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Catalytic Palladium Phosphination: Modular Synthesis of C_1-Symmetric Biaryl-Based Diphosphines

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Abstract: A new family of C_1-symmetric bis(diphenylphosphino)biphenyls have been prepared starting from readily available *ortho*,*ortho*′-dihalobiphenyl precursors by a palladium-catalyzed C–P coupling reaction. This process does not require the use of an additional ligand. To date, the synthesis of such diphosphines, by reaction of an intermediate biphenyldiyl dianion with $ClPPh_2$, mainly afforded the undesired cyclic phosphafluorene derivative. So far, no synthetic pathway has been found to avoid this intramolecular reaction. Herein we report the first general and external-ligand-free palladium-catalyzed phosphination reaction that allows the synthesis of a wide variety of substituted *ortho*,*ortho*′-bis(diphenylphosphino)biphenyls. With the aim of illustrating the scope and efficiency of this methodology, we applied it to the establishment of a straightforward access to C_1-symmetrical analogues of the most powerful ligands used in homogenous catalysis and extended it to more challenging substrates.

Keywords: biaryls · cross-coupling · lithiation · palladium · phosphorus

Introduction

As remarkable auxiliaries and scaffolds, chiral biaryls are widely used in a large number of efficient stereodifferentiating reactions.[1] In particular, atropisomeric C_2-symmetric binaphthyl or biphenyl diphosphine ligands such as BINAP,[2] BIPHEMP,[3] MeO-BIPHEP,[4] SEGPHOS,[5] SYNPHOS,[6] DIFLUORPHOS[7] and their analogues are well known as highly efficient chiral ligands for a variety of transition-metal-catalyzed asymmetric reactions (Scheme 1, top). The biphenyl backbone has an advantage over binaphthyl: By controlling the size of the substituents at the 6- and 6′- positions, the dihedral angle of the biphenyl backbone can be modulated. In fact, this angle is one of the key factors for ligand efficiency as regards conversion and enantiomeric excess in asymmetric catalysis.[5,7a,b,8]

On the other hand, the design of C_1-symmetric diphosphines has attracted increasing interest in recent decades because of the improved activity of some catalytic reactions.[8c,9] However, the synthesis of C_1-symmetric diphosphine ligands based on biaryl scaffolds has been less explored due to the difficulty of their synthesis. In addition, to elucidate the role of the *ortho* substituents of the biaryl backbone and, in particular, to compare the effect of C_2 and C_1 symmetry on catalytic reactions, it was considered desirable to establish a methodology to synthesize efficiently C_1-symmetrical biphenyl diphosphine ligand families (Scheme 1, bottom) analogous to their C_2-symmetric counterparts.

The synthesis of C_2-symmetric tetra-*ortho*-substituted biaryl diphosphines can essentially be achieved by three approaches. 1) Symmetrical bis(diphenylphosphino)biphenyls can be obtained by Ullmann coupling between two identical prefunctionalized aryl moieties bearing the phosphine group in the oxidized form (which might be reduced later), as exemplified in the synthesis of MeO-BIPHEP.[4] 2) A strategy based on palladium- or nickel-catalyzed phosphination of biaryl bis-triflates. This approach was successfully applied for the first time to the synthesis of BINAP.[10] 3) The use of an already pre-existing biaryl scaffold, most frequently a 2,2′-dibromobiaryl, which is submitted to halogen/metal exchange followed by trapping with $ClPPh_2$, as in the case of BIPHEMP.[3]

Unfortunately, these strategies cannot be applied to the synthesis of less sterically demanding C_1-symmetric tri-*ortho*-substituted derivatives. In fact, one major drawback was found. The use of 2,2′-dibromobiphenyl gave, after dilithiation followed by treatment with $ClPPh_2$, the cyclic derivative 5-phenyl-5*H*-benzo[*b*]phosphindole (or phosphafluorene)[11] instead of the expected 2,2′-bis(diphenylphosphino)-biphenyl[12] (Scheme 2). Schlosser and co-workers reported[11b] that the formation of the phosphafluorene derivative is a major limitation in the direct synthesis of 2,2′-bis(diphenylphosphino)biphenyl starting from their dihalo precursors. They even showed that reaction of 2,2′-biphenylylenedilithium with 2 equiv of $ClPPh_2$ affords a 1:1 mixture of phosphafluorene and PPh_3. Apart from this study, very few investigations regarding the formation of phosphafluorene as side-

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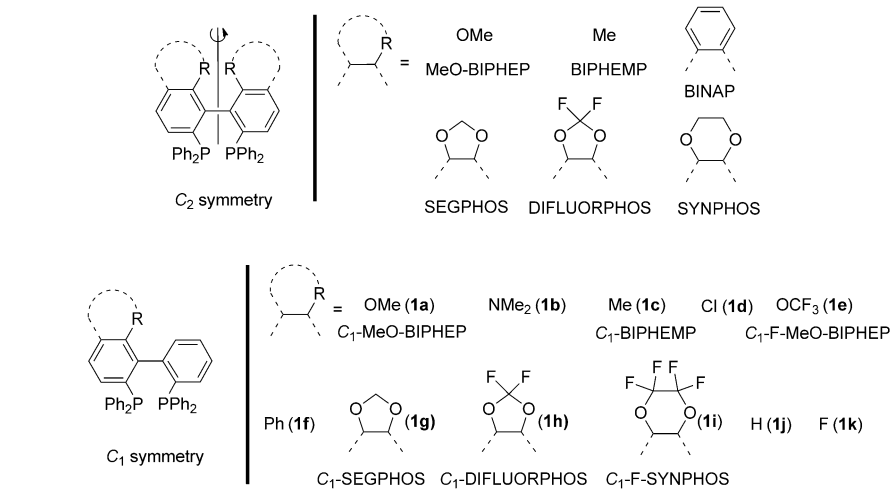
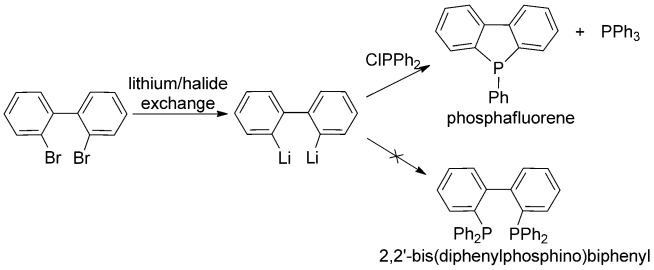


