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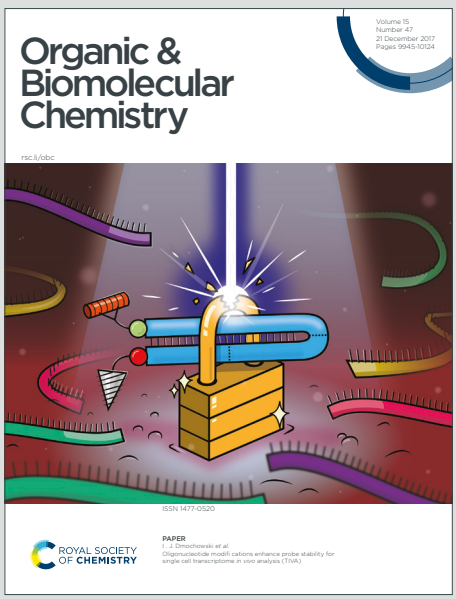

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ARTICLE

Investigations toward a Unified Reaction Pathway of Thermal and TBSOTf-Mediated Oxidopyrylium-Alkene (5 + 2) Cycloadditions

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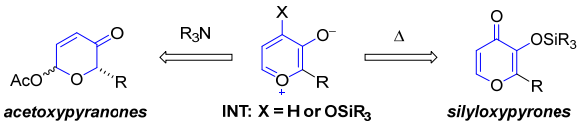
Oxidopyrylium-based (5 + 2) cycloadditions are crucial reactions to construct seven-membered carbocycles containing an ether bridge (i.e. oxabicyclo[3.2.1]octanes). Intramolecular silyloxypyrone-based (5 + 2) cycloadditions were investigated and revealed several features: 1) the TBDPS thermal process proceeds via a zwitterionic oxidopyrylium intermediate similar to previously reported TBS variants; 2) the TBSOTf-mediated reaction proceeds through a cationic oxidopyrylium intermediate; 3) quantum chemical calculations predict a stepwise process for an electron-rich dipolarophile for each set of conditions. The thermal silyloxypyrone-based (5 + 2) cycloadditions were extremely dependent on the nature of the dipolarophile and the silyl transfer group. The TBDPS enhances the rate compared to the TBS variant but only for less polarized alkenes. Relatively neutral alkenes were the least reactive for both, whereas electron-deficient and electron-rich dipolarophiles were more reactive providing evidence for ambident oxidopyrylium intermediates. TBSOTf-mediated cycloadditions, however, revealed evidence for a cationic intermediate that follows a more consistent mechanistic trend. Qualitative rate studies, Hammett linear free energy relationships, and theoretical calculations combine to provide evidence for both mechanistic scenarios.

Cycloadditions can be initiated by the input of thermal energy or an activating agent to access key transition states en route to a desired product.[1] Oxidopyrylium-based (5 + 2) variants[2] can be mediated by different pathways, but two widely utilized strategies involve acetoxypyranones or silyloxypyrones (Scheme 1). Activation of acetoxypyranones, established by Hendrickson[3] and Sammes,[4] typically requires a base to initiate deprotonation followed by release of the acetoxy (or related leaving group) to deliver the oxidopyrylium. Activation of silyloxypyrones (or related starting material), pioneered by Wender and Mascareñas,[5] takes advantage of either an internal group transfer process or an external Lewis acid to afford the oxidopyrylium moiety. Several variations of these methods have been reported[6] and our group has contributed to both activation pathways,[7] which are useful toward the total synthesis of natural products[8] and other applications.[9] The generally accepted mechanism[7b,10] involves silyl transfer to the oxidopyrylium followed by concerted cycloaddition. We previously reported silyloxypyrone-based cycloadditions that revealed crucial data regarding three components: silyl group transfer,[7g] tether proximity to the transfer group,[7g] and dipolarophile electronics.[7b] Relative rate comparisons of a wide variety of silylated maltol-derived substrates **1a-j** revealed an interesting result: only TBDPS-terminal olefin **1b** exhibited enhanced reactivity and transfer group dependence (Scheme 2A).[7g] Furthermore, several silylated kojic acid-derived substrates **3a-d** showed no dependence on the transfer group (Scheme 2B).[7g] Although enoates **1f-j** and **3c-d** were not affected by the silyl transfer group, enhanced conversion was observed compared to the terminal alkenes confirming the expected electronic effect of the ester that reduces the energy of the lowest unoccupied molecular orbital (LUMO). These combined results revealed a subtle interplay between transfer group, tether, and alkene. More recently, we undertook a detailed investigation of TBS-pyrones that revealed the substantial impact of dipolarophile electronics on the cycloaddition that illuminated a spectrum of reactivity[7b] passing through borderlands[11] of concerted and stepwise (Scheme 2C). Herein, we disclose TBDPS-thermal and TBSOTf-mediated[6o] (5 + 2) cycloadditions that proceed via zwitterionic and cationic intermediates, respectively (Scheme 2D). Taken together with our previous work,[7b,g] these qualitative rate studies, Hammett linear free energy relationship (LFER) findings, and theoretical calculations provide a coherent framework for a unified mechanistic pathway of silyloxypyrone-based (5 + 2) cycloadditions (*vide infra*) and lay the foundation for continued exploration of this intriguing reaction.

