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# A Novel Nucleophilic Substitution of in Situ Generated 3-*tert*-Butyldimethylsilyloxyalk-2-enylsulfonium Salts with Allylindium Reagents

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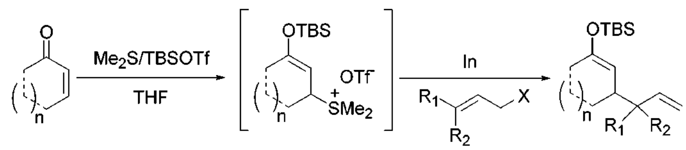
## ABSTRACT




**In situ generated 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts derived from the reaction of α,*β*-enones with dimethyl sulfide in the presence of TBSOTf undergo a novel nucleophilic substitution with in situ generated allylindium reagents from indium and allyl halides to give silyl enol ethers of *δ*,ϵ-unsaturated ketones, which correspond to Michael addition products, in good yields.**

The conjugate addition of organometallic reagents to α,*β*-unsaturated carbonyl compounds is one of the most useful and reliable methods for carbon–carbon bond formation. It has been normally achieved using organocopper and Grignard reagents in the presence of copper halide.[1] Although *β*-substituted silyl enol ethers are generally accessible from α,*β*-enones by conjugate addition of copper and Grignard reagents followed by enolate trapping, such procedures are sometimes not convenient and the requisite reagents are difficult to obtain.[2] Furthermore, as far as we are aware, there have been very few reports on the preparation of silyl enol ethers in which labile substituents such as alkoxycarbonyl or alkoxycarbonyl olefins are present at the *β*-position.[3] Our interests in extending the scope of the Michael addition reaction and subsequent application of indium metal to modern organic synthesis[4] have led us to investigate an indium-promoted Michael addition reaction. Generally, allylindium reagents react with α,*β*-unsaturated aldehydes to afford 1,2-addition products in good yields.[5] Reaction of 4-phenyl-3-buten-2-one, which is a unique example of an α,*β*-unsaturated ketone, with allylindium reagents produces a regioselective 1,2-addition product.[5] However, there are

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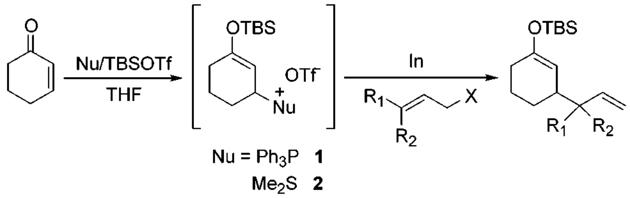
few reports on the Michael addition reaction to α,β-unsaturated ketones using allylindium reagents.[6] Recently, it was reported that indium-mediated allylation to 1,1-dicyano-2-arylethenes gave Michael addition products in aqueous media in good yields.[6a] Tetraorganoindium ate complexes reacted with α,β-unsatursated ketones in a 1,4-addition fashion.[6b] The reaction of allylindium with α,β-unsatursated carbonyl compounds, in which two electron-withdrawing groups were attached to alkenes, proceeded in a 1,2-addition mode, whereas a 1,4-addition reaction took place with 1,1-dicyano-2-arylethenes, which are extremely electron deficient olefins.[6c] Although several examples of the indium-mediated allylation of aldehydes and ketones have been reported,[7] as far as we are aware, few examples of the regioselective β-allylation to α,β-unsatursated ketones have been published.[6d] As part of our continuing effort to expand the synthetic utility of indium, we now report a novel nucleophilic substitution of in situ generated 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts with allylindium reagents to afford silyl enol ethers of α,β-unsaturated ketones, which correspond to Michael addition products (Scheme 1).

