Regioselective Syntheses of Substituted Pyridines and 2,2′-Bipyridines by Cobalt-Catalyzed [2+2+2] Cycloaddition of α,ω-Diynes with Nitriles

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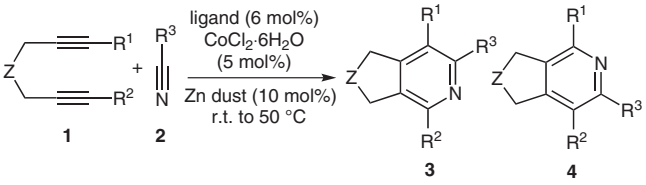
Abstract: In the presence of a 1,2-bis(diphenylphosphino)ethane–cobalt(II) chloride–zinc catalyst in 1-methylpyrrolidin-2-one at room temperature to 50 °C, α,ω-diynes reacted with nitriles by a [2+2+2] cycloaddition pathway to give annulated pyridines or 2,2′-bipyridines. The regioselectivity of the reaction is controlled by a combination of steric and electronic effects. The reaction of diynes with a terminal trimethylsilyl group gave the corresponding 3-(trimethylsilyl)pyridines exclusively; these products could be proto- or halodesilylated to give the corresponding protonated or halogenated pyridines or 2,2′-bipyridines.

Key words: cycloadditions, heterocycles, homogeneous catalysis, pyridines, regioselectivity

The catalytic cycloaddition of alkynes and nitriles in a [2+2+2] fashion provides a straightforward method for preparing substituted pyridines.[1,2] The regiochemistry of the reaction and its control are important in relation to utilizing the method in synthesis. Successful regiocontrol in a fully intermolecular reaction is possible but challenging,[3,4] whereas the regiochemistry of fully intramolecular reactions can be more readily controlled by altering the positions of the alkyne and nitrile groups or by the strain in the intermediates or products. Pyridines with unique tricyclic or spiro skeletons have been prepared by this method.[5] In contrast, comprehensive data on the regioselectivity of partially intramolecular reactions,[6] such as the cycloadditions of α,ω-diynes to nitriles or of ω-cyanoalkynes with alkynes, are not available.

The synthesis of pyridines by the cycloaddition of nonsymmetrical α,ω-diynes **1** to nitriles **2** gives two regioisomers **3** and **4** (Scheme 1). We assumed that the regioselectivity of this reaction might be controlled by steric or electronic effects or by the balance of the two. The reactions of 6-substituted (1-unsubstituted) 1,6-diynes catalyzed by $CpCo(CO)_2$[7a] (Cp = η^5-cyclopentadienyl) or Cp*RuCl(cod)[3b,5b,8] (Cp* = η^5-pentamethylcyclopentadienyl; cod = cyclooctadienyl) gave the corresponding 2,6-substituted pyridines predominantly rather than the 2,3-substituted pyridines. The selectivity of this reaction has been rationalized by considering the steric repulsion between the metallacyclopentadiene intermediate and the nitrile. Several examples that might be explained in terms of the electronic nature of the diyne substrate (and that of the corresponding metallacycle intermediates) have been reported by Schreiber and co-workers,[9] Tanaka et al.,[3c,10] Louie and co-workers,[11] and our research group[12] for reactions catalyzed by Cp-$Co(CO)_2$, cationic diphosphine–rhodium, N-heterocyclic carbene (NHC)–nickel, or diphosphine–cobalt systems, respectively. Here we report a regioselective [2+2+2] cycloaddition of diynes with nitriles catalyzed by a 1,2-bis(diphenylphosphino)ethane–cobalt(II) chloride hexahydrate–zinc [(dppe)$CoCl_2 \cdot 6H_2O$–Zn] reagent,[12] and we discuss the relationship between the selectivity and the substrate structure.



Scheme 1

During the course of our previous studies on alkyne cycloaddition,[12,13] we found that a $CoCl_2 \cdot 6H_2O$/Zn reagent catalyzed the cycloaddition of diynes and nitriles in the presence of a diphosphine ligand. A survey of phosphine ligands for the reaction of diyne **1** ($R^1 = R^2 = H$) in acetonitrile (80 equivalents as the solvent) showed that dppe was most effective ligand (Scheme 1; Table 1). Furthermore, we were able to reduce the amount of nitrile needed by using 1-methylpyrrolidin-2-one (NMP) as the solvent (runs 8 and 9).

The structures of the substrates used in this study are shown in Figure 1.

We then investigated the reactions of alkyl- and aryl-substituted diynes **1a–c**, **1f**, and **1e** with the nitriles **2a–d** (Scheme 2); the results are summarized in Table 2. The reactions of acetonitrile (**2a**) with diynes **1a–c** and **1f**, which contain electron-donating or -withdrawing groups at the *para*-position of the aryl substituent, gave the corresponding 3-arylpyridines **4** predominantly, with a slight variation in the regioselectivity (Table 2, entries 1–4). In contrast, substituents on the nitrile had a significant effect on the regioselectivity (entries 4–7): Aliphatic nitriles **2a** and **2b** (entries 1–5) gave the 3-arylpyridines **4** as the main products, whereas the aromatic nitriles **2c** and **2d** (entries 6 and 7) gave the corresponding 2-arylpyridines

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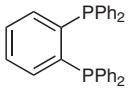
Table 1 Survey of Phosphine Ligands (Scheme 1; $R^1 = R^2 = H$, R = Me)

Entry[a]	Ligand	Time (h)	Yield (%)
1	–	24	–
2	$2PPh_3$	24	17
3	$Ph_2PCH_2PPh_2$ (dppm)	24	–
4	$Ph_2P(CH_2)_2PPh_2$ (dppe)	1	quant.
5	$Ph_2P(CH_2)_3PPh_2$ (dppp)	12	71
6	$Ph_2P(CH_2)_4PPh_2$ (dppb)	12	4
7		12	quant.
8	dppe (5 equiv of **2a** in NMP)[b]	12	52
9	dppe (20 equiv of **2a** in NMP)[b]	1	96

[a] MeCN (80 equiv), r.t.
[b] MeCN was replaced by NMP as the solvent.

