Asymmetric Catalysis on Sequentially-Linked Columns

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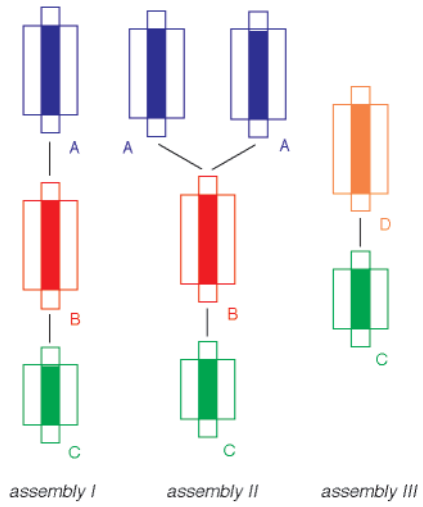
Abstract: We report a catalytic asymmetric reaction process that involves the use of solid-phase reagents and catalysts that constitute the packing of a series of "reaction columns". This process was applied to the catalytic asymmetric synthesis of β-lactams, to yield pure products with excellent enantio- and diastereoselectivity. We have identified several advantages to conducting chemical reactions on sequential columns, including ease of catalyst and reagent recovery and simplified purification steps that preclude the need for chromatography.

Introduction

Technological advances in synthetic chemistry have given chemists a large number of choices in the way that they conduct chemical reactions. In regard to chiral synthesis and drug discovery, asymmetric catalysis[1] and solid-phase chemistry[2] are especially important. Chiral catalysts are usually the most costly components of asymmetric reactions, and ideally they should be recoverable from the reaction mixture in a straightforward fashion.[3] In practice, this is rarely the case—the sensitive catalyst either decomposes or is difficult to reisolate chromatographically. Additionally, to be attractive to industry, the process should avoid the use of column chromatography, and additional reagents and solvents must be reusable whenever possible. With these considerations in mind, we have developed a catalytic, asymmetric reaction process involving the use of columns packed with solid-phase reagents and catalysts. Substrates are added to the top of a series of columns, and through gravity or pressure percolate through the packing, where they react to produce an enantioenriched product that is eluted at the bottom. Afterward, solvent-based regeneration of the system prepares it for another cycle of catalysis. We detail herein what we term "sequential column asymmetric catalysis" (sequential CAC) and apply it to the catalytic, asymmetric synthesis of β-lactams, affording products in good yields, good to excellent diastereoselectivity and enantioselectivity (ee). We also discuss how practical considerations of reagent expense and efficiency led us to design three assemblies (I, II, and III, Scheme 1) that can serve as prototypes for other reactions.

The concept of employing solid-phase reagents packed into columns has been relatively unexplored in academic chemistry. A recent paper details the use of HPLC columns for catalytic, asymmetric hydrolysis reactions.[4] In industry, reaction columns have been used for large-scale synthesis for quite some time; however, much of the technology is proprietary. The novelty of our approach rests on the use of *sequentially linked* columns that perform discrete functions in a reaction sequence. Taken to its logical limit, one can conceive of performing a fairly complex synthetic sequence all on reaction columns, including purification steps. Scheme 1 shows three generic assemblies consisting of jacketed columns and associated linkages. Column types labeled A, for example, contain stoichiometric reagents that convert precursors into substrates for the catalytic, asymmetric reaction. Column type B is packed with the appropriate asymmetric catalyst, loaded onto a suitable polymeric support. Column type C contains scavenger resins to remove byproducts effectively. Variations on this scheme can be imagined—for example, a column can contain both catalysts and reagents packed together (column type D). Each assembly is designed to duplicate stages in catalytic reactions, namely substrate preparation, catalysis, and purification steps.

Scheme 1. Sequential Column Asymmetric Catalysis Assemblies



We have published a number of preliminary reports concerning β-lactam synthesis using chiral nucleophiles as catalysts with ketenes and imines as the reacting substrates.[5] We realized advantages of conducting this type of reaction on a column, including obviating the need to isolate and/or manipulate highly reactive ketenes; separating the different solid-phase components

(1) (a) For a review, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479−483. (c) De Camp, W. H. *Chirality* **1989**, *1*, 2−6.

(2) (a) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817−827. (b) Blackburn, C. *Biopolymers* **1998**, *47*, 311−351.

(3) For a recent review see: (a) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217−1239. For recent examples see: (b) Kobayashi, S.; Kusakebe, K.; Ishitani, H. *Org. Lett*. **2000**, *2*, 1225−1227. (c) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc*. **2000**, *122*, 6500−6501.

(4) Jacobsen, E. N.; Annis, D. A. *J. Am. Chem. Soc*. **1999**, *121*, 4147−4154.

