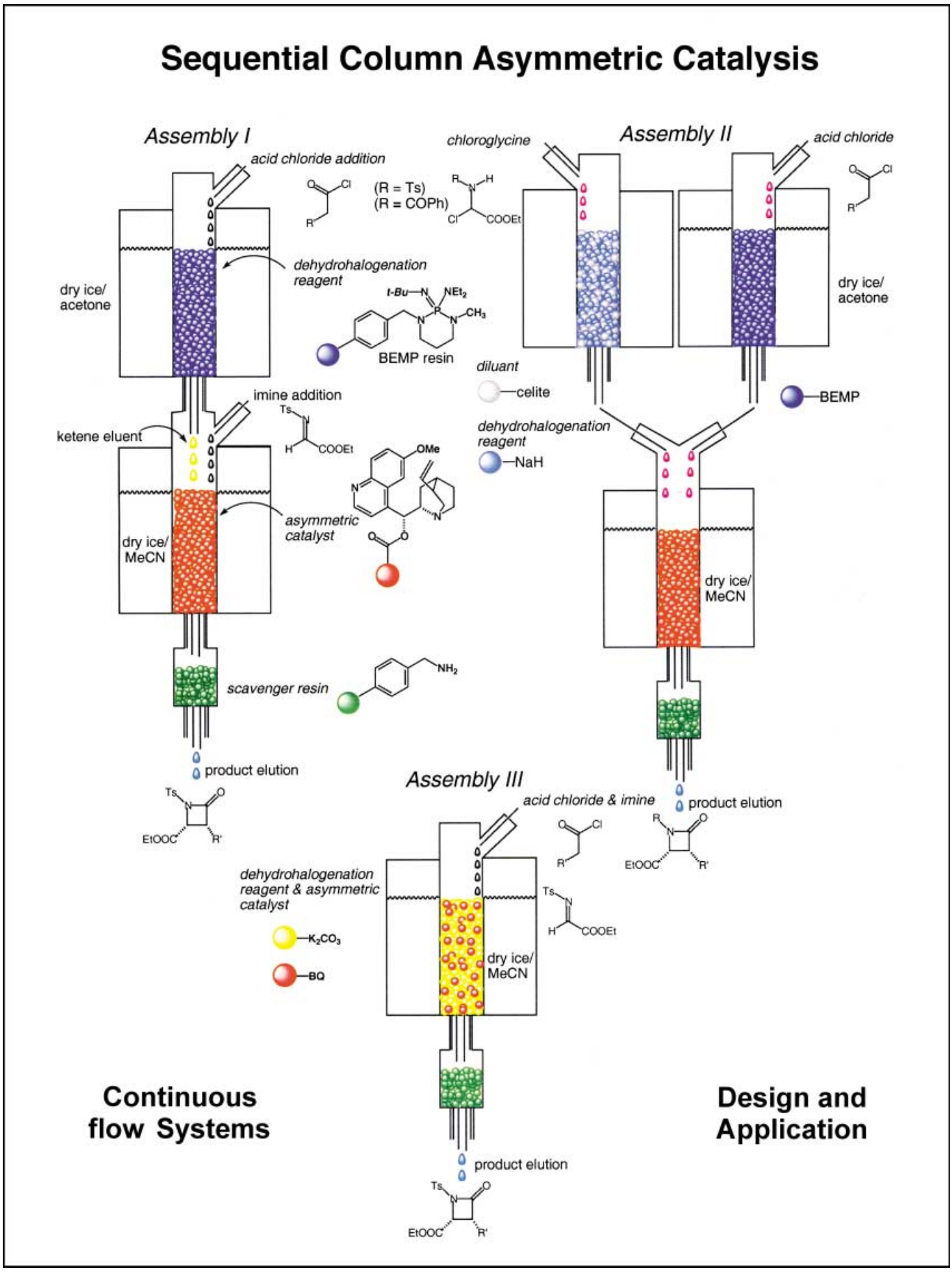

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Sequential Column Asymmetric Catalysis