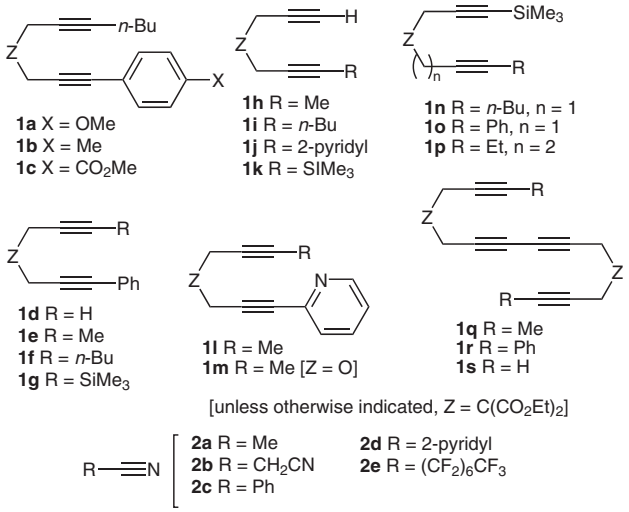


Figure 1 Substrate structures

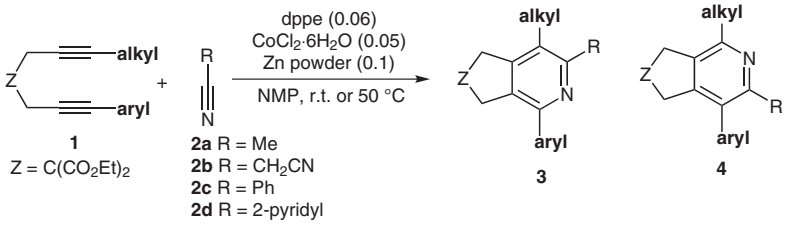
3. The extremely high selectivity in the reaction with 2-cyanopyridine (**2d**) compared with that of benzonitrile (**2c**) suggested that differences in the electronic nature of the nitriles may be responsible for changes in the selectivity. Tanaka et al.[3c] reported that the $Rh(cod)_2BF_4$/Segphos-catalyzed reaction of **1e** (R^1 = Me, R^2 = Ph) with malononitrile (**2b**) gave the 3-aryl derivative **4eb** with >84% regioselectivity, whereas our cobalt-catalyzed reaction of **1f** (R^1 = Bu, R^2 = Ph) with **2b** gave the opposite isomer **3fb** predominantly.

Table 2 Results for the Reactions Shown in Scheme 2

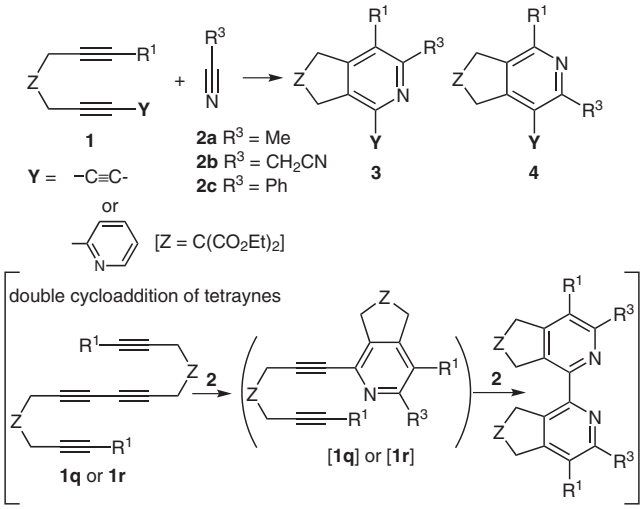
Entry	Diyne	Alkyl	Aryl	**2** (equiv)	Ratio **3**/**4**	Yield (%)
1	**1a**	Bu	4-$MeOC_6H_4$	**2a** (20)	15:85	91
2	**1b**	Bu	4-MeC_6H_4	**2a** (20)	12:88	89
3	**1c**	Bu	4-$MeO_2CC_6H_4$	**2a** (20)	16:84	96
4	**1f**	Bu	Ph	**2a** (20)	15:85	96
5	**1f**	Bu	Ph	**2b** (2)	18:82	80
6	**1f**	Bu	Ph	**2c** (20)	61:39	75
7	**1e**	Me	Ph	**2d** (5)	>99:1	47

In contrast, diyne substrates containing an alkynyl or a 2-pyridyl moiety as a terminal substituent gave the corresponding 3-alkynylpyridines or 3-(2-pyridyl)pyridines **4** exclusively in all cases, irrespective of the nitrile used (Scheme 3; Table 3). The strong electron-withdrawing nature of the alkynyl and 2-pyridyl groups may cause differentiation in the site reactivity of the corresponding cobaltacyclopentadiene intermediates (see below). The double (domino) cycloaddition of 1,6,8,12-tetrayne substrates **1q** and **1r** gave the corresponding 2,2′-bipyridines exclusively. The first cycloaddition gave the 2-alkynylpyridine (**1q** or **1r**) as a single isomer and the second addition followed a 2-pyridylpyridine formation pathway with complete selectivity.

Next, we investigated the regiochemistry of the reactions of diynes possessing a terminal alkyne group (Scheme 4; Table 4). The reactions with nitriles **2a**–**c** gave the corresponding 2,6-substituted pyridines **3** as the major products with moderate-to-complete selectivities (Table 4; entries 1–9). Although the large steric influence may account for the regioselectivity in entries 1, 5, and 8, other explanations could involving cooperative steric and electronic effects are possible (see below). A similar synthesis of 2,6-substituted pyridines has been reported for reactions catalyzed by Cp*RuCl (R^2 = Me, Ph, $R^3 = CO_2Et$, CH_2Cl)[3b] and $CpCo(CO)_2$ (under microwaves; R^2 = TMS, R^3 = alkyl).[7] It has been suggested that the formation of pyridines **4** might be disfavored by steric repulsion between R^3 and R^2 in the corresponding metallacyclic inter-



Scheme 2 Study on electronic effects in the alkynes and nitriles



Scheme 3 Reactions of alkynyl- or 2-pyridyl-substituted diynes

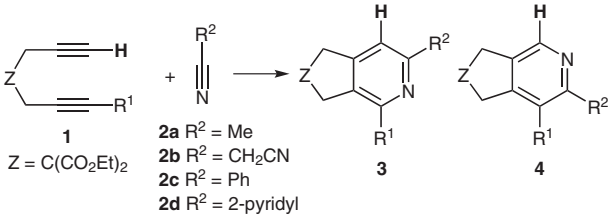
Table 3 Results of the Reactions Shown in Scheme 3

