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A Repetitive One-Step Method for Oligoarene Synthesis Using Catalyst-Controlled Chemoselective Cross-Coupling

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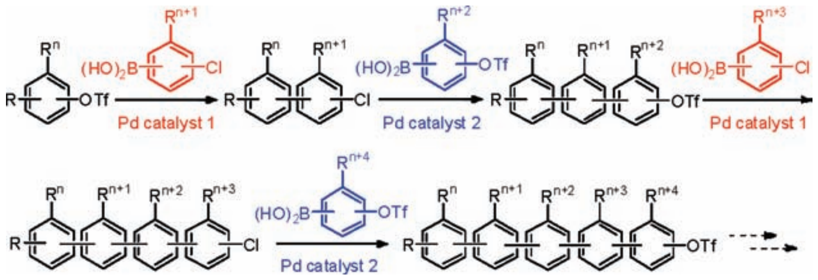
ABSTRACT



A method for oligoarene synthesis involving chemoselective cross-coupling as the key reaction was developed. Boronic acids with a chloro or trifluoromethanesulfonyloxy group were used as the monomer precursors with either of two chemoselective catalytic systems: Pd with P(*t*-Bu)$_3$, and Pd with 1,1′-bis(diphenylphosphino)ferrocene (DPPF). This method enabled elongation by one benzene unit in every step and thus reduced the number of steps required for elongation of oligoarene chains with well-defined lengths and sequences of substituted benzene rings.

Oligomers with well-defined chain lengths and structures are of interest as functional molecules, and the development of efficient methods for oligomer synthesis has been an important subject in organic chemistry.[1] Oligoarenes, which are composed of aromatic monomer units such as benzene rings connected through a single bond (Figure 1a), constitute an important class of oligomers,[2] and those with functional groups are widely used in electronic devices[3] and as self-assembling molecules,[4] biologically active compounds,[5] and catalytic molecules.[6] Herein, we report a new synthetic method that halves the number of steps required for elongation of oligoarene chains.

Oligopeptides are an important class of oligomers, and their established synthetic method involves the repetition of two steps: amide formation using N-protected amino acids and deprotection of the amino group. This has been a model in developing synthetic methods for other types of oligomers in which sequences of connected monomer units must be controlled. Oligoarenes with well-defined chain lengths and sequences have also been synthesized by methods in which two (or sometimes three)[5] steps required

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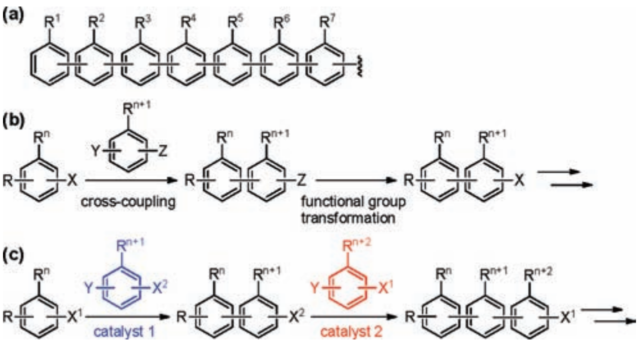
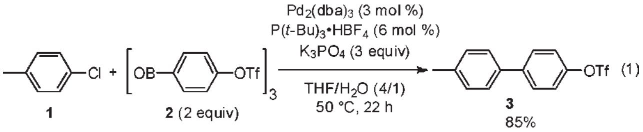


Figure 1. (a) General representation of an oligoarene. (b) The repetitive two-step method for oligoarene synthesis. X and Y are functional groups that form a carbon–carbon bond under cross-coupling conditions. Z is a group that remains intact under the cross-coupling conditions but can be converted to X in the subsequent step. (c) The repetitive one-step method using chemoselective cross-coupling: see text for details.

