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Biaryls via Suzuki Cross-Couplings Catalyzed by Nickel on Charcoal☆

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Abstract—Using the heterogeneous catalyst 'Ni/C', biaryl bonds can be made between functionalized aryl chlorides and boronic acids in good isolated yields. A standard set of conditions has been developed which applies to a variety of reaction partners. © 2000 Elsevier Science Ltd. All rights reserved.

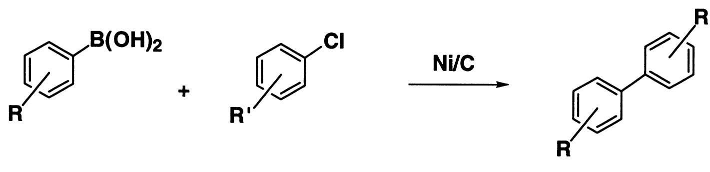
Introduction

Suzuki couplings which produce biaryl products are currently among the most highly prized processes in synthetic chemistry.[1] In just over the past year alone, *Chemical & Engineering News* has highlighted these C–C bond-forming reactions several times in large measure due to advances in Pd(0)-catalyzed processes which have allowed for the use of inexpensive aryl chlorides.[2] Unfortunately, overlooked in these reports is the contribution by Miyaura and co-workers,[3] which appeared in 1997, describing related couplings in solution albeit catalyzed by in situ generated Ni(0). A healthy number of subsequent papers on this theme have also highlighted the virtues of nickel catalysis involving chloroaromatics,[4] including a remarkable coupling under aqueous conditions described by Genet.[5] A feature common to many biaryl constructions is the involvement of catalysis under homogeneous conditions, whether palladium- or nickel-based. We have disclosed the first use of the heterogeneous catalyst, nickel on charcoal (Ni/C), as an especially inexpensive and environmentally friendly species which smoothly mediates Negishi couplings between functionalized aryl chlorides and organozinc halides.[6a] More recently, we have found that Kumada couplings with Grignards in hot THF can be effected with this catalyst.[6b] In this report, we describe details surrounding the experimental changes in conditions required for utilizing Ni/C to effect Suzuki biaryl couplings, as generalized in Scheme 1.

Results

Generation of the catalyst follows from procedures delineated in earlier work on related couplings.[6] Varying levels (0.50–0.75 mmol/g) of nickel(II) on charcoal are readily obtained by impregnating $Ni(NO_3)_2$ on commercially available charcoal of usually >200 mesh. This material, which is best stored under argon, is conveniently reduced to active Ni(0)/C simply upon stirring as a suspension in dioxane to which is first added triphenylphosphine (4 equiv.) and then *n*-BuLi (4 equiv.) at room temperature. After 15 min of continued stirring, the catalyst is ready for use.

Most Suzuki reactions tend to be carried out in dioxane.[1] A quick screening of solvents revealed that alternatives such



Scheme 1.

☆ It is with warmest congratulations and best wishes for continued good health and happiness that this contribution is dedicated to Prof. Harry H. Wasserman, who in this first year of the new millennium turns 80 years young.

Keywords: Suzuki couplings; biaryls; nickel; heterogeneous catalysis.

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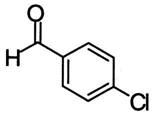
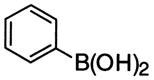
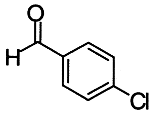
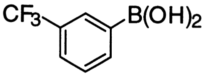
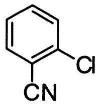
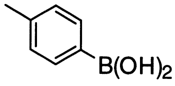
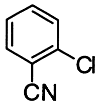
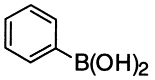
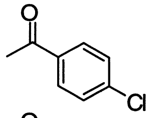
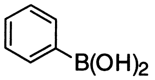
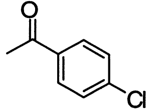
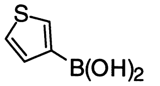
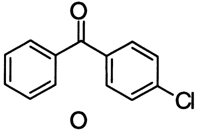
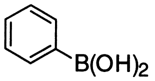
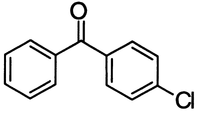
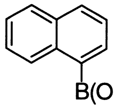
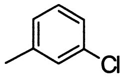
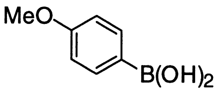
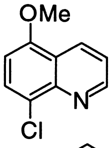
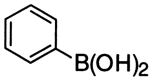
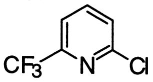
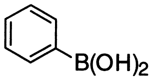
Table 1. Ni/C-catalyzed Suzuki couplings (for a representative procedure, as well as product characterization, see the Experimental section)

