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Tetrahydropyran Rings from a Mukaiyama−Michael Cascade Reaction

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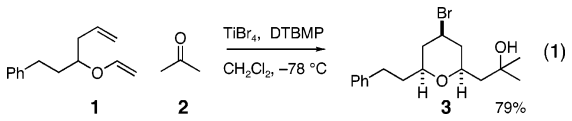
Reactions that form complex rings are vital tools in synthetic chemistry. The significance of [4 + 2] cycloadditions, such as the Diels−Alder reaction, cannot be overstated.[1] We have discovered a new annulation reaction that is formally a two-carbon plus four-carbon ring-forming reaction, but it proceeds through a cationic cascade. In the reaction, enones or acrylates combine with homoallylic enol ethers, such as **1**, to produce tetrahydropyrans. The scope and selectivity of the reaction have been elucidated in the preliminary studies described below.

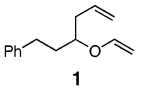
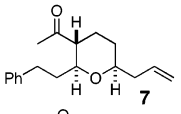
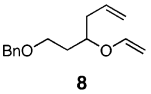
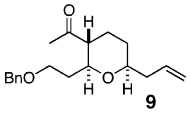
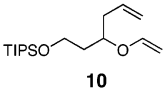
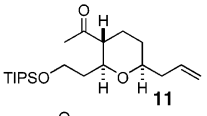
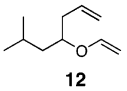
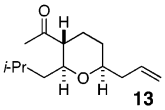
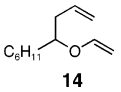
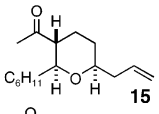
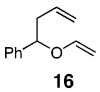
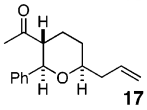
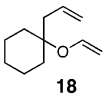
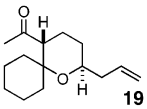


The Mukaiyama aldol−Prins cyclization, illustrated in eq 1, was the starting point for this investigation.[2] Ketones and aldehydes react with homoallylic enol ethers, such as compound **1**, to produce tetrahydropyran **3** by an initial Mukaiyama aldol reaction and subsequent Prins cyclization of the intermediate oxocarbenium ion. We had observed that α,β-unsaturated aldehydes led to complex mixtures in the reaction and decided to investigate enones. The reaction of 3-butene-2-one (**5**) and enol ether **1** promoted by $TiBr_4$ and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)[3] generated the unexpected tetrahydropyran **7** in high yield and as a single diastereomer.

The Mukaiyama−Michael cascade reaction of homoallylic enol ethers and 3-butene-2-one (**5**) is successful with a variety of substrates, and the scope of the reaction is outlined in Table 1. A variety of homoallylic enol ethers reacted rapidly with the enone at low temperature to produce tetrahydropyrans in 63−74% yields. All of the products except **17** were single diastereomers by NMR analysis, with all three substituents on the tetrahydropyran in equatorial positions. Robust oxygen protecting groups (entries 2 and 3) were compatible with the reactions, although more labile substituents, such as TBS, were cleaved under the strong Lewis acidic conditions. Most examples incorporated secondary aliphatic ethers, but both benzylic and tertiary ethers (entries 6 and 7) were effective. The enol ethers were readily prepared by exchange between ethyl vinyl ether and the corresponding homoallylic alcohols derived from allylmetal additions to simple aldehydes. Trisubstituted tetrahydropyrans are readily accessible by this new synthetic strategy.

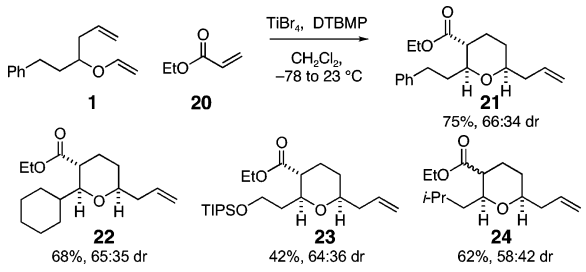
Ethyl acrylate (**20**) is a useful alkene component in the Mukaiyama−Michael cascade reaction. Scheme 1 shows several examples of the reaction of ethyl acrylate with a variety of enol ethers substrates. The reaction conditions are more vigorous; the temperature was increased to 23 °C during the course of the reaction to ensure complete consumption of starting material. In each case, a mixture of diastereomeric products was observed that were epimeric at the carboethoxy center. The efficiency of the reaction was more varied than with the enone, with yields ranging from less than 20 to 75%. Both enones and acrylates are useful substrates in the cascade cyclization reaction.

Table 1. Mukaiyama−Michael Cascade Reaction with 3-Butene-2-one (MVK)

Entry[a]	Enol Ether	Product[b]	Yield (%)
1	 **1**	 **7**	74
2	 **8**	 **9**	72
3	 **10**	 **11**	63
4	 **12**	 **13**	72
5	 **14**	 **15**	74
6[c]	 **16**	 **17**	65
7	 **18**	 **19**	74

[a] The enone (2.0 equiv), enol ether (1.0 equiv), and DTBMP (1.5 equiv) were combined in DCM at −78 °C, a solution of $TiBr_4$ (2.0 equiv) was added, and the reaction was stirred for 1 h before quenching. [b] Only a single diastereomer was observed by NMR spectroscopy. [c] Isolated as an 88:12 mixture of epimers at the methyl ketone center.

