ORGANIC LETTERS

2010
Vol. 12, No. 21
4800−4803

Pyridylalanine (Pal)-Peptide Catalyzed Enantioselective Allenoate Additions to *N*-Acyl Imines Proceed via an Atypical "aza-Morita−Baylis−Hillman" Mechanism

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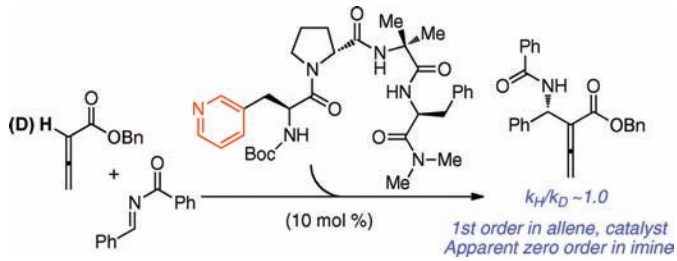
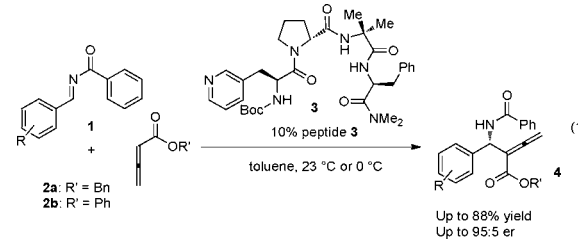
Received August 17, 2010

ABSTRACT



Mechanistic experiments, including kinetics and hydrogen/deuterium kinetic isotope effects, reveal an "atypical" rate-determining step in a pyridylalanine-peptide catalyzed enantioselective coupling of allenoates and *N*-acyl imines. Typically, acrylates participate in both the aldehyde-based "Morita−Baylis−Hillman (MBH)" reaction and the imine-based variant (the "aza-MBH") through similar mechanisms, with proton transfer/catalyst regeneration often rate-determining. In contrast, the title reaction exhibits kinetics wherein proton transfer is kinetically silent.

We recently reported a peptide-catalyzed enantioselective coupling of *N*-acyl imines **1** with allenic esters **2** (eq 1).[1] The reaction is catalyzed by peptide **3**, containing a Lewis basic pyridylalanine residue, and affords allene-substituted amides such as **4** in high yield and enantiomeric ratio (er). This transformation may be considered an allenoate aza-Morita−Baylis−Hillman (aza-MBH) reaction.[2]



The MBH reaction is a process that couples activated olefins with aldehydes, often using a Lewis basic catalyst,[3] typically an amine or phosphine.[4] It has attracted considerable attention, especially as a platform for asymmetric catalysis, and many examples have been reported.[5] Insight into the mechanism of the MBH reaction has been gleaned through detailed experimental and computational work.[6] For example,

(1) (a) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105. (b) For a report on the DABCO catalyzed coupling of allenoates with *N*-Boc imines, see: Guan, X.-Y.; Wei, Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 6343.

(2) For reviews on the aza-MBH reaction, see: (a) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev* **2009**, *109*, 1. (b) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.

(3) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

10.1021/ol101947s
Published on Web 09/28/2010

McQuade and Aggarwal independently showed that, in the absence of protic additives, certain MBH reactions are first order in an amine catalyst and in acrylate, but second order in aldehyde.[7] It is proposed that the second equivalent of aldehyde assists in the proton transfer step that follows carbon−carbon bond formation (Figure 1). It has also been

