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Short Note

5,5,7,7-Tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine

Roberto Bisaccia [1,2], Patrizia Scafato [1], Daniele Casarini [1] and Stefano Superchi [1,*]

[1] Department of Sciences, University of Basilicata, Via Dell'Ateneo Lucano 10, 85100 Potenza, Italy
[2] Flamma Group, Via Bedeschi, 22, 20040 Bergamo, Italy
* Correspondence: stefano.superchi@unibas.it

Abstract: 5,5,7,7-Tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine has been synthesized as a possible pro-chiral (or *tropos*) unit for the construction of a chiral catalyst and as a molecular chirality sensor for the absolute configuration assignment by chiroptical spectroscopy. A straightforward synthetic strategy for the preparation of the title compound in high overall yield through sequential addition of the four methyl groups on benzylic positions has been described. A VT-NMR study was used to determine the rotational barrier of the aryl–aryl bond in this biphenylazepine, revealing its torsional flexibility at room temperature, which makes the biphenylazepine suitable as both a chirality probe and a *tropos* moiety in chiral ligands.

Keywords: dibenz[*c*,*e*]azepines; chirality sensing; atropisomerism; nitrones

1. Introduction

Dibenz[*c*,*e*]azepines constitute an important class of compounds widely employed as chiral or *pro*-chiral scaffolds for the construction of chiral catalysts for asymmetric synthesis or probes for chiral molecular recognition. In particular, 1,1′-binaphthylazepines have been widely employed as chiral ligands in organometallic catalysis [1–5] and organocatalysis [6–10], while not-atropisomerically stable (i.e., *tropos*) 1,1′-biphenylazepines have been reported both as structural motifs for the construction of the chiral ligands [9–15] and as the chiroptical probes for the absolute configuration assignment to the chiral acids [16–19] and amines [14,20]. In fact, in 1,1′-biphenylazepines the low phenyl–phenyl rotational barrier allows, at room temperature, a free interconversion of the two possible *M* and *P* atropisomeric forms. This makes this molecular system a unique probe for detection of molecular chirality because, when this moiety is linked to a chiral compound, a central-to-axial chirality induction occurs and the stereogenic center(s) of the substrate induces a preferred biphenyl twist in the azepine, making this chiral itself. As reported above, this effect has been exploited to assemble chiral catalysts and reagents, joining the flexible biphenyl moiety to an atropisomerically stable binaphthyl moiety [10–14] or introducing one or two stereogenic centers on the benzylic positions [21,22], and to build chiroptical probes for the absolute configuration assignment to chiral acids [16–19] and amines [14,20]. In this latter application, the biphenylazepine moiety acts as a chirality sensor, assuming a preferred twist in dependence of the chiral substrate absolute configuration. The biphenyl twist is easily revealed by a diagnostic band in the electronic circular dichroism (ECD) spectrum. Therefore, from the sign of such a band the twist sign can be detected and the absolute configuration of the chiral substrate, from which the twist sign is determined, can be established.

Taking into account that the chirality induction in the biphenyl moiety is mainly determined by steric interactions between the substituents on the substrate stereocenter(s) and the benzyl carbons of the biphenylazepine, we decided to prepare the novel tetramethylated biphenylazepine **2** with the aim to enhance such steric interactions and eventually improve the chirality sensing ability of this probe.

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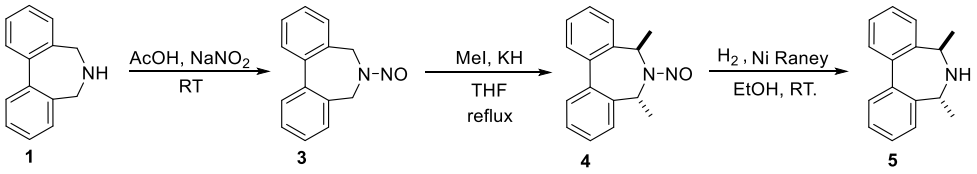
Citation: Bisaccia, R.; Scafato, P.; Casarini, D.; Superchi, S. 5,5,7,7-Tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine. *Molbank* **2023**, *2023*, M1554. https://doi.org/10.3390/M1554