Entry[a]	Diyne	R^1	Y	Z	**2** (equiv)	Ratio **3/4**	Yield (%)
1	**1r**	Ph	C≡C	$C(CO_2Et)_2$	**2a** (40)	>99:1	90%[b]
2	**1r**	Ph	C≡C	$C(CO_2Et)_2$	**2c** (10)	>99:1	86%[b]
3	**1q**	Me	C≡C	$C(CO_2Et)_2$	**2d** (2)	>99:1	47%[c]
4	**1l**	Me	2-Py[d]	$C(CO_2Et)_2$	**2a** (20)	>99:1	81%
5	[**1r**][e]	Ph	2-Py	$C(CO_2Et)_2$	**2a** (40)	>99:1	90%[b]
6	**1m**	Me	2-Py	O	**2a** (20)	>99:1	89%
7	[**1r**][e]	Ph	2-Py	$C(CO_2Et)_2$	**2c** (10)	>99:1	86%[b]
8	**1m**	Me	2-Py	O	**2d** (5)	>99:1	69%
9	**1m**	Me	2-Py	O	**2e** (1.5)	>99:1	64%

[a] 20 equiv of **2a** in NMP was used.
[b] Yield of 2,2′-bipyridine after double cycloaddition.
[c] Yield of monocyclized product (**1q**).
[d] 2-pyridyl.
[e] The reaction of the intermediate in the double cycloaddition.

mediate. In contrast, when 2-cyanopyridine (**2d**) was used, the regiochemistry of the product was completely changed by the substituent on the diyne **1** (Table 4, entries 10–12). Once more, we observed that, in terms of the regioselectivity, the relatively electron-deficient nitrile **2d** was much more sensitive to the electronic nature of the diyne than were the other nitriles.

In the case of the reaction of diynes terminated with a trimethylsilyl group (Scheme 5; Table 5), 3-(trimethylsilyl)pyridines were obtained exclusively without exception. Note that even substrates **1** containing a terminal alkyne group (R^1 = H) gave the more-sterically demanding 3-silylpyridines **3**. These results clearly showed that the reactions were electronically controlled. Note also that the selectivity is opposite to that observed in the $CpCo(CO)_2$- and the CpCo(CO)(dimethyl fumarate)-

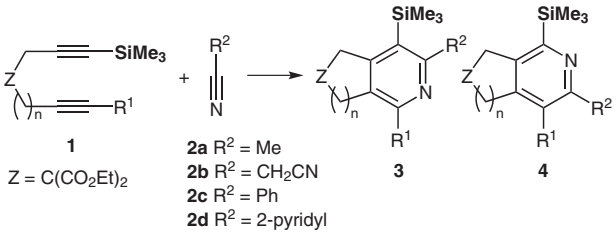


Scheme 4 Reactions of substrates **1** containing a terminal alkyne group

Table 4 Results for the Reactions Shown in Scheme 4

Entry	Diyne	R^2	**2** (equiv)	Ratio **3/4**	Yield (%)
1	**1i**	Bu	**2a** (20)	95:5	78
2	**1d**	Ph	**2a** (20)	66:34	66
3	**1s**	C≡C	**2a** (80)	>99:1	87[a]
4	[**1s**][b]	2-Py	**2a** (80)	>99:1	87[a]
5	**1i**	Bu	**2b** (2)	>99:1	57
6	**1d**	Ph	**2b** (2)	60:40	48
7	**1j**	2-Py	**2b** (1.5)	>99:1	71
8	**1i**	Bu	**2c** (20)	98:2	58
9	**1d**	Ph	**2c** (20)	>99:1	53
10	**1h**	Me	**2d** (20)	1:>99	78
11	**1i**	Bu	**2d** (20)	1:>99	67
12	**1d**	Ph	**2d** (20)	>99:1	78

[a] Yield of the double cycloaddition product.
[b] Reaction of the intermediate in the double cycloaddition.



Scheme 5 Reactions of trimethylsilyl-substituted diynes **1**

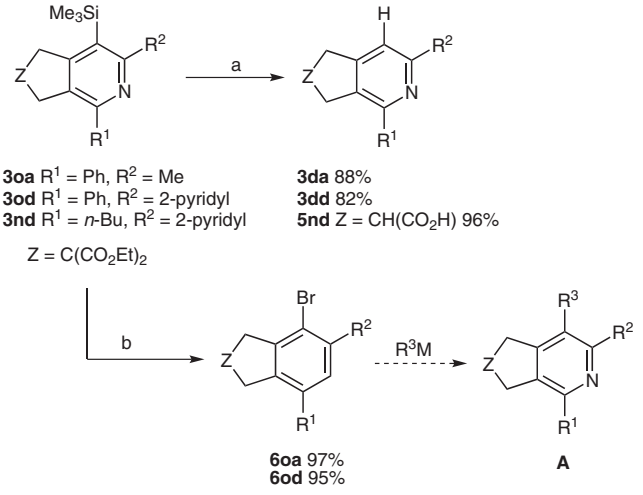
catalyzed reactions.[7] With respect to the reaction of alkyl- and silyl-substituted diynes, Louie and co-workers[11] reported that the $Ni(cod)_2$/NHC-catalyzed reaction of **2a** and a diyne (R^1 = Me) showed the same sense of regiochemistry as that of the reaction of **2a** and **1n** (Entry 2).

