One-Step Synthesis of Substituted α-Pyrones from Cyclobutenediones and Lithiated *O*-Silyl Cyanohydrins

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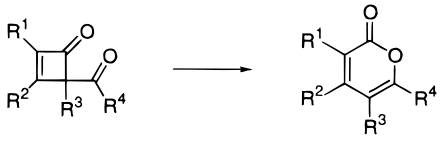
Introduction

The α-pyrone unit[1−5] is an important synthetic building block[6−10] that also is found in numerous biologically active, naturally occurring compounds.[11−19] Because of the ease and efficiency with which they rearrange,[20] 4-acylcyclobutenones are strategically attractive precursors to α-pyrones (eq 1). An acylcyclobutenone-based

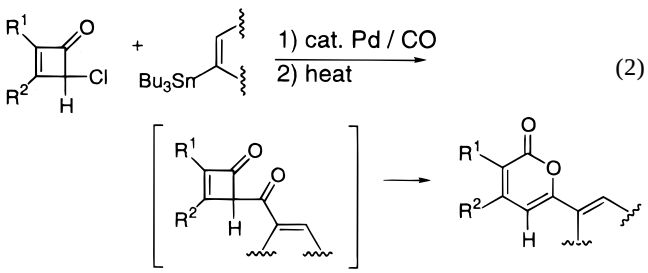


(1)

method for the synthesis of substituted α-pyrones involving the palladium-catalyzed carbonylative coupling of 4-chlorocyclobutenones with organotin reagents was previously disclosed (eq 2).[21] Herein is described a synthesis of 5-silyloxy-2-pyrones, which uses a highly effective addition of a lithiated *O*-silyl cyanohydrin to a cyclobutenedione followed by spontaneous silyl migration/cyanide expulsion to generate the key acylcyclobutenone (eq 3).

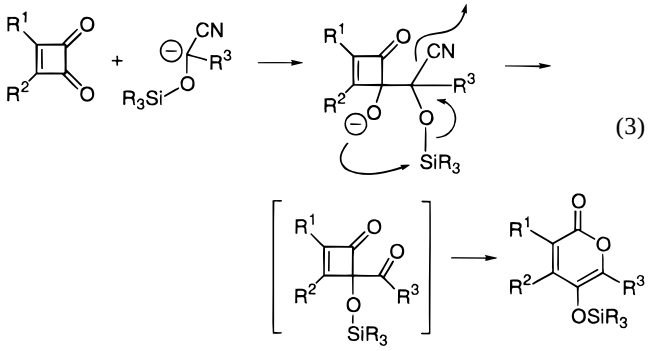
Results and Discussion

The addition of unsaturated nucleophiles to cyclobutenediones provides access to, inter alia, quinones and



(2)

phenols,[22−43] ring-fused α-pyridones,[44] and quinoline/isoquinoline quinones.[31,45] In an effort to extend this highly versatile chemistry to the synthesis of substituted α-pyrones, the addition of a lithiated *O*-silylated cyanohydrin to a cyclobutenedione with subsequent intramolecular 1,4-silyl migration and displacement of cyanide was envisioned. This process would generate in situ a 4-acylcyclobutenone, which is known to undergo facile rearrangement to a substituted 2-pyrone (eq 3).[21]



(3)

O-tert-Butyldimethylsilyl cyanohydrins (**1**, Table 1)

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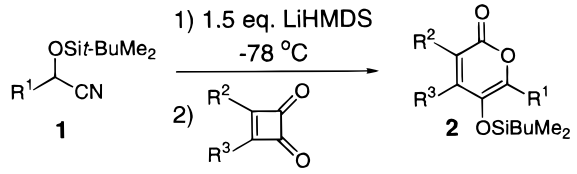
Table 1. Formation of Substituted α-Pyrones



no.	R^1	R^2	R^3	no.	yield (%)
1a	2-furyl	*i*-PrO	*i*-PrO	**2a**	71
1b	2-fluorophenyl	Et	Et	**2b**	61
1c	2-methyl-1-propenyl	*i*-PrO	*i*-PrO	**2c**	70
1d	4-chlorophenyl	*a*	*a*	**2d**	50
1e	*N*-methyl-2-pyrrolyl	phenyl	*i*-PrO	**2e**	71
1f	phenyl	phenyl	*i*-PrO	**2f**	86
1g	3-pyridyl	*tert*-butyl	MeO	**2g**	76
1h	phenyl	*tert*-butyl	MeO	**2h**	78[b]
1i	*N*-methyl-3-indolyl	*n*-butyl	*N*, *N*-dimethylamino	**2i**	57[b]

