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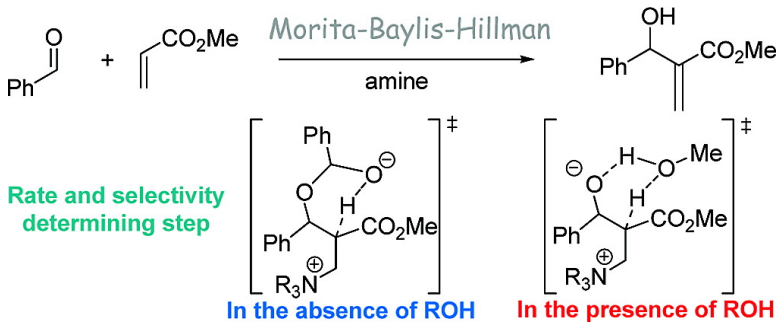


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# Mechanism of the Morita−Baylis−Hillman Reaction: A Computational Investigation

Raphaël Robiette,† Varinder K Aggarwal,* and Jeremy N. Harvey*

*Contribution from the School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, United Kingdom*

Received March 14, 2007; E-mail: jeremy.harvey@bristol.ac.uk; v.aggarwal@bristol.ac.uk

***Abstract:*** Accurate calculations are presented on the mechanism of the MBH reaction, focusing on the reaction between methyl acrylate and benzaldehyde, catalyzed by a tertiary amine. We address the mechanism under protic solvent-free conditions, but also consider how the mechanism and rate-limiting step change in the presence of alcohols. We have carefully calibrated the DFT method used in the calculations by carrying out high-level G3MP2 calculations on a model system. All of our calculations also treat the effect of solvent, described as a dielectric continuum. In the absence of protic solvent, we predict that deprotonation of the α-position is the rate-determining step and occurs through a cyclic transition state, with proton transfer to a hemiacetal alkoxide formed by addition of a second equivalent of aldehyde to the intermediate alkoxide. As first suggested by McQuade, this mechanism explains the observed second-order kinetics with respect to aldehyde concentration in the absence of protic solvent. In contrast, in the presence of methanol, we find a slightly lower energy pathway, in which the alcohol serves as a shuttle to transfer the proton from carbon to oxygen. Overall, the barrier to reaction for the latter mechanism is of 24.6 kcal/mol with respect to reactants at the B3LYP level of theory. The relative energy for the addition transition state of the amine-acrylate betaine adduct to the aldehyde is much lower, at 16.0 kcal/mol relative to reactants, so C−C bond formation should not be rate-limiting, except perhaps for some aliphatic aldehydes or imines. We discuss the implications of this mechanism for the design of asymmetric versions of the MBH reaction, given the overwhelming importance of the proton-transfer step.

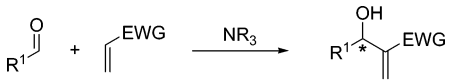
## Introduction

The Morita−Baylis−Hillman (MBH) reaction is an exquisite reaction as simple starting materials are converted into densely functionalized products in a catalytic process without generating waste or byproducts (Scheme 1).[1,2] As such, it has found numerous applications in synthesis. However, the reaction has traditionally suffered from low reaction rates leading to limited substrate scope, but recent developments that have focused on improving rates have changed that. Important landmarks include the following:

(i) The use of hindered (but still sufficiently nucleophilic) bases with high p$K_a$ including DBU and guanidines (leading to increased concentrations of the intermediate ammonium enolate).[3] Prior to this, it was believed that unhindered nucleophiles were required.

(ii) In a series of quinuclidine-based catalysts, the discovery of a simple correlation between the p$K_a$ of the conjugate acid of the amine and the rate of reaction in its presence led to the establishment that quinuclidine (which had the highest p$K_a$) was the optimum catalyst (it had been erroneously reported to be a poorer catalyst than DABCO).[4] Again, this leads to increased concentrations of the intermediate ammonium enolate.

***Scheme 1.*** Morita−Baylis−Hillman Reaction




$R^1$ = alkyl or aryl
EWG = CHO, $CO_2R$, COR, CN, ...

(iii) The use of hydrogen-bonding additives or solvents (MeOH/*t*-BuOH/$H_2O$) to promote reactions, which act by assisting the proton-transfer step.[5]

(iv) The use of Lewis acids with alcohol-based ligands (the Lewis acid−alcohol complex results in increased acidity of the OH groups, which promotes proton-transfer events).[6]

† Current address: Unité de Chimie organique et médicinale, Université catholique de Louvain, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium.

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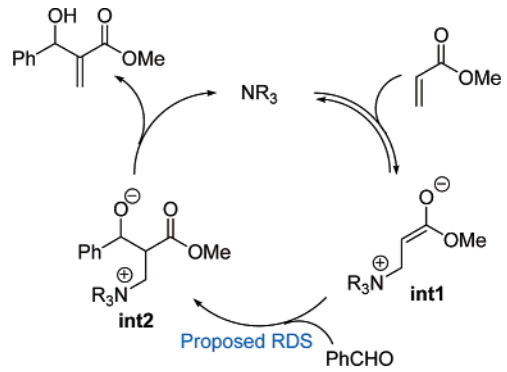


***Figure 1.*** Mechanism proposed by Hill and Isaacs for the MBH reaction.

These improvements in catalysts and conditions now allow even acrylamides to be employed in the MBH reaction.[7]

Asymmetric versions of the MBH reaction have also been developed.[8] Strategies include the use of chiral auxiliaries[9] and chiral catalysts (chiral amine,[10] protic source,[11] or Lewis acid[12]), with the use of bifunctional organocatalysts (chiral amine, or phosphine, catalysts bearing an alcohol function) having recently proven to be the most effective strategy.[13,14]

The mechanism of the reaction has been studied in detail. On the basis of pressure dependence, rate, and kinetic isotope effect (KIE) data, Hill and Isaacs were the first to suggest a mechanism similar to that in Figure 1.[15] This mechanism consists of reversible Michael addition of the nucleophilic amine catalyst[16] onto the acrylate to generate an enolate (**int1**), nucleophilic addition of this enolate to the aldehyde to give a second zwiterrionic intermediate (**int2**), and then proton transfer and elimination to yield the product and liberate the amine catalyst. This basic mechanistic sequence has since been supported by interception and structural characterization of each of these intermediates using electrospray ionization with mass and tandem mass spectrometry.[17]

While the global mechanistic sequence depicted in Figure 1 is widely accepted, the details of the mechanism and its kinetics have recently come under close scrutiny. Comparison of absolute rates over a number of half-lives of reaction of acrylonitrile and α-$^2$H acrylonitrile (EWG = CN) by Hill and Isaacs indicated a kinetic isotope effect of $1.03 \pm 0.1$ for the α-position.[15] From that, they concluded that no α-proton cleavage occurs in the rate-determining step (RDS) of the process and therefore suggested that addition of the enolate to the aldehyde was the RDS (see Figure 1).

According to this mechanism, it was proposed that the observed acceleration in the presence of protic additives occurs through activation of the aldehyde by hydrogen bonding.[5,18] However, hydrogen bonding to the aldehyde would have to compete with the enolate, which is a much better hydrogen-bond acceptor. Indeed, this more thermodynamically favorable interaction will stabilize the enolate and render it less reactive and so should slow down the reaction, albeit with an accumulation of the hydrogen-bonded enolate.

This conundrum prompted us to re-evaluate the kinetic data. Interestingly, in the course of our studies, we found that in the absence of protic additives the reaction shows autocatalysis, presumably because the product can act as a hydrogen-bond donor and promote the reaction.[19] Competition experiments between methyl acrylate and methyl α-$^2$H acrylate, in the absence of solvent and absence of added protic species, revealed a substantial KIE ($k_H/k_D = 5 \pm 2$) at the initial stage of the reaction (<20% conversion), that is, before autocatalysis takes place. Similar KIE's have been observed in DMSO by McQuade (at <10% conversion).[20] This author has, however, shown that the medium as well as the nature of the aldehyde have a great influence on the absolute value of the KIE for the α-position.[21] At higher conversion, our experiments indicated a much lower KIE, possibly suggesting a change in mechanism. However, this latter observation was not very reliable because the MBH product formed undergoes $^1$H/$^2$H exchange reactions with the starting acrylate, thereby limiting the accuracy of the measurements.

The following conclusions were drawn from these results: at the early stage of the reaction (i.e., in the absence of hydrogen-

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(21) KIE = $2.6 \pm 0.1$ ($5.2 \pm 0.6$) and $1.0 \pm 0.1$ ($2.4 \pm 0.1$), respectively, in DMSO and THF for the reaction of benzaldehyde (*p*-nitrobenzaldehyde) and labeled methyl acrylate in the presence of DABCO (see ref 20).

