The Stereodynamics of 5,5'-Disubstituted BIPHEPs

FRANK MAIER AND OLIVER TRAPP*

Ruprecht-Karls-Universität Heidelberg, Organisch-Chemisches Institut, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

ABSTRACT We investigated the stereodynamics of 5,5'-substituted tropos BIPHEP ligands (2,2'-bis(diphenylphosphino)-biphenyls) by enantioselective dynamic high-performance liquid chromatography (DHPLC) to elucidate the influence of the substitution pattern and electronics of the substituents (methyl, methoxy, and hydroxyl groups). By temperature-dependent dynamic HPLC measurements the activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ could be determined with high precision, revealing that the activation barrier of these 5,5'-substituted BIPHEP ligands ranges in a narrow band between 87.8 and 93.0 kJ mol^{-1}, making them highly attractive as deracemizable dynamic chiral ligands in asymmetric catalysis. Interestingly, the activation parameters are highly influenced by a hydroxyl or methoxy group in the 5,5'-position of the BIPHEP ligands. *Chirality 25:126–132, 2013.*

KEY WORDS: BIPHEP; dynamic HPLC; interconversion barrier; unified equation; kinetics

INTRODUCTION

Axial chiral ligand systems like Noyori's atropisomeric binap,[1] and tropos BIPHEP ligands used by Mikami *et al.*[2] are of high interest due to their broad applicability in asymmetric catalysis. An advantage of tropos ligands like BIPHEP (2,2'-bis(diphenylphosphino)-biphenyls) over atropos ligands is their dynamic rotational behavior, allowing to use synthetically easier accessible racemic mixtures of the ligand, which can be deracemized at low temperature to yield the desired enantiomerically pure catalyst. Mikami and Noyori reported first about a novel concept: the use of a racemic BIPHEP-Ru catalyst bearing a chiral amine to dynamically deracemize the BIPHEP-Ru complex.[3] Treatment of the racemic BIPHEP-Ru catalyst with a chiral amine led to the deracemization of the catalyst, which was used in hydrogenations of ketones to chiral alcohols with excellent enantioselectivities.[3] Mikami and colleagues made further contributions in enantioselective catalysis with the tropos BIPHEP-ligand by using either enantiopure diamine coligands in Pd-catalyzed hetero-Diels-Alder reactions[4] or enantiomerically pure counterions to deracemize BIPHEP-Au complexes, which were applied in intramolecular hydroaminations of allenes and enantioselective intermolecular carbon–carbon bond formations.[5–7] Brown *et al.* reported the use of enantiomerically pure bicyclo[3.3.1]nona-2,6-diene to deracemize BIPHEP-Rh complexes for use in asymmetric hydrogenations.[8] The deracemization of BIPHEP ligands using a chiral auxiliary represents a classic example of dynamic kinetic resolution (see Scheme 1).[9]

To understand and control the stereoselectivity of catalysts bearing tropos ligands it is important to know the factors that influence the dynamics and the kinetics of highly flexible systems. Thus, a robust and broadly applicable method to determine the dynamics and kinetics is required. Recently, we introduced a method using dynamic HPLC (DHPLC)[10–18] and a novel three-column HPLC setup to determine dynamics and kinetics in dependence of the stationary phase and solvent used.[19] In the past, dynamic chromatographic techniques were successfully employed to study the stereodynamics of substituted biphenyl compounds.[20–23]

In this study we focused on the influence of the substitution pattern of disubstituted BIPHEP oxides. Comparison of the investigated 5,5'-disubstituted BIPHEP oxides with 3,3'-disubstituted analogues enables detailed insight into substitution pattern effects on the Gibbs free energy $\Delta G^{\ddagger}$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Another advantage of tropos ligands is their potentially applicability in self-amplifying enantioselective processes.[24,25]

MATERIALS AND METHODS

General

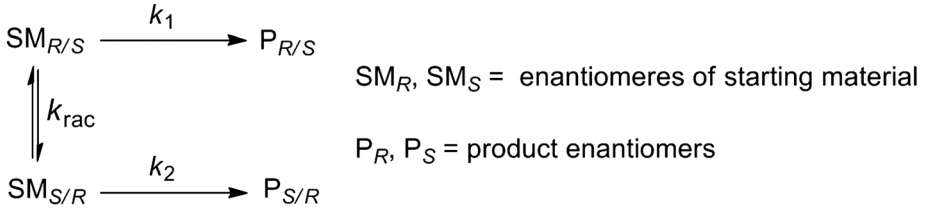
All chemicals used were purchased from Sigma Aldrich (Schnelldorf, Germany) or Acros Organics (Geel, Belgium). Nuclear magnetic resonance (^{1}H-NMR, ^{31}P-NMR) spectra were recorded at 300, 122, and 75 MHz, respectively, on a Bruker AC-300 spectrometer (Rheinstetten, Germany) in deuterochloroform, benzol-d_6, or methanol-d_4. High resolution mass spectra (ESI-HRMS) were acquired on a Jeol JMS-700 instrument. Infrared (FT-IR) spectra were recorded on a Thermo Fisher Nicolet 6700 FT-IR-Spectrometer (Dreieich, Germany).

