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Synthesis of hydroxylated oligoarene-type phosphines by a repetitive two-step method

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ABSTRACT

Hydroxylated oligoarene-type phosphines with various substitution patterns were synthesized. Such phosphines have potential as ligands for transition metal-catalyzed reactions. A successful route, which includes a repetitive Suzuki–Miyaura coupling–triflation sequence, reduction, and salt formation, was established starting from 2-bromophenyldicyclohexylphosphine oxide. Other key aspects of the method are the use of suitable triflation reagents and the formation of phosphines as HBF_4 salts. Interesting information was obtained from careful analysis of the byproducts in the triflation and reduction steps, and the mechanisms for their formation were proposed.

1. Introduction

Phosphines comprise one of the most important families of ligands for transition metals in various catalytic reactions because they bind strongly with transition metals and offer control of catalytic activity by altering the electronic and steric properties of the metal catalysts. The design and synthesis of useful new phosphines are important in the development of new types of synthetic reaction.

We recently developed hydroxylated oligoarene-type phosphines (HOPs, Fig. 1a) as ligands for transition metals.[1] HOPs are composed of an oligoarene backbone with a phosphino group at one end and a hydroxy group at the other.[2] The phosphino moiety was designed based on biphenylphosphines developed by Buchwald et al.[3] The hydroxy group was expected to function as an assisting group in catalytic reactions in which HOP is used as a metal ligand. For example, a metal oxido group (M^2-O in Fig. 1b), formed from the hydroxy group, could bind a substrate molecule through a functional group (Y), placing the reactive group (X) close to the catalytic transition metal (M^1) coordinated by the phosphino group, which should lead to acceleration of the catalytic reaction. The preparation of HOPs with various oligoarene lengths and substitution patterns was expected to afford a ligand library in which HOPs suitable for specific reactions could be found. After screening of the HOP library for palladium-catalyzed cross-coupling with Grignard reagents, we found that one of the HOPs exhibited high *ortho*-selectivity in cross-coupling of dihalogenated phenols or anilines.[4]

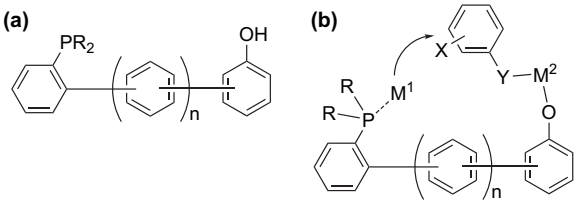
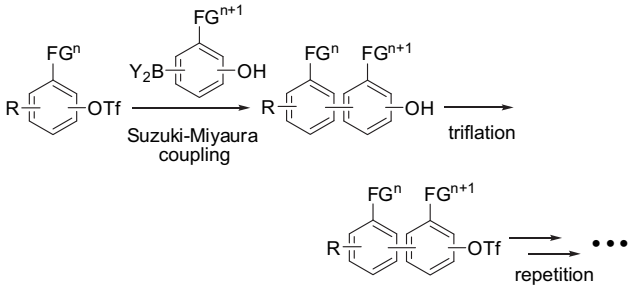


Figure 1. (a) HOP. (b) Expected intermediate of reactions using HOPs.

In order to synthesize HOPs, we planned synthetic routes based on a repetitive two-step method we recently developed for oligoarene synthesis.[5] This method involved a sequence of Suzuki–Miyaura coupling[6] and triflation using a hydroxyphenylboronic acid or its pinacol ester as a monomer (Scheme 1). The use of various monomers allows easy construction of oligoarene libraries.



Scheme 1. Repetitive two-step method for the synthesis of oligoarenes. Y_2B: $(HO)_2B$ or the corresponding pinacol ester.

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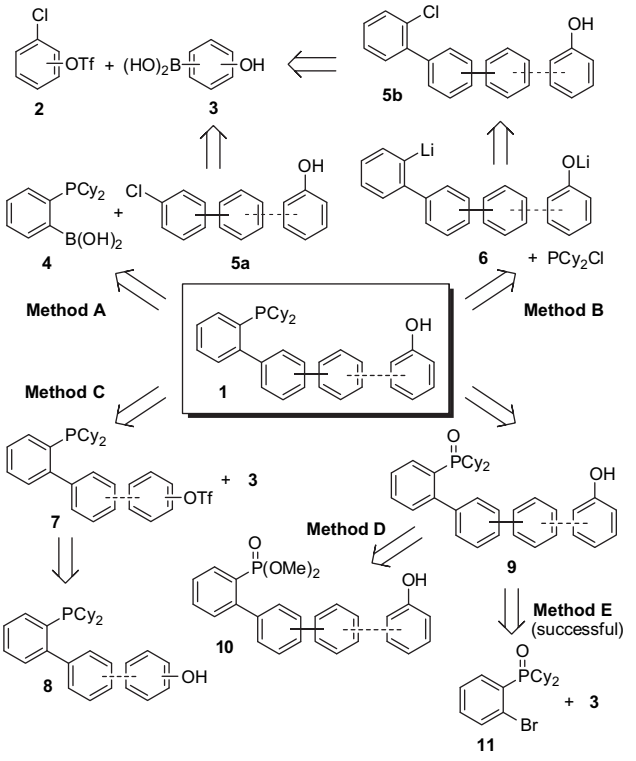
Our plan for HOP synthesis is outlined in Scheme 2. We first set molecules (**1**) having a dicyclohexylphosphino group (PCy_2) as synthetic targets because this group encourages the formation of active species in some types of transition metal-catalyzed reaction thanks to its electronic and steric properties.[7,8] The synthesis of a series of dialkylbiarylphosphine ligands had been already reported by Buchwald et al.[3] They are typically synthesized by the reaction of an aryl metal reagent with benzyne followed by treatment with dialkylchlorophosphane. In our study, however, we decided to develop another method because the need to introduce a hydroxy group and a variety of oligoaryl structures limits the application of this method.



