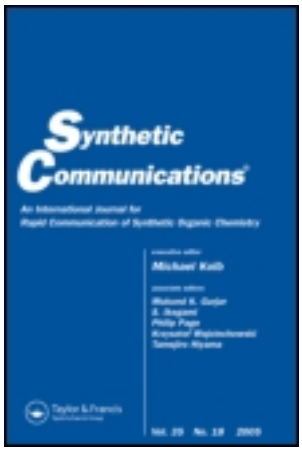

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SYNTHESIS OF DIARYL ETHERS USING AN EASY-TO-PREPARE, AIR-STABLE, SOLUBLE COPPER(I) CATALYST

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SYNTHESIS OF DIARYL ETHERS USING AN EASY-TO-PREPARE, AIR-STABLE, SOLUBLE COPPER(I) CATALYST

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ABSTRACT

We have found that bromo(triphenylphosphine)copper(I), an air-stable and soluble copper(I) complex, can be used as a catalyst in the synthesis of diaryl ethers. Using this catalyst, we have synthesized diaryl ethers from electron-rich aryl bromides and electron-rich phenols in the presence of cesium carbonate, in 17–24 h, in NMP. We also found that electron-deficient aryl bromides couple with phenols in the presence of cesium carbonate, in 6 h in NMP at 70°C, *without the catalyst*.

The classical copper-mediated Ullmann coupling is the reaction of choice for the synthesis of aryl ethers and triarylamines in large and industrial scales.[1,2] These reactions often require high temperatures (~ 200°C) and the use of copper salts in greater than stoichiometric amounts.[3,4] The reaction

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is also very sensitive to the substitution on the aryl halide. Due to these limitations, copper salts have largely been supplanted by Pd(0) catalysts.[5–8] However, it has been shown by Cohen in 1976 and more recently by others that if the solubility of the copper salts is increased, then S_NAr reactions tend to occur at milder temperatures and with catalytic amounts of the copper salt.[9–14] The possibility of milder reaction conditions, combined with its scope and robustness has renewed the interest in Ullmann-type reactions. In addition, there is an economic attractiveness for using copper over noble metals such as palladium.

Soluble copper(I) salts are often air- and moisture-sensitive (e.g. $Cu(CF_3SO_3 \cdot 0.5C_6H_6)$ and/or require the use of harsh conditions for their preparation.[15] In order to explore the full scope and mechanistic details of these copper-catalyzed reactions, there is a necessity for copper(I) salts that are chemically well-defined, stable, soluble in organic solvents and capable of systematic modification. In this regard, we are currently studying the use of copper-phosphine complexes as catalysts in the formation of aryl-carbon and aryl-heteroatom bonds. As a part of this study, we now report the use of $Cu(PPh_3)_3Br$ as a catalyst for the synthesis of diaryl ethers from electron-rich aryl bromides. This complex is extremely easy to prepare and is stable to air and ambient moisture.

Addition of $CuBr_2$ to a hot methanolic solution of triphenylphosphine gives $Cu(PPh_3)_3Br$ (**1**) as a crystalline white solid. This procedure obviates the need to reflux moisture-sensitive copper(I) bromide with triphenylphosphine for 3–4 h, a common procedure for making these complexes.[16–18] Using this procedure, $Cu(PPh_3)_3Cl$ and $Cu(PPh_3)_2NO_3$ have also been prepared in high yields. Complex **1** is soluble in organic solvents such as THF, dichloromethane, acetonitrile, chloroform, NMP, DMF, DMSO, toluene and benzene. However, it is not soluble in diethyl ether, hexane, ethanol or methanol. It can be stored under air for prolonged times, without any visible color change.

We chose to explore the synthesis of diaryl ethers using **1** as a catalyst. There has been a widespread interest in developing general strategies for the synthesis of diaryl ethers using Cu(**I**) or Pd(0) as catalysts.[19,20] This interest stems from the importance of diaryl ethers in organic synthesis, their occurrence in various biologically interesting compounds and the lack of general methods for their preparation. Recently, Buchwald and co-workers reported a general copper-catalyzed synthesis of diaryl ethers from phenols and aryl halides. Buchwald's protocol calls for the use of $Cu(CF_3SO_3 \cdot 0.5C_6H_6$ as the catalyst, cesium carbonate as the base, 5 mol% of ethyl acetate and sometimes the use of 1-napthoic acid. We report in here procedures for the synthesis of diaryl ethers that have the following advantages: (a) it dispenses with the need for the use of any additives or co-solvents; (b) in contrast to

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(CF_3SO_3•$0.5C_6H_6$, $Cu(PPh_3)_3Br$ is easy to prepare and is stable to air and ambient moisture; (c) $Cu(PPh_3)_3Br$ is soluble in organic solvents; and (d) it dispenses with the need for any catalyst for the synthesis of diaryl ethers from electron-deficient aryl halides and electron-rich phenols under mild conditions.