Academic Editor: Ian R. Baxendale

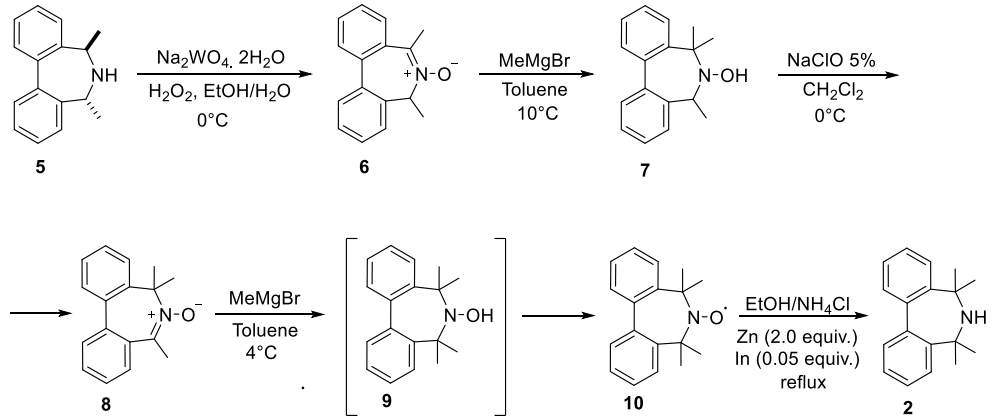
Received: 16 December 2022
Revised: 9 January 2023
Accepted: 11 January 2023
Published: 16 January 2023

2. Results and Discussion

The synthesis of the tetramethylazepine **2** [23] was carried out starting from the biphenylazepine **1** [**11**] following a two-step approach. First, two methyl groups were introduced in the benzylic positions by a double alkylation of the *N*-nitroso azepine **3** (Scheme 1); subsequently, the other two methyl groups were added in sequence by a repeated MeMgBr addition on azepine nitrones (Scheme 2) [24]. Accordingly, biphenylazepine **1** was first transformed in its *N*-nitroso derivative **3** by reaction with aqueous $NaNO_2$ in acetic acid [25]. After neutralization with 10 M NaOH, extraction with toluene, drying, and evaporation of solvent, *N*-nitroso azepine **3** was obtained in a 90% yield. This compound was then deprotonated in THF by treatment with excess of KH, providing a dark red solution that was treated with MeI at reflux for 18 h, giving double alkylation at the benzylic positions. After quenching with water and neutralization, evaporation of solvent provided a yellow oil that, after washing with pentane, afforded (±)-**4** as an orange solid residue in an 88% yield. Notably, NMR spectra showed the presence of a single diastereomer of (±)-**4**.



Scheme 1. Synthesis of dimethyl biphenylazepine **5**.



Scheme 2. Synthesis of dimethyl biphenylazepine **2**.

The *N*-nitroso dimethylazepine **4** could not be deprotonated further even with a large excess of NaH [24]. Therefore, the introduction of the other two methyl groups had to be obtained in a different way. Accordingly, the nitroso group was straightforwardly removed from the nitrogen of the azepine by treatment of the ethanolic solution of **4** with Raney Nickel under hydrogen atmosphere. After stirring overnight, dimethylazepine (±)-**5** [21,22] was obtained in an 80% yield after filtration of the mixture on celite and solvent removal. Analysis of the ^{1}H NMR spectrum revealed a single set of signals allied to the phenyl and methyl moieties, indicating the presence of a C_2 symmetry of the molecule and, then, a *trans* arrangement of the two methyl groups on the benzylic positions [21,22].

Afterwards, the second synthetic sequence allowed introduction of the other two methyl groups (Scheme 2).

