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Disposable Tethers in Type 2 Intramolecular Diels-Alder Cycloaddition Reactions. Applications in Stereochemical Control

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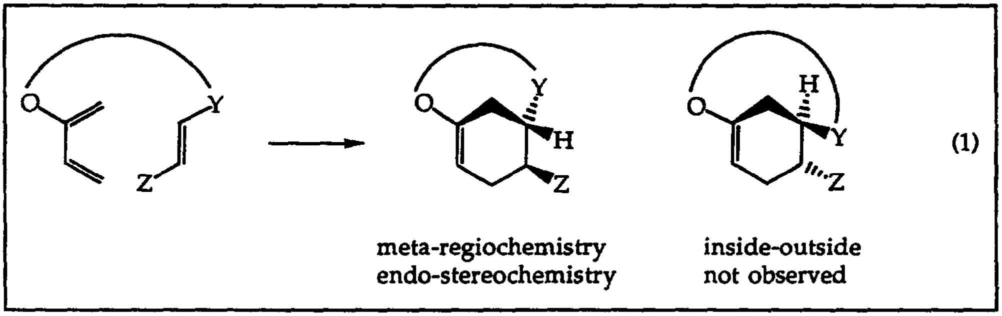
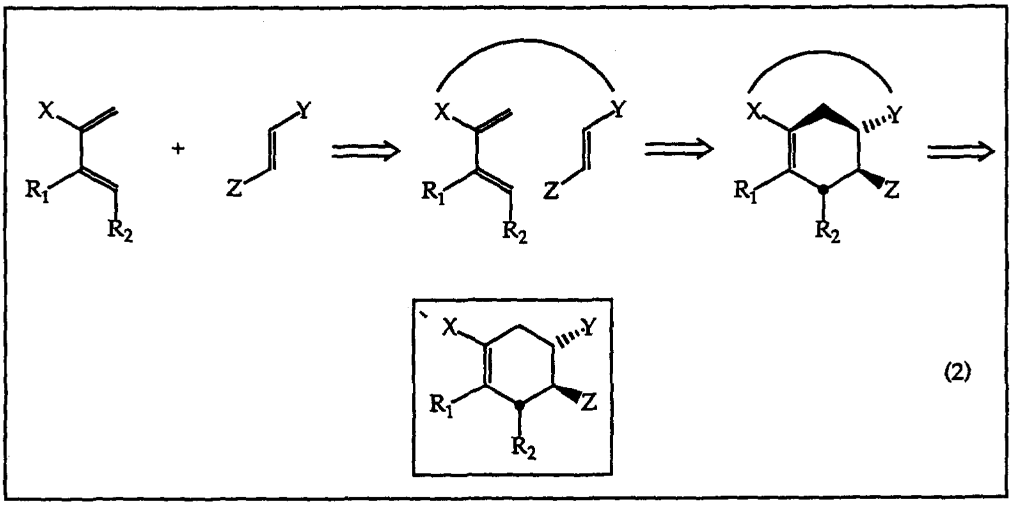
Summary: Temporary union of diene and dienophile in the type 2 intramolecular Diels-Alder cycloaddition provides a general strategy for controlling both regio- and stereochemistry of the cycloaddition.