for elongation by one arene unit are repeated.[7] These methods involve repetition of two steps: cross-coupling and the subsequent functional group transformation (Figure 1b). This type of stepwise synthesis allows the construction of multisubstituted oligoarenes with various substituents in a specific sequence. While these repetitive two-step methods may be improved to establish an efficient synthetic method, we envisioned the development of a more efficient method using chemoselective cross-coupling. The concept of this "repetitive one-step method" is shown in Figure 1c. Under conditions in which one catalyst promotes the reaction of Y with X^1 but not with X^2, while another promotes the reaction with X^2 but not with X^1, the molecule can be elongated by one benzene unit in every step. Without chemoselectivity between X^1 and X^2, uncontrolled polymerization would take place, producing a mixture of compounds with various molecular weights.[8] While chemoselective reactions have been utilized inrepetitive one-step synthesis of oligosaccharides[9] and dendrimers[10]—often called orthogonal synthesis—repetitive one-step synthesis of oligoarenes has not yet been achieved.[11] In the literature, there are several examples of catalyst-controlled chemoselective cross-coupling.[12] For example, Fu and co-workers reported an intriguing example of catalyst-controlled chemoselectivity between chloro and TfO groups in Suzuki–Miyaura coupling,[13–15] finding that a Pd catalyst bearing $P(t\text{-}Bu)_3$ reacted with chloroarenes preferentially over aryl triflates, which are known to be more reactive than chloroarenes in most cross-coupling reactions. Thus, we assumed that this chemoselective Suzuki–Miyaura coupling would be applicable to our repetitive one-step method for oligoarene synthesis (Figure 1c, Y = $(HO)_2B$, X^1 = Cl, X^2 = TfO).

As there have been no reports of chemoselective Suzuki–Miyaura coupling of chloroarenes with phenylboronic acids bearing a TfO group on the benzene ring, we first optimized the reaction conditions for cross-coupling based on those used by Fu and co-workers.[13] Phenylboronic acids bearing a TfO group were easily prepared from iodophenyl triflates through I–Mg exchange reactions.[16] Some boronic acids (e.g., **2**) were isolated as their trimeric anhydride forms (boroxines). Optimization of a model reaction of 4-chlorotoluene (**1**) with **2** led to the conditions shown in eq 1. As in Fu's examples,[13] the TfO group of the boronic acid remained intact under these conditions, and longer oligoarene byproducts were not produced. While KF also worked as a base, K_3PO_4 was found to be slightly more active, giving **3** in higher yield.



(1)

There are some examples in the literature of reactions of aryl triflates with phenylboronic acids bearing a Cl group.[17] Screening of catalytic conditions for a model reaction of **4** with **5** showed that the conditions shown in eq 2 were optimal. A combination of $Pd(OAc)_2$ (3 mol %)

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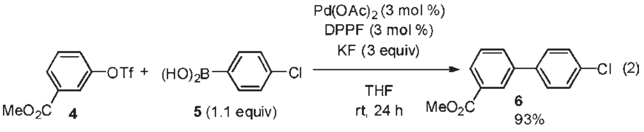
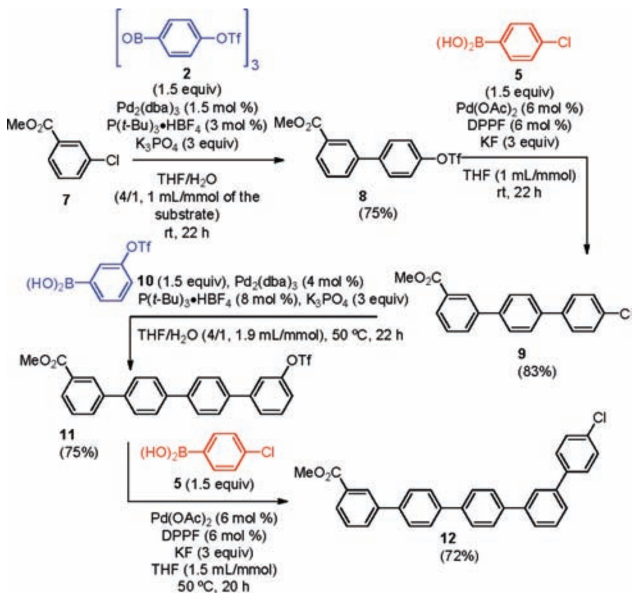
and PCy_3 (6 mol %) also gave **6** in good yield (75%), but a small amount of the terphenyl byproduct was formed through an overreaction (over-cross-coupling) at the Cl group. Therefore, we decided to use 1,1′-bis(diphenylphosphino)ferrocene (DPPF) for this chemoselective cross-coupling.[17b]