[a] R^2,R^3 = benzo. [b] Characterization and purification were facilitated by desilylation and then acetylization to provide the 5-acetoxypyrone

were prepared by following the procedure of Cava.[46] The *tert*-butyldimethylsilyl protecting group was chosen because of its greater hydrolytic stability relative to that of the trimethylsilyl group. The lithiated *O*-silyl cyanohydrins were generated by deprotonation with lithium hexamethyldisilazide at −78 °C in THF. Addition of a solution of the lithiated cyanohydrin via cannula into a −78 °C solution of a cyclobutenedione in THF gave the desired 2-pyrone, directly, after a low temperature quench and workup. As shown in Table 1, a variety of highly functionalized 5-silyloxy-2-pyrones (**2a**−**i**) were obtained in good to excellent yields using this protocol.

Efficient formation of pyrone **2i** required transmetalation of the deprotonated cyanohydrin from lithium to cerium in order to minimize competitive deprotonation of the enolizable proton of the *n*-butyl group on the cyclobutenedione. In addition, due to difficulty in the purification of the corresponding silyl ether-protected pyrone, this pyrone and **2h** were desilylated and then protected as the acetate for characterization purposes.

A particularly interesting aspect of this reaction is the ability of the 4-acylcyclobutenone to rearrange to a pyrone at or below room temperature, while most ring expansions of 4-aryl- or 4-vinylcyclobutenones require heating at temperatures in excess of 100 °C.[34] A similar result is seen when comparing the rates of cyclizations of *cis*-trienes and *cis*-dienones,[47] the latter of which possess significantly lower activation energies. In each case the more facile cyclization is attributed to greater polarization of the carbonyl group compared to a carbon−carbon double bond.

Conclusions

In conclusion, a method for the synthesis of highly substituted α-pyrones using cyclobutenedione precursors has been developed. Addition of an *O*-silylated cyanohydrin to a cyclobutenedione followed by 1,4-silyl migration and cyanide displacement results in the formation of a 4-acylcyclobutenone which undergoes spontaneous ring expansion to give the desired product in good to excellent yield.

Experimental Section

General Methods and Materials. All melting points were performed in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. All reactions were carried out under an inert atmosphere of nitrogen in flame-dried flasks. All solvents and reagents were purchased from commercial sources and were used as received, unless otherwise noted. Acetonitrile and THF were dried over 4 Å molecular sieves under an inert atmosphere. Flash chromatography was performed with EM Science Silica Gel 60 (230−400 mesh) with compressed air as the source of positive pressure. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60F-254 glass-backed plates of 0.25 mm thickness which were visualized with appropriate combinations of UV light, phosphomolybdic acid stain (10% phosphomolybdic acid in ethanol), and anisaldehyde stain (5 mL of *p*-anisaldehyde/95 mL of ethanol). $NaHCO_3$ refers to a saturated aqueous solution. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Starting Materials. The following compounds were prepared by literature methods: 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione,[48] 4-*tert*-butyl-3-methoxy-3-cyclobutene-1,2-dione,[48] 3,4-diisopropoxy-3-cyclobutene-1,2-dione,[48] 4-phenyl-3-isopropoxy-3-cyclobutene-1,2-dione,[48] 4-*n*-butyl-3-(*N*,*N*-dimethylamino)-3-cyclobutene-1,2-dione,[49] 3,4-diethyl-3-cyclobutene-1,2-dione,[44] and 3,4-benzo-3-cyclobutene-1,2-dione.[50,51]

General Procedure for the Preparation of Silylated Cyanohydrins. Distinctive CN stretching absorptions were not apparent in the infrared spectra of most of these cyanohydrins. Very weak bands possibly attributable to the CN stretch were seen between 2200 and 2300 wavenumbers.