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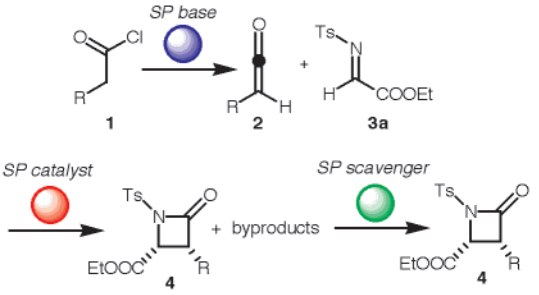
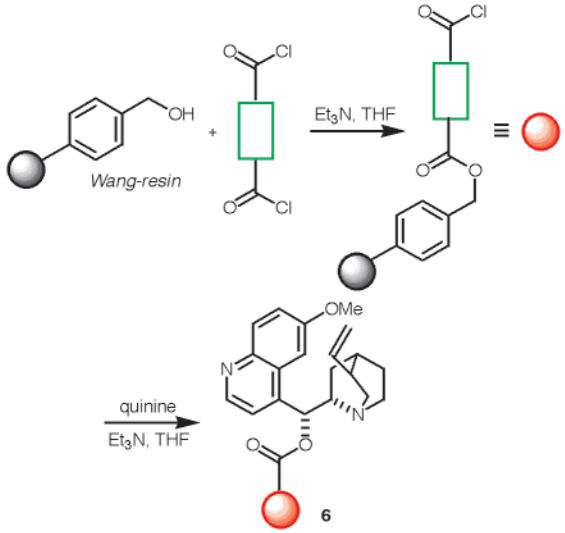
Scheme 2. Catalytic, Asymmetric Synthesis of β-Lactams with Solid Phase Reagents and Catalyst



easily, and recycling the polymers for additional catalytic reactions; and finally, avoiding strong agitation that can degrade resin beads.[6] Scheme 2 illustrates the chemical steps in the catalytic, asymmetric synthesis of β-lactams with solid-phase reagents and catalyst, including a ketene generation step (SP base), the catalytic step (SP catalyst), and a purification step (SP scavenger).

The well-precedented[7] in situ generation of ketenes with triethylamine (or other tertiary amines such as Hünig's base) is not applicable to our chemistry as the amine itself catalyzes the cycloaddition of ketene **2** and imino ester **3a**.[8] The presence of the byproduct hydrochloride salts compromises the reaction by lowering chemical yield and eroding diastereoselectivity.[5b] These facts prompted us to employ resin-bound dehydrohalogenation reagents to produce contaminant-free ketene solutions under inert atmosphere at reduced temperature. In our initial attempts, solid-phase bases such as Amberlite IRA-67,[9] a tertiary amine-based polymer, and resin-bound peralkylated guanidines[10] failed to promote ketene formation when phenylacetyl chloride **1a** in THF was passed through a packing of resin beads in a jacketed column at −78 °C. To our satisfaction, we found that the extremely basic resin BEMP **5**,[11] containing a triaminophosphoramide imine bound to a polymeric support,[12] produces ketenes rapidly and in high yield. By slowly passing a THF solution of phenylacetyl chloride **1a** through a jacketed addition funnel containing the polymer **5** (1.1 basic equivalent) at −78 °C, a straw-colored solution of phenylketene **2a** was eluted. 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 many other reactive ketenes. An advantage to placing BEMP resin **5** in a column is that in a reaction flask the resin was generally found to interfere with subsequent chemical reactions (it tended to destroy the imino ester and epimerize the β-lactam product).[13] Unfortunately, we found that the quality of BEMP seemed to be dependent on the supplier and lot number.[14] Less active lots of BEMP resin would sometimes let unreacted acid chloride through the column. We could compensate for lower quality BEMP by adding a larger excess of the resin to the column and by agitating the resin beads through magnetic stirring on the column. Usually, however, this was not necessary.

Scheme 3. Preparation of Polymer-Supported Quinine Derivatives



Results and Discussion

Preparation and Optimization of the Polymer-Supported Quinine Derivatives. In a preliminary report, we discovered that when a cold solution of phenylketene **2a** (−78 °C) is treated with 1 equiv of imino ester **3a** and 10 mol % benzoylquinine (BQ), β-lactam **4a** is formed in high ee and dr after purification by column chromatography.[5b] Under these conditions the catalyst is difficult to recover in a pure form from the reaction mixture, so that a solid-phase-based system was immediately deemed desirable. Moreover, the column asymmetric catalysis (CAC) 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 3) to synthesize the chiral packing of the catalytic reaction columns.[15]

Preliminary reactions were performed with quinine attached to carboxypolystyrene resin **7**,[16] using assembly I. After obtaining a relatively poor diastereomeric ratio (dr) of 3:1 (cis:trans) (Table 1, entry 1), we chose to derivatize the inexpensive and very high-loading Wang resin.[17] We felt that higher loading beads would be more effective as a catalyst. The other important

(5) (a) Wack, H.; Drury, W. J., III; Taggi, A. E.; Ferraris, D.; Lectka, T. *Org. Lett*. **1999**, *1*, 1985−1988. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (c) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett*. **2000**, *2*, 3963−3965.

(6) For other advantages over homogeneous systems see: (a) Kamahori, K.; Ito, K.; Itsuno, S. *J. Org. Chem*. **1996**, *61*, 8321−8324. (b) Itsuno, S.; Ito, K.; Maruyama, T.; Kanda, N.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 3329−3331.

(7) (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. (c) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792−3796.

(8) We have used α-imino ester **3a** 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 **3a** was first used in work by: (c) Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem*. **1984**, *49*, 5058−5064.

(9) Available from Aldrich (1.6 mequiv/mL exchange capacity).

(10) Polymer-supported base of the hindered tertiary base 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene available from Novabiochem (TBD-methyl polystyrene, 200−400 mesh, 2.0−3.0 mmol/g).

