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Asymmetric Synthesis of an Axially Chiral Antimitotic Biaryl via an Atropo-Enantioselective Suzuki Cross-Coupling

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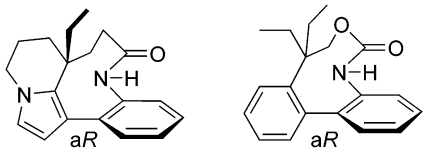
A catalytic asymmetric synthesis of the axially chiral bridged biaryl (−)-**2**, a structural analogue of natural (−)-rhazinilam possessing original antimitotic properties, is described. The key step is an intermolecular asymmetric Suzuki coupling, furnishing the nonbridged biaryl (−)-**6**, precursor of (−)-**2**, with up to 40% ee using binaphthyl ligand **7a**. Various known or new binaphthyl and ferrocenyl phosphines as well as phosphetanes were screened as ligands in this reaction, the conditions of which were optimized. The comparison with another Suzuki coupling system showed that **7a** is the most versatile ligand described to date for this type of transformation. This work gives the first application of the asymmetric Suzuki coupling to a biologically relevant target.

Introduction

(−)-Rhazinilam **1** is an alkaloid artifact isolated from various *Apocynaceae*.[1] Its tetracyclic structure comprises an axially chiral phenyl-pyrrole subunit bridged by a nine-membered lactam ring. It was found to have unique antimitotic properties, with in vitro inhibition of both tubulin assembly and disassembly and the formation of abnormal tubulin spirals.[2] As a consequence to these antitubulin properties, rhazinilam shows significant in vitro cytotoxicity toward various cancer cell lines,[2] but no activity was found in vivo. In the course of a program directed toward semi- and total synthesis of **1** and analogues, we found that compound (−)-**2**, obtained from



(−)-**1** (−)-**2**

chiral HPLC separation of (±)-**2**, had a 2-fold activity on microtubules assembly and disassembly compared to **1**, with a similar cytotoxicity toward cancer cells.[3,4] Compound **2** possesses a tricyclic structure encompassing an axially chiral biphenyl subunit and a nine-membered median carbamate ring. According to their X-ray crystal structure,[3,5] the nine-membered lactam or carbamate rings of **1** and **2** adopt a nearly superimposable boat-chair rigid conformation with perpendicular aryl groups, and a cis amide group, which presumably account for their similar biological activity. The absolute a*R* (or *M*) configuration at the biaryl axis has a crucial influence on the tubulin binding since the (+)-a*S* enantiomers of **1** and **2** are inactive.[3,6] Following our report on the racemic synthesis of **2** and analogues,[4] we initiated a study directed toward the asymmetric synthesis of the biologically active atropisomer (−)-**2**.

Axially chiral biaryls are common structure motifs in natural products and chiral ligands, and were the target of a number of synthetic approaches.[7] However, general methods that were truly applied to the synthesis of natural biaryl compounds or their analogues are quite rare. For instance, Meyers elaborated a method based on an aromatic nucleophilic substitution using a chiral oxazoline auxiliary,[8] as illustrated in the synthesis of (−)-steganone.[9] Uemura developed an efficient method using a diastereoselective Suzuki−Miyaura coupling of enan-

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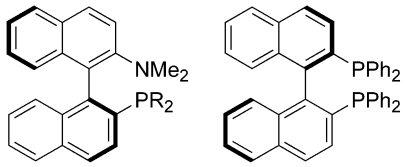
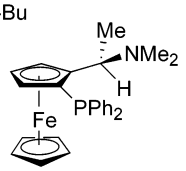
CHART 1. Ligands Described in Atropo-Enantioselective Suzuki Cross-Couplings



(*S*)-(+)-**7a** R=Cy
(*S*)-(+)-**7b** R=*i*-Pr
(*S*)-(+)-**7c** R=*t*-Bu

(*R*)-(+)-BINAP **8**

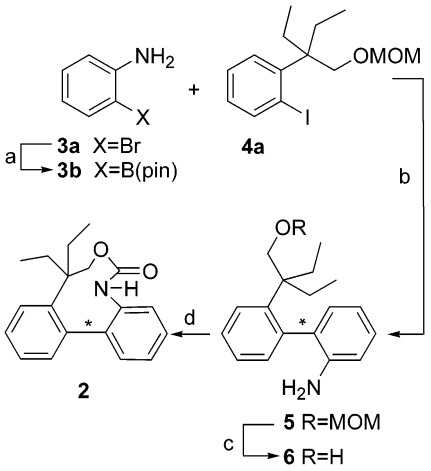


(*R*)-(*S*$_p$)-(−)-PFNMe **9**

tiopure (arene)chromium complexes,[10] which was applied to the formal synthesis of (−)-steganone and vancomycin.[11] Bringmann prepared a wide range of natural biaryl compounds such as the mastigophorenes or michellamine B via the "lactone method", consisting of the atroposelective ring cleavage of configurationally unstable lactone-bridged biaryls.[12] Nicolaou reported an atropodiastereoselective Suzuki cross-coupling using chiral ligands in the synthesis of vancomycin.[13] These last two methods offer the advantage of controlling the axial chirality by using *catalytic* chiral reagents, and therefore should influence further work on the asymmetric synthesis of axially chiral biaryls. In this direction, studies of atropo-enantioselective Suzuki coupling with chiral ligands appeared recently in the literature. All concerned the synthesis of binaphthyl or phenylnaphthyl compounds, which can be considered respectively as tetra- or tri-*o*-substituted biphenyls, and which are more configurationally stable than *di*substituted biphenyls such as **2**. Two different types of chiral ligands were used (Chart 1): binaphthyl ligands and ferrocenyl ligands. Ligands **7a**−**c** reported by Buchwald gave ee values up to 92%.[14] Colobert used BINAP **8** with ee values up to 30%.[15] Cammidge reported an atroposelective Suzuki coupling with known chelating ferrocenyl ligands such as **9**[16] with ee values up to 85%.[17]

We present therein the first application of the atropo-enantioselective Suzuki coupling to the synthesis of a biologically active axially chiral biphenyl compound.

SCHEME 1. Racemic Synthesis of Biphenylcarbamate 2[a,b]



[a] Reagents and conditions: (a, b) **3a** (1.0 equiv), Et_3N (4.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_2(*o*-biph) (0.2 equiv), (pin)BH (3.0 equiv), dioxane, 80 °C, 1 h, then water, **4a** (0.67 equiv), $Ba(OH)_2{\cdot}8H_2O$ (3.0 equiv), 100 °C, 1 h; (c) concd HCl/MeOH 1/4, reflux, 1 h; (d) $(Cl_3CO)_2C{=}O$ (1.0 equiv), pyridine (10 equiv), CH_2Cl_2, −78 °C, 30 min. [b] PCy_2(*o*-biph) = 2-(dicyclohexylphosphino)biphenyl, pin = pinacol, MOM = methoxymethyl.

