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RESEARCH ARTICLE

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Diastereoselective synthesis of a cyclic diamide-bridged biphenyl as chiral atropos ligand

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Abstract

Chiral compounds with a 1,2-diamine structure motif and their derivatives are of great interest in organic chemistry and are broadly used in asymmetric transformations, as chiral auxiliaries, (co)ligands, and ligand core structure. Here, we present a straightforward, diastereoselective synthesis for a diamide-bridged biaryl ligand. The ring closing reaction of the racemic atropos biphenyl 6,6′-dimethoxy-[1,1′-biphenyl]-2,2′-dicarboxylic acid with (*R*,*R*)-diaminocyclohexane yields the diasteromerically and enantiomerically pure cyclic (S_{ax},*R*,*R*)-BIPOL, which can be used as a versatile chiral ligand. By NMR spectroscopy, we observed the formation of intermolecular aggregates of the diamide-bridged BIPOL with anhydrous DMSO-d_6. DFT calculations at the B3LYP/6-31G* level of theory corroborate the high interconversion barrier for the biaryl axis of $\Delta G^{\ddagger} = 148.7$ kJ mol^{-1} and the favoured formation of (S_{ax},*R*,*R*)-BIPOL as single stereoisomer.

KEYWORDS

aggregates, atropos biaryls, DFT calculation, DOSY-NMR, interconversion barrier, (*R*,*R*)-diaminocylcohexane

1 | INTRODUCTION

Compounds derived from 1,2-diamines and their derivatives are of great interest and applied in a broad range of applications ranging from medicinal chemistry, as biologically active substances,[1,2] to synthetic organic chemistry, especially in the field of asymmetric synthesis, as versatile chiral auxiliaries,[1] ligands, and catalysts.[1] (*R*,*R*)- and (*S*,*S*)-1,2-Diaminocyclohexane[3] (DACH) and (*R*,*R*)- and (*S*,*S*)-diphenylethylenediamine (DPEN) are important chiral ligand backbones and building blocks in several highly efficient catalysts, because their enantiomerically pure forms are commercially available. Enantiomerically pure 1,2-diaminocyclohexane can be obtained at large scale by resolution as monotartrate salt using enantiomerically pure tartaric acid.[4]

In Jacobsen epoxidation, highly enantioselective DACH- and DPEN-derived manganese (III) salen catalysts are used, achieving excellent enantiomeric excesses (*ee*) (Figure 1A).[5] Trost et al. developed highly versatile DACH- and DPEN-based phosphines in 1992 (Figure 1B).[6] These and structurally related catalysts have since then been used in numerous Pd-catalyzed asymmetric allylic alkylations.[7–9] In addition, de Vries and coworkers recently reported the use of the (*S*,*S*)-DACH ligand (Figure 1B) in the Ru-catalyzed asymmetric hydrogenation of ketones such as acetophenone with excellent ee's of up to 96%.[10] Noyori et al. developed a DPEN-derived catalyst for the ruthenium (II)-catalyzed asymmetric transfer hydrogenation of ketones and imines that allows the beneficial use of formic acid-triethylamine as irreversible hydrogen donor instead of isopropanol