(11) 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.

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

(13) BEMP resin beads often stick to the walls of the reaction vessel decreasing the efficiency of the dehydrohalogenation.

(14) BEMP is available from both Fluka and Aldrich. The BEMP from Fluka was of higher quality.

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

(16) Carboxypolystyrene HL (100−200 mesh, 1.0−1.6 mmol/g) is available from Novabiochem.

Table 1. Polymer-Supported Quinine-Catalyzed Asymmetric Synthesis of β-Lactam **4a** from Phenylacetyl Chloride **1a** and Imino Ester **3a**[a]

entry	polymer-supported quinine derivative	dr[b]	% ee[c]	% yield[d]
1	**7**	3:1	90	52
2	**6a**	10:1	93	65
3	**6b**	13:1	90	62
4	**6c**	2:1	87	64

[a] The reaction was carried out with phenylacetyl chloride **1a** (0.13 mmol) and imino ester **3a** (0.13 mmol), using assembly I. [b] Determined by ^{1}H NMR of crude residue (cis:trans). [c] Determined by HPLC analysis with a Regis Technologies (*R*,*R*)-Whelk-01 Chiral HPLC column. [d] Isolated yield after crystallization of concentrated residue.

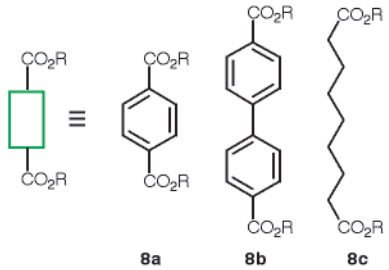


Figure 1. Linkers for polymer supported quinine derivatives.

consideration concerned the linker length and shape. Our hypothesis was that the linkers would in all probability affect the reaction chemistry in terms of rate and selectivity. One can argue that long, rigid linkers should project the catalytic quinine moiety more effectively away from the Wang resin bulk, thus mimicking solution chemistry more effectively. Short or "floppy" linkers would arguably allow close proximity of the catalytic moiety with the resin and thus lower the rate and affect selectivity in an unpredictable way. We derivatized the Wang resin with three different linkers to probe different possibilities (Figure 1). One linker is long and "floppy" (azelaic acid **8c**), and the others consist of a series of phenyl groups of varying length (**8a** and **8b**).[18] The Wang resin was treated with a large excess of the diacid chloride of each of the linkers to ensure predominant monoesterification. The quinine units were then attached to the derivatized resin by another simple esterification reaction to form solid-phase catalysts **6a**−**c**. Incorporation of quinine onto the resin averages 60%. Indeed we found that the length of the catalyst−solid-phase linker is crucial to the success of the reaction—short linkers give inferior results. Two factors could be in play here: presumably the steric encumbrance of the polymeric support has a negative effect (Table 1), and cross-linking of the resin could have an effect (although experimental evidence suggests that the degree of cross-linking is similar [within 10%] for resins **6a**−**c**).

The quinine-supported Wang resin **6a** (with the terephthaloyl linker **8a**) afforded β-lactam **4a** in 65% yield with 10:1 cis:trans dr. The enantioselectivity (ee) has been improved from 91% to 93% since our initial published results (entry 2).[5c] The slightly longer, more rigid quinine-supported Wang resin **6b** with the biphenyl linker **8b** improved the dr to 13:1 in comparable yield (62%) and with comparable ee (90%) (entry 3). The longer, floppy quinine supported Wang resin **6c** with the C_9 linker **8c** afforded β-lactam **4a** in 64% yield and dramatically dropped the dr to 2:1 with 87% ee (entry 4). These results confirmed our hypothesis that for whatever reason, a long, rigid linker is beneficial to reaction selectivity.

We found it necessary to run each newly synthesized resin a small number of times before we received consistent results. We noticed "bleeding" of quinine and other materials in all of our initial runs with each catalyst resin even after multiple washings during their preparations.[19] Once the resins have aged through several uses (5−10 runs), they have been employed multiple times with no significant loss in yield or selectivity. One resin batch has been used over 60 times and still maintains its efficacy to date.

Application of the Supported Quinine Derivatives in the Asymmetric Synthesis of β-Lactams Using Assembly I. In detail, assembly I 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 with a nucleophile-based solid-phase asymmetric catalyst. Between the two columns, the imine is added to the system. An additional column is optional (although in many cases highly desirable) and packed with a scavenger resin to remove any unreacted ketene or imine from the eluent. 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 **6a** (3 cm). The scavenger resin[20] **10** was loaded into a column and attached to the bottom of the apparatus. All columns were flushed with THF under nitrogen. The BEMP column was cooled to −78 °C with a dry ice/acetone mixture, and the catalyst loaded column was cooled to −43 °C by dry ice/acetonitrile.[21] A solution of phenylacetyl chloride **1a** in THF 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 middle column. Imino ester **3a** was then added through a port onto the middle 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. After passing through the scavenger resin column (which traps unreacted ketene and imine byproducts), the eluted reaction mixture was concentrated to afford β-lactam **4a** in 93% ee (Table 2, entry 1). Crystallization of the residue affords analytically pure material in 65% yield (>99% ee, 98/2 dr).