Scheme 2. Possible routes for the synthesis of HOPs.

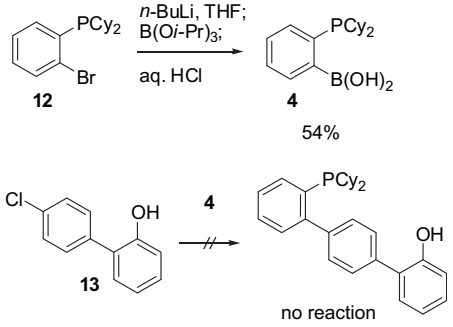
Method A and Method B involved routes in which the phosphino group was introduced in the last step to avoid complexity in the byproducts due to decomposition of the phosphino group during the reaction or purification process. We envisaged hydroxylated chloro-oligoarenes **5a** or **5b** as the precursors because we expected they would be readily available by the repetitive two-step method through chemoselective cross-coupling of OTf groups in the presence of a chloro group[9] starting from **2** (see Supplementary data). There were other precursor candidates, such as hydroxylated bromo-oligoarenes; however, the preparation of such molecules by the repetitive two-step method was expected to be more difficult and to require additional steps. The direction of oligoaryl chain elongation from the head (a benzene ring containing a chloro group) to the tail (a benzene ring with a hydroxy group) was expected to be more suitable for the production of ligand libraries than the opposite direction because a common intermediate could be utilized in the synthesis of a series of related structures. In Method C, we planned to utilize a strategy in which the phosphino group was introduced from the beginning and to apply the repetitive two-step method directly to triflates with a phosphino group, such as **7** with hydroxyphenylboronic acid (**3**) as the monomer unit. Methods D and E employed a strategy in which the phosphino group was protected as a phosphinyl group due to its stability toward oxygen and triflation. Method D involved the conversion of a dimethyl phosphonate into a dicyclohexylphosphine oxide by treatment with cyclohexyl Grignard reagent.[10] Method E, which was found to be the optimum route, utilized the phosphinyl group from the beginning.[11] Herein, we discuss the reasons for the difficulties with the unsuccessful routes and describe how these problems were overcome to establish the synthetic route for the HOP library through Method E.

2. Results and discussion

2.1. Method A

We attempted a synthetic route in which the $PCy_2C_6H_4$ unit was introduced in the final step using boronic acid **4** coupled with oligoaryl chloride **5a** (Method A, Scheme 2). Oligoaryl chloride **5a** would be synthesized by the repetitive two-step method using conditions reported by us[5b] (see Supplementary data).

Using **13** as a model substrate for the final stage of the HOP synthesis, we investigated the cross-coupling with **4**, which was synthesized through Br–Li exchange of the known compound **12**[12] with *n*-BuLi followed by borylation (Scheme 3). $B(Oi\text{-}Pr)_3$ was found to be better than $B(OMe)_3$ as a boron source as it avoided diarylation of the boron atom.[13] Product **4** was isolated as an air-stable solid. For the cross-coupling with **13**, several attempts were made using various conditions, including those previously reported by us.[5a] However, the desired product was not obtained, even at high temperatures or using other solvents (see Supplementary data). Other conditions,[3c,9] which had been reported to be efficient in constructing sterically demanding biaryl compounds also failed. Therefore, this route was finally abandoned.



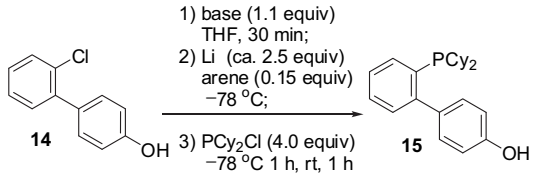
Scheme 3. Suzuki–Miyaura coupling of **13** with phosphinated boronic acid **4**.

2.2. Method B

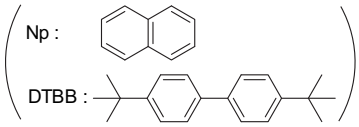
Another possibility for exploiting oligoaryl chlorides was the phosphination of lithiated compound **6** in the final step via lithiation of **5b** with Li metal[14] (Method B, Scheme 2).

To optimize the reaction conditions for the final step, we used a model 2-chlorobiphenyl containing a hydroxy group (**14**). Representative results are shown in Table 1. The phenolic hydroxy group of **14** must be deprotonated prior to the lithiation; in this regard, *n*-BuLi gave better results than NaH. In investigating electron carriers for the lithiation with Li metal, di-*tert*-butylbiphenyl (DTBB) gave better results than naphthalene. However, the desired product **15** was obtained only in ca. 30% yield. In addition, this strategy was unsatisfactory because the main byproducts formed by protonation of the lithiated intermediate were not easy to remove by silica gel column chromatography. Judging from these results, we decided to try other routes.

Table 1
Phosphination via lithiation with Li metal



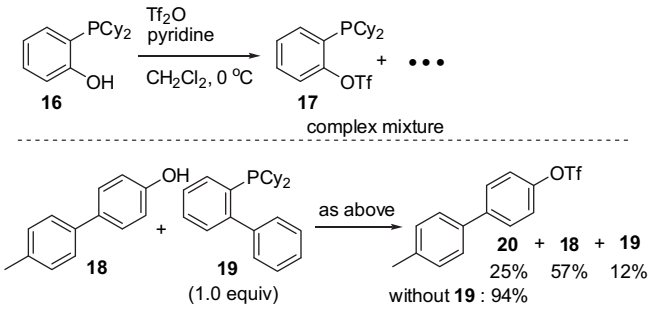
Entry	1) Deprotonation	2) Lithiation	Yield
1	NaH, rt	Np, 5 h	0%
2	NaH, rt	DTBB, 30 min	<6%
3	*n*-BuLi, 0 °C	DTBB, 30 min	<33%



2.3. Method C

The synthesis of hydroxylated oligoarene-type phosphines **1** was to be accomplished by the repetitive two-step method through the reaction of triflate **7** and hydroxyphenylboronic acid **3** (Method C, Scheme 2).