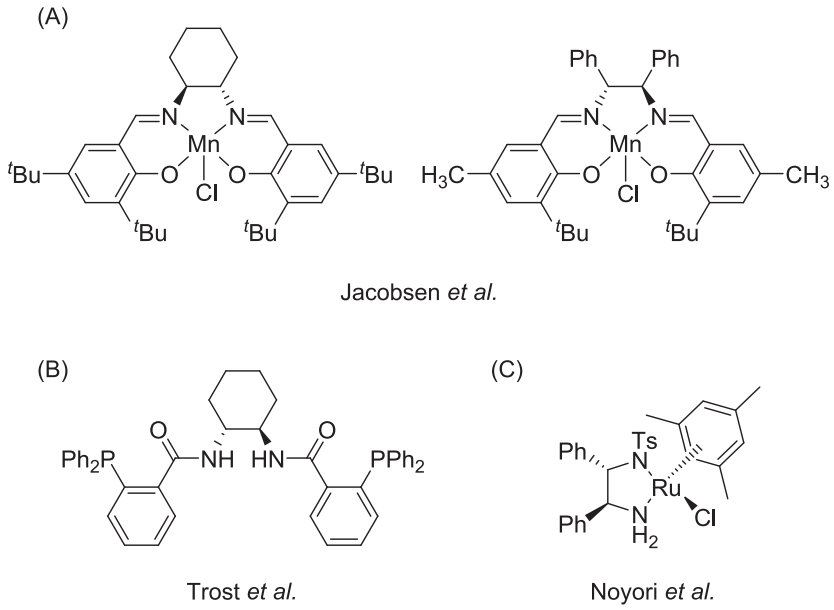


FIGURE 1 (A) DACH- and DPEN-modified salenes for Jacobson epoxidation; (B) Trosts phosphine ligand for asymmetric allylic alkylations, and (C) Noyoris catalyst for transfer hydrogenation

(Figure 1C).[11] This results in ee's of up to 99% for a large variety of aromatic ketones.[12,13] To date, Noyori's catalyst and structurally similar compounds are among the most widely used catalysts for asymmetric transfer hydrogenations.[14,15] The concept of chiral activation can provide highly activated catalysts for asymmetric transformations by inducing a ligand acceleration or modification.[16] Furthermore, tropos biphenyl derived ligands enable the synthesis of supramolecular catalysts, which can switch their sense of chirality by interaction with their own reaction product and therefore lead to asymmetric amplification and nonlinear effects.[17–19] Mikami and Noyori used (*S,S*)-DPEN as co-ligand for *rac*-TolBINAP-Ru complexes to selectively increase the reactivity of one of the catalyst enantiomer to enable the highly enantioselective reduction of ketonenes.[20] In racemic, stereodynamically flexible 2,2′-(diphenylphosphanyl)-1,1′-biphenyl (BIPHEP) catalysts, (*S,S*)-DPEN was used as chiral activator for the enantioselective hydrogenation of ketones.[21] By deracemization of the *rac*-BIPHEP-Ru complex with (*S,S*)-DPEN, remarkable ee's of up to 84% could be achieved.[22]

In addition, (*R,R*)-DACH and (*R,R*)-DPEN were used for the racemate resolution of binaphthol derivatives.[23] Mangeney et al. used the *N,N*′-dimethylated, enantiomerically pure DPEN to achieve a resolution of racemic aldehydes. The reaction leads to the formation of diastereomeric imidazolidines, through which the enantiomeric composition of the aldehydes can be determined even by achiral analytical techniques, for example, NMR.[24] Furthermore, phosphorous derivatives of C_2-symmetrical diamines served as chiral derivatization reagents in NMR spectroscopy to determine the ee of chiral alcohols, thiols, and amines.[25,26]

Very recently, we developed an approach to restrain the flexibility of the biphenol moiety by cyclization in the backbone and exemplified this with dihydroazepine-bridged biphenol phosphoramidite ligands.[27] The stereochemical flexibility can be varied by extension of the backbone cycle as shown for L-tartaric acid based biphenylbisphosphinite ligands with anilino linkers.[28] Here, we show a strategy to form an atropos biphenyl system with a highly rigid biphenyl axis starting from racemic 6,6′-dimethoxy-[1,1′-biphenyl]-2,2′-dicarboxylic acid, which is converted by a diastereoselective diamide ring closing reaction into the into the stereoisomerically pure (S_{ax},*R,R*)-BIPOL using (*R,R*)-diaminocyclohexane as bridging and stereodirecting group in the backbone.

2 | MATERIALS AND METHODS

2.1 | General methods

All reactions involving oxygen and/or moisture sensitive substances were carried out in heat dried glassware under an atmosphere of argon using standard Schlenk techniques. All chemicals were used as received from suppliers without further purification. Column chromatography was performed using silica gel (technical grade, pore size 60 Å, 70–230 mesh, 63–200 μm) provided by Sigma-Aldrich Chemie GmbH. Thin layer chromatography was performed on coated aluminum sheets (Machery-Nagel POLYGRAM SIL G/UV 254). Components were visualized by fluorescence quenching by irradiation with UV light (254 nm). Anhydrous solvents were taped from solvent purification system MBraun SPS-800 and used immediately.

