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A New Interpretation of the Baylis−Hillman Mechanism

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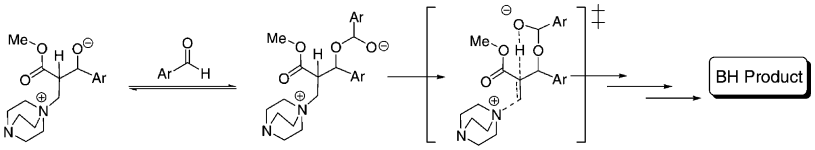


On the basis of reaction rate data, we have proposed a new mechanism for the Baylis−Hillman reaction involving the formation of a hemiacetal intermediate. We have determined that the rate-determining step is second order in aldehyde and first order in DABCO and acrylate. We have shown that this mechanism is general to aryl aldehydes under polar, nonpolar, and protic conditions using both rate data and two isotope effect experiments.

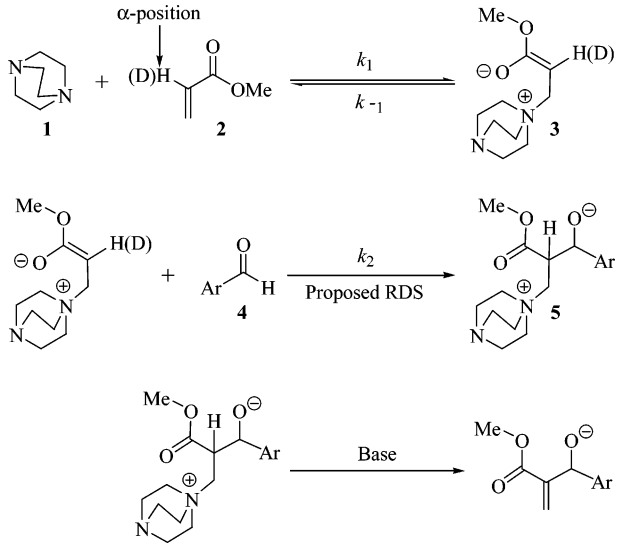
The Baylis−Hillman (BH) reaction, also known as the Morita−Baylis−Hillman reaction,[1] is an attractive method for forming carbon−carbon bonds and yields highly functionalized products with a new stereocenter.[2−4] The reaction became popular in the early 1980s with the first application to synthesis,[5] the first "arrow-pushing" mechanism,[6] and the first physical organic studies.[7] Since these original reports, the reaction has spawned an immense body of literature. One exemplar of the reaction's utility is Pfizer's ∼40-kg synthesis of *tert*-butyl 2-(hydroxymethyl)propenoate, a key intermediate en route to the Zn-metalloprotease inhibitor Sampatrilat.[8]

The significance of the BH reaction has prompted a number of mechanistic investigations. These studies provide some insight into the reaction, but leave many unanswered questions. On the basis of pressure dependence, rate, and kinetic isotope effect (KIE) data, Hill and Isaacs, using acrylonitrile,[7,9] suggested a mechanism similar to that in Scheme 1. The focus of their work was the pressure dependence of the BH reaction and, as such, they did not provide experimental or graphical information concerning the rate data. The authors observed a KIE of 1.03 ± 0.1 for the α-position, from which they concluded that no α-proton cleavage occurs in the rate-determining step (RDS).[9] Later, Bode and Kaye, using acrylates, supported the Hill and Isaacs mechanism (Scheme 1) with rate data and a rate law (eq 1).[10] Even

$$\text{rate} = K_1 k_2 [\mathbf{1}][\mathbf{2}][\mathbf{4}] \qquad (1)$$

with these mechanistic studies, a number of observations

SCHEME 1. The Published Baylis−Hillman Mechanism



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SCHEME 2. Dioxanone Baylis–Hillman Product

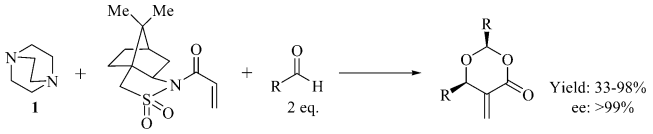
appear in the literature—including slow reaction rates,[2] dioxanone formation,[11–13] difficulty controlling stereochemistry,[3] autocatalysis,[14] and rate acceleration with protic additives[15–19]—that cannot be fully explained.

BH reactions are often sluggish, and methods to increase the reaction rate are numerous.[2] If eq 1 was valid, the reaction merely being third order does not explain why typical BH reactions are slow. Many third-order reactions are fast, including the Mitsunobu, Aldol-Tischencko, and Pd cross-coupling reactions. In general, electron-poor aldehydes and acrylates tend to provide faster reactions.[2] Even in cases in which additives are reported to accelerate the rate, the reaction still takes many hours to days to complete. For example, lanthanide salts in combination with triethanolamine are known to accelerate the reaction.[20] This method works well with *p*-nitrobenzaldehyde (pNBA) and methyl acrylate, yielding 90% product in 3 h, but it takes considerably longer with electron-rich anisaldehyde (2 days, 65%) and cyclohexanecarboxaldehyde (5 days, 37%).[21]

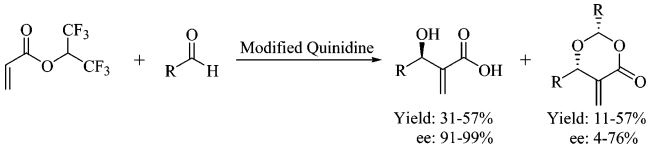
In addition to normal acyclic products, the BH reaction yields a dioxanone byproduct for which the published mechanism offers no clear explanation. This byproduct was first reported in 1990 by Drewes et al. and typically results when the acrylate ester is a reasonable leaving group and the aldehyde concentration is high (Scheme 2).[12,13,22]

Dioxanone formation was, surprisingly, an essential part of most successful asymmetric BH reactions. Given the published mechanism, the BH reaction should respond similarly to an aldol reaction.[23] In practice, however, chiral auxiliaries provide poor enantioselectivities except when dioxanones are the sole product.[4] For example, Leahy demonstrated high enantioselectivity using Oppolzer's sultam, as depicted in Scheme 3.[24] In this case, the reaction produced only the dioxanone, with both good yield and high enantioselectivity.