Accordingly, amine **5** was oxidized by treatment with $Na_2WO_4 \cdot 2H_2O$ and 35% aqueous H_2O_2 in a MeOH/H_2O mixture. After 6 h, the reaction was quenched with $Na_2S_2O_5$. After extraction, drying, and evaporation of solvent, dimethyl nitrone **6** was recovered in a 93% yield. The third methyl group was then introduced on nitrone **6** by a nucleophilic addition of MeMgBr in toluene. After quenching and treatment of the reaction mixture,

trimethyl hydroxylamine **7** was recovered, which partially spontaneously oxidized to nitrone **8**, as shown by both ^{1}H NMR and GC–MS analyses (see Supplementary Material). Therefore, compound **7** was not isolated but the mixture of **7** and **8** was directly oxidized to nitrone **8** by treatment with bleach (5% aqueous NaClO) overnight at room temperature [26]. After reaction treatments, trimethyl nitrone **8** was recovered in a 94% yield. Finally, the fourth methyl group was introduced on nitrone **8** by repeating the MeMgBr nucleophilic addition. The resulting product, tetramethyl hydroxylamine **9**, was not isolable because it spontaneously oxidized to provide the nitroxyl oxide **10** that was recovered in a 65% yield after chromatographic purification on silica gel column. Finally, the tetramethyl biphenylazepine **2** was obtained by indium-catalyzed reduction [27], treating compound **10** with metal zinc (2 equiv) and indium (0.05 equiv) at reflux in an ethanol/NH_4Cl satd. solution (pH~6). After treatment of the reaction mixture, compound **2** was recovered in a 75% yield. Notably, this synthetic sequence appears particularly straightforward for the obtainment of biphenylazepine **2**. In fact, most of the sequence reactions provided very high yields and only one step required chromatographic purification of the products. The desired title compound 5,5,7,7-tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **2** was thus obtained from the starting biphenylazepine **1** in a 25% overall yield after eight steps.

To employ the biphenylazepine **2** as the probe of molecular chirality and as the *tropos* moiety of the chiral ligands for asymmetric catalysis, it must be atropisomerically flexible, i.e., the aryl–aryl torsional barrier must be low enough (below 22 kcal/mol) to allow free interconversion between the *P* or *M* twist of the biphenyl at room temperature. Therefore, a VT-NMR study was undertaken to establish such torsional barrier (Figure 1) in both the tetramethylated biphenylazepine **2** and the usubstituted precursor **1**.

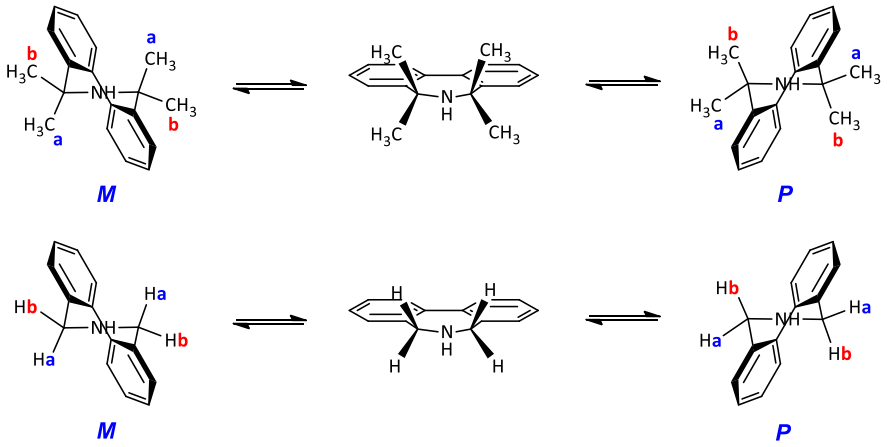


Figure 1. Conformational torsional equilibrium of tetramethyl biphenylazepine **2** (**top**) and unsubstituted biphenylazepine **1** (**bottom**).