The silyl-substituted pyridines that were obtained as the corresponding single regioisomers are synthetically useful. For instance, silylated pyridine **3oa** and 2,2′-bipyridines **3od** and **3nd** were smoothly protodesilylated[7,9] to give the regioisomerically pure products **3da**, **3dd**, and **5nd** (decarboxylation and saponification occurred during the reaction) (Scheme 6). The resulting cyclopenta[*c*]pyridine **5nd** had the opposite regiochemistry to that of the

Table 5 Results of the Reactions Shown in Scheme 5

Entry	Diyne	R^1	n	**2** (Equiv)	Ratio **3/4**	Yield (%)
1	**1k**	H	1	**2a** (20)	>99:1	39
2	**1n**	Bu	1	**2a** (20)	>99:1	83
3	**1o**	Ph	1	**2a** (20)	>99:1	91
4	**1p**	Et	2	**2a** (20)	>99:1	88
5	**1k**	H	1	**2b** (20)	>99:1	76
6	**1n**	Bu	1	**2b** (2)	>99:1	91
7	**1o**	Ph	1	**2b** (2)	98:2	68
8	**1o**	Ph	1	**2c** (5)	>99:1	99
9	**1n**	Bu	1	**2d** (2)	>99:1	91
10	**1o**	Ph	1	**2d** (2)	>99:1	82

pyridine **3id** derived from **1i** and **2d**. In addition, halodesilylation of the silylated pyridines gave the corresponding bromopyridines **6oa** and **6od** in good yields. From these 3-bromopyridine derivatives, regiochemically pure pyridines **A** can be synthesized by manipulations such as transition metal-catalyzed coupling reactions.[14] This indirect method permits the production of substituted pyridines possessing an opposite regiochemistry to that produced by the direct method. Studies on this reaction are underway, and the results will be reported elsewhere.

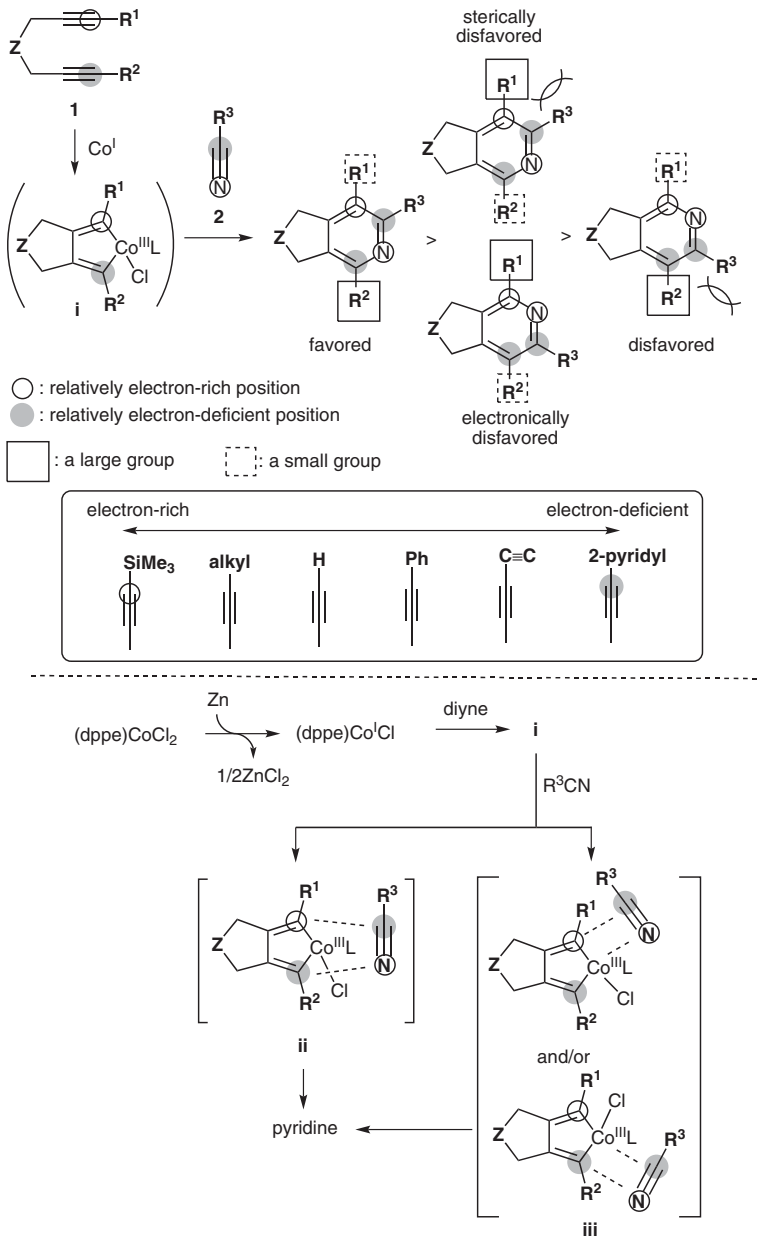


Scheme 6 Protodesilylation and halodesilylation of silyl-substituted pyridines

We postulate that the dppe–$CoCl_2 \cdot 6H_2O$–Zn-catalyzed pyridine-formation reaction might proceed through a (dppe)$Co^{I}Cl$ complex generated by the reduction of (dppe)$CoCl_2$ with zinc; this complex could react with diynes to provide cobaltacyclopentadiene intermediates **i** (Scheme 7). Although there are several exceptions (Table 1, entries 1–5; Table 4, entries 1, 5, and 7) involving reactions in which the contribution of steric factors might be relatively large, the regioselectivity observed in the majority of the reactions presented here can be systematically rationalized by considering differences in the electronic nature of the two alkyne groups in the diynes. Thus, the relatively electron-rich alkyne moiety in diyne **1** bonds to the electron-deficient position (the carbon atom) of the cyano group in nitrile **2**. It is plausible that an intermediate cobaltacycle of type **i**, derived from the corresponding **1**, might have a similar electronic nature, influenced by the substituents R^1 and R^2, and that the reaction proceeds by a pathway involving a [4+2] cycloaddition (**ii**) and/or an insertion reaction (**iii**). Thus, the regioselectivity observed here can be predicted accurately by considering the electronic nature of alkyne substituent, in the order TMS, alkyl, H, Ph, C≡C, 2-pyridyl (in other words, from electron rich to electron deficient) (Scheme 7). Overall, the regioselectivity can be altered by such electronic effects in conjunction with cooperative or competitive steric repulsion between the substituents of the diyne and the nitrile, as shown in Scheme 7. Confirmation of the mechanism for the conversion of metallacycle intermediates **i** into pyridines **ii** or **iii** will require further studies. However, a consideration of the regiochemical trends that we observed indicates that the method is potentially useful in synthesis.