Entry	Substrate	Boronic acid	% Ni/C[a]	Time (h)	Yield (% biaryl)[b]
A			6	7	**85**
B			10	18	**67**
C			5	18	**84**
D			10	18	**87**
E			10	18	**92**
F			10	18	**88**
G			6	18	**88**
H			6	24	**78**
I			10	18	**71**
J			10	18	**85**
K			10	18	**89**

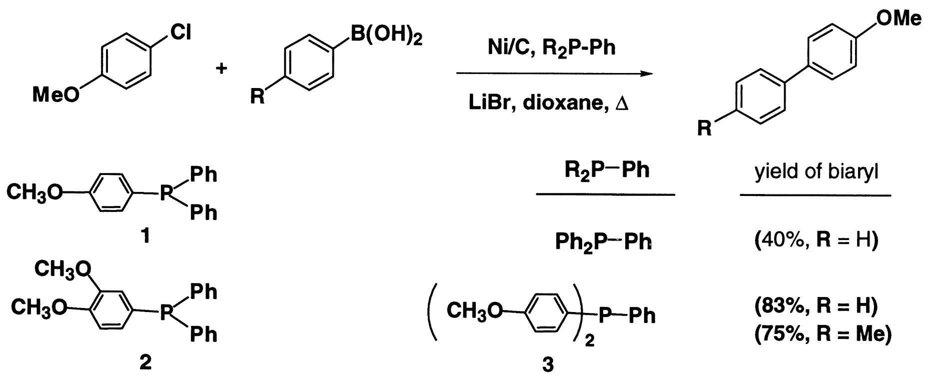
[a] Relative to chloroarene.

[b] Isolated, chromatographically purified materials.

as *N*-methylpyrrolidone (NMP), DME, and DMF were either totally ineffective or offered no improvement in terms of yields or rates for these heterogeneous events. Reactions in THF did produce biaryls but the extent of conversion was too low, perhaps due to the boiling point of the medium (66°C). Only vigorously boiling dioxane (bp 101°C) was acceptable in our hands.

Variations in the base used in Suzuki couplings have been numerous,[1] examples of which include Cs_2CO_3, K_3PO_4, CsF, K_2CO_3, KO–*t*-Bu, and $Ba(OH)_2$. All were examined for their impact on couplings under the influence of Ni/C in refluxing dioxane. Only one base, anhydrous K_3PO_4 (heated under high vacuum at ca. 125° for 1 h), was identified as effective. Changes in gegenion from potassium to lithium (i.e. Li_3PO_4) led to surprisingly inferior yields of biaryls under otherwise identical conditions. An experiment using a pre-formed borate salt ($Ar{-}BF_3^-K^+$)[7] in place of the corresponding boronic acid led only to recovered aryl chloride.

The nature and amount of the phosphine ligand present, likewise, can exert a dramatic impact on reaction rate and/or efficiency under Ni/C catalysis. Although the most common and least expensive ligand, triphenylphosphine (PPh_3), ultimately proved to be the best choice overall, others were evaluated. These included tricyclohexylphosphine (PCy_3),[8] tri-*iso*-butylphosphine,[8] dppf, racemic BINAP, dppe, (*t*-Bu)$_3$P,[5e] and Ph_3As.[9] Only PCy_3 was found to be somewhat comparable to PPh_3 conversion-wise, when employed in hot dioxane with K_3PO_4 as base.



Scheme 2.

Most of these phosphines actually inhibited biaryl formation, with starting materials being isolated upon work-up. The stoichiometry of phosphine present to Ni/C was also varied, with the typical 4:1 ratio giving the best yields of biaryl products. The extent of homocoupling found for the aryl chloride, oftentimes on the order of 10%, could be minimized (to ca. 5%) by incorporating LiBr in each reaction mixture. The impact of BHT[10,11] as an additive, however, was essentially nil.

