

# Ullmann Diaryl Ether Synthesis: Rate Acceleration by 2,2,6,6-Tetramethylheptane-3,5-dione

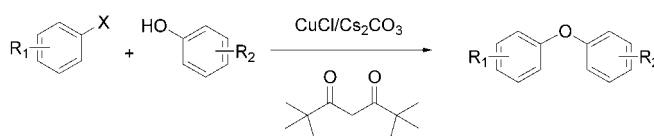
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## ABSTRACT



In the copper salt catalyzed ether formation from aryl bromides or iodides and phenols, 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) was found to greatly accelerate the ordinarily difficult reaction, making it occur under more moderate temperatures and reaction times. A series of aryl halides and phenols were shown to form ethers in NMP as the solvent, cesium carbonate as the base, and CuCl and TMHD as the catalysts. The reaction was shown to tolerate electron-rich aryl bromides and electron-neutral phenols.

Diaryl ethers are an important class of compounds in pharmaceuticals and agricultural chemicals. The Ullmann ether formation reaction, in which an aryl bromide or iodide reacts with a phenol under basic conditions in the presence of copper salt catalysts, has been the focus of a number of recent studies because it provides very direct access to diaryl ethers.<sup>1–3</sup> Although recent progress in palladium-catalyzed ether formation reactions has solved some problems in this area,<sup>4</sup> copper catalysts still hold the advantage of low cost for large-scale industrial applications.

The Ullmann ether formation has traditionally been carried out under rather harsh conditions, usually at high temperatures in pyridine solvent.<sup>3</sup> The yields are low to moderate, and reactions between electron-rich aryl halides and electron-deficient phenols typically do not work well. Recent work in Buchwald's group with copper(II) triflate catalyst has made it possible to carry out these reactions under milder conditions with a wider variety of substrates in good yields.<sup>2c</sup> Due to the relatively high cost of copper triflate and its air sensitivity, it is still desirable to develop more robust and more cost-effective processes for this important reaction. Recently, a number of groups have reported using pyridine-type ligands or phosphine-type ligands in catalytic amounts to accelerate or enhance the Ullmann reaction, allowing it to occur under more moderate conditions.<sup>2a,b</sup> We report here that 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) serves as a powerful ligand that accelerates the Ullmann coupling

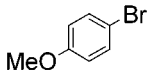
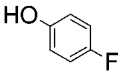
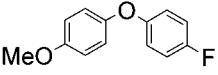
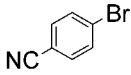
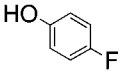
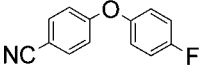
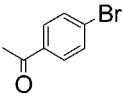
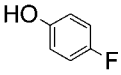
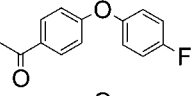
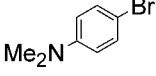
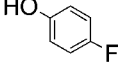
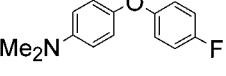
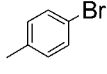
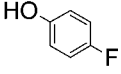
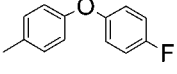

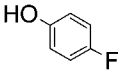
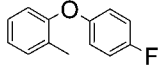

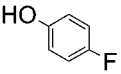
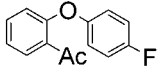
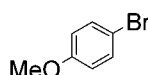
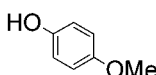
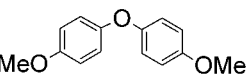
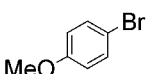
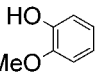
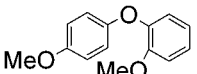
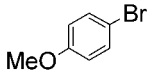
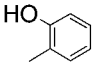
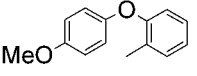
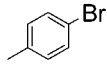
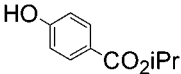
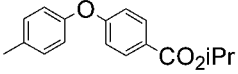
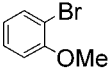
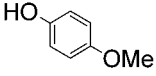
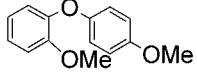
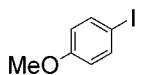
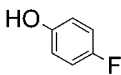
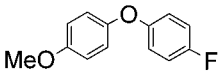
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**Table 1.** Ullmann Coupling Reaction in the Presence of 2,2,6,6-Tetramethylheptane-3,5-dione<sup>5</sup>

