DOI: 10.1002/adsc.200600300

First Modular Synthesis of Dissymmetric Biaryldiphosphine Ligands Allowing Tunable Steric and Electronic Effects

Frédéric R. Leroux[a,*] and Hanspeter Mettler[b]

[a] Laboratoire de Stéréochimie (UMR CNRS 7509), Université Louis Pasteur (ECPM), 67087 Strasbourg Cedex 2, France
Fax: (+33)-3-9024-2742; e-mail: frederic.leroux@ecpm.u-strasbg.fr
[b] LONZA AG, 3930 Visp, Switzerland
Fax: (+41)-27-947-5697

Received: June 22, 2006; Published online: January 8, 2007

Abstract: The first modular synthesis of a family of C_1-symmetric diphosphine ligands is presented. Their synthesis is based on unprecedented highly regioselective halogen/metal interconversions on a common polybrominated biaryl precursor. This methodology allows the functionalization of the *ortho*- and *ortho*′-positions of the biaryl core. Diphosphine ligands carrying only one substituent at the 6-position and the two phosphine substituents at the 2- and 2′-position become easily accessible. The two phosphine substituents may be identical (as in compounds **2** and **3**) or different (as in compounds **1** and **4**). All diphosphines were prepared on gram scale, and the enantiopure ligands were obtained by chromatography of the racemate on a chiral HPLC column. The asymmetric hydrogenation of β-keto esters, acetamidocinnamates and dimethyl itaconate revealed good to excellent asymmetric inductions of up to 99% *ee*, and are often close to those of the well-known C_2-symmetric MeO-BIPHEP.

Keywords: asymmetric catalysis; atropisomerism; biaryls; diphosphines; lithiation

Introduction

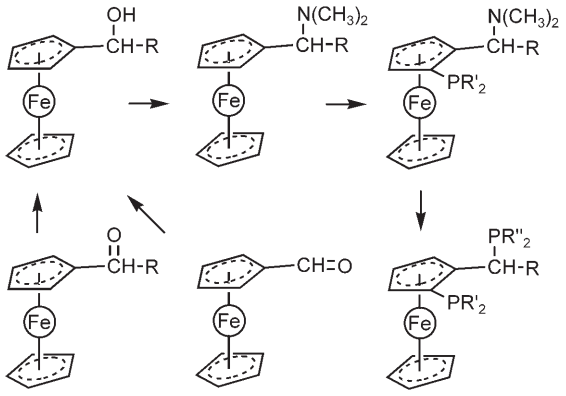
The use of chiral transition metal complexes as homogeneous catalysts is a well established and highly attractive strategy for the synthesis of optically active products. Chiral phosphorus compounds are very efficient ligands for many important reactions involving late transition metals. Consequently, the quest for new efficient ligand systems is a major challenge in catalysis research.[1–3]

Three dominant ligand classes, privileged because of their versatility and their enantioselective performance, can be recognized.

Diphosphines containing asymmetric carbon centers were the first to replace mono- and diphosphines[4–6] having stereogenic phosphorus atoms and were equally the first to gain practical importance. DIOP,[7] CHIRAPHOS[8] and, more recently, the DUPHOS family[9] have been featured by most impressive results in the area of asymmetric hydrogenation reactions.

Diphosphines supported on stereogenic atropisomeric biaryl scaffolds like MeO-BIPHEP,[10,11] SEGPHOS[12,13] and BINAP,[14,15] which is without any doubt the most popular of all ligands, became very efficient chiral inductors in most stereoselective reactions.

Finally, the option of planar chirality was explored leading to paracyclophane[16] and ferrocene[17–20] based diphosphines. Togni's JOSIPHOS ligand family[21–23] belonging to the latter category deserves particular attention, as it offers the unique advantage to enable a modular ligand construction with utmost structural flexibility (Scheme 1). The first variable is introduced as the aliphatic group R at the level of an (α-hydroxyalkyl)ferrocene which is either made by acylation of ferrocene followed by reduction or by addition of or-



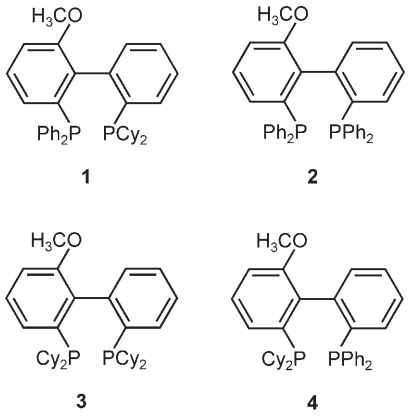
Scheme 1. Modular synthetic access to ferrocene based ligands.

ganozinc species to formylferrocene, a reaction which may even be accomplished enantioselectively when conducted in the presence of chiral auxiliaries. The alcohol is subsequently treated with acetic acid anhydride and dimethylamine to afford an α-aminoferrocene which can be resolved in its antipodes. Butyllithium-promoted deprotonation occurs exclusively at one of the two diastereotopic sites flanking the side chain. Using the appropriate chlorophosphine, any diorganylphosphino group can be now attached to this position. Finally, the dimethylamino group can be replaced by a second diorganylphosphino moiety or a suitable aliphatic, aromatic or heterocyclic amine (Scheme 1).

Such a modular access to a whole ligand family is much more difficult to realize in the field of atropisomeric biaryl ligands. Few examples are known so far and they only allow restricted structural diversity. Both the aryl phosphorus substituents and the biaryl backbone are tunable parts to modify the stereoelectronic profile of a ligand. So far, most modifications focused on the phosphorus substituents, influencing the steric hindrance around the metal and/or the electronic properties of the phosphorus center.[24–27] Steric modifications of the biaryl core were realized by Zhang,[28] Saito[12,13] and Genêt.[29,30] These groups could show that the dihedral angle between the two phenyl rings correlates well with the enantioselective performance of the ligand. However, the electronic design of atropisomeric diphosphine ligands has been less systematically studied.[31,32] It remains a challenge to prepare in parallel ligand families in a modular way allowing the fine-tuning of the steric and electronic properties of a ligand and thus to tailor the metal complex according to specific substrate needs.

Our objective was to apply the concept of modular ligand assembly (well known from the ferrocene-based JOSIPHOS ligand family) to the series of atropisomeric biaryls. A specific goal was to synthesize C_1-symmetric diphosphines that carry only one substituent at the 6-positions. For historical reasons, most of the diphosphine ligands in asymmetric catalysis are C_2-symmetric, although this symmetry is not a prerequisite. As a model compound we have chosen the well-known MeO-BIPHEP ligand due to its excellent and well documented catalytic properties. We decided to remove one of the methoxy substituents in order to get a C_1-symmetric diphosphine. In addition, all possible permutations of bisdiaryl-, bisdialkyl- and mixed diaryl-dialkyldiphosphines should be prepared in order to demonstrate the feasibility of a modular ligand construction (Scheme 2).

Polar organometallic chemistry allows one to perform highly selective reactions. Therefore, it seemed to us the ideal tool to realize our goal. As the objective had to cope with a high structural complexity, we decided, for reasons of logistic simplicity, to allow for the presence of just one kind of halogen, preferably bromine, in a common starting material. These bromine atoms should be replaced successively by a metal and ultimately by phosphorus groups or other substituents. However, this raised the question of how to discriminate chemically between formally identical halogen atoms.[33–36]



Scheme 2. Four target ligands demonstrating the modular construction of biaryl-based ligands.

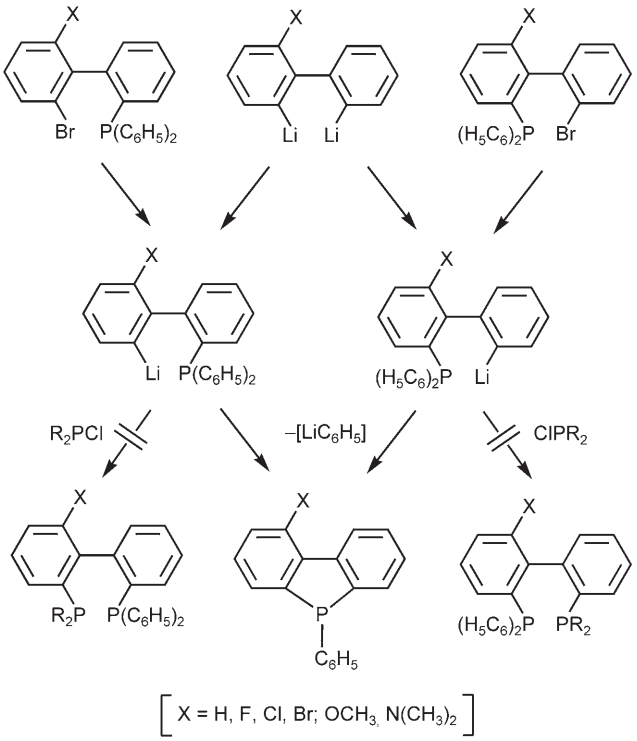
Results and Discussion

Ligand Synthesis

From our preliminary studies on the synthesis of biaryldiphosphines, we knew that there was a major obstacle to be overcome. Indeed, any 2′-diphenylphosphino-2-biphenyllithium generated as an intermediate would be unable to produce a diphosphine by condensation with a second chlorodiorganylphosphine component if a halogen atom, a methoxy- or a dimethylamino group occupies the 6-position (Scheme 3).[37,38] Due to the small torsion angle between the two phenyl rings, the intermediate would rather undergo an instantaneous nucleophilic substitution at phosphorus and cyclize under phenyllithium elimination to afford a "9-phosphafluorene" (1*H*-benzo[*b*]phosphindole).

