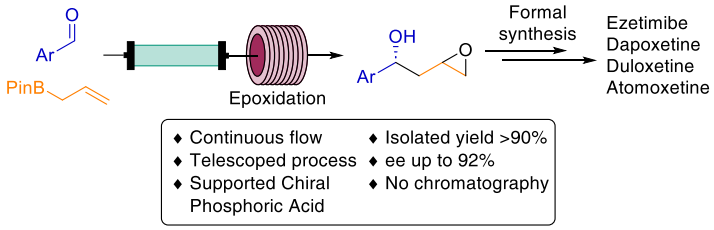
A Telescoped Continuous Flow Enantioselective Process to Access Chiral Intermediates of Atomoxetine, Dapoxetine, Duloxetine and Ezetimibe

Aitor Maestro*[a,b] Bence S. Nagy,[b] Sándor B. Ötvös,[b,c] C. Oliver Kappe*[b,c]

[a] Department of Organic Chemistry I, University of the Basque Country, UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain; [b] Institute of Chemistry, University of Graz, NAWI Graz, A-8010 Graz, Austria; [c] Center for Continuous Flow Synthesis and Processing (CC FLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), A-8010 Graz, Austria



ABSTRACT: A telescoped continuous flow process is reported for the enantioselective synthesis of chiral precursors of 1-aryl-1,3-diols, intermediates in the synthesis of Ezetimibe, Dapoxetine, Duloxetine and Atomoxetine. The two-step sequence consists of an asymmetric allylboration of readily available aldehydes using a polymer-supported chiral phosphoric acid catalyst to introduce asymmetry, followed by selective epoxidation of the resulting alkene. The process is highly stable for at least 7 h and represents a transition-metal free enantioselective approach to valuable 1-aryl-1,3-diols.

MAIN TEXT:

1-Aryl-1,3-diols of type **1** are important synthetic building blocks for the pharmaceutical industry.[1] They are key intermediates in the synthesis of numerous drugs, including ezetimibe (treatment of high blood cholesterol),[2] dapoxetine (premature ejaculation),[3] atomoxetine (attention deficit hyperactivity disorder)[4] and duloxetine (major depressive and anxiety disorders)[5] (Figure 1).

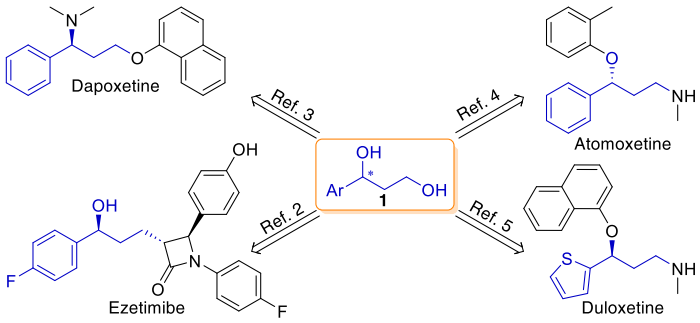


Figure 1: Relevant drugs synthesized from 1-aryl-1,3-diols 1.

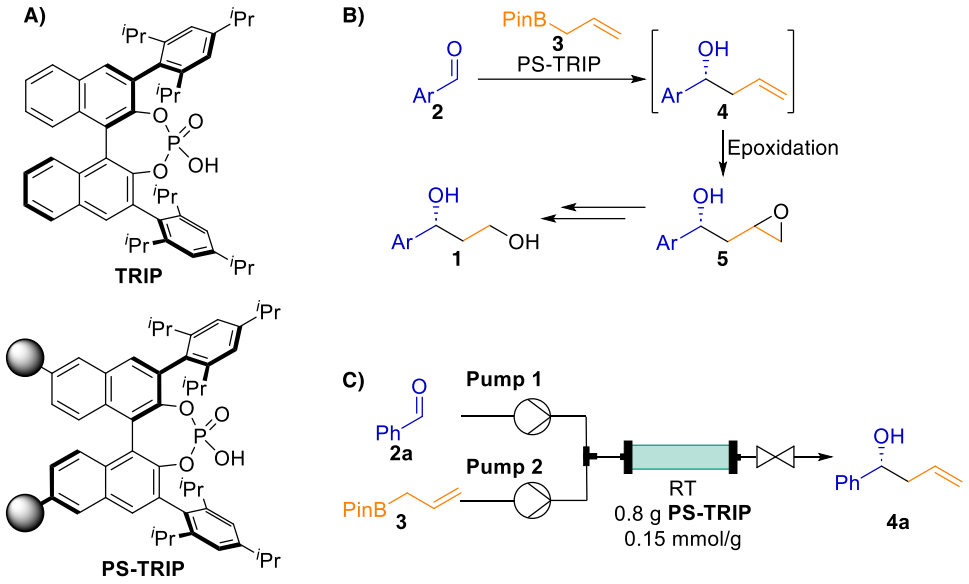
Several synthetic routes have been developed to access optically active 1-aryl-1,3-diols using transition metal-mediated enantioselective reactions[5,6] or organocatalysis.[7] While asymmetric catalytic methods are more atom-efficient and produce less waste, the high cost of chiral ligands and organocatalysts often makes the of use chiral auxiliaries the preferred option.[2,3,8] In order to maximize the efficiency of existing catalytic enantioselective transformations, there has been a growing interest in the development of recyclable catalysts during the last decade.[9] In particular, chiral phosphoric acids (CPAs) have seen widespread adoption due to their versatility.[10] Numerous applications of immobilized chiral CPAs have been reported to date, highlighting their significant potential to facilitate catalyst recovery.[11]

