



Copper-mediated synthesis of mono- and dichlorinated diaryl ethers



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ABSTRACT

An efficient synthesis of polychlorinated diphenyl ethers (PCDEs) using the Cu(OAc)₂-catalyzed Chan–Lam coupling reaction is described. A library of all possible mono- and dichlorinated diphenyl ether congeners was prepared and characterized using MS, ¹H, and ¹³C NMR spectroscopy, and Kovats retention indices. Our approach, using the optimized reaction conditions (i.e., reaction temperature, oxidizing atmosphere and base), significantly improves and simplifies the process compared to previously reported syntheses.

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Polychlorinated diphenyl ethers (PCDEs) are persistent environmental contaminants identified in various biota and abiota matrices.¹ With high lipophilicity and possible bioaccumulation and biomagnification in the food chain, these compounds are considered to exhibit potentially harmful effects in humans and the environment.² PCDEs are formed as a byproduct of the manufacture of technical chlorophenols,³ chlorinated phenoxyacetic acid, or during incomplete combustion in municipal waste incinerators.⁴ Unlike other well-known persistent organic pollutants, such as polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and biphenyls (PCBs), the distribution, experimental toxicities, or human health effects of PCDEs are less well described. For further investigations, the preparation and identification of PCDE congeners are clearly necessary. More than half of the 209 possible PCDE congeners (Fig. 1) with different numbers and positions of the chlorine atoms have been synthesized and characterized.⁵ However, to the best of our knowledge, a complete list of all possible mono- and dichlorinated diphenyl ethers (DEs) has not been published.

A large number of physiologically active compounds including antibiotics, antitumor, and anti-HIV agents contain the diaryl ether moiety.⁶ The search for efficient and convergent methods for the formation of such ethers has generated considerable interest. One of the most common methods for the O-arylation of phenols is the well-known copper-catalyzed Ullmann coupling reaction⁷ from aryl halides. However, applications of this reaction have been

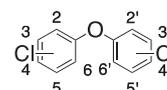


Figure 1. Polychlorinated diphenyl ethers (PCDEs).

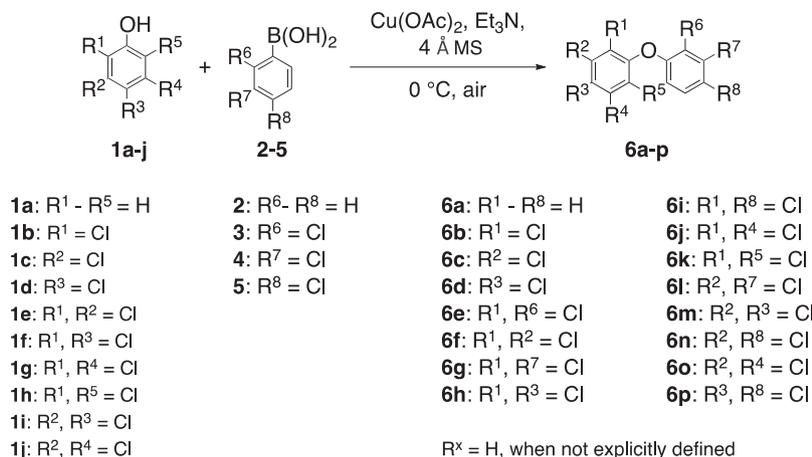
problematic due to the harsh conditions. The coupling reaction of diphenyliodonium salts with chlorinated phenols⁸ is successful, but requires inefficient preparation of diphenyliodonium salts in the first step, and overall is a time-consuming procedure.

A large volume of research deals with copper-mediated cross-coupling reactions of aryl boronic acids and phenols, which was first reported by Chan⁹ and Lam¹⁰ in 1998. In the present article, we report on the optimization and application of the Chan–Lam coupling reaction to the synthesis of a complete library of mono- and dichlorinated DEs (Scheme 1).

