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Chiral sulfinamidourea/Strong Brønsted Acid co-catalyzed enantioselective Povarov reaction to access tetrahydroquinolines

Hao Xu, **Hu Zhang**, and **Eric N. Jacobsen**

SUMMARY

This protocol describes a method for the laboratory synthesis of chiral tetrahydroisoquinolines, bicyclic organic framework present in a wide assortment of natural and synthetic biologically important compounds. The methodology involves the use of a two-catalyst system: an achiral strong Brønsted acid, together with a chiral urea derivative. The anion-binding properties of the urea lead to association of the ion pair that results from protonation of the imine substrate. Cycloaddition with electron-rich olefins in a [4+2] pathway, followed by spontaneous proton loss and rearomatization leads to the tetrahydroisoquinoline products in highly enantioenriched form.

INTRODUCTION

Strong Brønsted acids (HX) accelerate a wide variety of important reactions by protonating neutral substrates and thereby enhancing their electrophilicity and therefore their reactivity toward nucleophiles (Nu–H).[1] While the simple proton (H^+) itself is not chiral, asymmetric induction in Brønsted acid-catalyzed reactions can be achieved through the design of strong acids with chiral conjugate bases (X^{*-}). Chiral phosphoric acids,[2,3] *N*-triflyl phosphoramides,[4] aryl sulfonic acids,[5] and Lewis acid-assisted strong Brønsted acids[6] are representative examples of chiral strong Brønsted acids[7] that have been developed successfully (Figure 1A).

The anion-binding properties of neutral, chiral H-bond donors[8–10] introduce an alternate strategy for asymmetric induction in strong Brønsted acid-catalyzed reactions (Figure 1B). In this scenario, a chiral H-bond donor such as a urea can associate with a protonated substrate through the negatively charged conjugate base, and it may control the facial selectivity of subsequent nucleophilic addition reactions through appropriate non-covalent interactions in the resulting ion pair. This strategy was exploited successfully in the context of formal [4+2] cycloadditions of *N*-aryl imines with electron-rich olefins, also known as the Povarov[11] reaction (Figure 2).[12,13] This reaction is co-catalyzed by (*R*,*R*,*R*)-sulfinamide urea **1**[17] and *o*-nitrobenzenesulfonic acid (NBSA), and affords tetrahydroquinolines with up to three contiguous stereogenic centers directly from simple achiral precursors. Alternative and

H.X. designed and performed the experiments, and co-wrote the paper. H.Z. performed the synthesis of catalyst **1.** E.N.J. designed and supervised the experiments, analysed data, and co-wrote the paper.

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complementary enantioselective variants of the Povarov reaction have also been uncovered recently using chiral Lewis acid[14] and phosphoric acid catalysts.[15,16]

Under optimized conditions, the asymmetric catalytic Povarov reaction was found to proceed effectively in cycloadditions of enamide **3** or ene-carbamate **4** with a wide variety of *N*-aryl imines (Figure 3). High levels of enantioselectivity were observed in reactions that were performed under cryogenic conditions with a 2:1 ratio of catalyst **1** to NBSA. Reactions of benzaldimines **2** with vinylpyrrolidinone **3** afford pyrrolidinone-substituted tetrahydroquinolines $\mathbf{5_{exo}}$ with high enantio- and diastereoselectivities (Figure 4). Tricyclic hexahydropyrrolo-[3,2-c]quinolines $\mathbf{6_{exo}}$ were obtained under the same conditions through the cyclization of *N*-Cbz–protected 2,3-dihydropyrrole **4** with **2** (Figure 3). Although lower diastereoselectivities favoring the exo isomer were obtained in this reaction ($\mathbf{6_{exo}}$/$\mathbf{6_{endo}}$ = 1.4 to 4.2:1), the exo product was generated in high *ee* (90 to 98% *ee)* and could be isolated in diastereomerically pure form in useful yields (45 to 73%, Figure 5).

A very similar reaction protocol could be applied to highly enantioselective Povarov reactions between glyoxylate imines **7a** or **7b** with 2,3-dihydropyrrole **4** (Figure 6A). In this case, the catalytic reaction selectively affords the endo products (*dr* > 20:1, 95–97% *ee*). This transformation provides a direct route to the core tetrahydroquinoline structure of a variety of biologically active compounds, including martinelline (**9**, Figure 6B), a naturally occurring nonpeptide natural product that has been identified as a bradykinin B1 and B2 receptor antagonist.[18,19,20] An analogous reaction has also been applied successfully to the preparation of a 2328-membered library of 2,3,4-trisubstituted tetrahydroquinolines (Figure 6C).[13]

Experimental design

The catalytic asymmetric synthesis of a pyrrolidinone-substituted tetrahydroisoquinoline **5b** and a tricyclic hexahydropyrrolo-[3,2-c]quinoline **8b** are described in this protocol as two representative examples (Figure 7).