SCHEME 3. Leahy's Enantioselective Baylis–Hillman Reaction



SCHEME 4. Hatakeyama's Dioxanone Kinetic Resolution



The dioxanone diastereomer was also present in the few cases in which optically active Lewis bases provided high enantiomeric excess. Hatakeyama reported a modified quinidine that provided modest yields of nearly optically pure BH products.[25] As shown in Scheme 4, a significant fraction of the byproduct was the other enantiomer trapped as a dioxanone, so in essence the reaction was a kinetic resolution. Hatakeyama's example contrasts the many chiral Lewis bases that provide only modest enantioselectivity.[3]

The only example of a highly enantioselective BH reaction that does not rely on dioxanone formation uses an optically active 1,1′-bi-2-naphthol (BINOL). Schaus demonstrated that a modified BINOL catalyst in tandem with triethyl phosphine could react with 2-cyclohexenone and a range of aldehydes to provide BH products with high enantioselectivity.[26] Using the old mechanism, the authors suggested that the BINOL interacts with intermediate **3**, thus controlling the face of the enolate attacked by the aldehyde.

The BINOL catalysis is related to the observation that protic solvents accelerate BH reactions. Early on, 3-hydroxyquinuclidine (3-Hq) was found to be a more active catalyst than diazabicyclo[2.2.2]octane (DABCO).[10,27–29] The activity of 3-Hq was attributed to the formation of a 3-Hq-enolate hydrogen bond. Later, a number of groups reported that other protic additives such as ethylene glycol, formamide, and water also accelerate the reaction.[9,15] Auge suggested that the acceleration was due to stabilization of the 1,2 addition (k_2) or an increase in K_1

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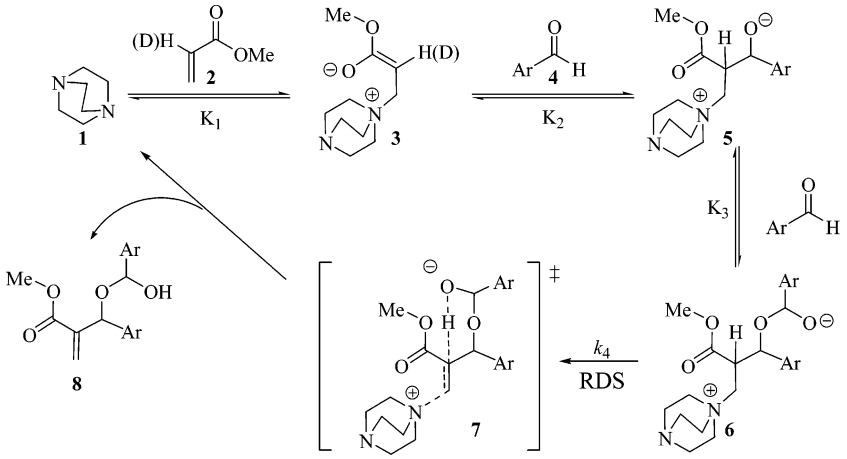
SCHEME 5. A New Mechanism for the Baylis–Hillman Reaction



(k_1/k_{-1}) (Scheme 1). Later, more thorough reports by Aggarwal, Hu, and Tang confirmed the acceleration of the BH reaction with solvent/water mixtures.[17–19] Despite many hypotheses for each of these phenomena, no current model can explain them all.

Recently, using *p*-nitrobenzaldehyde (pNBA) and methyl acrylate as substrates, we showed with rate and isotope data that the BH reaction is second order in aldehyde and that the α-position C–H bond breaks in the RDS.[30] On the basis of this order information, we altered the mechanism to include the second equivalent of aldehyde (Scheme 5). This mechanism features all of the intermediates previously proposed (and recently observed with mass spectroscopy)[31] but now includes the formation of a hemiacetal that subsequently goes on to eliminate DABCO in the RDS. The mechanism is bolstered by a primary KIE at the α-position and a large inverse secondary isotope effect at the aldehyde proton of pNBA. In this full paper, we expand the number and type of substrates studied. We also report the mechanism in protic solvents. Finally, we discuss how this new mechanism elucidates some of the unexplained nuances of BH chemistry.

Results

Order plots for each substrate were constructed with rate data collected by using the method of initial rates.[32] Each substrate/solvent combination studied was first order in acrylate and DABCO, but second order in aldehyde (Table 1). Previously, we found that DMSO significantly accelerates the rate of the BH reaction. We collected order plots using constant DMSO concentration to avoid any solvent-based changes in rate. DMSO concentration was held constant by using a small variable amount of THF to compensate for volume changes due to reagent concentration. To juxtapose the polar DMSO cases, order plots were also collected in THF. The 4-pyridinecarboxaldehyde (PYR) order plots featured in Figure 1 are representative of all order plots (see the Supporting Information for remaining plots).