Scheme 1. Mukaiyama−Michael Cascade Reaction with Ethyl Acrylate



The mechanism of the cascade reaction is outlined in Figure 1. The first step is assumed to be a Mukaiyama−Michael reaction

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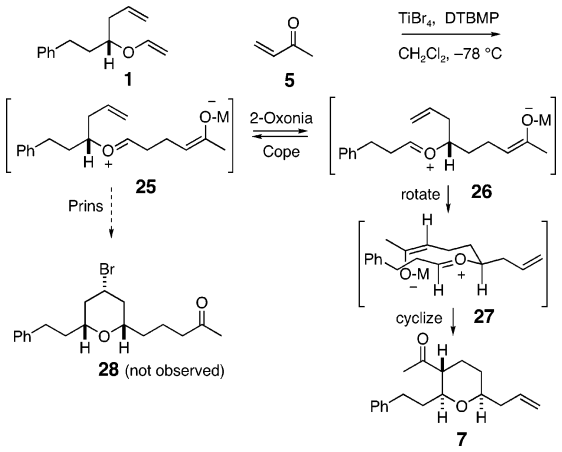
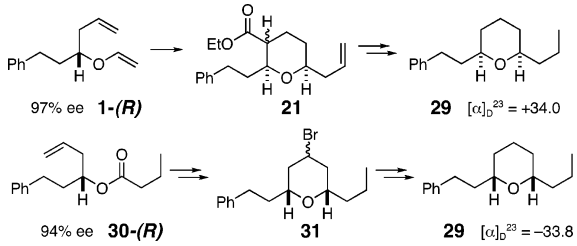


Figure 1. Proposed mechanism for the Mukaiyama−Michael cascade cyclization leading to **7** and the Mukaiyama−Michael Prins cyclization reaction leading to **28**, which was not observed with substrates **1** and **5**.

Scheme 2. Mukaiyama−Michael Cascade Reaction Leads to Inversion of Configuration but Retention of Optical Purity

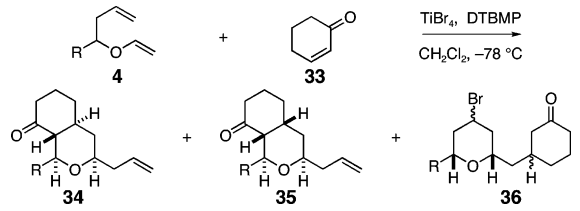


between reactants **1** and **5**, leading to zwitterion **25**.[4] Rapid equilibration of **25** and **26** by way of a 2-oxonia-Cope rearrangement[5] sets up the final cyclization between the oxocarbenium ion and the enolate in **27** to produce the tetrahydropyran **7**.[6] Bromo tetrahydropyran **28** might be formed by Prins cyclization of the initial Mukaiyama−Michael adduct **25**, but it was not observed in this case. We have demonstrated in model studies that the 2-oxonia-Cope rearrangement is very rapid for oxocarbenium ions related to **25**.[5j] The proposed sequence is conceptually related to an oxonia-Cope Prins sequence that we described recently.[7] Unlike that sequence, the current reaction was developed from a fortuitous observation and involves very simple substrates.

The sequence from oxocarbenium ion **25** to **26** to **27** suggests that the stereogenic center in the enol ether should be inverted in the product. The observations in Scheme 2 demonstrate that this is the case. A normal segment-coupling Prins cyclization of ester (*R*)-**30** leads to (*S*,*S*)-**29**, whereas the Mukaiyama−Michael cascade reaction of enol (*R*)-**1** leads to (*R*,*R*)-**29** in high optical purity.

Substituted enones also can be employed, but the outcome is more complicated. Table 2 outlines the reaction of several enol ethers with 2-cyclohexenone. The phenethyl enol ether (entry 1) reacts to give the expected cascade product **35** with high diastereoselectivity along with significant amounts of the Mukaiyama−Michael Prins adduct **36** (e.g., **28**, Figure 1). Previous work has demonstrated that the rate and equilibrium in 2-oxonia-Cope rearrangements are strongly influenced by the electronic properties of the R group.[5f] An R group favoring the rearranged oxocarbenium ion (e.g., **26**, Figure 1) would promote the cascade product, whereas a substituent favoring the starting oxocarbenium ion (i.e., **25**) would favor Prins products. The phenyl substituent stabilizes the rearranged oxocarbenium ion and leads to the diastereomeric cascade products **34** and **35** in good yield (entry 2). In contrast, chloromethyl substituent (entry 3) inhibits Cope rearrangement[5f] and favors the

Table 2. Influence of Substituents on the Cyclization Pathway



		Yields		
entry	R	**34**	**35**	**36**
1	$PhCH_2CH_2^-$	2%	43%	39%
2	Ph^-	46%	37%	
3	$ClCH_2^-$			68%

Mukaiyama−Michael Prins adduct **36**. Both the Prins product and cascade cyclization product were observed in the reactions of different enol ethers with 2-cyclohexenone, but the outcome responds to substrate modifications in a predictable manner.

We have discovered a new annulation reaction that leads to complex tetrahydropyrans from very simple substrates. The Mukaiyama−Michael cascade cyclization and the related Prins cyclization will be useful new tools for the synthesis of complex natural products.

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Supporting Information Available: Experimental data for the synthesis and characterizations of the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) $TiCl_4$ and 2,6-DTBMP also promote the reaction between **4** and **5** to give **6**, but in reduced yield (53%). Stoichiometric $TiBr_4$ was required for high conversion. Both $Ti(O\text{-}i\text{-}Pr)_4$ and TiF_4 were ineffective.

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