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APPLICATION OF A CU(I)-MEDIATED BIARYL CROSS-COUPLING REACTION TO THE SYNTHESIS OF OXYGENATED 1,1′-BINAPHTHALENES

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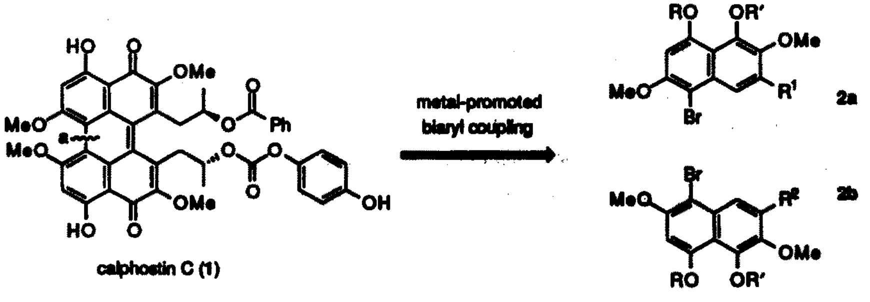
Abstract: *Application of an oxidative copper(I)-mediated biaryl cross-coupling protocol to the synthesis of highly oxygenated, differentially substituted 1,1′-binaphthalenes related to the perylenequinone calphostin C is detailed.*

In the course of our synthetic studies[2] on the protein kinase C inhibitor calphostin C (**1**),[3] we required effective methodology for the formation of a 1,1′-biaryl bond (bond a of **1**) by the transition metal-mediated coupling of highly oxygenated, *ortho*-substituted naphthalene systems. Our strategy necessitated that this bond be formed between differentially functionalized naphthalene subunits such as **2a** and **2b** (*i.e.*, $R^1 \neq R^2$) *via* a cross-coupling reaction. Previous approaches to the total synthesis of the calphostins[4] have used an $FeCl_3$-promoted dimerization reaction, which affords the desired homocoupled 1,1′-binaphthalene products in low yields, and provides no capability of effecting cross-coupling. We deemed that an effectual synthesis of calphostin C necessitated resolution of problems that are commonly encountered in transition metal-mediated biaryl cross-coupling reactions of hindered, electron-rich aromatic systems. During the course of our investigations on this matter, Lipshutz and co-workers[5] disclosed an oxidative Cu(I)-promoted biaryl cross-coupling procedure that proved ideal in our hands when applied to highly functionalized, electron-rich naphthalenes such as **2**. Herein, we communicate the application of this Cu(I)-based protocol for biaryl cross-coupling[5] to the formation of 1,1′-binaphthalene systems as a key step in the total synthesis of **1**.



calphostin C (**1**)

2a

2b

Initial efforts at Pd(0)-promoted cross-coupling of electron-rich, *ortho*-substituted naphthalenes were directed toward simple 2-alkoxy-1-halonaphthalenes. The most successful procedure involved Suzuki coupling.[6] Thus, lithiation of **3** with *n*-BuLi (THF, –78 °C) followed by reaction of the resulting aryllithium species with trimethyl borate afforded the boronic acid **4** ($X = B(OH)_2$) after aqueous workup; this reagent could be coupled with iodonaphthalene **5** using modified conditions detailed by Suzuki[6a] to afford 1,1′-binaphthalene **6** in a modest 39% yield. Alternatively, lithiation of **3** with *n*-BuLi followed by transmetallation with $ZnCl_2$ afforded the arylzinc reagent **4** (X = ZnCl), which could be coupled with iodide **5** using $Pd(PPh_3)_4$ in DME containing 10% v/v HMPA at 101 °C to afford **6** in 36% yield.[7a] Equally successful was the use of the catalyst $(CH_3CN)_2PdCl_2$ with **4** (X = ZnCl) and **5** in the same solvent at 65 °C,[7a] conditions that afforded **6** in 35% yield. Interestingly, *no coupling was observed in the absence of HMPA*. The use of the Ni(II) catalysts $(Ph_3P)_2NiCl_2$ or (dppp)$NiCl_2$ with aryl Grignard reagent **4** (X = MgBr)[7b] was unsuccessful in providing **6**.