However, we could show that the undesired ring closure can be avoided by the introduction of a later removable "dummy" substituent at the 6′-position. In fact, an increasing dihedral angle between the two phenyl rings favors the diphosphine formation with respect to the "9-phosphafluorene" formation.

Our first choice fell on bromine as "dummy" substituent. All four 2′-methoxy-2,6-biphenylenediphosphines **1**–**4** were prepared starting from 2,2′,6,6′-tetrabromobiphenyl.[35,39] The latter can be obtained by lithiation of 1,3-dibromobenzene, followed by copper-mediated aryl-aryl coupling, according to a new, low-temperature modification of the classic Ullmann cou-



Scheme 3. Formation of "9-phosphafluorenes".

pling.[40–42] 2,2′,6,6′-Tetrabromobiphenyl undergoes easily a bromine/lithium exchange using butyllithium in tetrahydrofuran at −75 °C. The methoxy substituent of the target ligands was easily introduced, by submitting the aryllithium intermediate to a borylation, oxidation and *O*-methylation sequence affording 2,2′,6-tribromo-6′-methoxybiphenyl (**5**; 82 %). A double bromine/lithium interconversion and subsequent condensation with two equivalents of chlorodiphenylphosphine gave 2-bromo-6′-methoxy-2′,6-bis-(diphenylphosphine) (**6**; 71 %) which could be readily reduced to the halogen-free diphosphine **2** (57 %).

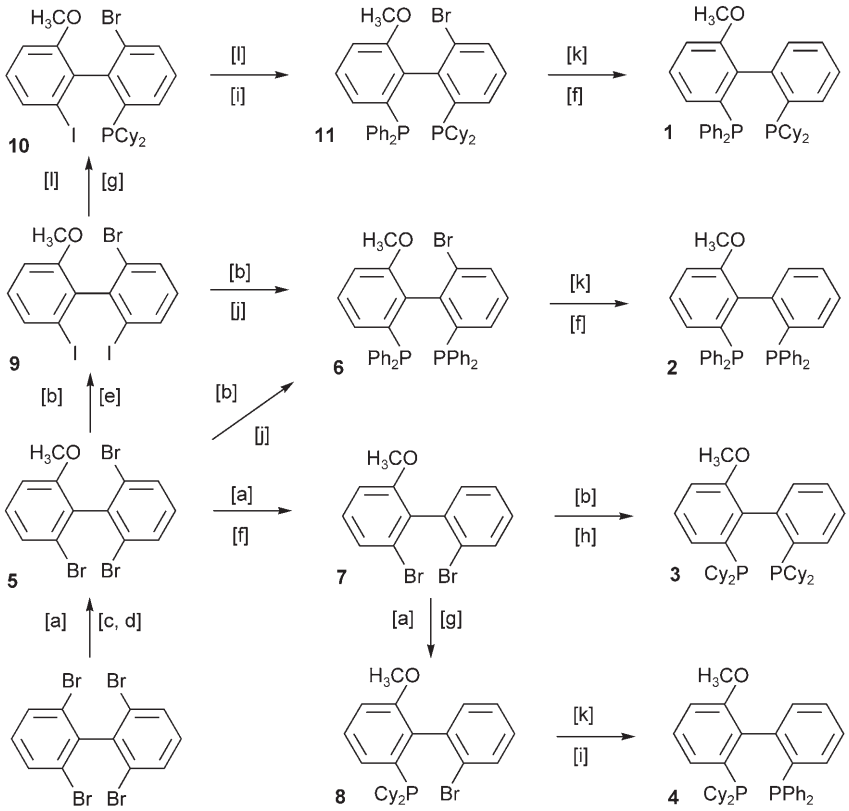
The intriguing question was whether one bromine of **5** would be exchanged preferentially if the two-fold halogen/metal permutation was not carried out simultaneously but successively. An effective discrimination between two bromine atoms as a function of their chemical environment has so far been observed only sporadically in such kind of processes.[34,36,43] 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 °C. Protolysis with methanol provided 2,2′-dibromo-6-methoxybiphenyl (**7**; 92 %) which was readily converted into 2,2′-bis(dicyclohexylphosphine)-6-methoxybiphenyl (**3**; 74 %) by double bromine/lithium exchange followed by trapping with two equivalents of chlorodicyclohexylphosphine. In contrast, the mixed P,P-dicyclohexyl-P′,P′-diphenyldiphosphine **4** was obtained in a yield of 56 % by stepwise bromine/lithium permutation. The bromophosphine **8** (79 %) acted hereby as an 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 halogen/metal permutations, the first followed by condensation with chlorodicyclohexylphosphine, led to the second mixed diphosphine **1** (62 %) *via* the bromoiodophosphine (**10**; 72 %) and the bromodiphosphine (**11**; 63 %) (Scheme 4).

All the methods employed were straightforward and expedient enough to provide the diphosphines **1**–**4** rapidly and in sufficient amounts. Several transformations described above revealed an unprecedented selectivity of the halogen/metal permutation mode. As one can deduce from the transformation of tribromo(methoxy)biphenyl (**5**) to the dibromo-(methoxy)biphenyl (**7**) and of the latter compound **7** to the phosphine **8**, it is always the halogen residing in the more electronegatively substituted ring which is replaced by lithium. We could show by *ab initio* calculations and equilibration studies, that a bromine atom stabilizes more efficiently a carbanion in its *meta* position than a methoxy substituent. This explains the regioselectivity of the bromine/lithium exchange of tribromo(methoxy)biphenyl (**5**). These results will be published elsewhere in due course.

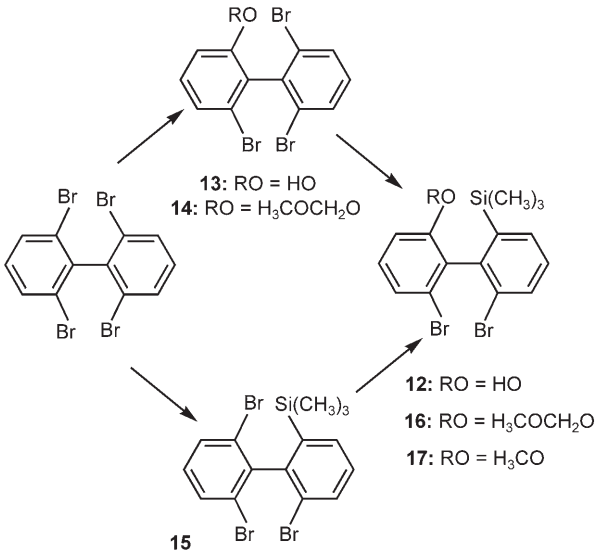
Racemate Resolution

The four racemic ligands **1–4** were separated in their enantiomers by means of semi-preparative HPLC chromatography on a CHIRALCEL® OD column. However, in order to avoid laborious individual resolution protocols in each single case, we decided to develop a second-generation approach (Scheme 5) using a common starting material which should be resolved at an early synthetic stage. Thus, 2,2′-dibromo-6-hydroxy-6′-(trimethylsilyl)biphenyl (**12**) was selected to become the new turntable. The trimethylsilyl group had to face two problems. First to avoid the undesired "9-phosphafluorene" formation and second to give rise to a resolvable biphenyl.

Consecutive treatment of 2,2′,6,6′-tetrabromobiphenyl with butyllithium, chlorotrimethylsilane, again butyllithium, fluorodimethoxyborane and alkaline hydrogen peroxide produced the phenol **12** in 56 % overall yield through 2,2′,6-tribromo-6′-(trimethylsilyl)biphenyl (**15**; 91 %). Alternatively, the phenol (**12**; 59 % overall) was obtained from 2,2′,6,6′-tetrabromobiphenyl by halogen/metal permutation followed by borylation and oxidation giving 2,2′,6-tribromo-6′-hydroxybiphenyl (**13**; 81 %), protection of the latter as the acetal (**14**; 88 %), another halogen/metal permutation and subsequent silylation (to the acetal **16**: 83 %)



Scheme 4. Modular synthetic access to atropisomeric biphenyl ligands. *Reagents and conditions:* [a] Butyllithium (1.0 equiv.) in tetrahydrofuran (THF) at −75 °C. [b] Butyllithium (2.0 equivs.) in THF at −75 °C. [c] (i) Fluorodimethoxyborane·diethyl etherate; (ii) aqueous sodium hydroxide/hydrogen peroxide. [d] Methyl iodide, potassium hydroxide in dimethyl sulfoxide. [e] Iodine (2.0 equivs.). [f] Methanol. [g] Chlorodicyclohexylphosphine (1 equiv.). [h] Chlorodicyclohexylphosphine (2.0 equivs.). [i] Chlorodiphenylphosphine (1.0 equiv.). [j] Chlorodiphenylphosphine (2.0 equivs.). [k] Butyllithium (2.0 equivs.) in toluene at +25 °C. [l] Butyllithium (1.0 equiv.) in diethyl ether (DEE) at −75 °C.

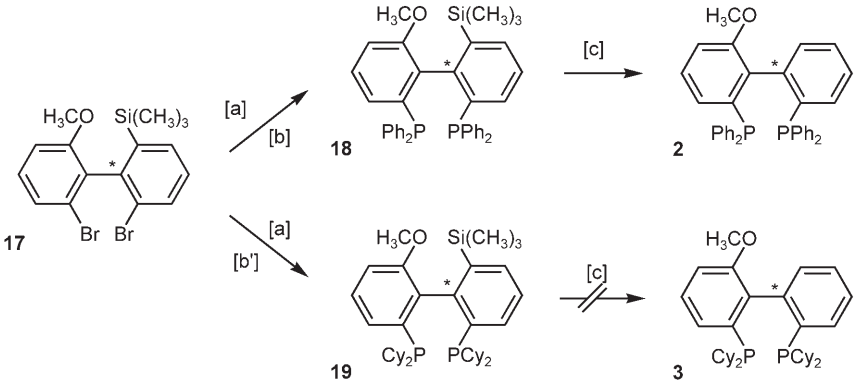


Scheme 5. Racemate resolution of a common precursor.

and deprotection. The methoxy-derivative **17** was obtained after alkylation of the phenol **13** with iodomethane.