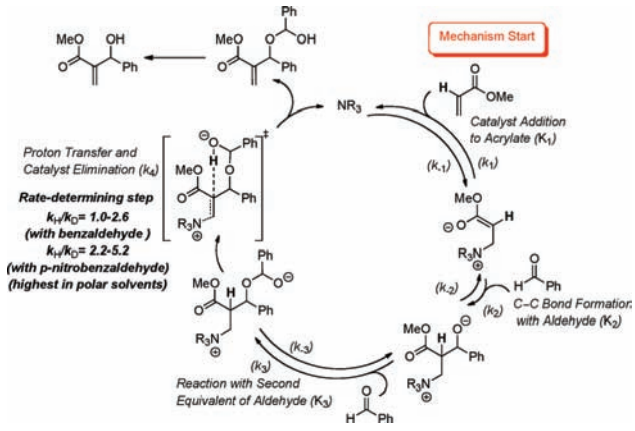


Figure 1. Proposed catalytic cycle for the MBH reaction in the absence of protic additives as reported by McQuade and Aggarwal. Quoted KIEs are for the acrylate α-proton (bold).

established that MBH reactions tend to show primary kinetic isotope effects (KIEs) for the α-proton of the acrylate or activated olefin, which supports proton transfer as being the rate-determining step in the reaction mechanism. However, the magnitude of the KIE may depend on the exact nature of the substrates, in addition to the polarity of the solvent (k_H/k_D = 1.0−5.2).[6]

Kinetic studies on the aza-MBH reaction by Jacobsen[8a] and by Leitner[8b] have also raised intriguing mechanistic proposals. These reactions were found to be first order in catalyst and in acrylate, which is in strong analogy to the classical MBH reaction. However, the reactions involved imines that either show rate saturation[8a] or exhibit a kinetic order of 0.5.[8b] Nevertheless, for these aza-MBH reactions, the proton transfer step has also been shown to be unambiguously rate-determining, in analogy to many MBH reactions involving aldehydes (Figure 2). A key piece of evidence in support of this finding is that the diazabicyclo[2.2.2]octane (DABCO) catalyzed aza-MBH

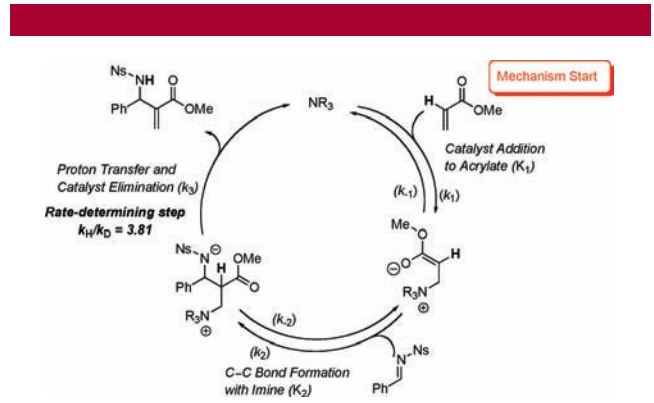


Figure 2. Proposed catalytic cycle for the aza-MBH reaction as reported by Jacobsen. The quoted KIE, with xylenes as the reaction solvent, is for the acrylate α-proton (bold).

reaction with methyl acrylate and *N*-nosyl imines displays a large primary KIE with k_H/k_D = 3.81, even in the relatively nonpolar solvent of xylenes.[8a]

Because of the complexity and lack of mechanistic generality of such reactions, we were interested to determine the kinetic parameters of the allenoate-imine coupling reaction. We report here that the allenoate aza-MBH reactions we have studied exhibit unique kinetic parameters and a mechanistic pathway that is distinct from several other aza-MBH reactions that have been previously studied.

We first carried out a series of rate studies employing allenoate **2a**, *N*-acyl imine **1** (R = H), and catalyst **3**. The kinetic order of each component was determined by constructing plots of k_{obs} versus concentration (Figures 3, 4).[9] The allenoate and catalyst plots each show a good linear correlation between the initial rate constant and the substrate or catalyst concentration, respectively (Figure 3). In addition, when the data are fit to a power curve, the exponent in each case is approximately equal to 1 (Table 1). We therefore conclude that the reaction is first order in allenoate and first order in peptide under the conditions we examined.

