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C_3-Thioester/-Ester Substituted Linear Dienones: A Pluripotent Molecular Platform for Diversification via Cascade Pericyclic Reactions

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Abstract. Substituted oxabicyclo derivatives bearing two quaternary carbon centers and five contiguous stereocenters have been synthesized from C_3-thioester/-ester substituted dienones, a simple and linear pluripotent molecular platform. The conversion proceeds from neat reactants, possibly via a thermally-driven pericyclic cascade manifold involving sequential *(E)-s-trans* to *(E)-s-cis* isomerization, oxa-6π-electrocyclization, and intermolecular, regioselective [4π + 2π] cycloaddition. The proposed mechanism has been substantiated by intermediate trapping experiments and DFT studies. Such dienones have also been exploited to effect stereoselective cross Diels-Alder cycloadditions with olefins and sequential Diels-Alder/retro-Diels-Alder reactions with activated alkynes. The reaction is greatly influenced by the substituent effect exerted by the C_3-thioester/-ester group.

Keywords: Pericyclic reaction; dimerization; neat reactants; cycloaddition; pluripotent molecular platform

Introduction

Reagent-based diversity-oriented synthesis[1] that utilizes a densely functionalized substrate (pluripotent molecular platform) with cascade or domino reaction sequences represents a powerful strategy in organic synthesis and can immensely improve the efficiency of a chemical reaction. In this strategy, a common multifunctional substrate is transformed into diverse topologically complex molecular frameworks by using different reactants and reaction conditions.[2] Several well-designed pluripotent molecular platforms have been developed by different research groups.[1-3] Katsumura and Vanderwal's groups have extensively studied substituted dienals possessing well-defined and dense array of interrelated functionalities.[4,5a-g] Katsumura and co-workers found that the introduction of an ester group at the C_3-position of dienals dramatically altered the course of the reaction due to the remarkable accelerating effect of this substituent. For instance, dienals underwent pericyclic rearrangement in refluxing toluene solution via [1,5]-H shift of the aldehyde hydrogen to afford the intermediary vinyl ketene intermediate which was subsequently captured by an alcohol, olefin, or imine to afford esters, cyclobutanones, or azacyclobutanones (Scheme 1).[4a] They also succeeded in accelerating the key 6π-aza-electrocyclization step for the synthesis of multisubstituted piperidine and pyridine derivatives from 1-azatrienes.[5a-g] The substituent effect was rationalized based on molecular orbital calculation which supports the contention that the substituent at the C_3-position of dienal reduces the activation energy of the process.[5a,5c,5h]

Although substantial progress has been made with the dienals, reagent-based cascade reactions of the corresponding C_3-carbonyl substituted dienones have not been reported until recently due to the paucity of methods available to access them.[6] Over the past few years, we have been involved in the development of synthetic methods for cyclopropanated furans,[6a] regioselective $E \rightarrow Z$ isomerization of olefins,[6b] and butenolides[6c-d] from dienones **1**. Recently, we have reported that neat **1** underwent dimerization due to a substituent-driven acceleration effect via sequential *s-trans* to *s-cis* isomerization/regioselective *E/Z* isomerization/Diels−Alder cycloaddition to provide cyclohexene derivatives **2** under direct excitation of the reactant by visible light absorption (Scheme 1).[6b] But dienones lacking such substitution did not undergo the transformation (Scheme 1).

In the light of the above findings and to convert densely functionalized dienones into diverse scaffolds,

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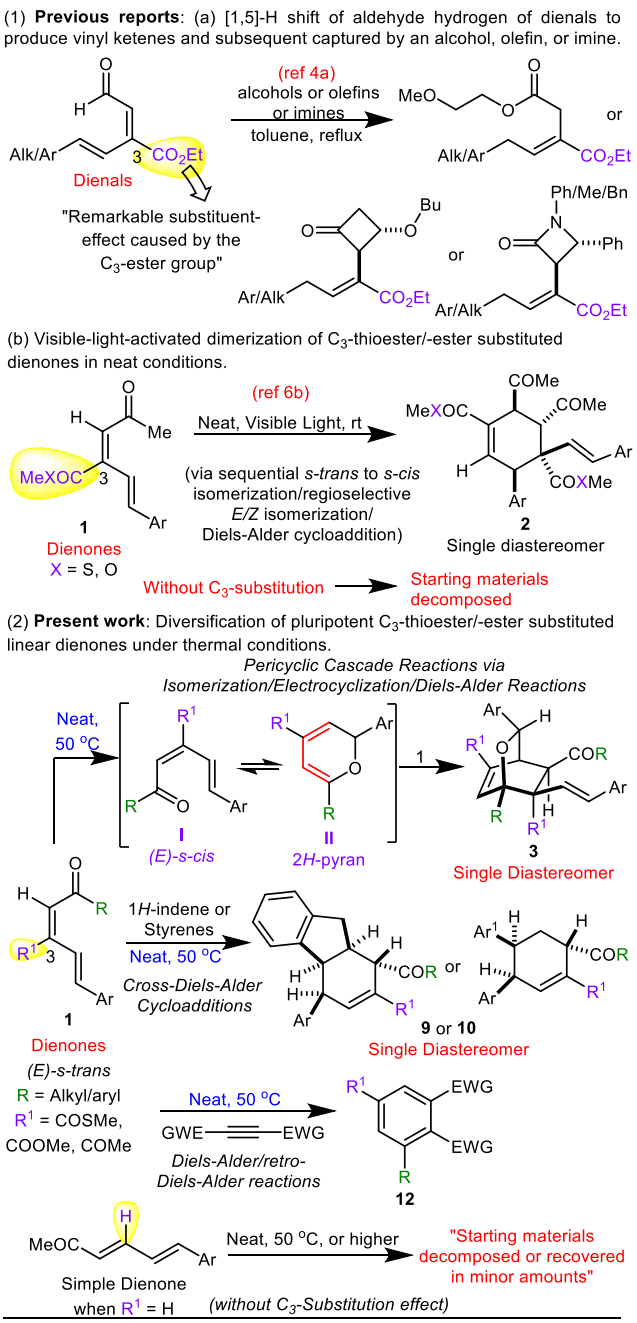

