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Negishi coupling strategy of a repetitive two-step method for oligoarene synthesis

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Abstract—A novel repetitive two-step method for oligoarene synthesis, based on Negishi cross-coupling of zinciophenoxides or zinciopyridinoxides with aryl triflates and subsequent triflation of the hydroxy group, was developed. Reaction conditions were optimized for the preparation of the arylzinc compounds and the palladium-catalyzed cross-coupling step.

We have recently reported on a synthetic method of multifunctionalized oligoarenes,[1,2] which can serve as useful molecules in various research areas that involve self-assembling molecules,[3,4] biologically active compounds,[5] and enzyme mimics.[6] The repetitive two-step methodology features the Suzuki–Miyaura coupling[7] of hydroxyphenylboronic acids or their derivatives as the key carbon–carbon bond-forming step (Fig. 1a).

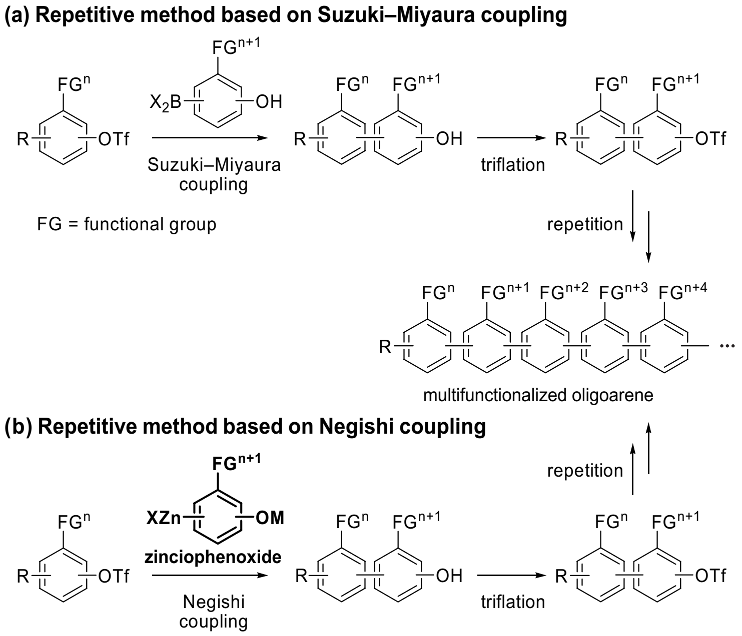

Figure 1. Repetitive two-step method for multifunctionalized oligoarene synthesis.

Keywords: Negishi coupling; Oligoarene; Palladium; Lithiation; Zinciophenoxide.

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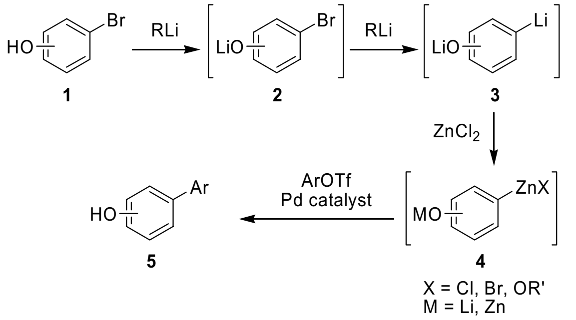


Scheme 1. Reaction plan for Negishi coupling of zinciophenoxides.

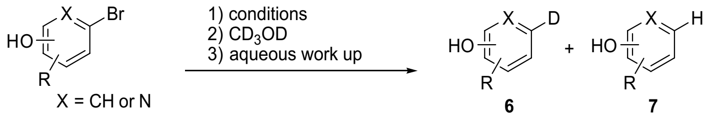
Repetition of the cross-coupling step and subsequent triflation of the hydroxy group were shown to afford the multifunctionalized oligoarenes with high efficiency. Although the Suzuki–Miyaura coupling methodology can be applied to the synthesis of various oligoarenes, there are limitations, such as the difficulty in preparing some functionalized boronic acids—for example, 2-pyridineboronic acids are known to hydrolyze rapidly.[8] Thus, to widen our repetitive two-step methodology for the synthesis of various oligoarenes, we investigated the use of an alternative cross-coupling step. Herein, we report the repetitive two-step method for oligoarene synthesis that features, as the key cross-coupling step, Negishi coupling[9] of an arylzinc species that contains an oxido group (Fig. 1b), specifically, phenylzincs (zinciophenoxides) and pyridylzincs (zinciopyridinoxides).

