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Synthesis of Highly Substituted Cyclohexenes via Mixed Lewis Acid-Catalyzed Diels–Alder Reactions of Highly Substituted Dienes and Dienophiles

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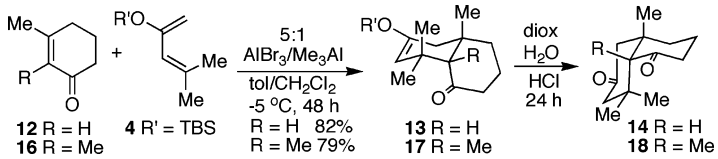
ABSTRACT



A high-yielding method is described for the rapid synthesis of very hindered cyclohexenes by the Diels–Alder reaction of hindered silyloxy dienes and dienophiles using the mixed Lewis acid catalyst system ($AlBr_3/AlMe_3$). Thus, reaction of the hindered diene 4 with various substituted enones gave good yields of the expected cycloadducts even though both partners are quite sterically hindered.

The Diels−Alder reaction has been a mainstay of synthetic organic chemistry for more than 70 years due to its predictable reactivity and control of the regio- and stereochemistry in the formation of the two new σ bonds in the intermolecular combination of a diene and dienophile.[1] However, despite its well-deserved reputation in synthesis, problems still exist in the application of these cycloadditions to certain cases. In particular, the use of Diels−Alder reactions to prepare highly substituted cyclohexene systems has generally met with failure owing to severe problems with steric hindrance.[2] Recently, we reported two examples of the preparation of a 6,6,5-tricyclic system, using the mixed Lewis acid system, $AlBr_3/AlMe_3$, via both the cycloaddition of hindered dienophiles with 2-silyloxydienes and the inverse-electron-demand Diels−Alder reaction of a hindered silyl enol ether with a 2-acyldiene.[3] We now report an examination of the scope of this process which demonstrates that it is quite general for the production of highly substituted cyclohexenes.

The cycloaddition of the silyloxydiene **1** with 1-acetyl-2-methylcyclopentene **2**[4] using a 10:1 mixture of $AlBr_3/AlMe_3$ at 0 °C for 4 h in toluene/dichloromethane solvent afforded an 88% yield of a 2.6:1 mixture of the stereoisomers **3x** and **3n**, favoring the exo product (Scheme 1). Since the cycloaddition is most likely a stepwise process (a Mukaiyama−Michael followed by an intramolecular Michael-like process) and the two bonds are not formed simultaneously,[5] the normal Alder endo transition state rules would not be in effect (no substantial secondary orbital overlap) and the stereochemistry would probably be controlled by steric hin-

(1) For reviews of the Diels−Alder reaction, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Hayashi, Y. *Cycloaddit.n React. Org. Synth.* **2002**, 5−55. (c) Willis, M. C. *Rodd's Chem. Carbon Comput., 2nd ed.* **2001**, *5*, 275−313. (d) Whiting, A. *Adv. Asymm. Synth.* **1996**, 126−145. (e) Oppolzer, W. Intermolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.1, pp 315−99.

(2) It is somewhat difficult to find references to the problems caused by severe steric hindrance in intermolecular Diels−Alder reactions, but one can find examples where the conditions for the successful cycloaddition are quite harsh. See, for example: (a) Engler, T. A.; Sampath, U.; Vander Velde, D.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399−16. (b) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Claiborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117−1118. (c) Gacem, B.; Jenner, G. *J. Phys. Org. Chem.* **2004**, *17*, 221−225.

(3) Jung, M. E.; Davidov, P. *Angew Chem.* **2002**, *41*, 4125−28.

(4) (a) Harding, K. E.; Trotter, J. W.; May, L. M. *J. Org. Chem.* **1977**, *42*, 2715−9. (b) Tabushi, I.; Fujita, K.; Oda, R. *Tetrahedron Lett.* **1968**, 5455−8.

