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The Development of the First Catalyzed Reaction of Ketenes and Imines: Catalytic, Asymmetric Synthesis of β-Lactams

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Abstract: We report practical methodology for the catalytic, asymmetric synthesis of β-lactams resulting from the development of a catalyzed reaction of ketenes (or their derived zwitterionic enolates) and imines. The products of these asymmetric reactions can serve as precursors to a number of enzyme inhibitors and drug candidates as well as valuable synthetic intermediates. We present a detailed study of the mechanism of the β-lactam forming reaction with proton sponge as the stoichiometric base, including kinetics and isotopic labeling studies. Stereochemical models based on molecular mechanics (MM) calculations are also presented to account for the observed stereoregular sense of induction in our reactions and to provide a guidepost for the design of other catalyst systems.

Introduction

The clinical relevance of β-lactams continues to expand at a surprising rate. Although their use as antibiotics is being compromised to some extent by bacterial resistance pressures,[1] recently β-lactams (especially nonnatural ones) have achieved many important nonantibiotic uses. Some of the most notable advances concern the development of mechanism-based serine protease inhibitors[2] of elastase,[3] cytomegalovirus protease,[4] thrombin,[5] prostate specific antigen,[6] β-lactamase,[7] and cell metastasis.[8] As a testament to the continuing importance of β-lactams to pharmaceutical science, a recent issue of *Tetrahedron* was devoted exclusively to β-lactam chemistry and synthesis. In the preface of this issue, a call was given to pharmaceutical companies to reintensify efforts to develop new types and uses of β-lactams, and refocus efforts away from antibiotic use.[9] The sheer importance of β-lactams has made this structural motif a worthwhile goal for the synthetic organic chemist,[10] thus the synthesis of these nonantibiotic β-lactams will be the focus of this contribution. While considerable effort has been put into synthetic methodology to construct the basic β-lactam skeleton, there have been few general methods proposed for their enantioselective synthesis. Current asymmetric methodology mainly uses chiral auxiliary-based systems that while effective, require an auxiliary that necessitates additional synthetic operations to install and remove. A general methodology built around a useful catalytic asymmetric reaction, as opposed to chiral auxiliaries, would be extremely useful. We herein summarize general and efficient methodology for the synthesis of the monobactam skeleton, which rests on the development of the first catalyzed reaction of ketenes (or their synthetic equivalents) and imines. We recently accomplished this mechanistically distinct, catalyzed reaction by making the ketene nucleophilic (through generation of a zwitterionic intermediate),[11] and the imine component nonnucleophilic, as in electron deficient α-imino ester **5a** (X = Ts, R = Et).[12,13] Many new classes of extremely useful β-lactams result from a successful asymmetric reaction of this type of imines with ketenes, including thrombin, prostate specific antigen, and cytomegalovirus protease inhibitors (Scheme 1).

There have been a few reported cases of catalytic, enantioselective syntheses of β-lactams. Alper reported a carbonylation of chiral and meso aziridines to produce optically enriched products in modest enantioselectivity (ee).[14] Tomioka et al.

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(10) A literature search found over 1600 articles describing the synthesis of β-lactams over the last 25 years.

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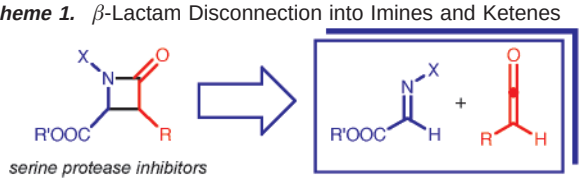
(13) We have also used *N*-acyl imino esters to form β-lactams as intermediates in the synthesis of substituted aspartic acids: Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387−390.

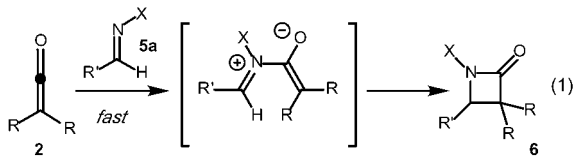
10.1021/ja0258226 CCC: $22.00

Scheme 1. β-Lactam Disconnection into Imines and Ketenes



described an interesting approach in which a chiral ether was used as a chelating catalyst for lithium enolates in their ring forming reactions with imines to form optically enriched β-lactams.[15] Finally, Doyle et al. have exploited the rhodium-catalyzed C−H insertion reaction of diazoacetates to construct the β-lactam skeleton for some specialized cases.[16] Biocatalytic methodology has also played a notable role in the synthesis of optically pure β-lactams.[17] These pioneering methods represent initial forays into this area, and outline a number of remaining challenges, including enantioselectivity and substrate generality.

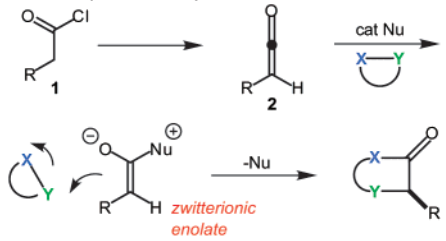
While there are many known syntheses of β-lactams, the Staudinger reaction is widely accepted as one of the simplest methods. It is a process that proceeds without a catalyst,[18] and its rate depends on the nucleophilicity of the imine. It is generally thought to be a stepwise [2+2] cycloaddition that is initiated by an imine nucleophile attacking a ketene, followed by cyclization of the azadiene intermediate (eq 1).[19] This



reaction has a very low energy of activation and thus proceeds rapidly even at reduced temperatures. Due to the wide range of available ketene and imine combinations, this method is considered one of the most useful and economical, although it is not apparently amenable to catalysis.

Many asymmetric versions of the Staudinger reaction involve the use of a chiral oxazolidinone substituted ketene.[20] Bose et al. have developed a diastereoselective β-lactam synthesis using a chiral auxiliary attached to the imine.[21] While these and other related procedures may be efficient in cases where the chiral auxiliary is part of the final target molecule, in most cases it is not and must be removed. In our system, achiral ketenes react with achiral imines to achieve asymmetric induction through the use of a chiral nucleophilic catalyst.

Scheme 2. Nucleophilic Catalysis with Ketenes



Results and Discussion

Asymmetric Catalysis with Ketenes. There has been a surge of interest in nucleophilic asymmetric catalysis as organic chemists have come to see the benefits and practicality offered by totally organic catalyst systems, especially their ease of handling and recovery.[22] In fact, some of the earliest discoveries in the field of asymmetric catalysis involved the use of organic nucleophiles. One pioneering study occurred in the labs of Pracejus, who used alkaloids to catalyze the alcoholysis of disubstituted ketenes to afford chiral alcohols in moderate enantioselectivity (ee).[23] In the 1980s, Wynberg developed an asymmetric β-lactone synthesis using ketenes, an activated aldehyde component, and cinchona alkaloid catalysts.[24] Tamai and Romo have also used ketenes for the asymmetric synthesis of β-lactones.[25] This list would possibly be much longer were it not for the fact that ketenes are often difficult to handle. It is clear that efficient, wide-ranging ketene generation would render many problems in asymmetric catalysis and mechanistic organic chemistry approachable for the first time.