entry	Ar-X	ArOH	ether product	reaction time (h)	assay yield %	isolated yield %	notes
1				10	70	55	5a
2				1.5	90	82	5b
3				4	83	60	5c
4				15	79	59	5d
5				7.5	86	63	5e
6				15	97	85	5f
7				24	67	61	5g
8				10	85	77	5h
9				10	80	66	5i
10				10	92	79	4e
11				47	56	51	5j
12				25	90	76	5i
13				6	74	68	5a

reaction more than previously described ligands, allowing some of the electronically unfavorable substrates to undergo ether formation readily.

To compare the effects of different ligands, we followed the kinetics and the reaction profile of 4-bromoanisole (4-methoxyphenyl bromide) with 4-fluorophenol in NMP at 130 °C in the presence of 2 equiv of cesium carbonate and 0.5 equiv of CuCl. Without any added ligand, the reaction was very slow (only 28% conversion after 1.5 h). By comparison, in the presence of 0.25 equiv of 2,2,6,6-tetramethylheptane-3,5-dione, 93% conversion was observed after 1.5 h. Analysis of related data shows that about 10 to 15-fold acceleration from the 0.25 equiv of dione was observed for this reaction.

The following are conversions under the same conditions in the presence of 0.25 equiv of other ligands: 8-hydroxyquinoline 82%, 2-aminopyridine 43%, and 1,10-phenanthroline 68%. The assay yields from all of these reactions were 63–77%. Pentane-2,4-dione (acac) also accelerated the reaction but not as much as 2,2,6,6-tetramethylheptane-3,5-dione. It is interesting to note that none of the ligands listed above accelerated the Ullmann coupling reaction when sodium *t*-pentoxide (a full equivalent relative to the phenol) was used as the base in NMP.

To investigate the scope of this additive, we applied similar conditions for Ullmann coupling between a variety of phenols and aryl halides. The results are summarized in Table 1. In

all the examples, we used 0.1 equiv of TMHD. As a general procedure, the aryl halide (11.3 mmol), the phenol (22.6 mmol), TMHD (1.1 mmol), and cesium carbonate (22.6 mmol) were added to 19 mL of anhydrous NMP. The mixture was degassed and filled with nitrogen. To this mixture was added CuCl (5.6 mmol), and the mixture was degassed and filled with nitrogen three times. This mixture was then heated to 120 °C under nitrogen and followed by HPLC until completion of the reaction. The reaction was diluted with MTBE and filtered. The filtrate was washed with 2 M HCl and then 0.6 M HCl, 2 M NaOH, and 10% NaCl. The desired product was isolated by flash column chromatography or direct crystallization from hexanes. The product purity was at least 98% by HPLC or GC in all examples, and the assay yields were relative to the isolated products as the standards.<sup>5</sup> The major advantages of the process reported here are the low cost and the simplicity of operation.

From Table 1, it can be observed that the Ullmann coupling reactions under these conditions follow the general trend that electron-donating groups on the phenol and electron-withdrawing groups on the halide make the reaction favorable and fast, as indicated by the higher yields and shorter reaction times for entries 2, 3, and 8 compared to 1 and 4. This has been a well-established trend in copper- and palladium-catalyzed ether formation reactions. Under the current conditions, 4-methoxyphenyl bromide and 4-*N,N*-dimethylaminophenyl bromide reacted with 4-fluorophenol

