Synthesis of 2,4,8-Trisubstituted 1,7-Naphthyridines by the Reaction of 4-(1-Aryl-2-methoxyethenyl)-3-isocyanopyridines with Excess Organolithiums

by **Kazuhiro Kobayashi***, **Taketoshi Kozuki**, **Shuhei Fukamachi**, and **Hisatoshi Konishi**

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan (phone/fax: +81-857-315263; e-mail: kkoba@chem.tottori-u.ac.jp)

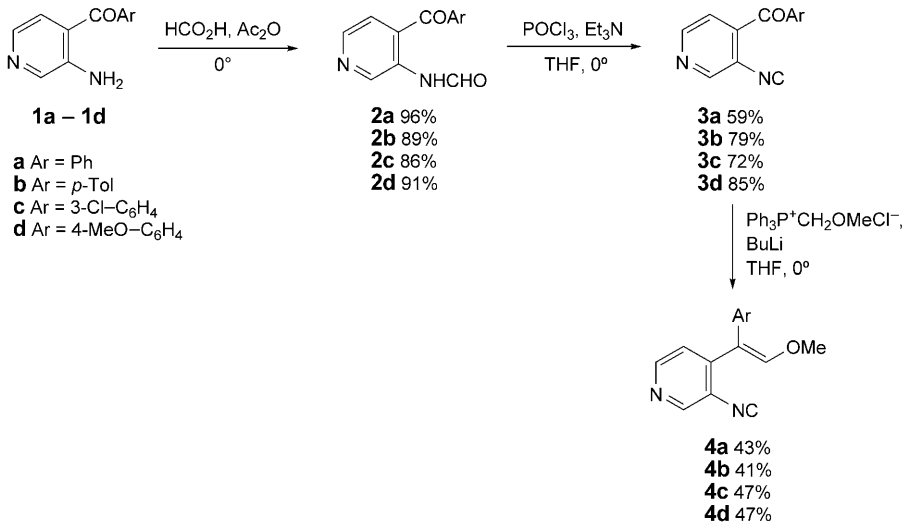
A convenient method for the synthesis of 2,4,8-trisubstituted 1,7-naphthyridines **6** by the reaction of (*E*)-4-(1-aryl-2-methoxyethenyl)-3-isocyanopyridines **4**, which could be easily prepared from commercially available 3-aminopyridine *via* aroylation of lithium (4-lithiopyridin-3-yl)pivalamide with *N*-methoxy-*N*-methylbenzamides, with excess organolithiums has been developed.

Introduction. – In previous papers, we reported an efficient synthesis of 2,4-disubstituted quinolines by the reaction of 1-(1-aryl-2-methoxyethenyl)-2-isocyanobenzenes with various organolithiums [1]. We anticipated that the use of 4-(1-aryl-2-methoxyethenyl)-3-isocyanopyridines **4** in place of 1-(1-aryl-2-methoxyethenyl)-2-isocyanobenzenes would give 2,4-disubstituted 1,7-naphthyridines. In this article, we report the results of our study on reactions of **4** with organolithiums. We found that 2,4-disubstituted naphthyridines could not be prepared satisfactorily, but that 2,4,8-trisubstituted naphthyridines **6** were obtained instead in reasonable yields by reacting **4** with excess organolithiums. 1,7-Naphthyridine derivatives have attracted considerable attention, mainly because some of these derivatives exhibit significant biological activities [2]. Although several efficient methods for the preparation of this class of heterocycles have been reported [3][1]), to date, there are no examples of the synthesis of 2,4,8-trisubstitued derivatives in the literature.

Results and Discussion. – 3-Aminopyridin-4-yl aryl ketones **1**, which could be easily prepared from commercially available 3-aminopyridine using the reaction of lithium (4-lithiopyridin-3-yl)pivalamide [4] with *N*-methoxy-*N*-methylbenzamides as described in the *Exper. Part*, were converted to (*E*)-4-(1-aryl-2-methoxyethenyl)-3-isocyanopyridines **4** *via* the route illustrated in *Scheme 1*. The first step was *N*-formylation of amino ketones **1** with HCOOH in the presence of Ac_2O at 0° to form *N*-(4-aroylpyridin-3-yl)formamides **2**. Dehydration of these formamides to form the corresponding isocyano derivatives **3** was accomplished on treatment with $POCl_3$ in THF in the presence of Et_3N as a base at 0°. These isocyano ketones were allowed to

[1]) See also pertinent references cited in [2].

Scheme 1



react with (methoxymethyl)triphenylphosphonium chloride in THF at 0° to give **4**; in each case, the (*E*)-isomer was obtained exclusively.

