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Rational design of novel ligands for environmentally benign cross-coupling reactions*

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Abstract: Transition-metal (TM) complexes of new phosphines, readily prepared by a straightforward three-step modular synthesis, were successfully employed in difficult cross-coupling reactions conducted under mild conditions (water, "open-flask", low temperature) that aspire to meet green chemistry criteria. High yielding catalyzed by bismuth or rhodium complexes oxidative arylation of naphthoquinone gave the key 2-arylnaphthoquinone intermediates for facile bismuth triflate-catalyzed Michael addition of secondary phosphine oxides. Subsequent O-methylation and reductions of the resulting products gave access to the target air-stable phosphine ligands in good overall yields (up to 60 %).

Keywords: asymmetric catalysis; *C*,*P*-complexation cross-coupling; green chemistry; phosphorus ligands.

INTRODUCTION

Transition-metal (TM)-mediated cross-coupling constitutes an important and rapidly developing class of organic transformations [1]. Among the variety of applied reaction conditions, those that include utilization of soluble palladium complexes of carbenes or phosphorus ligands as catalysts are the most successful. Such ligands not only maintain the catalyst in solution and at a low level of aggregation, but also subtly modify their electronic and steric properties. This threefold influence is crucial especially in cases of difficult coupling. First of all, monomolecular complex catalysts are more readily accessible by substrates, also ligands prevent breaking of the catalytic cycle by inactive palladium black formation and, if the catalysts are active and stable enough, they could be used in extremely small amounts. On the other hand, ligands could increase the electronic density at the TM center and therefore boost an oxidative addition reaction step. Eventually, steric factors play a twofold role: increasing steric hindrance accelerates reductive elimination of the products, and it could also generate a stereogenic environment around the metal atom to induce chirality in the reaction product. In this way, only a well-tuned ligand incorporating the foregoing design features has the potential to enhance efficiency and selectivity of the catalysts for difficult cases of cross-coupling reactions. This problem becomes even more difficult in the case of atroposelective aryl–aryl bond formation, since highly hindered products possessing at least three *ortho* substituents need to be created at low temperature with useful enantioselectivity, and in high chemical yield.

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Generally, to perform synthesis of multiple *ortho*-substituted biaryls by cross-coupling reactions, a new generation of highly electron-rich bulky phosphines and carbenes have been utilized. At the same time, limited availability of chiral carbenes stipulates that chiral phosphines are used almost exclusively for this purpose [2]. Actually, popular triarylphosphines and bis(phosphines), widely available also in optically pure forms, do not form catalysts efficient enough to couple multiply *ortho*-substituted aryls under conditions for Suzuki–Miyaura (SM), Negishi, Heck, and related reactions. Electron-rich bulky di- and especially trialkylphosphines form highly active catalytic systems for those cross-coupling reactions, but only a few of them are commercially available. The particular position in the range of efficient ligands for cross-coupling reactions is occupied by electronically rich and bulky biaryl core-based ligands of *C*,*P*-type of complexation [3]—e.g., dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (*S*-Phos) [4], 2'-(dicyclohexylphosphino)-*N*,*N*-dimethyl-1,1'-binaphthyl-2-amine (Cy-MAP) [5], dicyclohexyl(2'-methoxy-1,1'-binaphthyl-2-yl)phosphine (MOP) [3,6]—due to their extremely high activity and potential ability to incorporate a chiral axis as well as chirality at the phosphorus atom [7]. Despite enormous interest in new chiral phosphine ligands and a significant lack of such ligands that successfully catalyze cross-coupling reactions, general approaches to their rational design are still very rare.

DISCUSSION

Herein we would like to present the rational design, synthesis, and application in asymmetric cross-coupling reactions of the new air-resistant atropoisomeric ligand dicyclohexyl(1',2-dimethoxy-1,2'-binaphthyl-3'-yl)phosphine (*BisNap*-Phos), created particularly for the greener Suzuki and Heck reactions conducted in water at low temperature under air atmosphere.

Rational design of the ligands

As a starting point of our study we have used an assumption that a successful chiral phosphorus ligand should act through the *C*,*P*-complexation. The particularity of the *C*,*P*-ligands and *C*,*P*-ligands TM complexes arises from their atypical construction. In a free form, such ligands are remarkably air-resistant because of repulsion between oxygen and π-electron density of the remote aromatic ring assumed in the most stable conformations of the ligands (Fig. 1A) [8]. But in the formed palladium *C*,*P*-complex, a remote aromatic ring donates the π-electron density to palladium and stabilizes metal at the low coordination stage. Nevertheless, such a bond could easily dissociate by rebuilding the aromaticity to form very active coordinatively unsaturated palladium species (Fig. 1B) [3,9].

