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Iridium-Catalyzed Synthesis of Acylpyridines by [2 + 2 + 2] Cycloaddition of Diynes with Acyl Cyanides

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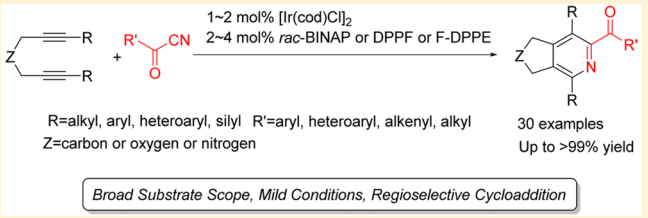
Supporting Information

ABSTRACT: 2-Acylpyridines were prepared by iridium-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with acyl cyanides. $[Ir(cod)Cl]_2$/*rac*-BINAP or F-DPPE is an efficient catalyst for this reaction. The scope and limitations of this reaction have been disclosed.



INTRODUCTION

Pyridines are among the most prevalent heterocyclic structural units in organic, medicinal, and supramolecular chemistry.[1] New synthetic methods for pyridines have the potential to impact the fields of both organic chemistry and material sciences.[2] However, the synthesis of functionalized pyridines is challenging because functionalization of the aromatic ring depends on electrophilic substitution. Electrophilic substitutions on the pyridine ring are unfavorable because electrophilic reagents, such a proton or Lewis acid, first attacks pyridine's nitrogen, thereby generating a pyridinium cation that is very resistant to electrophilic attacks. Since Friedel−Crafts acylation and alkylation fail with most pyridines, nucleophilic activated lithiopyridine is instead used for synthesis of acylpyridines. Lithiopyridine is generally prepared by regioselective metalation or metal−halogen exchange.[3] A major drawback of this method is its lack of compatibility with certain functional groups reactive to organolithium reagents. Moreover, this process is not environmentally benign because of the formation of a stoichiometric amount of metal salt waste. Another approach to acylpyridines is to choose an appropriate substrate for the construction of pyridine rings by classical Hantzsch synthesis.[4] Condensation of two molecules of 1,3-dicarbonyl compounds, one molecule of aldehyde, and ammonia affords 3,5-diacylpyridine. However, the varieties of possible products given by this classical approach are quite limited. In addition to such narrow scope, these condensation reactions often require harsh reaction conditions.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes with nitriles is an efficient route to pyridines.[5] The reaction proceeds under neutral conditions. In addition, catalytic [2 + 2 + 2] cycloaddition of alkynes with nitriles is an atom-economical and highly convergent reaction for constructing a multisubstituted pyridine ring. Since the pioneering work of Yamazaki and Wakatsuki on the synthesis of pyridines,[6] Co,[7] Rh,[8] Ru,[9] Fe,[10] and Ni[11] have been reported as catalysts for [2 + 2 + 2] cycloadditions of alkynes with nitriles. In the course of study on iridium-catalyzed [2 + 2 + 2] cycloaddition,[12] we previously reported that $[Ir(cod)Cl]_2$/BINAP is an efficient catalyst for [2 + 2 + 2] cycloaddition of α,ω-diynes with nitriles.[12c] One of the advantages of using an iridium catalyst over other transition metals is that a broader scope of nitriles can be utilized. We reported that the reaction of α,ω-diynes with cyanamides was successful for the synthesis of multisusbstituted 2-aminopyridine.[12d] These results prompted us to study the reaction of α,ω-diynes with acyl cyanides. There are few examples of cycloaddition reactions involving acyl cyanides, limited to Rh[8d] and Ru catalysis.[9e] The scope and limitation of acyl cyanides have not been studied. In this paper, we wish to report a detailed study on iridium-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with acyl cyanides to give acylpyridines.

RESULTS AND DISCUSSION

Diyne **1a** reacted with acyl cyanide **2a** to give **3aa** as the product. Our effort initially focused on the optimization of reaction conditions. The optimization was performed by the reaction of diyne **1a** with 1.2 equiv of acyl cyanide **2a** in the presence of 2 mol % of a catalyst. The results are summarized in Table 1. The catalytic activity depended on the ligand used. The reaction using $[Ir(cod)Cl]_2$ alone gave **3aa** in 15% yield (entry 1). PPh_3 inhibited the transformation (entry 2). The use of diphosphines in toluene at reflux was successful (entries 3, 5, 7, and 9), but the reactions using these diphosphines at room temperature gave **3aa** in poor yields (entries 4, 6, 8, and 10). The reaction using *rac*-BINAP yielded **3aa** quantitatively at reflux and in 92% at room temperature (entries 11 and 12). F-DPPE gave a result comparable to that given by *rac*-BINAP (entry 13). At room temperature, F-DPPE was less effective than *rac*-BINAP (entry 14). The final optimization of the reaction conditions was achieved using *rac*-BINAP or F-DPPE

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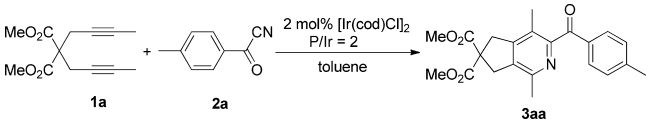
Table 1. Optimization of the Reaction Conditions[a]



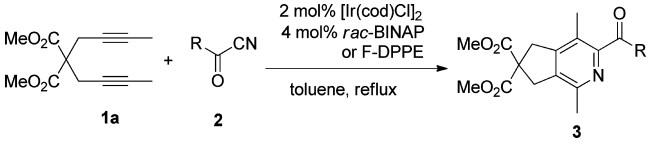
entry	ligand	temp (°C)	time (h)	yield[b] (%)
1	none	reflux	24	15
2	PPh_3	reflux	24	0
3	DPPE	reflux	1	82
4	DPPE	rt	24	9
5	DPPP	reflux	1	89
6	DPPP	rt	24	3
7	DPPB	reflux	1	90
8	DPPB	rt	24	1
9	DPPF	reflux	1	88
10	DPPF	rt	24	0
11	*rac*-BINAP	reflux	1	99
12	*rac*-BINAP	rt	1	92
13[c]	F-DPPE	reflux	1	94
14[c]	F-DPPE	rt	24	26

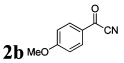
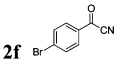
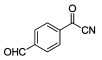
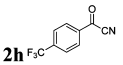
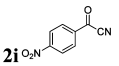
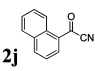
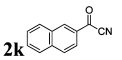
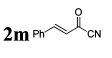
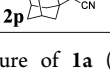
[a]A mixture of **1a** (0.5 mmol), **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), ligand (P/Ir atom = 2), and toluene (2.5 mL) was stirred under Ar. [b]Isolated yield. [c]F-DPPE is $(C_6F_5)_2PCH_2CH_2P(C_6F_5)_2$.

in toluene at reflux. In our previous paper,[12c] we reported that the nitrogen atom of the cyano group coordinates to an iridium center in an end-on fashion. F-DPPE is more electron-withdrawing than BINAP. The coordination of F-DPPE makes the iridium center more electron-deficient (more Lewis acidic) than if it had been coordinated by BINAP. A change of the ligand from BINAP to F-DPPE increases the electron-deficiency (Lewis acidity) of the iridium center to enhance the end-on coordination of the nitrogen atom of the cyano group. This effect improves the yield of the product.