Ahmed M. Hafez, Andrew E. Taggi, and Thomas Lectka*[a]

Abstract: Since the introduction of catalysts and reagents on solid-support, researchers have developed new reaction systems to take advantage of their insoluble nature by designing multistep reaction sequences, high-throughput purification techniques, and combinatorial synthesis methods. The continuous flow system is one of these advancements and represents the foundation of a new technique termed sequential column asymmetric catalysis (CAC). In this strategy, reagents and catalysts are attached to a solid-phase support and loaded onto sequentially-linked columns. The substrates are present in the liquid phase that flows through the column. As a substrate encounters each successive column, it grows in complexity. Consequently, one can imagine a number of flow systems that consist of columns attached in series and/or in parallel that synthesize a fairly complex molecule. Herein, we discuss the development of the sequential CAC technique, beginning with the most relevant antecedents.

Keywords: asymmetric catalysis · continuous flow systems · heterogeneous catalysis · lactams · supported catalysts

Introduction

As chemistry evolves and matures as a science, its technological facets are becoming increasingly more important. One example that has developed over the past forty years is automated solid-phase synthesis, pioneered in the laboratories of Robert Merrifield at Rockefeller University. Reduced to its essence, the idea was to build a complex polypeptide on a solid-phase scaffold by successive reactions in which reagents and solvents were introduced to the solid-phase support from the outside.[1] Recently, Merrifield's pioneering work has set the stage for the synthesis of very complex natural products on solid-phase supports, as well as Seeberger's automated synthesis of polysaccharides,[2] which expands on Danishefsky's efforts in oligosaccharide synthesis.[3]

An approach that can be thought of as the *reverse* of automated solid-phase synthesis also comes to mind. In this complementary strategy, *reagents and catalysts* are instead attached to a solid-phase support[4] and loaded onto sequentially-linked columns. The substrates are present in the liquid phase that flows through the column. As a substrate encounters each successive column, it grows in complexity. Consequently, one can imagine a number of flow systems that consist of columns attached in series and/or in parallel that synthesize a fairly complex molecule. We term this strategy sequential column asymmetric catalysis (sequential CAC), when at least one of the steps involves a catalytic, asymmetric transformation.[5] Almost immediately, however, this concept runs up against evident technical hurdles. For example, the solvent of choice in the flow system must be compatible with the packing of all the columns. Reagent columns must eventually be replaced or regenerated (possibly tedious or inefficient in practice), whereas catalytic columns may be used (at least in principle) indefinitely. Purification steps also provide a formidable challenge. Reactions must either proceed cleanly, with high yield and negligible byproducts, or else impurities must be effectively scavenged from the flow system.[6] In this concepts article, we discuss the development of the sequential CAC technique, beginning with the most relevant antecedents to our work.

Continuous Flow System Design and Application

Since the introduction of catalysts and reagents on solid support, researchers have developed new reaction systems to take advantage of their insoluble nature by designing multistep reaction sequences, high-throughput purification techniques, and combinatorial synthesis methods.[7] The continuous-flow system is one of these advancements and represents the backbone of the sequential CAC system. There have been several noteworthy examples of the synthesis of chiral materials in good to excellent enantiomeric excess (*ee*) through continuous flow systems. In 1986, Itsuno reported that polymer-supported (*S*)-(−)-2-amino-3-(*p*-hydroxyphenyl)-1,1-diphenyl-1-propanol (**1**) was an excellent chiral auxiliary reagent for asymmetric reduction of ketones with