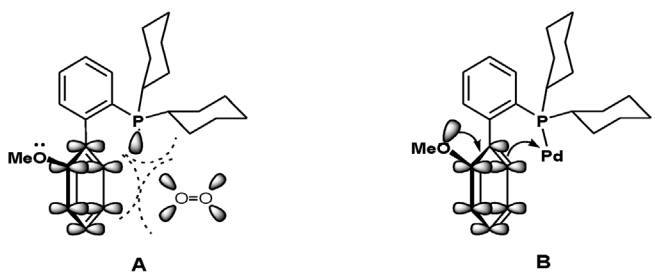


Fig. 1 Phenomena of air resistance and *C*,*P*-complexation of bulky electron-rich biarylphosphines.

Thus, *C*,*P*-ligands should bear: a biaryl core with high electronic density at both aromatic rings of the structure to push additional electronic density toward a metal atom for better stabilization of formed *C*,*P*-complex and for better activity of the complex in the oxidative addition reaction step; bulky

alkyl substituents at the phosphorus atom to protect phosphorus against the oxidation and accelerate reductive elimination of the product; protected *ortho* positions around the aryl–aryl bond to prevent palladocycle formation; atropoisomeric chirality for simple and more predictable stereocontrol. In addition to all of the above, we assumed an advantage of the binaphthalene core over the biphenyl core because of its spatially wider chiral differentiation ability.

First rationally designed according to these assumptions, mixed phenyl-naphthyl biaryl ligand *Nap*-Phos {dicyclohexyl[4-methoxy-3-(2-methoxyphenyl)naphthalen-2-yl]phosphine} [10] could possibly undergo *C*,*P*-complexation, nevertheless its X-ray analysis shows that in the 16-electron Pd(II) complexes $[Pd(nap\text{-}phos)(CH_3CN)_2Cl]BF_4$, palladium tends to undergo C–H activation reaction rather then adopt π-electron density of the methoxyphenyl group as indicated by the Pd–$C^{1'}C^{6'}$ distance of 2.94 Å, Pd–$C^{6'}$ distance of 2.96 Å, Pd–$C^{6'}$H distance of 2.79 Å, and Pd–H($C^{6'}$) distance of 2.79 Å (Fig. 2) [11].

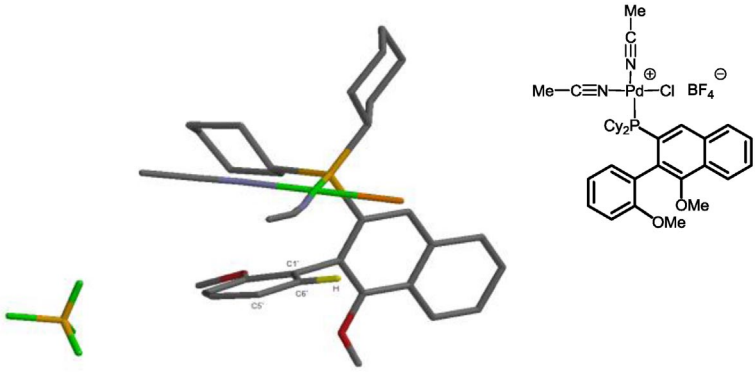
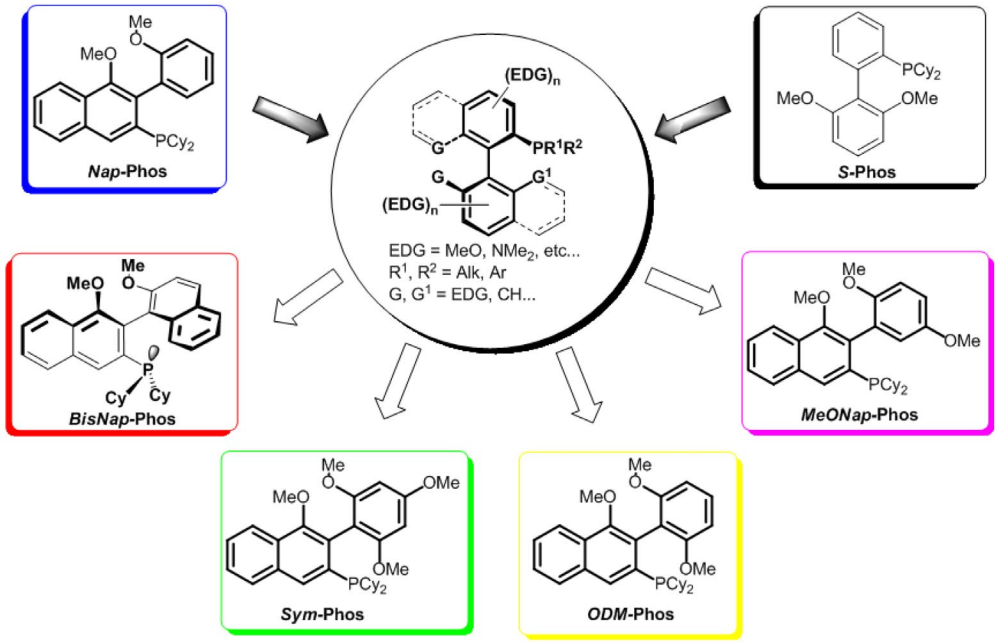