First, the reaction of (*E*)-3-isocyano-4-(2-methoxy-1-phenylethenyl)pyridine (**4a**) with PhLi was examined. Thus, **4a** was treated with an equimolar amount of PhLi in 1,2-dimethoxyethane (DME) at −78° for 3 h, as shown in *Scheme 2*. After the usual aqueous workup, only a trace amount of 2,4-diphenylnaphthyridine (**5**) was obtained, and the starting material **4a** was recovered almost quantitatively (*Table 1*, *Entry 1*). An

Scheme 2

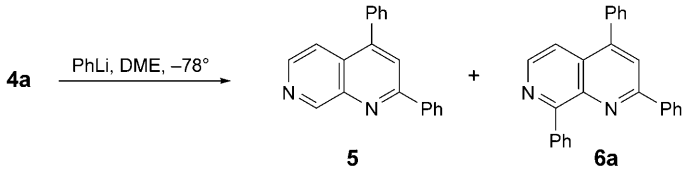


Table 1. *Results of Reactions of* **4a** *with PhLi in DME at* −78°

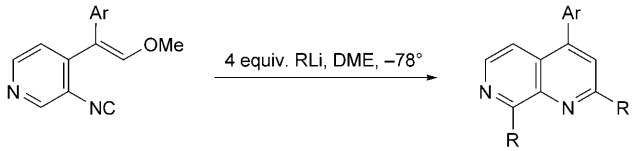
Entry	PhLi [equiv.]	Yield of **5** [%][a])	Yield of **6a** [%][a])
1	1	trace	0
2	2	14	4
3	3	7	25
4	4	0	47

[a]) Yields of isolated products.

extended reaction time and/or a higher reaction temperature (0°) led to similar results. Interestingly, use of 2 mol-equiv. of PhLi under similar conditions resulted in the formation of 2,4,8-triphenyl-1,7-naphthyridine (**6a**) in 4% yield along with 14% of **5a** (*Entry 2*). We assumed that the formation of **6a** was due to the preference of the addition of the second molecule of PhLi to C(8) of **5a**. For this reason, we focused our efforts on obtaining **6a** as the sole product in a reasonable yield. Compound **4a** was allowed to react with 3 mol-equiv. of PhLi to give **6a** in 25% yield along with 7% of **5a** (*Entry 3*). Subsequently, we found that treatment of **4a** with 4 mol-equiv. of PhLi gave **6a** in 47% yield after column chromatography on silica gel (*Entry 4*); no trace of **5a** was detected.

To examine the generality of the present procedure, we conducted reactions using four (*E*)-4-(1-aryl-2-methoxyethenyl)-3-isocyanopyridines **4** including **4a** and six organolithiums including PhLi under the conditions given in *Table 1*, *Entry 4*, as shown in *Scheme 3*, and obtained ten 2,4,8-disubstituted 1,7-naphthyridines including **6a**. The results are summarized in *Table 2*, which indicates that yields of the desired products, 2,4,8-trisubstituted 1,7-naphthyridines **6**, are generally modest. When alkyllithiums, such as BuLi and MeLi (*Entries 2* and *7*, resp.), were used, the yields of the corresponding products **6b** and **6g** are significantly lower than those with aryllithiums. It should be noted that there is no significant difference in yields between substrates **4** with an α-aryl substituent containing electron-donating or electron-withdrawing groups.

Scheme 3



4 **6**

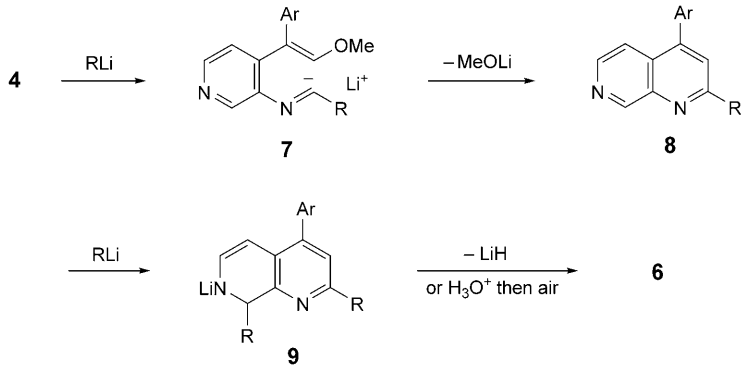
Table 2. *Preparation of 1,7-Naphthyridines* **6**

Entry	**4**	R in RLi	Ar	**6**	Yield[a]) [%]
1	**4a**	Ph	Ph	**6a**	47
2	**4a**	Bu	Ph	**6b**	25
3	**4b**	Ph	*p*-Tol	**6c**	45
4	**4b**	4-Cl–C_6H_4	*p*-Tol	**6d**	43
5	**4b**	4-MeO–C_6H_4	*p*-Tol	**6e**	47
6	**4c**	Ph	3-Cl–C_6H_4	**6f**	48
7	**4c**	Me	3-Cl–C_6H_4	**6g**	25
8	**4c**	*p*-Tol	3-Cl–C_6H_4	**6h**	47
9	**4d**	Ph	4-MeO–C_6H_4	**6i**	43
10	**4d**	4-Cl–C_6H_4	4-MeO–C_6H_4	**6j**	46

[a]) Yields of isolated products.