We initially examined the propensity of **1** to act as a catalyst for the formation of diaryl ethers using solvents such as toluene and *N*-methylpyrrolidinone (NMP). In NMP, we discovered that *o*- and *p*-cresol react with electron deficient aryl bromides such as 1-bromo-4-nitrobenzene and 4-bromobenzonitrile with Cs_2CO_3 to form the corresponding diaryl ether, at 70°C and in 6 h, *even in the absence of the copper catalyst* (see Table 1, entries 1–4). The reaction was however, incomplete in 6 h when Cs_2CO_3 was replaced with K_2CO_3 and does not occur if 4-*N*,*N*-dimethylaminopyridine (DMAP) was used as the base. In comparison, when the reaction was carried out in toluene, in addition to Cs_2CO_3, the copper catalyst was also required for the formation of the diaryl ether. These observations suggest that the formation of diaryl ethers from electron-deficient aryl bromides and electron-rich phenols might not require any catalysts such as Pd(0), if Cs_2CO_3 is used as a base and NMP as the solvent.

Table 1. Reactions of Electron-Rich Aromatic Bromides with Phenols in NMP or in Toluene

Entry	R	R′	Catalyst (mol%)	Solvent	Time (h)	Temperature (°C)	Isolated Yields (%)
1	*p*-NO_2	*p*-CH_3	0	NMP	6	70	88
2	*p*-NO_2	*o*-CH_3	0	NMP	6	70	86
3	*p*-CN	*p*-CH_3	0	NMP	6	70	80
4	*p*-CN	*o*-CH_3	0	NMP	6	70	85
5	*p*-CH_3	*o*-CH_3	20	NMP	17	100	75
6	*p*-CH_3	*p*-CH_3	20	NMP	17	100	70
7	*p*-$N(CH_3)_2$	*p*-CH_3	20	NMP	19	100	76
8	*p*-OCH_3	*p*-CH_3	20	NMP	24	100	75
9	*o*-OCH_3	*p*-CH_3	20	NMP	24	100	61
10	*o*-OH_3	*p*-CH_3	20	NMP	24	100	75
11	*o*-CH_3	*o*-CH_3	20	NMP	24	100	72
12	*p*-CH_3	*p*-CN	20	NMP	24	100	0
13	*p*-CH_3	*o*-$COOCH_3$	20	NMP	24	100	0
14	*o*-$COOCH_3$	*o*-CH_3	20	NMP	24	100	55
15	*p*-CN	H	20	Toluene	24	100	60
16	*p*-CH_3	*o*-CH_3	20	Toluene	24	100	27

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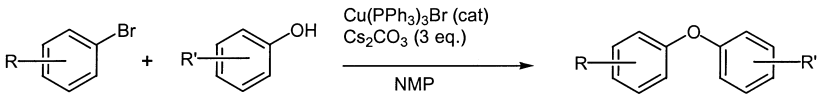
Furthermore, for electron-rich aryl bromides, the reactions were complete in 48 h in the presence of 5 mol% of **1** and 3 eq. of Cs_2CO_3, in NMP. The reactions do not proceed when K_2CO_3, KO*t*-Bu and DMAP were used as bases. Also, in contrast to the reactions with electron-deficient aryl bromides, the copper catalyst was necessary for diaryl ether formation. In general, we observed that the reactions were faster in NMP than in toluene.



Scheme 1.

We then probed the effect of the catalyst concentration on the reaction time. We found that when **1** was increased to 20 mol%, the reactions were complete (by TLC) in half the time, within 24 h and gave good yields (entries 5–11, Table 1). Similar reaction times and yields were observed, when **1** was used in stoichiometric amounts. We observed that the reaction mixtures needed to be well stirred owing to the low solubility of Cs_2CO_3 in NMP. All of the diaryl ethers reported in Table 1 have been characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses (see supporting information). The products from entry 1 and entry 6 in Table 1 have also been characterized by single crystal x-ray analyses.

