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Lewis Acid Induced Tandem Diels−Alder Reaction/Ring Expansion as an Equivalent of a [4 + 3] Cycloaddition

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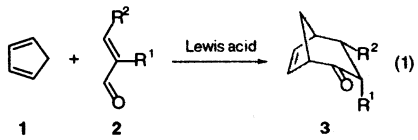
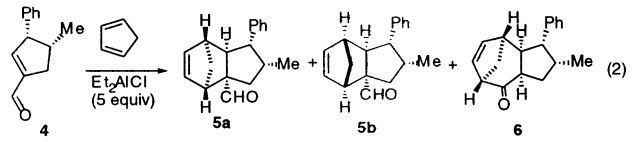
The Lewis acid-catalyzed Diels−Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes is one of the most widely studied reactions in organic synthesis.[1] Not only does the reaction have broad utility in total synthesis,[1] but also it has become a classic reaction for the evaluation of new chiral Lewis acids.[2] In this paper, we describe that, under appropriate conditions, the stereoselective formation of formal [4 + 3] cycloadducts **3** (eq 1) occurs instead of the usual Diels−Alder reaction. This transformation is shown to be a Lewis acid induced tandem Diels−Alder cycloaddition/ring expansion, and this interpretation has ramifications regarding the mechanism of other reported "[4 + 3] cycloadditions".[3]



The novel transformation was discovered during studies to explore the synthetic utility of the highly functionalized cyclopentenecarboxaldehyde **4** (eq 2).[4] Under forcing conditions, the reaction of **4** with excess diethylaluminum chloride (5 equiv), followed by quenching of the reaction at −78 °C, formed the Diels−Alder products **5a** and **5b** in 40% yield. On quenching the reaction at 0 °C, however, the major product was the formal [4 + 3] cycloadduct **6** (45% yield), containing four new stereocenters.

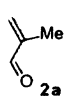
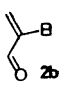
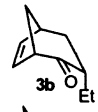
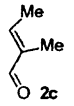
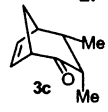
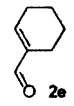
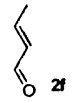
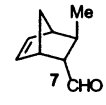


temp, °C	ratio **5a** : **5b** : **6**
-78	84 : 16 : 0
-78 to 0	7 : 21 : 72

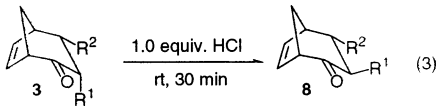
Having discovered this unexpected transformation, efforts were made to determine its generality (Table 1). A range of Lewis acids were explored, and the optimized conditions were 1.1 equiv of aluminum chloride with warming of the reaction mixture from −78 to 0 °C over the course of 2 h. The [4 + 3] cycloaddition is very effective between cyclopentadiene and 2-substituted (**2a**,**b**) and 2,3-disubstituted (**2c**−**e**) acrolein derivatives. In each case, the 3-*endo* diastereomer is formed with excellent diastereocontrol.[5] The presence of a 2-substituent in **2** is a requirement for this chemistry because the reaction with crotonaldehyde (**2f**) formed the Diels−Alder product **7**, which showed no tendency toward ring expansion. Ring strain also appears to be a factor as the reaction of **2a** with cyclohexadiene gave only the Diels−Alder product.

A particularly attractive feature of these [4 + 3] cycloadditions is that either the 3α or the 3β diastereomer of the cycloadduct can in many cases be selectively obtained. The 3α products **3** are the kinetic products, but for **3a**−**c**, epimerization to the 3β products is readily achieved as illustrated for the equilibration of **3** to **8** (eq 3). Treatment of **3a** with 1.0 equiv of HCl generated a 9:91 mixture of **3a** and **8a** from which the 3β isomer **8a** was readily isolated in 83% yield.

Table 1. [4 + 3] Cycloaddition of 1,3-Cyclopentadiene with α,β-Unsaturated Aldehydes[a]

substrate	product	yield, %[b]	de, %[c]
 2a	 3a	90	98
 2b	 3b	80	98
 2c	 3c	40	97
 2d	 3d	86	>98
 2e	 3e	21	>98
 2f	 7	71[d]	37

[a] Reaction conditions: 1.1 equiv of $AlCl_3$, 2.5 equiv of diene, −78 to 0 °C, CH_2Cl_2, 2 h. [b] Isolated yield after chromatographic purification. [c] The de was determined from a 500 MHz ^1H NMR spectrum of the crude reaction mixture. [d] Isolated yield of the mixture of *endo* and *exo* diastereomers.