A possible mechanism for the formation of 1,7-naphthyridines **6** from **4** and organolithiums starts with the addition of 1 equiv. of organolithium compound to the isocyano C-atom of **4**, which generates the imidoyl anion intermediates **7** (*Scheme 4*). Then, the 1,7-naphthyridine skeleton **8** is formed by the intramolecular attack of this anion to the C(α)-atom of the methoxyethenyl moiety with loss of MeOLi. Subsequently, **8** is attacked by a second equiv. of the organolithium compound at C(8) to form the intermediate **9**, from which elimination of LiH gives rise to **6**. Alternatively, formation of **6** may be accomplished by dehydrogenation of 7,8-dihydro-1,7-naphthyridines, formed by protonation of **9**, during workup and/or isolation procedures.

Scheme 4



In conclusion, we have demonstrated that 2,4,8-trisubstituted 1,7-naphthyridines could be prepared by the reaction of (*E*)-4-(1-aryl-2-methoxyethenyl)-3-isocyanopyridines with excess amounts of organolithiums. Although the yields of the products are not so high, in view of the ready availability of the starting materials as well as the ease of operations, the present procedure offers a convenient synthetic method for this class of heterocycles. Studies toward the synthesis of related heterocycles utilizing 3-isocyanopyridin-4-yl ketones are currently under way in our laboratory.

Experimental Part

General. All of the org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako* Gel C-200E. M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *Shimadzu FT-IR-8300* spectrophotometer. ^{1}H-NMR Spectra: in $CDCl_3$ with TMS as an internal reference, with a *JEOL ECP500* FT NMR spectrometer, at 500 MHz. ^{13}C-NMR Spectra: measured in $CDCl_3$ with TMS as an internal reference with a *JEOL ECP500* FT NMR spectrometer, at 125 MHz. LR- and HR-MS (EI, 70 eV): *JEOL JMS AX505 HA* spectrometer.

(3-Aminopyridin-4-yl)(phenyl)methanone (**1a**) and *(3-aminopyridin-4-yl)(4-methoxyphenyl)methanone* (**1d**) were prepared according to the method described in [4]. All other chemicals used in this study were commercially available.

N-*(4-Aroylpyridin-3-yl)-2,2-dimethylpropanamides.* These compounds were prepared by a successive treatment of 2,2-dimethyl-*N*-(pyridin-3-yl)propanamide [4] with 2 mol-equiv. of BuLi and *N*-methoxy-*N*-methylbenzamides under the conditions reported previously for the reaction of 2,2-dimethyl-*N*-lithio-*N*-(4-lithiopyridin-3-yl)propanamide with benzaldehyde [4].

2,2-Dimethyl-N-*[4-(4-methylbenzoyl)pyridin-3-yl]propanamide.* Yield: 68%. Pale-yellow solid. M.p. 151–153° (hexane/CH_2Cl_2). IR (KBr): 3318, 1678. ^{1}H-NMR: 1.34 (*s*, 9 H); 2.47 (*s*, 3 H); 7.33 (*d*, *J* = 7.8, 2 H); 7.37 (*d*, *J* = 4.1, 1 H); 7.67 (*d*, *J* = 7.8, 2 H); 8.45 (*d*, *J* = 4.1, 1 H); 9.90 (*s*, 1 H); 10.35 (br. *s*, 1 H). Anal. calc. for $C_{18}H_{20}N_2O_2$ (296.37): C 72.95, H 6.80, N 9.45; found: C 72.72, H 7.02, N 9.43.

N-*[4-(3-Chlorobenzoyl)pyridin-3-yl]-2,2-dimethylpropanamide.* Yield: 75%. Pale-yellow solid. M.p. 119–120° (hexane/Et_2O). IR (KBr): 3400, 1674. ^{1}H-NMR: 1.35 (*s*, 9 H); 7.35 (*d*, *J* = 4.6, 1 H); 7.48 (*t*, *J* = 7.8, 1 H); 7.61 (*d*, *J* = 7.8, 1 H); 7.63 (*d*, *J* = 7.8, 1 H); 7.76 (*s*, 1 H); 8.48 (*d*, *J* = 4.6, 1 H); 9.92 (*s*, 1 H); 10.34 (br. *s*, 1 H). Anal. calc. for $C_{17}H_{17}ClN_2O_2$ (316.79): C 64.46, H 5.41, N 8.84; found: C 64.36, H 5.58, N 8.78.

(3-Aminopyridin-4-yl)(aryl)methanones **1**. These compounds were prepared by acid hydrolysis under the conditions reported previously for the conversion of *N*-(4-benzoylpyridin-3-yl)-2,2-dimethylpropanamide into (3-aminopyridin-4-yl)(phenyl)methanone [4].