We first investigated whether triflation of a hydroxy group proceeded effectively in the presence of a phosphino group. As a model, triflation of **16**, which was synthesized according to the literature,[15] was attempted under conventional conditions (Scheme 4). However, the reaction was very complicated, and the desired compound **17** could not be isolated. To determine the reason for this failure, the effect of the presence of biphenylphosphine **19**[16] was examined in the triflation of biphenol **18**. The reaction produced **20** in low yield with recovery of the starting material **18** and a smaller amount of **19**, while triflation proceeded in high yield in the absence of **19**. These results indicated that the PCy_2 group of **19** consumed Tf_2O, and **19** itself decomposed in the reaction. To make matters worse, the PCy_2 group was gradually oxidized under air,[17] which meant that purification of intermediates was tedious. From these results we learned that the synthesis would be difficult as long as the PCy_2 group was used without a protecting group.

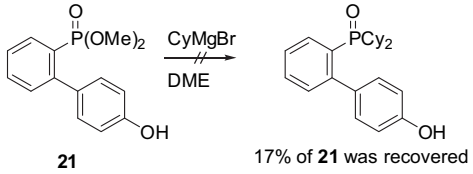


Scheme 4. Triflation of **16** or **18**.

2.4. Method D

We then designed a new route via phosphine oxide **9**, whose phosphorus atom is protected as an air-stable phosphinyl group (Methods D and E, Scheme 2). Phosphine oxide **9** may be synthesized either from phosphonate **10** or by oligoaryl chain elongation from a starting compound such as **11**. In Method D, we envisaged that a variety of substituents could be introduced onto the phosphorus atom in the final step if a dimethyl oligoarylphosphonate **10** was synthesized as a common intermediate and treated with various alkyl or aryl metal reagents. As the conversion of a dimethyl biarylphosphonate into a diphenylbiarylphosphine oxide by treatment with phenylmagnesium bromide had been reported by Buchwald et al.,[10] this scheme was considered a promising approach.

To test the feasibility of the final step, model compound **21** was subjected to a reaction with CyMgBr (Scheme 5). However, the desired compound was not obtained, and a crude NMR showed that most of the starting compound had decomposed. This failure was probably due to the steric hindrance by the cyclohexyl groups. Thus, Method D was concluded to be inappropriate for the HOP synthesis.



Scheme 5. Reaction of phosphonate with Grignard reagent.

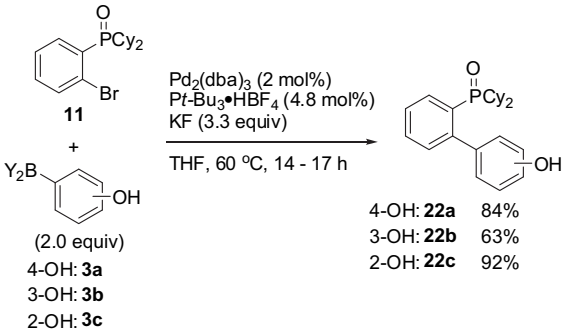
2.5. Method E

Method E utilized phosphine oxide **11** as a starting compound for oligoaryl chain elongation (Scheme 2). Various oligoaryl structures were expected to be constructed through the repetitive two-step method if the Suzuki–Miyaura coupling of **11** with a hydroxyphenylboronic acid proceeded. The *ortho* position of the phosphino group, which was nucleophilic in Method A, was electrophilic in this method. Generally, when conducting biaryl synthesis by Suzuki–Miyaura coupling, it is preferred that a bulky group is placed on the electrophilic side.[6] Thus, Suzuki–Miyaura coupling of **11** in Method E was expected to be more facile than that of **4** in Method A. After the synthesis of the oligoaryl chain, the desired products (**1**) were to be obtained by reduction of the phosphinyl group. This synthetic route was expected to be superior in terms of ease of operation, because the difference in the polarity between the desired phosphine and the starting phosphine oxide was expected to be sufficiently large to allow separation by silica gel column chromatography.

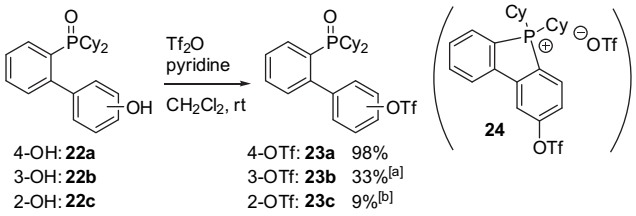
2.5.1. Suzuki–Miyaura coupling of (2-bromophenyl)dicyclohexylphosphine oxide with hydroxyphenylboronic acids. We first examined the key Suzuki–Miyaura coupling. The starting compound **11** was prepared by simple oxidation of **12** with H_2O_2. After optimizing the reaction conditions (see Supplementary data), we found that the reaction of **11** with hydroxyphenylboronic acids **3a**–**3c**[18] proceeded in high yield when P*t*-Bu_3 was used as a ligand for palladium, as reported by Fu et al.[9] (Scheme 6). The pure products were easily obtained by recrystallization or simple collecting of the solid formed after quenching, followed by washing with water and Et_2O. Under the optimized conditions, the reactions of all isomers with **3a**–**3c** to give **22a**–**22c** proceeded successfully. The reaction of the corresponding chloro compound, instead of bromo compound **11**, with hydroxyphenylboronic acid **3a** also proceeded, albeit in slightly lower yield (see Supplementary data).

