

# Cyclization Cascades Initiated by 1,6-Conjugate Addition

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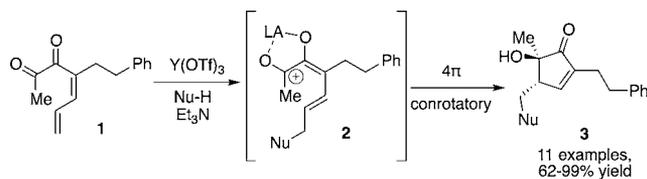
**S** Supporting Information

**ABSTRACT:** Dienyl diketones containing tethered acetates selectively undergo two different 1,6-conjugate addition-initiated cyclization cascades. One is a 1,6-conjugate addition/cyclization sequence with incorporation of the nucleophile, and the other is catalyzed by DABCO and is thought to proceed via a cyclic acetoxonium intermediate. The reaction behavior of substrates lacking the tethered acetate was also studied. The scope of both types of cyclization cascades, the role of the amine additive, and the factors controlling reactivity and selectivity in the two different reaction pathways is discussed.

Functionalized cyclopentenones containing quaternary stereogenic carbon centers are valuable building blocks for the preparation of interesting small molecules. Efficient, catalytic methods for the assembly of these targets via Nazarov cyclization have been studied extensively in recent years<sup>1</sup> and capitalize on the conservation of orbital symmetry<sup>2</sup> as a means to control relative stereochemistry. Typically, either a Brønsted or a Lewis acid is used to promote the  $4\pi$  cationic electrocyclozation.

Recently, we reported that 1,6-conjugate addition of a nucleophile to dienyl diketone **1** could initiate Nazarov cyclization, via pentadienyl cation **2** (Scheme 1).<sup>3</sup> Further

## Scheme 1. Conjugate Addition-Initiated Nazarov Cyclization

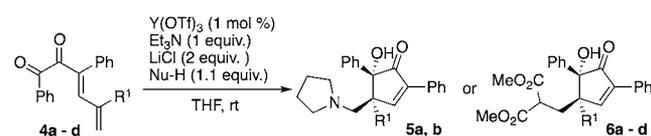


study of nucleophile-initiated cyclization of this kind has revealed a new type of cascade cyclization, which occurs under neutral reaction conditions, yet produces a stereochemical result consistent with cationic electrocyclozation. In this communication, we describe the two reaction pathways available to dienyl diketones upon treatment with nucleophiles and present a mechanistic rationale for the unusual reactivity observed.

A series of diketone substrates of type **4** were prepared for examination in the conjugate addition-initiated reaction. Substrates in which  $R^1 \neq H$  were of particular interest, since conrotatory cyclization would install adjacent tertiary and all-carbon quaternary centers stereospecifically in these systems.

We found that conjugate addition-initiated Nazarov cyclization proceeded smoothly with pyrrolidine to give products of type **5** (Table 1, entries 1 and 3) and with dimethyl malonate to

**Table 1. Lewis Acid Catalyzed Conjugate Addition/ Electrocyclization Cascade<sup>a</sup>**



entry	$R^1 =$	nucleophile	base	yield (product; %)
1	<b>4a</b> , H	pyrrolidine	$Et_3N$	<b>5a</b> ; 87
2	<b>4a</b> , H	dimethylmalonate (DMM)	$Et_3N$	<b>6a</b> ; 83
3	<b>4b</b> , Me	pyrrolidine	$Et_3N$	<b>5b</b> ; 85
4	<b>4b</b> , Me	DMM	$Et_3N$	<b>6b</b> ; 78
5	<b>4b</b> , Me	DMM	DABCO <sup>b</sup>	<b>6b</b> ; 72
6	<b>4c</b> , $(CH_2)_2OAc$	DMM	$Et_3N$	<b>6c</b> ; 89
7	<b>4c</b>	DMM	DABCO <sup>b</sup>	see Table 2
8	<b>4d</b> , $(CH_2)_3OAc$	DMM	$Et_3N$	<b>6d</b> ; 87