From Table 1, it can be surmised that **1** is a very effective catalyst for the coupling of electron-rich phenols and electron-rich aryl bromides (entries 5–11). It is also effective in the coupling of *o*-substituted aryl bromides and *o*-substituted electron-rich phenols (entry 11). However, **1** is ineffective in the coupling of electron-deficient phenols with electron-rich bromides (entries 12 and 13). This may be attributed to the delocalization of the charge on the phenoxide ion, making it a poor nucleophile. In fact, general methods that have been reported in the literature have focused on phenols with electron donating substituents.[11,14,21,22] In order to develop a complete set of reaction conditions for the synthesis of diaryl ethers, we are currently investigating the coupling of electron-deficient phenols with electron-rich and electron-deficient bromides. We also found that 4-bromobenzonitrile can couple with phenol, in toluene, to form the corresponding diaryl ether in 60% yield (entry 15). In direct comparison, when $Cu(CF_3SO_3)\cdot 0.5C_6H_6$ was used as the catalyst, 1-napthoic acid was required as an additive for the diaryl ether formation.[11]

In conclusion, we have shown that bromotris(triphenylphosphine)-copper(I), $Cu(PPh_3)_3Br$ is an effective catalyst for the formation of diaryl

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ethers from electron-rich bromides and phenols. In contrast to other Cu(I) catalysts, **1** is extremely easy to prepare and is air-stable. We have also shown that electron-deficient aryl bromides couple with phenols in the presence of Cs_2CO_3, with NMP as the solvent and do not require a catalyst. We are currently studying the mechanistic aspects of this reaction and the efficacy of **1** to act as a catalyst in other S_NAr reactions.

EXPERIMENTAL

General

All reactions for the synthesis of diaryl ethers were performed under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were purchased from Acros or from Aldrich and were used without further purification. Cesium carbonate (Acros, 99%) was stored in a glove box filled with argon. Flash chromatography was performed using ICN Flash Silica Gel, 230–400 mesh. The reported yields refer to isolated yields of the compounds, deemed pure by elemental analysis, ^{1}H NMR and ^{13}C NMR. All products were characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were recorded in parts per million (δ). The peak patterns are indicated as *s*, singlet; *d*, doublet; *t*, triplet; *dd*, doublet of doublets; and *m*, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The residual solvent peak was used as the internal reference. Elemental analyses were preformed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. The reported melting points are uncorrected. X-ray data were collected using a Nonius kappa-CCD diffractometer with Mo K_α ($\lambda = 0.71073$ Å) as the incident radiation. Diffraction data were collected at ambient temperature. The raw data were integrated, refined, scaled and corrected for Lorentz polarization and absorption effects, if necessary, using the programs DENZO and SCALEPAK, supplied by Nonius. Structures solutions and refinements were done (on F_o^2) using suite of programs such as SIR92, LSQ, SHELXS and SHELXL that are contained within the Nonius' MAXUS module. All structures were checked for any missing symmetry using MISSYM of PLATON.

Synthesis of bromotris(triphenylphosphine)copper(I) (1). In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100 mL) was heated to boiling and triphenylphospine (Acros, 6 g, 22.4 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuBr_2$ (Acros, 99+%, 1.24 g, 5.27 mmol) was added as a solid,

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in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper bromide, a white precipitate was formed. After the completion of the addition, the contents were stirred for 10 min and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give **1** (5.73 g, 85% yield, mp 164°C). It can also be recrystallized as white needles from hot methanol. Anal. calc. for $Cu(PPh_3)_3Br$: C, 69.71; H, 4.64; Cu, 6.83. Found: C, 69.67; H, 4.66; Cu, 6.20. We wish to point out that copper was analyzed using colorimetry, since there was a large interference from phosphorous in the ICP. For the same reason, we were unable to obtain a satisfactory P analysis. ^{31}P NMR (121 MHz) δ 0.5 (s). Crystal data for 1: Trigonal, $P3$ (no. 143), $a = 19.2150(3)$ Å, $b = 19.2150(3)$ Å, $c = 10.6220(3)$ Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 120.00°$, $V = 3396.39$ Å^3, $D_c = 1.364$ g cm^{-3}, $Z = 3$, number of unique reflections = 7487, number of parameters = 519, $R1$ (for $F_o > 4\ \sigma$) = 0.0397 and 0.0581 (all data), $wR2$ (for $F_o > 4\ \sigma$) = 0.1040 and 0.1183 (all data), GOF = 0.868, residual electron density = +0.340. The cell constants, contents and the space group are identical to that of the already reported structure of $Cu(PPh_3)_3Br$ (Cambridge Structural Database Refcode-FEYVAG).

Although **1** is stable to air and ambient moisture, we stored it in an argon-filled glove box. This is primarily due to the ease of setting up reactions, since Cs_2CO_3 had to be stored in a dry atmosphere as it is extremely hygroscopic.