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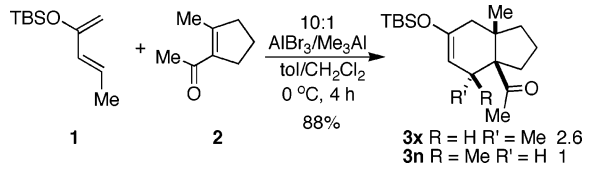
Scheme 1



drance. In this case, the trimethylene bridge is less sterically demanding than the methyl and acetyl groups on the dienophile and thus the exo isomer **3x** is the major product as shown in Figure 1.

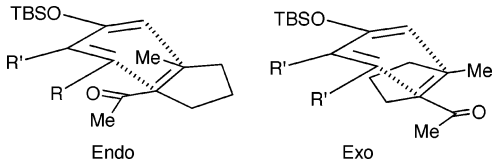
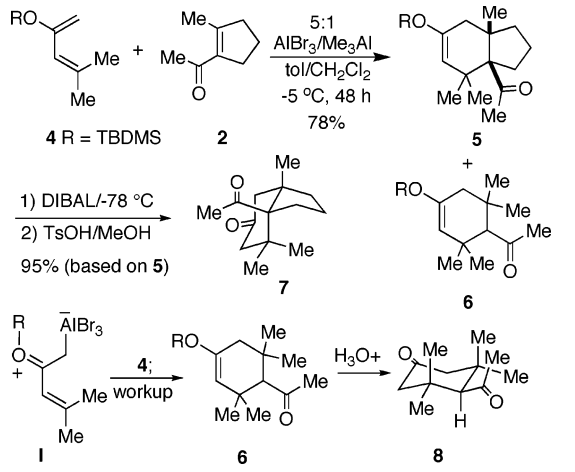


Figure 1.

More highly substituted dienes can also be used in this process. For example, the silyl enol ether **4** prepared from mesityl oxide was reacted with **2** using a 5:1 mixture of $AlBr_3/AlMe_3$ at −5 °C for 48 h to produce a 5:1 mixture of the desired cycloadduct **5** and the byproduct **6** in 78% yield (Scheme 2). Although these two compounds could not be

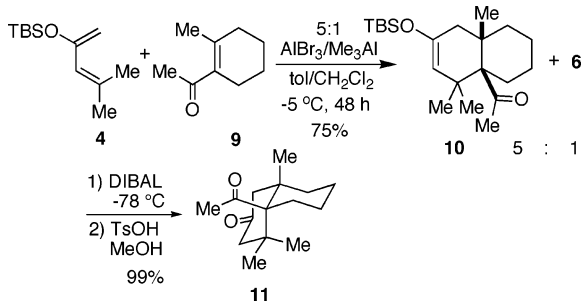
Scheme 2



separated, treatment of the mixture with DIBAL at −78 °C reduced the byproduct **6** and allowed the isolation, after silyl enol ether methanolysis, of the dione **7** in 95% yield (based on **5**). This ketone is an extremely congested molecule possessing three contiguous quaternary centers in a compact system. We propose that the byproduct arises via the following pathway: since the desired cycloaddition is quite slow under these conditions, the electron-rich silyl enol ether can react with the Lewis acid to produce the zwitterion **I**, which is a very activated dienophile and can add to the diene **4** to give **6**. The structure of **6** was proven by its preparation from **4** and mesityl oxide and its conversion to the dione **8**, which was identified by its high symmetry.

