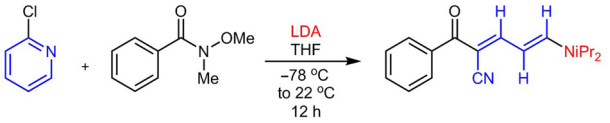
Synthesis H. J. Gim, M. E. Jung Paper

Formation of Aryl [1-Cyano-4-(dialkylamino)butadienyl] Ketones from Pyridines

Hyo Jin Gim
Michael E. Jung*

Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, CA 90095, USA
jung@chem.ucla.edu



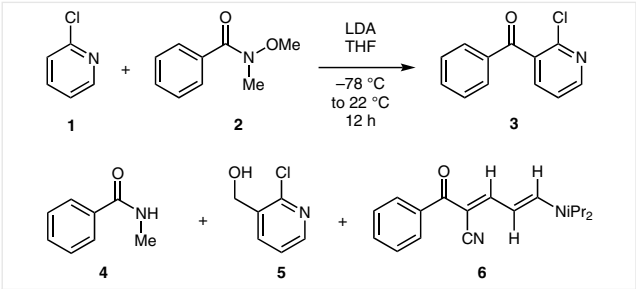
Received: 07.03.2019
Accepted after revision: 10.04.2019
Published online: 02.05.2019
DOI: 10.1055/s-0037-1611532; Art ID: ss-2019-z0154-op

Abstract Treatment of 2-chloropyridine with LDA and the Weinreb amide of benzoic acid afforded three unusual products, namely *N*-methylbenzamide, 2-chloropyridine-3-methanol, and the ring-opened addition product. This same final product could also be obtained from 2-chloro-3-benzoylpyridine on treatment with LDA. Mechanistic insight for the formation of these products is provided.

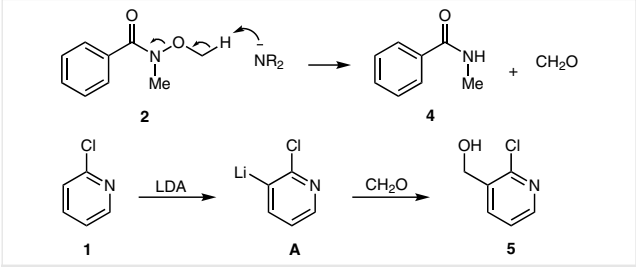
Key words pyridines, Weinreb amides, LDA, pyridine ring-openings, anions

For the synthesis of analogues of molecules that could potentially inhibit protein tyrosine kinase-σ,[1] we wished to prepare the simple phenyl 2-chloropyridyl ketone **3**. Although there was literature precedent for condensation of the 2-chloropyridin-3-yl anion with benzoyl chloride,[2,3] we decided to condense this anion with the more stable Weinreb amide **2** of benzoic acid.[4] When we treated 2-chloropyridine (**1**) with LDA in THF at –78 °C and added the Weinreb amide **2** and then let the mixture warm to 22 °C, we got little if any of the desired ketone **3** and rather isolated varying amounts of the three unexpected products, the simple *N*-methylbenzamide (**4**), 2-chloropyridine-3-methanol (**5**), and the ring opened addition product **6** (Scheme 1).

We believe that the first two products are formed by the mechanism shown in Scheme 2, namely the reaction of the Weinreb amide **2** with LDA to give, via an E_2-type reaction, elimination of formaldehyde with formation of the anion of the *N*-methylbenzamide (**4**). The formaldehyde generated in this reaction can then trap the 2-chloropyridin-3-yl lithium species, **A**, produced by the reaction of **1** and LDA, to produce, after workup, the 2-chloropyridine-3-methanol (**5**).