Ketene Generation. Ketenes are versatile, well-known substrates in organic synthesis. Their cumulated double bond structure imparts a unique spectrum of reactivity, and gives rise to a large number of mechanistically interesting transformations. Ketenes usually add substrates avidly across their C═C bond, a reaction which can be catalyzed by various nucleophilic Lewis bases (Scheme 2),[26] suggesting to us a strategy whereby the zwitterionic enolate could react with an electrophilic imine, were we to have in hand a generally useful ketene synthesis. There are many ways to synthesize ketenes through thermolytic, and photolytic reactions, although from a synthetic standpoint these methods suffer from drawbacks, requiring cumbersome apparatus, tricky conditions, or esoteric starting materials.[27] In addition, many methodological studies limit their scope to readily available (but less useful) disubstituted ketenes. In synthetic chemistry, ketenes are most often produced from inexpensive acid chlorides through dehydrohalogenation reactions with tertiary amines. This method works well for distillable disubstituted ketenes. More synthetically useful and chemically challenging monosubstituted ketenes are generally much more reactive, and must, with rare exception, be made in situ, where

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(22) For a comprehensive review see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.
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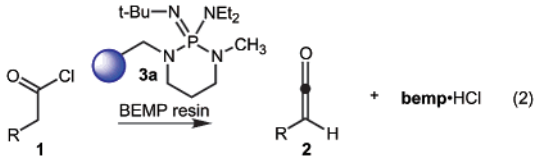
they are invariably stirred with precipitated and partially dissolved ammonium salt byproducts.[28] In some cases, the presence of these trialkylammonium byproducts presents no problem. However, we found that in many instances (vide infra), trialkylammonium salts were deleterious to established reactions.[29] Trialkylammonium salts have an appreciable solubility in almost all organic solvents and can serve as unwanted Brønsted acid catalysts. They are in equilibrium with the corresponding free amine bases that can act as nucleophiles or ligands; and because they are achiral, they may interfere with the desired reaction, producing racemic products.

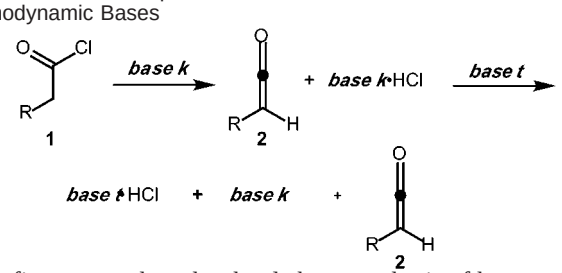
One possible solution is to use polymer-bound bases such as the highly basic resin BEMP **3a**,[30] a triaminophosphonamide imine bound to a polymeric support,[31] to form ketenes **2** from acid halides **1**.[32] We found that BEMP produces many ketenes rapidly when THF solutions of suitable acid chlorides **1** are passed through an addition funnel at −78 °C containing the polymer (eq 2).[33,34] Alternatively, the BEMP polymer can be



added to a solution of the acid chloride at low temperature. After a few minutes, filtration of the solid-supported base produces the desired solution of pure ketene. We previously investigated other polymer-supported bases such as guanidines and tertiary amines but found them to be ineffective for ketene generation.[35] Although they are attractive reagents, the primary drawback to the use of polymeric bases involves their expense (5 g of BEMP costs about $120).

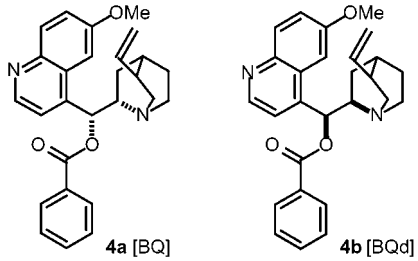
Shuttle Deprotonation. The use of tertiary amines for dehydrohalogenations of acid halides **1** to form ketenes for our reactions is complicated by the fact that they are usually too nucleophilic. The use of a stoichiometric base that is thermodynamically strong, but kinetically nonnucleophilic, could overcome this problem. This strategy, which we term "shuttle deprotonation", utilizes a catalytic, chiral nucleophile, which is kinetically active (**base k**), to dehydrohalogenate the acid chloride in the first step (Scheme 3). Exploiting the premise that proton transfers between heteroatoms are inherently fast,[36] the kinetically favored **base k** then rapidly transfers its proton to **base t**, the thermodynamically active, but kinetically restricted base, to regenerate itself for another catalytic cycle.

Scheme 3. Shuttle Deprotonation with Kinetic and Thermodynamic Bases



Our first approach to the shuttle base synthesis of ketenes in situ was the use of the strong organic base proton sponge (**3b**) as a nonnucleophilic thermodynamic base. We found that simply mixing 1 equiv of **3b** and acid chlorides **1** at low temperature usually does not produce detectable amounts of ketene. Although **3b** is a strong thermodynamic base, it is hindered and in most cases kinetically slow at deprotonating carbon-based acids.[37]

We found that a nucleophile such as benzoylquinine (BQ, **4a**), an inexpensive[38] and versatile asymmetric catalyst,[39] serves as an excellent shuttle base (**base k**) when added to a solution of various acid chlorides **1** in toluene at low temperature. In the case of diphenylketene **2b**, a yellow solution is formed along with a white precipitate over the course of a few minutes.[40] In an appropriate solvent like toluene, the ammonium salt of proton sponge was found to not interfere in many asymmetric reactions catalyzed by chiral nucleophiles. The main drawbacks to the use of the proton sponge-shuttle procedure include economical aspects (although proton sponge is a moderately priced chemical, in large quantities its use may be a cost factor) as well as the possibility that in rare instances the sponge itself may react in undesirable ways.[33]



Carbonate and Hydride Shuttle Bases. We have also looked at powdered carbonates as stoichiometric heterogeneous bases

(28) Even after filtration, solubilized salts may remain.
(29) Hegedus has found that trialkylammonium salts can interfere with the diastereoselectivity of the Staudinger reaction to produce β-lactams: Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784−5791.
(30) The pK_a of the conjugate acid of BEMP in DMSO is 16.2. See: O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.
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(34) For scaled up reactions, mechanical agitation of the polymer in the addition funnel is beneficial.
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(36) (a) Bell, R. P. *The Proton in Chemistry*; Cornell University Press: Ithaca, NY, 1973. (b) For discussions concerning proton sponge basicity, see: Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215−1270.
(37) Remarkably, there are some cases where the α-proton of the acid chloride is acidic enough to make it possible for proton sponge to perform the dehydrohalogenation without the assistance of BQ. See: Tidwell, T. T.; Fenwick, M. H. *Eur. J. Org. Chem.* **2001**, 3415−3419.
(38) Multigram quantities of benzoylquinine are easily synthesized in one step from benzoyl chloride and quinine. Also, BQ is benchtop stable indefinitely.
(39) Cinchona alkaloids have the status as general nucleophilic catalysts and ligands for many organic reactions, for example see: (a) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338−340. (b) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696−12697. (c) Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrère, L.; Gerlach, A.; Raabe, G. *Synthesis* 1719−1730. (d) Kacprzak, K.; Gawronski, J. *Synthesis*, **2001**, *7*, 961−998. (e) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984−6991. (f) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097−1100. (g) Alvarez, R.; Hourdin, M.-A.; Cave, C.; d'Angelo, J.; Chaminade, P. *Tetrahedron Lett.* **1999**, *40*, 7091−7094. (h) Martyres, D. *Synlett* **1999**, *9*, 1508−1515. (i) Studer, M.; Blaser, H.-U.; Okafor, V. *J. Chem. Soc., Chem. Commun.* **1998**, *9*, 1053−1054. (j) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899−4902. (k) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278−1291. (l) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568−7570. (m) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417−430.
(40) Tidwell has recently used our proton sponge shuttle base methodology to observe and study the reactivity of bisketenes: Allen, A. D.; Fenwick, M. H.; Jabri, A.; Rangwala, H.; Saidi, K.; Tidwell, T. T. *Org. Lett.* **2001**, *3*, 4095−4098.