To determine the free energy of the torsional inversion of biphenylazepine **2**, several VT-NMR experiments were carried out. At room temperature, ^{1}H NMR spectrum of **2** shows (Figure 2 and Figure S17 in the Supplementary Material), besides the biphenyl aromatic protons, two broad singlets at 0.92 and 1.55 ppm integrating six protons each. In fact, as a consequence of the not planarity of the twisted biphenyl system, the methyl groups on the benzylic positions are diastereotopic, so that the pseudo-axial and pseudo-equatorial methyls are anisochronous (Figure 1, top). The conformational inversion through a planar transition state gives rise to the topoisomerization of methyls (a) and (b): if methyl (a) is pseudo-axial in the twisted conformer *M*, it will be pseudo-equatorial in the *P* twisted conformer and *vice versa* for proton (b) (Figure 1, top).

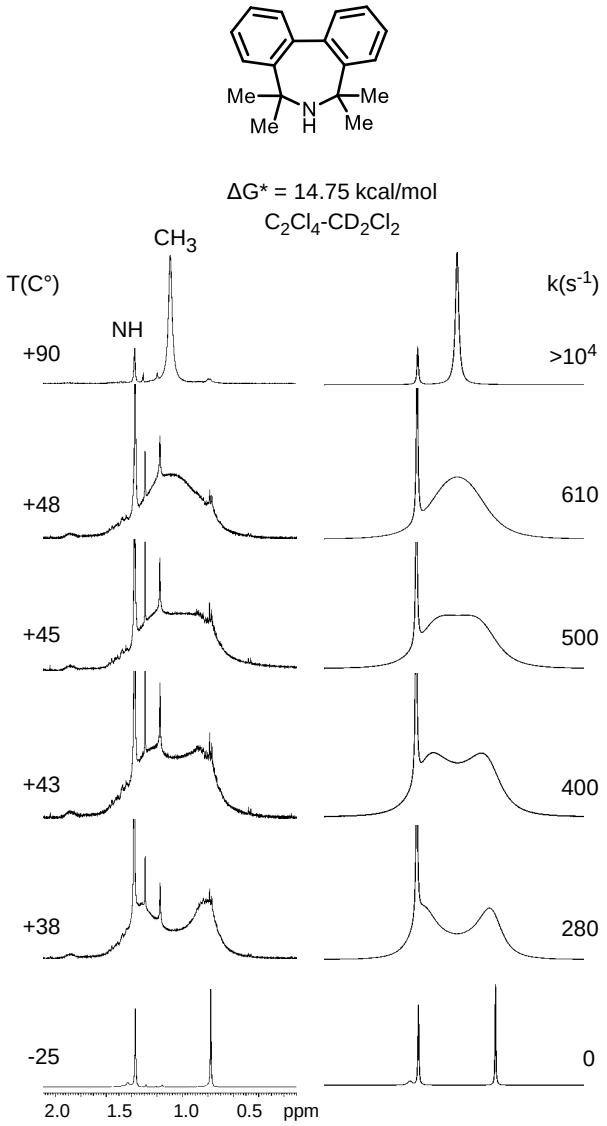
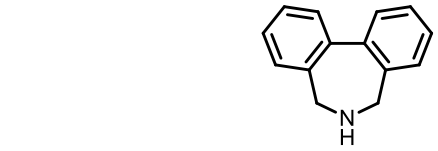


Figure 2. ^{1}H NMR spectra at 500 MHz in C_2Cl_4-CD_2Cl_2 for the signals of the two benzylic Me groups of biphenylazepine **2**. Experimental traces are shown on the left and the computer simulated ones on the right.

VT-NMR spectra (Figure 2) show that these two broad singlets, which are visible at low temperature (up to +43 °C), coalesce merging in a single broad singlet at +45 °C (coalescence temperature). At +90 °C, fast interconversion between the two *M* and *P* conformers occurs and the spectrum shows only one singlet centered at 1.23 ppm, which is the average value of the chemical shift of the axial and equatorial methyl groups. A 14.9 Kcal/mol torsional barrier for the twist interconversion at the coalescence temperature T_c was computed by the Eyring equation [28]. Such value indicates that, at room temperature, a free rotation around the aryl–aryl bond still occurs, thus making biphenylazepine **2** suitable as the chirality sensor and *tropos* moiety in the chiral ligands.