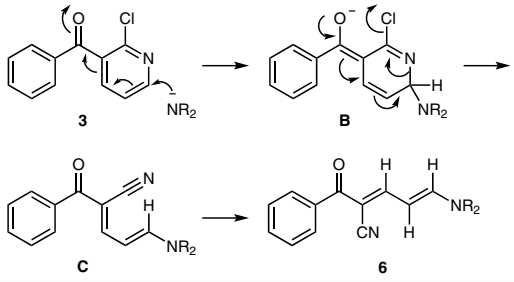


Scheme 1 Formation of unexpected products **4**–**6**



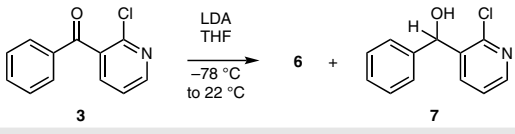
Scheme 2 Proposed mechanism for the formation of unexpected products **4** and **5**

The formation of the third product, the cyano aminodienone **6**, presumably involves the addition of diisopropylamide to the 6-position of the 2-chloro-3-benzoylpyridine (**3**) to generate the stabilized anionic intermediate **B**, which can then undergo an anionic-assisted cleavage of the C–N bond of the dihydropyridine with loss of chloride to form the cyano dienone **C**, which would rotate about the single bond to give the most stable conformer, namely the final product **6** (Scheme 3).



Scheme 3 Proposed mechanism for the formation of unexpected product **6**

There is literature precedent for such an elimination of halide from a 2-halopyridine with addition of nucleophiles.[5] The desired diaryl ketone **3** could be prepared by reacting the anion **A** formed from 2-chloropyridine (**1**) at low temperature with benzaldehyde followed by oxidation. We have also shown that treatment of the ketone **3** with LDA in THF at low temperature followed by warming to room temperature afforded a mixture of the same ring-opened product **6** and the product of reduction of the ketone with LDA, namely the alcohol **7** along with a small amount of a dimeric product, which will be discussed later (Scheme 4). Such reductions of hindered ketones with LDA are known and presumably occur via attack of the hydride from LDA onto the ketone carbonyl.[6]

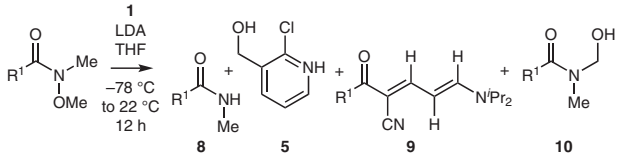


Scheme 4 Formation of **6** and alcohol **7** from ketone **3**

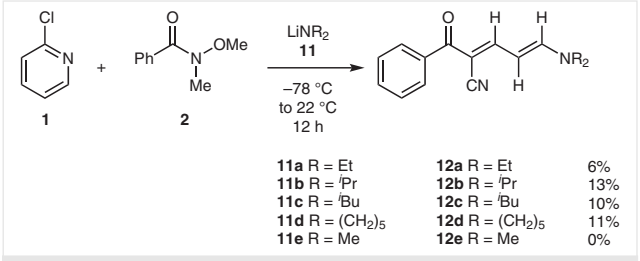
We then carried out a brief investigation of reaction scope and showed that other Weinreb amides **2a–f** also give the analogous ring-opened products, but in variable yields (Table 1). Thus the simple methyl ketone and the 3-chlorophenyl ketone afford the expected cyanoketones **9** under similar treatment with LDA, but in reduced yields. The 2- and 4-substituted phenyl systems gave poorer yields of the ring-opened product. In addition, in some cases, the hydroxymethyl amide **10** was also isolated, presumably from trapping of formaldehyde by the amide.

Likewise the basic amide can also be changed (Scheme 5). Thus treating 2-chloropyridine (**1**) and the Weinreb amide **2** with various lithium dialkylamides **11a–d** afforded the analogous cyanoketone **12a–d** in fair yields. Unhindered amides, e.g., lithium dimethylamide, and hindered amides, e.g., lithium hexamethyldisilazide, lithium diphenylamide, and LiTMP, gave none of the corresponding products. Since LiTMP did not promote the ring-opening, we could use it to

Table 1 Formation of Products from Other Weinreb Amides



Entry	Weinreb amide	R^1	Yield (%)			
			8	**5**	**9**	**10**
1	**2**	Ph	30	10	13	<1
2	**2a**	Me	0	0	9 (**9a**)	0
3	**2b**	2-ClC_6H_4	36 (**8b**)	30	<1	<1
4	**2c**	3-ClC_6H_4	29 (**8c**)	18	9 (**9c**)	<1
5	**2d**	4-ClC_6H_4	21 (**8d**)	6	3 (**9d**)	9 (**10d**)
6	**2e**	4-$CF_3C_6H_4$	10 (**8e**)	<1	<1	<1
7	**2f**	4-$MeOC_6H_4$	14 (**8f**)	0	1 (**9f**)	5 (**10f**)

