New Route to Biaryl Phosphanes with Axial Chirality as Ligands for Enantioselective Hydrogenations

Birgit Drießen-Hölscher,[a,*] Joachim Kralik,[a] Friederike Agel,[a] Christian Steffens,[a] Chunhua Hu[b]

[a] Institute of Technical Chemistry and Macromolecular Chemistry, RWTH Aachen and University of Paderborn, Faculty of Sciences, Technical Chemistry, Warburger Str. 100, 33098 Paderborn, Germany
Fax: (+49)-5251-603244, phone: (+49)-5251-603616; e-mail: bdh@tc.upb.de
[b] Institute of Inorganic Chemistry, RWTH Aachen, Templergraben 55, 52056 Aachen, Germany

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Dedicated to Professor Joachim Bargon on the occasion of his 65th birthday.

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Abstract: We have found a modular route for the synthesis of Cl-MeOBIPHEP ligands *via* the corresponding biphenol that allows us to introduce several substituents without the necessity to separate the enantiomers of each derivative. These new diphosphanes were used in the ruthenium-catalyzed enantioselective hydrogenation of dimethyl itaconate with ee values up to 97%.

Keywords: asymmetric hydrogenation; atropisomeric diaryl-core diphosphanes; crystal structure determination; dimethyl itaconate; homogeneous catalysis; P ligands; ruthenium

Abbreviations: Tf_2O: trifluoromethanesulfonic acid anhydride; DEIPA: diethylisopropylamine; DPPP: 1,2-bis(diphenylphosphino)propane; cod: 1,5-cyclooctadiene; dba: dibenzylideneacetone

Introduction

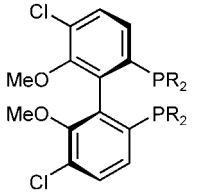
The use of chiral transition metal complex catalyzed reactions is well established and highly attractive for the synthesis of optically active products.[1] Atropisomeric diaryl-core diphosphanes like BINAP and MeOBIPHEP are attracting increasing interest because of their exceptional ability to induce asymmetry in numerous reactions.[2] Consequently, there also exists a large interest in expanding the library of axially chiral diphosphanes,[3] and the quest for new efficient ligand systems is still a major challenge in catalysis research.

Results and Discussion

Here we introduce new derivatives of bidentate chiral ligands **1b–e** which contain the 5,5′-dichloro-6,6′-dimethoxybiphenyl backbone (Figure 1). The ligand **1a** with phenyl groups at the phosphorus donors, called Cl-MeOBIPHEP, is already known and was originally synthesized *via* another route.[4]

Our aim was to find an easy route to diphenyldiphosphanes with several diarylphosphanyl substituents without the necessity to separate the enantiomers of each derivative. We were interested in modifying these ligands by varying the electronic and steric properties of the phosphorus donors.

The new derivatives **1b–e** were synthesized by reacting the readily available 4-chloro-3-methoxyphenol (**2**) with diiodomethane to form **3**, followed by the oxidative coupling of **3** to **4** (Scheme 1). The acetal **4** is cleaved in acidic media and yields the biphenol **5**.



1a, R = Ph
1b, R = *p*-fluorophenyl
1c, R = xylyl
1d, R = 2-furyl
1e, R = 2,5-dimethoxyphenyl

Figure 1. Cl-MeOBIPHEP (*R*)-**1**.

