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Biomimetic reduction of imines and heteroaromatics with chiral and regenerable [2.2]Paracyclophane-Based NAD(P)H model CYNAM

Zhou-Hao Zhu [a, c], Yi-Xuan Ding [a, c], Yong-Gui Zhou [a, b, *]

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China
[b] Zhang Dayu School of Chemistry, Dalian University of Technology, Dalian, 116024, China
[c] University of Chinese Academy of Sciences, Beijing, 100049, China

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ABSTRACT

In our previous work, we reported the synthesis of chiral and regenerable [2.2]paracyclophane-derived NAD(P)H models CYNAMs and their application in biomimetic asymmetric reduction of tetrasubstituted olefins. Herein, the biomimetic asymmetric reduction of imines and heteroaromatics has been successfully achieved using the chiral and regenerable CYNAMs and simple achiral phosphoric acid as the transfer catalyst, providing the chiral amines with up to 99% yield and 99% ee.

1. Introduction

Bionics is a novel discipline that utilizes biological structures and function principles to develop machinery or various new technologies. Additionally, as coenzymes that transfer protons and electrons, the reduced nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) participate in most of the redox metabolisms of the human body, such as citric acid cycle, glycolysis and amino acid decomposition [1–6]. Consequently, the biomimetic method of asymmetric transfer hydrogenation has been an important method for the synthesis of chiral molecules and various biomimetic asymmetric transfer hydrogenations based on coenzyme NAD(P)H have been studied in depth rapidly [7–10]. The first generation of biomimetic asymmetric reduction (BMAR) system is represented by Hantzsch ester (HEH, Scheme 1a) [11–21]. But the biggest disadvantage is that it's hard to realize the regeneration of NAD(P)H analogue [22–26] so that it normally needs stoichiometric NAD(P)H analogue to participate in the reactions. When the second generation represented by dihydrophenanthridine (DHPD, Scheme 1a) appears, due to the good regenerability of DHPD [27–31] under hydrogen gas, the catalytic BMAR of imines and heteroaromatics can be achieved using either a homogeneous ruthenium or iron catalyst. However, it is still difficult to synthesize and screen chiral organocatalysts or metal catalysts bearing complex structures, which hinders the practicability of the reaction. Very recently, our group has reported a new type of regenerable and planarly chiral ferrocene-based NAD(P)H models (FENAM, Scheme 1a). Accordingly, the BMAR of heteroaromatics, alkenes and imines has been realized using bench-stable simple Lewis acids, Brønsted acids or organic hydrogen bonding catalysts as hydrogen transfer catalysts [32–34]. In spite of remarkable contributions, an obvious drawback that the ferrocene skeleton is not resistant to strong Brønsted acids, Lewis acids and oxidative condition limits the further application in the biomimetic chemistry based on the coenzyme NAD(P)H.

In order to solve the problems above, we have designed and synthesized a more stable, rigid and sterically hindered regenerable and chiral [2.2]paracyclophane-based NAD(P)H models (CYNAMs, Scheme 1a) [35]. With simple achiral Lewis acid as the hydrogen transfer catalyst, it has been successfully applied to BMAR of tetrasubstituted olefins flavonoids (Scheme 1b) [35]. In order to further investigate the application prospects of CYNAMs, we elected to pursue this model for the BMAR of imines and

* Corresponding author. State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China.
E-mail address: ygzhou@dicp.ac.cn (Y.-G. Zhou).

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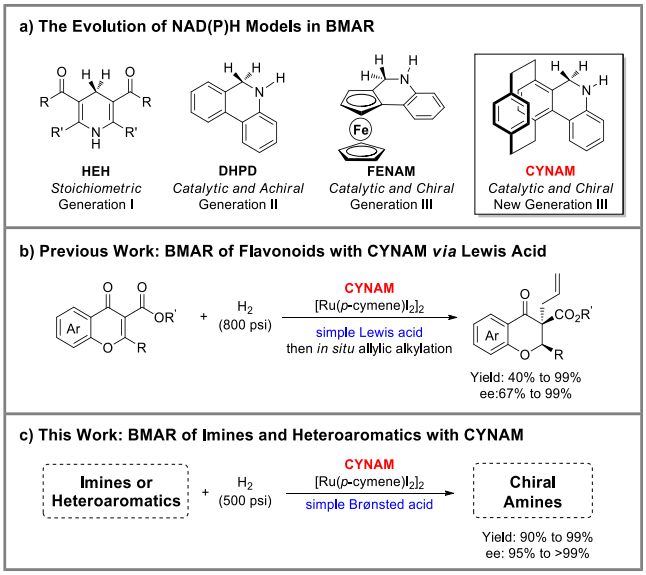


Scheme 1. A new type of NAD(P)H models and application in biomimetic asymmetric reduction (BMAR).

heteroaromatics. Finally, under the bench-stable simple Brønsted acid as the hydrogen transfer catalyst, the BMAR of imines and heteroaromatics could be achieved concisely with high yields and enantioselectivities (Scheme 1c).

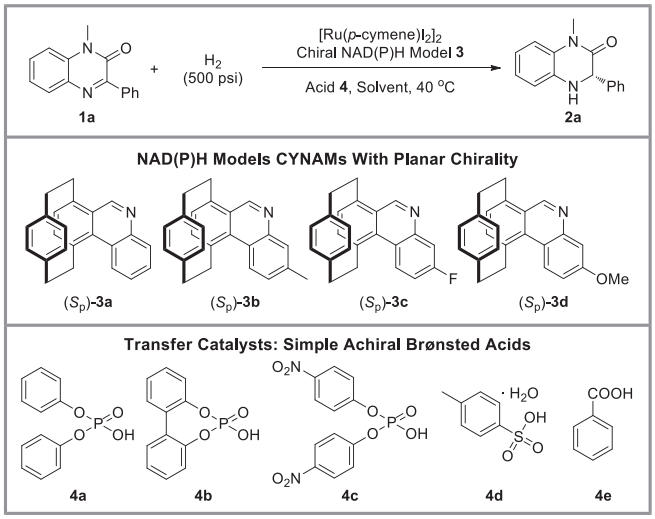
2. Results and discussion

To verify the efficiency of new planar chiral NAD(P)H models, quinoxalinone **1a** was chosen as the model substrate [36,37] for biomimetic asymmetric reduction with commercially available achiral diphenyl hydrogen phosphate **4a** as the transfer catalyst (Table 1).

