Continuous and convergent access to vicinyl amino alcohols†

Tomoya Nobuta,‡a Guozhi Xiao,‡a Diego Ghislieri,‡a Kerry Gilmore* and Peter H. Seeberger*ab

Five active pharmaceutical ingredients (APIs) containing the vicinyl amino alcohol moiety were synthesized using a convergent chemical assembly system. The continuous system is composed of four flow reaction modules: biphasic oxidation, Corey–Chaykovsky epoxidation, phenol alkylation, and epoxide aminolysis. Judicious choice of reagents and module order allowed for two classes of β-amino alcohols, aryl and aryloxy, to be synthesized in good (27–69%) overall yields.

The chemical synthesis of active pharmaceutical ingredients (APIs) is generally accomplished via a linear batch approach where a single process produces a single compound. Flow chemistry is a conceptual advance that allows for greater control over reaction conditions and the ability to combine several sequential flow reactors to achieve multistep processes. Chemical assembly systems (CAS) are based on telescoping sequential robust reaction units that are linked together in a non-iterative fashion. Multi-step syntheses of a wide range of compounds of similar or unique structural cores can be accessed in a divergent fashion (Fig. 1). Here, we report on the application of CAS to convergent syntheses, where two structural variations of a key epoxide intermediate can be trapped in an aminolysis reaction to produce two distinct classes of β-amino alcohols, including five APIs.

A variety of biologically active natural products, chiral auxiliaries, ligands, and APIs for the treatment of hypertension or as bronchodilators contain β-amino alcohols as an important structural core. Synthetic approaches to β-amino alcohols abound, including amino acid reduction, coupling reactions, α-functionalization, amino-hydroxylation, and epoxide ring opening. Two classes of pharmaceutically relevant compounds, aryl and aryloxy vicinal amino alcohols, should be accessible via convergent epoxidations followed by a final ring opening with an amine (Fig. 2).

Aryl epoxides should be accessible via a one-to-two step oxidation/Corey–Chaykovsky process. Employing robust and selective biphase alkyl-oxidation conditions we developed earlier, the first transformation is readily achieved and thus a continuous Corey–Chaykovsky epoxidation needed to be developed. Using benzaldehyde as a model system, a 0.5 M toluene solution was

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† Electronic supplementary information (ESI) available: Characterization data, full experimental procedures, copies of 1H and 13C NMR spectra of all new compounds. See DOI: 10.1039/c5cc06093a

‡ These authors contributed equally to this work.
mixed with an aqueous solution of trimethylsulfonium iodide ((CH₃)₃S(I)O), sodium hydroxide (NaOH), and a substoichiometric amount of phase transfer catalyst (tetrabutylammonium iodide (TBAI)). The resulting biphasic solution was passed through a 10 mL reactor held at 90 °C at a pressure of 2 bar. Clean conversions to styrene oxide were observed with (CH₃)₃S(I)O and NaOH in excess (1:4-2 equiv., Table 1 entries 1-3) after 24 minutes. Shorter reaction times, temperature, and the absence of TBAI resulted in decreased conversion (entries 5-7).

Using optimized conditions (97%, entry 2), we next turned to the amine ring-opening. While epoxide opening traditionally employed Lewis acids (LA), the elevated pressures and temperatures during microwave and flow transformations allow for clean reactions without LA catalysts. We aimed to combine epoxidation and ring opening by modifying established flow conditions. Thus, the crude epoxy solution containing styrene oxide was reacted with an aqueous solution of trimethylsulfonium iodide (1.7 equiv.), sodium hydroxide (1.7 equiv.), TBAI (0.1 equiv.) in water, flow rate: 0.33 mL min⁻¹, reactor size: 10 mL, temperature: 90 °C, residence time: 50 minutes at a 2:1 ratio, with the desired epoxide obtained in 56% yield (Fig. 3).

A number of hypertension medications such as propranolol, alpenolol, and metoprolol contain the arylxy b-amino alcohol motif. These targets were selected to expand the scope of the modular flow synthesis of vicinal amino alcohols. Typical phenol cyclizations require a large excess of epichlorohydrin equivalents in the presence of an inorganic base. However, homogeneous solutions would facilitate the development of a flow process. A biphasic solution, obtained by mixing aqueous sodium hydroxide solution with a phenol in neat epichlorohydrin, should provide the desired arylxy epoxy.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Me₃SOI</th>
<th>NaOH</th>
<th>TBAI</th>
<th>Residence time</th>
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<td>0.1</td>
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Table 2 Optimization of aminolysis (module 3) in flow

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<th>Entry</th>
<th>BuNH₂</th>
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<th>Temp. (°C)</th>
<th>Ratio</th>
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<tr>
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<td>7</td>
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<td>150</td>
<td>83</td>
<td>13 : 4</td>
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<tr>
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<td>130</td>
<td>64</td>
<td>13 : 23</td>
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<td>5</td>
<td>5</td>
<td>20</td>
<td>150</td>
<td>62</td>
<td>12 : 26</td>
</tr>
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</table>

*a Crude styrene oxide (2, 0.33 M in toluene), BuNH₂ in toluene/ethanol (1:0.5), flow rates each 0.2 mL min⁻¹. For full experimental details, see ESI. *b As determined by ¹H NMR. BPR: back pressure regulator.