2.5.2. Triflation. Next, we examined the triflation, which is another key reaction in the repetitive two-step method. The results showed that the yield depended on the position of the hydroxy group (Scheme 7). The reaction of **22a**, which had a hydroxy group on the 4-position, gave **23a** in high yield under general conditions using Tf_2O and pyridine; in contrast, the reaction of **22b** or **22c**, with a hydroxy group at the 3- or 2-position, gave a low yield even with

excess Tf_2O. In the reaction of **22b**, only a small amount of the starting material was recovered, while a significant amount of byproduct **24**, whose benzene rings were bridged by a phosphorus atom to form a five-membered ring,[19] was obtained. In contrast, in the reaction of **22c**, most of the starting material was recovered.

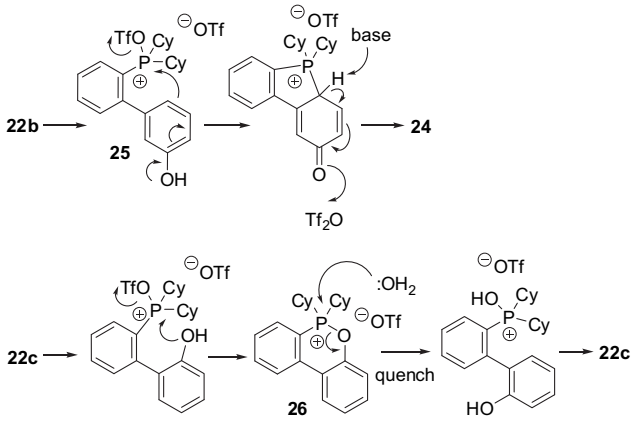


Scheme 6. Suzuki–Miyaura coupling of **11** with hydroxyphenylboronic acids. Y_2B: $(HO)_2B$ or anhydride form.



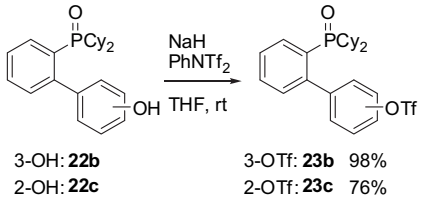
Scheme 7. Triflation of phosphinyl biphenol using Tf_2O. (a) 35% of the byproduct **24** was obtained. (b) 78% of the starting material was recovered.

The mechanism of formation of byproduct **24** allowed us to understand the positional dependence of the yield. The oxygen atom of the phosphinyl group may first react with Tf_2O to generate intermediate **25**. The formation of the five-membered ring of **24** is likely to occur via intramolecular electrophilic aromatic substitution with the phosphorus atom at the 6-position, enhanced by electron-pushing from the hydroxy group at the 3-position (Scheme 8). In the case of **22c**, on the other hand, the hydroxy group on the 2-position directly attacks the phosphorus atom to form the intermediate **26**, which contains a six-membered ring, and this is quenched by water to give the starting material (Scheme 8).



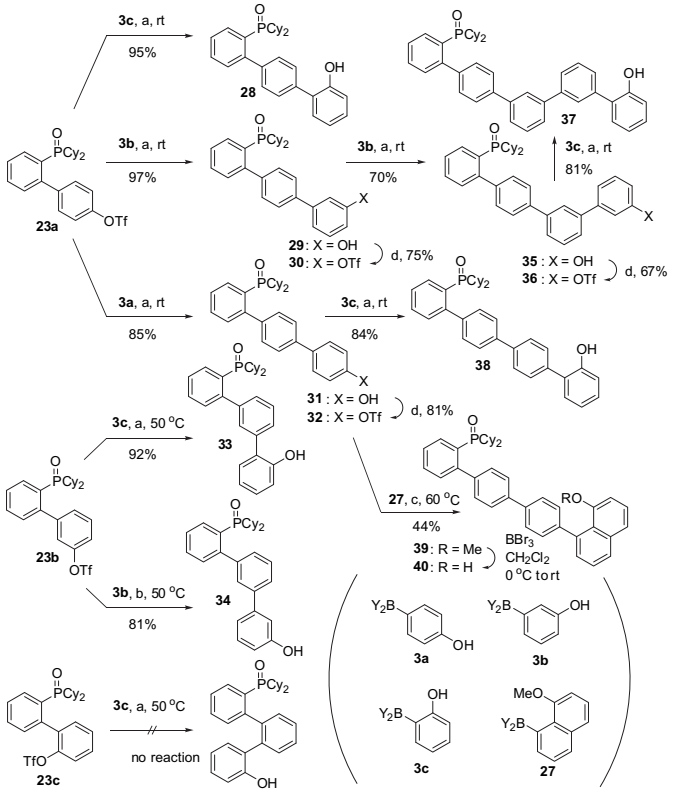
Scheme 8. Possible mechanisms for the formation of byproducts.

To improve the triflation step, other conditions were investigated. To our delight, a combination of NaH and $PhNTf_2$[20] was found to be successful, and the yields of **23b** and **23c** were improved dramatically (Scheme 9).



Scheme 9. Improvement of the triflation.