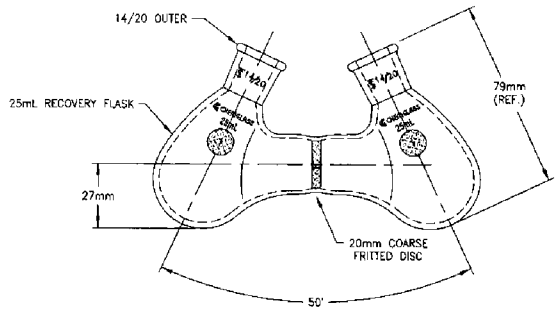
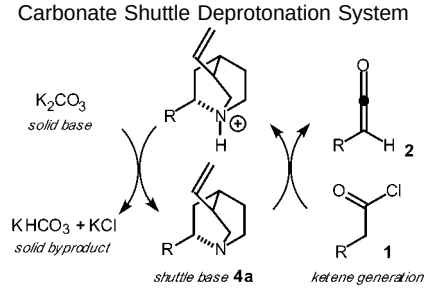


Figure 1. Schematic of the double reaction flask used with K_2CO_3.

Scheme 4. Carbonate Shuttle Deprotonation System

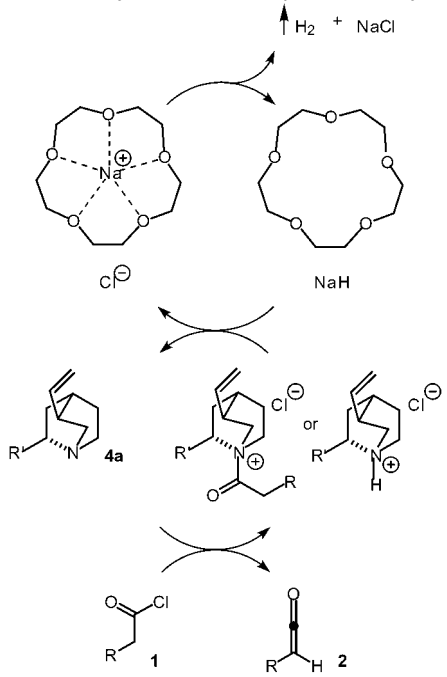


for monosubstituted ketene formation from acid halides **1** using a shuttle deprotonation strategy.[41] Carbonate salts are very inexpensive commodity chemicals,[42] they are nontoxic, and they are easily disposed of after use. Their insolubility in organic media can also be used to advantage.[43] Fine mesh K_2CO_3 is in contact with the organic phase, in which a small amount of a chiral nucleophile and an acid chloride are dissolved (Scheme 4). The catalytic shuttle base dehydrohalogenates the acid chloride to form ketene **2** and the ammonium salt of the base. The carbonate then deprotonates the ammonium salt, thus regenerating the shuttle base. Once the ketene has formed stoichiometrically, it can easily be separated from the solid phase by filtration if necessary.

We have simplified the above process by designing a piece of glassware that facilitates the ketene generation experiment (Figure 1). The apparatus consists of two recovery flasks linked by a fritted disc. The disc is located as low as possible in the assembly to allow it to be conveniently submerged in a cold bath. Simply by canting the assembly in one direction, the reaction liquor can be transferred from one side to another without removing the piece from the bath.

We recently improved upon our use of solid inorganic bases for ketene generation by developing a procedure using inexpensive NaH.[44] We found that using 10 mol % 15-crown-5 as a phase transfer cocatalyst to help solubilize the NaH,[45] in addition to 10 mol % BQ, allowed for the efficient formation of ketenes. Ketene formation was confirmed by observing the formation of the relatively stable diphenylketene both visually and spectroscopically. The use of NaH results in a much cleaner reaction, with NaCl and H_2 as benign byproducts. Our working hypothesis for the mechanism is presented in Scheme 5. Once again, a catalytic shuttle base, such as BQ, effects dehydrohalogenation of an acid chloride to the corresponding ketene. The acid chloride either forms an acylammonium salt with BQ and is deprotonated by NaH or the BQ deprotonates the acid chloride (possibly as its ammonium salt) and then shuttles the proton to the NaH, thus regenerating BQ for another catalytic cycle.

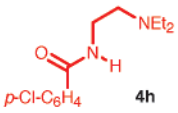
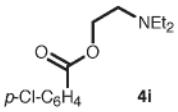
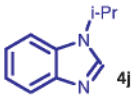
Scheme 5. Sodium Hydride Shuttle Deprotonation System



Catalyzing the Reaction. Having established several methods of ketene synthesis, we turned our attention to β-lactam forming reactions. In our preliminary work, we reported the catalytic, asymmetric reaction of imine **5a**[46] and ketenes **2** to produce β-lactams in high enantio- and diastereomeric excess, employing chiral cinchona alkaloid derivatives as catalysts.[11] Due to the fact that imine **5a** is electrophilic, the background rate of reaction with various ketenes is fortunately minimal. Imine electrophilicity thus necessitates an "umpolung" of ketene polarity; hence reaction with a nucleophile converts the ketene into the putative zwitterionic enolate. Due to this role reversal, this reaction is mechanistically distinct from the Staudinger reaction and thus should not be referred to as such (an idea kindly pointed out by the referees of our original publication). In an initial screen, we found that a diverse array of catalysts, including metal-based nucleophiles (Cp_2Co, $NaCo(CO)_4$),[47] tributyl phosphite, and amine-based nucleophiles such as triethylamine, promote the reaction of a ketene with α-imino ester **5a**. Initially we chose to examine catalyzed diastereoselectivity. For this purpose we chose methylphenylketene **2a**, which reacted with imine **5a** to

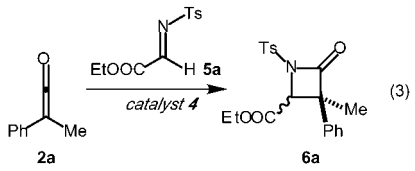
(41) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.
(42) Fine mesh size K_2CO_3 is available from Aldrich and many other companies.
(43) (a) Nelson, A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1583−1585. (b) Combined amine/carbonate base application: Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297−300. (c) Sasson, Y.; Bilman, N. *J. Chem. Soc., Perkin Trans. 2* **1989**, 2029−2033.
(44) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S. *Org. Lett.* **2002**, *4*, 627−629.
(45) In the case of β-lactams, the use of more polar solvents such as propionitrile and THF was found to decrease the diastereoselectivity greatly, possibly due to solubilized salts.
(46) We have used α-imino ester **5a** in the catalytic, asymmetric synthesis of α-amino acid derivatives: (a) Drury, W. J. III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006−11007. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J. III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090−6091. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998,** *120*, 4548−4549.
(47) Wack, H.; Drury, W. J. III; Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett.* **1999**, *1*, 1985−1988.

Table 1. Diastereoselectivity in the Nucleophile-Catalyzed Reaction of Methylphenylketene **2a** with Imine **5a**

entry	catalyst	yield[a]	dr (cis/trans)[b]
1	none	trace	-
2	Cp_2Co	**55%**	**25/75**
3	 **4h**	**75%**	**3/97**
4	 **4i**	77%	33/66
5	Et_3N	83%	55/45
6	dabco	62%	66/33
7	 **4j**	**79%**	**98/2**

[a] Yield after column chromatography. [b] dr (cis/trans) was determined by ^{1}H NMR of the crude residue.

