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Iridium-Catalyzed [2+2+2] Cycloaddition of α,ω-Diynes with Cyanamides

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Abstract: The complex $[Ir(cod)Cl]_2$/DPPF or *rac*-BINAP is an efficient catalyst for the [2+2+2] cycloaddition of α,ω-diynes with cyanamides. A wide range of cyanamides derived from secondary amines are good coupling partners for α,ω-diynes. The reaction of unsymmetrical α,ω-diynes possessing two different internal alkyne moieties with cyanamides is regioselective. A competitive experiment showed that cyanamide is more reactive than nitrile. This higher reactivity of cyanamide than nitrile was analyzed based on density functional theory (DFT) calculations at the B3LYP level.

Keywords: 2-aminopyridines; cyanamides; cycloaddition; diynes; iridium

Introduction

Heterocyclic compounds constitute an important class of compounds in organic chemistry.[1] New synthetic methods for heterocyclic compounds have been extensively studied. Transition metal-catalyzed cycloadditions provide a new and efficient route to complex heterocyclic compounds that are not accessible by conventional reactions.[2] In particular, reactions involving three π-components provide access to many complex heterocyclic compounds. Since the pioneering work of Yamazaki and Wakatsuki,[3] the [2+2+2] cycloaddition of alkynes with nitriles has been studied as an efficient and environmentally benign route to pyridines, in contrast to the traditional route based on a condensation reaction under strongly acidic or basic conditions. Co,[4] Ru,[5] Rh,[6] Ni[7] and Fe[8] have all been reported as catalysts for the [2+2+2] cycloaddition of alkynes with nitriles. Much attention has been paid to the scope of nitriles. Nitriles in which a functional group is directly connected to the nitrile carbon are especially important, because [2+2+2] cycloaddition with such nitriles gives functionalized pyridines. Despite its importance in pyridine synthesis, very few studies have examined [2+2+2] cycloaddition with functionalized nitriles. An interesting example is the Ru-catalyzed reaction, in which the scope of nitriles is limited. Only functionalized nitriles such as cyanoformate, α-halonitrile and dicyanide can be used for the reaction.[5] Simple nitriles cannot be used for the Ru-catalyzed reaction. Cyanamide is an important nitrile in which an amino group directly connects to a nitrile carbon.[9] Much attention has been paid to cyanamide as a substrate for a transition metal-catalyzed reaction.[10] With regard to [2+2+2] cycloaddition, the first example of the reaction of alkyne with cyanamide (H_2NCN) was reported by Bönnemann in 1984.[11] The reaction of cyanamide derived from a secondary amine with acetylene under photo-irradiation conditions was reported by Heller.[12] Maryanoff reported the $CpCo(CO)_2$-catalyzed reaction of α,ω-diynes with cyanamides (R_2NCN).[13] A series of cyanamides (R_2NCN) was examined by Maryanoff. Louie reported the Ni/NHC- and Fe-catalyzed reaction of α,ω-diynes with cyanamides.[14] Wan also reported the Fe-catalyzed reaction.[15] Only a single experiment has been reported with an Rh catalyst.[6d] However, a new catalyst is still needed to expand the reaction scope and improve the selectivity. 2-Aminopyridine is an attractive intermediate for the synthesis of biologically

active compounds.[16] The general method for the synthesis of 2-aminopyridines is the nucleophilic substitution of 2-halopyridines. A substitution reaction is useful for the construction of a simple 2-aminopyridine ring.[17] However, such a reaction is not suitable for the construction of a more complex multisubstituted 2-aminopyridine ring because of the need for further synthetic elaboration to introduce other substituents into the pyridine ring. Further development of the cycloaddition of alkynes with cyanamides has been desired as an efficient and convergent method for the construction of a multisubstituted 2-aminopyridine ring in a single operation.

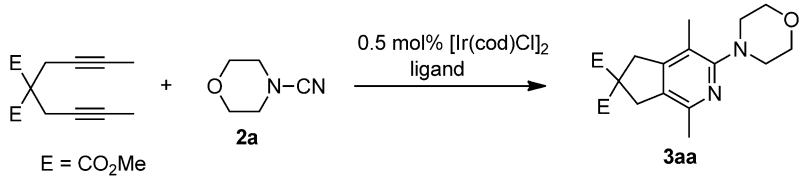
In the course of our study on iridium-catalyzed carbon-carbon bond-forming reactions,[18] we found that $[Ir(cod)Cl]_2$/BINAP was an efficient catalyst for the [2+2+2] cycloaddition of α,ω-diynes with nitriles.[19] One of the advantages of $[Ir(cod)Cl]_2$ catalyst over other transition metals, especially Cp- or Cp*-coordinated transition metals, is that we can alter the catalytic activity and selectivity by choosing appropriate phosphines. The iridium-catalyzed reaction has a broader scope of nitriles, since both functionalized nitriles and unactivated nitriles can be used. Our previous study[19] showed that α- or β-aminonitrile was a good coupling partner for α,ω-diynes. An amino group did not inhibit the reaction despite its ability to coordinate to the iridium center. This result prompted us to examine the cycloaddition with cyanamide in which an amino group is directly connected to a nitrile carbon. We report here the [2+2+2] cycloaddition of α,ω-diynes with cyanamides.

Results and Discussion

Screening of Ligands and Optimization of the Reaction Conditions

Diyne **1a** reacted with cyanamide **2a** to give 2-aminopyridine **3aa**. The phosphine ligand had a profound effect on the reaction. The screening of phosphine ligands was performed in the reaction of diyne **1a** with 1.2 equiv. of cyanamide **2a** in the presence of

Table 1. Reaction of diyne **1a** with cyanamide **2a**.[a]



Entry	Ligand	Conditions	Yield of **3aa** [%][b]
1	none	benzene, reflux, 24 h	0
2[c]	PPh_3	benzene, reflux, 24 h	0
3	DPPE	benzene, reflux, 13 h	76
4	DPPP	benzene, reflux, 24 h	0
5	DPPB	benzene, reflux, 24 h	2
6	DPPPen[d]	benzene, reflux, 24 h	0
7	DPPF	benzene, reflux, 1 h	>99
8	*rac*-BINAP	benzene, reflux, 1 h	97
9	F-DPPE[e]	benzene, reflux, 24 h	98
10	BIPHEP	benzene, reflux, 24 h	80
11	DPPBenzene	benzene, reflux, 24 h	66
12	DPPF	dioxane, 80 °C, 1 h	93
13	DPPF	DCE, 80 °C, 1 h	96
14	DPPF	THF, reflux, 1 h	>99
15	DPPF	benzene, 50 °C, 24 h	84
16	*rac*-BINAP	benzene, 50 °C, 24 h	80
17[f]	DPPF	benzene, r.t., 24 h	0
18	*rac*-BINAP	benzene, r.t., 24 h	5

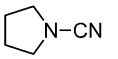
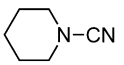
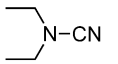
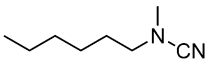
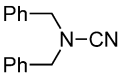
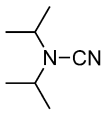
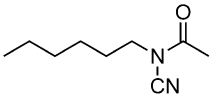
[a] A mixture of diyne **1a** (1 mmol), cyanamide **2a** (1.2 mmol), $[Ir(cod)Cl]_2$ (0.005 mmol), ligand (0.01 mmol) and solvent (2.5 mL) was stirred.
[b] Isolated yield based on the amount of **1a**.
[c] PPh_3 (0.02 mmol).
[d] 1,5-Bis(diphenylphosphino)pentane.
[e] 1,2-Bis[di(pentafluorophenyl)phosphino]ethane.
[f] **2a** (3 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), benzene (5 mL).

0.5 mol% $[Ir(cod)Cl]_2$ in refluxing benzene at a ratio of P/Ir = 2. The results are summarized in Table 1. $[Ir(cod)Cl]_2$ without any ligand and $[Ir(cod)Cl]_2$ with PPh_3 did not give **3aa** (entries 1 and 2). A bidentate phosphine ligand was effective. DPPE gave **3aa** in 76% yield (entry 3). DPPP, DPPB and DPPPen were inferior to DPPE (entries 4–6). DPPF gave the best result, and product **3aa** was obtained in quantitative yield (entry 7). *rac*-BINAP and F-DPPE were as effective as DPPF (entries 8 and 9). BIPHEP gave **3aa** in 80% yield (entry 10). DPPBenzene was less effective than BIPHEP (entry 11). DPPF, *rac*-BINAP and F-DPPE were selected as promising ligands. The effect of the solvent was examined at 80 °C (entries 12–14). Benzene gave **3aa** in a slightly higher yield than DCE and dioxane (entries 12 and 13). The reaction under refluxing THF gave **3aa** in quantitative yield (entry 14). The effect of temperature on the reaction was examined by using DPPF and *rac*-BINAP as a ligand. A decrease in the reaction temperature from 80 °C to 50 °C decreased the yield of **3aa** (entries 15 and 16). The reaction at room temperature did not give **3aa** (entries 17 and 18). The reaction temperature needed to be above 50 °C to obtain **3aa** in high yield. Notably, our Ir catalyst requires 0.5 mol% catalyst loading.

Scope of Cyanamides 2

We subjected various cyanamides **2b–j** to the reaction of **1a** under the optimized conditions as noted above. Diyne **1a** reacted with various cyanamides **2b–i** to give **3ab–ai**. The results are summarized in Table 2. Cyanamides derived from secondary amines are good coupling partners with diyne **1a**. The reactions of **1a** with **2b** and **2c** gave **3ab** and **3ac** in respective yields of 91% and 97% (entries 1 and 2). Similarly, cyanamides derived from acyclic secondary amines smoothly underwent cycloaddition with **1a**. Products **3ad** and **3ae** were obtained in respective yields of 93% and 92% (entries 3 and 4). Cyanamide **2f**, derived from an aromatic secondary amine, gave a good result, and product **3af** was obtained in quantitative yield (entry 5). An increase in the steric bulk of the cyanamide decreased the yield of the product. The reactions with **2g** and **2h** gave slightly lower yields compared to those with **2b–f** (entries 6 and 7). The reaction of **1a** with diisopropylcyanamide (**2i**), which is a more hindered cyanamide than **2a–h**, gave **3ai** in 31% yield (entry 8). In contrast, cyanamide derived from a primary amine such as *n*-hexylamine did not react with diyne **1a**, and the corresponding product was not obtained. Cyanamide **2j** bearing an acetyl group could be used for the reaction, and product **3aj** was obtained in 79% yield under more forcing conditions (entry 9).