Fig. 2 X-ray structure of $[Pd(nap\text{-}phos)(CH_3CN)_2Cl]BF_4$.

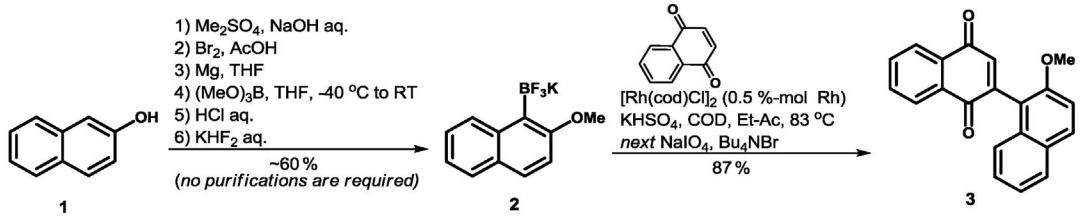
Nap-Phos palladium complexes were tested in several model coupling reactions and showed significant activity allowing the formation of sterically hindered biaryls in high yields [10].

The modifications of the *Nap*-Phos structure allow the design of a series of bulky phosphines with additional electron-donating substituents and both *ortho* positions in the remote aromatic ring blocked. Eventually, the proper substitution pattern should also secure an axial atropoisomeric chirality (Scheme 1).



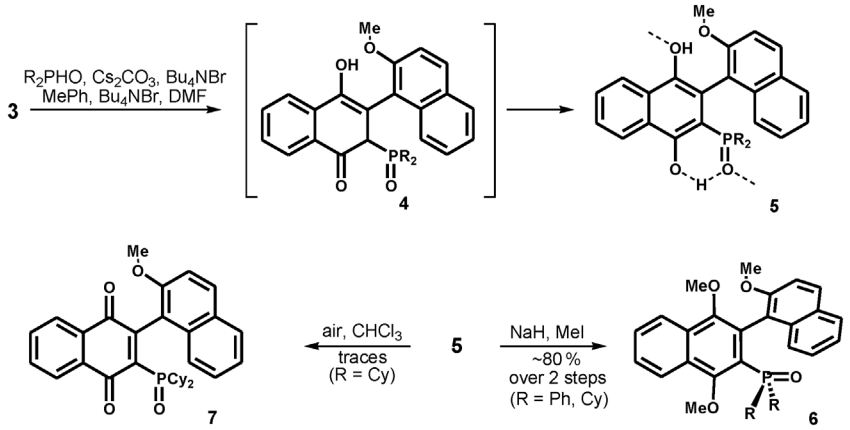
Scheme 1 Rationally designed ligands based on *Nap*-Phos structure.

We decided to exploit the developed synthetic approach leading to *Nap*-Phos [10] in connection with the new quinone arylation procedure [12] to design synthesis of chiral ligands in a cost-effective manner that began from the simplest starting materials and using facile methodologies. In a sequence of a few high-yield reactions, which did not require purification of the starting materials, 2-naphthol was converted into potassium 2-methoxynaphth-1-yl trifluoroborate **2** used subsequently for high-yield arylation of naphthoquinone (Scheme 2).



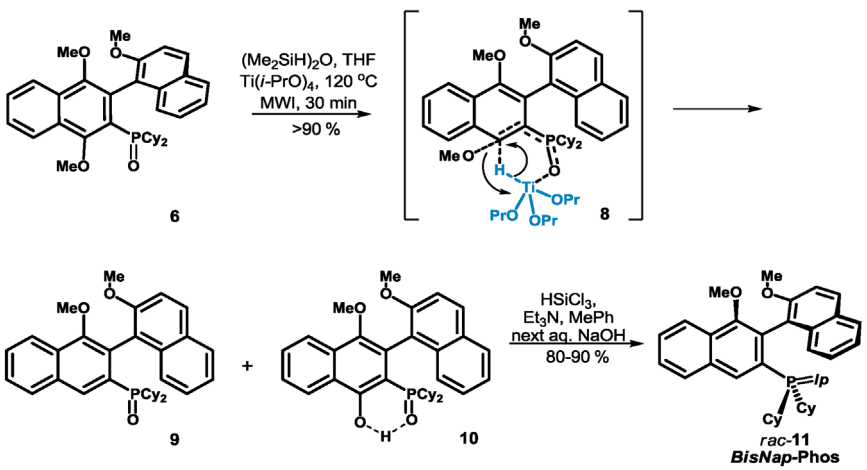
Scheme 2 Synthesis of 2-(2-methoxynaphth-1-yl)-naphthoquinone.

