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Ligand Tailoring: The First Modular Assembly of Atropisomeric Biarylbisphosphine Ligands

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Abstract: Strategies based on highly selective halogen–metal permutations have been devised and applied enabling the modular assembly of atropisomeric biaryl bisphosphines. After resolution on chiral column, the ligands were tested in benchmark hydrogenation reactions affording good to excellent enantioselectivity.

Key words: lithiation, phosphorus, catalysts, hydrogenation, biaryls

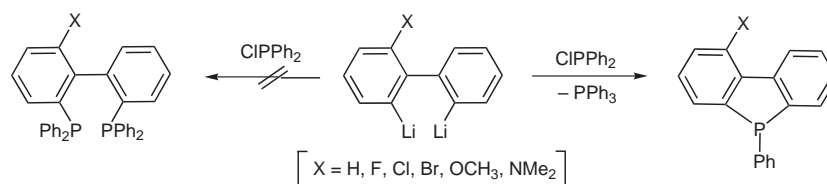
Chiral compounds qualifying as ligands for asymmetric catalysis continue to be designed and synthesized at a frenetic pace.^{1–3} If under such circumstances it appears difficult to keep track of all individual structures, one nevertheless recognizes three dominant classes which are privileged because of their versatility and their enantioselective performance. Bisphosphines containing asymmetric carbon centers were the first to supplant mono- and bisphosphines^{4,5} having stereogenic phosphorus atoms and were equally the first to gain practical importance. DIOP,⁶ CHIRAPHOS⁷ and, more recently, the DUPHOS family⁸ have been featured by most impressive results in the area of asymmetric hydrogenation reactions. Meanwhile competitors emerged such as BINAP,^{9,10} arguably the most popular of all ligands, MeOBIPHEP^{11,12} and SEGPHOS.^{13,14} Finally, the option of planar chirality was explored leading to paracyclophane¹⁵ and ferrocene^{16–18} based bisphosphines. The JOSIPHOS family^{19,20} belonging to the latter category deserves particular attention as it offers the so far unique advantage to enable ligand construction with utmost structural flexibility.

In the field of atropisomeric ligands, both the aryl phosphorus substituents and the biaryl backbone are tunable

parts to modify the stereoelectronic profile of a ligand. Numerous modifications of the phosphine substituent can be found in the literature, influencing the steric hindrance around the metal and/or the electronic properties of the phosphorus center.²¹ In addition, the groups of Zhang,²² Saito^{13,14} and Genêt²³ studied the steric modification of the biaryl core. However, the electronic design of atropisomeric bisphosphine ligands has been less systematically studied.²⁴ One difficulty is the possibility to synthesize atropisomeric ligand families in a modular way, as it is done for the JOSIPHOS family. Such a modular access to a whole ligand family allows the fine-tuning of the steric and electronic properties of a ligand depending on specific needs.

Our objective was to apply the concept of modular synthetic access²⁵ to the series of atropisomeric biaryls in order to prepare in a rational way a large family of biaryl-bisphosphine ligands having different tunable *ortho* substituents. A specific goal was to make biphenylene-2,2'-bisphosphines accessible that carry only one substituent at the 6-positions.

Polar organometallic chemistry is particularly suitable to realize this goal, due to the possibility to perform highly selective reactions. As our objective had to cope with a high structural complexity, we decided, for reasons of logistic simplicity, that it would be advantageous to allow for the presence of just one kind of halogen, preferably bromine, in a common starting material in order to replace them successively by metal and ultimately by phosphorus groups or other substituents. This raises the question of how to discriminate chemically between formally identical halogen atoms.



