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Experimental and Theoretical Investigation of the Synchronicity of Ambident Silyloxypyrone-Based (5 + 2) Cycloadditions

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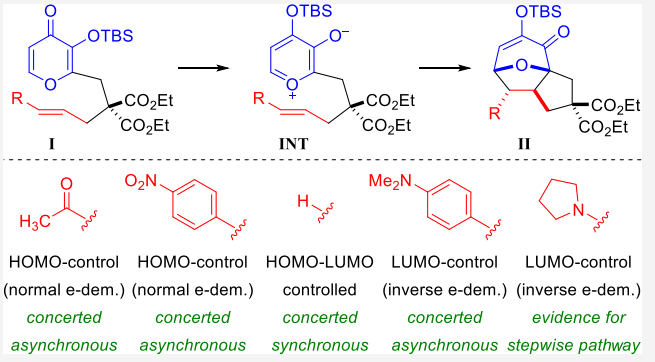
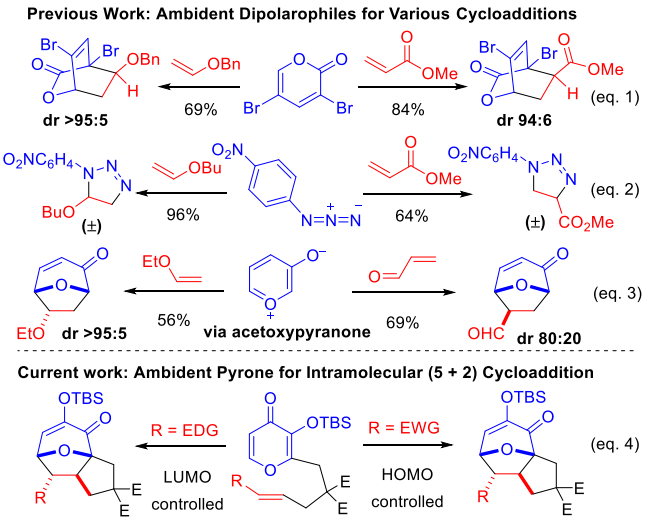
ABSTRACT: The reaction pathway of silyloxypyrone-based (5 + 2) cycloadditions was determined to be extremely dependent on the nature of the dipolarophile. Neutral alkenes were the least reactive, whereas both electron-deficient and electron-rich dipolarophiles were more reactive, thus providing evidence for ambident oxidopyrylium intermediates. Qualitative rate studies, Hammett linear free energy relationships, and theoretical calculations combined to provide evidence for a spectrum of reactivity that passes through the borderlands of concerted and stepwise.



INTRODUCTION

In contrast to extensively studied Diels−Alder[1] and Huisgen[2] cycloadditions, oxidopyrylium-based (5 + 2) cycloadditions[3] are less understood. However, these reactions are very useful toward the total synthesis of natural products[4] and other applications.[5] The generally accepted silyloxypyrone-based mechanism[6] involves silyl transfer to form an oxidopyrylium followed by concerted cycloaddition to give bridged, polycyclic ethers. Though many cycloadditions are assumed to be either synchronous or asynchronous but concerted,[7] evidence in support of stepwise pathways within Diels−Alder reactions[8] and 1,3-dipolar cycloadditions[2,9] has been reported. It should be noted that Domingo has extensively discussed cycloaddition reactions from an alternative perspective.[10] In addition, ambident dienes[11] that undergo Diels−Alder cycloaddition with both electron-rich and electron-deficient dienophiles (Scheme 1, eq 1) and dipolarophiles that display similar phenomena in 1,3-dipolar cycloadditions[12] have been described (Scheme 1, eq 2). Limited precedence for ambident reactivity of oxidopyrylium intermediates derived from acetoxypyranones[13] is also known (Scheme 1, eq 3), and a stepwise hetero-(5 + 2) cycloaddition between oxidopyrylium ylides and imines was recently reported.[14] Herein, we report evidence for ambident silyloxypyrone-based cycloadditions[3c,15] (Scheme 1, eq 4) supported by qualitative rate studies, Hammett linear free energy relationship (LFER) studies,[16] and theoretical calculations,[17] revealing a spectrum of reactivity that passes through the borderlands of concerted and stepwise.[18]

Scheme 1. Ambident Dipolarophiles in Cycloadditions



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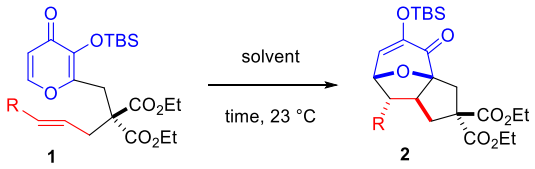
RESULTS AND DISCUSSION

Initial qualitative rate studies were obtained with substrates **1a–c** and excellent mass recovery was observed (Table 1).[19]

Table 1. Qualitative Rate Comparison of Various Dipolarophiles in Silyloxypyrone-Based (5 + 2) Cycloadditions



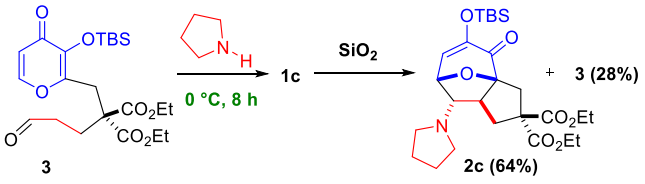
entry	R (1)	solvent	time (h)	% yield (2)[a]
1	C(O)Me (**1a**)	toluene	96	40 (**2a**)[b]
2	H (**1b**)	toluene	96	ND (**2b**)[c]
3	$(CH_2)_4N$ (**1c**)	tol-d_8	3	77 (**2c**)
4	$(CH_2)_4N$ (**1c**)	CD_3CN	3	78 (**2c**)
5	$(CH_2)_4N$ (**1c**)	THF-d_8	3	55 (**2c**)
6	$(CH_2)_4N$ (**1c**)	CD_2Cl_2	3	95 (**2c**)

[a]Determined by ^{1}H NMR analysis.[19] [b]45% recovered enone **1a**. [c]Not detected.

Electron-withdrawing enone **1a** reacted at room temperature, albeit quite slowly (entry 1). Olefin **1b** afforded no reaction at ambient temperature (entry 2) instead requiring heat to achieve conversion.[15c] Enamine **1c** gave substantial conversion at 23 °C to adduct **2c** after only 3 h in tol-d_8 (entry 3) and CD_3CN (entry 4) but was more efficient in CD_2Cl_2 (entry 6). Silyloxypyrone-based (5 + 2) cycloadditions generally require overcoming significant energy barriers via heating,[3c] thus further exploration was undertaken.

In order to test the limits of this enamine-based (5 + 2) cycloaddition below ambient temperature, unique parameters were necessary (Scheme 2). If a cycloaddition proceeds at

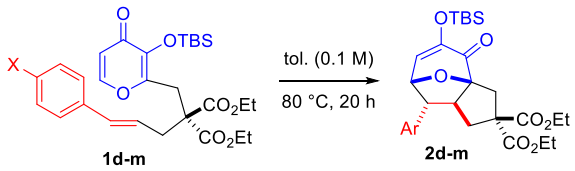
Scheme 2. Low-Temperature Silyloxypyrone-enamine (5 + 2) Cycloaddition



room temperature, then the substrate is likely to continue reacting upon isolation and purification thus skewing the results. Fortunately, in situ generation of enamine **1c** from aldehyde **3** can be reversed simply by passing the reaction mixture over silica gel. As such, enamine **1c** was generated at 0 °C which afforded substantial quantity of cycloadduct **2c** (64% yield), and aldehyde **3** (28% yield) was recovered upon direct column chromatography of the reaction mixture. A control reaction, which entailed quenching the reaction immediately upon addition of pyrrolidine, gave quantitative recovery of aldehyde **3**, indicating that the column does not affect the reaction.[19] To the best of our knowledge, this is the first silyloxypyrone-alkene (5 + 2) cycloaddition to proceed below room temperature.

LFER studies (i.e., Hammett plots) typically provide a straightforward method to gain information about a reaction pathway.[16,20] A graphical plot of σ (substituent constant) vs $\log[k/k_0]$ (or other correlation) often reveals a linear trend that lends credence to a proposed mechanism. In certain cases, however, a nonlinear plot may illuminate a subtle shift in mechanism.[21] To this end, we synthesized various styrene derivatives **1d–m** and subjected them to uniform conditions (Table 2). Electron-donating and electron-deficient substrates

Table 2. Linear Free–Energy Relationship of Styrenes



entry	X	% conv. (2)[a]	σ_p	log(rate/rate$_0$)
1	NMe_2	69.0 (**2d**)	−0.83	0.197
2	O*i*Pr	48.4 (**2e**)	−0.45	0.043
3	OMe	45.3 (**2f**)	−0.27	0.015
4	Me	44.3 (**2g**)	−0.17	0.005
5	H	43.8 (**2h**)	0.00	0.000
6	F	37.0 (**2i**)	0.06	−0.073
7	Cl	54.3 (**2j**)	0.23	0.093
8	CO_2Me	67.5 (**2k**)	0.39	0.188
9	CN	68.5 (**2l**)	0.66	0.194
10	NO_2	87.3 (**2m**)	0.78	0.300

[a]Determined by the average of two trials as measured by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

were more reactive than less polarized variants. 4-Dimethylaminostyrene 1d (entry 1) gave similar conversion as the electron-deficient ester-substituted **1k** (entry 8) and 4-cyano-substituted **1l** (entry 9), while the 4-nitrostyrene **1m** afforded 87% conversion (entry 10). However, less-polarized styrene derivatives such as phenyl **1h**, 4-fluoro **1i**, and 4-chloro **1j** were not as reactive (entries 5–7). When log rate/rate$_0$ was plotted against σ_p constants, a distinctly nonlinear Hammett plot was revealed (Figure 1). The nature of the plot reveals a shift in the reaction pathway with an inflection point near the phenyl **1h** (entry 5) and 4-fluorostyrene **1i** (entry 6). Indeed, when the trendlines are separated by general electronic trends, two distinctly linear Hammett plots are revealed. Thus, the negative slope (ρ) is indicative of acceleration of the rate by electron-donating groups, and the positive slope (ρ) is representative of acceleration of the rate by electron-withdrawing substituents.

