Stepwise Acid-Promoted Double-Michael Process: An Alternative to Diels–Alder Cycloadditions for Hindered Silyloxydiene–Dienophile Pairs
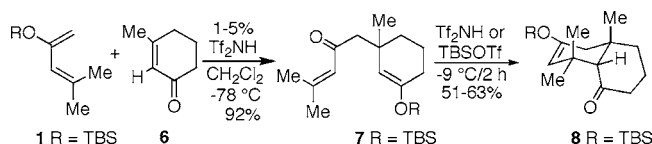
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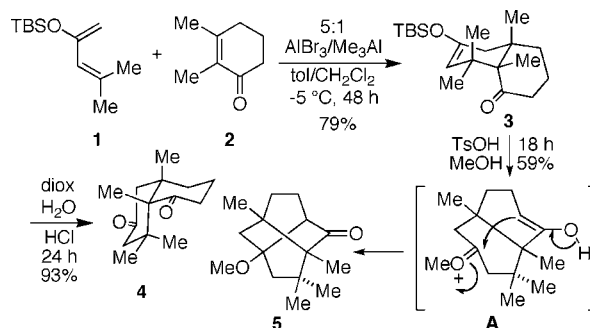
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ABSTRACT

The hindered diene **1** reacts with 3-methylcyclohexenone **6** catalyzed by triflimide to produce the Mukaiyama Michael product **7** (low-temperature quenching) or the [4+2] cycloadduct **8** (quenching at 0 °C). Reaction of the hindered diene **23** with 2-methylcyclohexenone **12** with 5:1 AlBr$_3$:AlMe$_3$ afforded a 71% yield of a 1.9:1 mixture of two cycloadducts. Hydrolysis of the major isomer gave the dione **27′**, a model for the BCD ring system of pentacyclic triterpenes.

The major drawback of the traditional Diels–Alder reaction is its severe limitation on substituents on the diene and dienophile partners due to the considerable amount of steric hindrance encountered with highly substituted substrates in the transition state for concerted (and nonsynchronous)[1] cycloadditions.[2,3] Recently, we have shown that very hindered cyclohexene systems can be prepared via a direct [4+2] cycloaddition between quite hindered 2-silyloxydienes and cyclic dienophiles catalyzed by a mixed Lewis acid, e.g., **1** and **2** giving **3** in excellent yield with a 5:1 mixture of AlBr$_3$: AlMe$_3$ (Scheme 1).[4] This ketone, which has three contiguous

(1) Diels–Alder reactions often proceed via a concerted but nonsynchronous transition state. (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092–4. (b) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 5650–9. (c) Boeckmann, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146–9.

(2) For reviews of Diels–Alder reactions, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 1668–98. (b) Hayashi, Y. *Cycloaddit. React. Org. Synth.* **2002**, 5–55. (c) Whiting, A. *Adv. Asymmetric Synth.* **1996**, 126–145. (d) Oppolzer, W. Intermolecular Diels–Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press, Oxford, UK, 1991; Vol. 5, Chapter 4.1, pp 315–99.

(3) 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.

Scheme 1

quaternary centers, can be hydrolyzed to the corresponding dione **4** in excellent yield. On treatment with acidic methanol,

(4) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–51.

it gives the methoxytwistanone **5** via an intramolecular aldol process as shown in **A**, which is presumably accelerated due to a vicinal gem-dimethyl effect.[5] We report here the novel stepwise acid-promoted double Michael reaction[6] of very hindered 2-silyloxydienes with hindered ketone dienophiles in the presence of the very strong Brønsted acid triflimide (Tf_2NH) to ultimately afford the products of a difficult [4+2] cycloaddition.

In our previous work, we used a 5:1 mixture of $AlBr_3$:$AlMe_3$ as a strong Lewis acid system in which we could guarantee the lack of even traces of HBr since it was thought that the presence of adventitious amounts of HBr would be detrimental to the desired Diels−Alder cycloaddition, in particular by causing decomposition of the electron-rich diene.[7] However, in an attempt to accelerate some hindered cycloadditions, we decided to carry out the reaction in the presence of triflimide, a very strong Brønsted acid.[8] Thus treatment of the 2-silyloxydiene **1** with 3-methylcyclohexenone **6** in the presence of 1−5% triflimide in dichloromethane at −78 °C for 2 h afforded, after quenching at −78 °C, the Mukaiyama Michael[9] product **7** in 92% yield (Scheme 2). Treatment of this new silyloxyenone **7** with

