Mechanistic Implications in the Morita–Baylis–Hillman Alkylation: Isolation and Characterization of an Intermediate

M. E. Krafft,* T. F. N. Haxell, K. A. Seibert, and K. A. Abboud

Department of Chemistry and Biochemistry, Florida State University and Department of Chemistry, University of Florida

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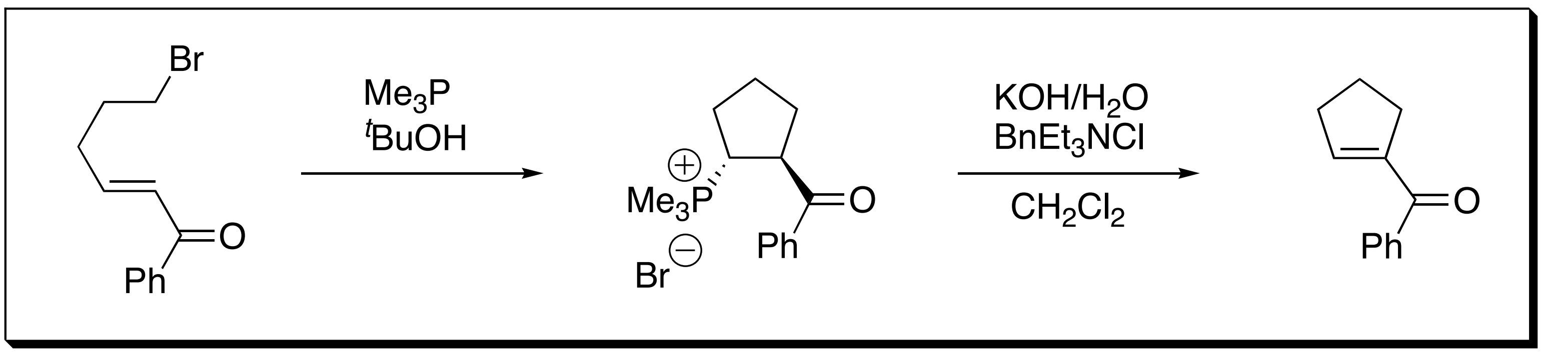
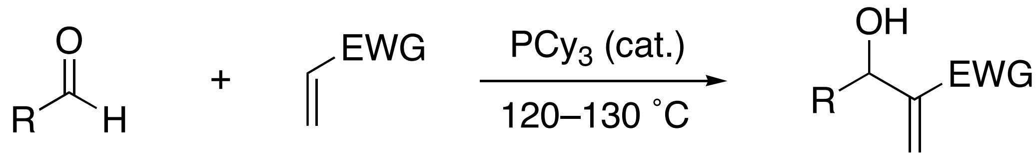


Presentation Outline

Introduction: the (Morita)–Baylis–Hillman Reaction

- First example



EWD = electron withdrawing group: CN or CO_2R

No immediate notice was taken probably because of the low conversions.

K. Morita *et al. Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

- German researchers used tertiary amine catalysts such as DABCO.

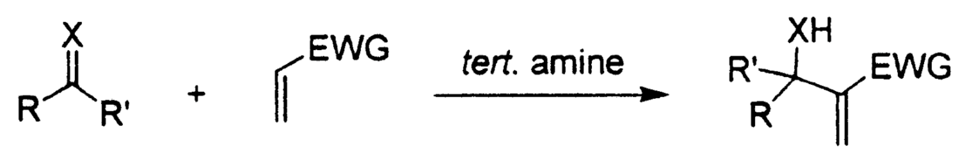
High conversions
Versatile (broad substrates *etc.*)

