Catalytic, Asymmetric Synthesis of β-Lactams

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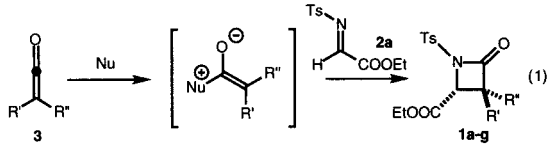
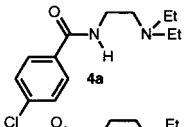
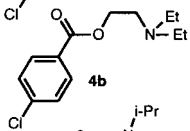
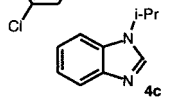
The paramount importance of β-lactams (**1**) to pharmaceutical science and biochemistry has been well established.[1] New chiral β-lactams are in demand as antibacterial agents, and their recent discovery as mechanism-based serine protease inhibitors[2] has kept interest in their synthesis at a high level.[3] However, most chiral methodology is auxiliary-based; only one catalytic, asymmetric synthesis of the β-lactam ring system is known, affording product in modest enantioselectivity.[4] Many asymmetric auxiliary-based β-lactam syntheses rely on the reaction of imines with ketenes, a process that generally proceeds without a catalyst.[3] We recently accomplished a catalyzed reaction of imines and ketenes by making the imine component non-nucleophilic, as in electron-deficient imino ester **2a**.[5] In this contribution, we report the catalytic, asymmetric reaction of imine **2a**[6] and ketenes **3** to produce β-lactams diastereoselectively and enantioselectively employing chiral nucleophilic amines as catalysts.[7]

When imine **2a** is mixed with test electrophile diphenylketene **3a,** it does not react at −78 °C and only very sluggishly at higher temperatures. However, in the presence of suitable nucleophilic catalysts, the reaction occurs smoothly to afford *rac*-β-lactam **1a** in good chemical yields at room temperature (eq 1, R′ = R″ = Ph). As a first step toward an asymmetric β-lactam synthesis, we



examined the diastereoselective amine catalyzed reaction. Methylphenylketene **3b** (R′ = Me, R″ = Ph), which reacts with imine **2a** to form two diastereomers (trans-**1b** R′ = Ph, R″ = Me; cis-**1b** R′ = Me, R″ = Ph), was our test electrophile (Table 1). The *cis*−*trans* diastereomeric ratio (dr) produced in the reaction of **2a** and **3b** catalyzed by triethylamine is about 1/1. We thought that a catalyst containing a nucleophilic center in tandem with an electrophilic center (e.g., a hydrogen bond donor) could potentially rigidify a proposed activated complex and afford products in higher dr.[8] As expected, the reaction of **2a** and **3b** catalyzed by 10 mol % bifunctional amine **4a** gave a *cis/trans* dr of 3/97. A significant role for the H-bond contact in **4a** is suggested, as the sterically similar catalyst **4b**, which does not contain a hydrogen bond donor, gave low diastereoselectivity (dr = 34/66). Similarly, when catalyst **4a** is used in the presence of a small quantity (10 mol %) of DMSO (a good hydrogen bond acceptor), the diastereoselectivity also erodes (dr = 40/60), implying an intramolecular H-bonding role for the electrophilic amide hydrogen. Remarkably, when benzimidazole **4c** is the catalyst, the *opposite* (*cis*) diastereomer is highly favored (dr 98/2).

Table 1. Diastereoselectivity in the Nucleophile-Catalyzed Reaction of Methylphenylketene **3b** with Imine **2a**

catalyst[a]	solvent	yield	dr (cis/trans)
NEt_3	THF	83%	55/45
 **4a**	THF	80%	3/97
 **4b**	THF	77%	34/66
 **4c**	THF	79%	98/2

[a] Reactions run with 10 mol% catalyst at −78 °C and allowed to slowly warm to room temperature overnight.

The successful development of diastereoselective amine-based catalysts prompted us to screen optically active cinchona alkaloid derivatives as potential enantioselective and diastereoselective catalysts.[9] The reaction of imine **2a** and ketene **3a**, catalyzed by 10 mol % benzoylquinine (BQ, **6a**)[10] affords product in toluene at −78 °C in 20% yield and 0% ee. We found that use of THF under similar conditions at −78 °C affords product in 35% yield and in 70% ee; running the reaction with minimal solvent increases the yield (92%) but annihilates enantioselectivity (0%). The most notable discovery was made when the reaction was run in higher dilution, (i.e., the concentration of imine, ketene, and catalyst were reduced by a factor of 10, to 0.1, 0.1, and 0.01 mM, respectively) affording product in 99% ee in THF at −78 °C,[11] although under these conditions the yield (36%) is still modest. Similarly, although we successfully employed methylphenylketene **3b** in highly diastereoselective reactions, it turned out to be a capricious substrate in enantioselective reactions.

