Oligoarenes as molecular backbones of catalysts: synthesis and applications

Kei Manabe* and Shunpei Ishikawa

Received (in Cambridge, UK) 8th May 2008, Accepted 30th May 2008
First published as an Advance Article on the web 4th July 2008
DOI: 10.1039/b807779g

This *feature article* highlights our recent work on oligoarene-type catalysts. We developed a synthetic method for multifunctionalized oligoarenes using a repetitive two-step strategy. The method was then applied to the preparation of oligoarene-type phosphines, which were used for palladium-catalyzed cross-coupling of halobenzenes with Grignard reagents.

Introduction

Oligoarenes, which are oligomers composed of aromatic rings such as benzene rings connected through a single bond (Fig. 1), constitute an important class of organic compounds.[1] They are widely used as molecular backbones in various research areas such as molecular electronics,[2] self-assembling molecules,[3] biologically active compounds,[4] and enzyme mimics.[5]

We have been interested in the use of functionalized oligoarenes as catalysts, because oligoarenes are attractive candidates for molecular backbones of bifunctional or multifunctional catalysts.[6] To create catalysts based on oligoarene structures, it is crucial to develop facile synthetic methods which can be applied to the synthesis of various types of multifunctionalized oligoarenes. In this *feature article*, we describe reported examples of synthetic methods for functionalized oligoarenes and our recent work on applications of oligoarene-type catalysts to selective synthetic reactions.

Concept of oligoarene-type catalysts

Before describing the synthetic methods for oligoarenes, we will first discuss the concept of oligoarene-type catalysts in this section.

Manabe Initiative Research Unit, RIKEN, Hirosawa, Wako 351-0198, Japan. Fax: +81-48-462-4662; Tel: +81-48-467-9394. E-mail: keimanabe@riken.jp

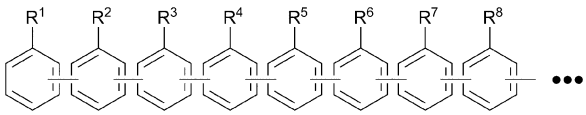


Fig. 1 Oligoarene.

Catalysis is a powerful tool in organic synthesis, and many efficient and practical catalysts have been created. Recently, the development of bifunctional or multifunctional catalysts has been an emerging and important field of synthetic chemistry.[7] These types of catalysts enable rate acceleration *via* multiple activation of substrate molecules or *via* substrate binding into a binding site. High chemo-, site-, and stereoselectivities can also be achieved. In designing such bifunctional catalysts it is essential to use molecular backbones that allow for precise positioning of various functional groups. In addition, creation of structural diversity is also a key aspect in the design of catalysts that are applicable to various types of reactions and substrates.

Peptides are promising candidates as molecular backbones for such catalysts.[8] The presence of intramolecular hydrogen bonding enables relatively easy prediction of conformation, and various combinations of amino acid monomer units easily generate structural diversity. Although there are many successful examples of peptide catalysts, peptide backbones themselves have certain limitations in terms of their usefulness as catalysts for various types of synthetic reactions. For

Kei Manabe

Kei Manabe completed his doctoral work in 1993 at the University of Tokyo. After working as a postdoctoral fellow at Columbia University, USA, he returned to the University of Tokyo and worked as an Assistant Professor, Lecturer, and Associate Professor. He joined RIKEN in 2005 where he is currently an Initiative Research Scientist.

Shunpei Ishikawa

Shunpei Ishikawa earned his BS degree in 2002 and MS degree in 2004 at the University of Tokyo. In 2005, he began his career as a researcher at RIKEN with Dr Kei Manabe.

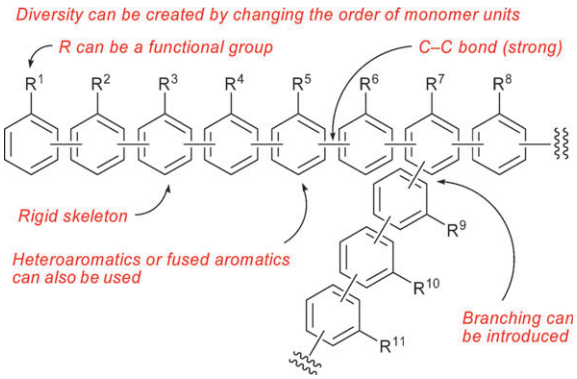
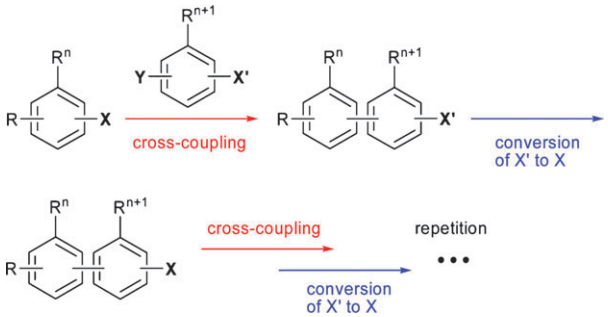


Fig. 2 Features of oligoarenes.



Scheme 1 Stepwise, repetitive synthesis of oligoarenes. X and Y are functional groups needed for cross-coupling, while X′ is untouched in the cross-coupling step.

example, amide N–H groups in the peptide backbone are incompatible with strong bases due to their acidic nature, and the amide C–N bond is susceptible to cleavage. Lewis basicity of carbonyl groups may interfere with Lewis acid catalysis. Because of these drawbacks, we considered alternative molecular systems for catalyst backbones.

Oligoarenes are an attractive candidate. They have several features that meet the requirements for the catalyst backbone (Fig. 2): (1) oligoarenes are composed of interconnected monomer units such as substituted benzene rings, and variation of the monomer units and the combination order leads to structural and functional diversity; (2) various aromatics, including heteroaromatics and fused aromatics, can be used as the monomer components, providing further diversity; (3) several functional groups can be introduced in a single monomer unit, and branching of the oligomeric chain is also possible; (4) the molecular skeleton contains no protic groups such as an amide N–H, which is found in peptides; (5) the C–C single bonds that connect two aromatic rings are strong and remain stable under various conditions; (6) the monomer skeleton consists of rigid aromatic rings, which makes it easier to design and predict the three-dimensional structures of the molecules, while rotation around the single bonds still gives some flexibility to the molecule; (7) oligomeric chains can be prepared *via* stepwise repetitive synthesis, which easily creates molecular diversity and generates molecules large enough to install many functional groups.[9]

Based on the ideas mentioned above, we began research on developing oligoarene-type catalysts. In order to use the oligoarene structure as a molecular backbone for catalysts, the development of an efficient synthetic procedure for multifunctionalized oligoarenes is crucial. While the synthetic procedure has yet to be established, several interesting methods have been reported to date. In the next section, we summarize the methods of oligoarene synthesis reported by other groups and ours.

