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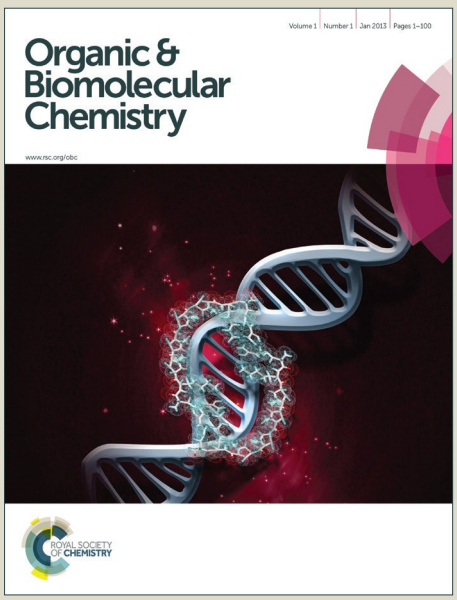

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ARTICLE

A Convenient Enantioselective CBS-Reduction of Arylketones in Flow-Microreactor Systems

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A convenient, versatile, and green CBS-asymmetric reduction of aryl and heteroaryl ketones has been developed by using the microreactor technology. The study demonstrates that it is possible to handle safely the borane solution within microreactors and that the reaction performs well using 2-MeTHF as greener solvent.

Introduction

In recent years microreactors and continuous flow technologies have been playing an important role both in academic research and in the industrial field, acting as a viable alternative to batch processes, and offering, in many cases, more sustainable synthetic routes.[1,2] These technologies reduce the wide gap between the academic and industrial development, allowing for an improvement of safety concerns and chemistry performance in terms of yield and selectivity. The use of continuous processes, within "micro- or meso-reactors", provides access to a wider profile of reaction conditions not accessible by traditional "batch" systems.

In fact, the high surface/volume ratio in microreactors allows for a rapid heat transfer and high thermal control. Usually, reactions conducted under cryogenic conditions in batch (i.e. -78 °C), could be conducted at higher temperature (i.e. 0 °C) in microreactors. In addition, pressure and temperature can be easily handled in flow.

The production in continuous flow has recently attracted the interest of the chemical and pharmaceutical industry, as it ensures lower costs, improved reliability, safety and sustainability. Recently a pharmaceutical roundtable study demonstrated the importance of continuous processes in the design of "Greener Processes".[3]

An interesting example is the continuous production of aliskiren hemifumarate, a direct renin inhibitor.[4] The production plant realised was able to perform reactions, separations, crystallization, drying and formulation up to the final tablets, all through a highly controlled and modular process. The production in continuous flow can be extended to a broader range of active pharmaceutical ingredients (API),[5] and the number of applications of flow technology in the production of API or other pharmaceutical products, is rapidly growing.[6] This aspect is particularly important considering the high environmental impact of the pharmaceutical industry. Thus, the search for new conditions in terms of solvent, temperature, stoichiometry and work-up operations as well as the use of flow technologies would help to reduce its burden.[7]

The needs for new technologies is also due to increasingly stringent regulations concerning the emission of wastes and the related environmental impact.[8]

In continuation of our research projects in the field of microreactor technology,[9] we became interested into the development of a continuous flow process for the asymmetric reduction of prochiral arylketones.

The asymmetric reduction of prochiral ketones, to produce enantioenriched alcohols, is an important step in the synthesis of many pharmaceutical molecules (Figure 1).[4b]

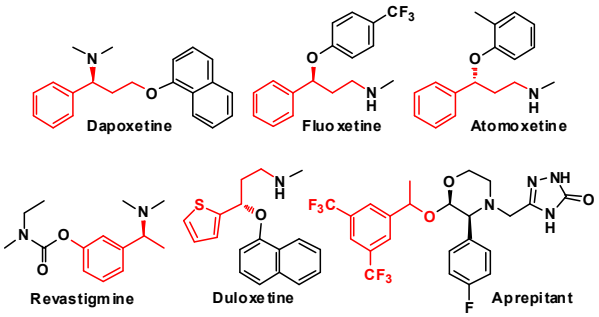

Figure 1. Drugs involving asymmetric reduction steps in their synthesis.