Scheme 1. Common biaryl scaffolds of the most efficient 2,2′-bis(diphenylphosphino)biphenyls ligands (top) and their C_1-symmetric targeted analogues **1a–k** (bottom).



Scheme 2. Formation of phosphafluorene instead of the expected 2,2′-bis(diphenylphosphino)biphenyl when using the classical methodology in less sterically demanding biaryls.

product have been carried out and no general approach has been developed to avoid its formation.[13]

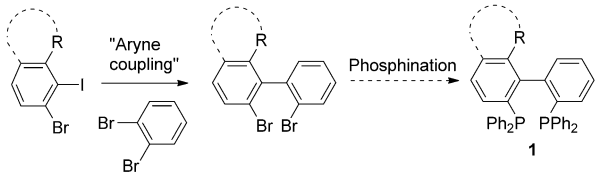
Similarly, our group has shown that an increased torsion angle between the two phenyl rings is necessary for the formation of bis(diphenylphosphino)biphenyls to prevail and, in some cases, the phosphafluorene has not been observed.[14] Continuing our research, we have reported the synthesis of the first C_1-symmetric MeO-BIPHEP analogue **1a**.[14] However, it required additional and laborious protection and deprotection of the biphenyl scaffold to avoid the undesired phosphafluorene formation.[15] In this paper we report on the first straightforward access to a whole family of C_1-symmetric tri-*ortho*-substituted bis(diphenylphosphino)biphenyls **1** in which, for the first time, the undesired formation of phosphafluorene is avoided.

Results and Discussion

For a rapid access to this ligand family, we devised the synthetic approach depicted in Scheme 3 based on the transition-metal-free "aryne" coupling reaction that we recently developed.[16] It allows the preparation of *ortho*,*ortho*′-dibromobiphenyl precursors, which can then be submitted to double phosphination reactions for which two strategies were investigated: The classical phosphination pathway, which relies on lithiation, and a new double palladium-catalyzed phosphination reaction.

Synthesis of the precursors: Substituted C_1-symmetric biaryl scaffolds were obtained by transition-metal-free "aryne" coupling in excellent yields either directly (**2d–k**) or by the functionalization of 2,2′,6-tribromobiphenyl (**3**; Scheme 4).[16d,17] We showed that the latter is an excellent turntable that allows the introduction of various *ortho* substituents like OMe (**2a**), NMe_2 (**2b**), Me (**2c**), and Ph (**2f**), which could not be obtained directly. Regioselective bromine/lithium exchange reactions can be performed on this substrate when submitted to lithiation in THF with 1 equiv of BuLi. Under these conditions only the bromine atom located in the most electronegative ring is selectively displaced.[18] Thus, 2,2′,6-tribromobiphenyl (**3**) was used as a molecular platform for the synthesis of most of the new ligands.

Lithiation pathway—solvent effects: When the *ortho*,*ortho*′-dibromobiphenyls **2** were submitted to a double halogen/lithium exchange in THF or Et_2O followed by trapping with 2 equiv of $ClPPh_2$, whatever the nature of the *ortho* substituent on the 2,2′-dilithiated biphenyl (X = Me, OMe, NMe_2, Cl, OCF_3, Ph, OCH_2O, OCF_2O, OCF_2CF_2O, H, F), the formation of phosphafluorenes was exclusively observed. This is consistent with the observation of Schlosser and co-workers.[11b] However, we anticipated that if THF was replaced by toluene, the outcome of the reaction could be modified in favor of the 2,2′-bis(diphenylphosphino)biphenyls. Indeed, it is known that aggregation plays an important role in organolithium chemistry. Coordinating ligands such as ethers can provide an alternative source of electron density for the electron-deficient lithium atoms. Ethers can stabilize aggregates by coordination to the lithium atoms and then allow organolithiums to shift to an entropically favored lower degree of aggregation.[19] For example, THF is a



Scheme 3. Synthetic approach to C_1-symmetric biaryl-based diphosphines **1**.

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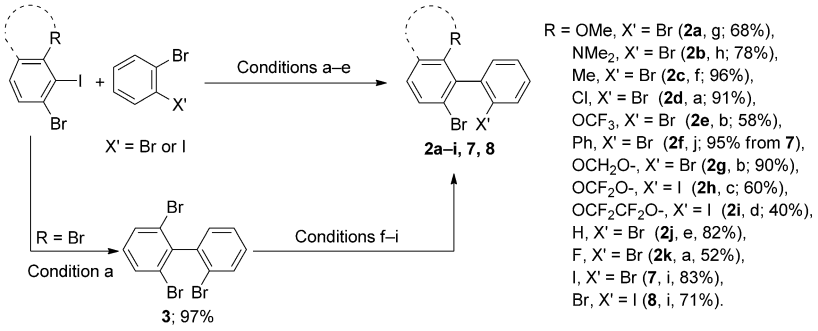