Scheme 1. C_3-ester/-thioester substituent-driven acceleration effect of dienals and dienones: previous and present work.

we planned to study their reactivity under thermal conditions. It was anticipated that C_3-C_4 single bond rotation of **1** would lead to the intermediate *(E)-s-cis*, capable of adopting a conformation in which it can undergo oxa-6π-electrocyclization to the reactive 2*H*-pyran intermediate. This could be subsequently trapped with a dienophile to deliver a range of bridged bicyclic molecules (Scheme 1). The anticipated product **3** was indeed isolated in minor amount when dienone **1** was stored neat at ambient temperature for a day. It may be pointed out that pericyclic cascade reactions,[7] the most versatile atom and step economical[8] transformation in synthetic organic chemistry, enable a straightforward access to complex and polycyclic products from simple starting materials. Recently, Diels-Alder dimerization of two identical 2*H*-pyrans has been showcased as useful pericyclic cascade reactions, which offer interesting applications in the biomimetic synthesis of natural products.[7d-g] However, the synthetic utility of monocyclic 2*H*-pyrans is somewhat restricted due to the substrate-dependent reversible nature of 6π-electrocyclization.[9] Increased steric interactions and the presence of specific electron-withdrawing groups in the π-conjugated system shift the equilibrium towards the 2*H*-pyran form.[10]

We now report solvent- and reagent-free,[11] atom- and step-economical, regio- and stereoselective thermally-driven cascade pericyclic reactions of pluripotent dienones, which underwent dimerization in neat condition, cross Diels-Alder cycloadditions with olefins, and sequential Diels-Alder/retro-Diels-Alder reactions with activated alkynes (Scheme 1).

Results and Discussion

The requisite dienones **1**[12] were readily prepared in pure form from the corresponding α-keto thioesters[13a-d] or esters[13e-f] following our previous reports. When **1a** was kept at ambient temperature (30 °C), **3a** was formed within a few days in 45% yield along with 50% of the recovered starting materials (Table 1, entry 1); the yellow crystalline solid slowly turned to a light green gummy liquid with the progress of the reaction. Extension of reaction time led to higher conversion to the product, while heating at 50 °C accelerated the transformation and improved the yield of **3a** to 64% (entry 2), although **1a** was recovered to the extent of 15%. But increasing the reaction temperature further (to 80 °C) proved counterproductive (entry 3). To improve the reaction efficiency, different additives were tried (Table 1, entries 4-9). But solid supports[14] such as silica gel, zeolite, silver-exchanged zeolite, montmorillonite (surface area 250 m^2/g), montmorillonite K 10 (surface area 220-270 m^2/g), and ionic liquids[15] such as 1-allyl-3-methylimidazolium dicyanamide, 1,3-dihydroxyimidazolium bis(trifluoromethylsulfonyl)-imide all proved unsuccessful. It is noteworthy that **1a** underwent decomposition in various solvents with the formation of minor amount of **3a** and substituted butenolide derivatives (not shown).[6c-d]

We next assessed the substrate scope of this dimerization reaction (Table 2). It was found that the C_3-thioester substituted dienones containing electron-withdrawing or electron-donating substituents on the C_5-aromatic ring (**1a-n**) gave the expected products **3a-n** bearing two quaternary carbon centers and five contiguous stereocenters as single diastereomers in moderate to good yields. Dienones containing phenyl

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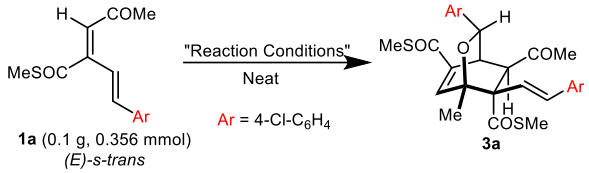
Table 1. Optimization studies for oxabicyclo derivatives.[a]



1a (0.1 g, 0.356 mmol)
(E)-s-trans

3a

entry	Reaction Conditions	time (h)	yield **3a** (%)
1	ambient temperature	120	45[b]
2	heated at 50 °C	47	64[b]
3	heated at 80 °C	15	<5[c]
4	Silica gel, 50 °C	48	25[c]
5	Zeolite, 50 °C	48	-[b]
6	Silver-exchanged zeolite, 50 °C	48	50[b]
7	montmorillonite or montmorillonite K 10, 50 °C	48	-[b]
8	1-allyl-3-methylimidazolium dicyanamide, 50 °C	48	-[c]
9	$(OH)_2$Im-NTf_2, 50 °C	48	-[c]

[a] *Reaction conditions*: **1a** was kept at ambient temperature or heated under the reaction conditions. Ambient temperature: 30 °C.

[b] Unreacted starting materials **1a** (for entry 1, 50%; entry 2, 15%; entry 5, 95%; entry 6, 16%; and entry 7, 92%) were isolated.

