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# *In situ* protection methodology for selective one-pot allylation and alkylation of ketones in the presence of α,β-unsaturated ketones

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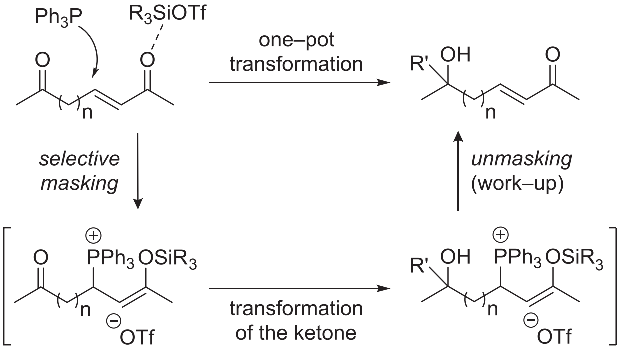
## ABSTRACT

Selective one-pot alkylation or allylation of ketones in the presence of α,β-unsaturated ketones (enones) were accomplished by using our in situ protection methodology. Enones selectively react with a combination of $PPh_3$ and silyl triflates in the presence of ketones to produce phosphonium silyl enol ethers, which act as protective groups for the enones during the alkylation or allylation of ketones, and can be easily deprotected to regenerate the parent enones on work-up.

## 1. Introduction

Ketones and α,β-unsaturated ketones (enones) display nearly identical reactivity, although ketones generally have slightly higher reactivity toward nucleophiles than enones. Only three different methods have described selective reductions of ketones in the presence of enones.[1] There are a few methodologies succeeding in the selective transformation between closely related carbonyl functions, ketones and enones. However, there is no general method for the selective alkylation of carbonyl functions in the presence of enones.

As part of our studies into the control of the reactivity of individual functional groups using in situ protection methodology with a combination of triphenylphosphine ($PPh_3$) and trifluoromethanesulfonic acid trimethylsilyl ester (TMSOTf),[2] we have recently reported selective transformations of carbonyl functions in the presence of enones.[3] Scheme 1 shows a selective transformation of a ketone as a representative example. This reaction involves the selective in situ protection of the enones as phosphonium silyl enol ethers. Subsequent transformation of other carbonyl functions (the ketone in Scheme 1) can then occur, followed by deprotection to regenerate the parent enones on work-up.



**Scheme 1.** Selective one-pot transformation of carbonyl functions in the presence of enones.

Research in this field has mainly involved reduction reactions. Alkylation, In(0)-mediated Barbier-type allylation[4] (Scheme 2, eq. 1) and Reformatsky-type reaction[5] (Scheme 2, eq. 2) has only been investigated with one substrate (**1a**) in Ref. 3. These were the first examples of ketone-selective alkylations in the presence of enones. We studied the alkylation in more detail using a range of substrates.

## 2. Results and discussion

Firstly, we examined the reactivity of a ketone in the presence of an enone using enone **3a** and various ketones (**4a**–**4f**). The results of the Barbier-type allylation using indium metal are shown in Table 1.

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**Scheme 2.** Ketone selective allylation (eq. 1) and reformatsky-type reaction (eq. 2).

An encouraging result was obtained in every case. In addition to alkyl ketones **4a**,**b**, aryl ketones **4c**–**f** reacted smoothly in spite of their substituents. The success of the Reformatsky-type alkylation reaction depended on which ketones was used, and several substrates gave no reaction, because the reactivity of the ketones were low (N.R., Table 2, entries 1, 3, 7). In these cases, the excess (4 equiv) nucleophile (iodo-In-acetate) which remained unchanged could not react with the salts from enones. When the enone was rebirthed on work-up, the nucleophile (iodo-In-acetate) was also quenched by the addition of tetra-n-butylammonium fluoride (TBAF). However, we could not find a trend to predict which substrates would react to give the desired product. We then examined the allylation reaction in more detail.

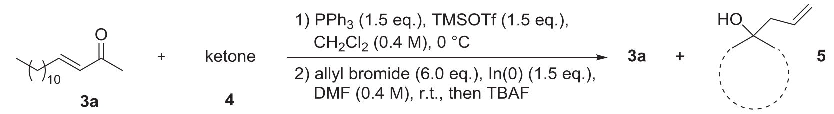
We studied the scope of the allylation reaction by using two different enones **3b** and **3c**, both of which have conjugated enone units (Table 3). The results show that pre-treatment with $PPh_3$ and TMSOTf can be used to protect not only aliphatic enone **3a** (Table 1), but also the aromatic enones **3b** and **3c,** in the presence of various ketones **4a**–**f**. Easily enolizable ketone **4c** was also selectively allylated in good yields (Table 3, entry 3). Moreover, acid-labile methoxy methyl (MOM) groups also tolerated the reaction conditions (Table 3, entry 5).

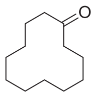
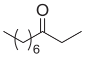
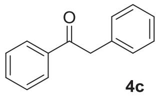
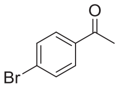
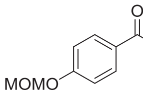
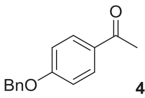
In addition to **1a,** aromatic keto-enone **1b** was submitted to the reaction conditions, and allylated alcohol **2c** was obtained in high yield with the enone unit intact (Scheme 3).

NMR analysis was used to demonstrate that phosphonium salt intermediates are selectively formed by treatment of keto-enones under the in situ protection conditions. Inspection of $^{13}$C NMR spectra (Fig. 1) shows that the resonances at 198 (D carbon), 148 (B carbon), and 131 (C carbon) ppm for the enone carbons of **1a** disappear when a $CDCl_3$ solution of **1a** is treated with $PPh_3$ (1.5 equiv) and TESOTf (1.5 equiv). Furthermore, new signals derived from the phosphonium silyl enol ether are observed at 204 (E carbon) and 154 (F carbon) ppm. The ketone carbon (A carbon) of **1a** (215 ppm) remains intact in the phosphonium silyl enol ether intermediate. These results indicate that the phosphonium salt intermediate is formed at the enone in the presence of the ketone.

Next, we examined the selective alkylation of ketones in the presence of enones. We first chose enone **3c** and ketone **4h** to optimize the conditions. A 1:1 mixture of **3c** and **4h** was treated with TMSOTf and $PPh_3$ to protect the enone. This was then treated with methylindium bromide (MeInBr), prepared from MeBr and

**Table 1**
Selective allylation of ketones in the presence of enones (In(0)-mediated Barbier-type allylation)



| Entry | Ketone (4) | Recovered enone (3a) | Allylated ketone (5) |
|---|---|---|---|
| 1 |  **4a** | 83% | 88% **(5a)** |
| 2 |  **4b** | 80% | 90% **(5b)** |
| 3 |  **4c** | 80% | 84% **(5c)** |
| 4 |  **4d** | 76% | 81% **(5d)** |
| 5 |  **4e** | 87% | 91% **(5e)** |
| 6 |  **4f** | 85% | 93% **(5f)** |