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Continuous Flow Synthesis of α-Halo Ketones: Essential Building Blocks of Antiretroviral Agents

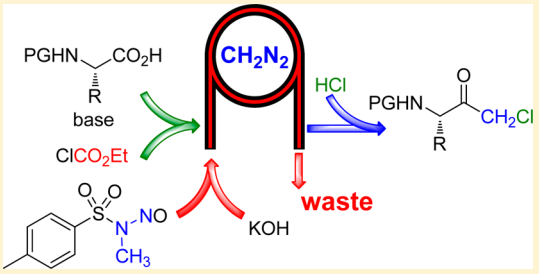
Vagner D. Pinho,[†] Bernhard Gutmann,[†] Leandro S. M. Miranda,[‡] Rodrigo O. M. A. de Souza,[‡] and C. Oliver Kappe*,[†]

[†]Institute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria

[‡]Biocatalysis and Organic Synthesis Group, Chemistry Institute, Federal University of Rio de Janeiro, CEP 22941 909 Rio de Janeiro, Brazil

Supporting Information

ABSTRACT: The development of a continuous flow process for the multistep synthesis of α-halo ketones starting from *N*-protected amino acids is described. The obtained α-halo ketones are chiral building blocks for the synthesis of HIV protease inhibitors, such as atazanavir and darunavir. The synthesis starts with the formation of a mixed anhydride in a first tubular reactor. The anhydride is subsequently combined with anhydrous diazomethane in a tube-in-tube reactor. The tube-in-tube reactor consists of an inner tube, made from a gas-permeable, hydrophobic material, enclosed in a thick-walled, impermeable outer tube. Diazomethane is generated in the inner tube in an aqueous medium, and anhydrous diazomethane subsequently diffuses through the permeable membrane into the outer chamber. The α-diazo ketone is produced from the mixed anhydride and diazomethane in the outer chamber, and the resulting diazo ketone is finally converted to the halo ketone with anhydrous ethereal hydrogen halide. This method eliminates the need to store, transport, or handle diazomethane and produces α-halo ketone building blocks in a multistep system without racemization in excellent yields. A fully continuous process allowed the synthesis of 1.84 g of α-chloro ketone from the respective *N*-protected amino acid within ~4.5 h (87% yield).



INTRODUCTION

In the last two decades a series of highly potent, orally bioavailable viral protease inhibitors have gained approval for HIV treatment (Figure 1).[1,2] HIV protease inhibitors are commonly used together with reverse transcriptase inhibitors for highly active antiretroviral therapy (HAART). Viral protease inhibitors, such as atazanavir (**3**) and saquinavir (**5**) (Figure 1), are listed by the World Health Organization as essential medicines for a basic health care system.[3] The protease inhibitors are peptidomimetics, resembling substrates in which the scissile bond is replaced by a nonhydrolyzable hydroxyethylene or hydroxyethylamine structure (Figure 1). In fact, most of the approved HIV protease inhibitors, such as nelfinavir (**1**), amprenavir (**2a**) (and its prodrug fosamprenavir **2b**), atazanavir (**3**), palinanavir (**4**), saquinavir (**5**), and darunavir (**6**) contain a chiral amino alcohol structure in the central core (Figure 1).[1,2] This crucial chiral moiety is usually introduced by a nucleophilic ring-opening of the respective *threo*- (**3**, Figure 1) or *erythro*- (**1**, **2** and **4** to **6**, Figure 1) *N*-protected aminoepoxide with the nitrogen of the C-terminal building block. A plethora of methods for the synthesis of the chiral aminoepoxide structures from their corresponding *N*-protected amino acids were developed in the past decade.[1] The most direct route involves halomethylation of an amino acid ester derivative to form an α-halo ketone (**7**), followed by reduction of the halo ketone to the alcohol.[1,4−7] Under suitable reaction conditions, both the *threo*- and the *erythro*-amino alcohol/epoxide can be produced from halo ketones **7** with excellent diasteroselectivity.[4,5]

A wide range of reagents and reaction conditions to accomplish the halomethylation of acid derivatives have been described in the scientific and patent literature.[1] The easiest and most cost-effective method, however, involves the condensation of an activated amino acid with anhydrous diazomethane (CH_2N_2) followed by an α,α-substitution reaction with a hydrogen halide (Scheme 1).[6,7]

Diazomethane is an exceptionally useful and powerful C1-building block in organic synthesis.[8] Unfortunately, CH_2N_2 is a volatile, highly irritating, poisonous, and carcinogenic compound (the boiling point of diazomethane is −23 °C). Furthermore, diazomethane is exceedingly heat, light, and shock sensitive and tends to decompose explosively. Ground glass joints, scratches in the glassware, or any other sharp edges have to be strictly avoided when working with diazomethane, and the use of specialized kits for the generation of diazomethane is recommended (kits are commercially available for the synthesis of up to 300 mmol of diazomethane in ether).[8a] The hazardous properties of diazomethane have in the past severely limited its widespread use in laboratories and