A. B. Baylis and M. E. D. Hillman, German Patent, 2155113, **1972**.

- Extended general scheme for the Baylis–Hillman Reaction

Some Features

1. Mild C–C bond forming reactions
2. Atom economical process
3. Synthetically useful products

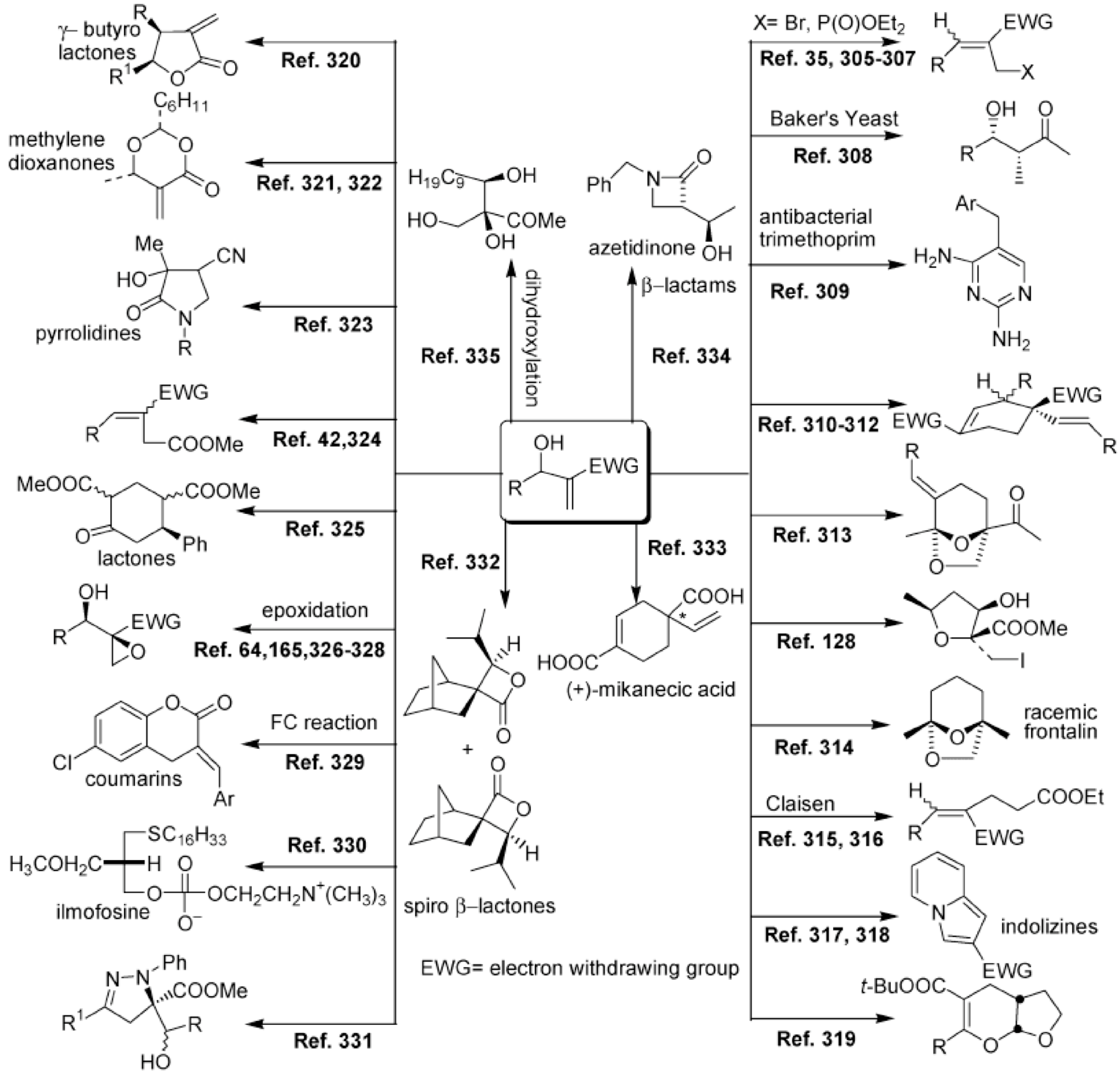


R= aryl, alkyl, heteroaryl; R' = H, COOR, alkyl
X= O, NCOOR, NTs, NSO_2Ph

EWG= electron withdrawing group :
COR, CHO, CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

D. Basavaiah *et al. Chem. Rev.* **2003**, *103*, 811.

Synthetic Applications of the Baylis–Hillman Adducts



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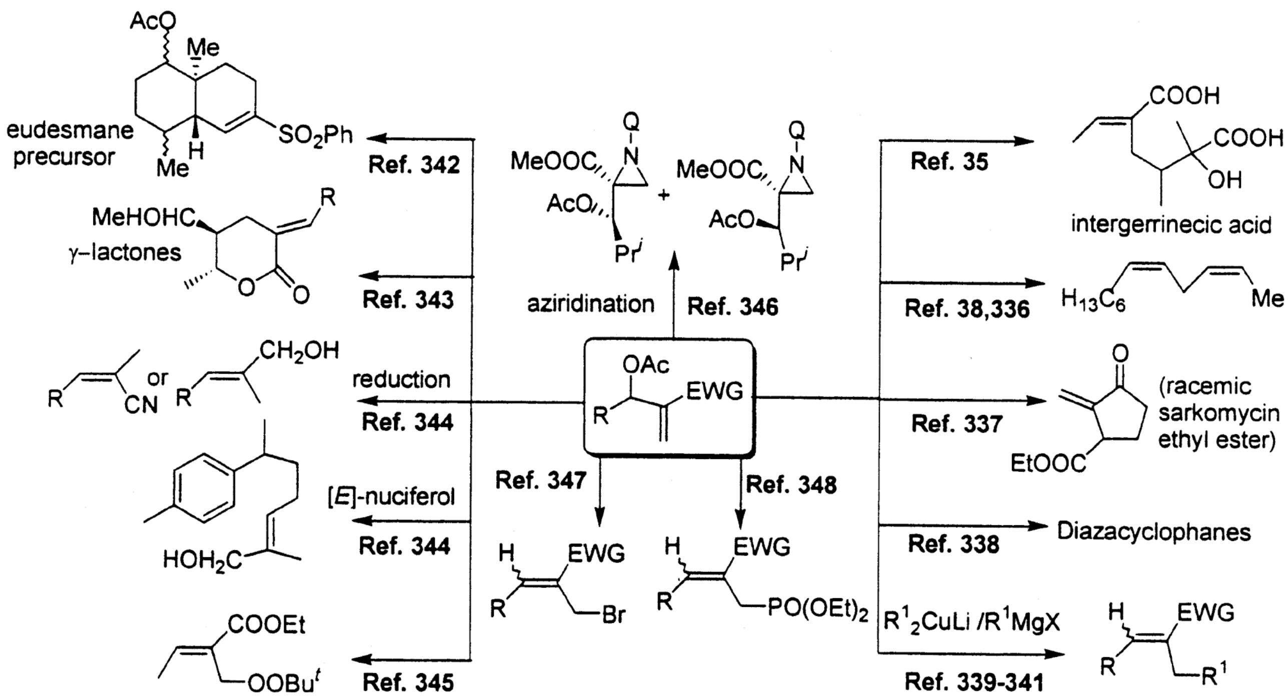
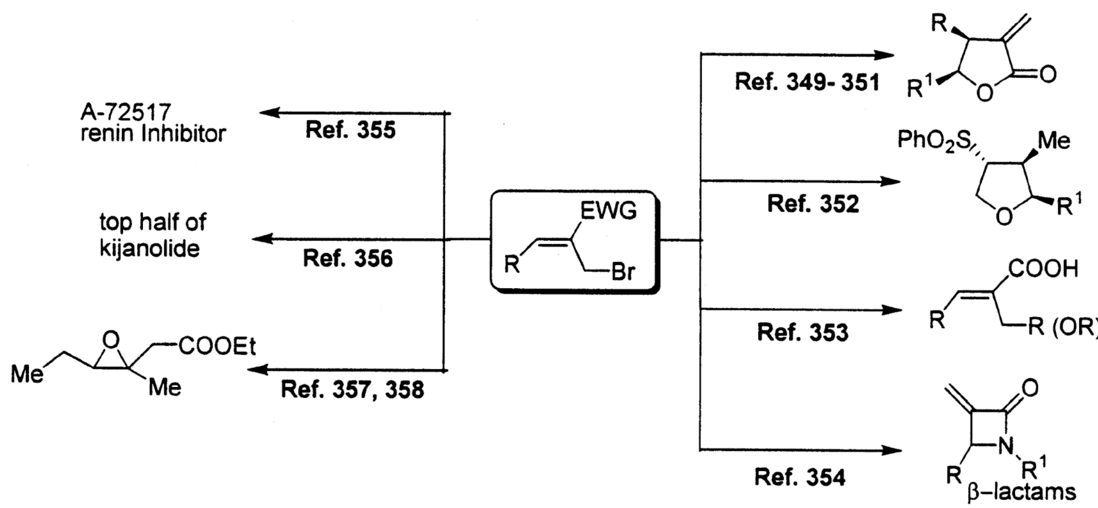
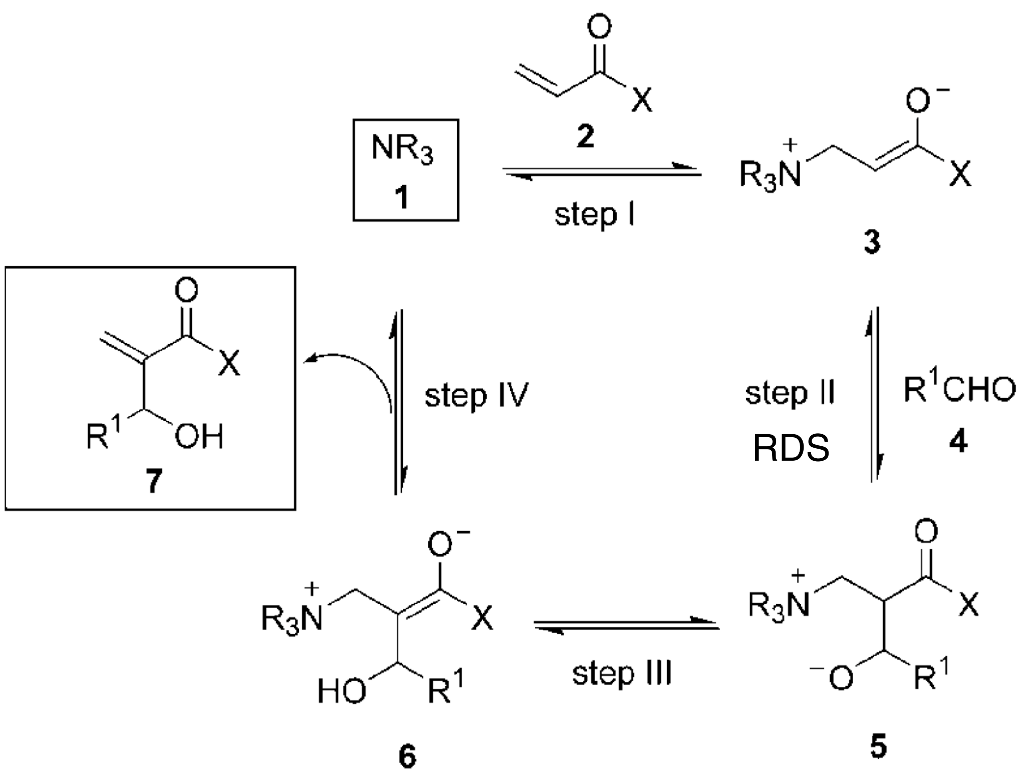
Synthetic Applications of the Baylis–Hillman Adducts