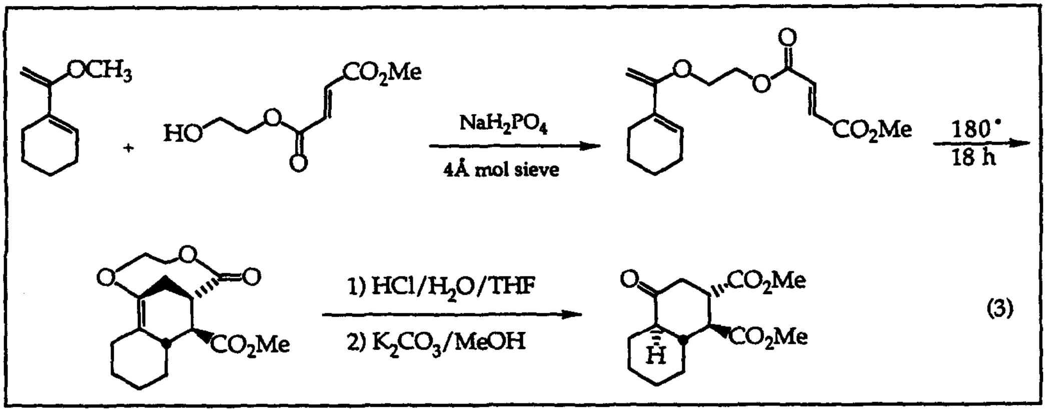
Most examples of type 2 intramolecular Diels-Alder cycloadditions[1-6] reveal a preference for "meta" or 1,3-cycloaddition regiochemistry and complete stereochemical control (equation 1). The origins of stereochemical control arise from avoidance of higher energy inside-outside bridged bicyclic cycloadducts. Apparently, serious nonbonded interactions develop in the transition states leading to these products. As part of our program to develop the synthetic applications of type 2 intramolecular Diels-Alder reactions, we have examined a number of *temporary* linkages between diene and dienophile to capitalize on the stereochemical constraints of the cycloaddition. Following cycloaddition, the temporary linkage can be removed providing a single stereoisomer of the cycloadduct (equation 2).



2-Oxydienes serve as carbonyl equivalents in the Diels-Alder reaction.[7] Because of their synthetic importance, we have examined strategies for temporarily joining this linkage to dienophiles prior to cycloaddition. Our first effort utilized a mixed ethylene glycol ester as the disposable tether. The Diels-Alder precursor was obtained by a two-stage transetherfication that involved formation of the mixed ketal (NaH_2PO_4 catalysis) followed by removal of MeOH (4 Å mol sieve, refluxing C_6H_6). The resulting dienol ether, which could be purified by chromatography on alumina (activity 3), underwent cycloaddition at 180 °C (18 h). It was necessary to include trace amounts of a hindered amine to eliminate a competing isomerization reaction of the oxydiene fragment under the cycloaddition conditions. Despite these competing side reactions, only a *single* cycloaddition product was observed for the reaction (equation 3). An acidic hydrolysis of the cycloadduct followed by base catalyzed transesterification removed the tether and afforded the *trans*-2-decalone in 25-45% overall isolated yield.[8] This example, although suffering from competing side reactions and low overall yields, demonstrates the principle of stereochemical control utilizing a disposable tether.

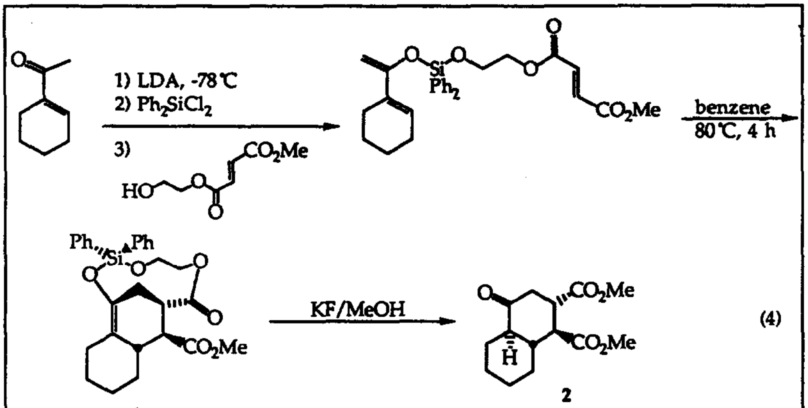


(2)



(3)

An alternative approach using a silicone connector met with greater success (equation 4). Synthesis of the cycloaddition precursor takes advantage of the differential reactivity of dihalodialkylsilanes for the preparation of the unsymmetrical silicone linkage.[9] Thus, condensation of the kinetic enolate of 1-acetylcyclohexene with diphenyldichlorosilane affords a good yield of the diphenylchlorosilyldienol ether. The Diels-Alder precursor is obtained upon condensation of the chlorosilane with hydroxyethyl methyl fumarate (87%). Cycloaddition proceeds under very mild conditions to afford a single cycloadduct 1 (90% yield).[10] The structure of the cycloadduct and the relative configuration of the three contiguous stereocenters was established unambiguously by X-ray crystallography (see figure).[11] Fluoride deprotection and methanol transesterification afforded a single ketodiester 2 (78%). The methodology is readily extended to allylic alcohols. Two examples are included in the figure below. In both cases, cycloaddition proceeds in high yield to give a single cycloadduct. The tether is readily cleaved (KF, MeOH) to afford the isomerically pure decalones in high yields.