Scope of Acyl Cyanides. The scope of acyl cyanides was examined under the optimized reaction conditions (Table 2). A broad scope of aroyl cyanides was introduced into this reaction. The electronic properties of the substituents in the benzene ring had a considerable effect on the product yield. The reaction of diyne **1a** with *p*-methoxy- and *p*-chlorobenzoyl cyanides **2b** and **2e** gave **3ab** and **3ae** in 95% and 98% yields, respectively (entries 1 and 6). *p*-Bromobenzoyl cyanide **2f** gave **3af** in a lower yield than *p*-methoxy- and *p*-chlorobenzoyl cyanides **2b** and **2e** (entry 7). Changing the ligand from *rac*-BINAP to F-DPPE increased the yield of **3af** to 88% (entry 8). With *p*-formyl, *p*-trifluoromethyl, and *p*-nitrobenzoyl cyanides **2g–i**, F-DPPE was better than *rac*-BINAP (entries 10, 12, and 14 vs entries 9, 11, and 13). Using F-DPPE instead of *rac*-BINAP improved the yields of **3ag–ai** to a preparatively useful range. Formyl, nitro, trifluoromethyl, and halo groups were tolerated under the reaction conditions. The functional group tolerance observed in this protocol allows the efficient preparation of functionalized aryl 2-pyridyl ketones, which are not easily accessible using conventional approaches.[13] The reaction of *o*-methylbenzoyl cyanide **2c** gave **3ac** in 88% yield (entry 3). The steric hindrance of two *o*-methyl groups decreased the yield. The reaction of *o*,*o*-dimethylbenzoyl cyanide **2d** using *rac*-BINAP gave **3ad** in 25% yield (entry 4). However, using F-DPPE increased the yield of **3ad** to 83% (entry 5). Both 1-naphthoyl and 2-naphthoyl cyanides **2j** and **2k** were good substrates for the reaction (entries 15 and 16). Heteroaroyl cyanide could be used. The reaction with **2l** gave

Table 2. Scope of Acyl Cyanides[a]



entry	2	ligand	time (h)	product	yield (%)[b]
1	**2b** 	*rac*-BINAP	1	**3ab**	95
2[c]	**2b**	*rac*-BINAP	24	**3ab**	9
3	**2c** 	*rac*-BINAP	1	**3ac**	88
4	**2d** 	*rac*-BINAP	20	**3ad**	25
5	**2d**	F-DPPE	1	**3ad**	83
6	**2e** 	*rac*-BINAP	1	**3ae**	98
7	**2f** 	*rac*-BINAP	24	**3af**	66
8	**2f**	F-DPPE	24	**3af**	88
9	**2g** 	*rac*-BINAP	24	**3ag**	19
10	**2g**	F-DPPE	3	**3ag**	86
11	**2h** 	*rac*-BINAP	24	**3ah**	65
12	**2h**	F-DPPE	24	**3ah**	100
13	**2i** 	*rac*-BINAP	24	**3ai**	13
14	**2i**	F-DPPE	24	**3ai**	72
15	**2j** 	*rac*-BINAP	1	**3aj**	94
16	**2k** 	*rac*-BINAP	2	**3ak**	95
17	**2l** 	*rac*-BINAP	1	**3al**	89
18	**2m** 	*rac*-BINAP	1	**3am**	85
19	**2n** 	*rac*-BINAP	24	**3an**	trace
20[d]	**2n**	F-DPPE	24	**3an**	89
21	**2o** 	*rac*-BINAP	1	**3ao**	82
22	**2p** 	*rac*-BINAP	1	**3ap**	87

[a]A mixture of **1a** (0.5 mmol), **2** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), *rac*-BINAP or F-DPPE (0.02 mmol), and toluene (2.5 mL) was stirred under Ar. F-DPPE is $(C_6F_5)_2PCH_2CH_2P(C_6F_5)_2$. [b]Isolated yield. [c]At room temperature. [d]$[Ir(cod)Cl]_2$ (0.02 mmol), F-DPPE (0.04 mmol).

product **3al** in 89% yield (entry 17). The reaction with alkenoyl cyanide **2m** gave **3am** in 85% yield (entry 18). The thiophene ring and carbon–carbon double bond were tolerated under the

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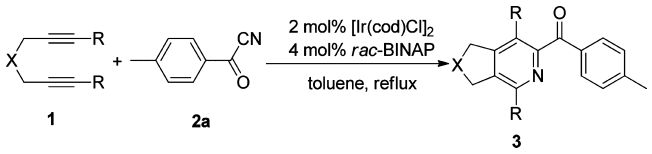
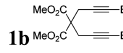
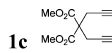
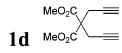
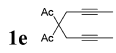
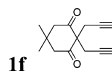
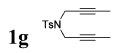
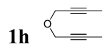
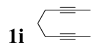
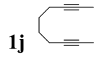
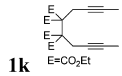
reaction conditions. The reaction with acetyl cyanide **2n** gave **3an** in 89% yield (entry 20). It is noteworthy that sterically hindered alkanoyl cyanides **2o** and **2p** smoothly reacted with diyne **1a** to give **3ao** and **3ap** in 82% and 87% yields, respectively (entries 21 and 22). The reaction with **2n** required greater catalyst loading than those with **2o** and **2p**. These results suggest that an enolizable alkanoyl cyanide such as **2n** is less reactive than a nonenolizable alkanoyl cyanide such as **2o** or **2p**.

Scope of Diynes. The effect of a substituent at the alkyne termini and the tether of a diyne was examined by using **2a** as the acyl cyanide. The results are summarized in Table 3. Ethyl-

Table 3. Scope of Diynes[a]



1 2a 3

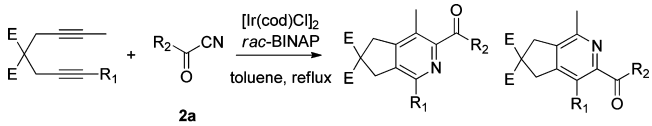
entry	1	time (h)	product	yield (%)[b]
1	 **1b**	5	**3ba**	88
2	 **1c**	1	**3ca**	96
3	 **1d**	24	**3da**	13
4[c]	**1d**	1	**3da**	68
5[d]	**1d**	16	**3da**	82
6	 **1e**	1	**3ea**	>99
7	 **1f**	1	**3fa**	98
8	 **1g**	1	**3ga**	90
9	 **1h**	14	**3ha**	80
10	 **1i**	2	**3ia**	89
11	 **1j**	24	**3ja**	0
12	 **1k**	24	**3ka**	45

[a]A mixture of **1** (0.5 mmol), **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), *rac*-BINAP (0.02 mmol), and toluene (2.5 mL) was stirred under refluxing toluene. [b]Isolated yield. [c]F-DPPE (0.02 mmol) was used in place of *rac*-BINAP. [d]F-DPPE (0.02 mmol) was used in place of *rac*-BINAP. Diyne **1a** was added to a reaction mixture for 3 h by a syringe pump.