NMR spectra were recorded on a Bruker Avance III HD spectrometer (400 MHz). NMR shifts are given in parts per million (ppm) and are referenced to the residual proton or carbon solvent signals.[29] Multiplicity is termed as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of a doublet), and m (multiplet). Assignment was done by means of two-dimensional experiments (^{1}H-^{1}H-COSY, ^{1}H-^{13}C-HSQC, and ^{1}H-^{13}C-HMBC). Mass spectra were acquired on a Thermo Finnigan LTQ FT Ultra FT-ICR (ESI) or Thermo Thermo Q Exactive Hybrid Quadrupole Orbitrap (ESI). For solid-state IR analysis, a Thermo Fisher Nicolet 6700 FT-IR-Spectrometer was employed. Crystallographic data was collected at the X-Ray Crystallography Laboratories of the Department of Chemistry and Pharmacy, LMU Munich, on a Bruker APEX-II Quazar area detector and on a STOE-IPDS system with Mo Kα radiation (λ = 0.71073 Å). DFT structure optimization and energy calculations were performed at the B3LYP/6-31G* level of theory using HyperChem 8, Gainesville, FL. HPLC-MS measurements were performed on an *Agilent Technologies 1200 HPLC-MS* (*Agilent Technologies*, Palo Alto, California, USA), equipped with a binary solvent pump, an autosampler, membrane solvent degasser, DAD detector and a quadrupole mass spectrometer *Agilent 6120*, equipped with an APCI source. All operations were controlled by the *Agilent ChemStation* software (Agilent Technologies, Palo Alto, California, USA). The solvents used (*n*-hexane, isopropyl alcohol and ethanol) were obtained from *Sigma-Aldrich* (HPLC-grade quality).

2.2 | (S_{ax})-(4a*R*,16a*R*)-10,11-Dimethoxy-1,2,3,4,4a,5,16,16a-octahydrotribenzo[b,f,h][1,4]diazecine-6,15-dione (S_{ax},*R*,*R*)-3

Rac-**2** (1.00 g, 3.31 mmol, 1.00 eq) and HOBt hydrate (1.10 g, 7.27 mmol, 2.20 eq.) were dissolved in anhydrous dichloromethane (200 ml). DIPEA (1.25 ml, 7.27 mmol, 2.20 eq.) was added, the solution was cooled in an ice bath and EDCI·HCl (1.40 g, 7.27 mmol, 2.20 eq.) was added. Subsequently (*R*,*R*)-diaminocyclohexane (455 mg, 3.98 mmol, 1.20 eq.) was added. After 15 min at lower temperature, the mixture was warmed to room temperature and stirring was continued for 18 h. The mixture was diluted with ethyl acetate, washed with 1 M HCl solution, $NaHCO_3$ and brine, dried over Na_2SO_4, and the solvent was evaporated. Column chromatography (SiO_2, pentane: ethyl acetate 3:1, R_f = 0.33) yielded the pure product as a light yellow solid (313 mg, 0.8 mmol, 25%).

^{1}H NMR (THF-d_8, 400.33 MHz, 300 K): δ = 1.26–1.38 (m, 2H), 1.39–1.52 (m, 2H), 1.75–1.81 (m, 2H), 1.86–1.93 (m, 2H), 3.61–3.70 (m, 8H), 6.44 (d, ^3J[H,H] = 9.5 Hz, 2H), 6.86 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.2 Hz, 2H), 6.94 (dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 1.2 Hz, 2H), 7.20 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.5 Hz, 2H) ppm. **^{13}C{^{1}H} NMR** (THF-d_8, 100.66 MHz, 300 K): δ = 26.4, 31.8, 56.3, 58.2, 112.4, 118.3, 124.4, 128.5, 140.8, 159.4, 172.5 ppm. **HRMS (ESI)**: m/z calcd. For $C_{22}H_{25}N_2O_4$ $[M + H]^+$: 381.1809; found: 381.1807. **IR (FT-ATR)**: = 686, 717, 730, 750, 783, 804, 818, 936, 962, 1000, 1037, 1047, 1094, 1146, 1204, 1256, 1298, 1317, 1359, 1427, 1458, 1517, 1579, 1592, 1644, 1669, 2931, 3305 cm^{-1}. **HPLC-MS:** Chiralpak IF (5 μm, 4.6 × 250 mm), 1 ml/min, *n*-hexane:*i*-PrOH 80:20 (v/v), (*R*,*R*,S_{ax})-**3** (*t* = 8.98 min).

