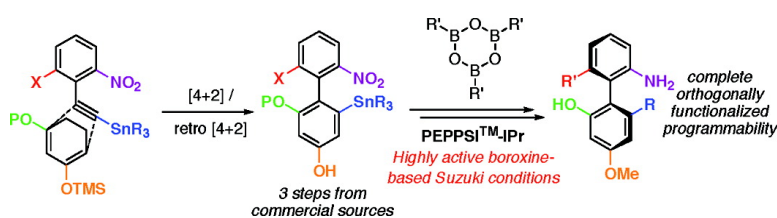


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Synthesis of Programmable Tetra-*ortho*-Substituted Biaryl Compounds Using Diels–Alder Cycloadditions/Cycloreversions of Disubstituted Alkynyl Stannanes

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The biaryl structural motif represents an important functionality in the biological and chemical communities.¹ In recent years, our laboratory² has been engaged in developing novel Diels–Alder based approaches to biaryls (DAB). This strategy has the distinct advantage of providing access to functional group combinations not readily available via traditional methods—particularly highly *ortho*-substituted biaryls. An ideal approach would provide ready access to an orthogonally functionalized biaryl template where two or more of the *ortho* substituents are available for subsequent functionalization. Consequently, this substitution pattern would require the use of an alkynyl halide or organometallic species as the dienophile in the cycloaddition process. While elegant work by Harrity, Hilt, Singleton, and others has demonstrated the utility of alkynyl boronates to undergo a net [4+2] process with suitably functionalized dienes,³ we are not aware of application of this technology to tetra-*ortho*-substituted biaryl synthesis. In this communication, we detail the successful construction of a series of unsymmetrical, programmable tetra-*ortho*-substituted biaryls containing *ortho*-oxygen and *ortho*-nitrogen functionality utilizing disubstituted alkynyl stannanes as dienophiles.

The key Diels–Alder cycloadditions/cycloreversions to form the highly substituted biaryl templates are shown in Table 1. The stannyl alkynes **1–4** were synthesized from their known corresponding 6-halo-2-nitrophenylacetylenes² using either Bu₃SnOMe (neat, 130 °C) or LDA, THF, and then Ph₃SnCl. The cycloaddition/cycloreversion sequence with chloro alkyne **1** proceeded in modest to good yields (48–75%) to provide the penta- or hexasubstituted biaryl products **11a–d** with *complete* orthogonal functionality between the five or six non-hydrogen substituents—four of which are *ortho* to the biaryl linkage. These biaryls **11a–d** are available in just 3 steps from commercially available reagents. While both alkyl and aryl groups are tolerated on the stannane, the alkyl groups consistently performed more efficiently in the biaryl formation. We attribute part of this superior reactivity to the relative robustness of the tributylacetylenic stannane as compared to the triphenylacetylenic stannane. Two oxygen substituents were required on the cyclic diene platform in order to facilitate reaction. Use of dienes such as 1-methoxy-1,3-cyclohexadiene, which had proven effective in previous DAB examples from our laboratory,² gave none of the desired biaryl product. Dimethyl dienes **6** and **10** were employed in cases where the resulting product was difficult to purify from the diene byproducts, particularly where oxidation of the dienes **5** and **8** to the corresponding benzene derivatives were competitive with cycloaddition.

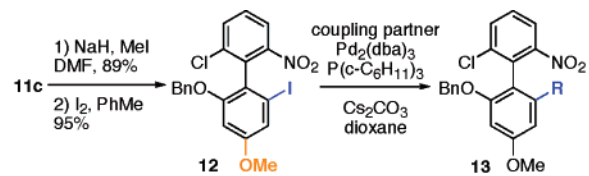
We then turned to functionalizing the biaryl templates (Table 2). Biaryl **11c** was selected as the platform for exploration of the reactivity of these compounds. For ease of subsequent functionalization, the *para*-phenolic moiety was protected as its methyl ether in excellent yield. We initially explored a range of Stille-based couplings with aryltributylstannane; however, we consistently

