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Scorpio-Ligand: Synthesis of Biphenyl-Dihydroazepine Phosphoramidite Ligands for Asymmetric Hydrogenation

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Dedicated to *Peter Kündig* on the occasion of his 75th birthday

A novel dihydroazepine-bridged BIPHEP phosphoramidite ligand with an amino acid moiety in the backbone was synthesized and evaluated in the Rh-catalyzed asymmetric hydrogenation. The scorpion tail-like amino acid backbone is capable of hydrogen bond formation and able to shift the rotamer composition of the biphenyl axis with the two scissor-like arms. Pivaloyl-L-valine was studied as chiral selector unit and compared with pivaloylglycine as the achiral reference substance. The enantiomerization barrier of the pivaloylglycine-modified biphenylamide was determined to be $\Delta G^{\ddagger}$ = 110 kJ/mol. In the case of pivaloyl-(*S*)-valine, the S_{ax} isomer is thermodynamically favored. Due to the relatively high barrier, the ligand is atropic at room temperature and allows the preparative separation of the stereoisomers. The obtained phosphoramidite ligands were separated by chiral HPLC. For the first eluting rotamer, Rh complex ([Rh(cod)(L)$_2$]BF$_4$) was generated *in situ* and examined in the enantioselective hydrogenation of 2-acetamidoacrylate and methyl 2-acetamido-3-phenylacrylate, achieving enantiomeric excesses of up to 94%.

Keywords: asymmetric hydrogenation • biphenyl ligand • chiral preparative HPLC • heterocycle • rhodium catalyst

Introduction

Chiral azepine and dihydroazepine biphenyls are utilized as ligands and organocatalysts in various enantioselective reactions. As bidentate compounds, such as diamines and aminophosphines, with a binaphthyl backbone, they found application in the enantioselective addition of alkyl lithium to aldehydes for the synthesis of chiral alcohols (Figure 1a),[1] the enantioselective dihydroxylation of olefins using OsO_4 (Figure 1a)[2] and the enantioselective palladium-catalyzed allylic alkylation (Figure 1b).[3] Bidentate aminoalcohols were used in the enantioselective addition of diethylzinc to aromatic aldehydes with high enantioselectivities (Figure 1c).[4,5] The dihydroazepine-bridged biphenyl shown in Figure 1d) was successfully used in the cross aldol reaction[6] as well as in the Mannich reaction.[7] Maruoka *et al.* used dihydroazepine-bridged catalyst for the regio- and stereoselective conjugate addition of aldehydes to β-tosyl enones with high syn selectivity and up to 94% *ee* (Figure 1e).[8] Modifying the naphthalene backbone to a biphenyl-based backbone and introducing substituents that can act as hydrogen bond donors, the enantioselective and diastereodivergent conjugate addition of aldehydes to electron-deficient olefins was accomplished with high enantiomeric excess and moderate anti-regioselectivity (Figure 1f).[9] Another application of azepine-bridged biaryls and their salts is the asymmetric epoxidation of olefins (Figure 1g and h).[10-12]

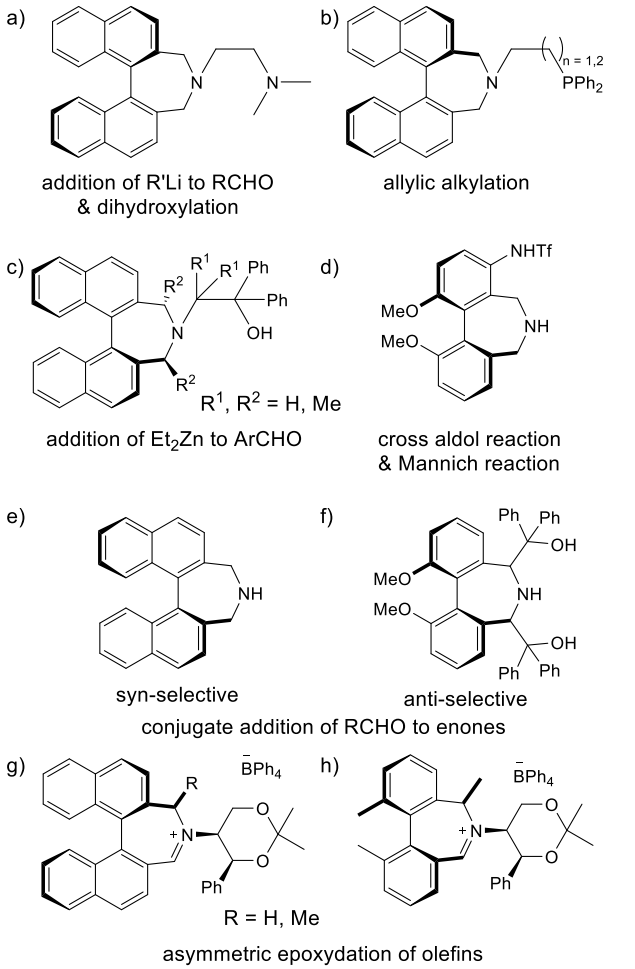

Figure 1. Examples for azepine- and dihydroazepine-bridged ligands and organocatalysts and their use in enantioselective reactions.

While the compounds shown in Figure 1 are *atropos* due to the implemented binaphthyl backbone as well as diortho substitution, lacking

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substituents in the 6,6'-positions compounds are stereodynamically flexible. However, by introducing substituents into the dihydroazepine ring, one of the isomers can be enriched. This was first recognized by Kündig *et al.* who were able to assign a predominant (S_{ax}) configuration to the amine in Figure 2a.[13,14] More recently, Zhang *et al.* reported an Ir-catalyzed intramolecular asymmetric reductive amination that succeeded in synthesizing various dihydroazepine compounds with up to 97% *ee* (Figure 2b).[15]

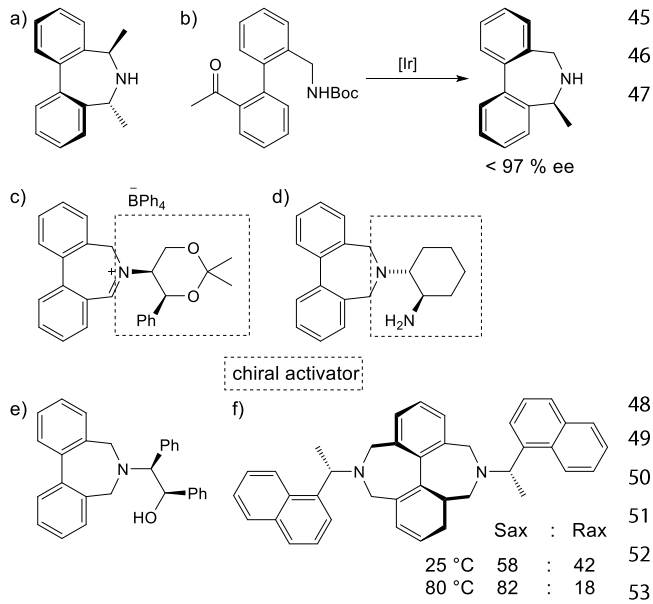
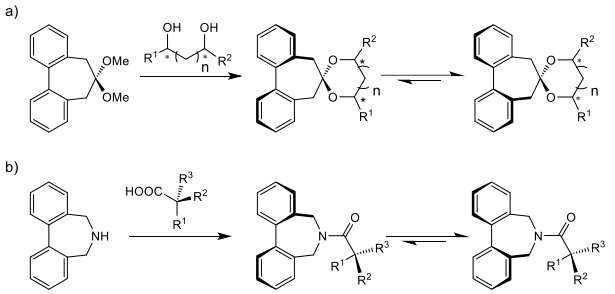


Figure 2. a) Kündig's amine, b) *atropos* selective synthesis of dihydrozepine-bridged compounds, c) and d) flexible biphenylazepines, e) biphenyldihydroazepine, and f) double-bridged biphenyl dihydroazepine stable at room temperature and flexible at 80 °C.

In addition to the introduction of substituents, the use of a chiral activator is another option to induce a shift out of the stereoisomer equilibrium by center-to-axis chirality transfer (Figure 2c[12] and d[16]). Scafato *et al.* employed the dihydroazepine-bridged biphenyl shown in Figure 2e as a ligand in the enantioselective aryl transfer to aromatic aldehydes, obtaining *ee*'s of up to 96%. Electronic circular dichroism spectroscopy (ECD spectroscopy) was used to investigate the chirality transfer of the chiral amino alcohol to the flexible biphenyl in favor of the (R_{ax}) configuration.[17] The enantiomeric excesses achieved with tropos ligand 2e are thus comparable to an atropos (R_{ax})-binaphthyl-based analogue, developed by Chan *et al.* with *ee*'s of up to 99% in the asymmetric arylation of aromatic aldehydes.[18] Lacour *et al.*[19] investigated double-bridged biphenyls in which the axis is atropic at room temperature but becomes stereodynamically flexible at elevated temperature. For the example shown in Figure 2f, the axis is oriented in favor of the (S_{ax}) configuration by kinetic control at room temperature (S_{ax}:R_{ax}) = 58:42. At 80 °C (20 h, benzene), the equilibrium shifts further toward the (S_{ax}) configuration (S_{ax}:R_{ax}) = 82:18.