First, the reduction was carried out in chloroform without ruthenium (II) complex as the regeneration catalyst or any NAD(P)H models CYNAMs respectively. As expected, there was no desired product obtained (<5% *conv.*, entry 1 and 2). However, when ruthenium (II) complex and NAD(P)H models CYNAMs were used but without any Brønsted acids, few desired product was obtained in 93% ee (10% *conv.*, entry 3). To our delight, when Brønsted acid **4a** was added, the reduction could proceed smoothly (94% *conv.*, 98% ee, entry 4). Then we set out to study the optimal reaction condition. In the first place, the evaluation of solvents suggested chloroform was optimal with regard to enantioselectivity and reactivity (entries 4–11). With the optimal solvent chloroform, further optimization of Brønsted acids was conducted. When employing a strong Brønsted acid (**4a-4d**) as the transfer catalyst, the enantioselectivity and reactivity could be enhanced (entries 4 and 12–14). On the contrary, when a weak Brønsted acid (**4e**) was used, the enantioselectivity and reactivity were not improved relative to the background reaction (entries 15) documenting the significance of acidity. Therefore, Brønsted acid **4a** was chosen to be the most suitable transfer catalyst. The reactivity and enantioselectivity could be improved to >95% and 99% ee respectively using NAD(P)H models CYNAMs (S_p)-**3d** (entries 16–18). Excellent isolated yield of **2a** (0.15 mmol) was achieved by prolonging the reaction time from 22 h to 48 h (98% yield, entry 19). At length, the optimal reaction condition was identified: **1** (0.15 mmol), [Ru (*p*-cymene)I_2]$_2$ (0.5 mol%), CYNAM (S_p)-**3d** (10 mol%), achiral transfer catalyst Brønsted acid **4a** (4 mol%), H_2 (500 psi), chloroform, 40 °C and 48 h.

With the optimized conditions in hand, the substrate scope of

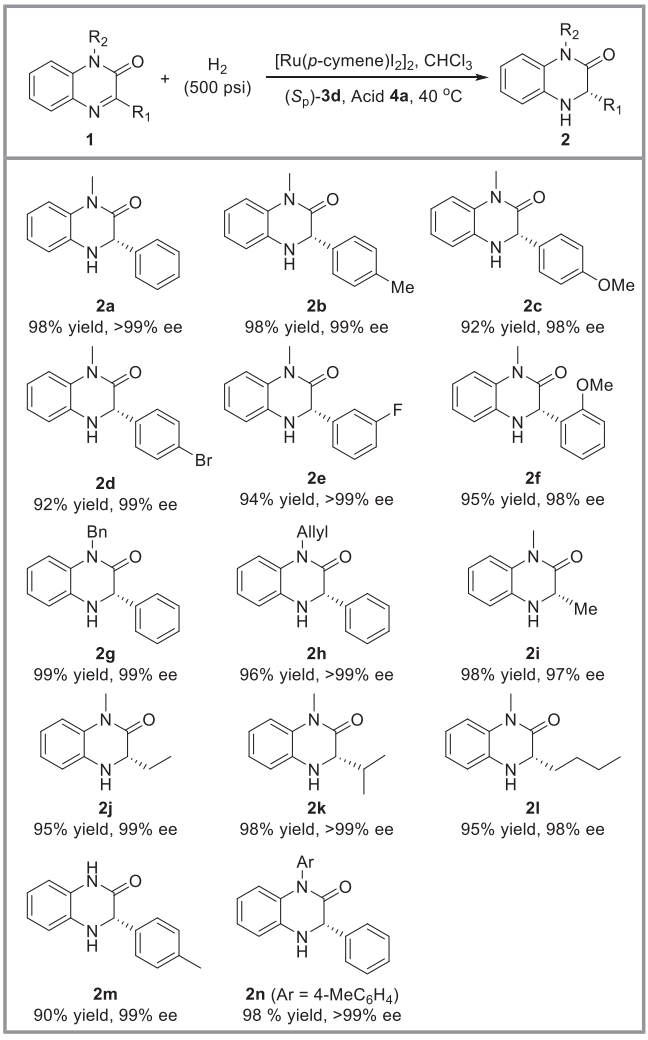
Table 1
Optimization of reaction parameters.[a].