TABLE 1. Aldehyde Order for Different Substrates Run in DMSO or THF

aldehyde[a]	solvent	aldehyde order
BA	DMSO	2.4
BA	THF	2.2
PYR	DMSO	1.9
PYR	THF	1.9
pNBA	DMSO	1.9
pNBA	THF	1.8

[a] BA = benzaldehyde; PYR = 4-pyridinecarboxaldehyde; pNBA = 4-nitrobenzaldehyde.

Using pNBA, we also examined the mechanism of the BH reaction in a series of protic conditions. The aldehyde shows a second-order dependence for each protic condition tested: THF/water, THF/formamide, and THF/methanol (Table 2). In addition, we examined the order in water, formamide, and methanol. We found that the order in each solvent was first order, but all displayed saturation at high concentration (Figure 2). In the case of water, the asymptote coincided with reagent insolubility. Methanol exhibits saturation at much lower concentration compared to formamide and water and showed the smallest rate enhancement. As such, we explored the potential of a methanol–aldehyde preequilibrium. NMR inspection of a solution of MeOH and pNBA reveals a significant hemiacetal concentration. We also compared the relative rates of pNBA reacting with methyl acrylate in DMSO, THF, THF/water, THF/formamide, and THF/methanol. As shown in Table 2, DMSO provided the fastest rate followed by THF/formamide.

To support the order results, we collected isotope effect data for both the α-position of methyl acrylate and the aldehyde proton (Table 3). All of the reactions run in DMSO show clear primary KIEs. Reactions run with pNBA show primary KIEs for all conditions. Unlike pNBA, the other substrates show KIEs between 1 and 2 in solvents other than DMSO. For the aldehyde proton, all reactions show large inverse secondary KIEs. To ensure that the α-position cleavage was still taking place when protic solvents were used, we measured the KIE in 2.75 M water in THF and found the value to be primary (2.07 ± 0.3). In addition to the KIE data, Table 3 contains relative rate data for each aldehyde in multiple solvents as well as a comparison of the entire data set.

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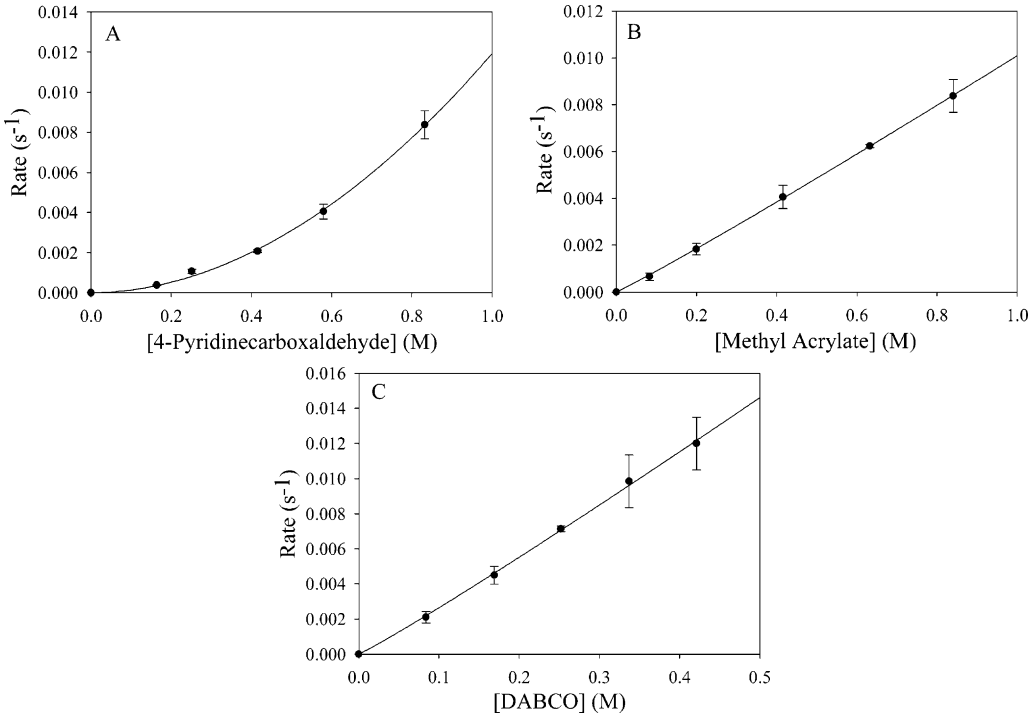


FIGURE 1. Order plots for reaction of 4-pyridinecarboxaldehyde, methyl acrylate, and DABCO in DMSO. (A) Rate as a function of 4-pyridinecarboxaldehyde; (B) rate as a function of methyl acrylate; and (C) rate as a function of DABCO. For raw data and plot fits, see the Supporting Information.