Next, arylated naphthoquinone **3** was used in base-catalyzed conjugate addition of secondary phosphine oxides (Cy_2PHO, Ph_2PHO) followed by double methylation reactions performed in one pot (Scheme 3). Pure phosphine oxide **5** could also be isolated. In such a case, the addition reaction should be carried out in the solvent mixture with a high ratio of toluene/dimethylformamide (DMF), then formed **5** must be filtered under inert atmosphere, thoroughly washed with toluene, and dried under reduced pressure. Pure **5** is quite air-resistant, nevertheless, it slowly oxidizes in neutral $CDCl_3$ solution if exposed to air and light to form corresponding quinone core **7** as the only product formed.



Scheme 3 Synthesis of phosphine oxides **5–7**.

Isolated phosphine oxide **6** apparently due to the proximity effect of *ortho* to phosphorus methoxy group could not be directly reduced to corresponding phosphine. Instead, phosphine oxide **6** smoothly underwent cleavage of the *ortho* to phosphorus methoxy group by treatment with titanium tetra-isopropyloxide-tetramethyldisiloxane mixture in tetrahydrofuran (THF) for 12 h at 90 °C under the argon atmosphere to form the *P*-oxidized precursor **9** of the new ligand *BisNap*-Phos in excellent yield (Scheme 4). We suppose that the reaction runs throughout transition state **8** in which the *ortho* to phosphorus carbon atom undergoes the nucleophilic attack by formal hydride of formed in situ titanium hydride species precoordinated by the P=O group. Some minor amounts of demethylation product **10** and free phosphine **11** are also formed as byproducts in this reaction. The demethoxylation step should be carefully monitored by ^{31}P NMR because of possible further reduction. Significant prolonging of the reaction time up to 96 h allows *BisNap*-Phos (**11**) to be obtained as the main product, nevertheless, its efficient chromatographic isolation is more complicated than isolation of corresponding phosphine oxide **9** due to oxidation on the SiO_2 support. Alternatively, demethoxylation of **6** performed in the microwave reactor at 120 °C for 30 min gives **9** in about 90 % isolated yield. The ratio of silica to the mixture to be separated should be optimized because of a risk of partial irreversible absorption of the

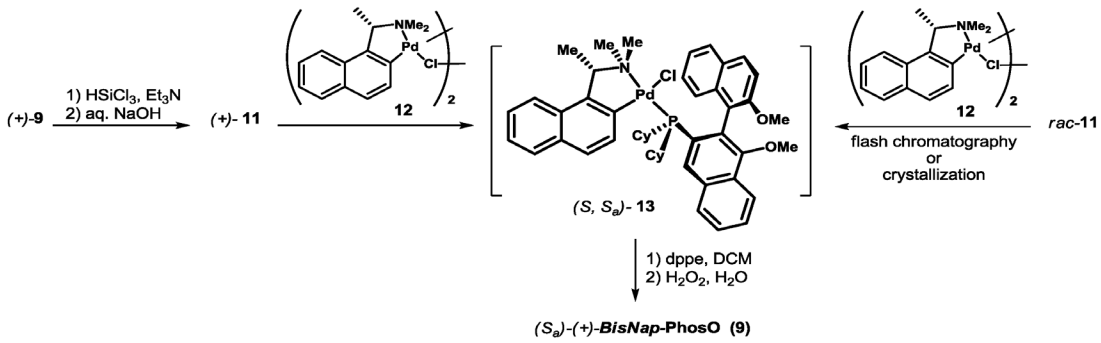


Scheme 4 Reductive conversion of the phosphine oxide **6** to phosphine **11**.

product during the chromatographic isolation. In fact, independently of the demethoxylation protocol the isolated product **9** could be slightly contaminated by hydroxyphosphine oxide **10**. However, **10** does not undergo further reduction to phosphine and can be easily removed at the final purification step. Eventually, pure **11** was obtained in classical reduction of **9** by $HSiCl_3$ in the toluene/Et_3N mixture at 110 °C followed by aq. NaOH treatment, solvent evaporation, and crystallization from methanol.

