

**NON-PHOTOCHEMICAL 2+2 CYCLOADDITIONS OF  
ACYCLIC ENONES AND ALKENES**

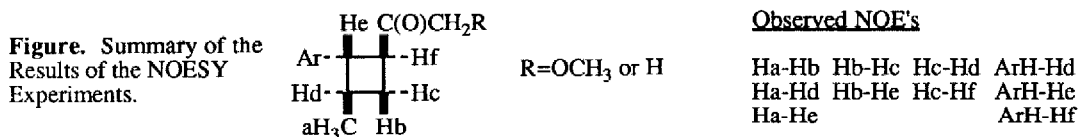
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**Abstract:** *An efficient synthesis of substituted cyclobutanes is reported via Ti(IV) catalyzed 2+2 cycloadditions of methoxymethyl vinyl ketone and methyl vinyl ketone with alkenes.*

The photochemical 2+2 cycloaddition of enones and olefins is one of the most versatile methods for the construction of cyclobutanes.<sup>1</sup> Unfortunately, this method generally fails for acyclic enones due to rotational deactivation of the excited state enone<sup>2</sup> and there has been much interest recently in thermal 2+2 cycloaddition reactions.<sup>3,4</sup> In general, thermal 2+2 cycloadditions of alkenes have been limited largely to a) reactions of fluorinated alkenes, b) reactions of highly strained alkenes and alkynes and c) reactions of electron rich alkenes with electron poor alkenes.<sup>3</sup> For example, cyclobutanes are formed from reaction of Michael acceptors and olefins with strong electron donating groups (-NR<sub>2</sub>, OR, SR).<sup>3,4</sup> Lewis acid catalyzed 2+2 cycloaddition of alkenes with alkynyl or allenyl esters and ketones have been well studied.<sup>5</sup> However, only a limited number of Lewis acid catalyzed 2+2 cycloadditions of enones with unactivated olefins have been reported<sup>6</sup> and the generality of these reactions is not clear. We now wish to report that Ti(IV) catalyzes 2+2 cycloadditions of styrenes and methoxymethyl vinyl ketone and, to a lesser extent, methyl vinyl ketone (MVK). To our knowledge, modification of enones with  $\alpha'$ -methoxy substituents represents a modest additional improvement in the design of acyclic enones which are capable of undergoing 2+2 cycloaddition reactions. The method represents a potentially general and versatile route to substituted cyclobutanes which are useful synthetic intermediates.<sup>4</sup>

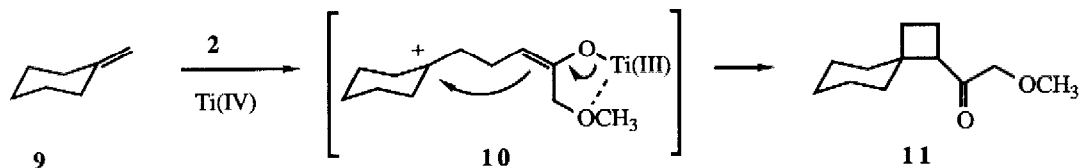
Thus, addition of styrenes **1** to a solution of methoxymethyl vinyl ketone **2**<sup>7</sup> (2 equiv) and a 1:1 mixture of TiCl<sub>4</sub>/Ti(OiPr)<sub>4</sub> (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at -78°C and then warming to -20°C produces, after addition of 1N HCl, extractive isolation and silica gel chromatography, a mixture of cyclobutane epimers **5** (Scheme and Table). Treatment of this mixture with methanolic K<sub>2</sub>CO<sub>3</sub> provides a single cyclobutane **6a-c**<sup>8</sup> in 56-89% overall yield from **1**. In a similar manner, the *cis*-styrenes **7a,c** also afford cyclobutanes **6a,c**

(24% and 50% yields, respectively). The stereochemical assignments in 6a-c are based on NOESY experiments, the results of which are summarized in the Figure.