Finally, we present some supplementary data on the amounts (equivalents) of nitriles that should be used. For the reaction of diynes containing a terminal alkyne group, the use of aliphatic or aromatic nitriles such as acetonitrile (**2a**), benzonitrile (**2c**), or 2-cyanopyridine (**2d**) in an excess of 80 equivalents when used as the solvent or in an excess of 5–20 equivalents in 1-methylpyrrolidin-2-one as the solvent is recommended for the successful synthesis of the required pyridines. These excesses of nitrile suppress the competitive formation of benzenes by [2+2+2] cycloaddition between the two diyne moieties as a side-reaction. Because the reactions of nitriles containing a coordinating group or of electron-deficient nitriles, such as malononitrile (**2b**) or cyanoperfluoroalkanes,[10,12b] proceed selectively at high rates, 1.5–2 equivalents of these nitriles can be used. When the two alkyne groups in diynes **1** are internal, the benzene-forming side-reactions are suppressed and the reactions require smaller excesses of the nitrile (2–5 equivalents).

^{1}H NMR spectra of samples dissolved in $CDCl_3$ were recorded at 600, 500, and 270 MHz, whereas ^{13}C NMR spectra were recorded at 150, 125 and 67.5 MHz on JEOL JNM-ECA600, JNM-ECA500, and JNM-EX270 spectrometers, respectively. Chemical shifts are reported in ppm relative to TMS (δ = 0.00) or residual $CHCl_3$ (δ = 7.26 for ^{1}H NMR) or $CDCl_3$ (δ = 77.0 for ^{13}C NMR). IR spectra were recorded on a Fourier-transform IR spectrometer (Shimadzu, IR Prestige-21 or JASCO FT/IR-4100). High-resolution mass spectra were acquired by using a JEOL Accu TOF T-100 spectrometer equipped for electrospray ionization. All reactions that were sensitive to oxygen and/or moisture were performed under argon. Anhydrous THF and NMP were purchased from Kanto Chemicals (Tokyo). All the other commercially sourced chemicals were used as received. Starting diynes **1** were prepared by conventional procedures. Data for compounds **3fa**, **4fa**, **3ed**, **3qd**, **3la**, **3ma**, **3md**, **3me**, **3ia**, **3da**, **4da**, **3jb**, **4hd**, **4id**, **3dd**, **3ka**, **3na**, **3oa**, **3pa**, **3kb**, **3nb**,



Scheme 7 Summary of regioselectivity and possible routes to opposite regioisomers

3nd, **5nd**, **6oa**, and 2,2′-bipyridines after the double cycloaddition of the **1r** + **2a**, **1r** + **2b**, **1r** + **2c**, and **1s** + **2a** substrate pairs have been published previously.[12]

Cycloaddition of Diyne 1 and Nitrile 2 Catalyzed by dppe–$CoCl_2 \cdot 6H_2O$–Zn Reagent; General Procedure

A soln of $CoCl_2 \cdot 6H_2O$ (6 mg, 0.025 mmol) and dppe (12 mg, 0.03 mmol) in NMP or MeCN (1 mL) at r.t. was added to a stirred mixture of Zn powder (3.5 mg, 0.05 mmol), diyne **1** (0.5 mmol), and nitrile **2** (1.5–80 equiv). [NMP (1 mL) was also added if 80 equiv of MeCN were used]. The mixture was then stirred at r.t. or 50 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, a small portion of EtOAc or Et_2O was added, and the mixture was passed through a pad of Celite that was washed with EtOAc or Et_2O. The filtrate was concentrated to dryness and the residue was purified by chromatography (silica gel, hexane–EtOAc) to separate the pyridine or bipyridine derivative(s).

Diethyl 1-Butyl-4-(4-methoxyphenyl)-3-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4aa) and Diethyl 4-Butyl-1-(4-methoxyphenyl)-3-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3aa) (Table 2, Entry 1)

4aa + 3aa

IR (neat): 2956, 2931, 2870, 1730, 1581, 1514, 1258, 1185 cm^{-1}.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.3, 158.7, 155.5, 154.3, 148.9, 130.8, 130.6, 130.4, 130.1, 113.9, 113.7, 61.9, 61.8, 60.0, 40.1, 38.6, 31.5, 31.4, 23.0, 22.9, 22.7, 14.03, 13.99, 13.98, 13.95.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{26}H_{34}NO_5]^+$: 440.2437; found: 440.2449.

4aa

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.15 (d, *J* = 8.6 Hz, 2 H, Ar), 6.97 (d, *J* = 8.6 Hz, 2 H, Ar), 4.24–4.13 (m, 4 H, OCH_2CH_3), 3.86 (s, 3 H, OCH_3), 3.59 (s, 2 H, $PyCH_2C$), 3.31 (s, 2 H, $PyCH_2C$), 2.72 (t, *J* = 7.9 Hz, 2 H, $PyCH_2CH_2$), 2.33 (s, 3 H, $PyCH_3$), 1.71–1.65 (m, 2

H, alkyl), 1.47–1.40 (m, 2 H, alkyl), 1.23 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.96 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$).

3aa

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.68 (d, J = 8.9 Hz, 2 H, Ar), 6.97 (d, J = 8.9 Hz, 2 H, Ar), 4.24–4.13 (m, 4 H, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 3.73 (s, 2 H, $PyCH_2C$), 3.55 (s, 2 H, $PyCH_2C$), 2.61 (t, J = 7.9 Hz, 2 H, $PyCH_2CH_2$), 2.56 (s, 3 H, $PyCH_3$), 1.71–1.65 (m, 2 H, alkyl), 1.55–1.48 (m, 2 H, alkyl), 1.23 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.96 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$).

Diethyl 1-Butyl-3-methyl-4-(4-tolyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4ba) and Diethyl 4-Butyl-3-methyl-1-(4-methylphenyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ba) (Table 2, Entry 2)

4ba + 3ba

IR (neat): 2956, 2922, 2857, 1747, 1589, 1454, 1270 cm^{-1}.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.3, 155.4, 154.1, 148.7, 136.9, 135.2, 130.9, 130.8, 129.2, 129.0, 128.8, 128.2, 61.9, 61.8, 60.0, 38.6, 35.9, 31.5, 22.9, 22.7, 21.2, 14.0, 13.96, 13.95.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{26}H_{34}NO_4]^+$: 424.2488; found: 424.2498.