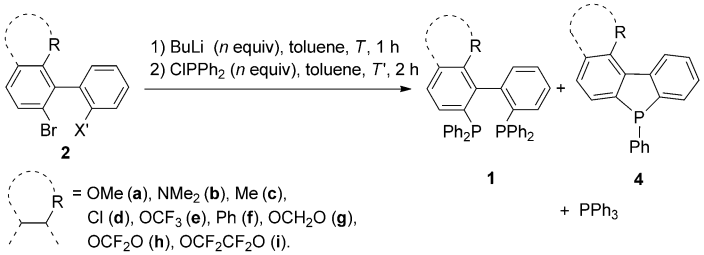
Scheme 4. Synthesis of *ortho,ortho'*-dibromobiphenyl precursors by "aryne" coupling. Reagents and conditions: (a) i. *t*BuLi (2 equiv), THF, −100 °C, 5 min then −78 °C, 1 h; ii. 1,2-dibromobenzene; (b) i. *t*BuLi (2 equiv), THF, −78 °C, 1 h; ii. 1,2-dibromobenzene; (c) i. *t*BuLi (2 equiv.), THF, −100 °C, 5 min then −78 °C, 1 h; ii. 1-iodo-2-bromobenzene; (d) i. BuLi (2 equiv), THF, −78 °C, 1 h; ii. 1-bromo-2-iodobenzene; (e) starting from 1,2-dibromobenzene with BuLi (0.5 equiv), THF, −78 °C; (f) i. BuLi (1 equiv), THF, −78 °C, 5 min; ii. MeI (96 %); (g) i. BuLi (1 equiv), THF, −78 °C, 5 min; ii. $BF(OMe)_2{\cdot}Et_2O$; iii. NaOH, H_2O_2, 0 °C; iv. K_2CO_3, MeI, acetone, 60 °C (68 %); (h) i. BuLi (1 equiv), THF, −78 °C, 5 min; ii. $PhSO_2N_3$; iii. $LiAlH_4$, Et_2O, 50 °C; iv. $NaCNBH_3$, CH_2O, AcOH, MeCN, 0 °C (78 %); (i) i. BuLi (1 equiv), THF, −78 °C, 5 min; ii. I_2, THF; (j) Na_2CO_3, $PhB(OH)_2$, $[Pd(PPh_3)_4]$, H_2O/MeCN (50:50), 90 °C, 3 h.

strong decoordinating solvent producing low degrees of aggregation, albeit with an increase in basicity and concomitantly an increase in nucleophilicity, whereas organolithiums in toluene or hydrocarbon solutions in general invariably form aggregates of hexamers or tetramers. These solvents favor the internal stabilization of lithiated species.[20]

Thus, when the reaction was performed in toluene, the formation of 2,2′-bis(diphenylphosphino)biphenyls **1** was observed together with phosphafluorenes **4** and triphenylphosphine (Table 1). The reaction conditions were chosen to ensure the complete double halogen/lithium exchange of the starting material and modification of the trapping conditions (temperature, order of addition, excess of $ClPPh_2$) had no significant influence on the ratio of diphosphine/phosphafluorene (**1**:**4**). All diphosphine ligands were stable in air and at room temperature. The low yields were due to the formation of phosphafluorenes as side-products.

In general, all the bis(diphenylphosphino)biphenyls **1** were obtained in moderate yields varying from 10 to 47 %. Nevertheless, the corresponding phosphafluorenes and triphenylphosphine were still formed. Even if these side-products could be separated from the desired diphosphine by standard chromatography on silica gel and/or by crystallization, the ring-closing reaction to yield phosphafluorenes remained a real limitation to the overall synthesis.[21] In spite of the significant progress, this result was not sufficiently satisfactory from a synthetic point of view and we decided to investigate a new approach: The palladium-catalyzed phosphination of halobiaryls.

Table 1. Reaction conditions for the synthesis of bis(diphenylphosphino)-biphenyls **1a–i**.



2	R	X′	*n* [equiv]	T[a] [°C]	T'[b] [°C]	Ratio **1**/**4**	Yield of **1** [%][c]
2a	OMe	Br	2	110	50	1.3:1.0	17
2b	NMe_2	Br	2	110	50	1.4:1.0	44
2c	Me	Br	2	110	50	1.9:1.0	30
2d	Cl	Br	2	110	50	1.4:1.0	23
2e	OCF_3	Br	2	110	50	n.d.	10
2f	Ph	Br	2	110	50	1.0:1.0	24
2g	OCH_2O	Br	2	110	50	1.6:1.0	18
2h	OCF_2O	I	3	25	25	2.7:1:0	47
2i	OCF_2CF_2O	I	3	25	25	2.0:1.0	34

[a] Metalation temperature. [b] Trapping temperature. [c] Isolated product yield of **1** after flash-chromatography on silica gel.

