Asymmetric Transfer Hydrogenation of Heterocyclic Compounds in Continuous Flow Using an Immobilized Chiral Phosphoric Acid as the Catalyst

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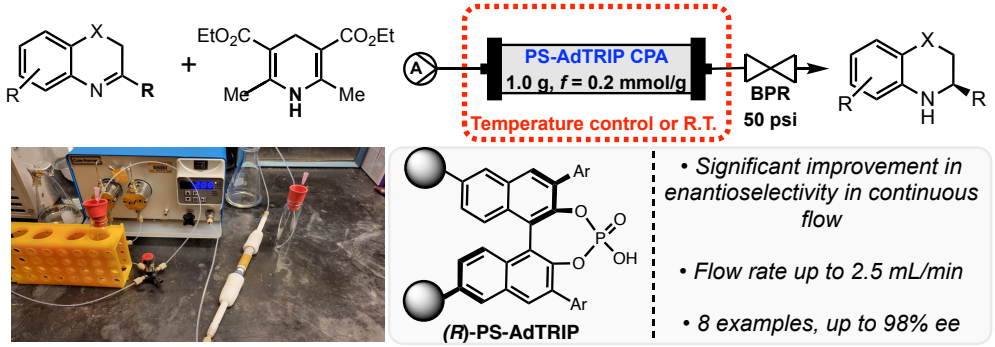
This manuscript is dedicated to Professor David A. Evans.

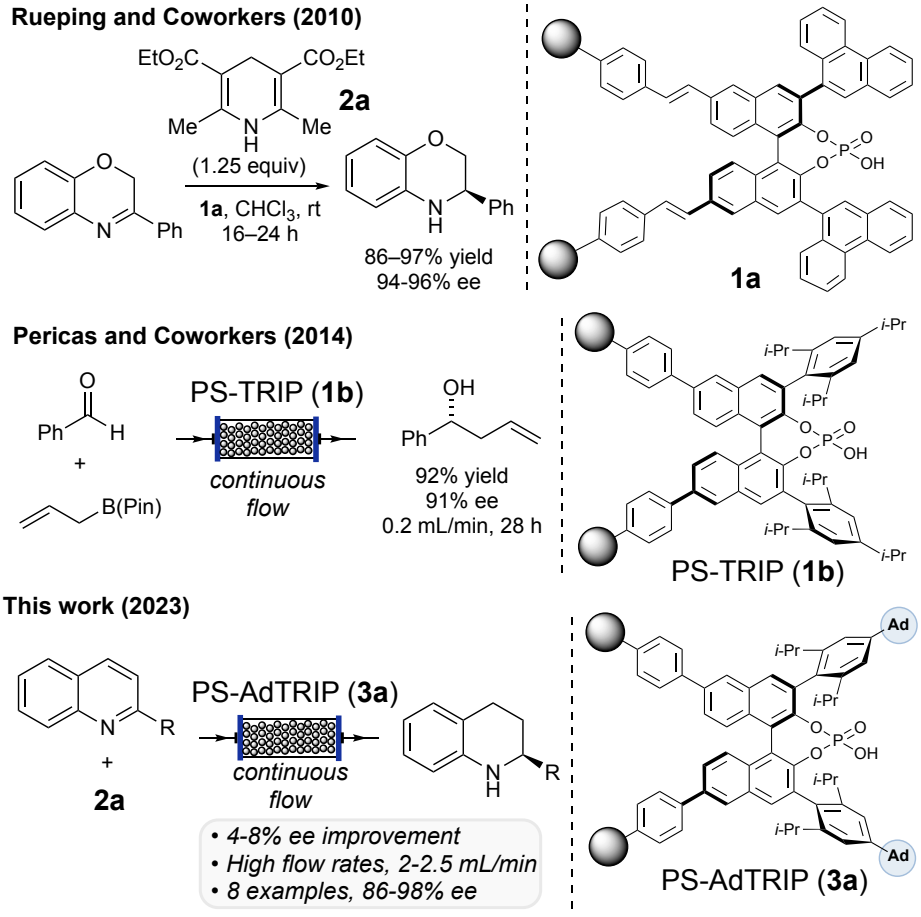


Abstract. This manuscript describes transfer hydrogenation of bicyclic nitrogen containing heterocyclic compounds using immobilized chiral phosphoric acid (R)-PS-AdTRIP catalyst 3a in batch and continuous flow. It was discovered that significant improvement in enantioselectivities was achieved in continuous flow with a fluidized bed reactor packed with (R)-PS-AdTRIP when the flow rate was increased from 0.2 mL/min to 2.0-2.5 mL/min. The optimized continuous flow conditions consistently provided 4-6% ee higher selectivity than transfer hydrogenation in batch with 2 mol% of (R)-PS-AdTRIP (3a) and were used to generate multiple chiral products with the same fluidized bed reactor.

For more than a century, the chemistry of heterocyclic compounds has attracted great interest from the synthetic community due to their significance to biomedicine and material science. Recent data suggests that more than 85% of all biologically active compounds contain heterocyclic motifs embedded in their structures.[1] Recent analysis of the US FDA approved pharmaceuticals highlights the importance of the nitrogen containing heterocycles as 59% of unique drugs contained at least one nitrogen heterocycle.[1c] The continuously increasing interest to nitrogen-containing heterocyclic compounds has fueled the development of many creative synthetic methodologies to access various nitrogen-containing scaffolds, particularly in their enantiopure forms.[2] These studies have been enabled by the recent advances in asymmetric catalysis, photocatalysis, transition metal catalysis and organocatalysis.[3] Among various methods for the synthesis of chiral heterocyclic compounds, dearomative reduction with a chiral catalysts has been one of the most important methods. Since the pioneering work of Rueping and coworkers that demonstrated the utility of chiral phosphoric acid (CPA)-catalyzed transfer hydrogenation of heterocyclic compounds with Hantzsch esters (HE),[4] numerous protocols for the synthesis of chiral nitrogen-containing heterocycles have emerged.[5] While these and related

transfer hydrogenations often proceed with excellent enantioselectivities under mild conditions and involve safe-to-handle reagents, such reactions often require high loadings of expensive CPAs, which are not easy to recover and recycle.[5] To demonstrate that some of these issues could be addressed by immobilizing CPA, Rueping and coworkers synthesized CPA **1** and successfully used it for the reduction of 3-phenyl-2*H*-benzo-[1,4]oxazine in excellent yield and enantioselectivity (*cf.* Figure 1).[6] The same study demonstrated that a stick containing catalyst **1a** could be recovered, washed, and recycled multiple times without the erosion in yields or selectivities. Following these studies, several different studies including the work of the Beller,[7] Blechert[8] and Pericas[9] groups have described the synthesis of various immobilized CPA catalysts and their use for the asymmetric reactions in batch including asymmetric transfer hydrogenation of substituted quinolines and substituted 2*H*-benzo-[1,4]oxazines.

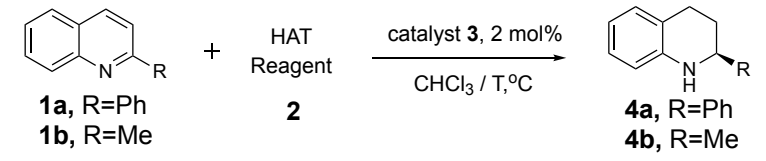
Figure 1. Key examples of using immobilized CPAs for asymmetric reactions in batch and continuous flow.