**Scheme 1**




Initial studies were performed with 3-*tert*-butyldimethylsilyloxycyclohex-2-enylphosphonium salts (**1**),[8] which could be prepared from phosphoniosilylation of 2-cyclohexen-1-one. **1** was treated with allylindium reagent to produce the *tert*-butyldimethylsilyl enol ether **19** of 3-allylcyclohexanone in 15% yield in THF at 60 °C for 2 h (Table 1, entry 11). We next turned our attention to the possibility of 3-*tert*-butyldimethylsilyloxycyclohex-2-enylsulfonium salts (**2**).[9] To obtain silyl enol ethers of α,β-unsaturated ketones in good yields, several reaction conditions were examined. Of the stoichiometric allylindium reagents examined, the best results were obtained with an allylindium reagent which was in situ generated from the reaction of 1 equiv of indium with 1.5 equiv of allyl halide. The use of indium in amounts less than 1 equiv and allyl halide in amounts less than 1.5 equiv resulted in a sluggish reaction and gave lower yields as well as longer reaction times. Because the sulfonium salt was thermally unstable, the reaction was carried out at low temperature (−78 °C) in THF.[9] To demonstrate the efficiency and scope of the present method, we applied this optimum condition to a variety of α,β-enones and allyl halides. The results are summarized in Table 1. The sulfonium salt **2** was treated with allyl bromide and indium to produce the conjugate addition product **19** in 65% yield (Table 1, entry 11). Reaction of **2** with indium reagents, which were derived from crotyl bromide and prenyl bromide in THF, afforded **20** and **21** in 62 and 61% yields, respectively, at −78 °C for 10 min (Table 1, entries 12 and 13). It is especially noteworthy that the substitution reaction showed exclusive γ-regioselectivity. Consequently, these two-step conversions in one pot correspond to the 1,4-addition of indium reagents to α,β-enones. Treatment of sulfonium salt **2** with indium reagent derived from ethyl iodoacetate gave **22** in 62% yield under the optimized conditions (Table 1, entry 14). Similarly, when **2** was reacted with ethoxycarbonyl allylindium reagent, the desired products **23** and **24** were obtained in 42% and 22% yields, respectively (Table 1, entry 15). It is of interest to note that sulfonium salts are easily displaced by indium reagents derived from ethyl iodoacetate and ethyl bromocrotonate; there have been very few reports on the preparation of silyl enol ethers in which substituents having labile alkoxycarbonyl or alkoxycarbonyl olefins are present at the β-position and lithium, magnesium, or cuprate reagents containing these groups cannot be easily prepared. Several sulfonium salts of other cyclic α,β-enones (**4** and **6**) underwent a novel nucleophilic substitution with the same efficiency. Also, the reaction worked well with a sulfonium salt of acyclic 4-hexen-3-one (**3**).

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(9) The low-temperature $^1$H NMR spectroscopy in $CDCl_3$ at −50 °C exhibited two singlets at δ 4.51 and 4.86 ppm resulting from an olefinic proton and the proton adjacent to dimethylsulfonium group. However, the $^1$H NMR at −20 °C was completely different from that at −50 °C indicating the decomposition of the sulfonium salt at above −20 °C. $^1$H NMR (300 MHz, $CDCl_3$, −50 °C) of 3-trimethylsilyloxy-2-cyclohexenyldimethylsulfonium trifluoromethanesulfonate: δ 0.20 (s, 9H), 1.85−2.63 (m, 6H), 2.98−3.01 (m, 6H), 4.51 (s, 1H), 4.86 (s, 1H).

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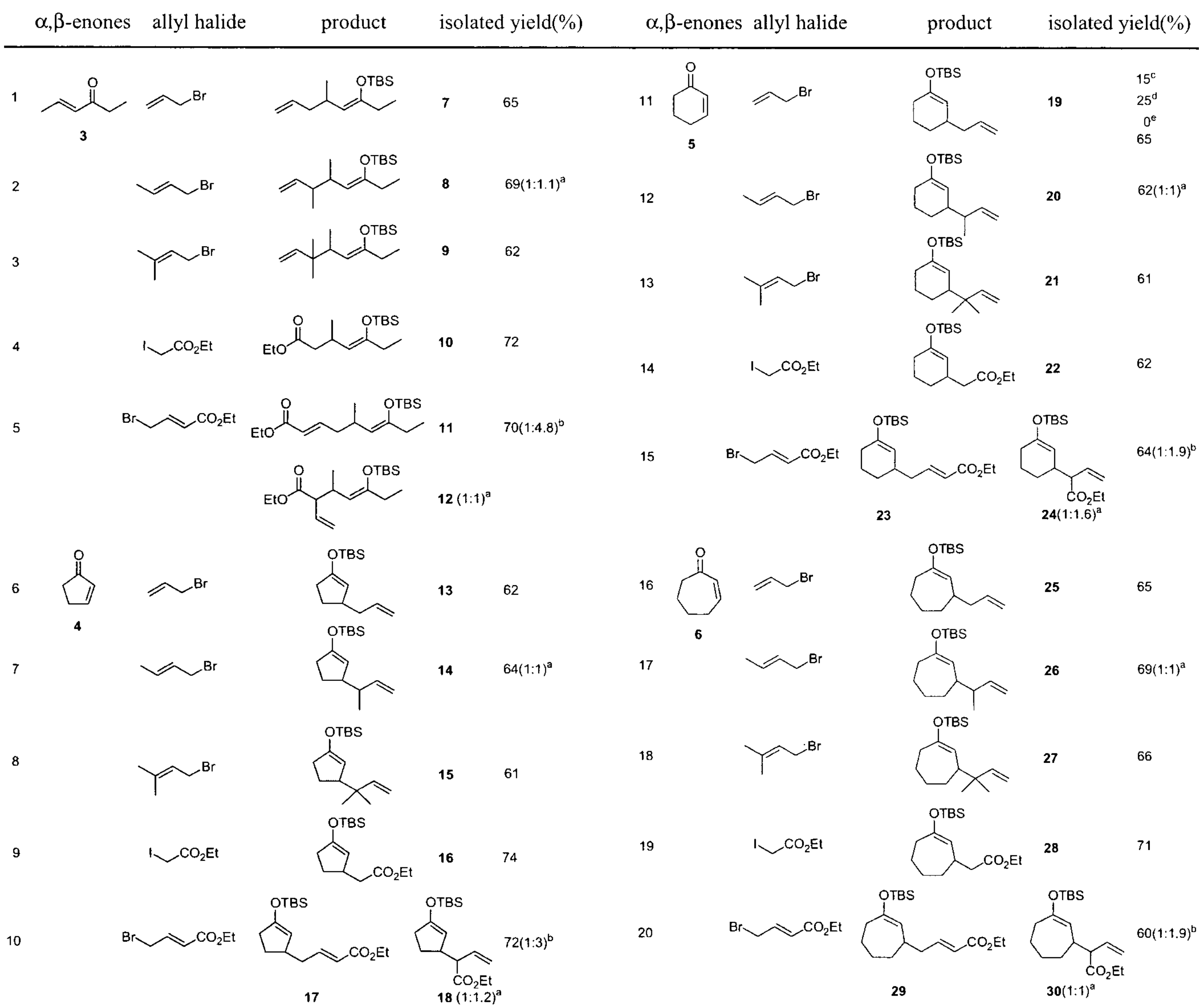
(12) **General Experimental Procedure.** To a stirred solution of 2-cyclohexen-1-one (96.0 mg, 1.0 mmol) in THF (1.5 mL) were added successively dimethyl sulfide (75.0 mg, 1.2 mmol) and TBSOTf (278 mg, 1.05 mmol) at −78 °C under a nitrogen atmosphere. After 10 min, allylindium reagent which is generated from allyl bromide (218.0 mg, 1.5 mmol) and indium (115 mg, 1.0 mmol) in THF (1.5 mL) was added and mixture was stirred at −78 °C for 30 min. The reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organics were washed with water and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane to give 3-allyl-1-*tert*-butyldimethylsilyloxy-1-cyclohexene (163 mg, 65%).