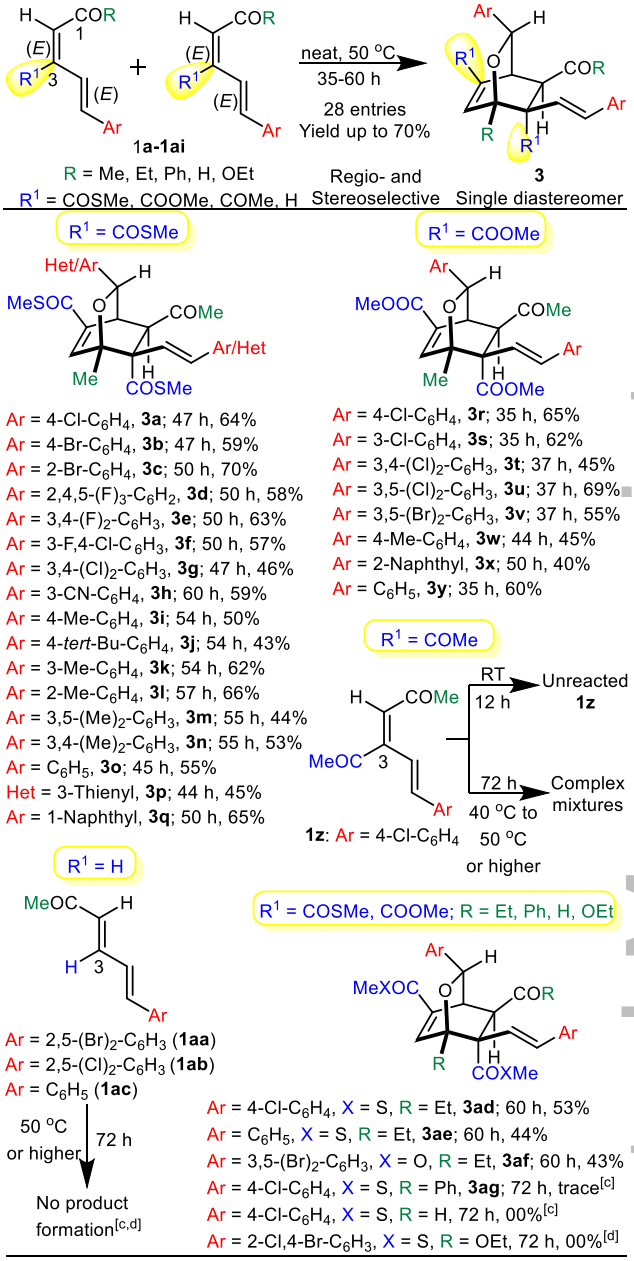
[c] Unidentified inseperable mixtures were formed. $(OH)_2$Im-NTf_2 = 1,3-dihydroxyimidazolium bis(trifluoromethylsulfonyl)imide

and improved the yield of **3a** to 64% (entry 2),

(**1o**), 3-thienyl (**1p**), or 1-naphthyl (**1q**) substituents at the C-5 position also furnished the expected products (**3o-q**). The replacement of the C_5-aromatic ring with an alkyl group like cyclohexyl was not tolerated (not shown), perhaps due to the need for extended conjugation for this pericyclic cascade reaction. Further investigation demonstrated that C_3-ester substituted dienones (**1r-y**) containing C_5-aromatic ring, which proved more reactive than the thioester analogous, could also be converted to the corresponding products in moderate to good yields (**3r-y**). But the expected product was not obtained when a dienone (**1z**) bearing C_3-COMe group was either stirred at room temperature or heated at 40 °C to 50 °C or higher temperature, possibly due to the presence of an additional C_3-keto group which leads to undesired side reactions. Moreover, the dimerization of substrates **1aa**, **1ab**, or **1ac**[16] lacking any substitution at the C_3-position was completely inhibited, which further supports the substituent-driven acceleration effect caused by the C_3-thioester/-ester group.[17a]

We next sought to extend the scope of this reaction by changing the C_1-group (Table 2). Replacement of the methyl group in dienone with an ethyl group continued to afford the corresponding products stereoselectively (**3ad**-**3af**), albeit a longer reaction time was needed (60 h). In contrast, the substrate **1ag** endowed with a C_1-phenyl group delivered the product **3ag** only in trace amount along with decomposed materials.[17b] The expected product was also not obtained when the C_1-methyl group was substituted with a hydrogen (**1ah**) or an ethoxy group

Table 2. Substrate scope for the C_3-substituent-driven rearrangement of dienones under thermal conditions.[a,b]



[a] *Reaction conditions*: Neat **1** (0.1 g) was heated at 50 °C.

[b] Along with product **3**, unreacted starting materials were also isolated.

[c] Complex inseparable mixtures.

[d] Unreacted starting dienones (**1**) isolated.

(**1ai**), attributed to the lack of sufficient electron density on the C_1-carbonyl group of dienones to undergo subsequent oxa-6π-electrocyclization. The structures of **3q** and **3y** were unambiguously established by single crystal X-ray diffraction analyses (Figure 1).[18]

A proposed mechanistic pathway for the formation of **3** is shown in Scheme 2. We presume that thermally induced *(E)-s-trans* to *(E)-s-cis*