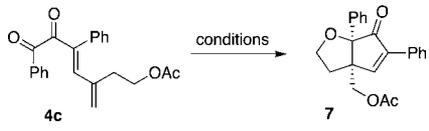
<sup>a</sup>Reaction conditions: Diketone **4** added to a stirring solution of  $Y(OTf)_3$  (1 mol %),  $LiCl$  (2 equiv), base (1 equiv), and the nucleophile in THF (1 M) at rt. <sup>b</sup>DABCO = 1,4-diazabicyclo[2.2.2]octane.

give products of type **6** (entries 2, 4–7, and 9). Both triethylamine and DABCO (1,4-diazabicyclo[2.2.2]octane) can be used as the basic additive for the reaction of substrate **4b** (entries 3 and 4). As would be expected in an electrocyclic reaction, only a single diastereoisomer was observed in each case. These reactions occur at ambient temperature, employ inexpensive reagents and catalysts, and are neither air- nor moisture-sensitive.

In the case of dienyl diketone **4c**, a dramatic change in reaction outcome was observed when DABCO was used instead of  $Et_3N$  as the basic additive (Table 1, entry 8). None of the expected product **6c** was obtained: instead, a new type of cyclization cascade took place resulting in cyclopentenone **7** (74% yield, Table 2). Strangely, no incorporation of the malonate nucleophile had occurred. This result is especially surprising in light of the entry 5 result, in which use of DABCO as the basic additive uneventfully produced malonate adduct **7b** (entry 4 vs 5; Table 1).

Received: August 25, 2012

Published: September 24, 2012

Table 2. Optimization of DABCO-Catalyzed Cyclization Cascade<sup>a</sup>


entry	Lewis acid	base	catalyst loading (mol %)	yield (%)
1	Y(OTf) <sub>3</sub>	DABCO	100	92
2 <sup>b</sup>	Y(OTf) <sub>3</sub>	Et <sub>3</sub> N	100	20
3 <sup>c</sup>	Y(OTf) <sub>3</sub>	DMAP	100	83
4	Y(OTf) <sub>3</sub>	DBU	100	64
5	Y(OTf) <sub>3</sub>	—	—	no reaction
6	—	DABCO	100	97
7	—	DABCO	10	96
8	—	DABCO	5	95
9 <sup>c</sup>	—	DABCO	1	54

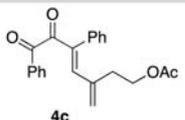
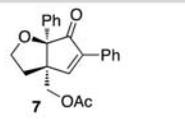
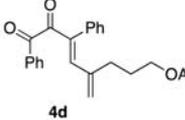
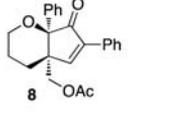
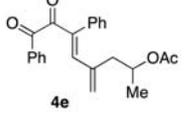
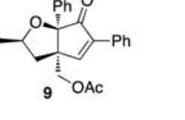
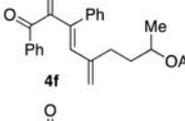
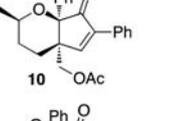
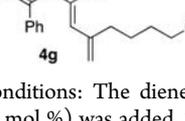
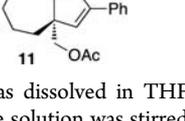
<sup>a</sup>All reactions run at 1 M concentration in THF at rt for 8 h, except when otherwise noted. <sup>b</sup>Heating to 50 °C was required for the reaction to occur. <sup>c</sup>Reaction took 24 h to reach completion.

When malonate was excluded from the reaction, the yield of product **7** improved to 92% (Table 2, entry 1). Further experimentation revealed that treatment of **4c** with Y(OTf)<sub>3</sub> and various amine bases also led to formation of **7** in good yield. While Et<sub>3</sub>N facilitated the reaction to some extent (20% yield; entry 2), long reaction times and elevated temperatures were required. Nucleophilic bases such as DMAP, DBU, and DABCO (entries 3 and 4) were found to be efficient promoters. Still, DABCO was the optimal promoter, and we were interested to find that when the Lewis acid was excluded, an even higher yield of **7** was obtained (entry 6, 97% yield). Furthermore, DABCO facilitated the reaction at catalytic levels (entries 7–9), operating with catalyst loadings as low as 1 mol % (54% yield). However, 10 mol % was found to be optimal, in terms of both yield (96%) and reaction time (1 h). The reaction was equally efficient when run open to air.

