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Tandem Michaël-Wittig Horner Reaction
One-Pot Synthesis of δ-Substituted α,β-Unsaturated Esters

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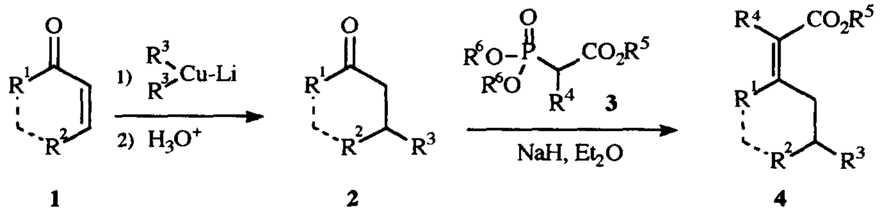
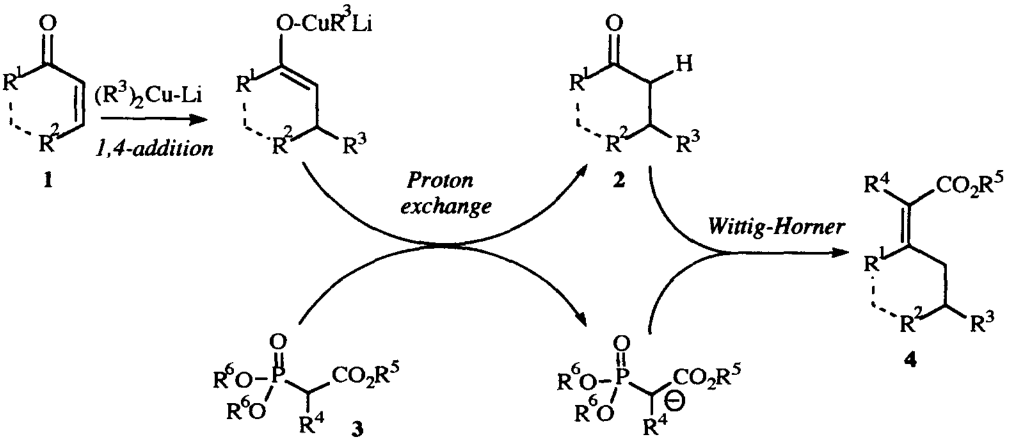
Abstract: A direct synthesis of δ-substituted α,β-unsaturated esters from unsubstituted aldehydes or ketones has been accomplished in high yield by a tandem 1,4-addition and Wittig-Horner reaction. The Copper-enolate obtained after the first step was able to deprotonate the highly acidic phosphonate generating thus the two components necessary for the second coupling reaction.

In connection with our work on the asymmetric photodeconjugation processes[1] and their application to the synthesis of natural products[2], we were recently interested to prepare α,β-unsaturated esters bearing in δ position different substituents. An obvious disconnection is presented on Scheme 1. 1,4-Addition of a cuprate[3,4] to an unsaturated aldehyde or ketone **1** could deliver after hydrolysis a β-substituted carbonyl compound **2**. This product could be further used for a next Wittig-Horner reaction[5]. Such coupling reactions require at this stage, the generation of a stabilized anion by deprotonation of a 2-phosphonoacid ester **3**.



Scheme 1

We have considered to perform this sequence in a one-step fashion using a new tandem process[6,7] according to Scheme 2. The enolate produced after the 1,4-addition on **1** could be able to deprotonate the phosphonoester **3**, regenerating at the same time compound **2**. Coupling between these two species could then deliver the expected α,β-unsaturated ester **4**.



Scheme 2

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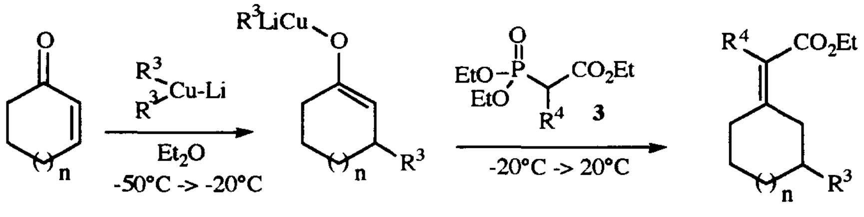
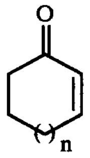
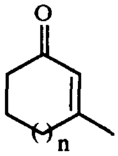
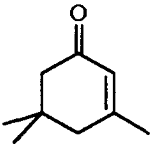
We report therein that such a process occurs giving in good yields the expected unsaturated esters[8]. Results with cycloalkenones and various cuprates are summarized in Table 1.

Table 1. Tandem Michaël-Wittig Horner reaction on cycloalkenones.



Substrate	n	Entry	Nucleophile $(R^3)_2$Cu-Li	Phosphonate **3** R^4	Adduct Yield	E/Z
	1	**1a**	Me_2Cu-Li	H	84% [a]	50/50
	1	**1b**	Me_2Cu-Li	H	70% [b]	50/50
	1	**1c**	Me_2Cu-Li	H	68% [c]	50/50
	1	**1d**	Me_2Cu-Li	Me	85% [a]	50/50
	1	**1e**	$(nBu)_2$Cu-Li	H	93% [a]	50/50
	1	**1f**	Ph_2Cu-Li	H	96% [a]	50/50
	1	**1g**	Ph_2Cu-Li	H	56% [c]	50/50
	0	**1h**	Me_2Cu-Li	H	68% [a]	52/48
	0	**1i**	$(nBu)_2$Cu-Li	H	89% [a]	50/50
	0	**1j**	Me_2Cu-Li	H	82% [a]	52/48
	1	**1k**	Me_2Cu-Li	H	83% [a]	77/23
		**1l**	Me_2Cu-Li	H	83% [a]	-
		1m	Me_2Cu-Li	F	64% [a]	-

a) Trapping of the enolate performed with phosphonate **3** (2 eq.).

b) Trapping of the enolate performed with a mixture of ammonium chloride (0.9eq.) and phosphonate **3a** (R^4=H) (1.2eq).