Palladium-catalyzed C–P cross-coupling reaction: Over the past few years, C–P coupling reactions have started to be studied but less systematically than the C–C, C–N, or C–O coupling reactions. Nevertheless, some catalytic systems have been successfully developed. Most of them allow the monophosphination of various substrates, in particular, substituted phenyl derivatives. However, double phosphination reactions have rarely been described and are performed starting from bis-triflate substrates.[10,22] Under the same reaction conditions, biphenyl and binaphthyl substrates exhibit different reactivities.[9e,10b,22d,e,23] In general, all these reactions have some critical drawbacks: 1) They have to be heated at reflux for 3 days, 2) triflate intermediates have to be accessible or otherwise have to be prepared, which requires two additional synthetic steps when starting from the dihalo precursor, and 3) they require the use of additional ligands to allow the coupling reaction. In contrast to the mono C–P coupling reactions mainly developed by Stelzer and co-workers,[24] very few double C–P coupling reactions of dihalobiphenyls have been reported so far. Murata and Buchwald reported only one example of a C–P coupling of 2,2′-dibromobiphenyl with dicyclopentylphosphine using $Pd(OAc)_2$ and DiPPF as catalyst, which afforded after 18 h the desired 2,2′-bis(dicyclopentylphosphino)biphenyl.[25] More recently, a bicyclic dibromo substrate afforded under microwave irradiation aza-BINAP-type ligands.[26]

Preliminary attempts to obtain 2,2′-bis(diphenylphosphino)biphenyls **1** from 2,2′-dibromobiphenyls and $HPPh_2$ with catalytic amounts of $Pd(OAc)_2$ failed. Irrespective of the

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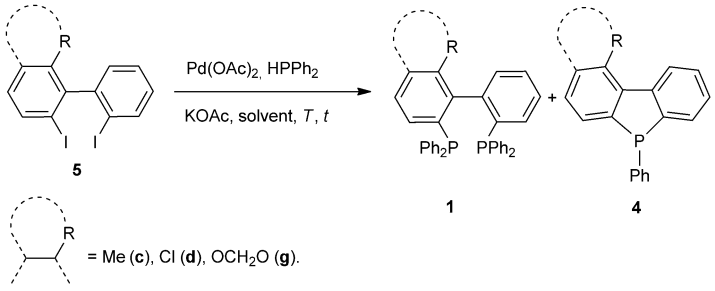
substrate used, it was all recovered. Therefore we considered the double C–P coupling reaction of the diiodo analogues. To convert the dibromobiphenyls **2a–k** and **3** into their diiodo analogues **5a–l**, they were submitted to a double Br/Li exchange in THF either with 2 equiv of BuLi (conditions a) or with 4 equiv of *t*BuLi (conditions b) followed by the addition of 2 equiv of iodine to afford most of the intermediates in very good yields (Table 2).

Inspired by the studies of Rohlík et al. on the phosphination of iodoaryl phosphonates,[27] a screening was carried out to determine the optimal phosphination conditions without addition of any external ligand. For this purpose, substrates **5c**, **5d**, and **5g** were selected as model substrates with structural and electronic diversity (Table 3). 2-Chloro-2′,6-diiodobiphenyl (**5d**) was treated with $HPPh_2$ in the presence of $Pd(OAc)_2$ and anhydrous KOAc as base in toluene, DMA (*N*,*N*-dimethylacetamide), or a mixture of toluene/DMA (13:1). In toluene, the outcome of the reaction seems to be dependent upon the amount of palladium (Table 3, entries 1–6). When the reactions were carried out with a small amount of palladium, incomplete conversion was achieved. Unexpectedly, under some conditions the corresponding phosphafluorene was formed in a non-negligible ratio relative to the corresponding diphosphine **1** (Table 3, entries 2 and 6). To the best of our knowledge, the formation of phosphafluorene side-products during catalytic phosphinations with $HPPh_2$ has never been reported. Interestingly, when DMA was used as co-solvent, the formation of phosphafluorene was avoided but the reaction was not complete even after 66 h (Table 3, entries 7–10). An increase in the amount of $Pd(OAc)_2$ had no beneficial effect when DMA was used as co-solvent or solvent. Note that attempts at phosphination at lower temperatures (50, 75, and 100 °C) did not afford the corresponding diphosphine **1**, but the starting material **5** together with some tentatively assigned monophosphine intermediates formed in the course of the reaction. Finally, at 130 °C, when only DMA was used as solvent with 2.2 equiv of KOAc, the reaction was complete after 2 h without any trace amounts of phosphafluorenes (Table 3, entry 11). The same trends were observed with 2,2′-diiodo-6-methylbiphenyl (**5c**) and 5-iodo-4-(2-iodophenyl)benzo[*d*][1,3]dioxole (**5g**; Table 3, entries 12 and 13).

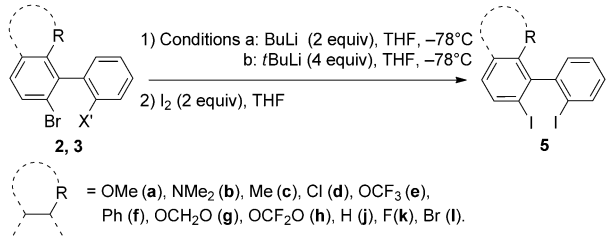
Table 3. Screening of the reaction conditions for the catalytic phosphination of model substrates **5c**, **5d**, and **5g**.



Entry	R	Solvent	*T* [°C]	KOAc [equiv]	$Pd(OAc)_2$ [mol %]	*t* [h]	**5** [%][a]	**1** [%][a]	**4** [%][a]
1	Cl	toluene	90	2.2	2	2	83	17	0
2						19	<5	77	23
3[b]		toluene	90	2.2	2	2	83	17	<5
4[b]						19	44	56	<5
5[b]						100	38	62	<5
6		toluene	90	2.2	10	20	<5	50	50
7		toluene/DMA	110	1.2	2	2	>95	<5	<5
8						18	53	47	<5
9						25	43	57	<5
10						66	27	73	<5
11		DMA	130	2.2	2	2	<5	>95	<5
12	OCH_2O	DMA	130	2.2	2	2	8	82	10
13	Me	DMA	130	2.2	2	2	<5	>95	<5

[a] Percentage determined by ^1H NMR spectra. Ratio within the limits of NMR detection. [b] $Pd(OAc)_2$ and $HPPh_2$ were mixed together in DMA before addition of reagents.