Scheme 1. Acetoxypyranone vs. Silyloxypyrone Activation



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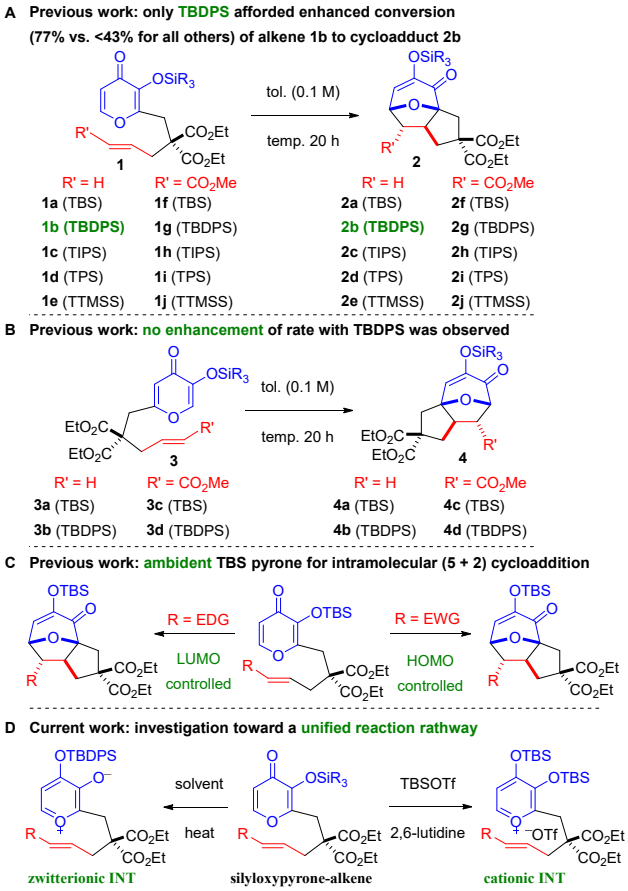
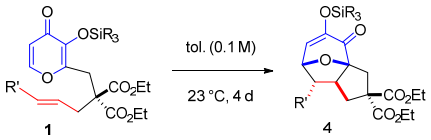
Scheme 2. Summary of Transfer Group, Tether, and Dipolarophile Effects on Silyloxypyrone-based (5 + 2) Cycloaddition Leading to Further Understanding toward a Unified Reaction Pathway



Results and Discussion

Building on the previous observation that the TBDPS transfer group showed no enhancement of enoate conversion (*vide supra*),[7g] we undertook a more thorough comparison of TBS- and TBDPS-pyrones[7b] with a range of substituents on the dipolarophile (Table 1 and Scheme 3). Ambient temperature qualitative rate studies afforded good mass recovery and, as expected, terminal olefins **1a**[7b] and **1b** both afforded no reaction (Table 1, entries 1-2). As the electron-withdrawing ability of the substituent increased, enhanced conversion was observed. Enoates **1f-g**[7g] gave minimal conversion (Table 1, entries 3-4),[7b] enones **1k**[7b] and **1l**[12] provided more substantial quantities of adducts **2k-l** (Table 1, entries 5-6), and nitro-enes **1m-n** afforded complete conversion (Table 1, entries 7-8),[12] thus confirming the effect of lowering the energy of the LUMO. These newly reported nitro-ene starting materials **1m-n** and corresponding cycloadducts **2m-n** were less stable than carbonyl substrates **1f-l**. Therefore, we do not believe that conversions of nitro-enes **1m-n** (entries 7-8) are reflective of rate enhancement by the TBDPS but rather reveal that the TBDPS is simply more stable and thus both are functioning similarly as transfer groups in the case of electron-poor dipolarophiles. Enamine **1o** was previously reported[7b] to proceed at ambient temperature (*in situ* via aldehyde **5**) and newly investigated variant **1p** further demonstrates that enhancement with the TBDPS transfer group is limited to less polarized alkenes (*vide infra*). Unique parameters were necessary to probe this variant below ambient temperature (Scheme 3). When a cycloaddition proceeds at room temperature, the substrate is likely to continue reacting upon isolation and purification, potentially skewing the results. By simply passing the reaction mixture over silica gel, *in situ* generation of enamines **1o-p** (not shown) from aldehydes **5/5'** is reversible, and the reaction is quenched. Therefore, enamine **1o** was formed at 0 °C to give cycloadduct **2o** (64% yield) and aldehyde **5** (28% yield) after column chromatography of the reaction mixture.[7b] A similar result in this study was obtained with the TBDPS variant **2p**.[12]

