DOI: 10.1002/chem.201204006

The Aza-Morita–Baylis–Hillman Reaction: A Mechanistic and Kinetic Study

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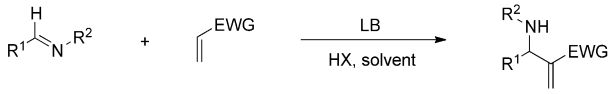
Abstract: The aza-Morita-Baylis–Hillman (aza-MBH) reaction has been studied in a variety of solvents, a selection of imine substrates and with various combinations of PPh_3 and *para*-nitrophenol as the catalyst system. The measured kinetic data indicates that the effects of solvent and protic co-catalyst are strongly interdependent. These results are most easily reconciled with a mechanistic model involving the reversible protonation of zwitterionic intermediates in the catalytic cycle, which is also supported by ^{31}P NMR spectroscopy and quantum chemical studies.

Keywords: kinetics · Lewis bases · NMR spectroscopy · reaction mechanisms · solvent effects · synthetic methods

Introduction

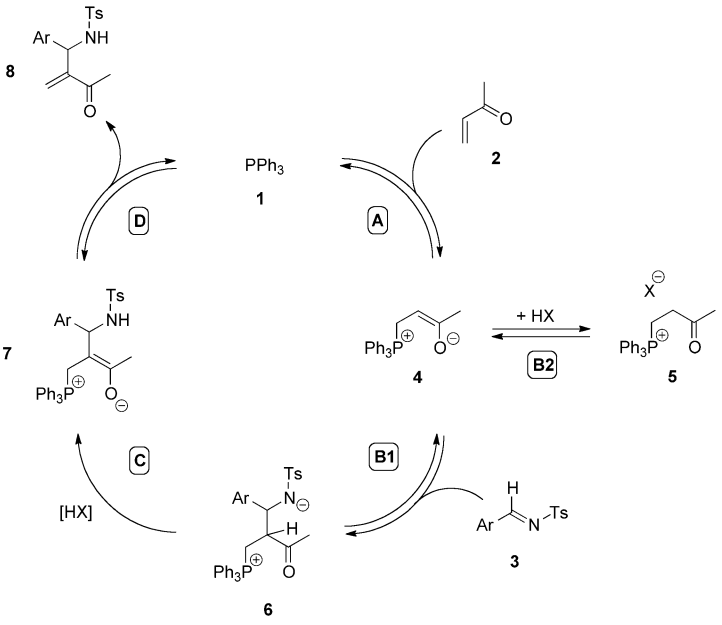
The aza-Morita–Baylis–Hillman (aza-MBH) reaction is a synthetically useful C–C bond-forming reaction involving the coupling of imines with Michael acceptors to highly functionalized amines (Scheme 1).[1]



Scheme 1. The aza-Morita–Baylis–Hillman (aza-MBH) reaction of imines with Michael acceptors. EWG = electron-withdrawing group; LB = Lewis base; HX = protic co-catalyst.

It can be mediated by nucleophilic Lewis bases, mainly including phosphanes and tertiary amines in various solvents.[2] The synergistic action of Lewis bases with Lewis acids or even Brønsted acids is often employed to accelerate the aza-MBH reaction.[3] The asymmetric aza-MBH reaction has been particularly successful with combinations of achiral Lewis bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or trialkyl phosphanes with chiral phenolic additives.[4,5] In some cases these components have been combined into covalently linked bifunctional catalysts providing highly stereoselective substrate turnover.[3d,6,7] Polar and/or protic solvents are known to accelerate MBH reactions, most likely due to the stabilization of zwitterionic intermediates as well as the acceleration of proton-transfer steps involved in the catalytic cycle.[8] Currently available mechanistic studies of the aza-MBH reaction indicate that reactions are first order in the Lewis-base catalyst and the Michael acceptor.[3c,d,4] The reaction is between zero and first order in imine, depending on the catalyst system used and the concentration of the imine itself. These results are readily discussed in terms of the mechanism shown in Scheme 2, here by using PPh_3 (**1**) as the Lewis-base catalyst and methylvinyl ketone (MVK, **2**) as the Michael acceptor in their reaction with tosylminines (**3**) as an example.