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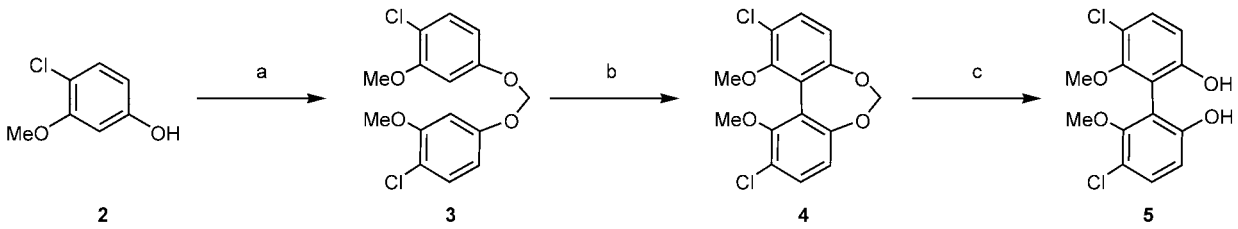
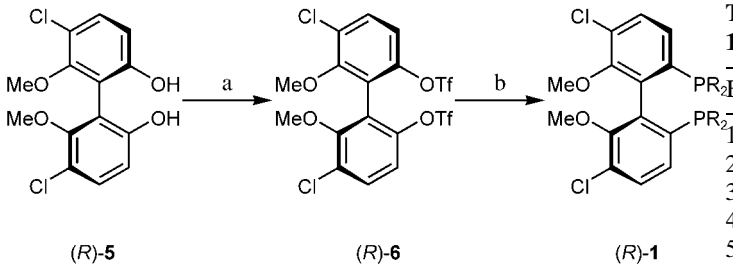


Scheme 1. Synthesis of the biphenol **5** starting from 4-chloro-3-methoxyphenol **2**. Reaction conditions: a) NaH, DMF, CH_2I_2, rt, 92%; b) 1. *n*-BuLi, THF, 0 °C; 2. $CuCl_2$, −40 °C, 77%; c) HCl, EtOH, reflux, 91%.



Scheme 2. Synthesis of the diphosphanes (*R*)-**1** starting from (*R*)-**5**. reaction conditions: a) Tf_2O, pyridine, toluene, 92%; b) $Pd_2(dba)_3 \cdot CHCl_3$, DPPP, DMSO, DEIPA, R_2PH, 100 °C, 20–62%.

Table 1. Yields of isolated Cl-MeOBIPHEP ligands (*R*)-**1a–e** and NMR data.

Entry	Ligand	Yield [%]	^{31}P NMR[a]	^{1}H NMR[b]
1	**1a**	62	−14.2	3.17
2	**1b**	20	−16.0	3.31
3	**1c**	42	−13.7	3.27
4	**1d**	24	−59.1	3.30
5	**1e**	53	−10.6	3.22

[a] Recorded in $CDCl_3$.
[b] Chemical shift of the OCH_3 proton resonances.

Compound (*R*)-**5** was separated by crystallization with *N*-benzylcinchonidinium chloride in a chemical yield of 29% (ee = 98%) and was then isolated in >99.9% ee after recrystallization from chloroform. The other enantiomer (*S*)-**5** could also be separated from the mother liquor. In order to bind a low-valent phosphorus centre to the aryl nucleus, (*R*)-**5** was reacted with trifluoroacetic anhydride to yield the biphenol ditriflate (*R*)-**6**. The last step, the substitution of the triflate groups of (*R*)-**6** with secondary phosphanes R_2PH was mediated by palladium(0) catalysts in the presence of a base (Scheme 2).[5]

The yields of the enantiomerically pure products (*R*)-**1a–e** are moderate or low, but the palladium catalyzed coupling has not yet been optimized. Table 1 lists the yields, the ^{31}P NMR and the ^{1}H NMR chemical shifts for the methoxy groups of (*R*)-**1a–e** (see also Supporting Information).

We determined the optical purity at the stage of the biphenol **5** by chiral HPLC. The absolute configuration of **1d** was assigned as (*R*) from the crystal structure determination. Bond lengths and angles show the expected values, and the two phenyl rings of the biaryl backbone are twisted against each other, the twist angle being 74.7° (Figure 2). We assume that the other derivatives have the same configuration because all were synthesized using the enantiomerically pure (*R*)-**5**.