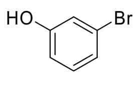
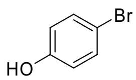
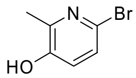
Although Negishi coupling of arylzinc compounds[10] has been widely used to construct C_{sp^2}–C_{sp^2} bonds, examples of the coupling reaction involving zinciophenoxides have been limited.[11] The most convenient method in preparing zinciophenoxides is presumably via dilithiation of halophenols, such as bromophenols (**1**–**3**), and subsequent transmetalation with zinc salts (**3** and **4**). Correspondingly, an effective procedure for the Negishi coupling step, as shown in Scheme 1, can be proposed.

To determine the reaction conditions for the dilithiation of bromophenols, deuteration experiments were carried out, some of which are listed in Table 1. In the presence of a functional group having an acidic hydrogen, the lithium–halogen exchange is often problematic due to the proton transfer from the starting molecule to the initially formed dilithiated species during the dropwise addition of the alkyllithium.[12] Although a combination of a metal hydride (such as NaH) and an alkyllithium has been widely used to circumvent this problem, we first investigated the preparation of dilithiated species using only the alkyllithium for experimental simplicity.

The results of the dilithiation and subsequent deuteration of various bromophenols and bromopyridinols revealed that the substrates can be classified into three groups. The first group can be exemplified by 3-bromophenol (**8**). Previous reports[13] on the dilithiation of **8** with *t*-BuLi describe conditions requiring fairly large volumes of the solvent (THF) (Table 1, entry 1). Under concentrated conditions, however, a significant degree of protonation was observed (entry 2). In contrast, fortunately, after screening various reaction conditions, our results show that, even under concentrated conditions, the use of *t*-BuLi in ether can afford high yield with high ratio between **6** and **7** (entry 4). This improvement by changing the solvents can be attributed to slow Li–Br exchange in ether compared with the diffusion rate of the added *t*-BuLi. The use of *t*-BuLi in ether was also favorable for other substrates of the first group, such as **11**–**13** (Chart 1). The second group can be exemplified by 4-bromophenol (**9**). In contrast to the first group, the use of *t*-BuLi in ether resulted in low yields (entries 6

Table 1. Deuteration experiments



Entry	Substrate	Conditions	Yield (%)[a]	**6**:**7**[a]
1	 **8**	*t*-BuLi, THF(15 mL/mmol), −78 °C, 5 min[b]	89	97:3
2		*t*-BuLi, THF (2 mL/mmol), −78 °C, 5 min[b]	>99	65:35
3		NaH, THF (2 mL/mmol), rt, 30 min then *t*-BuLi, −78 °C, 1 h[c]	96	83:17
4		*t*-BuLi, Et_2O (2 mL/mmol), −78 °C, 5 min[b]	95	>99:1
5	 **9**	*t*-BuLi, THF (2 mL/mmol), −78 °C, 5 min[b]	94	80:20
6		*t*-BuLi, Et_2O (2 mL/mmol), −78 °C, 5 min[b]	46	92:8
7		*t*-BuLi, Et_2O (2 mL/mmol), −78 °C, 1 h[b]	59	86:14
8		*t*-BuLi, Et_2O (1 mL/mmol), −78 °C, 5 min then THF (1 mL/mmol), 30 min[b]	97	87:13
9	 **10**	*t*-BuLi, Et_2O (1 mL/mmol), −78 °C, 5 min then THF (1 mL/mmol), 1 h[b]	55	80:20
10		NaH, THF (2 mL/mmol), rt, 30 min then *t*-BuLi, −78 °C, 1 h[c]	93	82:18

[a] Determined by ^1H NMR.

