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COMMUNICATION

A domino pericyclic route to polysubstituted salicylic acid derivatives: four sequential processes from enynones and ketene silyl acetals†

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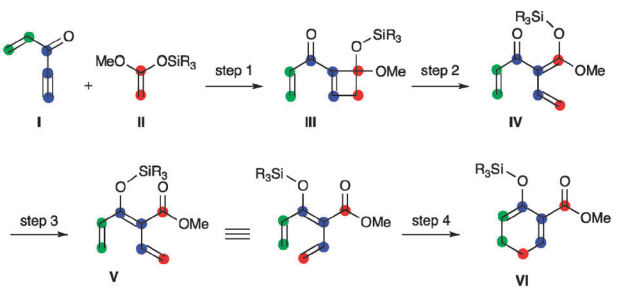
Alkenyl alkynyl ketones and ketene silyl acetals (KSAs) undergo regioselective [2 + 2]-cycloaddition under thermal conditions, triggering domino pericyclic reactions en route to various poly-substituted salicylic acid derivatives.

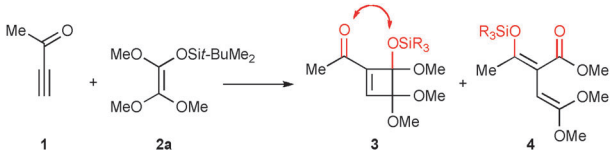
Domino reactions, *i.e.*, sequential one-pot chemical transformations without isolating intermediates, provide unique opportunities in organic synthesis.[1] Among attractive features, worth mentioning are rapid increase in the molecular complexity and reduction of the operational/material loads.

We report herein a domino pericyclic process en route to poly-substituted salicylic acid derivatives (Scheme 1). The [2 + 2] cycloaddition of enynone **I** to ketene silyl acetal (KSA) **II** (step 1)[2] is a prelude to a three-step domino process, electrocyclic ring opening (step 2),[3] 1,5-silatropy (step 3),[4] and 6π-electrocyclization (step 4),[5] allowing access to salicylate **VI**.



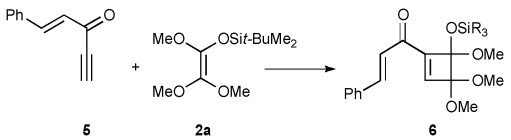
Scheme 1 Domino pericyclic reaction.

Two clues were drawn from our previous study.[2] Firstly, the [2 + 2] cycloaddition of alkynone **1** to KSA **2a** proceeded with rigorous regioselectivity, giving cycloadduct **3**[6,7] with the siloxy group near the carbonyl group. This regioselectivity provides cyclobutene **3** with a unique reactivity: the thermal electrocyclic opening is accompanied by a 1,5-silatropic reaction (steps 2 and 3, Scheme 1), giving 1,3-diene **4** as a side product (Scheme 2).



Scheme 2 Clue no. 1: potential reactivity in **3**.

The second clue was that *ene–yne* substrate **5** was found to react at its *yne* moiety to give dienone **6**, convincing us to test the *domino process* (Scheme 3).



Scheme 3 Clue no. 2.

As a test case, dienone **6** was exposed to thermal conditions (Table 1). Upon heating in xylene (140 °C), dienone **6** was quickly consumed (5 min), giving diester **7** in 82% yield (entry 1). Note that diester **7** is representing the formation of hexatriene **7′**, as the hydrolysis (**7′** → **7**) is quite facile in silica-gel chromatography. As entry 2 shows, on heating for a longer time, the initially formed hexatriene **7′** (judged by the amount of **7** by a TLC-assay) was gradually consumed, giving cyclohexadiene **8** (19% yield), the aromatized product **9** by thermal elimination of MeOH (49% yield) and some remaining diester **7**.[8,9] When the reaction was performed at a higher temperature (165 °C), the domino reaction including the final aromatization was driven to completion, giving salicylate **9** in 78% yield (entry 3). Addition of 2,6-lutidine, though not essential, realized a slightly faster reaction, giving **9** in 80% yield (entry 4).

We then attempted to perform all the steps *in one pot*, starting from the [2 + 2] cycloaddition of enynone **5** to KSA **2a** (Scheme 4). A mixture of enynone **5** and KSA **2a** was heated at 60 °C under solvent-free conditions, and the TLC assay confirmed the completion of the [2 + 2]-cycloaddition after 1 h. After the reaction mixture was diluted with mesitylene (0.1 M), heating was continued at 165 °C for 14 h, thereby affording salicylate **9** in 75% yield (listed as entry 1 in Table 2). Importantly, the dilution was essential at the stage of the