Synthesis of 5,5'-Disubstituted BIPHEPs

(5,5'-Dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine oxide) 1. The (5,5'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine oxide) **1** was synthesized according to modified sequences developed by Yuxue Liang *et al.*[26] and Wanbin Zhang *et al.*[27] A total of 16.4 g (132 mmol) 4-methoxyphenol was dissolved in 150 ml of dry nitromethane and $AlCl_3$ (17.6 g, 132 mmol) was added subsequently. After stirring for 15 min at room temperature, DDQ (DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (15.0 g, 66.1 mmol) dissolved in 200 ml of nitromethane was added dropwise and the reaction mixture was stirred for 1 h at room temperature. After addition of 2 M HCl the resulting mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel with petrol ether/EtOAc (10:1) as the eluent, yielding the product (8.5 g, 52%) as colorless crystals. ^{1}H-NMR (300 MHz, $CDCl_3$) $\delta = 6.96$ (*d*, $J = 8.8$ Hz, 2H), 6.88 (*dd*, $J = 8.8$, 3.1 Hz, 2H), 6.82 (*d*, $J = 3.1$ Hz, 2H), 5.37 (*bs*, 2H), 3.79 (*s*, 6H).

Afterwards pyridine (9.4 ml) was added to a solution of the product (3.44 g, 14.0 mmol) in 20 ml of CH_2Cl_2 and cooled to 0 °C. To this solution

*Correspondence to: Prof. Dr. Oliver Trapp, Ruprecht-Karls-Universität Heidelberg, Organisch-Chemisches Institut, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany. E-mail: trapp@oci.uni-heidelberg.de
Received for publication 26 July 2012; Accepted 21 September 2012
DOI: 10.1002/chir.22125
Published online 22 December 2012 in Wiley Online Library (wileyonlinelibrary.com).



Scheme 1. Classical dynamic kinetic resolution.

trifluoromethanesulfonic anhydride (Tf_2O, 9.40 ml, 57.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 12 h. The solvent was removed and the residue was diluted with EtOAc, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic extract was dried over $MgSO_4$ and the solvent was removed under vacuum to yield the product without further purification as colorless crystals (7.0 g, 98%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.31 (*d*, *J* = 9.0 Hz, 2H), 7.01 (*dd*, *J* = 9.0, 3.2 Hz, 2H), 6.95 (*d*, *J* = 3.2 Hz, 2H), 3.85 (*s*, 6H).

In the final step the reaction product (2.50 g, 4.90 mmol), diphenylphosphine oxide (3.00 g, 14.8 mmol), palladium acetate (110 mg, 0.49 mmol), and 1,4-bis(diphenylphosphino)butane (dppb, 220 mg, 0.52 mmol) were dissolved in dry and degassed DMSO (25 ml) and diisopropylethylamine (4.2 ml). After stirring the mixture at 110 °C for 6 h the next portions of diphenylphosphine oxide (1.00 g, 4.9 mmol), palladium acetate (55 mg, 0.25 mmol), and 1,4-bis(diphenylphosphino)butane (dppb, 110 mg, 0.26 mmol) were added and the reaction mixture was stirred at 110 °C for 12 h. After cooling the mixture to room temperature, CH_2Cl_2 (25 ml) was added and the organic phase was washed with 1 M HCl and brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with petrol ether/2-propanol (4:1) as the eluent, yielding product **1** (1.3 g, 45%) as a white solid. The dynamic separation of the enantiomers was performed on a Chiralpak IC (*n*-hexane/2-propanol 45/55 (v/v), 1.0 ml/min, temperature 20–70 °C, λ = 280 nm). ^{1}H-NMR (300 MHz, C_6D_6) δ = 8.04 – 7.95 (*m*, 6H), 7.22 – 7.00 (*m*, 18H), 6.52 (*dt*, *J* = 8.6, 1.9 Hz, 2H), 3.29 (*s*, 6H). ^{31}P-NMR (121.6 MHz, C_6D_6) δ = 40.02. ESI-HRMS *m/z* calc for $C_{38}H_{33}O_4P_2$ $[M+H]^+$: 615.1849; found: 615.1850. FT-IR [cm^{-1}]: 1589, 1558, 1437, 1264, 1233, 1115, 1029, 953, 816.

(5-Methoxy-5'-methyl-[1,1'-biphenyl]-2,2'-diyl) bis(diphenylphosphine oxide) 2. (5-Methoxy-5'-methyl-[1,1'-biphenyl]-2,2'-diyl) bis (diphenylphosphine oxide) **2** was prepared according to the preparation of product **1**, using 4-methoxyphenol and 4-methylphenol as starting material. (5-Methoxy-5'-methyl-[1,1'-biphenyl]-2,2'-diyl) bis(diphenylphosphine oxide) **2** was obtained as white solid in 26% overall yield over three steps. The dynamic separation of the enantiomers was performed on a Chiralpak IC (*n*-hexane/2-propanol 60/40 (v/v), 1.0 ml/min, temperature 10–50 °C, λ = 280 nm). ^{1}H-NMR (300 MHz, MeOD) δ = 7.79 – 7.24 (*m*, 20H), 7.18 – 7.02 (*m*, 3H), 6.74 – 6.67 (*m*, 2H), 6.58 (*t*, *J* = 3.0 Hz, 1H), 3.49 (*s*, 3H), 2.04 (*s*, 3H). ^{31}P-NMR (121.6 MHz, MeOD) δ = 31.39, 30.82. ESI-HRMS *m/z* calc for $C_{38}H_{33}O_3P_2$ $[M+H]^+$: 599.1899; found: 599.1908. FT-IR [cm^{-1}] 1592, 1558, 1438, 1224, 1169, 1114, 1030, 816, 723, 692.