(3-Aminopyridin-4-yl)(4-methylphenyl)methanone (**1b**). Yield: 81%. Pale-yellow solid. M.p. 115–117° (hexane/CH_2Cl_2). IR (KBr): 3435, 3327, 1651, 1613. ^{1}H-NMR: 2.45 (*s*, 3 H); 5.72 (br. *s*, 2 H); 7.24 (*d*, *J* = 5.5, 1 H); 7.29 (*d*, *J* = 7.8, 2 H); 7.62 (*d*, *J* = 7.8, 2 H); 7.95 (*d*, *J* = 5.5, 1 H); 8.28 (*s*, 1 H). Anal. calc. for $C_{13}H_{12}N_2O$ (212.25): C 73.56, H 5.70, N 13.20; found: C 73.51, H 5.94, N 13.10.

(3-Aminopyridin-4-yl)(3-chlorophenyl)methanone (**1c**). Yield: 81%. Yellow solid. M.p. 165–167° (hexane/THF). IR (KBr): 3445, 3306, 1634, 1607. ^{1}H-NMR: 3.89 (br. *s*, 2 H); 7.20 (*d*, *J* = 5.0, 1 H); 7.44 (*t*, *J* = 7.8, 1 H); 7.54 (*dd*, *J* = 7.8, 1.8, 1 H); 7.56 (*dd*, *J* = 7.8, 1.8, 1 H); 7.67 (*t*, *J* = 1.8, 1 H); 7.95 (*d*, *J* = 5.0, 1 H); 8.30 (*s*, 1 H). Anal. calc. for $C_{12}H_9ClN_2O$ (232.67): C 61.95, H 3.90, N 12.04; found: C 61.94, H 3.94, N 11.82.

N-*(4-Aroylpyridin-3-yl)formamides* **2**. These compounds were prepared by treating **1** with HCO_2H/Ac_2O under the previously reported conditions [5].

N-*(4-Benzoylpyridin-3-yl)formamide* (**2a**). Pale-yellow, viscous oil. R_f (THF/hexane 1:1) 0.35. IR (neat): 3308, 1699, 1668. ^{1}H-NMR: 7.39 (*d*, *J* = 5.0, 1 H); 7.54 (*dd*, *J* = 7.8, 7.3, 2 H); 7.68 (*tt*, *J* = 7.3, 1.4, 1 H); 7.77 (*d*, *J* = 7.8, 2 H); 8.48 (*s*, 1 H), 8.53 (*d*, *J* = 5.0, 1 H); 9.90 (br. *s*, 1 H); 9.91 (*s*, 1 H). Anal. calc. for $C_{13}H_{10}N_2O_2$ (226.23): C 69.02, H 4.46, N 12.38; found: C 68.97, H 4.50, N 12.27.

N-*[4-(4-Methylbenzoyl)pyridin-3-yl]formamide* (**2b**). Pale-yellow, viscous oil. R_f (AcOEt/hexane 1:2) 0.35. IR (neat): 3308, 1697, 1661, 1605. ^{1}H-NMR: 2.47 (*s*, 3 H); 7.33 (*d*, *J* = 7.8, 2 H); 7.38 (*d*, *J* = 5.0, 1 H); 7.69 (*d*, *J* = 7.8, 2 H); 8.46 (*s*, 1 H); 8.52 (*d*, *J* = 5.0, 1 H); 9.79 (br. *s*, 1 H); 9.88 (*s*, 1 H). Anal. calc. for $C_{14}H_{12}N_2O_2$ (240.26): C 69.99, H 5.03, N 11.66; found: C 69.72, H 5.23, N 11.47.

N-*[4-(3-Chlorobenzoyl)pyridin-3-yl]formamide* (**2c**). Beige solid. M.p. 115–117° (hexane/THF). IR (KBr): 3277, 1699, 1670. ^{1}H-NMR: 7.37 (*d*, *J* = 4.6, 1 H); 7.48 (*t*, *J* = 7.8, 1 H); 7.62 (*d*, *J* = 7.8, 1 H); 7.65 (*dd*, *J* = 7.8, 1.4, 1 H); 7.77 (*t*, *J* = 1.4, 1 H); 8.48 (*s*, 1 H); 8.55 (*d*, *J* = 4.6, 1 H); 9.84 (br. *s*, 1 H); 9.90 (*s*, 1 H). Anal. calc. for $C_{13}H_9ClN_2O_2$ (260.68): C 59.90, H 3.48, N 10.75; found: C 59.82, H 3.72, N 10.73.

N-*[4-(4-Methoxybenzoyl)pyridin-3-yl]formamide* (**2d**). Beige solid. M.p. 140–143° (hexane/CH_2Cl_2). IR (KBr): 3349, 1701, 1640. ^{1}H-NMR: 3.92 (*s*, 3 H); 7.00 (*d*, *J* = 8.7, 2 H); 7.39 (*d*, *J* = 5.0, 1 H); 7.80 (*d*, *J* = 8.7, 2 H); 8.44 (*s*, 1 H); 8.53 (*d*, *J* = 5.0, 1 H); 9.62 (br. *s*, 1 H); 9.84 (br. *s*, 1 H). Anal. calc. for $C_{14}H_{12}N_2O_3$ (256.26): C 65.62, H 4.72, N 10.93; found: C 65.52, H 4.72, N 10.70.