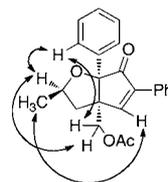
Once optimized conditions were identified, substrate scope was evaluated (Table 3). Acetate **4d** cyclized efficiently to produce cyclopentenone **8** in nearly quantitative yield (entry 2). Treatment of secondary acetates **4e** and **4f** gave **9** and **10**, respectively, as single diastereoisomers (entries 3 and 4). Figure 1 shows the key NOE correlations used to assign the stereochemistry of compound **9**. Acetate **4g** underwent cyclization to give cyclopentenone **11** in 84% yield (entry 5). For this experiment, elevated temperature was required to facilitate the reaction.

A mechanistic hypothesis consistent with the results shown in both Tables 1 and 3 is presented in Scheme 2. In the absence of DABCO, 1,6-conjugate addition of either pyrrolidine or malonate leads to adducts **2** (Scheme 1), which undergo electrocyclization. In the presence of DABCO, 1,6-conjugate addition of DABCO<sup>4,5</sup> to the dienyl diketone gives a zwitterionic DABCO adduct (see **12**, Scheme 2). We hypothesize that this species does not undergo 4π electrocyclization, and if formed reversibly. Thus, when both malonate and DABCO are present, the malonate adduct **6b** is formed (Table 1, entry 5), and DABCO acts as a simple base. However, if the substrate has an acetate tether (such as **4c–4g**, Table 3), another reaction pathway is available to DABCO adduct **12**. In these cases, we propose that the allylic quaternary ammonium moiety of **12** is displaced by the pendant acetate to produce cyclic zwitterion **13**, which contains a stereogenic center. The

Table 3. Substrate Scope<sup>a,b</sup>

entry	dienyl diketone	product	yield (%)
1			96%
2 <sup>c</sup>			98%
3 <sup>d</sup>			92%
4 <sup>e</sup>			91%
5 <sup>e</sup>			84%

<sup>a</sup>Reaction conditions: The diene was dissolved in THF (1 M), and DABCO (10 mol %) was added. The solution was stirred at rt until all starting material was consumed as judged by TLC. <sup>b</sup>Reaction time was 1 h unless otherwise stated. <sup>c</sup>Reaction time was 24 h. <sup>d</sup>Reaction time was 8 h. <sup>e</sup>Reaction was heated to 50 °C for 8 h.

Figure 1. Key NOE correlations for compound **9**.

intramolecular S<sub>N</sub>2 reaction is related to the anchimeric assistance acetates sometimes demonstrate during solvolysis,<sup>6</sup> and glycosylation,<sup>7</sup> but we could find only one example of a displacement reaction thought to proceed via a seven-membered acetoxonium intermediate.<sup>8</sup> This stereocenter then controls the torquoselectivity of the subsequent electrocyclization, which produces spirocyclic zwitterions **14**. The ring stereochemistry is consistent with conrotatory closure and analogous to the results of cyclization of the type **2** intermediate to cyclopentenones **5** and **6**. The cascade is concluded with intramolecular ether formation (Table 3). Remarkably, the proposal implies that seven-, eight-, and nine-membered zwitterions **13** readily participate as intermediates in the cyclization cascades.

In conclusion, two different cyclization cascades can be carried out beginning with 1,6-conjugate addition to a dienyl diketone. One is Lewis acid catalyzed and involves incorporation of a nucleophile, producing highly substituted cyclopentenones containing a quaternary stereogenic center. The second is a novel, metal-free cascade catalyzed by 1,6-conjugate addition of DABCO and involves three successive cyclizations: formation of a cyclic acetoxonium, putative 4π electrocyclization, and opening of the acetoxonium to form a cyclic ether. The stereochemical outcome of both reactions is