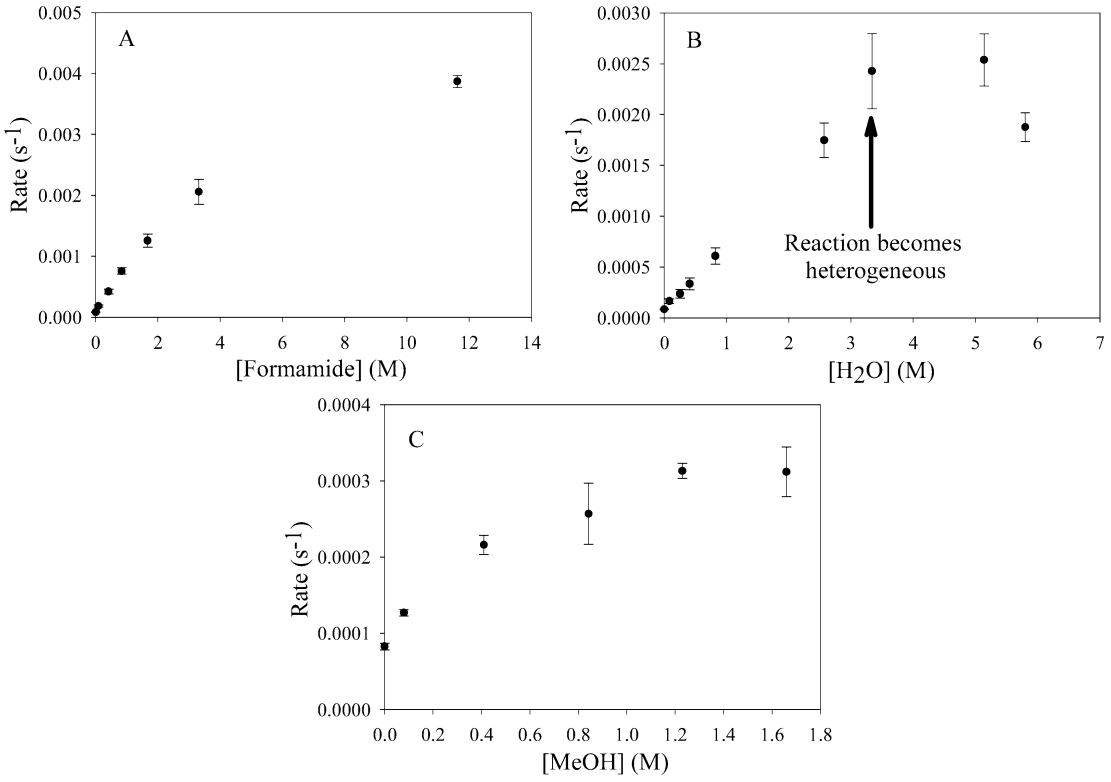


FIGURE 2. Order plots for reaction of *p*-nitrobenzaldehyde, methyl acrylate, and DABCO in THF with various protic additives. (A) Rate as a function of formamide; (B) rate as a function of water (the asymptote coincides with reagent precipitation); and (C) rate as a function of methanol.

For reference, two solvent polarity scales are also featured.

The rate law was derived by using either the steady-state approximation (SSA) or the equilibrium approximation. The equations describing each intermediate's concentration were derived by hand according to the reaction mechanism in Scheme 5 and then solved with Mathematica v. 5.0. The rate law derived by using the SSA,

TABLE 2. A Comparison of Relative Rates and Solvent Conditions for Reactions of pNBA, DABCO, and Methyl Acrylate

solvent[a]	protic additive	[protic] (M)	k_{rel}	order in pNBA
DMSO	N/A	0	49	1.9
THF	N/A	0	1	1.8
THF	H_2O	0.083	7	2.0
THF	H_2O	5.13	31	1.4[b]
THF	formamide	0.84	9	1.8
THF	formamide	11.62	47	2.0
THF	methanol	0.84	3	N/A
THF	methanol	1.7	4	N/A

[a] All reactions were run under general kinetics conditions (see the Experimental Methods section). [b] The intermediate order is due to aldehyde insolubility (see the Supporting Information for more details).

TABLE 3. Kinetic Isotope Data for Both α-Position Labeled Methyl Acrylate and Labeled Aldehydes for Reactions Run in Different Solvents

aldehyde[a]	solvent	k_H/k_D (α)	k_H/k_D (ald)	k_{rel}[b]	k_{rel}[c]	$E_T(30)$	ϵ[d]
BA	DMSO	2.6 ± 0.1	0.73 ± 0.05	7	7	45	47
BA	THF	1.0 ± 0.1	0.78 ± 0.10	1	1	37	8
BA	$CHCl_3$	1.2 ± 0.1	0.69 ± 0.09	2	2	39	5
PYR	DMSO	2.0 ± 0.2	N/A	54	9969	45	47
PYR	MeCN	2.1 ± 0.1	N/A	10	1814	46	37
PYR	$CHCl_3$	1.4 ± 0.1	N/A	1	184	39	5
pNBA	DMSO	5.2 ± 0.6	0.75 ± 0.05	36	4269	45	47
pNBA	MeCN	4.2 ± 0.1	N/A	7	877	46	37
pNBA	DMF	2.9 ± 0.2	N/A	10	1197	43	38
pNBA	THF	2.4 ± 0.1	0.80 ± 0.07	2	184	37	8
pNBA	$CHCl_3$	2.2 ± 0.2	0.72 ± 0.03	1	120	39	5

[a] BA = benzaldehyde; PYR = 4-pyridinecarboxaldehyde; pNBA = 4-nitrobenzaldehyde. [b] These k_{rel} values refer to relative rates for one aldehyde within the series of solvents. [c] These k_{rel} values refer to the rates of each reaction relative to benzaldehyde in THF, the slowest reaction we studied. [d] Dielectric constant. All reactions were run under general kinetics conditions (see the Experimental Methods section).

