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## New Trialkylsilyl Enol Ether Chemistry: New Regiospecific Methodology for the Synthesis of α,β-Unsaturated Cyclic Ketones

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Abstract: Treatment of TIPS enol ethers with PhIO/TMSN<sub>3</sub> followed by desilylation/elimination with fluoride ion gives good yields of the  $\alpha,\beta$ -unsaturated ketone.

While there have been many practical ways developed for the conversion of saturated ketones into  $\alpha$ ,  $\beta$ -unsaturated ketones, these various methodologies have notable draw backs.<sup>1</sup> For example, treatment of an enolate derivative 1a with sulfenylating or selenenylating reagents generates 2, but since the  $\alpha$ -SPh or  $\alpha$ -SePh derivative 2 is more acidic than 1, anion exchange can convert 1a back to into 1. As a consequence the conversion of 1 into 2 frequently requires excess base and electrophile. This can lead to further complications such as the introduction of more than one  $\alpha$ -SPh/ $\alpha$ -SePh group. The  $\alpha$ -functionalized derivative 2 is converted by oxidation into the corresponding sulfoxides/selenoxides 3 (diastereomers) and synelimination provides the  $\alpha,\beta$ -unsaturated ketone 4. The oxidation step can readily give problems of over-oxidation, particularly for sulfoxides, and both sulfoxides and selenoxides are susceptible to electrophilically induced Pummerer rearrangement.<sup>2,3</sup> Finally there are problems of regiospecificity. Since the sulfoxides/selenoxides 3 are a diastereomeric mixture, and the thermal syn-elimination requires synclinal alignment of the S=O/Se=O bond and the hydrogen atom, for cases where both exoand  $endo-\alpha,\beta$ -unsaturated ketones are structurally possible, mixtures can result. These problems can, individually and collectively, conspire to make the conversion of a saturated ketone into an  $\alpha,\beta$ -unsaturated ketone an inefficient process.<sup>4</sup>



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Recently we have reported the unprecedented direct  $\beta$ -azidonation of triisopropylsilyl enol ethers (TIPS) using the reagent combination PhIO/TMSN<sub>3</sub> /CH<sub>2</sub>Cl<sub>2</sub> at -15°C.<sup>5</sup> For example (entry 1) treatment of 5 with the above reagent gave 6 (89%), which was treated with tetra-n-butylammonium fluoride (TBAF)/THF at 0°C to give 7 (80%). In contrast using phenylselenoxide chemistry gave only 30% of 7.6 The intermediate  $\beta$ -azido TIPS enol ether need not be isolated but directly converted (TBAF) into the  $\alpha$ , $\beta$ -unsaturated ketone. The entries 2-12 are yields for the two steps and refer to chromatographically purified material. The reaction is completely regiospecific (entries 5/6 and 7/8), and for 23 where there is the possibility of





(In all cases the reactions are extremely clean as judged by tlc, and the lower yields are due to volatility).

regioisomeric azides we found that 24 and 25 were formed (ca. 6:1) which subsequently gave the enones 26 and 27. A particularly interesting example is shown in *entry 11*. The substrate 37 is made from cyclohexanone TIPS enol ether/PhIO/TMSN<sub>3</sub> followed by cyclohexanone TMS enol ether/Me<sub>2</sub>AlCl.<sup>7</sup> The  $\beta$ azidonation reaction reintroduces the azide functionality to give 38 which undergoes fluoride induced elimination to give the mixed ketone-enone 39. None of the existing methodology allows these manipulations without protection of the saturated carbonyl group. Indeed it is not at all obvious how mixed ketone-enones such as 39 could be made without this new enol TIPS enol ether chemistry. It is important to use the TIPS enol ether derivative in this chemistry since less sterically encumbered versions (TMS) are desilylated in the  $\beta$ -azidonation step to give the unfunctionalized ketone.

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