The most used methods involve bio-catalysis, heterogeneous catalysis with transition metals, use of stoichiometric amounts of chiral hydrides and homogenous asymmetric reduction based on oxazaborolidine.[10]

Herein we report the study on the development of a sustainable asymmetric reduction of arylketones under homogeneous conditions by using a microfluidic device, 2-MeTHF as greener solvent and without employing any additive. The Corey, Bakshi and

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Shibata (CBS) oxazaborolidine was employed as the catalyst to control the enantioselectivity.[11]

One of the main problems in CBS asymmetric reductions is the use of hazardous borane reagents difficult to handle on large scale and potentially benefiting from microreactor technology. Modified protocols have been introduced which, however, use genotoxic alky halides[12] or large amount of *N,N*-diethylaniline (DEAN)[13] and *N*-*t*-Bu-*N*-trimethylsilylamine as stabilizer for the borane.[14] Recently, Sanderson and coworkers developed a multi-steps flow synthesis of fluoxetine where the CBS asymmetric reduction of an arylketone was the stereo-determining step. Under optimised conditions, the reduction was accomplished in 10 minutes with 3 equivalents of borane-DEAN, 30% of catalyst, CH_2Cl_2/toluene as solvents and -7 °C.[15]

Results and discussion

We evaluated the possibility to develop a greener and continuous flow process for CBS asymmetric reduction of ketones, using chip-microreactors and employing a more sustainable solvent such as 2-MeTHF.[16] This is one of the ethereal solvents recommended for its low solubility in water (14g/100g at 23 °C), the relatively low boiling point (80 °C), deriving from renewable sources and amenable to be recycled. In particular 2-MeTHF can be obtained from levulinic acid or by hydrogenation of furfural which is, in turn, obtained from corn cobs and sugar cane, through an intramolecular cyclisation of pentoses.[17] Compared to THF, 2-MeTHF has a higher boiling point, lower solubility in water, allowing reactions at higher temperatures and giving superior performance in biphasic reactions, easiness to dry, and it is less irritating to eyes and respiratory system.[18] The microfluidic device employed in this study is reported in Figure 2. Exploiting the advantages of microreactors, we explored the possibility to handle the commercially available solution of BH_3 (1M in THF), without using any additive and to perform an in-line FT-IR analysis to speed up the optimization process.[19]

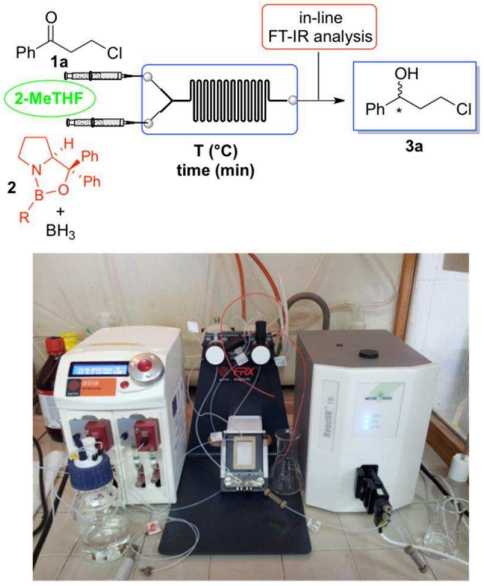

Figure 2. Scheme and equipment for a continuous flow CBS asymmetric reduction.

The optimization study was executed using a 2 inlets 1000 μL glass chip microreactor fed with a 0.2M 2-MeTHF solution of 1-phenyl-3-chloropropan-1-one **1a**, chosen as model substrate, and the progress of the reduction monitored by an ATR probe at steady state conditions. A 0.3M solution of BH_3 (85% 2-MeTHF, 15% THF), and oxazaborolidine **2** was introduced for the asymmetric reduction. Stoichiometry and residence time were adjusted according to the flow rate of the feeding solutions and response of the ATR probe. Results for this optimization study are reported in Table 1.

We started the study running the reactor at room temperature (24 °C) by using 2.5 equivalents of borane and 25 mol % of CBS catalyst (Table 1, entry 1). Under such reaction conditions, the reaction was complete in 10 minutes and the expected alcohol **3a** was obtained with 95% yield and a 91:9 enantiomeric ratio. Next, the amount of catalyst was reduced to 12 mol % and again a full conversion was observed while maintaining high enantioselectivity (Table 1, entry 2). However, reducing the amount of chiral catalyst to 8 mol %, and the amount of borane up to 1.5 equivalents (Table 1, entries 3,4), was detrimental for both yield (70%) and enantioselectivity (85:15). With the aim to improve the reaction performance, the temperature effect was also considered. Running the flow reactor under the conditions of entry 2 but at 0 °C (Table 1, entry 5) again a full conversion was observed (>95% yield) jointly to a very good enantioselectivity (er: 93:7). Lowering the amount of the catalyst to 5 mol % and using 1.5 equivalents of borane led to a good conversion (90% yield) with a modest enantiomeric ratio of 75:25 (Table 1, entry 6). Increasing the loading of the catalyst to 8 mol % and using 1.5 equivalents of borane, gave 94% yield of **3a** and an enatiomeric ratio of 91:9 (Table 1, entry 7). Reducing the catalyst to 5 mol % using 2 equivalents of borane resulted in lower yield (85%) while maintaining the enantioselectivity (Table 1, entry 8) thus showing that the amount of the catalyst is an important factor.

