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New Efficient and Stereoselective [2+2] Cycloadditions of Dimethylaluminum Enolates with Phenylvinylsulfoxide

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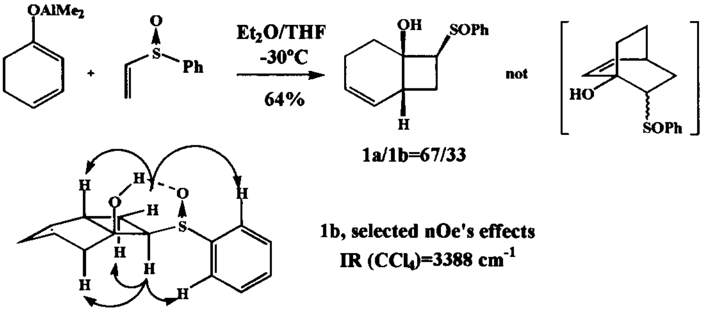
Abstract: Lewis-acidic enolates, such as dimethylaluminum enolates undergo cis-stereoselective [2+2] cycloadditions with phenylvinylsulfoxide. The method is quite general and gives good yields of synthetically valuable substituted cyclobutanols. The remaining sulfoxide handle can be further manipulated, giving access to diverse chemical functionalities.

During the course of our study[1] on "internally-catalyzed" Diels-Alder cycloadditions, we observed the unusual behavior of the phenylvinylsulfoxide dienophile when reacted with 1-dimethylaluminumoxy-1,3-cyclohexadiene[2]. Instead of the expected [4+2] Diels-Alder adduct[3], a mixture of two diastereomeric [2+2] cycloadducts were cleanly formed (scheme 1).

Upon inspection of the two compounds obtained, it was quickly realized that, in contrast to previous literature observations, a high cis relationship between the hydroxyl and the sulfoxide moieties was realized (assigments made from ^{1}H-NMR and IR spectra, as exemplified below for **1b**).



1a/1b=67/33

1b, selected nOe's effects
IR (CCl$_4$)=3388 cm^{-1}

Scheme 1

Although [2+2] cycloadditions between ketone lithium enolates and phenylvinylsulfoxide were reported[4], these reactions suffer from either low yield, poor cis/trans-selectivity and/or generality (only two exemples are reported and products are often contaminated with a Michael addition-type product).

The good yield and the cis-selectivity obtained for **1a/1b** together with the synthetic value of substituted cyclobutanols prompted us to examine this unusual and efficient transformation.

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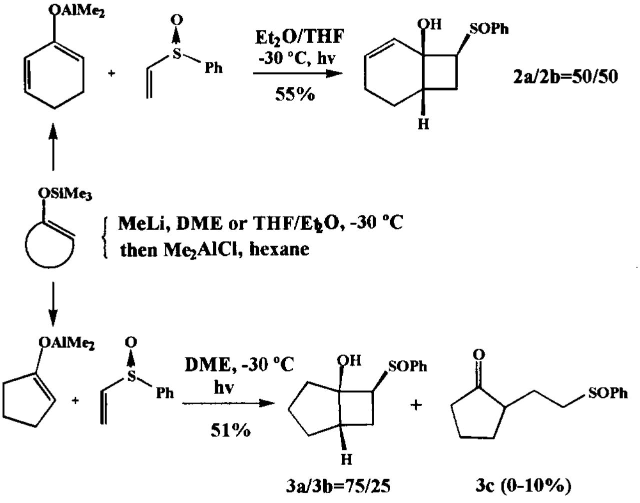
Starting from the readily available ketone trimethylsilyl enol ethers[5], aluminum enolates were generated through a one-pot, two-steps, silicon-lithium[2]-aluminum exchange reaction. The first experiment was carried out with the regioisomeric 2-dimethylaluminumoxy-1,3-cyclohexadiene. As anticipated, two major fused cis-cyclobutanols **2a/2b** were obtained (scheme 2). A minor amount (< 5%) of a third non characterized cycloadduct was also formed under these conditions. The same trends were observed for the cycloaddition of 1-dimethylaluminumoxy-1-cyclopentene.



Scheme 2

The following observations and comments worth mentioning:

a) Lower Lewis basicity ethers, such as Et_2O or DME, were the solvents of choice . A small amount of THF in diethylether was found necessary to catalyze the Stork silicon/lithium transmetallation.

b) Excess phenylvinylsulfoxide did not improve the yield, but as already mentioned in the literature[4b], irradiation (with a sunlamp) did. Mention should be made that in the complete dark, cycloaddition occured but with a lower yield (≈20-25%).