MATERIALS

REAGENTS

Catalyst **1** was prepared by the procedure in Box 1, as adapted from the literature procedure.[17]

Compounds **2b**, **4** and **7b** were prepared in accordance with literature procedures.[21,22,23]

2-Nitrobenzenesulfonic acid (Aldrich, cat. no. 127698)

2, 3-Dihydrofuran (Aldrich, cat. no. 200018)

1-Vinylpyrrolidin-2-one (**3**) (1-Vinyl-2-pyrrolidinone, Aldrich, cat. no. V3409)

Pyrrolidine (Aldrich, cat. no. W352316)

Benzyl chloroformate (Aldrich, cat. no. 119938)

Ethyl glyoxalate (Aldrich, cat. no. 50705)

4-Chloroaniline (Aldrich, cat. no. 477222)

Benzaldehyde (Aldrich, cat. No. B1334)

Methyl 4-aminobenzoate (Aldrich, cat. No. 274186)

Toluene, anhydrous

5 Å powdered molecular sieves

Et_3N (Aldrich)

Dichloromethane

Methanol

Hexanes

Ethyl acetate

Sodium sulfate, anhydrous

Brine (saturated aqueous NaCl solution)

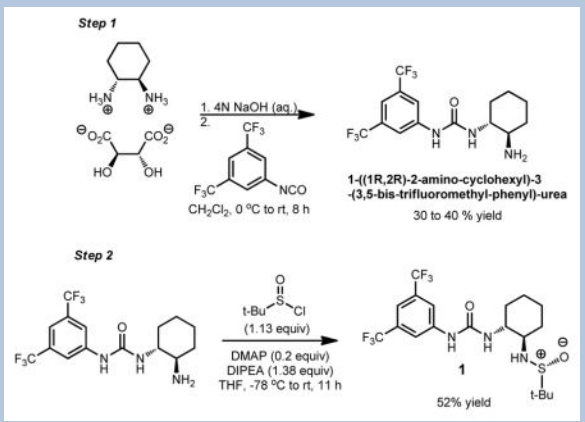
Saturated aqueous $NaHCO_3$

Thin-layer chromatography (TLC) (Silica gel $60F_{254}$, layer thickness 250 μm, EMD Chemicals Inc.)

Silica gel (Silica Gel for Flash Chromatography, 60Å, 40–63 μm, Sorbent Technologies, cat. no. 40930-25)

Box 1

Synthesis of Povarov catalyst 1



REAGENTS

- 3,5-Bis(trifluoromethyl)phenyl isocyanate (Aldrich, cat. No. 374857)
- (*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate[24]
- N,N-Diisopropylethylamine (Aldrich, cat. No. 387649)

- 4-(Dimethylamino)pyridine (Aldrich, cat. No. 107700)
- tert-butylsulfinyl chloride (Aldrich, cat. No. 569437)
- 1N HCl (EMD Chemicals Inc., cat. No. HX0603-4) solution
- Saturated $NaHCO_3$ (Mallinckrodt Chemicals, cat. No. 7412-06) aqueous solution
- 4N Sodium hydroxide (Macron Fine Chemicals, cat. No. 7708-06) aqueous solution
- THF, anhydrous (VWR)
- Dichloromethane (VWR)
- Methanol (VWR)
- Aqueous ammonia, 28~30% (wt/vol) (BDH, cat. No. BDH3014)
- Anhydrous sodium sulfate (VWR)
- Thin-layer chromatography (TLC) (Silica gel $60F_{254}$, layer thickness 250 μm, EMD Chemicals Inc.)
- Silica gel (Silica Gel for Flash Chromatography, 60Å, 40–63 μm, Sorbent Technologies, cat. no. 40930-25)

EQUIPMENT

- Syringe pump
- Rotary evaporator
- Chromatographic columns

Step 1 Synthesis of 1-((1R,2R)-2-amino-cyclohexyl)-3-(3,5-bis-trifluoromethyl-phenyl)-urea

● **TIMING 10 h**

PROCEDURE

1. Weigh out (*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate (7.77 g, 29.4 mmol) in a 125 mL Erlenmeyer flask, and dissolve in 20 mL dichloromethane.
2. Introduce 4N sodium hydroxide solution (40 mL) into the flask and stir the biphasic mixture with a magnetic stirring bar for 10 minutes.
3. Separate the two phases in a 250 mL separatory funnel, and wash the aqueous phase with dichloromethane (3×20 mL)
4. Dry the combined organic phases with anhydrous sodium sulfate (10 g), and filter the mixture through a funnel lined with filter paper.
5. Concentrate the filtrate in a 250 mL round-bottom flask by rotary evaporation to obtain crude (*R*,*R*)-1,2-Diammoniumcyclohexane.

6. Dissolve the crude (*R,R*)-1,2-Diammoniumcyclohexane in 40 mL dichloromethane and cool the solution to 0 °C.
7. Add a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (2.5 g, 9.8 mmol) in dichloromethane (10 mL) by syringe pump (2 mL/h).
8. After the completion of addition, stir the solution at room temperature for 3 hours, and then concentrate the solution by rotary evaporation.
9. Pack a chromatography column (4.0 cm i.d. x 16 cm length) with silica gel (100 g) using a mixture of dichloromethane/methanol/aqueous ammonia (95:5:1, vol/vol/vol) as eluent.
10. Dissolve the crude product in eluent (4 mL) and load it to the column.
11. Elute the column using the mixture of DCM/methanol/aqueous ammonia (gradient from 95:5:1 to 90:10:1, vol/vol/vol)
12. Analyze the contents of the collected fractions by thin-layer chromatography (DCM/methanol/aqueous ammonia, 90:10:1, vol/vol/vol); the R_f of the product is at approximately 0.1.
13. Combine fractions containing the product, dry with anhydrous sodium sulfate (50 g), filter, and concentrate by rotary evaporation.
14. Dry the product under high vacuum.