In addition, several different nanoparticle[10] and MOF-supported[11] CPA catalysts have been developed and used for asymmetric transformations in batch. Subsequently, the seminal work of the Pericas group highlighted the potential of such immobilized catalysts for the catalysis in continuous flow by passing the reagents through the fluidized bed reactor packed with the CPA

catalyst PS-TRIP (**2**) (*cf.* Figure 1).[9b-d] However, despite its great potential, the use of immobilized CPA catalysts for catalysis in continuous flow is limited to only several recent examples by the Pericas group.[12]

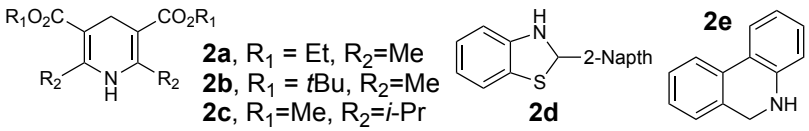
Scheme 1. Initial evaluation of immobilized CPAs **3a** and **3c** for the transfer hydrogenation of 2-substituted quinolines **1**.



1a, R=Ph
1b, R=Me

4a, R=Ph
4b, R=Me

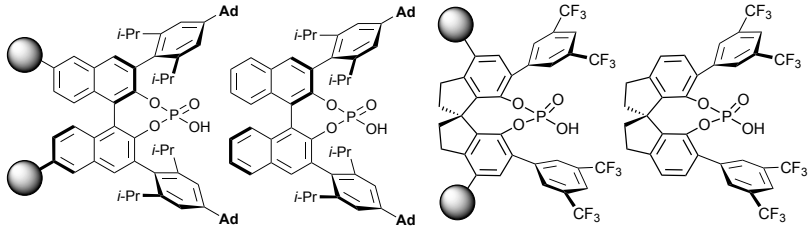
entry	catalyst	R	HAT	T, °C	time, h	conversion (yield),%	*ee*, %
1	**3a**	Ph	**2a**	60	4	90 (>95)	92
2	**3a**	Ph	**2a**	r.t.	18	92 (>95)	94
3	**3b**	Ph	**2a**	r.t.	18	88 (>95)	98
4	**3c**	Ph	**2a**	60	48	71 (84)	–42
5	**3d**	Ph	**2a**	60	48	61 (72)	–35
6	**3a**	Me	**2a**	r.t.	18	84 (87)	82
7	**3b**	Me	**2a**	r.t.	18	85 (93)	82
8	**3a**	Me	**2b**	r.t.	18	86 (>95)	81
9	**3a**	Me	**2c**	60	24	–	–
10	**3a**	Me	**2d**	60	24	–	–
11	**3a**	Me	**2e**	60	24	–	–



2a, R_1 = Et, R_2=Me
2b, R_1 = *t*Bu, R_2=Me
2c, R_1=Me, R_2=*i*-Pr

2d

2e

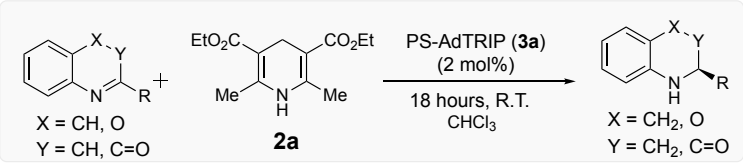


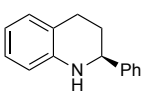
Ad-TRIP-PS (**3a**) Ad-TRIP (**3b**) PS-SPINOL (**3c**) **3d**

Recently, our group developed immobilized CPAs PS-AdTRIP (**3a**) and PS-SPINOL (**3c**) (*cf.* Figure 1 and Scheme 1) and demonstrated the utility of these catalysts for achieving regiodivergent functionalization of differentially protected monosaccharides.[13] The catalyst PS-AdTRIP (**3a**) has demonstrated excellent activity in these studies, and the same 50 mg of **3a** was used and recycled multiple times to generate six differentially protected *D*-glucose derivatives on a gram scale. Considering that TRIP CPA[14] is a privileged catalyst that demonstrates generally high selectivity

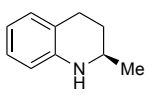
for a wide range of asymmetric transformations[5b] and that Ad-TRIP (**3b**) may exhibit a superior to TRIP catalytic profile,[15] our subsequent work focused on evaluating PS-AdTRIP (**3a**) in asymmetric reactions. This manuscript describes our work on applying **3a** as the general and recyclable catalyst for the enantioselective transfer hydrogenation of nitrogen containing heterocycles in batch and continuous flow. We demonstrate that a significant and consistent improvement of 4-6% ee is achieved if the reaction is carried in continuous flow using fluidized bed reactor packed with **3a** at flow rates as high as 2.5 mL/minute.

Scheme 2. Exploration of catalyst PS-AdTRIP (**3a**) for the in batch asymmetric reduction of quinolines, 2*H*-1,4-benzoxazines, and 2*H*-1,4-benzoxazin-2-ones.

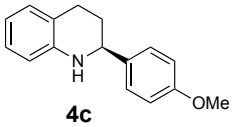




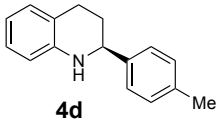
4a
PS-AdTRIP, 95%, 94% ee
BPPA, 96%, 0% ee



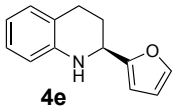
4b
PS-AdTRIP, 84%, 82% ee
BPPA, 83%, 0% ee



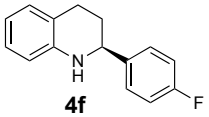
4c
PS-AdTRIP, 84%, 88% ee
BPPA, 77%, 0% ee



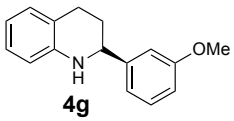
4d
PS-AdTRIP, 92%, 93% ee
BPPA, 99%, 0% ee



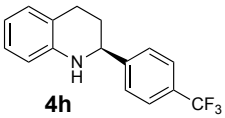
4e
PS-CPA, 97%, 84% ee
BPPA, 92%, 0% ee



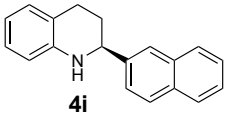
4f
PS-AdTRIP, 82%, 90% ee
BPPA, 93%, 0% ee



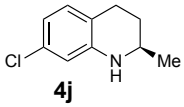
4g
PS-CPA, 99%, 93% ee
BPPA, 98%, 0% ee



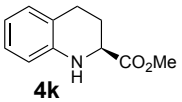
4h
PS-CPA, 69%, 94% ee
BPPA, 68%, 0% ee



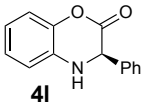
4i
PS-CPA, 79%, 93% ee
BPPA, 89%, 0% ee



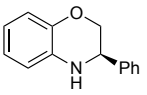
4j
PS-AdTRIP, 98%, 84% ee
BPPA, 99%, 0% ee



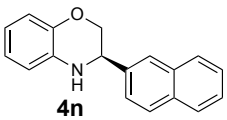
4k
PS-CPA, 74%, 89% ee
BPPA, 68%, 0% ee



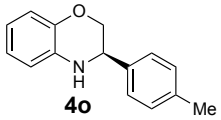
4l
PS-CPA, 68%, 92% ee
BPPA, 48%, 0% ee



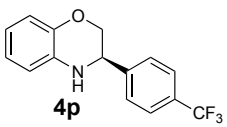
4m
PS-AdTRIP, 91%, 90% ee
BPPA, 89%, 0% ee