eq 2, can be further simplified to that of the equilibrium approximation if k_4 is assumed to be small (eq 3).

$$\text{rate} = \frac{k_1k_2k_3k_4[\mathbf{1}][\mathbf{2}][\mathbf{4}]^2}{k_2k_3k_4[\mathbf{4}]^2 + k_{-1}k_3k_4[\mathbf{4}] + k_{-1}k_{-2}k_{-3} + k_{-1}k_{-2}k_4} \quad (2)$$

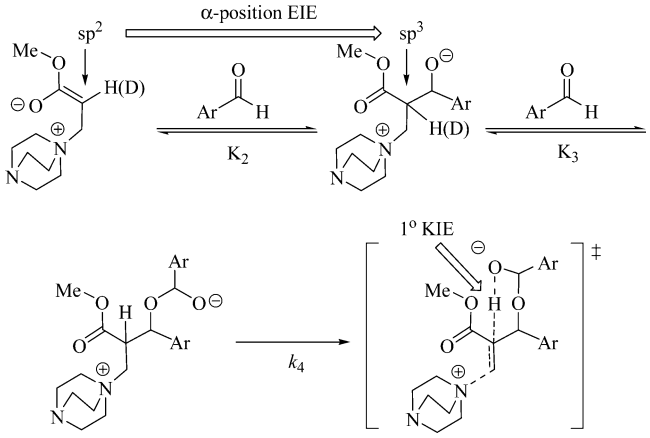
$$\text{rate} = \frac{k_1k_2k_3k_4[\mathbf{1}][\mathbf{2}][\mathbf{4}]^2}{k_{-1}k_{-2}k_{-3}} = K_1K_2K_3k_4[\mathbf{1}][\mathbf{2}][\mathbf{4}]^2 \quad (3)$$

The reversibility of the BH reaction was examined by heating the product of the reaction of methyl acrylate and pNBA with DABCO in DMSO. The reaction was monitored with gas chromatography (GC) for approximately 100 h, and no aldehyde formation was observed.

Discussion

In an initial communication, we showed, using pNBA as a substrate, that the BH reaction mechanism is second order in aldehyde.[30] On the basis of the order and isotope data, we proposed the mechanism featured in Scheme 5. We now report order and isotope effect data for three aryl aldehydes (BA, PYR, and pNBA), and we investigate the

SCHEME 6. The Origin of the EIE and the KIE



generality of the mechanism using a range of solvents. We found that aldehydes are second order, and methyl acrylate and DABCO are first order for each aldehyde examined (Table 1). To ensure that the mechanism was not an artifact of using DMSO as the solvent, we explored the order in both DMSO and THF, as polar and nonpolar solvents, respectively. We have found that the order is invariant with respect to solvent polarity (Table 1). We also examined the order in aldehyde under a variety of protic conditions and found that the reaction remains second order regardless of protic additive concentration (Table 2). These data indicate that the RDS stoichiometry is not influenced by solvent polarity or the presence of protic additives despite the observation that the rate is strongly influenced by the medium.

As in the initial communication, we measured isotope effects using two isotopically sensitive positions, the α-position on the acrylate and the aldehyde proton (Scheme 6 and 8).[30] The pNBA case, in DMSO, exhibits the largest α-position KIE (5.2) and provides the fastest overall rate. We interpret this result as a limiting case, and as such, 5.2 represents the maximum observable KIE. With use of the equilibrium approximation, the KIE_{obs} reduces to eq 4. Since the α-carbon's geometry only changes for K_2, the KIE_{obs} simplifies further to eq 5.

$$\text{KIE}_{\text{obs}} = \frac{(K_{1H}K_{2H}K_{3H})}{(K_{1D}K_{2D}K_{3D})}\,\frac{k_{4H}}{k_{4D}} \quad (4)$$

$$\text{KIE}_{\text{obs}} \approx \frac{K_{2H}}{K_{2D}}\,\frac{k_{4H}}{k_{4D}} \quad (5)$$

Therefore, the KIE_{obs} is a product of the inverse equilibrium isotope effect (iEIE; Scheme 6, top) and the KIE (Scheme 6, bottom). If we assume a value of 0.8 for the iEIE (typical values are between 0.6 and 0.9), then a true KIE for bond breaking is calculated by dividing 5.2 by 0.8, which provides 6.4. This value is close to the theoretical maximum for a primary KIE, 6.9.[33]

We examined the isotope effects for the substrates as a function of solvent (Table 3). We propose that all of the KIEs are primary for the α-position in both low- and high-polarity solvents. We observe that as the solvent polarity

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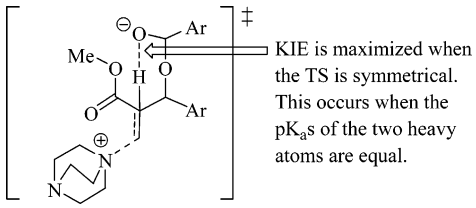
SCHEME 7. TS Geometry of Bond Breaking May Dictate KIE



decreases, the KIE at the α-position decreases and in low-polarity solvents, PYR and BA provided $KIE_{obs} < 2$. Variation in isotope effect as a function of solvent has been studied.[33] Changes in KIE_{obs} are ascribed to the solvent-dependent change in the ΔpK_a between the base and acid—in this case, the hemiacetal and the α-position proton. Therefore, we propose that for pNBA in DMSO, $\Delta pK_a \approx 0$ and consequently the KIE_{obs} is maximized. When comparing one aldehyde within a solvent series, we suggest that the ΔpK_a increases with decreasing polarity, reducing the magnitude of the KIE_{obs}.