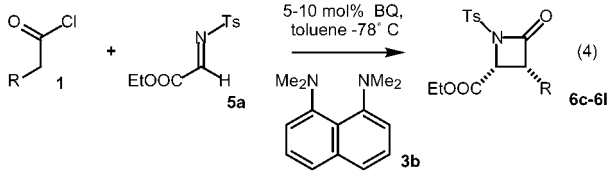
form the cis and trans diastereomers (Table 1 and eq 3). We identified two sets of catalysts: one that produced predominantly the trans β-lactam, and another group that produced the cis diastereomer of β-lactam **6a**. Despite the fact that simple tertiary



(3)

amines such as triethylamine usually catalyze the reaction in a nonselective fashion, we found that a bifunctional catalyst (**4h**, Table 1, entry 3) containing a nucleophilic center in tandem with a hydrogen bond donor may lead to a potentially rigidified activated complex affording products in a cis/trans ratio of 3:97.[48] When a small amount of DMSO was titrated into the reactions involving this catalyst, the reaction diastereoselectivity eroded,[49] implying a potential hydrogen bond interaction between the N−H of the amide and the ketene adduct with the nucleophilic center of the catalyst. Competitive H-bonding to DMSO apparently disrupts the rigidity of the activated complex. Surprisingly, we found that benzimidazole (**4j**) forms the opposite diastereomer (98/2 dr, entry 7).

Enantioselective Reactions. Next we investigated how our catalyst leads could be translated into a chiral environment. Due to our success with amine-based nucleophiles, we decided to investigate various alkaloids as potential catalysts. As a first step, we found that benzoylquinine (BQ, **4a**), a cinchona alkaloid, catalyzes the addition of diphenylketene **2b** to imino ester **5a** in 36% yield and 99% ee in toluene solvent at −78 °C. To further extend the scope and applicability of this reaction, we turned our attention to more reactive, synthetically useful monosubstituted ketenes. For example, the use of Hünig's base to generate phenylketene in situ afforded product **6c** in low yield and enantioselectivity with BQ catalyst **4a** at −78 °C in THF or toluene. It was obvious to us that Hünig's base was effectively competing with BQ as a catalyst in a nonselective fashion. At this point the necessity for a nonnucleophilic, yet thermodynamically strong base became apparent and as a result, we devised the shuttle base strategy for in situ ketene synthesis. We employed proton sponge **3b** as a nonnucleophilic "proton sink" and BQ (**4a**) as the shuttle base in toluene at −78 °C. The reaction afforded *cis*-lactam **6c** in 99% ee and good yield (65% yield, 99/1 dr, eq 4). In this reaction, **4a** plays two distinct



(4)

catalytic roles: namely as a dehydrohalogenation agent and as a nucleophilic catalyst. Additionally, we found that in all cases using benzoylquinidine **4b** instead of **4a** inverted the stereochemistry of the product. For example *ent*-**6c** was formed using **4b** in similar yield and selectivity as when **4a** was used (64% yield, 99% ee, 99/1 dr, Figure 2).

To exemplify the wide array of employable functionalities, β-lactams **6d**−**l** were synthesized from a variety of in situ generated ketenes in moderate to good yields (50−65%). All the products are formed with high ee and dr (cis/trans ratio), and were chosen in part for their potential utility in pharmaceutically active β-lactam synthesis (Figure 2). For example, lactam **6d** is an elastase inhibitor originally reported by DuPont-

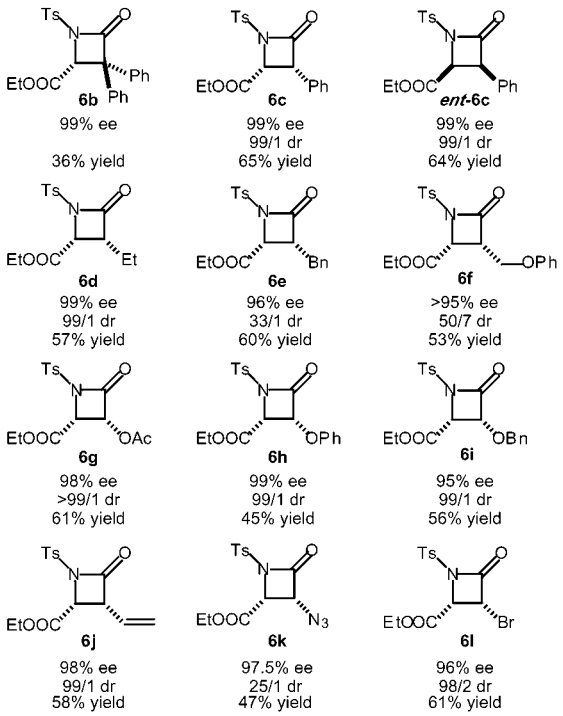


Figure 2. Representative β-lactams synthesized using proton sponge.

(48) (a) Hydrogen bond contacts have been postulated to play similar roles in other catalytic reactions: Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495−500. (b) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824−2827.

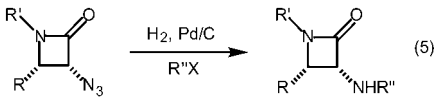
(49) For example, as DMSO is titrated in, the reaction diastereoselectivity erodes dramatically. H-bonding between DMSO and the catalyst can be discerned in the IR spectrum.

Table 2. A Comparison of the Four Ketene Generation Methods for **6i**

entry	base	rel cost[a]	% yield[b]	% ee[c]	dr[d]
1	BEMP	863	60	99	99/1
2	proton sponge/BQ	11	57	99	99/1
3	K_2CO_3/BQ	2	56	93	8/1
4	NaH/15-crown-5/BQ	1	60	99	25/1

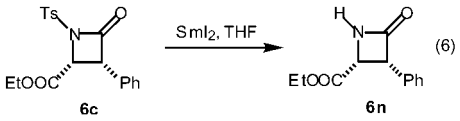
[a] Relative cost based on the least expensive $/g from the 2000/2001 Sigma Aldrich catalog. [b] Isolated yield after column chromatography. [c] Enantioselectivity determined by chiral HPLC. [d] dr (cis/trans) was determined by ^{1}H NMR of the crude residue.

Merck that has undergone clinical trials.[50] Furthermore, while 3-oxo-substituted ketenes are not amenable to the standard chiral auxiliary methodology, our process allows acetoxy, phenoxy, and benzyloxy β-lactams (**6g**−**i**) to be synthesized in good yield and with high selectivity. The azido-substituted β-lactam **6k** allows for the synthesis of 3-amino-substituted β-lactams, which are prevalent in pharmaceutical chemistry.[51] As a third example of a heteroatom substituent, we were able to use bromoacetyl chloride to form the corresponding β-lactam **6l** with similar selectivity and yield (96% ee, 98/2 dr). Formation of vinyl-substituted β-lactam **6j** (98% ee, 99/1 dr) occurs in preference to a theoretically possible [4+2] cycloaddition to form a six-membered lactam product. Enantiomers (for example, *ent*-**6c**) of our β-lactam compounds can be made with similar selectivity using the "pseudoenantiomeric" benzoylquinidine **4b**. The azido group on β-lactam **6k** provides a convenient handle for functionalization reactions. The azido group is known to be easily converted with retention of configuration to an amine or an amide substituent by catalytic hydrogenation followed by acylation (eq 5).[52]



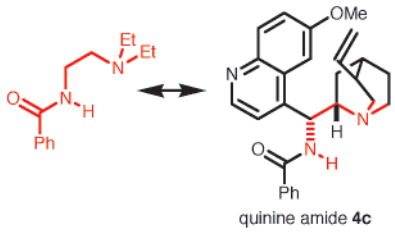
(5)

Similarly, the Ts group of many of our β-lactam products can be removed by treatment with 2 equiv of SmI_2 in THF to afford deprotected β-lactams such as **6n** in high yield (eq 6).