Step 2. Synthesis of Povarov catalyst **1**

● **TIMING 12 h**

PROCEDURE

1. Add THF (50 mL) into a 250 mL round-bottom flask, and cool the flask to −78 °C.
2. Add tert-butylsulfinyl chloride (0.23 mL, 1.84 mmol), N,N-Diisopropylethylamine (0.39 mL, 2.25 mmol), and 4-(Dimethylamino)pyridine (40 mg, 0.33 mmol) subsequently into the flask.
3. After stirring for 5 minutes, add 1-((1R,2R)-2-amino-cyclohexyl)-3-(3,5-bis-trifluoromethyl-phenyl)-urea (0.60 g, 1.63 mmol) in single portion into the flask.
4. Stir the reaction mixture at −78 °C for 4 hours and then warm up to room temperature slowly in 7 hours.
5. Quench the reaction with MeOH (5 mL), and remove the solvent using the rotary evaporator.
6. Dissolve the residue in ethyl acetate (20 mL) and wash the organic layer with 1N HCl (20 mL) and Saturated $NaHCO_3$ aqueous solution (20 mL)
7. Dry the organic layer with anhydrous sodium sulfate (10 g) and filter by filter funnel.
8. Remove the solvent in the filtrate using the rotary evaporator.

9. Pack a chromatography column (4.0 cm i.d. x 16 cm length) with silica gel (100 g) using a mixture of DCM/methanol (99.25:0.75, vol/vol) as eluent.
10. Dissolve the crude product in eluent (2 mL) and load it to the column.
11. Elute the column using the mixture of DCM/methanol (gradient from 99.25:0.75 to 97:3, vol/vol)
12. Analyze the contents of the collected fractions by thin-layer chromatography (DCM/methanol, 95:5, vol/vol); R_f of the product is found at 0.2.
13. Combine fractions containing the product and evaporate the solvent using rotary evaporator.
14. Dry the product under high vacuum.

EQUIPMENT

Round-bottomed flasks

Dual argon vacuum manifold with vacuum line

Rubber septa

Disposable syringes and injection needles

Rotary evaporator

Chromatographic columns

Immersion cooler

^{1}H NMR and ^{13}C NMR spectrometers

High Performance Liquid Chromatography (HPLC) or Supercritical Fluid Chromatography (SFC) and chiral analytical stationary phase

Electrospray (ESI) mass spectrometer

Infrared spectrometer

Polarimeter

REAGENT SETUP

All commercially available reagents were used as received unless noted otherwise. 2,3-Dihydrofuran and 1-vinylpyrrolidin-2-one were distilled prior to use. 5 Å molecular sieves were activated by flame-drying in a flask under vacuum and then storing in a vacuum oven at 120 °C. 2-Nitrobenzenesulfonic acid (NBSA) is obtained commercially as a hydrate. It can be used as a solid hydrate as described in the Procedure for the preparation of **5b**, or 0.1 M stock solutions can be prepared by dissolving NBSA·xH_2O in anhydrous diethyl ether with 5A activated sieves (20 mg sieves/1 mL solvent) and stored under argon up to 24 h.

PROCEDURE

Synthesis of 5b. Total time required: 80 h

1. In a 10 mL oven-dried round-bottom flask, charge *N*-benzylidene-4-chloroaniline **2b** (86 mg, 0.4 mmol), 2-nitro-benzenesulfonic acid (4.0 mg, 0.02 mmol), catalyst **1** (18.8 mg, 0.04 mmol), activated 5 Å molecular sieves (40 mg) at room temperature.
2. Introduce anhydrous toluene (5 mL) and a teflon-coated magnetic stir bar to the flask under a nitrogen atmosphere.
3. Cool the reaction mixture to −40 °C with an immersion cooler and stir for 10 min.
4. Add 1-vinylpyrrolidin-2-one **3** (0.30 mL of a 2.0 M toluene solution, 0.60 mmol) dropwise and allow the resulting solution to stir vigorously for 72 h.
5. Quench the reaction with pre-cooled Et_3N (−40 °C, 0.28 mL, 2.0 mmol).
6. Pour the resulting mixture into a separatory funnel filled with 5 mL of saturated $NaHCO_3$. Extract the organic material with ethyl acetate (10 mL x 2) and combine the organic phases.
7. Wash the organic phase with brine (10 mL).
8. Dry the organic phase over anhydrous sodium sulfate (ca. 10 g) and filter.
9. Transfer the organic solution into a 50-mL round-bottomed flask, and concentrate by rotary evaporation at 35 °C.
10. Purify the desired product by a flash chromatography column packed with silica gel (1.5 cm i.d. x 20 cm length) with hexanes/EtOAc as a eluent (gradient from 10:1 to 1:1) to afford **5b** as a colorless oil.