Rosini and Superchi *et al.* developed a method to determine the absolute configuration of chiral compounds, such as chiral 1,2- and 1,3-diols (Scheme 1a),[20] chiral primary amines[21] and chiral carboxylic acids (Scheme 1b),[22] using simple, chiroptical methods. The basic requirement for this type of absolute configuration determination is the coupling of the chiral compounds to chiroptically active chromophores. Center-to-axis chirality transfer of the covalently-bound chiral compounds to the flexible, chiroptically-active biphenyls induces a preferential twist of the biaryl axis. CD spectroscopic measurements can then be used to determine the sense of chirality of the axis in the chromophores and the absolute configuration of the chiral compound is deduced thereafter by indirect evidence. In this regard, Rosini and Superchi succeeded in identifying a general mechanism for the influence of the chiral compounds, depending on their sterics, on the preferred axial orientation of the flexible biphenyls.[22]



Scheme 1. Determination of the absolute configuration of a) chiral 1,2- and 1,3-diols and b) chiral carboxylic acids by coupling to 2,2'-bridged biphenyls as chromophores. A center-to-axis chirality transfer induces preferential twisting of the biphenyl axis, which can be studied by CD spectroscopy.

Here we present the synthesis and characterization of 6,6'-dihydroazepine-bridged-2,2'-biphenol-based ligands with amino acid- selector units in the dihydroazepine backbone (scorpio-type ligand), which can form intermolecular hydrogen bonds and, as chiral activators, can shift the rotamer equilibrium by chirality transfer to the biaryl axis. Pivaloyl-L-valine and L-proline were chosen as chiral selector units. For comparison the ligand with achiral pivaloylglycine in the backbone was prepared (Figure 3).

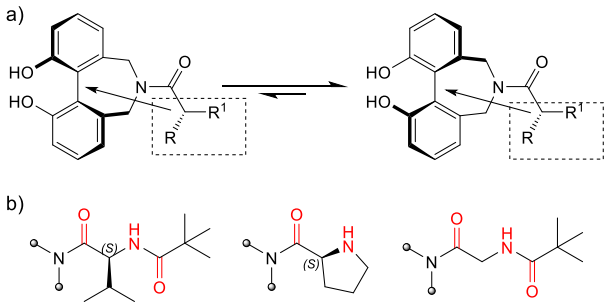


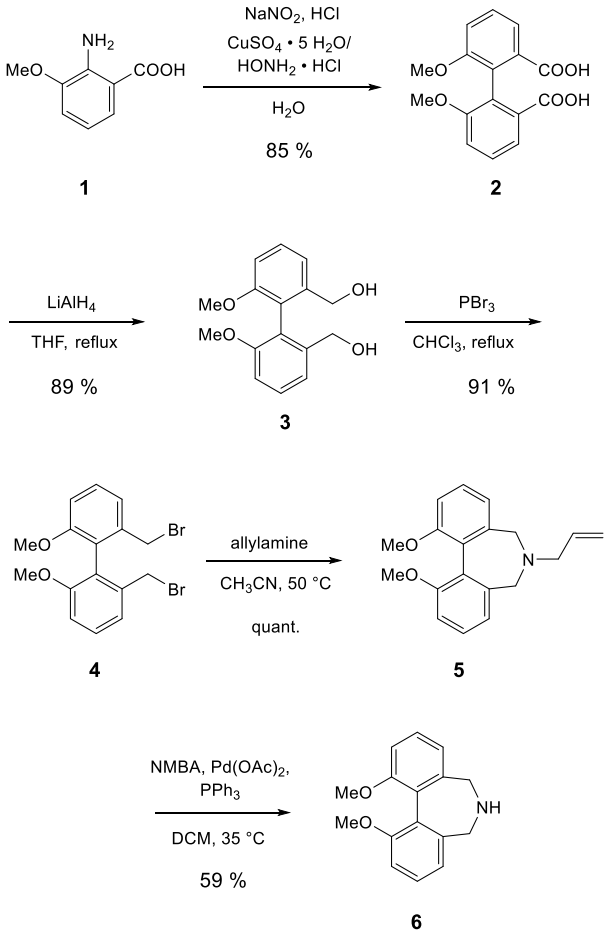
Figure 3. a) Targeted dihydroazepine-bridged biphenols. *N*-acylated with b) pivaloyl-L-valine, L-proline and pivaloylglycine, respectively.

L-Valine and L-proline derived selectors for stereodynamic biphenyls were introduced by Trapp *et al.* in self-amplifying supramolecular catalysts[23-32] and were originally developed as enantioselective selectors[33] in chiral stationary phases for chiral GC, i.e. Chirasil-Val,[34,35] and proline-based chiral stationary phases developed by Pirkle *et al.* for chiral HPLC.[36,37]

Furthermore, in this work we investigated in detail the stereodynamics and the performance of the chirality transfer to the axis in these scorpio-ligands. Finally, these ligands were employed in enantioselective Rh-catalyzed hydrogenations.

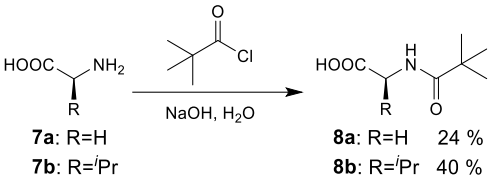
Results and Discussion

The dihydroazepine-bridged biphenyl was synthesized starting from 2-amino-3-methoxybenzoic acid **1**. For this purpose, 6,6'-dimethoxy-(1,1'-biphenyl)-2,2'-dicarboxylic acid **2** was first prepared in a modified Sandmeyer reaction with $NaNO_2$ and a Cu(I) catalyst in 85% yield.[38] This was followed by reduction of the dicarboxylic acid with $LiAlH_4$ to give the diol **3** in a yield of 89%. After bromination with PBr_3 (91%), the dibromide **4** was quantitatively cyclized with allylamine to give the bridged allyldihdroazepine **5**. Deprotection with 1,3-dimethylbarbituric acid (NMBA), $Pd(OAc)_2$, and PPh_3 afforded the dihydroazepine-bridged biphenyl **6** in a yield of 59% (Scheme 2).[3940]



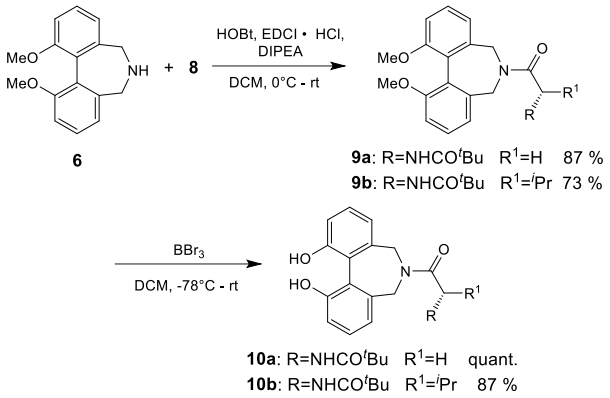
Scheme 2. Synthesis route of dihydroazepine-bridged biphenyl **6**.

The selectors pivaloylglycine **8a** and pivaloyl-L-valine **8b** were synthesized starting from the corresponding amino acids **7** using pivaloyl chloride and a 2M NaOH solution. The enantiomeric purity of pivaloyl-L-valine was then determined by analytical HPLC (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 85:15, t_1 = 5.68 min) and reference samples to 99% (Scheme 3).



Scheme 3. Synthesis of the selectors pivaloylglycine and pivaloyl-L-valine.

The coupling of the selector-modified biphenylamides **10a-b** was carried out using HOBt, EDCI·HCl, and DIPEA followed by deprotection with BBr_3 (Scheme 4).



Scheme 4. Synthesis of the selector-modified biphenylamides **10a-b**.

Coupling attempts with L-proline resulted in a polymerization of proline. Coupling of the dihydroazepine biphenyl with pivaloylglycine afforded **9a** in 87% yield. Subsequent deprotection was quantitative, and the biphenylamide **10a** was obtained as racemate, as confirmed by analytical HPLC (Chiralpak IA, 1 mL/min, *n*-hexane:*i*-PrOH, 85:15, t_1 = 9.6, t_2 = 13.6 min).

Racemization of the valine selector occurred upon coupling pivaloyl-L-valine with bridged dihydroazepine biphenyl **6** yielding **9b** as four stereoisomers in 73% yield in a ratio of 22:29:21:28 (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 80:20, t_1 = 5.3, t_2 = 6.6, t_3 = 12.6, t_4 = 15.4 min). We also observed racemization when other coupling reagents, such as COMU in DMF and EDCI·HCl/DMAP in DCM, were used. After deprotection, **10b** was obtained in 87% yield.