Table 1 Optimization study in continuous flow microreactor of the CBS asymmetric reduction of 3-chloro-1-phenylpropan-1-one **1**.

Entry	BH_3[a] (equiv)	CBS (%)	T (°C)	Solvent	t_R[b] (min)	Yield[c] (%)	er[d]
1	2.5	25	RT	2-MeTHF	10	> 95	91:9
2	2.5	12	RT	2-MeTHF	10	> 95	91:9
3	2	8	RT	2-MeTHF	10	70	85:15
4	1.5	8	RT	2-MeTHF	10	70	85:15
5	2.5	12	0	2-MeTHF	10	> 95	93:7
6	1.5	5	0	2-MeTHF	10	90	75:25
7	**1.5**	**8**	**0**	**2-MeTHF**	**10**	**94**	**91:9**
8	2	5	0	2-MeTHF	15	85	89:11
9	2.5	25	RT	THF	5	> 95	90:10
10	2	20	RT	THF	10	23	91:9
11	1	10	RT	THF	20	28	90:10

[a]entry 1-8: solvent mixture of 2-MeTHF 85% and THF 15% (deriving from commercial solution of BH_3 1M in THF). [b]Residence time. [c]Determined by ^{1}H-NMR using internal standard. [d]Determined by HPLC using a chiral stationary phase.

It is worth mentioning that under steady state conditions, reached by flowing twice the volume of the microreactor, the reaction was complete in 10 minutes under various conditions. The in-line

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monitoring offers several advantages reducing the optimization time and allowing for the automation of a continuous process.[20,21]

The progress of the reaction was followed by monitoring the disappearance of the C=O stretching signal at 1690 cm^{-1} and appearance of new signals in the range 1400-1350 cm^{-1}, ascribable to the reduction product.[22] In Figure 3 is reported the IR profile for the asymmetric reduction of **1a** under optimised conditions (Table 1, entry 7).

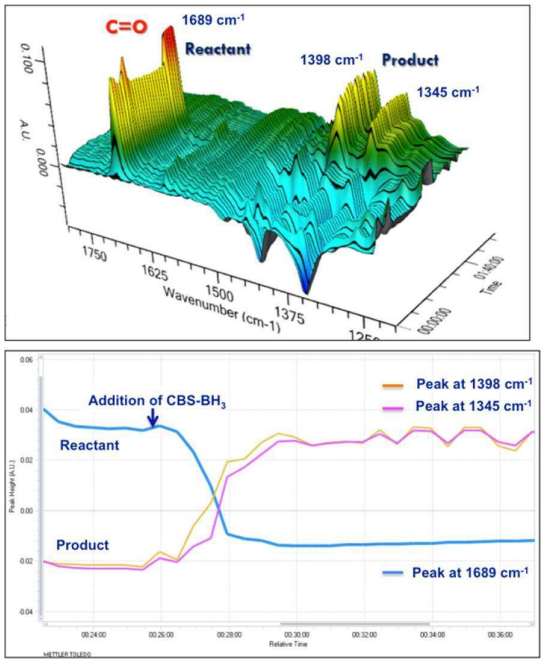
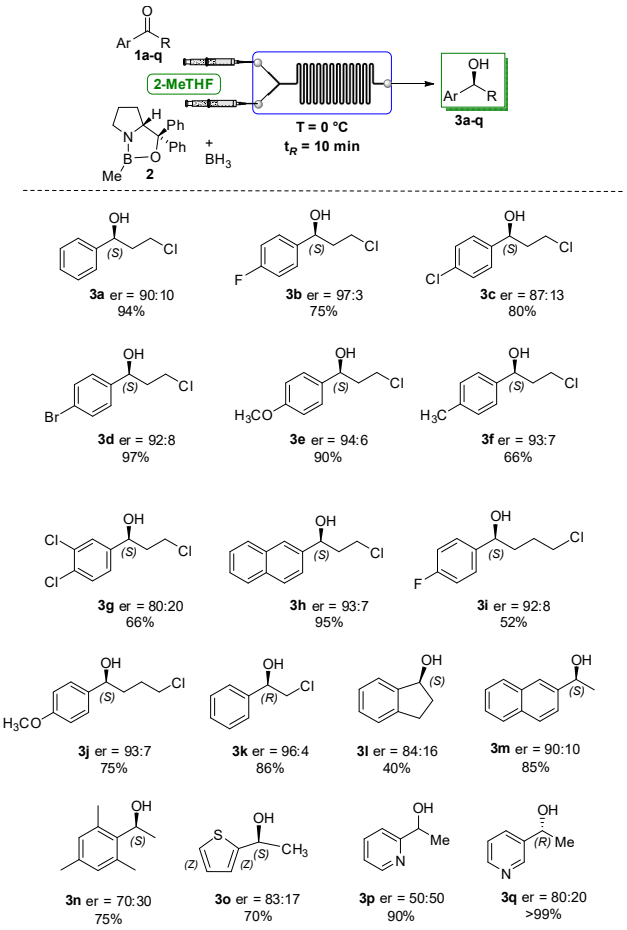


Figure 3.