D. Basavaiah *et al*. *Chem*. *Rev*. **2003**, *103*, 811.

Currently Accepted Mechanism for the (Morita)–Baylis–Hillman Reaction



■ This mechanism was proposed by Hill and Isaacs on the basis of pressure effects and kinetic isotope effects (KIE) studies.

J. S. Hill and N. S. Isaacs, *Tetrahedron Lett*. **1986**, *27*, 5007.
J. S. Hill and N. S. Isaacs, *J. Phys. Org. Chem.* **1990**, *3*, 285.

■Kinetic studies suggested that the reaction follows third-order kinetics overall or pseudo second-order if the concentration of amine is considered constant.

$$\text{Rate} = K_{obs}[\text{alkene}][\text{electrophile}][\text{amine}]$$

$$\text{Rate} = K_a\,[\text{alkene}][\text{electrophile}]$$
$$\text{where } K_a = K_{obs}[3^0\ \text{amine}]$$

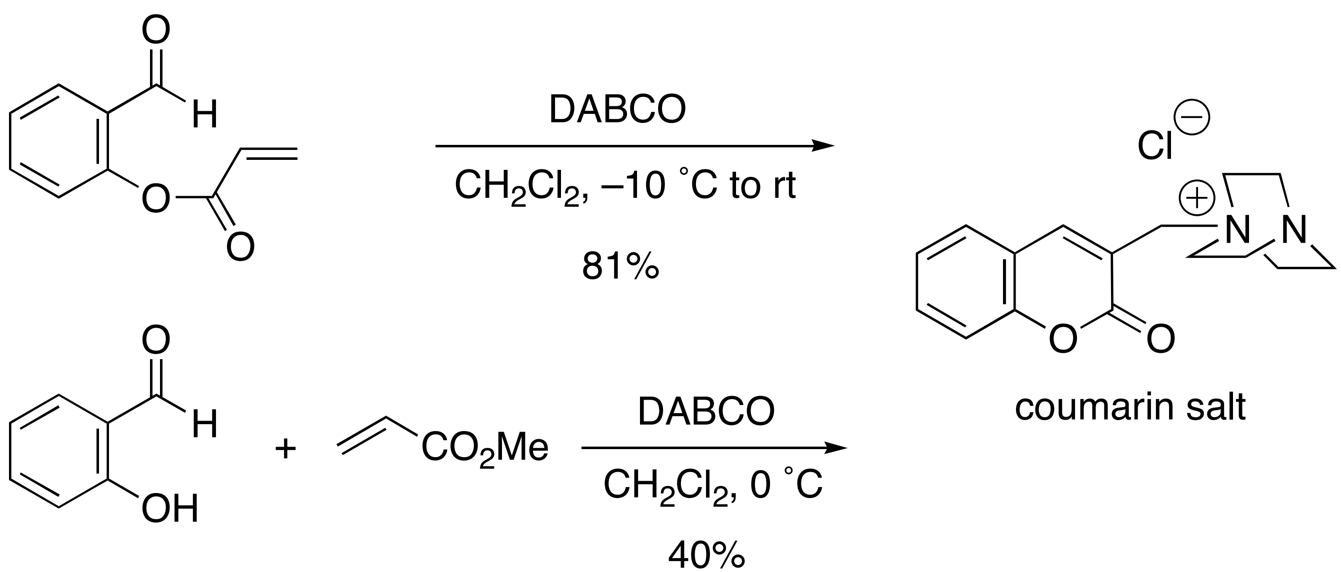
M. L. Bode and P. T. Kaye, *Tetrahedron Lett*. **1991**, *32*, 5611.