The assignment of the configurations of the four stereoisomers of the pivaloylvaline-modified biphenylamide was performed according to Rosini and Superchi *et al.*[21,22,39] They used flexible dihydrozepine biphenyls as chromophores to determine the absolute configuration of carboxylic acids by circular dichroism spectroscopy (CD spectroscopy). Due to the chirality transfer of the stereogenic carboxylic acids to the axially chiral biphenyl, a rotamer is thermodynamically preferred. The sign of the A band in the CD spectrum correlates with the chirality of the axis of the biphenyl. With a negative A band, the configuration (S_{ax}) is present, and with a positive A band, (R_{ax}) is present (Figure 4a). This approach, based on the observation of the sign of the A band of the CD signal, allows the determination of the absolute configuration of the carboxylic acid. Here, the preferred orientation of the axis, in the case of alkyl-substituted substances, is determined by their size and the resulting steric interactions.

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Figure 4 shows the orientation of the rotamers of dihydroazepine biphenylamide using an *N*-Boc-(*S*)-valine substituent.[20,39] For the (S_{ax}) configuration, the largest group (R_L), the isopropyl group, is sterically more favorably oriented than for the (R_{ax}) configuration. Therefore, the rotamer equilibrium is shifted to the (S_{ax}) configuration, for *N*-Boc-(*R*)-valine *vice versa*.[20,39]

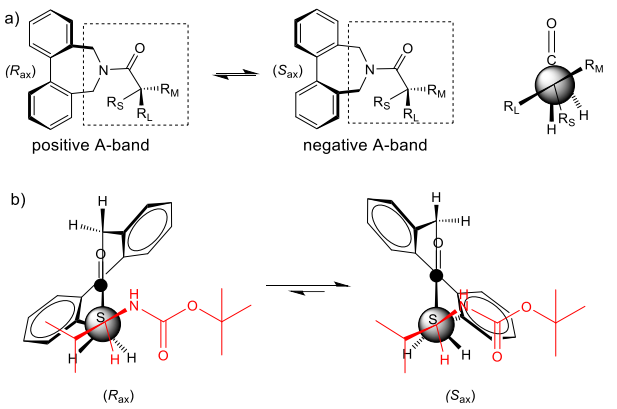


Figure 4. a) Illustration of rotamer equilibrium in alkyl-substituted biphenylamides and the corresponding sign of the A band. b) Relationship between the preferred orientation of the axis and the configuration of the chiral substituent *N*-Boc-(*S*)-valine, due to steric interactions.[20,39]

To determine the position of the A band of the pivaloylvaline-modified ligand **10b**, the UV spectrum of the ligand was first examined during the HPLC measurement, since only a single wavelength can be recorded per measurement with the available CD detector. Figure 5a shows the HPLC chromatogram of the ligand (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 90:10, 280 nm). Figure 5b shows the UV spectrum of the first eluting stereoisomer. The absorption maximum of the A band can be determined to be λ_{max} = 290 nm. In comparison to the dihydroazepine biphenylamides studied by Rosini and Superchi *et al.* (A band at λ_{max} = 250 nm), a bathochromically shifted A band results due to the OH substitution in the 2 and 2' position.

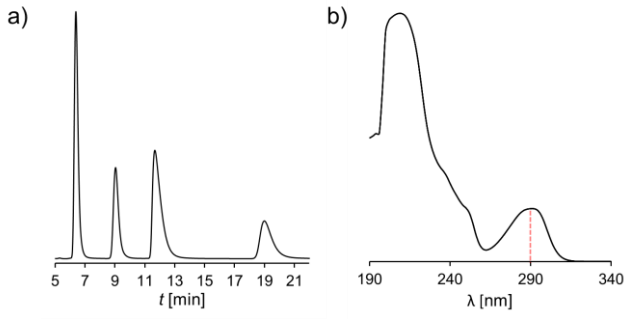


Figure 5. a) HPLC chromatogram of **10b** (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 90:10). b) UV spectrum of the first eluting stereoisomer, λ_{max} = 290 nm.

By coupling HPLC (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 90:10) with a CD detector, the sign of the CD signal and the configuration of the biaryl axis could be determined for all four stereoisomers (Figure 6). The four stereoisomers of **10b** are present in a ratio of 34:17:33:16, allowing isomer 1 and 3 and isomer 2 and 4 to be identified as enantiomeric pairs. The two isomers eluted first can be assigned to the (R_{ax}) configuration based on the positive CD signal, and the last two can be assigned to the (S_{ax}) configuration (negative signal). Assuming that the isopropyl group has the largest steric influence over the H atom and the pivaloyl group, the pivaloylvaline substituent of the first and last eluting isomers can additionally be assigned to the (*R*) configuration, since the (R_{ax}) configuration is preferred for pivaloyl-(*R*)-valine. Accordingly, the second and third isomers are the pivaloyl-(*S*)-valine substituent for which the (S_{ax}) configuration is preferred.

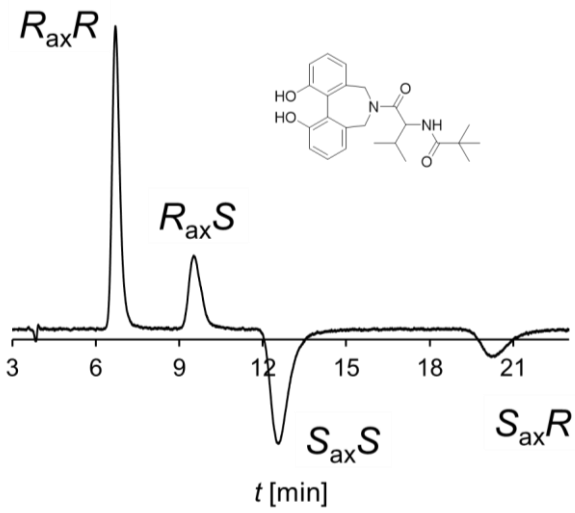


Figure 6. HPLC-CD signal of **10b** at 290 nm (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 90:10).

To investigate the stereodynamics of these four isomers, we separated them by semi-preparative HPLC, (Chiralpak IC, 20 mL/min, *n*-hexane:*i*-PrOH 90:10) and then annealed them individually for 18 h in *i*-PrOH at 80 °C. Partial inversion of the biphenyl axis into the corresponding ($S_{ax}R$) isomer was observed for the ($R_{ax}R$) isomer sample (Figure 7a). The resulting diastereomer mixture was in the ratio ($R_{ax}R$)/($S_{ax}R$) of 75:25. In contrast, diastereomerization to a mixture of ($R_{ax}S$)/($S_{ax}S$) in the ratio of 30:70 was observed for the ($R_{ax}S$) isomer (Figure 7b). We have to point out that the ratios of the inversion of ($R_{ax}R$)/($S_{ax}R$) and ($R_{ax}S$)/($S_{ax}S$) should theoretically be identical. The deviation indicates that the latter sample was not completely equilibrated.

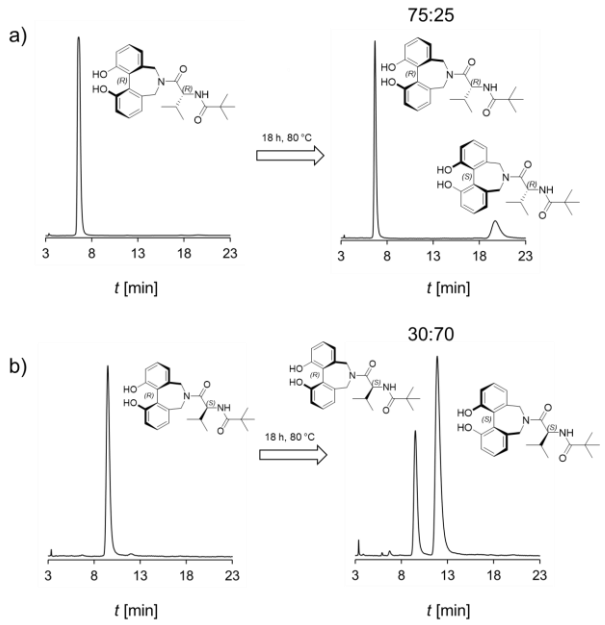


Figure 7. Change in composition of the isomers of **10b**. a) ($R_{ax}R$) and b) ($R_{ax}S$) separated at room temperature after 18 h at 80 °C.

Rotation about the biphenyl axis is by far the more likely process upon heating compared to isomerization of the chiral selector. Therefore, from the results of the temperature experiments, the assignment of the rotamers ($R_{ax}R$)/($S_{ax}R$) (peak 1/peak 4) and ($R_{ax}S$)/($S_{ax}S$) (peak 2/peak 3) in Figure 7 can be confirmed, since in each case diastereomerization was observed exclusively into the isomer to which a different axial configuration was assigned. Furthermore, for the (*S*)- or (*R*)-pivaloylvaline substituent, in each case a rotamer is thermodynamically preferred by chirality transfer to the axis. Through thermal influence, the diastereomeric ratio between the enantiomer pair ($R_{ax}R$)/($S_{ax}S$) and the enantiomer pair ($S_{ax}R$)/($R_{ax}S$) can thereby be adjusted to approximately 3:1.