Synthesis of 8b Timing 4 h

1. Charge a 10-mL oven-dried round-bottom flask with freshly made (*E*)-methyl 4-((2-ethoxy-2-oxoethylidene)amino)benzoate **7b** (94 mg, 0.4 mmol), catalyst **1**(7.6 mg, 0.016 mmol), benzyl 2,3-dihydropyrrole-1-carboxylate **4** (0.22 mL of a 2.0 M toluene stock solution, 0.44 mmol), and activated 5 Å molecular sieves (40 mg) at room temperature.
2. Introduce anhydrous toluene (5 mL) and a teflon-coated magnetic stir bar to the flask under a nitrogen atmosphere.
3. Cool the reaction mixture to −60 °C with an immersion cooler and stir for 10 min.
4. Add 2-nitrobenzenesulfonic acid (1.6 mg, 0.008 mmol, as 0.1M stock solution in Et_2O), dropwise and allow the resulting solution to stir vigorously for 1.5 h at −60 °C.
5. Quench the reaction with pre-cooled Et_3N (−60 °C, 0.28 mL, 2.0 mmol).

6. Pour the reaction mixture into a separatory funnel filled with 5 mL of saturated $NaHCO_3$. Extract the organic material with ethyl acetate (10 mL x 2) and combine the organic phases.
7. Wash the organic phase with brine (10 mL).
8. Dry the organic phase over anhydrous sodium sulfate (ca. 10 g) and filter.
9. Transfer the organic solution into a 50-mL round-bottomed flask, and concentrate by rotary evaporation at 35 °C.
10. Purify the desired product by a flash chromatography column packed with silica gel (1.5 cm i.d. x 20 cm length) with hexanes/EtOAc as a eluent, gradient from 10:1 to 1:2) to afford **8b** as a white foam.

TROUBLESHOOTING

Low yield

A low yield can result from acid-catalyzed imine hydrolysis due to adventitious water. Since the commercially available NBSA exists in its hydrated form, freshly activated 5 Å molecular sieves should be used in order achieve reproducibly high yields.

ANTICIPATED RESULTS

Analytical data

1-((2*R*,4*S*)-6-chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (5b)—Yield 82–86%

5b was determined to be 98% *ee* by Chiral SFC analysis (Pirkle Covalent (*S*, *S*) Whelk, 3.0 mL/min, 230 nm, 22% MeOH in supercritical CO_2, t_r(minor) = 7.63 min, t_r(major) = 6.59 min). $[\alpha]^{25}_D$= −83.1° (c = 3.1, CH_2Cl_2)

IR (film) ν_{max}, 3336 (m), 1667 (s), 1605 (m), 1490 (m), 1420 (s), 1285 (m), 1269 (s) cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.25–7.37 (m, 5 H) 7.03 (dd, *J* = 8.58, 2.40 Hz, 1 H) 6.95 (d, *J* = 2.29 Hz, 1 H) 6.54 (d, *J* = 8.70 Hz, 1 H) 5.19 (t, *J* = 5.27 Hz, 1 H) 4.43 (dd, *J* = 9.61, 3.66 Hz, 1 H) 4.34 (br. s., 1 H) 3.35–3.42 (m, 1 H) 3.16–3.23 (m, 1 H) 2.44 (t, *J* = 8.13 Hz, 2 H) 2.23–2.30 (m, 1 H) 1.96–2.14 (m, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 174.8, 143.7, 142.9, 128.7, 128.5, 127.8, 126.2, 126.2, 122.0, 119.1, 115.6, 53.4, 45.7, 45.2, 35.6, 31.2, 18.3.

HRMS (ESI-TOF) for $C_{19}H_{19}ClN_2O$ [M + Na^+] calculated 349.1078, found 349.1078.

(3a*R*,4*R*,9b*R*)-1-benzyl 4-ethyl 8-methyl 3,3a,4,5-tetrahydro-2*H*-pyrrolo[3,2-*c*]quinoline-1,4,8(9b*H*)-tricarboxylates (8b)—Yield 73–79%

8b was determined to be 95% *ee* by Chiral SFC analysis (Pirkle Covalent (*S*, *S*) Whelk, 3.0 mL/min, 230 nm, 20% MeOH, t_r(minor) = 14.31 min, t_r(major) = 13.31 min). $[\alpha]^{25}_D$= 125.3° (c = 4.1, CH_2Cl_2)

IR (film) ν_{max}, 3366 (m), 2951 (m), 1737 (s), 1698 (s), 1415 (s), 1281 (s), 1209 (m), 1131 (m), 1102 (m) cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) rotamers, δ ppm 8.26 (s, 0.5 H) 8.15 (s, 0.5 H) 7.74 (d, *J* = 7.33 Hz, 0.5 H) 7.50 (d, *J* = 7.33 Hz, 0.5 H) 7.28–7.45 (m, 5 H) 6.55 (d, *J* = 8.70 Hz, 1 H) 5.18–5.48 (m, 2.5 H) 4.78 (d, *J* = 12.13 Hz, 0.5 H) 4.21–4.41 (m, 4 H) 3.82 (d, *J* = 8.70 Hz, 3 H) 3.50–3.72 (m, 1 H) 3.32–3.46 (m, 1 H) 2.92 (d, *J* = 7.10 Hz, 1 H) 1.79–2.00 (m, 2 H) 1.33 (t, *J* = 7.21 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$) rotamers, δ ppm 170.4, 166.8, 156.3, 155.3, 145.4, 132.3, 131.9, 130.2, 128.5, 128.4, 127.8, 120.3, 113.8, 67.6, 67.0, 61.9, 55.8, 53.3, 53.2, 51.6, 44.7, 38.8, 38.3, 25.4, 23.3, 22.3, 14.2.