(Aryl)(3-isocyanopyridin-4-yl)methanones **3**. These compounds were prepared by dehydration of **2** with $POCl_3$/Et_3N under the conditions reported in [6].

(3-Isocyanopyridin-4-yl)(phenyl)methanone (**3a**). Yellow solid. M.p. 72–75° (dec.; hexane). IR (KBr): 2124, 1672. ^{1}H-NMR: 7.43 (*dd*, *J* = 5.0, 0.9, 1 H); 7.54 (*dd*, *J* = 8.2, 7.3, 2 H); 7.69 (*tt*, *J* = 7.3, 1.4, 1 H); 7.81 (*dd*, *J* = 8.2, 1.4, 2 H); 8.78 (*d*, *J* = 5.0, 1 H); 8.83 (*s*, 1 H). Anal. calc. for $C_{13}H_8N_2O$ (208.22): C 74.99, H 3.87, N 13.45; found: C 75.01, H 4.05, N 13.21.

(3-Isocyanopyridin-4-yl)(4-methylphenyl)methanone (**3b**). Pale-yellow solid. M.p. 72–73° (dec.; hexane/CH_2Cl_2). IR (KBr): 2126, 1669, 1604. ^{1}H-NMR: 2.46 (*s*, 3 H); 7.33 (*d*, *J* = 8.2, 2 H); 7.41 (*d*, *J* = 5.0, 1 H); 7.70 (*d*, *J* = 8.2, 2 H); 8.77 (*d*, *J* = 5.0, 1 H); 8.81 (*s*, 1 H). Anal. calc. for $C_{14}H_{10}N_2O$ (222.24): C 75.66, H 4.54, N 12.60; found: C 75.40, H 4.61, N 12.39.

(3-Chlorophenyl)(3-isocyanopyridin-4-yl)methanone (**3c**). Brown solid. M.p. 74–76° (dec.; pentane). IR (KBr): 2133, 1668. ^{1}H-NMR: 7.42 (*d*, *J* = 5.0, 1 H); 7.49 (*t*, *J* = 7.8, 1 H); 7.65–7.68 (*m*, 2 H); 7.80 (*t*, *J* = 1.8, 1 H); 8.81 (*d*, *J* = 5.0, 1 H); 8.85 (*s*, 1 H). Anal. calc. for $C_{13}H_7ClN_2O$ (242.66): C 64.34, H 2.91, N 11.54; found: C 64.17, H 2.98, N 11.51.

(3-Isocyanopyridin-4-yl)(4-methoxyphenyl)methanone (**3d**). Brown solid. M.p. 50–52° (pentane). IR (KBr): 2124, 1661. ^{1}H-NMR: 3.91 (*s*, 3 H); 6.99 (*d*, *J* = 8.7, 2 H); 7.40 (*d*, *J* = 5.0, 1 H); 7.78 (*d*, *J* = 8.7, 2 H); 8.76 (*d*, *J* = 5.0, 1 H); 8.80 (*s*, 1 H). Anal. calc. for $C_{14}H_{10}N_2O_2$ (238.24): C 70.58, H 4.23, N 11.76; found: C 70.40, H 4.39, N 11.68.

*4-[(*E*)-1-Aryl-2-methoxyethenyl]-3-isocyanopyridines* **4**. These compounds were prepared by reacting **3** with (methoxymethyl)(triphenyl)phosphonium chloride under the conditions reported for the conversion of (2-isocyanophenyl)(phenyl)methanone to 1-isocyano-2-(2-methoxy-1-phenylethenyl)-benzene [1b].

*3-Isocyano-4-[(*E*)-2-methoxy-1-phenylethenyl]pyridine* (**4a**). Pale-yellow oil. R_f 0.28 (THF/hexane 1:5). IR (neat): 2124, 1645, 1634. ^{1}H-NMR: 3.86 (*s*, 3 H); 6.73 (*s*, 1 H); 7.10 (*dd*, *J* = 8.2, 1.4, 2 H); 7.20 (*d*, *J* = 5.0, 1 H); 7.26 (*tt*, *J* = 7.3, 1.4, 1 H); 7.30 (*dd*, *J* = 8.2, 7.3, 2 H); 8.54 (*d*, *J* = 5.0, 1 H); 8.69 (*s*, 1 H). HR-MS: 236.0937 ($C_{15}H_{12}N_2O^+$; calc. 236.0950).

*3-Isocyano-4-[(*E*)-2-methoxy-1-(4-methylphenyl)ethenyl]pyridine* (**4b**). Yellow oil. R_f (THF/hexane 1:5) 0.28. IR (neat): 2126, 1636. ^{1}H-NMR: 2.33 (*s*, 3 H); 3.84 (*s*, 3 H); 6.69 (*s*, 1 H); 6.99 (*d*, *J* = 7.8, 2 H); 7.11 (*d*, *J* = 7.8, 2 H); 7.19 (*d*, *J* = 5.0, 1 H); 8.53 (*d*, *J* = 5.0, 1 H); 8.68 (*s*, 1 H). HR-MS: 250.1086 ($C_{16}H_{14}N_2O^+$; calc. 250.1106).