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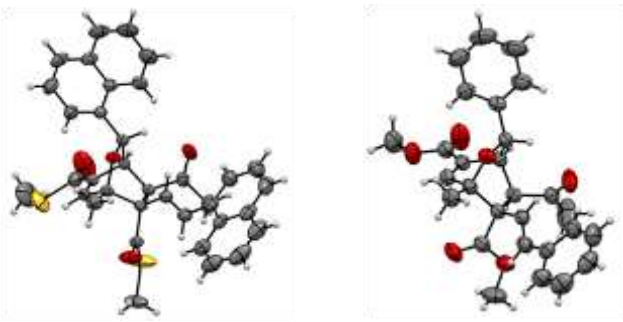
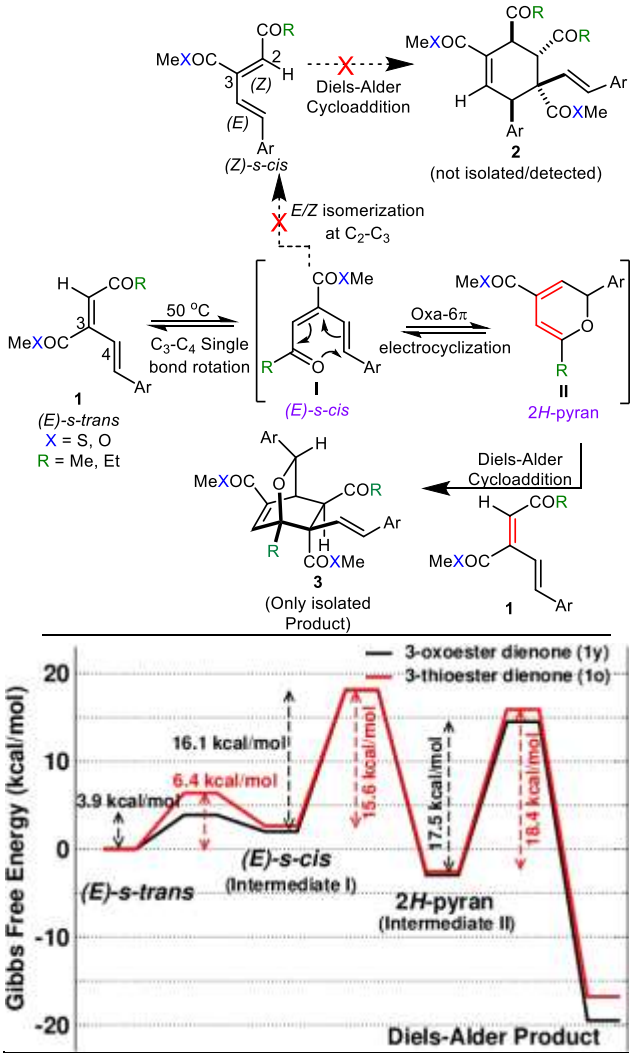


Figure 1. X-ray crystal structures of **3q** (CCDC 1871161) and **3y** (CCDC 1871167). Thermal ellipsoids are shown in 50% probability level.



Scheme 2. Proposed mechanism for the formation of **3** and results of DFT study of the reaction mechanism.

isomerization via C_3-C_4 single bond rotation could lead to the corresponding intermediate **I**, which might enable an oxa-6π-electrocyclic ring closure to afford the intermediate 2*H*-pyran (**II**). Subsequent intermolecular Diels-Alder cycloaddition of **II** with dienone **1** would furnish the desired product **3**.

We have quite recently reported that intermediate **I** underwent dimerization under photochemical conditions to yield **2** through an uphill *E*/*Z* isomerization of C_2-C_3 double bond followed by a Diels-Alder cycloaddition.[6b] In the present study carried out under thermal conditions, we observed the formation of dimerized product **3** exclusively. Concerning the differences in reactivity between the photochemical and thermal processes and subsequent formation of the different dimerized products **2** and **3**, respectively, we presume that a barrier of 35 kcal/mol (for **1o**)[6b] between *E* and *Z* isomers proves to be too large to be surmounted by the thermal events (at 50 °C reaction temperature), particularly in the absence of any catalyst and solvent. Therefore, intermediate **I** could not follow the *E*/*Z* isomerization pathway to deliver **2** under thermal conditions (Scheme 2). During our previous study under photochemical conditions also, we had not detected/isolated any dimerized product **3** arising from intermediate **I**.[6b] This may be ascribed to the fact that photoabsorption by the *E*-isomer excites the molecule to a higher energy state from where the formation of *Z*-isomer via the biradical mechanism may be a facile and viable process than oxa-6π-electrocyclization; subsequently the *Z*-isomer underwent rapid dimerization to afford **2** as the only isolated product.[6b] These results support the rationale behind the isolation of dimerized products **2** (previous work) and **3** (this work) exclusively under photochemical and thermal conditions, respectively.

It is interesting to note that the dimerization reactions summarized in Table 2 exhibit remarkable regio- and diastereoselectivity, only one isomer being formed in all cases.[19] Although several possible dimerization pathways are possible after the formation of 2*H*-pyran (step 2, Scheme 2), limited degrees of freedom and restricted molecular motions in the neat solid/liquid conditions of dienones may be responsible for the excellent stereochemical result. Moreover, we investigated the regioselectivity associated with the Diels-Alder cycloaddition step (step 3, Scheme 2) for the alternative products via DFT calculations. It shows that the activation energies associated with other regio- and diastereomeric products are higher than those of the experimentally observed product (see Figure S12 in the Supporting Information for details).

The mechanism proposed in Scheme 2 is corroborated by DFT calculations using substrates **1o** and **1y** as the representative cases.[20a] It outlined the reaction pathways by identifying the intermediates and the transitions states. The activation energy barriers for C_3-C_4 rotation of **1o** and **1y** to produce the corresponding intermediate **I** are estimated to be 6.4 and 3.9 kcal/mol, respectively. As shown in Figure 2 and 3, the highest occupied molecular orbitals of the *trans*- and *cis*- dienones have a very similar electron density distribution delocalized over the conjugated system. The antibonding overlap of the p_z orbitals of

C_3-C_4 seen in the HOMO of *trans*- and *cis*- isomers shows a modified interaction in the transition state, where the C_2-C_3 and C_4-C_5 double bonds are on orthogonal planes and the antibonding overlap of C_3-C_4 is quenched, leading to the stabilization of the transition state, as reflected by the lower HOMO energy in the transition state (Figure 2 and 3).[20a] This makes the isomerization reaction facile. The oxa-6π electrocyclization of intermediate **I** to produce intermediate **II** is estimated to involve activation energy barriers of 15.6 and 16.1 kcal/mol, for **1o** and **1y**, respectively. Finally, the Diels-Alder reaction of the intermediate **II** with dienone **1** involves barriers of 18.4 and 17.5 kcal/mol for **1o** and **1y**, respectively. Taken together, the DFT calculations show a smaller activation energy barrier for each step in the reaction involving **1y** as compared to **1o**, thus explaining the high reactivity of the former (Scheme 2). [20b-c]