(5,5'-Dihydroxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine oxide) 3. (5,5'-Dimethoxy-[1,1'-biphenyl]-2,2'-diyl) bis(diphenylphosphine oxide) **1** (2.43 g, 3.96 mmol) was dissolved in dry CH_2Cl_2 (50 ml) and BBr_3 (1 M in CH_2Cl_2, 15.9 ml, 15.9 mmol) was added drop wise at -78 °C and stirred overnight at room temperature. Water was added to the reaction mixture, extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4. The residue was washed thoroughly with ethyl acetate to remove byproducts. Product **3** was obtained as a white solid (2.0 g, 86%). The dynamic separation of the enantiomers was performed on a Chiralpak IA-3 (*n*-hexane/2-propanol/methanol 90/5/5 (v/v/v), 1.2 ml/min, temperature 10–40 °C, λ = 210 nm). ^{1}H-NMR (300 MHz, MeOD) δ = 7.79 – 7.29 (*m*, 20H), 7.02 (*dd*, *J* = 13.6, 8.6 Hz, 2H), 6.57 (*dt*, *J* = 8.6, 2.2 Hz, 2H), 6.38 (*dd*, *J* = 3.6, 2.3 Hz, 2H). ^{31}P-NMR (121.6 MHz, MeOD) δ = 31.17. ESI-HRMS *m/z* calc for $C_{36}H_{28}O_4P_2Na$ $[M+Na]^+$: 609.1355; found: 609.1356. IR [cm^{-1}]: 3165, 1561, 1437, 1184, 1104, 1044, 694. CCDC-903879 contain the supplementary crystallographic data for compound **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(5-Hydroxy-5'-methyl-[1,1'-biphenyl]-2,2'-diyl) bis(diphenylphosphine oxide) 4. (5-Methoxy-5'-methyl-[1,1'-biphenyl]-2,2'-diyl) bis (diphenylphosphine oxide) **2** (49.0 mg, 0.08 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and BBr_3 (1 M in CH_2Cl_2, 0.37 ml, 0.37 mmol) was added dropwise at -78 °C and stirred overnight at room temperature. Water was added to the reaction mixture, extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4. The residue was purified by preparative HPLC (column: Agilent prep-SIL, 100 mm, i.d. 30 mm, 10 µm particle size) (*n*-hexane/2-propanol (95:5)) to yield product **4** as a white solid (39 mg, 81%). The dynamic separation of the enantiomers was performed on a Chiralpak IA (*n*-hexane/2-propanol 70/30 (v/v), 1.0 ml/min, temperature 15–55 °C, λ = 280 nm). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.89 – 7.80 (*m*, 4H), 7.61 – 7.32 (*m*, 13H), 7.27 – 7.13 (*m*, 5H), 6.98 – 6.89 (*m*, 2H), 6.69 (*dd*, *J* = 13.2, 8.9 Hz, 1H), 6.28 (*d*, *J* = 3.9 Hz, 1H), 1.79 (*s*, 3H). ^{31}P-NMR (121.6 MHz, $CDCl_3$) δ = 30.47, 28.08. ESI-HRMS *m/z* calc for $C_{37}H_{31}O_3P_2$ $[M+H]^+$: 585.1743; found: 585.1743. FT-IR [cm^{-1}]: 2359, 1745, 1458, 1259, 804.

(5-Hydroxy-5'-methoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine oxide) 5. Product **5** was obtained as a byproduct (<5%) of the reaction to (5,5'-dihydroxy-[1,1'-biphenyl]-2,2'-diyl) bis(diphenylphosphine oxide) **3**. The dynamic separation of the enantiomers was performed on a Chiralpak IA-3 (*n*-hexane/2-propanol/methanol 90/5/5 (v/v/v), 1.2 ml/min, temperature 10–50 °C, APCI-MS trace). EI-HRMS *m/z* calc for $C_{37}H_{31}O_4P_2$ $[M+H]^+$: 601.1692; found: 601.1692.

Dynamic High-Performance Liquid Chromatography (DHPLC)

The stereodynamics of the 5,5'-disubstituted BIPHEPs were investigated by DHPLC, performed on an Agilent Technologies 1200 HPLC (Agilent Technologies, Palo Alto, CA, USA), with a quadrupole mass spectrometer Agilent 6120, equipped with an APCI source. Dynamic enantioselective separations were performed on Chiralpak IA, IA-3, IC, or IC-3 columns (IA + IC: 250 mm, i.d. 4.6 mm, particle size 5 µm; IA-3 + IC-3: 150 mm, i.d. 4.6 mm, particle size 3 µm), which were purchased from Chiral Technologies, Illkirch, France. The solvents used (*n*-hexane, 2-propanol, and methanol) were obtained from Sigma-Aldrich (HPLC-grade quality). Dynamic HPLC measurements of all compounds were performed with solutions of 1.0 mg substance in 1.0 ml of the solvent mixture, which was also used for the separation. Elution profiles with distinct plateau formation were measured between 10 and 70 °C. All measurements were repeated three times.

Determination of Reaction Rate Constants and the Gibbs Activation Energy

Reaction rate constants were determined using the unified equation, which allows for the direct calculation of the reaction rate constants k_1 and k_{-1} and Gibbs activation energies $\Delta G^{\ddagger}$ for all types of first-order reactions taking place in chromatographic or electrophoretic systems (for details, see [28–34] in the Literature Cited). Note that only the forward reaction rate constant k_1 is reported, because the reaction rate constant

k_{-1} is lower according to the interaction with the chiral selector and the resulting enantioselectivity $\Delta\Delta G_{R,S}$, which is mathematically considered by the principle of microscopic reversibility.[35–37] All calculations of the chromatograms were performed with the software DCXplorer (this software is available from the corresponding author upon request as an executable program running under the operating systems Microsoft Windows XP, Vista, and 7).[38]

Evaluation of Activation Parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$