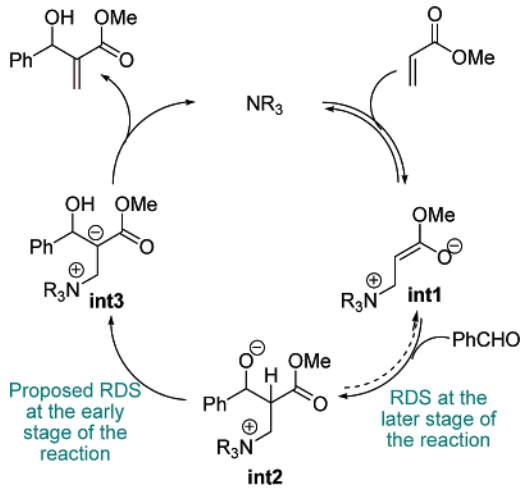


***Figure 2.*** Proposed rationale for the observed change in KIE during the reaction in the absence of protic additives.

bond donors), the RDS is the proton transfer (Figure 2). As the reaction proceeds, the product concentration builds up and an autocatalysis of the proton-transfer step takes place. These experiments therefore suggest that acceleration in the presence of hydrogen-bond donors is due to the promotion of the proton-transfer step by protic species.[22,23] It is worth noting that the fact that it needs a significant amount of product for the alcohol-catalyzed pathway to predominate (>20% conversion) suggests that this latter pathway is only slightly energetically more favored than the non-alcohol-catalyzed one. Based on the estimated value of the KIE and kinetic models, it was tentatively suggested that in the autocatalyzed stage of the reaction the rate-determining step is the addition to aldehyde. It should be pointed out, however, that McQuade reported a KIE value of $2.1 \pm 0.3$ in 2.75 M water in THF, which suggests that loss of the proton in the α-position can still be the RDS even in the presence of protic species.[20b]

These observations provide improved understanding of the global mechanism and kinetics of the reaction, but the question of the exact mechanism of proton transfer (**int2** → **int3**), in the absence and in the presence of protic species, however, still remains. For the early stage of the reaction, in the absence of alcohol, the possibility that a second molecule of amine acts as a shuttle to transfer the proton from carbon to oxygen was first suggested. This hypothesis was, however, eliminated by a study of the effect of doubling the catalyst loading, which caused only an approximately 1.75-fold increase in rate in the crucial early stages of reaction.[19] Another potential mechanism is an intramolecular four-membered direct proton transfer, but the strain induced in attaining the appropriate eclipsed conformation makes this mechanism unlikely. We had suggested that reaction was initiated by traces of water, enol, etc., present in the reaction.[19] Kinetic studies by McQuade have shown that the kinetics at the early stage of the reaction (i.e., in the absence of protic species) is second order in aldehyde (third order overall

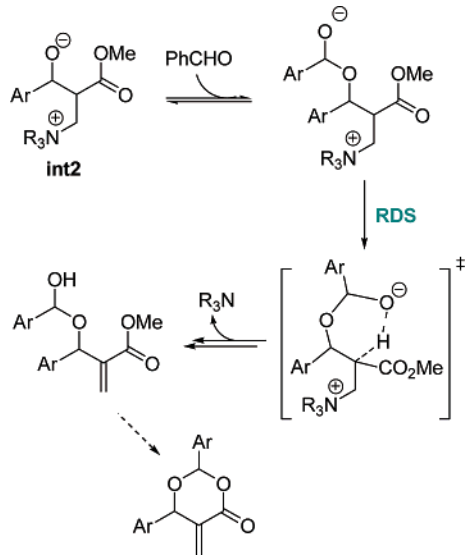


***Figure 3.*** McQuade's proposal for the mechanism of the MBH reaction in the absence of protic species.

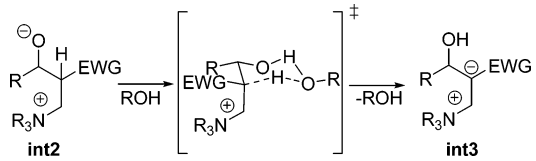


***Figure 4.*** Aggarwal's proposal for alcohol-catalyzed proton-transfer mechanism.

thus).[20,24] These kinetic observations indicate that the RDS, that is, the proton transfer, must involve a second molecule of aldehyde. Accordingly, McQuade suggested that the mechanism, in the absence of protic species, involves addition of **int2** onto a second molecule of aldehyde to form a hemiacetal intermediate, which undergoes proton transfer, via a six-membered transition state (Figure 3). This proposal is supported by KIE's as well as the observation in some cases of a dioxane product.[13h,25]

For the alcohol-catalyzed proton transfer, no experimental data enabling the identification of the mechanism were collected, but it was tentatively proposed that it was occurring via a concerted mechanism as depicted in Figure 4.[19,26]

In summary, despite the practical importance of the amine-catalyzed MBH reaction, a detailed atomistic account of its mechanism is still lacking. Particularly unclear issues concern the nature of the rate-determining step and the mechanism of proton transfer for the reaction in the absence and in the presence of alcohol, and the exact origin of the rate enhancement in the presence of alcohol. The present work addresses these issues, using computational methods and focusing on the MBH reaction

(22) Similar conclusions were drawn for the aza-Morita−Baylis−Hillman reaction, based on kinetic data. See: Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762−16763.

(23) For a recent example of an experimental and computational study of a process in which water has been shown to promote [1,2] proton transfer, see: Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470−3471.

(24) It must be noted that this is not in disagreement with previous kinetic studies. McQuade KIE values (ref 20) were indeed measured at the early stage of the reaction (<10% conversion), whereas Isaacs et al. data (ref 15) were obtained by comparison of absolute rates over a number of half-lives of reaction.

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(26) Using *p*-nitrobenzaldehyde, McQuade observed a second-order dependence for aldehyde in THF/$H_2O$ conditions, suggesting that the mechanism involving a hemiacetal intermediate is operative also in protic conditions (see ref 20b). As we will see in the Kinetics section, this is, however, specific to reaction of highly reactive aldehydes.

of methyl acrylate with benzaldehyde catalyzed by trimethyl amine, both in the absence of protic species and catalyzed by methanol.

Calculations on reactions of this type are highly challenging, due to the need to consider multiple possible reaction mechanisms, the large number of possible conformers and diastereomers, and the need to take solvent effects into account. To validate our chosen methodology, we have also studied the model reaction between acetaldehyde and the enolate $CH_3CH^-CO_2Me$ at a variety of different levels of theory. It is increasingly recognized that solvent effects should be included, at least with a continuum treatment, for organic reactions involving polar intermediates if accurate results are needed.[27,28] Accordingly, the present study includes the solvent, at the level of a continuum model, throughout, except for the model reaction system where gas-phase results were used. To describe cases where a molecule of protic solvent such as methanol is suggested to play a direct role in the mechanism, one molecule of methanol has been explicitly described in the calculations.

## Computational Details

The bulk of the computations have been carried out using the Jaguar 4.0 pseudospectral program package.[29] All species have been fully geometry optimized, unless mentioned otherwise, and the Cartesian coordinates are supplied in the Supporting Information. In the case of transition states, the "loose" geometry convergence parameters within Jaguar (which correspond to rms gradients below 0.0015 hartree/au) have been used. Test calculations using the standard convergence criteria led to insignificant changes in structure, but were much more time-consuming.

Geometry optimization was carried out using the well-established B3LYP hybrid density functional as implemented in Jaguar. The standard split valence polarized 6-31+G* basis set was used. Test optimization calculations of proton-transfer TSs (TS3) using additional p orbitals for the hydrogen atom involved in the bond breaking/making (6-31+G** basis set) did not lead to any change in structure.

The density of the grids used for integration in Jaguar is partly determined by the covalent radius on each atom, among other parameters. Using the standard covalent radius for the hydrogen atom involved in bond breaking/making leads, in some cases, to discontinuities in the potential energy surface as the breaking C−H bond length is varied, due to changes in the density of the grid. The corresponding changes in energy were small (max 2 kcal/mol) but prevented successful geometry optimization in some cases. Accordingly, the covalent radius of the hydrogen atom was set to 1.5 Å for optimization calculations of proton-transfer TSs. All given energies are obtained after corresponding fully analytical single-point calculations (i.e., without the pseudospectral method) using the fine DFT grid within Jaguar, and the larger 6-311+G** basis set.

All optimization and single-point calculations (except for the model system) were carried out using the polarizable continuum-Poisson method as incorporated in Jaguar.[30] The results are not expected to depend strongly on the parameters used for the continuum solvent, so we have used a single set of parameters for optimization calculations (unless mentioned), that is, a dielectric constant of 7.52, and a solvent probe radius of 2.5221 Å, which are suitable for tetrahydrofuran (THF), one of the most common solvents used in MBH reactions. Test optimization calculations in methanol (MeOH) (dielectric constant = 33.62; solvent probe radius = 2.002) did not lead to any significant change in structure or relative energies.

Frequency calculations for large molecules of the type studied here, especially if solvation effects need to be taken into account, are of prohibitive computational expense and have not been performed, so that we cannot be absolutely certain that the optimized structures have the desired character as minima or transition states, and cannot either include zero-point energy or thermal corrections. However, given the low symmetry of the molecules, it is extremely unlikely that the optimized structures correspond to anything else than minima or transition states. Moreover, the correct nature and sign of the selected vector for the TS optimization calculations have been thoroughly checked.

Rate constants and equilibrium constants depend on free energies, not electronic energies. As we have not calculated vibrational frequencies, we cannot directly compute free energies. However, the leading contribution to the entropic effects that lead to the difference between electronic energies and free energies is the loss or gain of rotational (or vibrational in solution) and translation degrees of freedom when forming one molecule out of two, or two molecules out of one. Roughly speaking, at and near room temperature, the gas-phase free energy of forming an adduct from two molecules is ca. 10 kcal/mol less exothermic than the corresponding electronic energy of adduct formation.[28a,31] In solution, the effect is suggested to be smaller, perhaps by ca. 50%.[32] We will use the resulting approximate value of 5 kcal/mol where required to discuss free energies.