A detailed computational study was undertaken to investigate the mechanism of the silyloxypyrone-based (5 + 2) cycloaddition. Initial conformational searches were carried out using xTB-CREST[22] and subsequent DFT calculations were carried out with Gaussian16.[23] The M06-2X functional with D3(0) dispersion correction[24] was used to locate stationary points, since this functional is known to perform well for main group thermochemistry and kinetic studies.[25] We employed a 6-31+G(d,p) basis set, and the SMD continuum solvation model for geometry optimizations.[26] The larger 6-311+G(2df,2p) basis set was used for computing single-point energies. Reported Gibbs free energies included thermal corrections from frequency calculations at the M06-2X-D3(0)/6-31+G(d,p) level, which was benchmarked with other functional/basis set combinations to confirm that qualitative conclusions did not change. In each case, silyl transfer was calculated to be fast and non-rate determining via

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J. Org. Chem. 2023, 88, 5972–5981

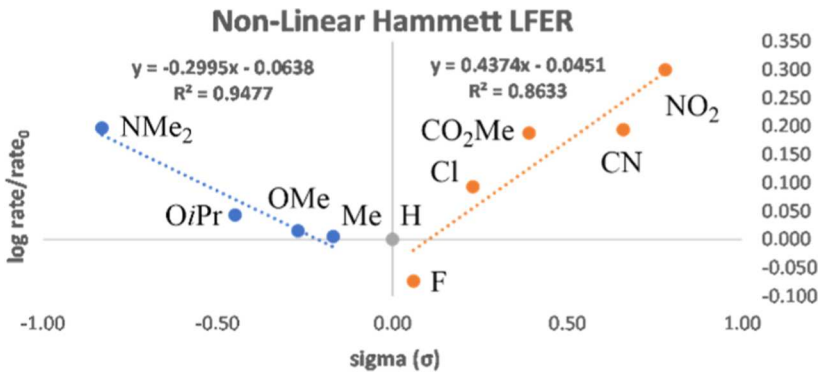


Figure 1. Hammett analysis: nonlinear trend.

a pentacoordinate species.[19] The overall barrier via rate-determining concerted asynchronous (5 + 2) cycloaddition for enone **1a** was predicted to be ~3 kcal/mol lower in energy than the corresponding synchronous concerted (5 + 2) cycloaddition for terminal alkene **1b** (Figure 2). This correlates

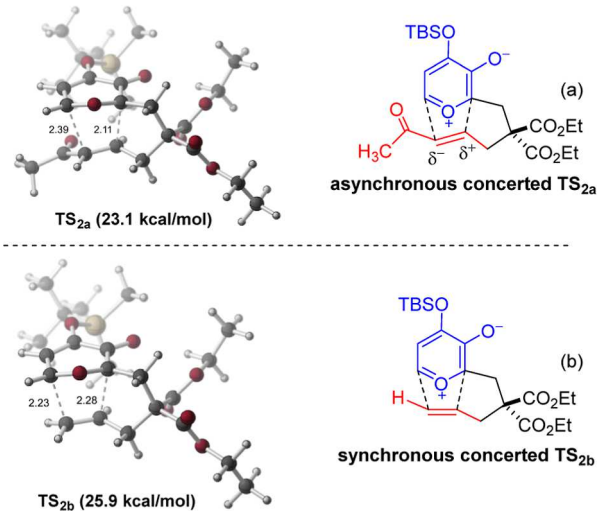


Figure 2. (a) Asynchronous enone; (b) synchronous terminal alkene.

to experimental results in which the more electrophilic enone **1a** was found to be more reactive than terminal olefin **1b** (cf. Table 1, entries 1−2). In contrast, the preferred pathway for enamine **1c** was predicted to be stepwise (Figure 3). The transition structure for the formation of the initial C−C bond ($\mathbf{TS}_{2c}$) en route to $\mathbf{INT}_{2c}$ was found to be rate limiting, and the subsequent transition structure ($\mathbf{TS}_{3c}$) was predicted to be slightly lower in energy. Exchanging the simple alkene for an enamine provides a species that is quite nucleophilic, affording an avenue for delocalization of cationic character that results from initial nucleophilic attack (i.e., iminium $\mathbf{INT}_{2c}$). Enone **1a** is apparently not electrophilic enough to promote formation of an analogous stepwise process with an anionic intermediate, but $\mathbf{TS}_{2a}$ reveals a significantly more asynchronous process as compared to $\mathbf{TS}_{2b}$ (Figure 2), suggesting that anion stabilization is occurring to some extent. It should be noted that a concerted pathway was located for enamine **1c**, but it was predicted to have a barrier that is 12.7 kcal/mol higher than that via $\mathbf{TS}_{2c}$. In addition, we were unable to locate a transition structure for nucleophilic attack of the enamine on the pyrone prior to silyl transfer. Overall, the stepwise conversion of enamine **1c** to cycloadduct **2c** was calculated

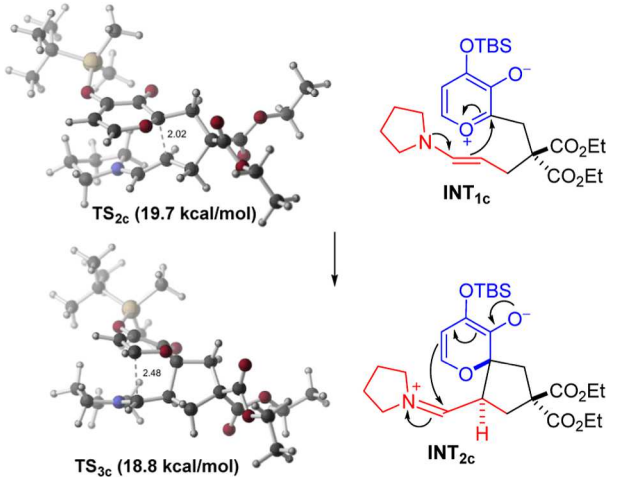
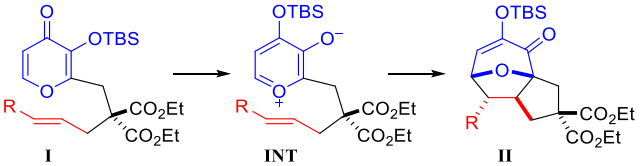


Figure 3. Transition structures of stepwise enamine.

to have the lowest energy barrier of the three substrates, consistent with the experimentally observed reactivity (cf. Table 1).

Frontier molecular orbital (FMO) calculations[2,17c,27] lend further credence to the ambident nature of these systems (Table 3). Cycloaddition of enone **1a** is controlled by the highest occupied molecular orbital (HOMO) of the oxidopyrylium (entry 1), whereas cycloaddition of enamine **1c** is controlled by the lowest unoccupied molecular orbital

Table 3. Summary of HOMO−LUMO Interactions



entry	R(1): FMO control[a]	pyrylium (eV)[b]	alkene (eV)[b]	D (eV)
1	C(O)Me(**1a**):HOMO	−6.53	−0.13	6.40
2	C(O)Me(**1a**):LUMO	−0.66	−8.60	7.94
3	H(**1b**):HOMO	−6.54	+1.64	8.18
4	H(**1b**):LUMO	−0.63	−8.40	7.77
5	$(CH_2)_4$N(**1c**):HOMO	−6.51	+2.50	9.01
6	$(CH_2)_4$N(**1c**):LUMO	−0.58	−6.04	5.46

[a]With respect to the oxidopyrylium. [b]The orbitals are visualized and computed by Multiwfn[28] based on the Kohn−Sham orbitals from SMD(toluene)/M06-2X/6-31G(d) level of theory.

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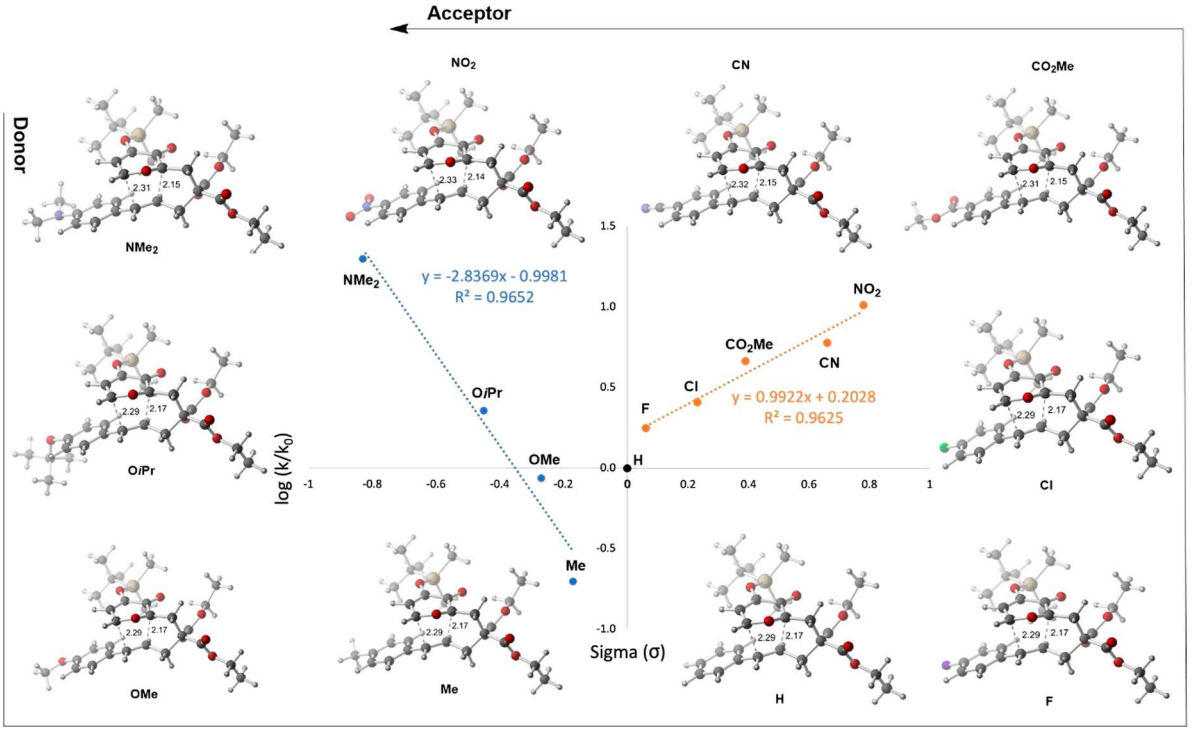

Figure 4. LFER graph given by computational study. The left regression trendline (in blue) derives from the points representing NMe_2, O*i*Pr, OMe, and Me substituents. The right regression trendline (in orange) derives from the points representing F, Cl, CO_2Me, CN, and NO_2 substituents. 3D structures are visualized by CYLView.[29] Critical TS bond lengths are labeled in angstrom.

(LUMO) of the oxidopyrylium (entry 6).[19] Although cycloaddition of the terminal alkene **1b** can be controlled by either the HOMO or LUMO of the oxidopyrylium, both pathways (entries 3−4) are less favorable than enone **1a** and enamine **1c**, thus requiring elevated temperature (cf. Table 1).