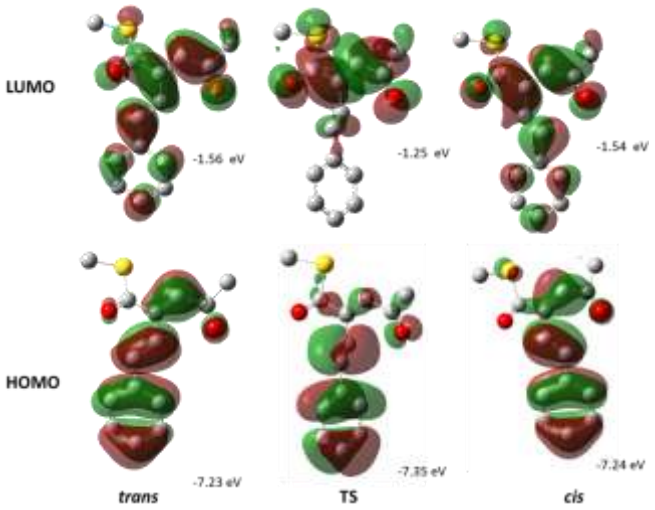


Figure 2. The HOMO and LUMO of *trans*- and *cis*-isomers of **1o** and those of the transition state separating the two.

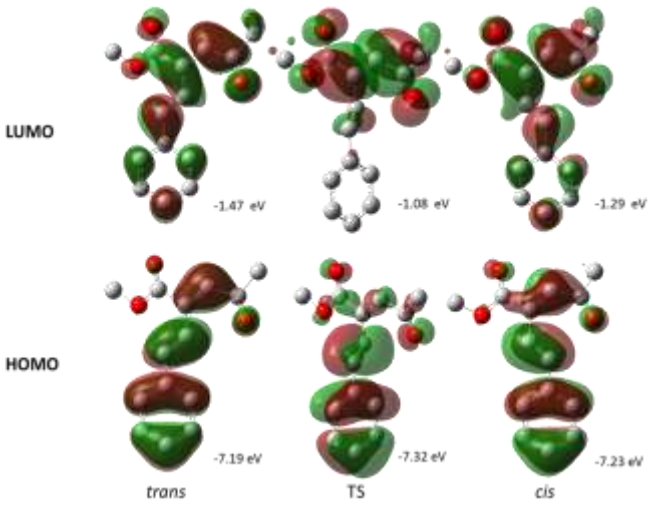
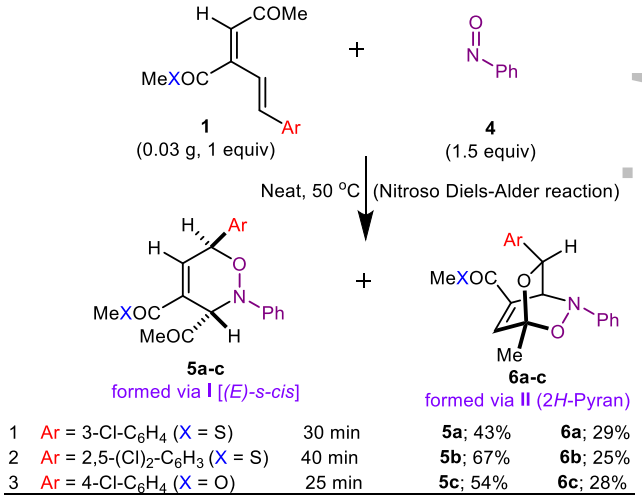


Figure 3. The HOMO and LUMO of *trans*- and *cis*-isomers of **1y** and those of the transition state separating the two.

Since we were unable to isolate the intermediates, trapping experiments with nitrosobenzene as a dienophile were conducted to better understand the intermediacy of **I/II** in Scheme 2. When **1** was mixed with 1.5 equiv of nitrosobenzene **4** and heated at 50 °C, two products each (**5a/6a**, **5b/6b**, or **5c/6c)** were isolated (Scheme 3). Analysis of the product mixtures revealed that the products **5a-c** must have formed via the intermediate **I**, whereas 6**a-c** originated from the intermediate **II**. The structures of **5b** and **6a** were unambiguously established by single crystal X-ray diffraction analyses (Figure 4).[18]



Scheme 3. Intermediate trapping experiments with nitrosobenzene **4** as a dienophile.

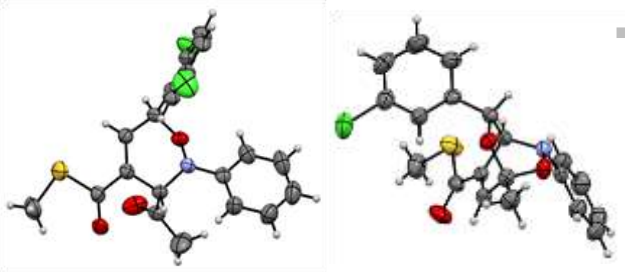
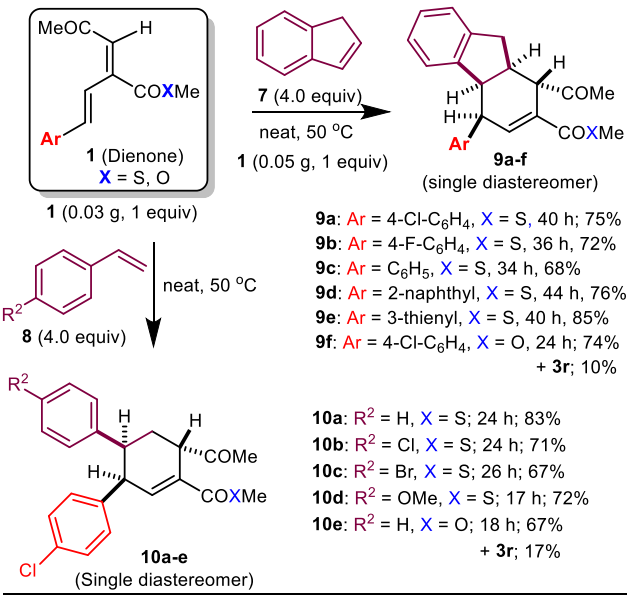


Figure 4. X-ray crystal structures of **5b** (CCDC 1871168) and **6a** (CCDC 1871169). Thermal ellipsoids are shown in 50% probability level.