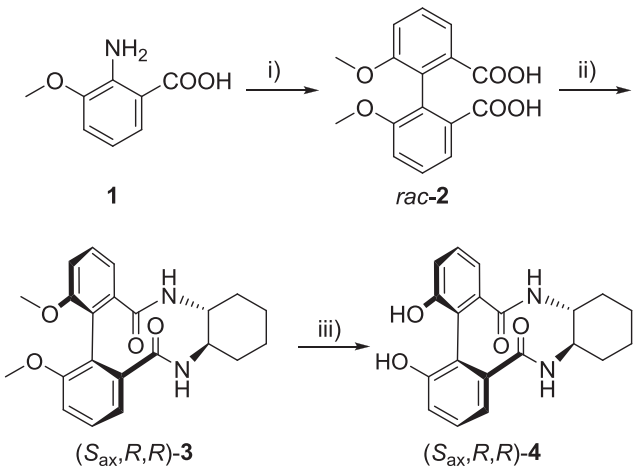
2.3 | (S_{ax})-(4a*R*,16a*R*)-10,11-Dihydroxy-1,2,3,4,4a,5,16,16a-octahydrotribenzo[b,f,h][1,4]diazecine-6,15-dione (S_{ax},*R*,*R*)-4

Dimethoxybiphenyl (S_{ax},*R*,*R*)-**3** (500 mg, 1.31 mmol, 1.00 eq.) was placed in a heat-gun dried Schlenk flask and dissolved in anhydrous and degassed dichloromethane (20 ml). The mixture was cooled at −78°C and BBr_3 solution, 1 M in dichloromethane, (6.60 ml, 6.57 mmol, 5.00 eq.) was added dropwise and stirred for 15 min. The cold bath was removed, and the reaction was stirred for 12 h at room temperature. At 0°C the mixture was slowly quenched with methanol and water and stirred for 1 h. The phases were separated, and the aqueous phase was extracted with dichloromethane and ethyl acetate. The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. (S_{ax},*R*,*R*)-**4** was obtained as white solid (448 mg, 1.27 mmol, 97%) and used without further purification.

^{1}H NMR (400.33 MHz, Acetonitrile-d_3, 300 K) δ = 1.20–1.30 (m, 2H), 1.38–1.51 (m, 2H), 1.60–1.78 (m, 2H), 1.77–1.86 (m, 14H, solvent signal), 3.40–3.68 (m, 2H), 5.95 (d, ^3J(H,H) = 2 Hz, 2H), 6.74 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.3 Hz, 2H), 6.80 (dd, ^3J(H,H) = 7.6 Hz, ^4J(H,H) = 1.2 Hz, 2H), 7.04–7.13 (m, 2H) ppm. OH signal was not observed. **^{13}C NMR** (100.66 MHz, Acetonitrile-d_3) δ = 25.8, 31.0, 59.0, 118.3, 120.9, 129.9, 140.3, 155.9, 173.7 ppm. **HRMS (ESI)**: m/z calcd. For $C_{22}H_{25}N_2O_4$ $[M + H]^+$: 353.1496; found: 353.1496. **IR (FT-ATR)**: = 672, 715, 753, 795, 809, 820, 907, 956, 987, 1003, 1052, 1090, 1143, 1188, 1282, 1319, 1360, 1443, 1511, 1579, 1597, 1649, 2856, 2931, 3174 cm^{-1}.

3 | RESULTS AND DISCUSSION

We developed a strategy for a straightforward diastereoselective synthesis of a biphenol scaffold with (*R*,*R*)-DACH as stereo-directing group (Scheme 1). The