Concerted but asynchronous (5 + 2) cycloaddition TSs were found for oxidopyrylium intermediates derived from **1d−m**, and the plot of computationally predicted free energy barriers vs substituent constants (σ_p) is also nonlinear (Figure 4). Strong electron donors and electron acceptors are predicted to activate the styrene toward cycloaddition as more advanced formation of the internal C−C bond correlates with reduced energy barriers.[19] It is important to note, however, that the magnitudes of the experimentally observed and computed effects (i.e., ρ values) are significantly different. This discrepancy could be the result of the fact that conversions rather than kinetics were used experimentally and/or that computations of the type used here do not account for explicit solvent effects and are not expected to be accurate to small fractions of a kcal/mol. We emphasize, however, that the key point is that both the experimental (Figure 1) and computed (Figure 4) plots are observed to be V-shaped.

■ CONCLUSIONS

Silyloxypyrone-based (5 + 2) cycloadditions were subjected to a variety of experiments to elucidate the reaction pathway. Utilizing qualitative rate comparisons, Hammett plots, and theoretical calculations, a comprehensive picture has emerged, illuminating unique mechanisms that are dependent on the electronic nature of the alkene. Of the three initially investigated dipolarophiles that probed the extremes of the borderlands, the terminal olefin is the closest to a concerted synchronous reaction. In the case of the enone, formation of a new C−C bond at the electrophilic β-position is more advanced in the transition state, thus the cycloaddition is concerted but asynchronous, representing a normal electron demand (5 + 2) cycloaddition controlled by the HOMO of the oxidopyrylium. The enamine, however, represents a unique stepwise mechanism that passes beyond the border of asynchronous, resembling an inverse electron demand (5 + 2) cycloaddition that is controlled by the LUMO of the oxidopyrylium. Based on conversion to cycloadduct at 0 °C and the theoretical calculations, this seems to be unprecedented for silyloxypyrone-based (5 + 2) cycloadditions. Styrenes were probed to investigate the internal portion of this spectrum of reactivity, utilizing experimental and theoretical LFERs. Less polarized styrenes were the closest to concerted synchronous, whereas both electron-rich and electron-deficient variants displayed more advanced internal C−C bond formation. A coherent understanding of the reactivity of silyloxypyrones has come into focus, thus providing new opportunities for discovery that will be reported in due course.

■ EXPERIMENTAL SECTION

All reactions were performed under an Ar atmosphere in oven-dried or flame-dried glassware. When heat was applied, an oil bath was utilized. All other commercially available anhydrous solvents and reagents were used as received. Sodium hydride (NaH) was a 60% dispersion in mineral oil. Thin-layer chromatography was performed with glass or aluminum plates (silica gel F_{254}, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with potassium permanganate. Flash column chromatography (FCC) was performed with silica gel 60A 40−63 μm (200−400 mesh). Mass spectral data were acquired using positive-mode electrospray ionization (ESI^+) and a high-resolution time-of-flight mass spectrometer. ^1H NMR spectra were acquired at 400 or 500 MHz and $^{13}C\{^1H\}$ NMR spectra were acquired at 100 or 125 MHz as

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noted. Chemical shifts are reported in ppm (δ) relative to the residual $CHCl_3$ (7.26) for ^1H NMR and the $CDCl_3$ shift (77.16 ppm) for $^{13}C\{^1H\}$ NMR. ^1H NMR coupling constants (J) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), ddt (doublet of doublet of triplets), dq (doublet of quartets), qq (quartet of quartets), ovlp (overlapping), br (broad), and app (apparent). Based on the intensity in the $^{13}C\{^1H\}$ spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses.

Enone Pyrone 1a. A solution of terminal alkene **1b** (592 mg, 1.35 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL, 0.09 M) was degassed for 10 min via streaming Ar. Methyl vinyl ketone (553 μL, 6.76 mmol, 5.0 equiv) and Grubbs–Hoveyda 2nd generation (GH II) catalyst (85 mg, 0.135 mmol, 0.1 equiv) were added sequentially, and the reaction was degassed with Ar for an additional 10 min. Upon stirring for 24 h at 23 °C, the reaction was concentrated. Purification by FCC (CH_2Cl_2/Et_2O 95:5) delivered enone **1a** as a dark oil (393 mg, 0.818 mmol, 61%): R_f = 0.07 (CH_2Cl_2/Et_2O 95:5); ^1H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 5.6 Hz, 1H), 6.69 (dt, J = 15.9, 7.6 Hz, 1H), 6.31 (d, J = 5.6 Hz, 1H), 6.03 (dt, J = 15.9, 1.2 Hz, 1H), 4.22 (ovlp q, J = 7.1 Hz, 4H), 3.47 (s, 2H), 2.75 (dd, J = 7.6, 1.2 Hz, 2H), 2.20 (s, 3H), 1.26 (t, J = 7.1 Hz, 6H), 0.98 (s, 9H), and 0.27 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 197.7, 173.9, 169.6(2), 152.9, 152.5, 144.3, 141.2, 134.7, 115.8, 62.1(2), 56.5, 36.4, 31.4, 26.9, 26.0(3), 18.8, 14.0(2), and −3.7(2); ESI-HRMS calcd for $C_{24}H_{36}O_8SiNa$ [M + Na]$^+$, 503.2077; found, 503.2063.

Terminal Alkene Pyrone 1b. Prepared according to a previous report[30] with consistent spectral data: ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J = 5.5 Hz, 1H), 6.29 (d, J = 5.5 Hz, 1H), 5.74 (ddt, J = 16.9, 10.3, 7.4 Hz, 1H), 5.10–5.04 (m, 2H), 4.21 (ovlp q, J = 7.1 Hz, 4H), 3.45 (s, 2H), 2.62 (dt, J = 7.4, 1.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H), 0.98 (s, 9H), and 0.27 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.2(2), 153.5, 152.7, 144.2, 132.5, 119.5, 115.8, 61.7(2), 57.0, 37.9, 31.0, 26.2(3), 19.0, 14.1(2), and −3.5(2).

Enamine Pyrone 1c. Aldehyde **S1** was prepared according to a previous report[15b] with consistent spectral data: ^1H NMR (500 MHz, $CDCl_3$): δ 9.69 (app s, 1H), 7.51 (d, J = 5.6 Hz, 1H), 6.30 (d, J = 5.6 Hz, 1H), 4.24–4.19 (m, 4H), 3.46 (s, 2H), 2.52 (app t, J = 7.7 Hz, 2H), 2.16 (t, J = 7.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H), 0.99 (s, 9H), and 0.27 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 200.2, 174.0, 170.2(2), 153.0, 152.7, 144.3, 115.8, 62.0(2), 55.9, 39.3, 31.5, 26.2(3), 25.2, 18.9, 14.1(2), and −3.5(2). Enamine **1c** was not characterized since it was generated in situ.

General Procedure[31] A for Synthesis of Styrene Pyrone 1d. To a solution of 4-dimethylamino styrenyl acetate **S1d** (1.6 g, 7.30 mmol, 1.0 equiv) in THF (50 mL, 0.15 M) were added KOAc (72 mg, 0.73 mmol, 0.1 equiv), bis(trimethylsilyl)acetamide (2.7 mL, 10.95 mmol, 1.5 equiv), and diethyl malonate (990 μL, 6.57 mmol, 2.0 equiv), and the solution was stirred until homogeneous (~10 min). In a separate flask, the catalyst was prepared by dissolving triphenylphosphine (957 mg, 3.65 mmol, 0.5 equiv) and $Pd_2(dba)_3$ (534 mg, 0.365 mmol, 0.05 equiv) in THF (10 mL) and stirred for 5 min. This catalyst solution was added to the previously prepared mixture and sparged with Ar for 10 min, and the resulting solution was heated to 70 °C and stirred for 4.5 h. The reaction was quenched slowly with H_2O (50 mL), extracted with Et_2O (3 × 75 mL), and separated. The combined organic extracts were washed with sat. aq NaCl, dried with Na_2SO_4, filtered, and concentrated. Purification by FCC (hexanes/EtOAc 90:10) afforded the cinnamyl diester (not shown). To a solution of this cinnamyl diester (750 mg, 2.35 mmol, 1.0 equiv) in THF (15 mL, 0.16 M) was added NaH (188 mg, 4.70 mmol, 2.0 equiv), and the solution was stirred for 15 min and then bromide **S2** (1.25 g, 2.82 mmol, 1.2 equiv) was added and stirred for an additional 1.5 h. The reaction was quenched slowly with H_2O (25 mL), extracted with Et_2O (3 × 50 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (25 mL), dried with Na_2SO_4, filtered, and concentrated. Purification by consecutive FCC (CH_2Cl_2/Et_2O 95:5; hexanes/EtOAc 70:30) afforded *tert*-butyldiphenylsilyl (TBDPS)-pyrone styrene **S3d** as a brown oil (278 mg, 0.408 mmol, 17% 2-step yield). A solution of **S3d** (140 mg, 0.205 mmol, 1.0 equiv) in THF (3 mL, 0.08 M) was added tetra-n-butylammonium fluoride (TBAF, 270 μL, 0.267 mmol, 1.2 equiv) at 23 °C and stirred for 1 h. The reaction was quenched slowly with sat. aq NH_4Cl (5 mL), diluted with Et_2O (20 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (5 mL), dried with $MgSO_4$, filtered, and concentrated. To a solution of crude enol in CH_2Cl_2 (3 mL) were added imidazole (45 mg, 0.656 mmol, 3.2 equiv) and *tert*-butyldimethylsilyl chloride (TBSCl, 128 mg, 0.615 mmol, 3.0 equiv) at 23 °C and stirred 24 h. The reaction was quenched slowly with H_2O (10 mL), diluted with CH_2Cl_2 (10 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (10 mL), dried with $MgSO_4$, filtered, and concentrated. Purification by FCC (hexanes/EtOAc 70:30) afforded TBS styrene pyrone **1d** as a brown oil (44 mg, 0.079 mmol, 39% 2-step yield): R_f = 0.33 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 5.6 Hz, 1H), 7.17 (app d, J = 8.8 Hz, 2H), 6.62 (app d, J = 8.8 Hz, 2H), 6.30 (d, J = 5.6 Hz, 1H), 6.29 (app d, J = 15.5 Hz, 1H), 5.87 (dt, J = 15.5, 7.8 Hz, 1H), 4.25–4.15 (m, 4H), 3.49 (s, 2H), 2.94 (s, 6H), 2.75 (dd, J = 7.8, 1.0 Hz, 2H), 1.24 (t, J = 7.2 Hz, 6H), 0.95 (s, 9H), and 0.25 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.1, 170.4(2), 153.8, 152.9, 150.2, 144.2, 134.6, 127.4(2), 125.8, 118.9, 115.8, 112.5(2), 61.8(2), 57.4, 40.7(2), 37.4, 31.0, 26.1(3), 18.9, 14.2(2), and −3.5(2); ESI-HRMS calcd for $C_{30}H_{43}NO_7SiNa$ [M + Na]$^+$, 580.2706; found, 580.2690.