4ba

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.24 (d, J = 7.9 Hz, 2 H, Ar), 7.11 (d, J = 7.9 Hz, 2 H, Ar), 4.24–4.13 (m, 4 H, OCH_2CH_3), 3.59 (s, 2 H, $PyCH_2C$), 3.31 (s, 2 H, $PyCH_2C$), 2.72 (t, J = 8.2 Hz, 2 H, $PyCH_2CH_2$), 2.41 (s, 3 H, $ArCH_3$), 2.32 (s, 3 H, $PyCH_3$), 1.71–1.64 (m, 2 H, alkyl), 1.48–1.39 (m, 2 H, alkyl), 1.23 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.97 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$).

3ba

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.61 (d, J = 8.2 Hz, 2 H, Ar), 7.25 (d, J = 8.2 Hz, 2 H, Ar), 4.24–4.13 (m, 4 H, OCH_2CH_3), 3.73 (s, 2 H, $PyCH_2C$), 3.55 (s, 2 H, $PyCH_2C$), 2.61 (t, J = 8.2 Hz, 2 H, $PyCH_2CH_2$), 2.56 (s, 3 H, $PyCH_3$), 2.39 (s, 3 H, $ArCH_3$), 1.56–1.49 (m, 2 H, alkyl), 1.48–1.39 (m, 2 H, alkyl), 1.24 (t, J = 7.6 Hz, 6 H, OCH_2CH_3), 0.98 (t, J = 7.9 Hz, 3 H, $CH_2CH_2CH_3$).

Diethyl 1-Butyl-4-[4-(methoxycarbonyl)phenyl]-3-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4ca) and Diethyl 4-Butyl-1-[4-(methoxycarbonyl)phenyl]-3-methyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ca) (Table 2, Entry 3)

4ca + 3ca

IR (neat): 2956, 2871, 1746, 1730, 1580, 1462, 1286, 1190 cm^{-1}.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.1, 166.9, 156.4, 153.5, 148.4, 143.2, 131.1, 130.0, 129.9, 129.6, 129.2, 129.1, 128.3, 62.0, 61.9, 60.0, 52.2, 39.9, 38.5, 31.4, 29.7, 23.0, 22.8, 22.7, 21.8, 14.01, 14.00, 13.97, 13.93.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{27}H_{34}NO_6]^+$: 468.2386; found: 486.2389.

4ca

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.11 (d, J = 7.6 Hz, 2 H, Ar), 7.32 (d, J = 7.6 Hz, 2 H, Ar), 4.26–4.14 (m, 4 H, OCH_2CH_3), 3.96 (s, 3 H, OCH_3), 3.60 (s, 2 H, $PyCH_2C$), 3.28 (s, 2 H, $PyCH_2C$), 2.74 (t, J = 7.9 Hz, 2 H, $PyCH_2CH_2$), 2.32 (s, 3 H, $PyCH_3$), 1.76–1.65 (m, 2 H, alkyl), 1.48–1.40 (m, 2 H, alkyl), 1.23 (t, J = 6.9 Hz, 6 H, OCH_2CH_3), 0.97 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$).

3ca

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.11 (d, J = 7.6 Hz, 2 H, Ar), 7.80 (d, J = 7.6 Hz, 2 H, Ar), 4.26–4.14 (m, 4 H, OCH_2CH_3), 3.94 (s, 3 H, OCH_3), 3.73 (s, 2 H, $PyCH_2C$), 3.57 (s, 2 H, $PyCH_2C$), 2.64 (t, J = 8.3 Hz, 2 H, $PyCH_2CH_2$), 2.58 (s, 3 H, $PyCH_3$), 1.75–1.64 (m, 2 H, alkyl), 1.56–1.49 (m, 2 H, alkyl), 1.23 (t, J = 6.9 Hz, 6 H, OCH_2CH_3), 0.98 (t, J = 6.9 Hz, 3 H, $CH_2CH_2CH_3$).

Diethyl 1-Butyl-3-(cyanomethyl)-4-phenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4fb) and Diethyl 4-Butyl-3-(cyanomethyl)-1-phenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3fb) (Table 2, Entry 5)

4fb + 3fb

IR (neat): 2957, 2931, 2871, 2251, 1747, 1583, 1462, 1430, 1268 cm^{-1}.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.0, 170.9, 157.2, 151.4, 149.7, 146.0, 136.1, 133.6, 133.3, 131.1, 129.1, 128.7, 128.4, 128.3, 128.2, 117.6, 62.1, 62.0, 60.3, 59.9, 40.2, 39.9, 39.0, 38.5, 31.5, 30.8, 29.3, 24.8, 24.4, 23.0, 22.7, 13.99, 13.96, 13.8.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{26}H_{31}N_2O_4]^+$: 435.2284; found: 435.2289.

4fb

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.49 (t, J = 7.6 Hz, 2 H, Ar), 7.43 (t, J = 7.6 Hz, 1 H, Ar), 7.25 (d, J = 7.6 Hz, 2 H, Ar), 4.26–4.15 (m, 4 H, OCH_2CH_3), 3.65 (s, 2 H, $PyCH_2CN$), 3.63 (s, 2 H, $PyCH_2C$), 3.33 (s, 2 H, $PyCH_2C$), 2.76 (t, J = 7.9 Hz, 2 H, $PyCH_2CH_2$), 1.76–1.69 (m, 2 H, alkyl), 1.48–1.40 (m, 2 H, alkyl), 1.24 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.98 (t, J = 7.9 Hz, 3 H, $CH_2CH_2CH_3$).

3fb

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.79 (d, J = 7.6 Hz, 2 H, Ar), 7.51–7.45 (m, 2 H, Ar), 7.45–7.39 (m, 1 H, Ar), 4.26–4.15 (m, 4 H, OCH_2CH_3), 3.95 (s, 2 H, $PyCH_2CN$), 3.80 (s, 2 H, $PyCH_2C$), 3.59 (s, 2 H, $PyCH_2C$), 2.67 (t, J = 8.2 Hz, 2 H, $PyCH_2CH_2$), 1.62–1.54 (m, 2 H, alkyl), 1.50–1.40 (m, 2 H, alkyl), 1.25 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 1.00 (t, J = 6.9 Hz, 3 H, $CH_2CH_2CH_3$).