To ready the apparatus for another catalytic cycle, the columns were separated and regenerated. The catalyst-loaded resin column was washed with methanol, methylene chloride, and diethyl ether 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^-,[12] and then dried under high vacuum at 120 °C. The scavenger resin was washed with a triethylamine solution in THF, methylene chloride, and diethyl ether and dried under high vacuum.[22] This reaction has been successfully run through the catalyst column 60 times with no significant loss in selectivity or yield (90% ee and 62% yield for run 60). The resin beads can either be stored in the column itself or removed to serve another purpose. When quinidine is similarly attached to the Wang resin and used in

(17) Wang resin (100−200 mesh, 1.6−3.0 mmol/g) is available from Novabiochem.

(18) Other examples of linker length's effect on selectivities: (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.

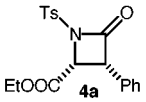
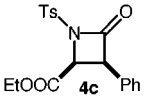
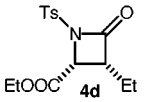
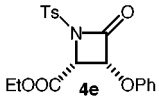
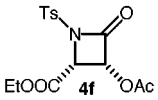
(19) See Experimental Section for detailed instructions on washing and drying the catalyst resins.

(20) Aminomethylated polystyrene (EHL, 200−400 mesh, 2.0−3.0 mmol/g) from NovaBiochem was employed as the scavenger resin.

(21) The optimal temperature for column asymmetric catalysis of phenylketene **2a** and imino ester **3a** was found to be −43 °C.

(22) Recycling of the scavenger resin is limited to 15−20 cycles due to the generation of polymer-bound amides.

Table 2. Polymer-Supported Quinine-Catalyzed Asymmetric Synthesis of β-Lactams **4** from Acid Chlorides **1** and Imino Ester **3a** with Quinine Derivative **6a**[a]

entry	product	dr[b]	% ee[c]	% yield[d]
1	 **4a**	10:1	93	65
2[e]	 **4c**	10:1	95	61
3	 **4d**	13:1	91	53
4	 **4e**	12:1	94	63
5	 **4f**	14:1	91	60

[a] The reaction was carried out with the appropriate acid chloride **1** (0.13 mmol) and imino ester **3a** (0.13 mmol), using assembly I with catalyst **6a**. [b] Determined by ^{1}H NMR of crude residue (cis/trans). [c] Determined by HPLC analysis with a Regis Technologies (*R*,*R*)-Whelk-01 Chiral HPLC column. [d] Isolated yield after crystallization of concentrated residue. [e] Polymer-supported quinidine on Wang resin used as catalyst.

place of the catalyst-loaded beads **6a** (entry 2), the other enantiomer **4c** of β-lactam **4a** is produced in 61% yield, 10:1 dr (cis:trans), and 95% ee (crystallization affords optically pure material >99% ee). Furthermore, these different catalyst columns can be used and stored as needed.

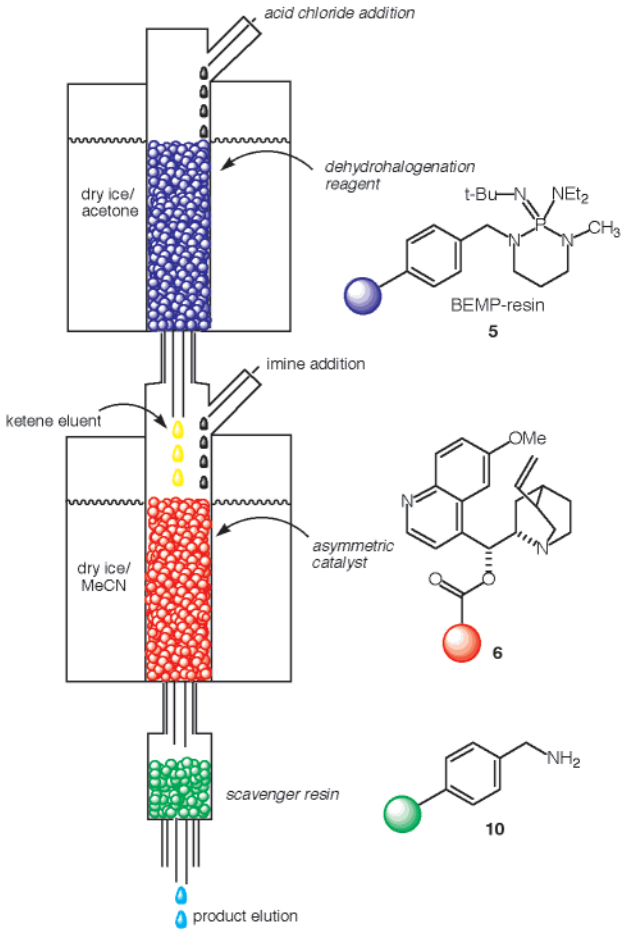
Several other β-lactams were produced by varying the acid chloride employed in the reaction. Butyryl chloride **1d**, when mixed with **3a** using assembly I, afforded β-lactam **4d** (entry 3) in modest yield (53%) and good selectivities (13:1 dr, 91% ee). Similarly, β-lactam **4e** (entry 4) was produced in 63% yield, 12:1 dr, and 94% ee. Acetoxyacetyl chloride **1f** was used with **3a** to afford **4f** in 60% yield (entry 5) with good selectivity (14:1 dr, 91% ee).