***tert*-Butyldimethylsilyloxy(2-furyl)acetonitrile, 1a.** This compound was prepared by a modification of a literature procedure.[46] To a room-temperature solution of 2-furancarbaldehyde (0.86 mL, 10.5 mmol, 1.00 equiv) in acetonitrile (60 mL) were added potassium cyanide (2.70 g, 42.2 mmol, 4.02 equiv), *tert*-butyldimethylsilyl chloride (1.91 g, 12.6 mmol, 1.20 equiv), and zinc iodide (0.053 g, 0.17 mmol, 0.02 equiv). The reaction mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, diethyl ether (50 mL) was added, and the organic layer was filtered, washed with water (2 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give *tert*-butyldimethylsilyloxy-(2-furyl)acetonitrile as a colorless oil (1.94 g, 8.17 mmol, 78%): TLC (silica gel, 4:1 hexane/ethyl acetate, R_f = 0.74); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, J = 1.0 Hz, 1 H), 6.53 (d, J = 3.3 Hz, 1 H), 6.39−6.41 (m, 1 H), 5.56 (s, 1 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 148.4, 143.6, 117.1, 110.6, 109.3, 57.9, 25.3, 18.0, −5.4. Anal. Calcd for $C_{12}H_{19}NO_2Si$: C, 60.72; H, 8.07; N, 5.90; O, 13.48; Si, 11.83. Found: C, 60.90; H, 8.15; N, 5.94.

***tert*-Butyldimethylsilyloxy(2-fluorophenyl)acetonitrile, 1b.** *tert*-Butyldimethylsilyloxy(2-fluorophenyl)acetonitrile, a colorless oil (2.67 g, 10.1 mmol, 91%), was analogously prepared from 2-fluorobenzaldehyde (1.16 mL, 11.0 mmol, 1.00 equiv), potassium cyanide (2.90 g, 44.6 mmol, 4.05 equiv), *tert*-butyldimethylsilyl chloride (1.98 g, 13.0 mmol, 1.18 equiv), and zinc iodide (0.060 g, 0.19 mmol, 0.02 equiv): TLC (silica gel, 4:1 hexane/ethyl acetate, R_f = 0.77); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.67 (dt, J = 7.6, 1.6 Hz, 1 H), 7.38−7.45 (m, 1 H), 7.26 (t, J = 7.9 Hz, 1 H), 7.10−7.15 (m, 1 H), 5.80 (s, 1 H), 0.96 (s, 9 H), 0.27 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.8, 157.6, 131.1, 128.0, 124.0, 123.8, 118.2, 115.6, 115.3, 58.0, 25.3, 18.0, −5.4. Anal. Calcd for $C_{14}H_{20}NOSiF$: C, 63.36; H, 7.60; N, 5.28; O, 6.03; Si, 10.58; F, 7.16. Found: C, 63.43; H, 7.66; N, 5.18.

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***tert*-Butyldimethylsilyloxy(2-methyl-1-propenyl)acetonitrile, 1c.** *tert*-Butyldimethylsilyloxy(2-methyl-1-propenyl)-acetonitrile, a pale yellow oil (2.12 g, 9.41 mmol, 86%), was analogously prepared from 3,3-dimethylpropenal (1.06 mL, 11.0 mmol, 1.00 equiv), potassium cyanide (2.90 g, 44.0 mmol, 4.00 equiv), *tert*-butyldimethylsilyl chloride (1.98 g, 13.0 mmol, 1.18 equiv), and zinc iodide (0.060 g, 0.19 mmol, 0.02 equiv): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.74$); IR (CH_2Cl_2, KCl, cm^{-1}) 673 (w); ^1H NMR ($CDCl_3$, 360 MHz) δ 5.31−5.34 (m, 1 H), 5.08 (d, $J = 8.5$ Hz, 1 H), 1.77 (s, 3 H), 1.72 (s, 3 H), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.7, 121.0, 119.2, 58.8, 25.3, 18.1, 17.9, −5.2. Anal. Calcd for $C_{12}H_{23}NOSi$: C, 63.94; H, 10.28; N, 6.21; O, 7.10; Si, 12.46. Found: C, 63.89; H, 10.27; N, 6.21.

***tert*-Butyldimethylsilyloxy(4-chlorophenyl)acetonitrile, 1d.** *tert*-Butyldimethylsilyloxy(4-chlorophenyl)acetonitrile, a pale yellow oil (2.6 g, 9.22 mmol, 84%), was analogously prepared from *p*-chlorobenzaldehyde (1.50 g, 11.0 mmol, 1.00 equiv), potassium cyanide (2.90 g, 44.0 mmol, 4.00 equiv), *tert*-butyldimethylsilyl chloride (1.98 g, 13.0 mmol, 1.18 equiv), and zinc iodide (0.060 g, 0.19 mmol, 0.02 equiv): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.65$); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.40 (s, 4 H), 5.48 (s, 1 H), 0.94 (s, 9 H), 0.23 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 135.0, 134.8, 128.8, 127.2, 118.7, 63.0, 25.2, 17.8, −5.4. Anal. Calcd for $C_{14}H_{20}NOClSi$: C, 59.66; H, 7.15; N, 4.97; O, 5.68; Cl, 12.58; Si, 9.96. Found: C, 59.72; H, 7.19; N, 4.99; Cl, 12.50.