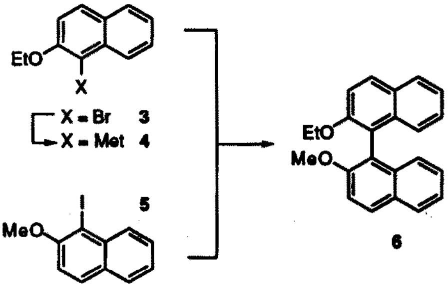
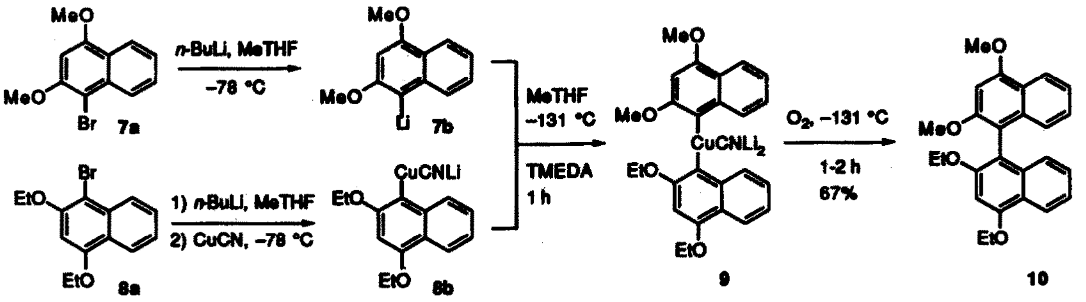
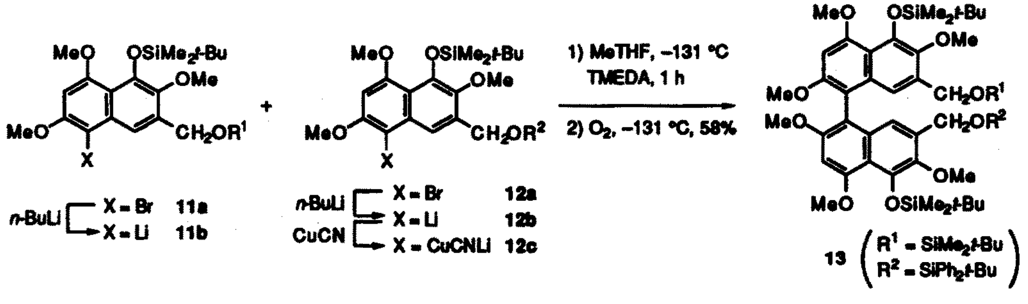


TABLE Pd-CATALYZED BIARYL CROSS-COUPLINGS			
4 (X =)	CATALYST	CONDITIONS	YIELD 6
$B(OH)_2$	$Pd(PPh_3)_4$	DMSO, K_3PO_4 75 °C	39%
ZnCl	$Pd(PPh_3)_4$	DME/HMPA 101 °C	36%
ZnCl	$(CH_3CN)_2PdCl_2$	DME/HMPA 65 °C	35%

