Biaryl Synthesis

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Diels–Alder Approach to Polysubstituted Biaryls: Rapid Entry to Tri- and Tetra-*ortho*-substituted Phosphorus-Containing Biaryls**

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Biaryl compounds have garnered considerable synthetic interest as a result of their presence as a structural motif in natural products[1,2] and their utility as ligands in metal catalysis.[3] While synthetic methods have been reported for the construction of selected biaryls, innovative strategies are needed to broaden their accessibility. Effective methods for the synthesis of biaryl linkages have progressed dramatically in recent years, primarily as a result of the use of palladium-mediated strategies, such as the Kharasch, Negishi, Stille, and Suzuki reactions.[1a] Of equal recent importance are the considerable contributions in the area of iron-catalyzed couplings[4] and the use of other metals, such as manganese,[5] nickel,[6] and copper.[7] Although these approaches have yielded valuable routes to the target functionality, limitations in their effectiveness have been observed. For example, although successful cases do exist,[8] tetra-*ortho*-substituted biaryls often prove difficult to construct.[2b,9] One rational for this lack of general availability is due to the added degree of difficulty in coupling two bis-*ortho*-substituted aryl precursors.[10]

A conceptually different approach to the synthesis of biaryls is the use of a Diels–Alder cycloaddition. Diels–Alder reactions are well documented for their generality and broad applicability.[11] Despite this factor, no general approach to biaryl compounds using a cycloaddition strategy has been reported.[12] One added advantage to this Diels–Alder approach is the ability to incorporate functional-group combinations (e.g., halogenated biaryls) that would not be readily accessible by traditional metal-mediated aryl–aryl couplings. In addition, the proper choice of substituents on the diene and dienophile should allow for the combination of the atom-economic benefits of cycloadditions with the power of subsequent metal-mediated couplings on the Diels–Alder adducts. Herein, we disclose our application of this concept to

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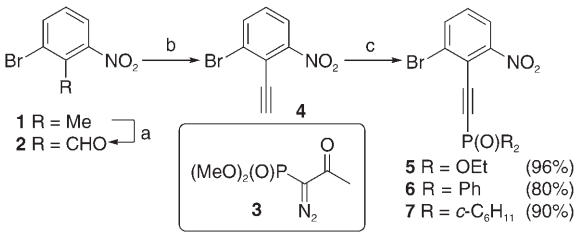
the rapid synthesis of a series of phosphorus-containing tri- and tetra-*ortho*-substituted biaryls.

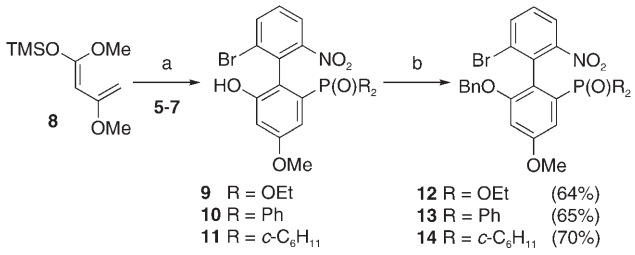
The dienophile subunit can be constructed quickly from the commercially available toluene derivative **1** (Scheme 1). Treatment of **1** with the *N*,*N*-dimethylformamide (DMF)



Scheme 1. Synthesis of phosphorus-containing dienophiles. Reagents and conditions: a) $(MeO)_2CH(NMe_2)$, DMF, 135 °C; then $NaIO_4$, DMF, H_2O, 0 °C (67%); b) **3**, K_2CO_3, MeOH (85%); c) LDA, $ClP(O)R_2$ (0.8 equiv).

dimethyl acetal at 135 °C followed by addition to a cooled (0 °C) solution of $NaIO_4$ in aqueous DMF yielded the aldehyde **2**.[13] This approach is based on a protocol developed by researchers at Pfizer;[14] however, use of their exact conditions led to formation of a significant amount of by-products. We found that cooling of the enamine solution to 0 °C and rapid addition to a vigorously stirred solution of $NaIO_4$ at 0 °C completely suppressed the formation of these impurities. Reaction of the aldehyde **2** with the Ohira–Bestmann reagent[15] **3** provided the desired alkyne **4**. Subsequent lithiation with lithium diisopropylamide (LDA; 1 equiv) followed by the addition of the requisite electrophiles (0.8 equiv) generated the dienophiles **5**–**7** in high yields (> 80%).