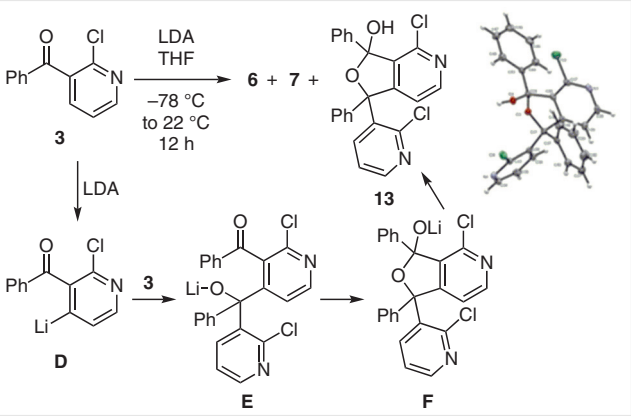


Scheme 5 Formation of other cyanoketones **12** from lithium dialkylamides **11**

prepare the desired 2-chloro-3-benzoylpyridine (**3**) from **1** and **2** in THF in 35% yield.

When the ketone **3** was reacted with LDA in THF at low temperature, in addition to the expected products, **6** and **7**, mentioned earlier (Scheme 4), we also isolated a small amount of a dimeric product, which was shown to be the lactol **13** (Scheme 6). We believe that the mechanism involves the deprotonation of the ketone **3** at the 4-position of the pyridine, *ortho* to the benzoyl unit, to give the anion **D**.[7] Condensation of this anion on the starting ketone **3** would then give the alkoxide **E**, which is perfectly set up to close on the adjacent ketone carbonyl to give the lactol anion **F**, which would protonate on workup to give the final product **13**. The structure of **13** was determined by a mixture of both high field proton and carbon NMR and mass spectrometric data and proven by a single crystal X-ray structure determination.[8]

We are currently looking at further examples of this rearrangement in simpler systems and will report those results in due course.



Scheme 6 Formation of dimeric product **13** from ketone **3**

All reactions were carried out under an argon atmosphere, unless otherwise specified. THF was distilled from benzoquinone ketyl radical under an argon atmosphere. Diisopropylamine (DIPA) was distilled from CaH_2 under an argon atmosphere. All other solvents were purified according to literature procedures. ^{1}H NMR spectra were recorded at 400 MHz and are reported relative to deuterated solvent signals. Melting points were recorded on Büchi melting point apparatus B-545. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Standard abbreviations are used for designating the splitting patterns. ^{13}C NMR spectra were recorded at 100 MHz. Data for ^{13}C NMR spectra are reported in terms of chemical shifts, which are reported in parts per million (ppm, δ). TLC was carried out using precoated silica gel sheets. Visual detection was performed using $KMnO_4$ or ceric ammonium nitrate stains. Flash chromatography was performed using SilicaFlash P60 (60 A, 40–63 μm) silica gel with compressed air. High-resolution mass spectrometry was taken on Waters LCT Premier mass spectrometer equipped with an ESI source.

For the preparation of Weinreb amides **2** and **2a–f** and product identification for **8** and **10**, see the Supporting Information.

(2-Chloropyridin-3-yl)(phenyl)methanone (3)

To a solution of 2,2,6,6-tetramethylpiperidine (882.2 mg, 1.06 mL, 6.245 mmol) in THF (6 mL) was slowly added *n*-BuLi (1.6 M solution in hexane, 3.6 mL, 5.765 mmol) at –78 °C and the reaction mixture was stirred at 0 °C for 30 min. Then 2-chloropyridine (**1**; 600 mg, 500 μL, 5.285 mmol) was added dropwise to the reaction mixture at –78 °C and the mixture was stirred for 30 min. A solution of Weinreb amide **2** (793.6 mg, 4.804 mmol) in THF (2 mL) was slowly added at –78 °C and the mixture was warmed to 22 °C and stirred for 12 h. After sat. aq NH_4Cl was added to the reaction mixture, it was diluted and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography (*n*-hexane/EtOAc 5:1) to obtain the desired product (363 mg, 1.668 mmol, 35%) as a light yellow liquid. Spectroscopic data for **3** match the literature data.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 4.8, 2.0 Hz, 1 H), 7.81–7.78 (m, 2 H), 7.43 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.65–7.61 (m, 1 H), 7.50–7.46 (m, 2 H), 7.38 (dd, *J* = 7.6, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 150.9, 147.8, 138.0, 135.8, 135.0, 134.2, 130.0, 128.9, 122.3.