The difference in free enthalpy ΔG° of the two rotamers ($R_{ax}R$)/($S_{ax}R$) and ($R_{ax}S$)/($S_{ax}S$) can be estimated:

$$\Delta G^\circ = -RT \cdot \ln K \qquad \text{with } K = \frac{A_1\,(R_{ax})}{A_2\,(S_{ax})} \qquad \text{(Eq. 1)}$$

This results in a value of ΔG° ($R_{ax}R$)/($S_{ax}R$) = -3.23 kJ/mol in favor of the (R_{ax}) isomer. For the second experiment, ΔG° ($R_{ax}S$)/($S_{ax}S$) was determined to be 2.49 kJ/mol. In this case, the (S_{ax}) isomer is thermodynamically favored. The difference in free enthalpy is due to incomplete equilibration in the second experiment.

The structurally very similar pivaloylglycine-modified biphenylamide **10a** was chosen for the detailed study of the racemization kinetics of the dihydroazepine biphenyls, since only two isomers are present here, facilitating the determination of the interconversion barrier.

Multidimensional stopped-flow three-column chromatography was used for measuring the enantiomerization kinetics[41-45] of pivaloylglycine modified biphenylamide ligand **10a**, which is a further development of the dynamic three-column chromatography.[46] The enantiomerization rate constants k_{enant} and the activation parameters $\Delta H^\ddagger$, $\Delta S^\ddagger$ and Gibbs free energy $\Delta G^\ddagger$ were determined. This technique enables the determination of rotational barrier too high to be investigated by dynamic HPLC. Furthermore, the analytes do not have to be separated preparatively by column chromatography prior to measurement.

Figure 8 shows the experimental setup of the three columns connected in series. On the middle, achiral column (Nucleodur), racemization takes place by increasing the temperature (here: in the range of 45 °C to 70 °C). Chiralpak IA 3 (particle size 3.00 µm, inner diameter 4.60 mm, length 15.0 cm) and Chiralpak IA (particle size 5.00 µm, inner diameter 4.60 mm, length 25.0 cm) columns were used for enantiomer separation. The three columns are connected to each other via capillaries.

On the first, chiral column (Chiralpak IA-3), operated at room temperature, the enantiomers are separated (Figure 8a) and then swept onto a second, achiral column (Nucleodur). There, the solvent flow is stopped and the temperature of the column is raised by a thermostat (temperatures in the range between 45 °C and 70 °C), allowing partial racemization of the separated enantiomers and determination of the rates $k_{rac} = 2\ k_{enant}$, depending on the column temperature *T* and the reaction time Δt. The interconversion changes the enantiomeric composition of the two peaks. The newly formed enantiomers are designated (*R'*) and (*S'*) (Figure 8b). To study the new enantiomeric composition, flow is resumed, and the enantiomers elute through a third, chiral column (Chiralpak IA). This column is again kept at room temperature, preventing progressive racemization. The re-separation leads to a third peak (peak overlap of peak (*S'*) and (*R'*)) with a retention time which lies between the two peaks of the original enantiomers (*S*) and (*R*) (Figure 8c).

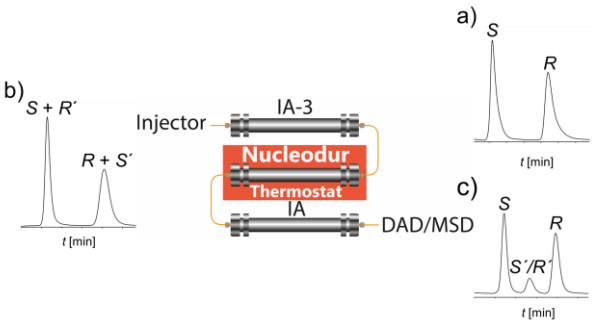


Figure 8. Schematic setup and corresponding chromatograms for measuring the racemization kinetics of the ligand by multidimensional stopped-flow three-column chromatography. The compound is purged at room temperature by the first, chiral column (IA-3), separating the enantiomers ((*S*) and (*R*)). On the second, achiral column (Nucleodur), the solvent flow is stopped, and the temperature is increased, resulting in racemization of the enantiomers. The flow is then resumed. The enantiomers elute at room temperature through the third, chiral column (Chiralpak IA) and are detected by UV spectroscopy (DAD) and mass spectrometry (MSD).

From the integrated chromatographic peak areas A_S, A_R and $A_{S';R'}$, the rate constant k_{enant} can then be calculated according to equation 2. The equation has already been used to calculate the rate constant in dynamic

three-column chromatography[46] as well as in multidimensional stopped-flow gas chromatography (sfMDGC).[47,48] The enantiomerization rate constants[49] k_{enant} are obtained according to the following equation:

$$k_{enant} = \frac{k_{rac}}{2} = \frac{1}{2\Delta t} \ln\left(\frac{er+1}{er-1}\right) = \frac{1}{2\Delta t} ln\left(\frac{A_S+A_R+A_{S',R'}}{A_S+A_R-A_{S',R'}}\right) \quad \text{(Eq. 1)}$$

Figure 9 shows the experimental peak profiles for determining the racemization kinetics of **10a** by multidimensional stopped-flow three-column chromatography. The corresponding integrated peak areas and the enantiomerization rate constants k_{enant} calculated are summarized in Table S1 in the supplementary information.

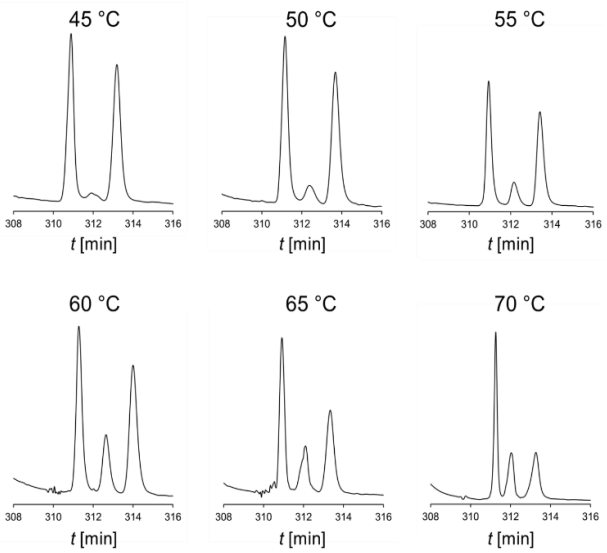


Figure 9. Experimental peak profiles for the determination of racemization kinetics of **10a** by multidimensional stopped-flow three-column chromatography (Chiralpak IA 3 (rt), Nucleodur (45 °C to 70 °C), Chiralpak IA (rt), 2 µL, 1 mL/min, *n*-hexane:EtOH, 60:40, 280 nm).

The Gibbs energy $\Delta G^{\ddagger}$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined by the Eyring equation regression analysis by plotting $\ln(k_{enant}/T)$ against T^{-1} (Figure 10).

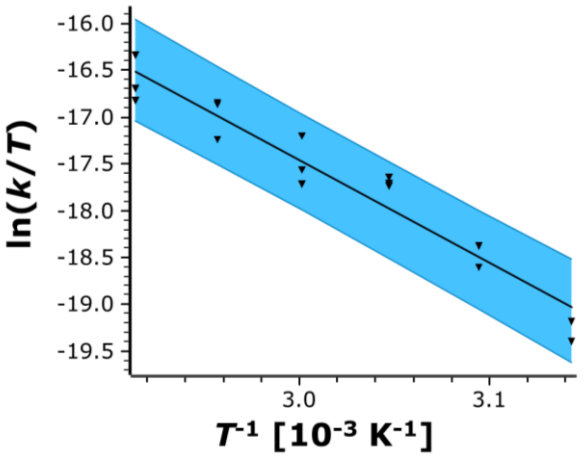
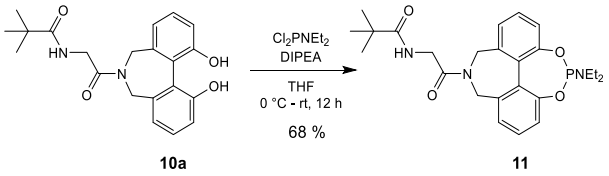


Figure 10. Eyring plot and linear regression with a confidence level of 95% for the determination of the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of enantiomerization from the multidimensional stopped-flow three-column chromatography experiment.

From the evaluation of the Eyring plot (correlation factor r = 0.9598, residual deviation σ_y = 0.2561), the following parameters were determined: $\Delta H^{\ddagger}$ = 91.72 ± 6.93 kJ/mol, $\Delta S^{\ddagger}$ = -61.8 ± 9.9 J/(K mol), and $\Delta G^{\ddagger}$(298.15 K) = 110.15 kJ/mol. The pivaloylglycine-modified biphenylamide **10a** is *atropos* at room temperature but can be interconverted at elevated temperatures. The significantly negative value for the activation entropy suggests a highly ordered transition state during atropisomerization.