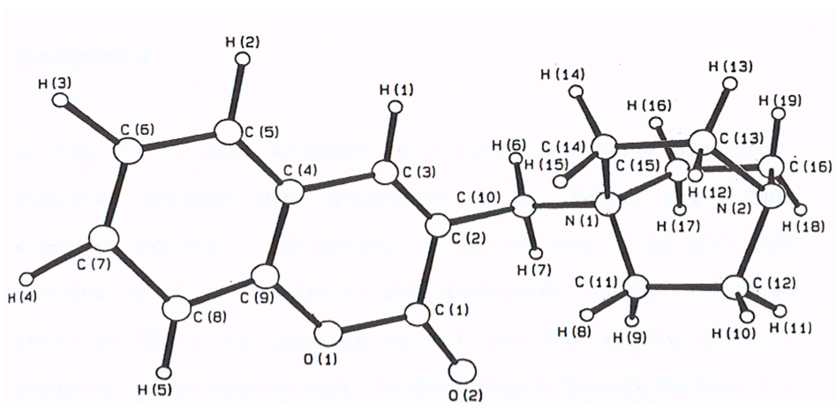
Although other interesting observations such as rate acceleration with protic additives, salt effects, MW effects have been appeared in the literature, those effects cannot be fully explained.

↓

We need more mechanistic study, especially, the certain evidence.

Some Evidences of Currently Accepted Mechanism



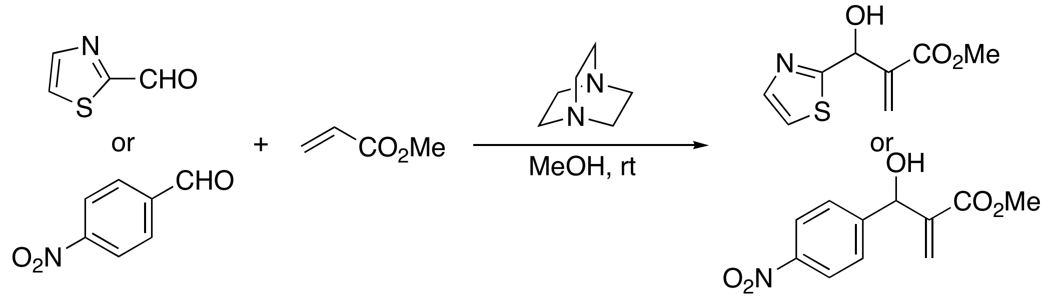


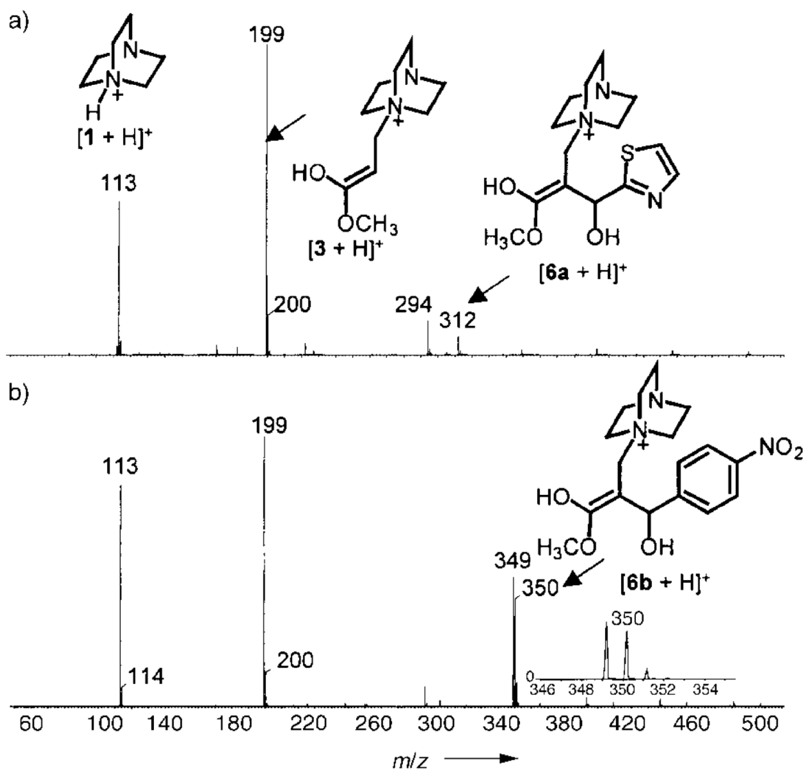
■This is the first experimental study have collected the evidence for the catalytic cycle.

■The authors explained that the counter ion presumably came from solvent.