Results and Discussion

The racemic synthesis of compound **2** was previously performed through a one-pot, two-step borylation−Suzuki coupling (BSC) reaction (Scheme 1, steps a and b).[4,18] The borylation reaction of compound **3a**, giving **3b** intermediately, is followed by in situ Suzuki cross-coupling with compound **4a**, furnishing biphenyl **5** in 78% yield. Then, after deprotection of the MOM group with HCl in methanol (step c), compound **2** is obtained by cyclization in the presence of trisphosgene (80% yield from **5**). The success of the BSC reaction relied on the use of the bulky and electron-rich PCy_2(*o*-biph) phosphine ligand described by Buchwald et al.[19] and barium hydroxide in dioxane/water as the base.[4]

To realize the asymmetric synthesis of **2**, we first determined its rotational energy barrier by thermal racemization experiments in DMF. Upon heating, the individual enantiomers are indeed slowly interconverted by rotation of the aromatic planes around the biphenyl axis. The (−)-**2** and (+)-**2** atropisomers could be separated on a few milligrams scale by analytical HPLC (Nucleodex column). The interconversion [(+)-**2** ⇄ (−)-**2**] was very slow up to 120 °C, but the rate constant of the racemization and the energy barrier could be determined at 140 and 160 °C (Table 1).

The separation of atropisomers at a given temperature requires a $\Delta G^{\ddagger}$ value of at least 23 kcal/mol.[20] The $\Delta G^{\ddagger}$ values found at 160 and 140 °C show that compound **2**

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TABLE 1. Experimental Activation Parameters for the Atropisomerization [(+)-2 ⇄ (−)-2]

T [°C]	k [s^{-1}]	$t_{1/2}$ [min]	$\Delta G^{\ddagger}$ [kcal/mol]
140	4.38×10^{-5}	263.5	32.7
160	8.22×10^{-5}	140.5	30.2

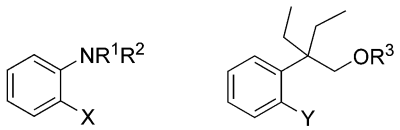
$\Delta H^{\ddagger}$= 84.3 kcal/mol; $\Delta S^{\ddagger}$= 125 cal/K·mol

has a stable axial chirality even at elevated temperatures. Then the configurational stability of the open-chain compounds **5** and **6** was evaluated qualitatively by analytical chiral HPLC experiments. The optically pure atropisomers (−)-**5** and (−)-**6**, which could only be obtained on a submilligram scale, were individually heated in dioxane under the Suzuki coupling conditions (1 h, 80−100 °C) and reinjected on the chiral column (Chiracel OJ). No racemization occurred for both of these compounds after 1 h at 80 °C, and 5% racemization occurred at 100 °C. This result was not predictable since there are very few examples of 2,2′-disubstituted biphenyls which are configurationally stable under those conditions.[21] This particular stability, which originates presumably in the presence of the quaternary carbon atom bearing bulky substituents, allowed us to envision the direct asymmetric synthesis of (+)-**5** and (−)-**5** via atroposelective Suzuki cross-coupling.

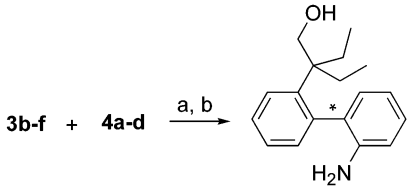
To this purpose, the coupling between boronate **3b** and iodide **4a** was first examined (Table 2). Compound **3b** was obtained from iodide **3c** in 61% yield via borylation in the presence of $PdCl_2$(dppf).[4,22] In this case $PdCl_2$(dppf) was used instead of $Pd(OAc)_2/PCy_2$(*o*-biph) (see Scheme 1, step a), to avoid traces of PCy_2(*o*-biph), which could interfere with the chiral phosphine in the next step. The asymmetric Suzuki coupling between **3b** and **4a** furnishing the biphenyl product **5** (Table 2, step a) was initially performed under the same conditions as the racemic coupling, using 2.5% Pd_2dba_3·$CHCl_3$ (5% Pd(0)), 6% of chiral ligand, and 2 equiv of barium hydroxide in dioxane/water 9/1. The reaction was stopped after 1 h at 80 °C in dioxane to avoid product racemization. The enantiomeric excesses (ee) were determined on compound **6** after MOM cleavage, since the separation of the atropisomers of **6** on a chiral HPLC column was better and more reproducible than that for compound **5**. To validate this ee determination, we checked that optically pure (−)-**5** or (+)-**5** did not racemize during the MOM-cleavage step (MeOH/HCl 4/1, 35 °C, 1 h, step b). A calibration of the peak areas for compound **6** allowed at the same time the determination of the yield for two steps.

Under these conditions, the ligands from the literature data (Chart 1) were first tested (Table 2). (*R*)-(+)-BINAP **8** (entry 1) gave very low yield of racemic **6**. Commercially available Hayashi's ferrocene ligand (−)-**9** gave **6** in 38% yield and with very low ee (entry 2). Buchwald's binaphthyl ligand (+)-**7a** bearing two cyclohexyl substituents was found to induce the highest enantioselectivity, with 70% of the (−)-atropisomer formed (ee 40%), and a 56% yield (entry 3). The analogous ligand (+)-**7b** bearing a

TABLE 2. Asymmetric Synthesis of 6 via Atropo-Enantioselective Suzuki Coupling: Screening of Known Chiral Ligands and Optimization of the Conditions[a]



3b R^1=R^2=H,X=B(pin) **4a** R^3=MOM,Y=I
3c R^1=R^2=H,X=I **4b** R^3=H,Y=I
3d R^1=R^2=H,X=$B(OH)_2$ **4c** R^3=$SiEt_3$,Y=I
3e R^1=H,R^2=*t*-Boc,X=B(pin) **4d** R^3=MOM,Y=B(pin)
3f R^1=R^2=O,X=I



6

entry	ligand	boronate	iodide	yield (%)[b]	ee (%)[b]	product
1	(+)-**8**	**3b**	**4a**	12	0	(±)-**6**
2	(−)-**9**	**3b**	**4a**	38	5	(+)-**6**
3	(+)-**7a**	**3b**	**4a**	56	40	(−)-**6**
4	(+)-**7b**	**3b**	**4a**	49	41	(−)-**6**
5	(+)-**7c**	**3b**	**4a**	8	3	(−)-**6**
6	(+)-**7a**	**3d**	**4a**	31	32	(−)-**6**
7	(+)-**7a**	**3e**	**4a**	38	0	
8	(+)-**7a**	**3b**	**4b**	0		
9	(+)-**7a**	**3b**	**4c**	0		
10	(+)-**7a**	**4d**	**3c**	0		
11	(+)-**7a**	**4d**	**3f**	0		