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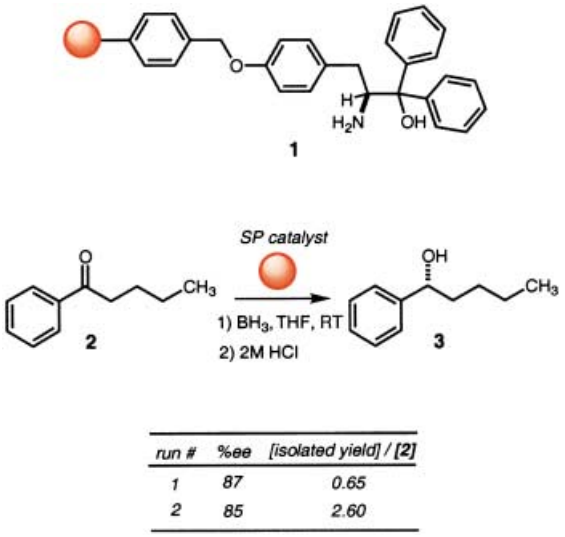
$BH_3 \cdot THF$ (Scheme 1).[8] During their investigation, they observed that after the reduction of the ketone with the polymeric reagent, careful filtration of the reaction mixture under N_2 followed by subsequent hydrolysis gave the optically active secondary alcohol quantitatively with high selectivity (>90% *ee*). After filtration, the chiral polymer containing the amino alcohol/borane complex could again induce chirality in the ketone reduction with borane.



run #	%ee	[isolated yield] / [2]
1	87	0.65
2	85	2.60

Scheme 1. Asymmetric reduction of an aromatic ketone by chiral auxiliary reagent **1**.

To prove that chiral products could be obtained if there were a continuous supply of borane and substrate ketone, Itsuno designed a piece of glassware made up of two flasks (A, B) connected by a glass-fritted filter (Figure 1). The asymmetric reduction with the chiral polymer, ketone, and borane in THF was conducted in flask A. The chiral product yielded from the reaction was filtered into flask B. Flask A was supplied with borane and substrate ketone for another run. Subsequent runs of this "batch system" produced the chiral alcohol with only a slightly lower optical activity than from the first run (run 1: 90% *ee*, run 5: 81% *ee*).

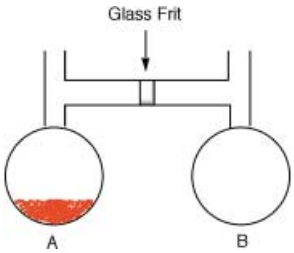


Figure 1. Schematic of a batch system.

With his batch system in hand, Itsuno applied this reaction to a continuous-flow system, thus obviating the repetition involved in the process. The continuous-flow system allows for the production of large quantities of highly optically enriched product with the use of only a small amount of the polymeric chiral auxiliary. The optimized procedure involves the slow injection through a syringe needle of ketone and borane in THF to the bottom of a THF-presaturated column that contains a polymeric $\mathbf{1} \cdot BH_3$ complex (Figure 2). The flow rate and ratio of borane and the ketone was controlled by the syringe pump. The THF solution output was hydrolyzed with 2 M HCl to give the chiral alcohol in high enantioselectivity.

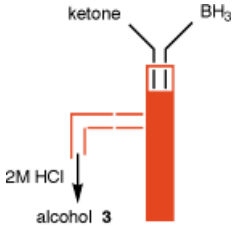
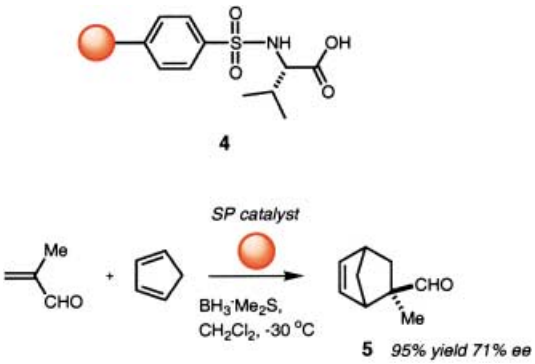


Figure 2. Schematic of a continuous flow system for reduction.

Itsuno later applied a continuous-flow system to the catalytic asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene (Scheme 2).[9] Cross-linked polymers



Scheme 2. Asymmetric Diels–Alder reaction by polymeric chiral catalyst **4**.

possessing chiral *N*-sulfonylamino acid residues **4** made up the packing of the flow system. Solutions of methacrolein and cyclopentadiene in CH_2Cl_2 were added to a column containing the insoluble polymer **4** pretreated with borane-methyl sulfide (Figure 3). A cooling jacket maintained the column at −30 °C. The chiral product **5** was eluted continuously from the bottom of the column in 71% *ee*.