Having established a standard set of conditions (i.e. Ni/C, $4PPh_3$, K_3PO_4, LiBr, dioxane, reflux), several representative couplings involving a variety of arylboronic acids and aryl chlorides were performed, the results from which are illustrated in Table 1. In the majority of cases, isolated yields of product biaryls are competitive with those observed from nickel-catalyzed reactions under homogeneous conditions.[6,7] Most reactions tended to go to completion within ca. 18 h, seemingly independent of either reaction partner. Although 5% Ni/C relative to educt could be used, slightly higher percentages (ca. 6–10%) were routinely employed. The presence of an electron-withdrawing group within the aryl chloride, as expected, activates the educt toward Ni/C insertion and helps to promote coupling with most types of boronic acids. Functional group tolerance in the aryl chloride is high, as aldehydes, ketones, and nitriles are unperturbed. Two representative heterocyclic systems bearing chloride were investigated and appear to readily couple (entries **J**[12a] and **K**[12b]), while the one case of a heteroaromatic boronic acid examined (entry **F**) served nicely as the nucleophilic component toward *para*-chloroacetophenone. Other boronic acids which led to successful biaryl products included those with either activating (entries **C**,[13] **I**) or deactivating (entry **B**) substituents, as well as one example involving a 1-naphthylboronic acid (entry **H**). Chloroanisole, however, was not fully consumed even after prolonged heating, typically leading to conversions in the 40% range. Eventually, by altering the nature of the aryl phosphine ligand from PPh_3 to the corresponding known bis-*para*-methoxyphenyl analog (**3**),[14] it was possible to secure good isolated yields of the desired biaryl derivatives (Scheme 2). Modifications in the substitution pattern on phosphorus, as in mixed aryl phosphines **1** and **2**, led to yields which were either comparable to, or lower than, those obtained using PPh_3.

Aryl chlorides **4**–**6**, when admixed with $PhB(OH)_2$ and treated under our standard coupling conditions, were consumed to a very limited extent (<5%). Among the numerous arylboronic acids screened for reactivity, both the *ortho*-methoxyphenyl derivative (**7**), and tetrazole **8**, led to no reaction irrespective of the aryl chloride selected (including activated cases). One experiment using phenylboronic acid *ester* **9** and *para*-chloroacetophenone appeared to stop at the point of ca. 30% conversion, and hence, boronates were not pursued further (see Fig. 1).

Discussion

Prior to this study, Ni/C as a catalyst had been applied successfully only to Negishi[6a] and Kumada couplings.[6b] From the standpoint of reactivity with respect to group 10 metal-mediated couplings, organozinc and Grignard reagents are among those most prone toward transmetalation, which is oftentimes regarded as the key rate-determining step.[15] Boronic acids, on the other hand, are considerably less reactive. Suzuki couplings involving these organometallics tend to require higher reaction temperatures and longer times relative to couplings with RZnX or RMgX,[1] notwithstanding the presence of a base in the reaction which is likely to establish an equilibrium

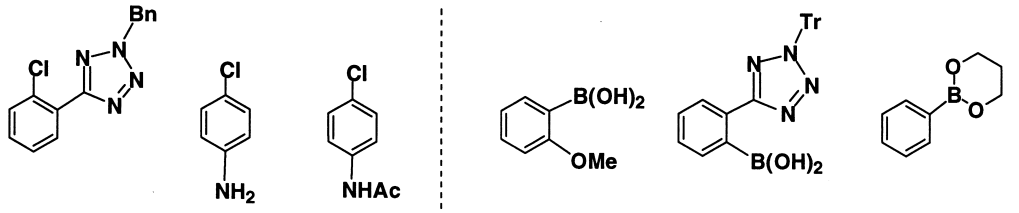


Figure 1.

percentage of the corresponding *ate* complex.[1] Thus, it is not unexpected that the higher boiling solvent dioxane, along with somewhat longer times, were required (along with K_3PO_4) to drive these heterogeneous processes to completion.

Given that at this time the nature of the active catalyst is completely unknown,[16] all of the reaction parameters have been empirically derived. Nonetheless, some insight regarding Ni(0)/C has been gleaned, and trends observed, from these as well as our earlier efforts.[6] The couplings appear to be especially sensitive to the nature and amount of phosphine present. Bidentate ligands (BINAP, dppf, dppe) appear to inhibit the extent of coupling relative to PPh_3 independent of the organometallic being used. In an effort to gauge the attraction of Ni(0)/C for monodentate phosphines, the catalyst was exposed to four equivalents of PPh_3 in THF at room temperature in the absence of an aryl chloride or nucleophilic partner. Filtration of this mixture followed by evaporation of solvent led to recovered PPh_3, but only roughly half of the amount initially in solution. Thus, if Ni(0)/C sequesters two phosphine ligands, and presumably must release one to allow for oxidative addition, bidentate ligands may deter this critical step. It appears premature, however, to comment on the steric and/or stereoelectronic subtleties surrounding the use of monodentate phosphines.