[a] Reagents and conditions: (a) iodide (1.0 equiv), $Ba(OH)_2$·$8H_2O$ (2.0 equiv), Pd_2dba_3·$CHCl_3$ (2.5 mol %), L* (6 mol %), boronate (1.5 equiv), dioxane/water 9/1, 80 °C, 1 h; (b) concd HCl/MeOH 1/4, 35 °C, 1 h. L* = chiral ligand (see Chart 1), Pd_2dba_3·$CHCl_3$ = tris(dibenzylideneacetone)dipalladium-chloroform adduct. [b] Determined by HPLC with a Chiracel OJ column.

diisopropyl group gave a comparable ee value with a slightly lower conversion (entry 4). By contrast, the yield and ee dropped with the di-*tert*-butyl-bearing phosphine (+)-**7c** (entry 5). This dramatic influence of the alkyl substituents on the phosphorus atom was previously observed with particular coupling substrates.[14]

Following these first results, the influence of the different reaction parameters was evaluated by using ligand **7a**. When boronic ester **3b** was replaced by boronic acid **3d**,[23] a lower yield and ee value were obtained (entry 6). With the bulky *t*-Boc-protected boronic ester **3e**[4,24] compound **6** was obtained in 38% yield after HCl-induced deprotection of both protecting groups, but in racemic form (entry 7). These observations highlight the influence of the steric hindrance of the boronate component on both reactivity and enantioselectivity. The choice of boronate **3b**, bearing a small amino group and a large pinacolboronic group, seems optimal.

On the other hand, when the alcohol function of the halide component **4a** was free (compound **4b**, entry 8) or

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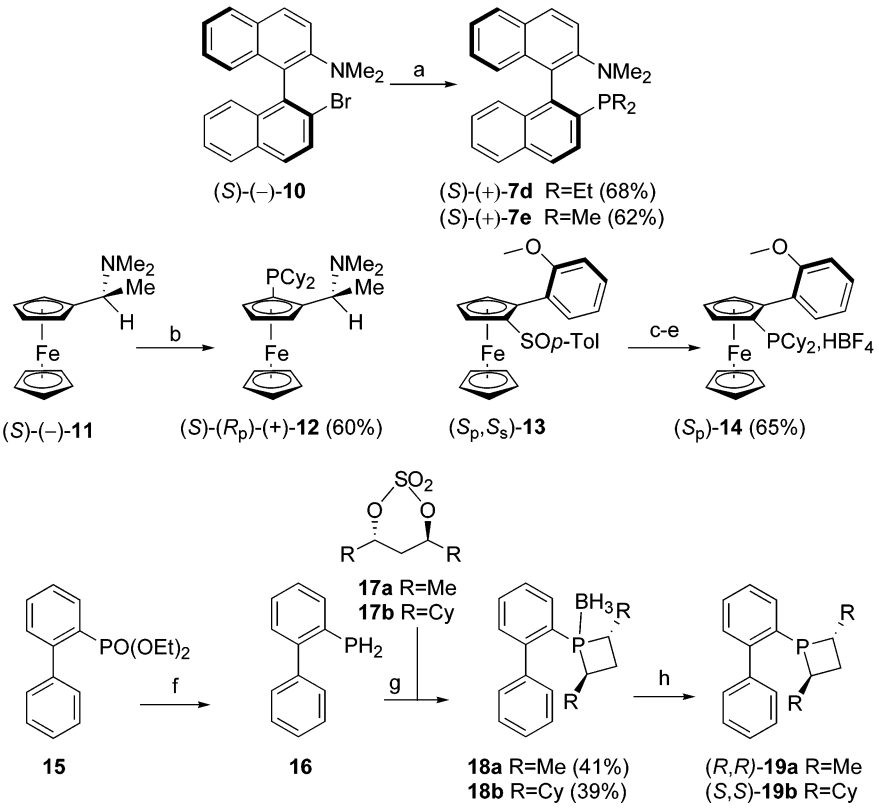
SCHEME 2. Synthesis of Dialkylmonoarylphosphine Ligands[a,b]



[a] Reaction conditions:(a) *n*-BuLi (1.1 equiv), $ClPR_2$ (1.3 equiv), THF, 25 °C, 18 h; (b) *n*-BuLi (1.3 equiv), $ClPCy_2$ (2.0 equiv), Et_2O, reflux, 3 h; (c) *t*-BuLi (3.0 equiv), $ClPCy_2$ (3.5 equiv), THF, −78 °C, 30 min, then $Me_2S{\cdot}BH_3$ (5.0 equiv); (d) DABCO (5.0 equiv), toluene, 50 °C, 30 min; (e) aq HBF_4, CH_2Cl_2; (f) $LiAlH_4$ (4.3 equiv), Et_2O −50 to 25 °C; (g) *sec*-BuLi (2.2 equiv), **17a** or **17b** (1.0 equiv), Et_2O, 0 °C, 2 h, then $Me_2S{\cdot}BH_3$ (1.5 equiv); (h) DABCO (2.0 equiv), toluene, 50 °C, 30 min. [b]DABCO=1,4-diazabicyclo[2.2.2]octane

protected with a triethylsilyl group (compound **4c**,[3] entry 9) no coupling occurred. Next the sense of the coupling was reversed, using **3c** (entry 10) or **3f** (entry 11) as the halide and **4d** as the boronate component. Indeed the nitro group of **3f** was thought to facilitate the oxidative insertion to Pd(0) and hence to improve the coupling with **4d**. However, the reaction between **4d** and **3b** or **3f** gave no coupling product, probably because **4d** is too sterically hindered. Among the different solvents tested, dioxane/water 9/1 gave the best results in terms of conversion and ee. Although in CH_3CN the ee value raised to 50%, the yield of the coupling was only 13%. Besides, the use of other bases than $Ba(OH)_2$ (e.g. CsF, NaO*t*-Bu, K_3PO_4) even combinated to other solvents than dioxane/water gave only poor yield of coupled material. The modification of the palladium source did not effect striking improvement: $Pd(OAc)_2$ (5 mol % + 10 mol % **7a**) gave the same result as Pd_2dba_3 (5 mol % + 6 mol % **7a**) while the use of $PdCl_2(CH_3CN)_2$ or $[Pd(\pi\text{-allyl})Cl]_2$ resulted in a decrease of the coupling yield. As observed previously by Buchwald, the change of the palladium/chiral ligand ratio did not affect the enantioselectivity, which fits with a 1:1 complex as the only active species.[14] Finally, when the temperature was decreased to 60 °C, **6** was formed in only 25%, and the enantioselectivity remained the same, which indicates that the reaction is under thermodynamic control. Further data were gained from monitoring the reaction at 80 °C at 15, 30, 45, and 60 min: while the yield of **6** was respectively 28, 52, 55 and 56%, the ee remained 40% throughout the experiment. This confirms that the observed ee value does reflect the enantioselectivity of the reaction and that no racemization of the product occurred. The reaction reached completion between 45 and 60 min, with consumption of all starting iodide **4a** and concomitant production of ca. 15% protodeiodinated byproduct.