Table 1. Synthesis of Biaryl Templates

1 X = Cl, M = SnBu₃ **5** R = R' = H, P = Me
2 X = Cl, M = SnPh₃ **6** R = H, R' = P = Me
3 X = Br, M = SnBu₃ **7** R = R' = H, P = Et
4 X = Br, M = SnPh₃ **8** R = R' = H, P = Bn
9 R = P = Me, R' = H
10 R = H, R' = Me, P = Bn

Entry	Alkyne	Diene	X	M	P	R	Yield
a	1	5	Cl	SnBu ₃	Me	H	75%
b	1	7	Cl	SnBu ₃	Et	H	70%
c	1	8	Cl	SnBu ₃	Bn	H	72%
d	1	9	Cl	SnBu ₃	Me	Me	48%
e	2	5	Cl	SnPh ₃	Me	H	54%
f	2	10	Cl	SnPh ₃	Bn	H	33%
g	3	5	Br	SnBu ₃	Me	H	75%
h	4	6	Br	SnPh ₃	Me	H	39%

Table 2. Exploration of Scope for Lower Ring

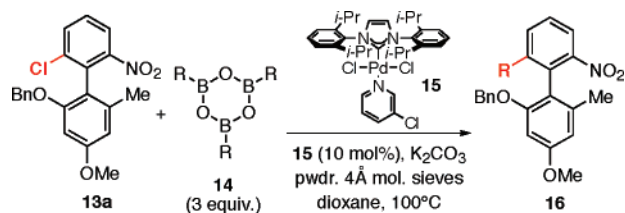


Entry	Coupling Partner (°C)	R	Yield
a	(MeBO) ₃ (80°C)	Me	92%
b	PhB(OH) ₂ (80°C)	Ph	82%
c	4-MeO-C ₆ H ₄ B(OH) ₂ (100°C)	4-OMe-C ₆ H ₄	86%
d	2-Me-C ₆ H ₄ B(OH) ₂ (100°C)	2-Me-C ₆ H ₄	74%
e	PhSnBu ₃ (45–80°C) ^a	Ph	63%
f	CH ₂ =CHCO ₂ Me (100°C)	E-CH=CH ₂ CO ₂ Me	73%

^a Alternate conditions used: Pd(PPh₃)₄, CuI, CsF, DMF.

observed little to no coupling with considerable amounts of protodestannylation. Consequently, we converted the aryl stannane into its corresponding iodide **12** in excellent yield. Optimum conditions for coupling the aryl iodide **12** employed the Pd₂(dba)₃/P(c-C₆H₁₁)₃ ligand system.⁴ We were able to readily functionalize the carbon–iodine bond through Suzuki couplings (entries a–d), a Stille coupling (entry e), and a Heck coupling (entries f). The success of the Stille coupling (entry e) combined with our inability to couple the methylated derivative of stannane **11c** supports our working hypothesis that the more sterically hindered of the two possible coupling partners should be functionalized as the aryl halide for optimum performance.

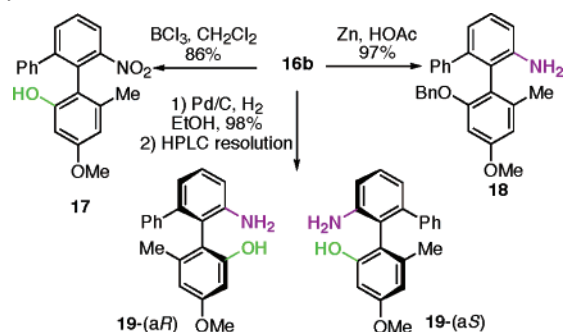
With an effective method for functionalizing the lower ring in hand, we next turned our attention cautiously to modifying the halogen in the upper ring. We were mindful of the inherent challenges of coupling of a highly substituted aryl chloride such

