

Supporting Information  
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## **Asymmetric Neber Reaction in the Synthesis of Chiral 2-(Tetrazol-5-yl)-2H-Azirines**

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## **Supporting Information**

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## 1. Experimental section

NMR spectra were run in deuterium chloroform (CDCl<sub>3</sub>) or hexadeuterodimethyl sulfoxide (DMSO-*d*<sub>6</sub>) and recorded at the following frequencies: proton (<sup>1</sup>H, 400 MHz), carbon (<sup>13</sup>C, 100 MHz). Chemical shifts are expressed in parts per million related to internal TMS and coupling constants (*J*) are in hertz. IR spectra were recorded on a Fourier-transform spectrometer. High-resolution mass spectra (HRMS) were obtained on an electrospray (ESI)TOF mass spectrometer. Melting points were determined in open glass capillaries.

Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. Compounds **5**, **13a**, **13b** and **10b** were prepared following known procedures.<sup>1,2</sup>

### 1.1 General procedure for the optimized asymmetric synthesis of 2*H*-azirines **7**, **14a** and **14b**

To a solution of the appropriate β-ketoxime **5** and **13a-b** (0.15 mmol), K<sub>2</sub>CO<sub>3</sub> (1.50 mmol, 10 equiv.) and tosyl chloride (0.17 mmol, 1.1 equiv.) in toluene (4 mL) under a nitrogen atmosphere, was added the organocatalyst (18 or 20 mol %) in toluene (1 mL). The mixture was stirred for 48 h at the appropriate temperature. The solvent was evaporated under reduced pressure, and the crude reaction was dissolved in ethyl acetate (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography [ethyl acetate/hexane (1:1)].

#### *3-Phenyl-(1-(4-nitrobenzyl)-1*H*-tetrazol-5-yl)-2*H*-azirine (**7**).*

The product was prepared following the general procedure, using different organocatalysts: Using quinidine as catalyst led to the formation of the desired product (*R*)-**7** in 87% yield and 66% *ee*. With quinine, azirine (*S*)-**7** was afforded in 61% yield and 44% *ee* and with organocatalyst **12**, (*R*)-**7** was obtained in 51% yield and 92% *ee*. The characterization data for **7** agreed with those previously reported.<sup>1</sup>

#### *2-(1-(4-Nitrobenzyl)-1*H*-tetrazol-5-yl)-3-(thiophen-2-yl)-2*H*-azirine (**14a**).*

The product was prepared following the general procedure, using different organocatalysts: Using quinidine as catalyst led to the formation of the desired product

(*R*)-**14a** in 86% yield and 55% *ee*. With quinine, (*S*)-**14a** was afforded in 52% yield and 29% *ee* and with organocatalyst **12**, (*R*)-**14a** was obtained in 44% yield and 74% *ee*. The characterization data for **14a** agreed with those previously reported.<sup>1</sup>

*3-(Furan-2-yl)-2-(2-(4-nitrobenzyl)-2H-tetrazol-5-yl)-2H-azirine (14b)*.

The product was prepared following the general procedure, using different organocatalysts: Using quinidine as catalyst led to the formation of the desired product (*R*)-**14b** in 71% yield and 24% *ee*. With quinine, azirine (*S*)-**14b** was afforded in 41% yield and 8% *ee* and with organocatalyst **12**, (*R*)-**14b** was obtained in 57% yield and 8% *ee*. The characterization data for **14b** agreed with those previously reported.<sup>1</sup>

## 1.2. Procedure for the synthesis of the organocatalyst 6-APA derived thiourea **12**

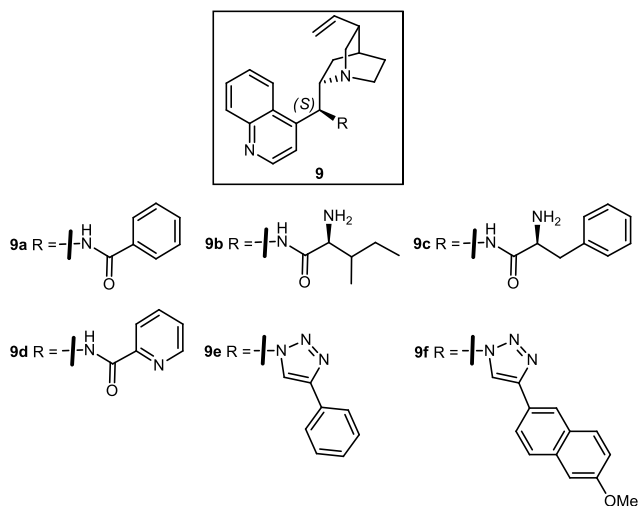
*(2S,6R)-Benzhydryl 6β-(3-(3,5-bis(trifluoromethyl)phenyl) thioureido)-aminopenicillanate (12)*