The optimal set of conditions was used in the investigation of new ligands in the atroposelective synthesis of biphenyl **6**. Our preliminary results with the known phosphines **7a**−**c**, **8**, and **9** as well as literature data[14] indicated that bulky electron-rich monophosphines were the most efficient ligands to perform this reaction. We decided therefore to synthesize chiral ligands having the schematic structure (Aryl)P(Alkyl)$_2$ (Scheme 2).

Binaphthyl ligands **7d**,**e** were synthesized in the same manner as **7a**−**c**,[14,25,26] following Buchwald's procedure from optically pure 2-*N*,*N*-(dimethylamino)-2′-bromo-1,1′-binaphthyl **10**.[14,25] A halogene−lithium exchange and the addition of the resulting organolithium derivative to a chlorophosphine furnished optically pure ligands **7**. These phosphines bearing respectively a diethyl and a dimethyl group were synthesized to complete the above observations on the influence of dialkyl substituents in the asymmetric coupling. Ferrocene ligands possessing planar chirality and additional central or axial chirality were also studied. To fit with our schematic view of the optimal

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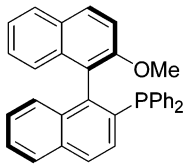
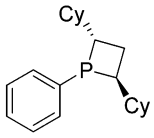
ligand as (Aryl)P(Alkyl)$_2$, the phenyl groups in ligand **9** were replaced by cyclohexyl groups to give the known (+)-**12** from *N*,*N*-dimethyl-1-ferrocenylethylamine (*S*)-(−)-**11** following the procedure described by Togni.[27] The ferrocenyl ligand **14**, fitting with the (Aryl)P(Alkyl)$_2$ structure, was also synthesized. The diphenylphosphino analogue of **14** (free phosphine) was used as ligand in the Pd(0)-catalyzed enantioselective hydrosilylation of styrene, giving up to 71% ee.[28] It possesses two sources of chirality: a planar chirality due to the ortho substitution of the ferrocene and an axial chirality at the ferrocene−anisole axis. It could be considered as a ferrocene analogue of ligands **7**. The chiral biaryl axis is indeed substituted in both cases in the 2 and 2′ positions by a coordinating group on one side (NMe_2 or OMe) and a dialkylphosphine group on the other. This ligand was synthesized from (S_P,S_S)-2-(*o*-anisole)-1-(*p*-tolylsulfinyl)-ferrocene **13** described by Johannsen,[28] the latter being prepared in two steps from ferrocene.[28b,29] Only one atropisomer can be obtained, the methoxy group taking position on the side of the ferrocene opposite to the iron atom. The cleavage of the chiral sulfoxide group was accomplished with *t*-BuLi, and the resulting lithiated ferrocene reacted with $ClPCy_2$ to form the free dicyclohexyl phosphine ligand. This phosphine was very unstable and difficult to purify. It was therefore protected via its borane complex, which could be purified by flash chromatography. However, when the free phosphine was liberated by using DABCO prior to introduction into the Suzuki coupling reaction, a rapid oxidation was observed. Nevertheless, upon addition of tetrafluoroboric acid in situ after treatment with DABCO, the stable phosphonium salt **14** could be isolated and fully characterized. This tetrafluoroboric acid protection described for air-sensitive phosphines by Fu[30] provides a convenient storage of the free phosphine, which is liberated in situ under the basic Suzuki coupling conditions. Finally, phosphetane ligands fitting with the (Aryl)P(Alk)$_2$ general structure were synthesized. Monodentate phosphetanes, which were described by Marinetti, were found to give stable rhodium complexes and moderate-to-high enantioselectivities in the rhodium-catalyzed hydrogenation of functionalized olefins.[31,32] These C_2-symmetric ligands bear different alkyl groups on the four-membered ring, arising from easily accessible *anti*-1,3-diols.[32] We chose to synthesize the phosphetanes **19a**,**b**, bearing a biphenyl group as the aryl substituent, which can be considered as chiral analogues of PCy_2(*o*-biph). They were synthesized via the addition of the dianion of the corresponding phosphine **16** on the cyclic sulfates **17a**,**b**.[32] The resulting air-sensitive phosphetanes were immediately protected with BH_3 to form the borane complexes **18a**,**b**. This protection was cleaved by DABCO just before use in the Suzuki cross-coupling.

TABLE 3. Asymmetric Synthesis of 6 via Atropo-Enantioselective Suzuki Coupling: Ligands Screening[a]



(*R*)-(+)-MOP-**20**



(*S*,*S*)-(−)-**21**

entry	ligand	yield (%)[b]	ee (%)[b]	product
1	(+)-**20**	51	7	(+)-**6**
2	(+)-**7d**	35	36	(−)-**6**
3	(+)-**7e**	35	30	(−)-**6**
4	(+)-**12**	28	8	(−)-**6**
5	(−)-**14**	39	10	(−)-**6**
6	(−)-**19a**	21	6	(+)-**6**
7	(−)-**19b**	37	17	(+)-**6**
8	(−)-**21**	19	0	(±)-**6**

[a] Conditions: see Table 2, step a. [b] Determined by HPLC with a Chiracel OJ column.

The results obtained with these new ligands in the synthesis of biphenyl **6** via atroposelective Suzuki coupling of **3b** and **4a** are summarized in Table 3.

Commercially available (*R*)-(+)-MOP **20**, a chiral triaryl monophosphine that was tested for the purpose of comparison with (*R*)-(+)-BINAP **8**, gave a higher yield than **8** but with low ee (entry 1). The screening of binaphthyl phosphines **7a**−**e** bearing different alkyl groups indicated that the influence of the phosphine cone angle is crucial. The value of this angle increases with the bulkiness of the phosphine substituents.[33] When the phosphine was too bulky (Table 2, entry 5, **7c** R = *t*-Bu) the palladium complex was inactive, while the yield and ee were optimal with the slightly less bulky dicyclohexyl phosphine **7a** (Table 2, entry 3). When the size of the dialkyl substituent is decreased, R = Cy > *i*-Pr > Et > Me (Table 2, entries 3 and 4; Table 3, entries 2 and 3), the yield and ee decreased as well. This effect may be related to the value of the phosphine cone angle, which increases from Me to *t*-Bu. The basicity of the phosphine, which is also related to the size of the alkyl groups,[33] may also contribute to the observed results. Nevertheless, there seems to be a suitable value of the phosphine cone angle with ligand **7a** giving optimal results in the atroposelective coupling. The Hayashi-type ferrocene ligand **12** gave dissatisfying results (Table 3, entry 4), with poor improvement of the enantioselectivity compared to the diphenyl analogue **9** (Table 2, entry 2). Similarly, ferrocene **14** gave (−)-**6** in 39% yield, but with low atroposelectivity (Table 3, entry 5). The new phosphetane ligands **19a** and **19b** gave quite interesting results. Whereas the dimethyl-substituted ligand **19a** furnished nearly racemic product (entry 6), there was a 10% increase in the enantioselectivity together with a better yield with the dicyclohexyl analogue **19b** (entry 7). The alkyl groups borne by the phosphetane ring seem therefore to have a crucial influence on the reactivity and enantioselectivity. On the other hand, phenyl phosphetane **21**[32] gave very low conversion and no enantioselec-