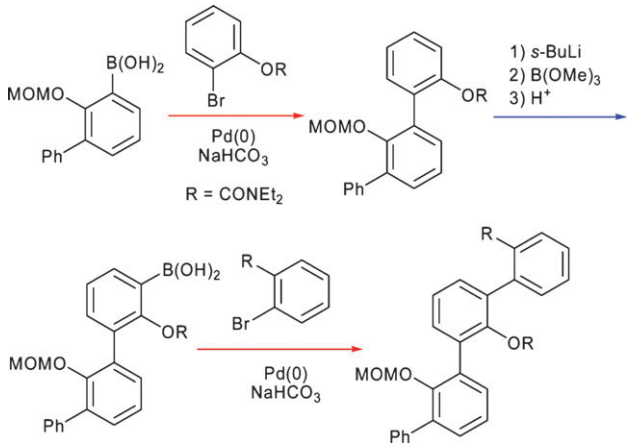
Synthesis of oligoarenes

The most reliable and efficient method to synthesize multifunctionalized oligoarenes should be stepwise elongation of oligoarene chains by repetitive addition of each monomer unit. Merely by changing the order of addition of each monomer unit, various oligoarenes could be easily prepared. The method is similar to the established method of polypeptide synthesis in which a coupling (amide bond formation with N-protected amino acids)–deprotection sequence is repeated. The C–C bond between two aromatics in oligoarenes is expected to be constructed by cross-coupling, which is one of the most extensively investigated reactions catalyzed by transition metals.[10] In fact, multiple cross-coupling plays a key role in the synthesis of polyarenes, which are mixtures of polymers with different molecular weights.[1b,c] For example, the Pd-catalyzed reaction of 4-bromophenylboronic acid produced polyarenes with up to 100 repeat units.[11] To synthesize monodisperse oligoarenes with high structural homogeneity and with various functional groups on specific aromatic rings, however, it is necessary to suppress polymerization in each cross-coupling step. In the literature there are some examples of stepwise elongation of oligoarene chains by repeating cross-coupling reactions that ensure the formation of only one C–C bond in each cross-coupling step, producing pure oligoarenes with high efficiency. The common feature of these examples is shown in Scheme 1. Although some of the previous examples were applied to oligoarenes with alkyl substituents only, some other methods, including ours, can be applied to multifunctionalized oligoarenes.

In this section, we focus on synthetic methods for oligoarenes with benzene rings as monomer units. Representative examples are shown below. Although there are several examples of repetitive synthesis of oligothiophenes,[12] they are not described here. It should also be noted that stepwise, repetitive methods have been successfully used in the synthesis of oligo(phenylene ethynylene)s.[1a,13]

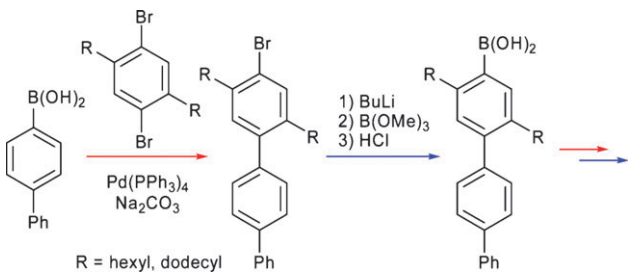
A repetitive method was reported by Cheng and Snieckus for oligoarene synthesis using Suzuki–Miyaura coupling[14] as the C–C bond-forming step (Scheme 2).[15] The use of directed *ortho*-metalation is a key aspect in preparing boronic acids in this synthetic sequence. The resulting boronic acid can be used for the next cross-coupling step to elongate the oligoarene chain. Thus, a repetitive sequence of Suzuki–Miyaura coupling and boronic acid formation produces oligoarenes. Directing groups such as –OMOM (MOM = methoxymethyl), $-OCONEt_2$, and $-CONEt_2$ are required for directed *ortho*-metalation.

Galda and Rehahn also reported oligoarene synthesis based on repetitive Suzuki–Miyaura coupling.[16] A Br–Li exchange reaction, rather than directed *ortho*-metalation, was used in



Scheme 2 Repetitive synthesis of oligoarene (Cheng and Snieckus).[15]

the boronic acid formation step (Scheme 3). Using this method, they obtained *para*-connected oligoarenes with up to 15 benzene rings. A drawback of this method was that a large excess of dibromoarene was required in the Suzuki–Miyaura coupling step to obtain the desired products in high yield. Simpkins *et al.* also reported a similar method for oligoarene synthesis.[17]

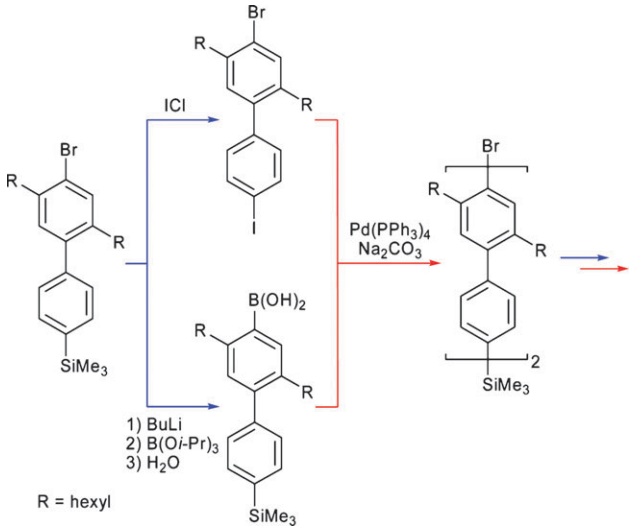


Scheme 3 Repetitive synthesis of oligoarenes (Galda and Rehahn).[16]

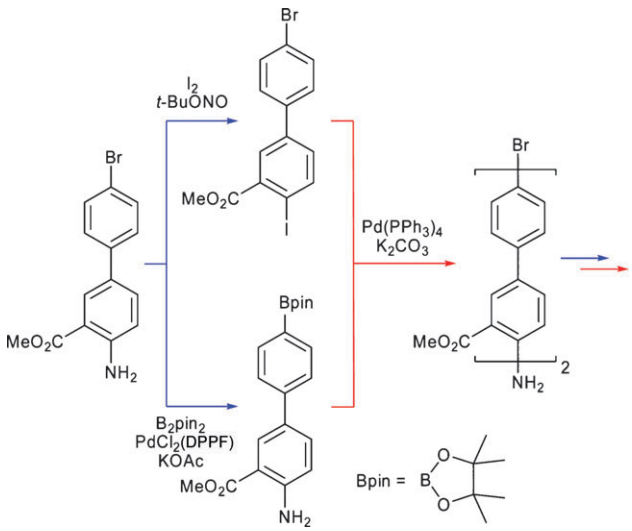
Hensel and Schlüter *et al.* used bromo-iodoarenes in their oligoarene synthesis based on iterative Suzuki–Miyaura coupling (Scheme 4).[18] The use of a large excess of dibromoarene as in the example of Scheme 3 can be avoided by employing the bromo-iodoarenes, in which the iodo group reacts preferentially in the cross-coupling step. Furthermore, the iodo group was readily prepared from a trimethylsilyl group by the action of iodine monochloride. Thus, the common intermediate bromo-trimethylsilylarene could be converted to both the corresponding boronic acid and the bromo-iodoarene, and these were coupled in the Suzuki–Miyaura coupling step. This efficient method for chain elongation is known as the iterative divergent–convergent approach.[1a,13]

Strongin *et al.* reported another iterative divergent–convergent method (Scheme 5).[19] The amino group in this substrate could be converted to an iodo group, and the bromo group to a boryl group by Pd-catalyzed borylation, which avoids the need for a strong nucleophile such as butyllithium.

