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Amine-Catalyzed Coupling of Allenic Esters to α,β-Unsaturated Carbonyls

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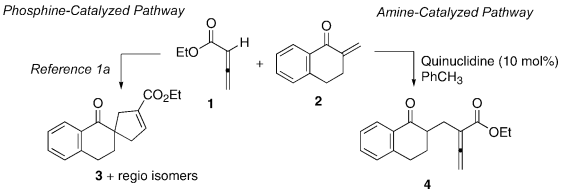
Organic reactions that lead to increases in molecular complexity are of great value in both target-oriented and diversity-oriented synthesis. In this context, the phosphine-catalyzed cycloaddition of allenic esters to enones represents a process that has received substantial attention in recent years (Scheme 1).[1] Thus, allene **1** and enone **2** undergo a reaction to give cycloadduct **3** in the presence of substoichiometric quantities of triphenyl phosphine. From a mechanistic point of view, the reaction is often represented as proceeding through a zwitterionic intermediate that serves as a dipole for a [3 + 2]-cycloaddition.[2] In the process of investigating whether nitrogen-based nucleophiles could induce similar reactivity, we found that a very different path is followed. Rather than a P-catalyzed cycloaddition, an N-catalyzed conjugate addition is observed. In this case, building blocks **1** and **2**, upon exposure to a catalytic quantity (10 mol %) of quinuclidine, afford product **4** in excellent yield (87%).

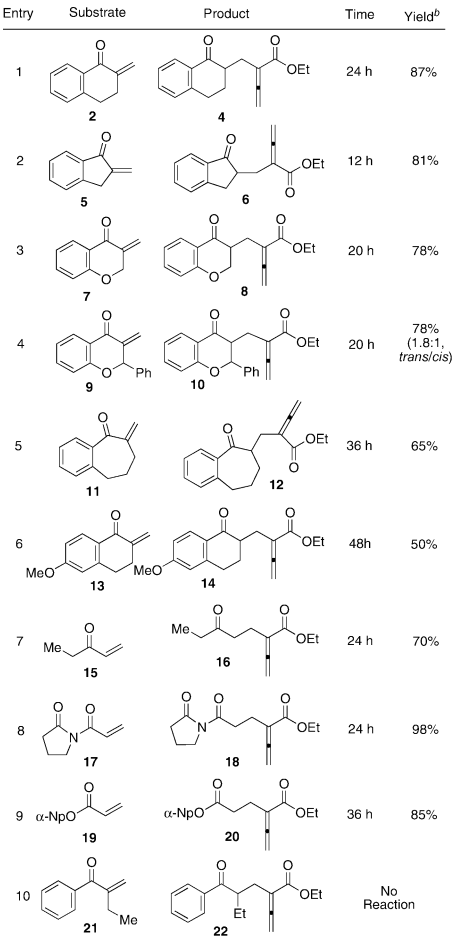
Scheme 1



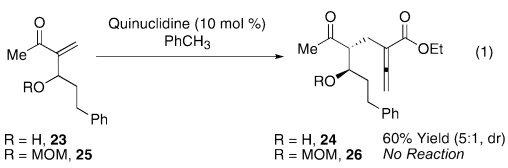
The reaction proceeds under very mild conditions (10 mol % quinuclidine, $PhCH_3$, 20 °C), and is efficient for a range of α,β−unsaturated carbonyl compounds.[3] Table 1 presents the substrate scope we have charted to date. Tetralone derivative **2** participates in the reaction, affording adduct **4** in 87% yield within 24 h (entry 1). Indanone analogue **5** participates in a faster reaction, delivering **6** in 81% isolated yield after 12 h (entry 2). Heterocyclic versions also participate; compound **7** undergoes reaction to give allenic ester **8** in 78% yield (entry 3); substituted enone **9** delivers a comparable yield of **10** (78%, entry 4) as a 1.8:1 mixture of diastereomers (trans/cis). Benzosuberone analogue **11** participated in a slower reaction, delivering **12** in 65% yield after 36 h (entry 5). Likewise, *p*-methoxy-substituted tetralone **13** delivers **14** in 50% yield after 48 h (entry 6). Acyclic enones such as ethyl vinyl ketone (**15**) deliver the linear substituted allenoate **16** in 70% yield. Imide **17** is an excellent substrate for the process, affording compound **18** in 98% isolated yield (entry 8). Ester **19** is also a good substrate for the reaction as product **20** is obtained in 85% yield (entry 9). Of note is that a number of substrates have been found to be unreactive under the reaction conditions. For example, while acyclic enone **15** reacts efficiently under the reaction conditions, enone **21** is unreactive (entry 10). Despite prolonged reaction times, and the subjection of the reagents to elevated temperatures, product **22** was not observed under the conditions that were explored.

Baylis−Hillman adducts such as **23** are also converted to product **24** under the standard reaction conditions (eq 1). Yet, MOM-ether **25** does not produce the corresponding allene-coupled product **26** under the reaction conditions.[4]

Table 1. Substrate Scope for Coupling of Ethyl Allenoate to α,β-Unsaturated Carbonyl Compounds[a]



[a] All reactions were conducted at room temperature in $PhCH_3$ in the presence of quinuclidine (10 mol %). [b] Yields refer to isolated yield after silica gel chromatography.