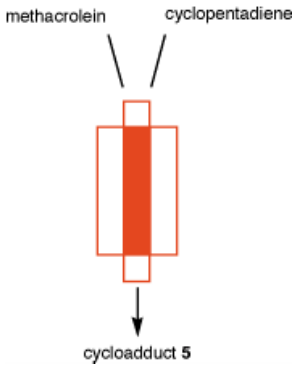


Figure 3. Schematic of a continuous flow system for cyclization.

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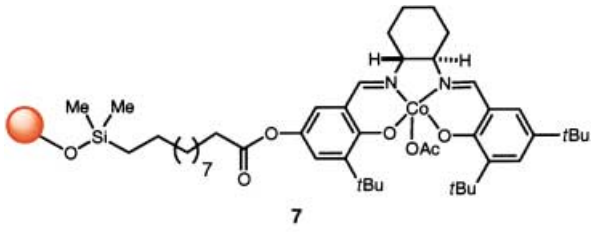
An especially notable recent advance originated in Jacobsen's labs, where catalytic, asymmetric hydrolysis reactions were successfully conducted on HPLC columns.[10] For example, epoxy alcohol **6** underwent a hydrolytic kinetic resolution with silica-supported chiral [Co(salen)] complexes **7** to give triol **8** (Scheme 3). For his continuous-flow system,



7

6 8

run #	% conversion	% ee	% yield
1	36	94.7	34
2	39	94.2	39

Scheme 3. Hydrolytic kinetic resolution of terminal epoxides by silica-bound chiral [Co(salen)] complex **7**.

Jacobsen employed a syringe pump as a solvent delivery device, an HPLC injector valve equipped with an injector loop for loading reagents into the reactant stream, a stainless steel HPLC column packed with **7** as the catalyst bed, and a receiver flask for the collection of product (Figure 4). A

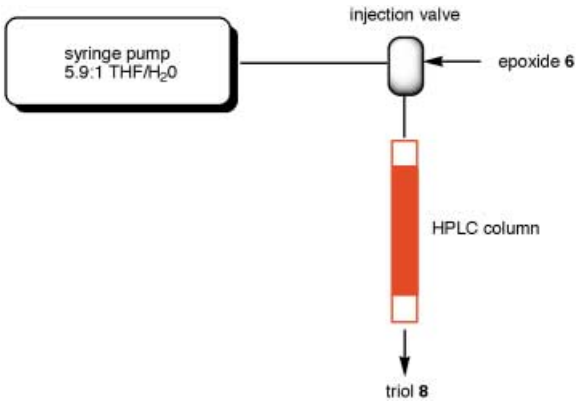


Figure 4. Schematic of continuous flow system for hydrolytic kinetic resolution.

solution of epoxy alcohol **6** in THF/water was injected into the system with a THF/water solvent stream and allowed to flow through the column. After removing the excess solvent and remaining starting materials, the desired triol **8** was obtained in high enantiomeric excess. The column could be regenerated by passing a small volume of acetic acid/toluene through it.

Development of Column Asymmetric Catalysis

The novelty of the CAC approach rests on the use of sequentially linked columns that perform discrete functions in a reaction sequence. We first thought of doing reactions on sequentially linked columns during the development of a catalytic, asymmetric synthesis of β-lactams using in situ generated ketenes, imines, and a chiral, organic nucleophile as catalyst.[11] Conducting this type of reaction on columns obviates the need to isolate and/or manipulate highly reactive monosubstituted ketenes. CAC also eases the separation of the different solid-phase components and allows for the recycling of the polymeric catalysts for additional reactions. Similar to other flow systems, CAC avoids strong agitation that can degrade resin beads when they are spinning in solution. Additionally, the use of a scavenger column avoids the need for column chromatography to purify the product.