In a first set of experiments, we used the ruthenium catalyzed hydrogenation of dimethyl itaconate (**7**) to study the potential of Cl-MeOBIPHEP ligands (*R*)-**1a–e** for asymmetric catalysis (Scheme 3). The number of publications on ruthenium catalyzed hydrogenations of dimethyl itaconate is rather small[6] and an excellent chiral catalyst to date is [Ru(BINAP)(CH_3CN)(cod)]BF_4 which leads to the formation of dimethyl succinate (**8**) with an enantiomeric excess of 95%.[7]

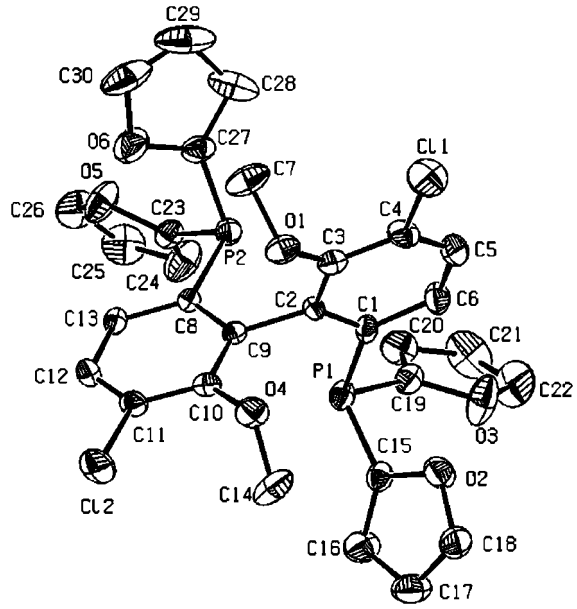
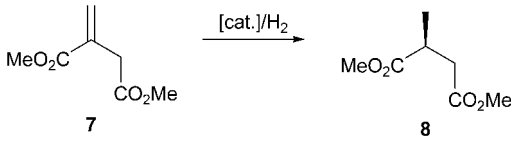


Figure 2. ORTEP illustration, with thermal ellipsoids drawn at the 30% probability level, of (*R*)-**1d** in the crystal.

Our catalysts can be synthesized by reacting [(cod) Ru(η^3-methallyl)$_2$], the diphosphanes (*R*)-**1a–e** (one equivalent) and trifluoroacetic acid (two equivalents) in methanol/dichloromethane as solvent mixture.[8] Formation of the complexes {[(*R*)-**1a–e**]Ru(OOCCF$_3$)$_2$} is complete after 70 hours at room temperature. The isolated compounds are yellow or orange solids which have been characterized by ^{31}P NMR spectroscopy. All Cl-MeOBIPHEP-containing ruthenium complexes catalyze the hydrogenation of dimethyl itaconate (**7**) with high enantioselectivities and almost complete conversion of the substrate after short reaction times (Table 2).

The enantioselectivities of all five complexes (ranging from 91 to 97% ee) are in some aspects even better than that with the best hydrogenation catalyst known to date. Electronic effects seem to be less important for asymmetric induction, as becomes evident by comparing entry 2 with entry 3. Steric effects seem to be more important because the ligands with the smaller aryl groups phenyl and furyl (entries 6 and 9) give somewhat lower ee values compared to the bulkier derivatives. The ruthenium catalysts formed with the Cl-MeOBIPHEP ligands not only show high asymmetric induction, but also show a significant catalytic activity. Activities are dependent on the ligand used: the electron-withdrawing *p*-fluorophenyl-substituted ligand **1b** shows lower activity (entry 2) than in the case of an electron-donating ligand (entry 3). At higher temperatures, the reaction is faster and quantitative conversion could be reached after 30 minutes (entries 6–8). The total number of catalytic turnovers is high. An initial turnover frequency of around 200 h^{-1}was determined.



Scheme 3. Hydrogenation of dimethyl itaconate (**7**).