For the model reaction, single-point energies at the B3LYP/6-31+G*(THF) geometries have been evaluated at several levels of theory: B3LYP/6-311+G**, MP2/6-311+G**, and QCISD(T)/6-31G*. G3(MP2)//B3LYP/6-31G* single-point energies[33] have also been calculated. MP2 calculations were performed using the Gaussian 03 program package,[34] with the QCISD(T) single-point calculations obtained using the MOLPRO program package.[35] Single-point calculations on the model and full systems have been carried out using the density-fitted Hartree−Fock[36] and local MP2 methods[37] in MOLPRO. For these calculations, the cc-pVTZ basis set was used, omitting the d polarization functions on hydrogen atoms, and including diffuse functions (aug-cc-pVTZ) on oxygen atoms. The reported energies, described below as SCS-MP2/cc-pVTZ, include scaling of the energy contributions from the different MP2 spin-components (SCS-MP2 method[38]) and include an approximate treatment of the solvation energy, given by the difference between the gas-phase and continuum solvent energies at the B3LYP/6-311+G** level of theory.

For the large reaction systems, there are usually several local minima or saddle points corresponding to each intermediate or transition state. This is due to the possibility of multiple conformations of substituents. We have made a systematic attempt to locate all possible local minima and saddle points, with the data presented referring to the lowest energy form unless mentioned otherwise.

The reactants for the system we consider are not chiral, and the corresponding MBH product has only one chiral center. However,

(27) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161−2200.
(28) For some recent examples, see: (a) Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747−5756. (b) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468−5471. (c) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2006**, *128*, 2394−2409.
(29) *Jaguar 4.0*; Schrödinger, Inc.: Portland, OR, 1991−2000.
(30) (a) Tannor, D. J.; Marten, B.; Murphy, R.; Friesner, R. A.; Sitkoff, D.; Nicholls, A.; Ringnalda, M.; Goddard, W. A., III; Honing, B. *J. Am. Chem. Soc.* **1994**, *116*, 11875−11882. (b) Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honing, B. *J. Phys. Chem.* **1996**, *100*, 11775−11788.
(31) George, P.; Siegbahn, P. E. M.; Glusker, J. P.; Bock, C. W. *J. Phys. Chem. B* **1999**, *103*, 7531−7541.
(32) See discussion in: Lau, J. K.-C.; Deubel, D. V. *J. Chem. Theory Comput.* **2006**, *2*, 103−106.
(33) Badoul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650−7657.
(34) Frisch, M. J.; et al. *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, 2003.
(35) Werner H.-J.; et al. MOLPRO Versions 2002.3 and 2006.1.
(36) Polly, R.; Werner, H.-J.; Manby, F. R.; Knowles, P. J. *Mol. Phys.* **2004**, *102*, 2311−2321.
(37) Werner, H.-J.; Manby, F. R.; Knowles, P. J. *J. Chem. Phys.* **2003**, *118*, 8149−8160.
(38) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095−9102.

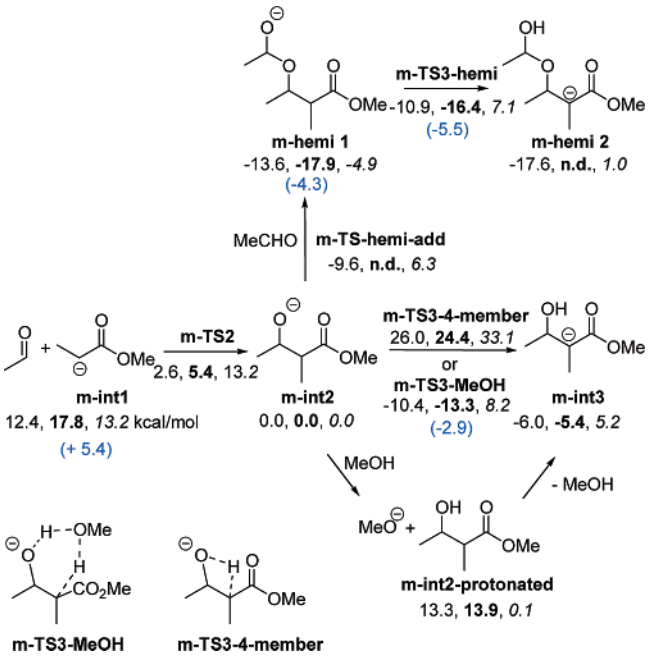



***Figure 5.*** Investigated pathways for model reaction. Energies (in kcal/mol relative to **m-int2**) were obtained by single-point calculations at the geometries optimized at the B3LYP/6-31+G*(THF) level of theory (roman font, gas-phase B3LYP/6-311+G**; bold, G3MP2; italics, B3LYP/6-311+G** with continuum THF; in brackets, error of the B3LYP method as compared to G3MP2).

several intermediates and transition states along the reaction pathway have two (or more) stereogenic carbons, which means that they can exist under two (or more) diastereomeric forms. The key intermediates and transition states of all diastereomeric pathways have been investigated (see Supporting Information). Data presented here refer to the pathway involving the lowest overall barrier unless mentioned otherwise.

## Results

**1. Model Reaction.** To select the most appropriate method for the studied system and check its reliability, we have investigated the model reaction between $CH_3CHO + CH_3CH^-CO_2Me$, for which accurate methods, such as CCSD(T) and G3(MP2), can be used. This model reaction does not allow us to describe the amine addition and elimination steps of the MBH process but enabled us nonetheless to investigate the other key steps, addition to the aldehyde and proton transfer. Because of the omission of the MBH reactants in the model reaction, in this section, energies will be given respective to intermediate **m-int2**. We will restrict here the discussion to the main points, with the full results presented in the Supporting Information. The investigated pathways are shown in Figure 5.

The energy of TSs and intermediates has been obtained at a variety of levels of theory. Taking the accurate G3(MP2)/B3LYP energies as a reference, we find that B3LYP method describes the studied system relatively well. Relative energies obtained, respectively, at B3LYP/6-31+G* and B3LYP/6-311+G** levels are similar (see Supporting Information), suggesting that basis set effects are not large in this system. The B3LYP/6-311+G**//B3LYP/6-31+G* method was thereby selected as the best compromise between cost and accuracy. Even at this level, however, the gas-phase energy of **int1** is underestimated (by ca. 5 kcal/mol), and the barriers to proton transfer in the absence (**m-TS3-hemi**) and in the presence (**m-TS3-MeOH**) of protic species are overestimated by ca. 5 and 3 kcal/mol, respectively.[39,40]

The overall reaction energy of the MBH reaction was also investigated at different levels of theory taking the reaction of methylacrylate and acetaldehyde as a model (see Supporting Information). The gas-phase reaction energies obtained at the B3LYP/6-311+G** and G3MP2 levels are, respectively, −7.7 and −12.4 kcal/mol, indicating an underestimation (by ca. 5 kcal/mol) of the exothermicity of the reaction by the DFT method. The value of −5.4 kcal/mol obtained at the B3LYP/6-311+G** level including continuum solvent shows that solvent effects only have a low influence on the overall reaction energy.

Solvent effects were found, however, to have a large influence on the relative stability of intermediates (see Figure 5) as expected by their charged, and hence highly polar, nature. Solvent effects will thus be taken into account throughout, both for optimization and for single-point calculations, at the level of a continuum model. For one step, protic solvent or a protic co-reactant is intimately involved in the mechanism, and we will model this solvent molecule explicitly.

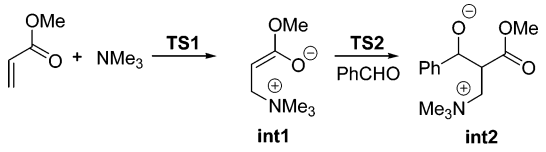
Our results on the model reaction support the pathway suggested by McQuade[20] for the reaction in the absence of sufficient amounts of protic species, that is, through formation of a hemiacetal, and the mechanism proposed by Aggarwal and Lloyd-Jones[19] for the alcohol-catalyzed proton transfer, that is, through **m-TS3-MeOH**. The simplicity of the model does not allow one, however, to draw firm conclusions.

**2. Realistic Model.** In this section, we will first discuss the mechanism of the enolate betaine formation and its addition to benzaldehyde. We shall then present our results concerning the mechanism of the proton transfer, first in the absence of protic species and then for the reaction catalyzed by methanol. For the latter case, it is necessary to include one methanol molecule in the reaction system throughout, not just for the key proton-transfer TS, so as not to get biased energies. For many species, it is relatively easy to choose the place in which to position the hydrogen-bonding methanol molecule so as to get the lowest or most meaningful energy. Nevertheless, for some intermediates or TSs, the "best" place to put the methanol molecule is not clear. Also, the "best" place may be different for two successive intermediates or for an intermediate and the following transition state. From close inspection of the results, it can be seen that the, in part, arbitrary decisions about where to place the explicit solvent molecule do slightly affect computed relative energies but this is a small effect. Where unclear, we signal the position of the methanol molecule in the text below.

(39) These apparent errors in the DFT energetics seem to be another example of some of the shortcomings of B3LYP that have been noted recently for describing systems with different numbers of different types of C−C, C−H, and C−O bonds. See, for example: (a) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schütz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896−5911. (b) Grimme, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4460−4464. (c) Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. v. R. *Org. Lett.* **2006**, *8*, 3631−3634. (d) Schreiner, P. R.; Fokin, A. A.; Pascal, R. A.; de Meijere, A. *Org. Lett.* **2006**, *8*, 3635−3638. (e) Friesner, R. A.; Knoll, E. H.; Cao, Y. *J. Chem. Phys.* **2006**, *125*, 124107. (f) Grimme, S.; Steinmetz, M.; Korth, M. *J. Org. Chem.* **2007**, *72*, 2118−2126.