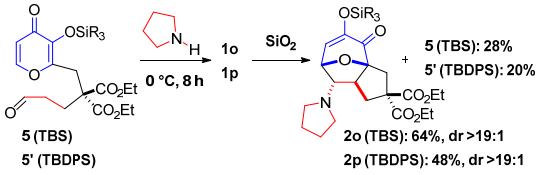
Table 1. Qualitative Rate Comparison of Various Dipolarophiles in Silyloxypyrone-based (5 + 2) Cycloadditions



entry	SiR_3	R'	% rec.[a] (**1**)	% yield[a] (**2**)
1	TBS[c]	H	>95 (**1a**)	<5 (**2a**)[b]
2	TBDPS	H	>95 (**1b**)	<5 (**2b**)[b]
3	TBS[d]	CO_2Me	77 (**1f**)	7 (**2f**)
4	TBDPS[d]	CO_2Me	78 (**1g**)	8 (**2g**)
5	TBS[c]	C(O)Me	54 (**1k**)	36 (**2k**)
6	TBDPS	C(O)Me	56 (**1l**)	37 (**2l**)
7	TBS	NO_2	<5 (**1m**)[b]	73 (**2m**)
8	TBDPS	NO_2	<5 (**1n**)[b]	84 (**2n**)

[a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Not detected. [c] Previously reported in ref. 7b (*J. Org. Chem.* 2023, *88*, 5972); included for comparison with new TBDPS data. [d] Previously reported in ref. 7g (*J. Org. Chem.* 2019, *84*, 10306); included for comparison with new TBDPS data.

Scheme 3. Low Temperature Enamine (5 + 2) Cycloaddition (Reproduced in part with permission from ref. 7b)



Linear free energy relationship (LFER) studies (i.e., Hammett plots) offer a powerful avenue to probe reaction pathways via substituent effects.[13] Plotting the substituent constant (σ) vs. the corresponding log [k/k_0] (or related rate parameter) typically reveals a linear trend that provides support for a consistent mechanism in operation, and non-linear Hammett plots afford compelling evidence for a change in mechanism across substituents.[14] We previously synthesized various styrenes with TBS[7b] (**1q-z**) and herein with TBDPS[12] (**1q'-z'**) transfer groups and subjected them to uniform conditions (Table 2). With both transfer groups, electron-donating and electron-deficient substrates were more reactive than less polarized variants. The TBDPS group slightly enhanced the reactivity as compared to the TBS further indicating that this phenomenon is limited to less polarized alkenes. For example, 4-dimethylaminostyrenes **1q/1q'** (Table 2, entry 1) gave similar conversion as the electron deficient ester-

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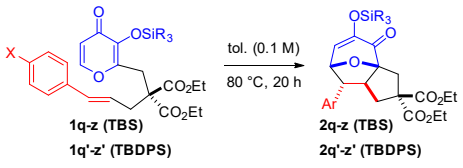
substituted **1x/1x'** (Table 2, entry 8) and 4-cyano-substituted **1y/1y'** (Table 2, entry 9), while the 4-nitrostyrenes **1z/1z'** afforded the highest conversion (Table 2, entry 10). Less-polarized derivatives such as phenyl **1u/1u'** and 4-fluoro **1v/1v'** were far less reactive by comparison (Table 2, entries 5-6). When log rate/rate$_0$ was plotted against σ_p constants, non-linear Hammett plots were revealed (Figures 1-2). These plots are consistent with a shift in reaction pathway with an inflection point near the phenyl **1u/1u'** (Table 2, entry 5) and 4-fluoro **1v/1v'** (Table 2, entry 6). In both cases, upon separation of the trendlines by sigma (σ) value, two distinctly linear Hammett plots are revealed. The negative slope (ρ) correlates to electron-donating group acceleration, whereas electron-withdrawing group acceleration is indicated by the positive slope (ρ).