Diels–Alder cycloaddition of the dienophiles **5**–**7** with the known Brassard diene **8**[16] followed by aromatization in situ using Et_3N[17] yielded the target tetra-*ortho*-substituted biaryls (Scheme 2). We initially employed tetrabutylammonium



Scheme 2. Synthesis of biaryls by Diels–Alder cycloaddition. Reagents and conditions: a) PhMe, 80 °C, 16 h; then Et_3N, 0 °C; b) BnBr, NaH, DMF, THF, 0 °C→RT; yields reported over two steps (Bn = benzyl).

fluoride (TBAF) to induce silyl deprotection and aromatization; however, the yields were inconsistent and lower than with the work-up with Et_3N. This approach provides access to aryl- and alkyl-substituted phosphine oxides and phosphonates. As a result of the highly crystalline nature of the tetra-*ortho*-substituted phenolic biaryls, protection of the phenol as its benzyl ether was employed to improve solubility for subsequent transformations. X-ray crystallographic analysis of biaryl **14** shows the perpendicular orientation of the biaryl linkage (Figure 1).[18]

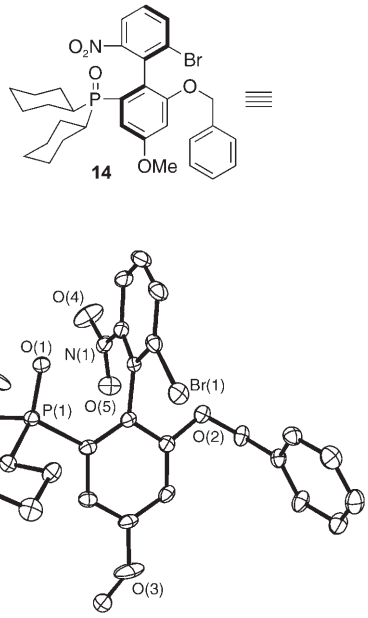
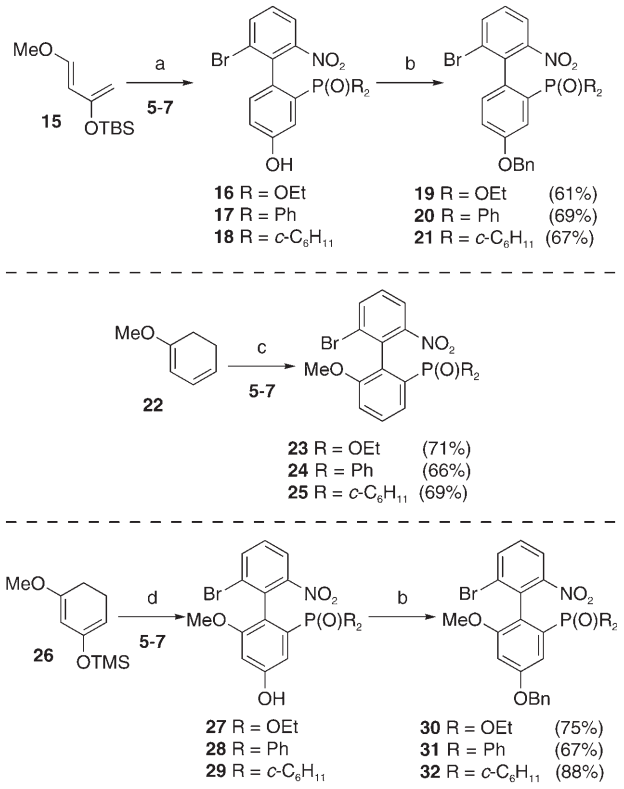


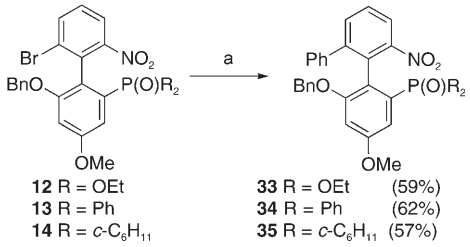
Figure 1. X-ray crystal structure of biaryl **14** as an ORTEP representation. Ellipsoids are shown at the 30% probability level.