SCHEME 1 Overview of the diastereoselective preparation of diamide-bridged biphenol (S_{ax},*R*,*R*)-**4** using (*R*,*R*)-DACH as directing group: (i) $NaNO_2$, HCl, $CuSO_4 \cdot 5\ H_2O$, $HONH_2 \cdot HCl$, 85%; (ii) (*R*,*R*)-diaminocyclohexane, HOBt hydrate, EDCI·HCl, DCM, 0°C – rt, 18 h, 25%; (iii) BBr_3 (1 M in DCM), DCM, −78°C – rt, 97%

synthesis started with 2-amino-3-methoxybenzoic acid **1** which was converted in a modified Sandmeyer reaction with $NaNO_2$ and a Cu(I) catalyst yielding the atropos[30] dicarboxylic acid *rac*-**2** (*rac*-6,6′-dimethoxy-[1,1′-biphenyl]-2,2′-dicarboxylic acid) in 85%.[31] In the next step, **2** was coupled with (*R*,*R*)-DACH using HOBt hydrate and EDCI·HCl to obtain the diamide-bridged biaryl (S_{ax},*R*,*R*)-**3** ((S_{ax})-(4a*R*,16a*R*)-10,11-dimethoxy-1,2,3,4,4a,5,16,16a-octahydrotribenzo[b,f,h] [1,4]diazecine-6,15-dione) in 25% yield, followed by deprotection of **3** with BBr_3. The diamide-bridged biphenol (S_{ax},*R*,*R*)-**4** ((S_{ax})-(4a*R*,16a*R*)-10,11-dihydroxy-1,2,3,4,4a,5,16,16a-octahydrotribenzo[b, f,h][1,4]diaz-ecine-6,15-dione) was obtained in 97% yield without further purification as a white solid.

The advantage of this strategy is, that the atropos dicarboxylic acid **2** can be easily racemized, which then results in a stereoconvergent synthesis with (*R*,*R*)-DACH of the targeted cyclic diamide-bridged biphenol (S_{ax},*R*,*R*)-**3** and (S_{ax},*R*,*R*)-**4**, respectively. Racemization of **2** can be achieved by formation of the intramolecular carboxylic acid anhydride using thionylcloride $SOCl_2$/triethylamine NEt_3, followed by refluxing in 1,4-dioxane and consecutive hydrolysis of the carboxylic anhydride.[30]

Furthermore, the here presented method can be used to deplete of one of the enantiomers of the atropos dicarboxylic acid **2** by reaction with (*R*,*R*)-DACH or (*S*,*S*)-DACH, respectively. This stereoselective depletion explains also the moderate yield of only 25% when (*R*,*R*)-DACH is used.

Coupling the racemic dicarboxylic acid *rac*-**2** with racemic *trans*-DACH ((*R*,*R*)-DACH and (*S*,*S*)-DACH) gives both enantiomers in approximately 50% yield. The obtained products were analyzed by chiral HPLC and compared with the chiral HPLC measurement of the single enantiomer (S_{ax},*R*,*R*)-**3** (Chiralpak IF (5 µm, 4.6 × 250 mm), 1 ml/min, *n*-hexane:*i*-PrOH 80:20 (v/v)) to assign the elution order. (S_{ax},*R*,*R*)-**3** is eluted at $t = 8.98$ min. As expected, two peaks in a ratio of 1:1 could be obtained for the coupling product from the reaction with *trans*-DACH ((S_{ax},*R*,*R*)-**3** ($t = 8.96$ min) and (R_{ax},*S*,*S*)-**3** ($t = 9.85$ min), $\alpha = 1.10$).

The diasteroselective synthesis of (S_{ax},*R*,*R*)-**3** was also confirmed by a XRD analysis of crystals, obtained by crystallization from DMSO, which verified the (S_{ax}) configuration (Figure 2). The dihedral angle of the biphenyl unit was determined to be 62.6°.

For the deprotected diamide-bridged biaryl (S_{ax},*R*,*R*)-**4** intermolecular aggregation could be observed by NMR spectroscopy (Figure 3). In contrast to aqueous DMSO-d_6, two species were identified in a 40:60 ratio in anhydrous DMSO-d_6. The second set of signals is downfield shifted, especially for the NH resonance ($\Delta\delta = 0.27$ ppm). This indicates that the second species has more pronounced hydrogen bonds than the first species, which is also seen in aqueous DMSO-d_6.