Since 1-acylcyclohexenes are generally less reactive than 1-acylcyclopentenes in cycloadditions, we wanted to test the reactivity of the higher homologue. Reaction of the substituted diene **4** with 1-acetyl-2-methylcyclohexene **9**[6] in the presence of 5:1 $AlBr_3/AlMe_3$ at −5 °C for 48 h gave a 5:1 mixture of the desired cycloadduct **10** and the byproduct **6** in 75% yield (Scheme 3). Reduction and methanolysis

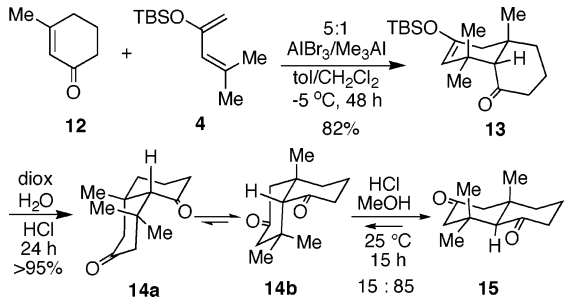
Scheme 3



afforded the dione **11** in 99% yield (based on **10**), which is also a very sterically encumbered molecule with three contiguous quaternary centers.

Substituted cyclic ketones can also be used as dienophiles in this process. For example, the relatively unhindered 3-methylcyclohex-2-en-1-one **12** reacted with the substituted diene **4** in the presence of 5:1 $AlBr_3/AlMe_3$ at −5 °C for 48 h to give the desired cycloadduct **13** in 82% yield (Scheme 4). As in most reactions with relatively unhindered dieno-

Scheme 4



philes, no more than a trace of the byproduct **6** was observed

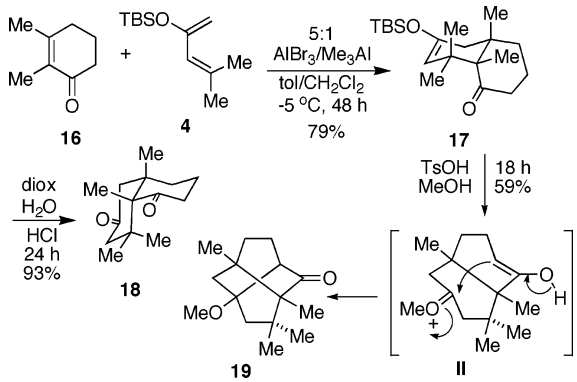
(5) Even though this is likely a stepwise process, it should still be considered a Diels−Alder reaction since Diels and Alder only described the reaction of a diene and dienophile to give a cyclohexene without implying any mechanistic detail; thus, this reaction should be considered a Diels−Alder reaction by their definition.

(6) (a) Groves, J. K.; Jones, N. *J. Chem. Soc. C* **1968**, 2898−900. (b) Hudlicky, T.; Srnak, T. *Tetrahedron Lett.* **1981**, *22*, 3351−4.

here. Acidic hydrolysis of the silyl enol ether afforded the expected dione, which can exist in two conformations, **14ab**. On treatment with acidic methanol, the ring juncture stereochemistry was epimerized to give an 85:15 mixture of the trans and cis diones **15** and **14**. This mixture could also be prepared by treatment of **13** directly with excess tosic acid in methanol. Molecular mechanics calculations (MM2) indicate a 1.3 kcal/mol difference in energy favoring **15** over **14b**. The fact that one can isomerize the cis ring juncture to the trans opens up the possibility of using this process for the synthesis of the AB ring system of various terpenoid natural products.

The value of a new synthetic method is determined by its ability to work even in difficult cases, and we believe that this new mixed Lewis acid catalyzed process meets this criterion. The very sterically hindered dienophile, 2,3-dimethylcyclohex-2-en-1-one **16**, reacted with the dimethyl-substituted diene **4** in the presence of 5:1 $AlBr_3/AlMe_3$ at −5 °C for 48 h to give the desired tetramethyl cycloadduct **17** in 79% yield (Scheme 5). Acidic hydrolysis as before