For sake of comparison, THF was employed to perform the same reaction into continuous flow microreactor (Table 1, entries 9-11). As reported in Table 1, the reaction performs well only using 25 mol % of catalyst and 2.5 equivalent of borane (entry 9). Lowering the loading of the catalyst caused a drop of the yields while maintaining the enantioselectivity (entries 10-11). The reason of this different behavior between THF and 2-MeTHF is unclear at the moment. Remarkably, these results demonstrate that the asymmetric reduction can be effectively run in continuous flow mode using a reduced amount of chiral catalyst, with respect to batch mode, using a greener solvent such as the 2-MeTHF and without any additive. Next, the scope of the process was investigated using several prochiral ketones of interest in medicinal chemistry programs (Scheme 2). The optimised conditions (Table 1, entry 7) were effective for the asymmetric reduction of aromatic ketones **1b-f** leading to the corresponding chloroalcohols **3b-f** with good yields and excellent enantiomeric ratios. In the case of 3,4-dichlorophenyl substituted ketone **1g**, 3 equivalents of BH_3 and 10 mol % of catalyst were needed to obtain a better yield (75%) and enantiomeric ratio (er: 80:20). It is worth pointing out that the CBS-reduction is the best strategy for the preparation of chiral 1-aryl-3-chloropropanols of the kind of **3a-h,** important for the synthesis of chiral four membered heterocycles[23] and APIs.[4] In fact, Yus recently reported that a Noyori-type asymmetric reduction was not effective with sulfinylhaloimines because of a competing β-elimination.[24] We tested the Noyori asymmetric reduction, in batch conditions, using **1a** as starting material, but only the corresponding product of β-elimination was observed.[25] Lower yields and enantioselectivity were observed in the reduction of indanone leading to **3l**, and in the reduction of aryl ketone bearing ortho substituents as in the case of **3n**. Heteroaryl ketones could be effectively reduced under flow conditions as in the case of **3o**. Pyridyl derivative **3p** was obtained as racemic mixture while compound **3q** was obtained enantioenriched, as established by the optical rotation value.



Scheme 2. Scope for the continuous flow CBS asymmetric reduction of prochiral ketones. Conditions: ketone (0.2 M) in 2-MeTHF, flow rate: 50μL/min, (*R*)-CBS catalyst (8%), BH_3 (0.3 M, 85% 2-MeTHF, 15% THF), flow rate: 50μL/min. Yields of isolated product are reported.

As mentioned previously, the enantioselective reduction of ketones to alcohols can represent an important step in the synthesis of several bioactive molecules and the availability of flow-methodology could be useful from a sustainability point of view. Thus, this continuous flow asymmetric reduction was tested in a microfluidic system including an in-line work up and a liquid/liquid separator at the output of the chip microreactor (Scheme 3). This integrated flow device allows to exploit the low solubility in water of 2-MeTHF. Nevertheless, the liquid/liquid separator was unable to perform a

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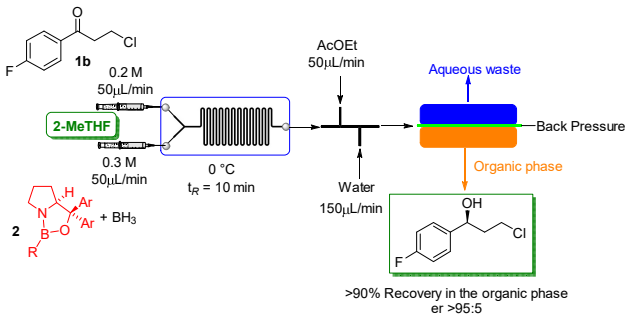
clear separation of the organic phase without introducing a small amount of AcOEt as organic solvent. The microfluidic system reported in Scheme 3, allows to recover >90% of the desired chloro alcohol **3b** and could be run for hours. However, for long runs, it was necessary to maintain the temperature of the BH_3 solution at 0 °C during the infusion, to minimise decomposition and loss of the reducing agent.[26]



Scheme 3. Integrated microfluidic device for CBS asymmetric reduction.

Conclusions

In summary, a sustainable, versatile, fast and environmentally friendly CBS-asymmetric reduction of aryl and heteroaryl ketones has been developed by using the microreactor technology. The study demonstrates that it is possible to handle safely the borane solution within microreactors and that the reaction performs well using 2-MeTHF as greener alternative to traditional solvents. In addition, the use of flow technology allows for a reduction of the amount of the chiral catalyst, avoid the use of an additive such as DEAN (*N*,*N*-diethylaniline) and the in-line monitoring and work up procedures helped to optimise the process.