General Procedure A for Synthesis of Styrene Pyrone 1e. To a solution of 4-isopropyl styrenyl acetate **S1e** (1.5 g, 6.20 mmol, 1.0 equiv) in THF (20 mL, 0.3 M) were added KOAc (61 mg, 0.620 mmol, 0.1 equiv), bis(trimethylsilyl)acetamide (2.3 mL, 9.30 mmol, 1.5 equiv), and diethyl malonate (897 μL, 5.90 mmol, 1.0 equiv), and the solution was stirred until homogeneous (~10 min). In a separate flask, the catalyst was prepared by dissolving triphenylphosphine (813 mg, 3.10 mmol, 0.5 equiv) and $Pd_2(dba)_3$ (284 mg, 0.310 mmol, 0.05 equiv) in THF (10 mL) and stirred for 5 min. This catalyst solution was added to the previously prepared mixture and sparged with Ar for 10 min, and the resulting solution was heated to 70 °C and stirred for 3 h. The reaction was quenched slowly with H_2O (50 mL), extracted with Et_2O (3 × 50 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (100 mL), dried with $MgSO_4$, filtered, and concentrated. Purification by FCC (hexanes/EtOAc 95:5) afforded the cinnamyl diester (not shown). To a solution of this cinnamyl diester (500 mg, 1.50 mmol, 1.0 equiv) in THF (15 mL, 0.1 M) was added NaH (120 mg, 3.00 mmol, 2.0 equiv), and the solution was stirred for 15 min and then bromide **S2** (798 mg, 1.78 mmol, 1.2 equiv) was added and stirred for an additional 1.5 h. The reaction was quenched slowly with H_2O (20 mL), extracted with Et_2O (3 × 20 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (75 mL), dried with $MgSO_4$, filtered, and concentrated. Purification by FCC (hexanes/EtOAc 80:20) afforded TBDPS-pyrone styrene **S3e** as a white foam (571 mg, 0.819 mmol, 20%, 2-step yield). To a solution of **S3e** (100 mg, 0.143 mmol, 1.0 equiv) in THF (1.5 mL, 0.1 M) was added TBAF (180 μL, 0.180 mmol, 1.3 equiv) at 23 °C and stirred for 1 h. The reaction was quenched slowly with H_2O (5 mL), diluted with Et_2O (10 mL), and separated. The combined organic extracts were washed with sat. aq NaCl (10 mL), dried with $MgSO_4$, filtered, and concentrated. To a solution of crude enol in CH_2Cl_2 (1.5 mL) were added imidazole (29 mg, 0.426 mmol, 3.0 equiv) and TBSCl (63 mg, 0.418 mmol, 3.0 equiv) at 23 °C and stirred for 3 h. The reaction was quenched slowly with H_2O (2 mL) and extracted into CH_2Cl_2 (3 × 2 mL). The combined organic extracts were washed with sat. aq NaCl (5 mL), dried with Na_2SO_4, filtered, and concentrated. Purification by FCC (hexanes/EtOAc 80:20 to 70:30) afforded TBS styrene pyrone **1e** as a clear oil (105 mg, 0.183 mmol, 50% 2-step yield): R_f = 0.46 (hexanes/EtOAc 60:40); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 5.5 Hz, 1H), 7.19 (app d, J = 8.7 Hz, 2H), 6.78 (app d, J = 8.7 Hz, 2H), 6.30 (app d, J = 15.8 Hz, 1H), 6.30 (d, J = 5.5 Hz, 1H), 5.93 (dt, J = 15.8, 7.6 Hz, 1H), 4.52 (sept, J = 6.1 Hz, 1H), 4.25–4.17 (m, 4H), 3.49 (s,

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J. Org. Chem. 2023, 88, 5972–5981

2H), 2.75 (dd, J = 7.6, 1.0 Hz, 2H), 1.32 (d, J = 6.1 Hz, 6H), 1.24 (t, J = 7.1 Hz, 6H), 0.92 (s, 9H), and 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.1, 170.3(2), 157.6, 153.6, 152.9, 144.2, 134.1, 129.7, 127.6(2), 121.0, 116.0(2), 115.8, 70.0, 61.8(2), 57.1, 37.2, 30.9, 26.1(3), 22.1(2), 18.9, 14.2(2), and −3.6(2); ESI-HRMS calcd for $C_{31}H_{44}O_8SiNa$ $[M + Na]^+$, 595.2703; found, 595.2675.

General Procedure B for Synthesis of Styrene Pyrones 1f−j. To a solution of malonate **S4** in THF (0.1 M) was added NaH (2 equiv) at 23 °C and stirred for 15 min. Then, a solution of cinnamyl bromide **S1f−j** (2−3 equiv) in THF (0.1 M) was added and stirred for 1.5 h. The reaction was quenched slowly with sat. aq NH_4Cl, diluted with Et_2O, and separated. The combined organic extracts were washed with sat. aq NaCl, dried with $MgSO_4$, filtered, and concentrated. Purification by FCC afforded TBDPS-pyrone styrenes **S3f−j**. To a solution of **S3f−j** in THF (0.1 M) was added TBAF (1.2 equiv) at 23 °C and stirred for 1 h. The reaction was quenched slowly with sat. aq NH_4Cl, diluted with Et_2O, and separated. The combined organic extracts were washed with sat. aq NaCl, dried with $MgSO_4$, filtered, and concentrated. Purification by FCC afforded the corresponding enol. To a solution of enol in CH_2Cl_2 (0.1 M) were added imidazole (1.6 equiv) and TBSCl (1.5 equiv) at 23 °C and stirred for 1 h. The reaction was quenched slowly with sat. aq NH_4Cl, diluted with CH_2Cl_2, and separated. The combined organic extracts were washed with sat. aq NaCl, dried with $MgSO_4$, filtered, and concentrated.

Styrene 1f. FCC (hexanes/EtOAc 80:20) afforded a colorless oil (263 mg, 0.485 mmol, 53% 2-step yield): R_f = 0.46 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 5.6 Hz, 1H), 7.22 (app d, J = 8.7 Hz, 2H), 6.80 (app d, J = 8.7 Hz, 2H), 6.31 (app d, J = 15.4 Hz, 1H), 6.30 (d, J = 5.6 Hz, 1H), 5.94 (dt, J = 15.4, 7.6 Hz, 1H), 4.24−4.18 (m, 4H), 3.80 (s, 3H), 3.50 (s, 2H), 2.75 (dd, J = 7.6, 1.1 Hz, 2H), 1.24 (t, J = 7.2 Hz, 6H), 0.93 (s, 9H), and 0.25 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.1, 170.3(2), 159.3, 153.6, 152.9, 144.2, 134.0, 129.9, 127.6(2), 121.2, 115.8, 113.9(2), 61.8(2), 57.1, 55.4, 37.2, 31.0, 26.1(3), 18.9, 14.2(2), and −3.6(2); ESI-HRMS calcd for $C_{29}H_{40}O_8SiNa$ $[M + Na]^+$, 567.2390; found, 567.2387.

Styrene Pyrone 1g. FCC (hexanes/EtOAc 70:30) afforded a colorless oil (317 mg, 0.168 mmol, 78% 2-step yield): R_f = 0.43 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 5.6 Hz, 1H), 7.18 (app d, J = 8.2 Hz, 2H), 7.07 (app d, J = 8.2 Hz, 2H), 6.34 (app d, J = 15.5 Hz, 1H), 6.30 (d, J = 5.6, 1H), 6.04 (dt, J = 15.5, 7.6 Hz, 1H), 4.24−4.17 (m, 4H), 3.50 (s, 2H), 2.76 (dd, J = 7.6, 1.2 Hz, 2H), 2.32 (s, 3H), 1.24 (t, J = 7.1 Hz, 6H), 0.94 (s, 9H), and 0.25 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.2(2), 153.5, 152.8, 144.1, 137.2, 134.4, 134.2, 129.1(2), 126.3(2), 122.3, 115.7, 61.7(2), 57.1, 37.1, 30.9, 26.0(3), 21.2, 18.8, 14.1(2), and −3.7(2); ESI-HRMS calcd for $C_{29}H_{40}O_7SiNa$ $[M + Na]^+$, 551.2441; found, 551.2418.

Styrene Pyrone 1h. Prepared previously as a colorless oil (1.50 g, 2.91 mmol, 87% yield) with the following spectral data:[15c] ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 5.6 Hz, 1H), 7.30−7.20 (m, 5H), 6.37 (dt, J = 15.7, 1.2 Hz, 1H), 6.31 (d, J = 5.6 Hz, 1H), 6.10 (dt, J = 15.7, 7.6 Hz, 1H), 4.22 (ovlp q, J = 7.1 Hz, 4H), 3.50 (s, 2H), 2.77 (dd, J = 7.6, 1.2 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H), 0.92 (s, 9H), and 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.1, 170.3(2), 153.5, 152.9, 144.2, 137.0, 134.6, 128.5(2), 127.6, 126.4(2), 123.5, 115.8, 61.8(2), 57.1, 37.1, 31.0, 26.0(3), 18.9, 14.2(2), and −3.6(2).

Styrene Pyrone 1i. FCC (hexanes/EtOAc 70:30) afforded a colorless amorphous solid (296 mg, 0.536 mmol, 36% 2-step yield): R_f = 0.36 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 5.5 Hz, 1H), 7.24 (app dd, J = 8.8, 5.5 Hz, 2H), 6.95 (app t, J = 8.8 Hz, 2H), 6.31 (app d, J = 15.8 Hz, 1H), 6.30 (d, J = 5.5 Hz, 1H), 6.00 (dt, J = 15.8, 7.6 Hz, 1H), 4.24−4.19 (m, 4H), 3.50 (s, 2H), 2.75 (dd, J = 7.6, 1.0 Hz, 2H), 1.25 (t, J = 7.2 Hz, 6H), 0.92 (s, 9H), and 0.24 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.2(2), 162.4 (d, J = 247.0 Hz), 153.4, 152.9, 144.2, 133.3, 133.2 (d, J = 3.6 Hz), 127.9(2) (d, J = 8.2 Hz), 123.3 (d, J = 2.7 Hz), 115.8, 115.4(2) (d, J = 20.9 Hz), 61.8(2), 57.0, 37.0, 31.0, 26.0(3), 18.9, 14.1(2), and −3.6(2); ^{19}F NMR (470 MHz) −114.7 (tt, J = 8.6, 5.5 Hz); ESI-HRMS calcd for $C_{28}H_{37}FO_7SiNa$ $[M + Na]^+$, 555.2190; found, 571.2171.