Efficient racemate resolution of phenol **12** was accomplished by preparative HPLC chromatography using a chiral stationary phase (CHIRALCEL® OD 20 μm, *n*-heptane/2-butanol, 100:2). The pure enantiomers (*R*)-**12** and (*S*)-**12** were converted into the methoxy compounds (*R*)-**17** (96 %) and (*S*)-**17** (95 %) by alkylation with iodomethane.

When 2,2′-dibromo-6-methoxy-6′-(trimethylsilyl)biphenyl (**17**) was treated with two equivalents of butyllithium and subsequently trapped with chlorodiphenylphosphine or chlorodicyclohexylphosphine, the respective diphosphines **18** (89 %) and **19** (76 %) were obtained (Scheme 6). Unfortunately, the protodesilylation underwent in the case of **18** very reluctantly (43 % of diphosphine **2**) and failed completely in the case of the diphosphine **19**. Although silanes are quite frequently used as protective groups in organometallic chemistry,[44] this approach leading to chiral biaryldiphosphines was unsuccessful and had to be abandoned. Presently, we are studying the use of chiral auxiliaries for the resolution of these biaryldiphosphines. These results will be presented elsewhere in due course.



Scheme 6. Attempt to use silylated precursors. *Reagents and conditions:* [a] Butyllithium (2.0 equivs.) in toluene at −75 °C. [b] Chlorodiphenylphosphine (2.0 equivs.). [b′] Chlorodicyclohexylphosphine (2.0 equivs.). [c] TBAF·H_2O in DMF at 120 °C, 3 days.

Benchmark Hydrogenation Studies

Most atropisomeric biaryldiphosphine ligands used for asymmetric hydrogenations have C_2-symmetry and, as a consequence, identically substituted phosphine groups.[3] The literature shows only very few C_1-symmetric examples in this ligand class, none of them having a high structural or electronic diversity.[27,45,46] It was therefore intriguing to investigate the behavior of the biaryldiphosphines **1–4** as ligands in asymmetric hydrogenation reactions.

Good results have been reported in the literature for the rhodium- and ruthenium-catalyzed asymmetric hydrogenations of olefins and ketones. Therefore, we chose to perform the benchmark reactions with β-keto esters and two acryl ester substrates in order to gather information on the applicability range of the new catalysts. 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 μm, *n*-heptane/EtOH, 2000:1).

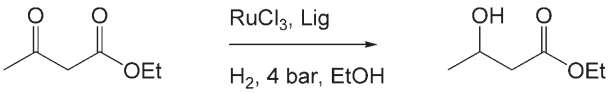
Hydrogenation of Ethyl Acetoacetate

The keto group in ethyl acetoacetate can be hydrogenated with a variety of catalysts. A very simple method for performing this reaction with easy available, stable $RuCl_3$ as precursor and *in situ* formation of the active catalyst was described by Madec et al.[47] and adopted for our benchmark studies. The reference ligand, MeO-BIPHEP gave a fast reaction with high *ee* (entry 5 in Table 1). A similar performance was found for ligand **2** (entry 2 in Table 1), whereas the other ligands gave slower reactions and lower *ee*s (entries 1, 3 and 4 in Table 1).

Hydrogenation of Ethyl 4-Chloroacetoacetate

If a coordinative functional group such as a chloride exists in the proximity of the carbonyl group of a β-

Table 1. Hydrogenation of ethyl acetoacetate using Ru complexes of ligands **1**–**4**.[a]



Entry	S/C	Ligand	Hydrogen uptake [h]	Total reaction time [h]	*ee* [%]	Conversion [%]	TOF [h^{-1}][b]
1	158	**1**	15	15	95	100	11
2	194	**2**	3.5	6	99	100	55
3	158	**3**	15	15	87	98	10
4	160	**4**	15	15	88	4	0.4
5	160	MeO-BIPHEP	3.0	7	99	100	53

[a] All reactions were conducted with 1.1 mol substrate in 7 mL EtOH at 4 bar hydrogen and 50 °C with $RuCl_3$ as catalyst precursor. The enantiomeric excesses were determined by GC analysis on a Lipodex-E column (25 m × 0.25 mm).
[b] The turnover frequency (TOF) is measured as mol of product per mol of catalyst per hour of hydrogen uptake time.

keto ester, lower enantioselectivity will be observed due to the competition of two different coordination patterns. However, the enantioselectivity can be improved under higher reaction temperatures. Under the Madec conditions with $RuCl_3$ as precursor and MeO-BIPHEP as ligand, the hydrogenation of ethyl 4-chloroacetoacetate gave 72% *ee* at 80°C and 92% *ee* at 120°C (entries 1 and 2 in Table 2). If the dimeric $[Ru(p\text{-cymene})Cl_2]_2$ was used as precursor, the *ee* values were 92% at 80°C and 95% at 120°C (entries 3 and 4 in Table 2). As the enantioselectivity of the reaction seems to be less temperature-dependent when starting from the dimeric ruthenium precursor, we chose to use these conditions for the benchmark tests. The temperature of 80°C will generally not lead to the optimal *ee* values but is more convenient for observing and measuring the reaction time and was therefore applied as standard for the benchmarks. Ligand **2** performed best from the new candidates with an *ee* only slightly lower compared to the reference ligand MeO-BIPHEP (entry 6 in Table 2). A similar enantioselectivity but much lower reactivity was observed for ligand **1** (entry 5 in Table 2). Whereas ligand **4** still allowed a decent *ee*, ligand **3** performed poor in enantioselectivity as well as reactivity (entries 7 and 8 in Table 2).

Hydrogenation of Acetamidocinnamic Acid Derivatives

Acetamidocinnamic acid and its derivatives are widely used substrates for testing new ligands in the asymmetric hydrogenation of a carbon-carbon double bond. In general, rhodium catalysts are used and electron-rich ligands are favored for achieving high reactivity as well as enantioselectivity.

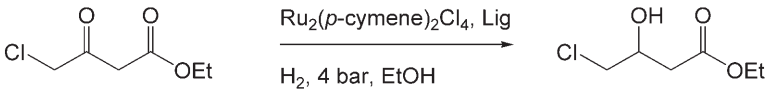
Matteoli et al.[48] described the ruthenium-catalyzed hydrogenation of the free acid in MeOH in the presence of BINAP as ligand and the dimeric $[Ru(benzene)Cl_2]_2$ as precursor. With an S/C ratio of 500, they reported a very long reaction time of 113 h at 40°C and 100 bar, leading to an enantioselectivity of only 50%. In our case the reaction was finished after 29 h at 40°C and 60 bar and with an S/C-ratio of 250, giving an *ee* of 45% (entry 1 in Table 3). A better enantioselectivity of 66% but very slow reaction was found for ligand **3** (entry 4 in Table 3). Ligand **2** gave approximately the same *ee* but much faster reaction compared to BINAP (entry 3 in Table 3). Very low enantioselectivities were achieved when using ligands **1** and **4** (entries 2 and 5 in Table 3).

Holz et al.[49] have used a cationic rhodium complex of MeDuphos for the asymmetric hydrogenation of the methyl ester and reported fast reactions with high enantioselectivities in dichloromethane (98.0% *ee*) as well as in methanol (97.5% *ee*). We observed an extremely slow hydrogenation in dichloromethane with much lower enantioselectivity (entry 1 in Table 4). The reaction in methanol however was as expected (97% *ee*, see entry 2 in Table 4) and we chose to use these conditions for the benchmark system. The MeO-BIPHEP ligand performed very poorly with this substrate and gives only 27% *ee* (entry 3 in Table 4). The three tested new ligands gave surprisingly high enantioselectivities of 90–94% (entries 4–6 in Table 4) and were reasonably active, with the exception of ligand **1**.

Hydrogenation of Dimethyl Itaconate

Many successful ligands have been reported for the hydrogenation of dimethyl itaconate. Among them

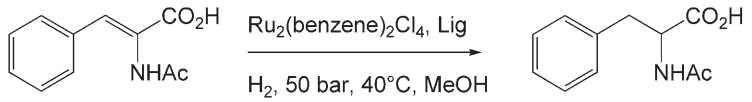
Table 2. Hydrogenation of ethyl 4-chloroacetoacetate using Ru-complexes of ligands **1**–**4**.[a]



Entry	S/C	Ligand	T [°C]	Hydrogen uptake [h]	Total reaction time [h]	*ee* [%]	Conversion [%]	TOF [h^{-1}][c]
1[b]	100	MeO-BIPHEP	80	1	15	72	100	99
2[b]	100	MeO-BIPHEP	120	2	4	92	100	49
3	200	MeO-BIPHEP	80	0.6	3	92	100	324
4	200	MeO-BIPHEP	120	$<0.5^b$	4	95	100	>400
5	200	**1**	80	48	48	87	100	4
6	200	**2**	80	2	4	88	100	95
7	200	**3**	80	15	18	45	98	13
8	200	**4**	80	2	3	80	100	102

[a] All reactions were conducted with 5 mmol substrate in 30 mL EtOH at 4 bar hydrogen with $Ru_2(p\text{-cymene})_2Cl_4$ as precursor. The enantiomeric excesses were determined by GC-analysis on a Lipodex-E column (25 m × 0.25 mm).
[b] $RuCl_3$ used as precursor, 15 mmol substrate, most of the substrate was hydrogenated during the heat-up phase.
[c] The turnover frequency (TOF) is measured as mol of product per mol of catalyst per hour of hydrogen uptake time.