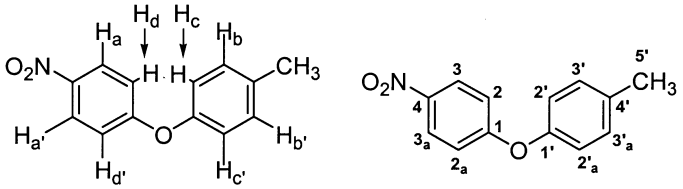
Cu-Catalyzed Coupling of Phenols with Aryl Halides

General procedure A: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 3.0 mmol) and $Cu(PPh_3)_3Br$ (20 mol% with respect to the aryl halide) and was sealed with a rubber septum. The sealed tube was taken out and the phenol (2 mmol), the aryl halide (2 mmol) and *N*-methylpyrrolidinone (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 100°C for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled and filtered to remove any insoluble residues. Water was then added to the filtrate, and the aryl ether was extracted in hexane. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced

pressure and the residue was then purified with by flash column chromatography on silica gel to obtain the analytically pure product.

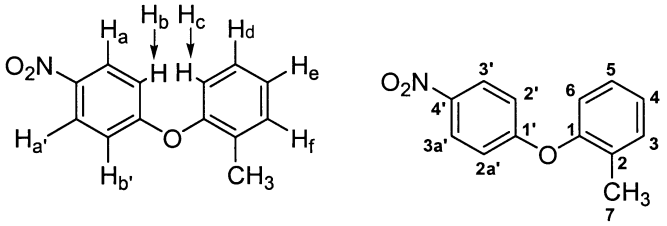
General procedure B (without the catalyst): In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with cesium carbonate (Acros, 3.0 mmol) and was sealed with a rubber septum. The sealed tube was taken out and the phenol (2 mmol), the aryl halide (2 mmol) and *N*-methylpyrrolidinone (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 70°C for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled and filtered to remove any insoluble residues. Water was then added to the filtrate, and the aryl ether was extracted in hexane. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified with by flash column chromatography on silica gel to obtain the analytically pure product.

1-Methyl-4-(4-nitrophenoxy)benzene (entry 1, Table 1). Procedure B was used to convert *p*-cresol and 1-bromo-4-nitrobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as white solid (0.40 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, $J = 7.0$, 2H-H_a, $H_{a'}$), 7.22 (dd, $J = 7.2$, 2H; H_b, $H_{b'}$), 6.96 (m, 4H; H_d, $H_{d'}$, H_c, $H_{c'}$), 2.31 (s, 3H-methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C_1), 152.1 ($C_{1'}$), 142.2 (C_4), 135.1 ($C_{4'}$), 130.7 ($C_{3'}$, $C_{3a'}$), 125.7 (C_3, C_{3a}), 120.3 (C_2, C_{2a}), 116.6 ($C_{2'}$, $C_{2a'}$), 20.7 (C_5). Anal. calcd for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80. Found: C, 68.04; H, 4.91; mp 65°C. Crystal data: Orthorhombic, *Pbca* (no. 61), $a = 7.4395(2)$ Å, $b = 12.4400(3)$ Å, $c = 24.8501(7)$ Å, $V = 2299.8(1)$ Å^3, $Z = 8$, number of unique reflections = 1573, number of parameters = 154, $R1 = 0.077$ (all data), wR ($w = 1/(\sigma^2(F_o^2) + 0.0300^*(F_o^2))) = 0.064$ (all data), GOF = 2.04, residual electron density = +0.27.

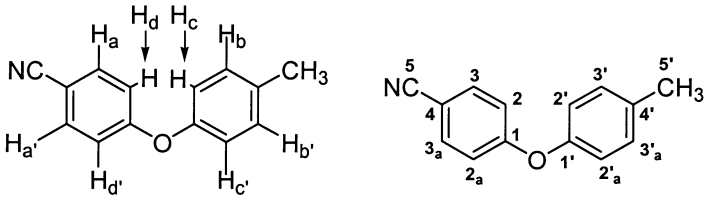


1-Methyl-2-(4-nitrophenoxy)benzene (entry 2, Table 1). Procedure B was used to convert *o*-cresol and 1-bromo-4-nitrobenzene to the title product.

Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as yellow oil (0.39 g, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, $J = 7.0$, 2H; H_a, $H_{a'}$), 7.34–7.16 (m, 3H; H_d, H_e, H_f), 7.02 (dd, $J = 7.7$, 1H; H_c), 6.92 (dd, $J = 7.0$, 2H; H_b, $H_{b'}$), 2.22 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C_1), 152.2 ($C_{1'}$), 142.1 ($C_{4'}$), 131.9 (C_3), 130.4 (C_2), 127.6 (C_5), 125.9 ($C_{3'}$, $C_{3a'}$), 125.8 (C_4), 121.0 (C_6), 115.8 ($C_{2'}$, $C_{2a'}$), 15.9 (C_7). Anal. calcd for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80. Found: C, 68.10; H, 4.85; mp 35°C.



4-(4-Methylphenoxy)benzonitrile (entry 3, Table 1). Procedure B was used to convert *p*-cresol and 1-bromo-4-cyanobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as white solid (0.3 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, $J = 8.8$, 2H; H_a, $H_{a'}$), 7.24 (dd, $J = 8.1$, 2H; H_b, $H_{b'}$), 6.90 (m, 4H; H_c, $H_{c'}$, H_d, $H_{d'}$), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (C_1), 152.2 ($C_{1'}$), 134.8 ($C_{4'}$), 133.9 (C_3, C_{3a}), 130.6 ($C_{3'}$, $C_{3a'}$), 120.2 (C_2, C_{2a}), 118.8 (C_5), 117.4 ($C_{2'}$, $C_{2a'}$), 105.3 (C_4), 20.7 ($C_{5'}$). Anal. calcd for $C_{14}H_{11}NO$: C, 80.38; H, 5.26; N, 6.69. Found: C, 79.93; H, 5.65; N, 6.24; mp 65°C.



4-(2-Methylphenoxy)benzonitrile (entry 4, Table 1). Procedure B was used to convert *o*-cresol and 1-bromo-4-cyanobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave

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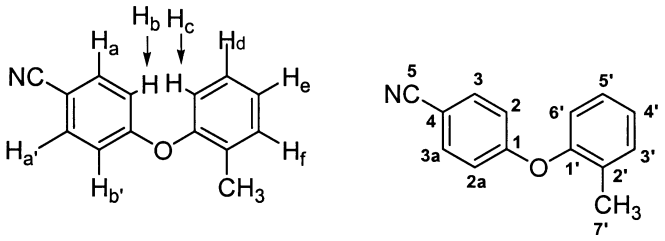
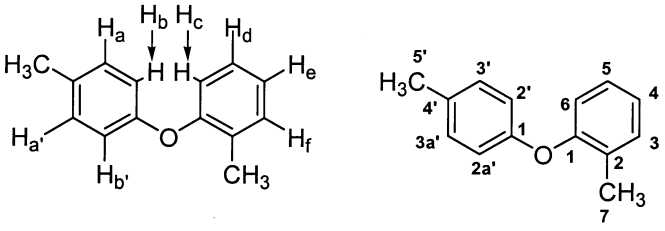
the analytically pure product as a white solid (0.35 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, $J = 6.9$, 2H; H_a, $H_{a'}$), 7.32–7.14 (m, 3H; H_d, H_e, H_f), 6.99 (dd, $J = 6.9$, 1H; H_c), 6.91 (dd, $J = 6.97$, 2H; H_b, $H_{b'}$), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (C_1), 150.8 ($C_{1'}$), 132.6 (C_3, C_{3a}) 130.4 ($C_{3'}$), 128.9 ($C_{2'}$), 126.0 ($C_{5'}$), 124.1 ($C_{4'}$), 119.6 ($C_{6'}$), 117.3 (C_5), 115.1 (C_2, C_{2a}), 103.6 (C_4), 14.4 ($C_{7'}$). Anal. calcd for $C_{14}H_{11}NO$: C, 80.38; H, 5.26. Found: C, 80.17; H, 5.40; mp 70°C.

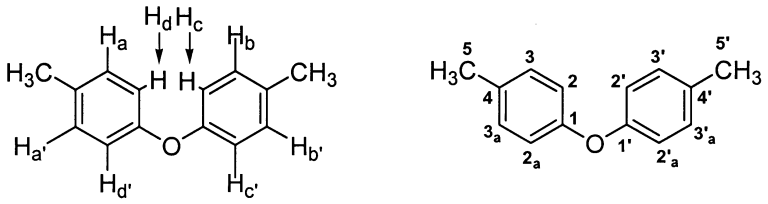


1-Methyl-2-(4-methylphenoxy)benzene (entry 5, Table 1). Procedure B was used to convert *o*-cresol and 1-bromo-4-methylbenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a colorless oil (0.29 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, $J = 8.5$, 1H; H_c), 7.07 (m, 3H; H_f, H_b, $H_{b'}$), 6.83 (m, 4H; H_e, H_d, H_a, $H_{a'}$), 2.11 (s, 3H-methyl protons), 2.10 (s, 3H-methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C_1), 154.9 ($C_{1'}$), 131.8 ($C_{4'}$), 131.3 (C_3), 130.1 ($C_{3'}$, $C_{3a'}$), 129.6 (C_2), 127 (C_5), 123.5 (C_4), 119.1 ($C_{2'}$, $C_{2a'}$), 117.5 (C_6), 20.6 ($C_{5'}$), 16.1 (C_7). Anal. calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.62; H, 7.22.