Diethyl 1-Butyl-3,4-diphenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4fc) and Diethyl 4-Butyl-1,3-diphenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3fc) (Table 2, Entry 6)

3fc + 4fc

IR (neat): 2958, 2931, 2870, 1747, 1565, 1454, 1258 cm^{-1}.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.26, 171.22, 157.7, 156.3, 151.0, 150.4, 149.3, 140.9, 139.7, 132.4, 132.0, 130.6, 129.9, 129.8, 129.1, 128.5, 128.3, 128.2, 128.1, 128.0, 127.6, 127.1, 126.9, 62.0, 61.9, 60.3, 59.9, 40.3, 40.2, 39.3, 38.6, 35.8, 31.9, 31.1, 29.6, 22.81, 22.77, 14.1, 13.99, 13.98, 13.7.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{30}H_{34}NO_4]$: 472.2488; found: 472.2484.

3fc

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.79 (d, J = 7.6 Hz, 2 H, Ar), 7.51 (d, J = 7.6 Hz, 2 H, Ar), 7.46–7.40 (m, 4 H, Ar), 7.39–7.34 (m, 1 H, Ar), 7.18–7.14 (m, 1 H, Ar), 4.28–4.15 (m, 4 H, OCH_2CH_3), 3.83 (s, 2 H, $PyCH_2C$), 3.66 (s, 2 H, $PyCH_2C$), 2.64 (t, J = 8.2 Hz, 2 H, $PyCH_2CH_2$), 1.50–1.43 (m, 2 H, alkyl), 1.31–1.20 (m, 2 H, alkyl), 1.27 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.83 (t, J = 7.6 Hz, 3 H, $CH_2CH_2CH_3$).

4fc

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.39–7.34 (m, 2 H, Ar), 7.29–7.21 (m, 4 H, Ar), 7.17–7.14 (m, 2 H, Ar), 7.10 (d, J = 8.2 Hz, 2 H, Ar), 4.28–4.15 (m, 4 H, OCH_2CH_3), 3.68 (s, 2 H, $PyCH_2C$), 3.46 (s, 2 H, $PyCH_2C$), 2.83 (t, J = 7.6 Hz, 2 H, $PyCH_2CH_2$), 1.80–1.74 (m, 2 H, alkyl), 1.50–1.43 (m, 2 H, alkyl), 1.25 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 0.98 (t, J = 7.6 Hz, 3 H, $CH_2CH_2CH_3$).

Diethyl 1-Butyl-3-(cyanomethyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ib) (Table 4, Entry 5)
IR (neat): 2959, 2933, 2871, 2252, 1729, 1600, 1455, 1265 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.16 (s, 1 H, Py), 4.23 (q, *J* = 7.2 Hz, 4 H, OCH_2CH_3), 3.86 (s, 2 H, $PyCH_2CN$), 3.59 (s, 2 H, $PyCH_2C$), 3.55 (s, 2 H, $PyCH_2C$), 2.70 (t, *J* = 7.6 Hz, 2 H, $PyCH_2CH_2$), 1.68–1.60 (m, 2 H, alkyl), 1.42–1.35 (m, 2 H, alkyl), 1.27 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3), 0.94 (t, *J* = 7.6 Hz, 3 H, $CH_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.0, 158.3, 151.2, 148.4, 133.4, 117.4, 115.7, 62.1, 59.7, 40.3, 38.0, 35.5, 30.9, 26.4, 22.6, 14.0, 13.9.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{20}H_{27}N_2O_4]$: 359.1971; found: 359.1968.

Diethyl 3-(Cyanomethyl)-1-phenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3db) and Diethyl 3-(Cyanomethyl)-4-phenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (4db) (Table 4, Entry 6)
3db + 4db
IR (neat): 2956, 2930, 2859, 2230, 1715, 1605, 1495, 1454, 1272 cm^{-1}.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{22}H_{22}N_2NaO_4]^+$: 401.1477; found: 401.1483.

3db
^1H NMR ($CDCl_3$, 600 MHz): δ = 7.75 (d, *J* = 6.9 Hz, 2 H, Ar), 7.49 (t, *J* = 6.9 Hz, 2 H, Ar), 7.43 (t, *J* = 6.9 Hz, 1 H, Ar), 7.31 (s, 1 H, Py), 4.25–4.16 (m, 4 H, OCH_2CH_3), 3.97 (s, 2 H, $PyCH_2CN$), 3.77 (s, 2 H, $PyCH_2C$), 3.65 (s, 2 H, $PyCH_2C$), 1.25 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.8, 154.4, 152.8, 149.0, 138.6, 133.0, 128.9, 128.5, 128.4, 117.3, 116.8, 62.1, 60.1, 40.2, 39.7, 26.6, 14.0.

4db
^1H NMR ($CDCl_3$, 600 MHz): δ = 8.46 (s, 1 H, Py), 7.51 (t, *J* = 6.9 Hz, 2 H, Ar), 7.45 (t, *J* = 6.9 Hz, 1 H, Ar), 7.26 (d, *J* = 6.9 Hz, 2 H, Ar), 4.26–4.14 (m, 4 H, OCH_2CH_3), 3.70 (s, 2 H, $PyCH_2CN$), 3.69 (s, 2 H, $PyCH_2C$), 3.35 (s, 2 H, $PyCH_2C$), 1.24 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.7, 150.1, 146.4, 144.3, 136.0, 135.5, 133.4, 129.2, 128.5, 128.4, 117.2, 62.0, 60.0, 39.6, 38.3, 24.8, 13.9.

Diethyl 4-Butyl-3-phenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ic) (Table 4, Entry 8)
IR (neat): 2958, 2931, 2870, 1730, 1601, 1453, 1253 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.95 (d, *J* = 6.9 Hz, 2 H, Ar), 7.44 (t, *J* = 6.9 Hz, 2 H, Ar), 7.40 (s, 1 H, Py), 7.36 (t, *J* = 6.9 Hz, 1 H, Ar), 4.23 (q, *J* = 7.2 Hz, 4 H, OCH_2CH_3), 3.63 (s, 2 H, $PyCH_2C$), 3.60 (s, 2 H, $PyCH_2C$), 2.79 (t, *J* = 7.6 Hz, 2 H, $PyCH_2CH_2$), 1.80–1.73 (m, 2 H, alkyl), 1.48–1.39 (m, 2 H, alkyl), 1.26 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3), 0.97 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_3$).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.3, 157.6, 156.0, 150.2, 140.0, 132.4, 128.6, 128.4, 127.0, 114.1, 62.0, 59.9, 40.5, 38.2, 35.7, 30.8, 22.7, 14.04, 14.00.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{24}H_{30}NO_4]^+$: 396.2175; found: 396.2173.