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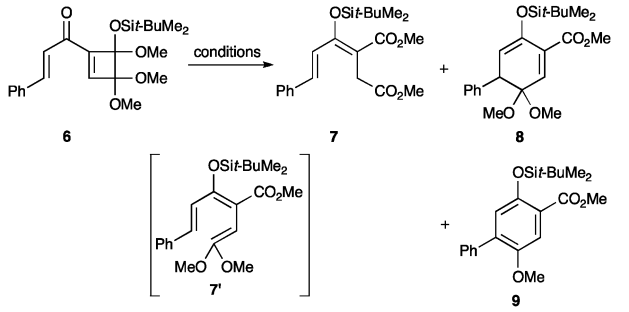
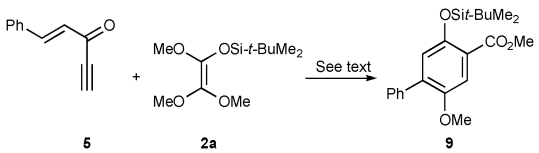
Table 1 Model experiments



Entry	Conditions	Yield of **7** (%)	Yield of **8** (%)	Yield of **9** (%)
1	Xylene, 140 °C, 5 min	82	—	—
2	Xylene, 140 °C, 12 h	24	19	49
3	Mesitylene, 165 °C, 14 h	—	—	78
4	Mesitylene, 2,6-lutidine, 165 °C, 10 h	—	—	80



Scheme 4 Domino pericyclic reaction to give salicylate **9**.

6π-electrocyclization, avoiding the competing polymerization of the hexatriene intermediate.

Table 2 summarizes the application of this one-pot protocol to various substrate combinations. Upon heating enynone **10** with KSA **2a**, the domino process occurred smoothly to give penta-substituted benzene **13** in 71% yield (entry 2). Similarly, the reaction of **11** with a cyclohexenyl group gave tetrahydronaphthalene **14** in good yield (entry 3).

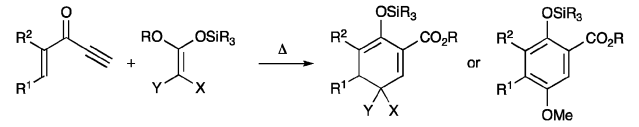
When KSA **2b** was used as the substrate (entry 4), the initially formed [2+2] cycloadduct was reactive, proceeding readily to the following steps at lower temperature.[10] Interestingly, however, the aromatization stage was relatively slow in this case, giving cyclohexadiene **15** as the product (86% yield), with the *cis* isomer predominating.

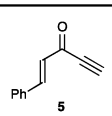
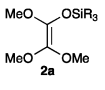
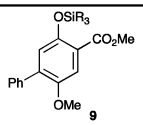
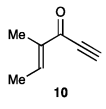
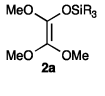
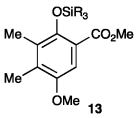
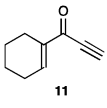
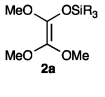
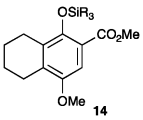
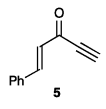
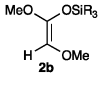
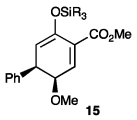
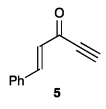
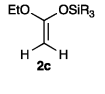
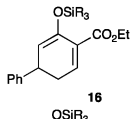
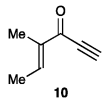
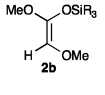
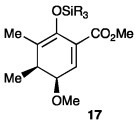
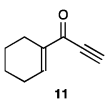
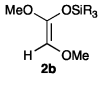
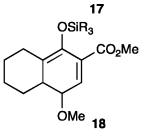
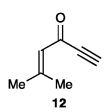
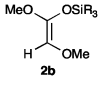
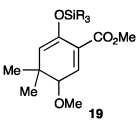
Less oxygenated KSA **2c** reacted also smoothly with enynone **5** (entry 5). In this case, better results were obtained by omitting the pre-heating at 60 °C at the stage of the [2+2] cycloaddition. By just applying higher reaction temperatures from the outset (140 °C, xylene), cyclohexadiene **16** was obtained in 62% yield.

Comparison of the reactivities of KSA **2a–c** (entries 1, 4, and 5) suggested that the domino pericyclic processes are more facile for less substituted cases (**2a** < **2b** < **2c**). The tendency is consistent with the reactivity order of the ring opening of the cyclobutene **A**[11] as well as the electrocyclic closure of the corresponding hexatriene **B** (Fig. 1).[12,13]

Similarly, the reactions worked well with ketones **10** and **11** by treatment with KSA **2b**, affording the poly-functionalized products **17** and **18** as single stereoisomers, respectively (entries 6 and 7). Furthermore, the pericyclic domino process proved applicable to substrate **12** with a β,β-substituted olefinic moiety (entry 8), and heating with KSA **2b** gave cyclohexadiene **19**.

Table 2 One-pot domino pericyclic reaction of enynone and KSA



Entry	Substrate	KSA	Conditions	Product[c]	Yield (%)
1[a]			60 °C, 1 h 165 °C, 14 h		75
2[a]			60 °C, 5 h 165 °C, 12 h		71
3[a]			60 °C, 8 h 165 °C, 12 h		66
4[b]			60 °C, 1 h 140 °C, 3 h		86[d]
5[b]			140 °C, 3 h		62
6[b]			60 °C, 7 h 140 °C, 2 h		56[e]
7[b]			80 °C, 5 h 140 °C, 8 h		50[e,f]
8[b]			60 °C, 10 h 140 °C, 5 h		60

[a] In mesitylene. [b] In xylene. [c] SiR_3 = Si*t*-BuMe_2. [d] *cis*/*trans* = 6:1. [e] Single isomer. [f] Stereochemistry was not determined.