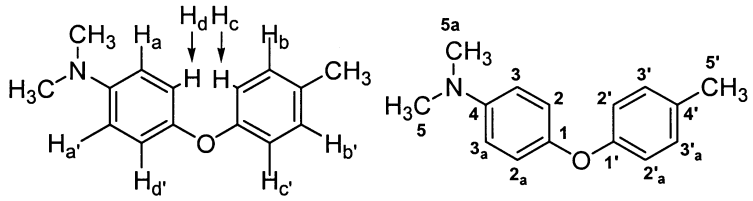


1-Methyl-4-(4-methylphenoxy)benzene (entry 6, Table 1). Procedure A was used to convert *p*-cresol and 1-bromo-4-methylbenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane)

gave the analytically pure product as a white solid (0.27 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, $J = 6.5$, 4H; H_a, H_a, H_b, H_b), 7.1 (dd, $J = 6.5$, 4H; H_c, H_c, H_d, H_d), 2.21 (s, 6H; C_5, $C_{5'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (C_1, $C_{1'}$), 132.3 (C_4, $C_{4'}$), 130 (C_3, C_{3a}, $C_{3'}$, $C_{3a'}$), 118.5 (C_2, C_{2a}, $C_{2'}$, $C_{2a'}$). Anal. calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.62; H, 7.07; mp 50°C. Crystal data: Orthorhombic, $P2_12_12_1$ (no. 19), $a = 5.9138(1)$ Å, $b = 7.8364(2)$ Å, $c = 24.6388(8)$ Å, $V = 1141.83(5)$ Å^3, $Z = 4$, number of unique reflections = 2167, number of parameters = 136, $R1 = 0.091$ (all data), wR (w = $1/(\sigma^2(F_o^2) + 0.0300^* F_o^2)$ = 0.047 (all data), GOF = 2.04, residual electron density = +0.33.



***N*,*N*-Dimethyl-4-(4-methylphenoxy)aniline (entry 7, Table 1).** Procedure A was used to convert *p*-cresol and 4-bromo-*N*,*N*-dimethylaniline to the title product. Purification by flash chromatography (1:1, dichloromethane/hexane) gave the analytically pure product as a white solid (0.34 g, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, 2H; H_b, H_b), 6.96 (dd, 2H; H_c, H_c), 6.81 (dd, 2H; H_d, H_d), 6.66 (dd, 2H; H_a, $H_{a'}$), 2.91 (s, 6H; dimethyl protons), 2.21 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 ($C_{1'}$), 146.4 (C_4), 145.8 (C_1), 129.8 ($C_{4'}$), 128.4 ($C_{3'}$), 118.9 (C_2), 115.7 ($C_{2'}$), 112.5 (C_3), 39.7 (C_5, C_{5a}), 19.0 ($C_{5'}$). Anal. calcd for $C_{15}H_{17}NO$: C, 79.29; H, 7.48. Found: C, 79.25; H, 7.68; mp 180°C.



1-Methoxy-4-(4-methylphenoxy)benzene (entry 8, Table 1). Procedure A was used to convert *p*-cresol and 4-bromoanisole to the title product.