Entry	Solvent	Acid	Model	*Conv.* (%)[b]	Ee (%)[c]
1[d]	$CHCl_3$	**4a**	(S_p)-**3a**	<5	–
2	$CHCl_3$	**4a**	–	<5	–
3	$CHCl_3$	–	(S_p)-**3a**	10	93
4	$CHCl_3$	**4a**	(S_p)-**3a**	94	98
5	CH_2Cl_2	**4a**	(S_p)-**3a**	89	98
6	THF	**4a**	(S_p)-**3a**	11	72
7	EtOAc	**4a**	(S_p)-**3a**	52	95
8	Toluene	**4a**	(S_p)-**3a**	67	98
9	MeOH	**4a**	(S_p)-**3a**	90	14
10	1,4-Dioxane	**4a**	(S_p)-**3a**	20	83
11	Benzene	**4a**	(S_p)-**3a**	70	97
12	$CHCl_3$	**4b**	(S_p)-**3a**	85	98
13	$CHCl_3$	**4c**	(S_p)-**3a**	84	98
14	$CHCl_3$	**4d**	(S_p)-**3a**	82	98
15	$CHCl_3$	**4e**	(S_p)-**3a**	13	93
16	$CHCl_3$	**4a**	(S_p)-**3b**	94	99
17	$CHCl_3$	**4a**	(S_p)-**3c**	88	99
18	$CHCl_3$	**4a**	(S_p)-**3d**	>95	99
19	$CHCl_3$	**4a**	(S_p)-**3d**	98[e]	>99

[a] Reactions were carried with **1a** (0.1 mmol), [Ru (*p*-cymene)I_2]$_2$ (0.5 mol%), **3** (10 mol%), Acid **4** (4 mol%), Solvent (2 mL), H_2 (500 psi), 40 °C, 22 h.
[b] Conversion was measured by analysis of ^{1}H NMR spectra of unpurified mixtures.
[c] Enantiomeric excess (Ee) values were determined by HPLC analysis with chiral column.
[d] [Ru (*p*-cymene)I_2]$_2$ was not used. [e] Isolated yield for the reaction with 0.15 mmol scale for 48 h.

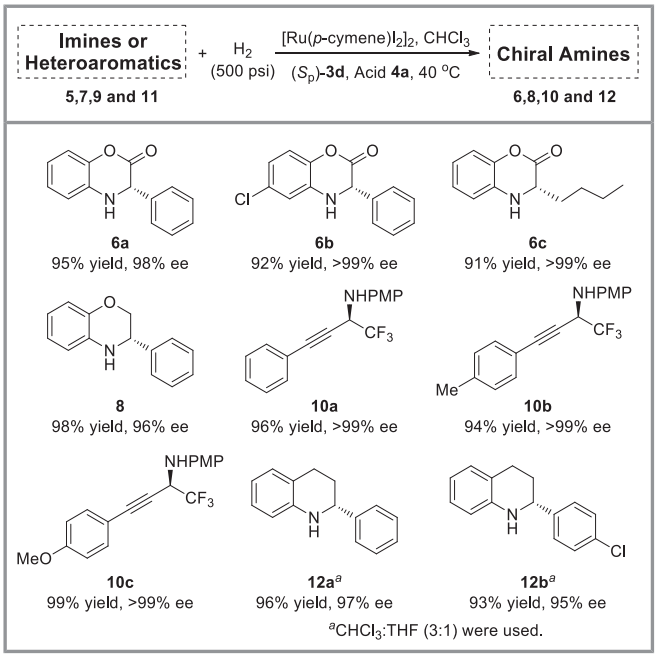
quinoxalinones was then explored (Scheme 2). In accordance with expectation, quinoxalinones **1** performed well under the optimized conditions. First, the steric and electronic properties of the substituent on aryl group were investigated. Either electron-donating or electron-withdrawing substituents on aryl group in *para*-position could both achieve excellent results (**2b**-**2d**). In terms of steric hindrance, the substituents on aryl group in *meta* or *ortho*-position rarely influenced the reaction, resulting in high yields and enantioselectivities (**2e** and **2f**). Similarly, the benzyl and allyl substituents on the nitrogen had no effect on the reaction. Both of excellent yields and enantioselectivities were obtained (**2g** and **2h**). As for the alkyl-substituted substrates, good reactivity could be obtained (**2i**-**2l**). In addition, along with the enhancement of steric hindrance of alkyl substituents, higher enantioselectivity could be achieved. In addition, quinoxalinone with free N–H **1m** could work smoothly under the optimized condition as well (**2m**). Last but not least, the aryl substituent on the nitrogen had no effect on the reaction too (**2n**).



Scheme 2. The BMAR of quinoxalinones.

Motivated by the above results, in order to further demonstrate the practicality of this strategy, we extended the biomimetic asymmetric reduction to other imines and heteroaromatic compounds, such as benzoxazinones [38–40], benzoxazines [41–44], alkynyl-substituted fluorinated ketimines [29,45] and heteroaromatic quinolines [38,46–55] (Scheme 3). Fortunately, these imines and heteroaromatics could be well compatible with this catalytic system. For benzoxazinones, whether it was an alkyl-substituted or aryl-substituted substrate, good yield and excellent enantioselectivity could be achieved (**6a**-**6c**). As the substrate of simple benzoxazine **7**, the reaction could also proceed smoothly, finally obtaining 98% yield and 96% enantioselectivity (**8**). Moreover, the carbon-nitrogen double bonds of linear alkynyl-substituted fluorinated ketimines could be selectively reduced with superior results (**10a**-**10c**). Last but not least, after fine-tuning the solvent, the 2-substituted heteroaromatic quinolines could also be reduced to the corresponding tetrahydroquinoline products with good yields and enantioselectivities (**12a** and **12b**).