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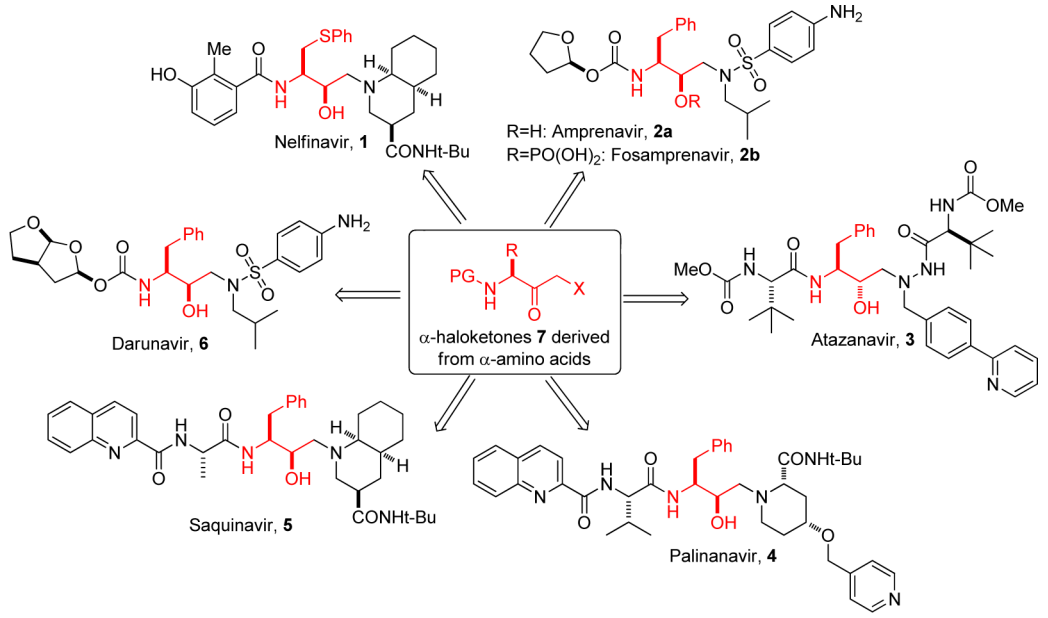
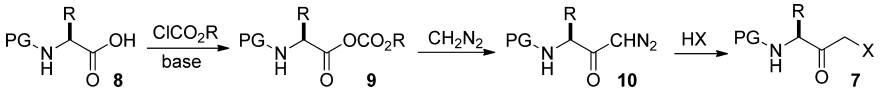


Figure 1. HIV protease inhibitors from α-halo ketones.

Scheme 1. Diazomethane Method for the Synthesis of α-Halo Ketones



industry. An industrial process capable of producing diazomethane on a scale up to 210 kg was published by Aerojet General Corp.[9] For the Aerojet process, diazomethane is generated by base-mediated decomposition of an *N*-methyl-*N*-nitrosoamine in a two-phase reaction mixture in the presence of a phase-transfer catalyst. Co-distillation of the organic solvent and the product gives an ethereal solution of diazomethane (less than about 3% by weight).[9] A continuous flow variant of this process was disclosed by Aerojet in 1998.[10] A further industrial process for the continuous production of up to 60 t per year of anhydrous CH_2N_2 was described by Proctor and Warr in 2002.[11] For this process, diazomethane was generated from a feed of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) in DMSO and a second feed of potassium hydroxide in water. The generated CH_2N_2 was continuously transported by a nitrogen stream to a reaction vessel, where it was consumed in a downstream reaction.[11] Recently, we and others presented strategies where generation, extraction, and consumption of diazomethane were integrated in continuous flow systems.[12−14] For the continuous flow process developed by DSM, the *N*-methyl-*N*-nitroso compounds were generated in an organic solvent in a first reactor and subsequently hydrolyzed by an aqueous base.[12] The diazomethane in the organic solvent was then separated through a hydrophobic membrane, whereas the aqueous phase of the reaction mixture was retained by the membrane and discarded. Kim et al. and our group used semipermeable, microporous, hydrophobic membranes, which selectively allow gases but not liquids to cross, for the generation of anhydrous CH_2N_2.[13,14] Diazomethane was produced from an aqueous feed of an *N*-nitroso precursor in a first chamber. Anhydrous CH_2N_2 gas subsequently diffused through the membrane into a second chamber where it was immediately utilized for chemical transformations.[13−15]

Continuous flow processes, long established for the production of commodity chemicals, are increasingly implemented also for the synthesis of fine chemicals and active pharmaceutical ingredients (APIs).[11−17] Fine chemicals and pharmaceuticals are generally significantly more complex than commodity chemicals and often require several steps for their synthesis and purification. Although most applications of continuous flow systems in organic synthesis focused on single-step transformations, several advanced systems for the continuous end-to-end production of APIs or the multistep synthesis of complex synthetic building blocks have been demonstrated recently.[17] In this context, a three-step continuous flow synthesis of the C-terminal biaryl building block of atazanavir (**3**, see Figure 1) was completed by our group in 2013.[18] Herein, we report the three-step continuous flow synthesis of chiral building blocks of type **7** (Scheme 1) from the respective amino acids and anhydrous diazomethane.

■ RESULTS AND DISCUSSION

For continuous-flow generation and separation of diazomethane we used a commercially available tube-in-tube (TiT) reactor.[14,19] The tube-in-tube reactor was originally developed in the Ley laboratory as a gas-addition tool for continuous gas−liquid reactions.[20,21] The inner tube of the module is a gas-permeable Teflon AF-2400 membrane with a thickness of 100 μm (0.8 mm inner diameter, 1 mm outer diameter, 4 m length).[19] Teflon AF-2400 is a copolymer of tetrafluoroethylene and perfluorodimethyldioxolane. It has an amorphous, intensely microporous structure that is highly permeable to small, unpolar molecules, while its chemical and mechanical resistance remains comparable to those typical for fluoropolymers.[20] Usually, a liquid substrate stream is carried within the membrane, while the gaseous stream is carried between the