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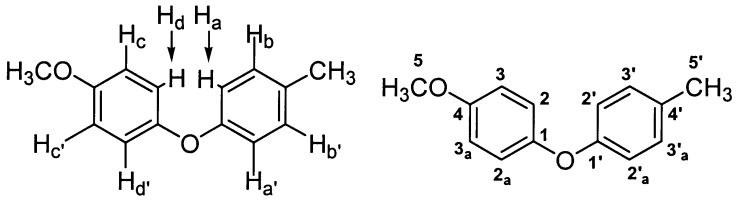
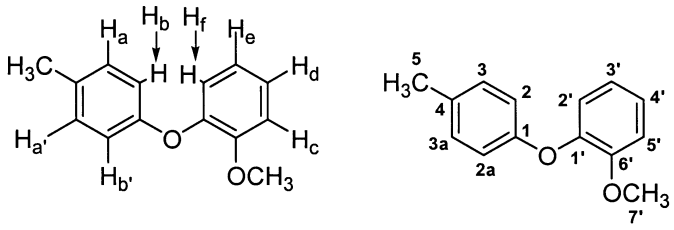
Purification by flash chromatography (30% dichloromethane/hexane) gave the analytically pure product as a white solid (0.42 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, $J = 8.3$, 2H; H_b, $H_{b'}$), 7.04 (dd, $J = 8.9$, 2H; H_d, $H_{d'}$), 6.99–6.89 (m, 4H; H_c, $H_{c'}$, H_a, $H_{a'}$), 3.91 (s, 3H; methoxy protons), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C_4), 155.5 ($C_{1'}$), 150.6 (C_1), 131.9 ($C_{4'}$), 129.9 ($C_{3'}$, $C_{3a'}$), 120.2 (C_2, C_{2a}) 117.6 ($C_{2'}$, $C_{2a'}$), 114.6 (C_3, C_{3a}). Anal. calcd for $C_{14}H_{14}O_2$; C, 78.5; H, 6.54. Found: C, 78.33; H, 6.66; mp 63°C.

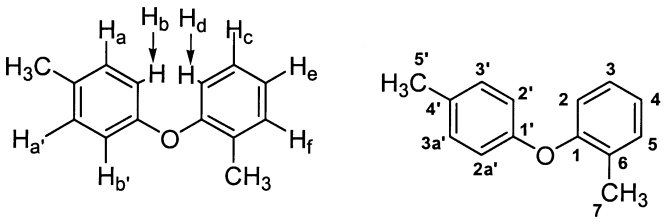


1-Methoxy-2-(4-methylphenoxy)benzene (entry 9, Table 1). Procedure A was used to convert *p*-cresol and 2-bromoanisole to the title product. Purification by flash chromatography (30% dichloromethane/hexane) gave the analytically pure product as a white solid (0.26 g, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.05 (m, 3H, H_f, H_e, H_d), 7.00 (dd, $J = 8.00$, 1H; H_c), 6.95–6.83 (m, 4H, H_a, $H_{a'}$, H_b, $H_{b'}$), 3.91 (s, 3H; methoxy protons), 2.2 (s, 3H; methyl protons); ^{13}C NMR δ 155.4 (C_1), 151.1 ($C_{6'}$), 145.6 ($C_{1'}$), 132.0 (C_4), 129.9 (C_3, C_{3a}) 124.2 ($C_{3'}$), 120.9 ($C_{4'}$), 120.2 ($C_{2'}$), 117.4 (C_2, C_{2a}), 112.6 ($C_{5'}$), 55.8 ($C_{7'}$), 20.6 (C_5). Anal. calcd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.54. Found: C, 78.2; H, 6.59; mp 75°C.

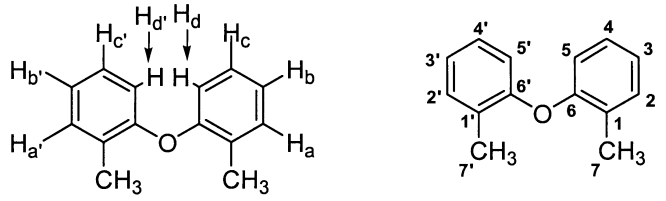


1-Methyl-2-(4-methylphenoxy)benzene (entry 10, Table 1). Procedure B was used to convert *o*-cresol and 1-bromo-2-methyltoluene to the title

product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a colorless oil (0.29 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, $J = 8.5$, 1H; H_c), 7.16–6.96 (m, 4H; H_f, H_b, $H_{b'}$, H_e), 6.86–6.76 (m, 3H; H_d, H_a, $H_{a'}$), 2.11 (s, 3H; methyl protons), 2.0 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C_1), 154.9 ($C_{1'}$), 131.8 ($C_{4'}$), 131.3 (C_3), 130.1 ($C_{3'}$, $C_{3a'}$), 129.6 (C_2), 127 (C_5), 123.5 (C_4), 119.1 ($C_{2'}$, $C_{2a'}$), 117.5 (C_6), 20.5 ($C_{7'}$), 16.1 (C_7). Anal. calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.83; H, 7.25; mp 155°C.