To a solution of benzhydryl 6β-aminopenicillanate **10b** (1.94 mmol, 0.74 g), under inert atmosphere in dry THF (3.5 mL) was added dropwise 3,5-bis(trifluoromethyl)phenyl isothiocyanate **11** (1.94 mmol, 0.35 mL). After stirring for 3 h at room temperature, the solvent was evaporated, and the crude product was purified by flash chromatography [eluting with ethyl acetate/hexane (1:2)] and recrystallized with diethyl ether/hexane. Yield: 48%; white solid; m.p.: 77.0-78.0 °C; IR (KBr)  $\nu$  = 682, 697, 1128, 1251, 1175, 1276, 1491, 1735, 2968, 2933, 3032, 3066, 3271, 3291  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.93 (s, 1H), 7.84 (s, 2H), 7.50 (s, 1H), 7.35-7.31 (m, 11H), 6.96 (s, 1H), 5.19 (d,  $J$  = 2 Hz, 1H), 4.25 (dd,  $J$  = 3.2 Hz,  $J$  = 1.2 Hz, 1H), 3.92 (s, 1H), 1.64 (s, 3H), 1.00 (s, 3H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 182.8, 170.6, 167.3, 139.1, 138.9, 133.9, 132.4 (q,  $J$  = 34.0 Hz, 2C), 128.8, 128.9, 128.6, 128.5, 128.2, 127.9, 127.7, 126.9, 126.8, 126.6, 124.1, 122.9 (m, 1C), 121.4, 78.7, 73.3, 66.5, 65.5, 65.1, 60.6, 26.3, 26.1 ppm;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 62.8 (s, 6F); HRMS (ESI)  $m/z$  calcd. for  $\text{C}_{30}\text{H}_{26}\text{F}_6\text{N}_3\text{O}_3\text{S}_2$  [ $\text{MH}^+$ ] 654.1314, found 654.1301.

### 1.3. Screening of *epi*-cinchonidine derivatives in the reaction model

The asymmetric Neber reaction of  $\beta$ -ketoxime **5** with a series of *epi*-cinchonidine derivatives in toluene and dichloromethane was also studied. The results are shown in table 1.

**Table 1.** *Epi*-cinchonidine derivative-assisted asymmetric Neber reaction of  $\beta$ -ketoxime **5**.



Entry	9	Solvent	Yield (%)	<i>ee</i> (%) <sup>a</sup>
1	<b>a</b>	Toluene	55	56 ( <i>R</i> )
2	<b>a</b>	CH <sub>2</sub> Cl <sub>2</sub>	41	43 ( <i>R</i> )
3	<b>b</b>	Toluene	30	24 ( <i>R</i> )
4	<b>b</b>	CH <sub>2</sub> Cl <sub>2</sub>	21	16 ( <i>R</i> )
5	<b>c</b>	Toluene	32	21 ( <i>R</i> )
6	<b>c</b>	CH <sub>2</sub> Cl <sub>2</sub>	19	21 ( <i>R</i> )
7	<b>d</b>	Toluene	52	18 ( <i>R</i> )
8	<b>d</b>	CH <sub>2</sub> Cl <sub>2</sub>	13	15 ( <i>R</i> )
9	<b>e</b>	Toluene	10	27 ( <i>R</i> )
10	<b>e</b>	CH <sub>2</sub> Cl <sub>2</sub>	21	6 ( <i>R</i> )
11	<b>f</b>	Toluene	4	14 ( <i>R</i> )
12	<b>f</b>	CH <sub>2</sub> Cl <sub>2</sub>	19	6 ( <i>R</i> )