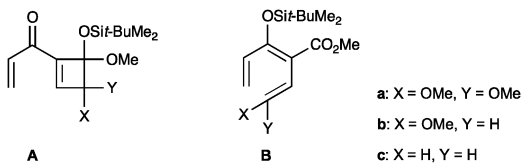
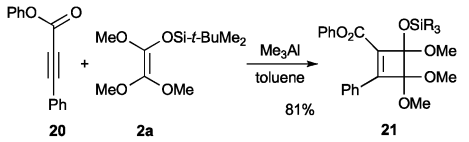


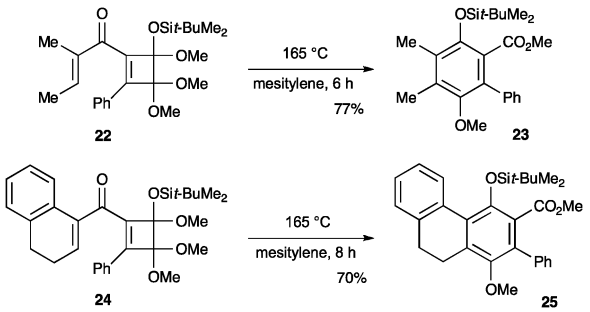
Fig. 1 Reactivity of substituted cyclobutenes and hexatrienes.

It is notable that the final 6π electrocyclization proceeded for a sterically congested hexatriene (not shown).

For exploring further scope of the domino process, we addressed the applicability to more substituted enynones. As the initial [2+2]-cycloaddition required the Me_3Al-promoted conditions for the β-substituted alkynes such as **20** (Scheme 5),[2] advanced substrates, dienones **22** and **24**,[14] were prepared from the [2+2]-cycloadduct **21** and subjected to the thermal conditions.



Scheme 5 [2 + 2] Cycloaddition of phenyl-substituted ynoate **20**.



Scheme 6 Domino pericyclic reaction of fully substituted cyclobutenes.

We were pleased to find that, upon heating, cyclobutene **22** having a 2-methylbut-2-enoyl group and a phenyl group on the four-membered ring underwent the domino reaction smoothly, giving hexa-substituted benzene **23** in 77% yield (Scheme 6). Similarly, the related substrate **24** with a cyclohexenylcarbonyl group was cleanly converted to poly-substituted dihydrophenanthrene **25**.

In summary, we described domino pericyclic reactions to poly-substituted 6-membered compounds by reaction of the alkenyl alkynyl ketone with KSA. Further studies are currently in progress.

Notes and references

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6 For reviews of cyclobutene derivatives, see: J. L. Segura and N. Martin, *Chem. Rev*., 1999, **99**, 3199.

7 For our contributions, see: (*a*) T. Matsumoto, T. Hamura, M. Miyamoto and K. Suzuki, *Tetrahedron Lett*., 1998, **39**, 4853; (*b*) T. Hamura, M. Miyamoto, T. Matsumoto and K. Suzuki, *Org. Lett*., 2002, **4**, 229; (*c*) T. Hamura, M. Miyamoto, K. Imura, T. Matsumoto and K. Suzuki, *Org. Lett*., 2002, **4**, 1675; (*d*) T. Hamura, T. Suzuki, T. Matsumoto and K. Suzuki, *Angew. Chem., Int. Ed*., 2006, **45**, 6294.

8 Initially formed triene as **IV** by the ring opening of **6** was not detected.

9 All new compounds were fully characterized by spectroscopic means and combustion analysis. For details, see ESI†.

10 Due to its high reactivity, the [2 + 2] cycloadduct easily isomerized to the corresponding ring opened product during purification.

11 For the conrotatory ring opening of substituted cyclobutenes, outward rotation becomes more preferred, as the donor character of the substituent increases. In the case of fully oxygenated cyclobutene **Aa** (X = Y = OMe), one of the two methoxy groups has to rotate inward, which is energetically unpreferable. For theoretical studies on torquoselectivity, see: (*a*) N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc*., 1985, **107**, 2099; (*b*) K. N. Houk, D. C. Spellmeyer, C. W. Jefford, C. G. Rimbault, Y. Wang and R. D. Miller, *J. Org. Chem*., 1988, **53**, 2125.

12 Calculation showed that steric effects pose a larger influence on the preference for inward/outward rotation of the substituent in the substituted 1,3,5-hexatrienes, see: J. D. Evanseck, B. E. Thomas IV, D. C. Spellmeyer and K. N. Houk, *J. Org. Chem*., 1995, **60**, 7134.

13 Stereochemistry of the cyclobutene and hexatriene intermediates in the reaction of KSA **2b** was not determined.

14 For preparation, see ESI.† See also ref. 2.