1-Methyl-2-(2-methylphenoxy)benzene (entry 11, Table 1). Procedure B was used to convert *o*-cresol and 1-bromo-2-methyltoluene to the title product. Purification by flash chromatography (1:3, dichloromethane/hexane) gave the analytically pure product as a colorless oil (0.29 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, $J = 7.3$, 2H; H_a, $H_{a'}$), 7.33 (dd, $J = 7.3$, 2H; H_c, $H_{c'}$), 7.23 (dd, $J = 7.2$, 2H; H_b, $H_{b'}$), 6.96 (dd, $J = 7.5$, 2H; H_d, $H_{d'}$), 2.51 (s, 6H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C_6, $C_{6'}$), 131.3 (C_2, $C_{2'}$), 128.8 (C_1, $C_{1'}$), 127.0 (C_4, $C_{4'}$), 123.0 (C_3, $C_{3'}$), 117.6 (C_5, $C_{5'}$), 16.1 (C_7, $C_{7'}$). Anal. calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.82; H, 7.14.



1-Methyl-2-(2-methylphenoxy)benzoate (entry 14, Table 1). Procedure A was used to convert *p*-cresol and 1-methyl-2-bromobenzoate to the title product. Purification by flash chromatography (1:1, dichloromethane/hexane)

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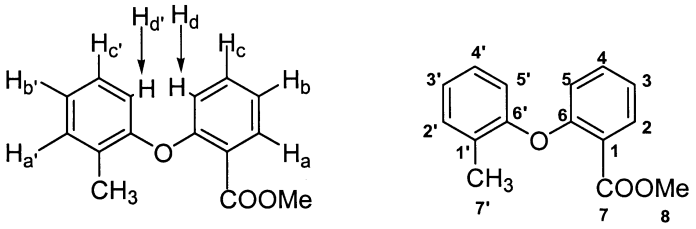
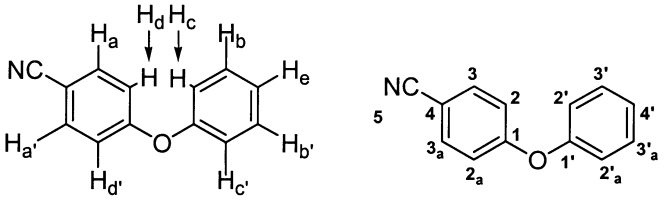
gave the analytically pure product as a colorless oil. (0.13 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, $J = 8.1$ Hz, 2H; H_a), 7.34 (t, $J = 7.91$ Hz, 1H; H_c), 7.28 (d, $J = 7.72$ Hz, 1H; H_b), 7.22 (m, $J = 7.72$ Hz, 3H), 7.11 (t, $J = 7.75$ Hz, 2H; $H_{d'}$, $H_{c'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C_7), 157.2 (C_1), 155.0 ($C_{6'}$), 133.8 (C_4), 132.2 (C_2), 131.8 ($C_{2'}$), 129.9 ($C_{1'}$), 127.5 ($C_{4'}$), 124.3 ($C_{3'}$), 122.8 (C_3), 122.2 (C_6), 119.1 ($C_{5'}$), 118.8 (C_5), 52.48 (C8), 16.57 ($C_{7'}$). Anal. calcd for $C_{13}H_9ON$: C, 74.38; H, 5.78. Found: C, 74.10; H, 5.83.



4-Phenoxybenzonitrile (entry 15, Table 1). Procedure A was used to convert phenol and 1-bromo-4-cyanobenzene to the title product. However, toluene was used as the solvent instead of NMP. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid. (0.12 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, $J = 8.1$ Hz, 2H; H_d, $H_{d'}$), 7.33 (dd, $J = 7.91$ Hz, 2H; H_a, $H_{a'}$), 7.03 (t, $J = 7.72$ Hz, 2H; H_e), 6.95 (d, $J = 7.72$ Hz, 2H; H_b, $H_{b'}$), 6.85 (d, $J = 7.75$ Hz, 2H; H_c, $H_{c'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 ($C_{1'}$), 154.6 (C_1), 134.0 (C_3, $C_{3a'}$), 130.1 (C_3, C_{3a}), 125 ($C_{4'}$), 120.3 (C_2, C_{2a}), 118.7 (CN), 117.8 ($C_{2'}$, $C_{2a'}$), 105.6 (C_4). Anal. calcd for $C_{13}H_9ON$: C, 80.0; H, 4.61. Found: C, 79.86; H, 4.66.



1-Methoxy-2-(4-methylphenoxy)benzene (entry 16, Table 1). Procedure A was used to convert *p*-cresol and 2-bromoanisole to the title product.

However, toluene was used as the solvent instead of NMP. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid (0.047 g, 27% yield). The ^{1}H and ^{13}C NMR was identical to that of entry 9.

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associated with it. For the syntheses of these soluble copper(I) salts, see: Kubas, G.J. Inorg. Synth. **1979**, *19*, 90–92.
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