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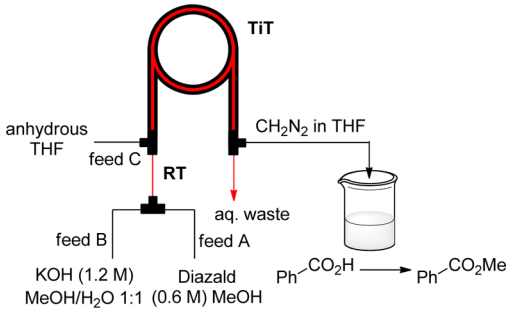
membrane and a thick-walled impermeable outer tube (polytetrafluoroethylene (PTFE); 1.59 mm inner diameter, 3.2 mm outer diameter, 4 m length). Gas diffuses from the outer to the inner chamber, thus enabling reliable and controllable saturation of the liquid feed with gases.[20] Since the introduction of the tube-in-tube module it has been heavily used for gas–liquid reactions, such as hydrogenation, carbonylation, ozonolysis, and the synthesis of carboxylic acids with carbon dioxide.[20,22]

For the generation of anhydrous diazomethane, Diazald and aqueous KOH were fed into the inner tube of the tube-in-tube reactor (Scheme 2).[14,23] CH_2N_2, an unpolar, low-molecular

Scheme 2. Generation of an Anhydrous, Ethereal Solution of CH_2N_2



weight molecule, is formed in the inner tube and subsequently diffuses through the hydrophobic, permeable wall into the outer chamber, where it dissolves and reacts in the solution carried within. To assess the efficiency with which diazomethane is generated and separated into the outer chamber, we first performed a series of experiments with different flow rates of the aqueous feed in the inner tube. Thus, 3.3 mL of a 0.6 M solution of Diazald in MeOH and an 1.2 M solution of KOH in MeOH/H_2O 1:1 were pumped into a T-mixer by two syringe pumps (Scheme 2). The combined stream passed through a short residence tube (rt; perfluoroalkoxy (PFA), 0.8 mm i.d., 2.0 mL internal volume, Scheme 2) and then further through the inner tube of the tube-in-tube reactor. The aqueous waste stream leaving the inner tube of the tube-in-tube reactor was directed into a flask containing acetic acid to decompose any diazomethane retained in the aqueous stream. Anhydrous THF was pumped through the outer tube by a third syringe pump at a flow rate of 200 μL/min (feed C, Scheme 2). Diazomethane from the inner tube dissolves in the THF, and the ethereal solution of CH_2N_2 thus generated was collected in a stirred flask containing 2.0 mmol of benzoic acid in THF. The whole setup was at room temperature. The mixture was finally analyzed by HPLC–UV/vis (Figure 2).

The reaction of benzoic acid with diazomethane can be considered to be quantitative and essentially instantaneous. The conversion of benzoic acid to methyl benzoate is thus a measure of the efficiency with which CH_2N_2 is extracted from the reaction of Diazald and KOH in the inner tube. Further, the reaction of Diazald with KOH is quite fast and highly exothermic (ΔH = −459 kJ/mol with respect to Diazald).[11] The diazomethane formed from Diazald and KOH, however, is not very stable in water and rapidly reacts with water to generate methanol (half-life = 750 s, at 20 °C and pH 7.2).[11] Therefore, a quick separation of CH_2N_2 from the aqueous phase is essential. The Teflon AF-2400 tubing has a large surface area but a small cross-sectional dimension and wall

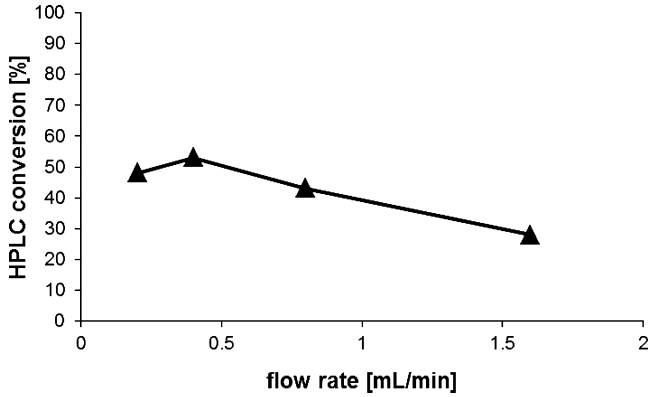


Figure 2. Generation, separation, and reaction of diazomethane with benzoic acid (HPLC conversion at 215 nm; flow rate = total flow rate of the two aqueous feeds).

thickness, thus allowing a fast gas diffusion rate across the membrane.[21] Indeed, the intense yellow color of diazomethane was apparent in the outer tube right from the inlet of the tube-in-tube reactor. The best conversion of benzoic acid to the ester was obtained for flow rates of 200 μL/min for the Diazald and KOH feeds (400 μL/min total flow rate; 5 min residence time), indicating a recovery of 53% of CH_2N_2 with respect to the introduced Diazald (Figure 2). Increasing the residence time of the aqueous stream in the inner tube above ∼5 min did not increase the conversion of benzoic acid any further (Figure 2), and apparently, a steady state of diazomethane formation/decomposition and mass transfer was attained.