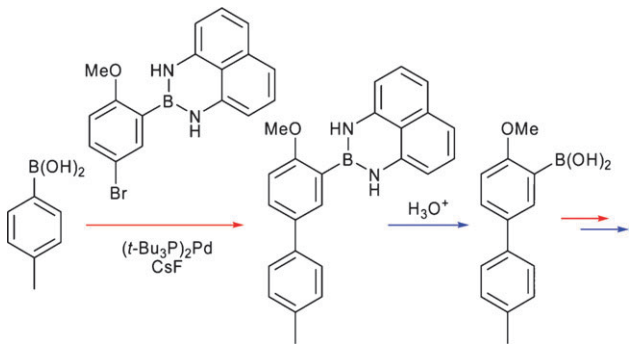
Suginome *et al.* reported a boron-masking strategy for repetitive Suzuki–Miyaura coupling to synthesize oligoarenes (Scheme 6).[20] They used bromoarylboronic acids in which the boronic acid moiety was deactivated with 1,8-diaminonaphthalene. These ''masked'' bromoarylboronic acids were



Scheme 4 Iterative divergent–convergent approach for oligoarene synthesis (Hensel and Schlüter *et al.*).[18]

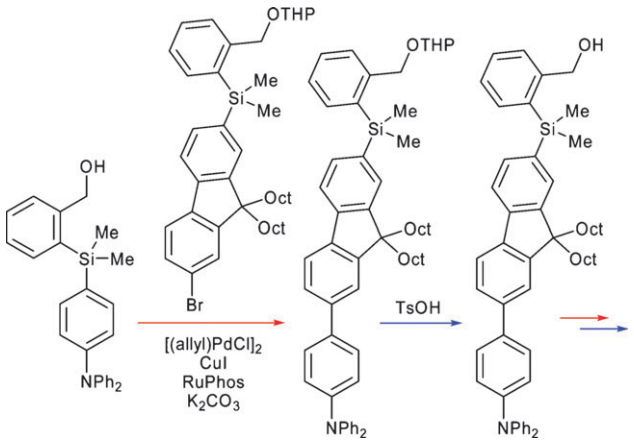


Scheme 5 Iterative divergent–convergent approach for oligoarene synthesis (Strongin *et al.*).[19] DPPF = 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 6 Boron-masking strategy for repetitive Suzuki–Miyaura coupling (Suginome *et al.*).[20]

used for Suzuki–Miyaura coupling with another ''unmasked'' boronic acid. The masked boryl group was then unmasked by acid treatment to liberate the boryl group [$B(OH)_2$] which was



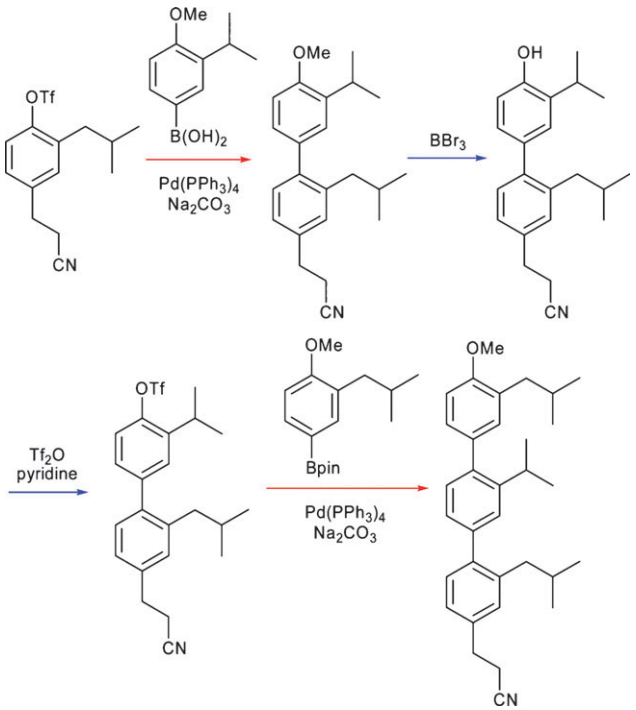
Scheme 7 Oligoarene synthesis based on repetitive Hiyama coupling (Nakao and Hiyama *et al.*).[22] RuPhos represents 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl.

used in the next cross-coupling step. The masked boronic acids were stable and purified by recrystallization or even by silica gel chromatography. For the unmasking process, 2 N aq. H_2SO_4 or 5 N aq. HCl was required. Another boron-masking strategy was reported by Gillis and Burke.[21] In their method, *N*-methyliminodiacetic acid was used to mask the boryl group, and unmasking was carried out under basic conditions.

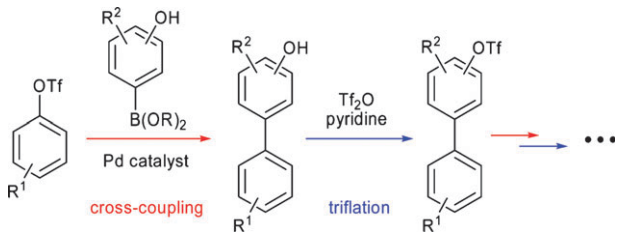
Nakao and Hiyama *et al.* reported an approach to oligoarenes by repetitive Hiyama coupling (Scheme 7).[22] This method is based on their finding of facile cross-coupling of organo[(2-hydroxymethyl)phenyl]dimethylsilanes under mild basic conditions in the presence of a Pd catalyst. When the hydroxy group is protected, the silyl moiety is unreactive under the cross-coupling conditions. Thus, the cross-coupling–deprotection sequence enables stepwise oligoarene synthesis as shown in Scheme 7. As the protecting group, not only THP (tetrahydropyranyl) but also an acetyl group can be used. Thus, the deprotection step can be either acidic (for THP) or basic (for acetyl).

In their synthesis of substituted *para*-terphenyl derivatives, Hamilton *et al.* used the repetitive Suzuki–Miyaura coupling approach using methoxyphenylboronic acids as precursors of the monomer units (Scheme 8).[4b] After Suzuki–Miyaura coupling of the boronic acid with an aryl trifluoromethanesulfonate (triflate), the methoxy group was converted to a hydroxy group by the action of boron tribromide, and the hydroxy group was then converted to the corresponding triflate with triflic anhydride. Hamilton's group also developed a synthetic method based on Negishi coupling using a methoxyphenylzinc species.[4a] This three step sequence of cross coupling–demethylation–triflation is applicable to the synthesis of longer oligoarenes.

In the course of our investigations on oligoarene-type catalysts, we also developed a synthetic method for multifunctionalized oligoarenes. At the outset of our synthetic work, our aim was to find a synthetic procedure having the following two features: (1) mild reaction conditions compatible with various functional groups; (2) quantitative yields for all steps in the synthetic sequence. In order to meet these criteria, we planned the synthetic scheme shown in Scheme 9.



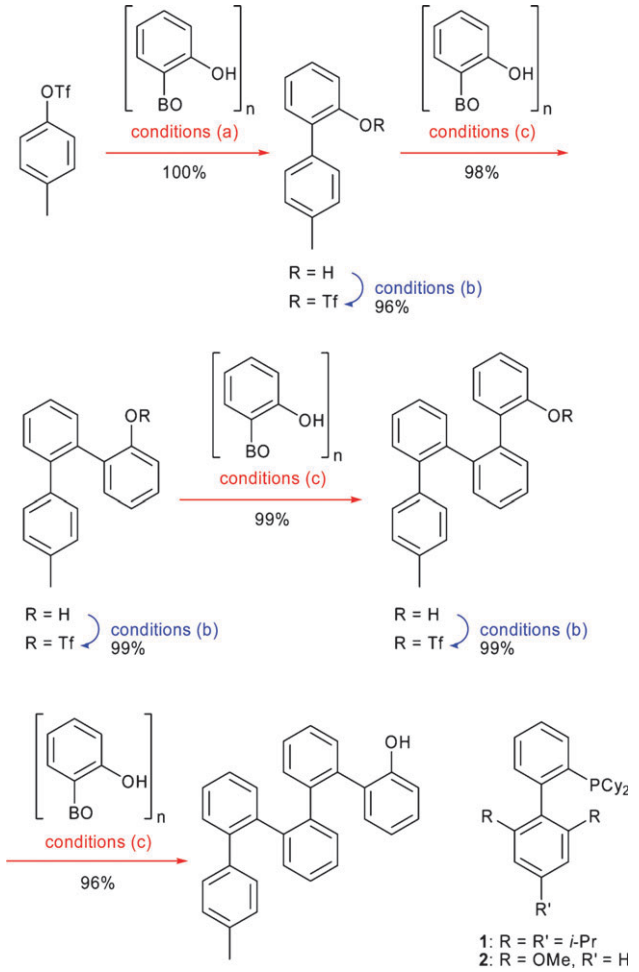
Scheme 8 Repetitive synthesis of terphenyls (Hamilton *et al.*)[4b]