HRMS (ESI-TOF) for $C_{24}H_{26}N_2O_6$ [M + Na^+] calculated 438.1791, found 438.1796.

References

1. Eigen M. Proton transfer acid-base catalysis: enzymatic hydrolysis. Part 1 elementary processes. Angew Chem Int Ed. 1964; 3:1–19.
2. Akiyama T, Itoh J, Yokota K, Fuchibe K. Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. Angew Chem Int Ed. 2004; 43:1566–1568.
3. Uraguchi D, Sorimachi K, Terada M. Organocatalytic asymmetric *aza*-Friedel-Crafts alkylation of furan. J Am Chem Soc. 2004; 126:11804–11805. [PubMed: 15382910]
4. Nakashima D, Yamamoto H. Design of chiral *N*-triflyl phosphoramide as a strong chiral Brønsted acid and its application to asymmetric Diels-Alder reaction. J Am Chem Soc. 2006; 128:9626–9627. [PubMed: 16866505]
5. Hatano M, Maki T, Moriyama K, Arinobe M, Ishihara K. Pyridinium 1,1′-binaphthyl-2,2′-disulfonates as highly effective chiral Brønsted acid-base combined salt catalysts for enantioselective Mannich-type reaction. J Am Chem Soc. 2008; 130:16858–16860. [PubMed: 19053478]
6. Ishihara K, Kaneeda M, Yamamoto H. Lewis-acid assisted chiral Brønsted acid for enantioselective protonation of silyl enol ethers and ketene bis(trialkyl silyl) acetals. J Am Chem Soc. 1994; 116:11179–11180.
7. Yamamoto H, Futatsugi K. “Designer acids”: Combined acid catalysis for asymmetric synthesis. Angew Chem Int Ed. 2005; 44:1924–1942.
8. Raheem IT, Thiara PS, Peterson EA, Jacobsen EN. Enantioselective Pictet-Spengler-type cyclizations of hydroxylactams: H-bond donor catalysis by anion binding. J Am Chem Soc. 2007; 129:13404–13405. [PubMed: 17941641]
9. Doyle AG, Jacobsen EN. Small-molecule H-bond donors in asymmetric catalysis. Chem Rev. 2007; 107:5713–5743. [PubMed: 18072808]
10. Schreiner PR, Wittkopp A. H-bonding additives act like Lewis acid catalysts. Org Lett. 2002; 4:217–220. [PubMed: 11796054]
11. Kouznetsov VV. Recent synthetic developments in a powerful imino Diels-Alder reaction (Povarov reaction): application to the synthesis of *N*-polyheterocycles and related alkaloids. Tetrahedron. 2009; 65:2721–2750.
12. Xu H, Zuend SJ, Woll MG, Tao Y, Jacobsen EN. Asymmetric Cooperative Catalysis of Strong Brønsted Acid-Promoted Reactions Using Chiral Ureas. Science. 2010; 327:986–990. [PubMed: 20167783]
13. Gerard B, et al. Application of a catalytic asymmetric Povarov reaction using chiral ureas to the synthesis of a tetrahydroquinoline library. ACS Combi Sci. 2012; 14:621–630.

14. Ishitani H, Kobayashi S. Catalytic asymmetric *aza* Diels-Alder reactions using a chiral lanthanide Lewis acid. Enantioselective synthesis of tetrahydroquinoline derivatives using a catalytic amount of a chiral source. Tetrahedron Lett. 1996; 37:7357–7360.
15. Akiyama T, Morita H, Fuchibe K. Chiral Brønsted acid-catalyzed inverse electron-demand *aza* Diels-Alder reaction. J Am Chem Soc. 2006; 128:13070–13071. [PubMed: 17017784]
16. Liu H, Dagousset G, Masson G, Retailleau P, Zhu JP. Chiral Brønsted acid-catalyzed enantioselective three-component Povarov reaction. J Am Chem Soc. 2009; 131:4598–4599. [PubMed: 19334771]
17. Tan KL, Jacobsen EN. Indium-mediated asymmetric allylation of acylhydrazones using a chiral urea catalyst. Angew Chem Int Ed. 2007; 46:1315–1317.
18. Witherup KM, et al. Martinelline and martinellic acid, novel G-protein linked receptor antagonists from the tropical plant *Martinella iquitosensis* (Bignoniaceae). J Am Chem Soc. 1995; 117:6682–6685.
19. Xia CF, Heng LS, Ma DW. Total synthesis of (+/−)-martinelline. Tetrahedron Lett. 2002; 43:9405–9409.
20. Batey RA, et al. A three-component coupling protocol for the synthesis of substituted hexahydropyrrolo[3,2-*c*]quinolines. Chem Commun. 1999:651–652.
21. Keinicke L, Fristrup P, Norrby PO, Madsen R. Nonradical Zinc Barbier Reaction for Diastereoselective Synthesis of Vicinal Amino Alcohols. J Am Chem Soc. 2005; 127:15756–15761. [PubMed: 16277518]
22. Kraus GA, Neuenschwander K. Facile synthesis of *N*-acyl-2-pyrrolines. J Org Chem. 1981; 46:4791–4792.
23. Trost BM, Marrs CM. A [3+2] cycloaddition and [4+3] cycloaddition approach to *N*-heterocycles via palladium-catalyzed TMM reactions with imines. J Am Chem Soc. 1993; 115:6636–6645.
24. Larrow JF, Jacobsen EN. (R,R)-N,N′-Bis(3,5-Di-tert-Butylsalicylidene)-1,2-Cyclohexanediamino Manganese(III) Chloride, A Highly Enantioselective Epoxidation Catalyst. Org Syn. 1998; 75:1.