***tert*-Butyldimethylsilyloxy(1-methyl-2-pyrrolyl)acetonitrile, 1e.** *tert*-Butyldimethylsiloxy(1-methyl-2-pyrrolyl)acetonitrile, a yellow oil (1.92 g, 7.67 mmol, 77% after flash chromatography), was analogously prepared from 1-methyl-2-pyrrolecarboxaldehyde (1.09 g, 10.0 mmol, 1.00 equiv), potassium cyanide (1.95 g, 30.0 mmol, 3.00 equiv), *tert*-butyldimethylsilyl chloride (1.51 g, 10.0 mmol, 1.00 equiv), and zinc iodide (0.064 g, 0.20 mmol, 0.02 equiv): TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.50$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 5% EtOAc in hexane); IR (CH_2Cl_2, KCl, cm^{-1}) 2306 (w); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.69 (app t, $J = 1.8$ Hz, 1 H), 6.23 (dd, $J = 3.3$, 1.8 Hz, 1 H), 6.08 (app t, $J = 3.3$ Hz, 1 H), 5.57 (s, 1 H), 3.79 (s, 3 H), 0.93 (s, 9 H), 0.15 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 125.9, 125.3, 118.0, 110.3, 107.0, 57.7, 34.3, 25.4, 17.9, −5.3, −5.5. Anal. Calcd for $C_{13}H_{22}N_2OSi$: C, 62.35; H, 8.86; N, 11.19; O, 6.39; Si, 11.22. Found: C, 62.47; H, 8.91; N, 11.17.

***tert*-Butyldimethylsilyloxy Phenyl Acetonitrile, 1f.** *tert*-Butyldimethylsilyloxy phenyl acetonitrile, a colorless oil (4.60 g, 18.60 mmol, 93% after flash chromatography), was analogously prepared from benzaldehyde (2.122 g, 20.0 mmol, 1.00 equiv), potassium cyanide (5.21 g, 80.0 mmol, 4.00 equiv), *tert*-butyldimethylsilyl chloride (3.618 g, 24.0 mmol, 1.20 equiv), and zinc iodide (0.115 g, 0.36 mmol, 0.02 equiv): TLC (silica gel, 10% EtOAc/hexane, $R_f = 0.38$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 5% EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48−7.40 (m, 5 H), 5.52 (s, 1 H), 0.94 (s, 9 H), 0.23 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 136.4, 129.1, 128.8, 126.0, 119.2, 63.9, 25.5, 18.1, −5.2, −5.3. Anal. Calcd for $C_{14}H_{21}NOSi$: C, 67.97; H, 8.56; N, 5.66; O, 6.47; Si, 11.35. Found: C, 68.19; H, 8.62; N, 5.49.

***tert*-Butyldimethylsilyloxy-3-pyridinylacetonitrile, 1g.** *tert*-Butyldimethylsiloxy-3-pyridinylacetonitrile, a yellow oil (2.71 g, 10.9 mmol, 73% after flash chromatography), was analogously prepared from 3-pyridinecarboxaldehyde (1.61 g, 15.0 mmol, 1.00 equiv), potassium cyanide (2.93 g, 45.0 mmol, 3.00 equiv), *tert*-butyldimethylsilyl chloride (2.26 g, 15.0 mmol, 1.00 equiv), and zinc iodide (0.096 g, 0.30 mmol, 0.02 equiv): TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.14$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 15% EtOAc in hexane + 1% Et_3N); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.71 (d, $J = 1.8$ Hz, 1 H), 8.66 (dd, $J = 7.8$, 1.5 Hz, 1 H), 7.84 (dt, $J = 7.8$, 1.8 Hz, 1 H), 7.39 (dd, $J = 7.8$, 1.8 Hz, 1 H), 5.56 (s, 1 H), 0.94 (s, 9 H), 0.26 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.5, 147.5, 133.7, 132.2, 123.6, 118.3, 61.9, 25.3, 17.9, −5.2, −5.4. Anal. Calcd for $C_{13}H_{20}N_2OSi$: C, 62.86; H, 8.12; N, 11.28; O, 6.44; Si, 11.31. Found: C, 62.60; H, 8.18; N, 11.14.