Application of the Catalytic, Resin-Bound Quinine in the Asymmetric Synthesis of β-Lactams Using Assembly II. As an illustration of the potential flexibility of our system, we have implemented our sequential CAC technique to conduct a reaction with four discrete steps: (1) formation of reactive ketenes in one column; (2) formation of imines in situ from corresponding α-chloroamines in another parallel column; (3) catalysis of the condensation of the ketene and imine to form a β-lactam product in the third column; and (4) removal of unwanted byproducts from the reaction stream with a scavenger resin. Ketenes **2** and imines **3** cannot be made simultaneously in a single column due to the different temperatures needed to effect reaction. To maximize utility, we modified our apparatus to accommodate this more elaborate application (Scheme 5).

Chloroglycine derivatives **9**[23] are very easily synthesized, handled, and stored, and serve as convenient and potentially widely applicable precursors to reactive imines such as **3**, which are more difficult to make and handle through our other standard procedures. The flexibility in the choice of R group

(23) Steglich, W.; Jager, M.; Jaroch, S.; Zistler, P. *Pure Appl. Chem.* **1994**, *66*, 2167−2170.

Scheme 4. Column Asymmetric Catalysis Assembly I



on **9** demonstrates its versatility; as an illustration of utility we have investigated, along with sulfonyl groups (Ts **9a**), the corresponding acyl groups (COPh **9b**). Acyl-substituted β-lactams are inhibitors of prostate specific antigen (PSA) and cytomegalovirus protease, for example.[24] Imines **3a**,**b** can be made at room temperature from chloroglycines **9a**,**b** by using a variety of dehydrohalogenation bases. We have utilized several polymer-supported bases, including BEMP **5**, TBD-methyl polystyrene,[10] and piperidinomethyl polystyrene,[25] to make imine **3a**,**b** from **9a**,**b** by means of mechanical stirring in THF. The solid-phase bases were filtered from the imine solution and the solution was added to assembly I, much the same way as the preformed imine **3a**, to afford β-lactam **4a** (Table 3), although this procedure is obviously more tedious. The application of these polymer-supported bases in a continuous flow system without any external agitation of the solution failed to generate the imine to any appreciable extent. These bases were presumably not basic enough (as positive charge builds up on spent resin, the basicity drops precipitously), and our column

(24) For PSA, see: (a) Adlington, R. M.; Baldwin, J. E.; Becker, G. W.; Chen, B.; Chen, L.; Cooper, S. L.; Hermann, R. B.; Howe, T. J.; McCoull, W.; McNulty, A. M.; Neubauer, B. L.; Pritchard, G. J. *J. Med. Chem.* **2000**, *44*, 1491−1508. (b) Adlington, R. M.; Baldwin, J. E.; Becker, G. W.; Chen, B.; Cooper, S. L.; Hermann, R. B.; Howe, T. J.; McCoull, W.; McNulty, A. M.; Neubauer, B. L.; Pritchard, G. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689−1694. For cytomegalovirus protease, see: (c) Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LaPlante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. C.; Déziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965−2973. (d) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Haché, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Déziel, R. *J. Med. Chem.* **1998**, *41*, 2882−2891.

(25) Available from Novabiochem (HL, 200−400 mesh, 3.3−3.8 mmol/g).

Scheme 5. Column Asymmetric Catalysis Assembly II

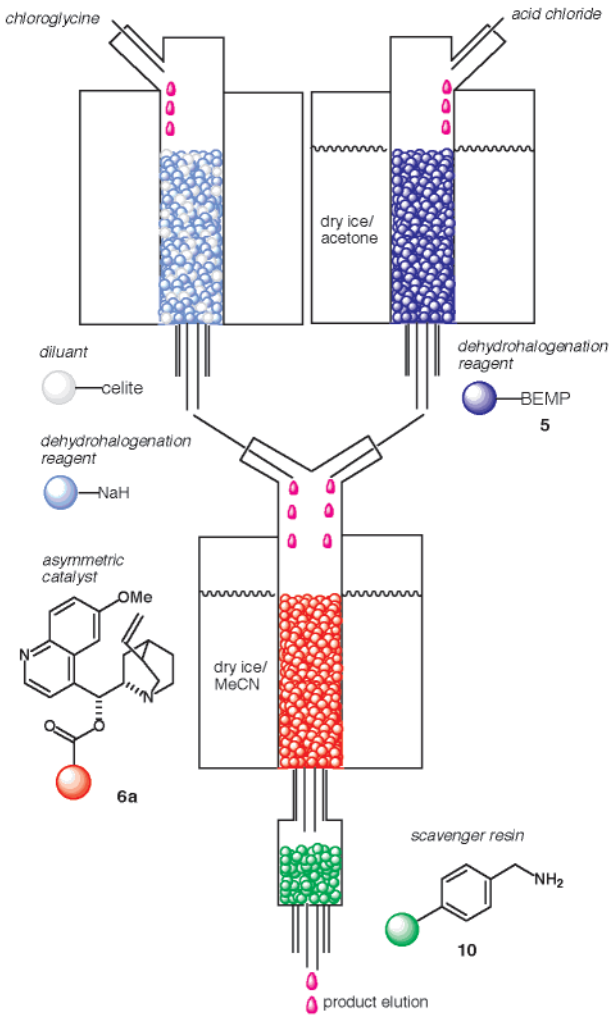


Table 3. Polymer-Supported Quinine-Catalyzed Asymmetric Synthesis of β-Lactam **4a** from Phenylacetyl Chloride **1a** and α-chloroamine **9a** with Quinine Derivative **6a**[a]

entry	polymer-supported base	dr[b]	% ee[c]	% ee[d]	% yield[e]
1	BEMP	8:1	88	>99	55
2	TBD-methyl polystyrene	10:1	91	>99	61
3	piperidinomethyl polysyrene	10:1	91	>99	59