[b] 3.4 equiv of *t*-BuLi was used.

[c] 1.05 equiv of NaH and 2.1 equiv of *t*-BuLi were used.

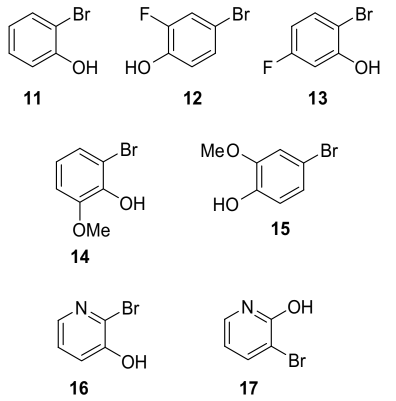


Chart 1.

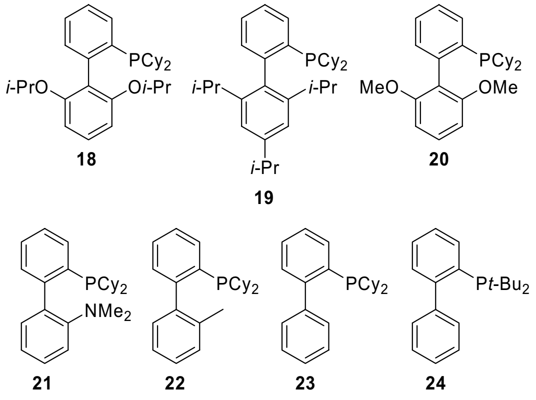


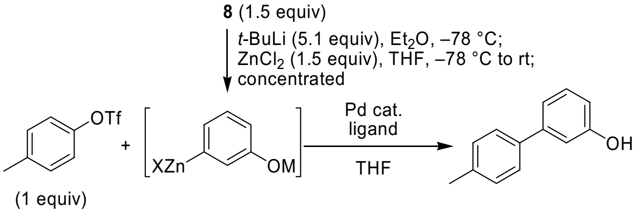
Chart 2.

and 7) probably due to extremely low solubility of the corresponding lithiated species in ether. However, satisfactory results were obtained by the addition of THF following the treatment with *t*-BuLi in ether (entry 8). The sequential addition of the two solvents (ether and THF) is critical for the substrates of the second group, which includes **9**, **14**, and **15**. Substrates that did not give satisfactory results under either conditions, as mentioned above, constitute the third group, which includes **10**, **16**, and **17**. For this group, the reaction requires a combination of NaH and *t*-BuLi (entry 10).

To optimize the conditions for the carbon–carbon bond-forming step, the Negishi coupling reaction was investigated using *p*-tolyl triflate and zinciophenoxide (as a model substrate) that was prepared by dilithiation of **8**, followed by transmetalation with $ZnCl_2$. Recently, Buchwald et al. reported that biphenylphosphine **18** (Chart 2) can serve as an extremely effective ligand for Pd-catalyzed Negishi coupling of arylzincs with aryl chlorides and bromides.[14] Using this catalytic system, the desired product was obtained at 45 °C in a high yield (Table 2, entry 1). As a note, an increase in the amount of $ZnCl_2$ required a longer reaction time (entry 2).

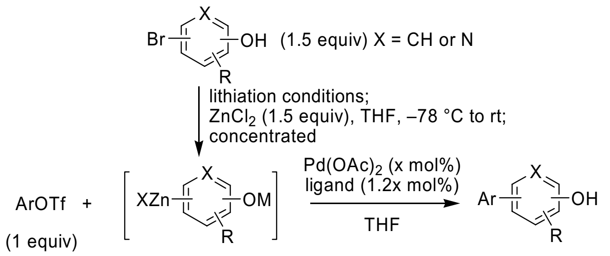
Since ligand **18** might not be the best ligand for our system, we screened various phosphine ligands. Based on the screening studies (entries 3–13), the activity of **19**[15] seemed to be higher than that of **18**, according to TLC analysis. Thus, we next compared the activity of **18** with

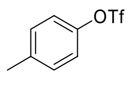
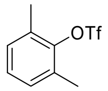
Table 2. Optimization of Negishi coupling step