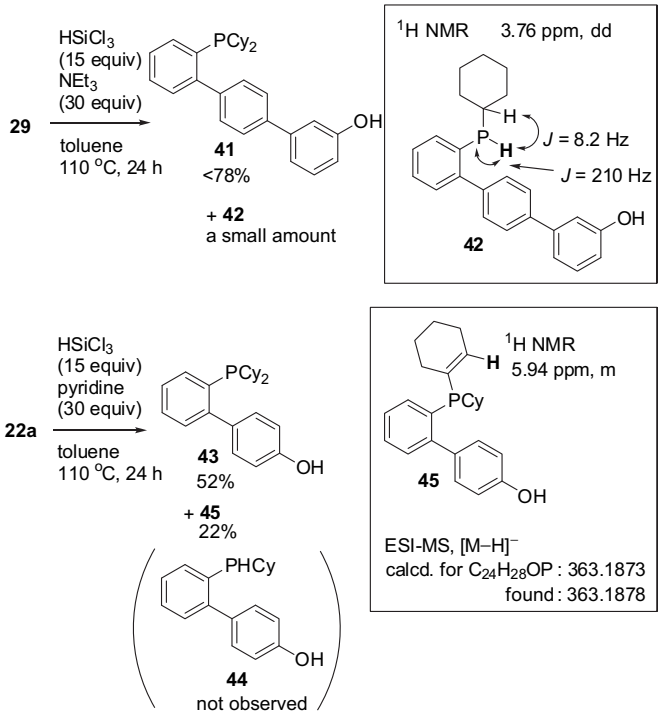
2.5.3. Elongation of the oligoaryl chain. Using the triflates thus obtained, elongation of the oligoaryl chain was next explored by applying the repetitive two-step method (Scheme 10). All steps proceeded well under conditions previously reported by us,[5a] with the exception of the failure for **23c** probably due to severe steric hindrance. The route allowed the construction of various substitution patterns. To introduce a hydroxynaphthyl group, boronic acid **27**[21] whose hydroxy group was protected as a methyl ether, was used, and thus a deprotection step with BBr_3 was carried out. For the Suzuki–Miyaura coupling of **23b** with **3b**, 2,6-dimethoxy-2′-dicyclohexylphosphinobiphenyl (S-PHOS)[3c] was used instead of 2,4,6-triisopropyl-2′-dicyclohexylphosphinobiphenyl (X-PHOS)[22] as a ligand for palladium, because the byproduct derived from X-PHOS was found difficult to separate from the desired product.



Scheme 10. Elongation of the oligoaryl chain by the repetitive two-step method. Conditions: (a) $Pd(OAc)_2$, X-PHOS, KF, THF/H_2O (4/1); (b) $Pd(OAc)_2$, S-PHOS, KF, THF/H_2O (4/1); (c) $Pd(OAc)_2$, X-PHOS, KF, THF; (d) Tf_2O, pyridine, CH_2Cl_2. Y_2B: $(HO)_2B$ for **3a** and **27**, anhydride form for **3b** and **3c**.[18]

2.5.4. Reduction of phosphinyl group. The final reduction step was explored under conventional conditions using $HSiCl_3$. Triethylamine or pyridine was used as a base in the reaction. Although the reactions themselves proceeded smoothly, the desired products were unexpectedly obtained as mixtures with small amounts of

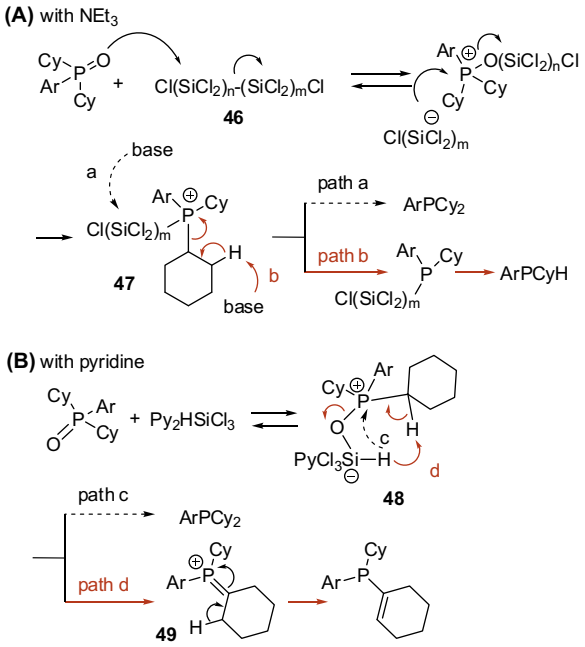
byproducts that were difficult to separate. ^{1}H NMR analysis indicated that the byproducts varied depending on the base used. In the reduction of **29** to give **41** in the presence of triethylamine, for example (Scheme 11), a doublet of doublets with a large coupling constant (210 Hz) was observed at 3.76 ppm; this is a typical value of a proton on a phosphorus atom.[23] This indicated that the byproduct lacked one cyclohexyl group as shown for **42**. Similar signals were observed after the reduction of other phosphine oxides such as **22a** and **28**. However, byproduct **44** was not observed in the reduction of **22a** to **43**, when pyridine was used as a base (Scheme 11). Instead, a characteristic multiplet derived from another byproduct was observed at 5.94 ppm in the NMR analysis. The structure of this byproduct, also confirmed by ESI-MS, was identified as **45**, which features a cyclohexenyl group on the phosphorus atom.



Scheme 11. Reduction of phosphinyl group using $HSiCl_3$ and NEt_3 or pyridine.

The mechanism of formation of these byproducts was assumed to be as shown in Scheme 12 based on the previously reported reduction mechanism of a phosphine oxide by $HSiCl_3$.[24] In the presence of triethylamine, the phosphine oxide reacted with perchloropolysilane **46** generated from $HSiCl_3$, and the perchloropolysilyl anion attacked the phosphorus atom with elimination of a perchloropolysilanol (Scheme 12A). The desired product was obtained if the base attacked the silicon atom in intermediate **47** (path a), while the byproduct lacking a cyclohexyl group was formed when the base deprotonated the β-hydrogen with elimination of cyclohexene (path b). On the other hand, pyridine formed a silicate like **48** (Scheme 12B). The desired product was obtained if the hydride attacked the phosphorus atom in intramolecular fashion (path c), while the byproduct containing a cyclohexenyl group was formed via **49** when the hydride deprotonated the α-hydrogen (path d).