The role of LiBr in this chemistry is another curiosity. Comparisons with LiCl and KBr revealed that a positive impact was made solely when LiBr is present in solution (although only three were screened). Using *p*-chlorobenzophenone and phenylboronic acid (in the presence of 5% Ni/C) as a test case, the extent of conversion was 69% in the absence of LiBr, while with LiCl present the level rose to 80%. LiBr further increased the conversion to 87%, which led us to employ this salt throughout the study. By contrast, LiBr plays no role in the corresponding Kumada couplings,[6b] while LiCl is the additive of choice in Negishi biaryl formations involving this heterogeneous catalyst.[6a]

A quantitative assessment of the level of catalyst bleed from the solid support was made by employing inductively coupled plasma (ICP) atomic emission spectroscopy.[6a,17] The sample was prepared from a crude reaction mixture by filtration, solvent evaporation, and then digestion with aqueous HNO_3, a sequence which prevents any loss of nickel that might otherwise occur during workup. The amount of nickel in solution was determined to be 0.44% of the initial 6 mol% invested relative to substrate. This level of catalyst in solution is far too low to be responsible for the couplings observed.[6a] Thus, it is quite likely that the desired C–C bond is being made on the surface of the charcoal.

Conclusions

Although essentially nothing is currently known concerning the surface chemistry of Ni(0) on charcoal, nonetheless, Ni/C functions as an effective heterogeneous catalyst for Suzuki couplings. In most cases, a set of generalized reaction parameters (dioxane, Δ, K_3PO_4, LiBr, PPh_3) suffice to afford biaryl bond formation between functionalized aryl chlorides and various aryl boronic acids. The results obtained compare favorably with those reported using homogeneous Ni(0) catalysis, yet imply a level of process simplification characteristic of heterogeneous conditions. Very little nickel is released from the charcoal during the coupling process, as established by ICP experiments. Ongoing work with Ni(0)/C suggests that several other bond constructions, including carbon-heteroatom arrays and C–Cl bond reductions, may be realized. These results are anticipated to form the basis of additional reports from our laboratories in the near future.

Experimental

Materials

All chloroarenes were purchased from Aldrich or Acros and were freshly distilled or dried azeotropically prior to use, and then stored at −15°C under inert atmosphere. Boronic acids were purchased from Frontier Scientific and were used without further purification. Dioxane was freshly distilled over Na/benzophenone ketyl. Anhydrous K_3PO_4, purchased from Aldrich, was crushed into a fine powder and dried under vacuum at 125°C for at least 1 h. All products were chromatagraphed on 200–425 mesh Fisher brand silica gel. All NMR spectra were taken in $CDCl_3$ on a 400 MHz Varian Inova system using TMS as internal standard. IR spectra were recorded on an ATI Mattson Infinity Series FT-IR spectrometer and reported in units of cm^{-1}. Mass spectra were acquired using a VG Autospec or an analytical VG-70-250 HF instrument.

General procedure for Suzuki couplings catalyzed by Ni/C

2-Cyanobiphenyl (Table 1, entry D). In a 10 mL round bottom flask under an inert atmosphere of argon was combined triphenylphosphine (75 mg, 0.28 mmol, 0.4 equiv.), and 0.75 mmol/g Ni/C (96 mg, 0.07 mmol, 0.1 equiv.). Dioxane (2.5 mL) was added via syringe and the mixture allowed to stir for 20 min. In a second flask was combined K_3PO_4 (547 mg, 2.58 mmol, 3.6 equiv.), LiBr (150 mg, 1.73 mmol), phenylboronic acid (135 mg, 1.08 mmol, 1.5 equiv.) and 2-chlorobenzonitrile (99 mg, 0.72 mmol). To the flask containing the Ni/C mixture was introduced dropwise via syringe *n*-butyllithium (2.55 M, 120 μL, 0.28 mmol, 0.4 equiv.) to form the active Ni(0)/C complex. The charcoal mixture was allowed to stir for 5 min and the flask was next placed in an icewater bath until frozen. The contents of the second flask were added to the frozen mixture and the flask was fitted with an argon purged condenser. The mixture was allowed to melt and then placed in a sand bath preheated to 135°C, where it was refluxed for 18 h. Upon cooling, the mixture was poured onto a fritted funnel containing a pad of Celite and washed with methanol (40 mL). The filtrate was collected and absorbed onto silica gel, and then subjected to column chromatography. The product eluted with 3% EtOAc/hexanes and was isolated as a white solid (112 mg, 87%).[4b]