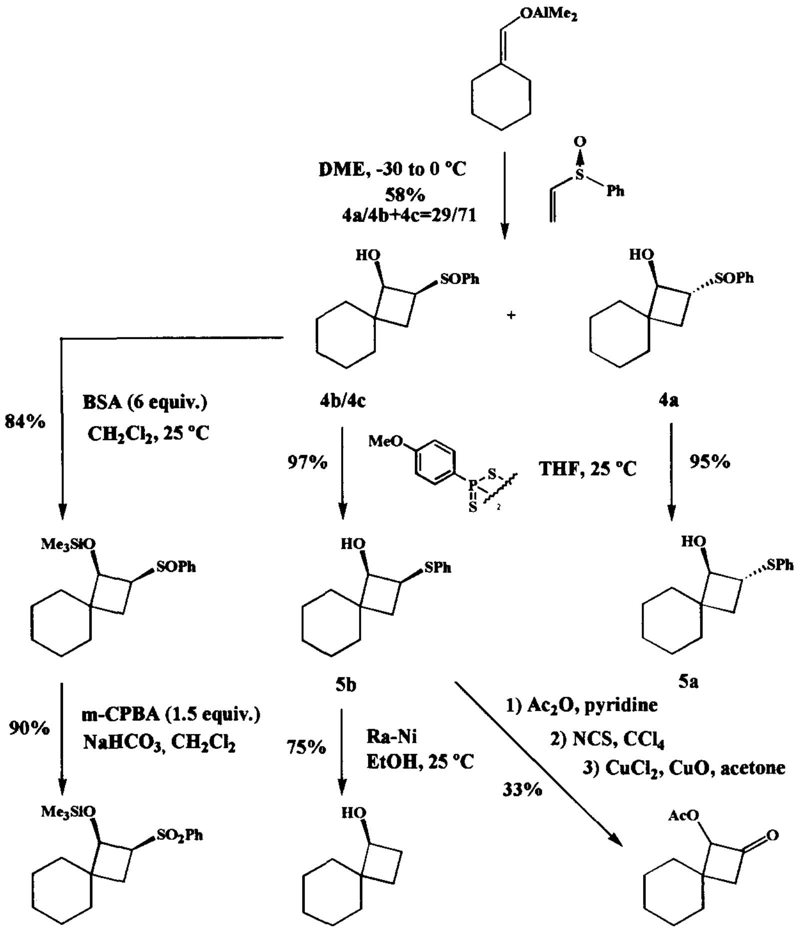
c) A Michael-addition adduct **3c**, resulting from a retroaldol reaction of the intermediate aluminum enolates of **3a/3b**, during the methanol quench was sometimes observed (0-10%).

d) Isolated cycloadducts were relatively stable crystalline solids (after flash chromatography).

e) No attempts were made to determine the relative stereochemistries at sulfur.

d) A tentative cycloaddition using ethynyltolylsulfoxide[6] (to generate the strained cyclobutenol system) failed, giving only a Michael-addition adduct.

As depicted in scheme 3, aldehyde aluminum enolates can also undergo this [2+2] cycloaddition. In that case, a relatively greater amount of trans stereoisomer **4a** is formed. The more polar (and still more abundant) cis stereoisomers **4b/4c** could not be separated by chromatography. To ascertain the relative hydroxyl/sulfoxide stereochemistry for **4b/4c** vs. **4a**, a reduction of the sulfur-oxygen bond was done using Lawesson's reagent[7]. Each fraction (**4a** and **4b/4c**) gave a different sufide **5a** and **5b** in high yields.



Scheme 3

Chemical transformations of cycloadducts **4b/4c** to give variously substituted cyclobutanes is illustrative of the power and simplicity of this protocol (scheme 3): The hydroxyl function can be protected with the mild silylating agent bis(trimethylsilyl)acetamide (BSA) in methylene chloride and the sulfoxide moiety oxydized to the sulphone using m-CPBA[8] (an alcohol protection is needed to avoid the facile retroaldol reaction). Otherwise, as stated before, sulfoxide is easily reduced to sulfide from which one can either access the cyclobutanol (Raney-Ni reduction[9]) or the α-acetoxycyclobutanone (Pummerer-type oxidation[10]).

In conclusion, we have shown that Lewis acid-containing enolates such as dimethylaluminum enolates, are extremely good partners for [2+2] cycloadditions with the otherwise relatively unreactive phenylvinylsulfoxide. The good yields and cis-stereochemistries observed here, when compared to literature results, are probably a direct consequence of the reactants pre-association (due to a strong aluminum-sulfoxide complexation) and strong steric interactions in the cyclic transition state. Reaction mechanism is not completely clear for the moment, in particuliar the role of irradiation which enhance both yields and kinetics but is not critical to the success of the transformation.

From a preparative point of view, this protocol is likely one of the best to prepare functionalized cyclobutanols, with the remaining sulfoxide moiety giving a powerful handle for further diversification.

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5. ***Typical procedure**: In an argon-inerted 50 mL glass round-bottom flask,1-trimethylsiloxycyclopentene (0.913 g, 5.84 mmol) is dissolved in dry DME (10 mL), then cooled to -30 °C. A solution of methyllithium (1.6M-Et*$_2$*O, 3.80 mL, 6.08 mmol) is added dropwise. Formation of the cyclopentanone lithium enolate is followed by TLC (pentane/acetone=3/1 eluent). After 10-20 min., a solution of dimethylaluminumchloride (1 M-hexanes,6.0 mL, 6.0 mmol) is added so the temperature does not exceed -20 °C (a characteristic white LiCl precipitate is formed). After stirring for 10 min. phenylvinylsulfoxide (1.095 g, 7.20 mmol) is introduced and the reaction flask irradiated with a sunlamp (100 W, placed at approx. 5 cm). Temperature is maintained at -30/-20 °C during the cycloaddition (followed by TLC, same eluent). After completion of the reaction, methanol (1 mL) is added followed by hydrochloric acid (2 N, 5 mL). Cycloadducts are extracted with ether (50 mL), and the organic phase washed with a saturated bicarbonate solution. Flash chromatography is effected on Amicon 20-45*μ* silicagel with a gradient eluent (pentane/acetone=5/1 to 2/1). **3a** (0.530 g, 2.23 mmol) and **3b** (0.176 g, 0.74 mmol) are isolated as white cristalline solids (combined yield= 51%). A variable amount of the Michael addition product **3c** (0 -10%) could be present with **3b**. **3a** and **3b** gave satisfactory analysis (*^{1}*H-NMR, IR, HRMS and/or microanalysis).*

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