Approaches to nonracemic ligand *BisNap*-Phos

In order to have access to the enantiopure ligand *BisNap*-Phos, a variety of enantioseparating agents and conditions were examined. Surprisingly, despite high basicity of P=O group of **9**, typical for phosphine oxides, protocols of enantioseparation via crystallization in the presence of chiral acids (such as DBTA and several others) completely failed and we have never seen any crystalline materials formed. The only successful method we have found to carry out the desired enantioseparation was double fractional crystallization of 1:1 complex of **9** and TADDOL, easily available from tartaric acids. After two crystallizations and short flash column separation, both isomers of over 98 % ee [13] *BisNap*-PhosO's (**9**) were isolated in 30 % average yield, unresolved phosphine oxide and recovered TADDOL were recycled for further crystallization. *BisNap*-PhosO, obtained in this way, underwent efficient reduction by $HSiCl_3$ in toluene/Et_3N without racemization. After simple basic workup and removing the solvents in vacuo, crude *BisNap*-Phos was crystallized from methanol to afford enantiomerically pure product. The absolute configuration of *BisNap*-Phos was established by means of X-ray analysis of its diastereomerically pure complexes **13** (Scheme 5) [14].

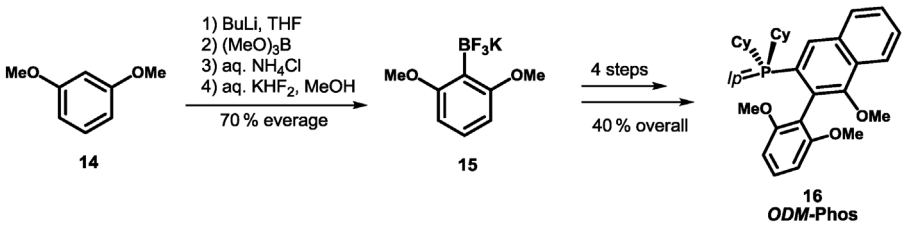


Scheme 5 Preparation of crystalline diastereomerically pure Pd complex of *BisNap*-Phos for X-ray analysis.

In fact, as indicated in Scheme 5, chiral palladocyclic complex **12** could also be used for rapid enantioseparation of racemic **11**, because free enantiopure **11** may be liberated from the separated diastereomerically pure complexes (S,S_a)-**13** or (S,R_a)-**13** by sequential treatment with a solution of HCl in acetone and an aqueous solution of NaCN. However, despite its rapidity such separation appears to be less practical than the TADDOL route.

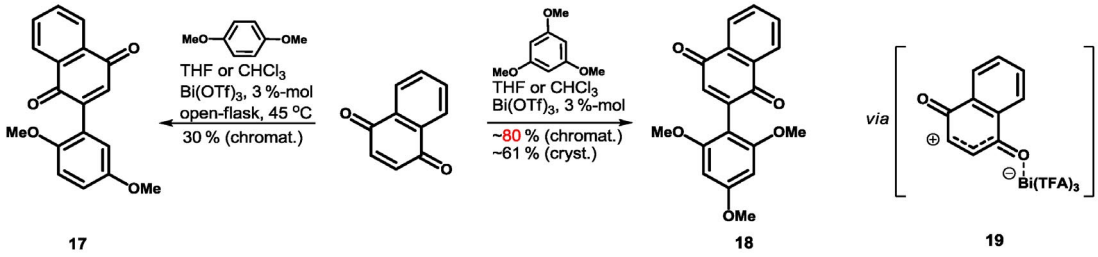
Other *C,P*-ligands

After some modifications, the synthetic protocol presented above could be also utilized to synthesize several new nonchiral ligands of *S*-Phos type. Thus, the ligand possessing bis-*ortho*-**dim**ethoxyphenyl group *ODM*-Phos {dicyclohexyl[3-(2,6-dimethoxyphenyl)-4-methoxynaphthalen-2-yl]phosphine, **16**} was prepared analogously to *BisNap*-Phos (Scheme 6).



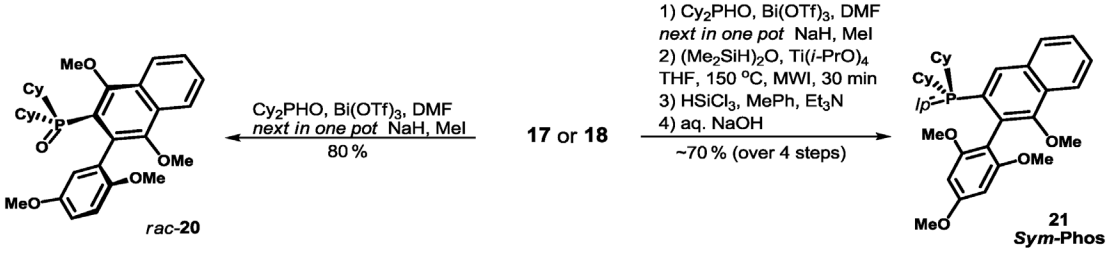
Scheme 6 Synthesis of *ODM*-Phos (**16**).