Table 2. Linear Free-Energy Relationship Comparison of TBS and TBDPS Styrenes (Reproduced in part with permission from ref. 7b)



entry	X	% yield [a] (**2**)[b]	σ_p	% yield[a] (**2'**)
1	NMe_2	69 (**2q**)	-0.83	87 (**2q'**)
2	O*i*Pr	48 (**2r**)	-0.45	65 (**2r'**)
3	OMe	45 (**2s**)	-0.27	65 (**2s'**)
4	Me	44 (**2t**)	-0.17	58 (**2t'**)
5	H	44 (**2u**)	0.00	47 (**2u'**)
6	F	37 (**2v**)	0.06	46 (**2v'**)
7	Cl	54 (**2w**)	0.23	68 (**2w'**)
8	CO_2Me	67 (**2x**)	0.39	77 (**2x'**)
9	CN	68 (**2y**)	0.66	85 (**2y'**)
10	NO_2	87 (**2z**)	0.78	94 (**2z'**)

[a] Determined by the average of two trials as measured by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [b] Previously reported in ref. 7b (*J. Org. Chem.* 2023, *88*, 5972); included for comparison with new TBDPS data.

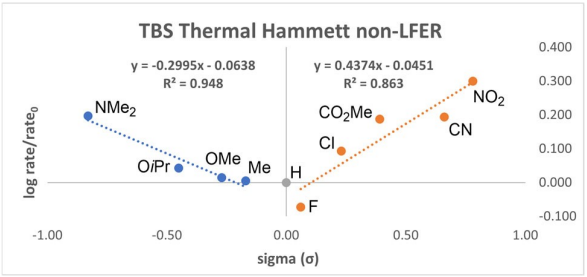


Figure 1. Hammett Analysis: TBS Thermal non-LFER (Reproduced with permission from ref. 7b; *J. Org. Chem.* 2023, *88*, 5972)

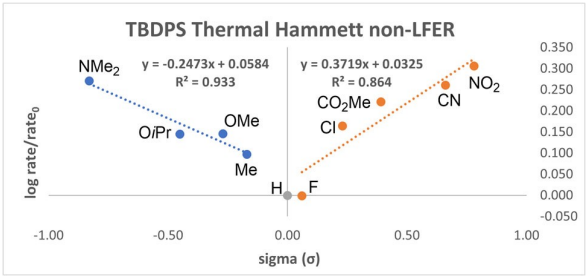
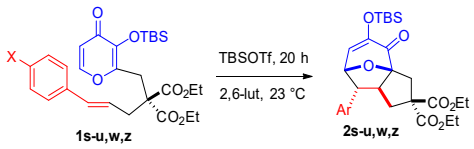


Figure 2. Hammett Analysis: TBDPS Thermal non-LFER

An alternative to thermal-mediated silyl transfer, TBSOTf-promoted (5 + 2) cycloadditions[6o] were explored with a subset of styrenes **2s,t,u,w,z** (Table 3) and **4e-i** (Table 4). Due to the proposed cationic intermediate (cf. Scheme 2D), these investigations afforded evidence of a more typical mechanistic pathway regardless of dipolarophile electronics. In each series, the reaction rate increased with enhanced electron density of the styrene substituent. Kojic acid substrates (Table 4) were more reactive than maltol variants (Table 3), with timeframes of 30 minutes vs. 20 hours, respectively. In both cases, Hammett plots revealed a straightforward linear trend (Figures 3-4) providing evidence for a rate-determining transition state involving accumulation of positive charge on the nucleophilic styrene via the proposed cationic oxidopyrylium species (*vide supra*). It was a challenge to ascertain an appropriate time course for all substrates since methoxy-substituted styrenes **1s** and **3e** were completely consumed with only minimal conversion of the nitro-substituted styrenes **1z** and **3i**. Thus, the results were slightly skewed, and the R^2-value improved upon calculation without the methoxy-substituted styrenes.

Table 3. Linear Free-Energy Relationship of Styrenes with TBSOTf



entry	X	% conv.[a] (**2**)	σ_p^+	log (rate/rate$_0$)
1	OMe	100 (**2s**)	-0.78	0.569
2	Me	98 (**2t**)	-0.31	0.560
3	H	27 (**2u**)	0.00	0.000
4	Cl	22 (**2w**)	0.11	-0.089
5	NO_2	4 (**2z**)	0.79	-0.829

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

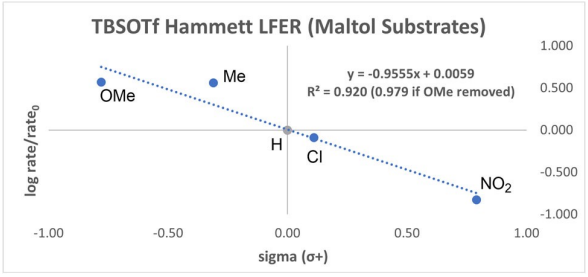


Figure 3. Hammett Analysis: TBSOTf (Maltol substrates)

