

# Facile $\beta$ -Alkylation and $\beta$ -Hydroxyalkylation of $\alpha,\beta$ -Unsaturated Lactones and Esters

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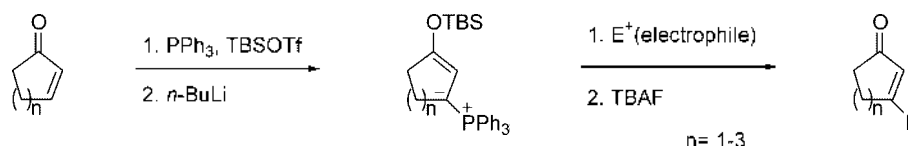
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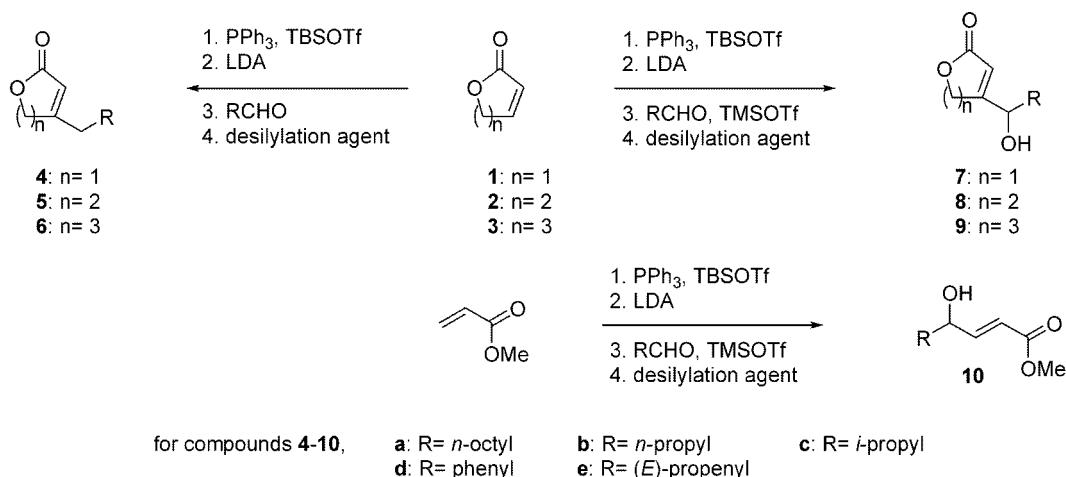
$\beta$ -Functionalization of  $\alpha,\beta$ -unsaturated carbonyl compounds has been generally achieved either by the organometallic conjugate addition procedures followed by enolate trapping and subsequent oxidation<sup>1</sup> or by the dipole reversal process involving the conversion of  $\alpha,\beta$ -unsaturated carbonyl compounds into  $\beta$ -acylvinyl anion equivalents.<sup>2-4</sup> In the case of enones, very efficient and practical  $\beta$ -functionalization methods utilizing the phosphoniosilylation process have been recently developed by Kozikowski<sup>3</sup> and Kim (Scheme 1).<sup>4</sup> However, as far as we are aware, there are no such  $\beta$ -functionalization methods available, in case of  $\alpha,\beta$ -unsaturated lactones and esters. Thus, we became interested in the development of phosphoniosilylation-based  $\beta$ -functionalization methods for  $\alpha,\beta$ -unsaturated lactones and esters. We now wish to report efficient and facile  $\beta$ -alkylation and  $\beta$ -hydroxyalkylation of  $\alpha,\beta$ -unsaturated lactones and esters (Scheme 2).

At the outset, scrutinizing the whole process of  $\beta$ -alkylation of enones, the feasibility of the phosphoniosilylation

and the ylide formation was envisaged to be the key to the success in  $\beta$ -alkylation of  $\alpha,\beta$ -unsaturated lactones. While the phosphoniosilylation of methyl acrylate, a model substrate, with triphenylphosphine and *t*-butyldimethylsilyl triflate (TBSOTf) proceeded rather smoothly, the subsequent phosphorane formation required further elaboration. Our initial attempt to generate the ylide from the phosphoniosilylation product of methyl acrylate using *n*-butyllithium was not fruitful, presumably due to the competing desilylation. However, upon examining various bases, lithium diisopropylamide (LDA) was found to be the most suitable for our purpose, although other strong bases with low nucleophilicity such as lithium bis(trimethylsilyl)amide and lithium 2,2,6,6-tetramethylpiperide could also be used with some success. When the Wittig reagent, derived from the phosphoniosilylation product of methyl acrylate, was reacted with benzaldehyde at -78 °C to rt, and then treated with tetra-*n*-butylammonium fluoride (TBAF) or saturated ammonium chloride solution in the same pot, the desired



Scheme 1



Scheme 2

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**Table 1.**  $\beta$ -Alkylation of  $\alpha,\beta$ -unsaturated lactones

Entry	$\alpha,\beta$ -unsaturated lactone	RCHO	Product	Yield (%) <sup>a</sup>
1	<b>2</b>	R - <i>n</i> -octyl	<b>5a</b>	72
2	<b>2</b>	R - <i>n</i> -propyl	<b>5b</b>	68
3	<b>2</b>	R - <i>i</i> -propyl	<b>5c</b>	64
4	<b>2</b>	R - phenyl	<b>5d</b>	66
5	<b>2</b>	R - ( <i>E</i> )-propenyl	<b>5e<sup>b</sup></b>	52
6	<b>1</b>	R - phenyl	<b>4d</b>	26 <sup>c</sup>
7	<b>3</b>	R - <i>n</i> -propyl	<b>6b</b>	40 <sup>c</sup>
8	<b>3</b>	R - phenyl	<b>6d</b>	43 <sup>c</sup>

<sup>a</sup>isolated yields based on  $\alpha,\beta$ -unsaturated lactone when TBAF was used as a protodesilylating agent otherwise mentioned. <sup>b</sup>a mixture of  $\beta,\gamma$  and  $\delta,\epsilon$ -unsaturated isomers was obtained. <sup>c</sup>saturated ammonium chloride solution was used instead of TBAF.

methyl (*E*)-4-phenyl-2-butenolate was obtained in 75% yield.