To evaluate the effect of the four methyl substituents on the aryl–aryl torsional barrier of biphenylazepine **2**, a comparison with the unsubstituted biphenylazepine **1** was carried out (Figure 3). VT-NMR spectra on **1** show an analogous situation as in **2**. However, in this case, the conformational inversion of the biphenyl twist exchanges the two benzyl hydrogens (a) and (b) (Figure 1, bottom) instead of the methyl groups as in **2**. If the exchange is fast (higher temperature), the ^{1}H NMR signal of the benzyl protons appears as a singlet, while a slow conformational interconversion occurs at lower temperature, giving rise to two separate signals for the (a) and (b) protons coupled as an AB spin system. Benzyl

protons coalesce at −65 °C; therefore, a ΔG* of 9.4 Kcal/mol can be calculated from the Eyring equation [28].



$\Delta G^* = 9.40$ kcal mol^{-1}

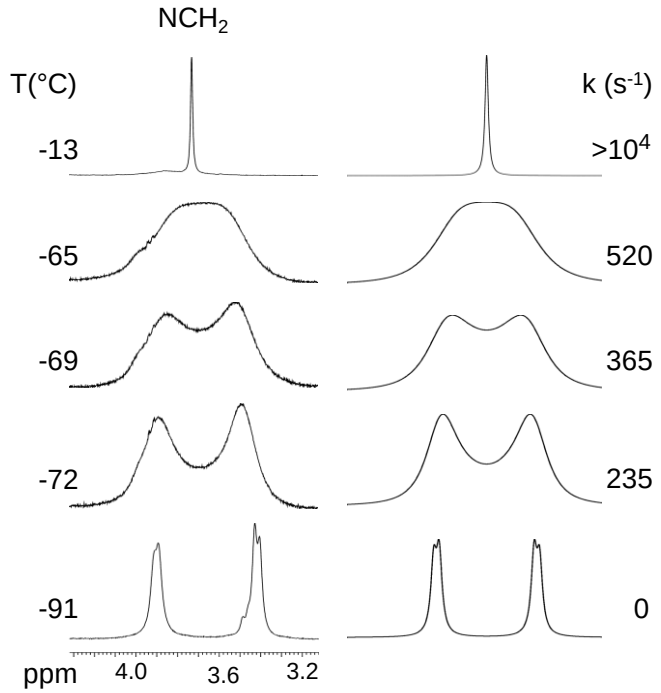


Figure 3. ^{1}H NMR spectra at 500 MHz in CD_2Cl_2 for the signals of the two benzylic hydrogens of biphenylazepine **1**. Experimental traces are shown on the left and the computer simulated ones on the right.

In summary, although in biphenylazepine **2** the presence of four benzylic methyls increases the rotational barrier of about 5.5 kcal/mol in respect to the unsubstituted derivative **1**, compound **2** is still conformational flexible at room temperature and then suitable to be employed as both the chirality probe and *tropos* unit.

3. Materials and Methods

NMR spectra were acquired on a Varian INOVA spectrometer running at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to TMS signal. ^{13}C NMR spectra were acquired in broad band decoupled mode. GC–MS analyses were carried out employing a HP 5 MS column, on a HP 6890 plus gaschromatograph equipped with HP 5973 mass detector. HRESI MS spectra were recorded on Agilent 6230B LC/MS TOF instrument [29]. Melting points were measured with a Kofler hotstage Reichert-Thermovar apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (Merck, Kieselgel 60, F254, 0.25) and column chromatography was performed on silica gel (Merck, Kieselgel 60, 0.063–0.200 mm). 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **1** was prepared as previously described [11]. CH_2Cl_2 and triethylamine were freshly distilled over CaH_2 prior to their use. THF, toluene, and

Et_2O were freshly distilled over sodium/benzophenone prior to their use. Unless otherwise specified, commercially available reagents and solvents were used without any purification.

