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An Unexpected Rate Acceleration−Practical Improvements in the Baylis−Hillman Reaction[†]

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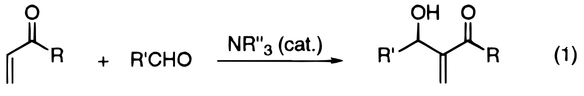
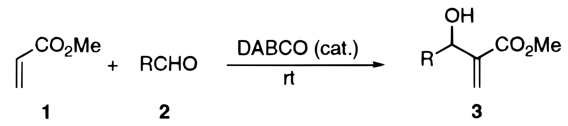
The formation of carbon−carbon bonds in a controlled manner lies at the core of organic synthesis.[1] Generally, these reactions require the preformation of a carbanionic or organometallic species followed by the addition of a carbon electrophile. One notable exception to this axiom is the Baylis−Hillman reaction, which entails a tertiary amine-catalyzed coupling of an acrylate and an aldehyde (eq 1).[2]

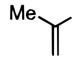
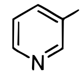


(1)

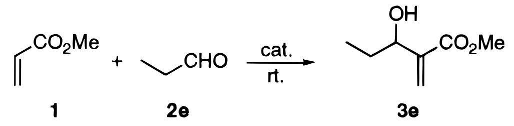
The Baylis−Hillman reaction produces a highly functionalized acrylate that can be used for the subsequent elaboration of a variety of useful compounds.[3] While it has served as the starting point for the synthesis of numerous natural and unnatural products,[4] it is not without drawbacks. Prominent among these is the rate at which the reactions typically occur. Reaction times of 1 week or more are common, and some reactions have been reported to take more than 1 month to complete (Scheme 1).[2,5] Furthermore, many aldehydes such as aromatic aldehydes are reluctant to serve as substrates at all under the relatively mild conditions.[6] It is therefore not surprising that a number of attempts have been made to circumvent the sluggish nature of this reaction, including the use of microwave and high pressure techniques, but these have given mixed results at best.[7] As part of our efforts focused on the development of an asymmetric Baylis−Hillman reaction,[8] we sought to improve the overall efficiency of this transformation in a general sense.

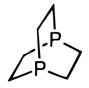
Scheme 1



	R	time	yield
a	t-BuPh$_2$SiOCH$_2$	30 d	30%
b		20 d	33%
c	Me	7 d	88%
d		4 h	82%

Scheme 2



cat.	time	yield
DABCO	10d	84%
	NR	
Me$_3$P	NR	
Chx$_3$P	6d	20%
Bu$_3$P	2d	80%

One significant drawback to the Baylis−Hillman reaction that we found was the undesired formation of self-aldol products from the initial aldehyde.[9] This problem manifested itself largely in cases where branched aldehydes such as isobutyraldehyde were used. We therefore sought to find a practical catalyst that would allow for the Michael addition to the acrylate component without predisposition to promote the aldol reaction (Scheme 2). Toward this end, tributylphosphine was the ideal catalyst.[10] While a number of trialkylphosphines and tertiary amines were explored, tributylphosphine was consistently found to be the most effective.[11]

As useful as the discovery of the phosphine catalyst has proven, it pales by comparison with the astonishing results observed by variation of the reaction temperature. Not surprisingly, the rate of formation of product is increased upon warming the reaction mixture above room temperature (Scheme 3). This is not a profitable process, however, as the yield eventually obtained is not greater than that derived at room temperature.[12] Surprisingly, however, we found that the reaction proceeded smoothly

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[†] This paper is dedicated to Clayton Heathcock, a true scholar, mentor, and friend, on the occasion of his 60th birthday.

(1) For a review of recent trends in organic synthesis, see: *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991.

(2) For reviews of the Baylis−Hillman reaction, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52,* 8001. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. See also: Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(3) For examples, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Williams, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2031. (c) Basaviah, D.; Bhavani, A. K. D.; Pandiaraju, S.; Sarma, P. K. S. *Synlett* **1995**, 243. (d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1995**, *60*, 4697.

(4) See, for example: Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58,* 2151.

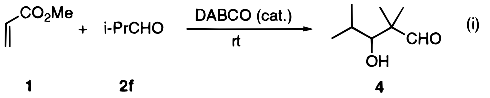
(5) Jenn, T.; Heissler, D. *Synlett* **1995**, 607.

(6) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48,* 6371.

(7) Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444. Hill, J. S.; Isaacs, N. S. *J. Chem. Res., Synop.* **1988**, 330.

(8) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* Submitted.