For the evaluation of activation parameters of the enantiomerization process of the BIPHEP molecules we determined the reaction rate constants at temperatures between 10 and 70 °C. Peak coalescence occurred at higher temperatures due to the fast interconversion process at elevated temperatures. The Gibbs free activation energy $\Delta G^{\ddagger}(T)$ was calculated according to the Eyring equation (Eq. [1]) with k_B as the Boltzmann constant ($k_B = 1.381 \times 10^{-23}$ J K^{-1}), T as the enantiomerization temperature [K], h as Planck's constant ($h = 6.626 \times 10^{-34}$ J sec), and R as the gas constant ($R = 8.31$ J K^{-1} mol^{-1}). The statistical factor κ was set to 0.5 for a degenerated interconversion process.

$$\Delta G^{\ddagger}(T) = -RT \ln \frac{k_1 h}{k k_B T} \quad (1)$$

The activation enthalpy $\Delta H^{\ddagger}$ was obtained from the slope and the activation entropy $\Delta S^{\ddagger}$ from the intercept of the Eyring plot ($\ln(k_1^{ue}/T)$ as a function of T^{-1}). Deviations of the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ have been calculated by analysis of the confidence interval of the linear regression with a level of confidence of 95%.

RESULTS AND DISCUSSION

The series of 5,5'-disubstituted BIPHEP oxides (5,5'-disubstituted-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine oxides) were synthesized according to modified sequences developed by Yuxue Liang *et al.*[26] and Wanbin Zhang *et al.*[27] (Scheme 2)

Products **1** and **2** could be synthesized from 4-methoxyphenol and 4-methylphenol in three steps with 23% and 26% yield, respectively. For the oxidative coupling of the starting materials DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) and $AlCl_3$ were used. The subsequent treatment of the compounds **1** and **2** with Tf_2O (trifluoromethanesulfonic anhydride) in the presence of Et_3N afforded the corresponding ditriflate derivative in almost quantitative yield. The diphenylphosphine oxides **3** and **4** were obtained by Pd-catalyzed phosphinoylation of the triflates with diphenylphosphine oxide ($HPPh_2O$) in DMSO at an elevated temperature. Demethylation with BBr_3 yields the corresponding hydroxyl-BIPHEP derivatives in yields up to 86%. Diphenylphosphine oxide **3** was fully characterized by single crystal X-ray analysis (see Fig. 1).

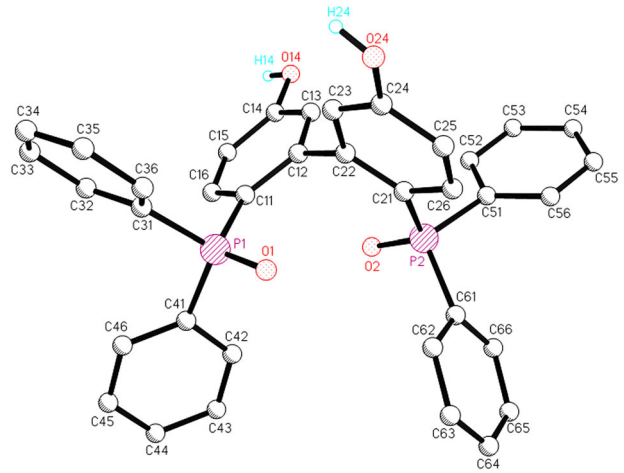
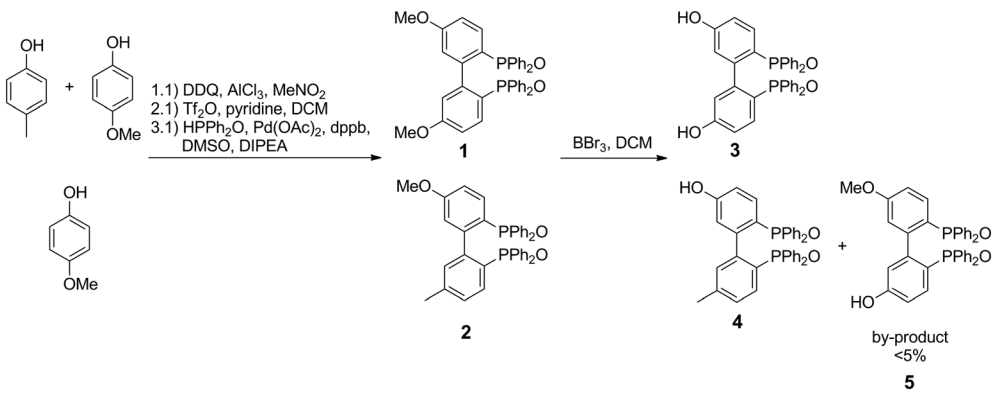


Fig. 1. Crystal structure of BIPHEP **3** determined by X-ray diffraction analysis. Selected bond distances [Å] and angles [°] are: P1-C11 1.7934(14), P2-C21 1.8009(14), C12–C22 1.4977(18), O1–P1–C11 115.33(6), O2–P2–C21 115.17(7), C12–C11–P1 123.42(10), C22–C21–P2 123.68(11). Dihedral angle between the two phenyl rings: C_{13}–C_{12}–C_{22}–C_{23}: 91.2°; C_{11}–C_{12}–C_{22}–C_{21}: 93.1°.