substituted diyne **1b** reacted with **2a** to give **3ba** in 88% yield (entry 1). Even more hindered phenyl-substituted diyne **1c** smoothly reacted with **2a** to give **3ca** in 96% yield (entry 2). The reaction was not limited to a methyl-substituted diyne. The reaction of terminal diyne **1d** with **2a** competed with self-dimerization and -trimerization of **1d**. Controlled addition of diyne **1d** to the reaction mixture using a syringe pump was necessary to obtain **3da** in high yield (entry 5). Diynes **1e** and **1f** bearing a ketone at the 5-position of 2,7-nonadiyne smoothly reacted with **2a** to give **3ea** and **3fa** in a nearly quantitative yield (entries 6 and 7). Tosyl amide-tethered diyne **1g** and oxygen-tethered diyne **1h** gave results comparable to those of quaternary carbon-tethered diynes **1a**, **1e**, and **1f**. Diyne **1g** and **1h** reacted with **2a** to give **3ga** and **3ha** in yields of 90% and 80%, respectively (entries 8 and 9). The reaction allows for the atom-economical synthesis of heteroatom-fused bicyclic 2-acylpyridines. The reaction of 2,7-nonadiyne (**1i**) with **2a** gave **3ia** in 89% yield (entry 10). On the other hand, the reaction of 2,8-decadiyne (**1j**) did not give the corresponding product (entry 11). Introducing a substituent at the 5- and 6-positions of 2,8-decadiyne enabled the reaction to occur. Diyne **1k** bearing the ethoxycarbonyl group at 5- and 6-positions reacted with **2a** to give **2ka** in 45% yield (entry 12). These results suggest that cyclization to a 5-membered bicyclic 2-acylpyridine do not always require a Thorpe−Ingold effect.[14] However, cyclization to a 6-membered bicyclic 2-acylpyridine requires a Thorpe−Ingold effect.

Regioselective Cycloaddition of Diyne with Acyl Cyanides. Regioselective cycloaddition of an unsymmetrical internal diyne with acyl cyanides has not been studied. The control of regioselectivity is challenging for the synthesis of multisubstituted 2-acylpyridines. We have reported that iridium catalyst provided regioselective cycloaddition with nitriles and cyanamides. Based on this advantage, we have developed a new method for the convenient synthesis of oligoheteroarenes without depending on a cross-coupling methodology. We examined the regioselectivity of the reaction of unsymmetrical diyne **4a−c** with acyl cyanide **2a** under the optimized conditions. The structure of the products was determined on the basis of 2D-NMR analysis (see the Supporting Information). The results are summarized in Table 4. The

Table 4. Reaction of 4a−d with 2a[a]



4 2a R2=4-methylphenyl 5 6

entry	diyne **4**	yield[b] (%)	ratio
1[a]	**4a**, R_1 = Ph, E = CO_2Me	94	**5aa**:**6aa** = 89:11
2[c]	**4b**, R_1 = 2-Py, E = CO_2Me	98	**5ba**:**6ba** = 91:9
3[d]	**4c**, R_1 = Me_3Si, E = CO_2Me	84	**5ca**:**6ca** = 1:>99
4[e]	**4d**, R_1 = Et, E = CO_2Et	95	**5da**:**6da** = 31:69

[a]A mixture of **4a** (1 mmol), **2a** (1.2 mmol), $[Ir(cod)Cl]_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol), and toluene (5 mL) was stirred under refluxing toluene for 1 h. [b]Isolated yield. [c]**4b** (0.5 mmol), **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), *rac*-BINAP (0.02 mmol), toluene (2.5 mL). Reflux for 1 h. [d]**4b** (0.5 mmol), **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol), toluene (2.5 mL). reflux for 7 h. [e]**4d** (0.5 mmol), **2a** (0.6 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), *rac*-BINAP (0.02 mmol), toluene (2.5 mL). reflux for 1 h.

reaction of phenyl-substituted diyne **4a** with **2a** gave an 89:11 mixture of **5aa** and **6aa** in 94% yield (entry 1). The major product **5aa** was α-phenylpyridine. 2-Pyridyl-substituted diyne **4b** underwent the reaction with **2a** to give a 91:9 mixture of **5ba** and **6ba** in 98% yield, favoring the formation of the 2,2′-bipyridine (entry 2). It is noteworthy that the reaction gave a functionalized 2,2′-bipyridine. The regioselectivity of the reaction of **4b** with **2a** was the same as that of the reaction

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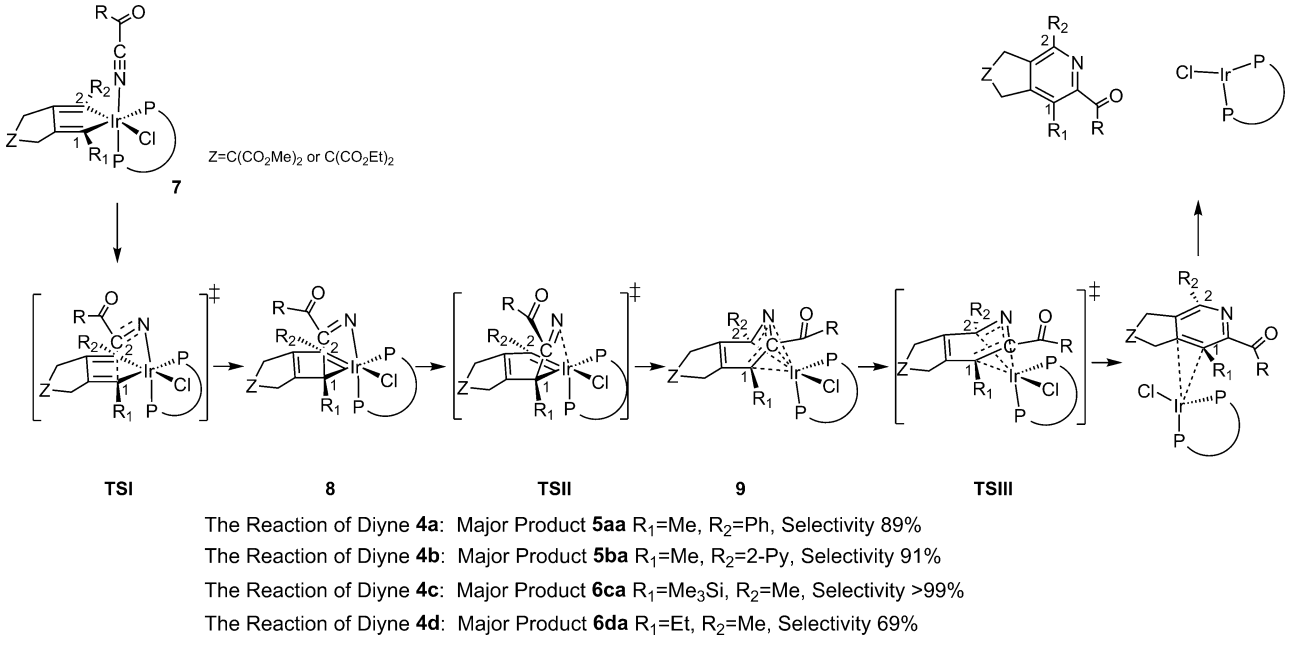
Scheme 1. Reaction Pathway for The Reaction of Unsymmetrical Diyne 4a−d



of **4a** with **2a**. The reaction of Me_3Si-substituted diyne **4c** with **2a** gave **6ca**, *β*-(trimethylsilyl)pyridine, in 84% yield as a single product (entry 3). The regioselectivity of the reaction of **4c** with **2a** was the opposite to that of the reaction of **4a** and **4b** with **2a**. The reaction of ethyl-substituted diyne **4d** with **2a** gave a 31:69 mixture of **5da** and **6da** in 95% yield (entry 4). The reaction of **4d** was less regioselective than the reaction of **4a−c**.