We then turned our attention to other, more reactive monoketenes, a fact that mandates their syntheses in situ from acid chlorides.[12] This transformation presents its own problems—the use of amine bases as dehydrohalogenating agents generates ammonium salts as interfering byproducts and often leaves

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(2) For a general account: Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. *Biochemistry* **1999**, *38*, 7989.

(3) Review: Palomo, C.; Aizpurua, J. M.; Iñaki, G.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *3223*, 3.

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(5) Wack, H.; Drury, W. J., III; Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett*. **1999**, *1*, 1985.

(6) We have used α-imino ester **2a** 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. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. Imine **2a** was first used in work by: (c) Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(7) Ring opening of β-lactams under mild conditions provides access to various optically pure β-amino acid derivatives whose synthesis is of recent interest, see: Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.

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(9) For other, excellent uses of cinchona alkaloids in asymmetric synthesis see: Ester synthesis; (a) Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157. Lactone synthesis; (b) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. Ketene dimerization; (c) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006. (d) Calter, M. A.; Guo, X. *J. Org. Chem*. **1998**, *63*, 5308. Baylis-Hillman reaction; (e) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc*. **1999**, *120*, 10219. Osmylation reactions; (f) Kolb, H. C.; VanNieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. Phase-transfer catalysis; (g) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1999**, *120*, 13000. (h) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. Peptide based catalysis; (i) Jarvo, E. R, Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J. Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**; *121*; 11638.

(10) Pracejus, H.; Maetie, H.; *J. Prakt. Chem.* **1964**, *24*, 195.

(11) For further details on the conduct of this reaction, including stereochemical proofs, see the Supporting Information.

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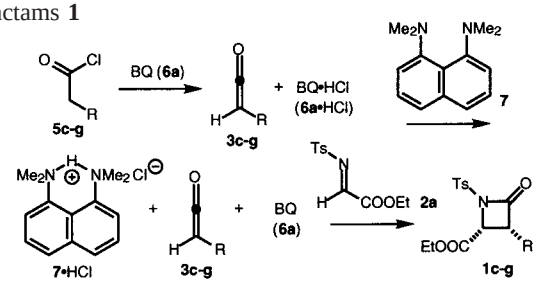
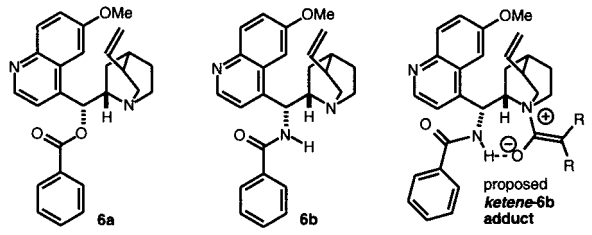
Scheme 1. Catalytic, Shuttle-Base Route to Optically Active β-Lactams **1**



residual base that catalyzes the β-lactam reaction racemically. For example, the use of Hünig's base to generate phenylketene in situ with BQ catalyst **6a** afforded racemic product **1c** in low yield at −78 °C in THF or toluene. One interesting approach to the synthesis of ketenes in situ would be the use of the strong organic base "proton sponge" **7** as a non-nucleophilic deprotonating agent. However, simply mixing 1 equiv of **7** and acid chloride **5c** at low temperature does not produce detectable amounts of ketene. Although **7** is a strong thermodynamic base, it is hindered and kinetically slow at deprotonating carbon-based acids.[14] Ideally, to make **7** effective as an HCl sink, a "relay" or "shuttle" base, that is, one that is thermodynamically weaker but kinetically active would serve to liberate HCl from the acid chloride and transfer it to **7**, which then precipitates as its HCl salt. Along those lines, we found that toluene precipitates salts well and affords the best conditions for monoketenes. In practice, BQ (**6a**) serves as an excellent shuttle base when added to the solution of phenylacetyl chloride **5c** and **7** in toluene at low temperature; a yellow solution of phenylketene **3c** was formed along with a white precipitate over the course of a few minutes (Scheme 1).[13] Imino ester **2a** was then added to the solution at −78 °C, and the characteristic ketene color disappeared over the course of 2 h to give *cis*-lactam **1c** in 96% ee (65% yield, 99/1 dr, Table 2, entry 2).[15] In this reaction, BQ plays two distinct catalytic roles as a dehydrohalogenation agent and a nucleophilic catalyst.