Encouraged by the successful  $\beta$ -benzylation of methyl acrylate, this four-step one pot procedure was employed to  $\alpha,\beta$ -unsaturated lactones. The results are shown in Table 1. This chemistry works well with aliphatic, aromatic, and unsaturated aldehydes in 5,6-dihydro-2*H*-pyran-2-one (**2**) series (entry 1-5). With crotonaldehyde (entry 5), a 1 : 2 mixture of (*E*)- and (*Z*)-4-buten-2-enylidenetetrahydropyran-2-ones, rather than the fully conjugated isomer, was obtained.<sup>5</sup> With 2(5*H*)-furanone (**1**) and 6,7-dihydro-5*H*-oxepine-2-one (**3**), the yields were relatively low (entry 6-8). With 2(5*H*)-furanone (entry 6), the yield was only 26% and was obtained a mixture of  $\alpha,\beta$ - and  $\beta,\gamma$ -unsaturated lactones, which could be isomerized to  $\alpha,\beta$ -unsaturated isomer by treating with DBU. This low yield was presumed to be in part due to the competing elimination of ring residue in the position beta to the phosphorus atom of a phosphonium salt during the ylide formation. It is also noteworthy that in most cases TBAF was a better protodesilylating agent than saturated ammonium chloride solution. In many cases the use of saturated ammonium chloride solution resulted in a mixture of  $\alpha,\beta$ - and  $\beta,\gamma$ -unsaturated lactones.

Kim has first shown that betaine intermediates can be successfully quenched by TMSOTf prior to the formation of oxaphosphetanes during the reaction of ylides with aldehydes.<sup>4a</sup> And he has further demonstrated that  $\beta$ -hydroxyalkylation of enones can be achieved by one-pot sequence of the phosphoniosilylation, the phosphorane formation, TMSOTf quenching of betaine intermediates and the desilylative elimination of triphenylphosphine. Our success in  $\beta$ -alkylation of  $\alpha,\beta$ -unsaturated lactones prompted us to test the possibility of  $\beta$ -hydroxyalkylation of  $\alpha,\beta$ -unsaturated lactones and esters by employing Kim's  $\beta$ -hydroxyalkylation procedure of enones.

When ylides, generated from phosphoniosilylation products of  $\alpha,\beta$ -unsaturated lactones and esters, were reacted with aldehydes and TMSOTf at -78 °C for 0.5 h, and the mixture was then treated with TBAF at -78 °C to rt, the desired  $\beta$ -hydroxyalkylated  $\alpha,\beta$ -unsaturated lactones (**7-9**) and esters

**Table 2.**  $\beta$ -Hydroxylation of  $\alpha,\beta$ -unsaturated lactones and esters

Entry	$\alpha,\beta$ -unsaturated lactone (ester)	RCHO	Product	Yield (%) <sup>a</sup>
1	<b>2</b>	R - <i>n</i> -octyl	<b>8a</b>	81
2	<b>2</b>	R - <i>n</i> -propyl	<b>8b</b>	85
3	<b>2</b>	R - <i>i</i> -propyl	<b>8c</b>	71
4	<b>2</b>	R - phenyl	<b>8d</b>	83(72) <sup>b</sup>
5	<b>3</b>	R - <i>n</i> -propyl	<b>9b</b>	21
6	<b>3</b>	R - phenyl	<b>9d</b>	26
7	Methyl acrylate	R - <i>n</i> -propyl	<b>10b</b>	76
8	Methyl acrylate	R - <i>i</i> -propyl	<b>10c</b>	87

<sup>a</sup>isolated yields based on  $\alpha,\beta$ -unsaturated lactone when TMSOTf was used as a betaine trapping agent otherwise mentioned. <sup>b</sup>TBSOTf was used instead of TMSOTf.

(**10**) were obtained in good yields. As reported in  $\beta$ -hydroxyalkylation of enones,<sup>4a</sup> the yields of products were influenced by the quenching method of the betaine intermediates. In our cases, the addition of aldehydes followed by fast addition of TMSOTf to ylides gave optimum results. As shown in Table 2, this chemistry also works well with aliphatic and aromatic aldehydes in 5,6-dihydro-2*H*-pyran-2-one series (entry 1-4) and methyl acrylate series (entry 7, 8). However, with 6,7-dihydro-5*H*-oxepin-2-one (entries 5, 6), the yields were relatively low as those in  $\beta$ -alkylation. With 2(5*H*)-furanone and  $\beta$ -substituted  $\alpha,\beta$ -unsaturated esters, this chemistry failed to give the corresponding  $\beta$ -hydroxyalkylated products. It should also be noted that in contrast to  $\beta$ -hydroxyalkylation of enones, TBSOTf could also be used as a trapping agent instead of TMSOTf, although yields of desired products were slightly lower (entry 4).

In summary, we have shown that the  $\alpha,\beta$ -unsaturated lactones and esters can efficiently be  $\beta$ -alkylated and  $\beta$ -hydroxyalkylated through the phosphoniosilylation process.

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- Isomerization of the mixture to the fully conjugated isomer could be effected by treating with DBU in refluxing toluene.