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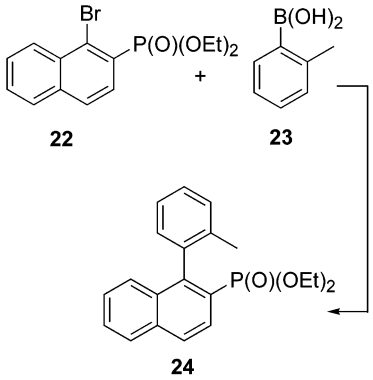
TABLE 4. Asymmetric Synthesis of Compound 24: Ligands Screening[a]



entry	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	(+)-**7a**	17	93	87
2	(+)-**7c**	17	~37	81[d]
3	(+)-**7d**	56	5	77
4	(−)-**9**	12	60	44
5	(+)-**12**	22	79	24
6	(−)-**14**	44	52	3
7	(−)-**19b**	61	10	40

[a] Reaction conditions: **22** (1.0 equiv), **23** (1.5 equiv), K_3PO_4 (3.0 equiv), Pd_2dba_3 (2.5 mol %), L* (6 mol %), NaI (3.0 equiv), toluene, 70 °C, 17−43 h. [b] Determined by GCMS analysis. [c] Determined by HPLC with a Chiracel OD column. [d] From literature data.

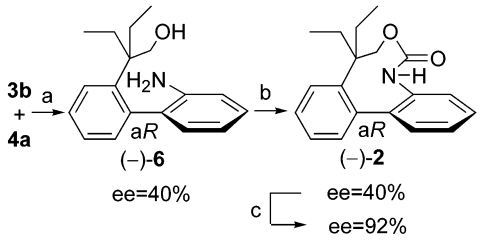
tivity (entry 8), which shows the positive influence of the biphenyl moiety on the ligand activity.

For comparative purpose, we chose to screen the best new ligands also on one of the systems described by Buchwald, i.e. the coupling of bromonaphthalene **22** and phenylboronic acid **23** (Table 4).[14] The corresponding phenyl-naphthyl product **24** has a much higher atropisomerization barrier than compound **5** and thus prolonged heating times (70 °C) could be utilized. Besides, the optimal reaction conditions (reagents, base, solvent) are markedly different in both systems. Indeed the conditions of this second system were not applicable to the synthesis of biphenyl **5** as shown above.

Indeed a few discrepancies were observed between the two systems. Whereas dicyclohexylphosphine **7a** gave also the best yield and ee value among the binaphthyl ligands series (entry 1), the di-*tert*-butyl analogue **7c** gave this time good enantioselectivity (entry 2), and the diethyl analogue **7d** gave good ee but with very poor yield (entry 3). In the ferrocene series, diphenylphosphine **9** (entry 4) gave a higher ee but a lower yield than the dicyclohexyl analogue **12** (entry 5). Ferrocene **14** gave, as in the preceding system, average yield and poor ee (entry 6). Finally, phosphetane **19b** gave also a moderate ee (40%, entry 7), but with a very low yield.

From these data, it appears that binaphthyl **7a** is the most versatile ligand that applied best to very different coupling systems. Other types of ligands such as ferrocene and phosphetanes are interesting new leads, but give substrate-dependent results. This substrate dependency is a recurrent feature of racemic Suzuki couplings and apparently also applies to the asymmetric couplings. Looking at both systems, it appears that the 40% ee value obtained for compound **6** with ligand **7a** is rather satisfying given its relatively unstable configuration compared to **24**. This moderate success originates in the reaction

SCHEME 3. Synthesis of Enantiomerically Enriched Carbamate (−)-2[a]



[a] Reaction conditions: (a) Table 2, entry 3; (b) $(Cl_3CO)_2C{=}O$ (1.0 equiv), pyridine (10 equiv), CH_2Cl_2, −78 °C, 30 min; (c) crystallization from CH_2Cl_2/heptane.

conditions ($Ba(OH)_2$ in dioxane/water) which allow the coupling to reach completion before racemization of the product.

With these results in hand, the asymmetric coupling with ligand **7a** was repeated on a 500-mg scale, giving, after MOM group cleavage, (−)-**6** in 66% isolated yield and 40% ee (Scheme 3, step a).

The latter was converted to the biologically active carbamate (−)-**2** (ee 40%) in 98% yield by reaction with trisphosgene. When this compound was allowed to recrystallize in a CH_2Cl_2/heptane mixture, the racemic mixture crystallized and the filtrate gave (−)-**2** with an ee of 92% as determined by chiral HPLC (35% yield). At this point, the (a*R*) absolute configuration of the intermediate compounds (−)-**5** and (−)-**6** could be deduced from the final formation of the atropisomer (−)-**2**, the (a*R*) configuration of which was known.[4] Whereas the Suzuki coupling gave a moderate enantioselectivity (ee 40%), it was sufficient to allow us to obtain (−)-**2** with an optical purity greater than 95% at the end of the synthesis, in only three steps and in 23% overall yield from **4a**.

Plausible intermediates for the enantioselective formation of biphenyl (−)-(a*R*)-**5** by asymmetric Suzuki coupling with ligand (+)-(a*S*)-**7a** are proposed in Figure 1. It was shown by Kocovsky et al. that the diphenylphosphino analogue of **7a** forms a P,C_σ five-membered palladacycle complex with $PdCl_2$ (analogous to complex **A**), at least in the solid state.[34] Although it is a matter of debate whether the actual catalytic species is this P,C_σ complex, the alternative seven-membered P,N complex, P-monoligated complex,[25,35] or even P,η^2-(C=C) complex,[36] we considered the X-ray structure of the P,C_σ palladium complex with the **7a** analogue as a relevant starting point for 3D visualization and preliminary molecular modeling of the Suzuki coupling intermediates.[37] We assume that the different types of palladium complexes should furnish similar intermediates. Thus, the (a*S*) ligand **7a** could form complex **A** (L = dba) with Pd_2dba_3, which undergoes

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(37) The molecular modeling studies have been performed with the MOE Package (Chemical Computing Group), using a MMFF94 force field. The geometry around the palladium atom has been deduced from X-ray data (MECDED molecule from Cambridge Data Base) and the atoms bound to the palladium have been fixed at their original place during the minimization.