Table 2. Reaction of diyne **1a** with cyanamide **2**.[a]

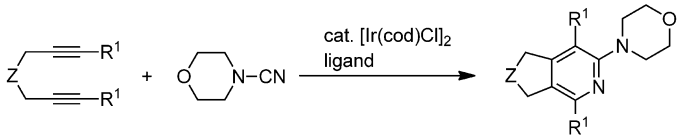
Entry	Cyanamide **2**		Product	Yield of **3** [%][b]
1[c]		**2b**	**3ab**	91
2		**2c**	**3ac**	97
3		**2d**	**3ad**	93
4		**2e**	**3ae**	92
5		**2f**	**3af**	99
6[d]		**2g**	**3ag**	85
7		**2h**	**3ah**	82
8[e]		**2i**	**3ai**	31
9[f]		**2j**	**3aj**	79

[a] A mixture of diyne **1a** (1 mmol), cyanamide **2** (1.2 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), ligand (0.02 mmol) and benzene (2.5 mL) was stirred under refluxing benzene for 1 h.
[b] Isolated yield based on the amount of **1a**.
[c] For 24 h.
[d] For 15 h.
[e] **2i** (2.5 mmol).
[f] $[Ir(cod)Cl]_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol), refluxing xylene (2.5 mL) for 24 h.

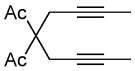
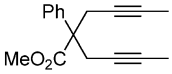
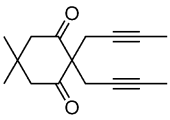
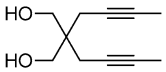
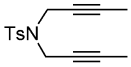
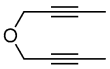
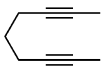
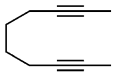
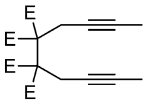
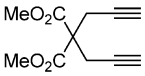
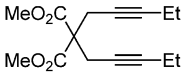
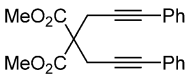
Scope of Diynes 1

We examined the reactions of various diynes **1b–m** with cyanamide **2a**. The results are summarized in Table 3. The tether structure of the diyne had a considerable effect on the reaction. Diyne **1b** derived

Table 3. Reaction of diyne **1** with cyanamide **2a**.[a]



1 **2a** **3**

Entry	Diyne **1**		Conditions	Product	Yield of **3** [%][b]
1		**1b**	benzene, reflux, 1 h	**3ba**	97
2[c]		**1c**	benzene, reflux, 1 h	**3ca**	99
3		**1d**	benzene, reflux, 1 h	**3da**	97
4		**1e**	benzene, reflux, 24 h	**3ea**	50
5[d]		**1f**	toluene, reflux, 24 h	**3fa**	79
6[e]		**1g**	toluene, reflux, 3 h	**3ga**	59
7[e]		**1h**	benzene, reflux, 24 h	**3ha**	59
8[f]		**1i**	xylene, reflux, 24 h	**3ia**	0
9	 E = CO_2Et	**1j**	benzene, reflux, 1 h	**3ja**	92
10		**1k**	xylene, reflux, 24 h	**3ka**	73
11		**1l**	benzene, reflux, 1 h	**3la**	92
12[g]		**1m**	benzene, reflux, 3 h	**3ma**	90

[a] A mixture of diyne **1** (1 mmol), cyanamide **2a** (1.2 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol) and solvent (2.5 mL) was stirred.
[b] Isolated yield based on the amount of **1**.
[c] Diyne **1c** (0.5 mmol), cyanamide **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.005 mmol), DPPF (0.01 mmol) and benzene (2.5 mL).
[d] Cyanamide **2a** (5 mmol), *rac*-BINAP (0.02 mmol).
[e] Diyne **1** (0.5 mmol), cyanamide **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), *rac*-BINAP (0.02 mmol) and solvent (2.5 mL).
[f] $[Ir(cod)Cl]_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and solvent (5 mL).
[g] *rac*-BINAP (0.02 mmol).

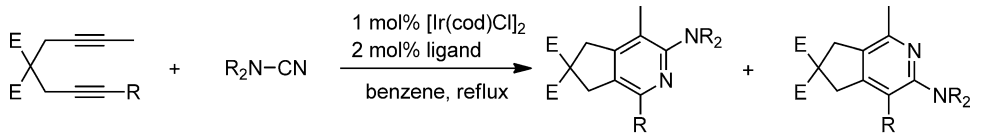
from acetylacetone and diyne **1c** derived from benzyl acetate reacted with **2a** to give **3ba** and **3ca** in nearly quantitative yields (entries 1 and 2). Similarly, diyne **1d** derived from methone underwent cycloaddition with **2a** to give **3da** in 97% yield (entry 3). These three diynes **1b–d** gave products in a yield that was comparable to that with diyne **1a** derived from malonate. As mentioned above, two carbonyl groups at the 5-position gave a good result. Two hydroxymethyl groups at the 5-position of 2,7-nonadiyne decreased the yield. The reaction of **1e** with **2a** gave **3ea** in 50% yield (entry 4). Heteroatom-tethered diynes were examined. The reaction of **1f** with **2a** gave **3fa** in 79% yield (entry 5). The reaction of ether-tethered diyne **1g** gave a lower yield than that with tosylamide-tethered diyne **1f** (entry 6). The reaction provides an atom-economical route to biologically important pyridine-based fused heterocycles.[20] Diyne **1h** with no substituents at the 5-position underwent the reaction with **2a** to give **3ha** in 59% yield (entry 7), which is lower than the yield with diynes **1a–d**. This result clearly showed that the Thorpe–Ingold effect is important for the reaction with cyanamide. With these three diynes **1f–h**, *rac*-BINAP was better than DPPF (entries 5–7). Various bicyclic pyridines with five-membered rings were formed by the reaction. We tried to form bicyclic pyridine with a six-membered ring. Diyne **1i** with no substituents at the 5- and 6-positions gave no product because of the lack of a Thorpe–Ingold effect[21] (entry 8). The substituents at the 5- and 6-positions were essential for cyclization to give a bicyclic pyridine with a six-membered ring. Diyne **1j** smoothly underwent cycloaddition with **2a** to give **3ja** in 92% yield (entry 9). Cyclization is effective for the formation of a six-membered ring. Terminal diyne **1k** could be used for the reaction. The reaction of **1k** with **2a** gave **3ka** in 73% yield under more forcing reaction conditions than those for **1a** (entry 10). With a terminal diyne, pyridine formation competed with the self-dimerization or self-trimerization of **1k**. Ethyl-substituted diyne **1l** reacted with **2a** to give **3la** in 92% yield (entry 11). The reaction of **1l** gave a yield comparable to that of **1a**. Phenyl-substituted diyne **1m** reacted with **2a** to give **3ma** in 90% yield (entry 12). *rac*-BINAP was better than DPPF for the reaction of **1m**. More-hindered diynes **1l–m** than **1a** could be used for the reaction.

Regioselective [2+2+2] Cycloaddition of Unsymmetrical Diynes 1n–q

In cycloaddition with nitriles, one of the advantages of an iridium catalyst over other transition metal catalysts is that the reaction is highly regioselective. We previously reported that unsymmetrical diynes possessing two different internal alkyne moieties underwent completely regioselective cycloaddition to give a single product.[19] The regioselectivity could be reasonably explained by the electronic effect of a substituent on an alkyne carbon. The regioselectivity of the reactions of unsymmetrical internal diynes with cyanamides has been examined.[14b,c,15] Further improvements to achieve a completely regioselective reaction have been desired. We examined the regioselectivity of the reaction with cyanamide. We subjected unsymmetrical diynes **1n–q** to the reaction with cyanamides **2a** and **2d** under the optimized conditions (Table 4). The structure of the products was determined on the basis of 2D-NMR analysis (see the Supporting Information, pp S27, S29, S31, S33, S35, S37, S39, S41, S43, S45, S47). Phenyl-substituted diyne **1n** underwent cycloaddition in the presence of DPPF ligand with **2a** to give a 70:30 mixture of **4na** and **5na** in 86% yield (entry 1). The regioselectivity was improved by the use of *rac*-BINAP instead of DPPF. The reaction of **1n** with **2a** in the presence of *rac*-BINAP ligand gave **4na** in 94% yield as a single product in which a Ph group was substituted at the α-position (entry 2). The reaction of **1n** with **2d** gave **4nd** in 96% yield as a single product with the same regioselectivity (entry 3). The reaction of 2-pyridyl-substituted diyne **1o** was also regioselective and gave 2,2′-bipyridine derivatives. Products **4oa** and **4od** were obtained as a single product in respective yields of 93% and 95% (entries 4 and 5). This reaction provides a new route to functionalized 2,2′-bipyridines, which is expected to have various applications. TMS-substituted diyne **1p** underwent cycloaddition with **2a** to give **5pa** in 90% yield as a single product in which the TMS group was substituted at the β-position (entry 6). The reaction of **1p** with **2d** gave **5pd** in 95% yield with the same regioselectivity (entry 7). Notably, both reactions exclusively gave the more hindered product. The regioselectivity of the reaction of **1p** was opposite that of **1n–o**. Ethyl-substituted diyne **1q** underwent cycloaddition with **2a** to give a 67:33 mixture of **4qa** and **5qa** in 94% yield (entry 8). The reaction of **1q** with **2d** gave a similar product distribution (entry 9).

The key intermediate in the cycloaddition is iridacyclopentadiene[22] which is formed by the oxidative cyclization of α,ω-diyne to iridium diphosphine species. The reaction of iridacyclopentadiene with cyanamide gives the 2-aminopyridine product. The regioselectivity of the reaction of an unsymmetrical diyne is determined when iridacyclopentadiene reacts with the carbon-nitrogen triple bond in cyanamide. In our previous paper,[19] we showed that the regioselectivity of the reaction with nitriles was controlled by an electronic effect. Specifically, the more electron-deficient α-carbon preferentially reacts with the more electron-rich nitrile nitrogen.

Table 4. Regioselective [2+2+2] cycloaddition of diynes **1n–q** with **2a** and **2d**.[a]



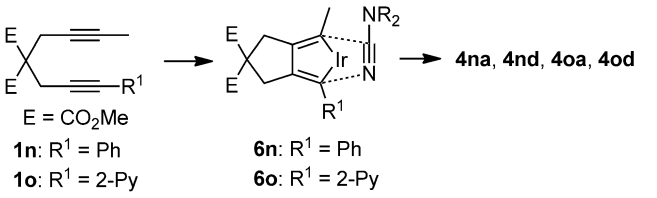
1 **2** **4** **5**

Entry	Diyne **1**	Cyanamide **2**	Ligand	Product	Yield [%][b]	Ratio **4**/**5**
1	**1n**: R = Ph, E = CO_2Me	**2a**	DPPF	**4na**, **5na**	86	70/30
2	**1n**: R = Ph, E = CO_2Me	**2a**	*rac*-BINAP	**4na**	94	> 99/1
3	**1n**: R = Ph, E = CO_2Me	**2d**	*rac*-BINAP	**4nd**	96	> 99/1
4[c]	**1o**: R = 2-Py, E = CO_2Me	**2a**	*rac*-BINAP	**4oa**	93	> 99/1
5[c]	**1o**: R = 2-Py, E = CO_2Me	**2d**	*rac*-BINAP	**4od**	95	> 99/1
6[d]	**1p**: R = Me_3Si, E = CO_2Me	**2a**	*rac*-BINAP	**5pa**	90	1/> 99
7[d]	**1p**: R = Me_3Si, E = CO_2Me	**2d**	*rac*-BINAP	**5pd**	95	1/> 99
8[e]	**1q**: R = Et, E = CO_2Et	**2a**	*rac*-BINAP	**4qa, 5qa**	94	67/33
9[f]	**1q**: R = Et, E = CO_2Et	**2d**	*rac*-BINAP	**4qd, 5qd**	94	73/27

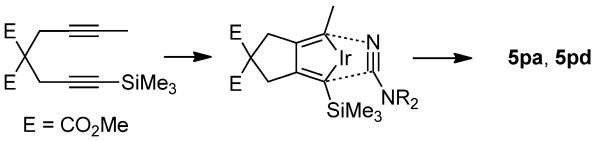
[a] A mixture of diyne **1** (1 mmol), cyanamide **2a** or **2d** (1.2 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), ligand (0.02 mmol) and benzene (2.5 mL) was stirred under refluxing for 24 h.
[b] Isolated yield based on the amount of **1**.
[c] For 1 h.
[d] $[Ir(cod)Cl]_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and benzene (5 mL).
[e] Diyne **1q** (0.95 mmol), cyanamide **2d** (1.23 mmol).
[f] Diyne **1q** (1.05 mmol), cyanamide **2d** (1.37 mmol).