On the other hand, the plot of k_{obs} versus imine concentration shows essentially a constant reaction rate for all of the imine concentrations evaluated (0.01−0.15 M).[10] This implies that the reaction could be zero order in imine. The kinetic order of the imine electrophile in this reaction is unusual in comparison to that observed for most other aza-MBH reactions[8] and in comparison to the aldehyde-based classical MBH.[6] Only recently have examples of aza-MBH processes been documented in which the imine is not found to factor into the rate-determining step.[11] Our observations suggest that the peptide-catalyzed allenoate variant follows this "atypical" or at least more recently documented pathway.

One explanation for the apparent zero order dependency of the reaction on imine concentration is the possibility of

(4) For reviews on the MBH reaction, see: (a) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(5) For a review, see: Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614.

(6) (a) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, *3*, 285. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980. (c) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147. (d) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706. (e) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513.

(7) In the presence of protic additives, the reaction becomes first order in aldehyde. See refs 6d and 6e.

(8) (a) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (b) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762.

(9) For reaction rate plots at the various concentrations, see Supporting Information.

(10) The imine concentration was not raised above 0.15 M due to its insolubility in toluene at higher concentrations. The slightly lower value of the rate constant at 0.15 M may be due to solubility issues.

(11) The following case exhibits similar kinetics, in the presence of protic additives. See: Yukawa, T.; Seelig, B.; Morimoto, H.; Matsunaga, S.; Berkessel, A.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 11988.

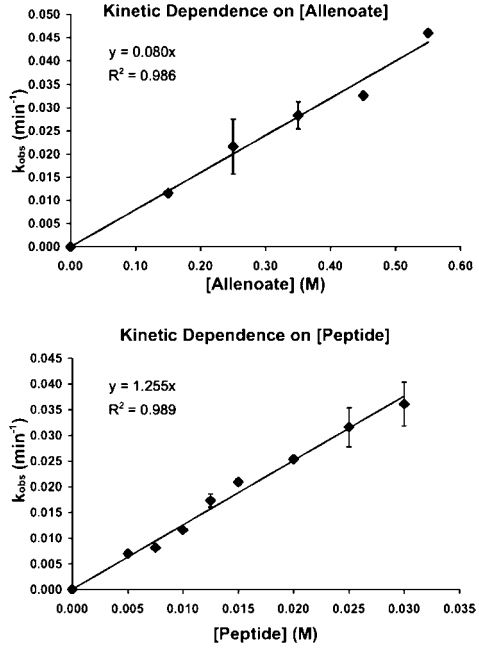


Figure 3. Kinetic order plots. (Top) Initial observed rate constant versus concentration of allenoate **2a**. Concentration of imine **1** was maintained at 0.10 M. Concentration of peptide **3** was maintained at 0.01 M. (Bottom) Initial observed rate constant versus concentration of peptide **3**. Concentration of allenoate **2a** was maintained at 0.15 M. Concentration of imine **1** was maintained at 0.10 M. All values of k_{obs} were measured by plotting the relative product formation (ratio of **4a** to 2,3-dimethylnaphthalene, the internal standard) with values $\leq$0.20 versus time at the specific concentrations of allenoate or peptide, respectively.[10] Linear fit equations and correlation constants are included. The $\pm$ error bar for each value of k_{obs} is equal to the corresponding standard deviation from the multiple trials.

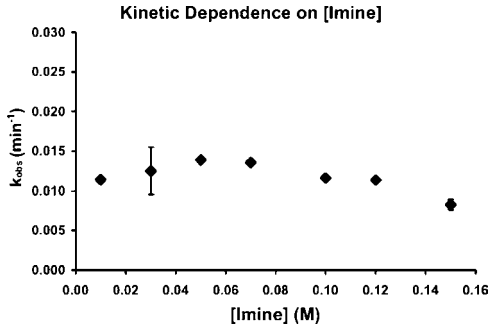


Figure 4. Kinetic order plot. Initial observed rate constant versus concentration of imine **1**. Concentration of allenoate **2a** was maintained at 0.15 M. Concentration of peptide **3** was maintained at 0.01 M. See Figure 3 legend and Supporting Information for additional details.