Once the suitability of the dienones **1** for dimerization via pericyclic cascade rearrangement was demonstrated, the feasibility of the significantly more challenging cross Diels-Alder cycloadditions with olefins was examined, since **1** underwent slow dimerization even at ambient temperature (Scheme 4). We observed that the desired hybrid cycloadducts **9a-f** and **10a-e** were obtained exclusively as single diastereomers in good yields with no trace of dimerization product when neat 3-thioester substituted dienones **1** were heated at 50 °C with excess 1*H*-indene **7** or styrenes **8**. However, when 3-

ester substituted dienone **1r** was independently employed in these reactions with **7** and **8**, 10-17% of dimerization product (**3r**) was also isolated along with the desired cycloadducts **9f** and **10e**, presumably because of the increased reactivity of **1r**. The structures of **9f** and **10c** were unambiguously established by single crystal X-ray diffraction analyses (Figure 5).[18,21]



Scheme 4. Stereoselective cross Diels-Alder cycloadditions with 1*H*-indene **7** and styrenes **8**.

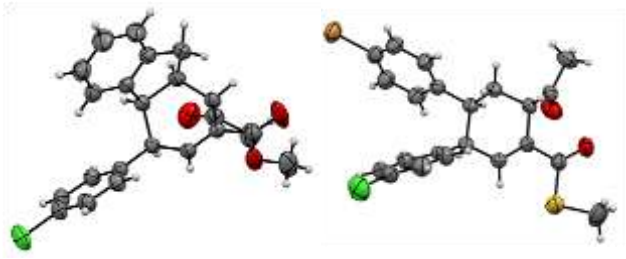
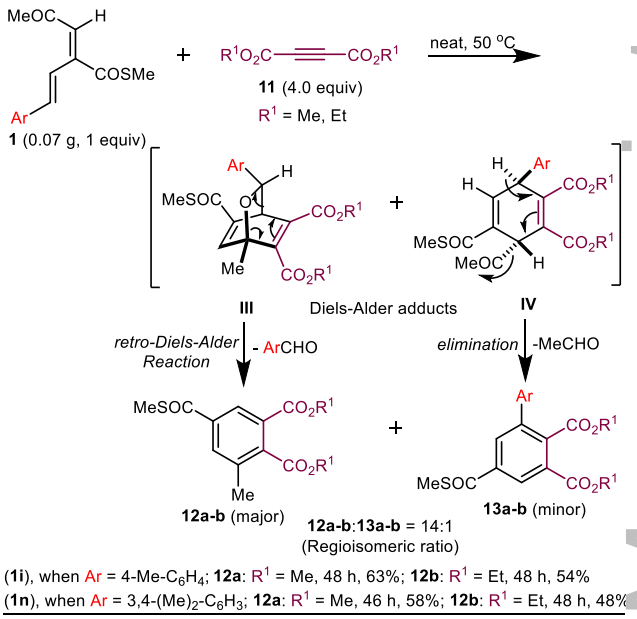


Figure 5. X-ray crystal structures of **9f** (CCDC 1871179) and **10c** (CCDC 1871178). Thermal ellipsoids are shown in 50% probability level.

To further highlight the potentiality of the pluripotent dienones, we next explored their utility in the synthesis of substituted aromatic rings by reacting with activated electron-poor alkynes as dienophiles (Scheme 5).[22] Indeed treatment of dienones **1i** and **1n** with acetylenedicarboxylate (**11**) in neat conditions at 50 °C afforded Diels-Alder adducts **III** and **IV**. Intermediate **III** underwent subsequent retro-Diels-Alder reaction to yield **12a-b** as separable major regioisomers in moderate yields, while in situ MeCHO elimination from the intermediate **IV** yielded minor product **13a-b**.[21] The selectivity of the reaction is high, affording **12a-b** and **13a-b** as 14:1 mixtures of isomeric benzene derivatives.

We next sought to extend the scope of this reaction by replacing the alkyl group of an acetylenic diester (**11**) with aromatic rings (Ph and C_6H_4-*p*-Me). But the expected products were obtained only in trace amounts along with the unreacted starting dienones (not shown), though the exact reason is not very clear at this moment. Moreover, alkynes such as diphenylacetylene and phenylacetylene were found to be completely inactive under the standard reaction conditions. Efforts to address this limitation and further optimization are presently ongoing in our laboratory and the findings will be reported in due course.



Scheme 5. Synthesis of substituted benzene derivatives from dienones.

Conclusion

In conclusion, we have demonstrated the use of linear C_3-thioester/-ester substituted dienones as pluripotent molecular platforms for reagent-based diversity-oriented synthetic strategies under thermal conditions. The neat substrates undergo highly regio- and stereocontrolled cascade pericyclic reactions due to the substituent-driven acceleration effect to produce oxabicyclo derivatives bearing two quaternary carbon centers and five contiguous stereocenters. The proposed mechanism has been corroborated through intermediate trapping experiments and DFT studies. The reactions of these dienones with olefins and activated alkynes have been shown to generate the corresponding cross-Diels-Alder cycloadducts and substituted benzene derivatives, respectively. Thus, through the use of branching paradigm under thermal conditions, we could generate a set of distinct and diverse molecular frameworks.