An important event that led to the development of CAC was the discovery that reactive ketenes could be made by passing a solution of an acid chloride through a column packed with a resin-bound phosphazine base, *tert*-butylimino-diethylaminodimethylperhydrodiazaphosphorine (BEMP). BEMP and other phosphazines are remarkably strong non-metallic bases first pioneered by Schwesinger in the 1980's.[12] Similarly to the work of Bolm, we attached quinine to a solid support to synthesize the chiral packing of the CAC system.[13]

Utilizing these techniques, we developed a system made up of different types of columns that constitute a CAC assembly (Figure 5). Each assembly is designed to duplicate stages in catalytic reactions, namely substrate preparation, catalysis, and purification steps. Columns labeled A contain stoichiometric reagents that convert precursors into substrates for the reaction. Column type B is packed with the asymmetric catalyst, loaded onto a suitable polymeric support. Columns labeled C contain scavenger resins to remove byproducts and effect purification. A mixed column D contains both catalysts and reagents packed together.

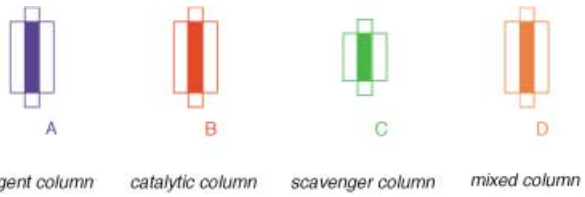


Figure 5. Column types that constitute sequential CAC assembly.

Although many different column assemblies can be imagined depending on the precise synthetic sequence that is desired, for the purposes of the β-lactam forming reaction, we chose to highlight three different assemblies (Figure 6). Assembly I possesses 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

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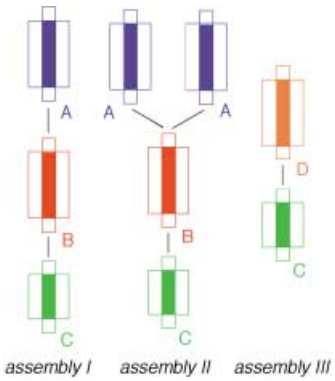
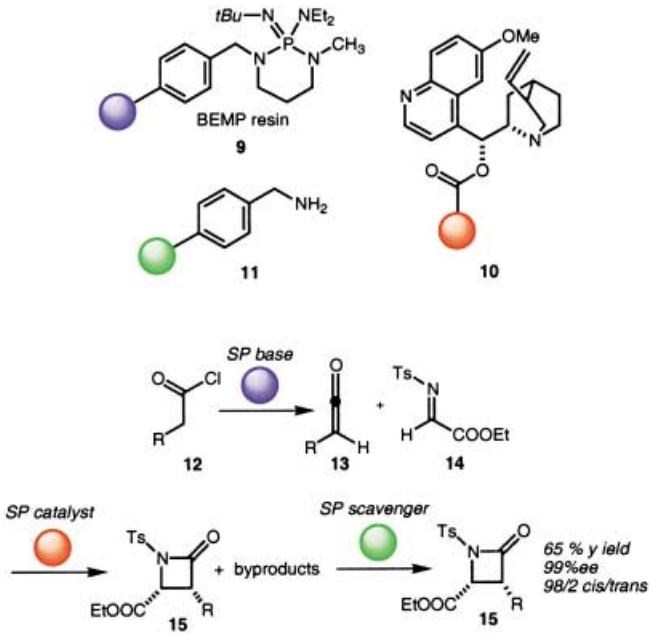


Figure 6. Column assemblies.

catalyst. In between the two columns, the imine is added to the system. An additional column is 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, the top column with the BEMP resin **9**, and the middle column with catalyst-loaded beads **10** (Scheme 4). The scavenger resin **11** was loaded into a column and attached