An excellent separation of the interconverting enantiomers was achieved by enantioselective HPLC using either the immobilized chiral stationary phase (CSP) Chiralpak IA or Chiralpak IC (both: 250 mm, i.d. 4.6 mm, 5 μm particle size). To economize the separation process we used, if possible, shorter separation columns with smaller particle size to achieve almost the same separation rates in much less time (column: Chiralpak IA-3 and IC-3; both: 150 mm, i.d. 4.6 mm, 3 μm particle size). Representative elution profiles of the enantiomers of BIPHEP **3** from the DHPLC experiments are depicted in Figure 2.

To determine the activation barrier $\Delta G^{\ddagger}$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of the enantiomerization by rotation about the σ bond, temperature-dependent dynamic HPLC experiments were performed between 10 °C and 50 °C. Due to rapid interconversion at higher temperatures complete coalescence of the enantiomers was observed. Reaction rate constants k_1 and k_{-1} of the enantiomerization of the BIPHEP oxides were calculated using the analytical function of the unified equation[28,38] considering three experiments at each temperature. Selected experimental data of BIPHEP **3** determined from the elution profiles and the calculated reaction rate constants are summarized in Table 1.



Scheme 2. Synthesis of BIPHEPs **1–5** by oxidative coupling of phenol derivatives using DDQ, subsequent treatment with trifluoromethanesulfonic anhydride and Pd-catalyzed phosphinoylation of the corresponding triflates with diphenylphosphine oxide. Demethylation of methoxy derivatives **1** and **2** was achieved by BBr_3 yielding compounds **3–4**.

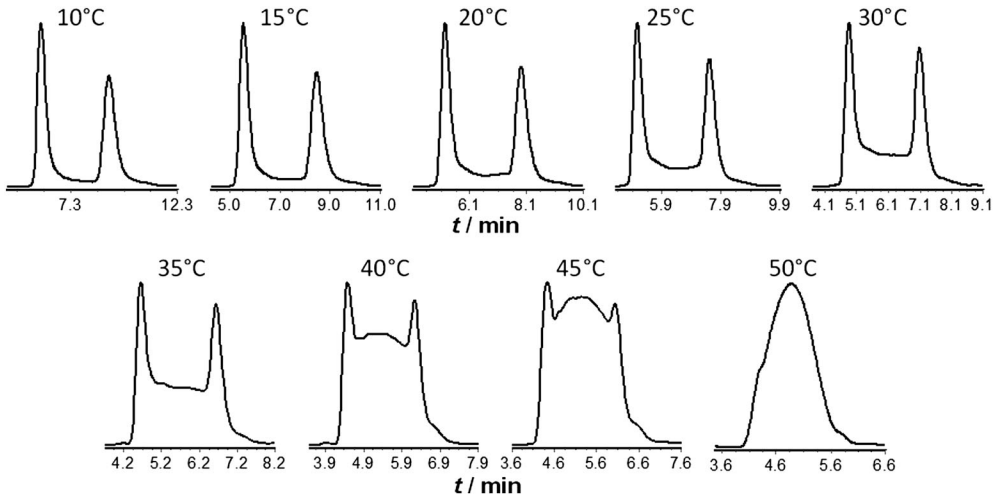


Fig. 2. Selected experimental interconversion profiles of the enantioselective DHPLC experiments of BIPHEP **3** between 10 and 50 °C. Chromatographic conditions: Column: Chiralpak IA-3, 250 mm, 4.6 mm, 3 μm particle size, (*n*-hexane/2-propanol/methanol 90/5/5 (v/v/v), 1.2 ml/ min, λ = 210 nm).

TABLE 1. Experimental data of the enantiomerization of BIPHEP 3 between 10 °C and 40 °C obtained by enantioselective DHPLC. Chromatographic conditions: Column, Chiralpak IA-3, 250 mm, 4.6 mm, 5 μm particle size, (*n*-hexane/2-propanol/methanol 90/5/5 (v/v/v), 1.2 ml/ min, λ = 210 nm)

T (°C)	t_R^A (min)	t_R^B (min)	h_p (%)	N 1	N 2	α	k_1 (10^{-4} sec^{-1})
10.0	5.905	9.105	3.62	834	820	1.65	3.98
10.0	5.891	9.091	3.59	887	817	1.65	4.07
10.0	5.880	9.080	3.50	883	815	1.66	3.98
15.0	5.560	8.494	4.01	959	905	1.64	4.88
15.0	5.557	8.484	4.09	1036	945	1.64	5.14
15.0	5.547	8.467	4.07	954	941	1.64	4.97
20.0	5.279	7.959	6.17	991	993	1.63	7.60
20.0	5.269	7.936	6.24	987	1039	1.62	7.67
20.0	5.269	7.935	6.12	987	1039	1.62	7.54
25.0	5.050	7.497	10.65	967	1139	1.60	12.5
25.0	5.037	7.464	10.63	961	1127	1.60	12.4
25.0	5.037	7.464	10.57	961	1127	1.60	12.4
30.0	4.839	7.065	19.02	950	1275	1.58	20.8
30.0	4.834	7.040	18.83	947	1264	1.58	20.5
30.0	4.814	7.020	18.77	1029	1256	1.58	21.3
35.0	4.650	6.657	34.58	942	1273	1.55	34.2
35.0	4.644	6.637	34.72	939	1264	1.55	34.3
35.0	4.635	6.629	34.60	1030	1356	1.55	35.2
40.0	4.502	6.275	66.36	867	1284	1.51	56.5
40.0	4.490	6.250	67.48	861	1272	1.50	56.3
40.0	4.485	6.232	67.07	947	1171	1.50	57.1

The activation enthalpy $\Delta H^{\ddagger}$ and activation entropy $\Delta S^{\ddagger}$ of the BIPHEPs were obtained by plotting $\ln(k_1/T)$ as a function of T^{-1}, according to the Eyring equation (see Fig. 3). Elution profiles showing coalescence at elevated temperature (>45 °C) were not considered for the calculation of activation parameters. The Gibbs free energy $\Delta G^{\ddagger}$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of all analyzed BIPHEP molecules are summarized in Table 2.