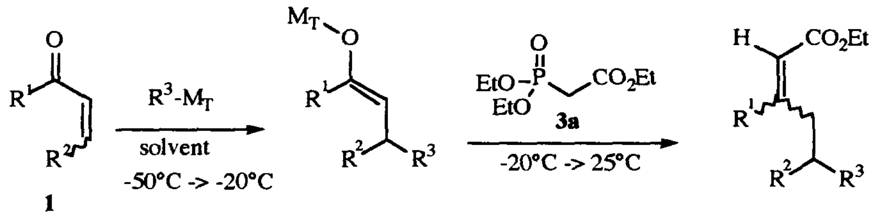
c) Trapping of the enolate performed with a mixture of acetic acid (0.9eq.) and phosphonate **3a** (R^4=H) (1.2eq).

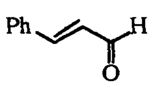
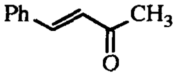
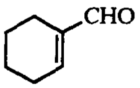
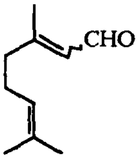
The yields of adducts were good to excellent whatever the substitution on 3 position of the enones, while the selectivity E/Z appeared poor due to the low interaction between the phosphonate and the new chiral center bearing substituent R^3. Moreover, the reaction was usually conducted with two equivalents of phosphonate **3**.

We found that this amount could be further reduced to 1.1eq. if another acidic compound like ammonium chloride (entry 1b) or acetic acid (entry 1c and 1f) was introduced just before the addition of **3**.

The reaction has been also tested on acyclic enones and also unsaturated aldehydes as reported in Table 2. Like above, the reaction took place with moderate to good yields. To suppress the propency of 1,2-addition of methyl cuprates on enals, the use of $Me_5Cu_3Li_2$ preconised by Clive *et al.* was tested[9] and verified. Furthermore, in connection with the synthesis of natural products, 1,4-reduction (R^3=H) followed by a Wittig-Horner olefination was conducted on Citral. In that case, this process suppressed the isolation of highly volatile intermediate and could therefore increase the yield in the adduct.

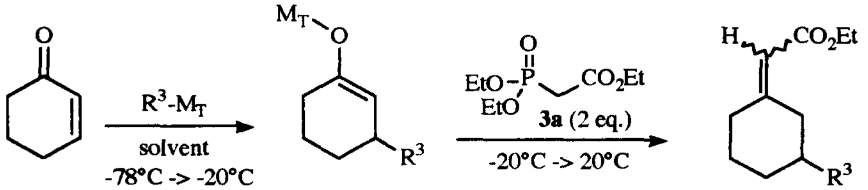
Table 2. Tandem Michaël-Wittig Horner reaction on acyclic enones and unsaturated aldehydes.

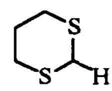
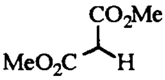
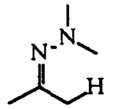


Entry	Substrate **1**	Nucleophile R^3-M_T	R^3	Conditions	Phosphonate **3a**	Adduct	
						Yield	E/Z
2a		Me_2CuLi	Me	Ether, -50°C	2 eq.	15%	95/5
2b		Me_5CuLi	Me	Ether, -50°C	5 eq.	47%	95/5
2c		Me_2CuLi	Me	Ether, -50°C	2 eq.	34%	85/15
2d		Me_5CuLi	Me	Ether, -50°C	5 eq.	72%	83/17
2e		Me_2CuLi	Me	Ether, -50°C	2 eq.	65%	62/38
2f		Me_2CuLi	Me	Ether, -50°C	2 eq.	81%	100/0
2g		DIBAH	H	THF/HMPA -50°C	1 eq.	41%	75/25

Finally, the reaction has been extended to the use of functionalized nucleophiles toward cyclohexenone. In Table 3, several examples are presented with an emphasis to the formation of adducts bearing masked ketone functionality like dithiane[11] (entry 3a) or hydrazone[12] (entry 3c). It should be mentionned that 1,4-addition of enolate of nitroalkane (e.g. nitroethane) was observed when the reaction was conducted in the presence of alumina.[13] Unfortunately, in that case, the second coupling was not observed and only nitroketones were isolated instead of the ε-nitro α,β-unsaturated esters.

Table 3. Tandem Michaël-Wittig Horner reaction with functionalized nucleophiles toward cyclohexenone



Nucleophile R^3-H	Entry	Conditions	Adduct Yield	E/Z
	**3a**	n-BuLi, HMPA	78%	55/45
	**3b**	n-BuLi, HMPA	92%	60/40
	**3c**	LDA, CuI, THF	76%	not det.

In conclusion, we have demonstrated that *tandem Michaël-Wittig Horner reaction* allows a rapid access to δ-substituted, α,β-unsaturated esters from alkenones or alkenals without isolation of relatively volatile intermediates. Work is now underway to apply this sequence in natural products synthesis.

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