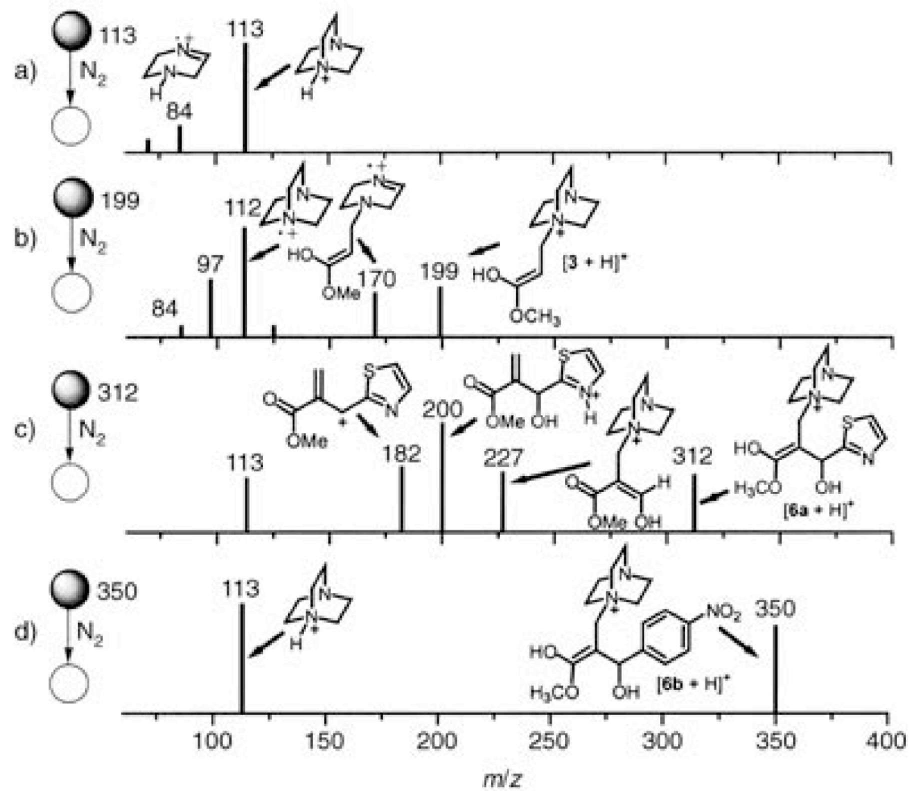
S. E. Drewes *et al*. *Synth*. *Commun*. **1993**, *23*, 2807.