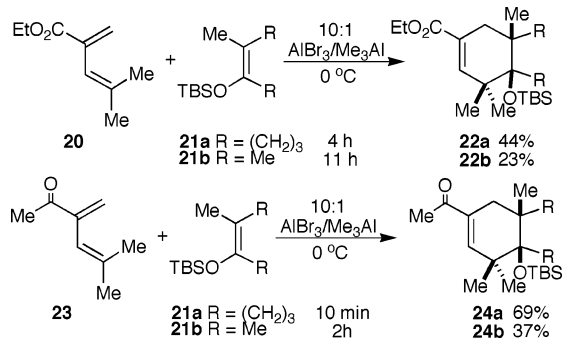
Scheme 5



gave the dione **18** in 93% yield. However, acidic methanolysis of the silyl enol ether did not afford the expected dione **18** but rather gave a different product which exhibited only a single ketone resonance at δ 219.0 in the ^{13}C NMR and one methoxy singlet at δ 3.2 in the ^{1}H NMR. We have assigned the methoxy twistanone structure **19** to this product. The formation of hydroxy twistanones from diones similar to **18** has been reported previously.[7] Here, the twistanone **19** is the major product of a 3:1:1 mixture along with the dione **18** and another, as yet, unidentified product. Presumably the reaction proceeds via the attack of the enol of the ketone on the α-methoxy carbocation (oxocarbenium ion) in an aldol-type process as shown in **II**. The mutual steric repulsion of the four methyl groups may well favor the cyclization in a kind of geminal and vicinal polyalkyl effect.[8]

We also decided to explore briefly the generality of the inverse-electron-demand Diels−Alder reaction[9] of a hindered silyl enol ether with a 2-acetyldiene that we reported earlier.[3] Reaction of the more hindered 4-methyl-1,3-pentadiene-2-carboxylate **20**[10a] with the two substituted dienophiles **21ab** with 10:1 $AlBr_3/AlMe_3$ at 0 °C gave modest yields (44% and 23%, respectively) of the cyclohexenecarboxylates **22ab**, which was not surprising since esters are known to be relatively poor electron-withdrawing groups and the dienes are less activated than our earlier one (Scheme 6). However,

Scheme 6



the corresponding 2-acetyldiene **23**[10b] gave higher yields (69% and 37%, respectively) of the desired cycloadducts **24ab** under much milder conditions. Therefore, the quite highly substituted cyclohexene esters and ketones **22** and **24** can be prepared very rapidly in fair to good yield directly from the activated dienes and the hindered dienophiles. We have not yet studied other electron-withdrawing groups as activating groups for this process on either the diene or dienophile but plan to do so soon.

In summary, we have demonstrated that highly substituted cyclohexene systems can be prepared directly by a Diels−Alder reaction in either the direct or inverse-electron-demand mode catalyzed by the novel mixed Lewis acid system $AlBr_3/AlMe_3$. The preparation of such systems and their use in synthesis is currently under study in our laboratory.

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Supporting Information Available: Spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Yordy, J. D.; Reusch, W. *J. Am. Chem. Soc.* **1977**, *99*, 1965−8. (b) Yordy, J. D.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 2086−8. (c) Bélanger, A.; Poupart, J.; Deslongchamps, P. *Tetrahedron Lett.* **1968**, 2127−8.

(8) Simple molecular mechanics calculations (MM2) indicate that the driving force for forming the twistanone **19** from the diketone is far greater than that for the formation of the unsubstituted twistanone presumably due to the buttressing steric effect of the four methyl groups. For a review of *gem*-dialkyl effects, see: Jung, M. E. *Synlett* **1999**, 843−46. Jung, M. E. *Synlett* **1990**, 186−90. Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, in press.

(9) As with the previous case, this reaction is presumably stepwise, namely a Mukaiyama−Michael addition followed by an intramolecular aldol condensation onto the very hindered ketone.

(10) (a) Prepared by Stille coupling of ethyl 2-tributylstannylacrylate with 1-bromo-2-methylpropene. (b) Prepared by Stille coupling of 2-tributylstannyl-1-butenol with 1-bromo-2-methylpropene followed by Swern oxidation.