**Table 1.** Indium-Mediated $\beta$-Allylation of $\alpha,\beta$-Unsaturated Ketones



| entry | $\alpha,\beta$-enones | product | isolated yield(%) |
|---|---|---|---|
| 1 | 3 | 7 | 65 |
| 2 | 3 | 8 | 69(1:1.1)[a] |
| 3 | 3 | 9 | 62 |
| 4 | 3 | 10 | 72 |
| 5 | 3 | 11 | 70(1:4.8)[b] |
| | | 12 (1:1)[a] | |
| 6 | 4 | 13 | 62 |
| 7 | 4 | 14 | 64(1:1)[a] |
| 8 | 4 | 15 | 61 |
| 9 | 4 | 16 | 74 |
| 10 | 4 | 17, 18 (1:1.2)[a] | 72(1:3)[b] |
| 11 | 5 | 19 | 15[c] 25[d] 0[e] 65 |
| 12 | 5 | 20 | 62(1:1)[a] |
| 13 | 5 | 21 | 61 |
| 14 | 5 | 22 | 62 |
| 15 | 5 | 23, 24(1:1.6)[a] | 64(1:1.9)[b] |
| 16 | 6 | 25 | 65 |
| 17 | 6 | 26 | 69(1:1)[a] |
| 18 | 6 | 27 | 66 |
| 19 | 6 | 28 | 71 |
| 20 | 6 | 29, 30(1:1)[a] | 60(1:1.9)[b] |

[a] The ratios in parentheses indicate diastereomeric ratio. [b] The ratios in parentheses indicate ratios of constitutional isomers. [c] Phosphonium salt was used. [d] 2-Cyclohexen-1-one:In:allyl bromide = 1.0:0.67:1.0. [e] $Me_2S$ was not used.

The reaction proceeds via an addition–substitution mechanism involving the formation of allylic sulfonium salts. Followed by addition of a dimethyl sulfide to $\alpha,\beta$-enones in the presence of *tert*-butyldimethylsilyl triflate produces the allylic sulfonium salts; then substitutions of dimethyl sulfide by in situ generated allylindium reagents would yield the desired products.

In summary, 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts underwent facile $\beta$-allylation with various in situ generated allylindium reagents to give 3-substituted silyl enol ethers.[12] Because the $\beta$-substituted silyl enol ethers are generally accessible to $\alpha,\beta$-enones by conjugate additions of copper and Grignard reagent followed by enolate trapping and few reports for the Michael addition reaction of indium reagents to $\alpha,\beta$-enones have been published,[5,6] the present method contrasts with and complements the existing synthetic methods. Also, since sulfonium salts have been utilized mainly in the generation of sulfur ylides[10] and seldom used as leaving groups,[11] the present method enhances the synthetic utility of 3-*tert*-butyldimethylsilyloxyalk-2-enylsulfonium salts. Extension of this study is now under investigation in this laboratory.

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