With regard to CPA-catalyzed enantioselective reactions with potential to synthesize optically active precursors of 1,3-diols **1**, Antilla and co-workers reported a highly enantioselective approach for allylboration of aldehydes using a 2,4,6-tris-isopropyl-derived CPA,[12] known as TRIP[13] (Scheme 1, A). A few years later, a copolymerization-based strategy was employed to immobilize TRIP onto a polystyrene resin, and the resulting supported catalyst (PS-TRIP) was successfully applied to

https://doi.org/10.26434/chemrxiv-2023-93llx **ORCID:** https://orcid.org/0000-0003-4726-9675

enantioselective allylboration reactions as a highly recyclable organocatalyst.[11j] Even though some of the immobilized CPAs have been shown to be exceptionally active and robust,[11b,d,j] they have not been widely utilized for the enantioselective synthesis of active pharmaceutical ingredients (APIs) and related compounds.[14]

Due to improved productivity, easier scalability, and waste reduction compared to more conventional batch procedures, telescoped continuous flow processes involving immobilized chiral catalysts have proven to be particularly useful for the multistep synthesis of optically active targets.[15] Building on our previous efforts in flow synthesis of chiral APIs and their advanced intermediates,[16] we hypothesized that merging PS-TRIP-catalyzed asymmetric allylboration with selective epoxidation of the resulting chiral alkene in an uninterrupted flow process would open a simple and efficient entry to optically active 1,3-diols as key intermediates of atomoxetine, dapoxetine, duloxetine and ezetimibe. The planned two-step process would produce enantioenriched epoxy alcohols **5** from readily available non-chiral aldehydes, which can then be easily transformed into the desired chiral diols **1** (Scheme 1B).[17] By carefully selecting reaction conditions, we aimed to eliminate the need for any chromatographic purification thereby facilitating larger-scale syntheses.

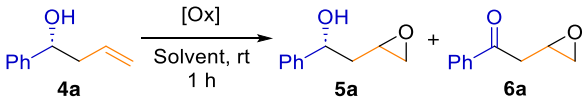


Scheme 1: A) CPAs used in the enantioselective allylboration of aldehydes. B) Proposed synthetic route to 1-aryl-1,3-diols. C) Continuous flow set up used for the allylboration step.

Our study began with optimizing the parameters of individual reaction steps. The activity of the PS-TRIP catalyst for asymmetric allylboration was explored in a flow set-up consisting of two separate reagent feeds: solutions of benzaldehyde **2a** (1.0 equiv.) and allylboronic ester **3** (1.2 equiv.), respectively. The reagent streams were pumped at a flow rate of 100 µL/min each and were combined before entering a packed bed reactor containing 0.8 g of the supported catalyst (Scheme 1, C). This corresponded to a residence time on the catalyst bed of approx. 15 min. Several solvents were evaluated with the purpose of making the overall process greener.[18] The effect of substrate concentration was also explored in order to maximize the productivity. The best results for obtaining alkene **4a** were achieved in 97% yield and 90% enantiomeric excess (ee) using a substrate concentration of 0.15 M in toluene as solvent (see the Supporting Information for details).