Phenyl[1-cyano-4-(diisopropylamino)butadienyl]ketones; General Procedure (Table 1)

To a solution of DIPA (586.1 mg, 817 μL, 5.792 mmol) in THF (5.5 mL) was slowly added *n*-BuLi (1.6 M solution in *n*-hexane, 3.36 mL, 5.378 mmol) at –78 °C and the reaction mixture was stirred for 1 h. Then 2-chloropyridine (**1**; 563.7 mg, 470 μL, 4.965 mmol) was added dropwise to the mixture at –78 °C and it was stirred for 30 min. A solution of the corresponding Weinreb amide **2** or **2a–f** (683.4 mg, 4.137 mmol) in THF (2 mL) was slowly added to the mixture at –78 °C and it was stirred for 1 h. Then the mixture was gradually warmed to 22 °C and stirred for 12 h. After sat. aq NH_4Cl was added to the mixture, it was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo.

The resulting crude residue from **2** was purified by flash column chromatography (*n*-hexane/EtOAc 3:1 to 1:1) to obtain in the order: **5**, **10** (R^1 = Ph), **6** (≡ **9**, R^1 = Ph), and **4** (≡ **8**, R^1 = Ph) (Table 1, entry 1).

N-Methylbenzamide (4 ≡ 8, R^1 = Ph)

Ivory powder; yield: 170.2 mg (1.259 mmol, 30%); mp 78.1–79.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.74 (m, 2 H), 7.43–7.40 (m, 1 H), 7.36–7.32 (m, 2 H), 6.87 (br s, 1 H), 2.93 (d, *J* = 4.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 134.6, 131.3, 128.5, 126.9, 26.8.

(2-Chloropyridin-3-yl)methanol (5)

Light yellow solid; yield: 58.5 mg (0.408 mmol, 10%); mp 61.7–62.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.89 (ddd, *J* = 7.7, 1.2, 0.8 Hz, 1 H), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1 H), 4.74 (s, 2 H), 3.66 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.0, 147.9, 137.0, 135.4, 122.8, 61.2.

(2*E*,4*E*)-2-Benzoyl-5-(diisopropylamino)penta-2,4-dienenitrile (6 ≡ 9, R^1 = Ph)

Yellow crystalline solid; yield: 151.9 mg, (0.538 mmol, 13%); mp 227.3–228.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 12.8 Hz, 1 H), 7.84–7.81 (m, 2 H), 7.48–7.41 (m, 3 H), 7.29 (d, *J* = 12.0 Hz, 1 H), 5.98 (dd, *J* = 12.4 Hz, 1 H) 4.18 (sept, *J* = 6.8 Hz, 1 H), 3.72 (sept, *J* = 6.4 Hz, 1 H), 1.29 (d, *J* = 6.4 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 159.7, 154.4, 139.2, 131.3, 128.3, 128.1, 120.4, 99.0, 93.4, 50.5, 48.6, 23.6, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O$: 283.1810; found: 283.1811.

N-(Hydroxymethyl)-*N*-methylbenzamide (10, R^1 = Ph)

Ivory solid (trace); mp 63.2–64.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 7.53–7.49 (m, 1 H), 7.44–7.41 (m, 2 H), 7.02 (br s, 1 H), 4.89 (d, *J* = 6.8 Hz, 2 H), 3.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 133.9, 132.0, 128.7, 127.1, 71.9, 56.2.