Some Evidences of Currently Accepted Mechanism





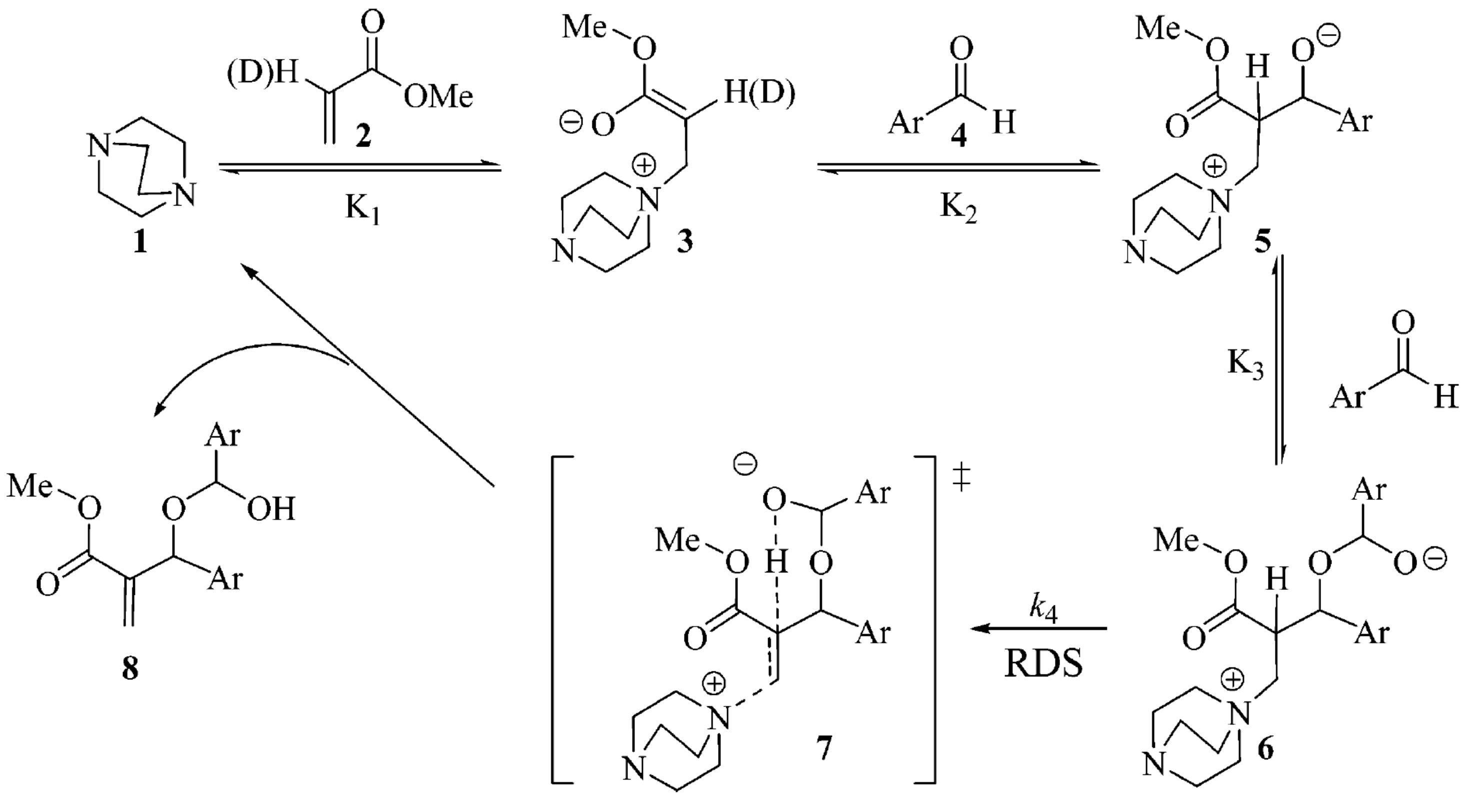
ESI(+)-MS spectra for the reactions



Characterization by ESI(+)-MS/MS spectra

F. Coelho, M. N. Eberlin *et al*. Angew. *Chem*., *Int*. *Ed*. **2004**, *43*, 4330.

New Interpretation of the Baylis–Hillman Mechanism

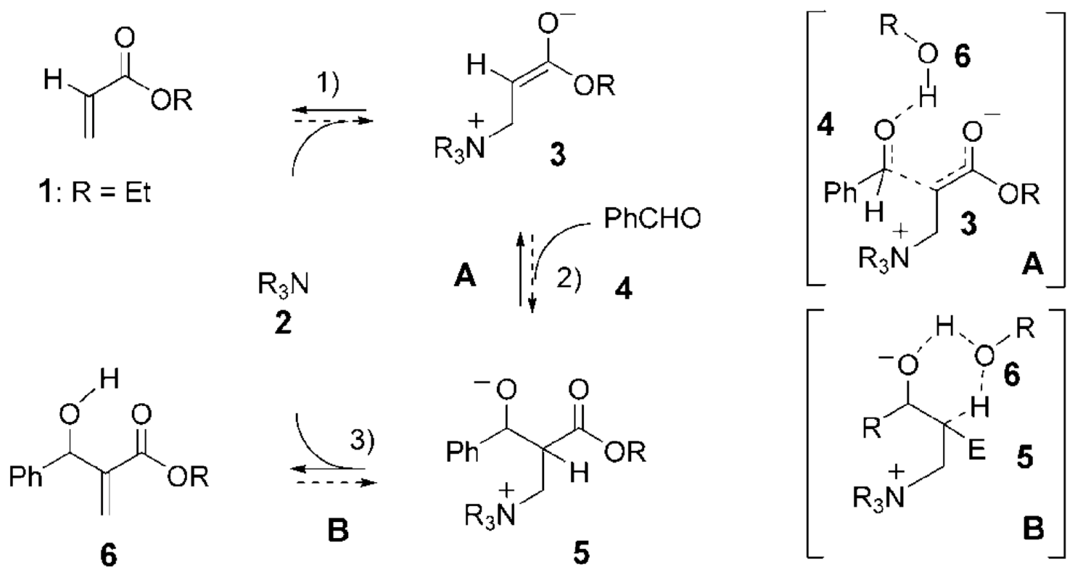


■ This new mechanism was proposed by McQuade *et al.* on the basis of reaction rate studies.

1. RDS is second order in aldehyde and first order in DABCO and acrylate (the proton transfer step).
   Rate = K_{obs}[aldehyde]^2[DABCO][acrylate]
2. The proposed mechanism was also supported using kinetic isotope experiments.
3. This mechanism is general to aryl aldehydes under polar, nonpolar, and protic conditions.

D. T. McQuade *et al*. *Org*. *Lett*. **2004**, *7*, 147.
D. T. McQuade *et al*. *J*. *Org*. *Chem*. **2005**, *70*, 3980.

New Interpretation of the Baylis–Hillman Mechanism



Previously suggested role of protic additives

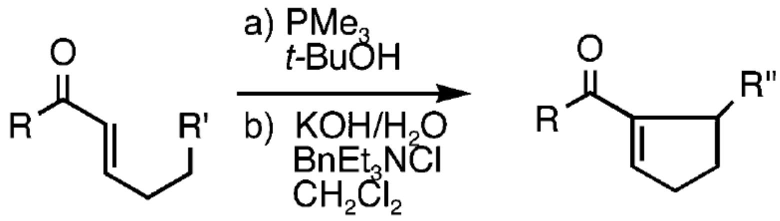
Alternative hypothesis

■ Aggarwal *et al.* also found that the RDS is the proton transfer step (step 3) based on kinetic studies.

■ Accoding their study, in the absence of protic solvents, step 3 is the RDS in the initial phase of the reaction and that once the concentration of the product has built up, step 2 becomes the RDS.

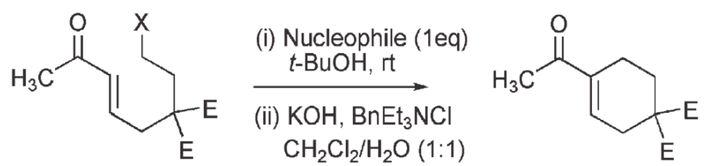
V. K. Aggarwal, G. C. Lloyd-Jones *et al.* Angew. *Chem., Int. Ed.* **2005**, *44*, 1706

Morita–Baylis–Hillman Alkylation and Allylation



MBH alkylation R'= CH_2Br R''= H
MBH allylation R'= $CH=CHCH_2Cl$ R''= $CH=CH_2$

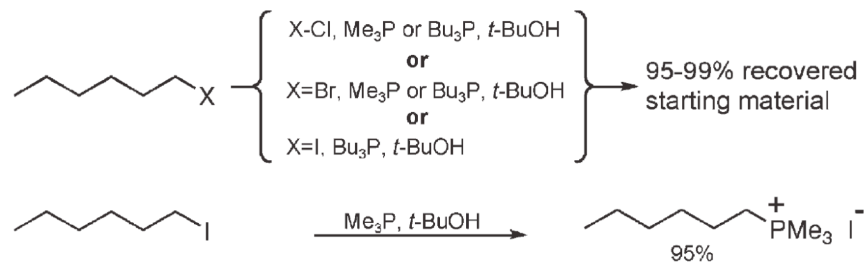
■ Amine nucleophiles (DABCO, quinuclidine, DBU, DMAP) were ineffective for these reactions.



1, X = Br; **4**, X = Cl; **5**, X = I **6**

Entry	X	Nucleophile	Time (h)	Yield (%)[a]
1	Cl	Bu_3P	72	12[b]
2	Cl	Me_3P	72	46[c]
3	Br	Bu_3P	3	99
4	Br	Me_3P	5	96
5	I	Bu_3P	3	87
6	I	Me_3P	24	[d]