Experimental section

General

The ^{1}H NMR, ^{13}C NMR spectra were recorded with a Bruker 500, Varian Inova 600 MHz or 400 MHz; all chemical shift values are reported in ppm (δ); the $CDCl_3$ was used as solvent. The high-performance liquid chromatography HPLC was performed with chiral stationary phases 5u Lux Cellulose -1 250 x 4.60 mm and CHIRALPAK AD- H ø 0.46 cm x 25 cm. The gas chromatography GC was performed with chiral column Cyclodex B 30m x 0.25mm x 0.25µm; inlet: (250°C) Split at 75 mL/min. The IR spectra have been carried out with a PERKIN - ELMER 283 spectrophotometer. The thin layer chromatography (TLC) was performed using silica gel plates (Merck) with fluorescence indicator F-254 and the visualisation was carried out with UV light (254nm). The flow apparatus is the FRX-400™ system by Syrris. Two Asia Syringe Pumps, equipped with Asia Green Syringes (250µL), glass chip microreactors (1000 µl – 3 inlet; 1000 µl -2 inlet) and a chip header were used. All the modules were connected by PTFE tubing and end fittings.

General procedure for the enantioselective synthesis of alcohols 3a-q in flow. The general procedure refers to the reduction of **1a**. The process could be executed using Asia® syringe pumps by Syrris that continuously deliver solutions of reactants from stock containers of suitable volume (minimum 50 mL). The following solutions were prepared and filtered with PTFE filters with a porosity of 0.2 µm: (i) 10 mL, 0.2 M in 2-MeTHF of ketone **1a** (2 mmol, 337.2 mg); (ii) 10 mL, 0.3 M of BH_3 in 85% 2-MeTHF, obtained by diluting with 2-MeTHF a 1 M commercial solution of BH_3 in THF. To solution (ii), the catalyst (*R*)-CBS **2** (8 mol% with respect to ketone **1a**) was added, and cooled at 0° C with an ice bath. Those solutions were pumped into the microreactor kept at 0° C with an ice bath at a flow rate of 50 µL/min. The solutions were delivered simultaneously into the flow system and collected under steady state conditions (after 20 minutes) for 1h (0.6 mmol of ketone). At the output of the microreactor, the flowing solution (100µL/min) was poured in acidic water (10%$_{aq}$ HCl) to deactivate the excess of borane. The catalyst may be removed during the purification on silica gel or by washing with a saturated solution of sodium bicarbonate $NaHCO_3$ (10 mL). The crude was extracted with ethyl acetate (3 x 2 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Pure products are obtained after column chromatography (hexane/ethyl acetate 8:2–9:1). Alternatively, the process can be executed using traditional syringe pumps and 10 or 20 mL gas-tight syringes (SGE) under the same conditions reported above. In this case, in order to reduce gas evolution (presumably borane), it is necessary to maintain the temperature at about 0° C during the infusion by keeping the syringe in contact with a plastic bag filled with ice replaced when required. Data for isolated products reported below matched those reported in the literature (references given).

(*S*)-3-Chloro-1-phenylpropan-1-ol (3a)[27] White solid, m.p. 30-32 °C (94% yield, 92 mg). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.28 (m, 5H), 4.95 (dd, 1H, *J* = 4.6 e 8.5 Hz), 3.77-3.72 (m, 1H), 3.59-3.54 (m, 1H), 2.28-2.22 (m, 1H), 2.13-2.07 (m, 1H), 1.99-1.94 (bs, 1H, exchange with D_2O). $[\alpha]^{19}_D$ = -25° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.9, 128.9, 128.1, 126.0, 71.6, 41.9, 41.7. FT IR (KBr, cm^{-1}) ν 3060, 2878, 1620, 1612, 1596, 1452, 1215, 1190, 1042, 1020, 988.
The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 90:10 (t_R major = 15.729 min, t_R minor = 16.774 min).
(*S*)-3-Chloro-1-(4-fluorophenyl)propan-1-ol (3b) Colorless oil (75% yield, 85 mg) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (dd, 2H, *J* = 5.3 e 8.6 Hz), 7.05 (t, 2H, *J* = 8.6 Hz), 4.94 (dd, 1H, *J* = 4.5 e 8.6 Hz), 3.76-3.71 (m, 1H), 3.57-3.52 (m, 1H), 2.25-2.18 (m, 1H), 2.09-2.02 (m, 1H), 1.93-1.70 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -25.7° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162 (dd, *J* = 247.9 Hz), 139.49, 127.45, 115.50 (dd, *J* = 21.3), 70.68, 41.59, 41.49, 29.70. FT IR (NaCl, cm^{-1}): ν 3381, 2032, 1891, 1715, 1605, 1511, 1224, 1054, 836, 661.
The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 97:3 (t_R major = 13.130 min, t_R minor = 12.385 min).
(*S*)-3-Chloro-1-(4-chlorophenyl)propan-1-ol (3c)[28] Colorless oil (80% yield, 98 mg) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.6 Hz), 4.95 (dd, 1H, *J* = 4.6 e 8.6 Hz), 3.77-3.72 (m, 1H), 3.58-3.53 (m, 1H), 2.24-2.17 (m, 1H), 2.09-2.03 (m, 1H), 1.94-1.81 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -10.6° (c = 1, $CHCl_3$) (Literature data:

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$[\alpha]^{20}_D$ = -15.6° c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.34, 133.71, 128.94, 127.29, 70.78, 41.67, 41.56. FT IR (NaCl, cm^{-1}): ν 3380, 2963, 1904, 1709, 1597, 1491, 1287, 1198, 1063, 927, 827, 735. The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 87:13 (t_R major = 13.871 min, t_R minor = 14.861 min).

(*S*)-3-Chloro-1-(4-bromophenyl)propan-1-ol (3d)[28] Colorless oil (97% yield, 145 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.1 Hz), 4.94 (dd, 1H, *J* = 4.6 e 8.6 Hz), 3.77-3.72 (m, 1H), 3.57-3.53 (m, 1H), 2.23-2.16 (m, 1H), 2.09-2.02 (m, 1H), 1.87-1.77 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -4.27° (c = 1, $CHCl_3$) (Literature data: $[\alpha]^{20}_D$ = -13.3° c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.86, 131.89, 127.63, 121.81, 70.82, 41.65, 41.52. FT IR (NaCl, cm^{-1}): ν 3465, 3184, 1562, 1450, 1114, 748, 618.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 92:8 (t_R major = 15.380 min, t_R minor = 16.808 min).

(*S*)-3-Chloro-1-(4-methoxyphenyl)propan-1-ol (3e)[29] Colorless oil (90% yield, 108 mg) ^1H NMR ($CDCl_3$, 600 MHz): δ 7.29 (d, 2H, *J* = 8.5 Hz), 6.90 (d, 2H, *J* = 8.5Hz), 4.89 (dd, 1H, *J* = 4.9 e 8.2 Hz), 3.81 (s, 3H), 3.75-3.69 (m, 1H), 3.56-3.52 (m, 1H), 2.27-2.22 (m, 1H), 2.10-2.04 (m, 1H), 1.94-1.86 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -10.5° (c = 1, $CHCl_3$) (Literature data: $[\alpha]^{20}_D$ = (*R*) +16° c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 126 MHz): *δ* 195.4, 164.0, 130.6, 129.6, 114.1, 55.7, 41.1, 39.2.[4] FT IR (NaCl, cm^{-1}): 3293, 2960, 2904, 1612, 1516, 1288, 1253, 1179, 1032, 834, 652.

The enantiomeric ratio was determined by HPLC using a chiral column ADH [hexane/i-PrOH (90:10)]; flow 1 mL/min; λ = 220 nm; er 94:6 (t_R major = 11.173 min, t_R minor = 10.553 min).

(*S*)-3-Chloro-1-(4-methylphenyl)propan-1-ol (3f)[30] White solid, m.p. 42-43°C (66% yield, 73 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, 2H, *J* = 7.8 Hz), 7.19 (d, 2H, *J* = 7.8 Hz), 4.92 (dd, 1H, *J* = 4.6 e 8.3 Hz), 3.76-3.71 (m, 1H), 3.59-3.54 (m, 1H), 2.36 (S, 3H), 2.28-2.21 (m, 1H), 2.12-2.05 (m, 1H), 1.90-1.83 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -13.2° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.85, 137.81, 129.46, 125.87, 71.34, 41.92, 41.54, 21.26. FT IR (KBr, cm^{-1}): ν 3306, 2917, 1416, 1286, 1049, 817.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 93:7 (t_R major = 13.908 min, t_R minor = 15.995 min).

(*S*)-3-chloro-1-(3,4-dichlorophenyl)propan-1-ol (3g) White solid, m.p. 44-47 °C (66% yield, 94 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, 1H, *J* = 2.0 Hz), 7.44 (d,1H, *J* = 8.2 Hz), 7.21 (dd, 1H, *J* = 2.0 e 8.2 Hz), 4.96 (dd, 1H, *J* = 4.2 e 8.6 Hz), 3.78-3.73 (m, 1H), 3.59-3.54 (m, 1H), 2.21-2.14 (m, 1H), 2.09-2.02 (m, 1H), 1.64-1.55 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -2.9° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.0, 132.8, 131.7, 130.6, 127.8, 125.1, 70.1, 41.3. FT IR (KBr, cm^{-1}): ν 3391, 2917, 1564, 1468, 1396, 1285, 1201, 1131, 1030, 885, 824, 666.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 80:20 (t_R major = 14.728 min, t_R minor = 15.375 min).