4-Carboxaldehydebiphenyl (Table 1, entry A). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chlorobenzaldehyde (101 mg, 0.72 mmol). The crude product was subjected to the standard workup and chromatography using 10% EtOAc/hexanes. The product was isolated as an off-white solid (112 mg, 85%).[18]

3′-Trifluoromethyl-4-carboxaldehydebiphenyl (Table 1, entry B). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chlorobenzaldehyde (101 mg, 0.72 mmol) and 3-trifluoromethylphenylboronic acid (205 mg, 1.08 mmol). The crude product was subjected to the standard workup and chromatography using 10% EtOAc/hexanes. The product was isolated as an oil (120 mg, 67%).[19]

4-Methylbiphenyl-2-carbonitrile; 'OTBN' (Table 1, entry C). The general procedure above was followed using 2-methylbenzonitrile (138 mg, 1.0 mmol), tolylboronic acid (136 mg, 1.5 mmol), Ni/C (100 mg, 0.5 mmol Ni/g, 0.05 mmol), triphenylphosphine (52 mg, 0.20 mmol), *n*-butyllithium (74 μL, 2.70 M, 0.20 mmol), lithium bromide (217 mg, 2.5 mmol), and potassium phosphate (636 mg, 3 mmol). The crude product was subjected to the standard workup and chromatography eluting with 5% EtOAc/hexanes. The product was isolated as a white crystalline solid (162 mg, 84%); R_f=0.5 (hexanes/ethyl acetate, 10/1); IR (CH_2Cl_2) 3047, 3027, 2950, 2921, 2863, 2224, 1596, 1517, 1478, 1443, 1285, 1266, 1186, 1107, 1047, 1006, 947, 821, 762; ^{1}H NMR (400 MHz) δ 7.77–7.74 (m, 1H), 7.65–7.61 (m, 1H), 7.53–7.40 (m, 4H), 7.32–7.29 (m, 21H), 2.43 (s, 3H); ^{13}C NMR (100 MHz) δ(145.7, 138.9, 135.4, 133.9, 133.0, 130.2, 129.6, 128.8, 127.5, 119.1, 111.4, 21.5; LREIMS 194(14), 193(100), 192(32), 191(5), 190(7), 165(21), 82(5); HREIMS calcd for $C_{14}H_{11}N$, 193.0892, found 193.0893.

4-Phenylacetophenone (Table 1, entry E). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chloroacetophenone (93 μL, 0.72 mmol). The crude product was subjected to the standard workup and chromatography using 10% EtOAc/hexanes. The product was isolated as a white solid (129 mg, 92%).[20]

3-(4-Acetylphenyl)thiophene (Table 1, entry F). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chloroacetophenone (93 μL, 0.72 mmol) and thiophene-3-boronic acid (138 mg, 1.08 mmol). The crude product was subjected to the standard workup and chromatography using 10% EtOAc/hexanes. The product was isolated as a white solid (127 mg, 88%).[21]

4-Phenylbenzophenone (Table 1, entry G). The general procedure above was followed using 4-chlorobenzophenone (312 mg, 1.44 mmol), phenylboronic acid (264 mg, 2.16 mmol), K_3PO_4 (1.09 g, 5.16 mmol, 3.6 equiv.), LiBr (150 mg, 1.73 mmol), PPh_3 (90 mg, 0.35 mmol, 0.12 equiv.) and 0.66 mmol/g Ni/C (130 mg, 0.09 mmol, 0.06 equiv.) and dioxane (3.0 mL). The crude product was subjected to the standard workup and chromatography using 10% EtOAc/hexanes. The product was isolated as a white solid (327 mg, 88%).[22]