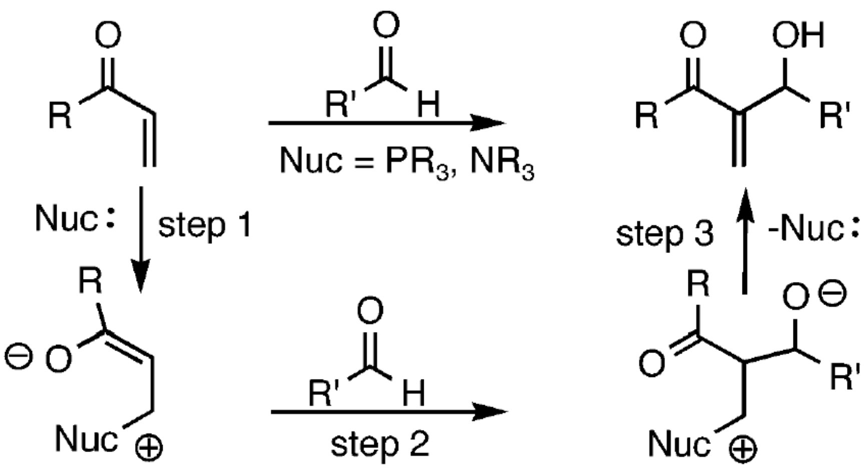
[a] Isolated yields after purification by silica gel chromatography.
[b] Excess Bu_3P (3 equiv.) added over 3 d; 18% recovery of chloride.
[c] Excess Me_3P (4 equiv.) added over 3 d; 10% recovery of chloride.
[d] Decomposition of enone.

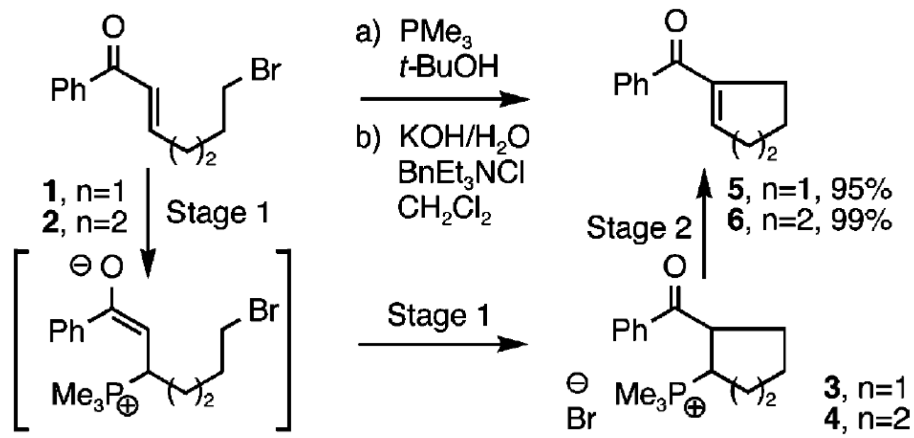


■ These results clearly point out the delicate balance of reactivity between the nucleophile and electrophilic centers in the molecule.

M. E. Krafft *et al*. *Chem*. *Commun*. **2005**, 5772.
M. E. Krafft *et al*. *J*. *Am*. *Chem*. *Soc*. **2005**, *127*, 10168.

Mechanistic Implications in the Morita–Baylis–Hillman Alkylation





One-pot, two-stage process

In the MBH alkylation, the resulting phosphonium counterion is a weakly basic halide ion.

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It is necessary to add base to promote the second stage of the reaction.

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Open the possibility for isolation and characterization of a reaction intermediate.

M. E. Krafft *et al. J. Am. Chem. Soc.* **2006**, *ASAP*.

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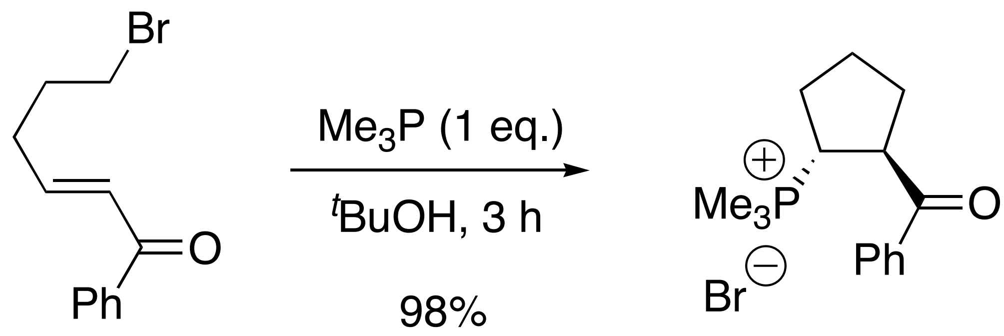

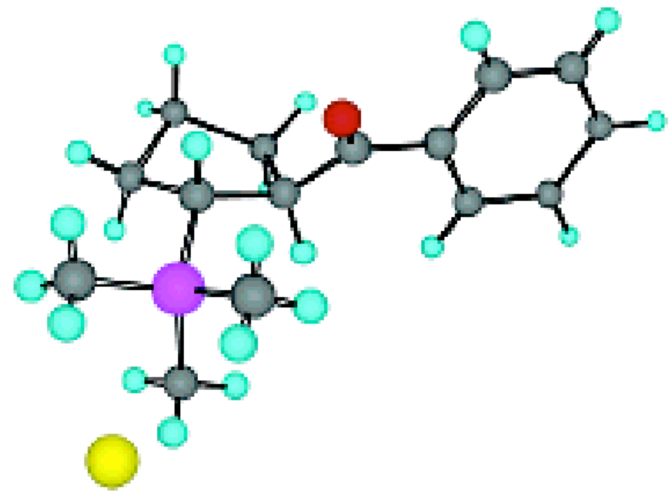

Recryst. from cyclohexane/CH_2Cl_2
under argon

■ X-ray analysis showed that the ring substituents are in the *trans* orientation.

■ NMR study suggested that the ketophosphonium salt was formed under kinetic conditions.

■ The authors claimed, for the first time, the isolation of a phosphonium salt from a MBH alkylation and its structure determination by X-ray.