Scheme 1

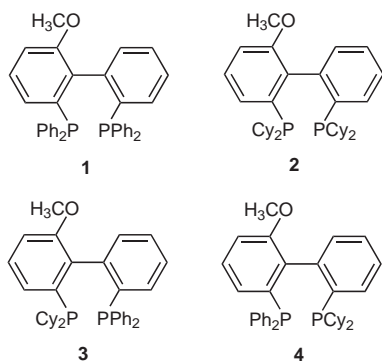


Figure 1

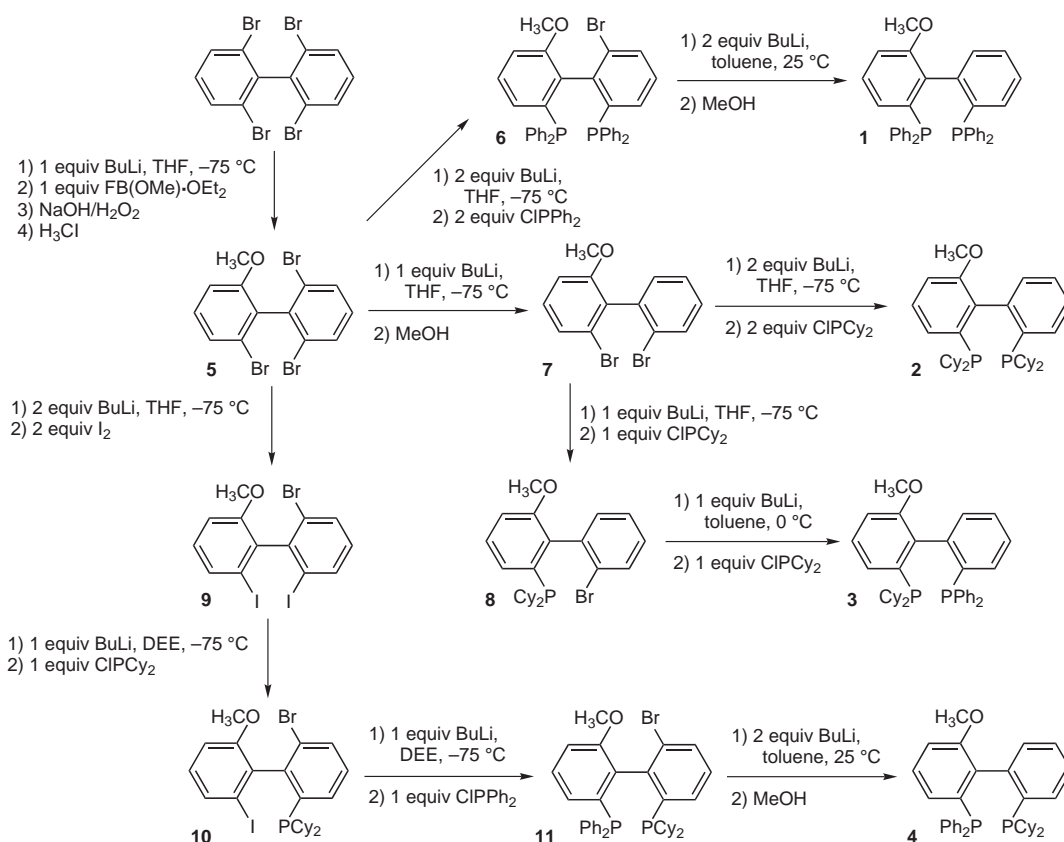
There was a major obstacle to be overcome. Any 2'-di-phenylphosphino-2-biphenyl lithium generated as an intermediate would be unable to produce a bisphosphine by condensation with a second chlorodiorganylphosphine component if a single fluorine, chlorine or bromine atom or a single methyl or methoxy group occupied the 6-position.²⁶ The intermediate would rather undergo an instantaneous nucleophilic substitution at phosphorus and cyclize under phenyllithium elimination to afford a 1*H*-benzo[*b*]phosphindole (Scheme 1).

The undesired ring closure can be avoided, as we have now found, by the introduction of a later removable 'dummy' substituent into the 6'-position. Our first choice fell on bromine.

We decided to use 2,2',6,6'-tetrabromobiphenyl as common starting material.²⁷ The feasibility of the project should be demonstrated on the modular synthesis of all four 2'-methoxy-2,6-biphenylenebisphosphines **1–4**, having a methoxy substituent, in analogy to MeOBIPHEP, and in addition all possible permutations of bis(diarylphosphine)-, bis(dialkylphosphine)- and mixed dialkyl/diarylphosphine substituents (Figure 1).

Starting from 2,2',6,6'-tetrabromobiphenyl, the first halogen was replaced by methoxy, affording 2,2',6-tribromo-6'-methoxybiphenyl (**5**; 82% yield), if the intermediate was consecutively subjected to borylation, oxidation and O-methylation.²⁸ A double bromine–lithium interconversion and subsequent condensation with two equivalents of chlorodiphenylphosphine gave 6'-bromo-2,2'-bis(diphenylphosphanyl)-6-methoxybiphenyl (**6**; 71% yield) which could be readily reduced to the halogen-free bisphosphine **1** (57% yield; Scheme 2).

