

A column-based ‘flush and flow’ system for the asymmetric α -chlorination of acid halides

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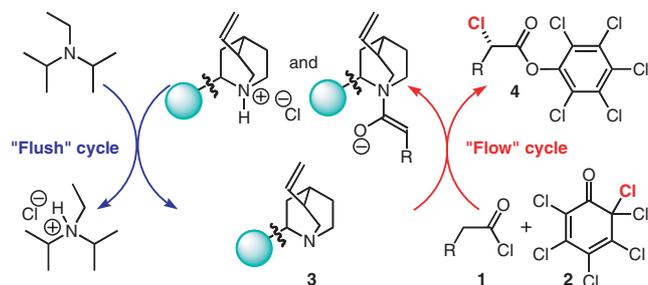
Abstract—We describe a column based flow system in which a cinchona alkaloid based reagent/catalyst solid-phase promotes the asymmetric α -chlorination of acid chlorides to afford highly optically active α -chloroesters in high enantiomeric excess and in good yields.

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1. Introduction

Herein, we report a simple, solid-phase ‘flow’ system for the enantioselective chlorination of acid halides, in which resin beads derivatized with a cinchona alkaloid serve as both the asymmetric promoter of the reaction and the stoichiometric dehydrohalogenating agent for enolate formation (Scheme 1). In most solid-phase¹ methodologies, the substrates are immobilized on solid support while the reagents are passed through in the mobile phase.² Our system, however, features the attachment of the reagent/catalyst to the solid support.³ The beads are loaded into a jacketed column, which serves as the reaction vessel, and are flushed with solvent to ensure complete saturation. The substrates are then added to the column in solution and allowed to flow through the solid-phase reagent with the products

eluting at the bottom of the column in a fairly pure form. The most interesting aspect of this particular system is that by alternating a Hünig’s base ‘flush’ cycle with the introduction of the substrates, the cinchona alkaloid-derived beads can be completely regenerated. Given the robustness of the beads to the flow of reagents and solvents, a theoretically unlimited number of flush/flow cycles can be done sequentially to afford the product again and again. This methodology thus provides an example of a process that is rendered catalytic by the addition of a periodic physical/chemical regeneration step. Also of note, by linking such columns together in sequence, a ‘synthesis machine’ can be fashioned in which each column carries out a discrete step of the overall synthesis. We recently demonstrated this concept via the convergent, five-step synthesis of BMS-27529⁴ entirely through a column-based flow system.⁵



Scheme 1. Column ‘flush and flow’ system for the enantioselective α -chlorination of acid chlorides.

In previous work, we discovered that when a solution of phenylketene is treated with 1 equiv of electrophilic chlorinating agent **2** in the presence of 10 mol % benzoylquinine, α -chloroester **4** is formed in 80% yield and high enantiomeric excess (99% ee) after purification by column chromatography.⁶ Under these conditions, the catalyst is difficult to recover from the reaction mixture in its pure form, so we looked to a solid-phase system based on our earlier success with reactive columns.⁷

2. Results and discussion

After our initial success with column asymmetric synthesis of β -lactams,⁷ we envisioned the extension of our

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methodology to other reactions and eventually onto more complex syntheses of medicinally or biologically important molecules. The linking and interchanging of columns could ultimately lead to the synthesis of a number of complex molecules.

The column assembly is depicted in Figure 1. First, a nitrogen-flushed, fritted, jacketed chromatography column⁸ was slurry-packed with quinine-loaded Wang resin **3**.⁹ THF was added via syringe until the solvent reached just above the surface. Phenylacetyl chloride **1a** (1.3 equiv) and 2,2,3,4,5,6-hexachloro-3,5-cyclohexadien-1-one **2** (1 equiv) were independently dissolved in a minimal amount of THF, and the jacketed column cooled to 0 °C with an ice/water bath. A small amount of the acid chloride (20%) was then added to the column. At this stage, the flow was started at a rate of 0.1 mL/min. It was necessary to provide a steady stream of nitrogen to ensure a constant flow rate. After the small primer of acid chloride was forced into the beads, small, equal amounts of acid chloride **1a** and chlorinating agent **2** in THF were loaded on top of the column packing. Once the level of the solution dropped to directly above the level of the surface, 1 mL of THF was added and forced into the beads. Then the next portions of reagents were added. Once all of the substrate mixture was added, THF was used to flush the product off the column. The entire process was complete in about 4 h. The eluent was collected, concentrated, and purified to afford **4a** in 58% yield and 94% ee (Table 1, entry 1).

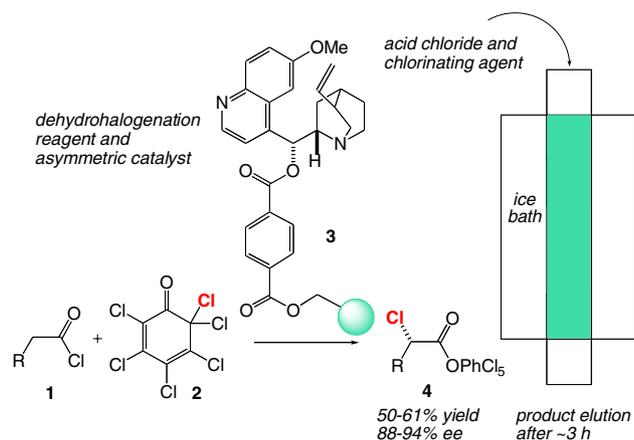


Figure 1. Column-based asymmetric synthesis of α -chloroesters.

To prepare the apparatus for another cycle, the column was flushed in sequence with THF, Hünig's base in THF solution (~10%), and two more times with THF.¹⁰ These beads have shown no loss of activity after numerous cycles; in fact, we have used one batch of beads more than 100 times.

To demonstrate the utility of this methodology, we have employed a variety of acid chlorides, ranging from aryl to aliphatic substituents.¹¹ The results of the screening can be seen in Table 1. There are several important advantages to conducting this type of reaction on a column as opposed to the conventional batch method.

Table 1. Reactions of acid chlorides **1** with chlorinating agent **2** using polymer-bound quinine derivative **3**

Entry	Acid chloride	Product	Yield ^a (%)	ee ^b (%)
1			58	94
2			52	93
3			50	92
4			40	90
5			61	93
6			55	88

^a Isolated yield after column chromatography.

^b Determined by chiral-phase HPLC.

First, it eliminates the need to isolate and/or manipulate highly reactive ketenes. No ketene preformation steps or precautions, other than an ice bath are necessary. Secondly, the catalyst can be easily recycled for innumerable additional runs and we avoid degradation of the catalyst beads that can be caused by vigorous mechanical stirring. Even the reaction time is drastically reduced. Most importantly, the system can ultimately be adapted to automation through the use of computer-mediated solvent pumps and flow meters.

3. Conclusion

In conclusion, we have expanded our column asymmetric methodology to include the enantioselective α -halogenation of acid chlorides, affording optically-active α -chloroesters in high enantioselectivity. It is noteworthy that the process has been rendered catalytic by an intermittent flush cycle using Hünig's base to deprotonate the beads and remove any hydrochloride salts.

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8. A standard chromatography column (1.3 cm inner diameter, 12 cm height) with a built-on jacket was used.
9. Wang resin VHL (100–200 mesh) was purchased from Novabiochem.
10. The beads can also be washed with methanol after the THF/Hünig's base wash and then dried under high vacuum at 120 °C.
11. All compounds were characterized by ¹H NMR, ¹³C NMR, IR, and elemental analysis. Compounds **4a–c**⁶ and **4f**⁵ have been synthesized previously.