Experimental Section

General Procedure and Representative Examples

General Procedure for the Synthesis of 3. C_3-thioester/-ester substituted neat *(E)-s-trans* dienones **1** (solid or gummy liquid) were heated at 50 °C. After completion of the reaction (TLC), the crude residue was purified by silica gel column chromatography [230–400 mesh; eluent: ethyl acetate/*n*-hexane] to obtain **3**.

***S*,*S*-dimethyl (1R*,3R*,4R*,7R*,8S*)-8-acetyl-3-(4-chlorophenyl)-7-((*E*)-4-chlorostyryl)-1-methyl-2-oxabicyclo[2.2.2]oct-5-ene-5,7-bis(carbothioate) 3a:** Prepared according to the general procedure discussed above: R_f = 0.3; eluent, EtOAc/*n*-hexane (15%); light red solid (0.064 g, 64%); mp 71–73 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (d, J = 8.0 Hz, 2 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.17 (d, J = 2.0 Hz, 1 H), 7.09 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 16.8 Hz, 1 H), 6.40 (d, J = 16.4 Hz, 1 H), 5.53 (s, 1 H), 3.69 (q, J = 2.4 Hz, 1 H), 3.34 (d, J = 2.0 Hz, 1 H), 2.32 (s, 3 H), 2.15 (s, 3 H), 2.14 (s, 3 H), 1.55 ppm (s, 3 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 206.8, 201.5, 188.7, 142.6, 140.3, 139.8, 135.0, 134.4, 134.0, 132.9, 128.9 (2 CH), 128.2 (2 CH), 127.8 (2 CH), 127.1 (2 CH), 125.6, 77.3, 71.6, 64.8, 55.9, 38.8, 32.2, 21.0, 13.3, 11.3 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1708, 1660, 1490, 1411, 1356, 1304, 1249, 1176, 1095, 1008, 820 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{26}Cl_2O_4S_2Na$ [M + Na]$^+$: 583.0548; found: 583.0532.

Dimethyl (1R*,3R*,4R*,7R*,8S*)-8-acetyl-3-(4-chlorophenyl)-7-((*E*)-4-chlorostyryl)-1-methyl-2-oxabicyclo[2.2.2]oct-5-ene-5,7-dicarboxylate 3r: Prepared according to the general procedure discussed above: R_f = 0.3; eluent, EtOAc/*n*-hexane (25%); white solid (0.065 g, 65%); mp 73–75 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.48 (d, J = 7.8 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 7.8 Hz, 2 H), 7.22 (s, 1 H), 7.12 (d, J = 7.8 Hz, 2 H), 6.52 (d, J = 16.8 Hz, 1 H), 6.31 (d, J = 16.8 Hz, 1 H), 5.66 (s, 1 H), 3.79 (s, 3 H), 3.64 (s, 1 H), 3.50 (s, 3 H), 3.32 (s, 1 H), 2.16 (s, 3 H), 1.59 ppm (s, 3 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 208.1, 173.0, 163.8, 145.6, 140.3, 134.6, 134.3, 134.0, 132.8, 132.6, 128.9 (2 CH), 128.1 (2 CH), 127.7 (2 CH), 127.0 (2 CH), 126.6, 76.6, 71.6, 59.0, 54.4, 52.8, 52.0, 38.3, 31.8, 21.1 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1721, 1490, 1441, 1367, 1274, 1216, 1080, 814, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}Cl_2O_6$ [M + H]$^+$: 529.1184; found: 529.1201.

General Procedure for the Synthesis of 9a-f. In a sealed tube, **1** (0.05 g, 1.0 equiv) was heated at 50 °C with 1*H*-indene (**7**, 4.0 equiv) under neat conditions for 24 – 44 h. After completion of the reaction (TLC), the crude residue was purified by silica gel column chromatography [230–400 mesh; eluent: ethyl acetate/*n*-hexane] to obtain **9a-f**.

***S*-methyl (1*R**,4*S**,4a*R**,9a*S**)-1-acetyl-4-(4-chlorophenyl)-4,4a,9,9a-tetrahydro-1*H*-fluorene-2-carbothioate 9a:** Prepared according to the general procedure discussed above: R_f = 0.3; eluent, EtOAc/*n*-hexane (6%); light yellow solid (0.053 g, 75%); mp 124–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 (d, J = 3.6 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 7.01 - 7.05 (m, 2 H), 6.90 (d, J = 8.4 Hz, 2 H), 6.74 (t, J = 7.8 Hz, 1 H), 5.83 (d, J = 7.8 Hz, 1 H), 4.21 (d, J = 2.4 Hz, 1 H), 4.02 (t, J = 9.0 Hz, 1 H), 3.85 (dd, J = 3.6, 9.0 Hz, 1 H), 3.56 - 3.61 (m, 1 H), 3.03 (dd, J = 9.0, 15.6 Hz, 1 H), 2.63 (dd, J = 8.4, 16.2 Hz, 1 H), 2.40 (s, 3 H), 2.23 ppm (s, 3 H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 206.0, 192.2, 145.2, 142.8, 142.7, 139.3, 137.9, 132.7, 130.7 (2 CH), 128.4 (2 CH), 127.2, 126.9, 125.3, 124.1, 52.6, 49.3, 43.8, 38.6, 38.5 (CH_2), 28.8, 11.7 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1711, 1645, 1413, 1144, 773, 697 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}ClO_2SNa$ [M + Na]$^+$: 419.0849; found: 419.0858.

General Procedure for the Synthesis of 10a-e. In a sealed tube, **1** (0.03 g, 1.0 equiv) was heated at 50 °C with substituted styrenes (**8**, 4.0 equiv) under neat conditions for 17 – 26 h. After completion of the reaction (TLC), the crude residue was purified by silica gel column chromatography [230–400 mesh; eluent: ethyl acetate/*n*-hexane] to obtain **10a-e**.

