxylate (28)—General Procedure B was used with diyne **25** (100 mg, 0.48 mmol) and cyanamide **2i** (96 mg, 0.48 mmol) in toluene (4.1 mL). The remaining residue was purified by flash column chromatography using dichloromethane to afford 160.7 mg of the title compound as a light-yellow viscous oil; yield 82 %. ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 7.5 Hz, 3 H), 1.27 (dt, J_1 = 5, J_2 = 10 Hz, 3 H), 1.48 (s, 9 H), 3.55 (s, 2 H), 3.56 (s, 2 H), 3.74 (s, 6 H), 3.86 (m, 2 H), 7.42 (s, 1 H), 8.17 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 20.2, 28.5, 31.2, 37.8, 40.4, 47.1, 53.3, 60.6, 80.8, 116.1, 132.3, 143.0, 150.9, 153.8, 154.6, 171.6 ppm. IR (neat): $\tilde{\nu}$ = 2959, 1739, 1704, 1390, 1276, 1142 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_6$ $[M + H]^+$ 407.2177; found 407.2189.

Dimethyl 3-(*N*-Butylacetamido)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (29)—General Procedure B was used with diyne **25** (100 mg, 0.48 mmol) and cyanamide **2j** (67 mg, 0.48 mmol) in toluene (4.1 mL). The remaining residue was purified by flash column chromatography using dichloromethane to afford 155.5 mg of the title compound as a light-yellow viscous oil; yield 93%. ^{1}H NMR ($CDCl_3$): δ = 0.84 (t, J = 7.5 Hz, 3 H), 1.27 (dt, J_1 = 5, J_2 = 10 Hz, 2 H), 1.47 (m, 2 H), 1.93 (br. s, 3 H), 3.61 (s, 4 H), 3.76 (br. s, 8 H), 7.04 (s, 1 H), 8.30 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9, 20.2, 23.2, 30.5, 37.9, 40.4, 48.4, 53.4, 60.4, 117.7, 128.7, 135.1, 144.7, 152.5, 154.7, 170.2, 171.4 ppm. IR (neat): $\tilde{\nu}$ = 2955, 2361, 1738, 1595, 1434, 1271 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{25}N_2O_5$ $[M + H]^+$ 349.1758; found 349.1760.

Dimethyl 3-[(Methyl)(phenyl)amino]-5*H*-cyclopenta[*c*]pyridine-6,6-(7*H*)-dicarboxylate (32)—General Procedure B was used with diyne **25** (100 mg, 0.48 mmol) and cyanamide **2p** (63.5 mg, 0.48 mmol) in toluene (4.1 mL). The remaining residue was