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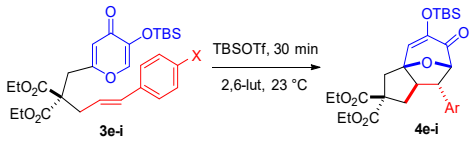
Table 4. Linear Free-Energy Relationship of Styrenes with TBSOTf



entry	X	% conv.[a] (**4**)	σ_p^+	log (rate/rate$_0$)
1	OMe	100 (**4e**)	-0.78	0.467
2	Me	89 (**4f**)	-0.31	0.415
3	H	33 (**4g**)	0.00	0.000
4	Cl	16 (**4h**)	0.11	-0.301
5	NO_2	1 (**4i**)	0.79	-1.480

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

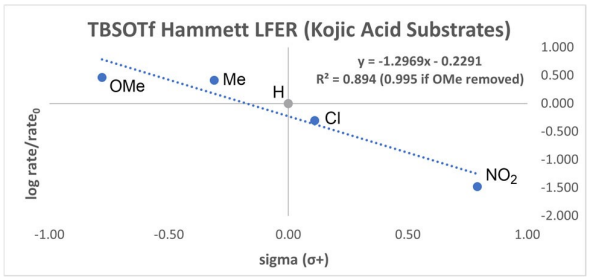
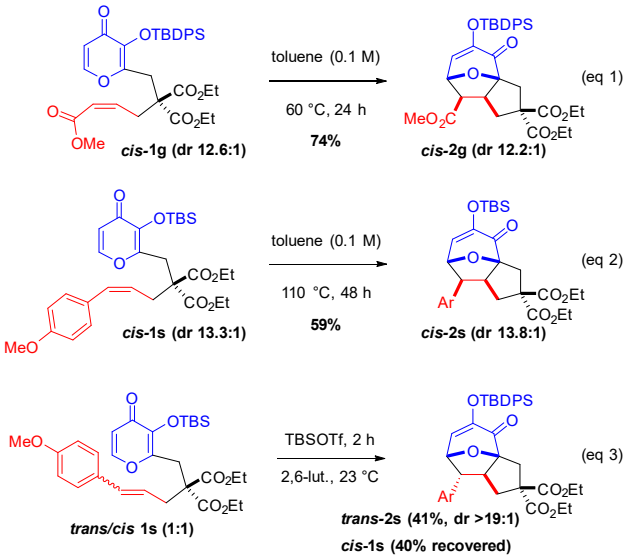


Figure 4. Hammett Analysis: TBSOTf (Kojic acid substrates)

To confirm the stereospecific nature of the thermal and TBSOTf-mediated (5 + 2) cycloadditions, two *cis* alkenes **1s** and **1g** were synthesized.[12] Cycloadditions utilizing these *cis* alkenes **1g** and **1s** (Scheme 4) complimented the stereospecific nature that was observed previously with various *trans* olefins.[7b,g] First, enoate *cis*-**1g** underwent smooth cycloaddition at 60 °C with complete stereospecificity (eq. 1). Styrenes **1s** were subjected to both sets of conditions (i.e. thermal and TBSOTf)[12] to investigate relative reactivity and stereospecificity (eq. 2-3). Styrene *cis*-**1s** was significantly less reactive than the corresponding styrene *trans*-**1s** and required increased heating (i.e. 110 °C) but afforded *cis*-**2s**, also with complete stereospecificity (eq. 2). To confirm this, a mixture of *trans/cis* (1:1) was utilized and, upon heating to only 80 °C, *trans*-**1s** underwent significant conversion, but minimal conversion to *cis*-**2s** was observed (not shown).[12] Upon activation with TBSOTf a similar trend was observed after 2 hours with an initial *trans/cis* ratio of 1:1. Nearly complete conversion of *trans*-**1s** (<5% remaining) to *trans*-**2s** (41% yield; maximum 50%) was detected while only trace conversion to *cis*-**2s** (<5%) and nearly complete recovery of *cis*-**1s** (40% yield; maximum 50%) was observed (eq. 3). Further conversion of *cis*-**1s** under these conditions, albeit slowly, was detected (not shown).[12]

Scheme 4. Stereospecific Cycloadditions with *cis*-Alkenes 1g/1s



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Quantum chemical calculations were undertaken to investigate the mechanism of these silyloxypyrone-based (5 + 2) cycloadditions. Initial conformational searches were carried out using XTB-CREST[15] and subsequent density functional theory (DFT) calculations were carried out with *Gaussian16*.[16] The M06-2X functional with the D3(0) dispersion correction[17] was used to locate stationary points, since this functional is known to perform well for main group thermochemistry and kinetic studies.[18] We employed the 6-31+G(d,p) basis set and the SMD continuum solvation model for geometry optimizations.[19] The larger 6-311+G(2df,2p) basis set was used for computing single point energies. Reported Gibbs free energies include 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.