Based on the experimental results and putative mechanism of NAD(P)H model-promoted biomimetic asymmetric reduction [27,33], a plausible mechanism for the chiral and regenerable [2.2] paracyclophane-based NAD(P)H model-enabled biomimetic asymmetric reduction of imines and heteroaromatics was illustrated (Scheme 4). In general, this catalytic biomimetic asymmetric

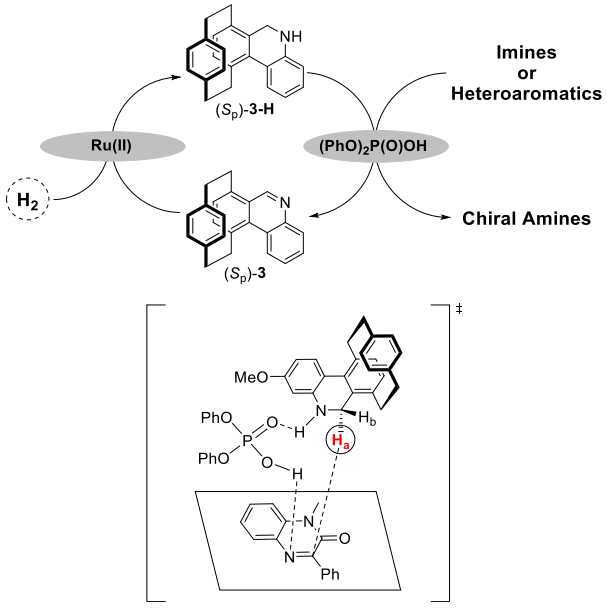


Scheme 3. The BMAR of other imines or heteroaromatics.

reduction comprised two cascade redox cycles promoted by two achiral catalysts. Firstly, chiral NAD(P)H model (S_p)-CYNAM **3** could be reduced to (S_p)-CYNAM **3**-**H** in situ by ruthenium (II) complex and hydrogen gas. Then, the reduced (S_p)-CYNAM **3**-**H** could realize enantioselective reduction of imines and heteroaromatics *via* coordination activation in the presence of the simple and achiral transfer catalyst Brønsted acid (Scheme 4).

3. Conclusion

In conclusion, we have successfully applied the new type of chiral and regenerable NAD(P)H models CYNAMs based on planar-



Scheme 4. Proposed mechanism and transition state.

chiral [2.2]paracyclophane skeleton to biomimetic asymmetric reduction of imines and heteroaromatics with simple and achiral Brønsted acid as a transfer catalyst. A broad range of highly enantiomerically enriched amines could be conveniently prepared with up to 99% yield and 99% ee. Efforts are underway to expand the applications of CYNAMs to other transformations in our laboratory.

4. Experimental section

4.1. General methods

All reactions were carried out under an atmosphere of nitrogen gas using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with Brucker spectrometer. ^{19}F was recorded at 376 MHz with Brucker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane (0) as internal standard when using $CDCl_3$ as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by TLC analysis. Optical rotations were measured by polarimeter. Enantiomeric excess was determined by HPLC analysis using chiral column described below in detail. The NADPH Models CYNAMs **3a-3d** could be synthesized according to the known literature procedure [35]. All Brønsted acids were commercially available and could be used without further purification.

4.2. General procedure for Brønsted acid-promoted biomimetic reduction of quinoxalinones

A mixture of [Ru (*p*-cymene)I_2]$_2$ (0.7 mg, 0.00075 mmol), diphenyl hydrogen phosphate (1.5 mg, 0.006 mmol), (S_p)-CYNAM **3d** (5.1 mg, 0.015 mmol) and quinoxalinones **1** (0.15 mmol) in chloroform (3 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C under hydrogen gas (500 psi) for 48 h. After carefully release of the hydrogen, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate to give the reductive products **2**. The enantiomeric excesses were determined by chiral HPLC.

4.2.1. (+)-(S)-1-Methyl-3-phenyl-3,4-dihydroquino-xalin-2(1H)-one (**2a**)

35 mg, 98% yield, pale yellow solid, known compound, R_f = 0.45 (hexanes/ethyl acetate 5/1), >99% e. e., $[\alpha]_D^{20}$ = +131.66 (*c* 0.66, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +153.0 (*c* 0.4, $CHCl_3$) for 92% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.26–7.17 (m, 3H), 6.93–6.82 (m, 2H), 6.82–6.73 (m, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.97 (s, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 139.1, 134.4, 128.7, 128.4, 128.3, 127.2, 123.8, 119.6, 114.8, 114.1, 60.8, 29.3. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 254 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 11.1 min (major), t2 = 14.0 min.

4.2.2. (+)-(S)-1-Methyl-3-(p-tolyl)-3,4-dihydroqui-noxalin-2(1H)-one (**2b**)

37 mg, 98% yield, white solid, known compound, R_f = 0.56 (hexanes/ethyl acetate 5/1), 99% e. e., $[\alpha]_D^{20}$ = +129.99 (*c* 0.74, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +106.2 (*c* 0.4, $CHCl_3$) for 89% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.88–6.81 (m, 2H), 6.80–6.73 (m, 1H), 6.67–6.60 (m, 1H), 4.90 (s, 1H), 4.04 (br s, 1H), 3.27 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 138.1, 136.2, 134.6, 129.4, 128.4, 127.0, 123.7, 119.4, 114.8, 114.0, 60.6, 29.2, 21.1. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 11.2 min (major), t2 = 15.0 min.

4.2.3. (+)-(S)-3-(4-Methoxyphenyl)-1-methyl-3,4-dihydroquinoxalin-2(1H)-one (**2c**)

37 mg, 92% yield, pale yellow solid, known compound, R_f = 0.30 (hexanes/ethyl acetate 5/1), 98% e. e., $[\alpha]_D^{20}$ = +130.15 (*c* 0.64, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +120.9 (*c* 0.4, $CHCl_3$) for 90% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.16 (m, 2H), 6.90–6.82 (m, 2H), 6.80–6.70 (m, 3H), 6.64 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.89 (s, 1H), 3.67 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.6, 134.6, 131.2, 128.4, 128.4, 123.7, 119.5, 114.8, 114.1, 114.0, 60.3, 55.3, 29.2. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 16.9 min (major), t2 = 20.0 min.