Diethyl 1,3-Diphenyl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3dc) (Table 4, Entry 8)
IR (neat): 3062, 2974, 2934, 1714, 1600, 1495, 1287 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.08 (d, *J* = 7.6 Hz, 2 H, Ar), 7.90 (d, *J* = 8.2 Hz, 2 H, Ar), 7.59 (s, 1 H, Py), 7.50 (t, *J* = 7.6 Hz, 2 H, Ar), 7.46 (t, *J* = 8.2 Hz, 2 H, Ar), 7.42 (t, *J* = 8.2 Hz, 1 H, Ar), 7.39 (t, *J* = 7.6 Hz, 1 H, Ar), 4.27–4.15 (m, 4 H, OCH_2CH_3), 3.84 (s, 2 H, $PyCH_2C$), 3.69 (s, 2 H, $PyCH_2C$), 1.27 (t, *J* = 7.3 Hz, 6 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.1, 156.0, 153.6, 151.9, 139.7, 139.5, 131.9, 128.7, 128.6, 128.5, 128.3, 127.0, 114.9, 62.0, 60.2, 40.3, 39.9, 14.0.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{26}H_{26}NO_4]^+$: 416.1862; found: 416.1865.

Diethyl 3-(Cyanomethyl)-1-phenyl-4-(trimethylsilyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3ob) (Table 5, Entry 7)
IR (KBr): 2980, 2903, 2250, 1730, 1556, 1445, 1365, 1259 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.83 (d, *J* = 6.9 Hz, 2 H, Ar), 7.49 (t, *J* = 6.9 Hz, 2 H, Ar), 7.43 (t, *J* = 6.9 Hz, 1 H, Ar), 4.25–4.14 (m, 4 H, OCH_2CH_3), 4.03 (s, 2 H, $PyCH_2CN$), 3.74 (s, 2 H, $PyCH_2C$), 3.67 (s, 2 H, $PyCH_2C$), 1.25 (t, *J* = 7.3 Hz, 6 H, OCH_2CH_3), 0.49 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.8, 158.6, 153.9, 153.0, 138.5, 132.0, 128.9, 128.5, 128.4, 127.2, 117.8, 62.1, 60.3, 42.3, 39.0, 28.7, 14.0, 1.54.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{25}H_{30}N_2NaO_4Si]^+$: 473.1873; found: 473.1874.

Diethyl 1,3-Diphenyl-4-(trimethylsilyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3oc) (Table 5, Entry 8)
IR (neat): 2980, 2900, 1747, 1540, 1384, 1268, 1198 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.78 (d, *J* = 6.9 Hz, 2 H, Ar), 7.45–7.35 (m, 8 H, Ar), 4.28–4.17 (m, 4 H, OCH_2CH_3), 3.79 (s, 2 H, $PyCH_2C$), 3.74 (s, 2 H, $PyCH_2C$), 1.26 (t, *J* = 7.6 Hz, 6 H, OCH_2CH_3), 0.06 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.2, 157.8, 153.0, 144.5, 139.5, 130.6, 129.3, 128.7, 128.4, 128.3, 127.8, 127.79, 172.3, 62.0, 60.4, 42.4, 39.1, 14.0, 1.15.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{29}H_{34}NO_4Si]^+$: 488.2257; found: 488.2257.

Diethyl 1-Phenyl-3-pyridin-2-yl-4-(trimethylsilyl)-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (3od) (Table 5, Entry 10)
IR (KBr): 2984, 2902, 1726, 1587, 1385, 1299, 1267, 1107 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.60 (d, *J* = 4.8 Hz, 1 H, Ar), 7.93 (d, *J* = 8.9 Hz, 1 H, Ar), 7.82–7.75 (m, 3 H, Ar), 7.45 (t, *J* = *J* = 7.6 Hz, 2 H, Ar), 7.39 (t, *J* = 7.6 Hz, 1 H, Ar), 7.30–7.27 (m, 1 H, Ar), 4.25–4.16 (m, 4 H, OCH_2CH_3), 3.79 (s, 2 H, $PyCH_2C$), 3.78 (s, 2 H, $PyCH_2C$), 1.25 (t, *J* = 7.3 Hz, 6 H, OCH_2CH_3), 0.14 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.0, 162.3, 160.8, 158.1, 152.9, 147.8, 139.5, 136.5, 131.6, 128.6, 128.4, 128.3, 128.2, 123.8, 122.9, 61.9, 60.4, 42.7, 39.1, 14.0, 1.69.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{28}H_{32}NaN_2O_4Si]^+$: 511.2029; found: 511.2017.

Diethyl 4-Bromo-1-phenyl-3-pyridin-2-yl-5,7-dihydro-6*H*-cyclopenta[*c*]pyridine-6,6-dicarboxylate (6od) (Scheme 6)
IR (neat): 2980, 2905, 1729, 1474, 1399, 1264, 1187 cm^{-1}.

^1H NMR ($CDCl_3$, 600 MHz): δ = 8.72 (d, *J* = 4.1 Hz, 1 H, Ar), 7.85–7.74 (m, 4 H, Ar), 7.46 (t, *J* = 7.6 Hz, 2 H, Ar), 7.40 (t, *J* = 7.6 Hz, 1 H, Ar), 7.35–7.31 (m, 1 H, Ar), 4.29–4.10 (m, 4 H, OCH_2CH_3),

3.93 (s, 2 H, PyCH_2C), 3.77 (s, 2 H, PyCH_2C), 1.27 (t, J = 7.3 Hz, 6 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.7, 157.5, 154.9, 153.0, 152.2, 148.6, 138.4, 136.4, 134.2, 128.7, 128.43, 128.41, 124.4, 123.2, 115.1, 62.2, 59.1, 42.5, 40.9, 13.9.

HRMS (ESI+, MeOH): *m/z* calcd for $[C_{25}H_{24}BrN_2O_4]^+$: 495.0919; found: 495.0920.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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