within a reasonable time frame (10–15 h) at 120 °C, giving the desired products in good yields (entries 1 and 4). This represents a significant improvement over the classical conditions, which generally do not work with aryl halides with strong electron-donating groups and phenols with electron-withdrawing groups.<sup>3</sup> In fact, the palladium-catalyzed reactions suffer the same drawback.<sup>4</sup> The electron-neutral phenols and aryl halides worked well under the current conditions, as indicated in entries 5, 6, and 10. Some tolerance of electron-withdrawing groups on the phenols was observed, as the reactions with 4-fluorophenol and isopropyl 4-hydroxybenzoate (entries 1–7 and 11) gave reasonable to good yields. The major side reaction in these Ullmann ether formations is the reduction of the aryl halides to the arene (Ar–Br to Ar–H). Phenols with extremely strong electron-withdrawing groups do not undergo the desired ether formation, and in those cases, the reduction of the aryl halide to the corresponding arene (Ar–Br to Ar–H) becomes the dominating reaction. For example, the reaction of 4-hydroxybenzaldehyde with 4-bromotoluene gave very little desired products and toluene was formed. Similar results were observed for the reaction between 4-methoxyphenyl bromide and 4-hydroxybenzonitrile. Neighboring groups on the phenols and the aryl bromide had various effects in the reaction. A methyl group had little effect, as indicated in entry 10. However, an ortho methoxy group slows the reaction and ortho acetyl even more (entries 7 and 9), perhaps due to chelating effects on the copper catalyst. The reaction is mildly basic, so it tolerates a variety of functional groups such as ketone, aldehyde, nitrile, amino, and hindered ester groups. Finally, the reaction of an aryl iodide is faster and higher yielding than the corresponding bromide, as indicated by entries 13 and 1.

The mechanism of Ullmann ether formation reactions has not been well established.<sup>6</sup> While it is not clear how the diketone accelerates the Ullmann coupling reaction under these conditions, the Cu(II) bis(2,2,6,6-tetramethylheptane-3,5-dionate) is a commercially available, stable solid and, to the best of our knowledge, has not been shown to be a superb catalyst for the Ullmann reaction. In fact, when we used it for the Ullmann coupling reaction between 4-methoxyphenyl bromide and 4-fluorophenol, it showed lower reactivity than the CuCl/TMHD combination, and it is also more expensive (note, however, that the reduction of the aryl halide as the side reaction was suppressed, though not eliminated). It was also observed that CuCl was soluble under the reaction conditions even without added ligands, so the role of the ligands was not simply to dissolve the copper salt. It was also observed that reducing the amount of the diketone from 0.25 to 0.1 equiv slowed the reaction. NMR studies of the reaction mixture indicated that when 4-fluorophenol and TMHD were dissolved in deuterated NMP in the presence of cesium carbonate, the phenol is partially deprotonated as indicated by the upfield shift of the aromatic proton chemical shifts. The diketone exists primarily as the ketone (as opposed to the enol) form. Upon addition of CuCl, a slight downfield shift of the phenol aromatic proton signals