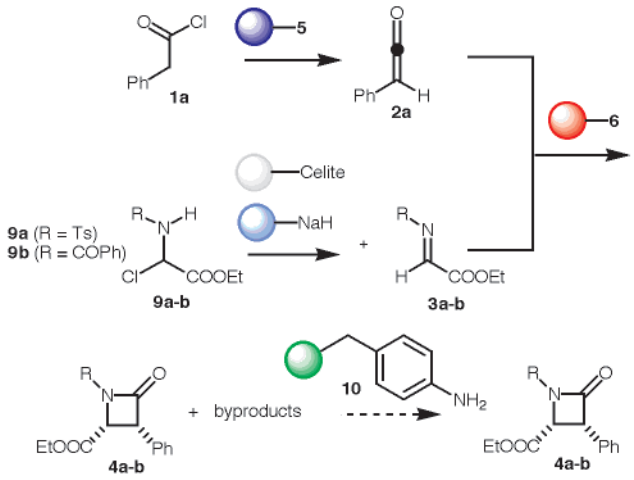
[a] The reaction was carried out with phenylacetyl chloride **1a** (0.13 mmol) and chloroglycine **9a** (0.13 mmol), using assembly I with catalyst **6a**. [b] Determined by ^{1}H NMR of crude residue (cis/trans). [c] Determined by HPLC analysis with a Regis Technologies (*R,R*)-Whelk-01 Chiral HPLC column. [d] Ee after crystallization of concentrated residue. [e] Isolated yield after crystallization of concentrated residue.

was not long enough to form the imine sufficiently. An alternative to making an impracticably long column was to find a strong, inexpensive base that could be packed into a shorter column. After considerable experimentation, we found that mixing Celite[26] with NaH in the column serves as the best packing to form the imine. NaH is the actual stoichiometric base that dehydrohalogenates the α-chloroamine **9a** to form imine **3a**, while the Celite acts as a diluant, slowing down the flow rate of the solution and thus allowing more time for the formation of the imine.

In detail, assembly II consists of three fritted, jacketed columns (each 2 cm wide), including two top columns (type A) for reagent synthesis, a catalytic column (type B) into which

(26) Celite 545 (diatomaceous earth) was employed in the reaction.

Scheme 6. Dual Ketene and Imine Generation from Powdered and Solid-Phase Bases in the Asymmetric Synthesis of β-Lactams



the reagent columns feed, and a scavenger resin column (type C) below the catalytic column. One of the top columns was packed with BEMP resin **5**, the other top column with the NaH/Celite mix (6:1 NaH:Celite w/w ratio, 3 cm). The catalytic column was loaded with catalyst beads **6a** (3 cm). The two top columns were connected to the catalyst column by a Claisen adapter. After all the columns were flushed with THF, the BEMP column was cooled to −78 °C with dry ice/acetone mixture. The NaH/Celite column was kept at room temperature, and the catalyst loaded column was cooled to −43 °C with a dry ice/acetonitrile mixture. A solution of phenylacetyl chloride **1** in THF was added to the top of the column and allowed to percolate by gravity through the BEMP resin and onto the catalyst-loaded resin of the middle column. Concurrently, the α-chloroamine **9a**, in a solution of THF, was added to the NaH/Celite column and allowed to drip by gravity through solid bases onto the catalyst-loaded resin of the middle column. The reaction was initiated by allowing a slow drip of THF from the bottom of the column to allow complete elution of the column contents over the course of 2 h. Surprisingly, little experimentation with regard to flow rates was undertaken before this fairly optimum "drip rate" was determined. After passing through the scavenger resin column the eluted reaction mixture was concentrated to afford fairly pure β-lactam **4a** in 90% ee and 10:1 dr (cis:trans). Simple crystallization of the residue affords optically and analytically pure material (>99% ee, 98/2 cis−trans dr) in 62% yield. Starting with chloroglycine **9b** and implementing a similar procedure affords β-lactam **4b** in 33% yield, 13/1 dr, and 92% ee.[27] There is reason to believe that a whole range of ketenes and acyl-substituted chloroglycines can be used in this procedure to produce a spectrum of β-lactam products.

Application of the Supported Quinine in the Asymmetric Synthesis of β-Lactams Using Assembly III. The expense of solid-phase-based BEMP prompted us to seek more economical ways of ketene generation. We recently reported a procedure for the synthesis of reactive ketenes by the use of an amine dehydrohalogenating catalyst and fine-mesh powdered K_2CO_3 as the stoichiometric base.[28] Our concept was to generate ketenes with columns of powdered K_2CO_3 to which chiral catalyst loaded beads have been added. This type of system satisfies the potential need for a shuttle base when using powdered

(27) Scavenger column was not used due to the propensity of primary amines opening *N*-acyl β-lactams.