In both cases, the desired products were difficult to purify by silica gel chromatography; moreover, the phosphino group was gradually oxidized under air during chromatography. To solve these problems, we decided to prepare HBF_4 salts to protect the phosphino group. Phosphine–HBF_4 salts are known to be stable to oxygen, to be easily treatable, and to release a free phosphine under basic conditions, as reported by Fu et al.[25]

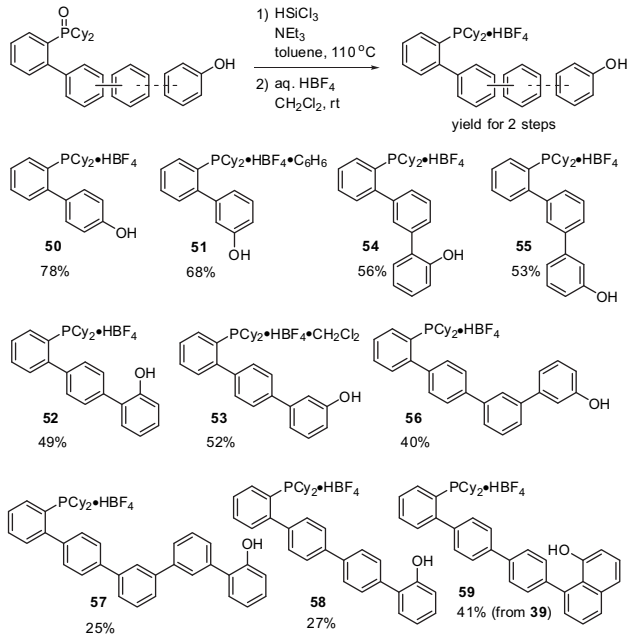


Scheme 12. Possible mechanisms of formation of byproducts.

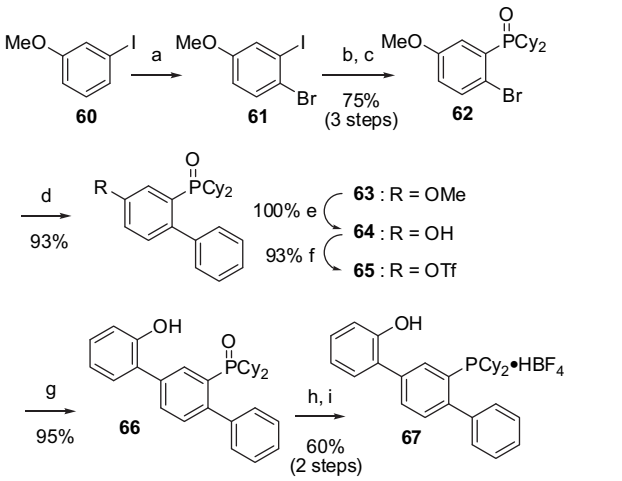
2.5.5. Salt formation of phosphines and completion of the synthesis. This method was applied to oligoarene-type phosphines (Scheme 13). After reduction with $HSiCl_3$ and NEt_3, the crude mixture was passed through a short silica gel column to remove a small amount of oxide and inorganic salts. The mixture of the desired product and a byproduct lacking one cyclohexyl group was dissolved in CH_2Cl_2 and treated with aqueous HBF_4, and the solution was stirred at rt for 15 min. The crude product was obtained after separation of the CH_2Cl_2 layer from water, followed by concentration. The crystallizing nature of most phosphines increased after salt formation, and isolation of the desired product by recrystallization was found to be possible for **50**, **51**, **52**, **53**, **58**, and **59**. Compounds **51** and **53** were obtained as crystals containing a solvent molecule. The use of gel permeation chromatography (GPC) was effective for **54**, **55**, **56**, and **57**, which were difficult to crystallize. Whereas HBF_4 salts were stable in $CDCl_3$, which was used for NMR analysis, they underwent gradual decomposition on the column during purification by GPC using $CHCl_3$ as a solvent. As a shorter retention time was required to suppress oxidation, collection of the pure fractions resulted only in lower yields. The structures of the final compounds were confirmed by elemental analysis.

2.6. Elongation by addition of an aryl chain to the phosphine-containing ring

Elongation by addition of an oligoaryl chain to the phosphine-containing ring of 2-dicyclohexylbiphenylphosphine was also possible; the key was methoxy group manipulation.[26] An example is shown in Scheme 14. The dicyclohexylphosphinylbiphenyl moiety was constructed by phosphination of **61**[27] prepared by bromination of **60**, oxidation with H_2O_2, and Suzuki–Miyaura coupling of **62**. Deprotection of the product (**63**) with BBr_3 and triflation afforded **64** and **65**, respectively, in excellent yields. Suzuki–Miyaura coupling of triflate **65** proceeded successfully, and reduction of **66** followed by salt formation gave phosphine **67** efficiently.



Scheme 13. Completion of ligand synthesis.



Scheme 14. Synthesis of **67**. Reagents and conditions: (a) Br_2, AcOH; (b) $Pd(OAc)_2$, 1,1′-bis(diisopropylphosphino)ferrocene, Cs_2CO_3, $HPCy_2$, 1,4-dioxane; (c) H_2O_2, CH_2Cl_2; (d) $Pd_2(dba)_3$, P*t*-$Bu_3\cdot HBF_4$, KF, $PhB(OH)_2$, THF; (e) BBr_3, CH_2Cl_2; (f) Tf_2O, pyridine, CH_2Cl_2; (g) **3c**, $Pd(OAc)_2$, X-PHOS, KF, THF/H_2O (4/1); (h) $HSiCl_3$, NEt_3, toluene; (i) aq HBF_4, CH_2Cl_2.