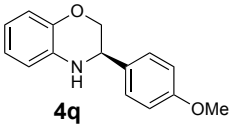
4n
PS-AdTRIP, 70%, 90% ee
BPPA, 66%, 0% ee



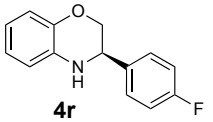
4o
PS-CPA, 96%, 92% ee
BPPA, 92%, 0% ee



4p
PS-CPA, 77%, 93% ee
BPPA, 88%, 0% ee



4q
PS-CPA, 78%, 92% ee
BPPA, 79%, 0% ee



4r
PS-AdTRIP, 88%, 89% ee
BPPA, 88%, 0% ee

Our initial studies commenced with evaluating the potential of immobilized on polystyrene support acids **3a** and **3c** as well as their non-immobilized counterparts **3b** and **3d** for the reduction of quinolines **1a** and **1b** with various reducing agents **2a-2e** (cf. Scheme 1). Subjecting **1a** to the reduction with Hantzsch ester **2a** catalyzed by **3a** (2 mol%) under the standard conditions developed by Rueping and coworkers (entry 1)[6] resulted in the formation of chiral product **4a** in excellent yield and enantioselectivity (90%, 92% ee). The selectivity was further improved to 94% ee by reducing the reaction temperature to r.t. although this increased the reaction time to 18 h (entry 2). Further investigation of the catalyst loading (*cf.* SI-Section III), revealed that the optimal catalyst loading is 2-10 mol%; however, higher or lower catalyst loading led to the erosion in enantioselectivity.

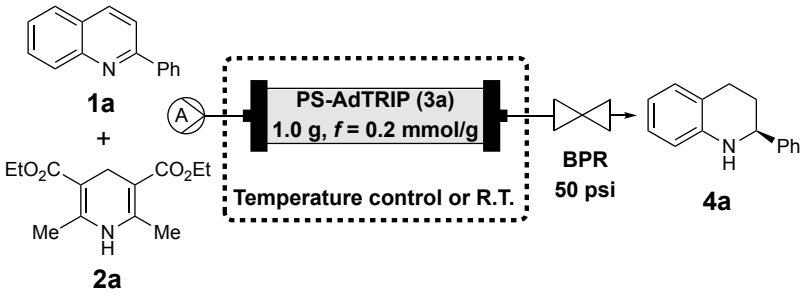
In a control experiment, standard Ad-TRIP catalyst **3b** was similarly active under the reaction conditions and provided the chiral product **4a** in 88% yield and 98% ee (entry 3). In contrast, SPINOL based CPAs **3c** and **3d** did not demonstrate good catalytic profiles in this reaction, and the formation of **4a** proceeded with low selectivities and required prolonged reaction times even at 60 ºC (entries 4 and 5). To evaluate the substrate tolerance, the reduction of 2-methylquinoline (**1b**) leading to **4b** was evaluated next (entries 6-11). Subjecting **1a** to the optimal reduction conditions with **3a** as the catalyst resulted in the formation of **4b** in 84% yield and 82% ee (entry 6). Similar results were also observed with Ad-TRIP (**3b**) as the catalyst (entry 7). As demonstrated in the pioneering work of MacMillan, Hantzsch ester substitution may have a significant impact on the reduction enantioselectivity.[16] However, further attempts to improve the selectivity by using bulkier Hantzsch esters such as **2b** and **2c** either resulted in similar outcome (**2b**, entry 8) or no formation of **4b** was observed (**2c**, entry 9). Similarly, the use of alternative reducing agents **2d**[17] and **23**[18] did not result in the formation of **4b** (entries 10 and 11).

Based on the studies above, the most optimal reaction conditions from Scheme 1, entry 2 were selected and used to evaluate the scope of the reduction with the immobilized catalyst PS-AdTRIP (**3a**) (Scheme 2). The variation in the C2-aromatic substitution of quinoline **1a** was found to be well-tolerated, and chiral products with the phenyl group containing both electrondonating (**4c**, **4d**, **4g**) and electronwithdrawing (**4f**, **4h**) substituents as well as C2-furanyl (**4e**) and C2-naphtyl (**4i**) groups were obtained with excellent enantioselectivities (84-94% ee). Similarly, modification in the structure of C2-methylquinoline led to the minor improvements in enantioselectivities and yields and reduced 7-chloro derivative **4j** and C2-carbomethoxy derivative **4k** were obtained in 84% ee and 89% ee, correspondingly. Considering that 2*H*-1,4-benzoxazines have been previously used as the substrates for the Hantzsch ester transfer hydrogenation with immobilized CPAs, the reduction of various 1,4-benozoxazines was investigated next. When compared side-by-side with their quinoline counterparts, 2*H*-1,4-benzoxazines **4m–4o**, **4p** and **4r** were formed in 1-3% lower ee; however, in the case of the 4-methoxy- group substituted substrate, the formation of 2*H*-1,4-benzoxazine **4q** proceeded with 4% higher enantioselectivity. Finally, to demonstrate that other modifications are tolerated, chiral 2*H*-1,4-benzoxazin-2-one **4l** was produced in 68% yield and 92% ee. Importantly, in all these studies, catalyst PS-AdTRIP (**3a**) was successfully recovered by filtration, washed, and recycled multiple times without the loss in activity (cf. SI-Section IV).

With the successful demonstration that PS-AdTRIP (**3a**) could be generally employed for the enantioselective synthesis of chiral heterocycles such as **4a-4r**, we investigated the possibility of carrying such transformations in continuous flow using a fluidized bed reactor packed with **3a** (Scheme 3). The solution of **1a** (50 mM) and **2a** (120 mM) in $CHCl_3$ was pumped through the

Omnifit® column equipped with a back-pressure regulator (BPR) and containing 1.0 g (0.2 mmol of active CPA) of PS-AdTRIP (**3a**). Our initial studies focused on identifying the optimal temperature and flow rate. The related studies on CPA-catalyzed continuous flow allylation and thiol addition reactions by the Pericas group utilized flow rates in the range of 0.2-0.5 mL/min,[9b-d] and we initially evaluated similar flow rates (0.05 to 0.2 mL/min) at 60 ºC (entries 1-4). While the formation of **4a** proceeded with full conversion in all these cases, the observed enantioselectivities were significantly lower than the observed 92% ee value for the in-batch reduction at 60 ºC carried earlier (cf. Scheme 1, entry 1). Lowering the reaction temperature to 45 ºC led to a significant improvement in enantioselectivity, and **4a** was obtained in 88% ee with the flow rates equal to 0.1 mL/min (entry 5) and 90% ee with the flow rates of 0.2 mL/min (entry 6). Further decreasing the temperature to room temperature (r.t.) did not result in diminished conversion; however, no increase in enantioselectivity was observed (entry 7). The results above suggest that the reduction of **1a** over the bed of **3a** in continuous flow is a fast process even at room temperature; however, improved enantioselectivity is consistently observed at higher flow rates.