4.2.4. (+)-(S)-3-(4-Bromophenyl)-1-methyl-3,4-dihydroquinoxalin-2(1H)-one (**2d**)

44 mg, 92% yield, pale yellow solid, known compound, R_f = 0.60 (hexanes/dichloromethane 1/3), 99% e. e., $[\alpha]_D^{20}$ = +131.27 (*c* 0.86, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +122.1 (*c* 0.4, $CHCl_3$) for 94% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2H), 7.21–7.15 (m, 2H), 6.91–6.78 (m, 3H), 6.68 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.93 (s, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.9, 134.0, 131.8, 128.9, 128.4, 123.9, 122.4, 112.0, 114.9, 114.2, 60.3, 29.3. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 10.3 min, t2 = 16.4 min (major).

4.2.5. (+)-(S)-3-(3-Fluorophenyl)-1-methyl-3,4-dihydroquinoxalin-2(1H)-one (**2e**)

36 mg, 94% yield, pale yellow solid, known compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), >99% e. e., $[\alpha]_D^{20}$ = +145.41 (*c* 0.72, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +121.8 (*c* 0.4, $CHCl_3$) for 91% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.15 (m, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.05–6.99 (m, 1H), 6.92–6.84 (m, 3H), 6.82–6.76 (m, 1H), 6.67 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.97 (s, 1H), 4.34 (br s, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 162.9 (d, $^1J_{F\text{-}C}$ = 245.2 Hz), 141.5 (d, $^3J_{F\text{-}C}$ = 6.7 Hz), 134.1, 130.2 (d, $^3J_{F\text{-}C}$ = 8.1 Hz), 128.2, 123.9, 122.8 (d, $^4J_{F\text{-}C}$ = 2.9 Hz), 119.8, 115.2 (d, $^2J_{F\text{-}C}$ = 21.1 Hz), 114.9, 114.3, 114.1, 60.3 (d, $^4J_{F\text{-}C}$ = 1.7 Hz), 29.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.17. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 13.2 min (major), t2 = 17.1 min.

4.2.6. (−)-(S)-3-(2-Methoxyphenyl)-1-methyl-3,4-dihydroquinoxalin-2(1H)-one (**2f**)

38 mg, 95% yield, pale yellow solid, known compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), 98% e. e., $[\alpha]_D^{20}$ = −195.91 (*c* 0.76, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = −168.4 (*c* 0.4, $CHCl_3$) for 74% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 1H), 7.04 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94–6.82 (m, 4H), 6.61 (dd, *J* = 7.3, 1.5 Hz, 1H), 5.47 (s, 1H), 3.88 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.2, 134.7, 129.4, 128.8, 127.5, 126.7, 123.6, 120.7, 119.4, 114.6, 114.5, 110.9, 55.8, 55.6, 29.2. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 13.5 min (major), t2 = 16.4 min.

4.2.7. (+)-(S)-1-Benzyl-3-phenyl-3,4-dihydroquino-xalin-2(1H)-one (**2g**)

47 mg, 99% yield, white solid, known compound, R_f = 0.50 (hexanes/ethyl acetate 5/1), 99% e. e., $[\alpha]_D^{20}$ = +94.99 (*c* 0.94, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +79 (*c* 0.2, $CHCl_3$) for 91% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.31 (m, 2H), 7.26–7.20 (m, 3H), 7.17–7.10 (m, 3H), 7.08–7.04 (m, 2H), 6.83–6.78 (m, 1H), 6.75–6.71 (m, 1H), 6.67–6.59

(m, 2H), 5.19 (d, J = 16.1 Hz, 1H), 5.06 (s, 1H), 4.98 (d, J = 16.1 Hz, 1H), 3.95 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 138.9, 136.7, 134.6, 128.8, 128.7, 128.4, 127.6, 127.2, 127.1, 126.5, 123.9, 119.6, 115.7, 114.3, 60.8, 45.9. HPLC (AD-H, elute: Hexanes/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 18.6 min (major), t2 = 20.3 min.

*4.2.8. (+)-(S)-1-Allyl-3-phenyl-3,4-dihydroquinoxa-lin-2(1H)-one (**2h**)*

38 mg, 96% yield, pale yellow solid, known compound, R_f = 0.52 (hexanes/ethyl acetate 5/1), >99% e. e., $[\alpha]_D^{20}$ = +119.72 (*c* 0.74, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +93.0 (*c* 0.2, $CHCl_3$) for 91% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2H), 7.26–7.17 (m, 3H), 6.90–6.80 (m, 2H), 6.77–6.70 (m, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.85–5.70 (m, 1H), 5.10–4.95 (m, 3H), 4.61–4.52 (m, 1H), 4.43–4.35 (m, 1H), 3.88 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.9, 134.6, 132.0, 128.7, 128.3, 127.5, 127.1, 123.8, 119.6, 116.7, 115.4, 114.3, 60.7, 44.7. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 10.6 min (major), t2 = 16.4 min.

*4.2.9. (+)-(S)-1,3-Dimethyl-3,4-dihydroquinoxalin-2(1H)-one (**2i**)*

26 mg, 98% yield, pale yellow oil, known compound, R_f = 0.40 (hexanes/ethyl acetate 5/1), 97% e. e., $[\alpha]_D^{20}$ = +104.99 (*c* 0.42, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +65.0 (*c* 0.2, $CHCl_3$) for 8% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–6.82 (m, 2H), 6.81–6.75 (m, 1H), 6.67–6.62 (m, 1H), 3.87 (q, J = 6.6 Hz, 1H), 3.77 (br s, 1H), 3.28 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 135.0, 129.2, 123.5, 119.7, 114.7, 114.2, 52.2, 29.1, 17.9. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 7.9 min (major), t2 = 8.4 min.