3. Conclusions

An efficient method for the synthesis of various hydroxylated oligoarene-type phosphines was established by applying a repetitive two-step procedure. The presence of a PCy_2 group rendered the synthesis of oligoarenes difficult due to its bulkiness and instability. Protection of the phosphorus atom as its oxide and salt formation with HBF_4 were the keys to overcoming the problems with the reaction and purification procedures. Unique mechanisms of formation of byproducts were suggested in the triflation and reduction steps, and the proper choice of the reagents was found to improve the yield and enable isolation. We hope these studies contribute not only to the synthetic study of oligoarene-type phosphines, but also to the development of new types of catalyst based on the oligoarene strategy.

4. Experimental section

4.1. Compound 22a: Suzuki–Miyaura coupling of 11 with 3a

2-Bromophenyldicyclohexylphosphine oxide **11** (3.72 g, 10.1 mmol), **3a** (2.78 g, 20.1 mmol), KF (1.93 g, 33.2 mmol), $Pd_2(dba)_3$ (184 mg, 0.201 mmol), and P*t*-$Bu_3\cdot HBF_4$ (140 mg, 0.483 mmol) were placed in a flask, and then evacuated and backfilled with argon. THF (20 mL) was added at rt, and the whole was then stirred at 60 °C for 17 h. The mixture was diluted with water and the resulting white precipitates were collected on a sintered glass funnel. Recrystallization from CH_2Cl_2/MeOH gave the desired product (**22a**) as a white solid in 84% yield (2 crops, 3.23 g). Mp 322.3–327.0 (dec) °C; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$=10/1) δ 0.97–1.79 (22H, m), 6.81 (2H, d, J=8.8 Hz), 6.95 (2H, d, J=8.8 Hz), 7.13–7.16 (1H, m), 7.38–7.45 (2H, m), 7.86–7.94 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$=10/1) δ 25.47, 26.11–26.27 (not resolved), 37.76 (d, J=66.1 Hz), 114.68, 126.99 (d, J=9.8 Hz), 129.06 (d, J=82.6 Hz), 129.75, 130.76 (d, J=3.2 Hz), 131.56 (d, J=9.9 Hz), 132.66 (d, J=3.3 Hz), 133.32 (d, J=6.6 Hz), 143.90 (d, J=8.2 Hz), 156.85 ppm; ^{31}P NMR (202 MHz, $CDCl_3/CD_3OD$=10/1) δ 52.63 ppm; IR (ATR) 3053, 2918, 2850, 1448, 1282, 1130, 839, 764 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{32}O_2P$ ($[M+H]^+$) 383.2134; found: 383.2152; Anal. Calcd for $C_{24}H_{31}O_2P$: C, 75.37; H, 8.17, found: C, 75.42; H, 8.05%.

4.2. Compound 23a: triflation of 22a

To a suspension of **22a** (1.40 g, 3.66 mmol) and pyridine (0.74 mL, 9.15 mmol) in CH_2Cl_2 (3.66 mL) was added trifluoromethanesulfonic anhydride (1.23 mL, 7.32 mmol) over 1 min at 0 °C, and the whole was then stirred at rt for 1 h. After the addition of HCl aqueous solution (10%, 30 mL), the product was extracted with EtOAc (40 mL). The organic layer was washed with water (20 mL×2) and brine (20 mL) successively, dried over Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane=1/2 to 4/1) gave the desired product (**23a**) as a white solid in 98% yield (1.84 g). Mp 117.3–120.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06–1.87 (22H, m), 7.22–7.25 (1H, m), 7.30 (2H, d, J=8.8 Hz), 7.35 (2H, d, J=8.8 Hz), 7.48–7.55 (2H, m), 7.81–7.86 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.61, 25.66, 26.02 (d, J=3.3 Hz), 26.29 (d, J=13.3 Hz), 26.42 (d, J=13.2 Hz), 37.58 (d, J=66.1 Hz), 118.73 (q, J=320.5 Hz), 120.29, 127.55 (d, J=9.9 Hz), 129.26 (d, J=79.3 Hz), 130.64 (d, J=3.3 Hz), 131.00, 131.57 (d, J=8.3 Hz), 132.64 (d, J=8.2 Hz), 142.21, 144.02 (d, J=6.6 Hz), 148.91 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ 48.19 ppm; IR (ATR) 2927, 2856, 1402, 1207, 1138, 872 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{31}F_3O_4PS$ ($[M+H]^+$) 515.1627; found: 515.1649; Anal. Calcd for $C_{25}H_{30}F_3O_4PS$: C, 58.36; H, 5.88, found: C, 58.34; H, 5.90%.

4.3. Compound 23b: triflation of 22b

To a suspension of NaH (60%, 133 mg, 3.33 mmol) in THF (27.7 mL) under argon was carefully added **22b** (1.06 g, 2.77 mmol) at rt and the whole was then stirred at rt for 30 min. After cooling to 0 °C, $PhNTf_2$ (1.19 g, 3.33 mmol) was added, and the whole was then stirred at rt for 1 h. The mixture was diluted with EtOAc (100 mL), and the organic layer was washed with water (25 mL) and brine (25 mL) successively, dried over Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane=1/1) gave the desired product (**23b**) as a white solid in 98% yield (1.40 g). Mp 136.5–138.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.88 (22H, m), 7.17 (1H, t, J=1.8 Hz), 7.21–7.24 (1H, m), 7.28–7.34 (2H, m), 7.48 (1H, t, J=7.8 Hz), 7.50–7.53 (2H, m), 7.83–7.88 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.63, 25.71 (d, J=3.3 Hz), 26.06 (d, J=3.3 Hz), 26.24 (d, J=13.2 Hz), 26.32 (d, J=13.3 Hz), 37.49 (d, J=66.1 Hz), 118.69 (q, J=320.5 Hz), 120.19, 121.97, 127.74 (d, J=11.5 Hz), 129.18,

129.32 (d, J=79.2 Hz), 129.65, 130.69, 131.55 (d, J=8.2 Hz), 132.84 (d, J=8.3 Hz), 143.46 (d, J=6.6 Hz), 144.42, 148.49 ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ 48.08 ppm; IR (ATR) 2929, 2856, 1417, 1198, 1146, 904, 814, 764 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{31}F_3O_4PS$ ($[M+H]^+$) 515.1627; found: 515.1643; Anal. Calcd for $C_{25}H_{30}F_3O_4PS$: C, 58.36; H, 5.88, found: C, 58.38; H, 5.95%.

