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

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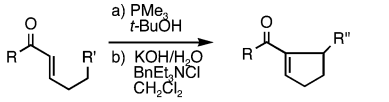
The Morita−Baylis−Hillman (MBH) reaction[1,2] gives rise to aldol products resulting from an organocatalyzed reaction at the α-carbon of unsaturated esters and ketones (eq 1). This carbon−carbon bond-forming reaction incorporates a wide variety of activated alkenes, electrophiles, and nucleophilic catalysts. Electrophiles that have been used include aldehydes, α-keto esters, 1,2-diketones, aldimines, α-bromo methyl enoates,[3] arenes,[4] and unsaturated moieties, such as enones[5] and vinyl sulfones.[6] Recently, this reaction has been further developed to include alkylations using sp^3-hybridized electrophiles (eq 2)[7] and allylations[8,9] of unsaturated carbonyl moieties (eq 3). To date, no intermediates in the MBH reactions have been isolated and characterized.[10] Herein we report the first isolation and characterization of a MBH alkylation intermediate and its potential consequences on current mechanistic hypotheses.

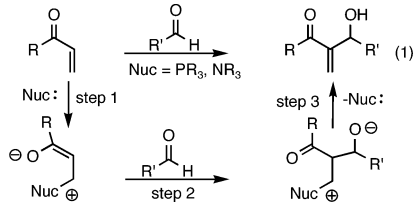
The generally accepted mechanism of the MBH reaction involves three steps (Scheme 1); nucleophilic addition to the enone, reaction of the aldehyde with the resulting zwitterionic intermediate, and base-promoted elimination. An electrostatic interaction between the positive center and the enolate oxygen is proposed to stabilize the zwitterionic intermediate formed in step 1 and is considered a key component necessary for success in the MBH reaction.[2] Recently, Shi and co-workers proposed that an interaction between an alcohol on a chiral phosphine {(*R*)-2′-diphenylphosphanyl-[1,1′]-binaphthalenyl-2-ol} and the Z(O)-zwitterionic enolate oxygen was responsible for enantioselectivity in an asymmetric aza-Baylis−Hillman reaction.[11] The rate-determining step has long been considered to be the aldehyde addition step;[2] however, recent work by McQuade suggests that the elimination step is rate determining.[12] McQuade found the MBH reaction, under aprotic, protic, polar, and nonpolar conditions, to be second order in aldehyde and therefore proposed a hemiacetal intermediate, which assists the proton transfer step. Aggarwal had similar findings in that the RDS is step 3, the proton transfer step. However, his data suggest that in the absence of protic solvents, while the initial RDS is the proton transfer step, once there is a build up of enough product, the RDS reverts back to the previously conceived one, the aldehyde addition step.[13]



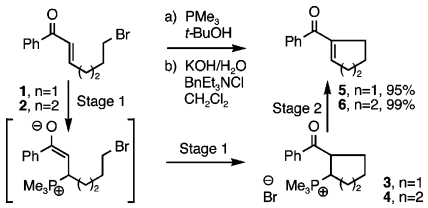
MBH alkylation R'= CH_2Br R"= H (2)
MBH allylation R'= $CH=CHCH_2Cl$ R"= $CH=CH_2$ (3)

When aldehydes are used as the electrophilic partner in the MBH reaction, a phosphonium alkoxide is generated in step 2 which involves the zwitterionic enolate adding to the aldehyde in an aldol reaction (Scheme 1). However, in the key C−C bond-forming step in either the MBH alkylation or allylation, the resulting phosphonium counterion is a weakly basic halide ion. In these MBH reactions, three steps are also involved in the mechanism; however, they are evident as two distinct and separate stages. The first stage encompasses the first 2 steps of the general mechanism and incorporates the addition of the nucleophile to the activated alkene followed by the cyclization step to form the *β*-phosphonoketone (Scheme 2). With only the weakly basic bromide anion generated in the carbon−carbon bond-forming step, it was necessary to add base to promote the second stage of the reaction (Scheme 2), which is a base-mediated elimination yielding the cyclic enone that is analogous to step 3 in the general mechanism (Scheme 1). With two distinct stages present, it opened the possibility for isolation and characterization of a reaction intermediate before addition of base. We now report, for the first time, isolation of a phosphonium salt from a MBH alkylation and its structure determination by X-ray crystallography. The stereochemical information obtained from the crystal structure and related transition state analyses may have important mechanistic implications for the MBH reaction.