With the more highly oxygenated systems **7a** and **8a**,[9] Suzuki borinate methodology[6] was completely unsuccessful in providing the desired 1,1′-binaphthalene **10**. This failure appeared to stem from hydrolytic instability of the boronic acid obtained from **7a** under literature reaction conditions.[6] Concurrent with the failure of the Suzuki and other coupling protocols,[7,8] the opportunity arose for the application of a novel Cu(I)-based method to this problem. Lipshutz and co-workers recently communicated methodology for the oxidative cross-coupling of kinetically formed, mixed biaryl higher-order cyanocuprates.[5] The application of this protocol to the synthesis of 1,1′-binaphthalene **10** proceeded smoothly, starting from bromonaphthalenes **7a** and **8a**. Thus, lithiation of **7a** by lithium-halogen exchange using *n*-BuLi (1.0 equiv) in 2-methyltetrahydrofuran (MeTHF) at –78 °C afforded aryllithium **7b**; similar treatment of **8a** followed by transmetallation of the intermediate aryllithium with copper cyanide (1.0 equiv) at –78 °C afforded the lower-order cyanocuprate **8b**. A solution of aryllithium **7b** at –78 °C was added dropwise *via* cannula to cuprate **8b** at –131 °C (EtOH/liq. N_2). After the addition of TMEDA (2.0 equiv), the higher-order cyanocuprate **9** was allowed to form for 1 h at –131 to –100 °C. A stream of dry, precooled (–78 °C) oxygen gas was bubbled vigorously through the reaction mixture at –131 °C using a fine fritted gas inlet tube for 2 h. Excess O_2 was removed by a pump/refill cycle with argon gas, and the reaction was quenched by the addition of satd. NH_4Cl/NH_4OH (9:1). Binaphthalene **10** was isolated by chromatography (Et_3N deactivated silica gel, CH_2Cl_2) in 67% yield.[10] A significant quantity of material was lost during chromatography due to instability of **10** to silica gel; the actual conversion typically ranged from 75-90%, as determined by ^1H NMR analysis of crude reaction extracts.[11]



This methodology was applied with equal success to oxygenated naphthalene systems of direct relevance to synthesis of calphostins C.[2] Using a reaction protocol identical to that described above,[5] bromonaphthalenes **11a** and **12a**[12] were lithiated with *n*-BuLi (MeTHF, –78 °C) to afford **11b** and **12b**, respectively. Naphthyllithium **12b** was transmetallated to the corresponding lower-order cyanocuprate **12c** by treatment with CuCN (1 equiv, –78 to 0 °C). A solution of organolithium reagent **11b** at –78 °C was added dropwise to cuprate **12c** at –131 °C (EtOH/liq. N_2), and after allowing the corresponding higher-order cuprate to form in the presence of excess TMEDA (1 h, –131 to –100 °C), the mixture was treated with a stream of precooled O_2 gas (1-2 h) at –131 °C. Using this procedure, cross-coupled 1,1'-binaphthalene **13** was obtained in 58% unoptimized yield[11] after chromatography (Et_3N deactivated silica gel, 10% EtOAc/hexanes).[13]



We have demonstrated an effective application of the Cu(I)-promoted biaryl cross-coupling reaction[5] of electron-rich, *ortho*-substituted naphthalene systems to the synthesis of 1,1'-binaphthalenes. The methodology detailed herein is capable of efficiently providing the highly functionalized, *unsymmetrical* binaphthalene **13**, which is of immediate relevance to our efforts[2] directed towards the total synthesis of the calphostin family of natural products,[3] and which was *unobtainable* using previously established protocols for biaryl coupling.[4,6,7]