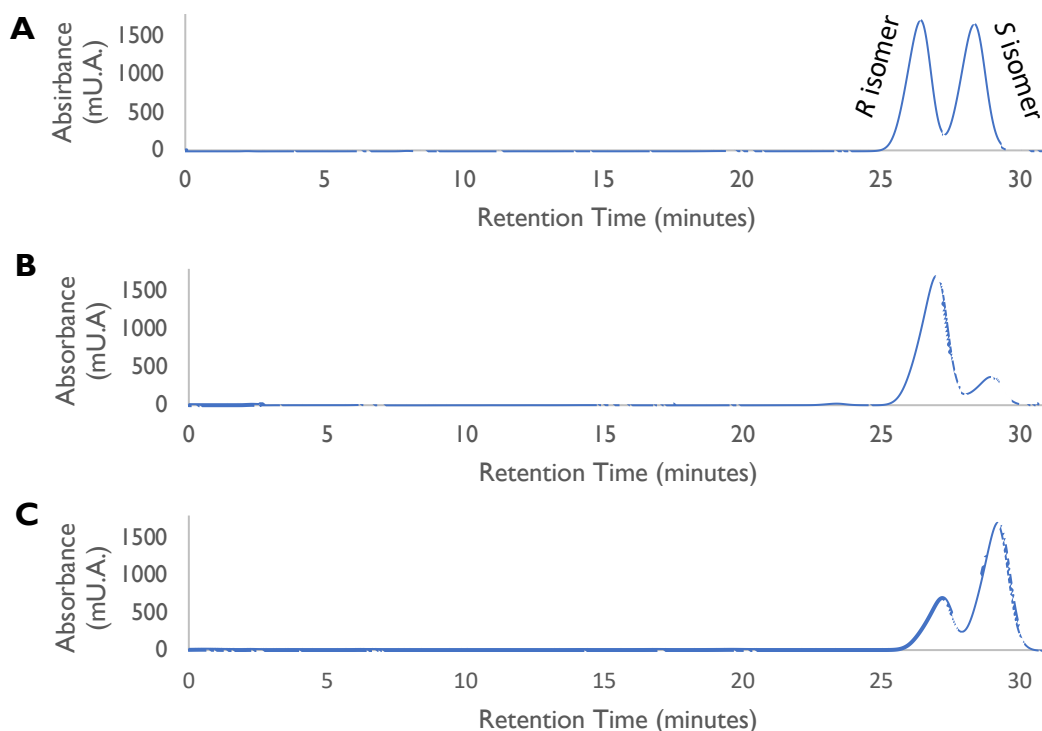
<sup>a</sup>Determined by HPLC analysis on a chiral stationary column.

## 2. HPLC methods

The enantiomeric excesses were obtained resorting on HPLC using a chiral column, CHIRALPAK IB (150x4.6 mm, 5  $\mu$ m) from Daicel Corporation. Before the sample analysis, a control test was carried out with a racemic mixture of 2-(tetrazol-5-yl)-2*H*-azirine (**7**, **14a** and **14b**) to ensure the efficiency of the separation of the two enantiomers. The HPLC methods were the following:

	Azirine <b>7</b>	Azirine <b>14a</b>	Azirine <b>14b</b>
<i><b>Eluent</b></i>	Acetonitrile/water (35/65)	Acetonitrile/water (30/70)	Acetonitrile/water (25/75)
<i><b>Flow Rate</b></i>	1 mL/min	1 mL/min	1 mL/min
<i><b>Temperature</b></i>	25 °C	26 °C	26 °C
<i><b>t<sub>1</sub></b></i>	≈ 26.5 min	≈ 23.4 min	≈ 55.5 min
<i><b>t<sub>2</sub></b></i>	≈ 28.5 min	≈ 26.0 min	≈ 58.5 min
<i><b>Analytical Injection</b></i>	20 $\mu$ L	20 $\mu$ L	20 $\mu$ L
<i><b>Absorption Wavelength</b></i>	250 nm	250 nm	250 nm
<i><b>Sample Concentration</b></i>	2 mg/mL	2 mg/mL	2 mg/mL

The areas are obtained by integration of the signals and in figure 1 are demonstrated examples of typical chromatograms obtained in the HPLC studies. Where **A** is a sample of a racemic mixture of 2*H*-azirine **7**, **B** is a sample of the quinidine-mediated Neber reaction product and **C** is a sample of the quinine-mediated Neber reaction product.