For reactions in the absence of TBSOTf, silyl transfer via a pentacoordinate species was calculated to be fast and non-rate determining in each case.[7b,12] The overall barrier via rate-determining concerted synchronous (5 + 2) cycloaddition for terminal alkene **1a** was predicted to be 1.9 kcal/mol higher in energy than the corresponding synchronous concerted (5 + 2) cycloaddition for terminal alkene **1b** (Figure 5). These predictions correlate to experimental results in which the TBDPS variant reacts faster than the TBS (cf. Scheme 2A), although an even larger difference (2.4 kcal/mol) is predicted for the kojic acid-derived analogs, which is not borne out in experiments (cf. Scheme 2B). These results with the TBDPS should be viewed with some caution (the issue is likely related to challenges in modeling the conformational properties of the TBDPS group). Nonetheless, barriers were predicted to be higher for kojic acid-derived substrates than for maltol-derived systems with both TBS (Figure 5) and TBDPS[12] transfer groups.

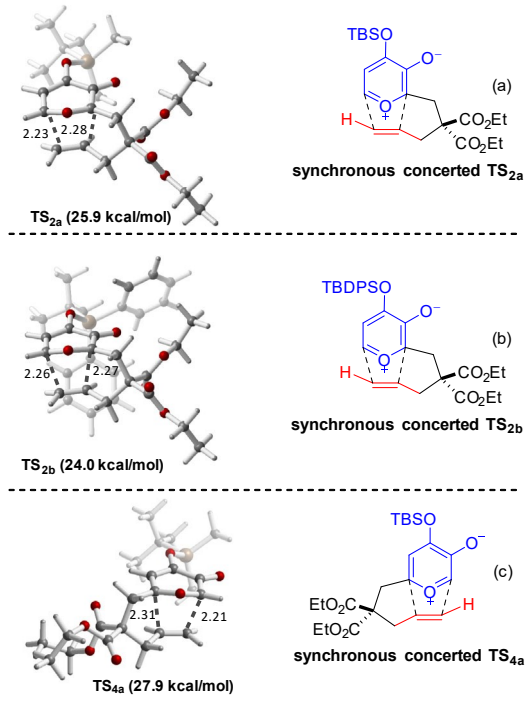

Figure 5. TSs of (a) maltol-derived terminal olefin (TBS);[7b] (b) maltol-derived terminal olefin (TBDPS); (c) kojic acid-derived terminal olefin (TBS)

Concerted but asynchronous (5 + 2) cycloaddition TSs were found for oxidopyrylium intermediates derived from **1q-z** and the plot of computationally predicted free energy barriers vs. substituent constants (σ_p) was previously shown[7b] to be non-linear in qualitative agreement with experimental results (cf. Figure 1). The same effect was found for TBDPS-containing systems **1q', 1u', 1z'** (Figure 6). Again, lower barriers were predicted for the TBDPS variants by ~2 kcal/mol, reinforcing the influence of this bulkier group on less polarized dipolarophiles. DFT calculations for cationic intermediates derived from TBSOTf show that the methoxy substituent promotes a stepwise (5 + 2) cycloaddition (Figure 7) while both H and NO_2 substituents promote an asynchronous concerted process.[12]

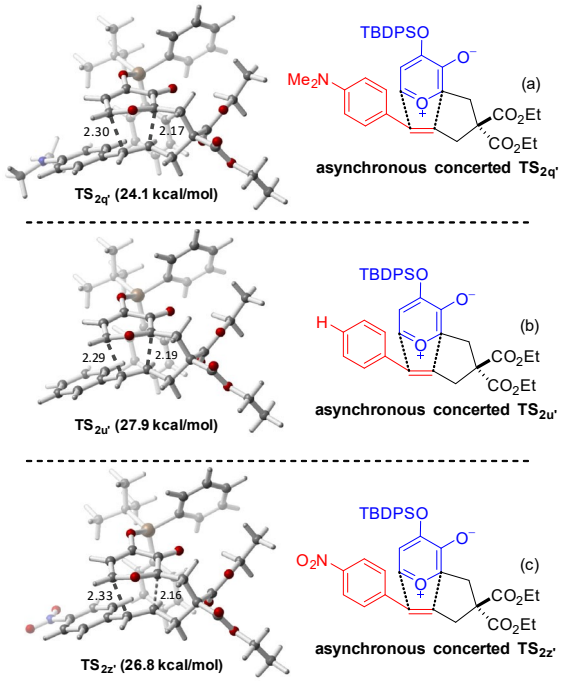

Figure 6. TSs of (a) dimethylaminostyrene (TBDPS); (b) styrene (TBDPS); (c) nitrostyrene (TBDPS)