purified by flash column chromatography using hexanes/ethyl acetate (1:2) to afford 135.5 mg of the title compound as a light-yellow viscous oil; yield 83%. ^{1}H NMR ($CDCl_3$): δ = 3.36 (s, 3 H), 3.43 (s, 3 H), 3.48 (s, 3 H), 3.71 (s, 6 H), 6.41 (s, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.21 (d, J = 10 Hz, 2 H), 7.37 (t, J = 7.5 Hz, 2 H), 8.04 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.5, 38.9, 40.4, 53.2, 60.6, 104.8, 125.3, 125.7, 126.3, 129.8, 142.8, 147.2, 150.8, 158.5, 171.9 ppm. IR (neat): $\tilde{\nu}$ = 3005, 2953, 2370, 1736, 1617, 1491, 1393, 1268 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{21}N_2O_4$ $[M + H]^+$ 341.1496; found 341.1496.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Horie H, Koyama I, Kurahashi T, Matsubara S. Chem Commun. 2011; 47:2658–2660.
2. Daka P, Xu Z, Alexa A, Wang H. Chem Commun. 2011; 47:224–226.
3. Di Nicola C, Effendy, Marchetti F, Nervi C, Pettinari C, Robinson WT, Sobolev AN, White AH. Dalton Trans. 2010; 39:908–922. [PubMed: 20066236]
4. Yip JHK, Suwarno, Vittal JJ. Inorg Chem. 2000; 39:3537–3543. [PubMed: 11196812]
5. Mutai T, Cheon J-D, Tsuchiya G, Araki K. J Chem Soc Perkin Trans. 2002; 2:862–865.
6. Tardioli S, Gooijer C, van der Zwan G. J Phys Chem B. 2009; 113:6949–6957. [PubMed: 19388641]
7. Sathyamoorthi G, Soong ML, Ross TW, Boyer JH. Heteroat Chem. 1993; 4:603.
8. Tursky M, Lorentz-Petersen LLR, Olsen LB, Madsen R. Org Biomol Chem. 2010; 8:5576–5582. [PubMed: 20959936]
9. Ueno M, Nobana T, Togo H. J Org Chem. 2003; 68:6424–6426. [PubMed: 12895080]
10. Kamal A, Reddy JS, Ramaiah MJ, Dastagiri D, Bharathi EV, Sagar MVP, Pushpavalli SNCVL, Ray P, Pal-Bhadra M. Med Chem Commun. 2010; 1:355–360.
11. Nam TG, Nara SJ, Zagol-Ikapitte I, Cooper T, Valgimigli L, Oates JA, Porter NA, Boutaud O, Pratt DA. Org Biomol Chem. 2009; 7:5103–5112. [PubMed: 20024105]
12. Carlucci G, Colanzi A, Mazzeo P, Quaglia MG. Int J Pharm. 1989; 53:257–259.
13. Acker, R-D.; Hamprecht, G. Preparation of 2-aminopyridine derivatives. US Patent. 4395555. 1981.
14. Ji H, Delker SL, Li H, Martásek P, Roman LJ, Poulos TL, Silverman RB. J Med Chem. 2010; 53:7804–7824. [PubMed: 20958055]
15. Chichibabin AE, Zeide OA. J Russ Phys Chem Soc. 1914; 46:1216–1236.
16. Chichibabin AE, Zeide OA. Ber Dtsch Chem Ges. 1923; 56B:1879–1885.
17. Wagaw S, Buchwald SL. J Org Chem. 1996; 61:7240. [PubMed: 11667641]
18. Patriciu OI, Fînaru AL, Massip S, Léger JM, Jarry C, Guillaumet G. Eur J Org Chem. 2009; 22:3753–3764.
19. Shen Q, Hartwig JF. Org Lett. 2008; 10:4109–4112. [PubMed: 18715012]
20. Lorimer AV, O'Connor PD, Brimble MA. Synthesis. 2008; 17:2764–2770.
21. Matsumoto K, Fukuyama K, Iida H, Toda M, Lown JW. Heterocycles. 1995; 41:237.
22. Perron-Sierra F, Saint Dizier D, Bertrand M, Genton A, Tucker GC, Casaram P. Bioorg Med Chem Lett. 2002; 12:3291. [PubMed: 12392735]