The intriguing question was whether one bromine would be exchanged preferentially if the twofold halogen–metal permutation was not carried out simultaneously but successively. An effective discrimination between two bromine atoms as a function of their chemical environment has so far been observed only sporadically in such kind of processes.²⁹ Fortunately, the reaction occurred exclusively in the doubly halogenated ring when 2,2',6-tribromo-6'-methoxybiphenyl (**5**) was treated with just one equivalent of butyllithium in tetrahydrofuran at $-75\text{ }^{\circ}\text{C}$.



Scheme 2

Protolysis with methanol provided 2,2'-dibromo-6-methoxybiphenyl (**7**; 92% yield) which was readily converted into 2,2'-bis(dicyclohexylphosphanyl)-6-methoxybiphenyl (**2**; 74% yield) and into the *P,P*-dicyclohexyl-*P',P'*-diphenylbisphosphine (**3**; 56% yield) by double and stepwise bromine–lithium permutation, respectively. In the latter case the bromophosphine **8** (79%) acted as the intermediate. Finally, 2,2',6-tribromo-6'-methoxybiphenyl (**5**) was converted into the diiodo compound **9** by double bromine–lithium interconversion and subsequent trapping with iodine. Two consecutive unilateral halogen–metal permutations, the first followed by condensation with chlorodicyclohexylphosphine, led to the *P',P'*-dicyclohexyl-*P,P*-diphenylbisphosphine (**4**; 62% yield) via the bromiodophosphine **10** (72% yield) and the bromobisphosphine **11** (32% yield). The introduction of iodine ascertains higher selectivity, as iodine is known to be displaced faster than bromine by several powers of ten (Scheme 2).

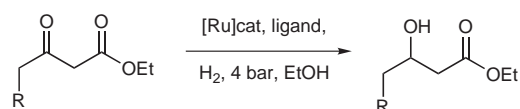
The four model compounds **1–4** are just meant to illustrate the almost inexhaustible possibilities for creating structural diversity. The aliphatic or aromatic substituents at phosphorus may be varied at will, the methoxy entity may be replaced by any other carbon or hetero unit and additional groups may be introduced. All the methods employed were straightforward and expedient enough to provide the bisphosphines **1–4** rapidly and in sufficient amounts. The access to the target compounds **1–4** relied on a combination of strategies, which deserve to be considered individually. First, the introduction of a removable 'dummy' substituent and taking it along almost to the end is essential for the success. Without the protection against planarization any transient 6- or 6'-methoxy-2'-diphenylphosphino-2-biphenyllithium would collapse to '9-phenyl-9-phosphafluorene' (9-phenyl-1*H*-benzo[*b*]phosphindole) under elimination of phenyllithium.²⁶ Second, dilithiated biaryls can be readily generated if, and only if, the two metal atoms are delivered to two separate rings rather than twice to the same ring. Thus, 2,2',6,6'-tetrabromobiphenyl and 2,2',6-tribromo-6'-methoxybiphenyl (**5**) produce the corresponding 2,2'-biphenylene dilithium neatly. Thirdly, and most importantly, all dibromo- and tribromobiphenyls exhibit rigorous site selectivity when exposed to just one equivalent of butyllithium. The halogen–metal exchange occurs exclusively in the ring that carries the more electronegative substituents. Such a distinct difference in permutation rates is without precedent. All transformations allow an easy preparation of the ligands on gram scale. The ligands are air- and temperature-stable compounds.

Most atropisomeric biaryl bisphosphine ligands used for asymmetric hydrogenations have C_2 -symmetry and, as a consequence, identically substituted phosphine groups.³ The literature only shows very few C_1 -symmetric examples in this ligand class, none of them having a high structural or electronic diversity.^{21d,30–32} It was therefore highly interesting to investigate the behavior of the biarylbisphosphines **1–4** as ligands in asymmetric hydrogenation

reactions. Tests were performed with two β -keto esters and two acrylates. All experiments were performed in screening type equipment with the objective to see differences between ligands for different substrates. Optimization of the hydrogenation conditions was not attempted.

The racemic ligands **1–4** were separated into their enantiomers by preparative HPLC chromatography using a chiral stationary phase (CHIRALCEL[®] OD 20 μ m, *n*-heptane–EtOH 2000:1).