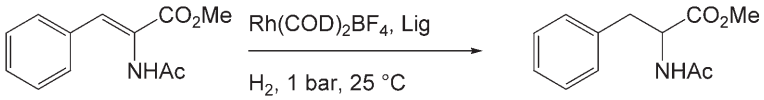
Table 3. Hydrogenation of acetamidocinnamic acid using Ru-complexes of ligands **1**–**4**.[a]



Entry	Ligand	Hydrogen uptake [h]	Total reaction time [h]	*ee* [%]	Conversion [%]	TOF [h^{-1}][c]
1	**BINAP**	<29[b]	29	45	100	>8
2	**1**	15	15	13	84	14
3	**2**	5	16	43	100	49
4	**3**	15	15	66	34	6
5	**4**	5	15	8	100	49

[a] All reactions were conducted with 2.5 mmol substrate in 5 mL MeOH at 50 bar hydrogen and 40 °C with $Ru_2(benzene)_2Cl_4$ as precursor. S/C ratio was 250. The enantiomeric excesses were determined by HPLC analysis on a Nucleodex beta PM column.
[b] Reaction at 60 bar pressure, exact uptake time not known due to data sampling problem.
[c] The turnover frequency (TOF) is measured as mol of product per mol of catalyst per hour of hydrogen uptake time.

Table 4. Hydrogenation of methyl acetamidocinnamate acid using Rh-complexes of ligands **1**–**4**.[a]



Entry	Ligand	Solvent	Hydrogen uptake [h]	Total reaction time [h]	*ee* [%]	Conversion [%]	TOF [h^{-1}][d]
1	MeDuphos[b]	CH_2Cl_2	24	24	83	6	0.3
2	MeDuphos[b]	MeOH	2.5	22	97	100	40
3	MeO-BIPHEP[c]	MeOH	4.0	24	27	98	25
4	**1**	MeOH	15	15	93	81	5
5	**3**	MeOH	3.3	15	90	100	29
6	**4**	MeOH	4.7	15	94	100	20

[a] All reactions were conducted with 0.5 mmol substrate in 6 mL solvent at 1 bar hydrogen and 25 °C with $Rh(COD)_2BF_4$ as precursor. S/C ratio was 100. The enantiomeric excesses were determined by GC analysis on a Lipodex-E column (25 m × 0.25 mm).
[b] 2 mmol substrate in 30 mL solvent, the finished $[Rh(MeDuphos)(COD)]BF_4$ complex was used.
[c] 2 mmol substrate in 30 mL solvent, reaction at 4 bar hydrogen.
[d] The turnover frequency (TOF) is measured as mol of product per mol of catalyst per hour of hydrogen uptake time.

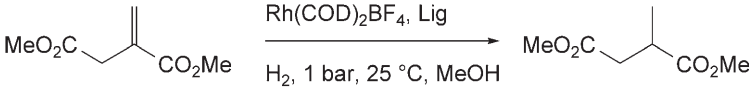
the cationic rhodium complexes of MeDuphos (97.0 % *ee* in THF at 1 bar pressure and 25 °C, see Holz et al.[49]) and Josiphos (98.5 % *ee* in MeOH at 1 bar pressure and 25 °C, see Togni et al.[50]). We decided to use the conditions as described by Togni for this benchmark system. The Josiphos ligand gave a fast reaction and a high enantioselectivity (entry 1 in Table 5). From the new candidates, ligand **1** was the only one leading to a high enantioselectivity however with a very slow reaction (entry 2 in Table 5). Ligands **2** and **4** showed a remarkably high reactivity but gave poor *ee*s (entries 3 and 5 in Table 5). Ligand **3**, finally, was neither very active nor stereoselective (entry 4 in Table 5).

Discussion of the Hydrogenation Results

The ruthenium-catalyzed reduction of the keto function in ethyl acetoacetate works well with the known MeO-BIPHEP ligand. The relative performance of the four new ligands is ligand **2** > ligand **1** > ligand **4** > ligand **3** for stereoselectivity and ligand **2** > ligand **1** ≈ ligand **3** > ligand **4** for activity. The relatively small change from MeO-BIPHEP to ligand **2** has obviously little influence on the hydrogenation. Replacing the phenyl substituents against the cyclohexyl substituents on one of the two phosphines leads to much lower activity and selectivity and one can differentiate between a matched case for ligand **1** and a mismatched case for ligand **4**. Low performance is noted with the very electron rich all-cyclohexyl ligand **3**.

The hydrogenation of 4-chloroacetoacetate follows a similar pattern at least in terms of selectivity. The

Table 5. Hydrogenation of dimethyl itaconate using Rh-complexes of ligands **1**–**4**.[a]



Entry	Ligand	Hydrogen uptake [h]	Total reaction time [h]	*ee* [%]	Conversion [%]	TOF [h^{-1}][c]
1	Josiphos[b]	2.5	9	97	100	73
2	**1**	15	15	89	57	7
3	**2**	3	6	2	100	59
4	**3**	15	15	24	60	7
5	**4**	2	15	30	100	89

[a] All reactions were conducted with 0.9 mmol substrate in 5 mL methanol at 1 bar hydrogen and 25 °C with $Rh(COD)_2BF_4$ as precursor. S/C ratio was 180. The enantiomeric excesses were determined by GC analysis on a Lipodex-E column (25 m × 0.25 mm).

[b] *R,S*-PPF-PCy_2.

[c] The turnover frequency (TOF) is measured as mol of product per mol of catalyst per hour of hydrogen uptake time.

relative performance of the four new ligands is ligand **2** ≈ ligand **1** > ligand **4** > ligand **3** for stereoselectivity and ligand **4** > ligand **2** > ligand **3** > ligand **1** for activity. It is most striking that ligand **4** which gave a slow hydrogenation with ethyl acetoacetate shows the highest activity for 4-chloroacetoacetate. None of the four new ligands is as active and selective as the benchmark ligand MeO-BIPHEP under the chosen conditions.

In the rhodium-catalyzed hydrogenation of methyl acetamidocinnamate, the relative performance of the three tested candidates was ligand **4** ≈ ligand **1** > ligand **3** for stereoselectivity and ligand **3** > ligand **4** > ligand **1** for activity. It is rather surprising that all three ligands give enantioselectivities of 90% or higher considering the much lower performance of the related MeO-BIPHEP ligand (25%). The presence of at least one cyclohexyl-substituted phosphine seems to play an important role for this application. The best match for high activity is presented by the fully cyclohexyl-substituted ligand **3**.

Very different results are obtained in the case of the ruthenium-catalyzed hydrogenation of acetoamidocinnamic acid. Here, we find a relative performance of ligand **3** > ligand **2** > ligand **1** > ligand **4** for stereoselectivity and ligand **2** = ligand **4** > ligand **1** > ligand **3** for activity. The electron rich fully cyclohexyl-substituted ligand **3** gives by far the highest enantioselectivity but, in contrast to the above benchmark, has the lowest activity of all four tested ligands. The enantioselectivities of both MeO-BIPHEP and the related ligand **2** are only mediocre with the latter showing a much higher activity. Very poor enantioselectivities are found when applying the ligands **1** and **4** with both cyclohexyl- and phenyl-substituted phosphines.

In the rhodium-catalyzed hydrogenation of dimethyl itaconate, the relative performance of the four new ligands is ligand **1** > ligand **4** > ligand **3** > ligand **2** for stereoselectivity and ligand **4** > ligand **2** > ligand **3** ≈ ligand **1** for activity. In this application we observe the interesting fact that the two "mixed" ligands, i.e., the ligands containing both cyclohexyl- and phenylphospine groups clearly outperform the other two ligands. The best match for enantioselectivity is ligand **1** with the cyclohexylphosphine located in the unsubstituted phenyl ring and the best match for activity is ligand **4** with the phenylphosphine located in the unsubstituted phenyl ring.

Conclusions

In summary, strategies have been devised and applied enabling the modular assembly of chiral biaryldiphosphines. 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 diphosphines **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 trimethylsilyl group or another removable "dummy" substituent is essential for the success. Without the protection against planarization any transient 6- or 6′-methoxy-2′-diphenylphosphino-2-biphenylyllithium would collapse to "9-phenyl-9-phosphafluorene" (9-phenyl-1*H*-benzo[*b*]phosphindene) under elimination of phenyllithium. Second, dilithiated biaryls can only be readily generated if the two metal atoms are delivered into two separate rings rather than in the same ring. Thus, 2,2′,6,6′-tetrabromobiphenyl,[36] and 2,2′,6-tribromo-6′-methoxybiphenyl (**5**) produce the corresponding 2,2′-biphenylenedilithium. Thirdly and most

importantly, all dibromo- and tribromobiphenyls exhibited rigorous site selectivity when exposed to just one equivalent of butyllithium. The halogen/metal exchange occurred exclusively in the ring carrying the more electronegative substituents, for example, bromine as opposed to hydrogen, lithiooxy or methoxy and methoxy as opposed to hydrogen, trimethylsilyl or diorganylphosphino. Such a distinct difference in permutation *rates* is without precedent.