23. Gupton JT, Idoux JP, Baker G, Colon C, Crews AD, Jurss CD, Rampi RC. J Org Chem. 1983; 48:2933.
24. Thomas S, Roberts S, Pasumansky L, Gamsey S, Singaram B. Org Lett. 2003; 5:3867–3870. [PubMed: 14535730]
25. Teague SJ. J Org Chem. 2008; 73:9765–9766. [PubMed: 18855484]
26. Ranu BC, Jana R, Sowmiah S. J Org Chem. 2007; 72:3152–3154. [PubMed: 17367198]
27. Sainte F, Serckx-Poncin B, Hesbain-Frisque AM, Ghosez L. J Am Chem Soc. 1982; 104:1428–1430.
28. Liu ZJ, Vors JP, Gesing ERF, Bolm C. Adv Synth Catal. 2010; 352:3158–3162.
29. Shafir A, Buchwald SL. J Am Chem Soc. 2006; 128:8742–8743. [PubMed: 16819863]
30. For reviews of transition-metal-catalyzed [2+2+2] cycloadditions, see: Varela JA, Saá C. Synlett. 2008:2571–2578.Heller B, Hapke M. Chem Soc Rev. 2007; 36:1085–1094. [PubMed: 17576476] Hua R, Abrenica MVA, Wang P. Curr Org Chem. 2011; 15:712–729.Varela JA, Saá C. Chem Rev. 2003; 103:3787–3801. [PubMed: 12964884] Chopade PR, Louie J. Adv Synth Catal. 2006; 348:2307–2327.Tanaka K. Synlett. 2007:1977–1993.
31. For recent examples of transition-metal-catalyzed [2+2+2] cycloadditions of alkynes and nitriles, see: Iwayama T, Sato Y. Chem Commun. 2009:5245–5247.Garcia L, Pla-Quintana A, Roglans A, Parella T. Eur J Org Chem. 2010:3407–3415.Garcia P, Moulin S, Miclo Y, Leboeuf D, Gandon V, Aubert C, Malacria M. Chem Eur J. 2009; 15:2129–2139. [PubMed: 19142937] Kadlcikova A, Hrdina R, Valterova I, Kotora M. Adv Synth Catal. 2009; 351:1279–1283.Young DD, Teske JA, Deiters A. Synthesis. 2009:3785–3790.Komine Y, Kamisawa A, Tanaka K. Org Lett. 2009; 11:2361–2364. [PubMed: 19473045] Garcia P, Evanno Y, George P, Sevrin M, Ricci G, Malacria M, Aubert C, Gandon V. Org Lett. 2011; 13:2030–2033. [PubMed: 21413688] Miclo Y, Garcia P, Evanno Y, George P, Sevrin M, Malacria M, Gandon V, Aubert C. Synlett. 2010:2314–2318.Geny A, Agenet N, Iannazzo L, Malacria M, Aubert C, Gandon V. Angew Chem. 2009; 121:1842.Angew Chem Int Ed. 2009; 48:1810–1813.Hsieh JC, Cheng CH. Chem Commun. 2008:2992–2994.Watanabe JI, Sugiyama YK, Nomura A, Azumatei S, Goswami A, Saino N, Okamoto S. Macromolecules. 2010; 43:2213–2218.
32. Bönnemann H, Brijoux W, Brinkmann R, Meurers W. Helv Chim Acta. 1984; 67:1616–1624.
33. Heller B, Reihsig J, Schulz W, Oehme G. Appl Organomet Chem. 1993; 7:641–646.
34. Boñaga LVR, Zhang HC, Maryanoff BE. Chem Commun. 2004:2394–2395.
35. Boñaga LVR, Zhang HC, Moretto AF, Ye H, Gauthier DA, Li J, Leo GC, Maryanoff BE. J Am Chem Soc. 2005; 127:3473–3485. [PubMed: 15755167]
36. Zhang HC, Boñaga LVR, Ye H, Derian CK, Damiano BP, Maryanoff BE. Bioorg Med Chem Lett. 2007; 17:2863–2868. [PubMed: 17350261]
37. Tanaka K, Suzuki N, Nishida G. Eur J Org Chem. 2006:3917–3922.
38. Hapko M, Kral K, Fischer C, Spannenberg A, Gutnov A, Redkin D, Heller B. J Org Chem. 2010; 75:3993–4003. [PubMed: 20481604]
39. McCormick MM, Duong HA, Zuo G, Louie J. J Am Chem Soc. 2005; 127:5030–5031. [PubMed: 15810832]
40. Louie J, Gibby JE, Farnworth MV, Tekavec TN. J Am Chem Soc. 2002; 124:15188–15189. [PubMed: 12487590]
41. Duong HA, Cross MJ, Louie J. J Am Chem Soc. 2004; 126:11438–11439. [PubMed: 15366880]
42. Tekavec TN, Louie J. Org Lett. 2005; 7:4037–4039. [PubMed: 16119961]
43. Tekavec TN, Louie J. J Org Chem. 2008; 73:2641–2648. [PubMed: 18318544]
44. Tekavec TN, Arif AM, Louie J. Tetrahedron. 2004; 60:7431–7437.
45. Tekavec TN, Zuo G, Simon K, Louie J. J Org Chem. 2006; 71:5834–5836. [PubMed: 16839179]
46. Böhm VPW, Weskammp T, Gstottmayr CWK, Herrmann WA. Angew Chem. 2000; 112:1672.Angew Chem Int Ed. 2000; 39:1602–1604.
47. Arduengo AJ III, Krafczyk R, Schmutzler R, Craig HA, Goerlich JR, Marshall WJ, Unverzagt M. Tetrahedron. 1999; 55:14523–14534.
48. Atkinson RS, Grimshire MJ. J Chem Soc Perkin Trans 1. 1986:1215–1217.
49. Nishida M, Shiga H, Mori M. J Org Chem. 1998; 63:8606–8608.

50. Nugent WA, Thorn DL, Harlow RL. J Am Chem Soc. 1987; 109:2788–2796.
51. Ross WJ, Harrison RG, Jolley MRJ, Neville MC, Todd A, Verge JP, Dawson W, Sweatman WJF. J Med Chem. 1979; 22:412–417. [PubMed: 430478]