Reaction of phosphane catalyst **1** with MVK is here assumed to yield zwitterionic adduct **4** in a first reversible



Scheme 2. General mechanism of the aza-MBH reaction of tosylimines (**3**) with MVK (**2**) and PPh_3 (**1**) as the catalyst.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204006.

step, followed by addition to tosylimine (**3**) to yield a second zwitterionic intermediate **6**. Subsequent intramolecular hydrogen-transfer, often catalyzed by protic co-solvents or co-catalysts, yields zwitterionic enolate **7**. The formation of second zwitterionic enolate **6** and its further transformation to enolate **7** are currently believed to represent the rate-limiting steps under most reaction conditions. This is in analogy to the Morita–Baylis–Hillman (MBH) reaction of aldehydes and Michael acceptors, in which the catalytic activity of protic co-solvents is firmly established.[9–11] Elimination of phosphane **1** to yield the final product **8** is then believed to occur in a reversible manner again. Protic additives may not only accelerate the intramolecular hydrogen-transfer step, but also act as a proton donor towards zwitterionic enolate **4**. The ion-pair intermediate **5** formed in this fashion has been detected spectroscopically by Leitner et al., in which exceedingly acidic additives HX were used as co-catalysts.[3c] Similar observations were also made by Raheem and Jacobsen in the related DABCO-catalyzed aza-MBH reaction.[3d] The very broad range of Lewis bases used in these reactions in combination with an equally broad range of solvents and acidic/protic co-catalysts suggests on first sight that no simple guidelines exist for efficient combinations of catalysts, co-catalysts, and solvents. For the example of triphenylphosphane (PPh_3, **1**) as the Lewis-base catalyst and *para*-nitrophenol (PNP, **9**) as the phenolic co-catalyst we show here that this is mainly due to large solvent effects, which substantially modify the effectiveness of Lewis-base catalysts and protic co-catalysts.

Results and Discussion

First experiments were performed for the reaction of *p*-chlorotosylimine **3a** with MVK by using PPh_3 as the catalyst in various aprotic solvents (Figure 1). For these studies no protic co-catalyst was added. The kinetics of the aza-MBH reaction were in these cases studied by using the decay of imine **3a**. The time/conversion plots can be analyzed using an effective first-order rate law (see the Supporting Information for details).

The reaction rate can thus be characterized by an effective first-order rate constant k_{eff} or, equivalently, by an effective reaction half-life $t_{1/2}$ ($=\ln 2/k_{eff}$). The latter option is particularly helpful as approximate values of the reaction half-life can also be obtained from visual inspection of conversion curves. The effective reaction half-life $t_{1/2}$ as well as the Gutmann acceptor numbers (AN) for the corresponding solvents are collected in Table 1. The reaction proceeds swiftly

Table 1. Reaction half-life $t_{1/2}$ and Gutmann acceptor numbers (AN) for the reactions shown in Figures 1 and 2.

Solvent	AN	$t_{1/2}$ [min]
$CDCl_3$	23.1	38.1 ± 0.1
CD_2Cl_2	20.4	85.4 ± 1.4
$[D_6]$DMSO	19.3	129.1 ± 0.6
$[D_7]$DMF	16.0	189.4 ± 3.1
$[D_8]$THF	8.0	679.6 ± 5.3

in chloroform as the solvent with reaction half-life $t_{1/2}(CDCl_3) = 38.1$ min, whereas the reaction is much slower in THF with $t_{1/2}([D_8]THF) = 679.6$ min. These solvent effects can be correlated with the Lewis acidity of the solvent as quantified by the Gutmann acceptor number AN,[12] which is also known as solvent polarity-polarizability for aprotic solvents (Table 1). The faster reactions observed in chloroform (a solvent with good electron-pair-acceptor ability) as compared with THF are compatible with the formation of (zwitterionic) enolate intermediates and their stabilization through dipole–dipole interactions with the surrounding solvent. A linear relationship between the Gutman acceptor number and reaction rates can be quantitatively expressed as indicated in Figure 2 with a good correlation coefficient. Similar solvent effects are known from other reactions involving anionic intermediates such as the epoxidation of al-