(9) Reaction of isobutyraldehyde with methyl acrylate under amine-catalyzed Baylis−Hillman conditions (eq i) leads to a mixture of products containing largely the self-aldol product **4** as opposed to **3f** (Brzezinski, L. J. Unpublished results).



(i)

(10) The use of tributylphosphine as a catalyst has been reported previously. See: Miyakoshi, T.; Omichi, H.; Saito, S. *Nippon Kagaku Kaishi* **1979**, 748. See also: *Chem. Abstr.* **1979**, *91*, 123360d.

(11) For the purposes of a direct comparison, the reaction of methyl acrylate and propionaldehyde was performed with DABCO for 2 days, and less than 10% of desired product **3e** was obtained.

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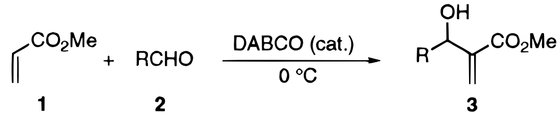
Scheme 3



	R	time	yield
c	Me	8h	74%
e	Et	8h	71%
f	i-Pr	12h	69%
g	i-Bu	12h	68%
h	$PhCH_2CH_2$	8h	67%
i	Ph	4h	68%

and very rapidly upon cooling to 0 °C. While the reaction between methyl acrylate and acetaldehyde at room temperature takes 1 week to reach completion, it is done in 8 h at 0 °C.[13] This apparent low-temperature acceleration can be extended to virtually any aldehyde, and even aromatic aldehydes undergo rapid conversion to the corresponding Baylis–Hillman adducts in short order. In addition, it works equally well with amine or phosphine catalysts.[14]

The pronounced acceleration of this reaction under the conditions described here elevates the Baylis–Hillman reaction into the realm of practically useful transformations. Work toward the use of these conditions in the synthesis of natural products is underway in our laboratories.[15]

Experimental Section[16]

General Procedure for the Baylis–Hillman Reaction. A solution of the aldehyde (120 mmol) and methyl acrylate (100 mmol) in dioxane (50 mL) was cooled to 0 °C in an ice bath, and DABCO (1 g, 0.09 mmol) was added. The reaction was kept cold until complete by thin-layer chromatography. While cold, 0.1 N HCl (100 mL) was added, and the layers were quickly separated. The aqueous phase was further extracted with ether, and the combined extracts were dried over sodium sulfate and concentrated. The crude product was then purified by distillation or column chromatography to give the desired products.

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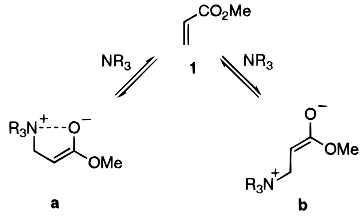
(12) At elevated temperatures, the polymerization of the acrylate apparently becomes a viable alternative. The formation of this byproduct makes purification of the desired Baylis–Hillman adducts exceedingly difficult and should typically be avoided. Roos and Rampersadh have observed that “gentle warming” effects a marked rate increase in the reaction with acetaldehyde and a slight increase with other aldehydes (Roos, G. H. P.; Rampersadh, P. *Synth. Commun.* **1993**, *23*, 1261), but they also observed polymerization at temperatures above 43 °C.

(13) This creates a surprising scenario where the apparent rate increases by deviation in either direction from room temperature. One way to rationalize this is to consider the two purported intermediates **a** and **b**. These should both be in equilibrium with the starting materials and would almost certainly react with aldehydes at different rates. It is reasonable to expect that the relative concentrations of **a** and **b** would be different at 0 °C vs at elevated temperatures, and the observed changes in the rate of the Baylis–Hillman reaction likely reflect this difference. Additional support for this possibility stems from the fact that low temperatures do not accelerate the addition of acrylonitrile to benzaldehyde,[17] and acrylonitrile is not capable of forming an ionically stabilized enolate such as **a**.



(14) While the reaction with tributylphosphine at low temperature rapidly generates the desired products with rapid efficiency, the ease with which the catalytic DABCO is removed makes it the preferred catalyst from a practical viewpoint.

(15) For example, see: Brzezinski, L. J.; Levy, D. D.; Leahy, J. W. *Tetrahedron Lett.* **1994**, *35*, 7601.

(16) For general experimental conditions, see: Provencal, D. P.; Leahy, J. W. *J. Org. Chem.* **1994**, *59*, 5496.

(17) Hill, J. S.; Isaacs, N. S. *J. Chem. Res., Synop.* **1988**, 330.