Next, various strategies were explored for the subsequent epoxidation, initially under batch conditions (Table 2). We found that hydrogen peroxide as oxidant resulted in overoxidation of the desired chiral alcohol (**5a**) to the corresponding ketone **6a**, making the process unsuitable for further development (Table 2, Entry 1). Dimethyldioxirane (DMDO), generated from acetone and Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in a buffered aqueous solution,[19] showed high conversion and selectivity (Table 2, Entry 2), but involved miscibility issues with toluene. In order to avoid solubility problems that could affect the reactivity in flow, we next evaluated organic peracids. Commercially available solutions of peracetic acid (PAA) showed high selectivity but only poor conversion (Table 2, Entry 3-4). Although the *in situ* generation of peracids under continuous flow conditions is well-known,[20] preliminary tests showed significant overoxidation to ketone **6a**, probably due to the large excess of H_2O_2 required in these reactions. Therefore, we finally tested *m*-chloroperbenzoic acid (*m*CPBA) as epoxidation agent. Gratifyingly, excellent conversion and selective epoxidation was achieved in the presence of 4.0 equiv. of *m*CPBA making it the preferred oxidant for further development (Table 2, Entries 5-7). The *m*CPBA-mediated selective epoxidation was then transferred to continuous flow using a simple coil reactor, ensuring conversions of ≥90% within residence times of around 10 min at 85 °C (see the Supporting Information for details).

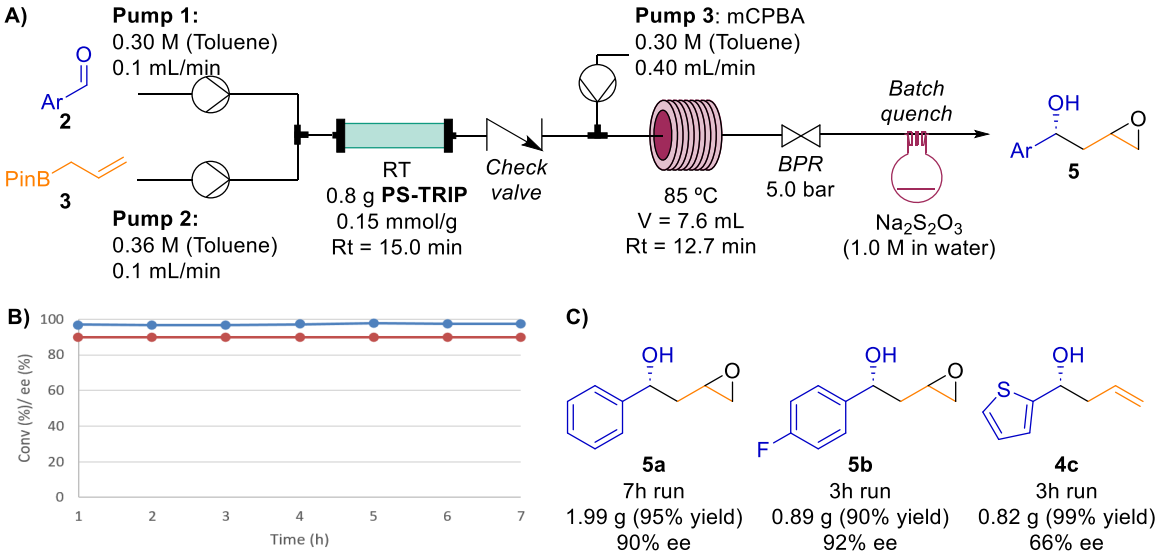
Table 2: Optimization of the epoxidation of 4a under batch conditions.



Entry	Ox (equiv.)	Solvent	5a(%)	6a(%)
1	H_2O_2 (1.2)	Acetone/H_2O 2:1	54	26
2	DMDO (2.0)	Acetone/H_2O 2:1	96	1
3	PAA (4.0)	Toluene	25	n.d.
4	PAA (8.0)	Toluene	30	n.d.
5	*m*CPBA (2.0)	Toluene	62	n.d.
6	*m*CPBA (3.0)	Toluene	80	n.d.
7	*m*CPBA (4.0)	Toluene	93	n.d.

General conditions: **4a** (0.1 mmol, 1 equiv.), oxidant (see Table), solvent (1.0 mL). Yield was determined by HPLC area %. n.d.: not detected.