With diynes **1n** and **1o**, a phenyl group or 2-pyridyl group is substituted at the α-carbon in iridacyclopentadienes **6n** or **6o**. The Hammett constant shows that a phenyl group and a 2-pyridyl group are more electron-withdrawing than a methyl group.[23] Thus, a phenyl- or 2-pyridyl-substituted α-carbon is more electron-deficient than a methyl-substituted α-carbon. Consequently, a phenyl- or 2-pyridyl-substituted α-carbon reacts with an electron-rich nitrile nitrogen to give **4na**, **4nd**, **4oa** and **4od** (Scheme 1).

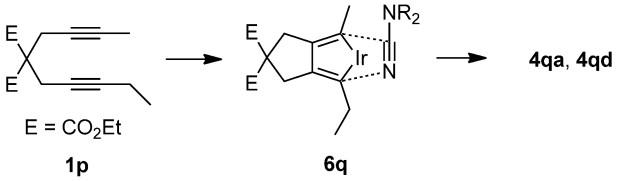
With diyne **1p**, a trimethylsilyl group is substituted at the α-carbon in iridacyclopentadiene **6p**. Based on the Hammett constant, a trimethylsilyl group is more electron-donating than a methyl group.[23] The electron-donating property of a trimethylsilyl group makes a trimethylsilyl-substituted α-carbon more electron-rich than a methyl-substituted α-carbon. Consequently, a trimethylsilyl-substituted α-carbon reacts with a more electron-deficient nitrile carbon to give **5pa** and **5pd**. The steric effect of a trimethylsilyl group should lead to the formation of the less-hindered product **4pa** and **4pd**. However, the absence of the less-hindered product shows that the steric effect does not determine the regioselectivity. Why doesn't the steric effect of a trimethylsilyl group determine the regioselectivity? The DFT calculation for the reaction mechanism in our previous paper showed consecutive bond formation between iridacyclopentadiene and nitrile (Scheme 2).[19] Nitrile coordinates to



Ph and 2-pyridyl groups are more electron-withdrawing than Me group.
More electron-deficient α-carbon reacts with nitrile nitrogen.

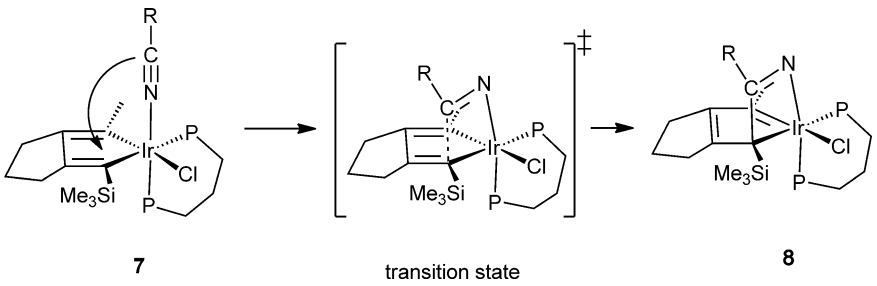


Me_3Si group is more electron-donating than Me group.
More electron-rich α-carbon reacts with nitrile carbon.



Et group and Me group are electronically the same.
Less-hindered α-carbon reacts with a substituted nitrile carbon.

Scheme 1. Regioselective reaction of iridacyclopentadienes **6n–q** with cyanamide **2**.

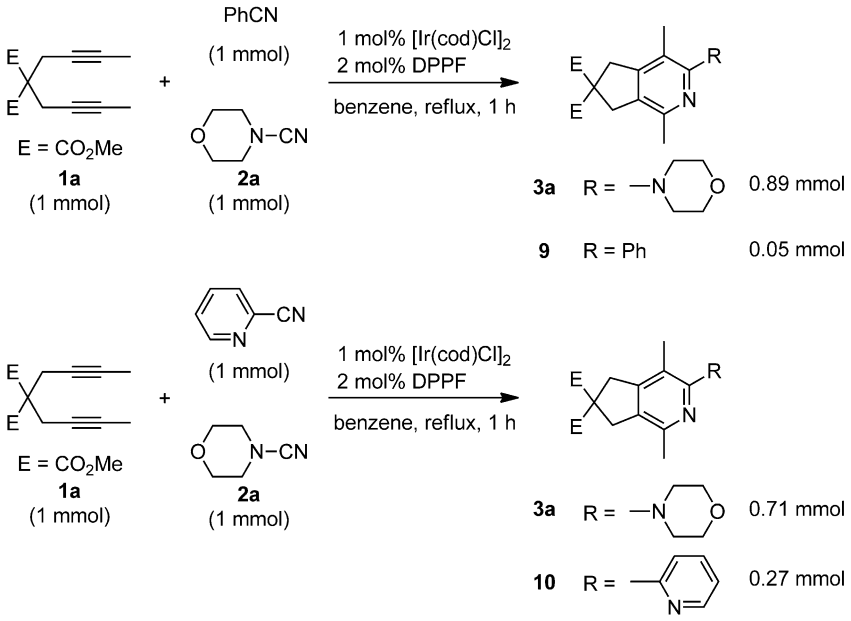


Scheme 2. Reaction of α-trimethylsilyl-substituted iridacyclopentadiene with nitrile.

the iridacyclopentadiene plane in an end-on mode. This end-on coordination delivers nitrile perpendicular to the iridacyclopentadiene plane in intermediate **7**. C–C bond formation *via* a transition state transforms an *sp*-hybridized nitrile carbon into an sp^2-hybridized imine carbon. The substituent on the nitrile carbon bends away from the newly formed C=N bond. In intermediates **7** and **8**, the distance between the TMS group and R group seems to be too large to allow for their effective steric interaction (Scheme 2). Thus, regioselection toward two α-carbons is only influenced by an electronic effect. With diyne **1q**, a methyl group and an ethyl group are substituted at the α-carbon in iridacyclopentadiene **6q**. These groups are electronically similar, but sterically different. To avoid steric repulsion between the Et group and the R_2N group, the less hindered Me-substituted α-carbon reacts with a nitrile carbon predominantly. The steric effect determines the regioselection in this case.

Competitive Reaction of Cyanamide 2a and Benzonitrile

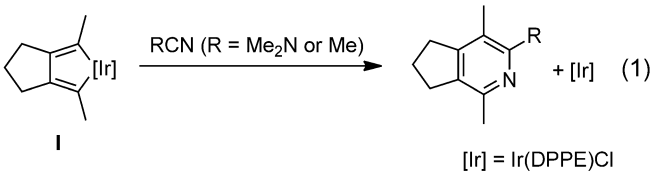
To compare the reactivity of cyanamide to that of nitrile, we performed a competitive experiment. The results are shown in Scheme 3. The reaction of 1 mmol of diyne **1a** with an equal amount of a mixture of **2a** and benzonitrile under the optimized conditions in Table 1 gave 0.89 mmol of **3a** and 0.05 mmol of **9**. Similarly, the reaction of 1 mmol of diyne **1a** with an equal amount of a mixture of **2a** and 2-cyanopyridine gave 0.71 mmol of **3a** and 0.21 mmol of **10**. In both reactions, the product derived from cyanamide **2a** was predominant. Based on these results, the order of the relative reactivities proved to be cyanamide **2a** > 2-cyanopyridine > benzonitirile.



Scheme 3. Competitive reaction of cyanamide **2a** and benzonitrile or 2-cyanopyridine.

Theoretical Calculations for the Difference in Reactivity between Cyanamide and Nitrile

To explain why cyanamide is more reactive than nitrile, we examined DFT calculations for the reaction mechanism. In our previous study, we examined the reaction mechanism of the model reaction system for iridium-catalyzed cycloaddition with nitriles by using DFT calculations, and proposed a reaction pathway where the iridacyclopentadiene generated by oxidative cyclization of α,ω-diyne reacts with nitrile to give the iridium pyridine complex *via* an azairidabicyclo[3.2.0]heptatriene complex.[19] Based on the results, we further carried out B3LYP DFT calculations[24,25] (LANL2DZ[26] for Ir atom and 6-31G*[27] for other atoms) to examine the reaction pathway from the iridacyclopentadiene to the η^4-complex in the model reaction [Eq (1)], and discuss the difference in the reactivity between Me_2NCN and MeCN.



The energy diagrams and optimized structures are shown in Figure 1 and Figure 2, respectively. The end-on coordination of Me_2NCN to iridacyclopentadiene **I** gives complex **II**. The relative Gibbs free energy at 298 K ($\Delta G^{298\,K}$) of **II** is 4.5 kcal mol^{-1}.[28] The first bond formation between the cyanamide carbon and the C-5 atom gives the azairidabicyclo[3.2.0]heptatriene complex **III** through transition state **TSI**.[29] The relative free energies of **TSI** and **III** are 20.4 and 9.5 kcal mol^{-1}, respectively, and the barrier height of **TSI** from **II** is 15.9 kcal mol^{-1}. Subsequent bond formation between the cyanamide nitrogen and the C-2 atom gives η^4-pyridine Ir complex **IV** *via* **TSII**. The relative free energy of **TSII** is 16.5 kcal mol^{-1}, and the barrier height of **TSII** from **III** is 7.0 kcal mol^{-1}, which is smaller than that of **TSI**.