4-Naphthylbenzophenone (Table 1, entry H). The general procedure above was followed using 4-chloroacetophenone (108 mg, 0.5 mmol), naphthylboronic acid (129 mg, 0.75 mmol), Ni/C (40 mg, 0.75 mmol Ni/g, 0.03 mmol), triphenylphosphine (32 mg, 0.12 mmol), *n*-butyllithium, (2.55 M, 47 μL, 0.12 mmol), lithium bromide (65 mg, 0.75 mmol), potassium phosphate (130 mg, 1.5 mmol), and dioxane (1.5 mL). The crude product was subjected to the standard workup and chromatography eluting with 5% EtOAc/hexanes. The product was isolated as a clear oil (154 mg, 78%); R_f=0.5 (hexanes/ethyl acetate, 10/1); IR (CH_2Cl_2) 3058, 2951, 2924, 2854, 1930, 1817, 1721, 1658, 1604, 1579, 1447, 1397, 1177, 1149, 938, 924, 858, 778, 702, 671, 633; ^{1}H NMR (400 MHz) δ 7.97–7.88 (m, 7H), 7.64–7.59 (m, 3H), 7.57–7.44 (m, 6H); ^{13}C NMR (100 MHz) δ 196.7, 145.4, 139.3, 137.9, 136.6, 134.0, 132.7, 131.4, 130.4, 130.3, 130.3, 128.6, 128.6, 128.5, 127.2, 126.6, 126.2, 125.8, 125.6; LREIMS 309.04(22), 308(100), 232(6), 231(51), 203(16), 202(34), 105(28.7), 77(28); HREIMS calcd for $C_{23}H_{16}O$, 308.1201, found 308.1203.

3-Methyl-4′methoxybiphenyl (Table 1, entry I). The general procedure above was followed using the same reagents and relative amounts with the exception of 3-chlorotoluene (88 μL, 0.72 mmol) and 4-methoxyphenylboronic acid (164 mg, 1.08 mmol). The crude product was subjected to the standard workup and chromatography using 2% EtOAc/hexanes. The product was isolated as a white solid (101 mg, 71%).[23]

5-Methoxy-8-phenylquinoline (Table 1, entry J). The general procedure above was followed using the same reagents and relative amounts with the exception of 8-chloro-5-methoxyquinoline (139 mg, 0.72 mmol). The crude product was subjected to the standard workup and chromatography, eluting with 50% EtOAc/hexanes. The product was isolated as a white solid (143 mg, 85%); ^{1}H NMR (400 MHz) δ 8.70 (dd, J=4.2, 1.7 Hz, 1H), 8.51 (dd, J=8.4, 1.7 Hz, 1H), 7.50 (dd, J=8.4, 4.03 Hz, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.50–7.38 (m, 5H), 6.95 (d, J=8.4 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (100 MHz) δ 154.7, 149.8, 140.7, 133.1, 130.2, 128.6, 127.5, 127.4, 127.0, 126.5, 122.5, 122.2, 107.5, 56.3; IR (KBr) 3061, 3016, 2941, 1597, 1502, 1308, 1097, 924, 782; LREIMS 235(9), 206(16), 195(22), 194(75), 192(88), 164(100), 128(62), 63(21); HREIMS calcd for $C_{16}H_{12}NO$ (M$^+$–H) 234.0921, found 234.0919.

2-Phenyl-6-trifluoromethylpyridine (Table 1, entry K). The general procedure above was followed using the same reagents and relative amounts with the exception of 2-chloro-5-trifluoromethylpyridine (131 mg, 0.72 mmol). The crude product was subjected to the standard workup and chromatography eluting with 5% EtOAc/hexanes. The product was isolated as a white solid (142 mg, 89%); ^{1}H NMR (400 MHz) δ 8.96 (s, 1H), 8.04 (d, J=8.1 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.50 (m, 2H), 7.30 (m, 2H); ^{13}C NMR (100 MHz)(δ(146.6, 134.4, 134.0, 133.8, 130.4, 129.2, 128.9, 128.7, 120.4; IR (KBr) 3063, 2924, 2852, 1603, 1565, 1334, 1129, 741, 692; LREIMS 223(100), 222(45), 154(60), 102(10), 51(11); HREIMS calcd for $C_{12}H_8NF_3$, 223.0609, found 223.0609.

4′-Methoxy-4-methylbiphenyl (Scheme 2). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chloroanisole (88 μL, 0.72 mmol), 4-tolylboronic acid (147 mg, 1.08 mmol) and bis-(4-methoxyphenyl)-phenylphosphine[14] (96 mg, 0.28 mmol). The crude product was subjected to the standard workup and chromatography using 2% EtOAc/hexanes. The product was isolated as a white solid (107 mg, 75%).[24]

4-Methoxybiphenyl (Scheme 2). The general procedure above was followed using the same reagents and relative amounts with the exception of 4-chloroanisole (88 μL, 0.72 mmol) and bis-(4-methoxyphenyl)-phenylphosphine[14] (96 mg, 0.28 mmol). The crude product was subjected to the standard workup and chromatography using 2% EtOAc/hexanes. The product was isolated as a white solid (110 mg, 83%).[4b]

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