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1. (a) Recipient of a Camille and Henry Dreyfus Foundation Distinguished New Faculty Award (1989-94), an American Cancer Society Junior Faculty Research Award (1991-93), and an American Cyanamid Faculty Award (1993). (b) Genentech Investigator in Biomolecular Chemistry (1990-1992).
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9. Naphthalenes **7a** and **8a** were prepared from commercially available 1,3-dihydroxynaphthalene (Aldrich) by the following reaction sequence: (a) (MeO)$_2$SO$_2$, K$_2$CO$_3$, acetone (100%) or NaH, EtBr, cat. *n*-Bu$_4$NI, (98%); (b) NBS, THF, 0 °C, 88-89%.
10. **2,4-Diethoxy-2′,4′-dimethoxy-1,1′-binaphthalene (10).** ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.26 (d, J = 8.5 Hz, 1 H, C8-H), 8.22 (d, J = 7.7 Hz, 1 H, C8′-H), 7.26 (m, 2 H, C5-H and C5′-H), 7.18 (m, 2 H, C7-H and C7′-H), 7.10 (m, 2 H, C6-H and C6′-H), 6.79 (s, 1 H, C3-H), 6.76 (s, 1 H, C3′-H), 4.27 (q, J = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 4.09 (s, 3 H, OCH$_3$), 3.94 (m, 2 H, OC*H*$_2$CH$_3$), 3.73 (s, 3 H, OCH$_3$), 1.59 (t, J = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 1.01 (t, J = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR (500 MHz, CDCl$_3$) δ 156.9, 156.8, 155.9, 155.3, 135.3, 127.2, 125.7, 123.2, 122.4, 122.3, 122.0, 113.4, 112.7, 97.7, 95.0, 66.2, 64.2, 57.6, 56.0, 15.6, 15.3; EIMS *m/e* (relative intensity) 402 (M$^+$, base), 373 (25), 342 (25), 313 (35), 241 (30), 185 (43).
11. In the FeCl$_3$-promoted homocoupling of naphthyllithium substrates, Broka[4b] recycles recovered debromonaphthalene by-products, thereby raising the "overall yield" of products. In the examples of cross-coupling reported herein, the major by-products of the reactions are the debrominated naphthalenes accompanied by small amounts (≤ 5%) of homocoupled products. It is possible, though not expedient, to recover these materials for reconversion to cross-coupling substrates; performing these reactions on a larger scale likely will alter the economics of this situation.
12. Prepared from previously described naphthalenes[2] by the sequence: (1) NaH, *t*-BuMe$_2$SiOTf, THF; (2) NBS, THF, –78°C, 90%; (3) (*i*-Bu)$_2$AlH, –78 °C, 96%; (4) *t*-BuPh$_2$SiCl or *t*-BuMe$_2$SiCl, imidazole, 90%.
13. **1,1′-(Di-*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3′-((*tert*-butyldimethylsilyloxy)methyl)-2,2′,6,6′,8,8′-hexamethoxy-5,5′-binaphthalene (13).** ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.51 (d, J = 6.7 Hz, 2 H, PhSi), 7.46 (d, J = 6.7 Hz, 2 H, PhSi), 7.38-7.20 (m, 6 H, PhSi), 7.14 (s, 1 H, C4-H), 6.86 (s, 1 H, C4′-H), 6.69 (s, 1 H, C7-H), 6.62 (s, 1 H, C7′-H), 4.72-4.60 (m, 4 H, ArCH$_2$O and ArCH$_2$′O), 3.94 (s, 3 H, OCH$_3$), 3.89 (s, 3 H, OCH$_3$), 3.94 (s, 9 H, OCH$_3$), 3.51 (s, 3 H, OCH$_3$), 1.04 (s, 9 H, SiC(CH$_3$)$_3$), 1.02 (s, 9 H, SiC(CH$_3$)$_3$), 0.73 (s, 9 H, SiC(CH$_3$)$_3$), 0.67 (s, 9 H, SiC(CH$_3$)$_3$), 0.13 (s, 6 H, Si(CH$_3$)$_2$), 0.11 (s, 6 H, Si(CH$_3$)$_2$), 0.09 (s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR (500 MHz, CDCl$_3$) δ 157.6, 154.9, 144.4, 144.2, 143.8, 135.8, 135.3, 135.1, 134.5, 134.4, 134.0, 133.8, 129.8, 127.9, 117.3, 117.1, 116.7, 113.4, 113.2, 95.7, 61.8, 61.3, 60.6, 60.5, 57.5, 55.3, 55.2, 27.0, 26.6, 26.2, 19.3, 19.1, 18.5, 0.383, –3.53, –3.55, –3.60, –3.64, –5.10, –5.13; EIMS, *m/e* (relative intensity) 1107 (M$^+$, 4), 983 (6), 365 (85), 297 (base); HRMS, *m/e* calcd for C$_{62}$H$_{90}$O$_{10}$Si$_4$: 1106.559; found: 1106.561.

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