(40) The addition of the enolate to acetaldehyde is found to be exothermic for the model reaction. As one will see in the next section, addition to benzaldehyde is conversely computed to be endothermic. The consequence is that **m-TS2** is a very "early" transition state, and thus similar to reactants, whereas in the realistic model case (addition to benzaldehyde), the addition of TS is very late and resembles the adduct very much. It is thereby more relevant to look at the relative energy of the adduct **m-int2** than at the energy of **m-TS2** to investigate the ability of a method to evaluate the energy of the addition TS in the case of addition to benzaldehyde.

***Table 1.*** Formation of **int2** (Energies (in kcal/mol Relative to Reactants) Are Obtained at the B3LYP/6-311+G**(THF) Level of Theory at the B3LYP/6-31+G*(THF) Geometries)




| | reactants | TS1 | int1 | TS2 | int2 |
|---|---|---|---|---|---|
| in the absence of MeOH | 0 | 11.6 | 11.2 | 20.1 | 20.5 |
| in the presence of MeOH | 0[a] | −[b] | 9.8[c] | 19.0[d] | 15.8 |

[a] Energy of separated acrylate and aldehyde, each complexed to a molecule of MeOH. [b] Not found (close in energy and geometry to **int1**). [c] Energy of separated **int1** and aldehyde, each complexed to a molecule of MeOH. [d] Additional TS involving a hydrogen bond between the developing negative charge on the aldehyde oxygen and one molecule of methanol (see Figure 6).

**A. Enolate Formation and Addition to the Aldehyde.** Our results concerning the two steps leading to formation of intermediate **int2**, the precursor of proton transfer, are presented in Table 1.

Addition of the amine to methyl acrylate is found to be endothermic with a very late (product-like) TS lying only slightly higher than the adduct (**int1**). Complexation of the alkoxide function of **int1** by one molecule of methanol leads to a stabilization to the enolate (**int1-MeOH**) of ca. 1.5 kcal/mol.

The *E* isomer of **int1** (with OMe trans to $CH_2NR_3^+$) is found to be more stable than its *Z* isomer (by 1.1 kcal/mol; B3LYP/6-31+G*(THF)). It has been previously suggested that the *E* isomer of this intermediate involves a stabilizing interaction between the positive center (ammonium in this case) and the enolate oxygen.[41,42] An analysis of the structure of **int1** reveals no specific interaction between the two groups, the higher stability of the *E* isomer being probably best accounted for by favorable electrostatic interactions.

The *E* isomer of **int1** is also the more reactive in addition to benzaldehyde,[43] which is found to be endothermic in our B3LYP calculations. Explicit complexation of **int2** by a molecule of methanol induces a decrease of reaction energy of ca. 3 kcal/mol. For the model reaction, we found the exothermicity of the analogous step to be underestimated by ca. 5 kcal/mol with B3LYP, so in the present case, addition of **int1** to benzaldehyde is likely to be only slightly endothermic or thermoneutral.

The optimized structures of the different **TS2** conformers and diastereomers are consistent with the importance of dipole−dipole interactions in determining orientation of approach of reactants in aldol-type TSs (Figure 6):[44] reactants are oriented in such a way that their respective dipoles point in opposite directions, and thereby there is maximum electrostatic stabilization.

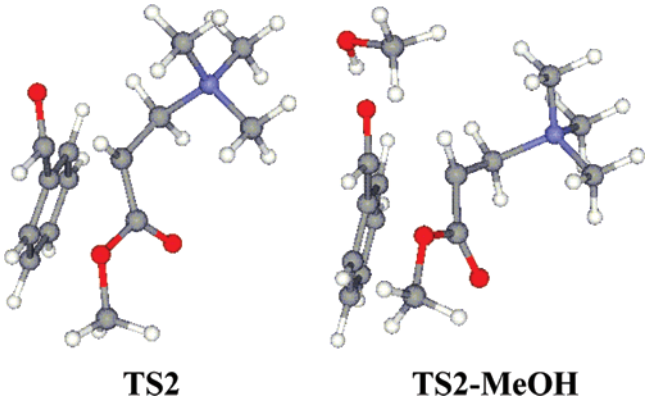



***Figure 6.*** Transition state structure for the addition to benzaldehyde step, in the absence (**TS2**) and in the presence (**TS2-MeOH**) of one molecule of methanol.

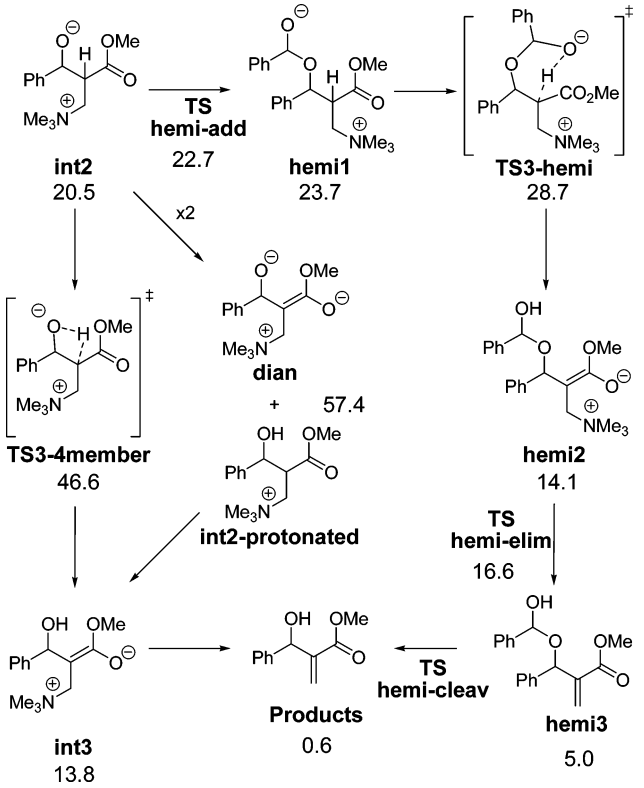



***Figure 7.*** Explored pathways for proton transfer in the absence of protic species. Energies are obtained at the B3LYP/6-311+G**(THF)//B3LYP/6-31+G*(THF) level of theory and are given in kcal/mol relative to reactants.

The activation energy of the addition to aldehyde is not significantly dependent on the complexation by a molecule of methanol. The presence of one molecule of MeOH does, however, stabilize **int1** and **int2**. Overall, a significant increase in rate is thus expected for **int2** formation in the presence of protic species.

**B. Proton-Transfer Mechanism in the Absence of Protic Species.** All of the explored mechanisms for the proton transfer in the absence of catalysis by protic species are reported in Figure 7.

The mechanism of intramolecular proton transfer involving a four-center transition state (**TS3-4member**) has been explored. The activation barrier associated with this mechanism

(41) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521−1522.
(42) Recent mechanistic studies indicate that this interaction should not be present in phosphine-catalyzed MBH reactions. See: Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174−4175.
(43) Reaction of the *Z* enolate has a barrier of 0.9 kcal/mol higher than that of the *E* (B3LYP/6-31+G*(THF)).
(44) (a) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789. (b) Heatchcock, C. H.; Davidsen, S. K.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027.

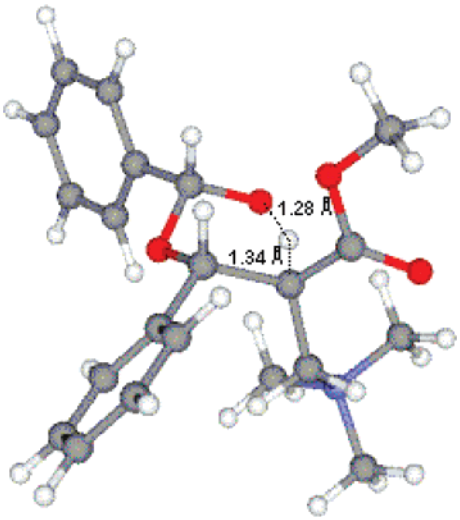


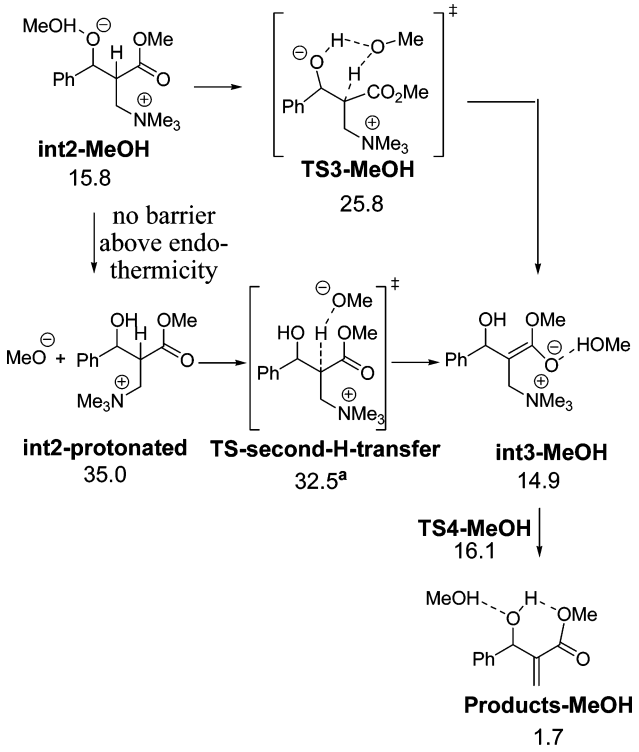

***Figure 8.*** Structure of proton-transfer TS in the absence of alcohol catalysis (**TS3-hemi**).

has been found to be, as previously believed,[19] highly unfavorable (26.1 kcal/mol).[45,46]

Calculations show that the mechanism in which **int2** acts as a base-catalyst, reacting with itself to give **dian** + **int2-protonated**, is also highly disfavored, with the intermediates lying at 57.4 kcal/mol above reactants. This is due to the high energy, even in continuum solvent, of the dianionic species. A similar mechanism involving deprotonation of **int2** by a second equivalent of the tertiary amine is expected to be even less favorable, given that amines are less basic than an alcolate, such as **int2**. Indeed, kinetic data show an overall first-order dependence of rate on concentration of amine,[19] not the second-order dependence that would be expected if the amine did deprotonate **int2** in the rate-limiting step.