Diels–Alder cycloadditions with acetylenic phosphonates are not limited to the Brassard diene (Scheme 3). Treatment of dienophiles **5**–**7** with the commercially available *tert*-butyldimethylsilyl (TBS) Danishefsky diene **15** followed by desilylation and aromatization in situ yielded the trisubstituted biaryls **16**–**18**. As demonstrated previously, benzylation of the resultant phenol was performed to improve solubility for subsequent transformations, and the yields were reported over the two steps (61–69%). We also found that oxygenated cyclohexadienes are active dienes for this process. The commercially available 1-methoxy derivative **22** gave the corresponding tetrasubstituted biaryls **23**–**25** in good yield (66–71%). Finally, use of the known 1,3-dialkoxy substrate **26**[19] efficiently provided the corresponding biaryls **30**–**32** in 67–88% yield after benzylation.

Metal-mediated couplings of the halide-containing biaryls could be accomplished in good yield (Scheme 4). As the pentasubstituted biaryls **12**–**14** possessed the highest degree of orthogonal functionalization, we decided to explore the coupling process with this series. After screening several of the commercially available catalyst systems developed for sterically challenging palladium couplings (including the Buchwald ligands,[20] $(P(c\text{-}C_6H_{11})_3/[Pd_2(dba)_3]$ (dba = dibenzylideneacetone),[21] $[Pd(dppf)Cl_2]$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene), and $Pd(OAc)_2$/1,3-bis(diphenylphosphino)propane (dppp)[22]), we found that the Fu $[Pd(PtBu_3)_2]$ catalyst[23] proved the most effective in generating the coupled adducts **33**–**35**. For both the Suzuki[23a] and Stille couplings,[23b] high catalyst loading (20 mol%) and



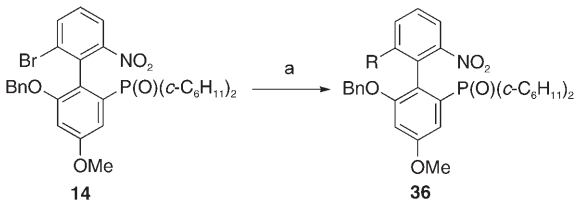
Scheme 3. Exploration of the diene scope in the Diels–Alder cycloaddition. Reagents and conditions: a) PhMe, 80 °C, 16 h; then TBAF, 0 °C; b) BnBr, NaH, DMF, THF, 0 °C→RT; yields reported over two steps; c) neat, 155 °C, 24 h; d) neat, 140 °C, 17 h.



Scheme 4. Negishi coupling of biaryls. Reagents and conditions: a) [Pd(P*t*Bu$_3$)$_2$] (10 mol%), PhZnCl (1.5 equiv), NMP/THF, 80 °C, 16 h. NMP = *N*-methylpyrrolidone.

excess boronic acid or stannane (3 equiv) were required to drive the reaction to completion. In contrast, the Negishi-style organozinc couplings[23c] proceeded in good yield with a more reasonable catalyst loading (10 mol%) and lower amounts of the organozinc species (1.5 equiv). It should be noted that nickel-catalyzed couplings are not effective on substrates such as **12**–**14** because of the NO_2 functionality.[23c,24]

Given the efficiency of the Negishi couplings with tetra-*ortho*-substituted biaryls **12**–**14** and phenylzinc chloride, a range of organozinc species was explored to gauge the potential utility in the metal-mediated couplings (Scheme 5). As shown in Table 1, these palladium-couplings proved successful with a variety of substituents on the organozinc moiety. Both electron-donating and electron-withdrawing groups are tolerated. One limitation can be found in our inability to achieve successful Negishi coupling with 2-methoxyphenylzinc chloride (Table 1, entry 3); however, *ortho*-substitution on the organozinc species is tolerated (entries 4 and 5). In fact, the more sterically hindered examples perform better in the coupling process. Finally, the pentafluorophenylzinc species could be cleanly coupled with bromide **14** to yield the pentafluorophenyl product **36f** (Table 1, entry 6).