In the case of MeCN, the examined reaction pathway corresponds to **II′**→**TSI′**→**III′**→**TSII′**→**IV′**, as shown in Figure 1. The initial end-on complex **II**, in which the σ-lone pair orbital at the nitrogen plays an important role, has almost the same free energy (4.5 kcal mol^{-1}) as the complex **II′** (4.2 kcal mol^{-1}). On the other hand, the relative free energy of **TSI** (20.4 kcal mol^{-1}) is slightly lower than that of **TSI′** (21.8 kcal mol^{-1}). Moreover, the relative energy of **TSII** (16.5 kcal mol^{-1}) is much lower than the energy of **TSII′** (22.2 kcal mol^{-1}). These results show that the

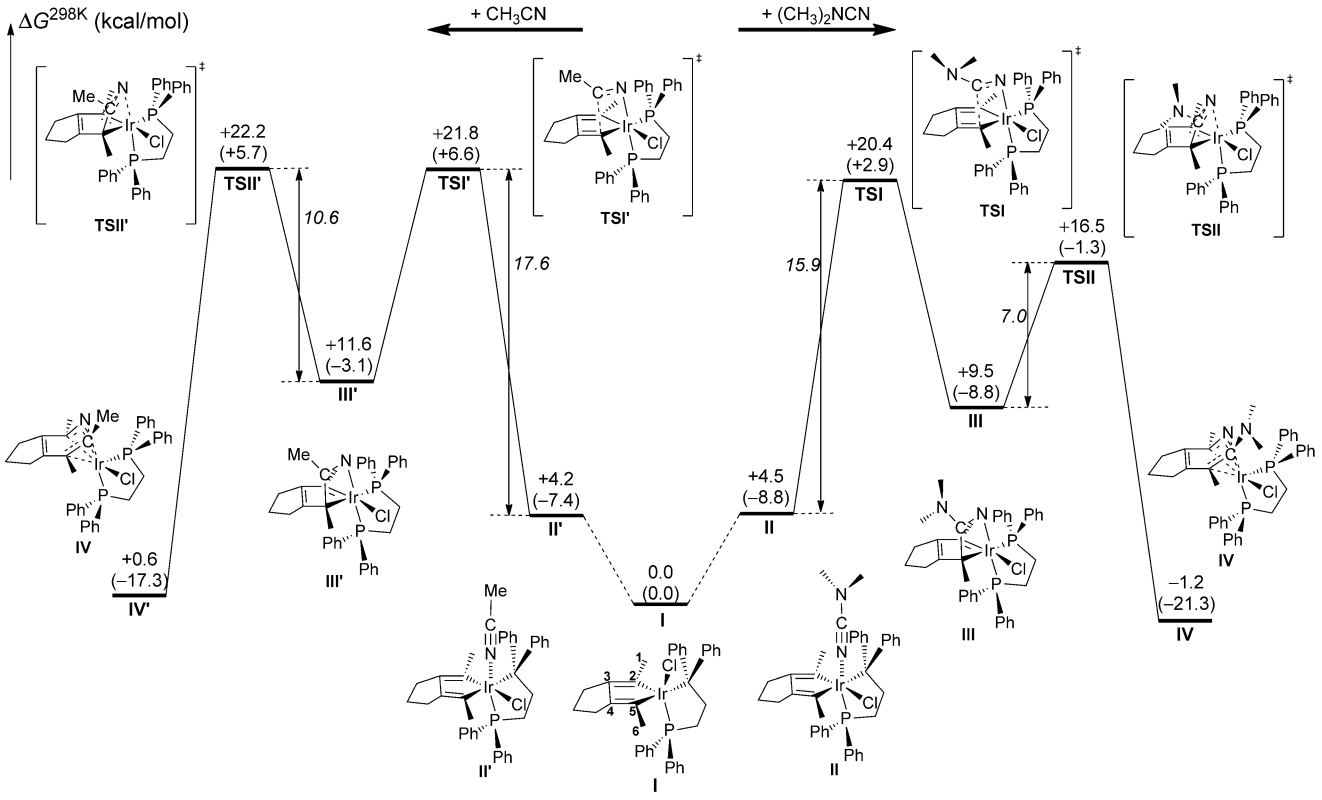


Figure 1. Relative Gibbs free energy ($\Delta G^{298\,K}$) diagram (kcal mol^{-1}) for the model reaction pathways. Relative energies (ΔE) are in parentheses.

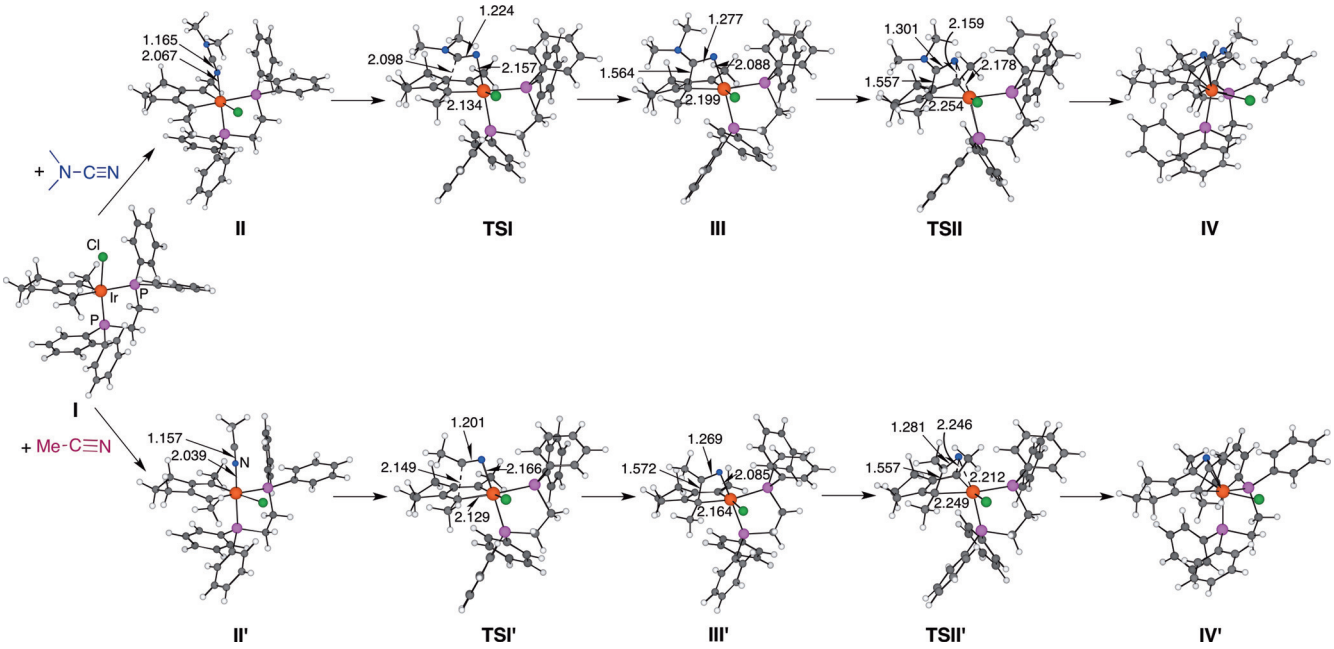


Figure 2. Optimized structures of stationary points for the model reaction pathways. Bond lengths are in angstroms.

reaction of **I** with Me_2NCN is preferred to that with MeCN.

At the first bond-formation step *via* **TSI′** for the reaction of MeCN, electron delocalization from the π occupied orbital (HOMO) in MeCN to the LUMO, which is localized at the Ir atom in iridacyclopentadiene, strengthens the Ir–N bond (Figure 3a), while electron delocalization from the HOMO of iridacyclopentadiene to the π* unoccupied orbital (LUMO) in MeCN is responsible for C–C bond formation (Figure 3b).

In the subsequent step *via* **TSII′**, electron delocalization from iridacyclopentadiene to MeCN (Figure 4a) participates not only in C–C bond formation but also in N–C bond formation. On the other hand, both electron delocalization from the π orbital in MeCN to the LUMO in iridacyclopentadiene (Figure 4b) and delocalization from the other π orbital in MeCN to the (LU+9)MO in iridacyclopentadiene (Figure 4c) contribute to N–C bond formation.

The orbital energy diagrams near frontier orbitals of MeCN and Me_2NCN are shown in Figure 5. The orbital energies of HO and (HO-1) MOs in Me_2NCN are higher than those of the corresponding two degenerate π orbitals in MeCN. This suggests that the π-nucleophilicity of the cyano group in Me_2NCN is stronger than that in MeCN. Thus, the electron delocalization from Me_2NCN to iridacyclopentadiene (Figure 3a, and Figure 4b, c) is enhanced. As a result, the relative energies of **TSI** and **TSII** are lower than those of **TSI′** and **TSII′**. This difference is responsible for the higher reactivity of cyanamide than nitrile.

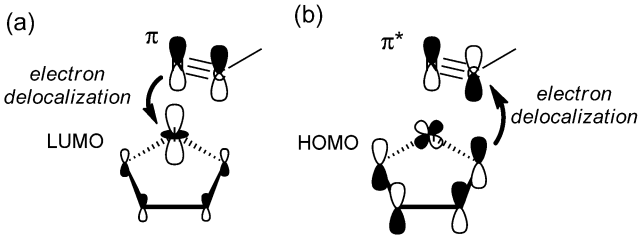


Figure 3. Orbital interactions between iridacyclopentadiene and MeCN at **TSI′**.

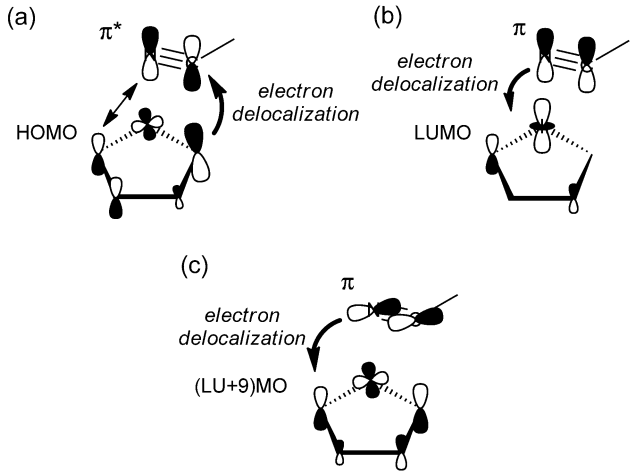


Figure 4. Orbital interactions between iridacyclopentadiene and MeCN at **TSII′**.

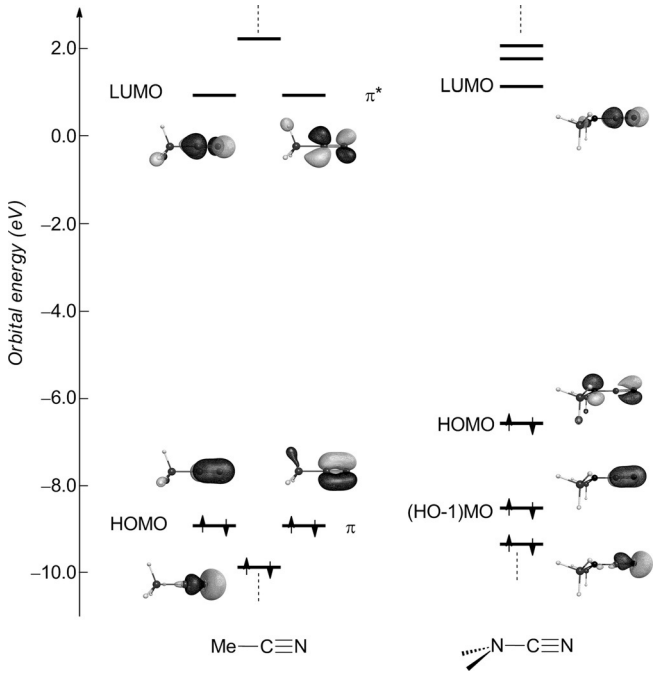


Figure 5. Orbital energy diagrams of MeCN and Me_2NCN at the B3LYP/6-31G* level.