6-Nitroso-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (**3**).

To a solution of 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **1** (5.82 g, 30.0 mmol) in acetic acid (232 mL) was dropwise added under stirring, a solution of $NaNO_2$ (5.3 g, 77.0 mmol) in water (85.6 mL). The resulting yellow solution was stirred at room temperature for 4 h, then cooled at 0 °C in ice bath and treated with 10.0 M aqueous NaOH (120 mL) until the reaction was alkaline. The mixture was extracted with toluene, the two layers separated, and the organic phases washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of solvent under vacuum, the *N*-nitroso derivative **3** was recovered as a yellow-orange solid (6.0 g, 26.8 mmol, 90% yield) and used without further purification. M.p. 109–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.60 (br s, 2H), 5.20 (br s, 2H), 7.30 ÷ 7.45 (m, 3H), 7.45 ÷ 7.60 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 47.50, 53.88, 128.35, 128.51, 128.67, 128.82, 129.14, 129.31, 129.46, 130.28, 130.77, 132.13, 139.56, 140.58. MS (EI): *m/z* 224 (M^+, 87), 194 (100), 179 (24), 166 (60), 165 (62), 152 (18). Spectroscopic data matched those already reported for compound **3** [25].

5,7-Dimethyl-6-nitroso-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (**4**).

A mineral oil dispersion of KH (5.0 g) was washed with hexane, then suspended in anhydrous THF (150 mL) and a solution of *N*-nitroso azepine **3** (2.8 g, 12.5 mmol) in anhydrous THF (50 mL) was added under stirring at room temperature. After 30 min, CH_3I (8.5 mL, 17.0 mmol) was added to the dark brown mixture. The mixture was heated at reflux overnight, then cooled at 0 °C in ice bath and water was added until complete dissolution of the white precipitate. The layers were separated and the aqueous phase was washed twice with Et_2O. The collected organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and solvent evaporation under vacuum, a dark orange liquid was recovered which, after washing with pentane provided **4** as an orange solid residue (2.78 g, 11.0 mmol, 88% yield). M.p. 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.89 (d, *J* = 7.3 Hz, 3H), 1.22 (d, *J* = 7.3 Hz, 3H), 5.93 (q, *J* = 6.7 Hz, 1H), 6.03 (q, *J* = 6.7 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.40÷7.60 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 18.92, 22.45, 55.05, 64.30, 128.64, 128.82, 129.41, 129.64, 129.67, 129.82, 130.16, 130.30, 136.07, 136.55, 139.18, 140.05. MS (EI): m/z 252 (M^+, 44), 222 (74), 207 (66), 193 (40), 180 (100), 165 (76).

5,7-Dimethyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (**5**).

To a solution of *N*-nitroso azepine **4** (2.0 g, 7.9 mmol) in anhydrous ethanol (50 mL), under nitrogen, activated Raney Nickel (400 mg) was added and hydrogen was bubbled overnight. The resulting white cloudy solution was filtered over celite and the filtrated washed with ethanol. The collected organic solution was concentrated under vacuum providing dimethyl amine **5** (1.40 g, 6.3 mmol, 80% yield) as a yellow viscous liquid which solidified on standing as pale yellow needles. M.p. 59–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.34 (d, *J* = 6.6 Hz, 6H), 1.82 (br s, 1H), 3.49 (q, *J* = 6.6, 2H), 7.40 ÷ 7.60 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 18.81, 50.77, 124.42, 127.68, 128.03, 128.36, 139.85, 141.43. MS (EI): m/z 223 (M^+, 7), 208 (100), 191 (11), 178 (10), 165 (24). Spectroscopic data matched those already reported for compound (*S*)-**5** [21,22].