	R^1	R^2	ratio **3** : **8**	yield of **8**, %
3a	Me	H	9 : 91	83
3b	Et	H	11 : 89	80
3c	Me	Me	0 : 100	92

The observation of the exclusive formation of Diels−Alder products **5a** and **5b** in the reaction of **4** at −78 °C suggests that the [4 + 3] cycloadducts are formed by a tandem Diels−Alder reaction/ring expansion. This was verified by preparing the Diels−Alder products, followed by treatment of the cycloadducts with a slight

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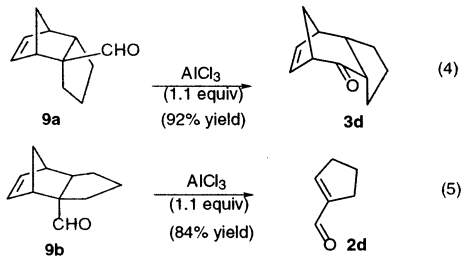
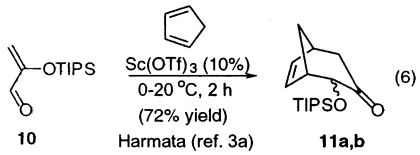
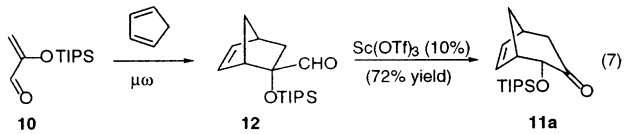
excess of aluminum chloride. In the case of the Diels−Alder products derived from **2a** and **2b**, very effective ring expansion to the [4 + 3] cycloadducts was observed. The reaction of aluminum chloride with the *exo* and *endo* isomers **9a** and **9b** derived from **2d** was especially interesting as the major *exo* isomer **9a** underwent an essentially quantitative rearrangement to the [4 + 3] cycloadduct **3d** (eq 4), while the minor *endo* isomer **9b** preferentially underwent a retro-Diels−Alder reaction (eq 5).[6] The retro-Diels−Alder reaction was a major side reaction for the Diels−Alder cycloadducts derived from **2c** and **2e**, which may explain why the yields for the formation of **3c** and **3e** (Table 1) are relatively low.



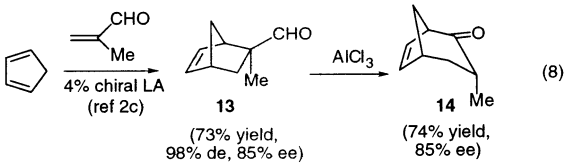
On the basis of these observations, it became of interest to reevaluate the recently published studies by Harmata on the scandium triflate-catalyzed reaction of the 2-siloxyacrolein **10** with cyclopentadiene, which results in the formation of [4 + 3] cycloadducts **11a**,**b** (eq 6).[3a] Although the mechanism of this reaction has not been fully elucidated, the working hypothesis has been a stepwise mechanism involving a zwitterionic intermediate, which preferentially forms the [4 + 3] cycloadduct rather than the [4 + 2] cycloadduct. A recent computational study on the reaction of 2-siloxyacrolein with furan supported a stepwise mechanism.[7] An alternative mechanistic possibility would be the tandem Diels−Alder reaction/ring expansion.



To test this possibility, attempts were made to isolate the Diels−Alder cycloadduct from the reaction of 2-siloxyacrolein **10** with cyclopentadiene. The scandium triflate-catalyzed reaction at −78 °C gave a mixture of **11a**,**b** and other unidentified products. The Diels−Alder product was eventually formed by a microwave-induced cycloaddition between **10** and cyclopentadiene (eq 7), but attempted purification of the product by conventional silica gel chromatography led to its rearrangement to a mixture of bicyclo-[3.2.1]octenones. Purification of the Diels−Alder product was possible using silica gel deactivated by triethylamine. Furthermore, the isolated *exo* isomer **12** was shown to readily undergo a scandium triflate-catalyzed rearrangement under Harmata's conditions[3a] to the *endo* product **11a**. Considering the facility of the rearrangement of **12** to **11a** and of the known ketol rearrangement of related Diels−Alder products,[8] it is conceivable that the Harmata [4 + 3] cycloaddition[3a] and related reactions[3b−d] are also examples of the tandem Diels−Alder reaction/ring expansion. The scandium triflate-catalyzed reaction of 2-methylacrolein with cyclopentadiene also generates [4 + 3] cycloadducts, but the yield is low and the diastereoselectivity is poor.



Due to the fact that a stoichiometric amount of Lewis acid is required to efficiently induce the formation of the formal [4 + 3] cycloadducts, the use of chiral Lewis acids for the direct transformation would not be practical. The asymmetric synthesis of the formal [4 + 3] cycloadducts, however, can be readily achieved in a two-step process beginning with a chiral Lewis acid-catalyzed asymmetric Diels−Alder reaction followed by aluminum chloride induced rearrangement (eq 8). For example, using Faller's ruthenium-based chiral Lewis acid,[2c] the Diels−Alder product **13** was obtained in 85% ee. Aluminum chloride induced rearrangement of **13** generated **14** in 74% yield with retention of the enantioselectivity. This is consistent with the formation of **14** from the direct rearrangement of **13** rather than a retro-Diels−Alder followed by a [4 + 3] cycloaddition, where loss of enantioselectivity would be expected.



In conclusion, we have discovered a remarkably simple method to achieve a formal [4 + 3] cycloaddition between cyclopentadiene and α,β-unsaturated aldehydes, which proceeds by a tandem Diels−Alder reaction/ring expansion. Further studies are in progress to determine the full scope of this chemistry.

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Supporting Information Available: Full experimental data for the compounds described in this paper (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) NOe studies support the relative configurations of compounds **3a**−**e**, **5a**, and **8a**−**c**. The relative configuration of **3d** was confirmed by the X-ray analysis of its 2,4-dinitrophenylhydrozone derivative. The X-ray crystallographic data have been submitted to the Cambridge Structural Database [Gerlits, O. O.; Coppens, P. Private Communication (1078) 2003, CCDC 219152].

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