Conclusions

We have developed a new and efficient catalyst for the cycloaddition of alkynes with cyanamides. Our catalyst system offers considerable advantages compared to previously reported catalyst systems. (i) The experimental procedure is more convenient than any previously reported. Pre-treatment of the catalyst system is not necessary. The procedure simply requires mixing of $[Ir(cod)Cl]_2$ and an appropriate diphosphine ligand in solvent before the addition of substrates. In the case of the Ni catalyst,[14c] air-sensitive $Ni(cod)_2$ and free NHC in DCE must be stirred for at least 4 h before the reaction. In the case of the Fe catalyst, an Fe(II) salt must be reduced to a low-valent Fe catalyst species by Zn before the reaction.[14b,15] (ii) The catalytic activity can be altered at will through the use of various commercially available phosphines. (iii) Electronically different unsymmetrical diynes undergo highly regioselective cycloaddition. The regioselectivity can be explained by electronic effects.

Cyanamide is a good substrate for the iridium-catalyzed [2+2+2] cycloaddition of α,ω-diynes. The reaction is an atom-economical route to 2-aminopyridines. The results described here should lead to new opportunities for the application of organoiridium chemistry in cycloaddition. Further theoretical studies will be needed to explore the substrate scope and mechanistic considerations.

Experimental Section

General Methods and Materials

^1H and ^{13}C NMR spectra were measured on JEOL JNM-ECP 500A, JEOL ECS-400 and JEOL ECX 500II spectrometers using TMS as an internal standard. Samples were dissolved in $CDCl_3$. GC analyses were performed on a Shimadzu GC-14B or a Shimadzu GC-2014 using 3.2 mm × 2 m glass columns packed with 5% OV-17 on 60/80 mesh Chromosorb WAW-DMCS. The products were purified by column chromatography on 63–210 mesh silica gel (Kanto Kagaku; Silica Gel 60N). High-resolution mass spectra were obtained with a JEOL Mstation JMS-700. All reagents and solvents were dried and purified before use by the usual procedures. $[Ir(cod)Cl]_2$ was prepared as described previously.[30] Diynes **1a–d**,[19] **1e**,[31] **1f**,[19] **1g** and **1h**,[32] **1j**,[19] **1k**,[33] **1l**,[19] **1m**,[34] **1n**,[19] **1o** and **1p**,[35] and **1q**[36] were prepared as described in the literature. Diyne **1i** was purchased. Cyanamides **2b**,[14c] **2c**,[14b] **2d**,[14c] **2f**,[14c] **2h**,[37] and 2i[15] were prepared as described in the literature. Cyanamide **2a** was purchased.

Procedure for the Preparation of Cyanamides

CAUTION: cyanogen bromide is toxic, handle in a ventilation hood. Care should be taken during both the set-up and work-up of cyanation reactions.

***n*-Hexylmethylcyanamide (2e):** *N*-Methylhexylamine (1.030 g, 8.94 mmol) was added to a solution of cyanogen bromide (552 mg, 5.21 mmol) dissolved in dry Et_2O/THF (1:1) (16 mL) at 0 °C. The solution was then stirred for 3 h. Solids were then filtered off through a pad of celite, and the filtrate was washed with H_2O. The organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography of the residue gave **2e** (hexane/AcOEt = 4/1; yield: 409 mg (2.92 mmol, 65%); yellow oil; $R_f = 0.55$ (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): $\nu = 2956$, 2929, 2860, 2210, 1465, 1379, 1313, 1258, 1209, 1167, 1107, 1061, 894, 784, 730, 638, 609, 598, 561 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.90$ (t, J = 7.0 Hz, 3H), 1.28–1.39 (m, 6H), 1.59–1.67 (m, 2H), 2.85 (s, 3H), 2.96 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 13.9$, 22.4, 26.0, 27.1, 31.3, 38.7, 52.9, 118.6; HR-MS (EI) $m/z = 140.1314$ $[M]^+$, calcd. for $C_8H_{16}N_2$: 140.1313.

Cyclohexylmethylcyanamide (2g): The title compound was prepared according to the procedure for the preparation of **2e** using *N*-methylcyclohexylamine (558 mg, 4.93 mmol) and cyanogen bromide (318 mg, 3.00 mmol). Column chromatography of the residue gave **2g** (CH_2Cl_2); yield: 312 mg (2.26 mmol, 92%); colorless oil; $R_f = 0.48$ (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): $\nu = 3006$, 2935, 2858, 2208, 1747, 1451, 1384, 1347, 1269, 1236, 1217, 1169, 1130, 1052, 992, 924, 892, 822, 752, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.15$–1.20 (m, 1H), 1.23–1.32 (m, 2H), 1.34–1.42 (m, 2H), 1.63–1.66 (m, 1H), 1.82–1.86 (m, 2H), 1.96–1.99 (m, 2H), 2.70 (tt, J = 4.0 and 10.5 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.8$, 25.1, 30.3, 36.8, 59.9, 117.6; HR-MS (EI) $m/z = 138.1157$ $[M]^+$, calcd. for $C_8H_{14}N_2$: 138.1157.

***N*-Cyano-*N*-*n*-hexylacetamide (2j):** *n*-Hexylamine (2.50 g, 24.70 mmol) in dry Et_2O (30 mL) was added to a solution of cyanogen bromide (1.570 g, 14.82 mmol) dissolved in dry Et_2O (50 mL) at 0 °C. The solution was stirred for 1 h. Solids

were then filtered off through a pad of celite, and the filtrate was washed with H_2O. The organic phase was dried with $MgSO_4$, and the solvent was removed under reduced pressure. *n*-Hexylcyanamide was obtained; yield: 1.220 g (9.67 mmol, 78%). This compound was used without further purification. *n*-Hexylcyanamide (976 mg, 7.73 mmol) in Et_2O (5 mL) was added to a suspension of NaH (385 mg, 60 wt% in paraffin oil, 9.63 mmol) in THF (25 mL) at 0 °C. The mixture was warmed to room temperature, after which acetyl chloride (717 mg, 9.13 mmol) was added. The reaction mixture was stirred for 1 h, and quenched with H_2O (1 mL). The crude reaction mixture was extracted with Et_2O (3× 15 mL), and concentrated. Column chromatography of the residue gave **2j** (hexane/AcOEt = 9/1); yield: 1.164 g (6.92 mmol, 90% yield); colorless oil; R_f = 0.58 (hexane/AcOEt = 4/1). IR (Zn/Se-ATR, neat): ν = 2956, 2931, 2861, 2232, 1727, 1462, 1371, 1348, 1244, 1180, 1139, 1037, 1001, 889, 811, 763, 727, 682, 630, 609, 586 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.90 (t, J = 6.5 Hz, 3H), 1.30–1.36 (m, 6H), 1.65–1.71 (m, 2H), 2.40 (s, 3H), 3.55 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 22.2, 22.4, 25.8, 27.5, 31.1, 46.1, 110.9, 169.3; HR-MS (EI): m/z = 169.1339 $[M+H]^+$, calcd. for $C_9H_{17}N_2O$: 169.1341.

Typical Procedure for the [2+2+2] Cycloaddition of Diyne (1) with Cyanamide (2)

A flask was charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol) and DPPF (5.5 mg, 0.01 mmol). The flask was evacuated and filled with argon. To the flask were added benzene (2.5 mL) and cyanamide (**2a**) (134 mg, 1.2 mmol). Diyne **1a** (236.2 mg, 1.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 1 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated under vacuum. Column chromatography of the residue gave **3aa** (*n*-hexane/AcOEt = 7/3); yield: 348 mg (1.0 mmol, >99%).

Competitive Experiment for the [2+2+2] Cycloaddition of Diyne (1a) with Cyanamide (2a) and Benzonitrile

A flask was charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol) and DPPF (11.0 mg, 0.02 mmol). The flask was evacuated and filled with argon. Benzene (1 mL) was added to the flask. To the flask were added a benzene (1.5 mL) solution of cyanamide **2a** (112 mg, 1.0 mmol) and benzonitrile (103 mg, 1.0 mmol). Diyne **1a** (236.2 mg, 1.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 1 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated under vacuum. Column chromatography of the residue gave a mixture of **3aa** and **9**[19] (AcOEt); yield: 325 mg. The molar ratio of **3aa**/**9** was determined to be 96:4 by NMR.

Competitive Experiment for the [2+2+2] Cycloaddition of Diyne (1a) with Cyanamide (2a) and 2-Cyanopyridine

A flask was charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol) and DPPF (11.0 mg, 0.02 mmol). The flask was evacuated and filled with argon. Benzene (1 mL) was added to the flask. To the flask were added a benzene (1.5 mL) solution of cyanamide **2a** (112 mg, 1.0 mmol) and 2-cyanopyridine (104 mg, 1.0 mmol). Diyne **1a** (236.2 mg, 1.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 1 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated under vacuum. Column chromatography of the residue gave a mixture of **3aa** and **10**[19] (AcOEt); yield: 341 mg. The molar ratio of **3aa**/**10** was determined to be 72:28 by NMR.

Dimethyl 1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]-pyridine-6,6(7*H*)-dicarboxylate (3aa): The title compound was obtained as a pale yellow oil; yield: 348 mg (>99%, 1.0 mmol scale); mp 93.5–95.0 °C; R_f = 0.48 (hexane/AcOEt = 11/9); IR (Zn/Se-ATR, neat): ν = 2962, 2909, 2862, 2840, 1730, 1587, 1434, 1420, 1364, 1256, 1196, 1160, 1109, 1062, 1034, 925, 850, 799, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.15 (s, 3H), 2.34 (s, 3H), 3.07 (dd, J = 4.5 Hz, J = 4.5 Hz, 4H), 3.49 (s, 2H), 3.51 (s, 2H), 3.77 (s, 6H), 3.83 (dd, J = 4.5 Hz, J = 4.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 21.5, 38.5, 39.8, 50.5, 53.1, 59.6, 67.2, 117.7, 128.1, 148.3, 150.3, 160.0, 171.9; HRMS (EI^+): m/z = 348.1685 $[M]^+$, calcd. for $C_{18}H_{24}N_2O_5$: 348.1685.

Dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ab): The title compound was obtained as a white solid; yield: 303 mg (91%, 1.0 mmol scale); mp 104.5–106.0 °C; R_f = 0.40 (hexane/AcOEt = 4/1); IR (Zn/Se-ATR, neat): ν = 2960, 2921, 2878, 2850, 1731, 1597, 1579, 1426, 1270, 1157, 1113, 943, 866, 756, 706, 607 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 1.85–1.90 (m, 4H), 2.15 (s, 3H), 2.29 (s, 3H), 3.41–3.47 (m, 8H), 3.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 15.7, 21.6, 25.4, 38.4, 39.9, 50.1, 53.0, 59.7, 113.3, 124.4, 147.2, 150.0, 158.8, 172.1; HR-MS (FAB): m/z = 333.1808 $[M+H]^+$, calcd. for $C_{18}H_{25}N_2O_4$: 333.1814; found .

Dimethyl 1,4-dimethyl-3-(piperidin-1-yl)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ac): The title compound was obtained as a brown oil; yield: 336 mg (97%, 1.0 mmol scale); R_f = 0.58 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2931, 2849, 1735, 1584, 1432, 1370, 1265, 1253, 1222, 1199, 1162, 1114, 1061, 857, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 1.54–1.72 (m, 6H), 2.14 (s, 3H), 2.33 (s, 3H), 2.98–3.02 (m, 4H), 3.48 (s, 2H), 3.50 (s, 2H), 3.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.2, 21.5, 24.5, 26.3, 38.5, 39.8, 51.4, 53.0, 59.6, 117.9, 127.3, 147.9, 149.9, 161.4, 171.9; HR-MS (FAB): m/z = 347.1958 $[M+H]^+$, calcd. for $C_{19}H_{27}N_2O_4$: 347.1971.

Dimethyl 3-(diethylamino)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ad): The title compound was obtained as a pale brown oil; yield: 312 mg (93%, 1.0 mmol scale); R_f = 0.40 (hexane/AcOEt = 4/1); IR (Zn/Se-ATR, neat): ν = 2965, 2931, 2869, 1736, 1585, 1433, 1259, 1163, 1095, 1059, 964, 952, 863, 804, 687, 601, 591 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (t, J = 6.9 Hz, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 3.11 (q, J = 7.0 Hz, 4H), 3.50 (d, J = 7.5 Hz, 4H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.3, 14.5, 21.6, 38.6, 40.0, 45.6, 53.0, 59.6, 119.2, 127.1, 147.7, 149.8, 160.2, 172.1; HR-MS (FAB): m/z = 335.1971 $[M+H]^+$, calcd. for $C_{18}H_{27}N_2O_4$: 335.1971.

Dimethyl 3-[hexyl(methyl)amino]-1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ae):

The title compound was obtained as a yellow oil; yield; 346 mg (92%, 1.0 mmol scale); R_f = 0.43 (hexane/AcOEt = 4/1); IR (Zn/Se-ATR, neat): ν = 2952, 2927, 2857, 1737, 1585, 1433, 1261, 1198, 1162, 1103, 1057, 965, 862, 768, 686, 645, 601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.87 (t, J = 6.5 Hz, 3H), 1.27–1.30 (m, 2H), 1.52–1.58 (m, 6H), 2.13 (s, 3H), 2.32 (s, 3H), 2.74 (s, 3H), 3.00 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H), 3.48 (s, 2H), 3.50 (s, 2H), 3.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.0, 14.6, 21.6, 22.6, 26.8, 27.9, 31.7, 38.6, 39.6, 39.9, 53.0, 54.5, 59.6, 117.6, 126.9, 147.7, 150.0, 161.5, 172.1; HR-MS (FAB): m/z = 377.2423 $[M+H]^+$, calcd. for $C_{21}H_{33}N_2O_4$: 377.2440.

Dimethyl 3-[methyl(phenyl)amino]-1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3af): The title compound was obtained as a pale yellow oil; yield: 366 mg (99%, 1.0 mmol scale); R_f = 0.54 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat): ν = 3006, 2953, 2919, 1734, 1590, 1498, 1434, 1264, 1164, 1105, 1064, 1036, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 1.88 (s, 3H), 2.40 (s. 3H), 3.34 (s, 3H), 3.53 (s, 2H), 3.59 (s, 2H), 3.78 (s, 6H), 6.59–6.64 (m, 2H), 6.73–6.80 (m, 1H), 7.13–7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.3, 21.6, 38.7, 38.8, 39.9, 53.1, 59.5, 115.5, 118.5, 122.1, 128.8, 130.5, 148.5, 150.1, 150.9, 156.4, 171.8; HR-MS (EI): m/z = 368.1748 $[M]^+$, calcd. for $C_{21}H_{24}N_2O_4$: 368.1736.

Dimethyl 3-[cyclohexyl(methyl)amino]-1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ag): The title compound was obtained as a white solid; yield: 317 mg; (85%, 1.0 mmol scale); mp 88.0–91.0 °C; R_f = 0.53 (hexane/AcOEt = 3/1); IR (Zn/Se-ATR, neat): ν = 2947, 2849, 1735, 1599, 1581, 1450, 1432, 1268, 1245, 1157, 1051, 866, 795, 767, 694, 648, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.04–1.15 (m, 1H), 1.17–1.28 (m, 2H), 1.43–1.53 (m, 2H), 1.58–1.62 (m, 1H), 1.73–1.79 (m, 4H), 2.12 (s, 3H), 2.31 (s, 3H), 2.69 (s, 3H), 3.02 (tt, J = 3.2 and 11.6 Hz, 1H), 3.49 (s, 2H), 3.50 (s, 2H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.7, 21.7, 26.05, 26.07, 29.9, 32.9, 38.6, 40.0, 53.0, 59.6, 60.6, 118.0, 126.7, 147.5, 149.9, 161.6, 172.1; HR-MS (EI): m/z = 374.2210 $[M]^+$, calcd. for $C_{21}H_{30}N_2O_4$: 374.2206.

Dimethyl 3-(dibenzylamino)-1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ah): The title compound was obtained as a brown oil; yield: 377 mg; (82%, 1.0 mmol scale); R_f = 0.55 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 3028, 2952, 2915, 1734, 1587, 1494, 1433, 1255, 1197, 1163, 1061, 949, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 2.24 (s, 3H), 2.29 (s, 3H), 3.48 (s, 4H), 3.75 (s, 6H), 4.24 (s, 4H), 7.15–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.3, 21.4, 38.6, 39.9, 53.0, 55.2, 59.5, 118.8, 126.5, 128.0, 128.1, 128.4, 139.6, 148.0, 150.2, 159.7, 172.0; HR-MS (EI): m/z = 458.2213 $[M]^+$, calcd, for $C_{28}H_{30}N_2O_4$: 458.2206.

Dimethyl 3-(diisopropylamino)-1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ai): The title compound was obtained as a white solid; yield: 113 mg (31%, 1.0 mmol scale): mp 81.1–82.5 °C; R_f = 0.55 (hexane/AcOEt = 3/1); IR (Zn/Se-ATR, neat): ν = 2975, 2958, 2920, 2871, 2845, 1747, 1733, 1585, 1434, 1377, 1302, 1253, 1175, 1058, 959, 849, 816, 671 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 0.99 (d, J = 6.5 Hz, 12H), 2.18 (s, 3H), 2.33 (s, 3H), 3.49–3.58 (m, 6H), 3.77 (s, 6H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.8, 21.2, 21.8, 38.9, 40.2, 49.4, 53.0, 59.5, 125.6, 129.4, 148.3, 149.1, 159.0, 172.1; HR-MS (FAB): m/z = 363.2301 $[M+H]^+$, calcd. for $C_{20}H_{31}N_2O_4$: 363.2284.

Dimethyl 3-(*N*-hexylacetamido)-1,4-dimethyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3aj): The title compound was obtained as a red oil; yield: 319 mg; (79%, 1 mmol scale); R_f = 0.40 (AcOEt); IR (Zn/Se-ATR, neat): ν = 2954, 2928, 2857, 1736, 1661, 1586, 1434, 1395, 1265, 1232, 1199, 1165, 1131, 1092, 1062, 1027, 952, 859, 828, 762, 728, 691, 631, 617, 555 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C, 500 MHz): δ = 0.85 (t, J = 7.0 Hz, 3H), 1.25–1.31 (m, 4H), 1.52–1.54 (m, 2H), 1.72 (s, 3H), 2.12 (s, 3H), 2.41 (s, 3H), 3.44 (br, 1H), 3.57 (s, 2H), 3.60 (s, 2H), 3.76–3.86 (m, 7H); ^{13}C NMR ($CDCl_3$, 55 °C, 125 MHz): δ = 13.6, 13.8, 21.4, 22.1, 22.3, 27.4, 29.2, 38.9, 40.0, 47.7, 53.0, 59.6, 123.7, 133.7, 150.9, 151.3, 152.8, 169.8, 171.4; HR-MS (EI): m/z = 404.2302 $[M]^+$, calcd. for $C_{22}H_{32}N_2O_5$: 404.2311.

6,6-Diacetyl-1,4-dimethyl-3-morpholino-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (3ba): The title compound was obtained as a brown solid; yield; 306 mg; (97%, 1.0 mmol scale); mp 131.3–132.8 °C; R_f = 0.45 (hexane/AcOEt = 9/11); IR (Zn/Se-ATR, neat): ν = 2963, 2944, 2893, 2849, 2822, 1697, 1589, 1422, 1361, 1258, 1205, 1162, 1134, 1113, 1034, 924, 851, 700, 587, 569 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 2.17 (s, 3H), 2.19 (s, 6H), 2.35 (s, 3H), 3.05–3.08 (m, 4H), 3.39 (d, J = 6.3 Hz, 4H), 3.81–3.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 21.6, 26.4, 35.4, 36.5, 50.5, 67.2, 74.3, 117.8, 127.8, 148.5, 150.1, 160.0, 201.4; HR-MS (FAB): m/z = 317.1859 $[M+H]^+$, calcd. for $C_{18}H_{25}N_2O_3$: 317.1865.

Methyl 1,4-dimethyl-3-morpholino-6-phenyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-6-carboxylate (3ca): The title compound was obtained as a brown oil; yield: 182 mg (99%, 0.5 mmol scale); R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat): ν = 2981, 2955, 2897, 2844, 1726, 1598, 1585, 1417, 1263, 1249, 1210, 1165, 1114, 1036, 967, 930, 867, 728, 698, 638, 607 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 2.19 (s, 3H), 2.39 (s, 3H), 3.07–3.29 (m, 6H), 3.62 (s, 3H), 3.82–3.95 (m, 6H), 7.23–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.4, 21.6, 40.5, 41.9, 50.6, 52.7, 58.9, 67.2, 117.7, 126.4, 127.1, 128.6, 129.2, 142.6, 148.1, 151.4, 159.8, 175.6; HR-MS (FAB): m/z = 367.2038 $[M+H]^+$, calcd. for $C_{22}H_{27}N_2O_3$: 367.2022.