To elucidate whether the second species is an aggregate or a conformational isomer of (S_{ax},*R*,*R*)-**4**, temperature-dependent ^{1}H NMR spectra were recorded in anhydrous DMSO-d_6 (40°C–80°C). However, no significant change in the ratio of the signals or a coalescence temperature could be observed (SI). Therefore, it can be deduced that the two species are not interconverting systems. This assumption could be confirmed by a NOESY spectra, because no cross signals can be seen between the NH resonances of the two species (SI). Additionally, a DOSY spectrum was recorded (Figure 4). It is obvious that the two sets of signals are species of different sizes and have different diffusion coefficients. The smaller species has a diffusion coefficient of log D = −9.74, the larger of log D = −9.86. As described above, the second, spatially larger species is subject to stronger hydrogen bonding due to the low shift of the NH resonance. From the DOSY experiment, it becomes apparent that the difference in diffusion coefficients (D = −9.74 and D = −9.86) is rather small. Because the NOESY experiment (SI) clearly shows that these are not interconverting species, we can conclude that the second species is an aggregate of (S_{ax},*R*,*R*)-**4** with anhydrous DMSO, which is suppressed by the addition of water.

To investigate the *atropos* property of ligand (S_{ax},*R*,*R*)-**4**, DFT calculations at the B3LYP/6-31G* level of theory were performed. The interconversion barrier $\Delta G^{\ddagger}$ of biaryl (S_{ax},*R*,*R*)-**4** could be determined to be 148.7 kJ mol^{-1}, which corroborates the highly *atropos* nature of the cyclic diamide-bridged biaryl. This is

FIGURE 2 ORTEP representation of the XRD crystal structure of (S_{ax},*R*,*R*)-**3** crystallized from DMSO. Ellipsoids are shown with 50% probability; blue: Carbon, light gray: Hydrogen, red: Oxygen, purple: Nitrogen, yellow: Sulphur

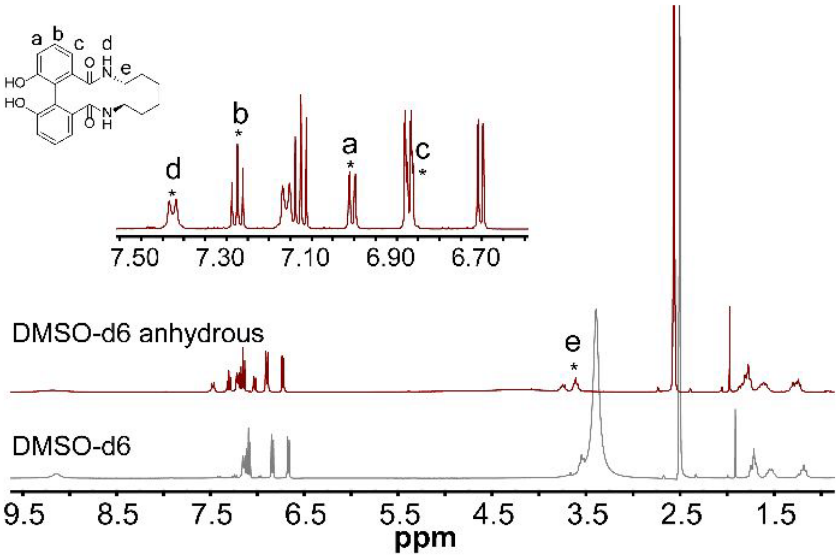


FIGURE 3 ^{1}H NMR spectra of (S_{ax},*R*,*R*)-**4** in DMSO-d_6, aqueous (gray) and in DMSO-d_6, anhydrous (red) and a magnified section of the aromatic region of the spectrum in DMSO-d_6, anhydrous (red). Two species are visible in anhydrous DMSO-d_6, in a 40:60 ratio (400.33 MHz, 298.15 K)

