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Column Asymmetric Catalysis for β-Lactam Synthesis

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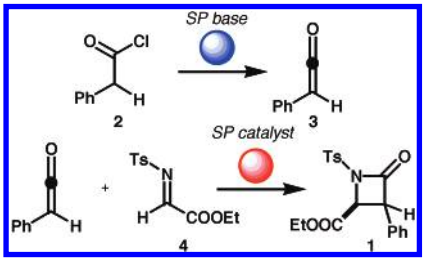
ABSTRACT



A catalytic asymmetric reaction process was designed involving the use of solid-phase reagents and catalysts that constitute the packing of a series of "reaction columns". This process was applied to the catalytic asymmetric synthesis of β-lactams, yielding pure product after crystallization with exceptional enantio- and diastereoselectivity.

In the realm of chiral synthesis and drug discovery, asymmetric catalysis[1] and solid-phase chemistry[2] are playing increasingly pivotal roles. Since chiral catalysts are often expensive, it is important that they be easily recovered from the reaction mixture.[3] In addition, to be industrially applicable, the product must be free of contaminants so as to avoid the need for extensive purification. Furthermore, additional reagents and solvents must be reusable whenever possible. Along these lines, we have designed a catalytic asymmetric reaction process involving the use of solid-phase reagents and catalysts that constitute the packing of reaction columns. Reagents are added to a series of columns, and gravity or pressure percolate these materials through the packing, where they react to produce an enantiopure product that is eluted at the bottom (Figure 1). After products have been collected, solvent-based regeneration of the solid-phase packing serves to ready the system for another cycle of reagents. Similarly, Jacobsen and others have developed continuous-flow reaction systems incorporating immobilized catalysts, demonstrating their advantages over homogeneous systems.[4] In this Letter, we demonstrate what we term *column asymmetric catalysis* and apply it to the catalytic, asymmetric synthesis of β-lactams, affording products in high yields and enantioselectivity (ee). We also discuss general features of our process and propose how this proof-of-principle can be applied to other practical problems in synthetic chemistry.

Figure 1 shows the assembly we designed for this purpose. It consists of two jacketed columns linked together by a ground glass joint; the top column is packed with a polymer-supported dehydrohalogenating agent that produces analytically pure, extremely reactive ketenes from inexpensive and widely available acid chlorides. The middle column is packed

(1) (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I. Ed.; John Wiley & Sons: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999.

(2) (a) *Solid-Phase Organic Synthesis*; Burgess, K., Ed; John Wiley & Sons: New York, 2000. (b) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley & Sons: New York, 2000. (c) Blackburn, C. *Biopolymers* **1998**, *47*, 311−351. (d) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817−827.

(3) The development of solid-phase chiral catalysts is of recent interest, see: (a) Kobayashi, S.; Kusakebe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225−1227. (b) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501.

(4) (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147−4154. (b) Kamahori, K.; Ito, K.; Itsuno, S. *J. Org Chem.* **1996**, *61*, 8321−8324.

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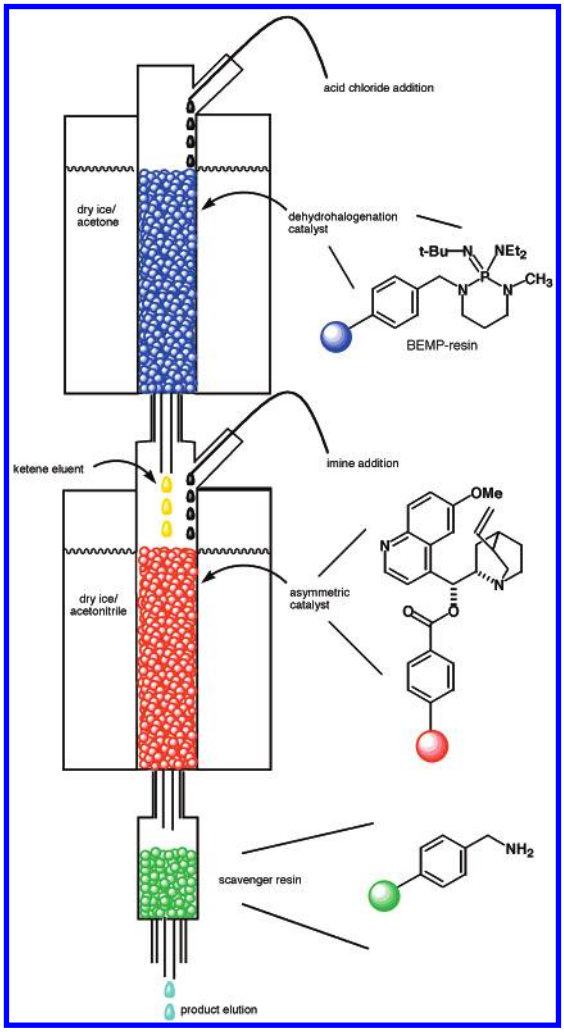
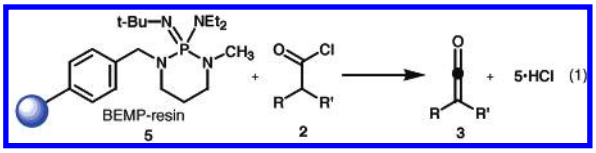