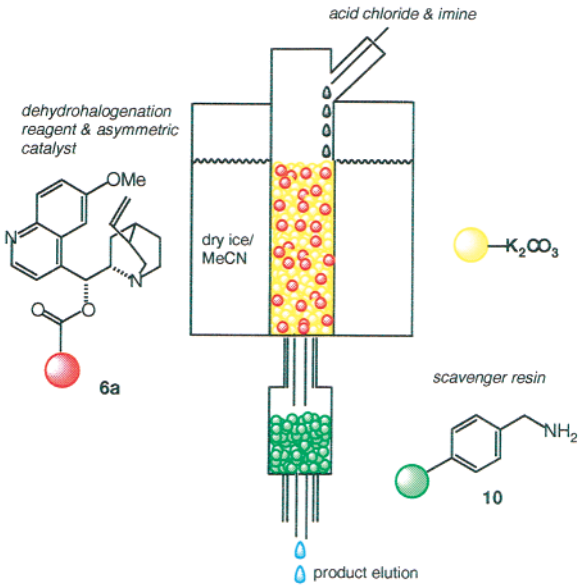
(28) Hafez, A. M.; Taggi, A. T.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.

Table 4. Polymer-Supported Quinine-Catalyzed Asymmetric Synthesis of β-Lactam **4a** from Phenylacetyl Chloride **1a** and Imino Ester **3a**[a]

entry	column packing	dr[b]	% ee[c]	% yield[d]
1	**6a**/K_2CO_3 (1/5)	3:1	88	58
	6a	7:1	91	61

[a] The reaction was carried out with phenylacetyl chloride **1a** (0.13 mmol) and imino ester **3a** (0.13 mmol), using assembly III with catalyst **6a**. [b] Determined by ^{1}H NMR of crude residue (cis/trans). [c] Determined by HPLC analysis with a Regis Technologies (*R*,*R*)-Whelk-01 Chiral HPLC column. [d] Isolated yield after crystallization of concentrated residue.

Scheme 7. Column Asymmetric Catalysis Assembly III



carbonates. The polymer-supported quinine beads effect dehydrohalogenation, and then presumably transfer their protons to the solid carbonate next door. As to the intriguing question of whether this transfer would involve bead-to-particle contact or is conducted through the flow medium was addressed by a control experiment. We attempted to produce solutions of ketene simply by filtering a solution of acid chloride through a cold column (−78 °C) containing powdered K_2CO_3, but were unsuccessful. *The catalyst beads are in fact needed to produce ketene on the column.* The implications of this experiment on the questions of packing, flow, and morphology remain to be sorted out.

In detail, assembly III consists of one fritted, jacketed column (2 cm wide, type D) that was loaded with a mixture of catalyst-loaded beads **6a** and powdered carbonate in a 5/1 w/w ratio. The scavenger resin **10** was loaded into a column and attached to the bottom of the apparatus. After flushing the columns with THF, the catalyst−carbonate loaded column was cooled to −43 °C with a dry ice/acetonitrile mixture. In an initial experiment, we found that when phenylacetyl chloride **1a** and imine **3a** were added to the quinine-supported resin **6a** and K_2CO_3 mix in a jacketed column at −43 °C, the reaction afforded β-lactam **4a** in 58% yield (Table 4, entry 1). The dr values of the product, however, seemed to be eroded by the presence of the K_2CO_3 (3:1 dr and 88% ee). Crystallization of the reaction material, however, provided optically pure material as an 98/2 mixture of diastereomers. The special appeal of reactions with assembly III is that they can be scaled up easily. For example, we made 1 g of pure lactam **4a** simply by increasing the amount of carbonate proportionally while employing the same loading of catalyst beads (10/1 ratio of carbonate to catalyst).

In a control experiment, by utilizing only the quinine-supported resin **6a** as both a dehydrohalogenating agent and catalyst (column type A), the β-lactam can be isolated in 61% yield with a 7:1 dr and an ee of 91% (entry 2). In the event, a solution of phenylacetyl chloride **1a** in THF was added to the top of the quinine-loaded column. Imino ester **3a** in THF was then added. The reaction was initiated by allowing a slow drip of THF from the bottom of the column to allow complete elution of the column contents over the course of 2 h. After passing though the scavenger resin the eluted reaction mixture was concentrated to afford crude β-lactam **4a** in 91% ee. Crystallization of the residue affords optically and analytically pure material in 61% yield.

Conclusions

One can envision the synthesis of considerably more complex enantioenriched compounds by using the sequential CAC methodology. Reactants can be passed through any number of discrete columns containing recyclable reagents connected in parallel or in series. It should be noted that the use of solid-supported catalysts and reagents, including scavenger resin columns, greatly simplifies the purification of the reaction products. In the future, we will apply the concept of serial CAC to the synthesis of more complex molecules in multistep and/or multicatalytic procedures.