Scheme 2
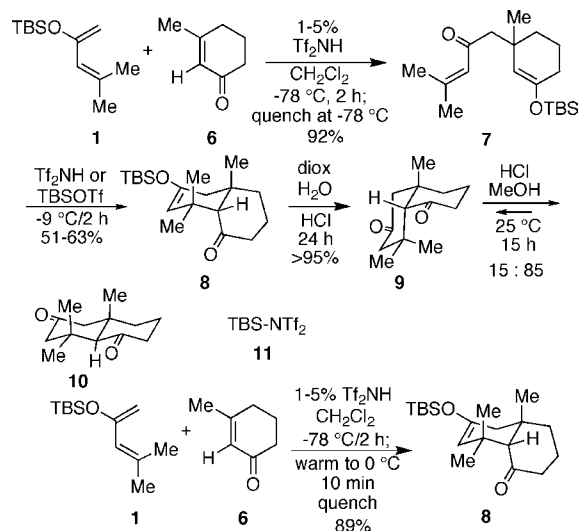
triflimide or silyl triflate (TBSOTf) gives the second, intramolecular Michael product, namely the ketone **8**, in 51−63% yield.[10] This would be the product of the direct

Diels−Alder [4+2] cycloaddition, which can be carried out by using our mixed Lewis acid catalyst. If one lets the reaction of **1** and **6** in the presence of triflimide warm to 0 °C before quenching, then the ketone **8** is produced in 89% isolated yield. Hydrolysis of the silyl enol ether of **8** gives the cis dione **9**, which can be equilibrated to a 15:85 mixture of **9** and **10**, favoring the more stable trans dione. Thus we have shown that the apparent cycloaddition of **1** and **6** in the presence of triflimide proceeds via the Mukaiyama Michael adduct **7**.

We believe that the true catalyst in this process is *tert*-butyldimethylsilyl triflimide, $TBSNTf_2$ **11**. The silyl triflimide **11** was prepared by the method of Ghosez, namely by addition of triflimide to the corresponding allylsilane.[11] Addition of this silyl triflimide **11** to a solution of **1** and **6** in dichloromethane does afford both the simple Michael adduct **7** and the double Michael product **8**, depending on time and conditions.

When the enone dienophile is unhindered (no β-alkyl group), the initial Michael reaction also works very well. Thus addition of **1** to 2-methylcyclohexenone **12** with either Tf_2NH or the mixed Lewis acid with quenching at −78 °C gave the Mukaiyama Michael product **13** in 95% yield (Scheme 3). However, hindrance at the α-carbon of the enone

Scheme 3
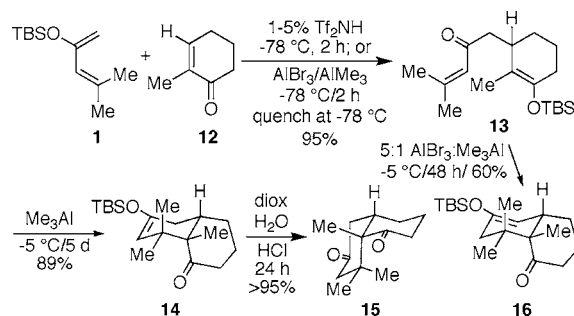
now slows the intramolecular Michael so that triflimide no longer is reactive enough to promote the second Michael process. However, the use of $AlMe_3$ converted **13**, in 89% yield, into the [4+2] cycloadduct **14**, which on hydrolysis affords the dione **15**. The mixed Lewis acid system afforded in 60% yield the double bond isomer **16**, which is calculated to be somewhat more stable than **14**.

We have found that the triflimide-catalyzed processes can be much cleaner than the cycloadditions using the mixed aluminum Lewis acid that we reported earlier. Thus reaction of the diene **1** with 1-acetyl-2-methylcyclopentene **17** in the presence of Tf_2NH was much cleaner giving the desired adduct **18** with much less of the diene-dimerization product **19** (Scheme 4). Again if one quenches the initial Tf_2NH

(5) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1766.

(6) For a review of base-catalyzed double Michael additions leading to bicyclic products, see: Jung, M. E. Stabilized Nucleophiles with Electron Deficient Alkenes and Alkynes. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 4, Chapter 1.1, pp 1−67.