***tert*-Butyldimethylsilyloxy(1-methyl-3-indolyl)acetonitrile, 1i.** *tert*-Butyldimethylsiloxy(1-methyl-3-indolyl)acetonitrile, a white amorphous solid (2.95 g, 9.820 mmol, 98% after flash chromatography), was analogously prepared from 1-methyl-3-indolecarboxaldehyde (1.59 g, 10.0 mmol, 1.00 equiv), potassium cyanide (1.95 g, 30.0 mmol, 3.00 equiv), *tert*-butyldimethylsilyl chloride (1.51 g, 10.0 mmol, 1.00 equiv), and zinc iodide (0.064 g, 0.20 mmol, 0.02 equiv): TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.35$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 5% EtOAc in hexane); mp 74.0−76.0 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, $J = 7.8$ Hz, 1 H), 7.34−7.17 (m, 4 H), 5.80 (s, 1 H), 3.75 (s, 3 H), 0.94 (s, 9 H), 0.22 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 137.3, 127.6, 125.3, 122.5, 120.0, 119.5, 119.1, 110.8, 109.6, 57.9, 32.8, 25.5, 18.1, −5.1. Anal. Calcd for $C_{17}H_{24}N_2OSi$: C, 67.95; H, 8.05; N, 9.32; O, 5.32; Si, 9.35. Found: C, 67.75; H, 8.12; N, 9.24.

General Procedure for the Preparation of 2-Pyrones. 5-*tert*-Butyldimethylsilyloxy-3,4-diisopropoxy-6-(2-furyl)-2-pyrone, 2a. To a −78 °C solution of *tert*-butyldimethylsilyloxy-(2-furyl)acetonitrile (0.200 g, 0.84 mmol, 1.05 equiv) in THF (4 mL) were added lithium hexamethyldisilazide, LiHMDS (1.80 mL, 1.00 M, 1.80 mmol, 2.24 equiv), by syringe. The solution was stirred for 20 min at −78 °C and then added via cannula into a solution of diisopropyl squarate (159 mg, 0.80 mmol, 1.00 equiv). After stirring for 20 min at −78 °C, the reaction was quenched with a saturated solution of $NaHCO_3$ (2 mL) and warmed to room temperature. The solution was extracted with diethyl ether (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatographic purification (flash column, silica gel, 0−20% ethyl acetate in hexanes) gave 5-*tert*-butyldimethylsilyloxy-3,4-diisopropoxy-6-(2-furyl)-2-pyrone, a white solid (231 mg, 0.565 mmol, 70%): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.51$); mp 88−90 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1702 (m), 1634 (w); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.44 (s, 1 H), 6.80 (d, $J = 3.4$ Hz, 1 H), 6.46−6.47 (m, 1 H), 5.25 (hept, $J = 6.2$ Hz, 1 H), 4.67 (hept, $J = 6.2$ Hz, 1 H), 1.30 (d, $J = 6.2$ Hz, 6 H), 1.27 (d, $J = 6.2$ Hz, 6 H), 0.95 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.8, 155.5, 145.4, 142.8, 136.8, 131.3, 129.3, 111.6, 111.4, 76.2, 74.1, 25.6, 22.4, 22.2, 18.3, −4.3. Anal. Calcd for $C_{21}H_{32}O_6Si$: C, 61.74; H, 7.89; O, 23.50; Si, 6.87. Found: C, 61.93; H, 7.95.

5-*tert*-Butyldimethylsilyloxy-3,4-diethyl-6-(2-fluorophenyl)-2-pyrone, 2b. 5-*tert*-Butyldimethylsilyloxy-3,4-diethyl-6-(2-fluorophenyl)-2-pyrone, an off-white solid (0.163 g, 0.43 mmol, 60%), was analogously prepared from 3,4-diethyl-3-cyclobutene-1,2-dione (0.099 g, 0.72 mmol, 1.00 equiv), *tert*-butyldimethylsilyloxy(2-fluorophenyl)acetonitrile (0.200 g, 0.75 mmol, 1.05 equiv), and LiHMDS (1.6 mL, 1.13 mmol, 1.50 equiv): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.43$); chromatographic purification (flash column, silica gel, 0−10% ethyl acetate in hexanes); mp 78−80 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1701 (m), 1633 (s), 1551 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.52 (m, 1 H), 7.30−7.36 (m, 1 H), 7.00−7.16 (m, 2 H), 2.51−2.53 (m, 4 H), 1.10−1.16 (m, 6 H), 0.83 (s, 9 H), −0.36 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.8, 161.5, 158.1, 153.5, 131.5, 131.4, 131.2, 126.3, 123.7, 123.7, 120.2, 120.0, 116.1, 115.8, 25.4, 21.1, 20.8, 17.9, 13.5, 13.3, −4.8. Anal. Calcd for $C_{21}H_{29}O_3SiF$: C, 66.99; H, 7.76; O, 12.75; Si, 7.46; F, 5.05. Found: C, 66.82; H, 7.73.