*4-[(*E*)-1-(3-Chlorophenyl)-2-methoxyethenyl]-3-isocyanopyridine* (**4c**). Yellow oil. R_f (THF/hexane 1:5) 0.29. IR (neat): 2123, 1636. ^{1}H-NMR: 3.87 (*s*, 3 H); 6.77 (*s*, 1 H); 6.94–6.98 (*m*, 1 H); 7.08–7.09 (*m*, 1 H); 7.19 (*d*, *J* = 5.0, 1 H); 7.22–7.24 (*m*, 2 H); 8.22 (*d*, *J* = 5.0, 1 H); 8.71 (*s*, 1 H). HR-MS: 270.0553 ($C_{15}H_{11}ClN_2O^+$; calc. 270.0560).

*3-Isocyano-4-[(*E*)-2-methoxy-1-(4-methoxyphenyl)ethenyl]pyridine* (**4d**). Colorless needles. M.p. 111° (hexane/Et_2O). IR (KBr): 2126, 1636. ^{1}H-NMR: 3.80 (*s*, 3 H); 3.84 (*s*, 3 H); 6.63 (*s*, 1 H); 6.84 (*d*, *J* = 9.2, 2 H); 7.02 (*d*, *J* = 9.2, 2 H); 7.18 (*d*, *J* = 5.0, 1 H); 8.52 (*d*, *J* = 5.0, 1 H); 8.68 (*s*, 1 H). Anal. calc. for $C_{16}H_{14}N_2O_2$ (266.29): C 72.16, H 5.30, N 10.52; found: C 72.07, H 5.37, N 10.26.

2,4,8-Triphenyl-1,7-naphthyridine (**6a**) (*Representative Procedure*). To a stirred soln. of **4a** (0.14 g, 0.59 mmol) in 1,2-dimethoxyethane (DME; 3 ml) at −78° was added PhLi (1.08M in cyclohexane/Et_2O; 2.4 mmol); the mixture was stirred for 3 h at the same temp. before addition of sat. aq. NH_4Cl (10 ml). The warmed mixture was extracted with Et_2O (3 × 10 ml), and the combined extracts were washed with brine and dried (anh. Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by CC (silica gel; THF/hexane 1:10) to give **6a** (0.10 g, 47%). Pale-yellow needles. M.p. 150–153° (hexane/CH_2Cl_2). IR (KBr): 1593. ^{1}H-NMR: 7.45–7.60 (*m*, 11 H); 7.70 (*d*, *J* = 5.5, 1 H); 8.07 (*s*, 1 H); 8.21 (*dd*, *J* = 8.2, 1.4, 2 H); 8.26 (*dd*, *J* = 8.2, 1.4, 2 H); 8.64 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 117.31; 121.55; 127.48; 127.66; 128.71; 128.83; 128.85; 128.88; 129.46; 129.86; 129.92; 131.59; 137.35; 138.65; 138.94; 141.72; 142.97; 148.49; 156.73; 160.51. MS: 358 (100, M^+). Anal. calc. for $C_{26}H_{18}N_2$ (358.44): C 87.12, H 5.06, N 7.82; found: C 87.22, H 5.14, N 7.66.

2,4-Diphenyl-1,7-naphthyridine (**5**). This compound was obtained by using less than 4 mol-equiv. of PhLi. Pale-yellow solid. M.p. 123–125° (hexane/Et_2O). IR (KBr): 1593. ^{1}H-NMR: 7.50–7.61 (*m*, 8 H); 7.75 (*dd*, *J* = 5.5, 0.9, 1 H); 8.03 (*s*, 1 H); 8.23 (*dd*, *J* = 7.8, 1.4, 2 H); 8.57 (*d*, *J* = 5.5, 1 H); 9.63 (*d*, *J* = 0.9, 1 H). ^{13}C-NMR: 117.77; 122.65; 127.59; 128.87; 128.91; 128.98 (2 C); 129.39; 129.98; 136.78; 138.74; 143.63; 148.83; 148.16; 154.74; 158.44. MS: 282 (100, M^+). Anal. calc. for $C_{20}H_{14}N_2$ (282.34): C 85.08, H 5.00, N 9.92; found: C 84.95, H 5.16, N 9.72.

2,8-Dibutyl-4-phenyl-1,7-naphthyridine (**6b**). Pale-yellow oil. R_f (THF/hexane 1:10) 0.42. IR (neat): 1597. ^{1}H-NMR: 0.99 (*t*, *J* = 7.3, 3 H); 1.00 (*t*, *J* = 7.3, 3 H); 1.43–1.55 (*m*, 4 H); 1.86–1.93 (*m*, 4 H); 3.03 (*t*, *J* = 7.3, 2 H); 3.56 (*t*, *J* = 7.8, 2 H); 7.38 (*s*, 1 H); 7.47–7.54 (*m*, 6 H); 8.39 (*d*, *J* = 6.0, 1 H). ^{13}C-NMR: 13.98; 14.07; 22.43; 22.98; 31.19; 31.88; 33.84; 38.69; 116.11; 124.82; 128.55; 128.66 (2 C); 129.41; 137.36; 141.92; 141.95; 147.34; 162.47; 165.17. MS: 318 (100, M^+). Anal. calc. for $C_{22}H_{26}N_2$ (318.46): C 82.97, H 8.23, N 8.80; found: C 82.88, H 8.35, N 8.77.