(2*E*,4*E*)-2-Acetyl-5-(diisopropylamino)penta-2,4-dienenitrile (9a) (Table 1, entry 2)

Compound **9a** (yellow solid, 93 mg, 0.423 mmol, 9%) was obtained from Weinreb amide **2a** (494 mg, 4.701 mmol) and 2-chloropyridine (**1**; 652.7 mg, 5.749 mmol) in THF (8 mL) using the general procedure; mp 163.8–164.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 12.4 Hz, 1 H), 7.24 (d, *J* = 12.4 Hz, 1 H), 5.80 (t, *J* = 12.4 Hz, 1 H), 4.13 (sept, *J* = 6.8 Hz, 1 H), 3.70 (sept, *J* = 6.8 Hz, 1 H), 2.34 (s, 3 H), 1.28 (d, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 156.8, 154.2, 120.4, 97.9, 94.3, 50.3, 48.4, 27.7, 23.5, 19.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O$: 221.1654; found: 221.1655.

(2*E*,4*E*)-2-(3-Chlorobenzoyl)-5-(diisopropylamino)penta-2,4-dienenitrile (9c) (Table 1, entry 4)

Compound **9c** (yellow solid, 81.7 mg, 0.258 mmol, 9%) was obtained from Weinreb amide **2c** (572.4 mg, 2.867 mmol) and 2-chloropyridine (**1**; 390.7 mg, 3.441 mmol) in THF (5.5 mL) using the general procedure; mp 242.9–244.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 12.8 Hz, 1 H), 7.76 (t, *J* = 1.6 Hz, 1 H), 7.73 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1 H), 7.44 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1 H), 7.36 (dd, *J* = 8.0, 7.6 Hz, 1 H), 7.33 (d, *J* = 12.4 Hz, 1 H), 5.99 (dd, *J* = 12.4 Hz, 1), 4.20 (sept, *J* = 6.8 Hz, 1 H), 3.74 (sept, *J* = 6.8 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.1, 159.8, 155.0, 140.9, 134.3, 131.2, 129.4, 128.4, 126,4 120.1, 99.4, 92.7, 50.7, 48.9, 23.6, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}ClN_2O$: 317.1421; found: 317.1422.

(2*E*,4*E*)-2-(4-Chlorobenzoyl)-5-(diisopropylamino)penta-2,4-dienenitrile (9d) (Table 1, entry 5)

Compound **9d** (yellow solid, 16.1 mg, 0.051 mmol, 3%) was obtained from Weinreb amide **2d** (408.2 mg, 2.045 mmol) and 2-chloropyridine (**1**; 278.6 mg, 2.454 mmol) in THF (4 mL) using the genearl procedure; mp 200.3–201.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 12.8 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 12.0 Hz, 1 H), 5.99 (dd, *J* = 12.4 Hz, 1 H), 4.19 (sept, *J* = 6.8 Hz, 1 H), 3.73 (sept, *J* = 6.8 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.2, 159.7, 154.8, 137.5, 137.4, 129.8, 128.3, 120.3, 99.2, 92.6, 50.6, 48.7, 23.5, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{22}ClN_2O$: 317.1421; found: 317.1420.

(2*E*,4*E*)-5-(Diisopropylamino)-2-(4-methoxybenzoyl)penta-2,4-dienenitrile (9f) (Table 1, entry 7)

Compound **9f** (9.6 mg, 0.031 mmol, 1%) was prepared from Weinreb amide **2f** (530 mg, 2.715 mmol) and 2-chloropyridine (**1**; 369.9 mg, 3.258 mmol) in THF (3 mL) using the general procedure; mp 188.1–189.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 12.8 Hz, 1 H), 7.91 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 12.0 Hz, 1 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 5.97 (dd, *J* = 12.4 Hz, 1 H), 4.18 (sept, *J* = 6.8 Hz, 1 H), 3.85 (s, 3 H), 3.71 (sept, *J* = 6.8 Hz, 1 H), 1.29 (d, *J* = 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1, 162.4, 159.6, 153.9, 131.6, 130.6, 120.8, 113.3, 98.7, 93.0, 55.3, 50.3, 48.4, 23.6, 19.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_2$: 313.1916; found: 313.1919.