For the synthesis of the α-halo ketone building blocks **7**, three successive reactions have to be performed (Scheme 1): activation of the amino acid **8** to the mixed anhydride **9**, condensation of the mixed anhydride and diazomethane to form the α-diazo ketone **10**, and finally hydrohalogenation of the diazo ketone to the α-halo ketone **7**. To accomplish the activation of the protected amino acid, a 4 mL residence loop (**RT1**; PFA, 0.8 mm i.d.; Table 1), a T-mixer (**TM1**), two injection valves (**SL1**, **SL2**), and two further syringe pumps were attached upstream to the outer tube of the tube-in-tube reactor (**TiT**, Table 1). For the first reactions, 2 mL of a solution containing *N*-Cbz-L-phenylalanine (0.64 mmol) and tributylamine (1.0 equiv; feed C) and 2 mL of ethyl chloroformate (0.70 mmol, 1.1 equiv; feed D) in THF were loaded into the sample loops of the two injection valves. When the flow reaction was started, the injection valves were switched to connect the sample loop in line with the carrier stream (THF). The two reaction solutions were carried into the T-mixer (**TM1**), and the merged stream then went through the tube reactor **RT1** at 0 °C. The mixture subsequently passed through the outer chamber of the tube-in-tube device, where the solution was saturated with the dry diazomethane from the inner tube (Table 1). The product solution from the outer tube was collected in a flask and stirred for further 15 min until conversion to the α-diazo ketone was completed. With flow rates of 200 μL/min for feed C and feed D (combined flow rate of 400 μL/min, 10 min residence time in **RT1**), a complete conversion of the *N*-Cbz-*L*-phenylalanine **8a** was achieved when 5.0 equiv of Diazald (3.2 mmol) were pumped through the inner tube. However, at a reaction temperature of 0 °C for the activation step, 34% of phenylalanine methyl ester, apparently formed from unactivated Cbz-phenylalanine and CH_2N_2, was detected in the reaction mixture (entry 1, Table 1).

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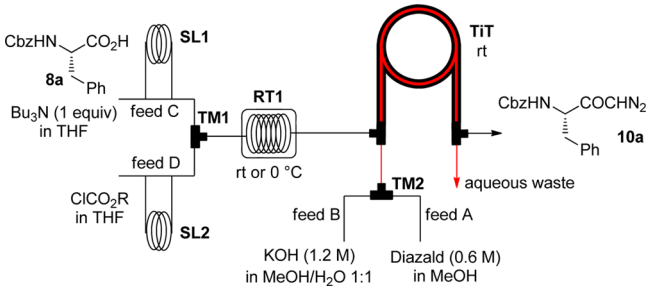
Table 1. Formation of α-Diazo Ketone 10a (and Cbz-Phe-OMe Side Product) in a Continuous Flow System[a]



entry	conc of **8a** (M)	activation agent R =	flow rate feed C/D [μL/min]	α-diazo ketone **10a**[a] (%)	Cbz-Phe-OMe[a] (%)
1[b]	0.16	Et (1.1 equiv)	200/200	66	34
2	0.16	Et (1.1 equiv)	200/200	86	14
3	0.16	Et (1.1 equiv)	400/400	77	23
4	0.16	Et (1.2 equiv)	400/400	93	7
5[c]	0.32	Et (1.2 equiv)	200/200	83	17
6	0.32	*i*-Bu (1.5 equiv)	200/200	98	2
7	0.32	Et (1.5 equiv)	200/200	98	2

[a]Amount of α-diazo ketone **10a** and Cbz-Phe-OMe according to HPLC at 215 nm. Conditions: room temperature; flow rate feed A/B: 200/200 μL/min. [b]Temperature of **RT1** was held at 0 °C in an ice bath. [c]Flow rate of the aqueous feed A/B was 400/400 μL/min rt = room temperature. For a graphical image of the setup see Figure S1 in the Supporting Information.

Still 14% of the ester was detected when the activation step was performed at room temperature under otherwise identical conditions (entry 2, Table 1). Increasing the amounts of ethyl chloroformate to 1.5 equiv decreased ester formation to 2% (entry 7, Table 1). The pure α-diazo ketone **10a** was isolated from this experiment in 82% after column chromatography. Importantly, even though the mixed anhydride intermediate **9a** is highly temperature sensitive, no racemization was observed under these conditions (see the Supporting Information).

The formation of the diazo ketone from the amino acid liberates 1 equiv of an acid.[8c] Acylation of diazomethane, therefore, generally requires at least 2 equiv of diazomethane to sequester the acid released in the reaction. In fact, 2 equiv of diazomethane is consumed for every molecule of ethyl chloroformate injected into the flow system. As mentioned above (Figure 2), a complete conversion of amino acid was obtained and essentially no side products were detected by HPLC using 1.5 equiv of ethyl chloroformate and 5 equiv of Diazald. This result suggests that at least 60% of the Diazald pumped through the inner tube is extracted into the outer tube in the form of anhydrous CH_2N_2 under the actual reaction conditions.

To convert the α-diazo ketone **10a** to the chloro ketone **7a**, the product solution from the outer tube was collected into a flask closed with a rubber septum. The mixture was stirred for 15 additional minutes to complete the diazo ketone formation. The flask was then cooled to 0 °C, and 2.6 mL of a 2 M solution of HCl in diethyl ether was added dropwise to the mixture with a syringe under vigorous stirring. The solvent was ultimately removed, and the chloro ketone **7a** was isolated by column chromatography (82% yield with respect to the amino acid **8a**). This general procedure was applicable for the synthesis of a range of α-chloro ketones in good yields (Figure 3), including the core building blocks of all the HIV protease inhibitors shown in Figure 1. For the synthesis of the α-bromo ketones, the diazo ketone solution was quenched with 1 equiv of HBr at 0 °C (from a 33% solution of HBr in AcOH diluted with 2 mL of dry THF).