1,4,5′,5′-Tetramethyl-3-morpholino-5*H*-2,3,6,7-tetrahydrocyclopenta[*c*]pyridine-6-spiro-2′-cyclohexan-1′,3′-dione (3da): The title compound was obtained as a white solid; yield: 346 mg (97%, 1.0 mmol scale); mp 206.2–208.0 °C; R_f = 0.40 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat): ν = 2952, 2913, 2886, 2843, 1730, 1696, 1589, 1421, 1323, 1254, 1115, 1064, 1032, 1020, 930, 852, 804, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 0.97 (s, 3H), 1.12 (s, 3H), 2.16 (s, 3H), 2.29 (s, 3H), 2.62 (d, J = 14.0 Hz, 2H), 2.82 (d, J = 14.3 Hz, 2H), 3.06 (q, J = 4.6 Hz, 4H), 3.30 (s, 2H), 3.36 (s, 2H), 3.83 (q, J = 4.3 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.2, 21.6. 27.4, 29.2, 30.5, 35.3, 39.1, 50.6, 51.3, 67.2, 70.5, 117.8, 126.8, 148.1, 151.1, 160.2, 206.3; HR-MS (FAB): m/z = 357.2184 $[M+H]^+$, calcd. for $C_{21}H_{29}N_2O_3$: 357.2178.

(1,4-Dimethyl-3-morpholino-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-6,6-diyl)dimethanol (3ea): The title compound was obtained as a pale orange solid; yield: 140 mg (50%, 0.95 mmol scale); mp 146.5–149.7 °C; R_f = 0.15 (AcOEt); IR (Zn/Se-ATR, neat): ν = 3407, 3276, 3203, 2951, 2924, 2865, 2846, 1656, 1581, 1420, 1362, 1252, 1108, 1031, 927, 847, 731, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ = 1.58 (br, 2H),

2.13 (s, 3H), 2.32 (s, 3H), 2.72 (s, 2H), 2.76 (s, 2H), 3.06–3.10 (m, 4H), 3.76–3.77 (m, 4H), 3.82–3.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3, 21.5, 36.4, 37.7, 48.5, 50.6, 67.3, 69.5, 118.5, 129.8, 149.0, 152.2, 159.7; HR-MS (EI): m/z = 292.1786 $[M]^+$, calcd. for $C_{16}H_{24}N_2O_3$: 292.1787.

4,7-Dimethyl-6-morpholino-2-tosyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (3fa): The title compound was obtained as a pale orange solid; yield: 306 mg (79%, 1.0 mmol scale): mp 166.0–169.0 °C; R_f = 0.50 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat): ν = 2948, 2911, 2847, 2812, 1608, 1596, 1423, 1341, 1260, 1150, 1116, 1100, 1035, 930, 834, 817, 714, 664, 589, 571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.09 (s, 3H), 2.28 (s, 3H), 2.42 (s, 3H), 3.04–3.07 (m, 4H), 3.80–3.83 (m, 4H), 4.50–4.52 (m, 4H), 7.32–7.35 (m, 2H), 7.77–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.2, 21.5 (2C), 50.4, 52.2, 53.2, 67.0, 116.2, 124.5, 127.5, 129.9, 133.6, 143.8, 146.5, 147.4, 160.5; HR-MS (FAB): m/z = 387.1606 $[M]^+$, calcd. for $C_{20}H_{25}N_3O_3S$: 387.1617.

4,7-Dimethyl-6-morpholino-1,3-dihydrofuro[3,4-*c*]pyridine (3ga): The title compound was obtained as a pale orange solid; yield: 71 mg (59%, 0.51 mmol scale); mp 105.0–108.0 °C; R_f = 0.53 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat): ν = 2973, 2905, 2845, 2817, 1595, 1455, 1420, 1389, 1365, 1304, 1262, 1137, 1110, 1061, 1029, 931, 922, 901, 847, 767, 687, 593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.13 (s, 3H), 2.32 (s, 3H), 3.09–3.12 (m, 4H), 3.83–3.86 (m, 4H), 5.00 (s 2H), 5.04 (s, 2H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.3, 21.6, 50.4, 67.0, 72.4, 72.8, 114.8, 127.3, 145.8, 149.8, 160.2; HR-MS (EI): m/z = 234.1370 $[M]^+$, calcd. for $C_{13}H_{18}N_2O_2$: 234.1368.

1,4-Dimethyl-3-morpholino-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (3ha): The title compound was obtained as an orange solid; yield: 73 mg (59%, 0.53 mmol scale); mp 41.2–44.5 °C; R_f = 0.50 (hexane/AcOEt = 3/1); IR (Zn/Se-ATR, neat): ν = 2956, 2918, 2852, 2832, 1584, 1421, 1363, 1301, 1259, 1114, 1068, 1035, 1014, 923, 849, 686, 584 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.07 (quint, J = 7.3 Hz, 1H), 2.15 (s, 3H), 2.34 (s, 3H), 2.76–2.84 (m, 4H), 3.06–3.09 (m, 4H), 3.82–3.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 14.3, 21.7, 24.5, 30.5, 31.9, 50.7, 67.3, 117.9, 120.4, 126.0, 132.2, 148.2, 154.5, 159.4; HR-MS (EI): m/z = 232.1569 $[M]^+$, calcd. for $C_{14}H_{20}N_2O$: 232.1576.

Tetraethyl 1,4-dimethyl-3-morpholino-isoquinoline-6,6,7,7(5*H*,8*H*)-tetracarboxylate (3ja): The title compound was obtained as a brown oil; yield: 493 mg (92%, 1.0 mmol scale); R_f = 0.53 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat): ν = 2981, 2958, 2908, 2849, 1730, 1572, 1427, 1365, 1262, 1239, 1199, 1116, 1037, 925, 864, 749, 736, 697, 580 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 1.20–1.26 (m, 12H), 2.15 (s, 3H), 2.37 (s, 3H), 3.03–3.07 (m. 4H), 3.32–3.34 (m, 4H), 3.82–3.85 (m, 4H), 4.14–4.23 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.5, 13.7, 22.1, 31.7, 32.9, 50.7, 53.4, 56.8, 57.0, 61.8, 61.9, 67.2, 119.3, 121.1, 142.0, 151.1, 158.6, 169.77, 169.82; HR-MS (EI): m/z = 534.2584 $[M]^+$, calcd. for $C_{27}H_{38}N_2O_9$: 534.2577.

Dimethyl 1,4-dimethyl-3-morpholino-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (3ka): The title compound was obtained as a white solid; yield: 234 mg; (73%, 1.0 mmol scale); mp 146.0–147.0 °C; R_f = 0.45 (hexane/AcOEt = 9/1); IR (Zn/Se-ATR, neat): ν = 2964, 2900, 2845, 2816, 1730, 1619, 1560, 1486, 1415, 1277, 1241, 1200, 1154, 1116, 1069, 1046, 966, 934, 883, 835, 761, 651, 595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 3.43–3.46 (m, 4H), 3.50 (s, 4H), 3.75 (s, 6H), 3.79–3.83 (m, 4H), 6.53 (s, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 37.3, 40.3, 46.0, 53.0, 60.5, 66.7, 102.6, 126.1, 142.9, 151.5, 159.2, 171.6; HR-MS (EI): m/z = 320.1367 $[M]^+$, calcd. for $C_{16}H_{20}N_2O_5$: 320.1372.

Dimethyl 1,4-diethyl-3-morpholino-5*H*-cyclopenta[c]pyridine-6,6(7*H*)-dicarboxylate (3la): The title compound was obtained as a brown oil; yield: 375 mg (92%, 1.08 mmol scale); R_f = 0.55 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat): ν = 2960, 2848, 1735, 1583, 1421, 1362, 1248, 1201, 1164, 1116, 1066, 966, 912, 853, 755, 665, 609 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 1.18 (t, J = 7.6 Hz, 3H), 1.23 (t, J = 7.6 Hz, 3H), 2.62 (q, J = 7.6 Hz, 4H), 3.07 (q, J = 4.6 Hz, 4H), 3.50 (s, 2H), 3.52 (s, 2H), 3.76 (s, 6H), 3.83 (q, J = 4.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.4, 13.5, 21.3, 28.3, 37.9, 39.3, 51.7, 53.0, 60.1, 67.3, 124.9, 128.4, 150.0, 153.4, 160.0, 171.8; HR-MS (FAB): m/z = 377.2089 $[M+H]^+$, calcd. for $C_{20}H_{29}N_2O_5$: 377.2076.

Dimethyl 3-morpholino-1,4-diphenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ma): The title compound was obtained as a pale orange solid; yield: 423 mg (90%, 1.0 mmol scale): mp 144.5–146.7 °C; R_f = 0.50 (hexane/AcOEt = 3/1); IR (Zn/Se-ATR, neat): ν = 2955, 2911, 2847, 1754, 1735, 1589, 1575, 1560, 1494, 1415, 1396, 1366, 1255, 1239, 1194, 1171, 1115, 1065, 993, 897, 851, 775, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.07–3.09 (m, 4H), 3.41 (s, 2H), 3.54–3.56 (m, 4H), 3.69 (s, 6H), 3.81 (s, 2H), 7.31–7.35 (m, 1H), 7.38–7.49 (m, 7H), 7.83–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 40.0, 40.2, 49.5, 53.0, 60.4, 66.8, 122.5, 126.2, 127.4, 128.2, 128.3, 128.4, 128.7, 129.0, 137.5, 139.7, 149.6, 151.7, 158.4, 171.6; HR-MS (EI): m/z = 472.2004 $[M]^+$, calcd. for $C_{28}H_{28}N_2O_5$: 472.1998.

Dimethyl 4-methyl-3-morpholino-1-phenyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (4na): The title compound was obtained as a white solid; yield: 384 mg (94%, 1.0 mmol scale); mp 166.2–168.5 °C; R_f = 0.48 (hexane/AcOEt = 11/9); IR (Zn/Se-ATR, neat): ν = 2965, 2891, 2849, 1731, 1595, 1560, 1415, 1362, 1254, 1212, 1164, 1115, 1072, 1037, 944, 900, 851, 784, 758, 703, 693, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.24 (s, 3H), 3.18–3.19 (m, 4H), 3.53 (s, 2H), 3.74 (s, 6H), 3.80 (s, 2H), 3.85–3.87 (m, 4H), 7.34–7.38 (m, 1H), 7.43–7.46 (m, 2H), 7.79–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.5, 39.4, 40.2, 50.5, 53.1, 60.1, 67.2, 119.2, 127.1, 128.0, 128.2, 139.8, 148.2, 151.9, 160.2, 171.7; HR-MS (FAB): m/z = 411.1933 $[M+H]^+$, calcd. for $C_{23}H_{27}N_2O_5$: 411.1920.