Entry	Pd cat. (mol %)	Ligand (mol %)	Temperature (°C)	Time	Yield (%)
1	$Pd_2(dba)_3$ (0.5)	**18** (2)	45	2 h	92
2	$Pd_2(dba)_3$ (0.5)	**18** (2)	45	17 h	92
3	$Pd_2(dba)_3$ (0.5)	**19** (2)	45	2 h	96
4	$Pd_2(dba)_3$ (0.5)	**20** (2)	45	2 h	89
5	$Pd_2(dba)_3$ (0.5)	**21** (2)	45	2 h	92
6	$Pd_2(dba)_3$ (0.5)	**22** (2)	45	2 h	92
7	$Pd_2(dba)_3$ (0.5)	**23** (2)	45	2 h	90
8	$Pd_2(dba)_3$ (0.5)	**24** (2)	45	2 h	70
9	$Pd_2(dba)_3$ (0.5)	DPPF (1)	45	2 h	87
10	$Pd_2(dba)_3$ (0.5)	PCy_2Ph (2)	45	2 h	10
11	$Pd_2(dba)_3$ (0.5)	PCy_3 (2)	45	2 h	0
12	$Pd_2(dba)_3$ (0.5)	P(*o*-tol)$_3$ (2)	45	2 h	0
13	$Pd_2(dba)_3$ (0.5)	PPh_3 (2)	45	2 h	9
14	$Pd_2(dba)_3$ (0.5)	**18** (2)	rt	10 min	5
15	$Pd_2(dba)_3$ (0.5)	**19** (2)	rt	10 min	95
16	$Pd(OAc)_2$ (1)	**19** (2)	rt	20 min	95
17	$Pd(OAc)_2$ (1)	**19** (1.2)	rt	20 min	95
18	$Pd(OAc)_2$ (0.5)	**19** (0.6)	rt	2 h	91
19	$Pd(OAc)_2$ (0.1)	**19** (0.12)	rt	24 h	24

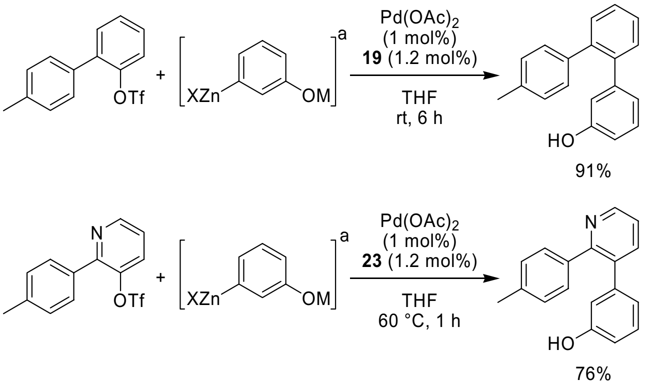
Table 3. Negishi coupling of various substrates



Entry	ArOTf	BrAr′	Lithiation conditions[a]	$Pd(OAc)_2$ (mol %)	Ligand	Temperature (°C)[b]	Time (h)[b]	Yield (%)
1		**9**	B	1	**19**	rt	1	92
2		**11**	A	1	**19**	45	2	80
3		**12**	A	1	**19**	45	2	80
4		**13**	A	1	**19**	rt	1	84
5		**14**	B	2	**19**	45	1	83
6		**15**	B	1	**19**	rt	2	70
7		**10**	C	2	**23**	60	1	78
8		**16**	C	2	**23**	60	2	78
9		**17**	C	2	**23**	60	1	75
10		**8**	A	2	**19**	45	20	94

[a] (A) *t*-BuLi (5.1 equiv), Et_2O, −78 °C, 30 min. (B) *t*-BuLi (5.1 equiv), Et_2O, −78 °C, 5 min, then THF, 30 min. (C) NaH (1.58 equiv), THF, rt, 30 min, then *t*-BuLi (3.15 equiv), −78 °C, 1 h.

[b] Temperature and reaction time for the Pd-catalyzed cross-coupling step.