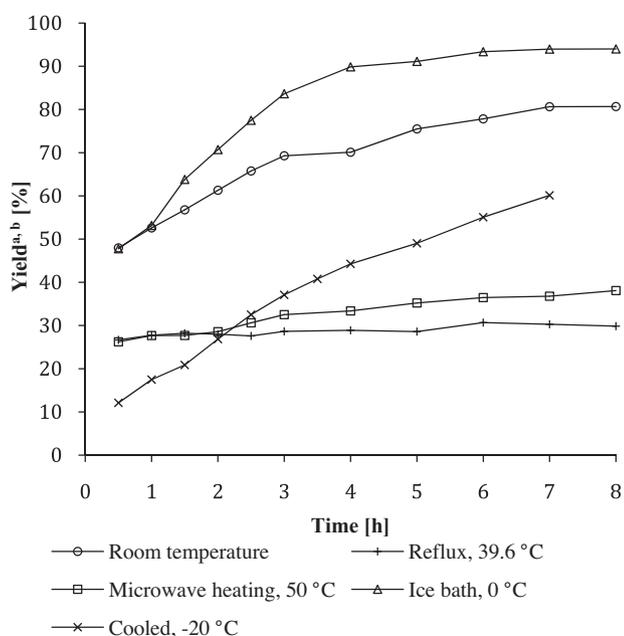
The formation of 2-chlorodiphenyl ether (**6b**) from phenylboronic acid (**2**) and 2-chlorophenol (**1b**) was selected as a model reaction. To investigate the behavior of the reactants, we first applied the usual Evans¹¹ coupling conditions (Fig. 2). At room temperature a reaction time of seven hours was required to give 2-chlorodiphenyl ether (**6b**) in 81% yield (GC). To improve this protocol we tried to increase the reaction temperature using conventional or microwave heating. Both, microwave and conventional heating led to low yields and immediate cessation of the reaction in both cases (30% and 37%, respectively, after 7 h). On the contrary, cooling the reaction mixture in an ice bath increased the yield, and after six hours, the reaction was complete yielding 93%

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Scheme 1. Synthesis of mono- and dichlorinated DE congeners.



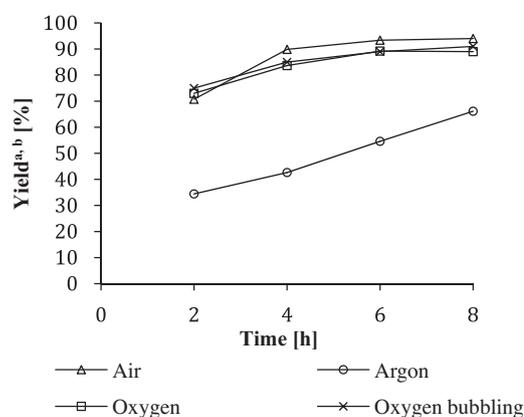
^a Yields determined by GC.

^b Reactions were performed using **1b** (1.0 mmol), **2** (2 mmol), Cu(OAc)₂ (1.0 mmol), Et₃N (5 mmol), 4 Å MS (1.0 g), CH₂Cl₂ (5 ml), air atmosphere.

Figure 2. Plot of the yield of **6b** against time for various reaction temperatures.

of the desired product. Attempts to further increase the yield by cooling to $-20\text{ }^{\circ}\text{C}$ were unsuccessful. The results seem to indicate that low temperatures are crucial for the stability of the reaction intermediates, and for our model reaction, a temperature of $0\text{ }^{\circ}\text{C}$ and reaction time of six hours were the most appropriate to achieve high yields.

Oxygen plays an important role in the proposed mechanism for the Chan–Lam coupling reaction. After initial transmetalation of the arylboronic acid and coordination of phenol, the aryl-Cu^{III}-phenol intermediate undergoes a plausible oxidation to give a Cu^{III} complex. Subsequent reductive elimination affords the product and a Cu^I species. Rapid oxidation of Cu^I to a Cu^{II} complex completes the catalytic cycle.¹² Therefore, during the optimization process, we focused our investigation on determining the influence of the oxidizing atmosphere on our model reaction. We compared the reaction under an inert (argon) atmosphere with oxidizing atmo-



^a Yields determined by GC.

^b Reactions were performed using **1b** (1.0 mmol), **2** (2 mmol), Cu(OAc)₂ (1.0 mmol), Et₃N (5 mmol), 4 Å MS (1.0 g), CH₂Cl₂ (5 ml), $0\text{ }^{\circ}\text{C}$.

Figure 3. Plot of the yield of **6b** against time using different reaction atmospheres.

spheres (air, oxygen and oxygen bubbling) (Fig. 3). In agreement with the proposed mechanism, we observed an important positive effect of the presence of oxygen over the use of an argon atmosphere. However, there was no significant difference between the reaction under an air atmosphere and that in an oxygen-rich atmosphere.

Also, the choice of an appropriate base is critical since the reaction yield is dependent on its nature. We have screened the effect of various tertiary amine bases and their molar ratios with respect to **1b** in our model O-arylation reaction (Table 1). Surprisingly, our first base of choice, triethylamine, was found to be the most active (Table 1, entries 1 and 2), and other bases all exhibited lower activity, with product yields of up to 58%.

Using the above-mentioned optimized reaction parameters,¹³ we have synthesized a complete library of mono- and dichlorinated DEs, that is, compounds **6a–p**. In the majority of cases very good reaction yields were achieved. The results are summarized in Table 2. Reaction yields were lower with sterically demanding phenolic substrates (Table 2, **6e** and **6k**), but we found no evidence of any effects due to electronic factors.