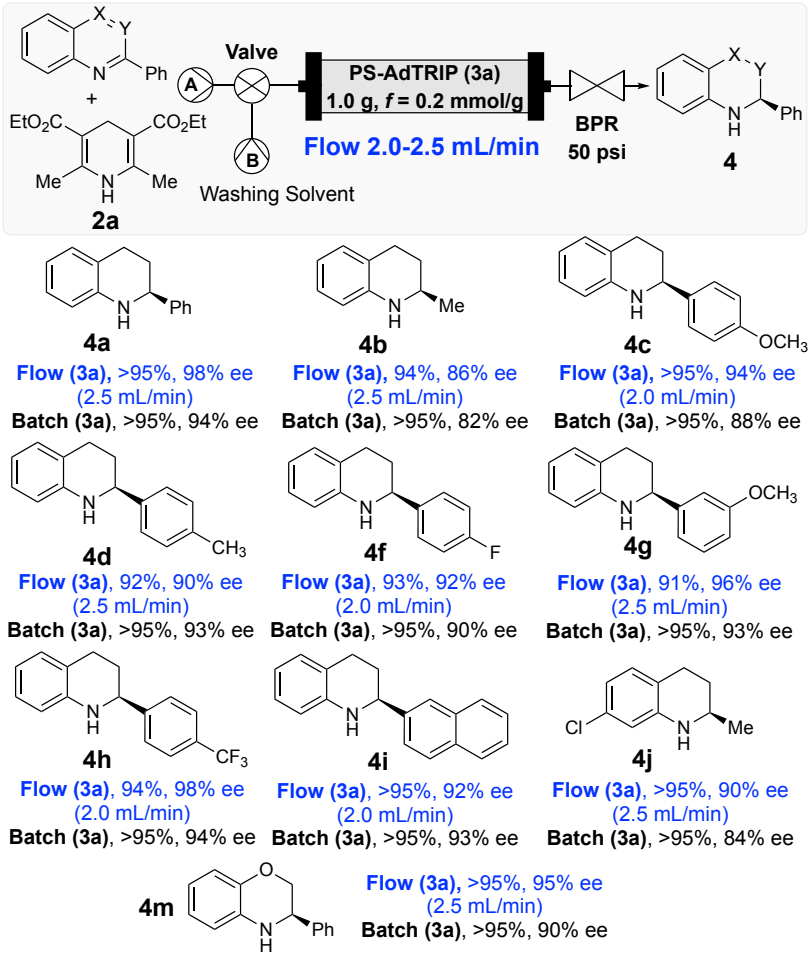
Scheme 3. Optimization of the continuous flow transfer hydrogenation of **1a** with Hantzsch ester **2a** over the reactor packed with PS-AdTRIP (**3a**).



entry	T, ºC	flow rate (mL/min)	BPR, psi	conversion (%)	ee, %
1	60	0.05	50	>95	78
2	60	0.10	50	>95	78
3	60	0.15	50	>95	80
4	60	0.20	50	>95	80
5	45	0.10	-	>95	88
6	45	0.20	-	>95	90
7	r.t.	0.20	-	>95	90
8	r.t.	0.50	-	>95	97
9	r.t.	0.75	-	>95	98
10	r.t.	1.00	-	>95	98
11	r.t.	1.50	-	>95	98
12	r.t.	2.00	-	>95	98
13	r.t.	2.50	-	94	98
14	r.t.	3.00	-	91	98

This may result from the reduction becoming reversible in the presence of the excess of catalyst **3a**, which leads to the epimerization of the product.[19] Such epimerization process should be suppressed if the residual time of **4a** on the surface of **3a** is lowered, which may be achieved at higher flow rates. Indeed, increasing the flow rate has led to significant increase in enantioselectivity for the formation of **4a** (entries 8-14). Remarkably, the reaction was found to proceed to significant extend even at flow rates as high as 2.5 mL/min, and the product **4a** was obtained in 98% ee and 94% conversion (entry 13). Further increase in the flow rate to 3.0 mL/min resulted in slightly lower conversion (91%), but similar enantioselectivity 98% ee (entry 14). It should be noted that the overall increase of the flow rate from 0.2 mL/min to 2.5 mL/min has led to +8% increase in enantioselectivity, and the enantioselectivity in continuous flow (98% ee) is higher than in batch (94% ee). It is also noteworthy that achieving high flow rates of 2.5 mL/min enables generating ~1.5 g (7.5 mmol) of **4a** per hour, which is a significant improvement in terms of the throughput when compared to the related processes.

With the optimized conditions in hand, our subsequent studies focused on demonstrating that the same Omnifit® column containing PS-AdTRIP catalyst **3a** could be used continuously to generate multiple chiral products **4** (Scheme 4). Thus, the original continuous flow set up has been modified to introduce a line with washing solvent ($CHCl_3$) that was used to wash the reactor containing **3a** between the runs. Thus, after the consumption of the reaction mixture containing heterocycle (1.0 mmol) and **2a** (2.4 mmol), the resin **3a** was washed for 10 minutes, and then next reaction mixture containing a different heterocyclic compound was introduced.

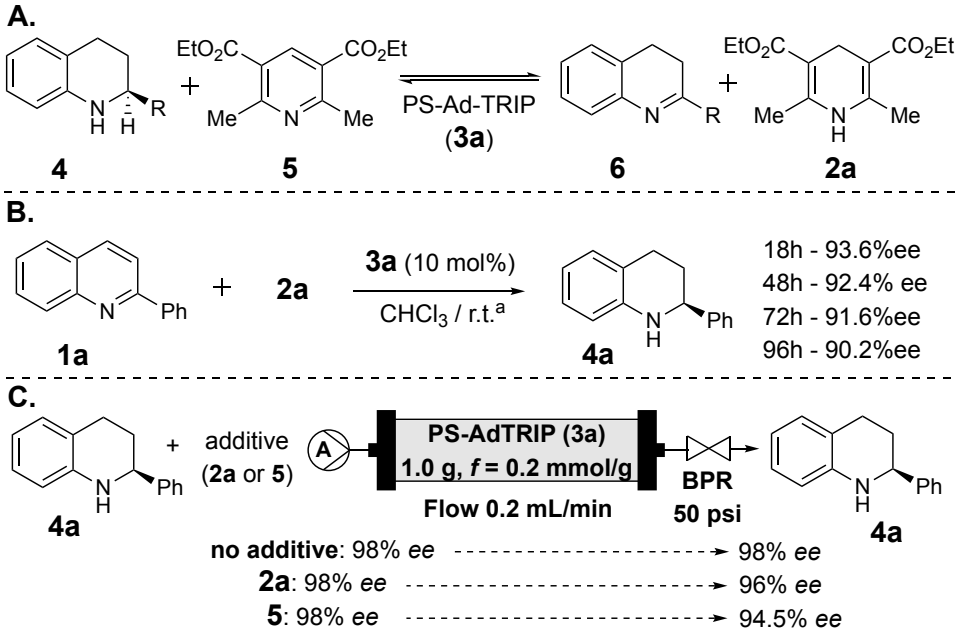


Scheme 4. Continuous flow reduction of multiple nitrogen-containing heterocyclic compounds using the same flow bed reactor packed with PS-AdTRIP (**3a**) catalyst.