Comparing one aldehyde to another, we found that α-proton KIEs vary in the following order pNBA > PYR > BA. This series correlates well with ^{13}C carbonyl chemical shifts, indicating that the electronic character of the carbonyl is important.[34] For example, the observed KIE for PYR in DMSO is 2.0. If we assume that the compounding iEIE is 0.8 then the real KIE should be ~2.5. This low value is due to the poor pK_a match between the α-proton and the hemiacetal, **6**. Despite the low KIE, the PYR order in both DMSO and THF remains 2, indicating that the proposed mechanistic model is valid. Once the iEIE is factored out, BA run in THF is the only substrate/solvent pair yielding a KIE value less than 2. Despite the low KIE_{obs}, the aldehyde order remains 2, supporting the mechanism depicted in Scheme 5. As such, we conjecture that the low KIE_{obs} represents a primary isotope effect.

For each of the aryl substrates, we also investigated the KIE associated with the aldehyde proton. As expected, each substrate yielded an observed KIE consistent with a large inverse secondary isotope effect. This inverse secondary KIE indicates that the aldehyde geometry changes from an sp^2 to an sp^3 center. As depicted in Scheme 8, because two aldehyde geometry changes must occur before the RDS, a strong inverse effect is expected and observed (eq 6).

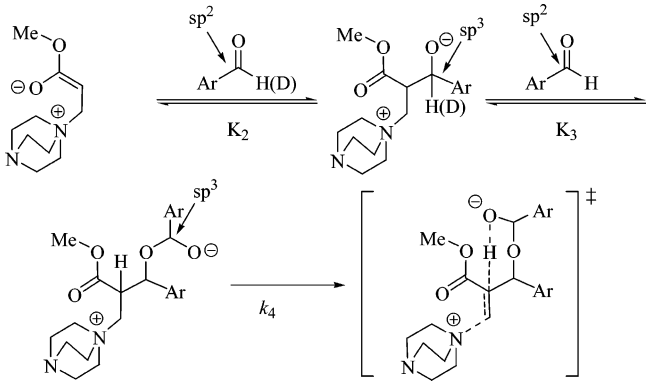
$$KIE_{obs} = \frac{K_{2H}}{K_{2D}} \frac{K_{3H}}{K_{3D}} \qquad (6)$$

The order and isotope effect data indicate that the mechanism provided in Scheme 5 is general for different aldehyde substrates when using methyl acrylate as the electron-poor alkene. We use these data and the proposed mechanism to resolve four unexplained features of the BH reaction: sluggish reaction rates, dioxanone formation, difficult stereocontrol, and acceleration with protic additives.

The rate law derived from the mechanism in Scheme 5 can be used to explain the dramatic difference in rate between substrates and why the BH reaction appears to

(34) http://www.aist.go.jp/RIODB/SDBS/menu-e.html.

SCHEME 8. The Origin of the Large Inverse Aldehyde Proton Kinetic Isotope Effect



equilibrate. The k_{obs} term has an inverse dependence on aldehyde concentration (eq 2). For aldehydes whose k_2, $k_3 \approx k_4$ the overall reaction rate is attenuated relative to aldehydes whose k_2, $k_3 \gg k_4$ (eq 2).

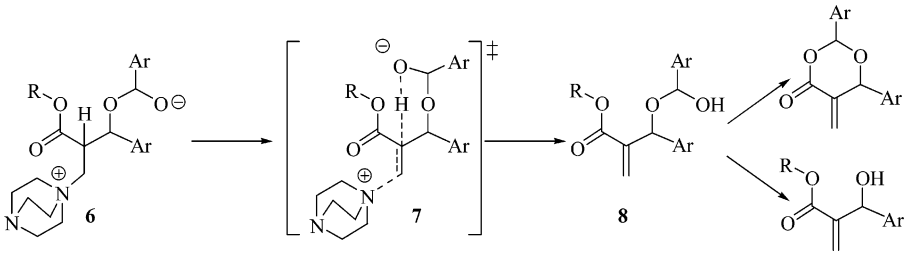
For fast BH substrates (electron-poor aldehydes, for example), we propose that the elimination rate, k_4, is slow relative to the other rate constants. This assumption simplifies the rate law to eq 3. This simplification removes the inverse aldehyde-dependent terms in k_{obs}. These terms do not alter the order but do alter the reaction rate. Alternatively in the case of sluggish substrates, we suggest that the assumption that k_4 is slow with respect to k_2 and k_3 becomes invalid, thus forcing the reaction into the inverse aldehyde-dependent regime. In addition, this rate law helps to explain why the reaction appears to equilibrate.[35] Since most BH reactions are run with a 1:1 ratio of aldehyde to methyl acrylate, as the reaction consumes aldehyde, k_2 and k_3 decrease, the equilibrium approximation becomes invalid, and the reaction slows dramatically as a function of aldehyde consumption.

The new mechanism also provides an explanation for the formation of dioxanone products. The proposed hemiacetal intermediate, **6**, can cyclize to yield dioxanone product (Scheme 9).[3] The hemiacetal intermediate does not provide irrefutable evidence, but it is a plausible intermediate en route to cyclic products, and others have proposed **8** as a post-rate-determining intermediate.[11,12] We are the first to provide any evidence supporting the presence of **7**.