Experimental Section

General Procedure for the Synthesis of Polymer-Supported Quinine Derivatives. Wang resin (2.0 g, 5.06 mmol, 2.53 mmol/g) was added via addition funnel to a solution of terephthaloyl chloride (2.57 g, 12.7 mmol) and triethylamine (1.74 mL, 12.7 mmol) in 30 mL of THF at 0 °C over 2 h. The reaction was allowed to warm to room temperature over 10 h. The resin was washed on a course glass frit with 50 mL of THF and 50 mL of diethyl ether to remove excess reagents and reaction byproducts. The derivatized resin was then dried under vacuum for 3 h. To the resin at 0 °C was added a solution of quinine (3.28 g, 10.1 mmol) and triethylamine (1.13 g, 11.1 mmol) in 60 mL of THF. The reaction was allowed to warm to room temperature over 10 h. Methanol (40 mL) was then added and the reaction stirred for 1 h. The resin was filtered off and washed with an additional 40 mL of methanol. The resin **6a** was then placed in a Soxhlet extractor and refluxed with acetone for 24 h. **6a** was removed from the extractor and dried under vacuum for 24 h. Incorporation of quinine catalyst was determined to be 60% based on the recovered quinine (2.3 g, 7.1 mmol). Anal. Found for **7**: C, 56.70; H, 4.91; N, 1.55. Found for **6a**: C, 81.73; H, 7.22; N, 2.51. Found for **6b**: C, 77.12; H, 6.58; N, 2.68. Found for **6c**: C, 81.32; H, 7.28; N, 2.87.

General Procedure for Column Catalysis Using Assembly I. Two fritted, jacketed columns (each 2 cm wide) were loaded under nitrogen, the top column with BEMP resin **5** (1.1 basic equivalents) and the bottom with catalyst-loaded beads **6a** (3 cm). The scavenger resin **10** was loaded into a column and attached to the bottom of the apparatus. All columns were flushed with THF under nitrogen. The BEMP column was cooled to −78 °C with dry ice/acetone mixture. The catalyst-loaded column was cooled to −43 °C with a dry ice/acetonitrile mixture. A solution of phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in THF (1 mL) was added to the top of the column and allowed to drip by gravity through the BEMP resin and onto the catalyst-loaded resin of the middle column. Imino ester **3a** (33 mg, 0.13 mmol in 0.5 mL of THF) was then added through a port onto the middle column. The reaction was initiated by allowing a slow drip of THF from the bottom of the column to allow complete elution of the column contents over the course of 2 h. After passing though the scavenger resin the eluted reaction mixture was concentrated to afford crude β-lactam **4a** in 93% ee and 10:1 cis:trans dr. Crystallization of the residue affords optically and analytically pure material in 65% yield. The standard reaction for assembly I can be scaled up by a factor of 10 or more (ca. 330 mg of acid chloride), using the same amount of catalyst resin with comparable results.

General Procedure for Column Catalysis Using Assembly II. Three fritted, jacketed columns (each 2 cm wide) were loaded under nitrogen, one of the top columns with BEMP resin **5** (1.1 basic equivalents) and the other top column with a NaH/Celite mix (3 cm), while the bottom was loaded with catalyst beads **6a** (3 cm). The two top columns were connected to the catalyst column by a Claisen adapter. The scavenger resin **10** was loaded into a column and attached to the bottom of the apparatus. All columns were flushed with THF under nitrogen. The BEMP column was cooled to −78 °C with a dry ice/acetone mixture. The NaH/Celite column was kept at room temperature. The catalyst-loaded column was cooled to −43 °C with a dry ice/acetonitrile mixture. A solution of phenylacetyl chloride **1a** (20 mg, 0.13 mmol) in THF (1 mL) was added to the top of the column and allowed to drip by gravity through the BEMP resin and onto the catalyst-loaded resin of the middle column. The α-chloroamine **9a** (33 mg, 0.13 mmol in 0.5 mL of THF) was then added to the NaH/Celite column and allowed to drip by gravity through solid bases and onto the catalyst-loaded resin of the middle column. The reaction was initiated by allowing a slow drip of THF from the bottom of the column to allow complete elution of the column contents over the course of 2 h. After passing though the scavenger resin the eluted reaction mixture was concentrated to afford crude *β*-lactam **4a** in 90% ee and 10:1 cis:trans dr. Crystallization of the residue affords optically and analytically pure material in 62% yield.

General Procedure for Column Catalysis Using Assembly III. One fritted, jacketed column (2 cm wide) was loaded under nitrogen with catalyst-loaded beads **6a** (0.30 mmol) and K_2CO_3 in a 1/5 w/w ratio (9 cm). The scavenger resin **10** was loaded into a column and attached to the bottom of the apparatus. All columns were flushed with THF under nitrogen. The catalyst/K_2CO_3 loaded column was cooled to −43 °C with a dry ice/acetonitrile mixture. A solution of phenylacetyl chloride **1a** (471 mg, 3.00 mmol) in THF (10 mL) was added to the top of the column and onto the catalyst-loaded resin of the middle column. Imino ester **3a** (774 mg, 3.00 mmol in 10 mL THF) was then added through a port onto the catalyst-loaded resin column. The reaction was initiated by allowing a slow drip of THF from the bottom of the column to allow complete elution of the column contents over the course of 2 h. After passing though the scavenger resin the eluted reaction mixture was concentrated to afford crude *β*-lactam **4a** in 89% ee and 3:1 cis:trans dr. Crystallization of the residue affords optically and analytically pure material in 58% yield.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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