Remarkably, in almost all the evaluated cases, a significant improvement in enantioselectivity for the continuous flow process in comparison to the reduction in batch was observed (Scheme 4). Thus, substrates **4a-4c**, **4f-4h**, **4j** and **4m** were generated with the improvement in the range of +4-6% ee. It should be noted that for substrates **4d** and **4i**, minor erosion in the ee was noted (–3% and –1%, correspondingly). It must be highlighted that all the chiral substrates in Scheme 2 were generated using the same reactor containing PS-AdTRIP (**3a**) in less than 48 h. Similar to the batch experiments, the multiple use of **3a** in flow did not result in eroded enantioselectivities or yields, and the same flow bed reactor consistently provided similar enantioselelctivity and reactivity for substrates in Scheme 4.

To confirm the hypothesis that lower products enantiopurities observed at lower flow rates are due to the epimerization arising from the oxidation of chiral product **4** with the oxidized Hantzsch ester **5** (*cf.* Scheme 5A), the controlled experiments summarized in Schemes 5B and 5C were performed. The reaction of substrate **1a** and Hantzsch ester **2a** was carried in batch in the presence of 10 mol% of **3a** in non-degassed chloroform as the solvent and the enantioselectivity was monitored at different times (Scheme 5B).

Scheme 5. Control experiments to determine the origins of enantioselectivity erosion at low flow rates. [a]The reactions mixture was not degassed, and the formation of **5** was detected as the reaction progressed.



As previously observed, the formation of product **4a** was complete after 18 h (93.6% ee). However, the continued exposure of the reaction mixture to catalyst **3a** indeed resulted in lower enantiopurity, and 90.2% ee was observed after 96 h. While these results seem to be counterintuitive since **2a** should not oxidize product **4a**, the careful analysis of the reaction mixture revealed that **2a** was slowly oxidized by the air present in the solution to form **5**, which caused the observed epimerization of **4a**. Subsequently, the continuous flow experiments in Scheme 5C were performed with the flow rate of 0.2 mL/min. When enantioenriched product **4a** (98% ee) was passed through the column containing PS-AdTRIP (**3a**), no change in enantiopurity was detected. At the same time, when the mixture of **4a** (98% ee) and Hantzsch ester **2a** was passed through the reactor containing **3a**, minor reduction of enantiopurity of **4a** to 96% ee was observed. Finally, when the mixture of **4a** (98% ee) and oxidized Hantzsch ester **5** was passed through **3a**, more significant epimerization was observed, and **4a** was isolated with 94.5% ee. These studies shed light onto the origins of the observed enantioselectivity dependence on flow rates and highlight the improvements in enantioselective catalysis obtained with continuous flow set up.

In summary, this manuscript describes transfer hydrogenation of nitrogen-containing heterocycles with immobilized chiral phosphoric acid PS-AdTRIP (**3a**) both in batch and in continuous flow. PS-AdTRIP (**3a**) was used as a recyclable catalyst for in batch enantioselective reduction of various quinolines, 2*H*-1,4-benzoxazines, and 2*H*-1,4-benzoxazin-2-ones using Hantzsch ester **2a** as the reducing agent. A continuous flow variant of this protocol features generally improved enantioselectivity when carried at high flow rates (2.0-2.5 mL/min or 7.5 mmol/h) and enables highly selective asymmetric reduction of ten different chiral heterocyclic

products in less than 48 hours using the same fluidized bed reactor containing PS-AdTRIP (**3a**). The subsequent control studies suggest that improvements in stereoselectivity at high flow rates may stem from less significant epimerization in continuous flow than in batch.

General Information and Methods

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Chloroform ($CHCl_3$) was filtered through a column (Innovative Technology PS-MD-5) of activated alumina under nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Heating was achieved by use of a metal heating block with heating controlled by electronic contact thermometer. Reactions were monitored by nuclear magnetic resonance (NMR) or thin layer chromatography (TLC) on silica gel precoated glass plates (0.25 mm, SiliCycle, SiliaPlate). TLC plate visualization was accomplished by irradiation with UV light at 254 nm or by staining with a cerium ammonium molybdate (CAM) solution. Continuous flow experiments were performed using Masterflex Constant Pressure Dual Piston Pump, Diba Omnifit EZ Solvent Plus Glass Column (10x100 mm, with two adjustable endpieces) and Zaiput Back-Pressure Regulator BPR-10. Column heating was performed using aluminum beads bath. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash column chromatography on SiO_2 using SiliCycle SiliaFlash P60 (230-400 mesh) to pack the columns for Teledyne ISCO CombiFlash Rf+ purification system. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

Instrumentation:

All spectra were recorded on Bruker Avance Neo 500 (500 MHz) spectrometer and chemical shifts (δ) are reported in parts per million (ppm) and referenced to the ^1H signal of the internal tetramethylsilane according to IUPAC recommendations. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(*S*) in Hz; integration). High resolution mass spectra (HRMS) were recorded on MicromassAutoSpecUltima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Optical rotations were measured at room temperature in a solvent of choice on a JASCO P-2000 digital polarimeter at 589 nm (D-line).

Procedures

General Procedure A for Batch Reduction. An oven-dried vial was charged with a magnetic stir bar, polymer-supported catalyst PS-AdTRIP CPA (**3a**)[13] (10 mg, *f* = 0.2 mmol/g, 200 μmol, 2 mol%), corresponding substrate **1** (0.1 mmol) and appropriate amount of reducing agent **HAT 2** (0.12 mmol or 0.24 mmol depending on substrate **1**). Vial was capped with septum, attached to Schlenk line using 22G needle and then evacuated and refilled with nitrogen 3 times. After that, 2 mL of $CHCl_3$ was added through the septum and the vial was placed on the stir plate (metal heating block was used when the heating was required). Reaction mixture was stirred for 18 hours after which TCL indicated the full consumption of the starting material. After that reaction mixture was filtered to isolate the immobilized catalyst that was subsequently washed with 2-3 mL of DCM. Filtrate was concentrated under reduced pressure and crude was analyzed via NMR to determine conversion. Purification was performed using CombiFlash Chromatograph system on SiO_2 using Hexane and EtOAc as solvents and gradient from 95:5 to 80:20 over 15 minutes. The identity of the purified product was confirmed by NMR and ESI-HRMS and its enantiomeric excess was analyzed by HPLC (using appropriate chiral column, see details below). ***Note***: In case of immobilized catalyst PS-SPINOL CPA (**3c**), 17 mg (204 μmol, 2 mol%) of resin was used due to lower functionality *f* = 0.12 mmol/g.[13]

General Procedure B for Reduction in Continuous Flow (*cf.* Supporting Information for Additional Details). Polymer-Supported Catalyst PS-AdTRIP CPA (**3a**), (1.0 g, *f* = 0.2 mmol/g) was placed in Omnifit® Glass Column and the stream of the $CHCl_3$ was pumped at 0.5 mL/min for 2 hours to swell the resin inside the column.

Subsequently, the column endpieces were adjusted to fit the volume of the swelled polymer. The reaction solution containing 1 mmol of the corresponding heterocycle **1** and 2.4 mmol of the Hantzsch ester **2a** (1.2 mmol if only mono reduction is needed) in 20 mL of $CHCl_3$ was placed in 40 mL glass vial and connected to the pump (line **A**). Reactants solution was pumped through the system at required flow rate and reaction products were collected in 40 mL glass vial. After full consumption of the reagents solution, valve was switched to line **B** and the $CHCl_3$ was pumped through the system with the same flow rate for 10 minutes to wash out all reaction products from the pump lines and column and was collected into vial with products. After the completion of these steps, the system is ready for the new run and next reagents solution is connected to line **A**. Collected solution after the flow run was concentrated under reduced pressure and purified using CombiFlash® Chromatograph system on SiO_2 using Hexane and EtOAc as solvents and gradient from 95:5 to 80:20 over 15 minutes.