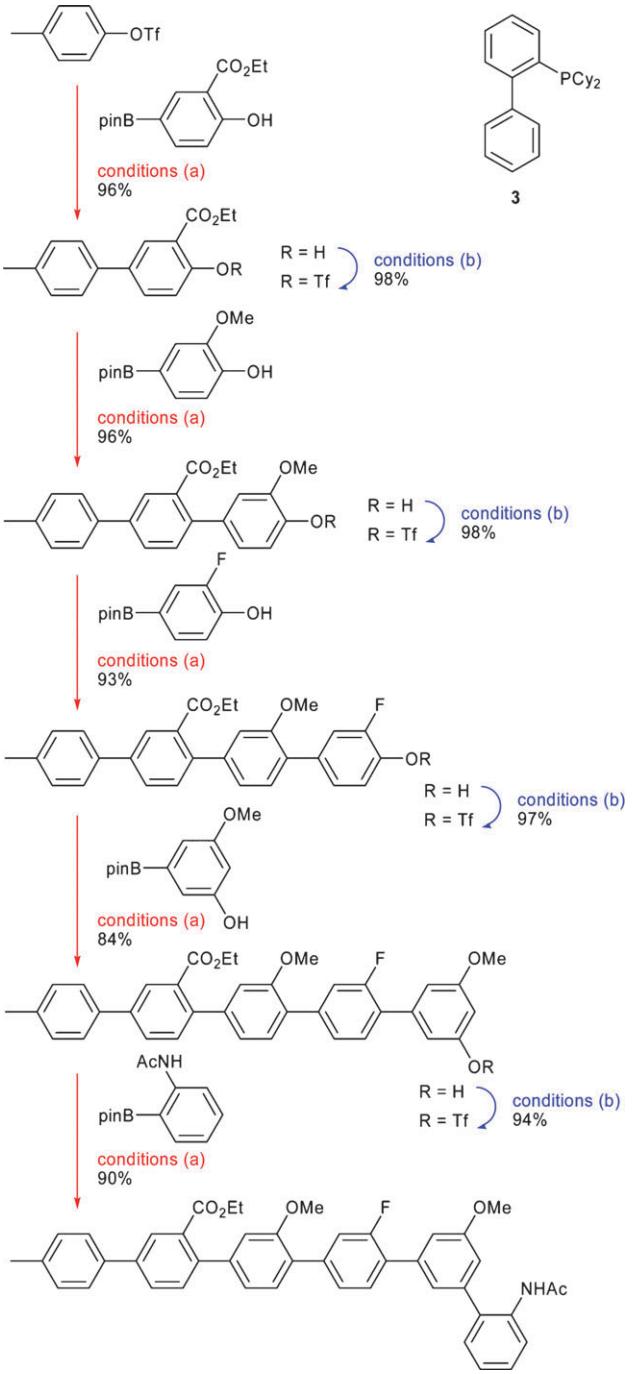
Scheme 9 Repetitive two-step strategy for oligoarene synthesis using hydroxyphenylboronic acids.

The synthetic sequence is composed of two steps, Suzuki–Miyaura coupling of hydroxyphenylboronic acids[23] (or their derivatives) and subsequent triflation of the hydroxy group. Triflation of hydroxy groups generally proceeds at room temperature or below in high yield under mild reaction conditions.[24] Therefore, we expected that repetition of these two steps would efficiently produce oligoarenes. Although this scheme is similar to the one shown in Scheme 8, the demethylation step is not required in our case.

We first optimized the reaction conditions of the Suzuki–Miyaura coupling of aryl triflates with hydroxyphenylboronic acids.[25] After screening various Pd sources, ligands, and solvents, we found that the reaction proceeded well at room temperature in a mixed solvent of THF and water in the presence of potassium fluoride, palladium acetate, and biphenylphosphine **1** or **2**, developed by Buchwald *et al.*[26] These conditions were then applied to oligoarene synthesis.[25] An example is shown in Scheme 10. 2-Hydroxyphenylboronic anhydride,[23] which generates the corresponding boronic acid in the presence of water, was used as the precursor of the monomer units. Each step proceeded almost quantitatively, giving an *ortho*-connected pentamer in high yield.



Scheme 10 Oligoarene synthesis using 2-hydroxyphenylboronic anhydride. Conditions: (a) $Pd(OAc)_2$ (2 mol%), **1** (2.4 mol%), KF, THF–H_2O (4 : 1), rt; (b) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (c) $Pd(OAc)_2$ (2 mol%), **2** (2.4 mol%), KF, THF–H_2O (4 : 1), rt.



Scheme 11 Oligoarene synthesis using hydroxyphenylboronic acid pinacol esters. Conditions: (a) $Pd(OAc)_2$ (2 mol%), **3** (2.4 mol%), $LiOH\cdot H_2O$, THF–H_2O (4 : 1), rt; (b) Tf_2O, pyridine, CH_2Cl_2, 0 °C or rt.

While oligoarene chains can be readily elongated by the method mentioned above, a problem still exists in this method, *i.e.*, difficulty in purification and characterization of the starting hydroxyphenylboronic acids, especially when a functional group is introduced on the benzene ring. On the other hand, boronic acid pinacol esters, which have also been used as coupling partners in Suzuki–Miyaura coupling, can usually be prepared, purified, and characterized without difficulty.[27] Thus, we next turned our attention to the use of the pinacol esters of hydroxyphenylboronic acids in the Suzuki–Miyaura coupling steps.[28]

After optimization of the reaction conditions, the Suzuki–Miyaura coupling of the pinacol esters of hydroxyphenylboronic acids was found to proceed well at room temperature in the presence of lithium hydroxide, palladium acetate, and biphenylphosphine **3**.[29] These cross-coupling conditions were successfully applied to the synthesis of a multifunctionalized oligoarene as shown in Scheme 11.[28] The simple combination of cross-coupling and subsequent triflation of the hydroxy group easily produced oligoarenes with various functional groups in high yield.

We also developed a similar method for oligoarene synthesis using Negishi coupling[30] of organozinc species as the key C–C bond-forming step.[31] This Negishi coupling strategy for oligoarene synthesis is complementary to the method based on Suzuki–Miyaura coupling.