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 benchmark tests have shown that no single ligand performs very well for a variety of substrates. Each of the four new ligands has its own merits and pitfalls, depending on the type of substrate as well as the specific catalytic system used. The variance in stereoselectivity and in activity caused by switching from phenylphosphine to cyclohexylphosphine is in some cases dramatic. It will now be very intriguing to investigate how a fine-tuning of the new ligands can be achieved by either variations in the alkyl- and arylphosphine substituents or by moving from 2-methoxybiphenyldiphosphines into related biphenyldiphosphines with other substituents in the 2-position.[35,51]

Experimental Section

General Remarks

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone and stored under nitrogen in Schlenk burettes. *N*,*N*-Dimethylformamide was dried by azeotropic distillation with toluene. Butyllithium, *sec*-butyllithium and *tert*-butyllithium were supplied by CheMetall AG, D-38685 Langelsheim. Other reagents were obtained from commercial sources and checked using refraction index for liquids and melting points for solids. Air- and moisture-sensitive compounds were stored in Schlenk tubes or Schlenk burettes. Reactions at low temperatures were performed using cold baths: water/ice at 0 °C, acetone/dry ice at −75 °C and diethyl ether/liquid nitrogen at −100 °C. The temperature acetone/dry ice is consistently indicated at −75 °C and "room temperature" as 25 °C. Melting ranges (mp) are reproducible after resolidification unless otherwise stated ("dec."), and were corrected using a calibration curve. ^{1}H NMR: Bruker DPX-400; chemical shift δ in ppm relative to tetramethylsilane ($\delta = 0.00$) or relative to deuterated solvent. Elemental analysis: Ilse Beetz, Microanalytisches Laboratorium, D-96301 Kronach or F. Hoffmann-La Roche, CH-4070 Basel. The expected percentages were calculated using the atomic weight numbers listed in the 1999 IUPAC recommendations.

2′-(Dicyclohexylphosphino)-2-(diphenylphosphino)-6-methoxy-1,1′-biphenyl (1)

At 0 °C, butyllithium (4.6 mmol) in hexanes (2.9 mL) was added to a solution of bromodiphosphine **11** (2.5 g, 3.9 mmol) in toluene (6.0 mL). After 1 h at 0 °C, methanol (1 mL) was added followed by water (10 mL) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 × 20 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. The residue was purified by silica gel chromatography (hexane:ethyl acetate = 9:1) affording the diphosphine **1**. Crystallization from ethyl acetate (10 mL) gave colorless prisms; yield: 1.36 g (62 %), mp 200–203 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.50$ (d, $J = 7.8$ Hz, 1H), 7.2 (m, 12H), 6.98 (t, $J = 7.5$ Hz, 1H), 6.83 (d, $J = 8.2$ Hz, 1H), 6.66 (ddd, $J = 7.7$, 3.2, 0.9 Hz, 1H), 6.57 (ddd, $J = 7.5$, 3.7, 1.2 Hz, 1H), 3.64 (s, 3H), 1.6 (m, 12H), 1.1 (m, 10H); ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -8.7$ (d, $J = 13.1$ Hz), −13.4 (d, $J = 13.2$ Hz); anal. calcd. for $C_{37}H_{42}OP_2$ (564.27): C 78.70, H 7.50; found: C 78.42, H 7.65.

The racemic diphosphine **1** was separated into its enantiomers by preparative chromatography using a chiral stationary phase. The column used was CHIRALCEL® OD 20 μm, the mobile phase was heptane/EtOH = 2000:1. From 360 mg racemic material 142 mg of (+)-6-dicyclohexylphosphanyl-2′-diphenylphosphanyl-2-methoxy-1,1′-biphenyl (+)-**1** and 123 mg of (−)-6-dicyclohexylphosphanyl-2′-diphenylphosphanyl-2-methoxy-1,1′-biphenyl (−)-**1** were isolated. The enantiomeric purity of both compounds was 100 % (measured by HPLC on an analytic CHIRALCEL® OD 10 μm column). (−)-**1:** $[\alpha]_D^{24}$: −1.4 (*c* 0.5 in CH_2Cl_2).

2′,6-Bis(diphenylphosphino)-2-methoxy-1,1′-biphenyl (2)

At 0 °C, butyllithium (50 mmol) in hexanes (30 mL) was added to a solution of compound **6** (16 g, 25 mmol) in toluene (0.1 L). After 45 min at 25 °C, methanol (2 mL) was added followed by water (25 mL) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 × 25 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. Crystallization from dichloromethane (50 mL) afforded colorless prisms; yield: 7.9 g (57 %); mp 227–228 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.3$ (m, 18H), 7.15 (dt, $J = 6.8$, 2.6 Hz, 4H), 7.06 (dt, $J = 7.3$, 1.7 Hz, 2H), 6.82 (dd, $J = 7.6$, 4.2 Hz, 1H), 6.77 (d, $J = 8.2$ Hz, 1H), 6.66 (dd, $J = 7.9$ Hz, 3.1, 1H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 157.1$ (d, $J = 2$ Hz), 144.1 (d, $J = 8$ Hz), 143.8 (d, $J = 8$ Hz), 138.3, 137.4, 136.3 (d, $J = 8$ Hz), 136.1 (d, $J = 7$ Hz), 134.5 (d, $J = 2$ Hz), 133.9 (dd, $J = 20$, 14 Hz), 133.3 (d, $J = 19$ Hz), 131.2 (dd, $J = 6$, 4 Hz), 128.8, 128.4, 128.2, 128.0, 127.9 (d, $J = 2$ Hz), 128.8, 127.6, 125.9 (d, $J = 2$ Hz), 110.6, 54.7; ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -13.1$ (d, $J = 17.8$ Hz), −13.6 (d, $J = 17.8$ Hz); anal. calcd. for $C_{37}H_{30}OP_2$ (552.59): C 80.42, H 5.47; found: C 80.53, H 5.52.

The separation was performed as described for **1**. (+)-**2**:$[\alpha]_D^{20}$: 6.0 (*c*0.5 in $CHCl_3$).

The same ligand **2** could be prepared starting from racemic or enantiopure diphosphine **18** (0.62 g, 1.0 mmol) and tetrabutylammonium fluoride hydrate (0.52 g, 2.0 mmol) in

N,*N*-dimethylformamide (5.0 mL). After heating at 100 °C for 20 h, 0.24 g (43 %) of diphosphine **2** were obtained.

2′,6-Bis(dicyclohexylphosphino)-2-methoxy-1,1′-biphenyl (3)

At −75 °C, butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of compound **7** (17 g, 50 mmol) in tetrahydrofuran (250 mL). After the addition was completed, the mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine (22 mL, 24 g, 0.10 mol) in tetrahydrofuran (50 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (100 mL). The mixture was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over sodium sulfate. The diphosphine **3** was obtained after evaporation of the solvents and crystallization form methanol (100 mL) as colorless cubes; yield: 43 g (74 %); mp 220–221 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56 (m sym., 1 H), 7.4 (m, 3 H), 7.16 (d, J = 7.5 Hz, 1 H), 7.08 (m sym., 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 3.66 (s, 3 H), 1.7 (m, 24 H), 1.2 (m, 20 H). 6.99 (ddd, J = 7.7, 2.9, 1.3 Hz, 1 H), 6.8 (m, 3 H), 6.63 (d, J = 8.6 Hz, 1 H), 3.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 157.5 (d, J = 9 Hz), 148.4 (d, J = 25 Hz), 141.7, 137.8 (d, J = 19 Hz), 136.2 (d, J = 18 Hz), 134.0, 132.4, 127.1, 125.0, 124.1, 108.9, 54.0, 35.9 (d, J = 16 Hz), 34.0 (d, J = 19 Hz), 32.5 (d, J = 16 Hz), 32.1 (d, J = 20 Hz), 31.7 (d, J = 16 Hz), 30.6, 29.7, 28.7 (d, J = 10 Hz), 28.0, 27.2, 26.4 (d, J = 13 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = −9.9 (d, J = 12.1 Hz), −11.5 (d, J = 12.2 Hz); anal. calcd. for $C_{37}H_{54}OP_2$ (576.79): C 77.05, H 9.44; found: C 77.17, H 9.14.

The separation was performed as described for **1**. The enantiomeric purity was 99.2 % for the (−)-isomer and 96.9 % for the (+)-isomer (measured by HPLC on an analytic CHIRALCEL® OD 10 μm column). (+)-**3**: $[\alpha]_D^{24}$: 16.4 (*c* 0.5 in CH_2Cl_2).

6-Dicyclohexylphosphanyl-2′-diphenylphosphanyl-2-methoxy-1,1′-biphenyl (4)

At 0 °C, butyllithium (25 mmol) in hexanes (30 mL) was added to a solution of compound **8** (11 g, 25 mmol) in toluene (100 mL). After 45 min the mixture was cooled to −75 °C and a 1.0 M solution of chlorodiphenylphosphine (4.4 mL, 5.5 g, 25 mmol) in toluene (25 mL) was added. The mixture was allowed to reach 25 °C. A saturated aqueous solution of ammonium chloride (50 mL) was added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. Crystallization from methanol (50 mL) gave the diphosphine as colorless cubes; yield: 7.9 g (56 %); mp 170–171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.3 (m, 16 H), 6.78 (d, J = 7.9 Hz, 1 H), 3.23 (s, 3 H); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = −11.3 (d, J = 10.7 Hz), −14.0 (d, J = 10.8 Hz); anal. calcd. for $C_{37}H_{42}OP_2$ (564.69): C 78.70, H 7.50; found: C 78.59, H 7.43; (−)-**4**: $[\alpha]_D^{20}$: −34.9 (*c* 0.5 in CH_2Cl_2).