M. E. Krafft *et al. J. Am. Chem. Soc.* **2006**, *ASAP*.

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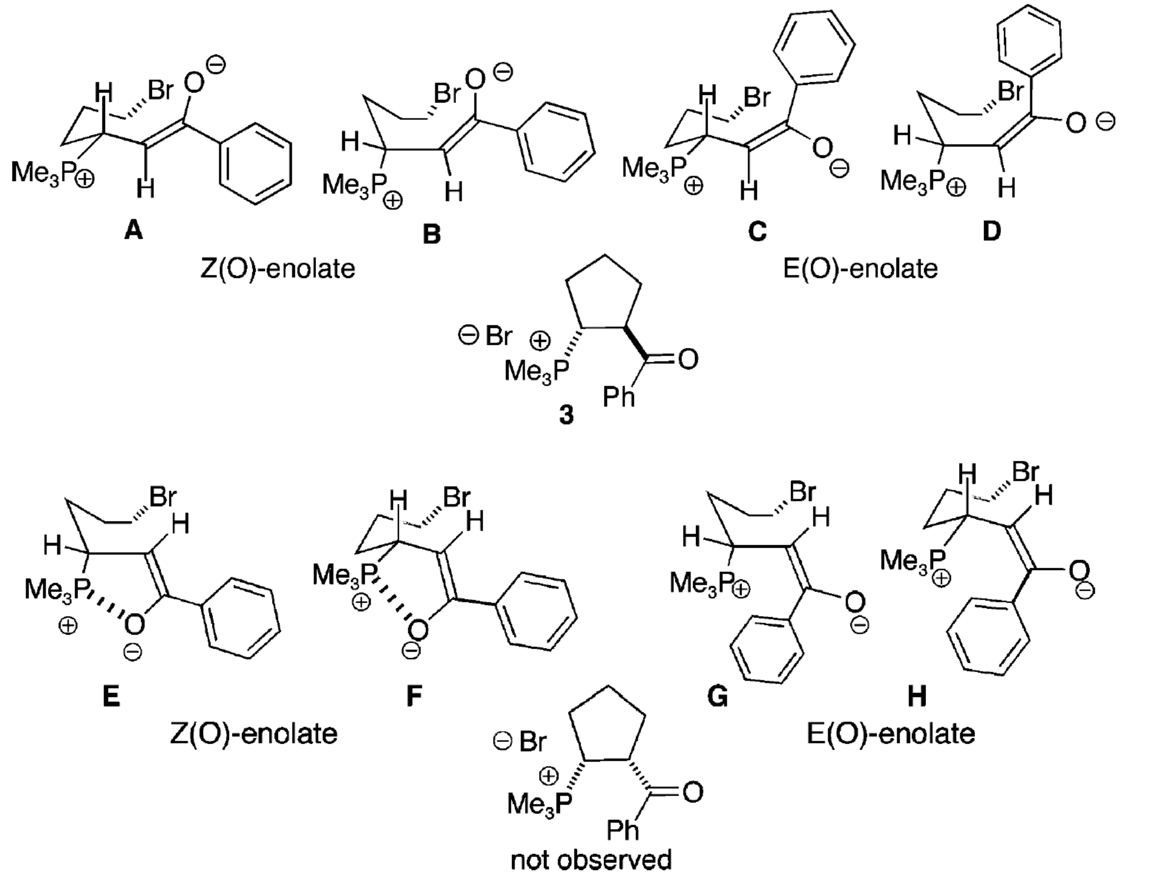
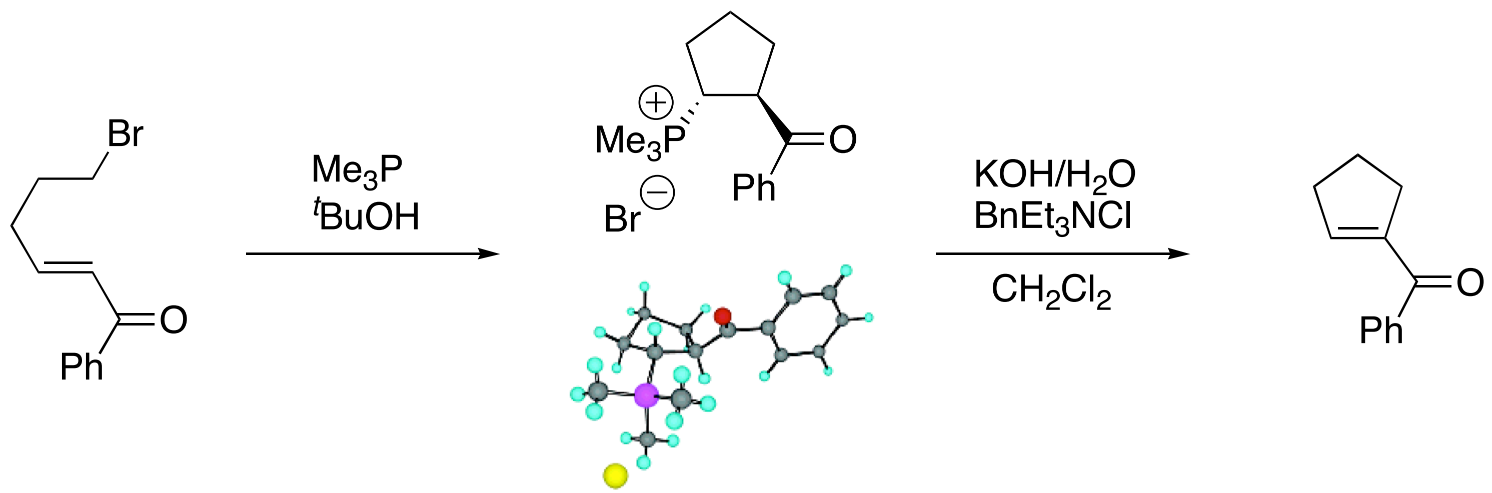


Interestingly, none of the four conformations exhibit any obious electrostatic interaction between the positively charged phosphorous and the negatively charged enolate oxygen, an attractive force that has been the cornerstone of the traditional MBH explanation.

M. E. Krafft *et al.* *J. Am. Chem. Soc.* **2006**, *ASAP*.

Summary

■ The authors have isolated for the first time a MBH intermediate exhibiting unprecedented *trans* geometry of the phosphonium salt and acyl group.



The lack of the previously accepted electrostatic stabilization of the zwitterionic intermediate Provides new insight into the MBH mechanism.

M. E. Krafft *et al*. *J. Am. Chem. Soc*. **2006**, *ASAP*.