The investigated Gibbs free energies $\Delta G^{\ddagger}$ of the 5,5'-disubstituted BIPHEP oxides varying from 87.8 kJ mol^{-1} for BIPHEP **3** to 93.0 kJ mol^{-1} for BIPHEP **1**. Apparently the more electron-rich BIPHEPs bearing methoxy substituents like BIPHEP **1** and **5** show a higher intrinsic rotation barrier

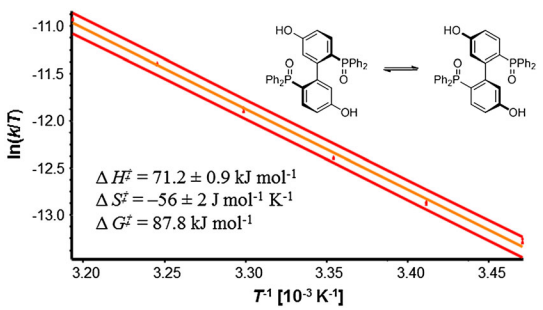
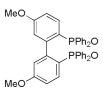
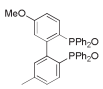
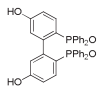
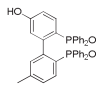
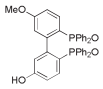


Fig. 3. Eyring plot of BIPHEP **3** between 15 °C and 40 °C.

TABLE 2. Activation parameters obtained by enantioselective DHPLC. Temperatures: a, 20 °C; b, 10 °C

BIPHEP		t_R^A (min)	t_R^B (min)	$\Delta G^{\ddagger}_{298K}$ (kJ mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	k_1 (10^{-4} sec^{-1})	CSP	Solvent *n*-hex:IPA:MeOH
1		9.5[a]	17.1[a]	93.0	40.8 ± 0.3	-175 ± 11	1.61	IC	45:55:0
2		13.8[b]	22.4[b]	90.5	69.5 ± 0.3	-70 ± 1	4.42	IC	60:40:0
3		5.9[b]	9.1[b]	87.8	71.2 ± 0.9	-56 ± 2	12.4	IA-3	90:5:5
4		6.9[b]	11.2[b]	88.5	57.9 ± 0.5	-103 ± 2	9.53	IA	70:30:0
5		7.9[b]	10.8[b]	90.6	38.9 ± 1.0	-173 ± 32	3.99	IA-3	90:5:5

than BIPHEPs with hydroxyl substituents in 5,5'-position. The $\Delta H^{\ddagger}$ values range between 38.9 ± 1.0 kJ mol^{-1} for BIPHEP **5** to 71.2 ± 0.9 kJ mol^{-1} for BIPHEP **3**. The activation entropy $\Delta S^{\ddagger}$ ranges from -56 ± 2 J mol^{-1} K^{-1} for BIPHEP **3** to -175 ± 11 J mol^{-1} K^{-1} for BIPHEP **1**. The negative values for the activation entropies indicate an increased organization of the substrate or its environment at the transition state. BIPHEPs **3** and **5** were measured under identical separation conditions. Here the activation entropy $\Delta S^{\ddagger}$ is more negative for the more electron-rich methoxy-substituted BIPHEP **5** compared to BIPHEP **3**, which might be explained by solvent effects increasing the sterical demand for rotation. Another explanation might be intermolecular interactions. We exclude stationary phase effects, because results of a previous publication indicate only a negligible influence for this compound class. Similar to a recently described effect by us about compensation of the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for 3,3'-disubstituted BIPHEP molecules,[19] we determined the same phenomena for the 5,5'-disubstituted BIPHEPs analyzed here. Comparison of BIPHEPs **2** and **5**, where $\Delta G^{\ddagger}$ has almost the same value (90.5 and 90.6 kJ mol^{-1}, respectively), have strongly different activation parameters ($\Delta H^{\ddagger}$: 69.5 ± 0.3 and 38.9 ± 1.0 kJ mol^{-1}; $\Delta S^{\ddagger}$: -70 ± 1 and -173 ± 32 J mol^{-1} K^{-1}, respectively).

With the determined data it is possible to compare the rotational barriers for the different substitution pattern of BIPHEP ligands (see Fig. 4). As expected, the unsubstituted BIPHEP has the lowest rotation barrier ($\Delta G^{\ddagger}$ = 86.8 kJ mol^{-1}) of the BIPHEPs shown in Figure 4.[19] To compare the rotation barriers of the substitution pattern of the 3,3'-, 5,5'-, and 6,6'-disubstituted BIPHEP ligands it is important to observe the same substituents. For methoxy-substituted BIPHEPs the rotation barrier of the 6,6'-disubstituted BIPHEP ligands is considerable higher due to steric hindrance. Even at elevated temperatures, this ligand shows atropisomerism. Compared to the 5,5'-disubstituted ligand the rotation barrier of the 3,3'-disubstituted analogue is slightly increased due to a buttressing effect that increases the steric hindrance along the σ bond.[39] Despite a higher rotation barrier for the 3,3'- and the 5,5'-analogue compared to the unsubstituted

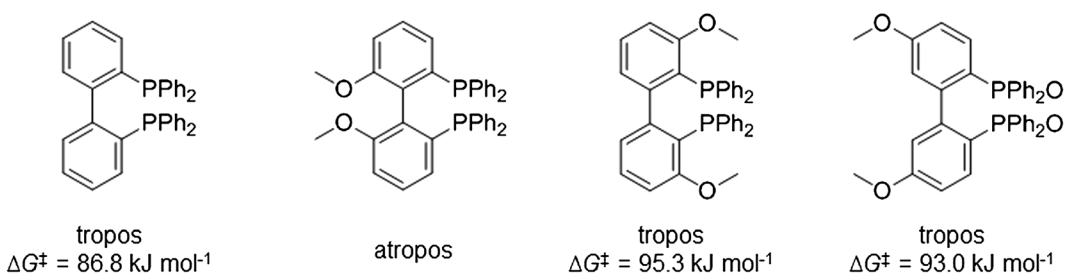


Fig. 4. Comparison of the rotation barriers of BIPHEP ligands with different substitution pattern.