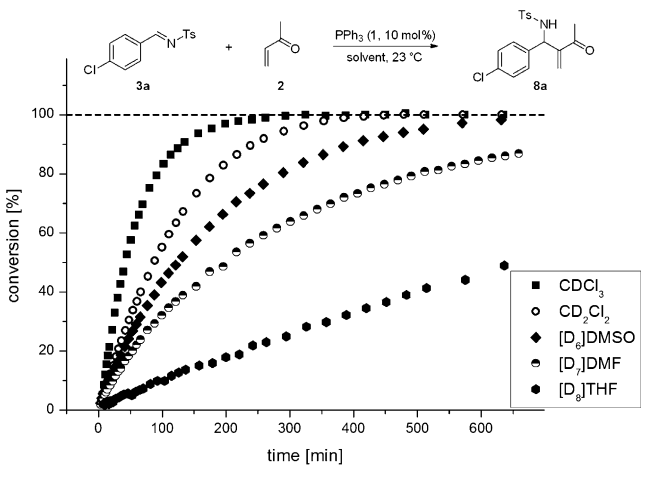


Figure 1. Conversion curves for the aza-MBH reaction of tosylimine **3a** with MVK (**2**) by using PPh_3 (**1**, 10 mol%) as the catalyst in selected solvents.

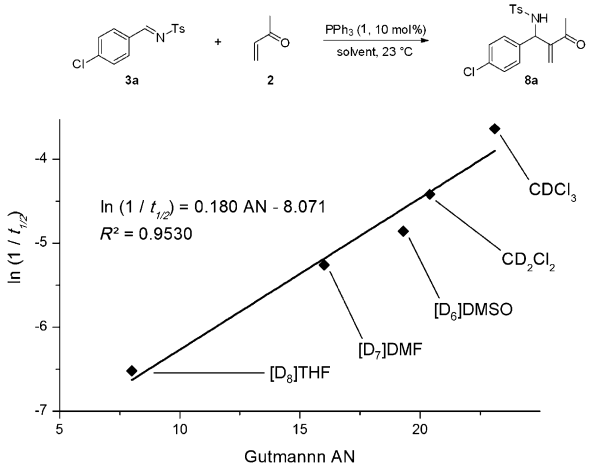


Figure 2. Correlation between Gutman acceptor number (AN) and relative reaction rates for the aza-MBH reaction of tosylimine **3a** with MVK (**2**) by using PPh_3 (**1**, 10 mol%) as the catalyst in selected deuterated solvents.

kenes and the aromatic nucleophilic substitution.[13] At this stage we exclude protic solvents such as CH_3OH, whose mode of action may also involve hydrogen-transfer catalysis (see below). The higher hydrogen-bond-donor abilities of aliphatic alcohols and amides do, however, indicate that the reaction may be even faster in these solvents as compared with chloroform.[15–17]

As a second step in this study we analyze the variation of reaction rate as a function of the imine substitution pattern. To avoid the simultaneous influence of electronic and steric effects we limit ourselves here to variations of the *para* substituent of the imine substrate in chloroform ($CDCl_3$) as the solvent. Conversion curves for imines with electron-withdrawing and electron-donating groups are shown in Figure 3.

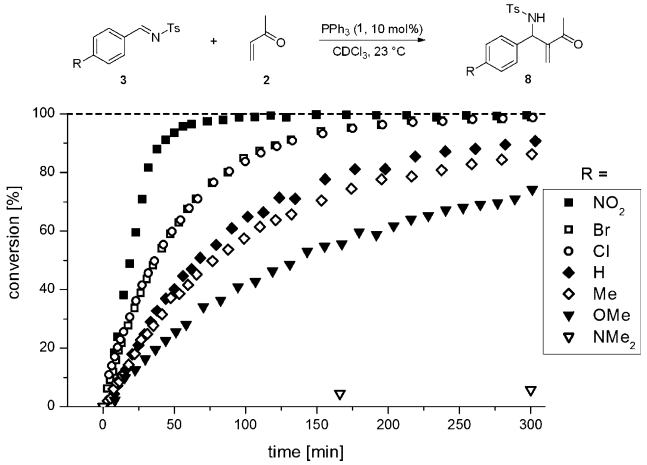


Figure 3. Conversion curves for the aza-MBH reaction of tosylimines with MVK (**2**) by using PPh_3 (**1**, 10 mol%) as the catalyst in $CDCl_3$.