The experimental setup described above is quite simple and flexible and thus very applicable for the screening of reaction conditions, exploring the scope of the reaction and the quick and convenient synthesis of small-scale compound libraries. Finally, however, the setup was modified and extended to accomplish the transformation of the Cbz-protected L-phenylalanine to the α-chloro ketone in a truly continuous, multistep reaction sequence (Scheme 3 and Figure S3 and S4 in the Supporting Information). Thus, a short residence loop (**RT2**; PFA, 0.8 mm i.d., 4 mL) was attached to the outer tube downstream to the tube-in-tube reactor to allow the completion of diazo ketone formation in the flow system, and a fifth pump was connected to the system via a T-piece to feed in the HCl quench-solution. The activation agent (feed D) and *N*-Cbz-L-phenylalanine **8a** (feed C) were pumped into the system at flow rates of 75 μL/min. The mixed anhydride **9a** was formed in a first 1 mL residence loop at room temperature (**RT1**, PFA, 0.8 mm i.d.). Diazomethane was generated from Diazald (feed A, 5 equiv) and KOH (feed B) in the inner tube of the tube-in-tube device at flow rates of 200 μL/min for each feed. The anhydride **9a** passed through the outer tube of the device, where it was combined with a continuous stream of anhydrous diazo-

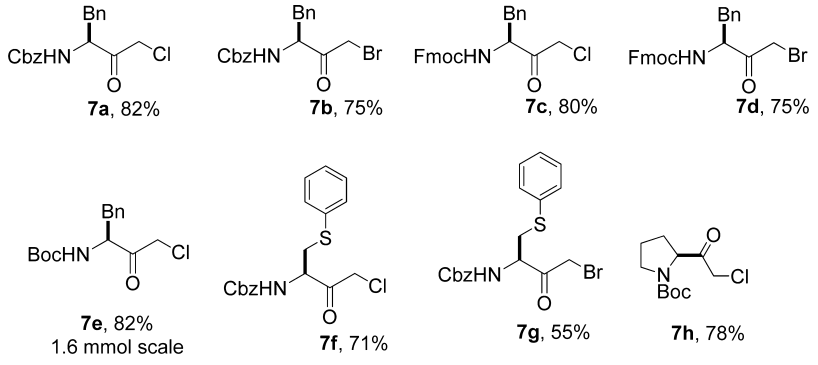


Figure 3. Yields of α-halo ketones after a three-step synthesis starting from *N*-protected amino acids.

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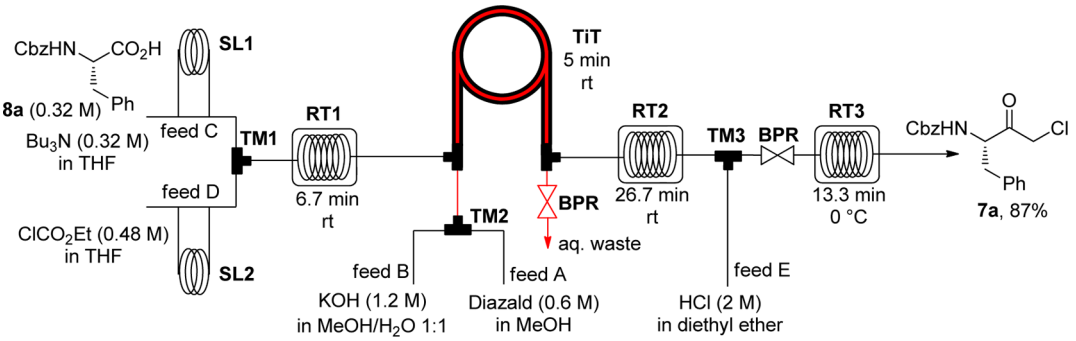
Scheme 3. Three-Step Continuous Flow Synthesis of α-Chloro Ketone 7a



methane from the inner tube. Again, the yellow color of CH_2N_2 was clearly visible in the outer tube, but the color slowly faded along the tube-in-tube device and then further in the residence loop **RT2**. Notably, thermal decomposition of CH_2N_2 released small amounts of nitrogen gas. Further, 1 equiv of CH_2N_2 is sequestered during diazo ketone formation (see above), and an additional 1 equiv of nitrogen gas is released. The released nitrogen pushes the reaction mixture through the tube-in-tube device and further through the residence module **RT2**. To obtain stable flow rates and predictable residence times throughout the flow system, back-pressure regulators (**BPR**, 3 bar) were attached after **RT2** and to the outlet of the inner tube of the tube-in-tube reactor. The product mixture passing **RT2** was finally merged with an excess of a 2 M ethereal solution of HCl in a T-mixer (**TM3**) at 0 °C (feed E; 80 μL/min, 1.33 equiv with respect to the total amount of used Diazald). The HCl reacts with the diazo ketone **10a** to furnish the α-chloro ketone **7a** in a third residence loop (**RT3**; PFA, 0.8 mm i.d., 3 mL) at 0 °C and any excess of CH_2N_2 is destroyed. The pure α-chloro ketone **7a** was collected and isolated by chromatography in 87% product yield after the continuous flow three-step reaction sequence (1.6 mmol scale; throughput: 1.25 mmol/h). The system was finally run continuously for ∼4.5 h (steady-state conditions) to produce 1.84 g of α-chloro ketone **7a** (87% yield).