*4.2.10. (+)-(S)-3-Ethyl-1-methyl-3,4-dihydroquino-xalin-2(1H)-one (**2j**)*

27 mg, 95% yield, pale yellow oil, known compound, R_f = 0.41 (hexanes/ethyl acetate 5/1), 99% e. e., $[\alpha]_D^{20}$ = +37.22 (*c* 0.54, $CHCl_3$), [lit [33].: $[\alpha]_D^{20}$ = −59.82 (*c* 0.56, $CHCl_3$) for 97% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86–6.79 (m, 2H), 6.78–6.71 (m, 1H), 6.66–6.60 (m, 1H), 3.90 (br s, 1H), 3.72 (dd, J = 7.9, 4.7 Hz, 1H), 3.27 (s, 3H), 1.81–1.70 (m, 1H), 1.69–1.58 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 134.4, 129.0, 123.5, 119.5, 114.6, 114.3, 57.9, 29.0, 24.8, 9.8. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 7.7 min (major), t2 = 9.0 min.

*4.2.11. (+)-(S)-3-Isopropyl-1-methyl-3,4-dihydroq-uinoxalin-2(1H)-one (**2k**)*

30 mg, 98% yield, colorless oil, known compound, R_f = 0.60 (hexanes/ethyl acetate 5/1), >99% e. e., $[\alpha]_D^{20}$ = +15.52 (*c* 0.58, $CHCl_3$), [lit [33].: $[\alpha]_D^{20}$ = −18.03 (*c* 0.56, $CHCl_3$) for 99% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86–6.78 (m, 2H), 6.77–6.70 (m, 1H), 6.66–6.59 (m, 1H), 3.77 (br s, 1H), 3.61 (d, J = 6.0 Hz, 1H), 3.29 (s, 3H), 2.15–2.05 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 134.5, 128.6, 123.5, 119.2, 114.5, 113.9, 62.1, 30.3, 29.0, 19.1, 17.7. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 7.5 min (major), t2 = 9.4 min.

*4.2.12. (+)-(S)-3-Butyl-1-methyl-3,4-dihydroquino-xalin-2(1H)-one (**2l**)*

31 mg, 95% yield, pale yellow oil, known compound, R_f = 0.57 (hexanes/ethyl acetate 5/1), 98% e. e., $[\alpha]_D^{20}$ = +30.16 (*c* 0.60, $CHCl_3$), [lit [33].: $[\alpha]_D^{20}$ = −35.15 (*c* 0.64, $CHCl_3$) for 96% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87–6.81 (m, 2H), 6.80–6.74 (m, 1H), 6.66–6.61 (m, 1H), 3.78 (dd, J = 8.3, 4.7 Hz, 1H), 3.73 (br s, 1H), 3.28 (s, 3H), 1.78–1.70 (m, 1H), 1.64–1.55 (m, 1H), 1.37–1.24 (m, 4H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 134.4, 129.0, 123.5, 119.6, 114.6, 114.4, 56.7, 31.3, 29.0, 27.6, 22.5, 14.0. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 8.0 min (major), t2 = 9.7 min.

*4.2.13. (+)-(S)-3-(p-Tolyl)-3,4-dihydroquinoxalin-2(1H)-one (**2m**)*

32 mg, 90% yield, pale yellow solid, known compound, mp = 149–150 °C, R_f = 0.40 (hexanes/ethyl acetate 3/1), 99% e. e., $[\alpha]_D^{20}$ = +72.67 (*c* 0.56, $CHCl_3$), [lit [58].: $[\alpha]_D^{25}$ = +81.2 (*c* 1.00, $CHCl_3$) for 99% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (br s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.92–6.86 (m, 1H), 6.72 (d, J = 4.2 Hz, 2H), 6.67 (d, J = 7.8 Hz, 1H), 5.01 (s, 1H), 4.25 (br s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 138.3, 136.1, 133.0, 129.5, 127.1, 124.8, 124.0, 119.3, 115.7, 113.7, 60.5, 21.2. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 14.5 min (major), t2 = 18.1 min.

*4.2.14. (−)-3-Phenyl-1-(p-tolyl)-3,4-dihydroquinox-alin-2(1H)-one (**2n**)*

46 mg, 98% yield, pale yellow solid, new compound, mp = 160–161 °C, R_f = 0.31 (hexanes/ethyl acetate 5/1), >99% e. e., $[\alpha]_D^{20}$ = −16.52 (*c* 0.92, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 6.7 Hz, 2H), 7.35–7.26 (m, 5H), 7.10 (d, J = 7.9 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.75 (d, J = 7.2 Hz, 1H), 6.63 (t, J = 7.7 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 5.17 (s, 1H), 4.47 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 139.0, 138.3, 134.8, 134.0, 130.5, 129.6, 128.8, 128.6, 128.3, 127.0, 123.8, 119.3, 116.9, 114.3, 61.1, 21.3. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 230 nm, 30 °C, flow rate: 1.0 mL/min), t1 = 11.3 min, t2 = 17.0 min (major). HRMS Calculated for $C_{21}H_{19}N_2O$ $[M+H]^+$ 315.1492, found: 315.1492.

4.3. General procedure for Brønsted acid-promoted biomimetic reduction of benzoxazinones

A mixture of [Ru (*p*-cymene)I_2]$_2$ (0.7 mg, 0.00075 mmol), diphenyl hydrogen phosphate (1.5 mg, 0.006 mmol), (S_p)-CYNAM **3d** (5.1 mg, 0.015 mmol) and benzoxazinones **5** (0.15 mmol) in chloroform (3 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C under hydrogen gas (500 psi) for 48 h. After carefully release of the hydrogen, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate to give the reductive products **6**. The enantiomeric excesses were determined by chiral HPLC.