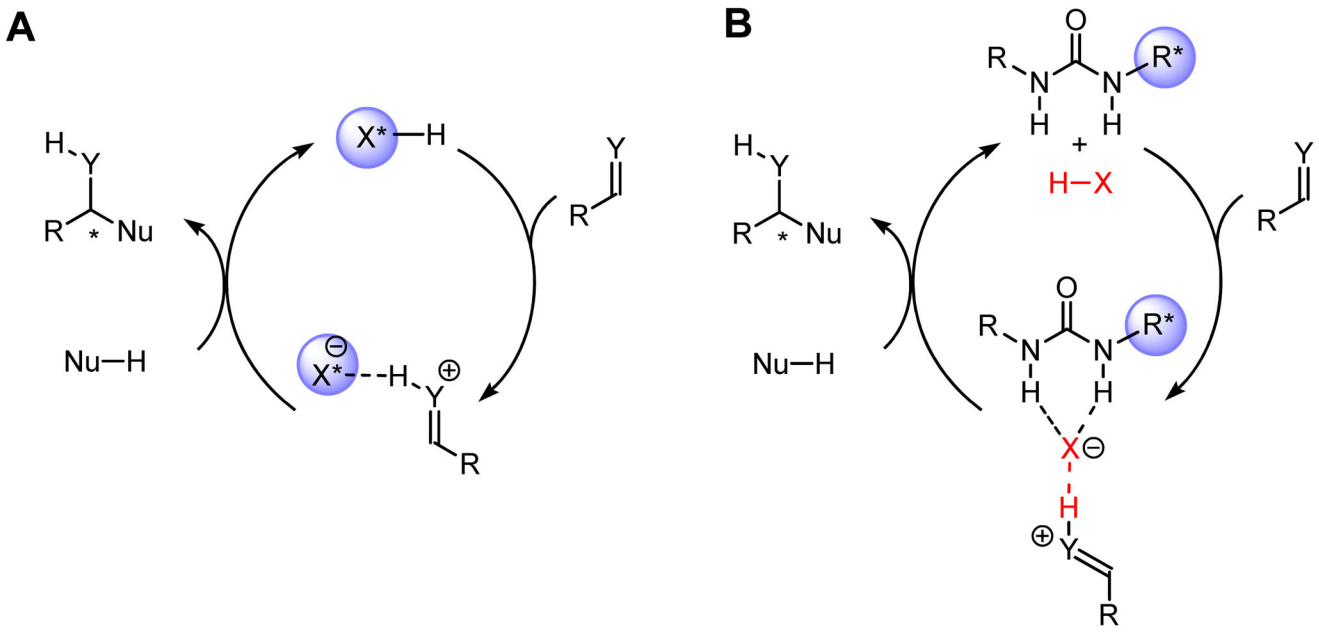


Figure 1.

Asymmetric catalysis by strong Brønsted acids. A) Use of chiral acids (H-X*). B) Use of achiral Brønsted acids (HX) together with a chiral urea co-catalyst.

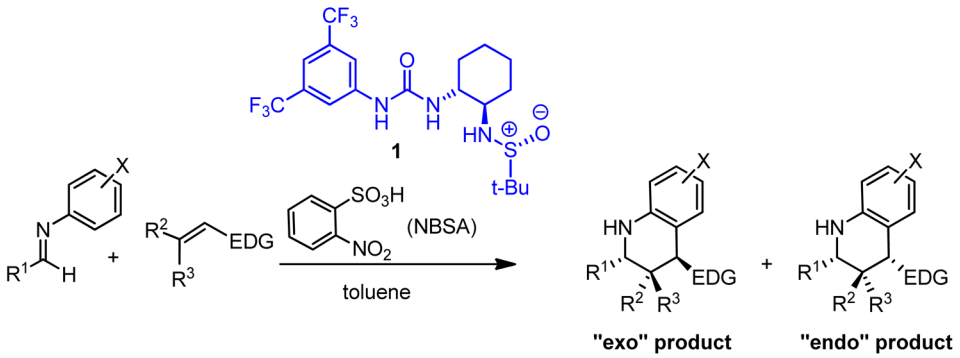


Figure 2.