(5) All products gave satisfactory mass spectrometry data (molecular ions were observed). All new compounds are characterized by satisfactory proton and <sup>13</sup>C NMR, elemental analysis (within 0.4% of theory), and HPLC or GC (≥98%). (a) oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 100 MHz) δ 7.04–6.85 (m, 8H), 3.81 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) δ 158.4 (d, *J* = 240.4 Hz), 155.9, 154.3, 150.7, 120.3, 119.2 (d, *J* = 8.2 Hz), 116.2 (d, *J* = 23.3 Hz), 115.0, 55.7. (b) Tanaka, A.; Terasawa, T.; Hagihara, H.; Ishibe, N.; Sawada, M.; Sakuma, Y.; Hashimoto, M.; Takasugi, H.; Tanaka, H. *J. Med. Chem.* **1998**, *41*, 4408. (c) Hogenkamp, D. J.; Nguyen, P.; Shao, B. Patent WO 2001/68612. Mp 68–71 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.97–7.90 (m, 2H), 7.13–7.01 (m, 4H), 6.99–6.93 (m, 2H), 2.53 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 196.7, 162.2, 159.6 (d, *J* = 243.5 Hz), 151.3, 132.0, 130.7, 121.8 (d, *J* = 8.5 Hz), 116.9, 116.8 (d, *J* = 23.5 Hz), 26.5. (d) Baliah, V.; Kanagasabapathy, V. M. *Indian J. Chem., Sect. B* **1978**, *16B*, 810. Mp 58–61 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.03–6.87 (m, 6H), 6.79–6.72 (m, 2H), 2.95 (s, 6H); <sup>13</sup>C (CDCl<sub>3</sub>, 100 MHz) δ 158.13 (d, *J* = 240.1), 154.9, 147.9, 147.7, 120.5, 118.7 (d, *J* = 8.10), 116.0 (d, *J* = 23.2), 114.0, 41.2. (e) oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.14 (d, 2H, *J* = 8.1 Hz), 7.07–6.92 (m, 4H), 6.89 (d, 2H, *J* = 8.2 Hz), 2.35 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 158.6 (d, *J* = 241.0 Hz), 155.3, 153.5, 132.9, 130.3, 120.0 (d, *J* = 8.2 Hz), 118.6, 116.2 (d, *J* = 23.3 Hz), 20.7. (f) oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.30–7.24 (m, 1H), 7.21–7.14 (m, 1H), 7.11–6.97 (m, 3H), 6.93–6.84 (m, 3H), 2.27 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 158.4 (d, *J* = 240.3 Hz), 155.0, 153.7, 131.6, 129.7, 127.2, 123.9, 119.1, 118.9 (d, *J* = 8.3 Hz), 116.2 (d, *J* = 23.3 Hz), 16.2. (g) oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 100 MHz) δ 7.88–7.80 (m, 1H), 7.48–7.39 (m, 1H), 7.22–7.13 (m, 1H), 7.13–7.04 (m, 2H), 7.04–6.96 (m, 2H), 6.86 (d, 1H, *J* = 8.3 Hz), 2.66 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 198.9, 159.2 (d, *J* = 242.5 Hz), 156.7, 152.2, 133.7, 130.6, 130.3, 123.5, 120.5 (d, *J* = 8.3 Hz), 118.6, 116.7 (d, *J* = 23.5 Hz), 31.6. (h) Wang, L.; Xi, H.; Sun, X.; Shen, Y.; Yang, Y.; Pan, Y.; Hu, H. *Synth. Comm.* **2000**, *30*, 227. (i) Mp 77–87 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.11–7.04 (m, 1H), 7.03–6.98 (m, 1H), 6.98–6.92 (m, 2H), 6.92–6.83 (m, 4H), 3.89 (s, 3H), 3.80 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.5, 151.1, 150.9, 146.8, 123.8, 121.0, 119.4, 119.3, 114.8, 112.7, 56.1, 55.7. (j) Mp 52–55 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.04–7.86 (m, 2H), 7.24–7.15 (m, 2H), 7.02–6.95 (m, 4H), 5.25 (sept, 1H, *J* = 6.2 Hz), 2.37 (s, 3H), 1.37 (d, 6H, *J* = 6.3 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 165.7, 162.1, 153.4, 134.2, 131.6, 130.5, 125.0, 120.1, 117.0, 68.2, 22.0, 20.8.

(6) For kinetic and mechanistic work, see: (a) Litvak, V. V.; Shein, S. M. *Zh. Organ. Khim.* **1975**, *11*, 92. (b) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496.

was observed, consistent with complexation of the phenolate with copper(I). At room temperature, the diketone peaks in the proton NMR were totally broadened after CuCl was added, consistent with complexation with the copper(I) and rapid equilibration among different species. All of the evidence is consistent with cocomplexation of the copper(I) by the diketone as well as the phenolate, which presumably made the rate-determining step faster.

In summary, we have developed a cost-effective, simple to use procedure for Ullmann diaryl ether synthesis that is applicable to a wide variety of substrates.

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**Supporting Information Available:** Detailed experimental procedures of the Ullmann ether preparations along with spectroscopic and elemental analysis data for all new compounds and previously partially characterized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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