4-(4-Methylphenyl)-2,8-diphenyl-1,7-naphthyridine (**6c**). Pale-yellow solid. M.p. 144–146° (hexane/Et_2O). IR (KBr): 1591. ^{1}H-NMR: 2.50 (*s*, 3 H); 7.39 (*d*, *J* = 8.2, 2 H); 7.44–7.52 (*m*, 6 H); 7.57 (*t*, *J* = 7.3,

2 H); 7.72 (*d*, *J* = 5.5, 1 H); 8.04 (*s*, 1 H); 8.20 (*d*, *J* = 7.3, 2 H); 8.26 (*d*, *J* = 7.3, 2 H); 8.63 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 21.32; 117.41; 121.49; 127.48; 127.65; 128.68; 128.88; 129.39; 129.54; 129.82; 130.05; 131.60; 134.44; 138.74; 138.91; 138.99; 141.77; 142.89; 148.55; 156.73; 160.51. MS: 372 (100, M^+). Anal. calc. for $C_{27}H_{20}N_2$ (372.46): C 87.07, H 5.41, N 7.52; found: C 87.05, H 5.52, N 7.32.

2,8-Bis(4-chlorophenyl)-4-(4-methylphenyl)-1,7-naphthyridine (**6d**). Pale-yellow crystals. M.p. 195–197° (hexane/Et_2O). IR (KBr): 1593. ^{1}H-NMR: 2.51 (*s*, 3 H); 7.40 (*d*, *J* = 7.8, 2 H); 7.47 (*d*, *J* = 7.8, 2 H); 7.49 (*d*, *J* = 8.7, 2 H); 7.54 (*d*, *J* = 8.7, 2 H); 7.74 (*d*, *J* = 6.0, 1 H); 8.01 (*s*, 1 H); 8.12 (*d*, *J* = 8.7, 2 H); 8.20 (*d*, *J* = 8.7, 2 H); 8.63 (*d*, *J* = 6.0, 1 H). ^{13}C-NMR: 21.34; 117.76; 121.27; 127.90; 128.69; 129.19; 129.35; 129.62; 130.13; 132.86; 134.12; 135.00; 136.24; 137.03; 137.32; 139.15; 141.57; 143.06; 148.97; 155.67; 159.15. MS: 440 (100, M^+). Anal. calc. for $C_{27}H_{18}Cl_2N_2$ (441.35): C 73.48, H 4.11, N 6.35; found: C 73.30, H 4.10, N 6.22.

2,8-Bis(4-methoxyphenyl)-4-(4-methylphenyl)-1,7-naphthyridine (**6e**). Pale-yellow solid. M.p. 102–104° (hexane/Et_2O). IR (KBr): 1603. ^{1}H-NMR: 2.49 (*s*, 3 H); 3.88 (*s*, 3 H); 3.94 (*s*, 3 H); 7.02 (*d*, *J* = 8.7, 2 H); 7.10 (*d*, *J* = 8.7, 2 H); 7.38 (*d*, *J* = 7.8, 2 H); 7.47 (*d*, *J* = 7.8, 2 H); 7.63 (*d*, *J* = 6.0, 1 H); 7.97 (*s*, 1 H); 8.17 (*d*, *J* = 8.7, 2 H); 8.28 (*d*, *J* = 8.7, 2 H); 8.56 (*d*, *J* = 6.0, 1 H). ^{13}C-NMR: 21.31; 55.36; 55.38; 113.13; 114.27; 116.83; 120.95; 128.89; 129.38; 129.49; 129.78; 131.51; 131.75; 133.06; 134.65; 138.77; 141.74; 142.52; 148.32; 156.16; 159.63; 160.22; 161.14. MS: 432 (100, M^+). Anal. calc. for $C_{29}H_{24}N_2O_2$ (432.51): C 80.53, H 5.59, N 6.48; found: C 80.39, H 5.50, N 6.40.

4-(3-Chlorophenyl)-2,8-diphenyl-1,7-naphthyridine (**6f**). Pale-yellow solid. M.p. 148–150° (hexane/Et_2O). IR (KBr): 1601, 1589. ^{1}H-NMR: 7.46–7.59 (*m*, 10 H); 7.65 (*d*, *J* = 5.5, 1 H); 8.05 (*s*, 1 H); 8.21 (*dd*, *J* = 8.2, 1.4, 2 H); 8.25 (*dd*, *J* = 8.2, 1.4, 2 H); 8.67 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 116.87; 121.51; 127.47; 127.66; 127.68; 128.80; 128.93; 129.00; 129.44; 129.54; 129.99; 130.11; 131.59; 134.89; 138.40; 138.77; 139.05; 141.63; 143.21; 146.92; 156.73; 160.59. MS: 392 (100, M^+). Anal. calc. for $C_{26}H_{17}ClN_2$ (392.88): C 79.48, H 4.36, N 7.13; found: C 79.48, H 4.57, N 7.08.