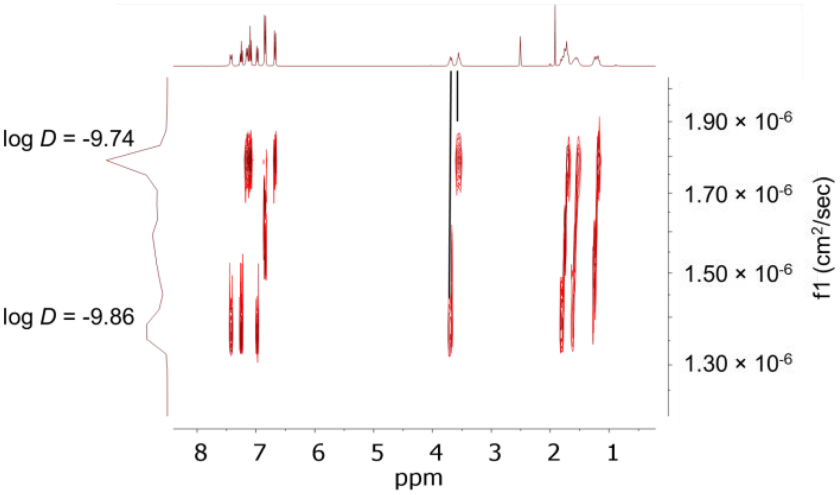


FIGURE 4 Section of the DOSY spectrum of (S_{ax},*R*,*R*)-**4** (400 MHz, 300 K, DMSO-d6). The diffusion coefficient log D = −9.74 corresponds to the constant of the monomeric compound, log D = −9.86 to that of the aggregate of (S_{ax},*R*,*R*)-**4** with anhydrous DMSO

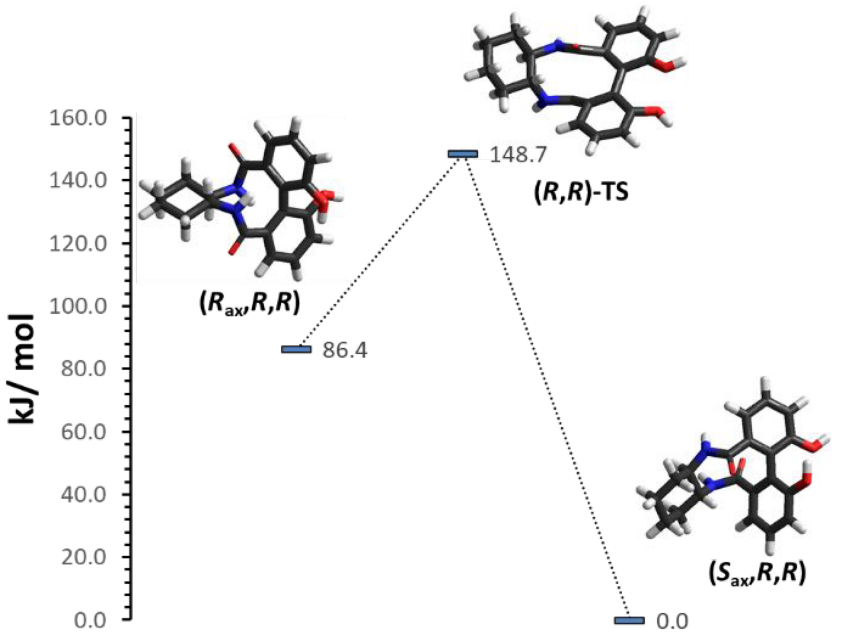


FIGURE 5 Energy profile of the interconversion of (S_{ax},*R*,*R*)-**4** to (R_{ax},*R*,*R*)-**4**. Energies were obtained by DFT calculations at the B3LYP/6-31G* level of theory

supported by the experimental XRD data and HPLC separations at elevated temperatures, which do not show any dynamic behavior. A rotation of the biaryl axis is therefore inhibited at room temperature. In addition, the change in the configuration of the axis would have to be accompanied by a conformational change of the cyclohexane ring, which leads to a structure that is less favorable by $\Delta\Delta G^{\circ}$ (298.15 K) = 86.4 kJ mol^{-1} (Figure 5). This means that the S_{ax} configured (S_{ax},*R*,*R*)-**4** is thermodynamically favored.

4 | CONCLUSION

In the present contribution, a cyclic diamide-bridged biaryl compound was prepared in a diastereoselective synthesis using (*R*,*R*)-DACH as directing moiety in the backbone of the ligand. The configuration of the chiral axis was determined by XRD crystallography. The aggregation behavior of (S_{ax},*R*,*R*)-**4** by hydrogen bond formation was examined by NMR measurements. Furthermore, the interconversion barrier of (S_{ax},*R*,*R*)-**4** was determined by DFT calculations to be $\Delta G^{\ddagger} = 148.7$ kJ mol^{-1}.

The here presented straightforward synthetic strategy offers the possibility to synthesize diamide-bridged biaryl compounds with a broad range of chiral diamines and allows the control of the dihedral angle. These well-defined atropos axially chiral biaryl compounds are versatile structures as ligands in asymmetric catalysis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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