2,6,6′-Tribromo-2′-methoxy-1,1′-biphenyl (5)

Butyllithium (0.10 mol) in hexanes (63 mL) was added at −75 °C to a solution of 2,2′,6,6′-tetrabromo-1,1′-biphenyl (47 g, 0.10 mol) in tetrahydrofuran (500 mL). The mixture was consecutively treated with fluorodimethoxyborane·diethyl ether[52,53] (19 mL, 16 g, 0.10 mol), a 3.0 M aqueous solution of sodium hydroxide (36 mL) and 30 % aqueous hydrogen peroxide (10 mL, 3.6 g, 0.10 mol). The reaction mixture was neutralized at 25 °C with 2.0 M hydrochloric acid (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with a 10 % aqueous solution of sodium sulfite (100 mL), dried over sodium sulfate and evaporated. The oily residue was dissolved in dimethyl sulfoxide (200 mL) before iodomethane (7.5 mL, 17 g, 0.12 mol) and potassium hydroxide powder (6.7 g, 0.12 mol) were consecutively added. After 1 h, water (500 mL) was added and the product was extracted with diethyl ether (3 × 100 mL). The organic layers were dried over sodium sulfate and evaporated. Crystallization from ethanol (0.10 L) afforded the product as colorless cubes; yield: 35 g (82 %); mp 184–185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (d, J = 8.3 Hz, 2 H), 7.3 (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); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 157.6, 139.5, 131.5, 130.5, 130.2, 125.1, 124.6, 124.3, 110.0, 56.3; anal. calcd. for $C_{13}H_9Br_3O$ (420.92): C 37.09, H 2.16; found: C 37.10, H 2.03.

6-Bromo-2,6′-bis(diphenylphosphino)-2′-methoxy-1,1′-biphenyl (6)

At −75 °C, butyllithium (0.10 mol) in hexanes (57 mL) was added to a solution of compound **5** (21 g, 50 mmol) in tetrahydrofuran (250 mL). The reaction mixture was treated with a 2.0 M solution of chlorodiphenylphosphine (18 mL, 22 g, 0.10 mol) in tetrahydrofuran (50 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (200 mL). The reaction mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from ethyl acetate (0.10 L) afforded colorless needles; yield: 23 g (71 %); mp 224–226 °C (decomposition); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56 (dd, J = 8.0, 1.3 Hz, 1 H), 7.38 (dt, J = 7.0, 1.6 Hz, 2 H), 7.3 (m, 12 H), 7.1 (m, 6 H), 6.99 (ddd, J = 7.7, 2.9, 1.3 Hz, 1 H), 6.8 (m, 3 H), 6.63 (d, J = 8.6 Hz, 1 H), 3.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 157.0 (dd, J = 10, 2 Hz), 144.0 (dd, J = 33, 7 Hz), 141.2 (dd, J = 13, 3 Hz), 138.4 (d, J = 14 Hz), 138.1 (dd, J = 10, 2 Hz), 137.3 (d, J = 1 Hz), 137.2, 137.1, 136.2 (dd, J = 14, 1 Hz), 135.5 (d, J = 7 Hz), 135.2 (d, J = 6 Hz), 135.0 (d, J = 11 Hz), 134.8 (d, J = 7 Hz), 134.6, 134.3, 134.1, 133.7 (d, J = 3 Hz), 133.6 (d, J = 3 Hz), 133.1, 132.9, 132.8, 129.3, 128.8, 128.4, 128.2, 128.1, 127.9, 127.8, 126.6, 110.5, 54.4; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = −10.1 (d, J = 24.6 Hz), −13.9 (d, J = 24.9 Hz); anal. calcd. for $C_{37}H_{29}BrOP_2$ (631.49): C 70.37, H 4.63; found: C 69.13, H 4.60.

2′,6-Dibromo-2-methoxy-1,1′-biphenyl (7)

At −75 °C, butyllithium (25 mmol) in hexanes (13 mL) was added to a solution of compound **5** (11 g, 25 mmol) in tetrahydrofuran (200 mL). Immediately after the addition was completed, methanol (2.0 mL) was added. After addition of water (100 mL) the organic phase was separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over sodium sulfate

before being evaporated. After crystallization from ethanol (25 mL) 2′,6-dibromo-2-methoxy-1,1′-biphenyl was obtained as colorless cubes; yield: 7.9 g (92%) mp 93–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.67$ (d, $J = 8.0$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.3 (m, 4H), 6.92 (d, $J = 8.1$ Hz, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 157.9$, 138.8, 132.3, 131.6, 131.4, 129.9, 129.1, 127.5, 127.1, 124.5, 124.2, 110.0, 56.1; anal. calcd. for $C_{13}H_{10}Br_2O$ (342.03): C 45.32, H 2.95; found: C 45.32, H 2.85.

(2′-Bromo-6-methoxy-1,1′-biphenyl-2-yl)dicyclohexylphosphine (8)

At −75 °C, butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of compound **7** (34 g, 0.10 mol) in tetrahydrofuran (500 mL). After the addition was completed, the mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine (22 mL, 24 g, 0.10 mol) in tetrahydrofuran (100 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (200 mL). The mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from a 9:1 mixture (v/v) hexanes/ethyl acetate (50 mL) afforded colorless needles; yield: 36 g (79%); mp 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.61$ (d, $J = 7.8$ Hz, 1H), 7.38 (t, $J = 7.9$ Hz, 1H), 7.33 (t, $J = 7.3$ Hz, 1H), 7.21 (dt, $J = 7.9$, 1.5 Hz, 2H), 7.14 (dd, $J = 7.6$, 1.8 Hz, 1H), 6.96 (d, $J = 8.2$ Hz, 1H), 3.72 (s, 3H), 1.7 (m, 12H), 1.2 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 157.8$, 133.1 (d, $J = 4$ Hz), 132.0, 128.6, 128.1, 126.2, 125.1, 124.7, 111.0, 55.8, 35.4 (d, $J = 18$ Hz), 34.3 (d, $J = 13$ Hz), 30.9 (d, $J = 15$ Hz), 30.1 (d, $J = 17$ Hz), 29.4 (d, $J = 6$ Hz), 35.4 (d, $J = 18$ Hz), 27.3, 26.4; ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -13.8$ (s); anal. calcd. for $C_{25}H_{32}BrOP$ (459.41): C 65.36, H 7.02; found: C 65.52, H 7.07.

2-Bromo-2′,6-diiodo-6′-methoxy-1,1′-biphenyl (9)

Butyllithium (30 mmol) in hexanes (19 mL) was added at −75 °C to a solution of **5** (6.3 g, 15 mmol) in tetrahydrofuran (75 mL). After 45 min, a solution of iodine (7.7 g, 30 mmol) in tetrahydrofuran (20 mL) was added. At 25 °C, a 10% aqueous solution of sodium thiosulfate was added (100 mL) followed by extraction with ethyl acetate (3 × 50 mL). The organic layer was dried over sodium sulfate before being evaporated to dryness. Crystallization from a 9:1 mixture (v/v) hexanes/ethyl acetate (30 mL) afforded colorless needles; yield 6.0 g (78%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.90$ (dd, $J = 7.9$, 1.1 Hz, 1H), 7.67 (dd, $J = 8.0$, 1.1 Hz, 1H), 7.57 (dd, $J = 7.9$, 0.9 Hz, 1H), 7.13 (t, $J = 8.1$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 6.93 (t, $J = 7.9$ Hz, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 156.9$, 145.8, 138.0, 132.5, 130.9 (2 C), 130.8, 130.5, 123.7, 111.0, 101.0, 100.7, 56.2; anal. calcd. for $C_{13}H_9BrI_2O$ (514.92): C 30.32, H 1.76; found: C 30.61, H 1.83.

2-Bromo-6-(dicyclohexylphosphino)-2′-iodo-6′-methoxy-1,1′-biphenyl (10)

At −75 °C, butyllithium (10 mmol) in hexanes (6.3 mL) was added to a solution of **9** (5.2 g, 10 mmol) in diethyl ether (50 mL). After the addition was completed, the mixture was treated with chlorodicyclohexylphosphine (2.2 mL, 2.3 g, 10 mmol). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over sodium sulfate. After concentration of the solvent, the residue was subjected to purification by silica gel chromatography (hexane:ethyl acetate = 9:1) to obtain the title compound as a yellowish oil; yield: 4.2 g (72%); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.58$ (d, $J = 7.9$ Hz, 1H), 7.5 (m, 2H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.01 (t, $J = 8.1$ Hz, 1H), 6.80 (d, $J = 8.3$ Hz, 1H), 3.62 (s, 3H), 1.6 (m, 12H), 1.1 (m, 10H); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 159.3$, 135.1 (d, $J = 7$ Hz), 131.0, 129.3, 128.7, 126.2, 125.1, 120.7, 113.0, 55.7, 35.4 (d, $J = 18$ Hz), 34.3 (d, $J = 13$ Hz), 30.9 (d, $J = 15$ Hz), 30.1 (d, $J = 17$ Hz), 29.4 (d, $J = 6$ Hz), 35.4 (d, $J = 18$ Hz), 27.3, 26.4; ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -2.1$ (s); anal.calcd. for $C_{25}H_{31}BrIOP$ (585.30): C 51.30, H 5.34; found: C 51.58, H 5.45.