Dimethyl 1-methyl-3-morpholino-4-phenyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (5na): The title compound was obtained as a white solid; yield: 107 mg (26%, 1 mmol scale); mp 135.0–137.8 °C; R_f = 0.48 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat): ν = 3057, 2990, 2951, 2910, 2854, 2838, 1754, 1724, 1577, 1436, 1417, 1369, 1274, 1254, 1195, 1163, 1150, 1114, 1068, 1048, 1033, 1020, 956, 926, 901, 853, 787, 756, 707, 692, 676, 644, 617, 573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.39 (s, 3H), 2.98–3.00 (m, 4H), 3.38 (s, 2H), 3.50–3.52 (m, 6H), 3.72 (s, 6H), 7.27–7.32 (m, 1H), 7.40–7.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.8, 38.3, 40.4, 49.6, 53.0, 59.8, 66.8, 121.2, 127.06, 127.12, 128.6, 129.0, 137.8, 149.9, 150.0, 158.3, 171.8; HR-MS (EI): m/z = 410.1838 $[M]^+$, calcd. for $C_{23}H_{26}N_2O_5$: 410.1842.

Dimethyl 3-diethylamino-4-methyl-1-phenyl-5*H*-cyclopenta[c]pyridine-6,6(7*H*)-dicarboxylate (4nd): The title com-

pound was obtained as a yellow oil; yield: 380 mg (96%, 1.0 mmol scale); R_f = 0.45 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2960, 2918, 2851, 1731, 1597, 1561, 1416, 1374, 1252, 1203, 1170, 1065, 1026, 965, 876, 756, 694, 627, 565 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.11 (t, J = 7.0 Hz, 6H), 2.21 (s, 3H), 3.21 (q, J = 7.0 Hz, 4H), 3.53 (s, 2H), 3.74 (s. 6H), 3.80 (s, 2H), 7.32–7.35 (m, 1H), 7.42–7.45 (m, 2H), 7.79–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.4, 14.8, 39.6, 40.2, 45.4, 53.0, 60.0, 120.3, 125.9, 127.7, 128.1, 128.3, 140.3, 147.6, 151.4, 160.4, 171.9; HR-MS (EI): m/z = 396.2041 $[M]^+$, calcd. for $C_{23}H_{28}N_2O_4$: 396.2049.

Dimethyl 4-methyl-3-morpholino-1-pyridyl-5*H*-cyclopenta[c]pyridine-6,6(7*H*)-dicarboxylate (4oa): The title compound was obtained as a white solid; yield: 381 mg (93%, 1.0 mmol scale); mp 206.0–208.0 °C; R_f = 0.50 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat): ν = 2968, 2954, 2890, 2843, 1730, 1583, 1556, 1423, 1413, 1362, 1278, 1254, 1196, 1162, 1117, 1100, 1076, 1050, 1037, 943, 925, 904, 851, 801, 760, 745, 706, 672, 645, 618, 558 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.25 (s, 3H), 3.19 (m, 4H), 3.52 (s, 2H), 3.76 (s, 6H), 3.88 (m, 4H), 4.15 (s, 2H), 7.19–7.22 (m, 1H), 7.74–7.77 (m, 1H), 8.33–8.34 (m, 1H), 8.64–8.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.6, 39.3, 41.4, 50.6, 53.0, 59.8, 67.1, 120.8, 122.2, 122.3, 129.4, 136.1, 146.0, 148.4, 152.6, 158.0, 159.5, 172.3; HR-MS (EI): m/z = 411.1799 $[M]^+$, calcd. for $C_{22}H_{25}N_3O_5$: 411.1794.

Dimethyl 3-diethylamino-4-methyl-1-pyridyl-5*H*-cyclopenta[c]pyridine-6,6(7*H*)-dicarboxylate (4od): The title compound was obtained as a white solid; yield: 377 mg (95%, 1.0 mmol scale); mp 96.5–98.0 °C; R_f = 0.58 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2999, 2952, 2871, 2836, 1732, 1583, 1462, 1417, 1340, 1246, 1205, 1166, 1069, 853, 797, 742, 690, 662, 561 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.11 (t, J = 7.0 Hz, 6H), 2.23 (s, 3H), 3.22 (q, J = 7.0 Hz, 4H), 3.53 (s, 2H), 3.76 (s, 6H), 4.15 (s, 2H), 7.17–7.20 (m, 1H), 7.72–7.76 (m, 1H), 8.31–8.32 (m, 1H), 8.63–8.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.2, 14.9, 39.4, 41.5, 45.4, 52.9, 59.8, 121.8, 122.1, 122.2, 128.2, 136.0, 145.4, 148.3, 152.2, 158.5, 159.6, 172.4; HR-MS (EI): m/z = 397.1998 $[M]^+$, calcd. for $C_{22}H_{27}N_3O_4$: 397.2002.

Dimethyl 1-methyl-3-morpholino-4-(trimethylsilyl)-5*H*-cyclopenta[c]pyridine-6,6(7*H*)-dicarboxylate (5pa): The title compound was obtained as a brown oil; yield: 365 mg (90%, 1.0 mmol scale); R_f = 0.53 (hexane/AcOEt = 11/9); IR (Zn/Se-ATR, neat): ν = 2953, 2916, 2851, 1736, 1572, 1434, 1402, 1377, 1360, 1255, 1201, 1165, 1115, 1071, 920, 904, 839, 754, 693, 644 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.35 (s, 9H), 2.38 (s, 3H), 2.95 (s, 4H), 3.47 (s, 2H), 3.61 (s, 2H), 3.77 (s, 6H), 3.81–3.83 (m. 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 1.9, 21.9, 37.7, 42.5, 52.7, 53.1, 59.4, 66.8, 122.6, 130.9, 153.5, 157.6, 168.1, 171.9; HRMS (FAB): m/z = 407.1989 $[M+H]^+$, calcd. for $C_{20}H_{31}N_2O_5Si$: 407.2002.

Dimethyl 3-(diethylamino)-1-methyl-4-(trimethylsilyl)-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate (5pd): The title compound was obtained as an yellow oil; yield: 372 mg (95%, 1.0 mmol scale); R_f = 0.50 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2954, 2895, 2870, 1738, 1571, 1556, 1434, 1402, 1371, 1358, 1251, 1201, 1163, 1071, 1051, 888, 839, 756, 688, 642, 604, 578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.34 (s, 9H), 0.95 (t, J = 7.5 Hz, 6H), 2.34 (s, 3H), 3.05 (q, J = 7.5 Hz, 4H), 3.45 (s, 2H), 3.58 (s, 2H), 3.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 1.7, 12.1, 21.9, 37.5, 42.3, 47.4, 53.0, 59.7, 121.8, 128.5, 152.0, 157.5, 167.1, 172.0; HR-MS (EI): m/z = 392.2131 $[M]^+$, calcd. for $C_{20}H_{32}N_2O_4Si$: 392.2131.

Diethyl 1-ethyl-4-methyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4qa): The title compound was obtained as a colorless oil; yield: 236 mg (64%, 0.95 mmol scale); R_f = 0.54 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2963, 2913, 2849, 1731, 1584, 1447, 1422, 1407, 1384, 1363, 1248, 1205, 1185, 1159, 1132, 1117, 1066, 1054, 1032, 939, 924, 859, 732, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (t, J = 8.0 Hz, 3H), 1.27 (t, J = 6.5 Hz, 6H), 2.15 (s, 3H), 2.62 (q, J = 8.0 Hz, 2H), 3.09–3.10 (m, 4H), 3.47 (s, 2H), 3.51 (s, 2H), 3.82–3.84 (m, 4H), 4.22 (q, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.5, 14.0, 14.3, 28.3, 38.0, 39.6, 50.6, 59.9, 61.8, 67.2, 117.4, 127.4, 150.5, 153.0, 159.9, 171.5; HR-MS (EI): m/z = 390.2154 $[M]^+$, calcd. for $C_{21}H_{30}N_2O_5$: 390.2155.

Diethyl 4-ethyl-1-methyl-3-morpholino-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (5qa): The title compound was obtained as a white solid; yield: 114 mg (30%, 0.95 mmol scale); mp 82.2–83.4 °C; R_f = 0.47 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat): ν = 2966, 2905, 2855, 2818, 1753, 1725, 1583, 1468, 1422, 1381, 1364, 1296, 1272, 1248, 1228, 1201, 1188, 1162, 1130, 1119, 1098, 1070, 1048, 1031, 1014, 955, 925, 861, 771, 736, 680, 615, 577 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.17 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.0 Hz, 6H), 2.34 (s, 3H), 2.62 (q, J = 7.5 Hz, 2H), 3.03–3.05 (m, 4H), 3.48 (s, 2H), 3.51 (s, 2H), 3.82–3.84 (m, 4H), 4.22 (q, J = 7.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.6, 14.0, 21.3, 21.6, 38.2, 39.3, 51.7, 60.1, 61.8, 67.3, 125.2, 129.5, 148.7, 150.1, 160.1, 171.4; HR-MS (EI): m/z = 390.2154 $[M]^+$, calcd. for $C_{21}H_{30}N_2O_5$: 390.2155.

Diethyl 3-(diethylamino)-1-ethyl-4-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4qd): The title compound was obtained as a pale yellow oil; yield: 271 mg (68%, 1.05 mmol scale); R_f = 0.48 (hexane/AcOEt = 17/3); IR (Zn/Se-ATR, neat): ν = 2970, 2933, 2871, 1732, 1597, 1583, 1448, 1422, 1367, 1337, 1251, 1209, 1181, 1159, 1098, 1054, 1012, 861, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.04 (t, J = 7.0 Hz, 6H), 1.21 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.0 Hz, 6H), 2.13 (s, 3H), 2.61 (q, J = 7.5 Hz, 2H), 3.12 (q, J = 7.0 Hz, 4H), 3.47 (s, 2H), 3.51 (s, 2H), 4.22 (q, J = 7.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.7, 13.2, 14.0, 14.5, 28.3, 38.1, 39.8, 45.6, 59.8, 61.8, 118.8, 126.4, 150.1, 152.4, 160.1, 171.7; HR-MS (EI): m/z = 376.2357 $[M]^+$, calcd. for $C_{21}H_{32}N_2O_4$: 376.2362.

Diethyl 3-(diethylamino)-4-ethyl-1-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (5qd): The title compound was obtained as a colorless oil; yield: 102 mg (26%, 1.05 mmol scale); R_f = 0.40 (hexane/AcOEt = 17/3); IR (Zn/Se-ATR, neat): ν = 2972, 2933, 2871, 1732, 1585, 1443, 1423, 1367, 1333, 1252, 1206, 1182, 1159, 1098, 1064, 860, 597, 582 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.01 (t, J = 6.5 Hz, 6H), 1.12 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.5 Hz, 6H), 2.33 (s, 3H), 2.61 (q, J = 7.5 Hz, 2H), 3.06 (q, J = 6.5 Hz, 4H), 3.48 (s, 2H), 3.52 (s, 2H), 4.22 (q, J = 7.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.4 (2C), 14.0, 21.4, 21.6, 38.4, 39.4, 47.1, 60.0, 61.8, 127.1, 128.8, 148.3, 149.6, 160.1, 171.6; HR-MS (EI): m/z = 376.2357 $[M]^+$, calcd. for $C_{21}H_{32}N_2O_4$: 376.2362.

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