Styrene Pyrone 1j. FCC (hexanes/EtOAc 70:30) afforded a yellow oil (238 mg, 0.131 mmol, 28% 2-step yield): R_f = 0.17 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 5.6 Hz, 1H), 7.24 (app d, J = 8.8 Hz, 2H), 7.20 (app d, J = 8.8 Hz, 2H), 6.31 (app d, J = 15.7 Hz, 1H), 6.30 (d, J = 5.6 Hz, 1H), 6.08 (dt, J = 15.7, 7.6 Hz, 1H), 4.22 (ovlp. q, J = 7.1 Hz, 4H), 3.50 (s, 2H), 2.75 (dd, J = 7.6, 1.2 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H), 0.93 (s, 9H), and 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.1(2), 153.3, 152.7, 144.2, 135.5, 133.2, 133.1, 128.6(2), 127.6(2), 124.4, 115.7, 61.8(2), 57.0, 37.0, 31.0, 26.0(3), 18.8, 14.1(2), and −3.7(2); ESI-HRMS calcd for $C_{28}H_{37}ClO_7SiNa$ $[M + Na]^+$, 571.1895; found, 571.1870.

General Procedure C for Synthesis of TBS-Pyrone Styrenes 1k−m. To a solution of malonate **S5** in THF (0.1 M) was added NaH (2 equiv) at 23 °C and stirred for 15 min. A solution of cinnamyl bromide **S1k−m** (2−3 equiv) in THF (0.1 M) was added and stirred for 1.5 h. The reaction was quenched slowly with sat. aq NH_4Cl, diluted with Et_2O, and separated. The combined organic extracts were washed with sat. aq NaCl, dried with $MgSO_4$, filtered, and concentrated.

Styrene Pyrone 1k. FCC (hexanes/EtOAc 70:30) afforded a yellow oil (483 mg, 0.843 mmol, 67%): R_f = 0.30 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (app d, J = 8.4 Hz, 2H), 7.54 (d, J = 5.6 Hz, 1H), 7.33 (app d, J = 8.4 Hz, 2H), 6.40 (app d, J = 15.7 Hz, 1H), 6.31 (d, J = 5.6 Hz, 1H), 6.23 (dt, J = 15.7, 7.5 Hz, 1H), 4.22 (q, J = 7.1 Hz, 4H), 3.81 (s, 3H), 3.51 (s, 2H), 2.78 (dd, J = 7.5, 1.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H), 0.82 (s, 9H), and 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.1(2), 166.8, 153.2, 152.9, 144.2, 141.3, 133.6, 129.8(2), 129.0, 126.6, 126.2(2), 115.8, 61.8(2), 56.9, 52.0, 37.0, 31.0, 26.0(3), 18.8, 14.1(2), and −3.7(2); ESI-HRMS calcd for $C_{30}H_{40}O_9SiNa$ $[M + Na]^+$, 595.2339; found, 595.2334.

Styrene Pyrone 1l. FCC (hexanes/EtOAc 70:30) afforded a yellow oil (141 mg, 0.261 mmol, 45%): R_f = 0.29 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (app d, J = 8.2 Hz, 2H), 7.54 (d, J = 6.0 Hz, 1H), 7.35 (app d, J = 8.2 Hz, 2H), 6.36 (app d, J = 15.6 Hz, 1H), 6.31 (d, J = 6.0 Hz, 1H), 6.25 (dt, J = 15.6, 7.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 4H), 3.50 (s, 2H), 2.78 (dd, J = 7.4, 1.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 6H), 0.91 (s, 9H), and 0.23 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.0(2), 153.1, 152.9, 144.2, 141.4, 132.9, 132.4(2), 128.1, 126.9(2), 119.0, 115.9, 110.9, 62.0(2), 56.8, 37.0, 31.1, 26.0(3), 18.8, 14.1(2), and −3.7(2); ESI-HRMS calcd for $C_{29}H_{37}NO_7SiNa$ $[M + Na]^+$, 562.2237; found, 562.2223.

Styrene Pyrone 1m. FCC (hexanes/EtOAc 80:20) afforded an orange oil; 2nd FCC (CH_2Cl_2/acetone 98:2) afforded a pale yellow oil (237 mg, 0.423 mmol, 31%): R_f = 0.34 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (app d, J = 8.8 Hz, 2H), 7.55 (d, J = 5.6 Hz, 1H), 7.41 (app d, J = 8.8 Hz, 2H), 6.42 (app d, J = 15.8 Hz, 1H), 6.32 (d, J = 5.6 Hz, 1H), 6.32 (dt, J = 15.8, 7.5 Hz, 1H), 4.23 (q, J = 7.1 Hz, 4H), 3.51 (s, 2H), 2.79 (dd, J = 7.5, 0.9 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H), 0.91 (s, 9H), and 0.24 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.0, 170.0(2), 153.05, 152.95, 147.1, 144.3, 143.3, 132.5, 129.2, 126.9(2), 124.0(2), 115.9, 62.0(2), 56.9, 37.1, 31.2, 26.0(3), 18.9, 14.2(2), and −3.6(2); ESI-HRMS calcd for $C_{28}H_{37}NO_9SiNa$ $[M + Na]^+$, 582.2135; found, 582.2130.

General Procedure D for (5 + 2) Cycloadditions (2a−c). To a 1 dram vial with a micro stir bar were added 0.05−0.10 mmol pyrone and 0.5−1.0 mL of solvent and stirred for the appropriate time and temperature. The solution was either carefully concentrated to avoid external heating and then treated with 1,3,5-trimethoxybenzene in $CDCl_3$ or the reaction was monitored directly by NMR with deuterated solvent. The quantity of both the starting material and product was calculated via comparison of diagnostic integrals. Each cycloaddition was either monitored by ^1H NMR analysis[19] or isolated as follows:

Isolated Yield of Cycloadduct 2a. A solution of silyloxypyrone **1a** (90 mg, 0.2 mmol, 1.0 equiv) in toluene (2 mL) was stirred for 24 h at 60 °C, concentrated, and purified by FCC (hexanes/EtOAc

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J. Org. Chem. 2023, 88, 5972−5981

70:30) to afford cycloadduct **2a** as a dark brown oil (61 mg, 0.136 mmol, 68%, dr > 19:1): R_f = 0.45 (hexanes/EtOAc 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (d, J = 4.9 Hz, 1H), 4.95 (dd, J = 6.0, 4.9 Hz, 1H), 4.28−4.14 (m, 4H), 3.68 (dd, J = 6.4, 6.0 Hz, 1H), 3.12 (d, J = 14.8 Hz, 1H), 2.91 (ddd, J = 10.2, 6.4, 2.8 Hz, 1H), 2.66 (ddd, J = 13.7, 2.8, 1.3* Hz, 1H) *long-range coupling, 2.53 (dd, J = 14.8, 1.3* Hz, 1H) *long-range coupling, 2.30 (dd, J = 13.7, 10.2 Hz, 1H), 2.19 (s, 3H), 1.26 (ovlp t, J = 7.2 Hz, 6H), 0.92 (s, 9H), 0.14 (s, 3H), and 0.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 204.1, 192.3, 171.2, 170.5, 146.7, 125.0, 97.7, 75.9, 64.9, 62.0, 61.9, 61.7, 45.4, 37.7, 37.2, 30.0, 25.6(3), 18.4, 14.1, 14.0, −4.71, and −4.74; ESI-HRMS calcd for $C_{24}H_{36}O_8SiNa$ $[M + Na]^+$, 503.2077; found, 503.2074.

Isolated Yield of Cycloadduct 2c. Control reaction: To a solution of silyloxypyrone-aldehyde **3** (35 mg, 0.077 mmol, 1.0 equiv) in $CDCl_3$ (660 μL) were added $MgSO_4$ (46 mg, 0.38 mmol, 5.0 equiv) and a solution of pyrrolidine (13 μL, 0.15 mmol, 2.0 equiv) in $CDCl_3$ (100 μL) delivered as 1/6th of a stock solution of 78 μL in 600 μL of $CDCl_3$. This mixture was quenched immediately by subjecting to FCC (Et_2O 100%) and further purified by FCC (CH_2Cl_2/Et_2O 90:10 to 80:20) which afforded unreacted aldehyde **3** as a yellow oil (35 mg, 0.077 mmol, >99%). Cycloaddition: To a solution of silyloxypyrone-aldehyde **3** (35 mg, 0.076 mmol, 1.0 equiv) in $CDCl_3$ (760 μL) were added $MgSO_4$ (46 mg, 0.38 mmol, 5.0 equiv) and a solution of pyrrolidine (13 μL, 0.15 mmol, 2.0 equiv) in $CDCl_3$ (100 μL) delivered as 1/6th of a stock solution of 78 μL in 600 μL of $CDCl_3$. This mixture was stirred for 8 h at 0 °C, concentrated, and quenched by subjecting to FCC (Et_2O 100%) and further purified by FCC (CH_2Cl_2/Et_2O 90:10 to 80:20) which afforded unreacted aldehyde **3** as a yellow oil (10 mg, 0.021 mmol, 28%) and cycloadduct **2c** as a yellow oil (25 mg, 0.049 mmol, 64%, dr > 19:1): R_f = 0.80 (CH_2Cl_2/Et_2O 50:50); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21 (d, J = 4.9 Hz, 1H), 4.67 (app t, J = 5.2 Hz, 1H), 4.25−4.11 (m, 4H), 3.08 (d, J = 14.8 Hz, 1H), 2.97 (app t, J = 5.2 Hz, 1H), 2.61 (dd, J = 13.0, 2.2 Hz, 1H), 2.53−2.40 (m, 6H), 2.33 (dd, J = 13.0, 10.1 Hz, 1H), 1.76−1.73 (m, 4H), 1.24 (ovlp t, J = 7.1 Hz, 6H), 0.93 (s, 9H), 0.15 (s, 3H), and 0.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.9, 170.9(2), 146.6, 127.1, 97.3, 78.0, 76.4, 62.0, 61.9, 61.7, 54.0(2), 49.9, 37.9, 37.4, 25.8(3), 23.6(2), 18.6, 14.2, 14.1, −4.5, and −4.7; ESI-HRMS calcd for $C_{26}H_{41}NO_7SiNa$ $[M + Na]^+$, 530.2550; found, 530.2535.

General Procedure E for (5 + 2) Cycloaddition (2d−m). To a 1 dram vial with a micro stir bar was added 0.05−0.10 mmol of pyrone and dissolved in 0.5−1.0 mL toluene. Upon stirring for the appropriate time and temperature and careful concentration on a vacuum pump to avoid external heating, a solution of 1,3,5-trimethoxybenzene in $CDCl_3$ was added and the resulting solution transferred to an NMR tube. The quantity of both starting material and product was calculated via comparison of diagnostic integrals and reported in the corresponding tables. Isolated yields were obtained by the following: A solution of silyloxypyrone (0.03−0.5 mmol) in toluene (0.1 M) was stirred for 2 d at 110 °C, concentrated, and purified by FCC to afford cycloadducts **2d−m**.