2-Bromo-6-(dicyclohexylphosphino)-2′-(diphenylphosphino)-6′-methoxy-1,1′-biphenyl (11)

At −75 °C, butyllithium (10 mmol) in hexanes (6.3 mL) was added to a solution of **10** (5.9 g, 10 mmol) in diethyl ether (20 mL). After 15 min chlorodiphenylphosphine (1.8 mL, 2.2 g, 25 mmol) was added. The mixture was allowed to reach 25 °C. A saturated aqueous solution of ammonium chloride (20 mL) was added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried over sodium sulfate before being evaporated. The residue was subjected to purification by silica gel chromatography (cyclohexane as eluent) to obtain the title compound as yellowish oil; yield: 4.1 g (63%); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.46$ (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 7.4$ Hz, 1H), 7.33 (dd, $J = 7.7$, 2.4 Hz, 1H), 7.2 (m, 12H), 6.82 (d, $J = 7.4$ Hz, 1H), 3.65 (s, 3H), 1.6 (m, 12H), 1.0 (m, 10H); anal. calcd. for $C_{37}H_{41}BrOP_2$ (643.57): C 69.05, H 6.42; found C 69.33, H 6.66; ^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = -8.7$ (d, $J = 13.1$ Hz), −13.4 (d, $J = 13.2$ Hz).

2′,6-Dibromo-6′-(trimethylsilyl)-1,1′-biphenyl-2-ol (12)

At −75 °C butyllithium (50 mmol) in hexanes (32 mL) was added to a solution of silane (**15**) (23 g, 50 mmol) in tetrahydrofuran (200 mL). The mixture was consecutively treated with fluorodimethoxyborane·diethyl ether[52,53] (9.5 mL, 8.0 g, 50 mmol), a 3.0 M aqueous solution of sodium hydroxide (18 mL) and 30% aqueous hydrogen peroxide (5.0 mL, 1.8 g, 50 mmol). At 25 °C, the mixture was neutralized with 2.0 M hydrochloric acid (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a 10% aqueous solution of sodium sulfite (50 mL), dried over sodium sulfate and evaporated. Crystallization form hexanes (50 mL) afforded **11** as colorless needles; yield: 13 g (64%); mp 93–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.78$ (dd, $J = 7.9$, 1.2 Hz, 1H), 7.69 (dd, $J = 7.3$, 1.3 Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 7.28 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.22 (t, $J = 8.1$ Hz, 1H), 6.98 (dd, $J = 8.0$, 1.2 Hz, 1H), 4.56 (s, 1H), 0.06 (s, 9H); anal. calcd. for $C_{15}H_{16}Br_2OSi$ (400.17): C 45.02, H 4.03; found C 44.96, H 4.27.

The same silane **12** was obtained in a 84% yield (3.36 g), when solution of acetal **14** (4.5 g, 10 mmol) in tetrahydrofuran (20 mL) was treated with a 3.0 M hydrochloric acid (20 mL) for 2 h. The racemic silane **12** was separated into its enantiomers by preparative chromatography using a chiral stationary phase. The column used was CHIRALCEL® OD 20 μm, the mobile phase was *n*-heptane/2-butanol = 100:1. The enantiomeric purity of both compounds was 100% (measured by HPLC on an analytic CHIRALCEL® OD 10 μm column). (+)-**12**: $[\alpha]_D^{20}$: +37.8 (*c* 1 in $CHCl_3$) and (−)-**12**: $[\alpha]_D^{20}$: −39.4 (*c* 1 in $CHCl_3$).

2,6,6′-Tribromo-1,1′-biphenyl-2-ol (13)

At −75 °C, butyllithium (50 mmol) in hexanes (31 mL) was added to a solution of 2,2′,6,6′-tetrabromo-1,1′-biphenyl (24 g, 50 mmol) in tetrahydrofuran (200 mL). The mixture was consecutively treated with fluorodimethoxyborane·diethyl ether[52,53] (9.5 mL, 8.0, 50 mmol), a 3.0 M aqueous solution of sodium hydroxide (18 mL) and 30% aqueous hydrogen peroxide (5.0 mL, 1.8 g, 50 mmol). At 25 °C, the mixture was neutralized with 2.0 M hydrochloric acid (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a 10% aqueous solution of sodium sulfite (50 mL), dried over sodium sulfate and evaporated. Crystallization form hexanes afforded **13** as slightly red prisms; yield: 17 g (81%); mp 118–119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (d, *J* = 8.1 Hz, 2H), 7.29 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.2 Hz,1H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) : δ = 153.3, 139.2, 137.5, 132.2, 131.3, 130.9, 125.9, 124.9, 123.9, 114.9; anal. calcd. for $C_{12}H_7Br_3O$ (406.90): C 35.42, H 1.73; found: C 35.31, H 1.73.

2,6,6′-Tribromo-2′-methoxymethoxy-1,1′-biphenyl (14)

A solution of phenol **13** (10 g, 25 mmol) in tetrahydrofuran (25 mL) was added to a 60% suspension of sodium hydride in mineral oil (1.0 g, 25 mmol) in tetrahydrofuran (25 mL) at 25 °C. After 30 min, a solution of chloromethyl methyl ether (2.2 mL, 2.2 g, 28 mmol) in tetrahydrofuran (10 mL) was added at 0 °C. The reaction mixture was allowed to reach 25 °C before water (50 mL) was added followed by extraction with ethyl acetate (3 × 50 mL). The combined organic layers were dried over sodium sulfate and evaporated. Crystallization from methanol afforded colorless platelets; yield: 9.92 g (88%); mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (d, *J* = 8.0 Hz, 2H), 7.38 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 5.13 (s,2H), 3.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) : δ = 155.0, 139.6, 131.7, 131.5, 130.5, 130.2, 125.6, 125.0, 124.2, 113.2, 94.3, 56.2; anal. calcd. for $C_{14}H_{11}Br_3O_2$ (450.95): C 37.29, H 2.46; found: C 37.35, H 2.58.

Trimethyl(2′,6,6′-tribromo-1,1′-biphenyl-2-yl)silane (15)

At −75 °C, butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of 2,2′,6,6′-tetrabromo-1,1′-biphenyl (47 g, 0.10 mol) in tetrahydrofuran (500 mL). Immediately after the addition was completed, the mixture was treated with chlorotrimethylsilane (13 mL, 11 g, 0.10 mol). At 25 °C, water was added (100 mL) and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over sodium sulfate and evaporated. After chromatography on silica (100 mL, 0.50 kg) with hexanes as eluent, **15** was obtained as a colorless oil. Crystallization from methanol afforded colorless platelets; yield: 41 g (88%); mp 175–179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.76 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.31 (t, *J* = 7.7 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) : δ = 146.2, 143.3, 141.8, 134.1, 133.2, 131.6, 130.4, 129.1, 125.7, 124.6, −0.1; anal. calcd. for $C_{15}H_{15}Br_3Si$ (463.08): C 38.91, H 3.27; found: C 38.84, H 3.04.

Trimethyl(6,2′-dibromo-6′-methoxymethoxy-1,1′-biphenyl-2-yl)silane (16)

At −75 °C butyllithium (25 mmol) in hexanes (16 mL) was added to a solution of acetal (**14**) (11 g, 25 mmol) in tetrahydrofuran (120 mL). Immediately after the addition was completed, the mixture was treated with chlorotrimethylsilane (3.3 mL, 2.8 g, 25 mmol). At 25 °C, water was added (100 mL) and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over sodium sulfate and evaporated. Crystallization from methanol afforded colorless platelets; yield: 9.22 g (83%); mp 90–92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.37 (m, 4H), 5.29 (d, *J* = 7.0 Hz, 1H), 5.10 (d, *J* = 7.0 Hz, 1H), 3.41 (s, 3H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 156.2, 155.3, 143.6, 142.4, 133.7, 133.0, 130.1, 128.5, 125.9, 125.6, 125.4, 113.2, 94.5, 56.2, −0.2; anal.calcd. for $C_{17}H_{20}Br_2O_2Si$ (444.24): C 45.96, H 4.54; found: C 46.06, H 4.13.

Trimethyl(6,2′-Dibromo-6′-methoxy-biphenyl-2-yl)silane (17)

Iodomethane (1.9 mL, 4.3 g, 30 mmol) was added to a suspension of phenol **12** (8.0 g, 20 mmol) and potassium carbonate (6.9 g, 50 mmol) in acetone (100 mL). The reaction mixture was heated at reflux for 12 h, before water (100 mL) was added followed by extraction with ethyl acetate (3 × 100 mL). The combined organic solvents were dried and evaporated. Crystallization from methanol afforded colorless prisms; yield: 7.29 g (88%); mp 184–185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.26 (m, 3H), 6.92 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 158.7, 144.0, 142.7, 134.1, 133.5, 132.5, 130.5, 129.0, 126.6, 125.9, 124.8, 109.9, 56.1, 0.1; anal. calcd. for $C_{16}H_{18}Br_2OSi$ (414.21): C 46.39, H 4.38; found: C 46.43, H 4.41.

Starting with enantiopure (+)- or (−)-**12** the corresponding methyl ethers (+)-**17**: $[\alpha]_D^{20}$: +13.1 (*c* 1 in $CHCl_3$) and (−)-**17**: $[\alpha]_D^{20}$: −13.5 (*c* 1 in $CHCl_3$) were obtained.