We first examined the hydrogenation reaction of acetoacetate and chloroacetoacetate (Scheme 3). The catalytic tests were performed in ethanol at 50 °C, and 80 °C, respectively, under 4 bar of hydrogen pressure with a substrate/catalyst ratio (S/C) of 100 (Table 1). The acetoacetate was preferentially hydrogenated using the MeOBIPHEP (99% ee, 100% conversion) related ligand **1** with fully aryl substituted phosphorus atoms (99% ee, 100% conversion). Similar results were obtained for chloroacetoacetate (88% ee, 100% conversion vs. 92% ee, 100% conversion for MeOBIPHEP). Both enantioselectivity and reactivity are highest with ligand **1** and much lower with ligand **2**, the mixed aryl/alkyl ligands **3** and **4** lying in-between.



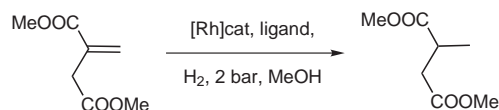
Scheme 3

Table 1 Hydrogenation of β -Ketoesters Using Ruthenium Complexes of Ligands **1–4**^a

R	Ru precursor	Ligand	Temp (°C)	Time (h)	ee (%)	Conversion (%)
H	RuCl ₃	1	50	3.5	99	100
H	RuCl ₃	2	50	15	88	4
H	RuCl ₃	3	50	15	87	98
H	RuCl ₃	4	50	15	95	100
H	RuCl ₃	MeOBIPHEP	50	3.0	99	100
Cl	Ru ₂ (<i>p</i> -cymene) ₂ Cl ₄	1	80	2	88	100
Cl	Ru ₂ (<i>p</i> -cymene) ₂ Cl ₄	2	80	15	45	98
Cl	Ru ₂ (<i>p</i> -cymene) ₂ Cl ₄	3	80	2	80	100
Cl	Ru ₂ (<i>p</i> -cymene) ₂ Cl ₄	4	80	48	87	100
Cl	Ru ₂ (<i>p</i> -cymene) ₂ Cl ₄	MeOBIPHEP	80	1	92	100

^a Reaction carried out with S/C of 100. The ee values were determined by HPLC analysis.

Next, we studied the hydrogenation of an olefin (dimethylitaconate). The hydrogenations were performed in methanol at 2 bar hydrogen pressure with a substrate/catalyst ratio (S/C) of 180 (Scheme 4).



Scheme 4

Table 2 Hydrogenation of Dimethyl Itaconate Using Rhodium Complexes of Ligands **1–4**^a

Rh precursor	Ligand	Temp (°C)	Time (h)	ee (%)	Conversion (%)
Rh(cod) ₂ BF ₄	1	22	3	2	100
Rh(cod) ₂ BF ₄	2	22	15	24	60
Rh(cod) ₂ BF ₄	3	22	2	30	100
Rh(cod) ₂ BF ₄	4	22	15	89	57
Rh(cod) ₂ BF ₄	JOSIPHOS ^b	22	3	71–97 ^c	100

^a Reaction carried out with S/C of 180.

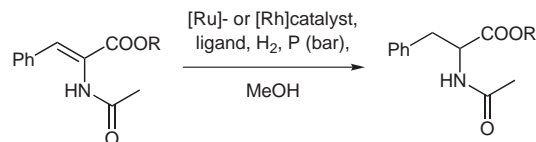
^b 1-(*S*)-[1(*R*)-(Dicyclohexylphosphanyl)ethyl]-2-(diphenylphosphanyl)ferrocene.

^c The ee is highly dependent on the hydrogen pressure. Reaction at 1 bar gave 97% ee, at 2 bar 71% ee.

A remarkably high diversity of the investigated ligands in terms of enantioselectivity as well as reactivity could be observed. While the ligands **1** and **3** give a fast and complete reaction with low ee, it is the complementary ligand **4**, which leads to a high enantioselectivity, albeit with a clearly lower hydrogenation rate. The all-alkyl ligand **2** performs poor in both respects, indicating that at least one electron-poor phosphorus atom needs to be present in the catalyst.

The third benchmark system, the hydrogenation of 2-acetaminocinnamic acid (Scheme 5), was performed in methanol according to the conditions given in Table 3.