As expected for reactions involving nucleophilic attack on the imine substrate we find here that the reaction rate for X = NO_2/CN is significantly faster than for X = OMe/NMe_2. For all imines the reaction eventually reaches full conversion, except for X = NMe_2 (the substituent with lowest σ_{para} value). For this latter imine the reaction is not only rather sluggish, but also reaches no more than 40% conversion even after extended reaction times.

The influence of the *para* substituent on the reaction rate can most easily be analyzed by the Hammett plot shown in Figure 4. Ignoring the results obtained for R = NMe_2, it is found that reaction rates vary systematically with the electronic nature of the *para* substituent, yielding $\rho = +0.92$ with a correlation coefficient of $R^2 = 0.978$. The ρ value found here is in the mid-range of what is typically found for nucleophilic addition reactions to aldehydes and imines (see ref. [14] for selected examples). The rates measured for R = NMe_2 deviate from this correlation and imply that the reaction becomes partially reversible for this particular system.

With the results for the Lewis-base-catalyzed substrate reaction in hand we can now turn to the effect of protic co-catalysts. The effects of phenols as co-catalysts have repeatedly been studied in the past for synthetic purposes, in particular in cases involving chiral phenols based on the 1,1′-bi-2-naphthol (BINOL) motif. The reaction of *p*-chlorotosylimine **3a** with MVK by using PPh_3 as the catalyst was therefore studied in the presence of *para*-nitrophenol (PNP, **9**) in various concentrations (Figure 5).

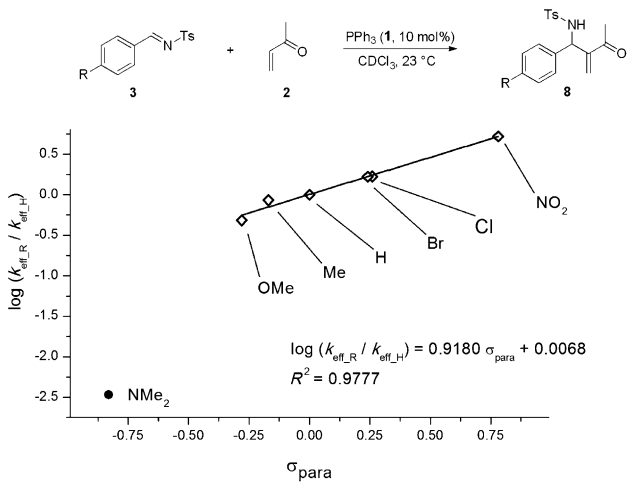


Figure 4. Hammett plot of the aza-MBH reaction of tosylimines with MVK (**2**) by using PPh_3 (**1**, 10 mol%) as the catalyst in $CDCl_3$.

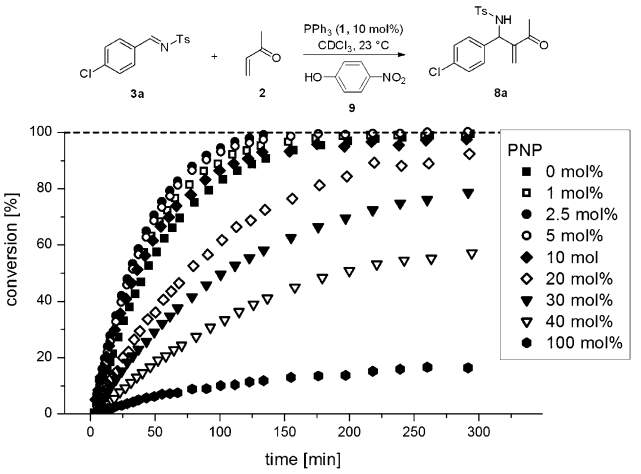


Figure 5. Conversion curves for the PPh_3 (10 mol%)-catalyzed aza-MBH reaction of *p*-chlorotosylimine **3a** with MVK (**2**, 120 mol%) in the presence of various concentrations of PNP (**9**) in $CDCl_3$.