The mechanism involving formation of a hemiacetal intermediate, as proposed by McQuade, has also been investigated.[20] Addition of **int2** onto a second molecule of aldehyde to form intermediate **hemi1** is very facile although slightly endothermic (by 3.2 kcal/mol). The following intramolecular proton transfer is exothermic (by 9.6 kcal/mol) and occurs with a low activation barrier (5.1 kcal/mol) via a six-membered ring TS in which the α-C−H bond is partially broken ($d_{C-H}$ = 1.34 Å; Figure 8). The hemiacetal intermediate so-formed, **hemi2**, can then decompose very easily into the MBH adduct, benzaldehyde, and $NMe_3$.

Our calculations provide strong support for the pathway proposed by McQuade and indicate an overall barrier of 8.2 kcal/mol from **int2** for the proton-transfer process. The overall energy barrier with respect to reactants is predicted to be 28.7 kcal/mol in THF. The true barrier is probably slightly lower than this, considering the errors in the B3LYP method highlighted in our calculations on the model system (see Figure 5). Assuming that B3LYP makes no error for the initial step, amine addition to form **int1** (this step is not treated in the model system), B3LYP can be expected to overestimate the height of **TS3-hemi** by 10.9 kcal/mol, giving a corrected barrier height of 17.8 kcal/mol. Single-point SCS-MP2/cc-pVTZ calculations using local correlation methods (with a correction for solvent effects from the B3LYP calculations) for this TS also suggest that its energy relative to reactants is overestimated by B3LYP. The predicted barrier height of 12.5 kcal/mol relative to reactants should be reasonable given that the same SCS-MP2 level of theory is in fair agreement with G3 for the model system (see the Supporting Information), although uncertainties associated with the correlation treatment and the definition of the domains in the local approach[37] mean that it is certainly not exact.




[a] optimized at the B3LYP/6-31+G*(MeOH) level of theory

***Figure 9.*** Explored pathways for methanol-catalyzed proton transfer. Energies (kcal/mol relative to reactants) are obtained at the B3LYP/6-311+G**(THF)//B3LYP/6-31+G*(THF) level of theory.

**C. Alcohol-Catalyzed Proton-Transfer Mechanism.** Results for the investigated pathways for methanol-catalyzed proton transfer are reported in Figure 9.

We first investigated the possibility of a two-step mechanism, that is, protonation−deprotonation. Protonation of **int2-MeOH** by methanol is endothermic by 19.2 kcal/mol. The product complex is unstable and upon attempted geometry optimizations reverts to **int2-MeOH** without any enthalpic barrier. The following step, deprotonation of the α-carbon by the methanolate, is exothermic and here too the barrier is very low; the B3LYP/6-311+G**(THF) single-point energy predicts it to lie slightly lower than the separated **int2-protonated** + methoxide species. The overall energy barrier for this two-step mechanism with respect to **int2-MeOH** is computed to be of 16.7 kcal/mol.

The concerted protonation−deprotonation mechanism (**TS3-MeOH**) is found to be more favorable, with an activation barrier

(45) A similar barrier has been obtained in a previous computational study for the equivalent step in phosphine-catalyzed MBH reaction (Xu, J. *J. Mol. Struct. (THEOCHEM)* **2006**, *767*, 61−66), as well as in a very recent study of the quinuclidine-catalyzed MBH reaction (Roy, D.; Sunoj, R. B. *Org. Lett.* **2007**, *9*, 4873−4876). This latter paper, published after submission of the present work, also contains thorough calibration and mechanistic studies that partly mirror our work.

(46) The mechanism involving a four-membered transition state (**TS3-4member**) has the particularity to be unimolecular, whereas all of the others are bimolecular, which should favor it from an entropy point of view. In terms of free energy, this benefit can be estimated (see Computational Details) to ca. 5 kcal/mol. This is not enough to compensate for the high energy barrier of this mechanism and make this pathway competitive with others.

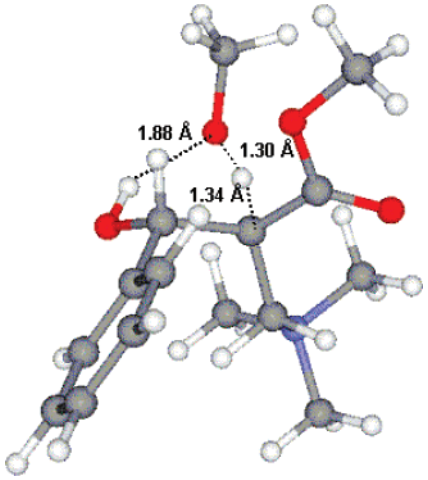



***Figure 10.*** Structure of methanol-catalyzed proton-transfer TS (**TS3-MeOH**).

of 10.0 kcal/mol with respect to **int2-MeOH**.[47] Calculations on the model system suggest, however, that the true barrier may be ca. 3 kcal/mol lower.

The concerted proton transfer occurs via a six-membered ring transition state (Figure 10). The structure of the TS reveals a concerted but asynchronous proton transfer: the α-C−H bond is only partially broken ($d_{C-H}$ = 1.34 Å), but the MeOH has almost completely transferred its proton to the alkoxide oxygen of **int2** ($d_{H-OMe}$ = 1.88 Å; $d_{H-OR}$ = 0.99 Å).

The enolate formed after the proton transfer (**int3**) subsequently undergoes an exothermic and very fast (<2 kcal/mol barrier) elimination to regenerate the amine catalyst and yield the MBH adduct.

Our results thereby support the concerted pathway for the alcohol-catalyzed proton-transfer mechanism with a barrier with respect to **int2-MeOH** of 10.0 kcal/mol (25.8 kcal/mol with respect to reactants).[47] Again, the data for the model reaction (see Figure 5) suggest an overestimation of the barrier by B3LYP, by 8.3 kcal/mol if one takes the correction factor directly from the model system, which would lead to a corrected barrier to reaction of 17.5 kcal/mol. Here too, SCS-MP2/cc-pVTZ single-point calculations confirm that B3LYP overestimates the barrier height, as they give a predicted value of 14.1 kcal/mol. Again, however, the uncertainties associated with this correlated method mean that this number should only be taken as a guideline.

Previous kinetic experiments suggest that in the absence of other hydrogen-bond donors the reaction shows autocatalysis. This is not surprising as in principle any molecule with an alcohol OH group, including the product, could play the same role as MeOH in **TS3**. Indeed, we have calculated the barrier to concerted proton transfer with the product instead of MeOH as the hydrogen-bond donor and obtained a similar value for the corresponding energy relative to reactants, of 26.2 kcal/mol.

(47) We note that single-point calculations (see Supporting Information) indicate that the barrier with respect to **int2-MeOH** is somewhat higher in continuum MeOH (13.8 kcal/mol). However, **int2-MeOH** is less stable in THF than in MeOH (15.8 and 10.8 kcal/mol, respectively). The result is a low decrease of overall activation barrier in continuum MeOH for alcohol-catalyzed mechanism (the barrier is 25.8 and 24.6 kcal/mol in continuum THF and MeOH, respectively). This agrees well with experimental results, suggesting that solvent polarity makes only a small contribution to the rate acceleration observed in protic solvents.[5g]

## Discussion

The overall reaction energy of the process is computed to be close to zero. By analogy with the model reaction, the stability of reactants is probably overestimated by the B3LYP method, such that the reaction should in reality be exothermic by about 5 kcal/mol, and the SCS-MP2 method indeed predicts a reaction energy of −4.7 kcal/mol. The entropy effects on the reaction energy are likely to be significant because it leads to the conversion of two molecules into one. Near room temperature, this is expected to make the reaction free energy in the gas phase less favorable by ca. 10 kcal/mol than the reaction energy.[31,48] In solution, the effect should be smaller, at ca. 5 kcal/mol.[32] Overall, the reaction is thereby expected to be near thermoneutral in free energy terms.[2b,49] One has to note, however, that the reactions involving alkyl aldehydes (or electron-poor aromatic aldehydes) are likely to be more exothermic due to the higher exothermicity (or lower endothermicity) of the addition step (**int1** → **int2**) in these cases.[50]

**A. Reaction Pathway in the Absence of Protic Species.** Our results are in very good agreement with the second-order kinetics with respect to aldehyde concentration, and first-order kinetics with respect to amine and acrylate concentrations observed experimentally in the absence of alcohol catalysis, and thereby give firm support to the mechanism proposed by McQuade (Figure 11).[20]

The first step of this process is addition of the amine to the acrylate to form an enolate (**int1**). Addition of this intermediate to the aldehyde then leads to **int2**, which reacts subsequently with a second equivalent of aldehyde to yield **hemi1**. This hemiacetal betaine species then undergoes an intramolecular proton transfer through a six-membered ring transition state (**TS3-hemi**). Elimination of the amine catalyst yields finally the hemiacetal **hemi3**, which usually decomposes into product and aldehyde, but can also in some cases cyclize to yield the corresponding dioxanone (see Figure 3).[20]

The energy profile obtained for this process is in very good agreement with the low reaction rate, which characterizes the MBH reaction (Figure 12). The overall enthalpic barrier is calculated to be 28.7 kcal/mol with respect to reactants at the B3LYP level of theory, although our calculations on the model system suggest a smaller barrier of ca. 18 kcal/mol. The loss in entropy expected upon going from four molecules (reactants) to one in **TS3-hemi** is expected to result in an overall free energy of activation that is roughly 15 kcal/mol higher than the energy of activation.