BIPHEP, these ligands are still tropos at room temperature. It should be noted that the rotation barriers of the oxidized BIPHEP molecules are approximately 2 kJ mol^{-1} higher than the barriers of the nonoxidized analogues.[19]

CONCLUSION

We synthesized and investigated the stereodynamics of 5,5'-substituted (hydroxy, methoxy, and methyl groups) tropos BIPHEP ligands (2,2'-bis(diphenylphosphino)-biphenyls) by temperature-dependent enantioselective dynamic HPLC in presence of the immobilized chiral stationary phases (CSP) Chiralpak IA or Chiralpak IC to elucidate the influence of the substitution pattern and electronics of the substituents. The obtained activation parameters, in particular the activation enthalpies $\Delta H^{\ddagger}$ and activation entropies $\Delta S^{\ddagger}$, reveal a strong influence of the substitution pattern and electronics of the substituents. Interestingly, the activation barriers are in a narrow range between 87.8 and 93 kJ mol^{-1}, which can be explained by enthalpy and entropy compensations.[40] Furthermore, the here-determined parameters allow the comparison of the stereodynamics of 3,3'- and 5,5'-substituted tropos BIPHEP ligands. These activation parameters can help in designing novel BIPHEP ligands, which can be deracemized for use in asymmetric catalysis.

ACKNOWLEDGMENTS

Generous financial support from the European Research Council (ERC) (Starting Grant No. 258740, AMPCAT, to O.T.) is gratefully acknowledged. We thank Dr. Frank Rominger for the X-ray analysis and structure elucidation of compound **3**.