We obtained other β-lactams from a variety of in situ generated ketenes (Table 2). For example, ethylketene **3d** (generated from butyryl chloride **5d)** affords *cis*-diastereomer **1d** in 57% yield[16] and 99% ee (entry 3).[17] Phenoxyketene **3e** (from phenoxyacetyl chloride **5e**) also produced the *cis*-diastereomer **1e** (45%) and 99% ee (entry 4). Other oxygen-substituted ketenes (acetoxyketene and benzyloxyketene) afforded products in high enantio- and diastereoselectivity (entries 5 and 6).[18] These β-lactams have historically presented a challenge for asymmetric synthesis due to the lack of a suitable chiral auxiliary on oxygen.[3] In analogy to our successful results using catalyst **4a** in a diastereoselective reaction, we sought to screen quinuclidine catalyst **6b** (note the similar



relationship of the amide proton donor to the nucleophilic center)

Table 2. Reaction of Ketenes **3** and Imine **2a** Catalyzed by BQ **6a** to Form β-Lactams **1**[a]

entry	acid chloride	ketene	product	% ee	dr (cis/trans)[c]	% yield[d]
1	**5a**[b]	**3a**	**1a**	99	--	36
2	**5c**	**3c**	**1c**	96	99/1	65
3	**5d**	**3d**	**1d**	99	99/1	57
4	**5e**	**3e**	**1e**	99	99/1	45
5	**5f**	**3f**	**1f**	98	>99/1	61
6	**5g**	**3g**	**1g**	95	99/1	56

[a] Reactions run with 10 mol% catalyst (0.13 mmol ketene, 0.13 mmol imine, and 0.14 mmol proton sponge) at −78 °C → 25 °C for 5 h in 2 mL of toluene. [b] Run in 10 mL of THF solvent. [c] Dr determined using ^{1}H NMR and confirmed by HPLC. [d] Yield of major diastereomer.

in an effort to gauge the effects on diastereoselectivity. In fact, we found that this catalyst affords product **1c** with high ee (89%) and good yield (65%) for phenylketene **3c** with the *cis* diastereomer favored (dr = 91/9). When the reaction is run under standard conditions in a solvent that can compete for hydrogen bond donors, such as propionitrile, the dr erodes to 1/1, once again implying a role for the hydrogen bond in the activated complex.[19]

The tosyl group on β-lactams can be readily removed by treatment with 2 equiv. SmI_2 in THF at room temperature for 20 min.[20] For example, **1g** afforded the deprotected product in 90% yield. This procedure is simple, mild, tolerates a number of functional groups on the β-lactam, and should prove useful for other β-lactam deprotections.

In conclusion, we have reported the first highly enantioselective synthesis of the β-lactam ring system using a nucleophile-catalyzed reaction of electron-deficient ketenes and imines. Our methodology is being applied to the synthesis of other biologically active classes of β-lactams, including α-amino-β-lactams, and further reports will be forthcoming.

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Supporting Information Available: Experimental procedures including the synthesis and characterization of compounds, stereochemical proofs, and crystal structure data for *cis*-**1b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001754G

(12) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742. Additional information can be found in: Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(13) A procedure for the in situ generation of ketenes, utilizing basic scavenger resins, is under development and will be published in due course.

(14) (a) Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* **1990**, *26*, 255. (b) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215.

(15) See the Supporting Information for general procedures.

(16) The nonoptimal yields may be due to slow polymerization of the imine.

(17) β-Lactam **1d** has been investigated by DuPont-Merck as an inhibitor of human elastase: Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990,** *46*, 2255.

(18) Ring opening of these β-lactams provides entry to various *syn*-alkyl-substituted aspartic acids. For a previous synthesis from β, β-disubstituted α-enamides through catalytic hydrogenation, see: (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. Synthesis from β-lactams; (b) Palomo, C.; Aizpurua, J. M.; Ontoria, J. M.; Iturburu, M. *Tetrahedron Lett.* **1992**, *33*, 4823.

(19) In propionitrile solvent, benzoylquinine **6a** functions as a highly diastereoeselective catalyst, yielding product **1c** with a dr of 95/5.

(20) SmI_2 is known to deprotect *N*-benzyloxy β-lactams: (a) Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, K.; Langenhan, J. M.; Sun, L.; Akhiezer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237.