(S)-2-phenyl-1,2,3,4-tetrahydroquinoline (4a). Known compound,[20] white solid, 19.8 mg, 95% yield, >95% NMR conv. in-flow (2.5 mL/min), 94% ee (batch), 98% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 – 7.38 (m, 2H), 7.37 (dd, *J* = 8.5, 6.6 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 2H), 6.67 (td, *J* = 7.4, 1.2 Hz, 1H), 6.58 – 6.53 (m, 1H), 4.46 (dd, *J* = 9.4, 3.3 Hz, 1H), 4.05 (s, 1H), 2.94 (ddd, *J* = 16.3, 10.7, 5.5 Hz, 1H), 2.75 (dt, *J* = 16.3, 4.8 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.01 (dddd, *J* = 12.9, 10.6, 9.3, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 144.94, 144.86, 129.4, 128.7, 127.6, 127.0, 126.7, 121.0, 117.3, 114.1, 77.4, 77.2, 76.9, 56.4, 31.1, 26.5.

HRMS (ESI+) (*m*/*z*): [M+H]$^+$ calcd for $C_{15}H_{15}NH^+$ 210.1277, found 210.1273.

$[\alpha]^{24}_D$ = –38.8 (c = 0.05M, $CHCl_3$).

HPLC: (Chiralpak IA column, 98:2 hexanes/isopropanol, 0.5 mL/min), tr = 12.1 min (minor, *R*), 15.1 min (major, *S*).

(R)-2-methyl-1,2,3,4-tetrahydroquinoline (4b). Known compound,[21] yellow oil, 12.4 mg, 84% yield, 94% NMR conv. in flow (2.5 mL/min), 82% ee (batch), 86% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 6.97 (tdd, *J* = 6.5, 2.4, 1.3 Hz, 2H), 6.62 (td, *J* = 7.4, 1.2 Hz, 1H), 6.48 (dd, *J* = 8.4, 1.3 Hz, 1H), 3.68 (s, 1H), 3.41 (dtd, *J* = 12.6, 6.3, 2.9 Hz, 1H), 2.90 – 2.80 (m, 1H), 2.74 (ddd, *J* = 16.4, 5.4, 3.5 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.60 (dddd, *J* = 12.8, 11.6, 9.9, 5.3 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 144.9, 129.4, 126.8, 121.2, 117.1, 114.1, 77.4, 77.2, 76.9, 47.3, 30.3, 26.7, 22.8.

HRMS (ESI+) (*m*/*z*): [M+H]$^+$ calcd for $C_{10}H_{13}NH^+$ 148.1121, found 148.1117;

$[\alpha]^{24}_D$ = +83.3 (c = 0.04M, $CHCl_3$).

HPLC: (Chiralpak OJ-H column, 95:5 hexanes/isopropanol, 1.0 mL/min), tr = 11.9 min (minor, *S*), 12.9 min (major, *R*).

(S)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (4c). Known compound,[20] white solide, 20.1 mg, 84% yield, >95% NMR conv. in flow (2.0 mL/min), 88% ee (batch), 94% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.29 (m, 2H), 7.02 (tt, *J* = 7.2, 1.2 Hz, 2H), 6.94 – 6.87 (m, 2H), 6.66 (td, *J* = 7.4, 1.2 Hz, 1H), 6.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 4.39 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.99 (s, 1H), 3.82 (s, 3H), 2.94 (ddd, *J* = 16.4, 11.0, 5.5 Hz, 1H), 2.75 (dt, *J* = 16.3, 4.6 Hz, 1H), 2.10 (dddd, *J* = 12.9, 5.5, 4.2, 3.2 Hz, 1H), 1.98 (dddd, *J* = 12.9, 10.9, 9.6, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 159.1, 144.9, 137.0, 129.4, 127.8, 127.0, 121.0, 117.2, 114.1, 114.0, 77.4, 77.2, 76.9, 55.9, 55.5, 31.2, 26.7.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{17}NOH^+$ 240.1383, found 240.1375.

$[\alpha]^{24}_D$ = –21.3 (c = 0.04M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 90:10 hexanes/isopropanol, 1.0 mL/min), tr = 8.6 min (major, *R*), 14.0 min (minor, *S*).

(S)-2-(p-tolyl)-1,2,3,4-tetrahydroquinoline (4d). Known compound,[20] white solide, 20.5 mg, 92% yield, 92% NMR conv. in-flow (2.5 mL/min), 93% ee (batch), 90% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.33 – 7.28 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.67 (td, *J* = 7.4, 1.2 Hz, 1H), 6.57 – 6.52 (m, 1H), 4.42 (dd, *J* = 9.5, 3.2 Hz, 1H), 4.02 (s, 1H), 2.94 (ddd, *J* = 16.3, 10.8, 5.5 Hz, 1H), 2.76 (dt, *J* = 16.3, 4.7 Hz, 1H), 2.38 (s, 3H), 2.12 (dddd, *J* = 13.0, 5.4, 4.3, 3.2 Hz, 1H), 2.00 (dddd, *J* = 12.9, 10.7, 9.5, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 144.93, 141.95, 137.21, 129.40, 129.36, 126.99, 126.58, 121.00, 117.20, 114.06, 77.41, 77.16, 76.91, 56.14, 53.56, 31.15, 26.61, 21.23.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{17}NH^+$ 224.1434, found 224.1431.

$[\alpha]^{24}_D$ = –25.5° (c = 0.05M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 90:10 hexanes/isopropanol, 1.0 mL/min), tr = 6.7 min (major, *S*), 11.9 min (minor, *R*).

(S)-2-(furan-2-yl)-1,2,3,4-tetrahydroquinoline (4e). Known compound,[4b] yellow solid, 19.3 mg, 97% yield, 84% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 (d, *J* = 2.0 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.66 (td, *J* = 7.4, 1.2 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 4.54 (dd, *J* = 8.4, 3.5 Hz, 1H), 4.14 (s, 1H), 2.87 (ddd, *J* = 15.4, 9.4, 5.6 Hz, 1H), 2.76 (dt, *J* = 16.4, 5.5 Hz, 1H), 2.26 – 2.09 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 157.0, 143.8, 141.6, 129.3, 126.9, 121.0, 117.6, 114.4, 110.2, 105.2, 49.7, 26.9, 25.6.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{13}NOH^+$ 200.1070, found 200.1067;

$[\alpha]^{24}_D$ = +31.2 (c = 0.039M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 90:10 hexanes/isopropanol, 0.5 mL/min), tr = 15.5 min (major, *S*), 16.7 min (minor, *R*).

(S)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline (4f). Known compound,[20] white solide, 18.6 mg, 82% yield, 93% NMR conv. in-flow (2.0 mL/min), 90% ee (batch), 92% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 2H), 7.09 – 6.99 (m, 4H), 6.67 (td, *J* = 7.4, 1.2 Hz, 1H), 6.58 – 6.53 (m, 1H), 4.44 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.01 (s, 1H), 2.93 (ddd, *J* = 16.3, 10.7, 5.5 Hz, 1H), 2.74 (dt, *J* = 16.4, 4.8 Hz, 1H), 2.11 (dddd, *J* = 13.1, 5.4, 4.5, 3.2 Hz, 1H), 1.97 (dddd, *J* = 12.9, 10.6, 9.3, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 162.1 (d, *J* = 245.3 Hz), 144.6, 140.5 (d, *J* = 3.1 Hz), 129.3, 128.1 (d, *J* = 8.0 Hz), 127.0, 120.9, 117.4, 115.4 (d, *J* = 21.3 Hz), 114.1, 55.6, 31.2, 26.3.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{14}NFH^+$ 224.1434, found 224.1431.