CONCLUSIONS

In conclusion, we have described a laboratory-scale multistep process for the synthesis of chiral α-halo ketones form *N*-protected amino acids which does not require any isolation or purification of intermediates. The amino acids were activated by ethyl chloroformate in the presence of a base to form the mixed anhydrides. The mixed anhydrides were subsequently converted to the α-diazo ketones with anhydrous diazomethane and finally treated with HCl or HBr to afford the corresponding α-halo ketones. The reaction sequence involving diazomethane is clearly the easiest and most cost-effective method to produce the chiral α-halo ketones. Diazomethane is an exceptionally useful and versatile C1 building block. Reactions with CH_2N_2 are usually very fast, can be performed under mild conditions, and often produce nitrogen as the only byproduct. However, the hazardous nature of CH_2N_2 has severely limited its widespread use in laboratories and industry. For the process described herein, diazomethane was formed in the inner tube of a tube-in-tube reactor. Anhydrous diazomethane diffuses through the gas permeable inner tube and immediately reacts with the mixed anhydride in the outer chamber. Any excess of CH_2N_2 is finally destroyed during the HCl or HBr quench. The continuous on-site-on-demand generation and separation/consumption of CH_2N_2 eliminates the need to store, transport or handle this highly toxic, odorless and explosive reagent and the total amount of hazardous material in the setup at any time is small. A fully continuous, multistep process on a 6.4 mmol scale finally allowed the synthesis of 1.84 g of enantiopure α-chloro ketone **7a**, a key intermediate for the synthesis of protease inhibitors such as Atazanavir, in 87% isolated yield (throughput: 1.25 mmol/h). During the course of this study, the continuous flow setup proved to be very robust and the system was run continuously for several hours without the need of any intervention.

EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded on a 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis (Shimadzu LC20) was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water−acetonitrile 90: 10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Diazald was synthesized following a literature procedure.[24] The known products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry and identified by comparison of the spectra with those reported in the literature. The new compounds **7c** and **7g** were further characterized by HRMS (TOF MS EI+). Proof of purity was obtained by ^{1}H NMR and HPLC−UV spectroscopy.

CAUTION: CH_2N_2 is a highly toxic, carcinogenic, and very explosive gas. The reactions present herein should not be undertaken without stringent hazard assessment and proper safety precautions put in place.

General Preparation of α-Halo Ketones (Figure 3). KOH (60 mmol) was dissolved in 50 mL of MeOH/H_2O 1:1 (feed B, 1.2 M), and 3.2 mmol of Diazald was dissolved in 5.4 mL of MeOH (feed A, 0.6 M). For feed C, the *N*-protected α-amino acid (0.64 mmol) and Bu_3N (0.64 mmol, 152 μL) were dissolved in 2 mL of dry THF (0.32M) and injected in a 5 mL sample loop (**SL1**; PTFE, 1.59 mm o.d., 0.8 mm i.d.; Table 1). For feed D, ethyl chloroformate (0.96 mmol, 122 μL) was dissolved in 2 mL of dry THF (0.48M) and injected in a second sample loop (**SL2**; PTFE, 1.59 mm o.d., 0.8 mm i.d.; Table 1). Feeds A and B were pumped into a T-mixer (**TM2**; PEEK, 1.59 mm o.d., 0.50 mm pore size, 1.7 μL internal volume.; Table 1) at room temperature by two syringe pumps (Asia Syrris) at flow rates of 200 μL/min each (2 equiv of KOH with respect to Diazald). The mixture went through a short PFA tubing (1.59 mm o.d., 0.8 mm i.d., 200 μL internal volume) and then further through the inner tube of the tube-in-tube reactor (**TiT**; Teflon AF-2400, 1.0 mm o.d., 0.8 mm i.d., 2 mL internal volume; Table 1). The aqueous

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waste stream leaving the inner tube of the reactor was quenched into AcOH. Feeds C and D were pumped from the sample loop into a T-mixer (**TM1**; PEEK, 1.59 mm o.d., 0.50 mm pore size, 1.7 μL internal volume.; Table 1) by two syringe pumps (Asia Syrris) at flow rates of 200 μL/min each. Feeds C and D went through a residence tube at room temperature (**RT1;** PFA, 1.59 mm o.d., 0.8 mm i.d., 4 mL internal volume) and then further through the outer tube of the tube-in-tube reactor (**TiT**; PTFE, 3.23 mm o.d., 1.59 mm i.d., 4.8 mL internal volume; Table 1). Seven minutes after the injection valves were switched to connect the sample loops **SL1**/**SL2** in line with the carrier stream, feed A was switched from pure solvent to the Diazald solution. The product stream form the outer tube was collected into a round-bottom flask under magnetic stirring. Product collection started 15 min after introducing the amino acid solution and the product stream was collected for 70 min in total. The flask was stirred for further 15 min at room temperature and was then cooled to 0 °C in an ice bath. For the synthesis of the α-chloro ketones, a 2 M solution of HCl in diethyl ether (1.28 mmol) was added dropwise with a syringe, and the reaction mixture was further stirred for 15 min at 0 °C. For the synthesis of the α-bromo ketones, a 33% solution of HBr in AcOH diluted with 2 mL of dry THF (0.64 mmol) was added dropwise with a syringe, and the reaction mixture was further stirred for 10 min at 0 °C. Then the solvent was removed, and the residue was purified by flash chromatography. For a detailed description of the experimental setup, see Figure S1 in the Supporting Information.