Cycloadduct 2d. FCC (hexanes/EtOAc 80:20) afforded a colorless oil (8.5 mg, 0.015 mmol, 52%, dr > 19:1): R_f = 0.67 (hexanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (app d, J = 8.9 Hz, 2H), 6.56 (app d, J = 8.9 Hz, 1H), 5.94 (d, J = 5.0 Hz, 1H), 4.80 (dd, J = 6.1, 5.0 Hz, 1H), 4.29−4.13 (m, 4H), 3.72 (dd, J = 6.5, 6.1 Hz, 1H), 3.17 (d, J = 14.7 Hz, 1H), 2.92 (s, 6H), 2.77 (ddd, J = 9.9, 6.5, 3.2 Hz, 1H), 2.67 (ddd, J = 13.6, 3.2, 1.1* Hz, 1H) *long-range coupling, 2.60 (dd, J = 14.7, 1.1* Hz, 1H) *long-range coupling, 2.31 (dd, J = 13.6, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.92 (s, 9H), 0.15 (s, 3H), and 0.14 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.9, 171.2, 171.0, 149.9, 146.4, 129.2(2), 127.0, 125.6, 112.7(2), 97.7, 79.7, 62.0, 61.9, 61.8, 55.7, 50.9, 40.7(2), 38.0, 37.4, 25.7(3), 18.5, 14.2(2), −4.4, and −4.5; ESI-HRMS calcd for $C_{30}H_{43}NO_7SiNa$ $[M + Na]^+$, 580.2706; found, 580.2704.

Cycloadduct 2e. FCC (hexanes/EtOAc 90:10 to 80:20) afforded a colorless oil (34 mg, 0.0594 mmol, 61%, dr > 19:1): R_f = 0.50 (hexanes/EtOAc 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (app d, J = 8.6 Hz, 2H), 6.80 (app d, J = 8.6 Hz, 2H), 5.90 (d, J = 5.0 Hz, 1H), 4.83 (dd, J = 5.9, 5.0 Hz, 1H), 4.51 (sept, J = 6.1 Hz, 1H), 4.29−4.14 (m, 4H), 3.76 (dd, J = 6.7, 5.9 Hz, 1H), 3.17 (d, J = 14.7 Hz, 1H), 2.78 (ddd, J = 9.9, 6.7, 3.2, 1H), 2.68−2.64 (m, 1H), 2.61 (d, J = 14.7 Hz, 1H), 2.34 (dd, J = 13.5, 9.9 Hz, 1H), 1.32 (ovlp d, J = 6.1, 6H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.91 (s, 9H), and 0.12 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.8, 171.2, 171.0, 157.2, 146.5, 129.9, 129.4(2), 126.6, 116.0(2), 97.7, 79.6, 70.1, 62.1, 61.9, 61.8, 55.8, 50.7, 38.1, 37.4, 25.7(3), 22.2, 22.1, 18.5, 14.2, 14.1, −4.5, and −4.6; ESI-HRMS calcd for $C_{31}H_{44}O_8SiNa$ $[M + Na]^+$, 595.2703; found, 595.2691.

Cycloadduct 2f. FCC (hexanes/EtOAc 85:15 to 70:30) afforded a colorless oil (41 mg, 0.08 mmol, 45%, dr > 19:1): R_f = 0.76 (hexanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (app d, J = 8.6 Hz, 2H), 6.83 (app d, J = 8.6 Hz, 2H), 5.89 (d, J = 5.1 Hz, 1H), 4.83 (dd, J = 6.1, 5.1 Hz, 1H), 4.28−4.14 (m, 4H), 3.79 (s, 3H), 3.78 (dd, J = 6.6, 6.1 Hz, 1H), 3.18 (d, J = 14.7, 1H), 2.78 (ddd, J = 9.9, 6.6, 3.3, 1H), 2.67 (ddd, J = 13.6, 3.3, 1.3* Hz, 1H) *long-range coupling, 2.61 (dd, J = 14.7, 1.3* Hz, 1H) *long-range coupling, 2.33 (dd, J = 13.6, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.1 Hz, 6H), 0.91 (s, 9H), 0.13 (s, 3H), and 0.12 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.7, 171.2, 170.9, 158.9, 146.5, 130.1, 129.4(2), 126.5, 114.1(2), 97.7, 79.6, 62.1, 61.9, 61.8, 55.7, 55.4, 50.8, 38.0, 37.4, 25.7(3), 18.5, 14.13, 14.12, −4.5, and −4.6; ESI-HRMS calcd for $C_{29}H_{40}O_8SiNa$ $[M + Na]^+$, 567.2390; found, 567.2382.

Cycloadduct 2g. FCC (hexanes/EtOAc 95:5 to 80:20) afforded a colorless oil (51 mg, 0.096 mmol, 47%, dr > 19:1): R_f = 0.56 (hexanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (app d, J = 8.4 Hz, 2H), 7.07 (app d, J = 8.4 Hz, 2H), 5.90 (d, J = 5.0 Hz, 1H), 4.85 (dd, J = 6.0, 5.0 Hz, 1H), 4.30−4.14 (m, 4H), 3.79 (dd, J = 6.7, 6.0 Hz, 1H), 3.18 (d, J = 14.7 Hz, 1H), 2.81 (ddd, J = 9.8, 6.7, 3.4 Hz, 1H), 2.67 (ddd, J = 13.6, 3.4, 1.1* Hz, 1H) *long-range coupling, 2.61 (dd, J = 14.7, 1.1* Hz, 1H) *long-range coupling, 2.33 (dd, J = 13.6, 9.8 Hz, 1H), 2.32 (s, 3H), 1.27 (ovlp t, J = 7.1 Hz, 6H), 0.91 (s, 9H), 0.125 (s, 3H), and 0.122 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.7, 171.2, 170.9, 146.5, 136.9, 135.1, 129.3(2), 128.3(2), 126.5, 97.7, 79.6, 62.1, 61.9, 61.8, 56.1, 50.6, 38.0, 37.3, 26.7(3), 21.1, 18.5, 14.13, 14.12, −4.5, and −4.6; ESI-HRMS calcd for $C_{29}H_{40}O_7SiNa$ $[M + Na]^+$, 551.2441; found, 551.2414.

Cycloadduct 2h. Prepared previously as a yellow oil (159 mg, 0.31 mmol, 62% yield) with the following spectral data:[15c] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.18 (m, 5H), 5.88 (d, J = 5.1 Hz, 1H), 4.89 (dd, J = 6.2, 5.1 Hz, 1H), 4.30−4.14 (m, 4H), 3.85 (dd, J = 6.6, 6.2 Hz, 1H), 3.19 (d, J = 14.8 Hz, 1H), 2.85 (ddd, J = 9.9, 6.6, 3.5 Hz, 1H), 2.68 (ddd, J = 13.5, 3.5, 1.3* Hz, 1H) *long-range coupling, 2.62 (dd, J = 14.8, 1.3* Hz, 1H) *long-range coupling, 2.35 (dd, J = 13.5, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.90 (s, 9H), and 0.11 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.6, 171.1, 170.9, 146.4, 128.9, 128.6(2), 128.4(2), 127.2, 126.3, 97.8, 79.4, 62.0, 61.9, 61.7, 56.4, 50.3, 38.0, 37.3, 25.6(3), 18.4, 14.10, 14.09, −4.57, and −4.64.

Cycloadduct 2i. FCC (hexanes/EtOAc 80:20) afforded a colorless oil (59 mg, 0.111 mmol, 56%, dr > 19:1): R_f = 0.70 (hexanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (app dd, J = 8.6, 5.3 Hz, 2H), 6.98 (app t, J = 8.6 Hz, 2H), 5.86 (d, J = 5.0 Hz, 1H), 4.86 (dd, J = 5.9, 5.0 Hz, 1H), 4.29−4.15 (m, 4H), 3.82 (dd, J = 6.7, 5.9 Hz, 1H), 3.18 (d, J = 14.7 Hz, 1H), 2.78 (ddd, J = 9.9, 6.7, 3.3 Hz, 1H), 2.67 (ddd, J = 13.5, 3.3, 1.2* Hz, 1H) *long-range coupling, 2.61 (dd, J = 14.7, 1.2* Hz, 1H) *long-range coupling, 2.34 (dd, J = 13.5, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.91 (s, 9H), 0.123 (s, 3H), and 0.117 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.5, 171.1, 170.8, 162.1 (d, J = 246.2 Hz), 146.7, 133.9 (d, J = 2.9 Hz), 129.2(2) (d, J = 8.2 Hz), 126.0, 115.5(2) (d, J = 20.9 Hz), 97.8, 79.4, 62.05, 61.96, 61.8, 55.7, 50.7, 38.0, 37.3, 25.6(3), 18.5, 14.14, 14.12, −4.5, and −4.6; ^{19}F NMR (470 MHz) −115.8 (tt, J = 8.6, 6.5 Hz); ESI-HRMS calcd for $C_{28}H_{37}FO_7SiNa$ $[M + Na]^+$, 555.2190; found, 555.2188.

Cycloadduct 2j. FCC (hexanes/EtOAc 90:10 to 60:40) afforded a colorless oil (41 mg, 0.07 mmol, 56%, dr > 19:1): R_f = 0.63 (hexanes/EtOAc 70:30); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (app d, J = 8.4 Hz, 2H), 7.12 (app d, J = 8.4 Hz, 2H), 5.86 (d, J = 5.0 Hz,

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J. Org. Chem. 2023, 88, 5972−5981

1H), 4.86 (dd, J = 6.0, 5.0 Hz, 1H), 4.30−4.18 (m, 4H), 3.82 (dd, J = 6.4, 6.0 Hz, 1H), 3.18 (d, J = 14.7 Hz, 1H), 2.78 (ddd, J = 9.9, 6.4, 3.4 Hz, 1H), 2.66 (ddd, J = 13.5, 3.4, 1.2* Hz, 1H) *long-range coupling, 2.61 (dd, J = 14.7, 1.2* Hz, 1H) *long-range coupling, 2.33 (dd, J = 13.5, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.1 Hz, 6H), 0.91 (s, 9H), 0.13 (s, 3H), and 0.12 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.5, 171.1, 170.8, 146.7, 136.7, 133.2, 129.7(2), 128.8(2), 125.8, 97.8, 79.4, 62.04, 61.99, 61.8, 55.9, 50.6, 37.9, 37.3, 25.7(3), 18.5, 14.15, 14.13, −4.5, and −4.6; ESI-HRMS calcd for $C_{28}H_{37}ClO_7SiNa$ $[M + Na]^+$, 571.1895; found, 571.1870.