Table 2. Synthesis of 2,2′-diiodobiphenyl precursors **5**.



Substrate	R	X′	Conditions	**5**	Yield [%][a]
2a	OMe	Br	b	**5a**	71
2b	NMe_2	Br	b	**5b**	65
2c	Me	Br	b	**5c**	86
2d	Cl	Br	a	**5d**	93
2e	OCF_3	Br	b	**5e**	81
2f	Ph	Br	b	**5f**	44
2g	OCH_2O	Br	a	**5g**	91
2h	OCF_2O	I	b	**5h**	69
2j	H	Br	a	**5j**	88
2k	F	Br	b	**5k**	80
3	Br	Br	a	**5l**	72

[a] Isolated product yield after flash chromatography.

Once the optimal reaction conditions had been found, they were applied to the diiodobiaryl series **5a–l**. A large number of target ligands were efficiently obtained and in most cases the formation of phosphafluorenes was prevented (Table 4).[28]

In general, the corresponding diphosphines were obtained in good-to-excellent yields in only one step and in a very short reaction time, even with the more sensitive fluorinated diphosphines. 2,2′-Bis(diphenylphosphino)biphenyl (**1j**; R = H) was prepared in a yield of 62 %. Although this compound is not useful from a catalytic point of view, it was not possible to obtain it by lithiation and trapping with $ClPPh_2$.[11b] We also successfully prepared its fluorinated analogue **1k** in good yield (73 %). The moderate yield obtained when R = NMe_2 (**1b**) can be explained by a likely co-

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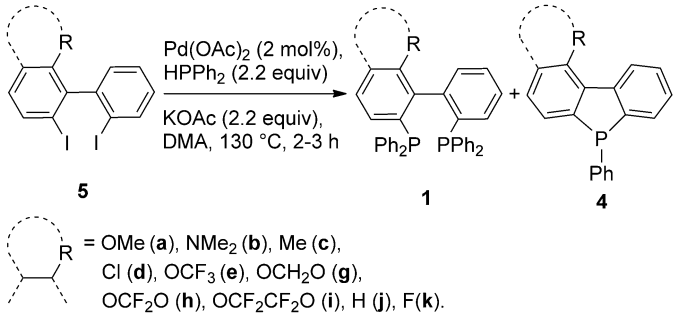
Table 4. Synthesis of 2,2′-bis(diphenylphosphino)biphenyl ligands by the catalytic C–P cross-coupling reaction under optimized conditions.



Entry	5	R	Time [h]	Ratio 1:4[a]	1	Yield of 1 [%][b]
1	**5a**	OMe	2.0	>95:5	**1a**	98
2	**5b**	NMe_2	3.0	86:14	**1b**	43
3	**5c**	Me	2.0	>95:5	**1c**	73
4	**5d**	Cl	3.0	>95:5	**1d**	95
5	**5e**	OCF_3	2.0	84:16	**1e**	53
6	**5g**	OCH_2O	3.0	88:12	**1g**	80
7	**5h**	OCF_2O	1.5	>95:5	**1h**	48
8	**5i**	H	3.0	63:37	**1j**	62
9	**5k**	F	1.5	>95:5	**1k**	73

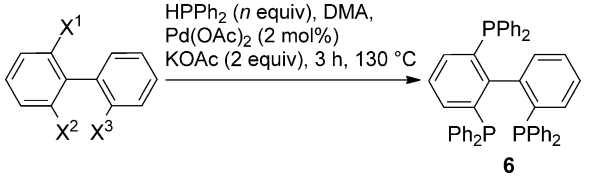
[a] Percentage determined by ^{1}H NMR spectroscopy. Ratio within the limits of NMR detection. [b] Isolated yield after flash chromatography.

ordination of the nitrogen atom to palladium, which modifies the nature of the catalytic species (Table 4, entry 2). We also noticed that *O*-alkyl-substituted derivatives are better substrates than their α-fluorinated ether analogues. In the case of R = OMe, 2,2′-bis(diphenylphosphino)biphenyl **1a** was obtained in a yield of 98% (Table 4, entry 1) compared with 53% when X = OCF_3 (**1e**; Table 4, entry 5). Similarly, the yield increased from 48% for **1h** (R = OCF_2O) to 80% for **1g** (R = OCH_2O).

To date, this is the first versatile double catalytic C–P cross-coupling protocol ever described. It allows a direct and rapid access to 2,2′-bis(diphenylphosphino)biphenyls in only one step in moderate-to-excellent yields and very short reaction times, allowing us to proceed on a gram scale. Interestingly, it did not require the addition of an external ligand. Moreover, in many cases (R = F, Cl, Me, OMe, OCF_2O), the formation of phosphafluorenes was completely avoided. When R = H, NMe_2, OCH_2O, and OCF_3, phosphafluorenes **4** were formed in only trace amounts and could be easily separated from the desired ligands **1**.

Probably one of the most interesting features of this double palladium catalytic phosphination reaction was observed when attempts were made to perform the reaction with 2-bromo-2′,6-diiodobiphenyl (**5l**; Table 5, entry 1). Surprisingly, the corresponding diphosphine was not detected at all. Instead, the triphosphine **6** was obtained in a yield of 50% (note that the biaryl was employed in excess compared with $HPPh_2$). The ^{31}P NMR spectrum of **6** displayed one doublet at $\delta = -12.5$ ppm (d, $J = 23$ Hz), which integrates for two phosphorous atoms, and a triplet at $\delta = -14.6$ ppm (d, $J = 23$ Hz), which integrates for one phosphorous atom. This suggests that a third unexpected phosphination reaction occurred at the bromide atom. Confirmation of its molecular structure was achieved by a single-crystal X-ray diffraction analysis (Figure 1). Aikawa and Mikami have used this achiral triphosphine, although its synthesis was not reported.[29]

Table 5. Synthesis of **6** starting from **5l**, **7**, **8**, or **3**.