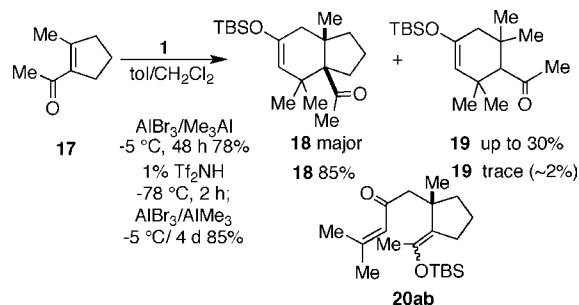(7) a) Jung, M. E.; Davidov, P. *Angew. Chem.* **2002**, *41*, 4125−28.

(8) The pK_a of triflimide is estimated to be −16 while that of triflic acid has been calculated to be −14. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(9) (a) Narasaka, N.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779−83. (b) For a review, see: Lee, V. Conjugate Additions of Carbon Ligands to Activated Alkenes and Alkynes. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 4, Chapter 1.3, pp 139−168.

(10) For an example of a triflimide-promoted Michael addition (and closure to the [2+2] product), see: Takasu, K.; Ishii, T.; Inanaga, K.; Ihara, M. *Org. Synth.* **2006**, *83*, 193.

(11) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497−5500.

Scheme 4

Scheme 4

17 → 18 major, 19 up to 30%

1
tol/CH₂Cl₂

AlBr₃/Me₃Al
-5 °C, 48 h 78%

1% Tf₂NH
-78 °C, 2 h;
AlBr₃/AlMe₃
-5 °C/ 4 d 85%

18 major
18 85%

19 up to 30%
19 trace (~2%)

20ab

Scheme 6

Scheme 6

23 + 12 → 24 (1.9 : 1) 25 + isomer

5:1
AlBr₃:Me₃Al
tol/CH₂Cl₂
-5 °C, 48 h
71%

TsOH
MeOH
20 h
90%

27 → **27'** ← **26**

reaction at low temperature, one isolates an 8:1 mixture of the stereoisomeric Mukaiyama Michael adducts **20ab**. We assume the less hindered *E* isomer is the major isomer formed.

We also wanted to examine the possible use of these cycloadditions for the synthesis of the trimethyldecalin portion of several naturally occurring terpenes, both of the bicyclic diterpene and pentacyclic triterpene classes. For this reason we examined the addition of **1** with the enone ester **21**[12] with triflimide, first at −78 °C, then warming to −40 °C, to give the desired cycloadduct **22** with very little of the diene dimer **19** (Scheme 5). We are currently looking at the
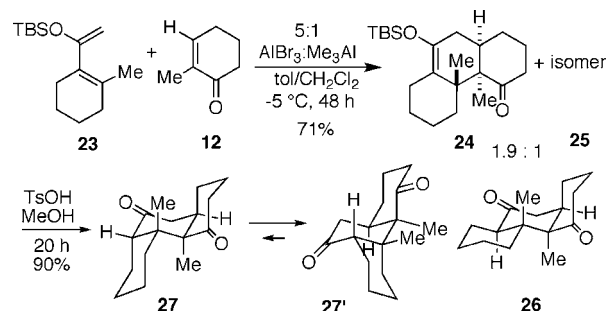
Scheme 5

Scheme 5

1 + 21 → 22 + 19 (minor)

5% Tf₂NH
CH₂Cl₂
-78 to -40 °C
2 h
86%
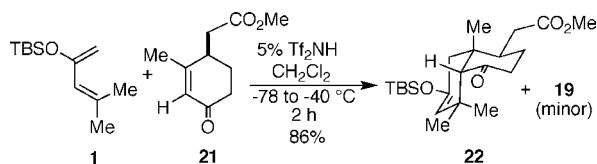
conversion of compounds such as **22** into biologically active diterpenes, e.g., haterumaimide E.[13]

We also examined the use of cyclic hindered dienes in these cyclizations as a route to the synthetically challenging BCD ring system of pentacyclic triterpenes which have two contiguous quaternary centers. We wanted to know whether cycloadditions of these hindered systems could be applied to the *trans*-C8,C14-dimethyl unit of pentacyclic triterpenes. Thus we reacted the hindered diene **23**[14] with 2-methylcyclohexenone **12** with the 5:1 mixture of Lewis acids at −5 °C for 2 d and isolated a 71% yield of a 1.9:1 mixture of two cycloadducts, **24** and a still unidentified isomer **25** (Scheme 6). It was impossible to determine the stereochem-