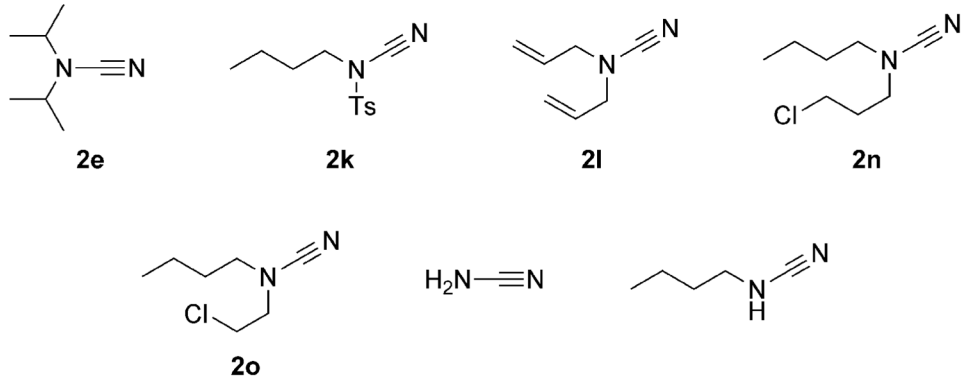


Figure 1.
Examples of cyanamides that are incompatible with the [Ni(cod)$_2$]/NHC-catalyzed cycloaddition.

Table 1

Ligand screening for the [2+2+2] cycloaddition reaction between **1** and **2a**.[a]

Entry	Ligand (mol-%)	Conv. [%][b]	Yield [%][b]
1	IPr (20)[c]	83	78
2	SIPr (20)[c]	100	98
3	IMes (20)[c]	100	98
4	P(*t*Bu)$_3$ (20)	91	45
5	P(Cy)$_3$ (20)	100	81
6	PPh$_3$ (20)	80	25
7	DPPE (10)[c]	47	17
8	BINAP (10)[c]	13	6
9	DPPF (10)[c]	11	6
10	P(OPh)$_3$ (20)	6	0
11	P(O*i*Pr)$_3$ (20)	86	11
12	TMEDA (20)[c]	65	0
13	[Ni(cod)$_2$] (10)	91	0

[a] Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, 10 mol-% [Ni(cod)$_2$], PhMe, room temp., 3 h.

[b] Determined by GC relative to naphthalene as an internal standard.

[c] SIPr = 1,3-bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazolin-2-ylidine, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, IMes = 1,3-bis(1,3,5-trimethylphenyl)imidazol-2-ylidene, DPPE = 1,2-bis(diphenylphosphanyl)ethane, BINAP = *rac*-(1,1′-binaphthalene-2,2′-diyl)bis(di-phenylphosphane), DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Table 2

Comparison of the reaction times for the reaction of **1** and **2a**.[a]

Entry	Ligand	Time [min]	Conv. [%][b]	Yield [%][b]
1	SIPr	15	30	29
2	SIPr	30	75	72
3	SIPr	60	100	98
4	IMes	15	98	98

[a]Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, 5 mol-% [Ni(cod)2], 10 mol-% ligand, PhMe, room temp.

[b]Determined by GC relative to naphthalene as an internal standard.

Table 3

Solvent screening for cycloaddition of **1** and **2a**.[a]

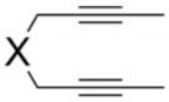
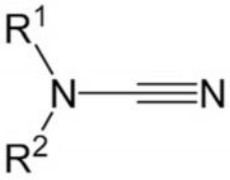
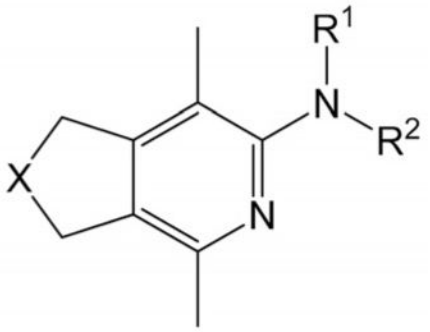
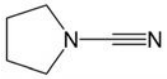
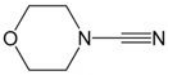
Entry	Solvent	Conv. [%][b]	Yield [%][b]
1	THF	95	67
2	Et_2O	100	86
3	benzene	33	4
4	pentane	100	98
5	1,4-dioxane	100	95
6	toluene	100	98