(2*E*,4*E*)-2-Benzoyl-5-(piperidin-1-yl)penta-2,4-dienenitrile (12d); Typical Procedure

To a solution of piperidine (265.6 mg, 308 μL, 3.119 mmol) in THF (3 mL) was slowly added *n*-BuLi (1.6 M solution in *n*-hexane, 2.33 mL) at –78 °C and the reaction mixture was stirred at 0 °C for 30 min. Then 2-chloropyridine (**1**; 303.5 mg, 2.633 mmol) was added dropwise to the reaction mixture at –78 °C and it was stirred for 30 min. A solution of Weinreb amide **2** (368 mg, 2.228 mmol) in THF (1 mL) was slowly added to the mixture at –78 °C and it was gradually warmed to 22 °C and stirred for 12 h. After sat. aq NH_4Cl was added to the mixture, it was diluted and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude residue was purified by column chromatography (*n*-hexane/EtOAc 1:1) to give **12d** (65.3 mg, 0.245 mmol, 11%) as a brown solid; mp 163.4–164.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 12.8 Hz, 1 H), 7.79–7.82 (m, 2 H), 7.40–7.49 (m, 3 H), 7.18 (d, *J* = 12.0 Hz, 1 H), 5.87 (dd, *J* = 12.4 Hz, 1 H), 3.46 (m, 4 H), 1.17 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.6, 159.4, 157.4, 139.0, 131.2, 128.3, 128.1, 120.2, 98.0, 93.9, 56.0, 47.0, 26.6, 25.1, 23.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O$: 267.1497; found: 267.1490.

(2*E*,4*E*)-2-Benzoyl-5-(diethylamino)penta-2,4-dienenitrile (12a)

Compound **12a** (yellow solid, 30.3 mg, 0.119 mmol, 6%) was obtained from Weinreb amide **2** (330 mg, 1.998 mmol) and 2-chloropyridine (**1**; 272.2 mg, 2.397 mmol) using Et_2NH in THF (3.5 mL); mp 114.8–116.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 12.8 Hz, 1 H), 7.79–7.81 (m, 2 H), 7.41–7.49 (m, 3 H), 7.21 (d, *J* = 12.0 Hz, 1 H), 5.81 (dd, *J* = 12.8, 12.4 Hz, 1 H), 3.41 (q, *J* = 7.2 Hz, 2 H), 3.37 (q, *J* = 7.2 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 159.4, 157.3, 139.1, 131.3, 128.4, 128.1, 120.1, 98.5, 94.1, 51.2, 43.6, 14.5, 12.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{19}N_2O$: 255.1497; found: 255.1502.

(2*E*,4*E*)-2-Benzoyl-5-(diisobutylamino)penta-2,4-dienenitrile (12c)

Compound **12c** (yellow solid, 82 mg, 0.264 mmol, 10%) was obtained from Weinreb amide **2** (436.5 mg, 2.642 mmol) and 2-chloropyridine (**1**; 360 mg, 3.171 mmol) using *i*-Bu_2NH in THF (4.5 mL); mp 121.0–122.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 12.8 Hz, 1 H), 7.81–7.84 (m, 2 H), 7.41–7.51 (m, 3 H), 7.21 (d, *J* = 12.0 Hz, 1 H), 5.83 (dd, *J* = 12.4 Hz, 1 H), 3.15 (d, *J* = 7.6 Hz, 2 H), 3.12 (d, *J* = 7.6 Hz, 2 H), 2.15 (m, 1 H), 1.97 (m, 1 H), 0.97 (d, *J* = 6.4 Hz, 6 H), 0.92 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7, 159.4, 158.9, 139.0, 131.3, 128.3, 128.1, 119.9, 98.8, 94.3, 64.9, 56.6, 27.9, 26.7, 20.2, 19.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}N_2O$: 311.2123; found: 311.2125.

Reaction of (2-Chloropyridin-3-yl)(phenyl)methanone (3) with LDA

To a solution of DIPA (108.2 mg, 151 μL, 1.069 mmol) in THF (1 mL) was slowly added *n*-BuLi (1.6 M solution in *n*-hexane, 0.6 mL, 0.980 mmol) at –78 °C and the reaction mixture was stirred for 1 h. The reaction mixture was warmed to 0 °C and (2-chloropyridin-3-yl)(phenyl)methanone (**3**; 193 mg, 0.891 mmol) in THF (0.2 mL) was slowly added and the mixture was stirred for 1 h at 0 °C. Then the mixture was warmed to 21 °C and stirred for 6 h. After adding sat. aq NH_4Cl to the mixture, it was diluted and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography (*n*-hexane/EtOAc 4:1) to give, in order: **7**, **13**, and **6** (30.2 mg, 0.107 mmol, 12%).