mesauring rates at catalyst saturation by the imine. Our experiments do not exclude this possibility. However, ^{1}H NMR spectra of the comixed catalyst and imine reveal minimal $\Delta\delta$ (0 to <0.05 ppm; relative to the independent spectra) for proton resonances at concentrations relevant to the reaction conditions. On the other hand, rate competition experiments with electronically perturbed imines reveal that a *p*-bromo-substituted imine is consumed faster than a *p*-methoxy-substituted imine (*p*-Br ~3 times faster than *p*-OMe). This result could be consistent with saturation by the imine, albeit at a quite low imine concentration.

Table 1. Kinetic Order of Allenoate and Peptide[a]

compound	kinetic order	linear fit correlation constant	exponent in power fit (correlation constant)
2a	1	0.985	0.998 (0.982)
3	1	0.989	0.993 (0.976)

[a] Linear and power fits as well as correlation constants were calculated using the trendline feature on Microsoft Excel. See Supporting Information section for plots with power trendlines.

We also explored isotope effects in the allenoate-imine coupling reaction. In particular, we probed the allenoate α-proton in order to establish any KIE. Intriguingly, and in contrast to the previously studied aza-MBH reactions discussed above,[8] k_H/k_D for the allenoate α-proton was 1.08 (Table 2).[12] This small KIE implies that the proton transfer step is not likely to be rate-determining.

Table 2. KIEs for Allenoate α-Proton[a]

parameter	average value	trial 1	trial 2	trial 3	SD
k_H (min^{-1})	0.0129	0.0119	0.0131	0.0137	0.000917
k_D (min^{-1})	0.0119	0.0110	0.0123	0.0125	0.000814
k_H/k_D	1.08	1.08	1.07	1.10	0.0155

[a] For each trial, the protio- and deutero-allenoate reactions were run simultaneously to minimize variables such as minor changes in temperature or humidity. The average value of k_H/k_D is taken as the overall KIE for the allenoate α-proton.

On the basis of the results described above, the rate equation for the allenoate aza-MBH reaction could be represented simplistically by eq 2 within the concentration range of our measurements.

$$d[P]/dt = k_{obs}[\text{allenoate}][\text{peptide}] \quad (2)$$

A possible mechanism for the allenoate aza-MBH reaction is shown in Figure 5. Peptide **3** first adds to allenoate **2a** to form zwitterionic intermediate **I**. Since the kinetic data support the absence of the imine in the rate-determining step, the catalyst addition to the allenoate could be rate-determining, in accord with eq 2. Intermediate **I** then adds to imine **1** to form a new C−C bond and intermediate **II**. The next step involves a fast proton transfer to form zwitterionic intermediate **III**, which then eliminates the catalyst to form coupled product **4a**. In the case where there could be saturation of the catalyst by imine, C−C bond formation could be rate-determining, with the reaction pseudo-zero

(12) For individual reaction rate plots for each trial and the procedure for the preparation of allenoate **2a-D**, see Supporting Information.

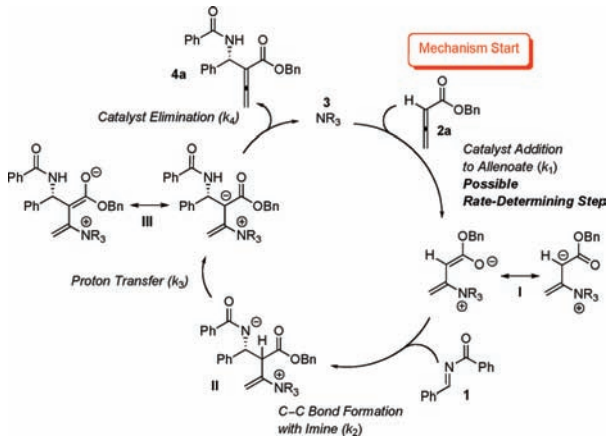


Figure 5. Possible mechanism for the allenoate-imine coupling.

order in imine. Nonetheless, in either case, it appears that neither proton transfer nor catalyst regeneration are rate-determining.