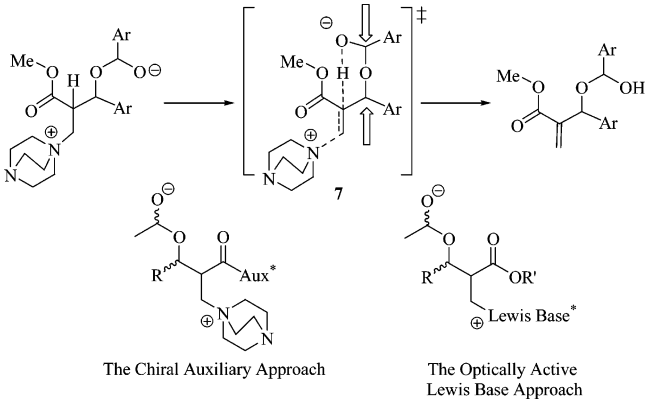
Our new mechanism can also explain why the BH stereochemistry is difficult to control. As depicted in Scheme 10, the elimination is both the RDS and the product distribution-controlling step. The elimination proceeds through a diastereometric, hemiacetal transition state (**7**). When an optically pure auxiliary or Lewis base is used, the number of stereocenters in the transition state increases from two to three, but there are still only four stereoisomers as the configuration of the base or auxiliary is fixed. These isomers provide four different pathways to products. Typically, chiral auxiliaries are successful in cases where only two pathways must be distinguished, and thus approaches beyond standard chiral auxiliaries or Lewis bases will be required to bias the reaction completely. Cyclization to the dioxanone can

(35) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371−6384.

SCHEME 9. A Hypothesis for the Formation of the Dioxanone Product



SCHEME 10. Stereocenters of the Hemiacetal



provide one method to enhance the stereoselectivity. In Leahy's case, the cyclization may be rate limiting and as such, the transition state leading to the cyclic product will be sensitive to stereochemistry by virtue of potential 1,3-diaxial interactions (see Scheme 3).

Auge, Aggarwal, Hu, and Tang report large rate enhancements caused by water and other polar protic additives. To extend the mechanism, we measured the order in aldehyde in the protic solvent/THF mixtures and the α-position KIE for one water/THF mixture. The reaction was found to be second-order in aldehyde under all protic conditions tested (Table 2). Also the KIE was >2, indicating a rate-limiting α-proton cleavage that is consistent with the proposed mechanism. In addition, the order in the additive was one for each protic additive tested—formamide, water, and methanol—using THF as the cosolvent. Each additive also showed saturation behavior, indicating that the protic additive may form a hemiacetal ground state at high protic concentrations. A first-order solvent dependence is also observed for polar aprotic solvents such as DMSO.[30]

The solvent-induced acceleration, under either protic or aprotic conditions, roughly follows the dielectric constant of the solvent or mixture. For instance, the acceleration caused by DMSO is very similar to the mixture of formamide and THF (Table 2). The first-order dependence on solvent could be interpreted as a medium effect or as a molecular interaction. Because the rate correlates with solvent polarity, we suggest that the rate increase is a medium effect in which the ionic transition states are stabilized in the presence of polar solvents.

In conclusion, we have used rate and isotope data to demonstrate that the mechanism featured in Scheme 5 is general for aryl aldehydes with different electronic properties. The mechanism is also valid when polar aprotic, nonpolar, and nonpolar/protic additive mixtures are used. This general mechanism is a useful model that can be used to explain the BH reaction's sluggishness, the difficulty in controlling its stereochemistry, the formation of dioxanone products, and the influence of protic additives.

Experimental Methods

General Procedures. Solvents and aldehydes were purified by using standard procedures. The purity of each aldehyde was evaluated with GC, ^{1}H NMR, and ^{13}C NMR. 4-Pyridinecarboxaldehyde was used immediately after purification. Solvent was used as the internal reference for both ^{1}H and ^{13}CNMR. GC analyses were carried out with a CP-Sil regular phase column (15.0 m × 0.25 mm i.d.). Response factors of authentic Baylis−Hillman products versus methyl benzoate (internal standard) were calculated for determining reaction conversion.

General Kinetic Procedure. All reactions were carried out with methyl acrylate, aldehyde, DABCO, and methyl benzoate at concentrations of 0.84, 0.83, 0.27, and 0.066 M, respectively. Reactions were started with the addition of methyl acrylate to a solution of aldehyde, DABCO, and methyl benzoate in a given solvent. The reactions were monitored by diluting 5−7 μL of the reaction mixture into 1.5 mL of CH_2Cl_2 at appropriate time intervals for GC analysis. For the acrylate, DABCO, and aldehyde order plots, the amount of DMSO and the reaction volume were held constant to eliminate solvent effects. THF was used as the nonreactive substitute for absent reagents. No substitutions were necessary when THF was the solvent for the order plot, as THF has no impact on rate. All reactions were monitored before 10% conversion. No byproducts were detected at high conversions. Relative rates were determined in Sigma Plot 8.0. Aberrant rates were eliminated by using the Student's t-test at the 95% confidence interval.