***S*-methyl (1'R*,2'S*,5'R*)-5'-acetyl-4''-chloro-1',2',5',6'-tetrahydro-[1,1':2',1''-terphenyl]-4'-carbothioate 10a:** Prepared according to the general procedure discussed above: R_f = 0.3; eluent, EtOAc/*n*-hexane (10%); white solid (0.034 g, 83%); mp 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 5.2 Hz, 1 H), 7.11 - 7.12 (m, 3 H), 7.03 (d, J = 8.0 Hz, 2 H), 6.67 - 6.70 (m, 2 H), 6.50 (d, J = 8.4 Hz, 2 H), 4.06 (d, J = 7.6 Hz, 1 H), 3.82 (t, J = 5.6 Hz, 1 H), 3.31 (ddd, J = 2.4, 5.4, 13.5 Hz, 1 H), 2.35 (s, 3 H), 2.30 (s, 3 H), 2.17 - 2.26 (m, 1 H), 1.91 ppm (d, J = 14.0 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 207.8, 193.1, 141.6, 141.4, 138.2, 135.5, 133.1, 131.3 (2 CH), 128.2 (2 CH), 128.0, 127.8 (2 CH), 126.8 (2 CH), 48.0, 47.0, 39.7, 28.9, 23.9 (CH_2), 11.6 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 3934, 2937, 1710, 1648, 1153, 1017 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}ClO_2SNa$ [M + Na]$^+$: 407.0849; found: 407.0850.

General Procedure for the Synthesis of 12a-b and 13a-b. In a sealed tube, **1i** or **1n** (0.07 g, 1.0 equiv) was heated at 50 °C with acetylenic diesters (**11a-b**, 4.0 equiv) under neat conditions for 46 - 48 h. After completion of the reaction (TLC), the crude residue was purified by silica gel column chromatography [230–400 mesh; eluent: ethyl acetate/*n*-hexane] to obtain **12a-b**. Two separable regioisomers [**12a-b**/**13a-b** = 14:1] was formed which was confirmed by the mixtures of ^{1}H NMR spectra.

Dimethyl 3-methyl-5-((methylthio)carbonyl)phthalate 12a: Prepared according to the general procedure discussed above: R_f = 0.3; eluent, EtOAc/*n*-hexane (10%); white solid (0.048 g, 63% from **1i** and 0.042 g, 58% from **1n**); mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 1.6 Hz, 1 H), 7.96 (d, J = 1.2 Hz, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 2.49 (s, 3 H), 2.39 ppm (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 191.2, 169.0, 165.4, 139.4, 137.4, 136.6, 132.6, 128.4, 126.3, 52.9, 52.8, 19.2, 12.0 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1726, 1656, 1310, 1266, 1082, 831, 788 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{14}O_5SNa$ [M + Na]$^+$: 305.0460; found: 305.0484.

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[17] a) In the absence of electron withdrawing substituent at the C_3 of dienones, the computed activation energy barriers for C_3-C_4 single bond rotation, oxa-6π electrocyclization, and Diels-Alder product formation are estimated as 9.6, 17.8 and 26.2 kcal/mol, respectively. These barriers are considerably higher than those obtained for 3-oxoester (**1y**) and 3-thioester (**1o**) substituted dienone. This explains the lack of product formation in the absence of an electron withdrawing group at the C_3-position. For details and the comparison of the activation energy barriers for the reaction with and without electron withdrawing groups at the C_3 position, see Figure S11 in the supporting information; b) **1ag** did not undergo oxa-6π-electrocyclization presumably due to the lack of sufficient electron density on the carbonyl group. The effect of a Ph group at the C_1-position of dienone could also be explained by activation energy parameter. For details and the comparison of the free energy profiles of the reaction, see Figure S10 in the Supporting Information.

[18] CCDC 1871161 (**3q**), 1871167 (**3y**), 1871168 (**5b**), 1871169 (**6a**), 1871179 (**9f**), 1871178 (**10c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

[19] The formation of a single diastereomeric product **3** was confirmed by the analysis of the crude product by LC-MS.

[20] a) The *trans*- and *cis*- isomers of dienones (**1o** and **1y**) and the transition states are optimized with DFT M06-2X/6-31G** method. For details, see computational details in the supporting information; b) The difference in the activation energy barriers between the ester (**1y**) and thioester (**1o**) for the Diels-Alder step is small (0.9 kcal/mol). This value may be within the margin of experimental error. It should also be noted that the initial step, i.e., C_3-C_4 sigma bond rotation requires higher activation energy (by 2.5 kcal) for the thioester than the oxoester, and the product (**3y**) derived from the oxoester is thermodynamically more stable than that obtained from the thioester (**3o**). All these observations allowed us to conclude that the reactivity of esters is higher than the thioesters; c) In Scheme 2, the first and second steps are unimolecular while the third step is bimolecular. The activation energy of the second step of Scheme 2 is obtained from the difference in the optimized energy of the transition state (between intermediate **I** and 2*H*-Pyran) and the intermediate **I** (Scheme 2). The activation energy barrier for the third step (a bimolecular Diels-Alder reaction) of Scheme 2 is obtained from the energy difference between the optimized transition state of the Diels-Alder reaction and the reactant of this reaction (i.e., one molecule of 2*H*-pyran and one molecule of *(E)-s-trans* (**1**)). To represent the overall reaction in a single energy profile, we equated the energy of 2*H*-Pyran obtained in the second step to the energy of the system containing 2*H*-Pyran and the reactant in the third step of the reaction (Scheme 2).

[21] It is noteworthy that the reaction did not proceed as expected in various solvents and mostly unreacted starting materials with traces of desired products were isolated.

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FULL PAPER

C_3-Thioester/-Ester Substituted Linear Dienones: A Pluripotent Molecular Platform for Diversification via Cascade Pericyclic Reactions

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