The determined Gibbs energy $\Delta G^{\ddagger}$ agrees very well with tetra-ortho substituted single lactone bridged biphenyls,[50,51] double bridged dihydroazepine biphenyls (~ 104 kJ/mol),[19] and di-ortho substituted biphenyls with sterically demanding substituents (-CF_3, -iPr, ~ 107 - 112 kJ/mol).[52]

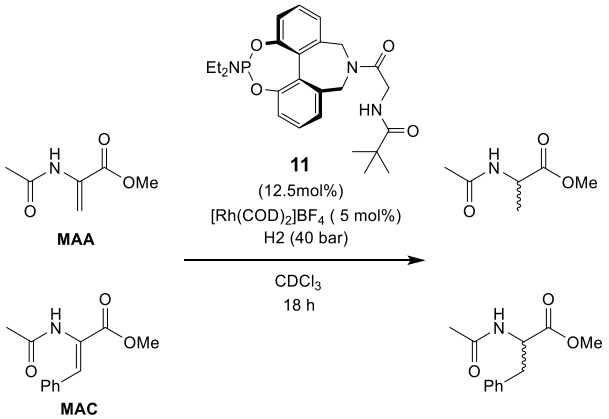
The corresponding phosphoramidite ligand was then synthesized from the pivaloylglycine-modified biphenylamide **10a.** The reaction was performed by reacting **10a** with Cl_2PNEt_2 and DIPEA in THF according to Scheme 5.



Scheme 5. Synthesis of phosphoramidite ligand **11.**

The absolute configuration was determined by the analysis of the sign of the CD signal of **11** at 280 nm coupled to chiral HPLC (Chiralpak IC, 1 mL/min, *n*-hexane:*i*-PrOH, 90:10, *vide supra*). The first eluting rotamer was assigned to the (S_{ax}) configuration based on the negative A band, and the second rotamer (positive A band) to the (R_{ax}).

For the hydrogenations, the first eluting rotamer (S_{ax}) was isolated by semi-preparative HPLC (Chiralpak IC, 20 mL/min, *n*-hexane:*i*-PrOH, 90:10). The synthesis of the Rh catalyst was performed in situ. $[Rh(COD)_2]BF_4$ and 2.5 eq. of the ligand were mixed in anhydrous and degassed $CDCl_3$ and stirred for 30 min. The hydrogenation substrate methyl 2-acetamidoacrylate (MAA) or methyl 2-acetamido-3-phenylacrylate (MAC) was then added, and the reaction mixture was transferred to an autoclave and hydrogenated at 40 bar (Scheme 6).



Scheme 6. Rh-catalyzed hydrogenations of MAA and MAC with *rac*-**11** and (S_{ax})-**11**.

In Table 1 the results of the hydrogenation experiments are summarized.

Table 1. Results of the Rh-catalyzed hydrogenations of MAA and MAC.

entry	ligand **11**	substrate	*T* [C°]	yield [%]	*ee* [%] *R*
1	*rac*	MAA	25	25	0
2	S_{ax}	MAA	25	100	84
3[a)]	S_{ax}	MAA	-20	52	94
4	S_{ax}	MAA	-40	100	84
5	S_{ax}	MAC	25	99	77
6	S_{ax}	MAC	-20	100	94
7	S_{ax}	MAC	-40	77	73

a) experiment stopped after 9h.

For MAA, an *ee* of 84% was obtained in favor of the (*R*)-enantiomer at room temperature (entry 2). At -20 °C, the *ee* increased to 94 % (entry 3). For MAC, an *ee* of 77% was obtained at room temperature (entry 5) and an *ee* of 94% at -20 °C. However, lowering the temperature to -40 °C did not improve the enantioselectivity for either MAA or MAC (entries 4 and 7).

Conclusions

In the present contribution pivaloylglycine- and pivaloylvaline-modified dihydroazepine-bridged biphenylamides were synthesized and characterized by HPLC and HPLC-CD measurements. These scorpio-type ligands are *atropos* at room temperature but interconvertible to each other at elevated temperature (80 °C). The influence of the selectors pivaloyl-(*S*)-valine and pivaloyl-(*R*)-valine on the preferred orientation of the biaryl axis was investigated. For pivaloyl-(*S*)-valine the (S_{ax}) configuration is thermodynamically preferred, for pivaloyl-(*R*)-valine the (R_{ax}) configuration. The core structure of dihydroazepine-bridged biphenyl **6** offers the possibility to synthesize a variation of ligands with different, chiral selectors by amide coupling. The chiral auxiliaries can be used to thermodynamically induce rotamer enrichment by central-to-axial chirality transfer. The pivaloylglycine-modified dihydroazepine-bridged BIPHEP phosphoramidite ligand (S_{ax})-**11** was successfully used after preparative separation in the Rh-catalyzed enantioselective hydrogenation of MAA and MAC. Enantiomeric excesses of up to 94% were achieved for MAA and MAC at -20 °C.

Experimental Section

General Experimental Details

All reactions involving the use of 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 done using silica gel (technical grade, pore size 60 Å, 70-230 mesh, 63-200 µm) produced by Sigma-Aldrich Chemie GmbH. Thin layer chromatography was performed on coated aluminum sheets (Macherey-Nagel POLYGRAM SIL G/UV 254). Components were visualized by fluorescence quenching during irradiation with UV light (254 nm). Anhydrous solvents were taped from solvent purification system MB SPS-800 and used immediately. Anhydrous and stabilized THF (250 ppm butylated hydroxytoluene) was purchased from Sigma-Aldrich Chemie GmbH. Manual degassing of solvents, if needed, was done by performing three consecutive freeze-pump-thaw cycles. Oxygen-free solvents were then put under an atmosphere of argon.

NMR spectra were recorded on Varian NMR-System (600 MHz) and Bruker Avance III HD (400 MHz). NMR shifts are given in parts per million (ppm) and are referenced to the residual proton or carbon solvent signals.[53] Multiplicity is termed as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of a doublet), ddt (doublet of a doublet of a triplet) 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). To improve comprehensibility, Atom numbering for NMR-assignments is not based on IUPAC nomenclature. The numbered structures are shown in the supporting information. Mass spectra were acquired on Thermo Finnigan LTQ FT Ultra FT-ICR (ESI) or Thermo Thermo Q Exactive Plus Hybrid Quadrupole Orbitrap (ESI). For solid-state IR analysis, Thermo Fisher Nicolet 6700 FT-IR-Spectrometer was employed. HPLC and 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). HPLC-CD 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 circular dichroism chiral detector (*Jasco Model CD-2095, Tokyo, Japan*). Preparative HPLC separations were performed on a *Agilent Technologies 1260 Infinity* (Agilent Technologies, Palo Alto, California, USA), equipped with a binary solvent pump, an autosampler, fraction collector and DAD detector. The solvents used (*n*-hexane, isopropyl alcohol and ethanol) were obtained from *Sigma-Aldrich* (HPLC-grade quality).

Compounds

6-Allyl-1,11-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepine **5**

This compound was synthesized according to a literature procedure,[39] which was slightly modified. To a solution of **4** (5.48 g, 13.7 mmol, 1.00 eq.) in acetonitrile (70 mL) allylamine (3.7 mL, 49.3 mmol, 3.60 eq.) was added and the mixture was stirred at 50°C for 4 h. Water (50 mL) was added and the aqueous layer was extracted with dichloromethane (3×40 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The product was obtained in quantitative yield as a dark yellow oil (3.98 g, 13.5 mmol, 97 %).

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^{1}H NMR (400.33 MHz, Chloroform-*d*, 300 K) δ = 3.03 – 3.13 (m, 4H, H7, H8), 3.60 (d, ^2J(H,H) = 12.3 Hz, 2H, H7), 3.84 (s, 6H, H11), 5.17 – 5.32 (m, 2H, H10), 5.98 (ddt, ^3J(H,H) = 16.9 Hz, ^3J(H,H) = 10.1 Hz, ^3J(H,H) = 6.7 Hz, 1H, H9), 6.96 (dd, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.1 Hz, 2H, H5), 7.00 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 1.1 Hz, 2H, H3), 7.33 (dd, ^3J(H,H) = 8.3 Hz, ^3J(H,H) = 7.4 Hz, 2H, H4). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.66 MHz, 300 K): δ =54.4 (2C, C7), 56.0 (2C, C11), 58.4 (C8), 110.8 (2C, C3), 118.2 (C10), 122.1 (2C. C5), 125.5 (2C, C1), 128.8 (2C, C4), 135.9 (2C, C6), 136.3 (C9), 156.7 (2C, C2) ppm. **HRMS (ESI)**: m/z calcd. for $C_{19}H_{22}O_4N$ [M+H]$^+$: 291.1645; found: 291.1642.

General procedure for the synthesis of biphenyl amides

N-protected amino acid (1.00 eq) and HOBt·xH_2O (1.25 eq.) were dissolved in dry dichloromethane and DIPEA (1.25 eq.) was added. The solution was cooled in an ice bath and EDCI·HCl (1.25 eq.) and 1,11-dimethoxy-6,7-dihydro-5H-dibenzo[c,e]azepin (1.25 eq.) were added. After 15 minutes at lower temperature, the mixture was warmed to room temperature and stirring was continued for 18 hours. The mixture was diluted with ethyl acetate and washed with 1M HCl solution, $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent was evaporated. The product was purified using column chromatography.