Preparation of α-Deuterio Methyl Acrylate (2d). The preparation was modified from that of Baldwin and Cianciosi.[36] DABCO (25 g, 0.22 mol) was dissolved in methanol-*d* (108 mL, 2.65mol) with stirring. Methyl acrylate (20 mL, 0.22 mol) was added, and the solution was stirred at room temperature for approximately 12 h. The solution was then diluted in *o*-dichlorobenzene (ODCB) and washed with water and brine. The organic phase was dried over Na_2SO_4 and fractionally distilled to remove **2d** from the ODCB. **2d** was isolated as a colorless liquid (7 g, 36%) and contained <2% ODCB, as determined by ^{1}H NMR spectroscopy. This volume difference was accounted for when running methyl-*d* acrylate kinetics. **2d** was approximately 87% deuterated and was stored cold over Na_2SO_4. The batch used for the H_2O/THF KIE was ∼80% *d*. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (m, 1H), 6.12 (m, 0.15 H), 5.83 (m, 1H), 3.75 (s, 3H).

Preparation of *C*,*C*-Dideuterio-*C*-(4-nitrophenyl)methanol (9). 4-Nitrobenzoyl chloride (8.0 g, 43.1 mmol) was dissolved in dry THF (200 mL) and added dropwise to a suspension of lithium aluminum deuteride (2.2 g, 51.8 mmol) in THF (100 mL) at −78 °C over 2 h. The reaction mixture was allowed to stir for an additional hour at −78 °C and then

(36) Baldwin, J. E.; Cianciosi, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 9401−9408.

allowed to warm to room temperature for 30 min. The reaction mixture was quenched with 1 N HCl, diluted with EtOAc, and filtered. The filtrate was washed with brine and water, dried over Na_2SO_4, and concentrated to produce a yellow solid (70%, 4.7 g). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.20 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 4.62 (s, 1H).[37] Complete characterization was carried out after **9** was converted to **10**.

Preparation of α-Deuterio-4-nitrobenzaldehyde (10). The material was prepared following the general procedure of More and Finney.[38] Product **9** (4.3 g, 27.7 mmol), *o*-iodoxybenzoic acid (IBX) (23.3 g, 83.2 mmol), and EtOAc (200 mL) were combined in a 500-mL round-bottom flask equipped with a condenser. **Caution**: IBX can explode on impact or heating.[39] The reaction mixture was stirred vigorously at 80 °C overnight, open to atmosphere. The reaction mixture was then cooled, filtered, and concentrated to produce a yellow solid. The solid was purified by flash chromatography on silica (preloaded with CH_2Cl_2, eluted with 4:1 hexanes:EtOAc) to produce a yellow crystalline solid (93%, 3.9 g). The spectroscopic data correspond to those in Wubbels et al. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H).[40] ^{2}H NMR (500 MHz, $CHCl_3$ spiked with $CDCl_3$) δ 10.02 (s, 1D). ^{13}C NMR (500 MHz, DMSO-d_6) δ 191.9 (t, J_{CD} = 28.2 Hz), 150.6, 140.0 (t, J_{CD} = 3.2 Hz), 130.6, 124.2.

Preparation of 2-[Hydroxy(4-nitrophenyl)methyl]acrylic Acid Methyl Ester (11). This compound was synthesized by using the general kinetic procedure with DMSO as the solvent. The spectroscopic characterization is consistent with the published characterization.[41] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 9.3 Hz, 2H), 6.38 (s, 1H), 5.86 (s, 1H), 5.62 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.4, 148.5, 147.4, 140.8, 127.3, 127.3, 123.6, 72.7, 52.2.

Preparation of 2-[Hydroxypyridin-4-ylmethyl]acrylic Acid Methyl Ester (12). PYR (1.07 g, 10 mmol) was added to a solution of DABCO (1.12 g, 10 mmol) in acetonitrile. Methyl acrylate (1.29 g, 15 mmol) was then added and the reaction was stirred at room temperature for 24 h. The product was isolated as a white powder (0.283 g, 14.7%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 6.4 Hz, 2H), 7.35 (d, J = 6.4 Hz, 2H), 6.38 (s, 1H), 5.89 (s, 1H), 5.53 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (500 MHz, CDCl3) δ 166.3, 152.5, 149.0, 140.7, 127.4, 121.6, 72.2, 52.2.[42]

Preparation of 2-[Hydroxyphenylmethyl]acrylic Acid Methyl Ester (13). This compound was synthesized by using the general kinetic procedure with DMSO as the solvent. Spectroscopic data are consistent with those in the literature.[43] H NMR (400 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5H), 6.33 (s, 1H), 5.82 (s, 1H), 5.56 (s, 1H), 3.72 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.8, 141.8, 141.2, 128.4, 127.8, 126.5, 126.2, 109.8, 73.7, 52.0.

Determination of the Final Location of ^{2}H. The reaction was run with pNBA and **2d**, using the general kinetic procedure with acetonitrile as the solvent. An aliquot of the reaction mixture was removed. Two resonances were observed in the ^{2}H NMR spectrum (400 MHz), 5.92 and 4.12 ppm, corresponding to the deuterated methyl acrylate and the deuterated alcohol in the product (benzene-d_6 as the internal standard).

Reversibility of the Baylis−Hillman Reaction. The product of the Baylis−Hillman reaction, **11** (0.21 mmol), was added to a solution of DABCO (0.0633 mmol) in 1 mL of DMSO. The reaction mixture was heated at 60 °C and sampled repetitively. At times ranging from 45 min to 100 h, no aldehyde was detected by GC.

Rate Law Determination. The rate law was simplified by using Mathematica (v. 5.0).

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Note Added after ASAP Publication. Two [D] terms were missing on p 154 of the Supporting Information published ASAP April 14, 2005; the corrected version was published April 15, 2005.

Supporting Information Available: Kinetics data, order plots, rate law derivation, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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