(2-Chloropyridin-3-yl)(phenyl)methanol (7)

Colorless oil; yield: 19.6 mg (0.089 mmol, 10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (dd, *J* = 4.8, 2.0 Hz, 1 H), 8.02 (ddd, *J* = 7.6, 2.0, 0.4 Hz, 1 H), 7.27–7.39 (m, 6 H), 6.14 (s, 1 H), 2.78 (br s, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 148.5, 141.4, 137.9, 136.9, 128.7, 128.2, 127.0, 122.9, 72.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}ClNO$: 220.0529; found: 220.0502.

4-Chloro-1-(2-chloropyridin-3-yl)-1,3-diphenyl-1,3-dihydrofuro[3,4-*c*]pyridin-3-ol (13)

White solid; yield: 42.7 mg (0.098 mmol, 11%); mp 257.2–258.3 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.53 (d, *J* = 5.5 Hz, 1 H), 8.38 (dd, *J* = 4.5, 2.0 Hz, 1 H), 8.00 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.81 (d, *J* = 5.0 Hz, 1 H), 7.74 (s, 1 H), 7.48 (dd, *J* = 8.0, 4.5 Hz, 1 H), 7.30–7.49 (m, 8 H), 7.20-7.22 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.6, 150.5, 149.2, 149.0, 146.1, 142.0, 140.9, 139.0, 137.3, 135.9, 128.5, 128.3, 127.9, 127.8, 126.9, 125.8, 122.6, 119.5, 107.4, 90.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{17}Cl_2N_2O_2$: 435.0667; found: 435.0666.

Funding Information

We thank the California Institute for Regenerative Medicine (CIRM) program at UCLA for support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611532.

References

(1) Zhang, Y.; Roos, M.; Himburg, H.; Termini, C. M.; Quarmyne, M.; Yan, X.; Zhao, L.; Kan, J.; Fang, T.; Li, M.; Pohl, K.; Diers, E.; Gim, H. J.; Damoiseaux, R.; Whitelegge, J.; McBride, W.; Jung, M. E.; Chute, J. P. *Nat. Commun.* manuscript submitted.

(2) (a) Marquise, N.; Nguyen, T. T.; Chevallier, F.; Picot, L.; Thiery, V.; Lozach, O.; Bach, S.; Ruchaud, S.; Mongin, F. *Synlett* **2015**, *26*, 2811. (b) Marquise, N.; Harford, P. J.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Gagez, A.-L.; Sable, S.; Picot, L.; Thiery, V.; Wheatley, A. E. H.; Gros, P. C.; Mongin, F. *Tetrahedron* **2013**, *69*, 10123.

(3) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.

(4) Weinreb, S. M.; Nahm, S. *Tetrahedron Lett.* **1981**, *22*, 3815.

(5) (a) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Synop.* **1982**, 278. (b) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Miniprint* **1982**, 2863. (c) Newkome, G. R.; Sauer, J. D.; Staires, S. K. *J. Org. Chem.* **1977**, *42*, 3524. (d) Utimoto, K.; Sakai, N.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 5601. (e) Vander Lans, H. M. N.; Den Hertog, J. J.; Van Veldhuizen, A. *Tetrahedron Lett.* **1971**, *12*, 1875.

(6) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, A. C. *J. Org. Chem.* **1978**, *43*, 2601.

(7) The formation of this anion is precedented in the literature: (a) Hedidi, M.; Maillard, J.; Erb, W.; Lassagne, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Dorcet, V.; Hamze, M.; Fajloun, Z.; Baratte, B.; Ruchard, S.; Bach, S.; Bentabed-Ababsa, G.; Mongin, F. *Eur. J. Org. Chem.* **2017**, 5903. (b) Hedidi, M.; Erb, W.; Lassagne, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Bentabed-Ababsa, G.; Mongin, F. *RSC Adv.* **2016**, *6*, 63185.

(8) (a) CCDC 1900152 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/getstructures. (b) We thank Dr. Saeed Khan for carrying out the single crystal X-ray determination.