Aryl vicinal amino alcohols produced by continuous synthesis. The sodium hydroxide solution (1.95 M, 1.3 equiv.) was combined with phenol in three equivalents of neat epichlorohydrin via a T-mixer and passed through a reactor (1 h reaction time at 35 °C). Two major alkylation products (10, 11) were observed in roughly a 2:1 ratio, with the desired epoxy 10 obtained in 56% yield (Table 3, entry 1). Addition of substoichiometric amounts of PTC resulted in an increased conversion of the intermediate halohydrin (11) into the desired product (entry 2). At a reaction temperature of 45 °C, 10 was obtained in 86% yield while no intermediate halohydrin was observed (entry 3). At higher temperatures, a diol was formed by sodium hydroxide mediated ring opening of the epoxide. Reducing the excess of epichlorohydrin to two equivalents (entry 5, final conditions) had no effect, while a further reduction of the reagent to one equivalent yielded sizable amounts of the API was obtained in 27% yield (Fig. 3).
of dimer 12 (entry 6). Shortening the residence time in the reactor to 46 minutes resulted in incomplete conversion (entry 4).

Using this method, chiral aryloxy epoxides can be generated efficiently. When enantiopure epichlorohydrin is reacted using the conditions described above, the reaction proceeds with 93.7% ee (Fig. 4).

Module 4 depends on the solubility of the intermediate aryloxide in the biphasic solution. In cases where a precipitate forms, as occurred during the synthesis of metoprolol 20, module 4 can split into a two-stage alkylation. Phenol was efficiently alkylated at 110°C after 60 minutes when epichlorohydrin served as solvent (3.1 M, 2 equiv.). By mixing the resulting solution with aqueous NaOH at 45°C, 84% of the desired epoxide could be obtained after only 30 minutes (Fig. 5).19

With a reliable process for the procurement of epoxide 10 in hand, the aminolysis module was connected (Table 2). Alkyl epoxides proved more active than aryl epoxides such that the ring opening proceeded at lower temperatures and shorter reaction times (Table 4). The epoxide solution was converted in just 20 min when mixed with five equivalents of isopropylamine in ethanol at 120°C (entry 4). The reaction proceeds efficiently at 100°C, but requires longer residence times (entry 2). Only one regioisomer and no amine dialkylation product were observed.

Finally, modules 3 and 4 were combined to yield the final sequence. The toluene phase is removed using a membrane-based separator and directly fed into module 3. Amino alcohol 16 was obtained in 48% yield from phenol, following off-line crystallization (Fig. 6). Several active pharmaceutical ingredients were prepared based on a judicious choice of starting materials. Racemic and chiral aryloxy β-amino alcohols can be prepared including propranolol (17, 51%),23 used to treat hypertension,24 alprenolol (18, 42%), an angina pectoris medication,25 and the hypertension drugs bupranolol (19, 69%),26 as well as metoprolol (20, 69%).

Described is the development of a convergent chemical assembly system consisting of four modules that reliably produces aryl and aryloxy β-amino alcohols in good yields. Modular flow units include biphasic oxidations,5 Corey–Chaykovsky epoxidations, aryloxy alkylations, and epoxide aminolysis.12 Aqueous in-line workup using liquid–liquid extractors resulted in continuous processes without intermediate purification. Starting from phenols or benzyl alcohols five active pharmaceutical ingredients for the treatment of hypertension, agina pectoris, and bronchodilation were produced. Enantiopure aryloxy β-amino alcohols can be prepared by starting from R/S epichlorohydrin.

![Fig. 4 Synthesis of (S)-2-((naphthalen-1-yloxy)methyl)oxirane using enantiopure (R)-epichlorohydrin.](image)

![Fig. 5 To accommodate water-soluble and insoluble phenoxides, two variants of module 4, were implemented.](image)

![Fig. 6 Overview over aryloxy vicinyl amino alcohols produced by continuous synthesis.](image)
Notes and references


9 Amino alcohol drugs such as Metoprolol, Atenolol were among the Top 200 brand name drugs by total prescriptions in 2012, see: N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, 87, 1348.


14 For details of the modification, see ESI. For the original description of the membrane-based separator, see J. G. Kralj, H. R. Sahoo and K. F Jensen, *Lab Chip*, 2007, 7, 256.


17 Typical conditions utilize epichlorohydrin in as much as 20-excess, see: ref. 16, p. 110.


19 See ESI for further details.