5,7-Dimethyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine-N-oxide (**6**).

To a solution of amine **5** (1.33 g, 6.0 mmol) in ethanol (30 mL) under nitrogen atmosphere $Na_2WO_4{\cdot}2H_2O$ (216 mg, 0.65 mmol, 11 mol%) and water (4.7 mL) were added. The solution was cooled at 0 °C in ice bath and 35% aqueous H_2O_2 (2.8 mL, 90.5 mmol) was added under stirring. After 30 min, the solution was left warming at room temperature and stirred overnight. The mixture was then concentrated under vacuum, diluted with CH_2Cl_2 and brine. The mixture was treated with $Na_2S_2O_5$ and the two layers separated. The aqueous phase was washed three times with CH_2Cl_2 and the collected organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The nitrone **6** was recovered as a waxy residue (1.31 g, 5.5 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.80 (d, *J* = 7.0 Hz, 3H), 2.3 (s, 3H), 4.50 ÷ 4.70 (m, 1H), 7.20 ÷ 7.50 (m,

5H), 7.50 ÷ 7.70 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 12.90, 19.16, 63.35, 123.97, 127.68, 127.94, 128.14, 128.44, 128.68, 128.85, 129.50, 129.66, 134.24, 138.19, 139.51, 141.45. MS (EI): m/z 237 (M^+, 50), 220 (20), 207 (59), 192 (100), 179 (40), 165 (48), 152 (12).

5,5,7-Trimetyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-6-ol (**7**).

To a solution of nitrone **6** (1.14 g, 4.8 mmol) in anhydrous toluene (80 mL) cooled at 10 °C was dropwise added, under nitrogen atmosphere, MeMgBr (5.5 mL, 16.4 mmol, 3.0 M in Et_2O). After 15 min, the solution was left warming at room temperature and stirred for 5 h. Then the solution was quenched with saturated aqueous NH_4Cl and solid NaCl until saturation. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The collected organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, providing 1.15 g of a crude mixture containing hydroxylamine **7** and nitrone **8** as revealed by GC–MS analysis. The mixture was not separated but directly oxidized to nitrone **8** in the following step. MS (EI): *m/z* 235 (M^+-H_2O, 2), 222 (100), 205 (10), 178 (11), 165 (12), 103 (8).

5,5,7-Trimetyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-N-oxide (**8**).

To a 0.5 M solution in CH_2Cl_2 of the crude mixture (600 mg) coming from the previous reaction and containing both hydroxylamine **7** and nitrone **8** was dropwise added at 0 °C a solution of 5% aqueous NaClO (6 mL). After 30 min, the solution was left warming at room temperature and stirred overnight. Then the solution was diluted with CH_2Cl_2 and the two layers separated. The aqueous layer was extracted three times with CH_2Cl_2 and the collected organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The trimethyl nitrone **8** was recovered as a brown solid (560 mg, 2.23 mmol, 94% yield). M.p. 110–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.22 (s, 3H), 2.19 (s, 3H), 2.43 (s, 3H), 7.45 (m, 5H), 7.64 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 14.46, 21.75, 25.16, 26.60, 125.34, 128.00, 128.40, 128.55, 128.64, 128.74, 129.01, 130.48, 133.92, 137.12, 139.25, 141,97, 142.89. MS (EI): *m/z* 251 (M^+, 8), 234 (8), 220 (12), 210 (16), 193 (100), 178 (50), 165 (11), 152 (8).

5,5,7,7-Tetramety-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-6-ol (**9**).