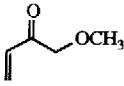
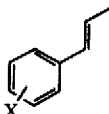

Titanium(IV) (2 equiv, as TiCl<sub>2</sub>(OiPr)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, -78°C) also catalyzes the reaction of anethole (1a, a vinylogous enol ether) with methyl vinyl ketone 3 to give cyclobutane 8a in 67-83% yield after treatment with K<sub>2</sub>CO<sub>3</sub>/MeOH. However, reactions of less nucleophilic styrenes 1b/c with MVK at -78°C to -20°C give moderate yields of 2+2 cycloadducts 8b/c. The assignment of stereochemistry in 8a-c is based on NMR (see Figure).

The cycloadditions of methoxymethyl vinyl ketone are not limited to styrenyl alkenes. Addition of methylene cyclohexane 9 to a mixture of 2 and TiCl<sub>4</sub>/Ti(OiPr)<sub>2</sub> [1:1, 2 equiv of Ti(IV)] at -78°C and then warming to -20°C followed by 1 N aqueous HCl quench gives cyclobutane 11 in 20-30% yield. To date, attempts to effect a similar 2+2 reaction between 9 and MVK have resulted in ≤ 10% yield of a 2+2 adduct. Attempts to improve the latter are in progress.



We reason that the process involves formation of a Ti(IV)-enone complex with a highly electrophilic β-carbon (Scheme). Alkylation of the complex by the alkene gives 4 (or 10) which then affords the cyclobutanes. The inferior results obtained with MVK suggest that the methoxy group in 2 may facilitate tighter binding to the Ti(IV) forming a Ti(IV)-enone chelate complex of sufficient reactivity for efficient alkylation by unactivated alkenes. Other workers have reported that Lewis acid catalyzed reactions of MVK and simple alkenes produce ene products.<sup>6a</sup>

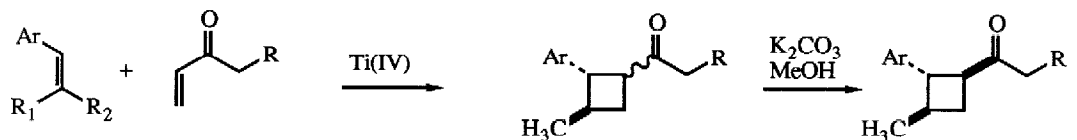
Table. Ti(IV) Catalyzed Reactions of Styrenes with Methoxymethyl Vinyl Ketone and with Methyl Vinyl Ketone.

Enone	Styrene		Ratio of Cyclobutanes <b>5</b>	Yield of <b>6</b> <sup>a</sup>
		X = OCH <sub>3</sub>	2:1	58-89% <sup>9</sup>
		X = CH <sub>3</sub>	1:1	69-78% <sup>9</sup>
		X = H	1:1	49-62% <sup>9</sup>
		X = OCH <sub>3</sub>	27:1 <sup>b</sup>	67-83%
		X = CH <sub>3</sub>	10:1 <sup>b</sup>	47-52%
		X = H	1:1	20-39%

a) Range for 2-3 experiments.

b) The major isomer is **6**. Reasons for this selectivity are unclear at this time and are under current investigation.

#### Scheme



**1a-c**,  
R<sub>1</sub>=H, R<sub>2</sub>=Me

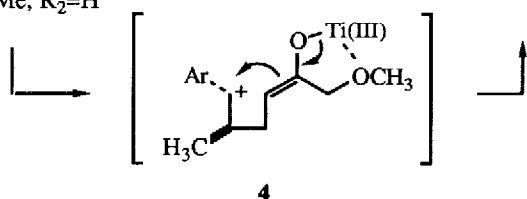
**2**, R=OCH<sub>3</sub>  
**3**, R=H

**5**

**6a-c**, R=OCH<sub>3</sub>  
**8a-c**, R=H

**7a,c**  
R<sub>1</sub>=Me, R<sub>2</sub>=H

a, Ar=4-MeOPh-; b, Ar=4-MePh-; c, Ar=Ph



We are continuing our investigations on the generality and applications of these novel cycloaddition reactions.

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## References and Notes

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8. All new compounds were characterized by 300 MHz  $^1\text{H}$  NMR, 75 MHz  $^{13}\text{C}$  NMR, IR and mass spectroscopy, including exact mass, on chromatographically homogeneous material.
9. The variable yields of 6a-c may be due to the difficulty in obtaining 2 in a consistently pure form.

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