Mechanistic Considerations in Regioselective [2 + 2 + 2] Cycloaddition. In our previous study, we examined the reaction mechanism in a model reaction system for iridium-catalyzed cycloaddition with nitriles by using DFT calculations and proposed a reaction pathway in which the iridacyclopentadiene[15] generated by the oxidative cyclization of *α,ω*-diyne reacts with a nitrile to give the iridium pyridine complex via an azairidabicyclo[3.2.0]heptatriene complex.[12c] Based on the results, the regioselectivity observed here can be reasonably explained (Scheme 1). The end-on coordination of the nitrogen atom of the cyano group to the iridacyclopentadiene gives intermediate **7**. The first C−C bond formation to give azairidabicyclo[3.2.0]heptatriene **8** determines the regioselectivity.

*i. In the Case of Diynes **4a** and **4b**.* To explain the regioselectivity, it is important to know which carbon atom (C1 or C2) is more reactive toward the carbon atom of the cyano group. Comparison of the electron densities at C1 and C2 is important for explaining the regioselectivity since the more electron-rich carbon at C1 and C2 should react with the electron-deficient carbon atom of the cyano group. The inductive effect of the substituent through the *σ*-bond affects the electron densities at C_1 and C_2, and this is generally evaluated in terms of the Hammett constant σ^I.[16] According to σ^I, aryl- and heteroaryl groups are electron-withdrawing, while an alkyl group is electron-donating. The methyl-substituted C_1 atom is more electron-rich than a phenyl- or 2-pyridyl-substituted C_2 atom. Therefore, the C_1 carbon reacts with the carbon atom of the cyano group to give azairidabicyclo[3.2.0]-heptatriene **8**. In addition, *π*-conjugation of the C_2═Ir bond with the benzene ring or 2-pyridyl ring increases the stability of azairidabicyclo[3.2.0]heptatriene **8**. This contributes to the formation of **8**. These two effects give **5aa** and **5ba** as the major products.

*ii. In the Case of Diyne **4c**.* According to σ^I, the inductive effect of a trimethylsilyl group is more electron-donating than that of an alkyl group.[17] This effect makes the trimethylsilyl-substituted C1 atom more electron-rich than the methyl-substituted C2 atom. The C1 carbon reacts with the carbon atom of the cyano group to give azairidabicyclo[3.2.0]-heptatriene **8**. C−C bond formation between C1 and the carbon atom of the cyano group via TSI transforms an sp-hybridized carbon atom of the cyano group into an sp^2-hybridized imine carbon. The substituent on the carbon atom of the cyano group bends away from the newly formed C═N bond. In intermediate **8**, the distance between the trimethylsilyl group and RCO group seems to be too large to allow for their effective steric interaction. Thus, the reaction of **4c** gives the more hindered **6ca** as the major product. The reaction of **4c** requires a greater catalyst loading than that of **4a,b,d** to obtain the product in high yield. This suggests that diyne **4c** is less reactive than **4a,b,d**.

*iii. In the Case of Diyne **4d**.* The reaction of **4d** is less regioselective than that of **4a−c**. The major product is **6da**. The first C−C bond formation occurs between ethyl-substituted C1 and the carbon atom of the cyano group. The inductive effects of a methyl group and an ethyl group are both electron-donating. However, an ethyl group might be slightly more electron-donating than a methyl group because an ethyl group is longer than a methyl group. This leads to preferential C−C bond formation at C1.

In cases i−iii, an electronic effect plays a major role in determining the regioselectivity. As mentioned above, end-on coordination delivers the nitrile perpendicular to the iridacyclopentadiene plane. The carbon atom of the cyano group approaches C1 or C2 from above the iridacyclopentadiene plane, and regioselectivity is determined by this C−C bond formation. An sp-hybridized carbon atom of the cyano group transforms into an sp^2-hybridized imine carbon through

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this C−C bond formation. The substituent on the carbon atom of the cyano group bends away from the newly formed C═N bond. The steric interaction between R1 or R2 and the RCO-group is not large enough to control the regioselectivity. This might explain why the steric effect does not play a major role in determining regioselectivity in cases i−iii.

CONCLUSION

In summary, we have developed an efficient synthesis of 2-acylpyridines by iridium-catalyzed cycloaddition of α,ω-diynes with acyl cyanide. Aliphatic, aromatic, and heteroaromatic acyl cyanides can be used for the reaction. This method gives various 2-acylpyridines not easily accessible by a conventional condensation reaction. Further applications and mechanistic studies are required to elucidate this useful transformation.

EXPERIMENTAL SECTION

General Methods and Materials. ^{1}H and ^{13}CNMR spectra were measured at 500 and 125 MHz using TMS as an internal standard. Chloroform-*d* was used as the solvent. GC analyses were performed 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. High-resolution mass spectra were obtained by using a double-focusing analyzer. Infrared spectra were recorded with an FT-IR spectrometer. All solvents were dried and distilled before use by the usual procedures. $[Ir(cod)Cl]_2$ was prepared as described in the literature.[18] Diynes **1a,b**,[12c] **1c**,[19] **1d**,[20] **1e−g**,[12c] **1h,i**,[21] **1k**,[12c] **4a**,[12c] **4b,c**,[22] and **4d**[23] were prepared according to previously published procedures. Diyne **1j** was purchased. Acyl cyanides **2a**,[24] **2b**,[25] **2c**,[26] **2d**,[27] **2e**,[25] **2f**,[28] **2h**,[24] **2i**,[28] **2j**,[29] **2k**,[30] **2l**,[29] **2m**,[31] and **2o**[32] were prepared by literature reports. Acyl cyanide **2n** was purchased. Adamantane-1-carbonyl chloride was purchased.

Procedure for the Preparation of Acyl Cyanides. *4-Formylbenzoyl Cyanide (**2g**).* 4-Formylbenzoyl chloride (10.11 g, 60 mmol)[33] was slowly added at room temperature to a stirred suspension of copper(I) cyanide (6.71 g, 75 mmol) in dry acetonitrile (19 mL). The mixture was stirred under reflux for 17 h. The resulting solution was cooled to room temperature and concentrated in vacuo. Distillation of the residue (0.8 kPa, 105−120 °C) gave **2g** (3.582g, 22.8 mmol, yield 38%): white solid;mp 69.4−70.1 °C; IR (neat) 1704, 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10−8.13 (m, 2H), 8.33−8.34 (m, 2H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.4, 130.2, 131.0, 136.9, 141.3, 167.3, 190.7; HRMS (EI) m/z $[M]^+$ calcd for $C_9H_5NO_2$ 159.0320, found 159.0325.