(*S*)-Benzyl (4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate (7a): 174 mg (82%, white solid); mp 108−109 °C (lit.[25] mp 105−106 °C); $[\alpha]_D^{20}$ +27.4 (*c* 2.35, $CHCl_3$), lit.[4f] $[\alpha]_D^{22}$ +30.9 (*c* 2.40, $CHCl_3$); $[\alpha]_D^{20}$ −48.5 (*c* 1.01, MeOH), lit.:[6a] $[\alpha]_D^{22}$ −51.1 (*c* 1.06, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.23 (m, 9H), 7.16 (d, *J* = 6.4 Hz, 2H), 5.36 (d, *J* = 7.1 Hz, 1H), 5.10 (s, 2H), 4.79 (q, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 16.2 Hz, 1H), 4.00 (d, *J* = 16.2 Hz, 1H), 3.20−2.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 155.8, 135.9, 135.2, 129.1, 129.0, 128.6, 128.4, 128.2, 127.5, 67.3, 58.7, 47.5, 37.7, 29.7; FT-IR (KBr, cm^{-1}) 3333, 3061, 2944, 1737, 1682, 1523, 1494, 1258, 825, 774, 697, 524; R_f 0.45 (2.5% EtOAc/DCM), R_f 0.37 (30% acetone/petroleum ether).

(*S*)-Benzyl (4-bromo-3-oxo-1-phenylbutan-2-yl)carbamate (7b): 180 mg (75%, white solid); mp 104−106 °C (lit.[6a] mp 103−104 °C); $[\alpha]_D^{20}$ +25.2 (*c* 1.03, $CHCl_3$), $[\alpha]_D^{20}$ −48.7 (*c* 1.03, MeOH), lit.[26] $[\alpha]_D^{20}$ −45.9 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.22 (m, 8H), 7.16 (d, *J* = 6.2 Hz, 2H), 5.34 (t, *J* = 7.6 Hz, 1H), 5.18−5.04 (m, 2H), 4.85 (q, *J* = 7.1 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 3.84 (d, *J* = 13.6 Hz, 1H), 3.10 (qd, *J* = 13.9, 7.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 200.5, 155.8, 135.9, 135.4, 129.1, 129.0, 128.6, 128.4, 128.1, 127.5, 67.3, 58.8, 38.0, 33.0; FT-IR (KBr, cm^{-1}) 3344, 3063, 3007, 2947, 1734, 1682, 1524, 1449, 1253, 1028, 977, 754, 699, 514; R_f 0.45 (30% EtOAc/petroleum ether).

(*S*)-(9*H*-Fluoren-9-yl)methyl (4-chloro-3-oxo-1-phenylbutan-2-yl)carbamate (7c): 215 mg (80%, white solid); mp 143−146 °C; $[\alpha]_D^{20}$ +10.7 (*c* 1.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.3 Hz, 2H), 7.65−7.04 (m, 11H), 5.46−5.21 (m, 1H), 4.89−4.62 (m, 1H), 4.54−4.37 (m, 2H), 4.27−4.06 (m, 2H), 3.96 (d, *J* = 16.1 Hz, 1H), 3.28−2.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 155.7, 143.5, 141.3, 135.3, 129.1, 129.0, 127.8, 127.5, 127.1, 125.0, 120.0, 69.0, 58.7, 47.4, 47.2, 37.6; FT-IR (KBr, cm^{-1}) 3314, 3027, 2942, 2873, 1736, 1679, 1529, 1464, 1259, 1031, 734, 521; HRMS (TOF MS EI+) calcd for $C_{18}H_{18}BrNO_3S$ $[M]^+$, 407.0191, found 407.0189; R_f 0.47 (2.5% EtOAc/DCM).

(*S*)-(9*H*-Fluoren-9-yl)methyl (4-bromo-3-oxo-1-phenylbutan-2-yl)carbamate (7d): 223 mg (75%, white solid); mp 148−149 °C (lit.[6a] mp 139−141 °C); $[\alpha]_D^{20}$ +3.8 (*c* 1.36, CH_2Cl_2), lit.[5d] $[\alpha]_D^{24}$ +5.4 (*c* 1.0, CH_2Cl_2), $[\alpha]_D^{20}$ +10.2 (*c* 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.66−7.49 (m, 2H), 7.37 (ddd, *J* = 24.1, 15.7, 8.4 Hz, 7H), 7.25−7.09 (m, 2H), 5.45−5.19 (m, 1H), 4.91−4.72 (m, 1H), 4.46 (d, *J* = 6.4 Hz, 2H), 4.21 (t, *J* = 6.1 Hz, 1H), 3.89 (t, *J* = 13.9 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 1H), 3.27−2.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 155.7, 143.6, 143.6, 141.3, 135.5, 129.1, 129.0, 127.8, 127.4, 127.1, 125.0, 120.0, 66.9, 58.8, 47.2, 37.8, 32.9; FT-IR (KBr, cm^{-1}) 3314, 3052, 3025, 2949, 1733, 1679, 1530, 1448, 1385, 1260, 990, 733, 696, 513; R_f 0.52 (2.5% EtOAc/DCM).

(*S*)-*tert*-Butyl (4-chloro-3-oxo-1-phenylbutan-2-yl)-carbamate (7e): 391 mg (82%, white solid); mp 103−105 °C (lit.[27] mp 102−103 °C); $[\alpha]_D^{20}$ +18.6 (*c* 2.0, $CHCl_3$), lit.:[28] $[\alpha]_D^{25}$ +17.0 (*c* 1.4 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.23 (m, 3H), 7.23−7.11 (m, *J* = 6.4 Hz, 2H), 5.21−4.91 (m, *J* = 6.9 Hz, 1H), 4.78−4.55 (m, 1H), 4.19 (d, *J* = 16.3 Hz, 1H), 4.00 (d, *J* = 16.3 Hz, 1H), 3.20−2.88 (m, *J* = 7.2 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 155.2, 135.6, 129.3, 129.1, 128.9, 127.4, 80.5, 58.4, 47.6, 37.7, 28.2; FT-IR (KBr, cm^{-1}) 3363, 2985, 2939, 1734, 1687, 1512, 1252, 1163, 1025, 939, 890, 703,646; R_f 0.50 (2.5% EtOAc/DCM).