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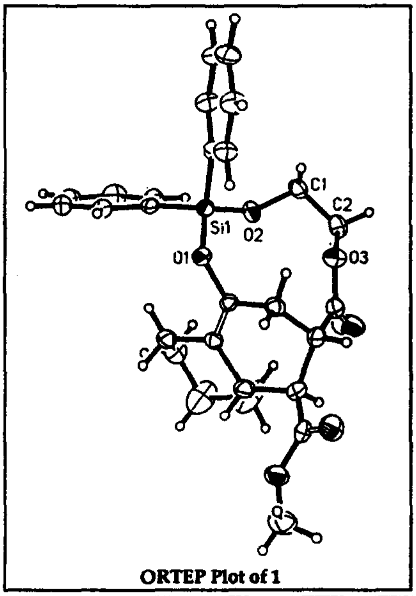

ORTEP Plot of 1

The temporary union of diene and dienophile in a type 2 manner as a stereochemical control strategy has been demonstrated. Applications of this strategy in organic synthesis will be the topic of later reports.

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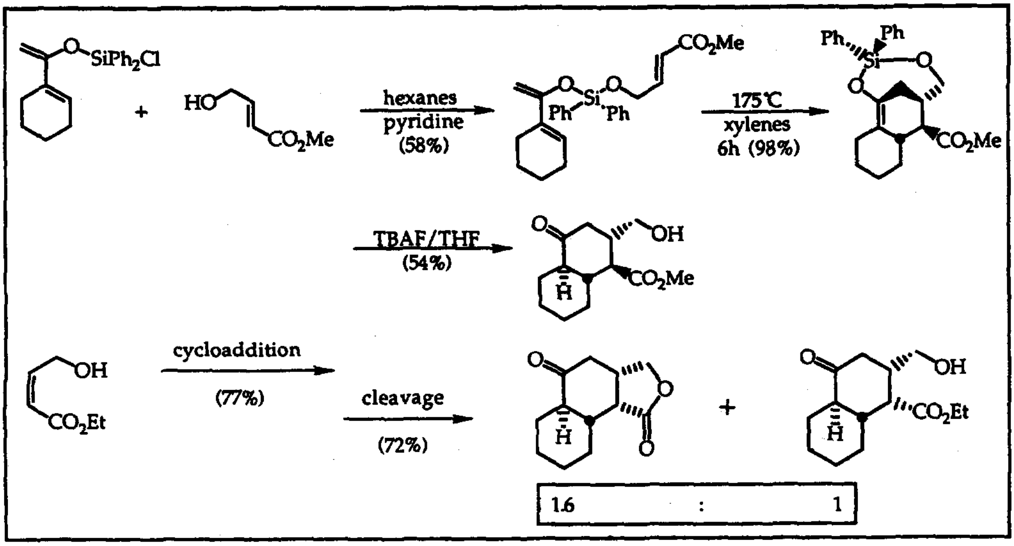

References and Footnotes

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8. All new compounds gave spectroscopic and analytical properties consistent with their assigned structures.
9. Walkup, R. D. *Tetrahedron Lett.* **1987**, *28*, 511.
10. Isolated yields were lower (53%) due to loss during chromatography.
11. Crystal data for cycloadduct 1: monoclinic space group $P2_1/n$, a = 9.7192(15) Å, b = 20.841(4) Å, c = 11.879(2) Å, β = 95.934(14)°, V = 2393.3(7) Å^3, Z = 4, d_{calcd} = 1.328 g cm^{-1}. Low temperature (213°K) intensity data were collected using the θ-2θ scan technique with Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least-squares techniques. Refinement of positional and thermal parameters (isotropic for hydrogen atoms) lead to convergence with R_F = 4.4%, R_{wF} = 4.6% and GOF = 1.97 for 428 variables refined against those 3486 data with $|F_o| > 3.0\ \sigma\ (|F_o|)$. Further details are provided as supplementary material.

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