Cycloadduct 2k. FCC (hexanes/EtOAc 90:10) afforded a colorless amorphous solid (26 mg, 0.045 mmol, 26%, dr > 19:1): R_f = 0.62 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (app d, J = 8.4 Hz, 2H), 7.26 (app d, J = 8.4 Hz, 2H), 5.85 (d, J = 5.0 Hz, 1H), 4.92 (dd, J = 6.0, 5.0 Hz, 1H), 4.29−4.14 (m, 4H), 3.92 (dd, J = 6.6, 6.0 Hz, 1H), 3.91 (s, 3H), 3.19 (d, J = 14.7 Hz, 1H), 2.86 (ddd, J = 9.9, 6.6, 3.3 Hz, 1H), 2.68 (ddd, J = 13.5, 3.3, 1.0* Hz, 1H) *long-range coupling, 2.62 (dd, J = 14.7, 1.0* Hz, 1H) *long-range coupling, 2.36 (dd, J = 13.5, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.1 Hz, 6H), 0.90 (s, 9H), 0.113 (s, 3H), and 0.107 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5, 171.1, 170.8, 166.8, 146.8, 143.5, 129.9(2), 129.3, 128.4(2), 125.7, 97.9, 79.3, 62.04, 61.99, 61.90, 56.5, 52.2, 50.3, 37.9, 37.3, 25.6(3), 18.5, 14.14, 14.12, −4.5, and −4.6; ESI-HRMS calcd for $C_{30}H_{40}O_9SiNa$ $[M + Na]^+$, 595.2339; found, 595.2335.

Cycloadduct 2l. FCC (hexanes/EtOAc 70:30) afforded a colorless oil (71 mg, 0.131 mmol, 89%, dr > 19:1): R_f = 0.60 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (app d, J = 8.4 Hz, 2H), 7.30 (app d, J = 8.4 Hz, 2H), 5.82 (d, J = 5.0 Hz, 1H), 4.91 (dd, J = 6.0, 5.0 Hz, 1H), 4.29−4.15 (m, 4H), 3.92 (dd, J = 6.7, 6.0 Hz, 1H), 3.19 (d, J = 14.8 Hz, 1H), 2.82 (ddd, J = 9.9, 6.7, 3.5 Hz, 1H), 2.67 (ddd, J = 13.6, 3.5, 1.1* Hz, 1H) *long-range coupling, 2.62 (dd, J = 14.8, 1.1* Hz, 1H) *long-range coupling, 2.35 (dd, J = 13.6, 9.9 Hz, 1H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.91 (s, 9H), 0.12 (s, 3H), and 0.11 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.2, 171.1, 170.7, 147.0, 143.8, 132.5(2), 129.2(2), 125.0, 118.6, 111.4, 97.9, 79.2, 62.1, 62.0, 61.9, 56.5, 50.4, 37.9, 37.3, 25.6(3), 18.5, 14.15, 14.12, −4.5, and −4.6; ESI-HRMS calcd for $C_{29}H_{37}NO_7SiNa$ $[M + Na]^+$, 562.2237; found, 562.2234.

Cycloadduct 2m. FCC (hexanes/EtOAc 85:15 to 70:30) afforded a colorless oil (84 mg, 0.16 mmol, 78%, dr > 19:1): R_f = 0.72 (hexanes/EtOAc 70:30); ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (app d, J = 8.7 Hz, 2H), 7.36 (app d, J = 8.7 Hz, 2H), 5.83 (d, J = 5.0 Hz, 1H), 4.94 (dd, J = 6.0, 5.0 Hz, 1H), 4.30−4.15 (m, 4H), 3.98 (dd, J = 6.7, 6.0 Hz, 1H), 3.20 (d, J = 14.8 Hz, 1H), 2.85 (ddd, J = 10.0, 6.7, 3.2 Hz, 1H), 2.68 (ddd, J = 13.6, 3.2, 1.2* Hz, 1H) *long-range coupling, 2.63 (dd, J = 14.8, 1.2* Hz, 1H) *long-range coupling, 2.36 (dd, J = 13.6, 10.0 Hz, 1H), 1.27 (ovlp t, J = 7.2 Hz, 6H), 0.90 (s, 9H), 0.13 (s, 3H), and 0.11 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 192.2, 171.1, 170.6, 147.3, 147.0, 145.9, 129.3(2), 124.9, 123.8(2), 97.9, 79.2, 62.04, 61.99, 61.90, 56.3, 50.5, 37.8, 37.2, 25.6(3), 18.5, 14.11, 14.09, −4.5, and −4.6; ESI-HRMS calcd for $C_{28}H_{37}NO_9SiNa$ $[M + Na]^+$, 582.2135; found, 582.2125.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00318.

General procedure D for (5 + 2) cycloadditions (**2a**−**c**); solvent screen for cycloaddition of enone **2a** and enamine **2c**; Arrhenius reaction kinetic studies for TBS-terminal alkene (**1b**); Arrhenius treatment and determination of experimental activation energy; Arrhenius reaction kinetic studies for TBS-enone; and stereochemical analysis of cycloadducts (PDF)

^1H NMR (500 MHz) and $^{13}C\{1H\}$ NMR (125 MHz) spectra (PDF)

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■ REFERENCES

(1) (a) Houk, K. N.; Liu, F.; Yang, Z.; Seeman, J. I. Evolution of the Diels−Alder Reaction Mechanism since the 1930s: Woodward, Houk with Woodward, and the Influence of Computational Chemistry on Understanding Cycloadditions. *Angew. Chem., Int. Ed.* **2021**, *60*, 12660−12681. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. The Diels−Alder Reaction in Total Synthesis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (c) Corey, E. J. Catalytic Enantioselective Diels-Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667. (d) Sauer, J.; Sustmann, R. Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey. *Angew. Chem., Int. Ed.* **1980**, *19*, 779−807. (e) Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98−122.