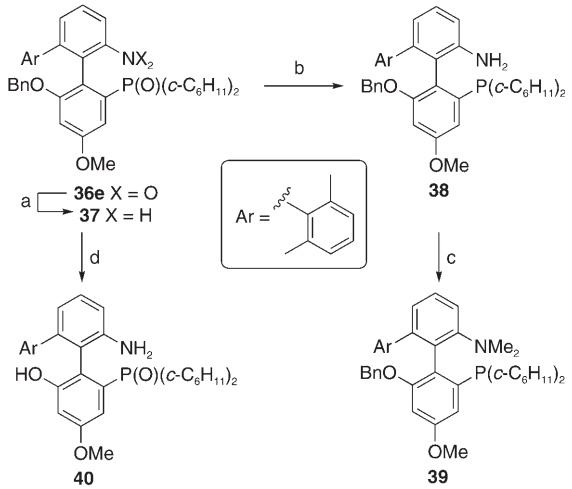
Scheme 5. Selected examples of Negishi couplings with biaryl **14**. Reagents and conditions: a) [Pd(P*t*Bu$_3$)$_2$] (10 mol%), RZnCl (1.5 equiv), NMP/THF, 80 °C, 16 h.

Table 1: Selected examples of Negishi couplings with biaryl **14**.

Entry	RZnCl[a]	Yield of **36** [%]
1	4-methoxyphenylzinc chloride	59
2	3-methoxyphenylzinc chloride	58
3	2-methoxyphenylzinc chloride	0
4	2-methylphenylzinc chloride	61
5	2,6-dimethylphenylzinc chloride[b]	66
6	pentafluorophenylzinc chloride	57

[a] The organozinc species was formed by addition of the in situ generated organomagnesium species to a solution of anhydrous zinc chloride in THF (1 M). [b] An extended reaction time (48 h) was employed for this coupling.

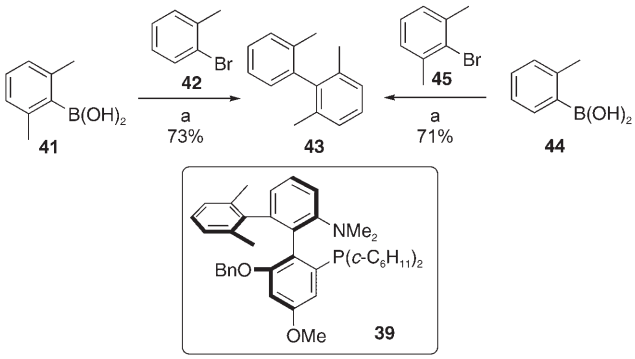
The reduction of selected biaryls was also studied (Scheme 6). The nitro arene **36e** can be cleanly converted into the corresponding amine **37** by reduction with Zn/AcOH.



Scheme 6. Reduction of selected biaryls. Reagents and conditions: a) Zn, HOAc, 16 h (85%); b) [Ti(O*i*Pr)$_4$], PMHS, THF, 80 °C, 48 h (61%); c) $NaBH_3CN$, paraformaldehyde, MeCN, AcOH (80%); d) BCl_3, CH_2Cl_2, 0 °C, 3 h (70%).

After screening a broad range of conditions for the conversion of the phosphine oxide **37** into its corresponding phosphine **38**, we found that this process could be accomplished in a reasonable yield using [Ti(O*i*Pr)$_4$]/poly(methylhydrosiloxane) (PMHS).[25] Reductive amination generated the dimethylaminophosphine **39**. Attempted removal of the benzyl moiety under hydrogenation conditions (Pd/C or PtO_2, H_2) gave problematic results. Fortunately, removal of the benzyl ether from **37** could be cleanly accomplished using BCl_3.

In order to show the utility of the synthesized materials, we chose to investigate palladium-mediated couplings using amino phosphine **39** as a ligand (Scheme 7). The structure of



Scheme 7. Utility of the synthesized biaryl **39** in the Suzuki coupling. Reagents and conditions: a) $Pd(OAc)_2$ (5 mol%), **39** (10 mol%), K_3PO_4, PhMe, 100°C, 20 h.

this catalyst is based on the pioneering work of Buchwald and co-workers.[26] Preliminary screening of **39** appears to indicate that a highly active catalyst is generated for Suzuki couplings, as demonstrated in the synthesis of the sterically challenging tri-*ortho*-substituted biaryl **43**. It is important to note that the control experiment (in the absence of phosphine) with boronic acid **41** and bromide **42** ($Pd(OAc)_2$ (5 mol%), K_3PO_4, PhMe, 100°C, 20 h) gave only a minor amount (18%) of the desired coupled material **43**. Use of PPh_3 as the ligand also gave inferior results. Further exploration in the scope and utility of our Diels–Alder approach to biaryls for the synthesis of novel ligand systems will be reported in due course.