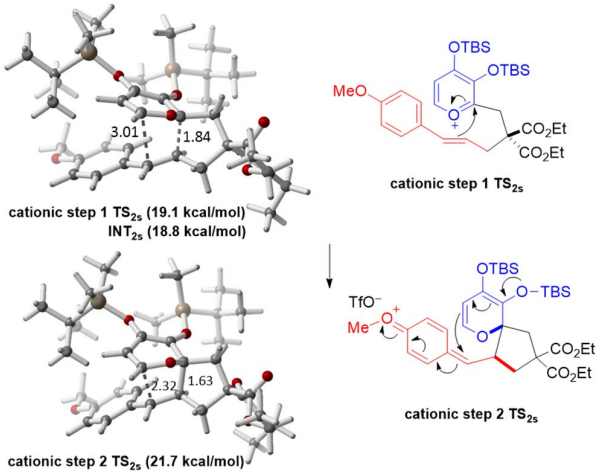

Figure 7. TSs of stepwise TBSOTf-mediated cationic (5 + 2) cycloaddition of methoxy styrene variant

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Comparison of previously calculated transition states[7b] for TBS variants with the newly calculated[12] enoate **2f** and nitro-ene **2m** reveals an interesting trend (Figure 8). The terminal olefin **1a** is the closest to a synchronous concerted transition state **2a** with an energy barrier of 25.9 kcal/mol. As electron-deficient substituents are introduced, the energy decreases and the mechanism shifts to concerted, but asynchronous along the following trend: enoate **2f** (23.4 kcal/mol), enone **2k** (23.1 kcal/mol), and nitro-ene **2m** (21.6 kcal/mol). This trend correlates to experimental results in which more electrophilic dipolarophiles react faster than the terminal olefin **1a** (cf. Table 1). However, enamine **1o**, which was far more reactive experimentally (cf. Scheme 3), was predicted to be stepwise with an initial rate-determining transition state **2o** energy of 19.7 kcal/mol followed by the second step which is only slightly lower in energy (18.8 kcal/mol).[7b] Interestingly, nitro-ene **2m** is not quite electrophilic enough to promote formation of an analogous stepwise process with an anionic intermediate, but decreased bond lengths suggest that the transition structure is progressively more asynchronous as the electron withdrawing ability of the substituent increases.

Based on these experiments and calculations, a unified mechanistic pathway is envisioned for both modes of activation (Scheme 5). Silyloxypyrones can be activated by either thermal or Lewis acid-mediated (i.e. TBSOTf) conditions. Thermal activation with either TBS or TBDPS as transfer group promotes the formation of zwitterionic oxidopyrylium intermediates and can be achieved at temperatures as low as 0 °C in the case of electron-rich enamines (cf. Scheme 3). Ample evidence suggests that the TBDPS transfer group enhances the rate as compared to the TBS, but only for less polarized alkenes (i.e. terminal **1b** and styrenes **1q-z**). Likely this is due to an entropic effect that results from steric interactions of the TBDPS and the diester functionality leading to slightly lower energy barriers for cycloaddition. When the alkenes are more polarized, however, the dipolarophile substituent effect is more significant than this TBDPS acceleration and lowers the activation energy regardless. By contrast, TBSOTf promotes the formation of a cationic oxidopyrylium intermediate, which proceeds more rapidly in the case of electron-rich methoxy styrenes (cf. Tables 3-4). Both intermediates (i.e. zwitterionic or cationic) readily undergo concerted (5 + 2) cycloaddition (synchronous or asynchronous depending on the dipolarophile substituent) with neutral or electron-deficient dipolarophiles. However, quantum chemical calculations revealed evidence of LUMO-controlled, inverse electron demand stepwise pathways for electron-rich dipolarophiles for each set of activation parameters. Hammett plots also afforded crucial insight into both sets of conditions (cf. Figures 1-4). In the case of the thermal-mediated zwitterionic-based cycloadditions, neutral alkenes were the least reactive, whereas both electron-deficient and electron-rich dipolarophiles were more reactive thus providing non-linear free energy relationships indicative of a change in mechanism. Hammett plots of the TBSOTf-mediated cycloadditions, however, revealed linear free energy relationships that are more in-line with a consistent mechanism throughout the reaction.