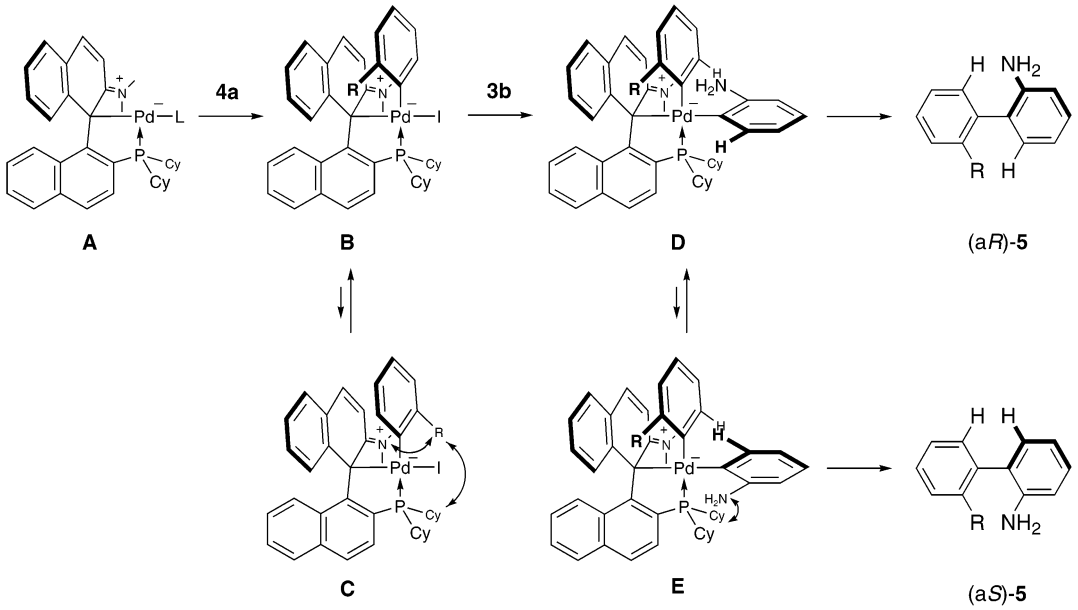

FIGURE 1. Possible mechanism for the atroposelective formation of (a*R*)-**5**, using ligand (a*S*)-**7a** (curved arrows indicate steric repulsions).

oxidative insertion of iodide **4a** bearing a bulky R substituent. This would, with the participation of π-stacking interactions, give complexes **B** or **C** having opposite orientations of the R substituent. Molecular mechanics indicated that complex **B** could be favored due to greater steric repulsions between R and the ligand in structure **C**. Transmetalation of boronic ester **3b** with the amino group anti to the R group could lead to two complexes **D** and **E** in which the amino group is respectively above and below the plane perpendicular to the R-bearing phenyl ring. Molecular mechanics again indicated that **D** could be favored over **E** due to a steric repulsion between NH_2 and a cyclohexyl group of the phosphine in **E**. Reductive elimination from **D** or **E** would lead respectively to the (a*R*) or (a*S*) biphenyl **5**, in favor of the (a*R*) atropisomer. According to the experimental data, it is likely that the overall enantioselectivity is set by the thermodynamic ratio of intermediates **D** and **E**. However, in the absence of more details concerning the catalytic cycle and the hybridation state of the palladium during this cycle, this mechanistic proposal should be taken with caution. It seems that the subtle adjustment of the steric and electronic interactions between the ligand and the substrate is better with binaphthyl ligand **7a** than with other ligands studied in this report. In particular ferrocene and phosphetane ligands probably give palladium complexes having very different shapes, and their optimization would require further structural analyses.

In conclusion, this work has shown a detailed study of the atropo-enantioselective Suzuki cross-coupling, which had not yet been applied to the synthesis of biologically relevant molecules. The influence of several reaction parameters were tested, and new chiral phosphine ligands were synthesized and screened. Whereas new phosphines did not equal the performance of binaphthyl **7a**, they provide interesting new leads for future ligand optimization, as improvements are clearly still needed in the synthesis of configurationally labile compounds such as **5** (maximum ee obtained was 40%). *Intra*molecular (versus *inter*molecular) coupling might also bring improvement in this direction, notwithstanding the failure of preliminary experiments in the synthesis of (−)-**2** (data not shown). As illustrated by the present synthesis of (−)-**2**, the atropo-enantioselective Suzuki coupling provides a rapid, straightforward, and efficient access to biologically relevant axially chiral biaryls compared to the previously described methods.

Experimental Section

Ligands **8**, **9**, **20**, and ferrocene **11** were commercially available. The physical data for compounds **2**,[4] **5**,[18a] **6**,[3] **a**nd **24**[14] were previously described. Compounds **3b**,[18a] **3d**,[23] **3e**,[24] **4a**,[18a] **4b**,[3] **4c**,[3] **7a**,[26] **7b**,[14] **7c**,[25] **10**,[25] **12**,[27] **13**,[28b,29] **15**,[38] **17a**,**b**,[39] **21**,[32] **22**,[14] **23**,[14] and **24**[14] were synthesized according to the described procedures. The optical purity of compound **10** (ee >99%) was determined by HPLC analysis (Diacel chiracel OJ, 3% 2-propanol in hexane, 0.5 mL/min).

General Procedure for Atroposelective Suzuki Coupling (Tables 2 and 3). A flame-dried resealable Schlenk tube was charged with aryl halide **4a** (100 mg, 0.3 mmol), arylboronate **3b** (94 mg, 0.45 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (182 mg, 0.6 mmol). The Schlenk tube was twice evacuated and backfilled with argon and capped with a rubber septum. Water and dioxane were pre-degazed by argon bubbling for 30 min. Water (0.1 mL) followed by 0.5 mL of dioxane were injected into the Schlenk tube. The chiral ligand (0.02 mmol) and $Pd_2dba_3 \cdot CHCl_3$ (8 mg, 0.008 mmol) were introduced followed by 0.5 mL of dioxane. The septum was replaced by a screwcap and the mixture was stirred at 80 °C for 1 h. The mixture was cooled to 25 °C, diluted with water, and extracted with methylene chloride. After being dried over magnesium sulfate and filtration, the solution was concentrated under vacuum. The crude material was purified by flash chromatography (silical gel, heptane/ethyl acetate 9/1, then 4/1) to afford **5** as an oil. To a

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solution of this compound in 1 mL of methanol at 0 °C was added 0.5 mL of concd HCl and the solution was stirred at 35 °C for 1 h. After being cooled to 0 °C, the solution was neutralized by concd sodium hydroxide, extracted by methylene chloride, dried over magnesium sulfate, and concentrated. The crude material was injected on HPLC, using a Chiracel OJ column. A calibration curve was previously elaborated with racemic **6** to determine the yields. The ee was determined by the difference of the two peak areas (hexane/propan-2-ol 95/5, flow rate 1 mL/min, (+)-**6** RT = 9 min, (−)-**6** RT = 15 min).