The addition of small amounts of PNP (**9**, 0–10 mol%) are able to accelerate the reaction in $CDCl_3$ by a small margin, whereas higher concentrations are found to slow down the reaction considerably. This is best seen when plotting the reaction half-life $t_{1/2}$ against the phenol concentration as shown in Figure 6. The additional data collected in Table 2 show that the rate deceleration at higher phenol concentrations is quite large. Moreover, the reaction does not yield more than 25% product in the presence of a full equivalent of PNP even after extended reaction times. Repeating this type of measurement for solvents of lower Gutmann acceptor number such as CD_2Cl_2 and [D_8]THF we can observe that the rate acceleration is significantly faster now

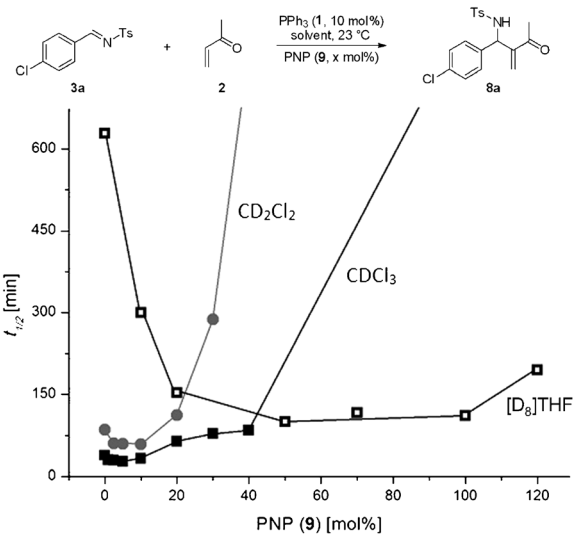


Figure 6. The effect of PNP (**9**) concentration on the relative rates of PPh_3 (10 mol%)-catalyzed aza-MBH reaction of *p*-chlorotosylimine **3a** with MVK (120 mol%) in $CDCl_3$, CD_2Cl_2, or $[D_8]$THF.

Table 2. Reaction half-life $t_{1/2}$ for the aza-MBH reaction shown in Figures 5 and 6.

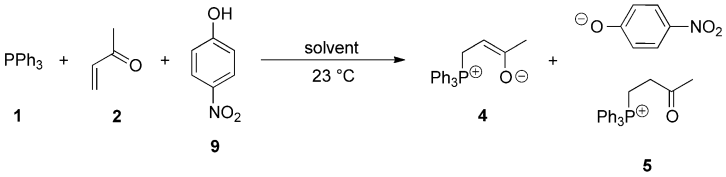
PNP (**9**) (x [mol%])	$t_{1/2}$ [min] in $CDCl_3$	$t_{1/2}$[min] in CD_2Cl_2	$t_{1/2}$[min] in $[D_8]$THF
1	30.0±0.1	nd[a]	nd[a]
2.5	29.0±0.3	60.1±1.0	nd[a]
5	27.1±0.2	59.1±0.9	nd[a]
10	32.1±0.2	58.4±0.8	300.0±3.6
20	63.8±0.9	112.0±2.0	153.7±2.4
30	78.0±0.6	287.6±11.3	nd[a]
40	84.3±1.2	nd[a]	nd[a]
50	nd[a]	191.5±12.0[c]	100.2±1.5
70	nd[a]	nd[a]	116.7±1.2
100	148.1±11.7[b]	77.3±22.9[d]	111.1±1.6
120	nd[a]	nd[a]	195.8±3.4

[a] Not determined. [b–d] Maximum yield of [b] 24, [c] 12, and [d] 7%.

and peaks (for THF) at a much higher concentration as compared with $CDCl_3$.

For THF as a frequently used solvent in asymmetric aza-MBH reactions the effects of added PNP are particularly pronounced with the largest rate enhancements achieved at PNP/imine ratios of around 0.5 to 1.0, which provides a larger window of opportunity for selecting phenolic additives. Similar results were also obtained by Shi et al. by using the combination of PNP and PPh_3 to catalyze the reaction of aldehydes with MVK.[19] To rationalize why PNP influences the reaction rates quite differently in the three solvents selected here, the fate of phosphane-derived species was followed by ^{31}P NMR spectroscopy over the course of the reaction.