6c **6n** (6)

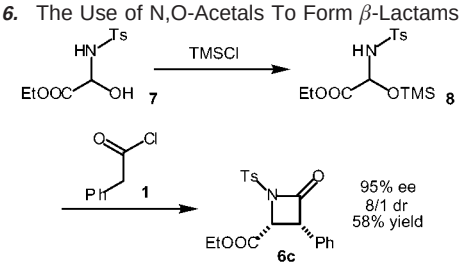
We compared our other three ketene generation methods to determine the possible effect on yield and selectivity. As expected, we found that the use of BEMP provided product **6i** with similar results (Table 2, entry 2, 58% yield, 99% ee, 99/1 dr) to that of proton sponge. When K_2CO_3 was used as the stoichiometric base, the enantioselectivity and diastereoselectivity were decreased somewhat (entry 3, 56% yield, 93% ee, 8/1 dr). Finally, we found that the use of NaH led to **6i** with similarly high selectivity (entry 4, 60% yield, 99% ee, 25/1 dr). Of the four stoichiometric bases employed NaH was by far the least expensive, being two times less expensive than K_2CO_3,



quinine amide **4c**

Figure 3. Homology between the structure of achiral bifunctional catalyst and the quinuclidine and amide groups of **4c**.

Scheme 6. The Use of N,O-Acetals To Form β-Lactams



eleven times less expensive than proton sponge, and *over 850 times* less expensive than BEMP.

Due to its similarity with trans-selective catalyst **4h** (entry 3, Table 1), quinine amide **4c**, made in three steps from quinine, was also investigated (Figure 3). We found that **4c** behaved similarly with respect to BQ in several reactions. For example, phenyl-substituted β-lactam **6b**, was obtained with somewhat decreased selectivity (89% ee, 10:1 dr) although not as the trans diastereomer. It appears that the other substituents on the skeleton of the alkaloid catalyst are effectively controlling the diastereoselectivity.

For many purposes tosyl groups are not ideal substituents for the nitrogen atom of β-lactams. Other sulfonyl groups would be more desirable for many applications. Along these lines, we have developed an alternative procedure for conducting the reaction that potentially allows for the use of other sulfonyl substituents (Scheme 6). Beginning with easy-to-make *N*,*O*-acetal **7** (readily available from glyoxylate and sulfonamide) in situ silylation with TMSCl presumably leads to intermediate **8**. We found in an earlier work that **8** can be converted to the imine in situ upon which it can react in an enantioselective fashion to form the desired products.[53] For example, **7** leads to product **6c** (58% yield, 95% ee, and 8/1 dr). In this work, we successfully employed a variety of different sulfonyl groups in our *N*,*O*-acetals.

In an effort to improve the overall yield, we investigated the effect of Lewis acids on the standard reaction of **1c** and **5a** catalyzed by BQ. To our surprise, we found that the simple addition of 10 mol % of inexpensive $In(OTf)_3$ to the 10 mol % BQ/proton sponge shuttle system *afforded β-lactam* ***6c*** *in 92% yield and comparable selectivity* (98% ee, 60:1 dr).[54]

Stereochemical Models. Given the size of the putative reactive complexes between the cinchona alkaloid derivatives and ketenes, their conformational flexibility, and all-organic nature, molecular mechanics (MM) calculations were judged

(50) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990**, *46*, 2255−2262.
(51) Azidoacetyl chloride has previously been used to make azido-substituted β-lactams by Bose. See ref 21.
(52) (a) Shibuya, M.; Jinbo, Y.; Kubota, S. *Chem. Pharm. Bull.* **1982**, *32*, 1303−1312. (b) Ojima, I.; Suga, S.; Abe, R. *Tetrahedron Lett.* **1980**, *21*, 3907−3910.
(53) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168−2169.
(54) A preliminary screen shows that this yield enhancement holds true for aliphatic and oxygen-substituted ketenes as well France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org.Lett.* **2002**, *4*, 1603−1605.

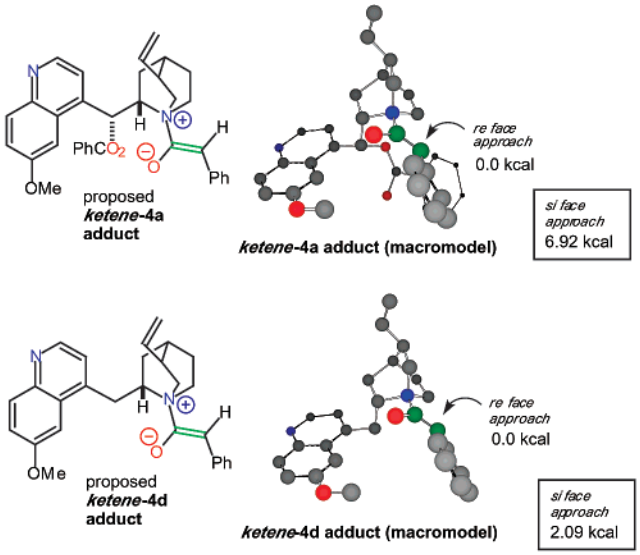


Figure 4. Stereochemical models of the putative zwitterionic intermediates of BQ, deoxy BQ, and phenylketene.

to be the best method to formulate useful stereochemical models for the β-lactam forming reactions. For example, Monte Carlo calculations employing the Macromodel program (AMBER force field) on the putative zwitterionic intermediate of BQ and phenylketene afforded several closely structurally related energetic minima represented by **ketene-4a**, a ketene−catalyst adduct in which the quinine moiety is preferably trans to the substituent across the C═C bond (Figure 4). The model shows that the *re*-face (top face) of the ketene C═C bond (highlighted in green) is completely open to the approach of an electrophile. The model correctly predicts the stereoregular sense of induction observed in the β-lactam forming reactions, and is consistent with other models proposed for cinchona alkaloid catalyzed processes.[24] In stark contrast, the lowest energy minimum in which the *si*-face is exposed is calculated to be almost 7 kcal/mol higher in energy.

Similar calculations on the adduct of phenylketene and deoxyquinine **4d** predict the same sense of induction (as observed, Figure 4) except for the fact that the lowest *si*-face conformation is now about 2 kcal/mol higher in energy, a smaller gap reflected in the diminished ee (72%) that we observed. This calculation suggests that the presence of the "oxy" stereogenic center in BQ is not critical to the sense of induction, and it is the steric bulk of the benzoyl group that is most critical in enhancing selectivity.

To confirm the validity of this conclusion, we investigated the consequence of epimerizing the "oxy" stereogenic center α to the ester oxygen (affording benzoylepiquinine, or BEQ). Macromodel calculations predict the *same sense* of induction as that seen in BQ-catalyzed reactions. As seen in model **ketene-4e**, the *re*-face of the ketene zwitterion is still exposed (Figure 5). The lowest energy corresponding *si*-face exposed conformer is some 6.69 kcal/mol higher in energy. When we performed a β-lactam forming reaction using BEQ (phenylacetyl chloride **1c**, imino ester **5a**) under standard conditions with proton sponge as the stoichiometric base, we obtained a 57% yield of the cis diastereomer **6c** in 97% ee, confirming our prediction. Thus, we can conclude that the orientation of the "oxy" center is not critical to selectivity.