In summary, we have demonstrated a novel method for the construction of highly substituted, orthogonally functionalized biaryl compounds previously not accessible by traditional methods. Subsequent manipulation of the resultant biaryls through palladium-coupling and/or reduction provides access to a significant range of substitution patterns. Finally, the potential utility of aminophosphine **39** as a ligand in challenging cross-coupling reactions has been demonstrated.

Experimental Section

14: Compound **8** (4.14 g, 20.4 mmol) was added to a pressure vessel containing **7** (2.24 g, 5.11 mmol) and PhMe (10.2 mL) at room temperature. The reaction mixture was heated at 80°C. After 18 h, the reaction mixture was cooled to 0°C and Et_3N (2.59 g, 3.58 mL, 25.6 mmol) was slowly added. After the orange solution had been stirred for 6 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (70 mL), diluted with EtOAc (70 mL), and washed with H_2O (70 mL) and saturated aqueous NaCl (70 mL). The dried extract ($MgSO_4$) was concentrated in vacuo. The crude product **12** was dissolved in DMF (25.6 mL) and cooled to 0°C. BnBr (17.5 g, 102 mmol, 11.8 mL) and NaH (1.02 g, 25.6 mmol, 60% in mineral oil) were added to this solution. After 8 h, the mixture was quenched with saturated aqueous NH_4Cl (100 mL), diluted with EtOAc (100 mL), and washed with H_2O (100 mL) and saturated aqueous NaCl (100 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel eluting with EtOAc/hexanes (50:50) to give **14** (2.26 g, 3.62 mmol, 70%) as a bright-yellow crystalline solid. M.p.: 202–203°C; IR (neat): $\tilde{\nu}$ = 2930, 1597, 1524, 1302 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J = 8.2, 1.2 Hz, 1H), 7.87 (dd, J = 8.0, 1.2 Hz, 1H), 7.33 (t, J = 8.6 Hz, 1H), 7.25–7.31 (m, 3H), 7.18–7.19 (m, 2H), 6.75 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 11.5, 2.2 Hz, 1H), 5.10 (s, 2H), 3.87 (s, 3H), 1.20–1.96 ppm (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (d, $J_{C,P}$ = 16 Hz, 1C), 158.2 (d, $J_{C,P}$ = 14 Hz, 1C), 150.7, 136.7, 136.5, 134.1 (d, $J_{C,P}$ = 1.9 Hz, 1C), 130.6, 129.8, 128.6, 128.4, 127.7, 127.6, 126.4, 125.8, 123.2, 107.6 (d, $J_{C,P}$ = 12 Hz, 1C), 101.5 (d, $J_{C,P}$ = 1.7 Hz, 1C), 70.6, 55.5, 38.2, 37.6 (d, $J_{C,P}$ = 3.9 Hz, 1C), 36.9, 26.8 (d, $J_{C,P}$ = 8.5 Hz, 1C), 26.7 (d, $J_{C,P}$ = 8.9 Hz, 1C), 26.6 (d, $J_{C,P}$ = 2.0 Hz, 1C), 26.5 (d, $J_{C,P}$ = 3.3 Hz, 1C), 26.4 (d, $J_{C,P}$ = 3.3 Hz, 1C), 25.9 (d, $J_{C,P}$ = 1.4 Hz, 1C), 25.7 (d, $J_{C,P}$ = 2.1 Hz, 1C), 25.0 (d, $J_{C,P}$ = 3.3 Hz, 1C), 24.7 (d, $J_{C,P}$ = 3.6 Hz, 1C); HRMS (FAB+) calcd for $C_{32}H_{38}NO_5PBr$ [M+H]: 626.1671; found: 626.1653.

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[18] CCDC-605862 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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