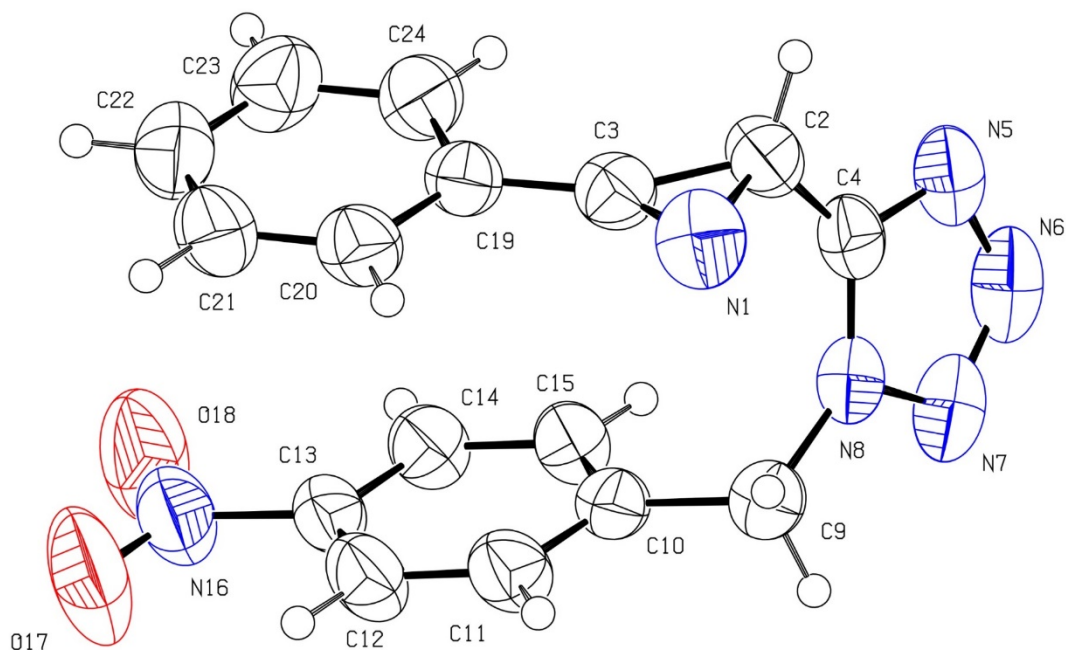


**Figure 1.** Typical chromatograms of (A) Racemic Mixture (B) Quinidine-mediated Neber reaction (C) Quinine-mediated Neber reaction for the model reaction.

### 3. Single crystal X-Ray Crystallography

The structure of 2*H*-azirine **7** was confirmed by single-crystal X-ray diffraction. Details of the data collection and crystallographic structure refinement are given in the supplementary data. The compound crystallizes in the centrosymmetric monoclinic space group  $P2_1/c$  with unit cell parameters  $a=15.228(4)$ ,  $b=7.231(2)$ ,  $c=13.866(4)$  Å,  $\beta = 97.008(11)^\circ$ . The unit cell contains 4 symmetry-related molecules (2 enantiomer pairs). An ORTEP plot of the molecule with the atom numbering scheme is depicted in Fig. 2.





**Fig 2.** ORTEP diagram of *2H*-azirines, with anisotropic displacement ellipsoids drawn at the 50% probability level.

Bond lengths and angles in this molecule are within the expected average ranges reported in the CCSD database, the exceptions being bond lengths C2–C4 (1.455(3) Å) and C19–C3 (1.440(3) Å) which are shorter than average values. The azirine N1=C3 double bond length is 1.256(3) Å whereas the N1–C2 single bond length is 1.549(3) Å. The C2–N1=C3 angle is 61.41(16)°. The phenyl and nitrobenzyl rings are in a *syn, syn* conformation and almost parallel, the angle between the least-squares planes of the two rings being 9.76(9)°. The tetrazole ring is almost perpendicular to each of the aromatic rings (dihedral angles of 85.11(8)° and 75.35(9)° for rings C10..C15 and C19..C24, respectively). The observed molecular conformation in the crystal maximizes the  $\pi$ - $\pi$  interaction between the electron clouds of the phenyl rings and minimizes steric repulsion effects. As the molecule lacks any strong H-bonding donor, the only significant intermolecular interactions spotted in the crystal structure involve C–H groups acting as donors (D) and N or O atoms as acceptors (A), namely C(15)–H(15)...N(5)<sup>i</sup>, *i* = 1-*x*, 1-*y*, 1-*z* (D...A = 3.435(4) Å) and C(22)–H(22) ...O(17)<sup>ii</sup>, *ii* = 2-*x*, -1/2+*y*, 3/2-*z* (D...A = 3.466(3)

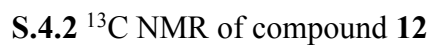
Å). In addition, the two short intramolecular contacts C(9)–H(9A)...N(1) (D...A = 3.102(3) Å) and C(15)–H(15) ...N(8) (2.861(3) Å) deserve to be remarked.