*1-Adamantane Carbonyl Cyanide (**2p**).* 1-Adamantane carbonyl chloride (3.97 g, 20 mmol) was slowly added at room temperature to a stirred suspension of copper(I) cyanide (2.68 g, 30 mmol) in dry acetonitrile (10 mL). The mixture was stirred under reflux for 17 h. The resulting solution was cooled to room temperature and concentrated in vacuo. Destillation of the residue (0.2 kPa, 75−80 °C) gave **2p** (2.797g, 14.8 mmol, yield 74%): white solid; mp 57.3−58.5 °C; IR (neat) 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70−1.73 (m, 3H), 1.79−1.82 (m, 3H), 1.88−1.89 (m, 6H), 2.15 (br, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2, 35.9, 36.4, 47.0, 112.1, 182.6; HRMS (EI) m/z $[M]^+$ calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1152.

General Procedure for the [2 + 2 + 2] Cycloaddition of Diyne (1) with Acyl Cyanide (2). A flask was charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol) and *rac*-BINAP (12.5 mg, 0.02 mmol). The flask was evacuated and filled with argon. To the flask were added toluene (2.5 mL) and acyl cyanide (**2a**) (87.1 mg, 0.6 mmol). Diyne **1a** (118.1 mg, 0.50 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 in vacuo. Column chromatography of the residue gave **3aa** (*n*-hexane/AcOEt = 6/4, 187.8 mg, 0.5 mmol, >99% yield).

*Dimethyl 1,4-dimethyl-3-(4-methylbenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3aa**):* yellow solid; yield 99%, 187.8 mg (0.50 mmol scale); mp 136.5−138.0 °C; R_f = 0.45 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1746, 1727, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 3.62 (s, 2H), 3.65 (s, 2H), 3.80 (s, 6H), 7.23−7.24 (m, 2H), 7.75−7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7, 21.6, 21.7, 39.3, 39.8, 53.3, 59.1, 125.5, 129.0, 130.7, 133.9, 134.8, 144.3, 149.5, 150.2, 153.9, 171.6, 195.5; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{22}H_{24}NO_5$ 382.1654, found 382.1644.

*Dimethyl 1,4-dimethyl-3-(4-methoxylbenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ab**):* white solid; yield 95%, 376.6 mg (1.00 mmol scale); mp 198.2−200.0 °C; R_f = 0.30 (AcOEt); IR (Zn/Se-ATR, neat) 1741, 1726, 1657 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 2.46 (s, 3H), 3.62 (s, 2H), 3.65 (s, 2H), 3.80 (s, 6H), 3.87 (s, 3H), 6.90−6.93 (m, 2H), 7.84−7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7, 21.7, 39.3, 39.8, 53.3, 55.5, 59.2, 113.6, 125.4, 129.5, 133.0, 134.7, 149.5, 150.2, 154.1, 163.8, 171.7, 194.5; HRMS (FAB) m/z $[M]^+$ calcd for $C_{22}H_{23}NO_6$ 397.1525, found 397.1523.

*Dimethyl 1,4-dimethyl-3-(2-methylbenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ac**).* Yellow solid; yield 88%, 155.8 mg (0.47 mmol scale); mp 139.4−141.8 °C; R_f = 0.39 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1734, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3H), 2.40 (s, 3H), 2.54 (s, 3H), 3.63 (s, 4H), 3.80 (s, 6H), 7.16−7.19 (m, 1H), 7.26−7.27 (m, 1H), 7.33−7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.0 MHz) δ 14.8, 21.5, 21.6, 39.2, 39.8, 53.2, 59.1, 125.2, 126.0, 131.7, 131.8, 132.2, 135.1, 136.6, 140.0, 149.6, 150.3, 154.4, 171.6, 198.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{22}H_{24}NO_5$ 382.1654, found 382.1671.

*Dimethyl 1,4-dimethyl-3-(2,4,6-trimethylbenzoyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3ad**):* yellow solid; yield 83%, 169.4 mg (0.50 mmol scale); mp 171.6−172.1 °C; R_f = 0.29 (hexane/AcOEt = 4/1); IR (Zn/Se-ATR, neat) 1730, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 6H), 2.29 (s, 3H), 2.30 (s, 3H), 2.51 (s, 3H), 3.59 (s, 2H), 3.64 (s, 2H), 3.79 (s, 6H), 6.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.4, 19.7, 21.2, 21.8, 39.4, 39.9, 53.3, 59.1, 128.0, 128.1, 134.4, 136.5, 138.0, 139.3, 149.9, 150.5, 152.1, 171.7, 202.8; HRMS (EI$^+$) m/z $[M]^+$ calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1900.

*Dimethyl 1,4-dimethyl-3-(4-chlorobenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ae**):* white solid; yield 98%, 197.8 mg (0.50 mmol scale); mp 145.3−147.1 °C; R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1749, 1731, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 3H), 2.45 (s, 3H), 3.63 (s, 2H), 3.65 (s, 2H), 3.81 (s, 6H), 7.40−7.43 (m, 2H), 7.82−7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.7, 39.3, 39.8, 53.3, 59.1, 126.3, 128.6, 132.1, 135.0, 135.4, 139.7, 149.9, 150.3, 152.8, 171.6, 194.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{21}H_{21}ClNO_5$ 402.1108, found 402.1123.

*Dimethyl 1,4-dimethyl-3-(4-bromobenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3af**):* yellow solid; yield 88%, 194.9 mg (0.50 mmol scale); mp 162.5−164.2 °C; R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1748, 1731, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 2.45 (s, 3H), 3.63 (s, 2H), 3.65 (s, 2H), 3.80 (s, 6H), 7.57−7.59 (m, 2H), 7.74−7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.6, 39.3, 39.8, 53.3, 59.1, 126.4, 128.5, 131.5, 132.1, 135.37, 135.40. 149.9, 150.2, 152.7, 171.6, 194.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{21}H_{21}BrNO_5$ 446.0603, found 446.0600.

*Dimethyl 3-(4-formylbenzoyl)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ag**):* yellow solid; yield 86%, 170.8 mg (0.50 mmol scale); mp 145.2−147.1 °C; R_f = 0.50 (hexane/AcOEt = 2/3); IR (Zn/Se-ATR, neat) 1728, 1698, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 3H), 2.45 (s, 3H), 3.65 (s, 2H), 3.66 (s, 2H), 3.81 (s, 6H), 7.94−7.96 (m, 2H), 8.02−8.04 (m, 2H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 21.7, 39.3, 39.9, 53.3, 59.1, 127.1, 129.3, 131.2, 135.9, 138.8, 141.4, 150.1, 150.3, 152.2, 171.6, 191.8, 194.6; HRMS (EI$^+$) m/z $[M]^+$ calcd for $C_{22}H_{21}NO_6$ 395.1369, found 395.1384.