2,2′-Bis-diphenylphosphanyl-6-methoxy-6′-trimethylsilanylbiphenyl (18)

At 0 °C, butyllithium (25 mmol) in hexanes (16 mL) was added to a solution of silane **17** (10 g, 25 mmol) in toluene (50 mL). After 45 min, the reaction mixture was treated with a 2.0 M solution of chlorodiphenylphosphine (9.0 mL, 11 g, 50 mmol) in toluene (25 mL). The mixture was allowed

to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (200 mL). The reaction mixture was extracted with ethyl acetate (3×100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from ethyl acetate afforded colorless cubes; yield: 13.9 g (89 %); mp 214–216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.59 (dd, J=7.4, 1.6 Hz, 1H), 7.5 (m, 4H), 7.3 (m, 16H), 7.09 (ddd, J=7.4, 3.5, 1.3 Hz, 1H), 7.04 (symm. m, 3H), 6.58 (d, J=8.32 Hz, 1H), 3.08 (s, 3H), −0.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ=157.1 (d, J=2 Hz), 144.1 (d, J=8 Hz), 143.8 (d, J=8 Hz), 138.3, 137.4, 136.3 (d, J=8 Hz), 136.1 (d, J=7 Hz), 134.5 (d, J=2 Hz), 133.9 (dd, J=20, 14 Hz), 133.3 (d, J=19 Hz), 131.2 (dd, J=6, 4 Hz), 128.8, 128.4, 128.2, 128.0, 127.9 (d, J=2 Hz), 128.8, 127.6, 125.9 (d, J=2 Hz), 110.6, 54.7; ^{31}P NMR ($CDCl_3$, 162 MHz): δ=−12.2 (d, J=38.1 Hz), −14.9 (d, J=38.8 Hz); anal. calcd. for $C_{40}H_{38}OP_2Si$ (624.78): C 76.90, H 6.13; found: C 76.59, H 6.02.

Starting with enantiopure (+)-**17** the corresponding diphosphine (+)-**18** was obtained; $[\alpha]_D^{20}$: +16.4 (*c* 1 in $CHCl_3$).

2,2′-Bis-dicyclohexylphosphanyl-6-methoxy-6′-trimethylsilanyl-biphenyl (19)

At 0 °C, butyllithium (25 mmol) in hexanes (16 mL) was added to a solution of silane **17** (10 g, 25 mmol) in toluene (50 mL). After 45 min, the reaction mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine (11 mL, 12 g, 50 mmol) in toluene (25 mL). The mixture was allowed to reach 25 °C and treated with a saturated aqueous solution of ammonium chloride (0.20 L). The reaction mixture was extracted with ethyl acetate (3×100 mL), and the combined organic layers were dried over sodium sulfate. Evaporation of the solvents and crystallization from ethyl acetate afforded colorless cubes; yield: 12.3 g (76 %); mp 173–175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.55 (d, J=8.3 Hz, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.30 (t, J=7.4 Hz, 2H), 7.04 (d, J=7.7 Hz, 1H), 6.79 (d, J=8.3 Hz, 1H), 3.63 (s, 3H), 1.6 (m, 21H), 1.2 (m, 23H), −0.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ=157.5 (d, J=9 Hz), 148.4 (d, J=25 Hz), 141.7, 137.8 (d, J=19 Hz), 136.2 (d, J=17 Hz), 134.0, 132.4, 127.1, 125.0, 124.1, 108.9, 54.0, 35.9 (d, J=16 Hz), 34.0 (d, J=19 Hz), 32.5 (d, J=16 Hz), 32.1 (d, J=20 Hz), 31.7 (d, J=16 Hz), 30.6, 29.7, 28.7 (d, J=10 Hz), 28.0, 27.2, 26.4 (d, J=13 Hz), 0.48; ^{31}P NMR ($CDCl_3$, 162 MHz): δ=−10.4 (d, J=45 Hz), −11.3 (d, J=45 Hz); anal. calcd. for $C_{40}H_{62}OP_2Si$ (648.97): C 74.03, H 9.63; found: C 73.78, H 9.71.

Acknowledgements

The authors are indebted to the Bundesamt für Berufsbildung und Technologie (Bern) for financial support in the framework of a KTI project (contract 5474.1 KTS) and the COST-D24 action WG0006–02. F.L. is much indebted to Prof. M. Schlosser, Lausanne, for countless precious advice.

References

[1] *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.
[2] *Asymmetric Catalysis in Organic Synthesis*, (Ed.: R. Noyori), Wiley, New York, **1994**.
[3] T. Ohkuma, M. Kitamura, R. Noyori, *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.
[4] L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed.* **1968**, *7*, 942.
[5] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106.
[6] W. S. Knowles, M. J. Sabacky, *J. Chem. Soc., Chem. Commun.* **1968**, 1445.
[7] T. P. Dang, H. B. Kagan, *J. Chem. Soc., Chem. Commun.* **1971**, 481.
[8] M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1978**, 5491.
[9] M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518.
[10] R. Schmid, M. Cereghetti, B. Heiser, P. Schönholzer, H. Hansen, *Helv. Chim. Acta* **1988**, *71*, 897.
[11] R. Schmid, J. Foricher, M. Cereghetti, P. Schönholzer, *Helv. Chim. Acta* **1991**, *74*, 370.
[12] T. Saito, T. Yokozawa, X.-y. Zhang, N. Sayo, *Eur. Pat. Appl.* 850,945 (to Takasago Int. Corp.; filed on 26 Dec. 1996); *Chem. Abstr.* **1998**, *129*, 124055.
[13] N. Sayo, T. Saito, T. Yokozawa, *Eur. Pat. App.* 945,457 (to Takasago Int. Corp.; publ. on 29 Dec. 1999); *Chem. Abstr.* **1999**, *131*, 251749.
[14] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932.
[15] K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, *J. Chem. Soc., Chem. Commun.* **1982**, 600.
[16] P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207.
[17] G. Argouarch, O. Samuel, O. Riant, J.-C. Daran, H. B. Kagan, *Eur. J. Org. Chem.* **2000**, 2893.
[18] G. W. Gokel, I. K. Ugi, *J. Chem. Educ.* **1972**, *49*, 294.
[19] T. Hayashi, M. Sawamura, Y. Ito, *Tetrahedron* **1992**, *48*, 1999.
[20] D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. K. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389.
[21] A. Togni, *Angew. Chem. Int. Ed.* **1996**, *35*, 1475.
[22] A. Togni, N. Bieler, U. Burckhardt, C. Köllner, G. Pioda, R. Schneider, A. Schnyder, *Pure Appl. Chem.* **1999**, *71*, 1531.
[23] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062.
[24] H. Kumobayashi, T. Miura, N. Sayo, T. Saito, X. Zhang, *Synlett* **2001**, 1055.
[25] K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064.
[26] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[27] R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Müller, M. Scalone, G. Schoettel, U. Zutter, *Pure Appl. Chem.* **1996**, *68*, 131.
[28] Z. Zhang, H. Qian, J. Longmire, X. Zhang, *J. Org. Chem.* **2000**, *65*, 6223.
[29] S. Duprat de Paule, N. Champion, V. Vidal, J.-P. Genêt, P. Dellis, *FR* 2830254 (to SYNKEM, filed on 28 Sep. 2001).
[30] S. Duprat de Paule, N. Champion, V. Vidal, J.-P. Genêt, P. Dellis, *WO* 03029259 (to SYNKEM, filed on 16 Sep. 2002).
[31] S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Angew. Chem. Int. Ed.* **2004**, *43*, 320.
[32] F. Leroux, J. Gorecka, M. Schlosser, *Synthesis* **2004**, 326.
[33] The preparation of organolithium reagents and intermediates, F. Leroux, M. Schlosser, E. Zohar, I. Marek, in: *Chemistry of Organolithium Compounds*, Vol. 1, (Ed.: Z. Rappoport), Wiley, Chichester, **2004**, p 435.
[34] M. Schlosser, in: *Organometallics in Synthesis: A Manual*, (Ed.: M. Schlosser), Wiley, Chichester, **2002**, p 1.
[35] F. Leroux, H. Mettler, *Synlett* **2006**, 766.
[36] F. Leroux, N. Nicod, L. Bonnafoux, B. Quissac, F. Colobert, *Lett. Org. Chem.* **2006**, *3*, 165.
[37] O. Desponds, M. Schlosser, *J. Organomet. Chem.* **1996**, *507*, 257.
[38] T. K. Miyamoto, Y. Matsuura, K. Okude, H. Ichida, Y. Sasakik, *J. Organomet. Chem.* **1989**, *373*, C8.
[39] A. Rajca, A. Safronov, S. Rajca, C. R. Ross, J. J. Stezowski, *J. Am. Chem. Soc.* **1996**, *118*, 7272.
[40] F. Leroux, T. U. Hutschenreuter, C. Charriere, R. Scopelliti, R. W. Hartmann, *Helv. Chim. Acta* **2003**, *86*, 2671.
[41] F. Leroux, M. Maurin, N. Nicod, R. Scopelliti, *Tetrahedron Lett.* **2004**, *45*, 1899.
[42] F. Leroux, M. Schlosser, *Angew. Chem. Int. Ed.* **2002**, *41*, 4272.
[43] F. Leroux, H. Mettler, *Synlett* **2006**, 766.
[44] M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[45] G. Michaud, M. Bulliard, L. Ricard, J.-P. Genêt, A. Marinetti, *Chem. Eur. J.* **2002**, *8*, 3327.
[46] T. Benincori, S. Rizzo, F. Sannicolo, *J. Heterocyclic Chem.* **2002**, *39*, 471.
[47] J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genêt, *Tetrahedron* **2001**, *57*, 2563.
[48] U. Matteoli, V. Beghetto, A. Scrivanti, *J. Mol. Cat. A: Chemical* **1999**, *140*, 131.
[49] J. Holz, A. Monsees, H. Jiao, J. You, I. V. Komarov, C. Fischer, K. Drauz, A. Borner, *J. Org. Chem.* **2003**, *68*, 1701.
[50] A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijanit, *J. Am. Chem. Soc.* **1994**, *116*, 4062.
[51] H. Mettler, F. Leroux, M. Schlosser, *WO* 2006/002729 – *WO* 2006/002731 (to Lonza AG, Switz., filed on June 6, 2005).
[52] G. Rauchschwalbe, A. Zellner, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 3903.
[53] M. Schlosser, L. Franzini, *Synthesis* **1998**, 707.