N-(2-(1,11-Dimethoxy-5,7-dihydro-6H-dibenzo[c,e]azepin-6-yl)-2-oxoethyl)pivalamide ***9a***

9a was synthesized according to the general procedure using pivaloylglycine (239 mg, 1.50 mmol, 1.00 eq.), HOBt·xH_2O (398 mg, 1.88 mmol, 1.25 eq.), DCM (50 mL), DIPEA (320 µL, 1.88 mmol, 1.25 eq), EDCI·HCl (359 mg, 1.88 mmol, 1.25 eq.) and dihydroazepine **6** (500 mg, 1.65 mmol, 1.10 eq.). Column chromatography (SiO_2, dichloromethane:ethyl acetate 10:1, R_f = 0.23) yielded the pure product as a light yellow solid (518 mg, 13.1 mmol, 87 %).

It has to be noted, that for some atoms separate resonances were observed. This is caused by the C_1-symmetric molecular structure. Corresponding signals are marked as such (X and X´).

^{1}H NMR ($CDCl_3$, 598.74 MHz, 300 K): δ = 1.24 (s, 9H, H13), 3.51 (d, ^2J(H,H) = 13.5 Hz, 1H, H7/H7´), 3.82 – 3.87 (m, 7H, H14/H14´, H7/H7´), 4.05 (d, ^2J(H,H) = 17.4 Hz, 1H, H9), 4.25 (d, ^2J(H,H) = 17.5 Hz, 1H, H9), 4.39 (d, ^2J(H,H) = 13.0 Hz, 1H, H7/H7´), 5.24 (d, ^2J(H,H) = 13.6 Hz, 1H, H7/H7´), 6.93 (m, 1H, H10), 6.96 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.0 Hz, 1H, H3/H3´), 6.00 – 7.06 (m, 3H, H3/H3´, H5, H5´), 7.33 – 7.39 (m, 2H, H4, H4´) ppm. **^{13}C{^{1}H} NMR** ($CDCl_3$, 150.57 MHz, 300 K): δ = 27.7 (3C, C13), 38.9 (C12), 42.2 (C9), 46.5 (C7/C7´), 48.0 (C7/C7´), 55.99 (C14/C14´), 56.02 (C14/C14´), 111.5 (C3/C3´), 111.8 (C3/C3´), 121.2 (C5/C5´), 122.0 (C5/C5´), 125.2 (C1/C1´), 125.3 (C1/C1´), 129.73 (C4/C4´), 129.74 (C4/C4´), 134.5 (C6/C6´), 135.1 (C6/C6´), 157.0 (C2/C2´), 157.1 (C2/C2´), 166.4 (C8), 178.7 (C11) ppm. **HRMS (ESI)**: m/z calcd. for $C_{23}H_{29}N_2O_4$[M+H]$^+$: 397.2122; found: 397.2134. **IR (FT-ATR)**: $\tilde{\nu}$ = 1632, 1460, 1429, 1256, 1237, 1200, 1076, 788, 747, 729 cm^{-1}.

N-(1-(1,11-Dimethoxy-5,7-dihydro-6H-dibenzo[c,e]azepin-6-yl)-3-methyl-1-oxobutan-2-yl)pivalamide ***9b***

9b was synthesized according to the general procedure using pivaloyl-L-valine (298 mg, 1.37 mmol, 1.00 eq.), HOBt·xH_2O (365 mg, 1.72 mmol, 1.25 eq.), DCM (50 mL), DIPEA (300 µL, 1.72 mmol, 1.25 eq), EDCI·HCl (329 mg, 1.72 mmol, 1.25 eq.) and dihydroazepine **6** (519 mg, 1.72 mmol, 1.25 eq.). Column chromatography (SiO_2, dichloromethane:ethyl acetate 10:1, R_f = 0.34, 0.45) yielded the pure product as a light yellow solid (437 mg, 997 µmol, 73 %).

It has to be noted, that for some atoms separate resonances were observed. This is caused by the C_1-symmetric molecular structure. Corresponding signals are marked as such (X and X´). Due to racemization, the compound was obtained as mixture of a major (a) and a minor (b) diastereomer (a:b 60:40).

Major isomer a: **^{1}H NMR** (400.33 MHz, Methylene Chloride-d_2, 300 K) δ = 0.83 – 0.90 (m, 6H, H11a), 1.21 (s, 9H, H15a), 1.93 – 2.05 (m, 1H, H10a), 3.40 (d, ^2J(H,H) = 13.5 Hz, 1H, H7a/H7a´), 3.76 – 3.89 (m, 7H, H7a/H7a´, H16a, H16a´), 4.82 (d, ^2J(H,H) = 12.9 Hz, 1H, H7a/H7a´), 4.94 (dd, ^3J(H,H) = 8.8 Hz, ^2J(H,H) = 6.4 Hz, 1H, H9a), 5.10 (d, ^2J(H,H) = 13.4 Hz, 1H, H7a/H7a´), 6.39 (d, ^3J(H,H) = 8.7 Hz, 1H, H12a), 6.98 – 7.08 (m, 4H, H3a, H3a´, H5a, H5a´), 7.32 – 7.40 (m, 2H, H4a, H4a´) ppm. **^{13}C{^{1}H} NMR** (100.66 MHz, Methylene Chloride-d_2, 300 K) δ = 17.8 (C11a), 19.8 (C11a), 27.9 (3C, C15a), 32.2 (C10a), 39.2 (C14a), 47.1 (C7a/C7a´), 49.3 (C7a/C7a´), 54.4 (C9a), 56.29 (C16a, C16a´), 56.31 (C16a, C16a´), 111.7 (C3a/C3a´), 111.8 (C3a/C3a´), 121.7 (C5a/C5a´), 122.1 (C5a/C5a´), 125.8 (C1a/C1a´), 126.0 (C1a/C1a´), 129.8 – 130.0 (C4a, C4a´), 135.7 (C6a/C6a´), 136.2 (C6a/C6a´), 157.4 (C2a), 170.6 (C8a), 178.3 (C13a) ppm. *Minor isomer b*: **^{1}H NMR** (400.33 MHz, Methylene Chloride-d_2, 300 K) δ = 0.83 – 0.90 (m, 3H, H11b), 1.04 (d, ^3J(H,H) = 6.8 Hz, 3H, H11b), 1.17 (s, 9H, H15b), 2.10 – 2.23 (m, 1H, H10b), 3.34 (d, ^2J(H,H) = 13.4 Hz, 1H, H7b/H7b´), 3.76 – 3.89 (m, 7H, H7b/H7b´, H16b, H16b´), 4.61 (d, ^2J(H,H) = 13.0 Hz, 1H, H7b/H7b´), 4.89 (dd, ^3J(H,H) = 8.7 Hz, ^2J(H,H) = 4.8 Hz, 1H, H9b), 5.33 (d, ^2J(H,H) = 13.4 Hz, 1H, H7b/H7b´), 6.44 (d, ^3J(H,H) = 8.7 Hz, 1H, H12b), 6.98 – 7.08 (m, 4H, H3b, H3b´, H5b, H5b´), 7.32 – 7.40 (m, 2H, H4b, H4b´) ppm. **^{13}C{^{1}H} NMR** (100.66 MHz, Methylene Chloride-d_2, 300 K) δ = 17.2 (C11b), 20.5 (C11b), 27.9 (3C, C15b), 32.6 (C10b), 39.2 (C14b), 46.0 (C7b/C7b´), 49.0 (C7b/C7b´), 56.29 (C16b, C16b´) 56.34 (C16b, C16b´), 111.6 (C3b/C3b`), 111.9 (C3b/C3b´), 121.5 (C5b/C5b´), 122.1 (C5b/C5b´), 125.8 (C1b/C1b´), 126.3 (C1b/C1b´), 129.8 – 130.0 (C4b, C4b´), 135.3 (C6b/C6b´), 135.9 (C6b/C6b´), 157.7 (C2b), 170. 3 (C8b), 178.2 (C13b) ppm. C9b is behind solvent signal. **HRMS (ESI)**: m/z calcd. for $C_{26}H_{35}N_2O_4$ [M+H]$^+$: 439.2592; found: 439.2591. **IR (FT-ATR)**: $\tilde{\nu}$ = 1614, 1585, 1575, 1524, 1461, 1432, 1304, 1255, 1201, 1075, 785, 757, 746, 729, 662 cm^{-1}.

General procedure for the deprotection of dimethoxybiphenylamide

Dimethoxybiphenylamide (1.00 eq.) was placed in a heat-gun dried Schlenk flask and dissolved in anhydrous and degassed dichloromethane. The mixture was cooled to – 78 °C and BBr_3 solution (1M in DCM, 5.00 eq.) was added dropwise and stirred for 15 minutes. 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 one was extracted with

dichloromethane and ethyl acetate. The combined organic phase was dried over Na_2SO_4 and evaporated under reduced pressure.

N-(2-(1,11-dihydroxy-5,7-dihydro-6H-dibenzo[c,e]azepin-6-yl)-2-oxoethyl)pivalamide ***10a***

10a was synthesized according to general procedure for the deprotection employing dimethoxy-biphenylamide **9a** (350 mg, 880 µmol, 1.00 eq.), BBr_3 (1M in DCM, 4.41 mL, 4.41 mmol, 5.00 eq.) and dichloromethane (20 mL). The product was obtained as a white solid (316 mg, 857 µmol, 97 %).