(*R*)-Benzyl (4-chloro-3-oxo-1-(phenylthio)butan-2-yl)-carbamate (7f): 158 mg (71%, white solid); mp 91−92 °C; $[\alpha]_D^{20}$ +12.7 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.17 (m, 10H), 5.74−5.50 (m, 1H), 5.10 (s, 2H), 4.84−4.64 (m, 1H), 4.20 (q, *J* = 16.0 Hz, 2H), 3.39 (ddd, *J* = 31.1, 14.1, 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 155.7, 135.8, 133.8, 130.7, 129.4, 128.6, 128.4, 128.1, 127.5, 67.4, 57.0, 47.0, 35.6; FT-IR (KBr, cm^{-1}) 3337, 3280, 3059, 3030, 2938, 1737, 1680, 1524, 1262, 1169, 1082, 779, 732, 634, 469; R_f 0.42 (30% EtOAc/petroleum ether).

(*R*)-Benzyl (4-bromo-3-oxo-1-(phenylthio)butan-2-yl)-carbamate (7g): 143 mg (71%, yellowish solid); mp 94−95 °C; $[\alpha]_D^{20}$ +10.1 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.12 (m, 10H), 5.82−5.54 (m, 1H), 5.10 (s, 2H), 4.90−4.69 (m, 1H), 4.00 (s, 2H), 3.40 (ddd, *J* = 20.2, 14.1, 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 155.7, 135.8, 133.9, 130.8, 129.4, 128.6, 128.4, 128.1, 127.5, 67.4, 57.0, 35.9, 32.3; FT-IR (KBr, cm^{-1}) 3307, 3278, 3063, 3029, 2939, 1733, 1682, 1529, 1270, 1255, 1039, 1023, 892, 732, 688; HRMS (TOF MS EI+) calcd for $C_{25}H_{22}ClNO_3$ $[M]^+$, 419.1288, found 419.1286; R_{+f} 0.45 (30% EtOAc/petroleum ether).

(*S*)-*tert*-Butyl 2-(2-chloroacetyl)pyrrolidine-1-carboxylate (7h): 123 mg (78%, colorless oil); $[\alpha]_D^{20}$ −73.7 (*c* 2.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 4.65−4.40 (m, 1H), 4.27 (d, *J* = 23.9 Hz, 2H), 3.66−3.34 (m, 2H), 2.38−2.06 (m, 1H), 2.05 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 202.2, 201.8, 154.7, 153.5, 80.8, 80.3, 63.4, 62.8, 47.1, 46.9, 46.7, 46.1, 30.5, 29.4, 28.4, 28.3, 28.1, 24.6, 23.8, 23.7; FT-IR (neat, cm^{-1}) 2976, 2933, 2881, 1824, 1743, 1685, 1390, 1365, 1245, 1158, 1115, 1078, 771, 665; R_f 0.47 (40% EtOAc/petroleum ether).

Continuous Flow Synthesis of (*S*)-Benzyl (4-Chloro-3-oxo-1-phenylbutan-2-yl)carbamate (7a) (Scheme 3). Feed A (0.6 M solution of Diazald in MeOH) and feed B (1.2 M solution of KOH in $MeOH/H_2O$ 1:1) were pumped into a T-mixer (**TM2**) by two syringe pumps at flow rates of 200 μL/min each (Asia Syrris). The combined mixture went through a PFA tubing (200 μL internal volume) and then further through the inner tube of the tube-in-tube reactor (**TiT**, room temperature). The mixture leaving the inner tube was quenched into conc AcOH. Feed C (20 mL of a 0.32 M solution of *N*-Cbz-L-phenylalanine **8a** and Bu_3N in dry THF) and feed D (20 mL 0.48 M solution of ethyl chloroformate in dry THF) were pumped into a T-mixer (**TM1**) by two further syringe pumps at flow rates of 75 μL/min each (Asia Syrris). The combined mixture went through a coil reactor (**RT1**, 1 mL internal volume, room temperature) and then further through the outer tube of the tube-in-tube reactor (**TiT**). The mixture leaving the outer tube went through a second coil reactor (**RT2**, 4 mL internal volume, room temperature). Feed E (2 M solution of HCl in Et_2O) was pumped into the system at a flow rate of 80 μL/min (Asia Syrris). Feed E was combined with the product stream leaving **RT2** in a T-mixer (**TM3**, 0 °C), and the resulting stream went through a third coil reactor (**RT3**, 2 mL internal volume, 0 °C). The product was collected in a flask closed with a rubber septum at 0 °C. After collection was finished, the solvent was removed and the residue was purified by flash chromatography with DCM/EtOAc as eluent (0−10%) to give 1.85 g (87%) of the title compound. For a detailed description of the experimental setup see Figure S4 in the Supporting Information.

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■ ASSOCIATED CONTENT

Supporting Information

Pictures and detailed description of the continuous flow setup; ^{1}H and ^{13}C NMR spectra of all compounds; chiral HPLC of α-diazo ketone **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: oliver.kappe@uni-graz.at.

Notes

The authors declare no competing financial interest.

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