Conclusions

To summarize, we have found a new route for the synthesis of Cl-MeOBIPHEP ligands (*R*)-**1a–e** and used these diphosphanes for the synthesis of chiral ruthenium complexes. The complexes with the general formula {[(*R*)-**1a–e**]Ru(OOCCF$_3$)$_2$} have been successfully used in the enantioselective hydrogenation of dimethyl itaconate (ee values up to 97%). In conclusion, the highly flexible synthesis of Cl-MeOBIPHEP ligands *via* the biphenol opens a broad range of possible modifications for further optimization of this ligand family by electronic and steric variations. Most of the research results reported here are encompassed by pending patent[9] applications. Further work will include investigations into other enantioselective reactions using these ligands.

Experimental Section

Typical Procedure for the Preparation of (*R*)-1

A solution of 79 mg (0.19 mmol) DPPP in 10 mL DMSO is added to 0.220 g (0.19 mmol) [Pd(PPh$_3$)$_4$] under argon. To the resulting suspension 0.99 g (5.3 mmol) diphenylphosphane, 0.85 g (6.6 mmol) DEIPA and a solution of 1.00 g (1.7 mmol) ditriflate (*R*)-**6** in 10 mL DMSO are added in this order. The resulting clear yellow solution is heated to 100 °C. After the reaction is complete, the solvent is removed under vacuum, and the residue dissolved in 10 mL methanol. Crystallization at −25 °C afforded (*R*)-**1** as a white, crystalline solid; yield: 0.70 g (62%).

Catalyst Preparation

To a solution of 155 mg (0.484 mmol) [Ru(cod)(methallyl)$_2$] in 5 mL CH_2Cl_2 are added 432 mg (0.484 mmol) (*R*)-1a under argon. After stirring for 1 h, 79 μL (1.025 mmol) trifluoroacetic acid are added and the mixture is stirred for 72 h under the exclusion of light. The solvent is removed under reduced pressure to give complex {[(*R*)-1**a–e**]Ru(OOCCF$_3$)$_2$} in quantitative yield.

Table 2. Hydrogenation of dimethyl itaconate (7**)** with {[(*R*)-**1a–e**]Ru(OOCCF$_3$)$_2$} as catalysts.[a]

Entry	Catalyst	Temperature [°C]	Conversion [%]	% ee
1	[(**1a**)Ru(OOCCF$_3$)$_2$]	22	100	92 (*S*)
2	[(**1b**)Ru(OOCCF$_3$)$_2$]	22	70	95 (*S*)
3	[(**1c**)Ru(OOCCF$_3$)$_2$]	22	100	95 (*S*)
4	[(**1d**)Ru(OOCCF$_3$)$_2$]	22	0	–
5	[(**1e**)Ru(OOCCF$_3$)$_2$]	22	100	92 (*S*)
6	[(**1a**)Ru(OOCCF$_3$)$_2$]	50	100	92 (*S*)
7	[(**1b**)Ru(OOCCF$_3$)$_2$]	50	100	96 (*S*)
8	[(**1c**)Ru(OOCCF$_3$)$_2$]	50	100	97 (*S*)
9	[(**1d**)Ru(OOCCF$_3$)$_2$]	50	17	93 (*S*)

[a] Reaction conditions: 0.02 mmol Ru; 2.0 mmol **7**; 5 mL MeOH, 1 bar H_2; reaction time: 60 minutes for the experiments at 22 °C and 30 minutes for experiments at 50 °C; conversion and enantiomeric excesses were determined by GC.

Asymmetric Hydrogenation of Dimethyl Itaconate (7)

To a 60-mL glass autoclave with a magnetic stirrer are added under argon dimethyl itaconate (7, 2.0 mmol), 0.100 g diglyme, and catalyst (*R*)-**1a** (1 mol %) in 5 mL methanol. The autoclave is sealed and pressurized to 1 bar with hydrogen. The reaction mixture is stirred for 1 h at room temperature, the pressure then released. Conversion was determined by GC of the crude reaction mixture, while the enantiomeric excess was determined by chiral GC after distillation under reduced pressure.

Crystallographic data (excluding structure factors) for the structure **1d** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-156383. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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