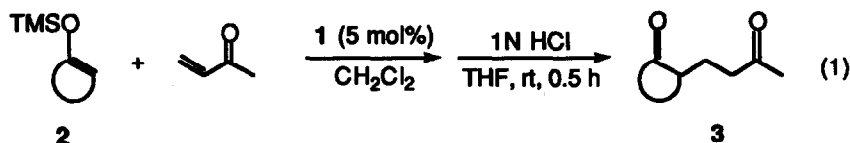


ORGANOTIN TRIFLATES AS FUNCTIONAL LEWIS ACIDS.
A NEW ENTRY TO SIMPLE AND EFFICIENT ROBINSON ANNULATION

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SUMMARY: An efficient Robinson annulation has been established through the Michael addition of enol silyl ethers to α -enones catalyzed by dibutyltinbis(triflate) followed by the MeONa-mediated intramolecular aldol condensation of the adducts.

The Robinson annulation is a classical but still widely used methodology for synthesis of polycyclic compounds.¹ Unfortunately, however, the original procedure consisting of Michael addition of enolates to α,β -unsaturated systems has some restrictions.² Under highly basic conditions, some of the acceptors readily polymerize and intermediary enolates frequently undergo intramolecular proton transfer resulting in dialkylation. For example, methyl vinyl ketone (MVK), the most commonly demanded acceptor, is susceptible to these side reactions. In fact, the coupling of cyclohexanone (CHN) with MVK has seldom been realized although this is the simplest donor-acceptor combination. Several improvements have appeared, most of which fall into one of the following categories: (1) development of milder reaction conditions, (2) modification of the acceptors to increase the rate of the initial addition reaction and/or to decrease the reactivity of the resulting enolates, and (3) decreasing of the basicity of the enolate components. In line with category 1, Marshall et al. isolated ketols which were then dehydrated to the final products.³ This procedure afforded the ketol from 2-methylcyclohexanone (MCH) and MVK in 52% yield, but resulted in only a 17% yield for the CHN-MVK reaction. Heathcock et al. utilized acidic conditions (H_2SO_4) to obtain the MCH-MVK adduct in 55% yield, but did not refer to the CHN-MVK combination.⁴ The representatives of modified acceptors (category 2) are Mannich bases,⁵ β -haloketones,⁶ and the MVK-iron complex⁷ which work to some extent. The successful CHN-MVK coupling to give pure $\Delta^{1,9}$ -octalone-2 was achieved only by employing the Stork's α -silylated MVK.⁸ In category 3, Stork et al. devised the enamine method.⁹ Despite considerable success, this method suffered from the double bond isomerization of the CHN-MVK adduct. The Mukaiyama's enol silyl ether method is a promising alternative.¹⁰ Although this procedure is successful by use of an MVK acetal, the employment of MVK itself induces serious side reactions with conventional Lewis acids. We have now found that the Mukaiyama-type Michael reaction is dramatically improved under the influence of catalytic $Bu_2Sn(OTf)_2$ (1). This methodology provides not only a new category for the Robinson annulation (the promotor-controlled strategy), but also a practical solution to the problems which have remained unanswered for a long time.¹¹

Table 1. The Michael Addition of Silyl Nucleophiles **2** to MVK.

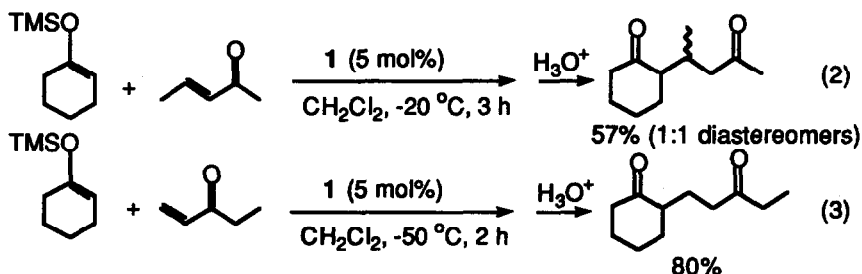
entry	2	conditions	3	yield, %
1		-78 °C, 4 h		70
2		-78 °C, 10 h		76 ^a
3		-78 °C, 3 h		64
4		-50 °C, 8 h		77 ^b
5		-50 °C, 3 h		61 ^c
6		-78 °C, 5 h		61

^a Cis-trans mixture (63:37). ^b Cis-trans mixture (84:16).