Table 3. Exploration of Scope for Suzuki Reaction in Upper Ring

Entry	R	Yield
a	Me	74%
b	Ph	83%
c	4-MeO-C ₆ H ₄	70%
d	3-MeO-C ₆ H ₄	75%
e	2-Me-C ₆ H ₄	63%
f	2,6-Me-C ₆ H ₃	0%
g	4-CF ₃ -C ₆ H ₄	50%

as **13a** through our own unsuccessful previous experience with tetra-*ortho*-substituted aryl chlorides in our phosphorus-containing biaryls.^{2b} As a methyl moiety is the least sterically demanding of the carbon-based nucleophiles, we used commercially available methyl boroxine as the coupling partner for the initial investigation. We screened a wide range of coupling systems including those developed by Fu [(*t*-Bu₃P)₂Pd]⁵ and Buchwald [Pd(OAc)₂, S-Phos].⁶ We were disappointed to observe only poor or no reaction in all cases. We next turned our attention to the recently developed and commercially available PEPPSI-IPr catalyst (**15**) by Organ and co-workers.⁷ We were quite pleased to observe clean conversion to the Suzuki product **16a** in good yield (74%). When we explored alternate boron-based nucleophiles such as PhB(OH)₂, we were surprised to observe no reaction—even at high catalyst loading and with excess boronic acid. As our boron source for the successful coupling to produce **16a** had employed the boroxine **14**, we felt it would be prudent to screen the analogous phenyl boroxine **14b**⁸ in the reaction protocol. We were quite gratified to find clean construction of the tetra-*ortho*-substituted biaryl **16b**. Optimum conditions employed 3 equiv of the boroxine **14** and powdered 4 Å molecular sieves in order to remove any adventitious water. To the best of our knowledge, the unique and powerful role of the boroxines in Suzuki couplings has not been previously reported.⁹ These conditions have proven to be the most reactive that we have found during our studies in challenging C–C bond forming reactions.² Additionally, reasonable functional group tolerance was observed using this reaction protocol. Electron donating substituents in the *ortho*, *meta*, and *para* positions of the aryl boroxine are all tolerated. One limitation appears to be the 2,6-dimethylphenyl boroxine **14f**. Successful coupling with electron deficient boroxine **14g** was also observed in reasonable yield (50%).

Orthogonal and/or tandem functionalization of these highly substituted biaryls could be readily accomplished (Scheme 1). Selective formation of the *ortho*-anilino or *ortho*-phenolic functionalities were demonstrated using Zn/HOAc or BCl₃, respectively. Tandem reduction using Pd/C, H₂ revealed the anilino phenol **19** in excellent yield. This biaryl could be readily resolved using chiral HPLC separation (Daicel OD column). These axially chiral anilino phenols **19-(aR)** and **19-(aS)**¹⁰ should be of considerable interest to the synthetic community as they closely resemble the 2-amino-2'-hydroxy-1,1'-binaphthyl (NOBIN) class of binaphthalene-based ligands. Interestingly, while NOBIN has been utilized in asymmetric catalysis—including in Carreira's asymmetric aldol methodology,¹¹ little variation of the binaphthalene core structure has been explored to date.

Scheme 1. Further Functionalization of Tetra-*ortho*-Substituted Biaryl **16b**

In conclusion, a DAB strategy has been developed for the construction of highly functionalized biaryl templates utilizing arylacetylenic stannanes and cyclic dienes. The sequential functionalization of a representative template compound **11c** has been demonstrated. Highly active boroxine-based, anhydrous Suzuki coupling conditions have been developed which should be of considerable interest to the synthetic community. Finally, the ability to resolve an axially chiral anilino phenol has been demonstrated. Further application of this DAB strategy will be reported in due course.

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Supporting Information Available: Complete experimental procedures, including ¹H and ¹³C spectra, of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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