Entry	Substrate	X^1	X^2	X^3	n [eq]	Yield of **6** [%][a]
1	**5l**	Br	I	I	2.2	50
2	**5l**	Br	I	I	3.2	91
3	**7**	I	Br	Br	3.2	88
4	**8**	Br	Br	I	3.2	79
5	**3**	Br	Br	Br	3.2	18

[a] Isolated product yield after flash chromatography.

This result encouraged us to investigate the polyphosphination reactions of polyhalobiaryls (Table 5). The triple C–P cross-coupling reaction under stoichiometric conditions afforded the corresponding triphosphine **6** in an excellent yield of 91% (Table 5, entry 2). It is interesting to note that 1) three consecutive C–P coupling reactions can be performed almost quantitatively and in one pot on the same substrate and 2) that C–P coupling with a bromo substrate is possible. Next we repeated the reaction by using the 2,2′-dibromo analogue **7** and in this case biphenyl-2,2′,6-triyltris(diphenylphosphine) (**6**) was obtained in a yield of 88% (Table 5, entry 3). We also tried to determine whether the relative position of the iodine atom on the biphenyl backbone has an influence on the outcome of the reaction. Thus, we performed the reaction with 2,6-dibromo-2′-iodobiphenyl (**8**) instead of 2,2′-dibromo-6-iodobiphenyl (**7**), but the outcome of the reaction was the same and the product was obtained once again in an excellent yield (79%; Table 5, entry 4). Finally, we wondered whether the reaction would

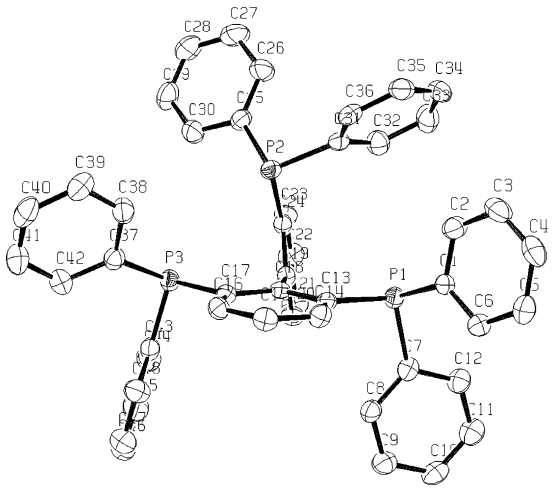


Figure 1. Molecular structure of compound **6** in the solid state.

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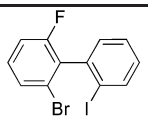
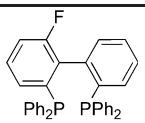
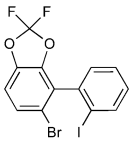
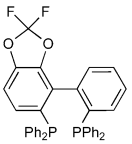
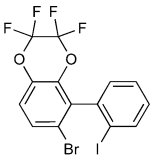
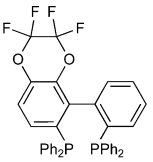
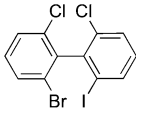
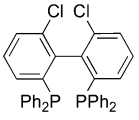
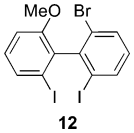
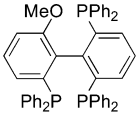
be as efficient in the absence of any iodine atoms as it is with the iodo substrates. Thus, the triple phosphination was performed on 2,2′,6-tribromobiphenyl (**3**), which yielded the triphosphine **6**, but in a lower yield (Table 5, entry 5).

Irrespective of the substrate employed, the crude reaction mixture was extremely clean and revealed only one product. In general, C–P coupling reactions on these substrates were extremely rapid. After 45 min, the trihalobiphenyls were consumed and biphenyl-2,2′,6-triyltris(diphenylphosphine) (**6**) was exclusively formed. This suggests that autocatalysis may be responsible for the rate and efficiency of the reaction. It may also be assumed that the limiting step of the overall process is the first C–P coupling reaction. Indeed, when the first phosphine is introduced on to the biphenyl backbone, it can favor palladium insertion into the other C–X bonds (X = Br or I) on its skeleton. This could explain the absence of side-products such as the mono- and/or diphosphines. For instance, when we applied the reaction conditions to the dibromo precursor **2d** (R = Cl), even after 12 h no coupling product was observed. This means that the presence of at least one iodine atom is necessary to start the cascade phosphination and to guarantee the formation of the polyphosphinated biaryl in good yield.