Aside from the catalyst signal for PPh_3 at $\delta = -4.7$ ppm, only one additional signal can be detected in the ^{31}P NMR spectrum at $\delta = +25.7$ ppm in the reaction mixture lacking imine **3** (cf., Scheme 3). By using a combination of different



Scheme 3. Reaction of PPh_3 (**1**) with MVK (**2**) and PNP (**9**), lacking imine (**3**).

NMR techniques and theoretical NMR shift calculations it can be shown that this signal corresponds to intermediate **5** and not to the initially formed zwitterionic intermediate **4** or oxidized catalyst $OPPh_3$ (see the Supporting Information for details). This is illustrated in Figure 7 (A–D) with ^{31}P NMR spectra for a sample of pure PPh_3 (A), a sample containing only triphenylphosphane oxide (B), a mixture containing PPh_3 (0.32 M), MVK (3.2 M), and PNP (0.16 M) (C), and the mixture in C but after addition of imine **3a** (0.16 M) (D). In this latter case we expect formation of zwitterionic intermediate **4** as well as the formation of cationic adduct **5** as described in Scheme 3.

The experimentally measured ^{31}P NMR shifts for $OPPh_3$ and **5** of $\delta = +29.5$ and $\delta = +25.7$ ppm are closely matched by theoretical calculations of these species with values of $\delta = +29.6$ and $+26.6$ ppm, respectively. The zwitterionic species **4**, in contrast, is predicted to appear at $\delta =$

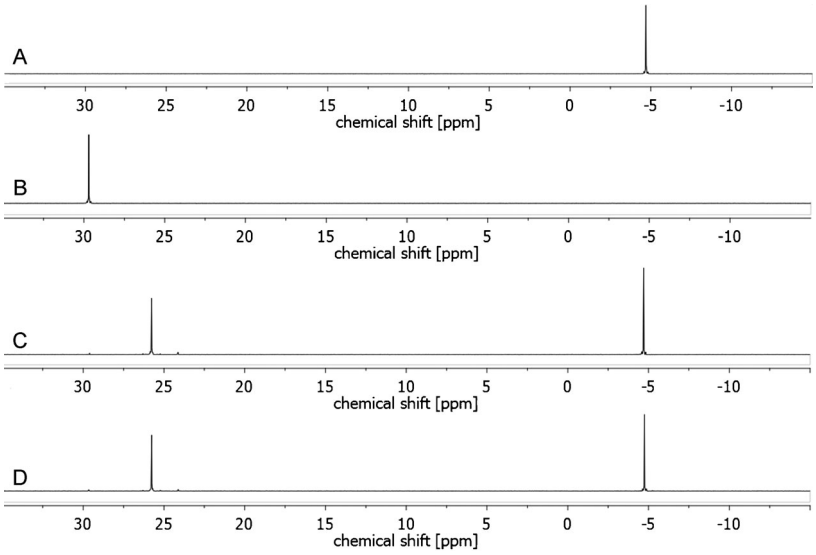


Figure 7. ^{31}P NMR spectra of: A) triphenylphosphane (**1**); B) triphenylphosphane oxide; C) reaction mixture without imine **3a** (containing intermediate **5**); and D) reaction mixture with imine **3a** (containing intermediate **5**).