Generalized Povarov reaction co-catalyzed by *o*-nitrobenzenesulfonic acid and chiral urea **1** (R^1, R^2, R^3, and X are organic substuents; EDG = electron-donating group).

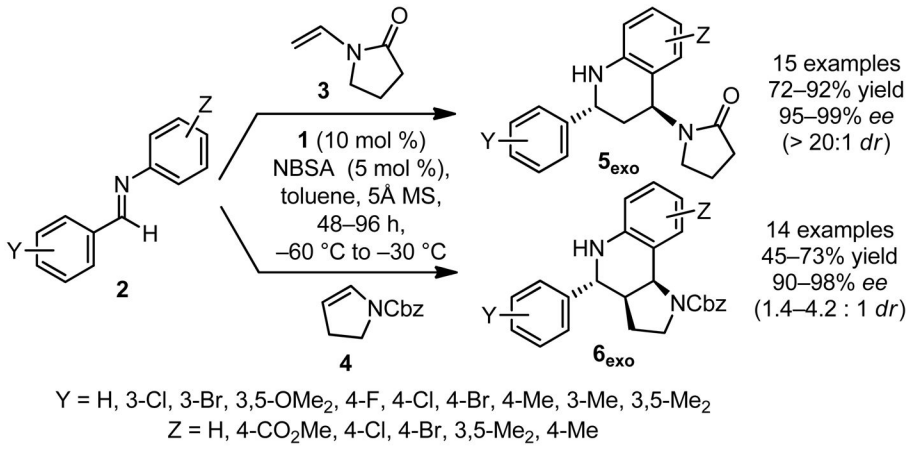


Figure 3.

Asymmetric Povarov reactions catalyzed by **1**/NBSA with enamide **3** or enecarbamate **4** as the nucleophilic reacting partners

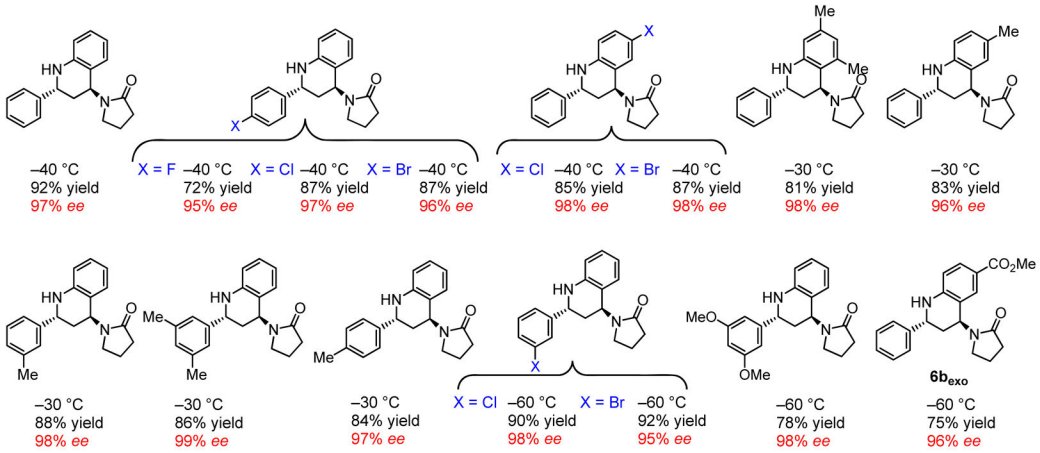


Figure 4.

Scope of the catalytic asymmetric Povarov reaction of *N*-aryl imines and enamide **3.**