2-Acetaminocinnamic acid was hydrogenated over Ru catalysts at elevated temperature and pressure. The enan-



Scheme 5

tioselectivities were only moderate with the all-alkyl ligand **2** performing best, followed by the all-aryl ligand **1**. Use of the mixed ligands **3** and **4** results in very poor ee. A completely different picture was found upon hydrogenating 2-acetaminocinnamic acid methyl ester over Rh catalysts at low pressure and room temperature. Here, the mixed aryl-alkyl ligand **3** performs very well, giving high ee as well as fast reaction rates (94% ee and 100% conversion, better than MeDUPHOS). Use of the alternative mixed ligand **4** results in a slower hydrogenation and lower enantioselectivity (Table 3).

In summary, strategies have been devised and applied enabling the modular assembly of chiral biarylphosphines. The four model compounds **1–4** are just meant to illustrate the almost inexhaustible possibilities for creating structural diversity. The aliphatic or aromatic substituents at phosphorus may be varied at will, the methoxy entity may be replaced by any other carbon or hetero unit and additional groups may be introduced. All the methods employed were straightforward and expedient enough to provide the bisphosphines **1–4** rapidly and in sufficient amounts.

The four ligands **1–4** behave very differently in the catalytic hydrogenation and their relative performance is strongly dependent on the substrate. It is interesting to note that each ligand has the best ee performance in one of the test reactions and that ligands **1** and/or **3** are among the best concerning reaction rates in all cases. The findings underline the importance to be able to prepare biarylphosphine ligands in a modular way in order to answer rapidly and efficiently on catalytic needs.

Table 3 Hydrogenation of Acetamino Cinnamates Using Ruthenium and Rhodium Complexes of Ligands **1–4**

R	Ligand	S/C	Temp (°C)	P (bar)	Time (h)	ee (%)	Conversion (%)
H	1 ^a	500	40	50	5	43	100
H	2 ^a	500	40	50	15	66	34
H	3 ^a	500	40	50	6	8	100
H	4 ^a	500	40	50	15	13	84
H	BINAP ^a	500	40	60	15	45	100
Me	2 ^b	100	25	2	3.3	90	100
Me	3 ^b	100	25	2	4.7	94	100
Me	4 ^b	100	25	2	15	81	93
Me	MeDUPHOS ^b	100	25	2	10	91	100

^a Catalyst precursor was Ru₂(benzene)₂Cl₄.

^b Catalyst precursor was Rh(cod)₂BF₄.

Acknowledgment

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- (28) **Representative Procedure for the Selective Bromine–Lithium Exchange.**
n-BuLi (0.10 mol) in hexanes (63 mL) was added at $-75\text{ }^{\circ}\text{C}$ to a solution of 2,2',6,6'-tetrabromo-1,1'-biphenyl (47 g, 0.10 mol) in THF (500 mL). The mixture was consecutively treated with fluorodimethoxyborane diethyl ether (19 mL, 16 g, 0.10 mol), a 3.0 M aq solution of NaOH (36 mL) and 30% aq H₂O₂ (10 mL, 3.6 g, 0.10 mol). The reaction mixture was neutralized at $25\text{ }^{\circ}\text{C}$ with 2.0 M HCl (100 mL) and extracted with Et₂O (3 × 100 mL). The combined organic layers were washed with a 10% aq solution of Na₂SO₃ (100 mL), dried over Na₂SO₄ and evaporated. The oily residue was dissolved in DMSO (200 mL) before MeI (7.5 mL, 17 g, 0.12 mol) and KOH powder (6.7 g, 0.12 mol) were consecutively added. After 1 h, H₂O (500 mL) was added and the product was extracted with Et₂O (3 × 100 mL). The organic layers were dried over Na₂SO₄ and evaporated. Crystallization from EtOH (100 mL) afforded 35 g (82%) product as colorless cubes; mp $184\text{--}185\text{ }^{\circ}\text{C}$. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.64$ (d, $J = 8.3$ Hz, 2 H), 7.30 (m, 2 H), 7.11 (t, $J = 8.1$ Hz, 1 H), 6.96 (dd, $J = 7.2, 2.2$ Hz, 1 H), 3.77 (s, 3 H). ¹³C NMR (101 MHz, CDCl₃): $\delta = 157.6, 139.5, 131.5, 130.5, 130.2, 125.1, 124.6, 124.3, 110.0, 56.3$. Anal. Calcd (%) for C₁₃H₉Br₃O (420.92): C, 37.09; H, 2.16. Found: C, 37.10; H 2.03.
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