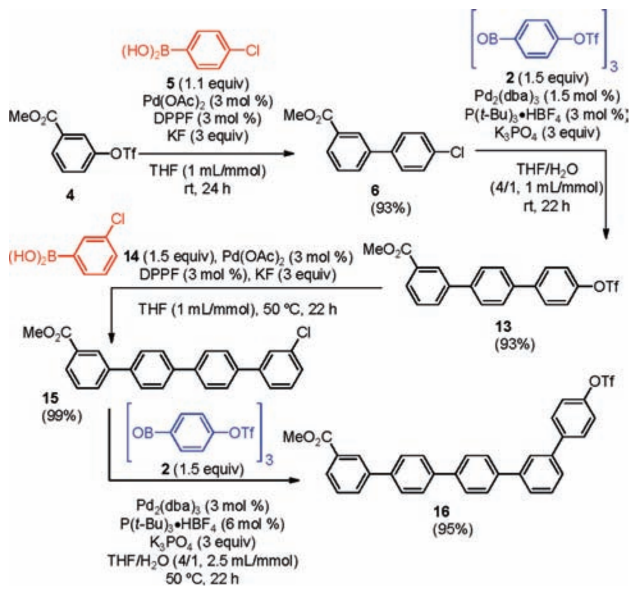
We then applied the reaction conditions to oligomer synthesis, as shown in Scheme 1. The synthesis began with chloroarene **7**. Alternating use of the Cl-selective and TfO-selective conditions afforded **12** in 4 steps, demonstrating that the repetitive one-step method really worked. The yields in each step were not excellent (72–83%), but over-cross-coupling was not observed. Slight modifications of the conditions in eqs 1 and 2 were required for some steps: the third and fourth steps were found to require higher temperatures, greater amounts of the catalysts, and larger volumes of solvents to increase the fluidity of the reaction mixtures. While the target quinquephenyl was arbitrarily chosen, this result strongly suggests that the method under discussion is applicable to the synthesis of various types of oligoarene.

Scheme 1. Synthesis of Quinquephenyl **12**



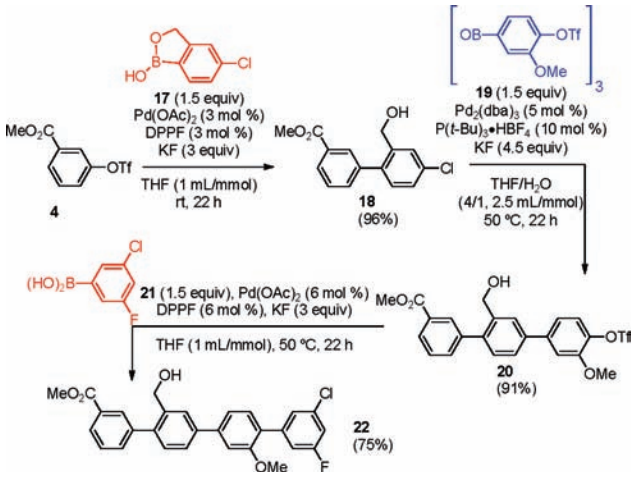
In this repetitive one-step method, the alternating use of triflates and chlorides in a different order was expected to work equally well. To demonstrate this, we started with aryl triflate **4**, instead of **7**, with the aim of synthesizing the same quinquephenyl backbone as **12** (Scheme 2). In this way, quinquephenyl **16** was produced in 4 steps by using the two catalytic systems alternately. In this case, the yields in the steps (93–99%) were higher than those in the previous synthesis (Scheme 1). Although the reason for the higher yields is unclear, we assume that slight differences in the solubility of the substrates are responsible.