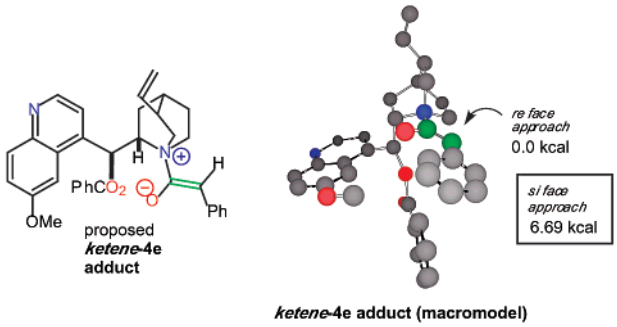


Figure 5. Stereochemical models of the putative zwitterionic intermediate of BEQ (**4e**) and phenylketene.

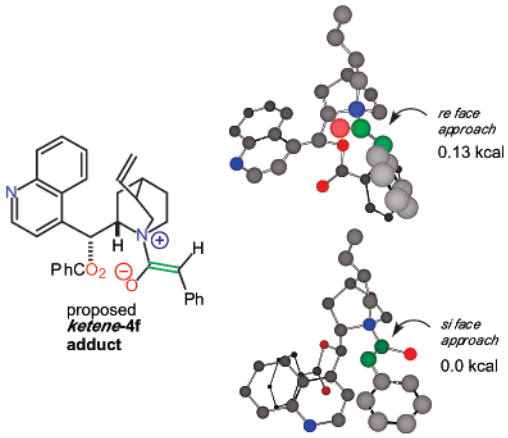


Figure 6. Stereochemical models of the putative zwitterionic intermediate of BC and phenylketene.

Another surprising effect that we observed concerns the catalyst benzoylcinchonidine (BC, **4f**), in which the methoxy group of complex **ketene-4a** is absent. MM calculations on the complex of **4f** with phenylketene (Figure 6) reveal two very closely spaced low-energy minima. One minimum has its *si*-face exposed, the other, only 0.13 kcal higher in energy, has its *re*-face exposed. For all purposes, the calculation predicts that a racemic β-lactam product should result. In this event we found that the product of the reaction of imino ester **5a** with phenylketene is indeed racemic. *We therefore conclude that the presence of the methoxy group is critical for selectivity.* Operationally, it appears that the methoxy group serves to anchor the quinoline moiety proximate to the ketene-derived enolate. When the methoxy group is absent, the quinoline moiety may spin away to another isoenergetic conformation, allowing the face of the ketene to flip. We have proposed that quinine amide **4c** engages in hydrogen bonding with the ketene enolate in the activated complex **ketene-4c**, yielding product with the same sense of induction as BQ. Macromodel calculations were performed on model complex **ketene-4c**, and a low-energy complex was found in which an intramolecular hydrogen bond stabilized the oxygen of the ketene enolate, leaving the *re*-face exposed to attack of an electrophile (Figure 7). The corresponding low-energy structure with the *si*-face exposed is 3.84 kcal/mol higher in energy. The energy difference between the two faces is a factor of 2 smaller than that of BQ, explaining the decreased selectivity when using **4c** (89% ee). This calculation suggests, however, that hydrogen bonding can be used as an organizing principle in the catalyst design of ketene reactions. The performance of various cinchona alkaloid derivatives in

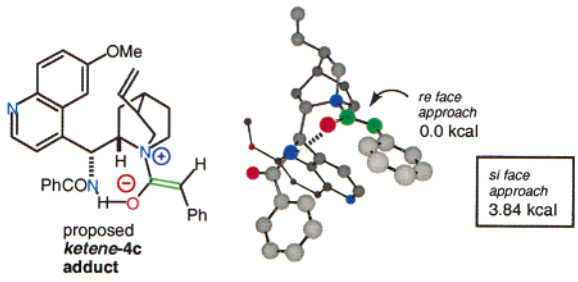


Figure 7. Stereochemical model of the zwitterionic intermediate when using benzamidoquinine **4c**.

Table 3. Summary of the Selectivities Imparted by Cinchona Alkaloid-Derived Catalysts

catalyst	% ee	dr
benzoylquinine **4a**	99	99/1
benzoylquinidine **4b**	99 (ent)	99/1
benzoyl-epi-quinine **4e**	99	99/1
benzamidoquinine **4c**	89	10/1
deoxyquinine **4d**	72	2/1
benzoylcinchonidine **4f**	5	5/1

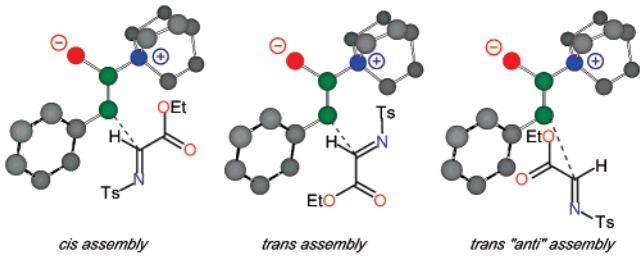


Figure 8. Stereochemical models of cis and trans diastereoselectivity.

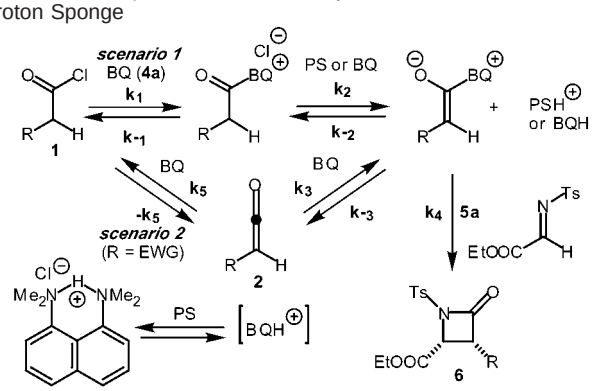
our reactions is summarized in Table 3. Depending on the nature of substituents on the alkaloid catalyst, selectivities range from >99% ee to virtually racemic. As a final comment, these calculations demonstrate that the selectivity of cinchona alkaloid catalyzed ketene reactions can, in certain circumstances, be predicted with some accuracy. They also suggest that on this basis other effective nucleophilic catalysts can be designed and synthesized as desired.

Models for Diastereoselectivity. One of the hallmarks of these BQ-catalyzed reactions is predominant cis diastereoselectivity for a wide variety of ketenes. To shed light on these results, we performed MM calculations (Macromodel, AMBER force field) in which we dock imino ester **5a** to the zwitterionic enolate (derived from BQ and phenylketene) at 2.2 Å to represent, albeit in the crudest fashion, a transition state distance.

The lowest energy assembly is derived from interaction with the *re*-faces of **4a** and **5a**, leading to the cis product. The structures represented in Figure 8 show interaction between the enolate, in model form, and **5a**. The imine C=N bond in the cis assembly is antiperiplanar to the enolate C=C bond (in green), a low-energy "open" transition state orientation is proposed to account for the diastereoselectivity of the Mukaiyama aldol reaction.[55] The lowest energy trans assembly is

(55) (a) Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 2951−2962. (b) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707−709.