$[\alpha]^{24}_D$ = –25.47 (c = 0.044M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 90:10 hexanes/isopropanol, 1.0 mL/min), tr = 8.0 min (major, *S*), 13.5 min (minor, *R*).

(*S*)-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (4g). Known compound,[22] colorless oil, 23.7 mg, 99% yield, 91% NMR conv. in-flow (2.5 mL/min), 93% ee (batch), 96% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.28 (t, *J* = 7.8 Hz, 1H), 7.06 – 6.95 (m, 4H), 6.84 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.66 (td, *J* = 7.4, 1.2 Hz, 1H), 6.58 – 6.52 (m, 1H), 4.43 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.04 (s, 1H), 3.82 (s, 3H), 2.94 (ddd, *J* = 16.3, 10.8, 5.5 Hz, 1H), 2.75 (dt, *J* = 16.3, 4.7 Hz, 1H), 2.13 (dddd, *J* = 13.0, 5.4, 4.4, 3.2 Hz, 1H), 2.00 (dddd, *J* = 13.0, 10.8, 9.4, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 159.9, 146.6, 144.7, 129.6, 129.3, 126.9, 120.9, 118.9, 117.2, 114.0, 112.8, 112.1, 56.3, 55.3, 31.0, 26.5.

HRMS (ESI+) (*m*/*z*): [M+H]$^+$ calcd for $C_{16}H_{17}NOH^+$ 240.1383, found 240.1368;

$[\alpha]^{24}_D$ = –40.5 (c = 0.58M, $CHCl_3$).

HPLC: (Chiralpak IA column, 98:2 hexanes/isopropanol, 1.0 mL/min), tr = 8.9 min (minor, *R*), 11.1 min (major, *S*).

(*S*)-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline (4h). Known compound,[23] yellowish solid, 19.1 mg, 69% yield, 94% NMR conv. in-flow(2.0 mL/min), 94% ee (batch), 98% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.08 – 6.99 (m, 2H), 6.69 (td, *J* = 7.4, 1.2 Hz, 1H), 6.58 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.53 (dd, *J* = 8.9, 3.4 Hz, 1H), 4.06 (s, 1H), 2.92 (ddd, *J* = 15.9, 10.2, 5.4 Hz, 1H), 2.72 (dt, *J* = 16.4, 5.0 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.00 (dddd, *J* = 13.0, 10.2, 8.9, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) 148.9 (d, *J* = 1.2 Hz), 144.2, 129.7 (q, *J* = 32.2 Hz), 129.4, 127.1, 126.9, 125.5 (q, *J* = 3.8 Hz), 124.20 (q, *J* = 272.0 Hz), 120.8, 117.6, 114.1, 55.8, 30.9, 26.0.

HRMS (ESI+) (*m*/*z*): [M+H]$^+$ calcd for $C_{16}H_{14}NF_3H^+$ 278.1151, found 278.1151.

$[\alpha]^{24}_D$ = –47.2 (c = 0.32M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 7.8 min (major, *S*), 12.9 min (minor, *R*).

(*S*)-2-(naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline (4i). Known compound,[20] white solid, 20.5 mg, 79% yield, >95% NMR conv. in-flow(2.0 mL/min), 93% ee (batch), 92% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.92 – 7.80 (m, 4H), 7.60 – 7.40 (m, 3H), 7.06 (td, *J* = 7.4, 5.1 Hz, 2H), 6.70 (td, *J* = 7.4, 1.2 Hz, 1H), 6.61 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.62 (dd, *J* = 9.3, 3.4 Hz, 1H), 4.15 (s, 1H), 2.98 (ddd, *J* = 16.2, 10.7, 5.4 Hz, 1H), 2.79 (dt, *J* = 16.3, 4.8 Hz, 1H), 2.21 (dtd, *J* = 13.2, 5.1, 3.5 Hz, 1H), 2.11 (dddd, *J* = 12.9, 10.6, 9.2, 5.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 144.7, 142.3, 133.4, 133.0, 129.4, 128.4, 127.9, 127.7, 127.0, 126.2, 125.8, 125.1, 124.9, 121.0, 117.3, 114.1, 56.4, 31.0, 26.5.

HRMS (ESI+) (*m*/*z*): [M+H]$^+$ calcd for $C_{19}H_{17}NH^+$ 260.1434, found 260.1442.

$[\alpha]^{24}_D$ = –25.4 (c = 0.43M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 9.6 min (major, *S*), 16.8 min (minor, *R*).

(R)-7-chloro-2-methyl-1,2,3,4-tetrahydroquinoline (4j). Known compound,[21] yellowish solid, 17.8 mg, 98% yield, >95% NMR conv. in-flow (2.5 mL/min), 84% ee (batch), 90% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 6.85 (d, *J* = 8.0 Hz, 1H), 6.54 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 3.75 (s, 1H), 3.39 (dqd, *J* = 9.4, 6.3, 3.0 Hz, 1H), 2.81 – 2.64 (m, 2H), 1.92 (ddt, *J* = 12.5, 5.5, 3.3 Hz, 1H), 1.55 (dddd, *J* = 12.9, 11.2, 9.7, 5.3 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 145.8, 132.0, 130.3, 119.4, 116.7, 113.4, 77.4, 77.2, 76.9, 47.1, 29.9, 26.2, 22.6.

HRMS (ESI+) (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{12}ClNH^+$ 182.0731, 184.0702, found 182.0732(100%), 184.0701(33%).

$[\alpha]^{24}_D$ = +77.9 (c = 0.035M, $CHCl_3$).

HPLC: (Chiralpak OJ-H column, 92:8 hexanes/isopropanol, 1.0 mL/min), tr = 11.8 min (minor, *S*), 13.4 min (major, *R*).

Methyl (*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylate (4k). Known compound,[24] white solid, 14.1 mg, 74% yield, 89% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.01 (td, *J* = 7.8, 1.6 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.65 (td, *J* = 7.4, 1.2 Hz, 1H), 6.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.37 (s, 1H), 4.05 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.78 (s, 3H), 2.84 (ddd, *J* = 15.1, 9.3, 5.4 Hz, 1H), 2.76 (dt, *J* = 16.3, 5.5 Hz, 1H), 2.29 (dtd, *J* = 12.9, 5.6, 3.8 Hz, 1H), 2.01 (dtd, *J* = 13.0, 9.1, 5.2 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 173.7, 143.0, 129.1, 127.1, 120.5, 117.7, 114.6, 77.3, 77.1, 76.8, 53.9, 52.4, 25.8, 24.7.

HRMS (ESI+) (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{13}NO_2H^+$ 192.1019, found 192.1015.

$[\alpha]^{24}_D$ = +27.8 (c = 0.048M, $CHCl_3$), lit: –31.3 for R-enantiomer.