LITERATURE CITED

1. Noyori R. Asymmetric catalysis: science and opportunities. Adv Synth Catal 2003;345:15–32.
2. Mikami K, Aikawa K, Yusa Y, Jodry JJ, Yamanaka M. Tropos or atropos? That is the question! Synlett 2002;10:1561–1578.
3. Mikami K, Korenaga T, Terada M, Ohkuma T, Pham T, Noyori R. Konformativ flexible Biphenyl-Phosphanliganden für Ru-katalysierte enantioselektive Hydrierungen. Angew Chem 1999;111:517–519; Conformationally flexible biphenylphosphane ligands for Ru-catalyzed enantioselective hydrogenation. Angew Chem Int Ed 1999;38:495–497.
4. Mikami K, Aikawa K, Yusa Y. Asymmetric activation of the Pd catalyst bearing the tropos biphenylphosphine (BIPHEP) ligand with the chiral diaminobinaphthyl (DABN) activator. Org Lett 2002;4:95–97.
5. Aikawa K, Kojima M, Mikami K. Axial chirality control of gold(BIPHEP) complexes by chiral anions: application to asymmetric catalysis. Angew Chem Int Ed 2009;48:6073–6077.
6. Kojima M, Mikami K. Enantioselective intramolecular hydroamination of N-alkenyl ureas catalyzed by tropos BIPHEP-Gold(I) complexes with Au-Au interaction. Synlett 2012;23:57–61.
7. Kojima M, Mikami K. Enantioselective intermolecular carbon-carbon bond formation of glyoxylate imines with allylstannanes catalyzed by tropos BIPHEP-Gold(I) complexes with Au-Au interactions. Chem Eur J 2011;17:13950–13953.
8. Punniyamurthy T, Mayr M, Dorofeev AS, Bataille CJR, Gosiewska S, Nguyen B, Cowley AR, Brown JM. Enantiomerically pure bicyclo[3.3.1] nona-2,6-diene as the sole source of enantioselectivity in BIPHEP-rh asymmetric hydrogenation. Chem Commun 2008;5092–5094.
9. Noyori R, Ikeda T, Ohkuma T, Widhalm M, Kitamura M, Takaya H, Akutagawa S, Sayo N, Saito T. Stereoselective hydrogenation via dynamic kinetic resolution. J Am Chem Soc 1989;111:9134–9135.
10. Gasparrini F, Misiti D, Pierini M, Villani C. Enantiomerization barriers by dynamic HPLC. Stationary phase effects. Tetrahedron: Asymmetry 1997;8:2069–2073.
11. Trapp O, Schoetz G, Schurig V. Determination of enantiomerization barriers by dynamic and stopped flow chromatographic methods. Chirality 2001;13:403–414.
12. Gasparrini F, D'Acquarica I, Pierini M, Villani C. Chromatographic resolution and enantiomerization barriers of axially chiral 1-naphthamides. J Sep Sci 2001;24:941–946.
13. Trapp O, Caccamese S, Schmidt C, Böhmer V, Schurig V. Enantiomerization of an inherently chiral resorcarene derivative: determination of the interconversion barrier by computer simulation of the dynamic HPLC experiment. Tetrahedron: Asymmetry 2001;12:1395–1398.
14. Trapp O, Trapp G, Schurig V. Direct calculation and computer simulation of the enantiomerization barrier of oxazepam in dynamic HPLC experiments—a comparative study. J Biochem Biophys Methods 2002;54:301–313.
15. D'Acquarica I, Gasparrini F, Pierini M, Villani C, Zappia G. Dynamic HPLC on chiral stationary phases: a powerful tool for the investigation of stereomutation processes. J Sep Sci 2006;29:1508–1516.
16. Wolf C. Stereolabile chiral compounds: analysis by dynamic chromatography and stopped-flow methods. Chem Soc Rev 2005;34:595–608.
17. Wolf C. Dynamic stereochemistry of chiral compounds—principles and applications. Cambridge: RSC Publishing; 2008.
18. Ciogli A, Bicker W, Lindner W. Determination of enantiomerization barriers of hypericin and pseudohypericin by dynamic high-performance liquid chromatography on immobilized polysaccharide-type chiral stationary phases and off-column racemization experiments. Chirality 2010;22:463–471.
19. Maier F, Trapp O. Quantifizierung der Stationärphasen- und Lösungsmitteleinflüsse auf die Stereodynamik von BIPHEP-Liganden durch dynamische Drei- Säulen-HPLC. Angew Chem 2012;124:3039–3043; Effects of the stationary phase and the solvent on the stereodynamics of BIPHEP ligands quantified by dynamic three-column HPLC. Angew Chem Int Ed 2012;51:2985–2988.
20. Wolf C, König WA, Roussel C. Influence of substituents on the rotational energy barrier of atropisomeric biphenyls—studies by polarimetry and dynamic gas chromatography. Liebigs Ann 1995;781–786.
21. Wolf C, König WA, Roussel C. Conversion of a racemate into a single enantiomer in one step by chiral liquid chromatography: studies with rac-2,2'-diiodobiphenyl. Chirality 1995;7:610–611.
22. Wolf C, Hochmuth DH, König WA, Roussel C. Influence of substituents on the rotational energy barrier of atropisomeric biphenyls II. Liebigs Ann 1996;357–363.
23. Ceccacci F, Mancini G, Mencarelli P, Villani C. Determination of the rotational barrier of a chiral biphenyl: comparison of theoretical and experimental data. Tetrahedron: Asymmetry 2003;14: 3117–3122.
24. Soai K, Shibata T, Morioka H, Choji K. Asymmetric autocatalysis and amplification of enantiomeric execss of a chiral molecule. Nature 1995;378:767–768.
25. Shibata T, Yonekubo S, Soai K. Eine nahezu ideale asymmetrische autokatalyse mit (2-alkinyl-5-pyrimidyl)alkanolen. Angew Chem 1999;111:746–748; Practically perfect asymmetric autocatalysis with (2-alkynyl-5-pyrimidyl)alkanols. Angew Chem Int Ed 1999;38:659–661.
26. Liang Y, Wang Z, Ding K. Generation of self-supported Noyori-type catalysts using achiral bridged-BIPHEP for heterogeneous asymmetric hydrogenation of ketones. Adv Synth Catal 2006;348:1533–1538.
27. Wang C, Yang G, Zhuang J, Zhang W. From tropos to atropos: 5,5'-bridged 2,2'-bis(diphenylphosphino)biphenyls as chiral ligands for highly enantioselective palladium-catalyzed hydrogenation of α-phthalimide ketones. Tetrahedron Lett 2010;51:2044–2047.
28. Trapp O. Unified equation for access to rate constants of first-order reactions in dynamic and on-column reaction chromatography. Anal Chem 2006;78:189–198.
29. Trapp O. Fast and precise access to enantiomerization rate constants in dynamic chromatography. Chirality 2006;18:489–497.
30. Trapp O, Sahraoui L, Hofstadt W, Könen W. The stereodynamics of 1,2-dipropyldiaziridines. Chirality 2010;22:284–291.
31. Trapp O. The unified equation for the evaluation of degenerated first order reactions in dynamic electrophoresis. Electrophoresis 2006;27:2999–3006.
32. Trapp O. The unified equation for the evaluation of first order reactions in dynamic electrophoresis. Electrophoresis 2006;27:534–541.
33. Trapp O. A novel software tool for high throughput measurements of interconversion barriers: DCXplorer. J Chromatogr B 2008;875:42–47.

34. Trapp O, Bremer S, Weber SK. Accessing reaction rate constants in on-column reaction chromatography: an extended unified equation for reaction educts and products with different response factors. Anal Bioanal Chem 2009;395:1673–1679.
35. Bürkle W, Karfunkel H, Schurig V. Dynamic phenomena during enantiomer resolution by complexation gas chromatography. J Chromatogr 1984;288:1–14.
36. Trapp O, Schurig V. Stereointegrity of Tröger's base: gas-chromatographic determination of the enantiomerization barrier. J Am Chem Soc 2000;122:1424–1430.
37. Trapp O, Schurig V. Chromwin—a computer program for the determination of enantiomerization barriers in dynamic chromatography. Comput Chem 2001;25:187–195.
38. Trapp O. The unified equation for the evaluation of first order reactions in dynamic electrophoresis. Electrophoresis 2006;27:534–541.
39. Rieger M, Westheimer H. The calculation and determination of the buttressing effect for the racemization of 2,2', 3,3'-tetraiodo-5,5'-dicarboxybiphenyl. J Am Chem Soc 1950;72:19–28.
40. Dunitz JD. Win some, lose some: enthalpy-entropy compensation in weak intermolecular interactions. Chem Biol 1995;2:709–712.