5-*tert*-Butyldimethylsilyloxy-3,4-diisopropoxy-6-(2-methyl-1-propenyl)-2-pyrone, 2c. 5-*tert*-Butyldimethylsilyloxy-3,4-diisopropoxy-6-(2-methyl-1-propenyl)-2-pyrone, a pale yellow oil (0.175 g, 0.44 mmol, 70%), was analogously prepared from diisopropyl squarate (0.126 g, 0.63 mmol, 1.00 equiv), *tert*-butyldimethylsilyloxy(2-methyl-1-propenyl)acetonitrile (0.150 g, 0.67 mmol, 1.05 equiv), and LiHMDS (1.00 mL, 1.00 M, 1.00 mmol, 1.58 equiv): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.62$); chromatographic purification (flash column, silica gel, 0−20% ethyl acetate in hexanes); IR (CH_2Cl_2, KCl, cm^{-1}) 1698 (s), 1643 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.01 (s, 1 H), 5.24 (hept, $J = 6.2$ Hz, 1 H), 4.62 (hept, $J = 6.2$ Hz, 1 H), 2.07 (s, 3 H), 1.89 (s, 3 H), 1.28 (m, 12 H), 0.98 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.8, 155.9, 145.3, 141.8, 131.7, 128.7, 113.4, 76.2, 74.3, 28.2, 26.1, 22.8, 22.6, 20.8, 18.7, −3.9. Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60; H, 9.15; O, 20.17; Si, 7.08. Found: C, 63.66; H, 9.15.

3,4-Benzo-5-*tert*-butyldimethylsilyloxy-6-(4-chlorophenyl)-2-pyrone, 2d. 3,4-Benzo-5-*tert*-butyldimethylsilyloxy-6-(4-chlorophenyl)-2-pyrone, a white solid (0.319 g, 0.82 mmol, 49%), was analogously prepared from 3,4-benzocyclobutene-1,2-

dione (0.223 g, 1.69 mmol, 1.00 equiv), *tert*-butyldimethylsilyloxy(4-chlorophenyl)acetonitrile (0.500 g, 1.78 mmol, 1.05 equiv), and LiHMDS (2.70 mL, 1.00 M, 2.70 mmol, 1.60 equiv): TLC (silica gel, 4:1 hexanes/ethyl acetate, $R_f = 0.62$); chromatographic purification (flash column, silica gel, 0−20% ethyl acetate in hexanes); mp 160−163 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1724 (s), 1703 (w), 1626 (w); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, $J = 7.8$ Hz, 1 H), 7.73−7.84 (m, 4 H), 7.54 (t, $J = 7.2$ Hz, 1 H), 7.39 (d, $J = 8.3$ Hz, 2 H), 1.04 (s, 9 H), −0.26 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.1, 141.8, 136.4, 134.9, 134.3, 132.5, 130.5, 129.9, 129.7, 128.5, 128.4, 122.4, 120.8, 25.8, 18.2, −4.2. Anal. Calcd for $C_{21}H_{23}O_3SiCl$: C, 65.18; H, 5.99; O, 12.40; Si, 7.26; Cl, 9.16. Found: C, 65.30; H, 6.05; Cl, 9.22.

5-(*tert*-Butyldimethylsiloxy)-4-isopropoxy-6-(1-methyl-2-pyrrolyl)-3-phenyl-2-pyrone, 2e. 5-(*tert*-Butyldimethylsiloxy)-4-isopropoxy-6-(*1*-methyl-2-pyrrolyl)-3-phenyl-2-pyrone, a yellow solid (0.623 g, 1.42 mmol, 71%), was analogously prepared from *tert*-butyldimethylsiloxy(1-methyl-2-pyrrolyl)-acetonitrile (0.53 g, 2.10 mmol, 1.05 equiv), LiHMDS (3.00 mL, 1.00 M, 3.00 mmol, 1.50 equiv), and 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (0.43 g, 2.00 mmol, 1.00 equiv): TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.30$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 10% EtOAc in hexane); mp 154.5−155.5 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1695 (s), 1625 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.24 (m, 5 H), 6.70 (dd, $J = 2.7$, 1.8 Hz, 1 H), 6.59 (dd, $J = 3.6$, 1.8 Hz, 1 H), 6.14 (dd, $J = 3.6$, 2.7 Hz, 1 H), 4.24 (hept, $J = 6.0$ Hz, 1 H), 3.74 (s, 3 H), 1.06 (d, $J = 6.0$ Hz, 6 H), 0.89 (s, 9 H), −0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.0, 162.4, 142.9, 132.5, 132.4, 130.2, 127.9, 127.7, 125.5, 122.8, 114.5, 114.0, 108.1, 75.9, 35.7, 25.6, 22.0, 18.1, −4.9. Anal. Calcd for $C_{25}H_{33}NO_4Si$: C, 68.30; H, 7.57; N, 3.19; O, 14.56; Si, 6.39. Found: C, 68.17; H, 7.63; N, 3.13.