Scheme 1



Scheme 2



In a typical MBH alkylation, treatment of enone **1** with PMe_3 followed by addition of base under phase-transfer conditions (100 mol % of KOH, 10 mol % of $BnEt_3NCl$, DCM/H_2O 0.1 M) yielded 95% of cycloalkenone **5** in a one-pot, two-stage process (Scheme 2). Upon addition of 1 equiv of PMe_3 to enone **1** in *t*-BuOH, a precipitate forms in 3 h. Filtration yields 98% of a solid, whose ^1H NMR spectrum suggested that it was phosphonium salt **3**, an assumed intermediate in the process.[2,14] Recrystallization of the solid from cyclohexane/CH_2Cl_2 under argon yielded X-ray quality crystals. The structural representation for ketophosphonium salt **3** is illustrated in Figure 1. A striking characteristic of the intermediate evident in the crystal structure is that the ring substituents are in the *trans* orientation. To determine whether the ketophosphonium

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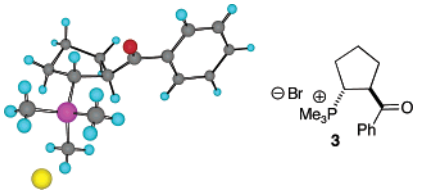
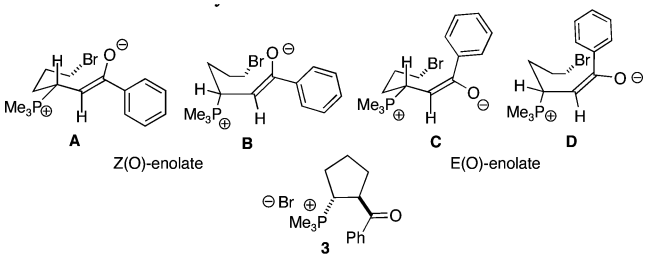
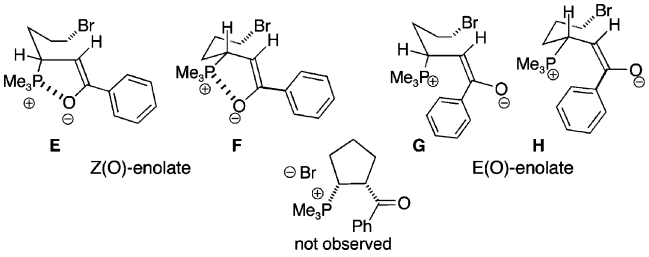


Figure 1. Structural representation for phosphonium salt **3**. Br is disordered with a half water molecule; Br(2) and the water are removed for clarity.

Scheme 3



Scheme 4



salt **3** was formed under kinetic or thermodynamic conditions, enone **1** was treated with 1 equiv of PMe_3 in $(CD_3)_3COD$ (0.17 M) for 5 min. A lower concentration was used to ensure that the intermediate remained in solution. Intermediate **3** that precipitated during the reaction conducted at a higher concentration was identical to ketone **3** that was isolated from the solution. Analysis of intermediate **3** by 500 MHz ^{1}H NMR spectroscopy revealed that no deuterium was incorporated either α to the ketone or phosphonium salt, strongly suggesting the intermediate isolated is the kinetic product. Furthermore, analysis of the resulting enone showed no deuterium incorporation at the alkene *β*-position.

The stereochemistry of the *trans*-disubstituted phosphonium ketone **3** can be correlated with potential transition state conformations leading to its formation. Consideration of both chair-like and boat-like conformations and the Z(O)- and E(O)-enolates leads to four viable transition states giving rise to intermediates bearing *trans* stereochemistry (Scheme 3, **A**, **B**, **C**, **D**). Steric interactions present in the boat-like conformations (**B**, **D**) should result in a higher transition state energy. Either of the chair-like conformations could be considered likely transition states. However, it is remarkable that none of the four conformations exhibit any obvious electrostatic interaction between the positively charged phosphorus and the negatively charged enolate oxygen, an attractive force that has been the cornerstone of the traditional MBH explanation. With the E(O)-enolates, electrostatic interaction is sterically prohibited, whereas reactions proceeding through the Z(O)-enolate could develop electrostatic interactions, but these transition states would lead to the *cis*-disubstituted intermediate that is not observed (Scheme 4, **E**, **F**). Electrostatic interactions in ketophosphonium salts were recently described as a control element in a regioselective intramolecular aldol cyclization.[15]

The generally accepted explanation regarding the putative intermediate in the conventional MBH reaction takes advantage of an electrostatic interaction between the positively charged phosphorus and the enolate oxygen as a necessary stabilizing interaction driving the C−C bond-forming step.[2] However, any intermediate exhibiting this type of electrostatic interaction will necessarily lead to the *cis*-disubstituted phosphonium ketone (Scheme 4, **E** and **F**). Our results, in which the *trans* intermediate salt has been isolated from the MBH alkylation under kinetically controlled conditions, suggest that this electrostatic interaction, while typically an electronically favorable interaction, is not the overriding electronic influence defining the stereochemical outcome of the cyclization. These results obtained in the MBH alkylation also suggest that the oxygen−phosphorus electrostatic interaction in the transition state, long considered to be a key component in the traditional MBH reaction, is not a requirement for successful MBH alkylation. Extrapolation of these results to MBH reactions with aldehydes may provide insight on successful and unsuccessful procedures in particular those involving asymmetric induction.

In summary, we 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 in this alkylation provides new insight into the MBH mechanism. Further work on the mechanism of the MBH reaction and application of these findings is in progress.

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Supporting Information Available: Experimental procedures and spectral data for the preparation of **1**, **2**, **5**, and **6**, and X-ray crystallographic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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