2-Aminophenylboronic Acid (3d). To a stirred solution of BCl_3 in CH_2Cl_2 (1 M, 9 mL, 9 mmol) at −78 °C was added dropwise a solution of pinacol (2-aminophenyl)boronate **3b** (300 mg, 1.37 mmol) in CH_2Cl_2 (1.4 mL). The mixture was stirred at −78 °C for 15 min, allowed to warm to 25 °C, and stirred at 25 °C for 3 h. The solution was then concentrated under reduced pressure and methanol (3 mL) was carefully added. Trimethyl borate and methanol were removed by evaporation under vacuum. Water (10 mL) and diethyl ether (10 mL) were added, and the aqueous layer was separated and washed with 2 × 15 mL of diethyl ether. Removal of water under vacuum and recrystallization from MeOH/$CHCl_3$ gave boronic acid **3d**[23] (96 mg, 52%).

Pinacol [2-(1-(Methoxymethoxy)methyl-1-ethylprop-1-yl)phenyl]boronate (4d). Compound **4a** (241 mg, 0.69 mmol) was submitted to a classical palladium-catalyzed borylation,[18a] using triethylamine (386 μL, 2.8 mmol), palladium(II) acetate (7.8 mg, 0.035 mmol), PCy_2(*o*-biph) (48.5 mg, 0.14 mmol), and pinacolborane (301 μL, 2.1 mmol), to afford **4d** as an oil (171 mg, 71%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (t, 6H), 1.38 (s, 12H), 1.88 (m, 4H), 3.33 (s, 3H), 3.84 (s, 2H), 4.62 (s, 2H), 7.15−7.30 (m, 3H), 7.44 (d, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.2, 24.7, 28.4, 46.3, 55.2, 70.6, 83.7, 96.8, 124.7, 127.1, 128.7, 133.7, 148.3 ppm; IR (film) ν 2975, 1594 cm^{-1}; HRMS (LSIMS) calcd for $C_{20}H_{34}BO_4$ [(M + H)$^+$] 349.2550, found 349.2559.

(+)-2-*N*,*N*-Dimethylamino-2′-dimethylphosphino-1,1′-binaphthyl (7e). A round-bottom flask was charged with (−)-2-*N*,*N*-(dimethylamino)-2′-bromo-1,1′-binaphthyl (**10**, 500 mg, 1.34 mmol) and purged with argon. THF (10 mL) was added, the resulting solution was cooled to −78 °C, and a solution of *n*-butyllithium in hexane (1.6 M, 0.913 mL, 1.5 mmol) was added dropwise. The solution was stirred at −78 °C for 1 h. Dimethylchlorophosphine (0.137 mL, 1.7 mmol) was added dropwise and the reaction mixture was stirred for 1 h at −78 °C, allowed to warm to 25 °C, and stirred for 17 h at 25 °C. A saturated aqueous ammonium chloride solution was added and the reaction mixture was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The crude material was recrystallized from methylene chloride/methanol to give (+)-**7e** as colorless crystals (297 mg, 62%); mp = 228−229 °C; [α]$^{23}_D$ 128.4 (*c*1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, J = 15 Hz, 3H), 1.26 (d, J = 15 Hz, 3H), 2.47 (s, 6H), 6.84 (d, J = 8.8 Hz, 1H), 7.07 (t, J = 8.8, 1H), 7.19−7.32 (m, 3H), 7.42 (t, J = 6.3 Hz, 1H), 7.48 (d, J = 9 Hz, 1H), 7.79−7.97 (m, 5H) ppm; ^{31}P (121.5 MHz, $CDCl_3$) δ −55.7 ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (d, J_{C-P} = 16.7 Hz), 15.2 (d, J_{C-P} = 11.2 Hz), 43.6, 119.3, 123.4, 125.6, 125.9, 126.1, 126.4, 126.9, 127.7, 127.9, 129.0, 129.4, 133.2, 133.6, 134.4, 139.0 (d, J_{C-P} = 12.2 Hz), 142.5 (d, J_{C-P} = 33.4 Hz), 149.7 ppm (observed complexity due to P−C splitting); IR (film) ν 2771, 1593 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{25}NP$ [(M + H)$^+$] 548.1725, found 548.1732.

(+)-2-*N*,*N*-Dimethylamino-2′-diethylphosphino-1,1′-binaphthyl (7d). Compound **7d** was synthesized as described above for compound **7e** from **10** (500 mg, 1,34 mmol) and diethylchlorophosphine (0.236 mL, 1.73 mmol). (+)-**7d** was obtained as colorless crystals (348 mg, 68%); mp 105 °C; [α]$^{25}_D$ 106.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.52 (dt, J = 15, 8.3 Hz, 3H), 1.04 (dt, J = 15, 7 Hz, 3H), 7.22−7.32 (m, 2H), 1.73 (m, 2H), 2.47 (s, 6H), 6.81 (d, J = 8.8 Hz, 1H), 7.08 (t, J = 9.0 Hz, 1H), 7.22−7.32 (m, 4H), 7.46 (m, 2H), 7.79 (m, 2H), 7.93 (m, 2H) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ −26.1 ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.1 (d, J_{C-P} = 11.9 Hz), 10.6 (d, J_{C-P} = 15.2 Hz), 21.2 (d, J_{C-P} = 15 Hz), 21.3 (d, J_{C-P} = 11.5 Hz), 43.7, 119.2, 123.4, 125.8, 126.0, 126.4, 127.3, 127.7, 128.0, 128.1, 129.2, 133.9, 134.6, 136.8 (d, J_{C-P} = 16.5 Hz), 144.4 (d, J_{C-P} = 30.2 Hz), 150.0 ppm (observed complexity due to P−C splitting); IR (film) ν 2957, 1594 cm^{-1}; HRMS (LSIMS) calcd for $C_{26}H_{29}NP$ [(M + H)$^+$] 386.2038, found 386.2038.