Application: oligoarene-type phosphines

As an application of oligoarene structures to catalytic molecules, we designed hydroxylated oligoarene-type phosphines (HOPs, Fig. 3a)[32,33] as ligands for transition metals, based on

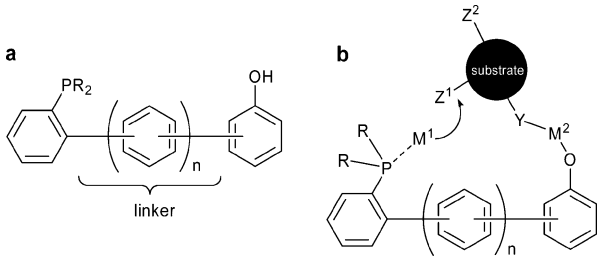
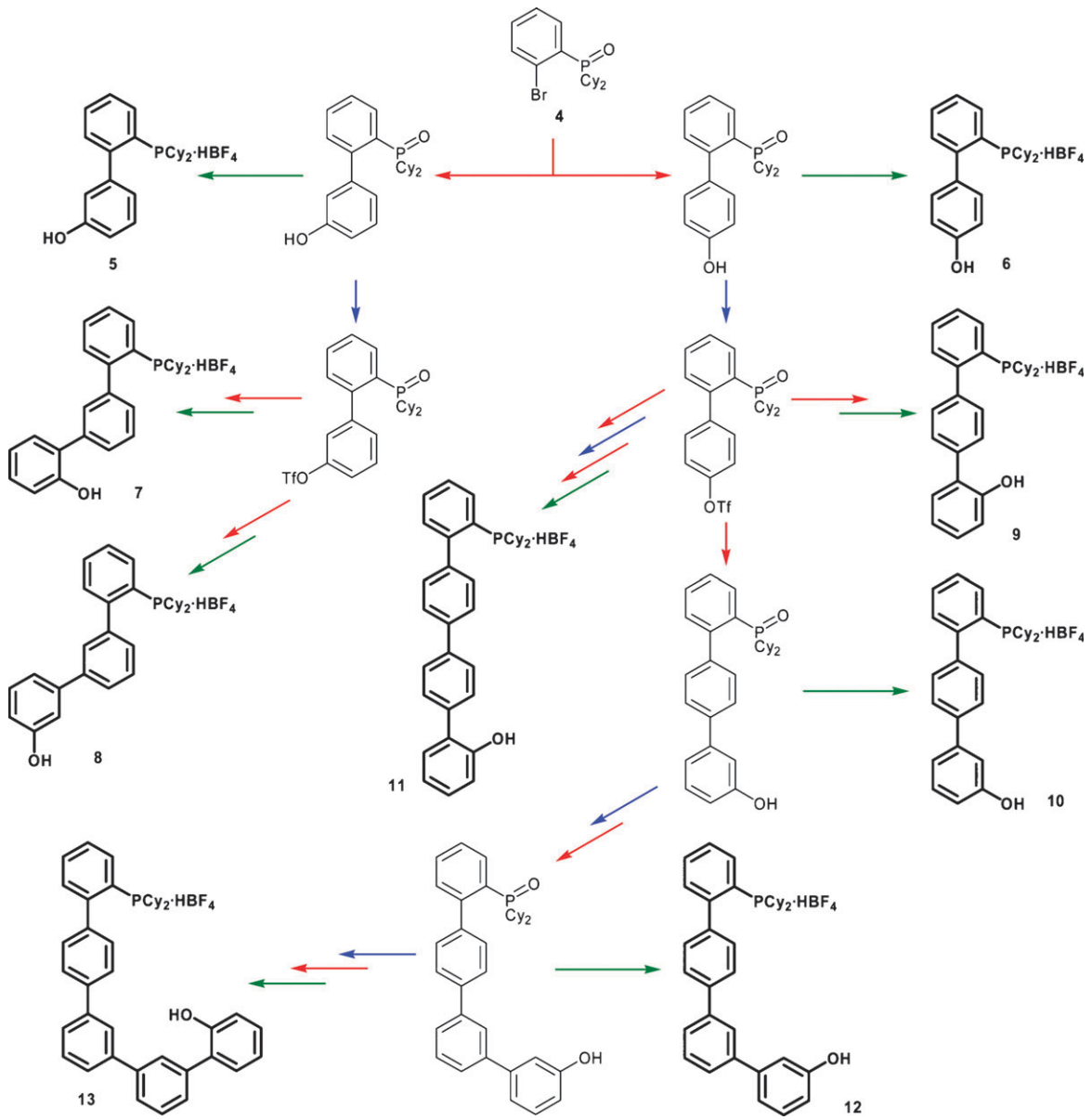


Fig. 3 (a) Hydroxylated oligoarene-type phosphine (HOP). (b) Proposed intermediate in the reaction using a HOP–metal complex as a catalyst.

biphenylphosphines developed by Buchwald *et al.*[26,29a] It was expected that a library of HOPs would be prepared by our repetitive two-step method for oligoarene synthesis, and that HOPs would work as bifunctional ligands: the phosphino group coordinates to a soft transition metal and the hydroxy group, as the anionic oxide form, coordinates to a hard metal. If the metal oxido group (M^2–O in Fig. 3b) can bind a substrate through a functional group (Y), this binding would place the reactive group (Z^1) close to the catalytic transition metal (M^1) coordinated by the phosphino group, leading to rate acceleration of the catalytic reaction. In addition, when the substrate has more than one reactive position (Z^1, Z^2, *etc.*), site-selectivity would be realized by placing only one of the reactive groups in the vicinity of the catalytic metal. Optimizing length and substitution pattern (*ortho*-, *meta*-, *para*-) of the linker moiety would give suitable HOPs for specific reactions and also enable high substrate specificity and reaction selectivity. Thus, we initiated the synthetic study of HOPs with various lengths and substitution patterns using the stepwise, repetitive method mentioned in the previous section.



Scheme 12 Synthetic scheme of HOPs **5**–**13**. Red arrow: Suzuki–Miyaura coupling with a hydroxyphenylboronic acid. Blue arrow: triflation of the hydroxy group. Green arrow: reduction of the phosphinyl group with $HSiCl_3$ and Et_3N, and subsequent salt formation with HBF_4.

Synthesis of hydroxylated oligoarene-type phosphines

On the basis of the method using hydroxyphenylboronic acids, we readily synthesized a library of HOPs (**5**–**13**) as shown in Scheme 12.[34] Since the HOPs have the common 2-dicyclohexylphosphinobiphenyl core structure, we started the synthesis from the phosphinophenyl side of the oligoarene chain, using phosphine oxide **4** as the starting key compound, which was easily prepared from 2-bromoiodobenzene. Because the PCy_2 group is gradually oxidized in air, the group was protected as the corresponding oxide form throughout the synthesis. This protection also facilitates the triflation step, because the triflating agent, Tf_2O, reacts with the PCy_2 group to afford undesired products. The phosphine oxides were finally reduced with trichlorosilane to give the phosphines, which were purified and stored in the form of the HBF_4 salts.[35]

Application to site-specific cross-coupling

We next used the HOPs as precursors of oligoarene-type catalysts.[34] We chose Pd-catalyzed cross-coupling of haloarenes with Grignard reagents for the reaction. Transition metal-catalyzed cross-coupling with Grignard reagents is a widely used method for C–C bond formation,[36] especially in biaryl synthesis. Considering the high catalytic activity of Pd complexes formed with biphenylphosphines such as **1**–**3**,[26,29] the HOPs were also expected to be active when complexed with Pd. We envisaged that rate acceleration of the oxidative addition step would be realized through the reaction intermediate shown in Fig. 3b (M^1 = Pd, M^2 = Mg, Z^1 = halogen). In addition, if the position of Z^1 is more susceptible to reaction than that of Z^2, a site-selective reaction in which Z^1 reacts with the Pd atom preferentially over Z^2 would be realized (Z^1 and Z^2 = the same halogen). In this proposed structure, the proper position and orientation of Z^1 relative to M^1, which are crucial factors for rate acceleration, are governed by the correct selection of the linker moiety of the HOPs. We hoped that screening of the HOP library in the cross-coupling would lead to finding a HOP with a proper structure. Thus, we tested HOPs **5**–**13** and many other reference ligands for the Pd-catalyzed cross-coupling with Grignard reagents.