Scheme 2. [a]Prepared by the same procedure as shown in Table 2.

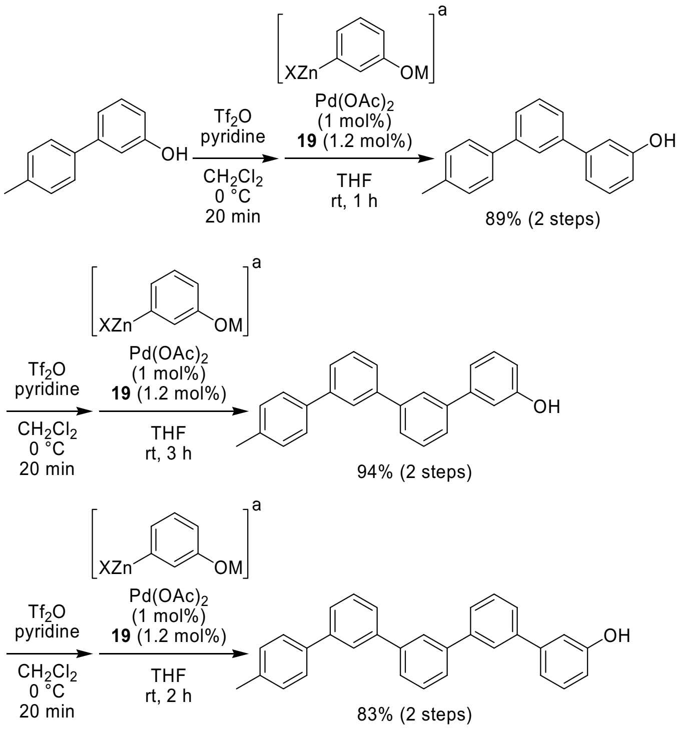
that of **19** at room temperature and found that **19** was indeed much more active than **18** (entry 14 vs 15). It is noteworthy that, even at room temperature, the reaction proceeded rapidly to give the product in excellent yields. The use of $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ was also found to be effective (entry 16), and the amount of the ligand can be reduced to 1.2 mol % (entry 17). As expected, lower loading of the catalyst led to significant retardation of the coupling reaction (entries 18 and 19).

As shown in Table 3, the reaction conditions were successfully applied to various zinciophenoxides and zinciopyridinoxides. Although higher temperatures were required in some cases, the products were obtained in good yields. Interestingly, **23**[16] was found to be the most effective ligand for the less reactive zinciopyridinoxides (entries 7–9). Interestingly, a bulky triflate (2,6-dimethylphenyl triflate) also gave the coupling product in a high yield (entry 10).

Subsequently, our Negishi coupling strategy was applied towards the synthesis of oligoarenes. As shown in Scheme 2, trimers were readily synthesized from the corresponding triflates and the zinciophenoxide (derived from **8**). In spite of the bulky *ortho*-aryl group of the triflates, high yields of the products were obtained. Again, the use of **23** as the ligand was favorable for the pyridyl-containing substrate.

As shown in Scheme 3, our Negishi coupling strategy was also used for the facile synthesis of a pentamer. In each triflation step, purification of the triflated product was unnecessary—the crude mixture obtained after work up was directly used for the next Negishi coupling step to give the coupling product in a high yield.

In summary, a repetitive two-step method for oligoarene synthesis based on Negishi coupling strategy was developed. For the preparation of zinciophenoxides and zinciopyridinoxides, the selection of appropriate conditions for the lithiation of bromophenols and bromopyridinols is crucial. In the Pd-catalyzed cross-coupling step, **19** was found to be an effective ligand for most substrates, whereas **23** was favorable for pyridyl-containing substrates. The availability of this Negishi coupling strategy, in addition to the Suzuki–Miyaura coupling strategy reported previously,[1,2] provides access to the synthesis of various multifunctionalized oligoarenes. Further studies to develop functional molecules based on these strategies are currently underway.



Scheme 3. [a]Prepared by the same procedure as shown in Table 2.

Acknowledgments

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Supplementary data

Experimental procedures and spectral data of the products. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.048.

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