In the case of the syntheses that utilize *p*-dimethoxy- or *sym*-1,3,5-trimethoxybenzene as substrates, giving only single S_E2 monosubstituted product, the synthetic pathway to the ligand could be notably simplified. We decided to use tandem bismuth triflate [15] catalyzed Friedel–Crafts alkenylation [16] followed by air oxidation to obtain 2-arylnaphthoquinones (Scheme 7).



Scheme 7 Arylation of naphthoquinone in $Bi(OTf)_3$-catalyzed Friedel–Crafts reaction.

The second synthetic step consisting of conjugate addition of dicyclohexylphosphine oxide to **17** or **18** was also run under bismuth triflate-catalyzed conditions (Scheme 8). Contrary to common basic activation of phosphorus nucleophile requiring oxygen-free conditions, we decided to activate 2-arylnaphthoquinones to make them more electrophilic by complexation with $Bi(OTf)_3$ afforded the complex similar to **19** (Scheme 7). Thus, both arylation and phosphorylation reactions could be run in one pot, nevertheless, the better overall yields were obtained when isolated 2-arylnaphthoquinone was utilized (Scheme 8). After the double O,O'-methylation, the *ortho* to phosphorus methoxy group was removed as previously in the reaction with TMDS/Ti(*i*-PrO)$_4$, run in the microwave reactor for 30 min at 120 °C. Eventually, the ligand *Sym*-Phos (**21**) was obtained in the classical $HSiCl_3/Et_3N$ reduction followed by crystallization from methanol. In this way, the ligand *Sym*-Phos was obtained starting from naphthoquinone and 1,3,5-trimethoxybenzene in 40 % yield overall with only one chromatographic isolation step and 60 % yield when two chromatographic isolation steps were applied. The obtained lig-



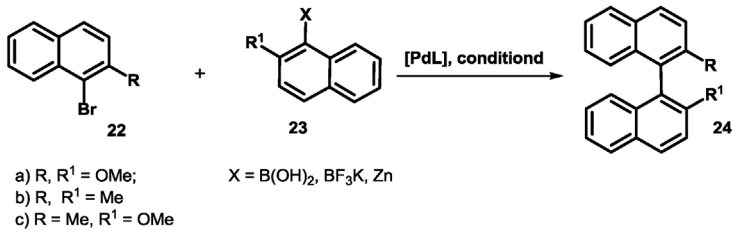
Scheme 8 Synthesis of phosphine oxide **20** and *Sym*-Phos ligand **21**.

and **21** does not significantly oxidize when exposed to air and therefore does not require storage and handling in an inert gas atmosphere.

Model catalytic reactions

The new ligands could only be evaluated by their efficiency to perform selective catalyst-mediated reactions they were designed for. In the initial point of our study we aimed for the design of straightforward and inexpensive syntheses of potentially active ligands for cross-coupling reactions, particularly for new aryl–aryl bond formation performed in an enantioselective manner. Proper selection of the model reaction for examination of the ligand which would point to its virtues does not appear to be a trivial task. Several issues should be taken into consideration: What are the reactions this ligand was designed for? Is it a general model reaction or a single case? Could the new ligand-based catalyst activate unreactive substrates (e.g., electronically rich halogenoarenes or electron-deficient arylboronic acids)? Is it suitable for sterically hindered and *ortho*-substituted substrates? Could it ensure a high level of enantiodiscrimination in asymmetric coupling reactions? Does it require special storing or handling conditions (air, moisture, temperature, or light sensitivity)? What is the toxicity of the starting materials, solvents, or formed wastes? Could we run usually sensitive reactions in an open flask at ambient temperature? etc. Eventually, a simple and representative model was selected—we decided to start by examining the ligand in the SM coupling reaction leading to 2,2'-dimethoxybinaphthyl (**24a**). Synthesis of **24a** required the application of a deactivated electron-rich double *ortho*-substituted bromide **22a** and boronic acid derivatives **23a**-$B(OH)_2$ or **23a**-BF_3K. A few examples of this SM coupling are also already known [9,10]. There are also asymmetric versions of the synthesis of **24a** [17].