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*Dimethyl 1,4-dimethyl-3-(4-trifluoromethylbenzoyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3ah**):* yellow solid; yield >99%, 226.1 mg (0.52 mmol scale); mp 144.0−145.7 °C; R_f = 0.55 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 3H), 2.45 (s, 3H), 3.65 (s, 2H), 3.67 (s, 2H), 3.81 (s, 6H), 7.69−7.71 (m, 2H), 7.99−8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.6, 39.3, 39.8, 53.3, 59.1, 123.7, (q, J = 272.4 Hz), 125.1, (d, J = 3.5 Hz), 127.0, 131.0, 134.1 (q, J = 32.3 Hz), 135.8, 139.6, 150.1, 150.3, 171.5, 194.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{22}H_{21}F_3NO_5$ 436.1372, found 436.1380.

*Dimethyl 1,4-dimethyl-3-(4-nitrobenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ai**):* pale orange solid; yield 72%, 146.6 mg (0.49 mmol scale); mp 137.4−139.0 °C; R_f = 0.46 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1731, 1694, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.34 (s, 3H), 2.44 (s, 3H), 3.66 (s, 2H), 3.67 (s, 2H), 3.81 (s, 6H), 8.04−8.06 (m, 2H), 8.26−8.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.0, 21.6, 39.3, 39.9, 53.3, 59.0, 123.2, 127.9, 131.6, 136.4, 142.0, 150.0, 150.32, 150.34, 151.3, 171.5, 193.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_7$ 413.1349, found 413.1357.

*Dimethyl 3-(1-naphthoyl)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3aj**):* white solid; yield 94%, 197.5 mg (0.50 mmol scale); mp 119.6−120.5 °C; R_f = 0.51 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1748, 1724, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.29 (s, 3H), 2.40 (s, 3H), 3.65 (s, 4H), 3.81 (s, 6H), 7.39−7.43 (m, 1H), 7.53−7.57 (m, 1H), 7.61−7.64 (m, 1H), 7.88−7.90 (m, 1H), 8.00−8.01 (m, 1H), 8.93−8.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 21.6, 39.3, 39.8, 53.3, 59.1, 124.1, 126.1, 126.2, 126.4, 128.2, 128.4, 131.4, 132.8, 133.6, 133.9, 134.0, 135.1, 149.6, 150.4, 154.9, 171.6, 198.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{25}H_{24}NO_5$ 418.1654, found 418.1655.

*Dimethyl 3-(2-naphthoyl)-1,4-dimethyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ak**):* white solid; yield 95%, 209.3 mg (0.53 mmol scale); mp 169.8−171.2 °C; R_f = 0.55 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1744, 1729, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 2.48 (s, 3H), 3.66 (s, 2H), 3.69 (s, 2H), 3.82 (s, 6H), 7.50−7.53 (m, 1H), 7.58−7.61 (m, 1H), 7.87−7.91 (m, 3H), 8.04−8.06 (m, 1H), 8.28 (br,1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.7, 39.3, 39.9, 53.3, 59.1, 125.3, 125.8, 126.6, 127.8, 128.2, 128.6, 129.8, 132.4, 133.4, 133.9, 135.0, 135.8, 149.7, 150.4, 153.8, 171.7, 195.8; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{25}H_{24}NO_5$ 418.1654, found 418.1650.

*Dimethyl 1,4-dimethyl-3-(thiophene-2-carbonyl)-5H-cyclopenta-[c]pyridine-6,6(7H)-dicarboxylate (**3al**):* yellow solid; yield 89%, 167.4 mg (0.50 mmol scale); mp 145.0−146.2 °C; R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1726, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.40 (s, 3H), 2.52 (s, 3H), 3.63 (s, 2H), 3.65 (s, 2H), 3.80 (s, 6H), 7.11−7.13 (m, 1H), 7.69−7.70 (m, 1H), 7.87−7.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2, 21.4, 39.2, 39.9, 53.3, 59.1, 127.5, 127.6, 135.6, 135.9, 136.1, 142.4, 149.9, 150.3, 151.5, 171.6, 186.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{19}H_{20}NO_5S$ 374.1062, found 374.1047.

*Dimethyl 3-cinnamoyl-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3am**):* brown solid; yield 85%, 169.8 mg (0.50 mmol scale); mp 129.5−131.8 °C; R_f = 0.55 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1730, 1685, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.46 (s, 3H), 2.51 (s, 3H), 3.63 (s, 2H), 3.64 (s, 2H), 3.79 (s, 6H), 7.37−7.42 (m, 3H), 7.63−7.65 (m, 2H), 7.71 (d, J = 16 Hz, 1H), 7.87 (d, J = 16 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.0 MHz) δ 15.5, 21.8, 39.3, 39.8, 53.3, 59.1, 124.8, 128.1, 128.6, 128.8, 130.2, 135.2, 136.3, 143.9, 150.1, 150.2, 151.8, 171.6, 192.5; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{24}NO_5$ 394.1654, found 394.1659.

*Dimethyl 3-acetyl-1,4-dimethyl-5,7-dihydro-6H-cyclopenta[c]-pyridine-6,6-dicarboxylate (**3an**):* yellow solid; yield 89%, 136.1 mg (0.50 mmol scale); mp 99.5−101.2 °C; R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1742, 1726, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3H), 2.46 (s, 3H), 3.60−3.60 (m, 4H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.6, 21.7, 28.5, 39.3, 39.8, 53.2, 59.1, 127.6, 136.6, 149.9, 150.1, 150.8, 171.5, 202.8; HRMS (FAB) m/z $[M]^+$ calcd for $C_{16}H_{19}NO_5$ 305.1263, found 305.1260.

*Dimethyl 1,4-dimethyl-3-pivaloyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3ao**):* yellow liquid; yield 82%, 145.9 mg (0.51 mmol scale); R_f = 0.50 (hexane/AcOEt = 13/7); IR (Zn/Se-ATR, neat) 1736, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 9H), 2.14 (s, 3H), 2.41 (s, 3H), 3.56 (s, 2H), 3.59 (s, 2H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 21.6, 27.4, 39.2, 39.9, 44.6, 53.2, 59.1, 124.1, 134.0, 149.2, 149.4, 154.9, 171.7, 211.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{19}H_{26}NO_5$ 348.1811, found 348.1803.

*Dimethyl 3-(adamantane-1-carbonyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3ap**):* white solid; yield 87%, 184.3 mg (0.50 mmol scale); mp 114.0−115.5 °C; R_f = 0.50 (hexane/AcOEt = 13/7); IR (Zn/Se-ATR, neat) 1736, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.69−1.75 (m, 6H), 2.00−2.03 (m, 9H), 2.11 (s, 3H), 2.42 (s, 3H), 3.56 (s, 2H), 3.59 (s, 2H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.6, 28.0, 36.5, 38.5, 39.1, 46.8, 53.2, 59.0, 123.6, 133.7, 149.0, 149.4, 155.2, 171.6, 210.9; HRMS (FAB) m/z $[M]^+$ calcd for $C_{25}H_{31}NO_5$ 425.2202, found 425.2198.