The difference in the rate-determining step of the allenoate aza-MBH versus other acrylate aza-MBH[8a] reactions is notable, especially considering that the reactions were conducted in similar solvents (toluene vs xylenes; no protic additives). These analogies imply that the nature of the allenoate, the catalyst, or a combination of factors could cause the mechanistic dichotomy. One proposal for the relative ease in proton transfer in the allenoate reaction, as compared to the acrylate reaction, is that intermediate **III** (Figure 5), formed upon proton transfer, contains a resonance stabilized allylic anion in the formal zwitterionic species.[13] The analogous intermediate in an acrylate-based aza-MBH reaction is not allylic. The allylic nature could stabilize intermediate **III** relative to intermediate **II**, lowering the activation energy associated with proton transfer, and therefore make this step substantially faster in the allenoate reaction.

We wished to further establish if the alternative mechanism is due to the nature of the pyridyl moiety of the catalyst (e.g., in comparison to DABCO), the peptide-based functionality, or the nature of the allenoate. Therefore, we ran an analogous KIE study with pyridine as the catalyst, rather than peptide **3**. It was found that the k_H/k_D for the allenoate α-proton was 1.03 (Table 3), nearly identical to that observed with peptide-catalyst **3**.[12] As in the **3**-catalyzed reaction, this

(13) For a discussion of related P-initiated zwitterions, see: Khong, S. N.; Tran, Y. S.; Kwon, O. *Tetrahedron* **2010**, *66*, 4760, references therein.

Table 3. KIEs for Allenoate α-Proton with Pyridine Catalyst[a]

parameter	average value	trial 1	trial 2	SD
k_H (min^{-1})	0.00099	0.00097	0.00102	0.000035
k_D (min^{-1})	0.00096	0.00096	0.00097	0.0000071
k_H/k_D	1.03	1.01	1.05	0.028

[a] See Table 2 legend and Supporting Information for details.

lack of a primary KIE supports the assertion that a step other than proton transfer is rate-determining in the pyridine-catalyzed case. Moreover, the pyridine-catalyzed reaction is significantly slower than the peptide-catalyzed variant, indicating that the peptide may be better able to activate the substrate. This fact also suggests that pyridine and the Pal-based catalysts may themselves function through different mechanisms, with different rate-determining steps.

The exclusion of the proton transfer step as rate-determining brings new insight to some of our previously discovered empirical observations. For example, a decrease in temperature (from 23 to 0 °C) leads to slower reactions. However, with allenoate **2b**, where the benzyl ester has been changed to a phenyl ester, the rate is significantly faster such that high yields of product are obtained in only 1 h at 0 °C.[1a] Since **2b** may contain a more electrophilic sp-hybridized carbon than that of benzyl ester **2a**, catalyst addition could be faster with **2b** than with **2a**. These rate differences could be consistent with catalyst addition being the rate-determining step.

In summary, we have determined that the allenoate aza-MBH follows a divergent mechanism in comparison to several other MBH and aza-MBH reactions. Our experiments are consistent with an alternative rate-determining step in which events prior to proton transfer appear to be the bottleneck in these reactions. The nature of the zwitterionic intermediates, with possible electronic delocalization due to the presence of the allenoate, in addition to other factors, could contribute to this behavior.

Acknowledgment. We are grateful to the National Science Foundation (CHE-0848224) for support. We thank Professor Kenneth B. Wiberg (Yale University) and Professor Seth Herzon (Yale University) for discussions.

Supporting Information Available: Kinetic procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101947S