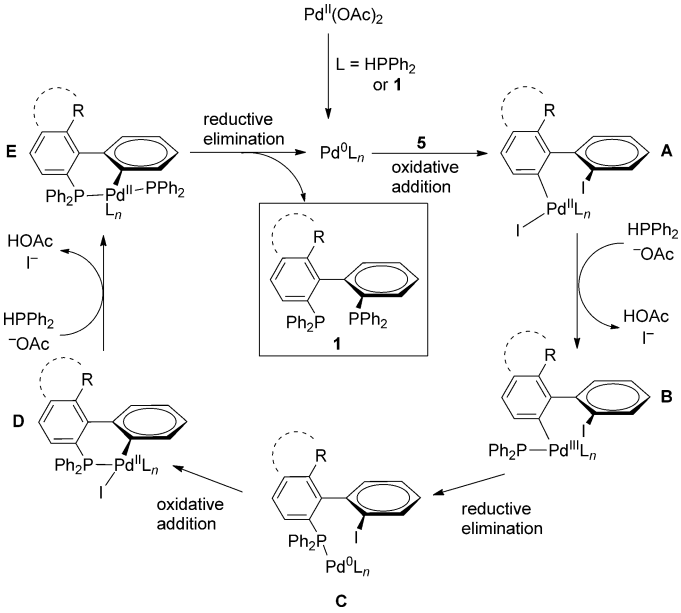
We then extended our study to other 2-bromo-2′-iodobiaryls. Starting with **9**, diphosphine **1k** was obtained in good yield (70%; Table 6, entry 1), similar to the yield obtained starting from the 2,2′-diiodo analogue **5k** (Table 4, entry 9). Thus, complete iodination of the substrate is not necessary. The synthesis of 2,2′-bis(diphenylphosphino)biphenyl **1h** from its diiodo precursor in a yield of 48% has already been described (Table 4, entry 7). The yield surprisingly increased to 72% starting from 5-bromo-2,2-difluoro-4-(2-iodophenyl)benzo[*d*][1,3]dioxole (**2h**; Table 6, entry 2). The tetrafluorinated ligand **1i** was also obtained in this way in a yield of 47% (Table 6, entry 3). To study the limits of our system, we studied the double phosphination of more sterically hindered substrates. The reaction conditions were successfully applied to tetra-*ortho*-substituted biaryls like 2-bromo-6,6′-dichloro-2′-iodobiphenyl (**10**), which afforded the corresponding diphosphine **11** in an excellent yield of 80% (Table 6, entry 4). Even a triple phosphination was efficiently performed with a global yield of 67% starting from 2,2′,6,6′-tetrasubstituted biphenyl **12** (Table 6, entry 5).

Table 6. Extension of the method to various 2-bromo-2′-iodobiaryls.[a]

Entry	Substrate	Product	Yield [%][b]
1	 **9**	 **1k**	70
2	 **2h**	 **1h**	72
3	 **2i**	 **1i**	47
4	 **10**	 **11**	80
5	 **12**	 **13**	67[c]

[a] Reaction conditions: $Pd(OAc)_2$ (2 mol%), $HPPh_2$ (2.2 equiv), KOAc (2.2 equiv), DMA, 130°C, 3 h. [b] Isolated yield after flash chromatography. [c] Reaction conditions: $HPPh_2$ (3 equiv) and KOAc (3 equiv).

Suggested mechanism for the catalytic phosphination: A similar mechanism to those studied and described by Buchwald,[30] Hartwig,[31] and Barluenga[32] and their co-workers for C_{sp2}–N coupling[33] can be formulated for the present double C–P cross-coupling reaction (Scheme 5). The first step is the formation of a catalytic species involving Pd^0. After oxidative addition of the iodobiaryl (intermediate **A**), $HPPh_2$ might coordinate the metal center prior to its deprotonation by KOAc to give intermediate **B** ($pK_a(HPPh_2/^-PPh_2) = 22$; $pK_a(HOAc/^-OAc) \approx pK_a(KOAc/^-OAc) = 4$).[34] Reductive elimination leads to the formation of the first monophosphine, which remains coordinated to Pd^0 (intermediate **C**) and which can intramolecularly assist the second oxidative addition to give intermediate **D**. A second coordination/deprotonation sequence



Scheme 5. Proposed mechanism for the catalytic double phosphination reaction.

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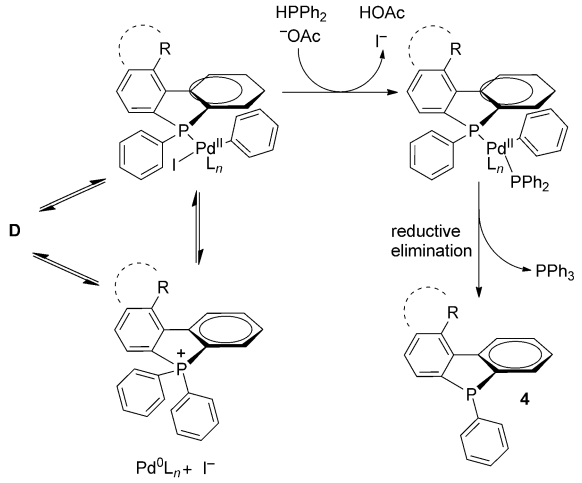
of $HPPh_2$ gives intermediate **E**. Then the last reductive elimination leads to the formation of the 2,2′-bis(diphenylphosphino)biphenyl **1** with regeneration of the Pd^0 catalytic species (Scheme 5).

The trace amounts of phosphafluorenes formed can be explained by an exchange of the aryl groups bonded to the coordinated phosphine in intermediate **D**. After aryl migration, reductive elimination gives PPh_3, which was detected in the crude reaction mixture by ^{31}P NMR spectroscopy. According to Cheng and Kong, this kind of aryl exchange occurs in $[Pd(PPh_3)_2(C_6H_4\text{-}p\text{-}CH_3)I]$.[35] Marcuccio and co-workers have also observed an aryl migration in Suzuki–Miyaura coupling reactions[36] and Chenard and co-workers reported similar observations in Stille coupling reactions.[37] In addition, such a Pd–aryl/P–aryl exchange has been observed in numerous processes[38] like Heck reactions,[39] aminations,[40] amidations,[41] ketone α-arylations,[42] cyanations,[43] and C–S coupling reactions.[44] Kwong and Chan even used this exchange as the key step in the catalytic monophosphination of biaryl triflates with PPh_3 to obtain the PYPHOS ligands.[45] On the other hand, several studies[35,46] have shown that this exchange is an equilibrium process between different palladium species and that is controlled by the steric and electronic profiles of the coordinated ligands (Scheme 6). These authors proved that the migration is favored by electron-donor substituents. This is in agreement with our observations that phosphafluorenes are mainly formed when $R = OCF_3$, NMe_2, and OCH_2O. On the other hand, Kong[35] noticed that additional amounts of ligand prevent this migration. In our case, the ligand is $HPPh_2$ itself and/or the diphosphine **1** obtained, which is in excess (2 equiv) relative to the palladium species. This could explain why the phosphafluorene **4** is formed only as a minor product in comparison with the 2,2′-bis(diphenylphosphino)biphenyl **1**.