*Dimethyl 1,4-diethyl-3-(4-methoylbenzoyl)-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ba**):* yellow oil; yield 88%, 189.9 mg (0.53 mmol scale); R_f = 0.42 (hexane/AcOEt = 4/1); IR (Zn/Se-ATR, neat) 1735, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (t, J = 8.0 Hz, 3H), 1.22 (t, J = 8.0 Hz, 3H), 2.40 (s, 3H), 2.61 (q, J = 7.5 Hz, 2H), 2.76 (q, J = 7.5 Hz), 3.67 (d, J = 4.5 Hz, 4H), 3.79 (s, 6H), 7.22−7.24 (m, 2H), 7.76−7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.0 MHz) δ 12.7, 14.5, 21.5, 22.3, 28.4, 38.5, 39.0, 53.1, 59.5, 128.8, 130.6, 131.6, 134.0, 134.3, 144.0, 149.1, 153.6, 154.9, 171.4, 195.2; HRMS (FAB) m/z $[M]^+$ calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1908.

*Dimethyl 3-(4-methoylbenzoyl)-1,4-diphenyl-5H-cyclopenta[c]-pyridine-6,6(7H)-dicarboxylate (**3ca**):* white solid; yield 96%, 242.0 mg (0.50 mmol scale); mp 193.6−194.5 °C; R_f = 0.50 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1732, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.59 (s, 2H), 3.73 (s, 6H), 3.96 (s, 2H), 7.17−7.19 (m, 2H), 7.25−7.31 (m, 5H), 7.40−7.48 (m, 3H), 7.74−7.76 (m, 2H), 7.80−7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 40.0, 40.7, 53.2, 59.9, 127.9, 128.41, 128.43, 128.6, 128.7, 128.9, 129.0, 130.5, 131.6, 133.98, 134.0, 135.5, 138.6, 144.0, 150.7, 151.8, 154.4, 171.3, 194.6; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{32}H_{27}NO_5$ 505.1889, found 505.1897.

*Dimethyl 3-(4-methylbenzoyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3da**):* yellow solid; yield 82%, 144.7 mg (0.50 mmol scale); mp 115.8−117.2 °C; R_f = 0.49 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1732, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 3H), 3.71 (d, J = 5.5 Hz, 4H), 3.78 (s, 6H), 7.27 (d, J = 8.0 Hz, 2H), 7.89 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 38.3, 40.2, 53.2, 59.9, 120.5, 128.7, 131.0, 133.7, 139.0, 143.6, 144.1, 150.6, 154.2, 171.2, 193.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{20}H_{20}NO_5$ 354.1341, found 354.1346.

*1,1′-[1,4-Dimethyl-3-(4-methylbenzoyl)-6,7-dihydro-5H-cyclopenta[c]pyridine-6,6-diyl]diethanone (**3ea**):* yellow solid; yield >99%, 176.6 mg (0.50 mmol scale); mp 133.8−135.3 °C; R_f = 0.36 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1720, 1701, 1665, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3H), 2.23 (s, 6H), 2.40 (s, 3H), 2.46 (s, 3H), 3.52 (s, 2H), 3.54 (s, 2H), 7.22−7.24 (m, 2H), 7.74−7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.6, 21.6, 21.7, 26.4, 35.9, 36.3, 73.9, 125.5, 129.0, 130.6, 133.8, 134.5, 144.3, 149.3, 150.3, 153.9, 195.3, 203.4; HRMS (FAB) m/z $[M]^+$ calcd for $C_{22}H_{23}NO_3$ 349.1678, found 349.1670.

*1′,4,4,4′-Tetramethyl-3′-(4-methylbenzoyl)-5′,7′-dihydrospiro-(cyclohexane-1,6′-cyclopenta[c]pyridine)-2,6-dione (**3fa**):* white solid; yield 98%, 187.2 mg (0.49 mmol scale); mp 198.0−199.7 °C; R_f = 0.41 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1728, 1697, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 3H), 1.11 (s, 3H), 2.20 (s, 3H), 2.41 (s, 3H), 2.42 (s, 3H), 2.71 (d, J = 14 Hz, 2H), 2.81 (d, J = 14 Hz, 2H), 3.45 (s, 2H), 3.47 (s, 2H), 7.22−7.24 (m, 2H), 7.74−7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.0 MHz) δ 14.7, 21.71, 21.73, 27.9, 28.8, 30.6, 36.6, 38.5, 51.4, 69.8, 125.6, 129.0, 130.7, 133.95, 133.98, 144.3, 149.8, 150.2, 154.0, 195.5, 205.9; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{25}H_{28}NO_3$ 390.2069, found 390.2082.

*(4,7-Dimethyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(4-methylphenyl)methanone (**3ga**):* orange solid; yield 90%, 182.9 mg (0.49 mmol scale); mp 193.8−195.2 °C; R_f = 0.33 (hexane/AcOEt

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= 3/2); IR (Zn/Se-ATR, neat) 1661 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.15 (s, 3H), 2.40 (s, 3H), 2.41 (s, 3H), 2.44 (s, 3H), 4.63 (s, 2H), 4.66 (s, 2H), 7.22−7.24 (m, 2H), 7.36−7.37 (m, 2H), 7.71−7.72 (m, 2H), 7.80−7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5, 21.5, 21.7, 52.8, 53.2, 124.2, 127.5, 129.1, 130.0, 130.6, 131.3, 133.55, 133.59, 144.1, 144.6, 146.0, 149.1, 154.7, 194.7; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_3S$ 421.1586, found 421.1573.

*(4,7-Dimethyl-1,3-dihydrofuro[3,4-c]pyridin-6-yl)(p-tolyl)-methanone (**3ha**):* white solid; yield 80%, 90.3 mg (0.42 mmol scale); mp 134.0−135.8 °C; R_f = 0.43 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat) 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 5.15−5.16 (m, 2H), 5.18−5.19 (m, 2H), 7.24−7.26 (m, 2H), 7.77−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.7, 21.8, 72.9, 73.2, 123.2, 129.1, 130.7, 133.9, 144.4, 147.9, 149.0,. 154.3, 195.2; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1268.

*(1,4-Dimethyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)(p-tolyl)-methanone (**3ia**):* white solid; yield 89%, 103.9 mg (0.44 mmol scale); mp 95.4−97.8 °C; R_f = 0.50 (hexane/AcOEt = 13/7); IR (Zn/Se-ATR, neat) 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.13−2.18 (m, 1H), 2.20 (s, 3H), 2.41 (s, 3H), 2.45 (s, 3H), 2.90−2.97 (m, 4H), 7.22−7.24 (m, 2H), 7.77−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9, 21.7, 21.8, 23.9, 31.2, 31.8, 125.5, 129.0, 130.7, 134.3, 138.7, 144.0, 150.2, 153.0, 153.6, 196.1; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1461.

*Tetraethyl 1,4-dimethyl-3-(4-methylbenzoyl)isoquinoline-6,6,7,7-(5H,8H)-tetracarboxylate (**3ka**):* yellow liquid; yield 45%, 128.2 mg (0.50 mmol scale); R_f = 0.45 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1729, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26 (m, 12H), 2.15 (s, 3H), 2.41 (s, 3H), 2.47 (s, 3H), 3.41 (s, 2H), 3.45 (s, 2H), 4.20−4.27 (m, 8H), 7.22−7.24 (m, 2H), 7.74−7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 14.4, 21.7, 22.2, 32.2, 32.4, 56.7, 62.1, 126.5, 129.1, 130.7, 133.9, 141.7, 144.4, 153.0, 169.6, 195.9; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{31}H_{38}NO_9$ 568.2547, found 568.2554.