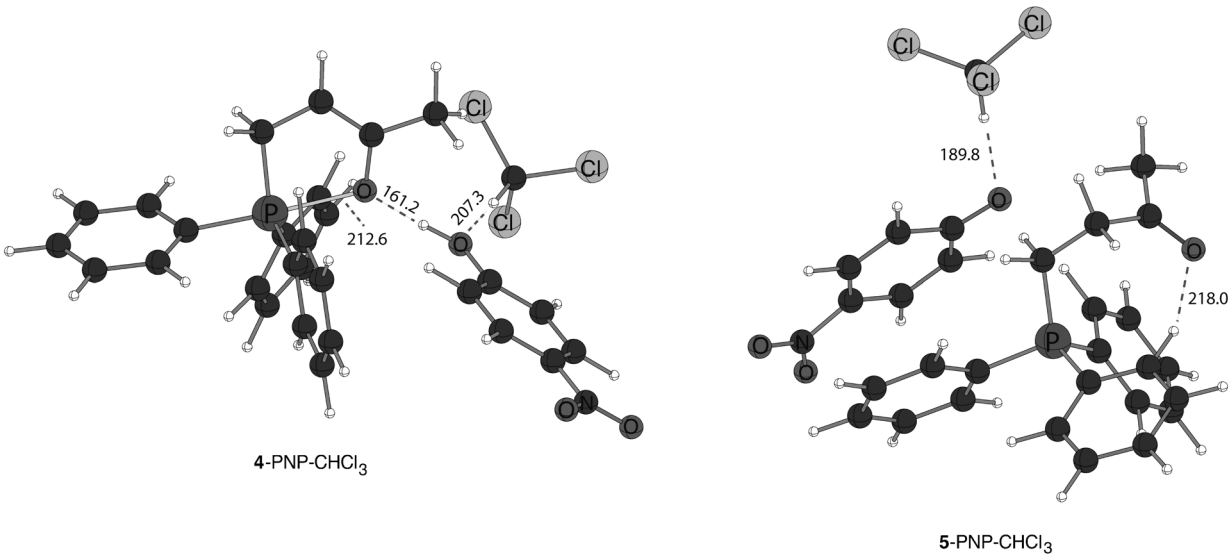


Figure 8. Structures of intermediates **4** and **5** complexed to chloroform and *para*-nitrophenol (**4**) or *para*-nitrophenolate (**5**), as obtained at MPW1K/6-31G(d) level of theory.

−12.0 ppm in the ^{31}P NMR spectrum. Following a computational protocol developed recently for the calculation of ^{31}P NMR spectra in solution, the solute/solvent interactions are here accounted for through the simultaneous presence of one explicit chloroform molecule and a polarizable continuum model (PCM) for bulk solvation effects.[18] In addition, calculations for **5** include *para*-nitrophenolate as the counterion to model an overall neutral ion pair (Figure 8). Calculations for zwitterion **4** are effectively based on the same overall system and thus include *para*-nitrophenol as a neutral complexation partner. In line with the calculated shifts, the structure of protonated intermediate **5** can best be described as a true phosphonium ion, whereas zwitterionic intermediate **4** is located half-way between a tetra- and a pentacoordinated phosphorous atom.

The amount of intermediate **5** formed is strongly dependent on the amount of added PNP and, to a lesser extent, on the solvent used (see the Supporting Information). Addition of 0.5 equiv PNP relative to PPh_3 yields slightly less than 50% of intermediate **5**, whereas after addition of 2 equiv PNP, practically no free catalyst **1** can be detected. This trend is, to a slightly lesser extent, also seen in the other two solvents CD_2Cl_2 and [D_8]THF. The proportion of protonated intermediate **5** is slightly lower in these solvents as compared with $CDCl_3$, but the differences remain rather moderate. Together with measurements at intermediate phenol concentrations (see the Supporting Information) the data shown for $CDCl_3$ in Figure 8 can be fitted to a simple equilibrium model with intermediate **5** and *para*-nitrophenolate anion as the only products by using an equilibrium constant $K=4$ at 300 K (cf., Figure 9). These measurements also indicate that the equilibrium is fully established within minutes after mixing all components.

The pre-equilibrium formation of intermediate **5** is not perturbed in a significant way through the addition of imine substrate **3a**. This was shown by the addition of 50 mol% imine to the mixture used for experiment C in Figure 7, which does not result in any significant change in the signals for catalyst **1** and intermediate **5**, and also leads to no new signals for the equally possible intermediates **6** or **7**.