Preliminary ligand testing was run under usual for SM reaction conditions involving use of $Pd(OAc)_2$ (2 mol %), L/Pd = 2, K_3PO_4, anhydrous DMF, 120 °C, 18 h and showed significant activity of the catalyst based on ligands **11** and **21** comparable with that observed when *S*-Phos was utilized (Table 1). It is worth mentioning that, according to our knowledge, the best published yield in the cross-coupling leading to **24a** (78 %) was achieved with utilization of 10 mol % 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)-biphenyl (**25**) used in combination with 2.5 mol % Pd_2dba_3 run in toluene at 110 °C [9] (Scheme 9).



Scheme 9 Model SM coupling reactions used for the examination of ligands efficiency.

The observed notable stability of biaryl core-based dicyclohexylphosphines and high activity of their palladium complexes in the cross-coupling reactions should allow those transformations to be performed in an open flask at moderately low temperature. Moreover, an aqueous medium should be also compatible with the SM coupling protocol.

Table 1 Examination of ligands efficiency in the model SM reaction leading to **24a** according to Scheme 9.

Entry	Ligand	Yield, %
1	Ph_3P	trace
2	*S*-Phos	85
3	*Nap*-Phos	58
4	*Sym*-Phos	82
5	*BisNap*-Phos	72
6	**25**	78[a]

Reaction conditions: **22a** (1mmol), **23a**-$B(OH)_2$ (1.5 mmol), $Pd(OAc)_2$ (2 mol %), L/Pd = 2, K_3PO_4, dry DMF, 120 °C, 18 h.
[a]2.5 mol % Pd_2dba_3 and toluene was utilized instead of $Pd(OAc)_2$ and DMF [9].

Contrary to a common approach we used water as a reaction medium, 0.3 % sodium dodecylsulfate (SDS) was added to prevent precipitation of starting materials in a block but to form fine emulsion or suspension. We found that the optimal reaction temperature for this synthesis is 60 °C, below which high conversion was not observed in reasonable time and above it the product yield decreased perhaps due to faster ligand oxidation. Among the number of the tested bases, Na_2CO_3 appears to be a base of choice. The optimal ratio of ligand to palladium was 2, and $Pd(OAc)_2$ as well as $[Pd(CH_3CN)_2Cl]BF_4$ [18] were found to be best precursors of the catalyst (Table 2).

Table 2 Examination of the ligands efficiency in coupling reactions run in water, according to Scheme 9.

Entry	Substrates	Ligand	Base	Yield, %
1	**22a, 23a**-$B(OH)_2$	Ph_3P	K_2CO_3	trace
2	**22a, 23a**-$B(OH)_2$	$PhPCy_2$	K_2CO_3	0
3	**22a, 23a**-$B(OH)_2$	rac. *BisNap*-Phos	K_2CO_3	69
4	**22a, 23a**-$B(OH)_2$	*S*-Phos	K_2CO_3	63
5	**22a, 23a**-$B(OH)_2$	*S*-Phos	Na_2CO_3	95
6	**22a, 23a**-BF_3K	*S*-Phos	Na_2CO_3	95
7	**22a, 23a**-BF_3K	*S*-Phos	Na_2CO_3	69[a]
8	**22a, 23a**-BF_3K	*Sym*-Phos	Na_2CO_3	92[b]

Reaction conditions: **22** (1 mmol), **23** (1.5 mmol), $Pd(OAc)_2$ (2 mol %), L/Pd = 2, base (3 equiv), 0.3 % SDS in water, 60 °C, 18 h.
[a]No SDS used.
[b]Brij® used instead of SDS.

Asymmetric cross-coupling reactions

Asymmetric SM coupling leading to **24a** is indeed a difficult synthetic task. Among only a few published examples of its enantioselective synthesis, the best results in terms of ee were achieved in the Negishi coupling (54 % ee) performed with utilization of 5 mol % palladium catalyst and 20 mol % ferrocene core-based ligand (R,S_P)-(–)-(2-diphenylphosphino-ferrocenyl)-ethyldimethylamine (**26**) run in THF at 50 °C [17]. Nevertheless, even in this noteworthy case chemical yield did not exceed 70 %. In our hands, SM reaction run in dry DMF at 110 °C and utilizing 5 mol % of separately prepared complex *rac*-[Pd(bisnap-phos)]Cl_2 (ligand/Pd ratio = 1/1) gave 80 % yield of **24a**. Analogous experiments

performed with enantiomerically pure complexes were run with catalyst loading lowered to 2.5 mol %, albeit at the cost of yield. The decreasing of the amount catalysts effected in chemical yield decreasing to 35–40 %, while the observed optical yields 33–37 % ee had encouraged us to further optimize the reaction conditions (Table 3).

Table 3 Comparision of the results of the asymmetric syntheses of **24a** run in organic solvents with the utilization of different chiral catalysts, according to Scheme 9.