istry of the major compound **24** although NOE experiments did not show a correlation between the two methyl groups. The silyl enol ether was hydrolyzed to give a dione that we expected to have the *trans*-decalin structure, e.g., compound **26**. Therefore we were surprised to see an NOE correlation between the two methyl groups since in neither **26** nor **27** would one expect such a correlation. We postulated that because of the two severe 1,3-diaxial interactions of the methyl groups with the rings of the perhydrophenanthrene system, compound **27** might exist preferentially in the conformation **27′**, which would show the observed NOE. A single-crystal X-ray structure confirmed that assignment. Thus the cycloaddition−hydrolysis of **23** and **12** gives the desired contiguous quaternary centers in the desired trans orientation as the major component of a 1.9:1 mixture.

Also the [4+2] cycloaddition of the hindered diene **23** with another hindered dienophile **28** promoted by the mixed Lewis acid catalyst gave a 6.4:1 mixture of the two cycloadducts **29** and **30** favoring the all-cis stereoisomer in 88% yield (Scheme 7). The stereochemical determination was again done by a single-crystal X-ray structure.

Scheme 7

Scheme 7

23 + 28 → 29 (6.4 : 1) 30

5:1
AlBr₃:Me₃Al
tol/CH₂Cl₂
-5 °C, 48 h
88%
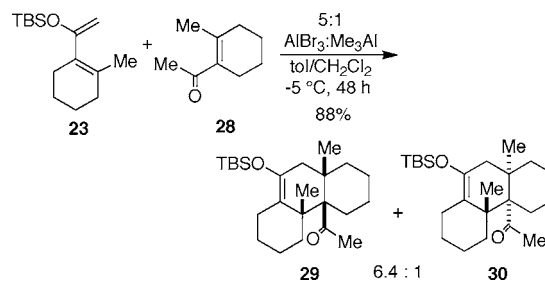
Finally the most hindered diene we have examined thus far, the trimethylcyclohexenyl silyl enol ether **31**,[15] underwent a [4+2] cycloaddition with the hindered dienophile 2-methylcyclohexenone **12** promoted by the mixed Lewis acid catalyst to give the cycloadduct **32** in an unoptimized 61%

(12) The enone ester is prepared from 3-ethoxycyclohexenone by alkylation of the anion (LDA) with ethyl bromoacetate, followed by addition of methyl Grignard reagent and hydrolysis in an overall yield of 79%. See: Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257−65.

(13) Uddin, M. J.; Kokubo, S.; Suenaga, K.; Ueda, K.; Uemura, D. *Heterocycles* **2001**, *54*, 1039−1047.

(14) This diene is unknown but the TMS analogue is known. (a) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−602. (b) Stanetty, P.; Mihovilovic, M. D.; Mereiter, K.; Vollenkle, H.; Renz, F. *Tetrahedron* **1998**, *54*, 875−894.

(15) This diene is prepared from 2-acetyl-1,3,3-trimethylcyclohexene in good yield. See: Jung, M. E.; Murakami, M. *Org, Lett.* **2006**, *8*, 5857−59.

yield after 8 days at −5 °C. Acidic methanolysis afforded an 8:2 mixture of the tetramethyldiones **33** and **34** in which the stereochemical determination was done by extensive NOESY experiments on all three compounds, **32**−**34**. Thus the trans-diaxial arrangement of the two quaternary methyls is favored in both the less substituted system **24** and the more highly substituted one **32**. This is a good model for the BCD ring system of pentacyclic triterpenes.

Scheme 8
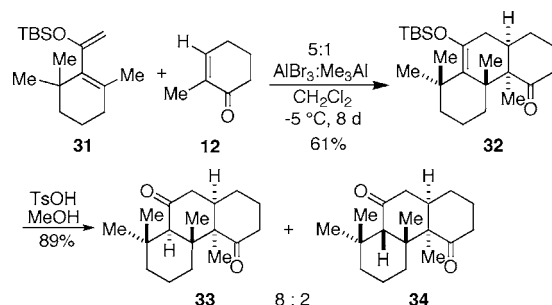
In summary, we have described the stepwise double Michael process in which a very hindered 2-silyloxydiene reacts with an enone in the presence of triflimide to give either the initial Michael product (quenching at low temperature) or the [4+2] cycloadduct. In addition we have reported the synthesis of very hindered perhydrophenanthrene systems related to the central core of pentacyclic triterpenes. Further studies on the use of these concepts and intermediates for the synthesis of natural products are in progress and will be reported in due course.

Supporting Information Available: Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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