Following step-by-step optimization, we combined the PS-TRIP-catalyzed asymmetric allylboration of benzaldehyde (**2a**) and the subsequent epoxidation in a telescoped flow sequence to access epoxy alcohol **5a**, chiral intermediate of atomoxetine and dapoxetine (Scheme 2, A). Downstream to the packed bed reactor, the *m*CPBA feed served a double role. Apart from functioning as an epoxidation agent, it also quenched any unreacted allyl pinacol ester, thereby preventing racemic background reactions in case of uncompleted allylboration. In order to safely quench any excess oxidant, the

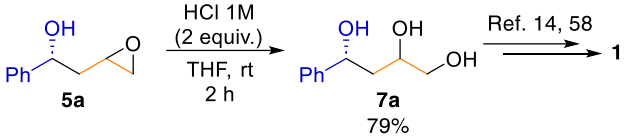


Scheme 2. A) Optimal set-up for the telescoped asymmetric allylboration/epoxidation process. B) Yield (blue) and ee (red) of 5a over the time (HPLC). C) Chiral intermediates for the synthesis of APIs.

outlet of the reactor was directed into a stirred solution of $Na_2S_2O_5$. With the optimized set-up in hand, we performed a continuous long run for 7 h. The overall process was followed by off-line HPLC with samples taken and analyzed in every hour. We were pleased to find no decrease in either the conversion or in the enantioselectivity, showing the robustness of the process (Scheme 2, B). Contrary to previous reports on enantioselective allylboration reactions,[11j,12,21] the present process did not require any a chromatographic purifiction but a simple acid/base extractive work up to isolate the desired chiral adduct in sufficiently pure form.

In order to also obtain potential precursors of ezetimibe and duloxetine, the two-step flow synthesis was next attempted using 4-fluorobenzaldehyde (**2b**) and 2-thiophenecarboxaldehyde (**2c**) as substrate, respectively (Scheme 2, C). Epoxy alcohol **5b** was smoothly produced from aldehyde **2b** during a continuous 3 h run (90% yield, 92% *ee*) under conditions identical to those applied in the synthesis of **3a**. In the targeted synthesis of oxirane **5c** from aldehyde **2c**, the epoxidation step resulted in a complex mixture, probably due to the polymerization of the thiophene ring.[22,] In this case, the process was stopped after the allylboration step (performed using the set-up shown in Scheme 1, C; see also the Supporting Information for details) to afford alkene **4c** in 99% yield and 66% ee.

In order to illustrate the applicability of epoxides **5** in the synthesis of 1-aryl-1,3-diols **1**, we performed the ring opening of epoxide **5a** in acidic media, obtaining triol **7a** in high yield (Scheme 3). Further transformations of triols **7** to the corresponding diols **1** are known in the literature.[14,58]



Scheme 3: Formal synthesis of 1-aryl-1,3-diols 1.

In summary, we have developed a telescoped continuous flow process using an immobilized CPA-mediated enantioselective allylboration as the key step followed by *m*CPBA-mediated selective alkene epoxidation. Our strategy consists of a transition metal-free catalytic method to access triols **7** and diols **1** in high yield and enantiocontrol by using a robust immobilized organocatalyst. By exploiting an uninterrupted flow process, chiral epoxides **5** were attained in a simple and efficient manner, without the need for any chromatographic purification. With a cumulative residence time of less than 30 min, the protocol enabled a notable chemical intensification compared to earlier methodologies.

ASSOCIATED CONTENT

Supporting Information

General procedures and characterization data are available (PDF)

AUTHOR INFORMATION

Corresponding Author

Aitor Maestro − Department of Organic Chemistry I, University of the Basque Country, UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain; Institute of Chemistry, University of Graz, NAWI Graz, A-8010 Graz, Austria; orcid.org/0000-0003-4726-9675; Email: aitor.maestro@ehu.eus

C. Oliver Kappe − Institute of Chemistry, University of Graz, NAWI Graz, A-8010 Graz, Austria; Center for Continuous Flow Synthesis and Processing (CC FLOW), Research Center Pharmaceutical Engineering GmbH (RCPE), A-8010 Graz, Austria; orcid.org/0000-0003-2983-6007; Email: oliver.kappe@uni-graz.at

Author Contributions

The manuscript was written through contributions of all authors. / All authors have approved the final version of the manuscript.

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