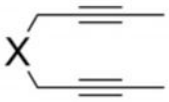
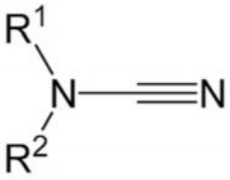
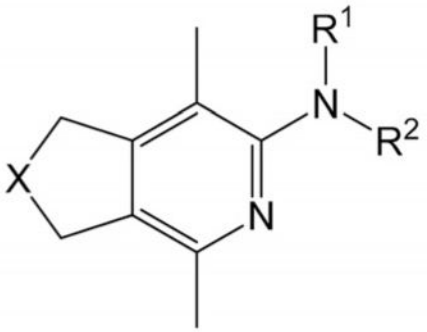
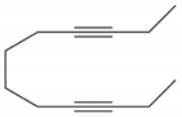
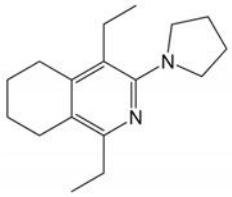
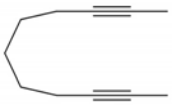
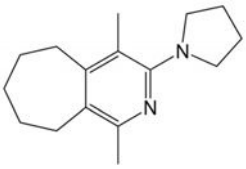
[a] Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, 5 mol-%[Ni(cod)2], 10 mol-% IMes, room temp., 30 min.

[b] Determined by GC relative to naphthalene as an internal standard.

Table 4

Cycloaddition of cyanamides and internal diynes.[a]

Entry	Diyne	Cyanamide	Yield[b]
			
1	X = $C(CO_2Me)_2$ **1**	 **2a**	**3**, 93%
2	**1**	$R^1 = R^2 = Me$ **2b**	**4**, 99%
3	**1**	$R^1 = R^2 = Et$ **2c**	**5**, 93%
4	**1**	$R^1 = R^2 = n$Pr **2d**	**6**, 89%
5	**1**	 **2f**	**7**, 97%
6	**1**	R^1 = Me, R^2 = PMB **2g**	**8**, 87%
7	**1**	$R^1 = R^2$ = Bn **2h**	**9**, 88%
8	**1**	**2i** $R_1 = n$Bu R_2 = Boc	**10**, 82%
9	**1**	$R^1 = n$Bu, R^2 = Ac **2j**	**11**, 87%
10	**1**	$R^1 = n$Bu, $R^2 = CH_2CO_2Me$ **2m**	**12**, 81%
11	**1**	R^1 = Me, R^2 = Ph **2p**	**13**, 90%
12	X = NTs **14**	**2a**	**15**, 84%
13	X = O **16**	**2a**	**17**, 94%

Entry	Diyne	Cyanamide	Yield[b]
			
14	 **18**	**2a**	 **19**, 92
15	 **20**	**2a**	 **21**, 76%

[a] Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, 5 mol-% [Ni(cod)2], 10 mol-% IMes, PhMe, room temp., 30 min.

[b] Isolated yield, average of at least two runs.

[c] No reaction.

Table 5

Cycloaddition reactions of the terminal malonate diyne.[a]

Entry	Diyne	Cyanamide	Yield[b]
1	**25**	**2a**	**26**, 80%
2	**25**	**2f**	**27**, 86%
3	**25**	**2i**	**28**, 82%
4	**25**	**2j**	**29**, 93%
5	**25**	**2g**	**30**, n.r.[c]
6	**25**	**2m**	**31**, n.r[c]
7	**25**	**2p**	**32**, 83%

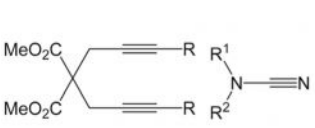
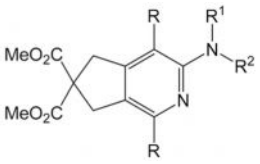
[a]Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, PhMe, 5 mol-% [Ni(cod)2], 10 mol-% SIPr, room temp., 60 min.

[b]Isolated yield, average of at least two runs.

[c]No reaction.

Table 6

Yields from in situ generated Ni–carbene catalyst (rsm = recovered starting material).[a]

Entry	Diyne	Cyanamide	Yield[a]
			
1	R = CH_3 **1**	**2a**	**3**[b], 80%
2	**1**	**2i**	**10**[b], 70%
3	**1**	**2j**	**11**[b], 79%
4	**1**	**2m**	**12**[b], 78%
5	**1**	**2p**	**13**[b], 85%
6	R = H **25**	**2a**	**26**[c], 75%
7	**25**	**2i**	**28**[c], 50% (20% rsm)
8	**25**	**2j**	**29**[c], 30% (32% rsm)
9	**25**	**2p**	**30**[c], 80%

[a] Isolated yields (average of at least two runs).

[b] Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, PhMe, 5 mol-% [Ni(acac)$_2$], 10 mol-% IMes·HCl, 25 mol-% *n*BuLi, room temp., 60 min.

[c] Reaction conditions: 0.1 M diyne, 0.1 M cyanamide, PhMe, 5 mol-% [Ni(acac)$_2$], 10 mol-% SIPr·HBF_4, 25 mol-% *n*BuLi, room temp., 60 min.