Scheme 2. Synthesis of Quinquephenyl **16**

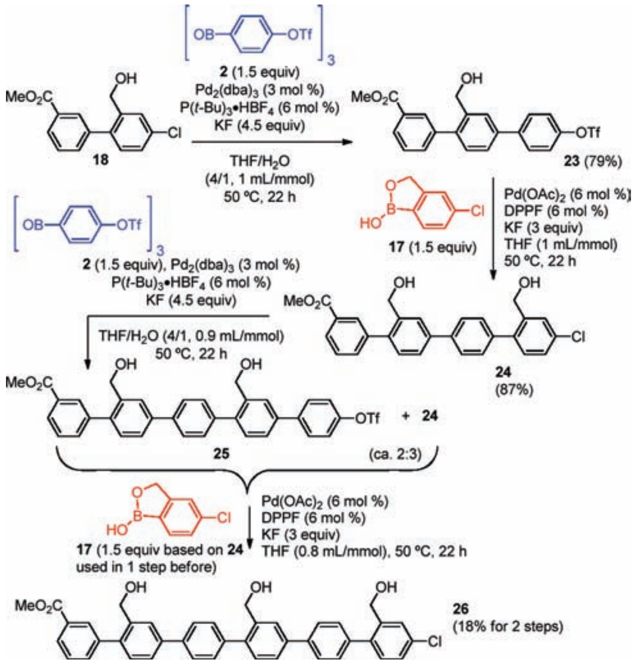


We next carried out the synthesis of multisubstituted oligoarenes using boronic acids with substituents. An example is shown in Scheme 3. Multisubstituted quaterphenyl **22** was produced in good yield. It should be mentioned that the cross-coupling conditions for chloroarene **18** had to be modified in this synthesis. When **18** was subjected to the conditions described above ($Pd_2(dba)_3$, $P(t\text{-}Bu)_3 \cdot HBF_4$, K_3PO_4), some aldehydes and a byproduct in which the Cl group was substituted with H were obtained (7–9%). These byproducts are likely to be produced through Pd-mediated oxidation of the hydroxymethyl

Scheme 3. Synthesis of Quaterphenyl **22**



Scheme 4. Synthesis of Sexiphenyl **26**



group and Pd-mediated reduction of the Cl group with the hydride generated by the oxidation step.[18] However, we were pleased to find that the use of KF instead of K_3PO_4 suppressed the formation of these byproducts to a significant extent. Therefore, we used KF as the base, albeit slightly less active, throughout the synthetic route. The result shown in Scheme 3 demonstrates that various functional groups, including ester, free hydroxy, alkoxy, and fluoro groups, can be installed into oligoarene structures.

Another example of multisubstituted oligoarene synthesis is shown in Scheme 4. The third step from **24** to **25** resulted in modest yield. In addition, **25** and remaining **24** could not be separated. Therefore, the mixture (**24**:**25** = ca. 2:3) was subjected to the next reaction with **17** without isolation of **25**. The reaction preferentially occurred at the TfO group of **25** over the Cl group of **24** to produce sexiphenyl **26**, which was now isolated with ease. The results of synthesis of these arbitrarily chosen oligoarenes strongly suggest that combinatorial uses of monomer precursors should enable preparation of various oligoarenes by this method.

In conclusion, we have developed a repetitive one-step method for synthesizing multisubstituted oligoarenes. The key reaction is catalyst-controlled chemoselective Suzuki–Miyaura coupling. The monomer precursors were phenylboronic acids bearing a Cl group or a TfO group, which were used in an alternating fashion to elongate the oligoarene chain by one benzene unit in every step. In principle, by using various monomer precursors and combining them in different ways, a variety of oligoarenes should be produced with ease. Combinatorial syntheses of functional molecules are now underway in our laboratory.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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