It has to be noted, that for some atoms separate resonances were observed. This is caused by the C_1-symmetric molecular structure. Corresponding signals are marked as such (X and X´).

^{1}H NMR (400.33 MHz, DMSO-d_6, 300 K) δ = 1.12 (s, 9H, H13), 3.18 (d, ^2J(H,H) = 13.1 Hz, 1H, H7/H7´), 3.59 (d, ^2J(H,H) = 12.9 Hz, 1H, H7/H7´), 3.91 (dd, ^2J(H,H) = 16.7 Hz, ^3J(H,H) = 5.6 Hz, 1H, H9), 4.17 (dd, ^2J(H,H) = 16.8 Hz, ^3J(H,H) = 5.5 Hz, 1H, H9), 4.60 (d, ^2J(H,H) = 12.9 Hz, 1H, H7/H7´), 5.03 (d, ^2J(H,H) = 13.2 Hz, 1H, H7/H7´), 6.84 (dd, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.2, 1H, H3/H3´), 6.91 – 6.99 (m, 2H, H5, H5´), 7.04 (dd, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.2 Hz, 1H, H3/H3´), 7.16 – 7.31 (m, 2H, H4, H4´), 7.52 (t, ^3J(H,H) = 5.5 Hz, 1H, H10), 9.42 (s, 2H, H14) ppm. **^{13}C{^{1}H} NMR** (100.66 MHz, DMSO-d_6, 300 K) δ = 27.4 (3C, C13), 38.0 (C12), 41.2 (C9), 45.9 (C7/C7´), 47.1 (C7/C7´), 116.2 (C3/C3´), 116.3 (C3/C3´), 120.1 (C5/C5´), 120.3 (C5/C5´), 123.7 (C1/C1´), 128.87 (C4/C4´), 128.92 (C4/C4´), 135.36 (C6/C6´), 135.38 (C6/C6´), 154.23 (C2/C2´), 154.24 (C2/C2´), 166.8 (C8), 177.5 (C11) ppm. **HRMS (ESI)**: m/z calcd. for $C_{21}H_{25}N_2O_4$ $[M+H]^+$: 369.1809; found: 369.1813. **IR (FT-ATR)**: $\tilde{\nu}$ = 1621, 1522, 1455, 1439, 1349, 1291, 1275, 1258, 1234, 1205, 1024, 1007, 798, 773, 761, 730, 711 cm^{-1}.

N-(2-(1,11-Dihydroxy-5,7-dihydro-6H-dibenzo[c,e]azepin-6-yl)-2-oxoethyl)pivalamide ***10b***

10b was synthesized according to general procedure for the deprotection by employing dimethoxy-biphenylamide **9b** (350 mg, 880 µmol, 1.00 eq.), BBr_3 (1M in DCM, 4.41 mL, 4.41 mmol, 5.00 eq.) and dichloromethane (20 mL). Column chromatography (SiO_2, *n*-pentane:ethyl acetate 3:1, R_f = 0.15) yielded the pure product as a white solid (316 mg, 857 µmol, 87 %).

It has to be noted, that for some atoms separate resonances were observed. This is caused by the C_1-symmetric molecular structure. Corresponding signals are marked as such (X and X´). Due to racemization, the compound was obtained as mixture of major (a) and minor (b) diastereomers (a:b 64:36).

Major isomer a: **^{1}H NMR** (400.33 MHz, Methylene Chloride-d_2, 300 K) δ = 0.88 (d, ^3J(H,H) = 6.7 Hz, 3H, H11a), 1.05 (d, ^3J(H,H) = 6.8, 3H, H11a), 1.29 (s, 9H, H15a), 2.01 – 2.10 (m, 1H, H10a)2.88 (d, ^2J(H,H) = 12.8 Hz, 1H, H7a/H7a´), 2.06 (d, ^2J(H,H) = 13.3 Hz, 1H, H7a/H7a´), 3.96 (d, ^2J(H,H) = 12.8 Hz, 1H, H7a/H7a´), 4.84 (dd, ^3J(H,H) = 8.9 Hz, ^3J(H,H) = 3.8 Hz, 1H, H9a), 5.20 (d, ^2J(H,H) = 13.3 Hz, 1H, H7a/H7a´), 6.35 (dd, ^3J(H,H) = 7.3 Hz, ^4J(H,H) = 1.3 Hz, 1H, H5a/H5a´), 6.85 (d, ^3J(H,H) = 8.8 Hz, 1H, H12b), 6.87 – 6.94 (m, 1H, H5a/H5a´), 7.06 – 7.14 (m, 2H, H3a, H3a´), 7.16 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.3 Hz, 1H, H4a/H4a´), 7.22 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.4 Hz, 1H, H4a/H4a´), 7.54 (s, 1H, H16a/H16a´), 10.79 (s, 1H, H16a/H16a´) ppm. **^{13}C{^{1}H} NMR** (100.66, MHz, Methylene Chloride-d_2, 300K) δ = 16.9 (C11a), 20.3 (C11a), 27.8 (3C, C15a), 33.1 (C10a), 39.6 (14a), 45.9 (C7a/C7a´), 48.5 (C7a/C7a´), 117.0 (C3a/C3a´), 119.4 (C3a/C3a´), 122.8 (C5a/C5a´), 123.2 (C5a/C5a´), 124.1 (C1a/C1a´), 125.3 (C1a/C1a´), 130.0 (C4a/C4a´), 130.1 (C4a/C4a´), 134.7 (C6a/C6a´), 136.4 (C6a/C6a´), 152.4 (C2a/C2a´), 154.5 (C2a/C2a´), 168.8 (C8a), 180.3 (C13a) ppm. C9a is behind solvent signal.

Minor isomer b: **^{1}H NMR** (400.33 MHz, Methylene Chloride-d_2, 300 K) δ = 0.75 (d, ^3J(H,H) = 6.7 Hz, 3H, H11b), 0.89 (d, ^3J(H,H) = 6.8 Hz, 3H, H11b), 1.92 – 2.00 (m, 1H, H10b), 3.13 (d, ^2J(H,H) = 12.6 Hz, 1H, H7b/H7b´), 3.21 (d, ^2J(H,H) = 13.3 Hz, 1H, H7b/H7b´), 4.45 (d, ^2J(H,H) = 12.7 Hz, 1H, H7b/H7b´), 4.80 (dd, ^3J(H,H) = 9.3 Hz, ^3J(H,H) = 8.0 Hz, 1H, H9b), 4.97 (d, ^2J(H,H) = 13.3 Hz, 1H, H7b/H7b´), 6.54 (d, ^3J(H,H) = 9.6 Hz, 1H, H12b), 6.57 (dd, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.3 Hz, 1H, H5b/H5b´), 6.79 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.4 Hz, 1H, H4b/H4b´), 6.87 – 6.94 (m, 2H, H3b/H3b´, H5b/H5b´), 7.06 – 7.14 (m, 1H, H3b/H3b´), 7.26 (dd, ^3J(H,H) = 8.2 Hz, ^3J(H,H) = 7.4 Hz, 1H, H4b/H4b´), 7.82 (s, 1H, H16b/H16b´), 9.62 (s, 1H, H16b/H16b´) ppm. **^{13}C{^{1}H} NMR** (100.66, MHz, Methylene Chloride-d_2, 300K) δ = 18.5 (C11b), 19.1 (C11b), 27.8 (3C, C15b), 33.2 (C10b), 39.5 (C14b), 47.1 (C7b/C7b´), 49.2 (C7b/C7b´), 54.1 (C9b), 117.7 (C3b/C3b´), 118.6 (C3b/3Cb´), 122.6 (C5b/C5b´), 123.0 (C5b/C5b´), 124.5 (C1b/C1b´), 124.6 (C1b/C1b´), 130.0 (C4b/C4b´), 130.2 (C4b/C4b´), 135.4 (C6b/Cb´), 136.8 (C6b/C6b´), 153.0 (C2b/C2b´), 153.7 (C2b/C2b´), 169.7 (C8b), 179.8 (C13b) ppm. C9b is behind solvent signal. **HRMS (ESI)**: m/z calcd. for $C_{24}H_{31}N_2O_4$ $[M+H]^+$: 411.2279; found: 411.2277. **IR (FT-ATR)**: $\tilde{\nu}$ = 1615, 1582, 1531, 1499, 1444, 1367, 1345, 1273, 1248, 1208, 1168, 1017, 794, 759, 729, 718, 689, 668 cm^{-1}.

N-(2-(11-(Diethylamino)-4,6-dihydro-5H-10,12-dioxa-5-aza-11-phosphadibenzo[ef,kl]heptalen-5-yl)-2-oxoethyl)pivalamide ***11***

Selector-modified diol **10a** (150 mg, 410 µmol, 1.00 eq.) was dissolved in dry, degassed and stabilized THF (2.5 ml) and triethylamine (170 µl, 1.02 mmol, 2.50 eq.) was added. The mixture was cooled in an ice bath and diethylaminophosphorous dichloride (65.0 µl, 450 µmol, 1.1 eq.) was added dropwise. The mixture was warmed to room temperature and stirred for 18 hours. For work-up, the suspension was passed through a pad of dry, neutral alumina under inert conditions and was eluted with more THF (2 x 3 mL). Combined fractions were evaporated *in vacuo* using an external cooling trap. The resulting residue was washed with *n*-pentane (3 x 3 ml) to give the product as a white solid (130 mg, 277 µmol, 68 %).