(2) (a) Breugst, M.; Reissig, H.-U. The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition. *Angew. Chem., Int. Ed.* **2020**, *59*, 12293−12307. (b) Huisgen, R. 1,3-Dipolar Cycloadditions Past and Future. *Angew. Chem., Int. Ed.* **1963**, *2*, 565−598.
(3) (a) Bejcek, L. P.; Murelli, R. P. Oxidopyrylium (5 + 2) cycloaddition chemistry: Historical Perspective and recent advances (2008-2018). *Tetrahedron* **2018**, *74*, 2501−2521. (b) Singh, V.; Murali Krishna, U.; Vikrant; Trivedi, G. K. Cycloaddition of oxidopyrylium species in organic synthesis. *Tetrahedron* **2008**, *64*, 3405−3428. (c) Mascareñas, J. L. The (5 + 2) Cycloaddition Chemistry of β-Alkoxy-γ-pyrones. *Adv. Cycloaddit.* **1999**, *6*, 1−54.
(4) (a) Gao, K.; Zhang, Y.-G.; Wang, Z.; Ding, H. Recent development on the (5 + 2) cycloadditions and their application in natural product synthesis. *Chem. Commun.* **2019**, *55*, 1859−1878. (b) Liu, X.; Hu, Y.-J.; Fan, J.-H.; Zhao, J.; Li, S.; Li, C.-C. Recent synthetic studies toward natural products *via* (5 + 2) cycloaddition reactions. *Org. Chem. Front.* **2018**, *5*, 1217−1228. (c) Ylijoki, K. E. O.; Stryker, J. M. (5 + 2) Cycloaddition Reactions in Organic and Natural Product Synthesis. *Chem. Rev.* **2013**, *113*, 2244−2266.
(5) (a) Fuhr, K. N.; Hirsch, D. R.; Murelli, R. P.; Brenner-Moyer, S. E. Catalytic Enantioselective Intermolecular [5 + 2] Dipolar Cycloadditions of a 3-Hydroxy-4-pyrone-Derived Oxidopyrylium Ylide. *Org. Lett.* **2017**, *19*, 6356−6359. (b) Toda, Y.; Shimizu, M.; Iwai, T.; Suga, H. Triethylamine Enables Catalytic Generation of Oxidopyrylium Ylides for [5+2] Cycloadditions with Alkenes: An Efficient Entry to 8-Oxabicyclo[3.2.1]octane Frameworks. *Adv. Synth. Catal.* **2018**, *360*, 2377−2381. (c) Suga, H.; Iwai, T.; Shimizu, M.; Takahashi, K.; Toda, Y. Efficient generation of an oxidopyrylium ylide using a Pd catalyst and its [5+2] cycloadditions with several dipolarophiles. *Chem. Commun.* **2018**, *54*, 1109−1112. (d) Wilkerson-Hill, S. M.; Sawano, S.; Sarpong, R. Bis(1-cyanovinyl acetate) Is a Linear Precursor to 3-Oxidopyrylium Ions. *J. Org. Chem.* **2016**, *81*, 11132−11144. (e) D'Erasmo, M. P.; Meck, C.; Lewis, C. A.; Murelli, R. P. Discovery and Development of a Three-Component Oxidopyrylium [5 + 2] Cycloaddition. *J. Org. Chem.* **2016**, *81*, 3744−3751. (f) Mei, G.; Liu, X.; Qiao, C.; Chen, W.; Li, C.-C. Type II Intramolecular [5+2] Cycloaddition: Facile Synthesis of Highly Functionalized Bridged Ring Systems. *Angew. Chem., Int. Ed.* **2015**, *54*, 1754−1758. (g) Aimon, A.; Karageorgis, G.; Masters, J.; Dow, M.; Craven, P. G. E.; Ohsten, M.; Willaume, A.; Morgentin, R.; Ruiz-Llamas, N.; Lemoine, H.; Kalliokoski, T.; Eatherton, A. J.; Foley, D. J.; Marsden, S. P.; Nelson, A. Realisation of small molecule libraries based on frameworks distantly related to natural products. *Org. Biomol. Chem.* **2018**, *16*, 3160−3167. (h) Hirsch, D. R.; Schiavone, D. V.; Berkowitz, A. J.; Morrison, L. A.; Masaoka, T.; Wilson, J. A.; Lomonosova, E.; Zhao, H.; Patel, B. S.; Datla, S. H.; Hoft, S. G.; Majidi, S. J.; Pal, R. K.; Gallicchio, E.; Tang, L.; Tavis, J. E.; Le Grice, S. F. J.; Beutler, J. A.; Murelli, R. P. Synthesis and biological assessment of 3,7-dihydroxytropolones. *Org. Biomol. Chem.* **2018**, *16*, 62−69.
(6) (a) Zaragoza, R. J.; Aurell, M. J.; Domingo, L. R. The role of the transfer group in the intramolecular (5 + 2) cycloadditions of substituted β-hydroxy-γ-pyrones: a DFT analysis. *J. Phys. Org. Chem.* **2005**, *18*, 610−615. (b) Lopez, F.; Castedo, L.; Mascarenas, J. L. A Theoretical Rationalization of the Asymmetric Induction in Sulfinyl-Directed [5C + 2C] Intramolecular Cycloadditions. *J. Org. Chem.* **2003**, *68*, 9780−9786. (c) Domingo, L.; Zaragoza, R. J. Toward an Understanding of the Mechanisms of the Intramolecular (5 + 2) Cycloaddition Reaction of γ-Pyrones Bearing Tethered Alkenes. A Theoretical Study. *J. Org. Chem.* **2000**, *65*, 5480−5486.
(7) Beno, B. R.; Houk, K. N.; Singleton, D. A. Synchronous or Asynchronous? An "Experimental" Transition State from a Direct Comparison of Experimental and Theoretical Kinetic Isotope Effects for a Diels-Alder Reaction. *J. Am. Chem. Soc.* **1996**, *118*, 9984−9985.
(8) (a) Loesche, A.-C.; Bruckner, R. Dienolates of Cycloalkenones and α,β-Unsaturated Esters Form Diels−Alder Adducts by a Michael/Michael-Tandem Reaction Rather Than in One Step. *Eur. J. Org. Chem.* **2019**, *2019*, 562−573. (b) Linder, M.; Brinck, T. Stepwise Diels-Alder: More than Just an Oddity? A Computational Mechanistic Study. *J. Org. Chem.* **2012**, *77*, 6563−6573. (c) Bongini, A.; Panunzio, M. A Hetero Diels-Alder Concerted vs. Aldol Stepwise Mechanism in the Cyclization of Silyloxyazadienes with Aldehydes: A Theoretical Study. *Eur. J. Org. Chem.* **2006**, 972−977. (d) Guimaraes, C. R. W.; Udier-Blagović, M.; Jorgensen, W. L. Macrophomate Synthase: QM/MM Simulations Address the Diels-Alder versus Michael-Aldol Reaction Mechanism. *J. Am. Chem. Soc.* **2005**, *127*, 3577−3588. (e) Singleton, D. A.; Schulmeier, B. E.; Hang, C.; Thomas, A. A.; Leung, S.-W.; Merrigan, S. R. Isotope effects and the distinction between synchronous, asynchronous, and stepwise Diels-Alder reactions. *Tetrahedron* **2001**, *57*, 5149−5160.
(9) (a) Huisgen, R. 1,3-Dipolar cycloadditions. 76. Concerted nature of 1,3-dipolar cycloadditions and the question of diradical intermediates. *J. Org. Chem.* **1976**, *41*, 403−419. (b) Daru, A.; Roca-Lopez, D.; Tejero, T.; Merino, P. Revealing Stepwise Mechanisms in Dipolar Cycloaddition Reactions: Computational Study of the Reaction between Nitrones and Isocyanates. *J. Org. Chem.* **2016**, *81*, 673−680. (c) Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. Concerted vs. Stepwise Mechanism in 1,3-Dipolar Cycloaddition of Nitrone to Ethene, Cyclobutadiene, and Benzocyclobutadiene. A Computational Study. *J. Org. Chem.* **2000**, *65*, 6112−6120.
(10) (a) Domingo, L. R.; Ríos-Gutiérrez, M.; Perez, P. A molecular electron density theory study of the participation of tetrazines in aza-Diels−Alder reactions. *RSC Adv.* **2020**, *10*, 15394−15405. (b) Ríos-Gutiérrez, M.; Domingo, L. R. Unravelling the Mysteries of the [3+2] Cycloaddition Reactions. *Eur. J. Org. Chem.* **2019**, 267. (c) Domingo, L. R.; Saez, J. Understanding the mechanism of polar Diels−Alder reactions. *Org. Biomol. Chem.* **2009**, *7*, 3576.
(11) (a) Afarinkia, K.; Bahar, A.; Neuss, J.; Ruggiero, A. 2(H)-1,4-Oxazin-2-ones as ambident azadienes. *Tetrahedron Lett.* **2004**, *35*, 3995−3998. (b) Cho, C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H.; Koo, S. Diels-Alder Cycloadditions of 3,5-Dibromo-2-pyrone: A New Ambident Diene. *J. Org. Chem.* **2002**, *67*, 290−293. (c) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. Stille couplings of 3-(trimethylstannyl)-5-bromo-2-pyrone for the syntheses of 3-aryl-5-bromo-2-pyrones and their ambident dienyl characters. *Tetrahedron Lett.* **2002**, *43*, 5779−5782. (d) Levandowski, B. J.; Hamlin, T. A.; Bickelhaupt, F. M.; Houk, K. N. Role of Orbital Interactions and Activation Strain (Distortion Energies) on Reactivities in the Normal and Inverse Electron-Demand Cycloadditions of Strained and Unstrained Cycloalkenes. *J. Org. Chem.* **2017**, *82*, 8668−8675. (e) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. Inverse electron demand Diels-Alder reactions in chemical biology. *Chem. Soc. Rev.* **2017**, *46*, 4895−4950. (f) Jiang, X.; Wang, R. Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels-Alder Reaction. *Chem. Rev.* **2013**, *113*, 5515−5546.
(12) (a) Huisgen, R.; Szeimies, G.; Möbius, L. 1.3-Dipolare Cycloadditionen, XXIV. Triazoline aus organischen Aziden und α.β-ungesättigten Carbonylverbindungen oder Nitrilen. *Chem. Ber.* **1966**, *99*, 475−490. (b) Huisgen, R.; Möbius, L.; Szeimies, G. 1.3-Dipolare Cycloadditionen, XIV: Die Anlagerung organischer Azide an Enoläther: Orientierung und Triazolin-Zerfall. *Chem. Ber.* **1965**, *98*, 1138−1152.
(13) (a) Sammes, P. G.; Whitby, R. J. On the Preparation and Chemical Reactivity of 2-Benzopyrylium-4-olate. *J. Chem. Soc., Perkin Trans. 1* **1987**, *1*, 195−202. (b) Sammes, P. G.; Street, L. J. The Preparation and Some Reactions of 3-Oxidopyrylium. *J. Chem. Soc., Perkin Trans. 1* **1983**, *1*, 1261−1265. (c) Hendrickson, J. B.; Farina, J. S. A New 7-Ring Cycloaddition Reaction. *J. Org. Chem.* **1980**, *45*, 3359−3361.
(14) Zhao, C.; Glazier, D. A.; Yang, D.; Yin, D.; Guzei, I. A.; Aristov, M. M.; Liu, P.; Tang, W. Intermolecular Regio- and Stereoselective Hetero-[5+2] Cycloaddition of Oxidopyrylium Ylides and Cyclic Imines. *Angew. Chem., Int. Ed.* **2019**, *58*, 887−891.
(15) (a) Corrie, S. I.; Pearce, A. C.; Grabowski, J. P.; Randolph, K. A.; Guo, W.; Tantillo, D. J.; Mitchell, T. A. Boron-tethered oxidopyrylium-based (5 + 2) cycloadditions. *Tetrahedron Lett.* **2022**, *107*, 154094. (b) Rokey, S. N.; Simanis, J. A.; Law, C. M.; Pohani, S.;

https://doi.org/10.1021/acs.joc.3c00318
J. Org. Chem. 2023, 88, 5972−5981

Willens Behrends, S.; Bulandr, J. J.; Ferrence, G. M.; Goodell, J. R.; Mitchell, T. A. Intramolecular asymmetric oxidopyrylium-based (5 + 2) cycloadditions. *Tetrahedron Lett.* **2020**, *61*, 152377. (c) Bulandr, J. J.; Grabowski, J. P.; Law, C. M.; Shaw, J. L.; Goodell, J. R.; Mitchell, T. A. Investigation of Transfer Group, Tether Proximity, and Alkene Substitution for Intramolecular Silyloxypyrone-Based (5 + 2) Cycloadditions. *J. Org. Chem.* **2019**, *84*, 10306−10320.

(16) Hammett, L. P. The Effect of Structure upon the Reactions of Organic Compounds. Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96−103.

(17) (a) Lu, Y.; Tantillo, D. Comparison of (5 + 2) Cycloadditions Involving Oxidopyrylium and Oxidopyridinium Ions − Relative Reactivities. *J. Org. Chem.* **2021**, *86*, 8652−8659. (b) Kaufman, R. H.; Law, C. M.; Simanis, J. A.; Woodall, E. L.; Zwick, C. R., III; Wedler, H. B.; Wendelboe, P.; Hamaker, C. G.; Goodell, J. R.; Tantillo, D. J.; Mitchell, T. A. Oxidopyrylium-Alkene (5 + 2) Cycloaddition Conjugate Addition Cascade (C3) Sequences: Scope, Limitation, and Computational Investigations. *J. Org. Chem.* **2018**, *83*, 9818−9838. (c) Wang, S. C.; Tantillo, D. J. Theoretical Studies on Synthetic and Biosynthetic Oxidopyrylium-Alkene Cycloadditions: Pericyclic Pathways to Intricarene. *J. Org. Chem.* **2008**, *73*, 1516−1523.

(18) Tantillo, D. J. Recent Excursions to the Borderlands between the Realms of Concerted and Stepwise: Carbocation Cascades in Natural Products Biosynthesis. *J. Phys. Org. Chem.* **2008**, *21*, 561−570.

(19) See Supporting Information.

(20) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195.

(21) Crawford, J. M.; Kingston, C.; Toste, F. D.; Sigman, M. S. Data Science Meets Physical Organic Chemistry. *Acc. Chem. Res.* **2021**, *54*, 3136−3148.

(22) Grimme, S. Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations. *J. Chem. Theory Comput.* **2019**, *15*, 2847−2862.

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*. Revision A.03; Gaussian, Inc.: Wallingford CT, 2016.

(24) Grimme, S. Density functional theory with London dispersion corrections. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, *1*, 211−228.

(25) (a) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215−241. (b) Zhao, Y.; Truhlar, D. G. Construction of a generalized gradient approximation by restoring the density-gradient expansion and enforcing a tight Lieb−Oxford bound. *J. Chem. Phys.* **2008**, *128*, 184109−184118.

(26) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980**, *72*, 650−654. (b) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.

(27) Chen, S.; Hu, T.; Houk, K. N. Energy of Concert and Origins of Regioselectivity for 1,3-Dipolar Cycloadditions of Diazomethane. *J. Org. Chem.* **2021**, *86*, 6840−6846.

(28) Lu, T.; Chen, F. Multiwfn: A multifunctional wave function analyzer. *J. Comput. Chem.* **2012**, *33*, 580−592.

(29) Legault, C. Y. *CYLview, 1.0b*; Universitéde Sherbrooke, 2009. http://www.cylview.org.

(30) Lopez, F.; Castedo, L.; Mascareñas, J. L. A Practical Route to Enantiopure, Highly Functionalized Seven-Membered Carbocycles and Tetrahydrofurans: Concise Synthesis of (+)-Nemorensic Acid. *Chem. Eur. J.* **2002**, *8*, 884−899.

(31) Tietze, L. F.; Hippe, T.; Steinmetz, A. Palladium-catalyzed allylic substitution on solid support. *Chem. Commun.* **1998**, 793−794.

https://doi.org/10.1021/acs.joc.3c00318
J. Org. Chem. 2023, 88, 5972−5981