4-(3-Chlorophenyl)-2,8-dimethyl-1,7-naphthyridine (**6g**). Pale-yellow solid. M.p. 124–126° (hexane/Et_2O). IR (KBr): 1605, 1591. ^{1}H-NMR: 2.82 (*s*, 3 H); 3.11 (*s*, 3 H); 7.36 (*d*, *J* = 6.0, 1 H); 7.39 (*s*, 1 H); 7.45–7.50 (*m*, 4 H); 8.39 (*d*, *J* = 6.0, 1 H). ^{13}C-NMR: 21.36; 25.62; 115.89; 125.36; 127.52; 127.59; 128.81; 129.38; 129.97; 134.76; 138.85; 142.17; 142.36; 145.96; 158.91; 161.54. MS: 268 (100, M^+). Anal. calc. for $C_{16}H_{13}ClN_2$ (268.74): C 71.51, H 4.88, N 10.42; found: C 71.41, H 5.02, N 10.21.

4-(3-Chlorophenyl)-2,8-bis(4-methylphenyl)-1,7-naphthyridine (**6h**). Pale-yellow crystals. M.p. 124–126° (hexane/Et_2O). IR (KBr): 1611, 1587. ^{1}H-NMR: 2.43 (*s*, 3 H); 2.49 (*s*, 3 H); 7.33 (*d*, *J* = 8.2, 2 H); 7.38 (*d*, *J* = 8.2, 2 H); 7.45–7.47 (*m*, 1 H); 7.52–7.53 (*m*, 2 H); 7.58 (*t*, *J* = 0.9, 1 H); 7.59 (*d*, *J* = 5.5, 1 H); 8.00 (*s*, 1 H); 8.11 (*d*, *J* = 8.2, 2 H); 8.18 (*d*, *J* = 8.2, 2 H); 8.63 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 21.35; 21.43; 116.57; 121.31; 126.49; 127.40; 127.68; 128.45; 128.92; 129.45; 129.67; 130.07; 131.58; 134.86; 135.78; 135.96; 138.72; 139.23; 140.19; 141.69; 143.01; 146.74; 156.63; 160.38. MS: 420 (100, M^+). Anal. calc. for $C_{28}H_{21}ClN_2$ (420.93): C 79.89, H 5.03, N 6.66; found: C 79.62, H 5.11, N 6.42.

4-(4-Methoxyphenyl)-2,8-diphenyl-1,7-naphthyridine (**6i**). Pale-yellow solid. M.p. 157–160° ($CHCl_3$). IR (KBr): 1608, 1593. ^{1}H-NMR: 3.94 (*s*, 3 H); 7.12 (*d*, *J* = 8.7, 2 H); 7.46–7.59 (*m*, 8 H); 7.75 (*d*, *J* = 5.5, 1 H); 8.04 (*s*, 1 H); 8.21 (*d*, *J* = 8.2, 1.4, 2 H); 8.26 (*d*, *J* = 8.2, 1.4, 2 H); 8.64 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 55.44; 114.32; 117.40; 121.41; 127.47; 127.64; 128.67; 128.87; 129.60; 129.80; 130.11; 130.77; 131.58; 138.74; 138.99; 141.81; 142.85; 148.19; 156.71; 160.21; 160.49. MS: 388 (100, M^+). Anal. calc. for $C_{27}H_{20}N_2O$ (388.46): C 83.48, H 5.19, N 7.21; found: C 83.39, H 5.21, N 6.93.

2,8-Bis(4-chlorophenyl)-4-(4-methoxyphenyl)-1,7-naphthyridine (**6j**). Pale-yellow solid. M.p. 255–257° (hexane/AcOEt). IR (KBr): 1611, 1595. ^{1}H-NMR: 3.94 (*s*, 3 H); 7.17 (*d*, *J* = 8.7, 2 H); 7.48–7.55 (*m*, 6 H); 7.75 (*d*, *J* = 5.5, 1 H); 7.99 (*s*, 1 H); 8.12 (*d*, *J* = 8.7, 2 H); 8.20 (*d*, *J* = 8.7, 2 H); 8.63 (*d*, *J* = 5.5, 1 H). ^{13}C-NMR: 55.50; 114.44; 117.76; 121.23; 127.90; 128.71; 129.20; 129.32; 130.24; 130.77; 132.87; 135.01; 136.24; 137.08; 137.34; 141.66; 143.04; 148.65; 155.71; 159.20; 160.39. MS: 456 (100, M^+). Anal. calc. for $C_{27}H_{18}Cl_2N_2O$ (457.35): C 70.91, H 3.97, N 6.13; found: C 70.85, H 4.03, N 6.36.

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