The fact that Baylis−Hillman adducts participate in this quinuclidine-catalyzed reaction prompted us to explore whether a Baylis−Hillman reaction might be coupled to the allenoate conjugate addition since both processes are in fact now known to be catalyzed by nucleophilic amines.[5] Such a process would constitute a three-

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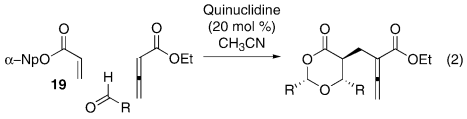


Table 2. Substrate Scope for Three-Component Coupling of Ethyl Allenoate, Aldehydes and Acrylate **19**[a]

Entry	Aldehyde	Product	Time	Yield[b]
1	R_1 = $PhCH_2CH_2$	**27**	18 h	88 %
2	R_2 = $MeCH_2CH_2$	**28**	18 h	80%
3	R_3 = *i*-Bu	**29**	18 h	60%
4	R_4 = Et	**30**	18 h	65%

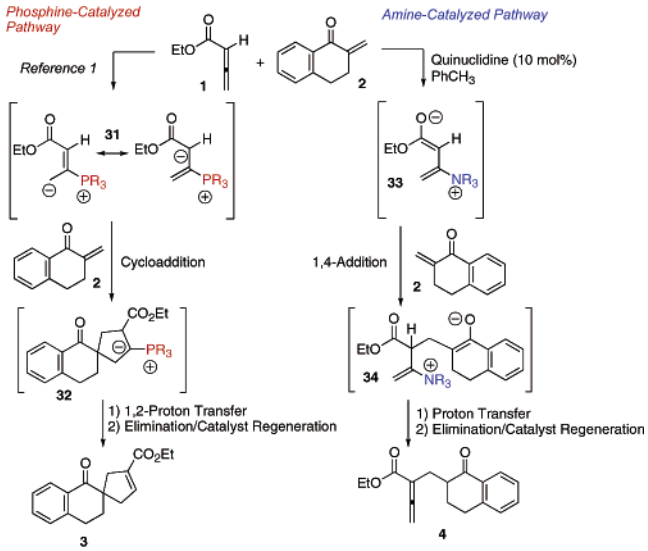
[a] All reactions were conducted at room temperature in CH_3CN in the presence of quinuclidine (20 mol %). [b] Yields refer to isolated yield after silica gel chromatography.

component coupling (TCC)[6] between an α,β-unsaturated carbonyl compound (e.g., acrylate **19**), an aldehyde, and the allenoate **1**. Indeed, when **19** (1.0 equiv) is subjected to a Baylis−Hillman reaction (4.0 equiv of aldehyde)[7] and allenoate **1** (4.0 equiv) is introduced into the same flask after an appropriate interval (12 h), TCC products may be isolated in good yield (eq 2, Table 2).[8] For example, with hydrocinnamaldehyde, product **27** is obtained in 88% yield (entry 1). Saturated aldehydes represent good substrates for the reaction, with *n*-butyraldehyde affording product **28** in 80% yield (entry 2); 3-methyl-butyraldehyde delivers **29** in 60% yield (entry 3). Propionaldehyde also affords comparable reaction efficiency, wherein allene **30** is obtained in 65% isolated yield. In each case, products **27**−**30** are obtained as predominantly single diastereomers (>20:1 trans/cis by ^{1}H NMR spectroscopic analysis).[4,9]

The divergent reactivity exhibited by the starting materials in the presense of different nucleophiles represents an example of conditionally dependent reactivity (Scheme 2). In the case of the phosphine-catalyzed reaction, the catalyst may react with the allene to generate zwitterionic enolate **31**. This species may then undergo cycloaddition with **2** to deliver spirocyclic ylide **32**. Facile 1,2-proton transfer then yields **3**, and regeneration of catalyst. This mechanism, as proposed by others,[10] benefits from the ability of phosphorus to support the ylide-like structure **32**. In contrast, the amine-catalyzed pathway does not benefit from analogous stabilization. Rather, zwitterionic enolate **33** may undergo 1,4-addition to **2** to deliver **34**. This newly generated enolate does not undergo a second C−C bond-forming step to form the spirocycle because the ammonium ion-substituted adduct cannot similarly stabilize the ylide. Thus, proton transfer and tautomerization ensues, yielding adduct **4** with concomitant regeneration of the amine catalyst. While this mechanistic hypothesis remains to be verified, it does account for the conditionally dependent reactivity of **1** and **2** in the presence of different nucleophilic catalysts.

In conclusion, we have presented an efficient, amine-catalyzed coupling of allenoate esters and α,β-unsaturated carbonyl compounds. The scope of the reaction has been defined under a very mild set of conditions. Significantly, the implications of the discovery have been extended to include a three-component coupling reaction where two distinct catalytic C−C bond-forming events unite three building blocks under the influence of a unique catalyst.

Scheme 2



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Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The stereochemical assignment is in the Supporting Information.
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