Our results indicate that the rate-determining step in this case is the proton-transfer step. This is in good agreement with McQuade's kinetic experiments and observed KIE's at the early stage of the reaction (see Introduction).[19,20]

The above mechanism does not, however, account for the experimentally observed acceleration in the presence of protic species. The rate-determining step **TS3-hemi** involves proton

(48) The gas-phase entropic contribution to the overall free energy of reaction for the MBH reaction of acrylonitrile and acetaldehyde has been recently calculated to be 11.4 kcal/mol, at the B3LYP/6−311+G* level. See ref 45.

(49) For experiments supporting this, see: Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371−6384.

(50) The reaction energy for the addition of **int1** onto benzaldehyde, *para*-nitrobenzaldehyde, and acetaldehyde is endothermic by 9.3, 1.9, and 1.8 kcal/mol, respectively (B3LYP/6-311+G**(THF)//B3LYP/6-31+G*-(THF)).

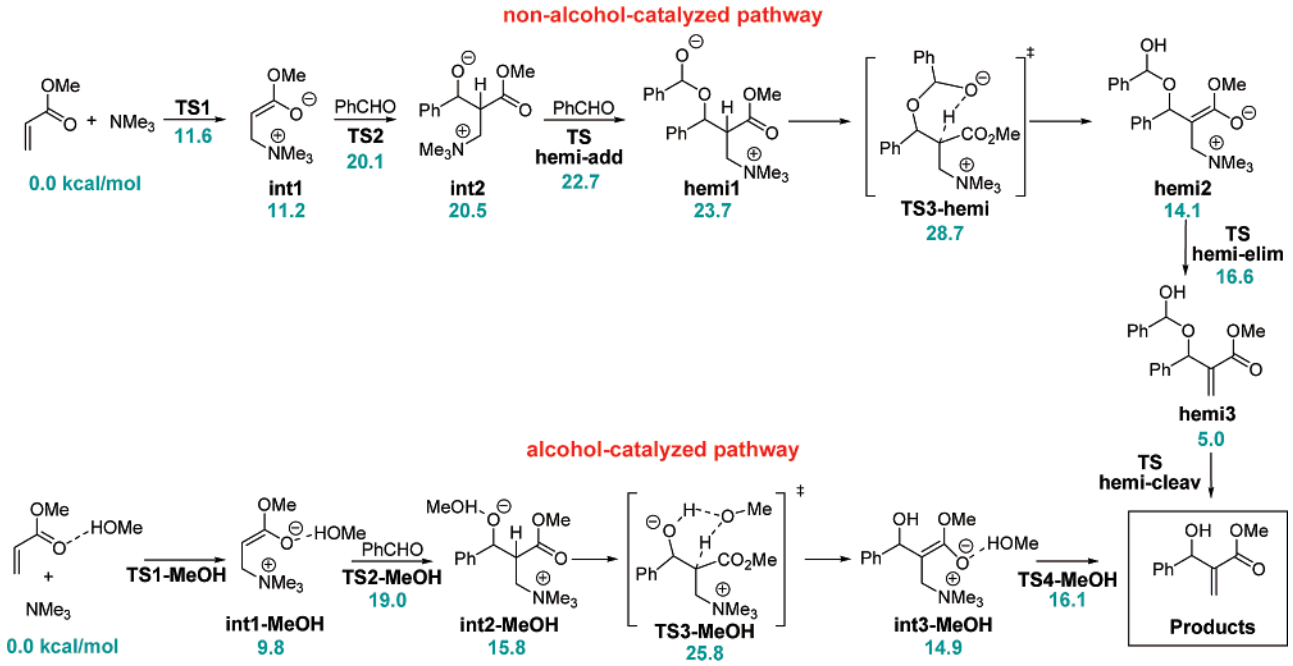



***Figure 11.*** Mechanism of the MBH reaction in the absence and in the presence of alcohol catalysis with energies (kcal/mol) of important intermediates and transition states shown.

transfer, and hydrogen bonding from protic species would not be expected to stabilize **TS3-hemi** much better than reactants. Previous experimental results suggest that the higher polarity of alcohol solvents does not on its own explain the observed acceleration either.[5g] This is confirmed by single-point calculations, indicating that increasing the polarity of the solvent (MeOH instead of THF) stabilizes intermediates **int2** and **hemi1** (by 4.8 and 3.6 kcal/mol, respectively)[51] but has no significant influence on the energy relative to reactants of **TS3-hemi**, that is, on the overall barrier (**TS3-MeOH** lies at 28.7 and 28.0 kcal/mol in THF and MeOH, respectively). In other words, a protic and more polar solvent (MeOH instead of THF) helps formation of **int2** and **hemi1** by stabilizing them, but these effects are compensated by an increase in the barrier to proton transfer. These results indicate thus that another mechanism must occur in the presence of protic species, as suggested previously by our kinetic experiments.[19]

**B. Alcohol-Catalyzed Reaction Pathway.** Numerous experimental studies have shown that the rate of the MBH reaction is increased in the presence of hydrogen-bond donors.[5] Our recent kinetic data and KIEs suggest moreover that another mechanism is effective in the case of alcohol catalysis (see Introduction).[19] The present computational results are in good agreement with these observations, in that we have found a lower-energy pathway involving a concerted proton transfer catalyzed by one molecule of MeOH (or of product).[52]

(51) Relative energy of **hemi1** is 23.7 and 20.1 kcal/mol in THF and MeOH, respectively, and **int2** lies at 20.5 and 15.7 kcal/mol in THF and MeOH, respectively.

(52) The B3LYP calculations give an overall barrier of 28.7 and 25.8 kcal/mol for the aldehyde- and alcohol-catalyzed pathways, respectively. If one corrects these calculated barrier heights, by simply taking the difference between the B3LYP and G3MP2 energies in the model system calculations of Figure 5, the calculated activation energies for the two pathways are, respectively, 17.8 and 17.5 kcal/mol. This leads to a small difference in the energy barrier for the two pathways, with the alcohol-catalyzed pathway slightly favored as found experimentally. Given the remaining potential for error in the G3MP2 calculations on the model system, and the additional errors possible in the B3LYP calculations on the real system, the overall agreement with experiment seems reasonable.

The first steps of the overall mechanism in the presence of methanol lead to the formation of **int2**, as in the absence of hydrogen-bond donors. Hydrogen bonding with methanol stabilizes **int1** and **int2** and makes their formation thermodynamically more favored than in the absence of protic species. The presence of methanol enables **int2** to undergo a concerted proton transfer via **TS3-MeOH** to give **int3**, which then decomposes easily into the product and the amine catalyst (see Figure 11).

From our kinetic experiments, it was tentatively suggested that the RDS of the alcohol-catalyzed process is addition to aldehyde (at >20% conversion when the product promotes proton transfer).[19] As mentioned above, these experiments were, however, not very reliable because of $^{1}H/^{2}H$ exchange reactions between the MBH product and the starting acrylate limiting the accuracy of the measurements. Later, McQuade reported a KIE value of 2.1 ± 0.3 in 2.75 M water in THF, which suggests that the RDS involves loss of the proton in the α-position even in the presence of protic species. Our calculations are in good agreement with this observation, indicating that addition to aldehyde should be reversible with the rate-determining step being instead proton transfer (see Figure 12).

However, the use of aliphatic aldehydes (or substitution of aromatic aldehydes by electron-withdrawing groups) will stabilize **int2** relative to **int1** (addition more exothermic)[50] but is expected to have little effect on the activation barrier to proton transfer (Figure 13). Addition to aldehyde (**TS2-MeOH**) might therefore be non-reversible in these cases.

**C. Kinetics.** Even taking into account the errors involved in our B3LYP calculations, the significant calculated energy barrier for the non-alcohol-catalyzed pathway (28.7 kcal/mol) accounts for the traditionally observed low reaction rates. The loss in entropy upon going from four molecules (reactants) to the single species in **TS3-hemi** means that the overall free energy of activation will be even higher (by ca. 15 kcal/mol).