Scheme 6. Pd–aryl/P–aryl exchange.

Conclusion

In this work we have shown how a new class of C_1-symmetric bis(diphenylphosphino)biphenyl ligands can be prepared starting from a few common precursors obtained by a transition-metal-free "aryne" coupling reaction. The difficulties previously encountered in synthesizing these kinds of ligands, that is, an undesired intramolecular cyclization of a transient 2-diphenyphosphanyl-2′-biphenylyllithium to yield a phosphafluorene, has been overcome to a certain extent by a solvent effect on the lithiation/trapping sequence to afford the desired diphosphine as the major product.

As an alternative, the C–P cross-coupling reactions were performed on a series of 2,2′-diiodobiaryls and some 2-bromo-2′-iodobiaryls under the optimized conditions. This catalytic system turns out to be a direct and rapid route to 2,2′-bis(diphenylphosphino)biphenyls giving moderate-to-excellent yields without the addition of any ligand. To the best of our knowledge this is the first versatile external-ligand-free C–P coupling reaction of dihalobiaryls. It is an extremely fast double C–P cross-coupling reaction relative to the C–P coupling reactions starting from bis(triflates) that have been described in the literature. In particular, the reaction time was in general reduced from 3 days to 3 h. Interestingly, the formation of phosphafluorenes was avoided in most cases. When X = H (**1j**), NMe_2 (**1b**), OCH_2O (**1g**), and OCF_3 (**1e**), it was only observed as a minor product and could be easily separated chromatographically from the desired diphosphine. The formation of this side-product was a priori completely unexpected under palladium-catalyzed conditions but can be explained by aryl migration. The double palladium-catalyzed phosphination reaction is perfectly reproducible and allows the preparation of ligands in multi-gram quantities. We also applied the same reaction conditions to more challenging substrates and proved that it was possible to perform up to three coupling reactions on the same polyhalogenated substrate and to obtain the corresponding polyphosphines in very good yields.

Overall, the methodology presented in this study allows new pathways to be considered for the synthesis of more sophisticated diphosphines based on C_1- or C_2-symmetric biaryl scaffolds. The direct synthesis of enantiomerically pure C_1-symmetric biaryl-based diphosphines is currently under investigation, as well as the introduction of chirality at the phosphorus atom.

Experimental Section

Full experimental details are given in the Supporting Information.

General description for the catalytic C–P coupling protocol towards bis-(diphenylphosphines): An oven-dried Schlenk tube was evacuated and refilled with argon. Potassium acetate (2.20 mmol, 0.22 g, 2.2 equiv), diiodobiaryl (1.00 mmol, 1 equiv), and diphenylphosphine (2.20 mmol, 0.41 g, 0.38 mL, 2.2 equiv) were added to a solution of *N*,*N*-dimethylacetamide (9.00 mL) and then a solution of *N*,*N*-dimethylacetamide (1.00 mL) containing palladium acetate (1.50 mg, 2 mol %) was added. The solution turned red and was immediately placed in an oil bath at 130 °C. Once the

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reaction had finished the reaction mixture was allowed to cool down to room temperature. Water (40 mL) was added and the aqueous phase was extracted with dichloromethane (3×50.0 mL). The combined organic layers were dried over sodium sulfate. Evaporation of the solvent followed by column chromatography on silica gel with cyclohexane/ethyl acetate (19:1) afforded the corresponding bis(diphenylphosphino)biphenyls.

X-ray crystallographic data for 6: Single crystals of **6** were obtained by slow diffusion of pentane into a dichloromethane solution of the compound. $C_{48}H_{37}P_3$, $M_r = 706.69$, orthorhombic, $P2_12_12_1$, $a = 12.8102(2)$, $b = 13.0470(3)$, $c = 22.5088(6)$ Å, $V = 3762.00(14)$ Å^3, $Z = 4$, $D_x = 1.248$ Mg m^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $\mu = 0.192$ cm^{-1}, $F(000) = 1480$, $T = 173$ K. The sample (0.25×0.22×0.20 mm) was studied on a Kappa CCD diffractometer with graphite-monochromatized $Mo_{K\alpha}$ radiation. The structure was solved with SIR-97,[47] which revealed the locations of the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms were found by performing a Fourier difference analysis. The whole structure was refined with SHELX-97[48] and full-matrix least-square techniques (use of F^2 magnitude; x, y, z, β_{ij} for carbon and phosphorus atoms, x, y, z in the riding mode for hydrogen atoms; 460 variables and 8415 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(F_o^2) + (0.0807P)^2]$ for which $P = (F_o^2 + 2F_o^2)/3$ with the resulting $R = 0.0442$, $R_w = 0.1405$, and $S_w = 1.078$; $\Delta\rho < 0.345$ e Å^{-3}. Flack parameter: 0.09(8).

CCDC-823921 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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