We chose bromophenols as substrates for the Pd-catalyzed cross-coupling, because the phenolic oxygen atom was expected to act as the interacting group (Y in Fig. 3b) after being deprotonated by a Grignard reagent present in excess. Phenylmagnesium bromide was used as the Grignard reagent. In the ligand screening experiments, the three isomers of bromophenol, *o*-, *m*-, and *p*-bromophenol (***o***-, ***m***-, and ***p*-14**), were separately subjected to the catalytic conditions with each ligand. The results are summarized in Fig. 4. For HOPs **5**–**13**, the HBF_4 salts were used directly, because the corresponding free phosphines were liberated in the presence of the Grignard reagent. The results of commercially available biphenylphosphines **1** and **3** are also shown. The yields of the coupling products (***o***-, ***m***-, and ***p*-15**) were significantly affected by the ligands. From the experiments at 50 °C, it was found that ***m*-14** was generally more reactive than the other isomers for each ligand, except when ligands **5** and **9** were used. In particular, hydroxylated terphenyl phosphine **9** showed unusually high activity for ***o*-14**, and the yield

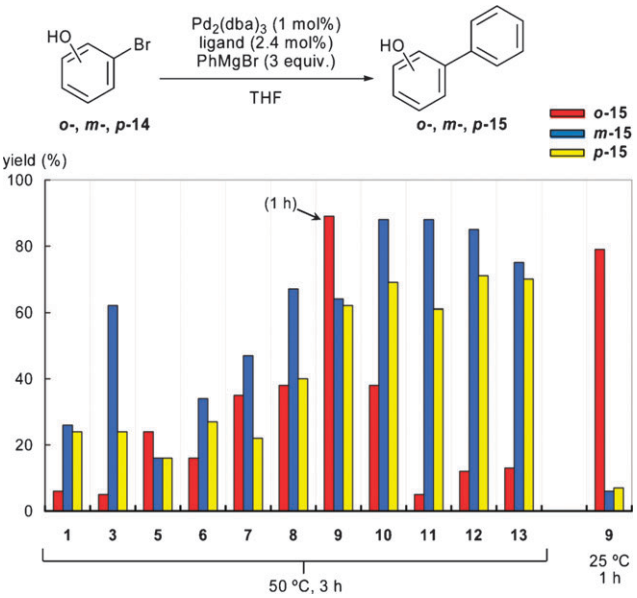
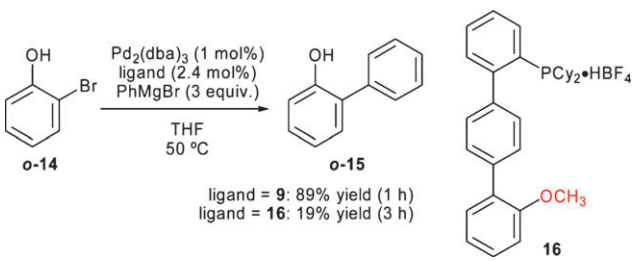


Fig. 4 Screening of ligands in Pd-catalyzed cross-coupling of bromophenols with PhMgBr. dba = dibenzylideneacetone.

was higher even with a shorter reaction time (1 h). The preference of ligand **9** for ***o*-14** over ***m***- and ***p*-14** was further demonstrated at 25 °C where the yield of ***o*-15** was significantly higher than the yields of ***m***- and ***p*-15**. This result indicates that the complex of ligand **9** with Pd specifically accelerates the reaction of the *ortho*-isomer.

In general, oxidative addition of Pd to a C–X bond is slow at more electron-rich carbons compared with oxidative addition at less electron-rich carbons.[37] Since bromophenols **14** have an electron-donating hydroxy group, which is converted to the more electron-donating oxido group under the reaction conditions, it is expected that oxidative addition to the C–Br bond of the *ortho*- and *para*-isomers is slower. If the rate-determining step is the oxidative addition step,[38] the *meta*-isomer should be the most reactive isomer. In fact, most of the ligands shown in Fig. 4 exhibited higher activity for ***m*-14**. It is surprising, therefore, that ligand **9** showed the strong preference for ***o*-14**. Furthermore, this high activity for ***o*-14** was observed only for ligand **9**. This suggests that the phosphino group and the hydroxy group of **9** are properly arranged to accelerate the reaction of ***o*-14**.

To confirm the need for the hydroxy group of ligand **9**, reference ligand **16** was used for the cross-coupling (Scheme 13). The much lower activity using **16** than **9** indicates that the hydroxy group of **9** plays a significant role in rate acceleration.



Scheme 13 Ligand **9** *vs.* ligand **16**.

We assume that the reaction proceeds *via* an intermediate similar to Fig. 3b, in which the Mg oxido group of the ligand holds the C–Br bond *ortho* to the oxido group of bromophenoxide close to the Pd atom coordinated by the phosphine.

Application to site-selective cross-coupling of dihalophenols and dihaloanilines

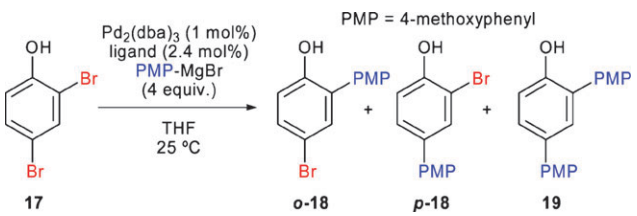
Site-selectivity is an important issue in the cross-coupling of halogenated arenes when the arene molecules have more than one substituent of the same halogen atom. If one of the halogen atoms is site-selectively converted to another group, this type of selective cross-coupling can be a powerful tool to synthesize multiply substituted arenes. For multiply halogenated heteroarenes such as dihalothiophenes and dihalopyridines, many examples of site-selective cross-coupling have been reported.[39] In contrast, only a few examples have been reported for dihalogenated benzene derivatives.[37,40] The cross-coupling of these substrates mainly occurs at less electron-rich carbons, *i.e.*, at more electron-poor carbons. For example, Singh and Just reported a selective cross-coupling in which dibromoanilines underwent coupling preferentially at the position *meta* to the electron-donating amino group over the *ortho*- or *para*-positions.[37] On the other hand, electron-withdrawing groups such as nitro and carbonyl groups are known to promote cross-coupling at the *ortho*- or *para*-positions over the *meta*-position.[37,40] Thus, it is generally difficult to achieve site-selective cross-coupling that occurs preferentially at more electron-rich carbons. If the carbons are at more sterically hindered positions, the reactions are even more difficult to achieve.

The results of the site-*specific* cross-coupling using ligand **9** prompted us to investigate site-*selective* cross-coupling of dihalophenols with Grignard reagents.[41] We chose 2,4-dibromophenol (**17**) as the substrate and studied the effects of ligands on the site-selectivity in the cross-coupling with 4-methoxyphenyl Grignard reagent. The results are summarized in Table 1. PPh_3, PCy_3, **1**, and **3** gave products ***o*-18** and ***p*-18** with low selectivity in low yields (entries 1, 2, 5, and 6). For t-$Bu_3P{\cdot}HBF_4$ and DPPF the reactions occurred site-selectively at the position *para* to the hydroxy group to afford ***p*-18** as the major product (entries 3 and 4). In contrast, ligand **9** reversed the site-selectivity and preferentially afforded ***o*-18** in good yield (entry 7). While a small amount of diarylated compound **19** was still obtained, the yield of ***p*-18** was 0%! In addition, ligand **9** greatly shortened the reaction time to 2 h. It is also noteworthy that reference ligand **16** did not show any site-selectivity (entry 8), indicating the importance of the hydroxy group of **9**. We further examined the effects of the phosphino group and found that another hydroxylated terphenyl phosphine, **20**, which has a PPh_2 group instead of PCy_2, suppressed the formation of **19** and improved the yield of ***o*-18** up to 89% (entry 9).