*4.3.1. (+)-(S)-3-Phenyl-3,4-dihydro-2H-benzo[b] [1,4]oxazin-2-one (**6a**)*

32 mg, 95% yield, white solid, known compound, R_f = 0.60 (hexanes/ethyl acetate 5/1), 98% e. e., $[\alpha]_D^{20}$ = +117.18 (*c* 0.64, $CHCl_3$), [lit [37].: $[\alpha]_D^{20}$ = +106.5 (*c* 0.4, $CHCl_3$) for 97% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 5H), 6.98–6.89 (m, 2H), 6.80–6.74 (m, 1H), 6.71 (d, J = 7.9 Hz, 1H), 4.94 (s, 1H), 3.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 140.9, 136.4, 132.4, 129.0, 127.5, 125.2, 120.4, 117.0, 115.0, 59.3. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 230 nm, 30 °C, flow rate: 0.7 mL/min), t1 = 10.8 min, t2 = 14.6 min (major).

*4.3.2. (+)-(S)-6-Chloro-3-phenyl-3,4-dihydro-2H-benzo[b] [1,4]-oxazin-2-one (**6b**)*

36 mg, 92% yield, white solid, known compound, R_f = 0.60 (hexanes/dichloromethane 1/1), >99% e. e., $[\alpha]_D^{20}$ = +142.35 (*c* 0.72, $CHCl_3$), [lit [27].: $[\alpha]_D^{15}$ = −109.9 (*c* 0.90, $CHCl_3$) for 89% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 5H), 6.97 (d, J = 8.2 Hz, 1H), 6.88–6.80 (m, 2H), 5.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5,

139.3, 136.0, 133.2, 130.2, 129.2, 129.1, 127.3, 120.1, 118.0, 114.7, 58.8. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 230 nm, 30 °C, flow rate: 0.7 mL/min), t1 = 10.4 min, t2 = 14.9 min (major).

4.3.3. (+)-(S)-3-Butyl-3,4-dihydro-2H-benzo[b] [1,4]oxazin-2-one (**6c**)

28 mg, 91% yield, white solid, known compound, R_f = 0.70 (hexanes/ethyl acetate 10/1), >99% e. e., $[\alpha]_D^{20}$ = +26.25 (*c* 0.56, $CHCl_3$), [lit [33].: $[\alpha]_D^{20}$ = −43.75 (*c* 0.56, $CHCl_3$) for 99% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97–6.87 (m, 2H), 6.80–6.73 (m, 1H), 6.73–6.68 (m, 1H), 3.84 (dd, *J* = 7.7, 5.2 Hz, 1H), 3.56 (br s, 1H), 1.90–1.80 (m, 1H), 1.75–1.65 (m, 1H), 1.42–1.26 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 141.1, 132.3, 125.0, 120.3, 116.8, 115.1, 54.8, 30.9, 27.4, 22.4, 13.9. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 230 nm, 30 °C, flow rate: 0.7 mL/min), t1 = 18.1 min, t2 = 23.4 min (major).

4.4. General procedure for Brønsted acid-promoted biomimetic reduction of benzoxazine

A mixture of [Ru (*p*-cymene)I_2]$_2$ (0.7 mg, 0.00075 mmol), diphenyl hydrogen phosphate (1.5 mg, 0.006 mmol), (S_p)-CYNAM **3d** (5.1 mg, 0.015 mmol) and 3-phenyl-2*H*-benzo [*b*] [1,4]oxazine **7** (0.15 mmol) in chloroform (3 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C under hydrogen (500 psi) for 48 h. After carefully release of the hydrogen, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate to give the reductive product **8**. The enantiomeric excesses were determined by chiral HPLC.

4.4.1. (+)-(S)-3-Phenyl-3,4-dihydro-2H-benzo[b] [1,4]oxazine (**8**)

31 mg, 98% yield, pale yellow oil, known compound, R_f = 0.80 (hexanes/dichloromethane 2/5), 96% e. e., $[\alpha]_D^{20}$ = +153.22 (*c* 0.62, $CHCl_3$), [lit [57].: $[\alpha]_D^{22}$ = −147.8 (*c* 1.14, $CHCl_3$) for 98% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 5H), 6.79–6.69 (m, 2H), 6.65–6.55 (m, 2H), 4.43–4.38 (m, 1H), 4.22–4.17 (m, 1H), 3.94–3.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.1, 133.7, 128.9, 128.4, 127.3, 121.5, 119.1, 116.7, 115.5, 70.9, 54.3. HPLC (OD-H, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 230 nm, 30 °C, flow rate: 0.7 mL/min), t1 = 11.9 min, t2 = 15.7 min (major).

4.5. General procedure for Brønsted acid-promoted biomimetic reduction of alkynyl ketimines

A mixture of [Ru (*p*-cymene)I_2]$_2$ (0.7 mg, 0.00075 mmol), diphenyl hydrogen phosphate (1.5 mg, 0.006 mmol), (S_p)-CYNAM **3d** (5.1 mg, 0.015 mmol) and alkynyl ketimines **9** (0.15 mmol) in chloroform (3 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C under hydrogen gas (500 psi) for 48 h. After carefully release of the hydrogen, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate to give the reductive products **10**. The enantiomeric excesses were determined by chiral HPLC.

4.5.1. (−)-(R)-4-Methoxy-N-(1,1,1-trifluoro-4-phenylbut-3-yn-2-yl)aniline (**10a**)

44 mg, 96% yield, yellow oil, known compound, R_f = 0.80 (hexanes/ethyl acetate 30/1), >99% e. e., $[\alpha]_D^{20}$ = −255.32 (c 0.88, $CHCl_3$), [lit [31].: $[\alpha]_D^{20}$ = = −231.28 (c 1.16, $CHCl_3$) for 95% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 2H), 7.29–7.18 (m, 3H), 6.78–6.66 (m, 4H), 4.67 (q, *J* = 6.2 Hz, 1H), 3.68 (s, 3H), 3.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 138.8, 132.0, 129.1, 128.4, 123.8 (q, *J* = 279.9 Hz), 121.5, 119.58, 117.0, 114.9, 86.3, 80.8 (q, *J* = 2.1 Hz), 55.7, 52.2 (q, *J* = 33.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.64. HPLC (AD-H, elute: n-Hexane/i-PrOH = 95/5, detector: 254 nm, 30 °C, flow rate: 0.8 mL/min), t1 = 11.3 min, t2 = 12.2 min (major).