5-(*tert*-Butyldimethylsiloxy)-3,6-diphenyl-4-isopropoxy-2-pyrone, 2f. 5-(*tert*-Butyldimethylsiloxy)-3,6-diphenyl-4-isopropoxy-2-pyrone, a light yellow solid (0.753 g, 1.72 mmol, 86%), was analogously prepared from (*tert*-butyldimethylsiloxy)-phenylacetonitrile (0.55 g, 2.20 mmol, 1.10 equiv), LiHMDS (3.00 mL, 1.00 M, 3.00 mmol, 1.50 equiv), and 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (0.43 g, 2.00 mmol, 1.00 equiv): TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.40$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 5% EtOAc in hexane); mp 156.8−158.5 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1693 (s), 1620 (m), 1543 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92−7.89 (m, 2 H), 7.51−7.31 (m, 8 H), 4.24 (hept, $J = 6.0$ Hz, 1 H), 1.09 (d, $J = 6.0$ Hz, 6 H), 0.94 (s, 9 H), −0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.2, 162.6, 147.9, 133.0, 132.3, 131.2, 130.2, 129.5, 128.5, 128.1, 128.0, 127.9, 114.7, 76.0, 25.7, 22.0, 18.1, −4.5. Anal. Calcd for $C_{26}H_{32}O_4Si$: C, 71.52; H, 7.39; O, 14.66; Si, 6.43. Found: C, 71.43; H, 7.39.

3-*tert*-Butyl-5-(tert-butyldimethylsiloxy)-4-methoxy-6-(3-pyridinyl)-2-pyrone, 2g. 3-*tert*-Butyl-5-(*tert*-butyldimethylsiloxy)-4-methoxy-6-(3-pyridinyl)-2-pyrone, a light yellow solid (0.589 g, 1.510 mmol, 76%), was analogously prepared from (*tert*-butyldimethylsiloxy)-3-pyridinylacetonitrile (0.52 g, 2.10 mmol, 1.05 equiv), LiHMDS (3.00 mL, 1.00 M, 3.00 mmol, 1.50 equiv), and 3-*tert*-butyl-4-methoxy-3-cyclobutene-1,2-dione (0.34 g, 2.00 mmol, 1.00 equiv): TLC (alumina, 20% EtOAc in hexane, $R_f = 0.36$); chromatographic purification (flash column, silica gel, 2 × 15 mm, (1) 200 mL 5% Et_3N in hexane to treat silica gel, (2) 10% EtOAc in hexane + 1% Et_3N); mp 116.0−118.0 °C; IR (CH_2Cl_2, KCl, cm^{-1}) 1707 (s), 1630 (m), 1540 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.08 (br s, 1 H), 8.56 (br d, $J = 4.2$ Hz, 1 H), 8.08 (dt, $J = 8.1$, 1.8 Hz, 1 H), 7.33 (dd, $J = 8.1$, 4.8 Hz, 1 H), 3.84 (s, 3 H), 1.42 (s, 9 H), 0.89 (s, 9 H), −0.15 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.3, 161.6, 149.8, 149.3, 144.2, 134.9, 133.0, 127.4, 123.8, 123.1, 61.2, 35.8, 30.1, 25.7, 18.0, −4.8. Anal. Calcd for $C_{21}H_{31}NO_4Si$: C, 64.75; H, 8.02; N, 3.60; O, 16.43; Si, 7.21. Found: C, 64.62; H, 8.03; N, 3.68.