^c Mixture (78:22). Stereochemistry has not been assigned.

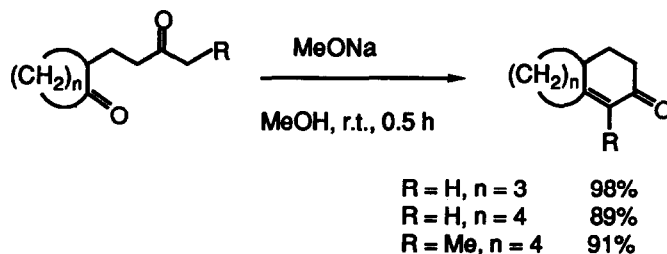
In the context of our studies with organotin triflates,¹² we have found that **113** catalyzes the addition reaction of enol silyl ethers **2** with MVK (eq 1). For instance, to a dichloromethane solution (5 ml) of **1** (27 mg, 0.05 mmol) were added 1-trimethylsilyloxy-1-cyclohexene (170 mg, 1.0 mmol) and MVK (91 mg, 1.3 mmol), in this order, at -78 °C. The reaction mixture was stirred for 5 h at this temperature and quenched with 1N HCl. Usual workup and column chromatography on silica gel (97:3 hexane-ethyl acetate) gave 2-(3-oxobutyl)cyclohexanone (117 mg, 70%), the first CHN-MVK coupling products employing unmasked MVK. Neither polymerization of MVK nor double alkylation was observed. Our results are summarized in Table 1.¹⁴ Apparently, the MVK adducts **3** are obtained with a wide variety of enol silyl ethers. Note that the reaction proceeds

specifically to give the corresponding regioisomers from the respective isomeric enol silyl ethers of MCH (entries 3,4). These results compliment the conventional methods where alkylation usually occurs at the more highly substituted α -carbon except the enamine method.⁹ Quite naturally, α -enones other than MVK are also employable (eq. 2 and 3).

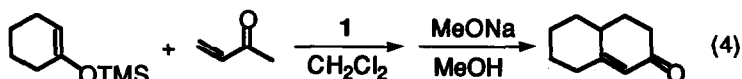


Completion of the Robinson annulation sequence involved cyclization of the Michael adducts thus obtained with MeONa-MeOH ⁸ (Scheme 1).¹⁵

Scheme 1



Of more importance is a one-pot synthesis of $\Delta^{1,9}$ -octalone-2 directly from the enol silyl ether of CHN and MVK (eq 4). A mixture of these two reactants in a 1.3:1 molar ratio¹⁶ was stirred in dichloromethane containing 0.05 equiv of 1 at -78°C . After 5 h, MeONa in methanol was added to this solution, and then, the mixture was stirred at room temperature for 3 h. Usual workup provided the octalone in 68 % yield based on MVK.



In conclusion, organotin triflate is acidic enough to trigger the Michael addition but moderate enough that polymerization of α -enones and double alkylation are entirely suppressed. Consequently, the serious side reactions which otherwise occurs frequently are retarded in the present case. Finally, it should be noted that the actual promotor is 1, but not trimethylsilyl triflate (TMSOTf) which may be formed in situ through transmetalation between a silyl enolate and 1. Complex side reactions arise when TMSOTf is employed in place of 1.

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- 15) The isomer, $\Delta^{9,10}$ -octalone-2, was not detected in the case where $\text{R} = \text{H}$ and $n = 4$ on the basis of ^{13}C NMR and GLC analyses.
- 16) Employment of MVK in excess induced side reactions to some extent.

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