HPLC: (Chiralpak IA column, 80:20 hexanes/isopropanol, 0.5 mL/min), tr = 12.5 min (minor, *R*), 15.6 min (major, *S*).

(*R*)-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (4l). Known compound,[20] yellow solid, 15.3 mg, 68% yield, 92% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 (dqd, *J* = 17.1, 5.0, 2.1 Hz, 5H), 7.04 (ddd, *J* = 13.8, 7.8, 1.4 Hz, 2H), 6.87 (td, *J* = 7.8, 1.5 Hz, 1H), 6.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.07 (d, *J* = 2.0 Hz, 1H), 4.25 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 165.2, 140.9, 136.4, 132.4, 129.0, 129.0, 127.5, 125.2, 120.4, 117.0, 114.9, 77.3, 77.0, 76.8, 59.3.

HRMS (ESI+) (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{11}NO_2H^+$ 226.0863, found 226.0869.

$[\alpha]^{24}_D$ = +101.4 (c = 0.069M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 70:30 hexanes/isopropanol, 0.7 mL/min), tr = 10.1 min (major, *R*), 13.1 min (minor, *S*).

(R)-3-phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (4m). Known compound,[20] white solid, 19.2 mg, 91% yield, >95% NMR conv. in-flow (2.5 mL/min), 90% ee (batch), 95% ee (in-flow).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 – 7.37 (m, 4H), 7.35 (ddd, *J* = 7.4, 4.1, 2.1 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.83 (td, *J* = 7.6, 1.5 Hz, 1H), 6.75 – 6.66 (m, 2H), 4.52 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.30 (ddd, *J* = 10.6, 3.2, 1.4 Hz, 1H), 4.01 (dd, *J* = 10.7, 8.5 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.7, 139.3, 134.0, 129.0, 128.5, 127.3, 121.6, 119.1, 116.7, 115.5, 71.1, 54.4.

HRMS (ESI+) (*m*/*z*): [M+H]$^{+}$ calcd for $C_{14}H_{13}NOH^{+}$ 212.1070, found 212.1073.

$[\alpha]^{24}_{D}$ = –137.1 (c = 0.52M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 9.4 min (major, *R*), 12.8 min (minor, *S*).

(R)-3-(naphthalen-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (4n). Known compound,[20] white solide, 18.3 mg, 70% yield, 90% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.91 – 7.83 (m, 4H), 7.56 – 7.48 (m, 3H), 6.93 – 6.82 (m, 2H), 6.78 – 6.70 (m, 2H), 4.68 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.37 (dd, *J* = 10.8, 3.0 Hz, 1H), 4.14 – 4.06 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.7, 136.6, 134.0, 133.5, 133.4, 128.8, 128.1, 127.9, 126.5, 126.4, 126.3, 125.1, 121.7, 119.1, 116.8, 115.6, 71.1, 54.4.

HRMS (ESI+) (*m*/*z*): [M+H]$^{+}$ calcd for $C_{18}H_{15}NOH^{+}$ 262.1226, found 262.1231.

$[\alpha]^{24}_{D}$ = –146.0 (c = 0.035M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 15.4 min (major, *R*), 29.3 min (minor, *S*)

(R)-3-(p-tolyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (4o). Known compound,[20] colorless oil, 21.6 mg, 96% yield, 92% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.27 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.86 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.81 (td, *J* = 7.6, 1.5 Hz, 1H), 6.74 – 6.65 (m, 2H), 4.48 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.27 (dd, *J* = 10.6, 3.0 Hz, 1H), 3.99 (dd, *J* = 10.6, 8.7 Hz, 1H), 3.97 (s, 1H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.7, 138.3, 136.3, 134.1, 129.6, 127.2, 121.6, 119.0, 116.7, 115.5, 71.2, 54.1, 21.3.

HRMS (ESI+) (*m*/*z*): [M+H]$^{+}$ calcd for $C_{15}H_{15}NOH^{+}$ 226.1226, found 226.1228.

$[\alpha]^{24}_{D}$ = –121.9 (c = 0.064M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 7.4 min (major, *R*), 14.1 min (minor, *S*).

(R)-3-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (4p). Known compound,[25] white solide, 21.5 mg, 77% yield, 93% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 6.90 – 6.81 (m, 2H), 6.73 (ddd, *J* = 17.0, 7.7, 1.6 Hz, 2H), 4.60 (dd, *J* = 8.2, 3.0 Hz, 1H), 4.29 (dd, *J* = 10.7, 3.0 Hz, 1H), 4.06 – 3.97 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.5, 143.4 (q, *J* = 1.4 Hz), 133.4, 130.6 (q, *J* = 32.5 Hz), 127.6, 125.8 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 121.7, 119.3, 116.8, 115.5, 70.5, 53.9.

HRMS (ESI+) (*m*/*z*): [M+H]$^{+}$ calcd for $C_{15}H_{12}F_3NOH^{+}$ 280.0948, found 280.0944.

$[\alpha]^{24}_{D}$ = –99.5 (c = 0.38M, $CHCl_3$).

HPLC: (Chiralpak IA column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 9.4 min (major, *R*), 18.1 min (minor, *S*).

(R)-3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (4q). Known compound,[20] yellow oil, 18.8 mg, 78% yield, 92% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.29 (m, 2H), 6.96 – 6.89 (m, 2H), 6.86 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.81 (td, *J* = 7.6, 1.5 Hz, 1H), 6.70 (td, *J* = 7.6, 1.6 Hz, 1H), 6.67 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.46 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.25 (dd, *J* = 10.6, 3.0 Hz, 1H), 3.97 (dd, *J* = 10.6, 8.7 Hz, 1H), 3.82 (s, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 159.8, 143.6, 134.1, 131.3, 128.4, 121.5, 119.0, 116.7, 115.5, 114.3, 71.2, 55.5, 53.7.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{15}NO_2H^+$ 242.1163, found 242.1176.

$[\alpha]^{24}_D$ = -108.5 (c = 0.040M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 7.4 min (major, *R*), 14.1 min (minor, *S*).

(R)-3-(4-fluorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (4r). Known compound,[20] white solid, 20.1 mg, 88% yield, 89% ee (batch).

^{1}H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.34 (m, 4H), 7.12 – 7.04 (m, 4H), 6.89 – 6.79 (m, 4H), 6.75 – 6.65 (m, 4H), 4.50 (dd, *J* = 8.6, 3.0 Hz, 2H), 4.26 (dd, *J* = 10.7, 3.0 Hz, 2H), 3.97 (dd, *J* = 10.7, 8.5 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 162.7 (d, *J* = 246.8 Hz), 143.5, 134.96 (d, *J* = 3.1 Hz), 133.7, 128.8 (d, *J* = 8.2 Hz), 121.5, 119.1, 116.6, 115.7 (d, *J* = 21.5 Hz), 115.4, 70.9, 70.9, 53.5.

HRMS (ESI+) (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{12}FNOH^+$ 230.0980, found 230.0976.

$[\alpha]^{24}_D$ = –103.5 (c = 0.044M, $CHCl_3$).

HPLC: (Chiralpak OD-H column, 80:20 hexanes/isopropanol, 1.0 mL/min), tr = 8.5 min (major, *R*), 14.9 min (minor, *S*).

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Supporting Information

The supporting information for this article is available online.

Primary Data

NO.

Conflict of Interest

PS-AdTRIP (3a) is the subject of the U.S. provisional patent (No. 63/397,220)

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