Scheme 7. Proposed Mechanism of β-Lactam Formation with Proton Sponge



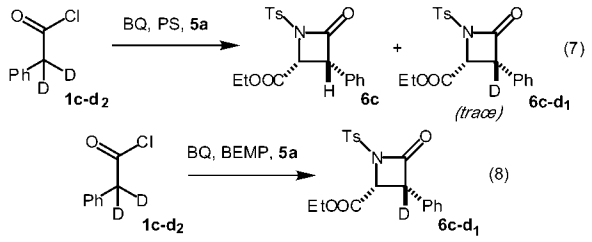
several kilocalories higher in energy than the cis, reflecting our experimental results. In this case, the C=C enolate bond and the C=N imine bond are gauche, rather than anti to each other, once again an orientation that has been proposed to be higher in energy. The alternative trans "anti" conformation suffers from apparent close contact of the carboethoxy and phenyl groups.

Mechanism of β-Lactam Formation with Proton Sponge as the Base. We investigated the mechanism of the β-lactam formation reaction, with proton sponge as the base, through rate studies and deuterium-labeling experiments. The studies outlined below allow us to propose a detailed mechanism, shown in Scheme 7. We were especially interested in two questions: namely, what is the rate determining step of the reaction, and are ketenes necessarily formed in all cases, or is it possible that in certain instances, the reaction preempts ketene formation to proceed directly to the β-lactam from a zwitterionic intermediate?

For example, if k_4[zwitterion][imino ester] > k_3[zwitterion] (where k_3 encompasses the possible rate dependence on any other species) then free ketene will not, or need not, be formed to any appreciable extent. Of course, if the imino ester **5a** is withheld from the reaction, then free ketene should be formed. By varying the concentrations of acid chloride, imine, proton sponge, and catalyst, we found that the initial rate of reaction is dependent on the concentrations of acid chloride and catalyst. The concentrations of proton sponge and imine have *no effect* on the rate of product formation. A plausible rate determining step for the reaction involves one of three scenarios: (1) formation of the acylammonium salt as an initial intermediate, (2) a concerted dehydrohalogenation of the acid chloride by BQ to yield the ketene directly, or (3) the (rate determining) deprotonation of the acylammonium salt by a second molecule of BQ. Scenario 3 can be ruled out since we know that the rate of reaction is first order in BQ (we would expect second order behavior for this step in the former scenario) and zero order in proton sponge. The first and second scenarios are more difficult to distinguish, although the second should give rise to a substantial primary kinetic isotope effect (KIE) for an *irreversible* ketene forming reaction.

Consequently, we sought also to illuminate mechanistic details by a series of kinetic isotope studies and deuterium-labeling experiments. We measured a KIE of only 1.1 for the reaction of **1c**-d_2 as compared to **1c**, a fact which, upon the surface, appears to rule out scenario 2. To our surprise, when *2,2-d*$_2$-phenylacetyl chloride (**1c**-d_2) was allowed to react to form β-lactam product to completion under standard conditions, the

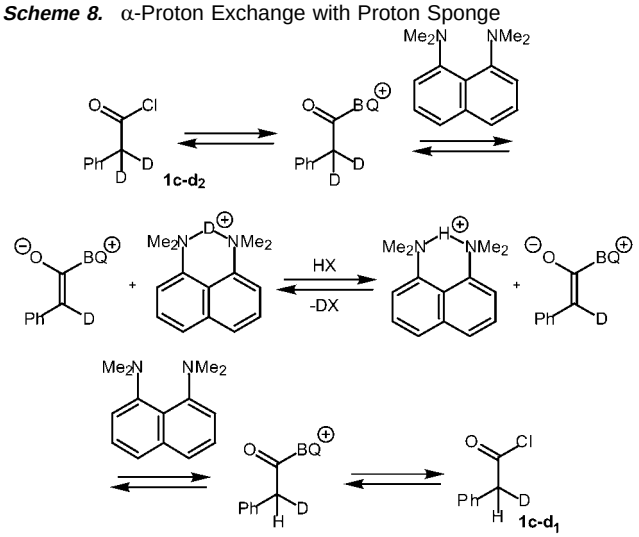
products contained only trace amounts of deuterium (eq 7). However, when **1c**-d_2 was treated with BEMP resin to form phenylketene directly, labeled product **6c**-d_1 was isolated in good



yield (eq 8). We interpret this result to imply that, with PS as the stoichiometric base, the ketene (or zwitterionic enolate) is formed reversibly. The pK_a difference between the enolate and proton sponge is expected to be small enough in an organic solvent to ensure reversibility. It should be noted that when scrupulous regard is paid to excluding moisture, the reaction of eq 7 yields **6c**-d_1 predominately. Consequently, the isotope effect of 1.1 that we measured is more likely a normal equilibrium effect than a KIE (involving formation of an sp^2-bound H or D) and scenario 2 cannot be ruled out on this basis. Precedent suggests that acylammonium salt intermediates are involved in the synthesis of the majority of ketenes; however, for acid halides possessing certain electron-withdrawing groups in the α-position, direct dehydrohalogenation (scenario 2) may operate.[37,56]

We can conclude that in the presence of trace amounts of water (or other Brønsted acids HX), the deuteron in PS·DCl exchanges for a proton (Scheme 8), forming PS·HCl, which can protonate the enolate, thus effecting the exchange. Under the conditions of our reaction, we obviously have enough adventitious HX or water present to promote an almost complete exchange. When solid-phase based BEMP (a powerful base) is employed, ketene is formed irreversibly, so the deuterium label is preserved in the product.

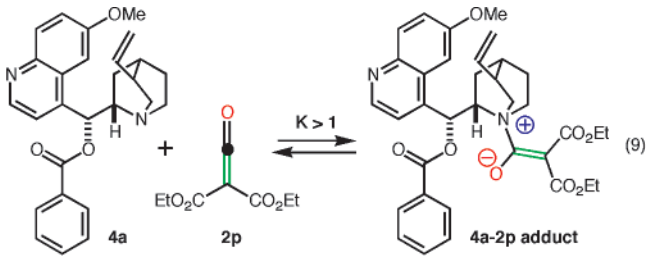
Scheme 8. α-Proton Exchange with Proton Sponge



As a confirming experiment to determine if a second molecule of BQ could be acting as a shuttle base (scenario 1), we ran a reaction where we replaced BQ with a nucleophile that is unlikely to act as a competent base. When the reaction was run under standard conditions with PPh_3[57] (instead of BQ), proton sponge, and **1c**, only a trace of product **6c** was observed. This lends credence to the idea that a second molecule of BQ could be acting as a shuttle base and transferring the proton from the acylammonium salt to proton sponge, regenerating the catalyst.

We have also examined the formation of diphenylketene from proton sponge and BQ by ReactIR. In the absence of imine **5a**, an equilibrium between acid chloride and free ketene is established over time, as witnessed by the observed IR frequencies for the ketene and acyl chloride C═O stretches, a spectroscopic conformation of the kinetic data that we assembled for phenylketene. If the experiment is performed under identical conditions in the presence of imine, no free ketene is observed (although we obviously cannot strictly rule out its intermediacy in low concentrations). What allows us to conclude that free ketene need not be involved in this particular reaction is the fact that the rate of ketene formation in experiment one is less than the rate of product formation in experiment two. Whether this conclusion holds for all manner of ketenes cannot be concluded at this point. *However, we can conclusively state that scenario 2, which requires the formation of free ketene, cannot be the predominate reaction mode in this case.* Although the question of whether free ketene is formed in the reaction is mainly semantic, there could be a practical consequence. For example, if free ketenes are not formed, then reactions such as ketene dimerization, which in some cases may require the presence of free ketene, should be suppressed.