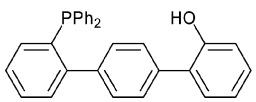
The site-selective cross-coupling was applied to other substrates, and representative examples are shown in Scheme 14. High *ortho*-selectivity was induced by **9** or **20** not only for dibromophenols but also for dibromoanilines. The results of 2,5-dibromophenol and 2,5-dibromoaniline are worth mentioning because the cross-coupling occurred preferentially at more electronically negative and more sterically hindered carbons. In all cases, the yields of the corresponding isomeric products were less than 0.5%.

We also performed the reaction with 4-bromo-2-chlorophenol (**21**).[42] In normal cross-coupling, bromo groups are more reactive than chloro groups. However, when ligand **20** was used, the chloro group at the *ortho*-position reacted preferentially over the bromo group at the *para*-position (Scheme 15). This unusual selectivity was not observed in the reaction with

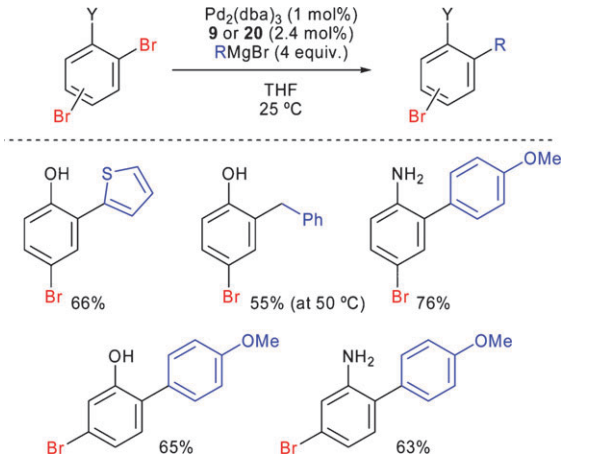
Table 1 Effect of ligands on site-selective cross-coupling of **17**



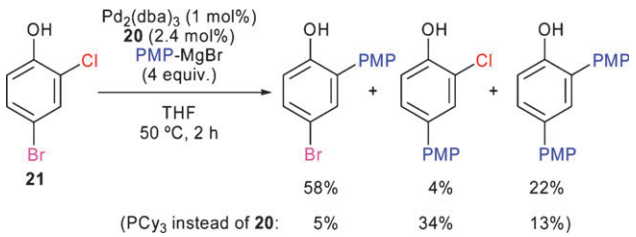
Entry	Ligand	Reaction time/h	Yield (%)		
			***o*-18**	***p*-18**	**19**
1	PPh_3	24	22	16	14
2	PCy_3	24	21	14	38
3	t-$Bu_3P{\cdot}HBF_4$	24	0	40	25
4	DPPF	24	1	77	1
5	**1**	24	5	5	1
6	**3**	24	8	12	3
7	**9**	2	71	0	16
8	**16**	24	13	18	7
9	**20**[a]	2	89	0	4

[a] 

20



Scheme 14 Site-selective cross-coupling of dibromophenols and dibromoanilines.



Scheme 15 *Ortho*-selective cross-coupling of 4-bromo-2-chlorophenol.

PCy_3. This result further emphasizes the effects of the hydroxylated terphenyl phosphines on the rate acceleration at the position *ortho* to hydroxy and amino groups.

Conclusions

We described here a strategy to create new catalysts. Oligoarenes can be regarded as useful molecular backbones to construct catalytic molecules. We and others have developed synthetic methods for multifunctionalized oligoarenes, based on stepwise, repetitive cross-coupling. Our method was successfully applied to the synthesis of a library of hydroxylated oligoarene-type phosphines. One of the linker structures of the phosphines was found to be suitable for the ligand to Pd in site-specific and site-selective cross-coupling. The *ortho*-acceleration observed in the reactions of dihalophenols and dihaloanilines with Grignard reagents is outstanding. Although we have developed only a single example of catalyst by the oligoarene strategy, we hope that use of oligoarene structures as molecular backbones of catalysts can provide a promising strategy to develop new types of catalysts.

Acknowledgements

We thank Ms Haruka Saito (née Shimizu) for her contribution in this work. Our work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

1 (*a*) J. M. Tour, *Chem. Rev.*, 1996, **96**, 537; (*b*) A. J. Berresheim, M. Müller and K. Müllen, *Chem. Rev.*, 1999, **99**, 1747; (*c*) A. D. Schlüter and Z. Bo, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-i. Negishi, John Wiley & Sons, New York, 2002, ch. III.2.17.2; (*d*) A. C. Grimsdale and K. Müllen, *Angew. Chem., Int. Ed.*, 2005, **44**, 5592; (*e*) F. J. M. Hoeben, P. Jonkheijm, E. W. Meijer and A. P. H. J. Schenning, *Chem. Rev.*, 2005, **105**, 1491; (*f*) K. Tsubaki, *Org. Biomol. Chem.*, 2007, **5**, 2179.
2 J. M. Tour, *Acc. Chem. Res.*, 2000, **33**, 791.
3 (*a*) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995, ch. 9; (*b*) N. Sakai, J. Mareda and S. Matile, *Acc. Chem. Res.*, 2005, **38**, 79; (*c*) Y.-S. Yoo, J.-H. Choi, J.-H. Song, N.-K. Oh, W.-C. Zin, S. Park, T. Chang and M. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 6294; (*d*) H. Goto, H. Katagiri, Y. Furusho and E. Yashima, *J. Am. Chem. Soc.*, 2006, **128**, 7176.
4 (*a*) B. P. Orner, J. T. Ernst and A. D. Hamilton, *J. Am. Chem. Soc.*, 2001, **123**, 5382; (*b*) J. T. Ernst, O. Kutzki, A. K. Debnath, S. Jiang, H. Lu and A. D. Hamilton, *Angew. Chem., Int. Ed.*, 2002, **41**, 278.
5 D. J. Cram, P. Y.-S. Lam and S. P. Ho, *J. Am. Chem. Soc.*, 1986, **108**, 839.
6 K. Manabe, *J. Synth. Org. Chem., Jpn.*, 2007, **65**, 1113.
7 (*a*) R. Breslow, *Supramol. Chem.*, 1993, **1**, 111; (*b*) M. C. Feiters, in *Comprehensive Supramolecular Chemistry*, ed. D. N. Reinhoudt, Pergamon, Oxford, 1996, vol. 10, ch. 11; (*c*) *Multimetallic Catalysts in Organic Synthesis*, ed. M. Shibasaki and Y. Yamamoto, Wiley-VCH, Weinheim, 2004; (*d*) J.-A. Ma and D. Cahard, *Angew. Chem., Int. Ed.*, 2004, **43**, 4566; (*e*) M. Kanai, N. Kato, E. Ichikawa and M. Shibasaki, *Synlett*, 2005, 1491; (*f*) S. Das, G. W. Brudvig and R. H. Crabtree, *Chem. Commun.*, 2008, 413.
8 (*a*) L. J. Prins and P. Scrimin, in *Functional Synthetic Receptors*, ed. T. Schrader and A. D. Hamilton, Wiley-VCH, Weinheim, 2005, ch. 1; (*b*) S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601; (*c*) E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, 2007, **107**, 5759.
9 There are many artificial oligomer systems other than oligoarenes. For reviews, see: (*a*) D. Seebach and J. L. Matthews, *Chem. Commun.*, 1997, 2015; (*b*) S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173; (*c*) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.*, 2001, **101**, 3893; (*d*) I. Huc, *Eur. J. Org. Chem.*, 2004, 17; (*e*) N. Franz, G. Kreutzer and H.-A. Klok, *Synlett*, 2006, 1793; (*f*) *Foldamers: Structure, Properties and Applications*, ed. S. Hecht and I. Huc, Wiley-VCH, Weinheim, 2007.
10 *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004.
11 M. Rehahn, A.-D. Schlüter and G. Wegner, *Polymer*, 1989, **30**, 1060.
12 (*a*) A. Minato, K. Suzuki, K. Tamao and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 1984, 511; (*b*) P. R. L. Malenfant, L. Groenendaal and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1998, **120**, 10990; (*c*) T. Kirschbaum, R. Azumi, E. Mena-Osteritz and P. Bäuerle, *New J. Chem.*, 1999, **23**, 241; (*d*) G. Biden, A. De Nicola, V. Enée and S. Guillerez, *Chem. Mater.*, 1998, **10**, 1052.
13 (*a*) J. Zhang, J. S. Moore, Z. Xu and R. A. Aguirre, *J. Am. Chem. Soc.*, 1992, **114**, 2273; (*b*) J. S. Moore, *Acc. Chem. Res.*, 1997, **30**, 402.
14 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. Suzuki and H. C. Brown, *Organic Synthesis* via *Boranes, Suzuki Coupling*, Aldrich Chemical Company, Milwaukee, 2003, vol. 3.
15 W. Cheng and V. Snieckus, *Tetrahedron Lett.*, 1987, **28**, 5097.
16 P. Galda and M. Rehahn, *Synthesis*, 1996, 614.
17 A. J. Blake, P. A. Cooke, K. J. Doyle, S. Gair and N. S. Simpkins, *Tetrahedron Lett.*, 1998, **39**, 9093.
18 (*a*) P. Liess, V. Hensel and A. D. Schlüter, *Liebigs Ann.*, 1996, 1037; (*b*) V. Hensel and A. D. Schlüter, *Chem.–Eur. J.*, 1999, **5**, 421.
19 M. W. Read, J. O. Escobedo, D. M. Willis, P. A. Beck and R. M. Strongin, *Org. Lett.*, 2000, **2**, 3201.
20 H. Noguchi, K. Hojo and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758.
21 E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 6716.