5-Acetoxy-3-(*tert*-butyl)-4-methoxy-6-phenyl-2-pyrone, 2h. 5-Acetoxy-3-(*tert*-butyl)-4-methoxy-6-phenyl-2-pyrone, a white solid (0.494 g, 1.56 mmol, 78%), was analogously prepared from (*tert*-butyldimethylsiloxy)phenylacetonitrile (0.55 g, 2.20 mmol, 1.10 equiv), LiHMDS (3.00 mL, 1.00 M, 3.00 mmol, 1.50 equiv), and 3-*tert*-butyl-4-methoxy-3-cyclobutene-1,2-dione (0.34 g, 2.00 mmol, 1.00 equiv) with the following modification: The crude product was treated in THF with acetic anhydride (0.31 g, 3.04 mmol, 1.52 equiv) and TBAF (0.55 g, 3.04 mmol, 1.05 equiv) for 30 min. After the usual workup, flash chromatography, and recrystallization from CH_2Cl_2/hexane, the product was obtained: TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.12$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 15% EtOAc in hexane); mp 110.5−111.8 °C (methylene chloride/hexane); IR (CH_2Cl_2, KCl, cm^{-1}) 1780 (s), 1717 (s), 1643 (m); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73−7.70 (m, 2 H), 7.39−7.35 (m, 3 H), 3.77 (s, 3 H), 2.20 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 167.5, 162.1, 161.4, 149.8, 130.2, 129.2, 128.4, 127.9, 127.1, 122.6, 61.5, 35.7, 29.7, 20.3. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; O, 25.29. Found: C, 68.20; H, 6.39.

5-Acetoxy 3-(*n*-butyl)-4-(dimethylamino)-6-(1-methyl-3-indolyl)-2-pyrone, 2i. $CeCl_3 \cdot 7H_2O$ (1.27 g, 3.400 mmol, 1.70 equiv) was dried on the vacuum pump at 150−155 °C for 2 h and cooled to room temperature, and then anhydrous THF (5 mL) was added. After stirring for 1 h under nitrogen at room temperature, the slurry was cooled to −78 °C. A THF solution of LiHMDS (3.00 mL, 1.00 M, 3.00 mmol, 1.50 equiv) was added to a flask charged with (*tert*-butyldimethylsiloxy)(1-methyl-3-indolyl)acetonitrile (0.90 g, 3.00 mmol, 1.50 equiv) in 5 mL of THF at −78 °C under nitrogen. The mixture was stirred at −78 °C for 20 min and then transferred via cannula into the cold slurry of $CeCl_3$ in THF made above. After stirring for 20 min, the cerium reagent was transferred to a solution of 3-*n*-butyl-4-(*N*,*N*-dimethylamino)-3-cyclobutene-1,2-dione (0.36 g, 2.00 mmol, 1.00 equiv) in 5 mL of THF, which was precooled to −78 °C, and the reaction mixture was stirred for 1 h at −78 °C. TMEDA (0.395 g, 3.40 mmol, 1.70 equiv) was added and stirring was continued for 20 min. The reaction mixture was then quenched with 10 mL of saturated $NaHCO_3$, and the usual workup was carried out. The crude product was treated in THF for 30 min with acetic anhydride (0.41 g, 4.00 mmol, 2.00 equiv) and TBAF (0.784 g, 3.00 mmol, 1.50 equiv). 5-Acetoxy-3-(*n*-butyl)-4-(*N*,*N*-dimethylamino)-6-(1-methyl-3-indolyl)-2-pyrone was isolated as a yellow foam (0.435 g, 1.14 mmol, 57%) after the usual workup and flash chromatography: TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.31$); chromatographic purification (flash column, silica gel, 2 × 15 mm, (1) 30% EtOAc in hexane + 1% Et_3N, (2) 50% EtOAc in hexane + 1% Et_3N); IR (CH_2Cl_2, KCl, cm^{-1}): 1772 (s), 1733 (m), 1686 (s), 1627 (s), 1543 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 (dd, $J = 6.6$, 1.8 Hz, 1 H), 7.51 (s, 1 H), 7.29−7.18 (m, 3 H), 3.73 (s, 3 H), 2.91 (s, 6 H), 2.53 (t, $J = 7.5$ Hz, 2 H), 2.15 (s, 3 H), 1.55 (br pent, $J = 7.2$ Hz, 2 H), 1.42 (pent, $J = 7.2$ Hz, 2 H), 0.95 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 168.0, 164.1, 156.6, 148.2, 136.7, 130.7, 126.6, 124.9, 122.5, 122.0, 120.9, 110.5, 109.5, 105.6, 42.5, 33.1, 30.8, 26.9, 22.8, 20.5, 13.9. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32; O, 16.73. Found: C, 68.89; H, 6.97; N, 7.25.

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