CCDC 1958457 contains the crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

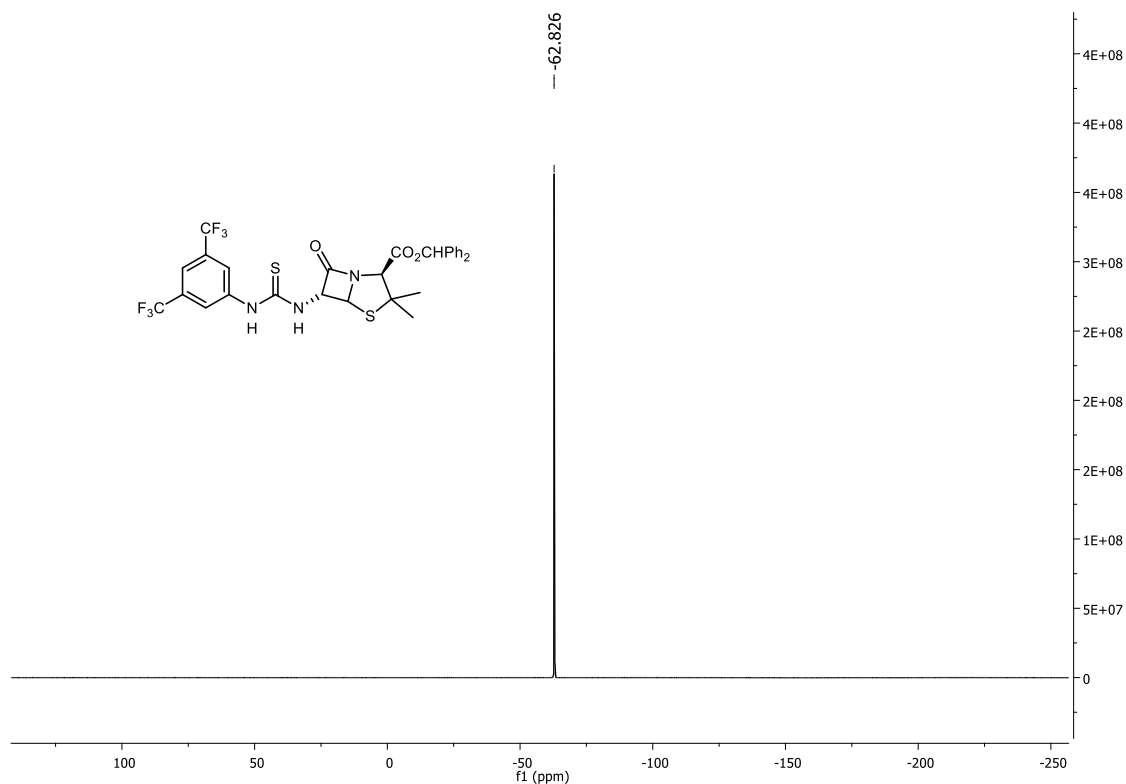
Data were collected at room temperature on an X-ray single crystal diffractometer equipped with a kappa-geometry goniometer, a 4K CCD detector (Bruker APEXII) and a sealed, fine focus, X-ray tube, emitting MoK $\alpha$  radiation ( $\lambda$  = 0.71073 Å). The *bremsstrahlung* radiation and the K $\beta$  component were filtered by a graphite monochromator. Data collection and data reduction were performed using the Bruker APEXIII software package.<sup>3</sup> The measurements were performed on a small single crystal with plate habit coated with perfluorinated ether. The crystal was fixed on top of a thin glass fiber and transferred to the diffractometer. Initial lattice parameters were determined from a preliminary data collection consisting of set of 33 detector frames. A subsequent data collection was performed on a full sphere, using omega and phi scans of 0.5° width. The data acquisition time was 10 s per frame. Reflections were merged and corrected for Lorentz and polarization effects, scan speed, and background using SAINT V8.38A<sup>4</sup> included in the APEXIII package. Absorption corrections, including odd and even spherical harmonics up to rank 3 and 6, respectively, were performed using SADABS-2016/2.<sup>5</sup>

Space group assignment was based upon systematic absences, *E* statistics, and successful refinement of the structure in space group *P*2<sub>1</sub>/*c*. The structure was solved by a dual-space method using SHELXT 2014/5<sup>6</sup> and refined by full matrix least-squares (minimizing  $\Sigma w(F_o^2 - F_c^2)^2$ ) using SHELXL-2018/1.<sup>7</sup> The weighting scheme was  $w = 1/[s^2(F_o^2) + (0.0435P)^2 + 0.4764P]$  where  $P = (F_o^2 + 2F_c^2)/3$ , as suggested by SHELXL-2018/1. The final quality factors of the refinement were  $R_1(I > 2s) = 0.0409$ ,  $wR_{all} = 0.1177$  and GOF = 1.034 for 2665 for independent reflections and 218 refined parameters, including one extinction coefficient. Default SHELXL-2018/1 values for neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were used. The ORTEP plot of the molecule was generated by PLATON.<sup>8</sup> CCDC 1958457 contains additional crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

### S.4.1 <sup>1</sup>H NMR of Compound 12



### S.4.3 $^{19}\text{F}$ of compound **12**



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