22 Y. Nakao, J. Chen, M. Tanaka and T. Hiyama, *J. Am. Chem. Soc*., 2007, **129**, 11694.
23 H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, *J. Am. Chem. Soc*., 1957, **79**, 3077. The boronic anhydrides of hydroxyphenylboronic acids exist as aggregated forms whose real aggregation states are unclear because of the complexity associated with the phenolic OH groups.
24 P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, 1982, 85.
25 S. Ishikawa and K. Manabe, *Chem. Lett*., 2006, **35**, 164.
26 (*a*) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc*., 2003, **125**, 6653; (*b*) H. N. Nguyen, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc*., 2003, **125**, 11818; (*c*) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc*., 2005, **127**, 4685.
27 (*a*) D. G. Hall, in *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005 ch. 1; (*b*) T. Ishiyama and N. Miyaura, in *Boronic Acids*, ed. D. G. Hall, Wiley-VCH, Weinheim, 2005 ch. 2.
28 S. Ishikawa and K. Manabe, *Chem. Commun*., 2006, 2589.
29 (*a*) J. P. Wolfe and S. L. Buchwald, *Angew. Chem., Int. Ed*., 1999, **38**, 2413; (*b*) O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem*., 2000, **65**, 9268.
30 E.-i. Negishi, in *Handbook of Organopalladium Chemistry, for Organic Synthesis*, ed. E.-i. Negishi, John Wiley & Sons, New York, 2002, ch. III.2.1.
31 H. Shimizu and K. Manabe, *Tetrahedron Lett*., 2006, **47**, 5927.
32 Examples of oligoarene-type phosphines: (*a*) H.-B. Yu, Q.-S. Hu and L. Pu, *J. Am. Chem. Soc*., 2000, **122**, 6500; (*b*) K. Goto, Y. Ohzu, H. Sato and T. Kawashima, *Phosphorus, Sulfur Silicon Relat. Elem*., 2002, **177**, 2179; (*c*) T. Matsumoto, T. Kasai and K. Tatsumi, *Chem. Lett*., 2002, **31**, 346; (*d*) T. Iwasawa, T. Komano, A. Tajima, M. Tokunaga, Y. Obora, T. Fujihara and Y. Tsuji, *Organometallics*, 2006, **25**, 4665; (*e*) K. Matsui, S. Takizawa and H. Sasai, *Synlett*, 2006, 761.
33 Examples of hydroxylated phosphines: (*a*) T. Hayashi, T. Mise and M. Kumada, *Tetrahedron Lett*., 1976, **17**, 4351; (*b*) Y. Hatanaka, K. Goda, F. Yamashita and T. Hiyama, *Tetrahedron Lett*., 1994, **35**, 7981; (*c*) N. Yoshikai, H. Mashima and E. Nakamura, *J. Am. Chem. Soc*., 2005, **127**, 17978. See also ref. 32*e*.
34 S. Ishikawa and K. Manabe, *Chem. Lett*., 2007, **36**, 1302.
35 M. R. Netherton and G. C. Fu, *Org. Lett*., 2001, **3**, 4295.
36 Cross-coupling of Grignard reagents: (*a*) M. S. Kharasch and C. F. Fuchs, *J. Am. Chem. Soc*., 1943, **65**, 504; (*b*) M. Tamura and J. Kochi, *J. Am. Chem. Soc*., 1971, **93**, 1487; (*c*) R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun*., 1972, 144; (*d*) K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc*., 1972, **94**, 4374; (*e*) M. Yamamura, I. Moritani and S.-I. Murahashi, *J. Organomet. Chem*., 1975, **91**, C39; For reviews: (*f*) J. Tsuji, *Palladium Reagents and Catalysts*, John Wiley & Sons, West Sussex, 2004, p. 335; (*g*) T. Takahashi and K.-i. Kanno, in *Modern Organonickel Chemistry*, ed. Y. Tamaru, Wiley-VCH, Weinheim, 2005, p. 41; (*h*) I. Cepanec, *Synthesis of Biaryls*, Elsevier, Oxford, 2004, p. 83.
37 R. Singh and G. Just, *J. Org. Chem*., 1989, **54**, 4453.
38 (*a*) R. Martin and S. L. Buchwald, *J. Am. Chem. Soc*., 2007, **129**, 3844; (*b*) N. A. Bumagin and E. A. Luzikova, *J. Organomet. Chem*., 1997, **532**, 271.
39 For reviews: (*a*) S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245; (*b*) I. J. S. Fairlamb, *Chem. Soc. Rev*., 2007, **36**, 1036; See also: (*c*) C. Y. Legault, Y. Garcia, C. A. Merlic and K. N. Houk, *J. Am. Chem. Soc*., 2007, **129**, 12664.
40 (*a*) Y. Ishii, N. Chatani, S. Yorimitsu and S. Murai, *Chem. Lett*., 1998, **27**, 157; (*b*) S. M. Dirk, D. W. Price, Jr, S. Chanteau, D. V. Kosynkin and J. M. Tour, *Tetrahedron*, 2001, **57**, 5109; (*c*) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani and S. Murai, *J. Am. Chem. Soc*., 2004, **126**, 2706; (*d*) L. Ackermann and A. Althammer, *Angew. Chem., Int. Ed*., 2007, **46**, 1627; (*e*) I. N. Houpis, J.-P. V. Hoeck and U. Tilstam, *Synlett*, 2007, 2179; (*f*) T. Wang, B. J. Alfonso and J. A. Love, *Org. Lett*., 2007, **9**, 5629; See also: (*g*) D. R. Fahey, *J. Am. Chem. Soc*., 1970, **92**, 402.
41 S. Ishikawa and K. Manabe, *Chem. Lett*., 2007, **36**, 1304.
42 S. Ishikawa and K. Manabe, *Org. Lett*., 2007, **9**, 5593.