4.5.2. (−)-(R)-4-Methoxy-N-(1,1,1-trifluoro-4-(p-tolyl)but-3-yn-2-yl)aniline (**10b**)

45 mg, 94% yield, pale yellow oil, known compound, R_f = 0.70 (hexanes/dichloromethane 1/1), >99% e. e., $[\alpha]_D^{20}$ = −261.29 (*c* 0.84, $CHCl_3$), [lit [31].: $[\alpha]_D^{20}$ = −288.76 (*c* 0.90, $CHCl_3$) for 95% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.86–6.72 (m, 4H), 4.80–4.67 (m, 1H), 3.76 (s, 3H), 3.76 (br s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 139.4, 139.0, 131.9, 129.1, 123.8 (q, *J* = 280.2 Hz), 118.4, 116.9, 114.9, 86.5, 80.2 (d, *J* = 2.0 Hz), 55.7, 52.2 (q, *J* = 33.7 Hz), 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.72. HPLC (AS-H, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, 30 °C, flow rate: 0.8 mL/min), t1 = 8.5 min, t2 = 9.4 min (major).

4.5.3. (−)-(R)-4-Methoxy-N-(1,1,1-trifluoro-4-(4-methoxyphenyl)-but-3-yn-2-yl)aniline (**10c**)

50 mg, 99% yield, pale yellow oil, known compound, R_f = 0.70 (hexanes/dichloromethane 2/5), >99% e. e., $[\alpha]_D^{20}$ = −236.88 (*c* 1.00, $CHCl_3$), [lit [31].: $[\alpha]_D^{20}$ = −239.65 (*c* 1.20, $CHCl_3$) for 95% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 2H), 6.93–6.66 (m, 6H), 4.83–4.62 (m, 1H), 3.79 (s, 3H), 3.76 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 154.1, 139.0, 133.5, 123.8 (q, *J* = 280.0 Hz), 116.9, 114.9, 114.0, 113.5, 86.3, 79.5 (d, *J* = 1.8 Hz), 55.7, 55.3, 52.2 (q, *J* = 33.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.74. HPLC (AD-H, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, 30 °C, flow rate: 0.8 mL/min), t1 = 20.3 min, t2 = 21.7 min (major).

4.6. General procedure for Brønsted acid-promoted biomimetic reduction of quinolines

A mixture of [Ru (*p*-cymene)I_2]$_2$ (0.7 mg, 0.00075 mmol), diphenyl hydrogen phosphate (1.5 mg, 0.006 mmol), (S_p)-CYNAM **3d** (5.1 mg, 0.015 mmol) and quinolines **11** [56] (0.15 mmol) in $CHCl_3$/THF (3:1) (3 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The hydrogenation was performed at 40 °C under hydrogen (500 psi) for 48 h. After carefully release of the hydrogen, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using hexanes and ethyl acetate to give the reductive products **12**. The enantiomeric excesses were determined by chiral HPLC.

4.6.1. (+)-(R)-2-Phenyl-1,2,3,4-tetrahydroquinoline (**12a**)

30 mg, 96% yield, colorless oil, the known compound, R_f = 0.70 (hexanes/ethyl acetate 10/1), 97% e. e., $[\alpha]_D^{20}$ = +39.50 (*c* 0.60, $CHCl_3$), [lit [27].: $[\alpha]_D^{19}$ = −35.7 (*c* 0.80, $CHCl_3$) for 91% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 4H), 7.22–7.17 (m, 1H), 6.97–6.87 (m, 2H), 6.57 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 4.34 (dd, *J* = 9.3, 3.1 Hz, 1H), 4.11 (br s, 1H), 2.88–2.79 (m, 1H), 2.68–2.61 (m, 1H), 2.07–2.00 (m, 1H), 1.96–1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 144.6, 129.4, 128.7, 128.6, 127.5, 127.0, 126.6, 121.1, 117.4, 114.2, 56.3, 31.0, 26.4. HPLC (AS-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 254 nm, 30 °C, flow rate: 0.7 mL/min), t1 = 7.1 min (major), t2 = 15.9 min.

4.6.2. (+)-(R)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoline (**12b**)

34 mg, 93% yield, white solid, the known compound, R_f = 0.70

(hexanes/ethyl acetate 20/1), 95% e. e., $[\alpha]_D^{20} = +42.64$ (*c* 0.68, $CHCl_3$), [lit [27].: $[\alpha]_D^{20} = -36.0$ (*c* 0.92, $CHCl_3$) for 91% e. e.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 4H), 6.96–6.87 (m, 2H), 6.58 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 7.9 Hz, 1H), 4.32 (dd, *J* = 9.1, 3.2 Hz, 1H), 4.01 (br s, 1H), 2.86–2.76 (m, 1H), 2.65–2.58 (m, 1H), 2.04–1.96 (m, 1H), 1.91–1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 143.3, 133.1, 129.4, 128.7, 128.0, 127.0, 120.9, 117.6, 114.2, 55.6, 31.0, 26.2. HPLC (AS-H, elute: *n*-Hexane/*i*-PrOH = 85/15, detector: 254 nm, 30 °C, flow rate: 0.8 mL/min), t1 = 8.0 min (major), t2 = 15.7 min.

Declaration of competing interest

The authors declare that they have no known competing financialinterestsor personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131968.

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