(*S*)-3-chloro-1(2-naphtyl)propan-1-ol (3h) Colorless oil (95% yield, 126 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87-7.83 (m, 4H), 7.50-7.46 (m, 3H), 5.14 (m, 1H, *J* = 4 e 8 Hz), 3.81-3.76 (m, 1H), 3.61-3.57 (m, 1H), 2.37-2.30 (m, 1H), 2.23-2.19 (m, 1H), 2.07-2.05 (bs, 1H, exchange with D_2O). FT IR (NaCl, cm^{-1}): ν 3400, 2923, 1721, 1455, 1259, 1051, 856, 800, 747, 699.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 1 mL/min; λ = 254 nm; er 93:7 (t_R major = 19.15 min, t_R minor = 23.11 min).

(*S*)-4-Chloro-1-(4-fluorophenyl)butan-1-ol (3i)[31] Colorless oil (52% yield, 63 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (dd, 2H, *J* = 5.2 e 8.5 Hz), 7.05 (t, 2H, *J* = 8.5 Hz), 4.73 (dd, 1H, *J* = 5.4 e 7.2 Hz), 3.61-3.53 (m, 2H), 1.96-1.75 (m, 5H, 2 x CH_2 e 1H OH). $[\alpha]^{20}_D$ = 40° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): 162.2 (d, *J* = 246 Hz), 140.0 (d, *J* = 3 Hz), 127.4 (d, *J* = 8 Hz), 115.4 (d, *J* = 21 Hz), 73.2, 19 44.9, 36.2, 28.8. FT IR (NaCl, cm^{-1}): ν 3383, 1604, 1508, 1222, 1157, 1070.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 92:8 (t_R major = 22.574 min, t_R minor = 23.558 min).

(*S*)-4-Chloro-1-(4-methoxyphenyl)butan-1-ol (3j)[32] Colorless oil (75% yield, 96 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.68-4.65 (m, 1H), 3.81 (s, 3H), 3.59-3.51 (m, 2H), 1.95-1.73 (m, 4H), 1.66-1.53 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -29.13° (c = 1, $CHCl_3$) (Literature data: $[\alpha]^{20}_D$ = -37.3° c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.2, 136.5, 127.1, 114.0, 73.54, 55.3, 45.0, 36.1, 29.1. FT IR (NaCl, cm^{-1}): ν 3211, 2955, 1462, 1035, 832, 651.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (90:10)]; flow 0.5 mL/min; λ = 220 nm; er 93:7 (t_R major = 12.313 min, t_R minor = 11.662 min).

(*R*)-2-Chloro-1-phenylethanol (3k)[33] Colorless oil (86% yield, 80 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.33 (m, 5H), 4.90 (dd, 1H, *J* = 3.4 e 8.7 Hz), 3.75 (dd, 1H, *J* = 3.4 e 11.4 Hz), 3.65 (dd, 1H, *J* = 8.7 e 11.4 Hz), 2.61-2.39 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = -49° (c = 1, $CHCl_3$). (Literature data: $[\alpha]^{22}_D$ = -53.1°, c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.86, 128.65, 128.43, 126.02, 74.03, 50.88. FT IR (NaCl, cm^{-1}): ν 3400, 3050, 2960, 1455, 1070, 705.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 96:4 (t_R major = 31.869 min, t_R minor = 25.876 min).

(*S*)-2,3-diHydro-1H-inden-1-ol (3l)[34] White solid, m.p. 60-63 °C (40% yield, 32 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43 (m, 1H), 7.24 (m, 3H), 5.26 (t, 1H, *J* = 6.07 Hz), 3.10-3.04 (m, 1H), 2.86-2.80 (m, 1H), 2.54-2.47 (m, 1H), 1.99-1.92 (m, 1H), 1.64-1.53 (bs, 1H, exchange with D_2O). $[\alpha]^{20}_D$ = +20° (c = 1, $CHCl_3$). ^{13}C NMR ($CDCl_3$, 75 MHz, 35˚C): δ 145.02, 143.30, 143.29, 128.30, 126.69, 124.87, 124.16, 76.44, 35.94, 29.77. FT IR (KBr, cm^{-1}): ν 3336, 2939, 1607, 1478, 1459, 1329, 1213, 1096, 1056, 958, 742.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 84:16 (t_R major = 19.522 min, t_R minor = 22.149 min).