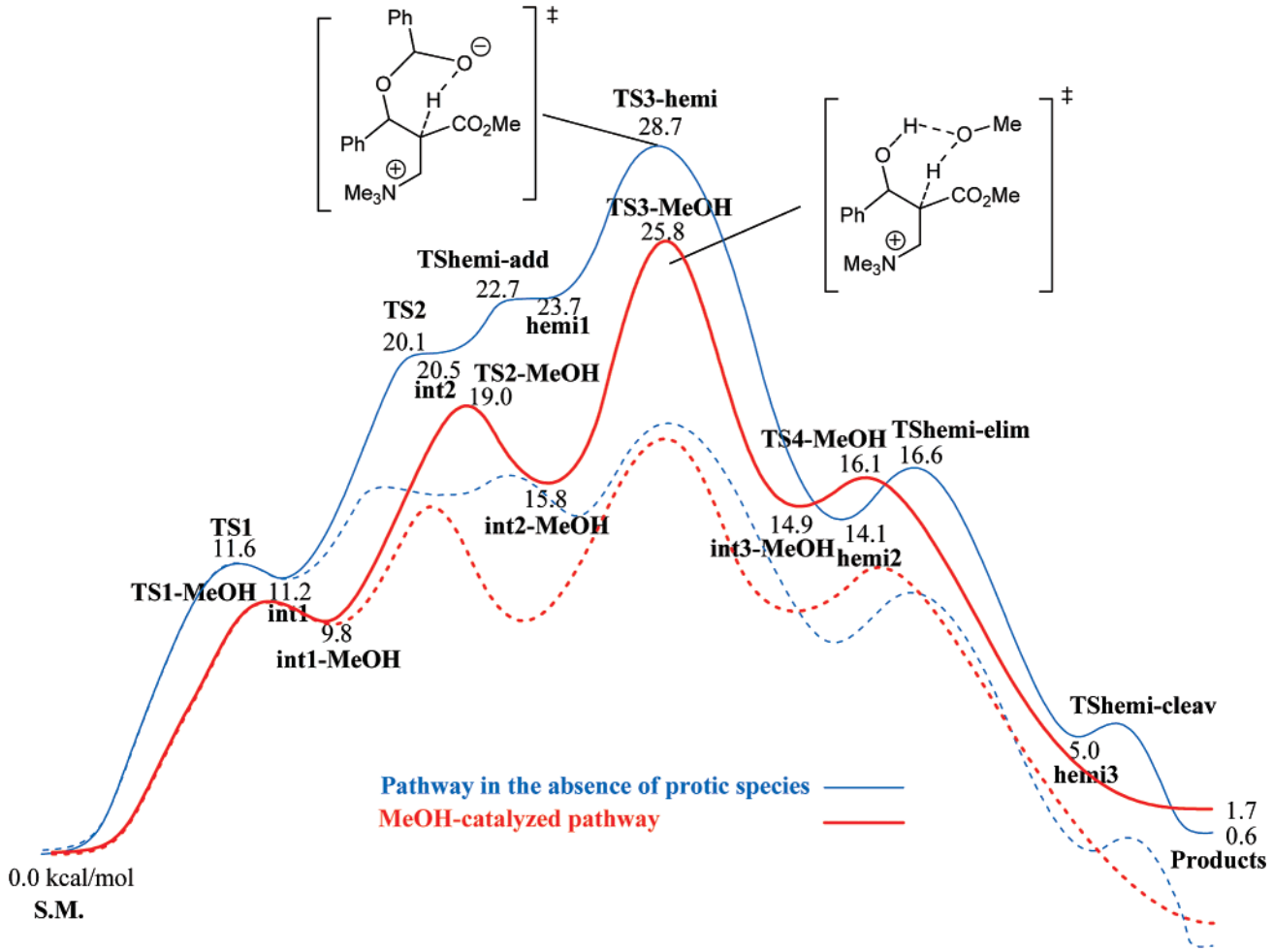



***Figure 12.*** Calculated potential energy surface (kcal/mol) for the MBH reaction in the absence (blue) and in the presence (red) of alcohol catalysis, at the B3LYP/6-311+G**(THF)//B3LYP/6-31+G*(THF) level of theory. The dotted curves correspond to qualitative energy profiles, taking into account the estimated errors in the B3LYP method.

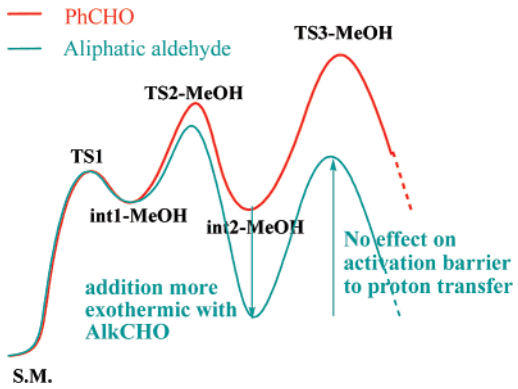



***Figure 13.*** Influence of the nature of the aldehyde on the energy profile.

It is well documented that a rate acceleration is observed in the presence of hydrogen-bond donors.[5] Our kinetics experiments have shown furthermore that in the absence of protic additives autocatalysis takes place in the reaction of benzaldehyde with methyl acrylate.[19] This autocatalysis starts, however, to be effective only at ca. 20% conversion, indicating that the barriers for the two processes (alcohol-catalyzed and non-alcohol-catalyzed) are rather close in energy. Our calculations are in very good agreement with these observations. Taking into account the error in the B3LYP energies suggested by the model system calculations, the overall enthalpic barrier to the alcohol-catalyzed proton-transfer mechanism is only slightly smaller (see Figure 12, dotted lines) than the energy barrier for the reaction involving 2 equiv of benzaldehyde and hemiacetal intermediates.[52] We note, however, that single-point calculations (see Supporting Information) indicate an additional decrease of overall energy barrier for the alcohol-catalyzed reaction with increasing polarity of the solvent.[47]

Moreover, from a kinetic point of view, the non-alcohol-catalyzed pathway involves two additions to aldehyde prior to RDS, whereas the alcohol-catalyzed one is first order in aldehyde and alcohol. In the case of reaction in protic solvents, the higher concentration of alcohol over aldehyde favors thus even more the alcohol-catalyzed pathway.

However, due to this difference in aldehyde order, the overall barrier of the pathway in the absence of alcohol is expected to be more sensitive to the nature of the aldehyde than the alcohol-catalyzed process, which means that a more reactive aldehyde (e.g., alkyl aldehydes or *p*-nitrobenzaldehyde) will favor the aldehyde-catalyzed reaction more than the alcohol-catalyzed one. In these cases, the mechanism involving addition onto a second molecule of aldehyde could thus well become the lowest lying pathway, even in the presence of protic species. Indeed, in reactions of *p*-nitrobenzaldehyde with methylacrylate, McQuade observed a second-order dependence for aldehyde under THF/$H_2O$ conditions.[20b]

Our B3LYP calculations find the transition state for addition of the initial betaine **int1** to the aldehyde (**TS2**) to form **int2** to be significantly lower than the TSs for proton transfer (i.e., 19.0 and 25.8 kcal/mol relative to reactants in MeOH for the methanol-catalyzed process). Hence, in almost all cases proton transfer should be rate-limiting. However, our G3MP2 calculations on the model system suggest that B3LYP overestimates the energy of **TS3-MeOH** and **TS3-hemi** relative to **int2**, and hence probably also to **TS2**. Also, with some activated aldehydes, the relative energy of **int2** is likely to be lower still. Hence, it is just possible that, in some cases, addition of aldehyde to **int1** could become rate- and selectivity-determining (see Figure 13).

**D. Implications for Stereoselectivity.** The MHB product has only one stereogenic center but several intermediates, and TSs have more than one chiral center. For instance, in the case of the alcohol-catalyzed mechanism, the selectivity-determining TS (**TS3-MeOH**) has 2 stereogenic centers, which means that 4 diastereomers can be formed.[53] In the case of the aldehyde-catalyzed pathway, **TS3-hemi** has 3 chiral centers, so there are 8 possible diastereomers. This complexity is expected to significantly decrease selectivity: a chiral catalyst has to enable discrimination between 4 or 8 diastereomers and not 2 as in traditional processes. This will be especially important here as our calculations indicate that the diastereomers of most intermediates and TSs lie rather close in energy and so are easily accessible (see Supporting Information).

Our kinetic studies have shown that in the absence of protic additives autocatalysis of the reaction takes place (at ca. 20% conv. for the reaction of benzaldehyde with methyl acrylate).[19] Moreover, our calculations, supported by KIEs,[19] revealed that the mechanism of the reaction is different in the absence and in the presence of hydrogen-bond donors. As a result, in the absence of protic additives, there is a change in mechanism during the course of the reaction, and hence in the nature of the TS where selectivity is determined. The achievement of high asymmetric induction is thus made difficult in this reaction. This is most probably one of the causes of the moderate success of asymmetric MBH reactions using a chiral auxiliary[9] or amine catalyst,[10] in the absence of protic additives.[54]

The nature of the lowest energy pathway may also well depend on the nature of the aldehyde: due to the difference in aldehyde order between the two mechanisms, reaction of a more reactive aldehyde (e.g., alkylaldehydes or *p*-nitrobenzaldehyde) will lower more the overall activation energy of the non-alcohol-catalyzed pathway (which is second order in aldehyde) than the barrier to the alcohol-catalyzed process (first order in aldehyde). In these cases, aldehyde-catalyzed reaction could thus well become more favored than the alcohol-catalyzed one, even in the presence of protic species. This is probably one of the causes of the difficulty of developing a general version of the asymmetric MBH reaction. Indeed, the highly diastereoselective BHR using Oppolzer's sultam only works well for alkylaldehydes.[9b]

(53) This is true for reactions involving acrylate unsubstituted in $\beta$-position, by far the most common case encountered in literature. Substitution of the acrylate in $\beta$-position would lead to the creation of an additional stereogenic center in the first step of the reaction, and hence multiply the number of possible diastereomers of all intermediates and TSs by 2.

(54) It has been shown that increased selectivities could be achieved when working in a protic solvent for reactions with a chiral auxiliary and reactions catalyzed by a chiral amine (see, respectively, refs 9a and 10b).