Figure 1. Column asymmetric catalysis assembly.

with a nucleophile-based solid-phase asymmetric catalyst. Between the two columns, an imine is added to the system. An optional third column is packed with a scavenger resin to remove any unreacted ketene or imine from the eluent.[5] The advantages of conducting this type of reaction on a column include (1) obviating the need to isolate and/or manipulate highly reactive ketenes, (2) separating the different solid-phase components easily, (3) recycling the polymer supported reagents and catalysts for additional catalytic reactions, and, finally, (4) avoiding vigorous agitation that can degrade resin beads.

The well precedented[6] in situ generation of ketenes using triethylamine (or other tertiary amines such as Hünig's base) is problematic because the amine itself catalyzes the cycloaddition of ketene **3** and imino ester **4**.[7] Additionally, the byproduct hydrochloride salts also interfere with the catalytic, asymmetric reaction.[8] To overcome these difficulties, we employed resin-bound dehydrohalogenation reagents to allow for the simple isolation of the ketene solution under inert atmosphere at reduced temperature. Standard solid-phase bases such as Amberlite IRA-67, a tertiary amine-based polymer, failed to promote ketene formation to any appreciable extent when phenylacetyl chloride **2** in THF was passed through it in a jacketed column at −78 °C. However, the extremely basic resin BEMP **5**,[9] containing a triaminophosphoamide imine bound to a polymeric support,[10] was found to produce ketenes rapidly and quantitatively (eq 1).



Simply by passing a solution of acid chloride **2** in THF over polymer **5** (1.1 basic equivalents), a yellow solution of phenylketene **3** was eluted instantaneously in high yield. We found that we could also form highly reactive ketenes such as ethylketene, phenoxyketene, benzyloxyketene, acetoxyketene, and phthalamidoketene and believe that this approach should be amenable to the formation of pure solutions of most reactive ketenes. The prime advantage to placing BEMP resin **5** separately on a column is that in a reaction flask the resin was generally found to destroy the imino ester and epimerize the β-lactam product.

In preliminary work, we discovered that when a cold solution of phenylketene (−78 °C) is treated with 1 equiv of imino ester **4** and 10 mol % of benzoylquinine (BQ), β-lactam **1** is formed in 65% yield, 98% de, and 96% ee after purification by column chromatography.[7] Under these conditions the catalyst is difficult to recover in a pure form from the reaction mixture, so a solid phase-based system was immediately deemed desirable. Moreover, the column asymmetric catalysis system eliminated the shortcomings of performing this reaction with the solid-phase components in a conventional reaction flask. In the next step, we attached quinine units to a solid support (Scheme 1) in order to synthesize the chiral packing of the middle reaction column.[11] We chose to derivatize the inexpensive Wang resin with an excess of terephthaloyl chloride. Quinine units were then attached to the derivatized resin by a simple esterification reaction to form solid-phase catalyst **6**. It is significant to note that the length of the catalyst−solid-phase linker is

(5) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881.

(6) (a) Palomo, C.; Aizpurua, J. M.; Inaki, G.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (b) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(7) We have used α-imino ester **4** 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.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. Imine **4** was first featured in work by: (c) Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058−5064.