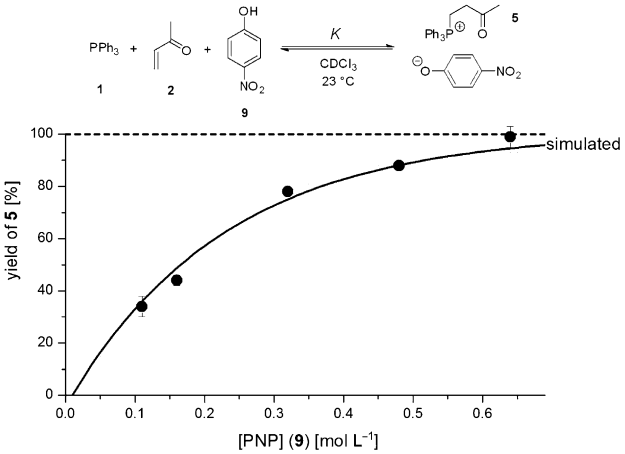


Figure 9. Ratio of protonated intermediate **5** relative to PPh_3 in the reaction shown in Scheme 3 with different amounts of PNP (**9**) in $CDCl_3$.

Taken together these results can best be rationalized assuming rapid pre-equilibrium formation of intermediate **5** through protonation of the zwitterionic adduct **4** with the added PNP co-catalyst (steps **A** and **B2** in Scheme 2). The subsequent reaction of **4** with imine **3** then leads to aza-MBH products in the overall rate-limiting steps **B1** and **C**. Given the only moderate solvent effects on the pre-equilibrium formation of intermediate **5**, the rather large effect of added PNP on the overall reaction rate documented in Figure 6 must be connected to the rate-limiting steps **B1** and **C**. Due to the rather swift overall reactions in the more Lewis-acidic solvent $CDCl_3$ in the absence of PNP we may speculate that added PNP has only a moderate effect on these rate-limiting steps. Addition of larger amounts of PNP

thus reduces the reaction rates through the conversion of most of the catalyst **1** to the more stable intermediate **5**. This differs from the situation in [D_8]THF, in which the pre-equilibrium formation of intermediate **5** also offers no advantage for the overall reaction, but where the catalytic effects of PNP on the rate-limiting steps **B1**/**C** is much more pronounced. Results obtained by Shi et al.,[7b,c] Jacobsen et al.,[3d] and Sasai et al.[6a] in stereoselective aza-MBH reactions promoted by phenol-containing bifunctional catalysts are also in line with this mechanistic model. The highest stereoselectivities in these studies were found in apolar media such as ethers or ether/hydrocarbon mixtures, whereas the results obtained in chloroform or CH_2Cl_2 were rather disappointing. This also implies that catalyst/co-catalyst systems optimized for one particular organic solvent will not necessarily be effective in other reaction media.

Experimental Section

General procedure for the kinetic measurement of aza-MBH reactions: Stock solution A (0.5 mL, prepared from MKV (0.9 mmol), tosylimine (0.75 mmol), and trimethoxybenzene as an internal standard (0.2 mmol) in $CDCl_3$ (5 mL) and stock solution B (0.1 mL, prepared from the catalyst PPh_3 (0.1875 mmol) in $CDCl_3$ (5 mL)) were mixed in an NMR tube under a nitrogen atmosphere. The reaction was then followed by monitoring the disappearance of the tosylimine signals by using ^{1}H NMR spectroscopy. The actual conversion data were obtained by using the signals of trimethoxybenzene as an internal reference.

Acknowledgements

These studies were supported through a CSC fellowship to Y.L. Further financial support has been provided by the deutsche Forschungsgemeinschaft (DFGZI 436/12–1) and the Sino-German Program.

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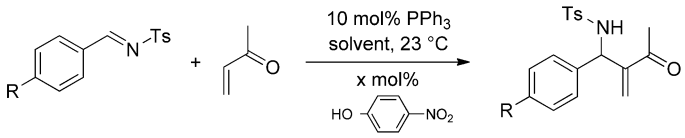
Received: November 8, 2012
Revised: February 10, 2013
Published online: ■■ ▮▮, 2013



Examining the aza-MBH: The aza-Morita–Baylis–Hillman (aza-MBH) reaction has been studied in a variety of solvents, with a selection of imine substrates, and with various combinations of PPh_3 and *para*-nitrophenol as the catalyst system (see scheme). The measured kinetic data indicates that the effects of solvent and protic co-catalyst are strongly interdependent. ^{31}P NMR spectroscopy and quantum chemical studies support a mechanistic model that involves the reversible protonation of zwitterionic intermediates in the catalytic cycle.

Reaction Mechanisms