Catalyst	Substrates	L/Pd, mol %	*T*, °C	*t*, h	ee, %	Yield, %
rac-[Pd(bisnap-phos)]Cl_2	**22a, 23a**-$B(OH)_2$	5/5	110	16	n/a	80[a]
(R_a)-[Pd(bisnap-phos)]Cl_2	**22a, 23a**-$B(OH)_2$	2.5/2.5	110	16	33 (*R*)	35[a]
(R,R_a)-**13**	**22a, 23a**-$B(OH)_2$	2.5/2.5	110	16	37 (*R*)	40[a]
25 + Pd_2bda_3	**22a, 23a**-$B(OH)_2$	10/5	110	24	n/a	78[b]
Nap-Phos + $Pd(OAc)_2$	**22a, 23a**-$B(OH)_2$	10/2	150	18	n/a	58[a]
26 + Pd_2bda_3*$CHCl_3$	**22a,** (**23a**-)$_2$Zn	20/5	50	24	54 (*S*)	70[c]
26 + $Pd(OAc)_2$	**22a,** (**23a**-)$_2$Zn	20/5	50	48	49 (*S*)	70[c]
(+)-*BisNap*-Phos + $Pd(OAc)_2$	**22a, 23a**-$B(OH)_2$	5/2.5	100	12	40 (*R*)	50[a]

Solvent used: [a]DMF; [b]toluene [9]; [c]THF [17].

As presented above, the utilization of aqueous medium to run SM coupling in the case of utilization of appropriate ligands allows us to significantly decrease the reaction temperature, which could boost the enantioselectivity of the reactions. Again, reactions run in water bring better chemical yield compared to that observed in the case of dry organic solvent even at lower reaction temperature. We were also able to run those reactions under "open-flask" conditions.

In fact, as can be seen from Table 4, entry 2, we reached a somewhat lower level of asymmetric induction (46 % ee) than the highest, but still low, we found in the literature for coupling leading to **24a** (54 % ee) [17]. We think that it might well be due to the nature of the selected model, which does not allow reaching high ee. Because in another model reaction leading to **24c** run under similar reaction conditions, a high chemical yield of 85 % was observed and asymmetric induction reached a much better level of 77 % ee (Table 4, entry 3). In addition, we have checked the assumption that differentiation of the functional groups around the newly formed aryl–aryl bond should favor better enantiodifferentiation. This assumption was not confirmed by the preliminary results obtained for the last model synthesis of **24b** formed in excellent yield, but only moderate ee's were obtained under the same conditions (Table 4, entries 4 and 5). Surprisingly, for both combinations of the substrates [**22b**, **23a**-$B(OH)_2$ vs. **22a**, **23b**-$B(OH)_2$] the same yield, ee, and absolute configuration of the product were observed. We believe that an explanation of this phenomenon could be possible only after the mechanism of asymmetric induction in cross-coupling reaction is better understood.

Table 4 Comparision of the results of the asymmetric syntheses of **24a–c** run in water with the utilization of *BisNap*-Phos palladium complexes.

Entry	Substrates	Product	Base	ee, %	Yield, %[a]
1	**22a**, **23a**-BF_3K	**24a**	K_2CO_3	37 (*R*)	(56)
2	**22a**, **23a**-$B(OH)_2$	**24a**	Na_2CO_3	46 (*R*)	86 (97)
3	**22b**, **23b**-$B(OH)_2$	**24b**	Na_2CO_3	77 (*R*)	79 (85)
4	**22b**, **23a**-$B(OH)_2$	**24c**	Na_2CO_3	70 (*S*)	98
5	**22a**, **23b**-$B(OH)_2$	**24c**	Na_2CO_3	70 (*S*)	88

Reaction conditions: **22** (1 mmol), **23** (1.5 mmol), $Pd(PhCN)_2Cl_2$ (2 mol %), (+)-*BisNap*-Phos (4 mol %), base (3 mmol), 0.3% SDS in water, 60 °C, 18 h.
[a]GC/MS or HPLC/MS yield shown in parentheses.

CONCLUSIONS

Summing up, we have described herein a new rational design and high-yield straightforward synthesis of very effective air-stable phosphorus *C,P*-ligands, also chiral nonracemic, based on utilization of inexpensive, nontoxic starting materials and readily affordable reaction conditions with limited numbers of chromatographic isolation steps. The ligands obtained are able to form highly active palladium complexes acting as excellent catalysts for difficult SM reactions giving excellent yields and good asymmetric induction even in the case of syntheses run under "open-flask" conditions in water at moderately low reaction temperature. The results of further studies along these lines will be reported separately in due time.

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