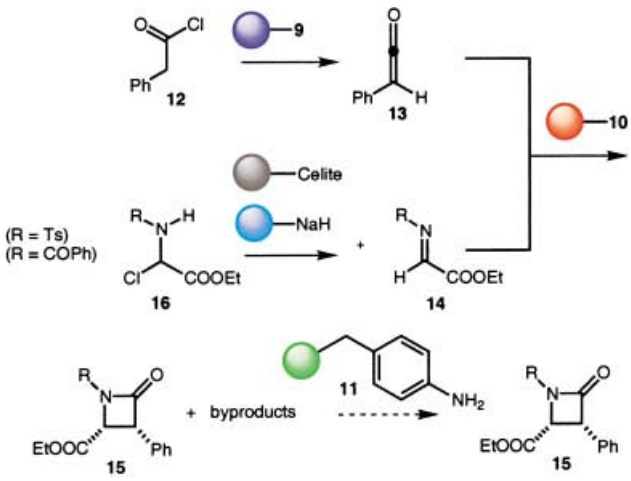


Scheme 4. Catalytic, asymmetric synthesis of β-lactams with solid phase reagents and catalyst.

to the bottom of the apparatus. The BEMP column was cooled to $-78\,^{\circ}C$, and the catalyst loaded column was cooled to $-43\,^{\circ}C$. A solution of phenylacetyl chloride **12** 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 **14** 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. After passing through the scavenger resin column, the eluted reaction mixture was concentrated to afford β-lactam **15** in 93 % *ee*. Crystallization of the residue affords analytically pure material in 65 % yield (> 99 % *ee*, 98/2 dr).

To prepare 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, then 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 $120\,^{\circ}C$. This reaction was successfully run through the catalyst column sixty times with no significant loss in selectivity or yield (90 % *ee* and 62 % yield for run 60). The resin beads can either be stored as needed in the column itself, or removed to serve another purpose.

Assembly II is similar except that there are now two reagent columns on top allowing the sequential CAC technique to conduct a reaction with four discrete steps: 1) formation of reactive ketenes, 2) formation of imines in situ from corresponding α-chloroamines, 3) catalyzed condensation of the ketene and imine to form a β-lactam product, and 4) removal of unwanted byproducts from the reaction stream using a scavenger resin. We found that mixing Celite 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 **16** to form imine **14**, 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 (Scheme 5).



Scheme 5. Dual ketene and imine generation from powdered and solid-phase bases in the asymmetric synthesis of β-lactams.

In Assembly III, a mixed column rests on top and a scavenger column rests below. Our concept was to generate ketenes with columns of powdered K_2CO_3 to which chiral catalyst loaded beads have been added. The polymer-supported quinine beads effect dehydrohalogenation, and then presumably transfer their protons to the neighboring solid carbonate. The special appeal of reactions with assembly III is that they can be scaled up easily. For example, we made one gram of pure lactam **15** simply by increasing the amount of carbonate proportionally, while employing the same loading of catalyst beads (10/1 ratio of carbonate to catalyst).

Since the assemblies are constructed from modular columns, a large number of variations can be imagined, some

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practical, and some, like that depicted in Figure 7, more hypothetical or fanciful. The apparatus would be designed to duplicate steps in a convergent chemical synthesis. A complex or practical enough variety can be thought of as a "synthesis machine," although such a device remains far from reality. Whether concepts such as sequential CAC evolve into a generally applicable strategy for conducting reaction sequences is still speculative.

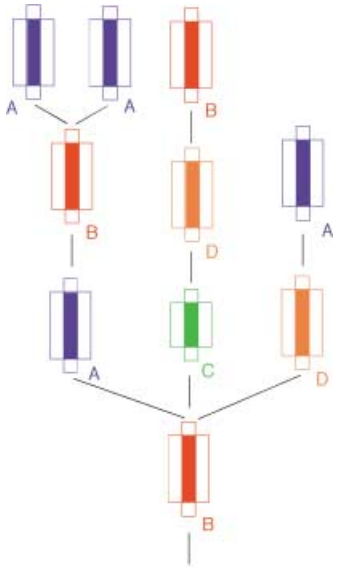

Figure 7. Hypothetical assemblies constructed from modular columns.

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