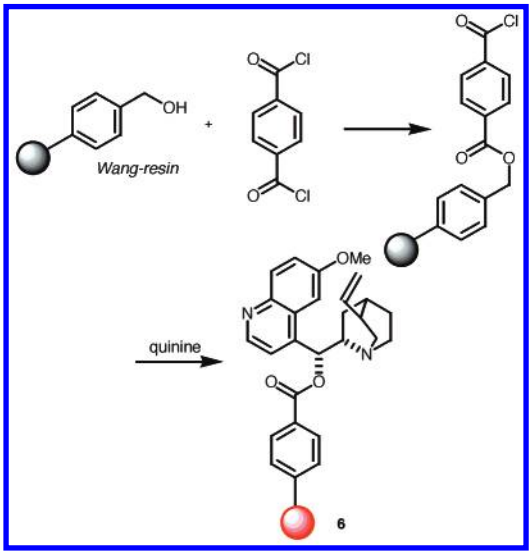
(8) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(9) 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.

(10) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.

(11) For other examples of polymer-supported asymmetric catalysts utilizing cinchona alkaloids, see: Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21−27.

Scheme 1. Synthesis of Solid-Phase Catalyst **6**



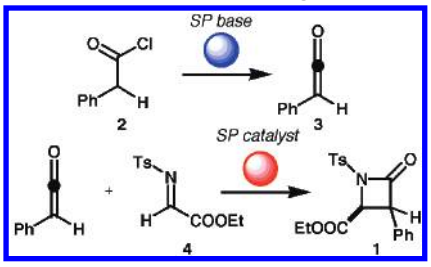
crucial to the success of the reaction; short linkers give inferior results, presumably due to the steric encumbrance of the polymeric support.[12]

Assembly of the system began by loading two fritted, jacketed columns (each 2 cm wide) under nitrogen, the top column with the BEMP resin **5** and the middle column with catalyst-loaded beads **6** (3 cm). The scavenger resin was loaded into a column and attached to the bottom of the apparatus. All columns were flushed with THF (3 mL) under nitrogen. The BEMP column was cooled to −78 °C with a dry ice/acetone mixture. The catalyst-loaded column was cooled to −43 °C by dry ice/acetonitrile.[13] An ambient temperature solution of phenylacetyl chloride **2** (0.14 mM) in THF (0.5 mL) was added to the top column and allowed to percolate by gravity through the BEMP resin and onto the lower catalyst-loaded resin of the bottom column (Scheme 2). Imino ester **4** (0.13 mM in 0.5 mL of THF) was then added through a port onto the lower column. The reaction was initiated by allowing a slow drip of THF from the catalyst column, enough to allow complete elution of the column contents dropwise over the course of 2 h. An additional amount of THF (3 mL) was added to flush the column free of reagants. After passing through the scavenger

(12) The use of shorter linkers decreased the diastereoselectivity to 7:1 possibly because the catalyst was constrained to a nonoptimal conformation. (a) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003−3006. (b) Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Lett.* **1992**, *32*, 5175−5178.

(13) The optimal temperature for column asymmetric catalysis of phenylketene **3a** and imino ester **4** was found to be −43 °C.

Scheme 2. Synthesis of Optically Enriched β-Lactams through Dual Solid-Phase Reagents



resin column, the eluted reaction mixture was concentrated to afford crude β-lactam **1** in 91% ee. Without further purification, crystallization of the residue affords optically and analytically pure material in 65% yield.

To ready the apparatus for another catalytic cycle, the columns were separated and regenerated. The catalyst-loaded resin column was washed with methanol and dried under high vacuum. The BEMP resin was regenerated by rinsing with phosphazene base P_4-*t*-Bu in THF/MeCN (1:1), until the eluent was free from Cl^-, and then dried under high vacuum at 120 °C.[14] The scavenger resin was washed with ammonia and dried under high vacuum. In the extreme, the reaction has been successfully run through the catalyst column 20 times with no significant loss in selectivity or yield (90% ee and 62% yield for run 20).

One can envision practical applications for the synthesis of enantiopure compounds using this methodology. Reactants can be passed through discrete columns containing recyclable reagents, which upon degradation can be swapped out of the production stream and regenerated. The use of reagents on solid support greatly simplifies the purification of the crude reaction mixture, allowing for shorter production times and thus lower costs under certain circumstances. We are currently applying our concept of column asymmetric catalysis to other asymmetric reactions involving solid-phase catalysts.

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Supporting Information Available: General experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.