Spectroscopic Observation of a Zwitterionic Enolate. Reaction of a ketene and an amine base to form a zwitterionic intermediate is a reversible process whose equilibrium constant should be dependent on the basicity of the amine as well as the electrophilicity of the ketene. Considering the reaction of BQ with diphenylketene, for example, the equilibrium constant is almost certainly much less than one, making the derived enolate difficult to observe spectroscopically (eq 9). To observe stable,



characterizable zwitterionic intermediates, we employed the much more electrophilic ketene **2p** in order to favor formation of the intermediate. Dicarboethoxyketene **2p** is known to form adducts with DMAP,[58] and consequently we studied its reaction with BQ through IR and NMR spectroscopy. A preliminary DFT calculation we performed (B3LYP/6-31G*) revealed a stable adduct **9** of an electronically similar electrophilic ketene with a quinuclidine core, suggesting the viability of an experiment to observe the enolate intermediate directly. Interestingly, the distance from the quinuclidine N to the ketene carbonyl carbon

(56) Brady, W. T.; Scherubel, G. A. *J. Org. Chem.* **1974,** *39*, 3790−3791. (b) Brady, W. T.; Scherubel, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7447−7449. (c) Walborsky, H. M. *J. Am. Chem. Soc.* **1952**, *74*, 4962−4963.

(57) We had previously found that triphenylphosphine catalyzed the reaction of **2b** with **5a**.

(58) Gompper, R.; Wolf, U. *Liebigs Ann. Chem.* **1979**, 1388−1405.

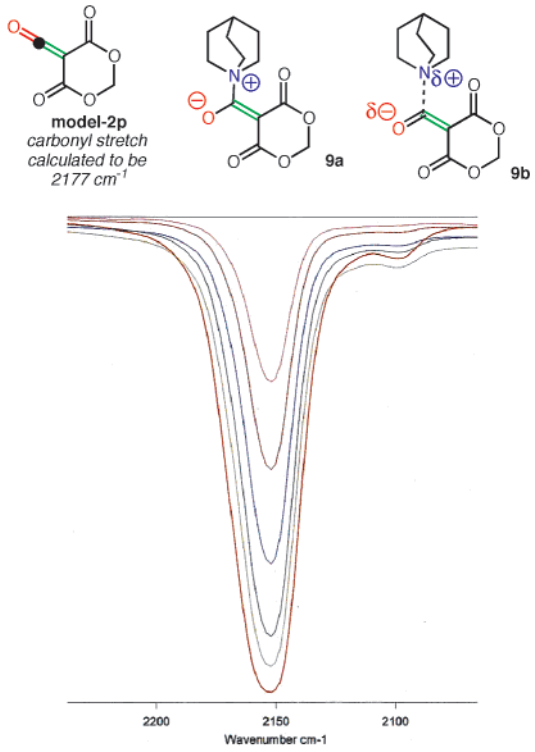


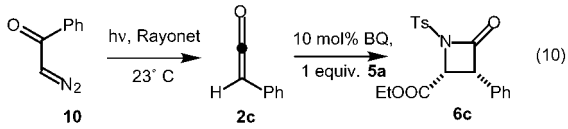
Figure 9. Diagnostic ketene stretch at 2155 cm^{-1} for the **4a**−**2p** adduct.

is calculated to be long (1.70 Å), whereas the zwitterionic C−O^- bond in **9a** is very short (1.19 Å)—virtually a C═O bond, facts perhaps better represented by **9b**. Other adducts derived from less electrophilic ketenes are often not computationally stable and dissociate during the calculation.

A solution of the ketene in toluene revealed a carbonyl stretch at 2155 cm^{-1} (Figure 9). As BQ was added, this peak diminished in intensity, and the ester carbonyl peaks shifted to lower wavenumber, consistent with formation of a zwitterion.[59] A new resonance of strong intensity was observed at 1730 cm^{-1}, in good agreement with the calculated vibrational frequency of 1741 cm^{-1} (scaled)[60] for a coupled stretch of an ester carbonyl group and the "C−O" bond of the ketene zwitterion. The reaction of BQ with ketene **2p** is not instantaneous, but equilibrium is reached after about 5 min; whereupon the IR spectrum remains stable, contraindicating a catalytic chemical reaction. Quenching the reaction with MeOH affords a quantitative yield of the corresponding triester, affirming that another competing chemical process is not occurring.

In summary, the kinetics experiments, precedent, and IR spectroscopic data we have gathered are all consistent with the formation of an acylammonium salt in the rate determining step and subsequent zwitterion formation, followed by fast reaction with imine **5a** (Scheme 7). Formation of the crucial zwitterionic intermediate is reversible, and putative β-lactam ring closure and ejection of the catalytic nucleophile to form the product also must be fast steps in the reaction.

Photochemical Generation of Phenylketene. Another experiment conclusively determined that free monosubstituted ketenes *can* be precursors in the reaction (as we believe they must be for the carbonate and hydride shuttle deprotonation procedures). For example, when diazoketone **10** is photolyzed, it produces phenylketene **2c** through a standard Wolff rearrangement (eq 10). We photolyzed **10** in the presence of imino



(10)

ester **5a** and BQ catalyst to form lactam **6c** in 52% yield (dr 5/1, ee 93%). The yield and product selectivity obtained are similar, if slightly less than the proton sponge promoted experiments, and suggest that zwitterionic intermediates can be formed from chemically distinct precursors.

Conclusion

We have reported a catalytic, asymmetric route to β-lactams using chiral amines to catalyze a reaction between ketenes (or derived zwitterionic enolates) and corresponding electron-deficient imines. Kinetics experiments, labeling studies, and direct observation of intermediates, as well as stereochemical models, have helped to formulate a proposed mechanism for the reaction. Further work will center on a trans-selective asymmetric β-lactam forming process.

Experimental Section

General Procedure for β-Lactams 6 with Proton Sponge.[61] To a solution of phenylacetyl chloride (20 mg, 0.129 mmol) in toluene (0.5 mL) at −78 °C[62] was added proton sponge **3b** (31 mg, 0.142 mmol) in toluene (0.5 mL) immediately followed by benzoylquinine **4a** (6 mg, 0.0129 mmol) and α-imino ester **5a** (33 mg, 0.129 mmol). The reaction was allowed to stir for 5 h as it slowly warmed to room temperature. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (15% EtOAc/hexanes) on a plug of silica gel to yield **6c** (65% yield, 33 mg).

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Supporting Information Available: General procedures for using BEMP, K_2CO_3, and NaH as the stoichiometric base, compound characterization, and kinetic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0258226

(59) See Supporting Information for the full IR spectrum.
(60) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.
(61) A large-scale reaction (2.6 mmol) was carried out to form **6c** by multiplying the amounts of reagents and solvents by a factor of 20. Similar values for ee, dr, and yield were received.
(62) It was found that the optimal conditions for in situ generation of ketenes **2b**, **2h**, and **2i** were to stir the solution of proton sponge and acid chloride at 0 °C for 30 min and then reduce the temperature to −78 °C proceeding with the standard reaction conditions. These conditions better effect dehydrohalogenation for more stable ketenes.