Usually there were several typical side products (Scheme 2) detected (GC/MS) in the crude reaction mixture. Even under seemingly anhydrous conditions (activated powdered 4 Å molecular sieves, dried solvent), we detected traces of by-products associated

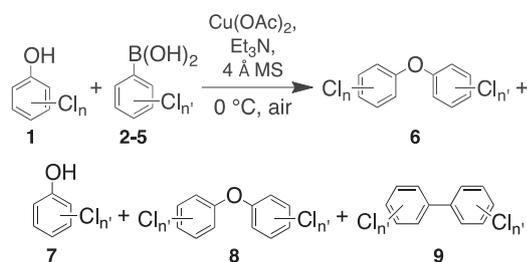
Table 1
Effect of the base in the preparation of **6b**^a

| Entry | Base | Equiv ^b | Yield ^c (%) |
|-------|------|--------------------|------------------------|
| 1 | | 2 | 80 |
| 2 | | 5 | 93 |
| 3 | | 2 | 10 |
| 4 | | 5 | 34 |
| 5 | | 2 | 19 |
| 6 | | 5 | 23 |
| 7 | | 2 | 10 |
| 8 | | 5 | 44 |
| 9 | | 2 + 2 | 58 |
| 10 | | 2 + 2 | 58 |
| 11 | | 2 | 48 |
| 12 | | 5 | 56 |
| 13 | | 2 | — |
| 14 | | 5 | 3 |
| 15 | | 2 | 6 |
| 16 | | 5 | 9 |

^a Reaction conditions: **1b** (1.0 mmol), **2** (2 mmol), Cu(OAc)₂ (1.0 mmol), 4 Å MS (1.0 g), CH₂Cl₂ (5 ml), 0 °C, under air atmosphere.

^b Molar ratio of base with respect to **1b**.

^c Yield determined by GC.

**Scheme 2.** By-products in the PCDE congener synthesis.

with the presence of water.¹¹ Phenylboronic acid undergoes O-arylation with water and gives the corresponding phenol **7**. Subsequent coupling of newly generated phenol **7** affords diaryl ether **8**. This was supported, among others, by the observation of **1a** and **6a** in the reaction of phenylboronic acid (**2**) with 2-chlorophenol (**1b**). Also, biphenyl **9** was detected as the product of homocoupling of arylboronic acids. With 2-chlorophenylboronic acid, 2,2'-dichlorobiphenyl was observed as the major product. Therefore, we avoided the use of this sterically hindered phenylboronic acid, when possible.

We have also performed control experiments using phenol and chlorinated phenylboronic acids for the preparation of monochlorinated DEs **6b–d**. The yields were comparable for 3-chloroDE (**6c**) and 4-chloroDE (**6d**), but as mentioned above, 2-chlorophenylboronic acid (**3**) gave 2,2'-dichlorobiphenyl as the major product.

All the PCDE congeners were purified using silica gel flash chromatography and compounds **7**, **8**, and **9** were completely separated from the desired product. The purified products were characterized by MS, ¹H, and ¹³C NMR spectroscopy (see Supplementary data), and using Kovats¹⁴ retention indices (Table 2). Both retention indices and mass spectra are crucial in routine environmental analysis. Although it is difficult to distinguish between congeners with the same number of chlorine atoms, mass spectral patterns give important clues about the chlorine positions. We found the molecular ion (M⁺) to be the major peak in all cases except for those with

Table 2
Synthesis of mono and dichlorinated DEs from chlorinated phenols and (chlorinated) phenylboronic acids

| No. ^a | PCDE | Chlorine position | Phenol | Phenyl-boronic acid | Yield ^b (%) | RI ^c |
|------------------|-----------|-------------------|-----------|---------------------|------------------------|-----------------|
| — | 6a | — | 1a | 2 | 85 | 1436.9 |
| 1 | 6b | 2 | 1b | 2 | 89 | 1613.4 |
| 2 | 6c | 3 | 1c | 2 | 86 | 1620.8 |
| 3 | 6d | 4 | 1d | 2 | 90 | 1637.1 |
| 4 | 6e | 2,2' | 1b | 3 | 8 ^d | 1621.1 |
| 5 | 6f | 2,3 | 1e | 2 | 84 | 1820.1 |
| 6 | 6g | 2,3' | 1b | 4 | 81 | 1794.6 |
| 7 | 6h | 2,4 | 1f | 2 | 81 | 1782.3 |
| 8 | 6i | 2,4' | 1b | 5 | 70 | 1818.5 |
| 9 | 6j | 2,5 | 1g | 2 | 74 | 1770.3 |
| 10 | 6k | 2,6 | 1h | 2 | 54 | 1743.0 |
| 11 | 6l | 3,3' | 1c | 4 | 81 | 1806.5 |
| 12 | 6m | 3,4 | 1i | 2 | 79 | 1824.6 |
| 13 | 6n | 3,4' | 1c | 5 | 84 | 1828.0 |
| 14 | 6o | 3,5 | 1j | 2 | 65 | 1764.8 |
| 15 | 6p | 4,4' | 1d | 5 | 80 | 1850.2 |

^a Suggested numbering analogous to PCBs.⁸

^b Yields are given for isolated products.