*Dimethyl 4-methyl-3-(4-methylbenzoyl)-1-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**5aa**):* white solid; yield 84%, 372.1 mg (1.00 mmol scale); mp 134.6−136.2 °C; R_f = 0.40 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat) 1749, 1723, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.32 (s, 3H), 2.41 (s, 3H), 3.67 (s, 2H), 3.78 (s, 6H), 3.91 (s, 2H), 7.24−7.26 (m, 2H), 7.36−7.38 (m, 1H), 7.41−7.44 (m, 2H), 7.73−7.75 (m, 2H), 7.84−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.8, 21.7, 39.5, 40.7, 53.2, 59.6, 127.0, 128.35, 128.39, 128.44, 129.0, 130.8, 133.8, 134.0, 138.9, 144.2, 150.3, 151.2, 154.1, 171.4, 195.0; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{27}H_{25}NO_5$ 443.1733, found 443.1732.

*Dimethyl 1-methyl-3-(4-methylbenzoyl)-4-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**6aa**):* yellow solid; yield 10%, 47.4 mg (1.00 mmol scale); mp 146.1−147.8 °C; R_f = 0.26 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat) 1731, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 3H), 2.54 (s, 3H), 3.55 (s, 2H), 3.70 (s, 2H), 3.77 (s, 6H), 7.13−7.15 (m, 2H), 7.19−7.28 (m, 5H), 7.63−7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 21.9, 39.2, 40.3, 53.2, 59.4, 127.7, 128.4, 128.9, 129.0, 130.4, 130.5, 134.0, 135.0, 135.7, 144.0, 148.9, 152.1, 154.1, 171.5, 195.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{27}H_{26}NO_5$ 444.1811, found 444.1819.

*Dimethyl 4-methyl-3-(4-methylbenzoyl)-1-(pyridin-2-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (**5ba**):* white solid; yield 89%, 198.1 mg (0.50 mmol scale); mp 157.5−158.4 °C; R_f = 0.54 (hexane/AcOEt = 7/3); IR (Zn/Se-ATR, neat) 1735, 1724, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 3H), 2.43 (s, 3H), 3.66 (s, 2H), 3.79 (s, 6H), 4.29 (s, 2H), 7.21−7.26 (m, 3H), 7.67−7.71 (m, 1H), 7.84−7.86 (m, 2H), 8.19−8.20 (m, 1H), 8.65−8.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.1, 21.8, 39.3, 42.2, 53.1, 59.4, 122.7, 122.8, 128.5, 129.0, 130.8, 134.1, 135.8, 136.3, 144.1, 147.8, 148.4, 152.0, 153.2, 157.1, 171.9, 194.9; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{26}H_{24}N_2O_5$ 444.1685, found 444.1677.

*Dimethyl 1-methyl-3-(4-methylbenzoyl)-4-(pyridin-2-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (**6ba**):* yellow solid; yield 9%, 20.1 mg (0.50 mmol scale); mp 130.8−132.1 °C; R_f = 0.54 (hexane/AcOEt = 1/1); IR (Zn/Se-ATR, neat) 1733, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 3H), 2.56 (s, 3H), 3.69 (s, 2H), 3.74 (s, 2H), 3.77 (s, 6H), 7.10−7.16 (m, 3H), 7.35−7.36 (m, 1H), 7.58−7.62 (m, 1H), 7.69−7.71 (m, 2H), 8.48−8.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 22.1, 38.9, 40.5, 53.3, 59.5, 122.3, 124.3, 128.9, 129.9, 130.5, 133.9, 135.5, 136.2, 143.8, 149.0, 149.4, 152.8, 154.4, 154.7, 171.4, 195.0; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{26}H_{24}N_2O_5$ 444.1685, found 444.1682.

*Dimethyl 1-methyl-3-(4-methylbenzoyl)-4-(trimethylsilyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**6ca**):* white solid; yield 84%, 185.8 mg (0.50 mmol scale); mp 122.4−124.5 °C; R_f = 0.53 (hexane/AcOEt = 3/2); IR (Zn/Se-ATR, neat) 1738, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.22 (s, 9H), 2.41 (s, 3H), 2.46 (s, 3H), 3.59 (s, 2H), 3.72 (s, 2H), 3.79 (s, 6H), 7.23−7.25 (m, 2H), 7.78−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.89, 21.7, 21.9, 38.1, 42.6, 53.2, 59.5, 126.5, 129.1, 130.9, 133.9, 134.0, 144.2, 152.9, 156.0, 160.9, 171.5, 196.6; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{24}H_{29}NO_5Si$ 439.1815, found 439.1806.

*Diethyl 1-ethyl-4-methyl-3-(4-methylbenzoyl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (**5da**):* pale yellow solid; yield 30%, 63.9 mg (0.50 mmol scale); mp 59.8−62.2 °C; R_f = 0.38 (hexane/AcOEt = 8/2); IR (Zn/Se-ATR, neat) 1727, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 6H), 2.22 (s, 3H), 2.41 (s, 3H), 2.74 (q, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.65 (s, 2H), 4.25 (q, J = 7.0 Hz, 4H), 7.22−7.24 (m, 2H), 7.77−7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.9, 14.0, 14.7, 21.7, 28.6, 38.8, 39.6, 59.4, 62.1, 125.7, 128.9, 130.8, 134.1, 134.3, 144.1, 149.9, 153.7, 155.0, 171.2, 195.4; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{25}H_{29}NO_5$ 423.2046, found 423.2038.

*Diethyl 4-ethyl-1-methyl-3-(4-methylbenzoyl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (**6da**):* white solid; yield 65%, 139.7 mg (0.50 mmol scale); mp 71.1−71.8 °C; R_f = 0.5 (hexane/AcOEt = 8/2); IR (Zn/Se-ATR, neat) 1731, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.5 Hz, 6H), 2.40 (s, 3H), 2.45 (s, 3H), 2.58 (q, J = 7.5 Hz, 2H), 3.62 (s, 2H), 3.64 (s, 2H), 4.25 (q, J = 7.5 Hz, 4H), 7.21−7.23 (m, 2H), 7.73−7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 14.6, 21.67, 21.72, 22.5, 38.9, 39.1, 59.5, 62.1, 128.9, 130.7, 131.6, 134.0, 135.2, 144.2, 149.1, 150.3, 153.7, 171.1, 195.4; HRMS (EI^+) m/z $[M]^+$ calcd for $C_{25}H_{29}NO_5$ 423.2046, found 423.2042.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00668.

^1H and ^{13}C NMR spectra for the acyl cyanides **2g**, **2p**, and the products **3aa**−**ap**, **3ba**−**ia**, **3ka**, **5aa**, **5ba**, **5da**, **6aa**, **6ba**, **6ca**, and **6da**, HMBC spectra for the product **5aa**, **5ba**, **5da**, **6aa**, **6ba**, **6ca**, and **6da** (PDF)

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Notes

The authors declare no competing financial interest.

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