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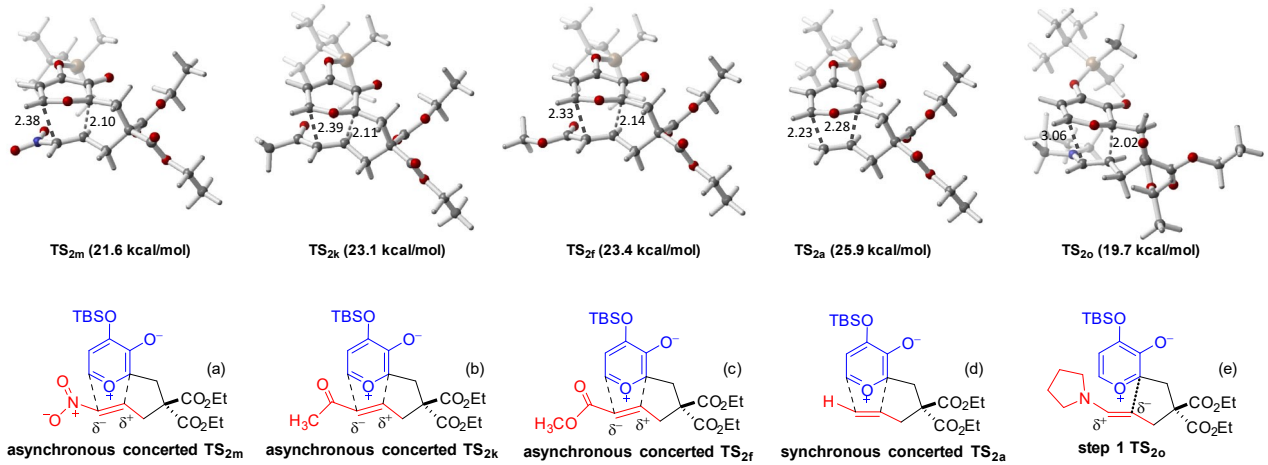
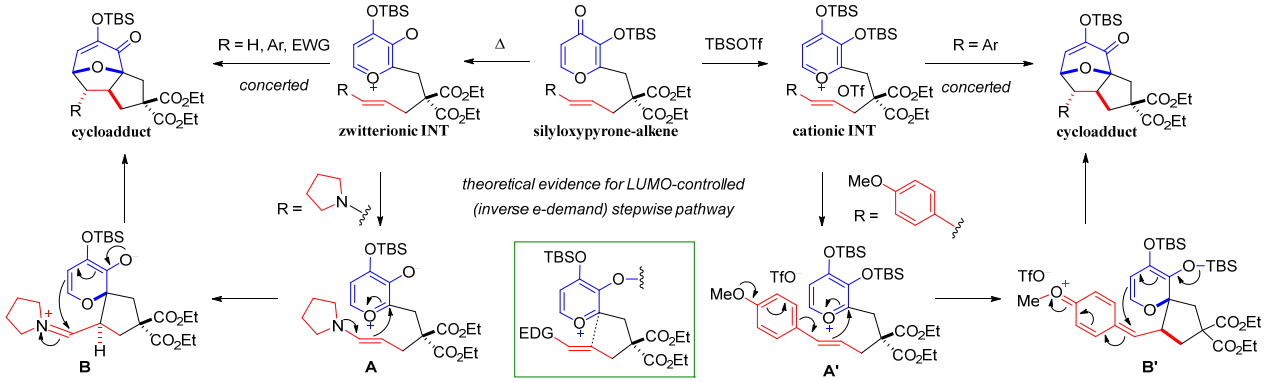


Figure 8. TSs of substitute olefins: (a) nitro; (b) ketone;[7b] (c) ester; (d) H;[7b] (e) amine[7b] (TBS only for simplicity)

Scheme 5. Unified Mechanism for Thermal (TBS only for simplicity) and TBSOTf-mediated (5 + 2) cycloadditions



Conclusions

Silyloxypyrone-based (5 + 2) cycloadditions were investigated using both thermal and TBSOTf-mediated processes that revealed similarities and differences between these modes of activation. Thermal-mediated (5 + 2) cycloaddition proceeds through a zwitterionic oxidopyrylium intermediate, whereas TBSOTf-mediated (5 + 2) cycloaddition proceeds via cationic, bis-silylated intermediates. Qualitative rate studies, Hammett plots, and quantum calculations combined to illustrate a dichotomy between these two pathways. In the case of thermally induced variants with both TBS and TBDPS, both electron-deficient and electron-rich dipolarophiles were more reactive than neutral alkenes thus providing evidence for ambident zwitterionic oxidopyrylium intermediates. Several examples reveal that the TBDPS lowers the activation barrier, but only for less polarized olefins. Although most thermal-initiated reactions were concerted, theoretical evidence for a stepwise reaction pathway of electron-rich enamines was predicted. In TBSOTf-mediated cycloadditions, by contrast, electron-rich dipolarophiles are the most reactive and electron-deficient dipolarophiles are the least reactive. This observation is suggestive of cationic intermediates that demonstrate a more linear free energy relationship. Theoretical evidence for a stepwise reaction pathway of the electron-donating methoxy styrene was also predicted. Overall, several dipolarophiles were investigated utilizing both modes of activation to probe the range of reactivity, which revealed a variety of mechanistic nuances between concerted and stepwise borderlands. A deep appreciation of these important mechanistic details is enabling opportunities to discover novel transformations to be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information. All computational structures are available in the ioChem-BD repository: https://doi.org/10.19061/iochem-bd-6-585

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