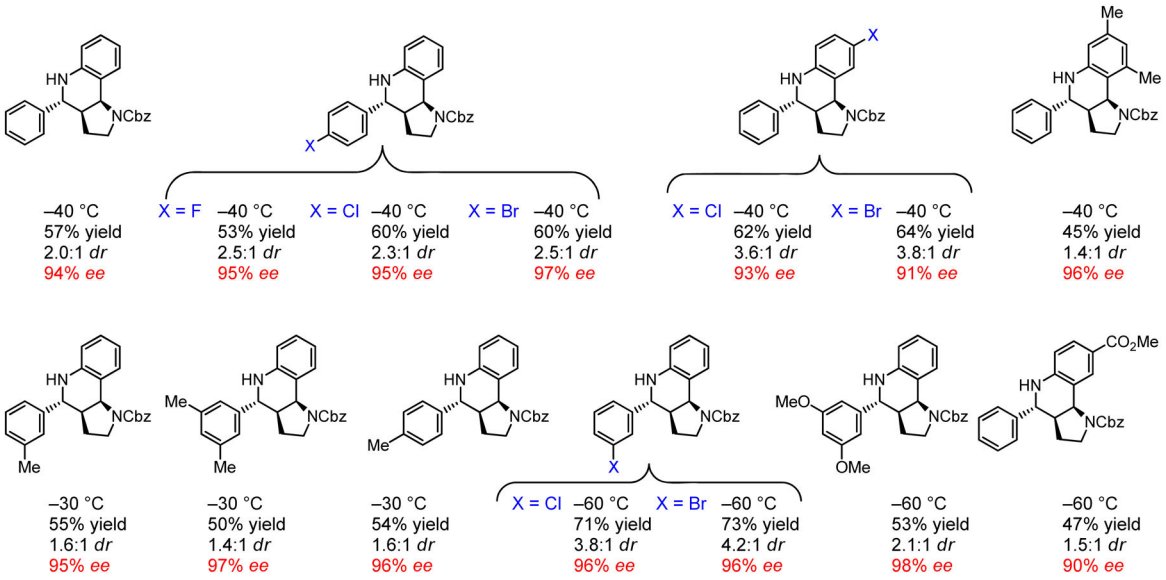


Figure 5.

Scope of the catalytic asymmetric Povarov reaction of *N*-aryl imines and enecarbamate **4**.

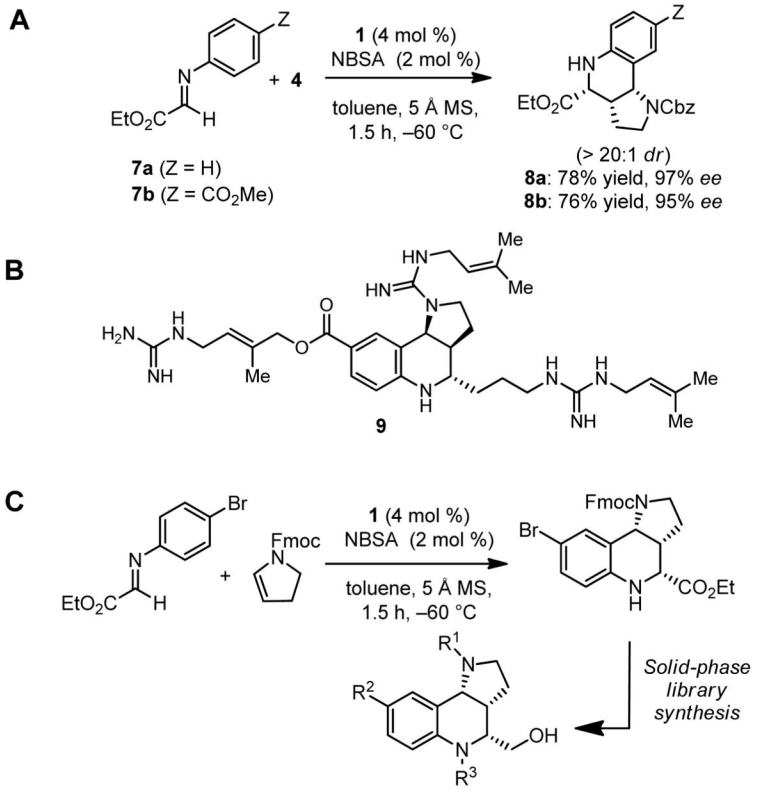


Figure 6.

A) Catalytic asymmetric Povarov reaction of ethyl 2-(arylimino)acetates and enecarbamate **4**; B) The enantioselective synthesis of **8b** constitutes a formal enantioselective synthesis of martinelline (**9**). C) Application to a 2328-membered library of 2,3,4-trisubstituted tetrahydroquinolines (R^1, R^2, R^3 = organic diversity elements.

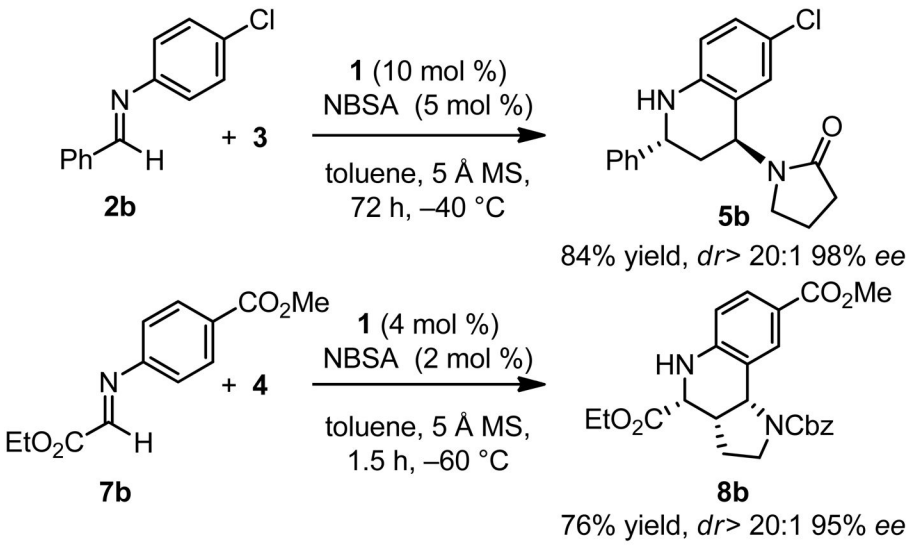


Figure 7.
Protocols for the asymmetric synthesis of **5b** and **8b**.