^c Retention indices.^{14,15}

^d 2,2'-Dichlorobiphenyl was isolated as the major product.

ortho-chlorines **6b,e–k**. This mass spectrometric *ortho* effect¹⁶ was observed for monochlorinated diphenyl ethers, where the loss of Cl[•] from (M⁺) is the lowest-energy process. In agreement with this the ions (M–Cl)⁺ for **6b** or (M–2Cl)⁺ for **6e–k** were observed as the base peaks in the mass spectrum. Also for 2,4-(**6h**) and 2,4'-(**6i**) substituted congeners, the ion M⁺ was almost as intense as the fragment (M–2Cl)⁺.

In conclusion we have developed a copper-catalyzed protocol for the synthesis of chlorinated diaryl ethers. This protocol was successfully applied to the synthesis of mono- and dichlorinated DEs.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, analytical instrumentation, ¹H and ¹³C NMR, and mass spectra) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.06.035>. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

- (a) Lake, J. L.; Rogerson, P. F.; Norwood, C. B. *Environ. Sci. Technol.* **1981**, *15*, 549; (b) Stafford, C. J. *Chemosphere* **1983**, *12*, 1487; (c) Kuehl, D. W.; Durhan, E.; Butterworth, B.; Linn, D. *Environ. Int.* **1984**, *10*, 45; (d) Paasivirta, J.; Tarhanen, J.; Soikkeli, J. *Chemosphere* **1986**, *15*, 1429; (e) Koistinen, J.; Vuorinen, P.; Paasivirta, J. *Chemosphere* **1993**, *27*, 2365; (f) Koistinen, J.; Paasivirta, J.; Suonpera, M. *Environ. Sci. Technol.* **1995**, *29*, 2541.
- For reviews, see: (a) de Boer, J.; Denneman, M. *Rev. Environ. Contam. Toxicol.* **1998**, *157*, 131; (b) Koistinen, J. In *The Handbook of Environmental Chemistry*; Paasivirta, J., Ed.; Springer: Berlin, 2001; Vol. 3K, pp 157–201; (c) Domingo, J. *Environ. Int.* **2006**, *32*, 121.
- Frankki, S.; Persson, Y.; Tysklind, M.; Skyllberg, U. *Environ. Sci. Technol.* **2006**, *40*, 6668.
- Kurz, J.; Ballschmiter, K. *Fresenius J. Anal. Chem.* **1995**, *351*, 98.
- (a) Norström, Å.; Andersson, K. *Chemosphere* **1977**, *5*, 237; (b) Kurz, J.; Ballschmiter, K. *Fresenius J. Anal. Chem.* **1994**, *349*, 533; (c) Nevalainen, T.;

- Koistinen, J.; Nurmela, P. *Environ. Sci. Technol.* **1994**, *28*, 1341; (d) Kurz, J.; Ballschmiter, K. *Chemosphere* **1999**, *38*, 573.
- (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700; (b) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032; (c) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **2002**, *52*, 2957.
 - (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382; (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853; (c) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211.
 - Gara, A.; Andersson, K.; Nilsson, C. A.; Norstrom, A. *Chemosphere* **1981**, *10*, 365.
 - Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.
 - Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.
 - Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
 - Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735.
 - General procedure for the preparation of compounds 6a–p:** To a solution of phenol (**1a–j**) (1.0 mmol) and phenylboronic acid (**2–5**) (2 mmol) in dry CH₂Cl₂ (5 ml) were added powdered activated 4 Å molecular sieves (1.0 g), Cu(OAc)₂ (1.0 mmol) and Et₃N (5 mmol). The mixture was cooled to 0 °C and stirred for 6 h under an air atmosphere. The reaction was quenched with an excess of *n*-hexane and precipitated catalyst and molecular sieves were separated by filtration. The filtrate was evaporated under vacuum and the residue was purified by flash chromatography (hexane, two parallel silica gel columns) to afford pure product (**6a–p**).
 - (a) Kovats, E. *Helv. Chim. Acta* **1958**, *41*, 1915; (b) van der Dool, H.; Kratz, P. D. *J. Chromatogr.* **1963**, *11*, 463.
 - Operating conditions for retention indices measurements:** TR-5MS, 30 m/0.25 mm/0.25 μm, N₂, 8 °C/min, *T*_{start} = 100 °C, *T*_{end} = 300 °C.
 - (a) Granth, I. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1503; (b) Schwarz, H. *Top. Curr. Chem.* **1978**, *73*, 231.