(*S*)-1-(2-Naphthyl)-ethanol (3m)[35] White solid, m.p. 73-74 °C (85% yield, 88 mg) ^1H NMR ($CDCl_3$, 500 MHz): δ 7.85-7.82 (m, 4H), 7.53-7.46 (m, 3H), 5.08 (q, 1H, *J* = 6.5), 1.68 (bs, 1H, exchange with D_2O), 1.59 (d, 3H, *J* = 6.5). $[\alpha]^{20}_D$ = -34° (c = 1, $CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 143.3, 133.3, 132.9, 128.3, 127.9, 127.7, 126.1, 125.8, 123.9, 123.8, 70.4, 25.1. FT IR (KBr, cm^{-1}): ν 3347, 3052, 2970, 2924, 1598, 1505, 1408, 1362, 1273, 1123, 1072, 1024, 899, 861, 823, 740.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 90:10 (t_R major = 11.179 min, t_R minor = 12.040 min).

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(*S*)-1-(2,4,6-triMethyl-phenyl)-ethanol (3n)[36] Colorless oil (75% yield, 74 mg) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.82 (s, 2H), 5.37 (q, 1H, *J* = 6.7), 2.42 (s, 6H), 2.25 (s, 3H), 1.52 (d, 3H, *J* = 6.7). $[\alpha]^{20}_D$ = -21.8° (c = 1, $CHCl_3$). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 137.6, 136.3, 135.6, 130.0, 67.4, 21.5, 20.6, 20.4. FT IR (NaCl, cm^{-1}): 3209, 2925, 1611, 1449, 1365, 1076, 893, 850.

The enantiomeric ratio was determined by GC using a chiral column Cyclodex B carrier gas: hydrogen; isothermal 180°C; flow 1.1 mL/min; FID = 260° C; er 70:30 (t_R major = 5.464 min, t_R minor = 5.299 min).

(*S*)-1-(2-Thienyl)ethanol (3o)[35a] Colorless oil (70% yield, 54 mg) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.25 (m, 1H), 7.00-6.97 (m, 2H), 5.15 (q, 1H, *J* = 6.2 Hz), 2.05-1.83 (bs, 1H, exchange with D_2O), 1.63 (d, 3H, *J* = 6.2 Hz). $[\alpha]^{20}_D$= -12° (c = 1, $CHCl_3$) (Literature data: $[\alpha]^{20}_D$ = -15.7°, c = 0.8, $CHCl_3$). ^{13}C NMR (75 MHz, CDCl3): δ 150.0, 126.6, 124.3, 123.1, 66.1, 25.2. FT IR (NaCl, cm^{-1}): ν 3336, 3104, 3072, 2973, 2927, 2873, 1720, 1537, 1445, 1435, 1370, 1310, 1287, 1232, 1185, 1150, 1065, 1037.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 83:17 (t_R major = 22.100 min, t_R = minor 21.172 min).

1-(2-Pyridyl)ethanol (3p)[35a,b] Colorless oil (90% yield, 66 mg) ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.53 (d, 1H, *J* = 4.5 Hz), 7.68 (t, 1H, *J* = 8 Hz), 7.28 (d, 1H, *J* = 8 Hz), 7.2 (m, 1H), 4.89 (q, 1H, *J* = 6.7 Hz), 4.47-4.16 (bs, 1H, exchange with D_2O), 1.49 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.4, 146.6, 142.0, 133.5, 123.4, 66.9, 25.0. FT IR (NaCl, cm^{-1}): ν 3205, 2971, 2926, 2866, 2370, 1736, 1620, 1595, 1580, 1480, 1424, 1369, 1314, 1291, 1261, 1216, 1190, 1167, 1088, 1044, 1028, 1008.

The enantiomeric ratio was determined by HPLC using a chiral column Lux- 1 Cellulose [hexane/i-PrOH (95:5)]; flow 0.5 mL/min; λ = 220 nm; er 50:50.

1-(3-Pyridyl)-ethanol (3q)[35c] Colorless oil (>99% yield, 73 mg) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.53 (s, 1H), 8.45 (d, 1H), 7.75-7.72 (m, 1H), 7.29-7.26 (m, 1H), 4.93 (q, 1H, *J* = 6,4), 2.82 (bs, 1H, exchange with D_2O), 1.51 (d, 3H, *J* = 6.4 Hz). $[\alpha]^{20}_D$ = +12.9° (c = 1, $CHCl_3$) (Literature data: $[\alpha]^{20}_D$ (*R*) = +19.6° (c = 1g/100ml, $CHCl_3$, er = 97.5 : 3.5). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.4, 146.6 , 142.0, 133.5, 123.4, 66.9, 25.0. FT IR (NaCl, cm^{-1}): ν 3205, 2971, 2926, 2866, 2370, 1736, 1620, 1595, 1580, 1480, 1424, 1369, 1314, 1291, 1261, 1216, 1190, 1167, 1088, 1044, 1028, 1008. er 80:20 (estimated on the basis of $\alpha]^{20}_D$ value).

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