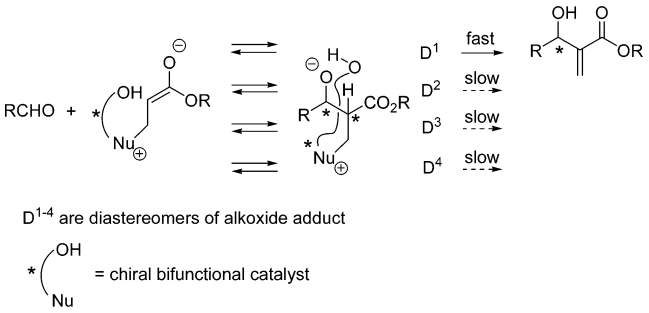



***Figure 14.*** Origin of stereoselection in the MBH reaction.

Our calculations show that formation of **int2** is reversible, and hence that proton transfer is the selectivity-determining step, in both the non- and alcohol-catalyzed pathways.

If one wishes to obtain good enantiomeric excesses, it is therefore advisable to (1) work in the presence of hydrogen-bond donors and (2) control stereoselectivity of the proton-transfer step. This may explain the recent success of bifunctional organocatalysts (amines covalently attached to a protic function several carbons away). The success of these systems can be attributed to the suitable positioning of H-bond donors for selective intramolecular proton transfer of one of the alkoxide diastereomers and not the others. The alkoxide diastereomer that undergoes the fast selective proton-transfer reaction may also be the diastereomer that is preferentially formed, but this is not a prerequisite (Figure 14). One should note, however, that the bifunctional catalysts give good selectivities only if no other protic additives, which could competitively catalyze proton transfer, are present (see, for example, ref 14a).

As mentioned above, in the case of aliphatic (or activated aromatic aldehydes), addition to aldehyde may well become less or non-reversible, and hence addition of the enolate to the aldehyde becomes the selectivity-determining step. If there is a high degree of stereocontrol in the addition step and it is coupled with reduced reversibility, this would explain the higher enantiomeric excesses often obtained for reactions with aliphatic aldehydes, as compared to aromatic aldehydes (see, for instance, refs 11b,c and 13a,d,f).[55] It is interesting to note that this lower or non-reversibility of the addition is also likely to be the origin of the higher success of the asymmetric aza version of the MBH reaction: addition to *N*-sulfonated imines, the most common type of imines in aza-MBH reaction, is more exothermic than addition to aldehydes.

In any case, enantioselectivity of the process is likely to be influenced by the degree of non-reversibility of the addition of the enolate to the aldehyde, and hence by the nature of the aldehyde. This stresses the importance of controlling stereoselectivity of both key steps, addition to aldehyde and proton transfer, if a general asymmetric version of the MBH reaction is to be achieved. Ideally, a chiral catalyst will favor a major diastereomer in the enolate addition step, and the catalyst will also promote a fast proton-transfer step associated with the same major diastereomer.

(55) This observation could also be due to a higher reversibility of the overall reaction in the case of aromatic aldehydes. However, to our knowledge, no variation of enantiomeric excess with time has ever been reported.

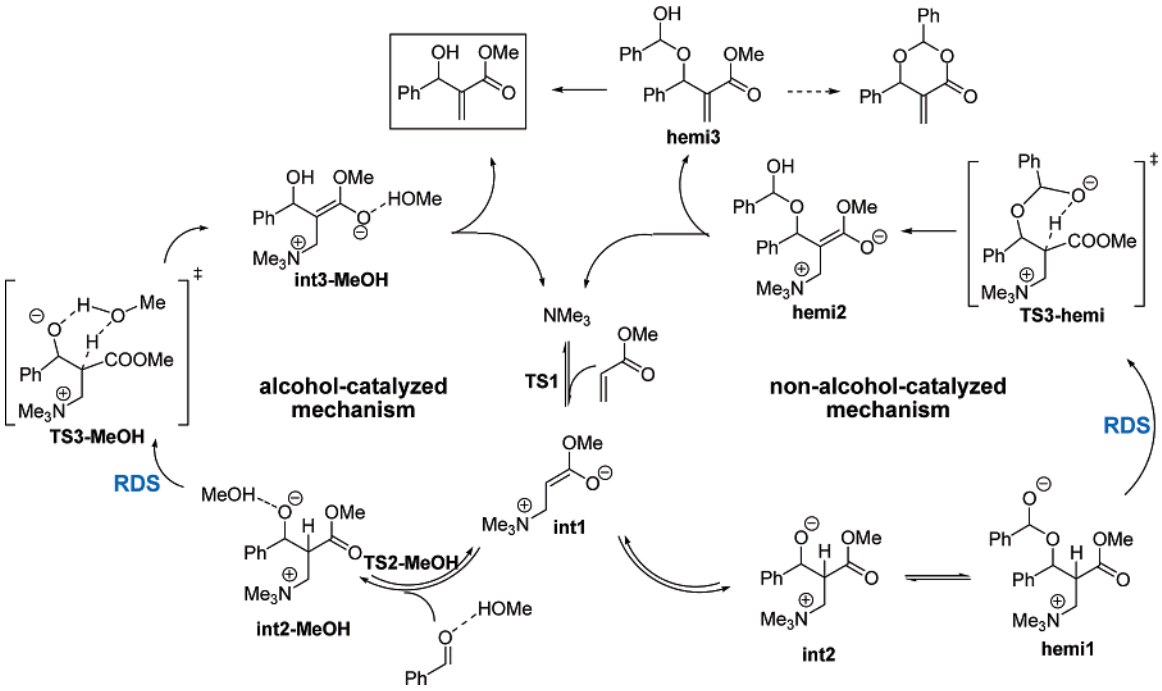



***Figure 15.*** Mechanisms for the MBH reaction.

## Conclusion

We have used density functional theory calculations, calibrated with high-level G3MP2 computations, and including solvation effects, to model each step in the Morita−Baylis−Hillman reaction. Our results show good agreement with the experimental observations: formation of the ammonium enolate (**int1**) and subsequent addition to the aldehyde leading to **int2** are both endothermic processes (by 11.2 and 9.3 kcal/mol, respectively). This is followed by rate-limiting proton transfer to give the MBH adduct. The computed energy profile is consistent with the substantial kinetic isotope effect observed for the α-position,[19,20] with the high overall activation energy (28.7 kcal/mol) in good agreement with the experimentally observed slow rate for the reaction.

Two mechanisms have been identified for the proton-transfer process: (i) addition of a second aldehyde to form a hemiacetal alkoxide followed by rate-limiting proton transfer as suggested by McQuade[20] (non-alcohol-catalyzed pathway) and (ii) an alcohol-catalyzed pathway in which an alcohol acts as a shuttle to transfer a proton from the α-position to the alkoxide of **int2** (Figure 15). Taking into account the error in the B3LYP energies suggested by the model system calculations, the overall enthalpic barrier to the alcohol-catalyzed proton-transfer mechanism is estimated to be slightly smaller than the energy barrier for the first pathway (see Figure 12; dotted lines).[52] The mechanism involving 2 equiv of benzaldehyde and hemiacetal intermediates is thereby likely to dominate in the absence of proton donors (early phase of the reaction), and the second pathway will usually dominate as the aldehyde is consumed and the alcohol concentration (the product is an alcohol) increases. This result is in good agreement with our kinetic experiments, showing that autocatalysis starts to be effective at ca. 20% conversion.[19]

One has to note, however, that, due to its second order in aldehyde, the non-alcohol-catalyzed pathway will be more sensitive to the nature of aldehyde and could well become the more favored pathway in reaction of more reactive aldehydes (e.g., alkyl aldehydes), even in the presence of protic species.

Morita−Baylis−Hillman reactions are often conducted in the presence of protic donors (e.g., MeOH or $H_2O$) as such conditions enhance rates.[5] Our results give for the first time a clear understanding of the origin of this rate enhancement: hydrogen-bond donors activate the reaction by allowing the proton-transfer step to occur via a concerted lower-energy mechanism in which one molecule of alcohol (or water) act as a shuttle to transfer the proton from the α-position to the alkoxide of **int2**. Even under such conditions though proton transfer remains the RDS.

Our B3LYP calculations find the barrier to formation of **int2** (20.1 and 19.0 kcal/mol in the absence and presence of MeOH, respectively) to be significantly lower than the TSs for proton transfer (28.7 and 25.8 kcal/mol in the absence and presence of MeOH, respectively). Although our G3MP2 calculations on the model system suggest that B3LYP slightly overestimated the energy of **TS3-hemi** and **TS3-MeOH** relative to **TS2**, these results show that formation of **int2** is reversible in both the non- and alcohol-catalyzed pathways, highlighting the importance of the proton-transfer step, which is the rate- and selectivity-determining step of the reaction. The successful bifunctional catalysts that have been developed all seem to have the potential to promote proton transfer intramolecularly. The high selectivity is likely to result from fast proton transfer of one of the diastereomers while the others revert back to starting materials. However, our calculations show that in reactions with aliphatic aldehydes and activated aromatic aldehydes (and activated imines − for the aza analogue of these reactions) **int2** formation is likely to be less reversible and may even become non-reversible, which suggests that the development of a general

asymmetric version of the MBH reaction requires the stereocontrol of both key steps, addition to aldehyde and proton transfer.

While high enantioselectivities may have occurred fortuitously for the previously constructed successful catalysts in the past, we now present a sound basis for the design of future catalysts for this important reaction.

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**Supporting Information Available:** Full results on model reaction. Tables with optimized Cartesian coordinates for all species discussed in the text, together with corresponding total energies at the different levels of theory. Complete refs 34 and 35. This material is available free of charge via the Internet at http://pubs.acs.org.

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