4.4. Compound 28: Suzuki–Miyaura coupling of 23a with 3c

Triflate **23a** (713 mg, 1.39 mmol), **3c** (216 mg, 1.80 mmol), KF (266 mg, 4.57 mmol), $Pd(OAc)_2$ (6.1 mg, 0.0277 mmol), and X-PHOS (15.9 mg, 0.0333 mmol) were placed in a flask, and then evacuated and backfilled with argon. A THF/H_2O (4/1) solution (1.39 mL) was added at rt, and the whole was then stirred at rt for 13 h. The mixture was diluted with water (10 mL), and the product was extracted with EtOAc (20 mL) and CH_2Cl_2 (20 mL×2). The combined organic layers were dried over Na_2SO_4 and concentrated. Recrystallization from hexane/CH_2Cl_2/MeOH and purification of the mother liquid by column chromatography (silica gel, chloroform/MeOH=30/1) gave the desired product (**28**) as a white solid in 95% yield (603 mg). Mp 261.8–265.0 (dec) °C; ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD=10/1) δ 1.09–1.84 (22H, m), 6.89 (1H, t, J=7.6 Hz), 6.94 (1H, d, J=7.6 Hz), 7.15–7.28 (3H, m), 7.20 (2H, d, J=8.0 Hz), 7.41–7.50 (2H, m), 7.49 (2H, d, J=8.0 Hz), 7.67 (1H, dd, J=7.6, 10.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD=10/1) δ 25.52, 25.53, 25.86 (d, J=3.3 Hz), 26.20 (d, J=11.5 Hz), 26.25 (d, J=11.5 Hz), 37.30 (d, J=67.7 Hz), 116.46, 119.77, 126.94 (d, J=9.8 Hz), 127.88 (d, J=82.6 Hz), 128.12, 128.37, 128.70, 130.23, 130.69, 131.62 (d, J=8.2 Hz), 131.74 (d, J=8.2 Hz), 137.78, 139.92, 139.94, 146.17 (d, J=6.6 Hz), 153.91 ppm; ^{31}P NMR (202 MHz, $CDCl_3$/CD_3OD=10/1) δ 51.43 ppm; IR (ATR) 3064, 2931, 2854, 1446, 1132, 750 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{34}O_2P$ ($[M-H]^-$) 457.2302; found: 457.2305; Anal. Calcd for $C_{30}H_{35}O_2P$: C, 78.57; H, 7.69, found: C, 78.55; H, 7.72%.

4.5. Compound 52: reduction of 28 and salt formation with HBF_4

To a toluene (10.0 mL) suspension of **28** (306 mg, 0.668 mmol) in a sealed tube filled with argon were added NEt_3 (2.79 mL, 20.0 mmol) and $HSiCl_3$ (1.01 mL, 10.0 mmol) at −78 °C, and the whole was then stirred at 0 °C for 30 min, then at 110 °C for 24 h. After cooling to rt, a saturated aqueous $NaHCO_3$ solution and MeOH were added, and the mixture was filtered through Celite and washed with EtOAc and MeOH. The phases were separated and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexane=1/5) gave the reduced product. The product was then dissolved in CH_2Cl_2 (7.92 mL), and to the solution was added HBF_4 aqueous solution (42 wt %, 0.56 mL). The whole was stirred at rt for 15 min, and then diluted with CH_2Cl_2. The phases were separated and the organic layer was dried over $MgSO_4$ and concentrated. Recrystallization from hexane/CH_2Cl_2 gave colorless block containing CH_2Cl_2 molecules. The blocks were dissolved in MeOH, then concentrated, and dried in vacuo at 100 °C. The desired product **52** was obtained as a white solid in 49% yield (174 mg). Mp 111.4–138.7 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.18–1.47 (10H, m), 1.70–1.89 (10H, m), 2.72–2.81 (2H, m), 6.91–6.95 (2H, m), 7.20 (1H, dt, J=1.2, 7.6 Hz), 7.33 (2H, d, J=8.2 Hz), 7.32–7.34 (1H, m), 7.65 (1H, dd, J=4.6, 7.6 Hz), 7.75 (2H, d, J=8.2 Hz), 7.74–7.78 (1H, m), 7.89 (1H, t, J=7.6 Hz), 7.99 (1H, dd, J=7.6, 12.2 Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 26.16, 26.78 (d, J=14.9 Hz), 26.78 (d, J=14.9 Hz), 27.76 (d, J=3.3 Hz), 28.63, 30.33 (d, J=41.1 Hz), 116.97, 121.12, 128.56, 130.07 (d, J=13.2 Hz), 130.19, 130.30, 131.12, 131.55, 133.25 (d, J=8.2 Hz), 134.61 (d, J=9.9 Hz), 135.75, 137.94 (d, J=4.9 Hz), 141.41, 150.51 (d, J=6.6 Hz), 155.51 ppm (one carbon signal (C–P) was not observed due to broadening); ^{31}P NMR (162 MHz, CD_3OD) δ 17.12 (br t, J=67 Hz (P–D)) ppm; IR (ATR) 3406, 2935, 2854, 1448, 1061, 1005, 768 cm^{-1}; HRMS (ESI) m/z calcd for $C_{30}H_{34}OP$ ($[M-H]^-$) 441.2353; found: 441.2350; Anal. Calcd for $C_{30}H_{36}BF_4OP$: C, 67.94; H, 6.84, found: C, 67.90; H, 6.93%.

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Supplementary data

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