It has to be noted, that for *some atoms separate resonances were observed.* This is caused by the C_1-symmetric molecular structure. Corresponding signals are marked as such (X and X´). Due to phosphorus chirality, the compound was obtained as mixture of (a) and (b) diastereomer (a:b 50:50).

^{1}H NMR ($CDCl_3$, 400.33 MHz, 300 K): δ = 1.07 (t, ^3J(H,H) = 7.0 Hz, 12H, H15a/H15b), 1.24 – 1.26 (m, 18H, H13a/H13b), 2.87 – 3.04 (m, 4H, H14a/H14b), 3.05 – 3.22 (m, 4H, H14a/H14b), 3.56 (d, ^2J(H,H) = 13.7 Hz, 1H, H7a/H7a´/H7b/H7b´), 3.62 (d, ^2J(H,H) = 13.7 Hz, 1H, H7a/H7a´/H7b/H7b´), 3.88 (d, ^2J(H,H) = 13.2 Hz, 1H, H7a/H7a´/H7b/H7b´), 3.96 (d, ^2J(H,H) = 13.2

Hz, 1H, H7a/H7a´/H7b/H7b´), 4.04 – 4.16 (m, 2H, H9a/H9b), 4.25 – 4.36 (m, 2H, H9a/H9b), 4.42 – 4.56 (m, 2H, H7a/H7a´/H7b/H7b´ (2×)), 5.30 (d, ^2J(H,H) = 13.7 Hz, 1H, H7a/H7a´/H7b/H7b´), 5.34 (d, ^2J(H,H) = 13.7 Hz, 1H, H7a/H7a´/H7b/H7b´), 6.87 – 6.97 (m, 2H, H10a, H10b), 7.13 – 7.31 (m, 8H, H3a, H3a´, H3b, H3b´, H5a, H5a´,H5b, H5b´), 7.31 – 7.37 (m, 2H, H4a/H4a´/H4b/H4b´ (2×)), 7.38 – 7.44 (m, 2H, H4a/H4a´/H4b/H4b´ (2×)) ppm. **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.66 MHz, 300 K): δ = 14.8 (4C, d, ^3J(C,P) = 2.3 Hz, C15a, C15a´, C15b, C15b´), 27.7 (6C, C13a, C13b), 38.41 (4C, d, ^2J(C,P) = 21.7 Hz, C14a, C14a´, C14b, C14b´), 38.9 (2C, C12a, C12b), 42.2 (2C, C9a,C9b), 46.3 (C7a/C7a´/C7b/C7b´), 46.4 (C7a/C7a´/C7b/C7b´), 47.78 (C7a/C7a´/C7b/C7b´), 47.81 (C7a/C7a´/C7b/C7b´), 121.97 (C5a/C5a´/C5b/C5b´), 122.2 (C5a/C5a´/C5b/C5b´), 122.7 (d, ^3J(C,P) = 2.0 Hz, C5a/C5a´/C5b/C5b´), 123.0 (d, ^3J(C,P) = 1.9 Hz, C5a/C5a´/C5b/C5b´), 124.79 (C5a/C5a´/C5b/C5b´), 125.4 (C5a/C5a´/C5b/C5b´), 125.80 (C5a/C5a´/C5b/C5b´), 126.5 (C5a/C5a´/C5b/C5b´), 128.8 (d, ^3J(C,P) = 1.8 Hz, C1a/C1a´/C1b/C1b´), 128.9 (d, ^3J(C,P) = 1.8 Hz, C1a/C1a´/C1b/C1b´), 129.86 – 129.94 (2C, C4a/C4a´/C4b/C4b´ (2×)), 130.04 – 130.15 (2C, C4a/C4a´/C4b/C4b´ (2×)), 130.4 (d, ^3J(C,P) = 4.3 Hz, C1a/C1a´/C1b/C1b´), 130.6 (d, ^3J(C,P) = 4.2 Hz, C1a/C1a´/C1b/C1b´), 134.4 (C6a/C6a´/C6b/C6b´), 134.5 (C6a/C6a´/C6b/C6b´), 135.05 (C6a/C6a´/C6b/C6b´), 135.14 (C6a/C6a´/C6b/C6b´), 150.9 (2C, d, ^2J(C,P) = 13.2 Hz, C2a/C2a´/C2b/C2b´ (2×)), 152.1 (2C, d, ^2J(C,P) = 8.0 Hz, C2a/C2a´/C2b/C2b´), 152.2 (d, ^2J(C,P) = 8.0 Hz, C2a/C2a´/C2b/C2b´), 166.3 (C8a/C8b), 166.4 (C8a/C8b), 178.67 (C11a/C11b), 178.72 (C11a/C11b) ppm. **^{31}P{^{1}H} NMR** ($CDCl_3$, 162.00 MHz, 300 K): δ = 150.87 (a/b), 150.9 (a/b) ppm. **HRMS (ESI)**: m/z calcd. for $C_{25}H_{33}N_3O_4P$ $[M+H]^+$: 470.2203; found: 470.2204. **IR (FT-ATR)**: $\tilde{\nu}$ = 1634, 1449, 1431, 1253, 1227, 1203, 1175, 1016, 938, 848, 831, 812, 776, 748, 729, 701, 669 cm^{-1}.

Hydrogenation experiment

For hydrogenation experiments with phosphoramidite ligand *rac*-**11** (Table 1, entry 1), the Rh complex was generated *in situ*. Therefore, *rac*-**11** (5.00 mg, 10.6 µmol, 2.50 eq.) and $[Rh(cod)_2]BF_4$ (1.70 mg, 4.26 µmol, 1.00 eq.) were dissolved in 0.5 mL anhydrous and degassed $CDCl_3$. After 30 min MAA (12.2 mg, 85.2 µmol, 20.0 eq) was added to the mixture. For hydrogenation experiments with phosphoramidite ligand (S_{ax})-**11**, the first eluting isomer of precursor (Table 1, entry 2 – 6) was separated using preparative HPLC (Chiralpak IC, 20 mL/min, *n*-hexane:isopropanol, 90:10, $t_{(Sax)}$ = 13.90 min, $t_{(Rax)}$ = 16.15 min). The solvent was removed directly, and the ligand stored under inert gas until use. The Rh complex was prepared *in situ*. Therefore, (S_{ax})-**11** (2.50 mg, 5.33 µmol, 2.50 eq.) and $[Rh(cod)_2]BF_4$ (0.86 mg, 2.13 µmol, 1.00 eq.) were dissolved in 0.5 mL anhydrous and degassed $CDCl_3$. After 30 min MAA (6.10 mg, 42.6 µmol, 20.0 eq) or MAC (9.34 mg, 42.6 µmol, 20.0 eq) was added to the mixture. This solution was transferred into a nitrogen filled stainless steel reactor loaded with a standard NMR tube and a small stirring bar. If necessary, the reactor was cooled in a bath of 2-propanol utilizing a cryostatic cooling. The reactor was pressurized with hydrogen gas (40 bar) to initiate the catalysis. The autoclave was reopened after 18 h. The solution was passed through a short pipet filled with silica (ca. 3 cm) using ethyl acetate as eluent. Evaporation gave the hydrogenation product as a yellow oil. Enantiomeric ratio and conversion were determined by chiral GC (MAA: (6-TBDMS-2,3-Ac)-β-CD, 25 m, i.d. 250 µm, film thickness 250 nm, 100-kPa helium, 130°C, FID detection, t_{Subst} = 6.26 min, t_R = 8.84 min, t_S = 10.78 min) or chiral HPLC (MAC: Chiralpak ODH, hexane:ethanol 97:3, 1.5 ml/min, 20 °C, 210 nm , t_{Subst} = 6.87 min, t_R = 16.74 min and t_S = 19.49 min). Assignment of absolute configuration was accomplished by comparing measurements to those of previously prepared enantiopure samples.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

S.A. performed the experiments and analyzed the data. S.A. and O.T. designed the experiments and wrote the manuscript.

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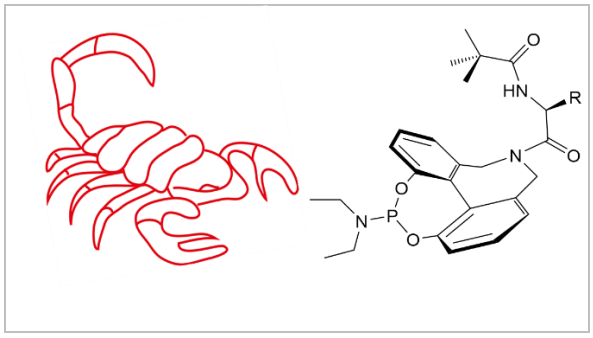

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Scorpio-type pivaloyl amino acid modified dihydroazepine-bridged BIPHEP phosphoramidite ligands were prepared and used in the Rh-catalyzed enantioselective hydrogenation with ee's of up to 94%.

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