(*S*)-(−)-2-(*o*-Anisole)-1-(dicyclohexylphosphanyl)ferrocene, Tetrafluoroboric Acid Salt (14). A flame-dried round-bottom flask was charged with (S_P,S_S)-2-(*o*-anisole)-1-(*p*-tolylsulfinyl)ferrocene (**13**, 159 mg, 0.371 mmol), THF (2 mL) was added, and the reaction was cooled to −78 °C. Dicyclohexylchlorophosphine (0.286 mL, 1.3 mmol) and a solution of *tert*-butyllithium in hexane (1.5 M, 0.742 mL, 1.11 mmol) were added sequentially dropwise. The reaction mixture was stirred at −78 °C for 30 min. A solution of borane−methyl sulfide complex in THF (2.0 M, 0.925 mL, 1.85 mmol) was then added dropwise. The solution was allowed to warm to 25 °C, and stirred for 1 h at that temperature, followed by quenching with a 2 M NaOH solution and extraction with diethyl ether. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silical gel, heptane/ethyl acetate 9/1, then 4/1) to afford **14** borane complex (125 mg, 67% yield). This compound (35.2 mg, 0.07 mmol) was charged in a flame-dried round-bottom flask, DABCO (78.6 mg, 1.4 mmol) and toluene (1.5 mL) were added, and the reaction mixture was stirred at 60 °C for 1 h. The solution was cooled to 25 °C and concentrated under reduced pressure. CH_2Cl_2 (5 mL) and tetrafluoroboric acid (48% aqueous solution, 5 mL) were added to the residue and the solution was stirred for 30 min. After separation, the organic layer was dried over magnesium sulfate and concentrated under vacuum to afford phosphonium **14** (39 mg, 96.3%); [α]$^{23}_D$ −3.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83−2.53 (m, 22H), 3.84 (s, 3H), 4.46 (s, 5H), 4.78 (m, 1H), 4.82 (m, 2H), 5.92 and 7.58 (br d, J_{H-P} = 498 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 8.4, 1H), 7.64 (dd, J = 7.5, 2.1 Hz, 1H) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 22.7 ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.0, 25.1, 26.1, 26.2, 26.3, 26.4, 26.6, 26.7, 27.8, 28.2, 30.5, 31.1, 31.2, 31.8, 55.6, 71.8, 72.7 (d, J_{C-P} = 9.8 Hz), 73.7 (d, J_{C-P} = 12.1 Hz), 75.8 (d, J_{C-P} = 9.8 Hz), 111.1, 121.4, 122.5, 130.4, 133.0, 156.8 ppm (observed complexity due to P−C splitting); IR (film) ν 2930, 1450 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{38}FeOP$ [(M − BF_4)$^+$] 489.2010, found 489.2020.

(*R*,*R*)-2,4-Dimethyl-1-biphenylphosphetane Borane Complex (18a). A flame-dried Schlenk tube was charged with $LiAlH_4$ (1.1 g, 29.6 mmol), diethyl ether (5 mL) was added, and the solution was cooled to −50 °C and stirred at this temperature for 30 min. A solution of diethyl 2-biphenylphosphonate (**15**,[38] 2 g, 6.89 mmol) in 11 mL of diethyl ether was then introduced dropwise into the Schlenk tube, stirred for 30 min at 0 °C, and allowed to warm to 25 °C for 2 h.Water (5 mL) and 5 mL of NaOH (20% aqueous solution) were introduced dropwise. A white precipitate formed. The supernatant was cannulated off, dried over magnesium sulfate, and carefully evaporated under reduced pressure to furnish the air-sensitive phosphine **16**; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.28 and 4.29 (d, J_{H-P}= 202 Hz, PH_2), 6.95−7.42 (m, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −121.6. This compound was directly introduced in the next step. To a solution of phosphine **16** (233 mg, 1.25 mmol) and (*S*,*S*)-pentane-2,4-diol cyclic sulfate (**17a**, 208 mg, 1.25 mmol) in diethyl ether (17 mL) at 0 °C was added dropwise a solution of *sec*-butyllithium in hexane (0.9 M, 3.1 mL, 2.75 mmol). After the solution was warmed to 25 °C and stirred for 30 min, excess BH_3·Me_2S (2 mmol) was added. Water was carefully added, the solvent was evaporated, the residue was dissolved in diethyl ether, and the solution was washed with water and dried over magnesium sulfate. After

evaporation, the crude material was purified by flash chromatography (neutral alumina, 2% diethyl ether/cyclohexane) and the product was recrystallized from CH_2Cl_2/heptane to furnish **18a** (131 mg, 41%); mp 96 °C, $[\alpha]^{25}_D$ −78.2 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (dd, J_{P-H} = 18.8 Hz, J = 6.9 Hz, 3H), 0.94 (dd, J_{P-H} = 12.9 Hz, J = 5.8 Hz, 3H), 1.85 and 2.00 (dt, J_{P-H} = 42.4 Hz, J = 10.2 Hz, 1H), 2.30 (m, 1H), 2.46 (m, 2H), 7.34−7.51 (m, 9H) ppm; ^{31}P NMR (160 MHz, $CDCl_3$) δ 53.8 (d, J_{P-B} = 55.5 Hz) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 17.2 (d, J_{C-P} = 8 Hz), 29.9 (d, J_{C-P} = 39.3 Hz), 30.2 (d, J_{C-P} = 39.0 Hz), 35.0 (d, J_{C-P} = 12.2 Hz), 127.0 (d, J_{C-P} = 9.8 Hz), 128.0, 128.7, 129.0, 130.1, 130.2 (d, J_{C-P} = 21.7 Hz), 130.9 (d, J_{C-P} = 5.7 Hz), 131.4 (d, J_{C-P} = 10.7 Hz), 141.1, 145.0 (d, J_{C-P} = 3.7 Hz) ppm; IR (film) ν 2957, 2371, 1587 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}P$ [$(M - BH_3)^{+\bullet}$] 254.1224, found 254.1216.

***(S,S)*-2,4-Dicyclohexyl-1-biphenylphosphetane Borane Complex (18b).** Compound **18b** was synthesized from phosphine (**16,** 429 mg, 2.31 mmol) and (*R*,*R*)-1,3-dicyclohexylpropane-1,3-diol cyclic sulfate (**17b**, 295 mg, 2.31 mmol). **18b** was obtained as a coloress oil (366 mg, 39%). $[\alpha]^{25}_D$ −19.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.2−2.2 (m, 26H), 7.4−7.7 (m, 9H) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 53.3 ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.9, 26.0, 26.1, 26.2, 26.3, 27.7 (d, J_{C-P} = 14.1 Hz), 29.2 (d, J_{C-P} = 7.9 Hz), 30.4 (d, J_{C-P} = 11.8 Hz), 32.6 (d, J_{C-P} = 4.9 Hz), 32.8 (d, J_{C-P} = 4.8 Hz), 37.4 (d, J_{C-P} = 6.0 Hz), 38.0, 41.2 (d, J_{C-P} = 36.2 Hz), 43.1 (d, J_{C-P} = 36.8 Hz), 126.9 (d, J_{C-P} = 9.0 Hz), 127.2 (d, J_{C-P} = 6.4 Hz), 127.9, 128.5, 128.9 (d, J_{C-P} = 23.0 Hz), 129.4, 130.2, 131.6 (d, J_{C-P} = 6.1 Hz), 132.6 (d, J_{C-P} = 9.1 Hz), 141.2, 145.8 (d, J_{C-P} = 5.4 Hz) ppm; IR (film) ν 2925, 2368, 1587 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{36}P$ [$(M - BH_3)^{+\bullet}$] 390.2476, found 390.2484.

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Supporting Information Available: Copies of ^{1}H, ^{13}C, ^{31}P NMR spectra for compounds **4d**, **7d**,**e**, **14**, and **18a**,**b**, as well as HPLC chromatograms of compounds **6** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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