To a solution of nitrone **8** (510 mg, 2.0 mmol) in anhydrous toluene (40 mL) cooled at 4 °C under nitrogen atmosphere, MeMgBr (2.5 mL, 7.4 mmol, 3.0 M) was added. After 15 min, the solution was left warming at room temperature and stirred for 5 h, then quenched with saturated aqueous NH_4Cl and solid NaCl was added until saturation. The two layers were separated and the aqueous layer extracted three times with CH_2Cl_2. The collected organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The recovered crude was purified by column chromatography (SiO_2; petroleum ether:diethyl ether 1:1) providing hydroxylamine **9,** which spontaneously oxidized to nitroxyl oxide **10** as dark green crystals (322 mg, 1.3 mmol, 65% yield). M.p. 123–125 °C. This compound is paramagnetic; therefore, its ^{1}H NMR spectrum provided very broad bands that prevented any further characterization. The compound was used in the subsequent step without any purification.

5,5,7,7-Tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (**2**).

Nitroxyl oxide **10** (612 mg, 2.4 mmol) was dissolved in a 2:1 solution of ethanol and 10% aqueous NH_4Cl (33 mL; pH ≈ 6), and zinc powder (298 mg, 4.6 mmol) and indium (13 mg, 0.11 mmol) were added. The mixture was heated 10 h at reflux, then cooled at room temperature, filtered over celite and extracted with ethyl acetate. To the organic solution saturated aqueous Na_2CO_3 (15 mL) was added and the two layers separated. The organic phase was died over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Biphenylazepine **2** was recovered as pale yellow crystals (450 mg, 1.8 mmol, 75% yield). M.p. 70–71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.92 (br s, 6H), 1.55 (br s, 6H), 2.2 (br s, 1H), 7.33 (m, 2H), 7.37 (m, 4H), 7.46 (d, *J* = 8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 26.22, 28.63, 50.66, 120.33, 123.00, 123.09, 125.40, 137.70, 139.20. MS (EI): *m/z* 251 (M^+, 8), 236 (100), 219 (13), 194 (30), 179 (48), 110 (15). HRESIMS (+) *m/z* 251.1669 $[M + H]^+$ (calculated for $C_{18}H_{22}N$ 251.1674).

4. Conclusions

A novel straightforward synthetic strategy for the synthesis of 5,5,7,7-tetrametyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine **2** has been described. The reactions sequence provides very high yields and requires only one chromatographic purification step. A VT-NMR study was employed to determine the rotational barrier of the aryl–aryl bond in biphenylazepine **2**, showing that this compound is conformational flexible at room temperature and then suitable to be used as both the chirality probe and *tropos* moiety in the chiral ligands for asymmetric catalysis.

Supplementary Materials: The following supporting information can be downloaded at online, Figure S1: ^{1}H NMR spectrum of compound **3**; Figure S2: ^{13}C NMR spectrum of compound **3**; Figure S3: GC–MS analysis of compound **3**; Figure S4: ^{1}H NMR spectrum of compound **4**; Figure S5: ^{13}C NMR spectrum of compound **4**; Figure S6: GC–MS analysis of compound **4**; Figure S7: ^{1}H NMR spectrum of compound **5**; Figure S8: ^{13}C NMR spectrum of compound **5**; Figure S9: GC–MS analysis of compound **5**; Figure S10: ^{1}H-NMR spectrum of compound **6**; Figure S11: ^{13}C NMR spectrum of compound **6**; Figure S12: GC–MS analysis of compound **6**; Figure S13: GC–MS analysis of mixture of compounds **7** and **8**; Figure S14: ^{1}H NMR spectrum of compound **8**; Figure S15: ^{13}C NMR spectrum of compound **8**; Figure S16: GC–MS analysis of compound **8**; Figure S17: ^{1}H-NMR spectrum of compound **2**; Figure S18: ^{13}C-NMR spectrum of compound **2**; Figure S19: GC–MS analysis of compound **2**.

Author Contributions: Conceptualization, S.S.; methodology, R.B. and D.C.; validation, P.S. and D.C.; investigation, R.B. and D.C.; data curation, P.S.; writing—original draft preparation, S.S.; writing—review and editing, S.S.; visualization, S.S. and D.C.; supervision, S.S.; project administration, S.S.; funding acquisition, S.S. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support from University of Basilicata (R.I.L. 2020 grant) is gratefully acknowledged.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

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