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Ultrafast Chemistry: Cobalt Carbonyl-Mediated Synthesis of Diaryl Ketones under Microwave Irradiation

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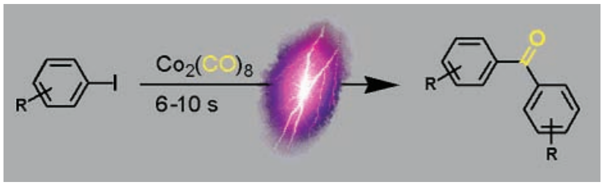
ABSTRACT



By combining the advantages of metal activation, in situ carbon monoxide delivery, and microwave heating, benzophenones were efficiently synthesized in 6–10 s. These ultrafast carbonylation reactions occur under air by flash heating of aryl iodides in the presence of dicobalt octacarbonyl.

The ultimate goal of the emerging disciplines of high-speed chemistry[1] and automated organic synthesis[2] is to perform organic transformations at an ever-increasing rate. The synthetic chemist of today is expected to synthesize the desired products not only in high yields and purities but also very quickly. Supporting high-throughput production is a large component of basic chemistry research in areas such as the development of supported reagents[3] and fluorous technologies[4,5] for fast purifications. Further, to meet the high expectations regarding reaction rates, both for optimization work and target synthesis, organic chemists have begun to explore microwave flash heating to accelerate slow reactions.[6] Notwithstanding the use of modern and highly efficient single mode microwave synthesizers, reported reaction times are seldom below 5 min.[7]

Despite these advances in our ability to purify the products and to enhance slow chemistry, the crucial aspect of performing high-speed gaseous organic reactions has not improved until recently. To avoid risky and complicated handling or highly specialized equipment, carbonylation processes employing in situ liberation of carbon monoxide in sealed vessels have been developed.[8−10] In a research program dedicated to the disclosure of new and rapid metal-catalyzed protocols,[11] we now wish to report that direct synthesis of symmetric benzophenones from aryl iodides can be directly accomplished in the presence of dicobalt octacarbonyl. **The reaction proceeds cleanly to full conversion in the absence of carbon monoxide atmosphere after less than 10 s of microwave irradiation!**

Our primary objectives were (a) to identify a highly convenient and robust in situ carbonylation procedure for generation of benzophenones and (b) to minimize the reaction

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[1] Larhed, M.; Hallberg, A. *Drug Discov. Today* **2001**, *6*, 406−416.
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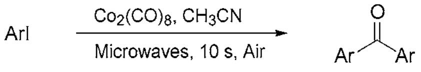
times. Inspired by the pioneering work of Brunet,[12] a series of aryl iodides (**1a**−**k**) were microwave heated together with 0.66 equiv of $Co_2(CO)_8$, the latter acting as a combined Ar−I activator and carbon monoxide source (Scheme 1). The aryl iodides were chosen to cover aspects of sterical hindrance, different electronic properties, and potentially reactive functional groups. Initial screening experiments revealed that inert atmosphere, bases or other additives were unnecessary. Further, the solvents acetonitrile and propionitrile drastically expedited the formation of benzophenones (**2**), while the use of benzene, THF, DMAc, and DMF afforded only minor yields of product. Addition of small amounts of water inhibited the process.

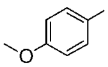
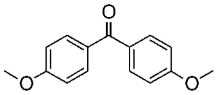
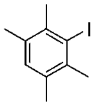
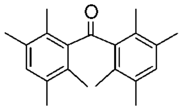
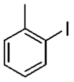
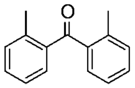
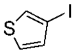
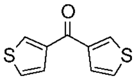
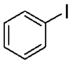
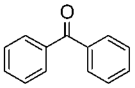
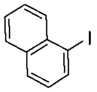
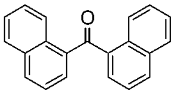
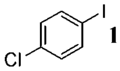
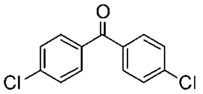
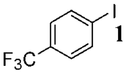
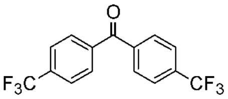
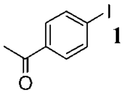
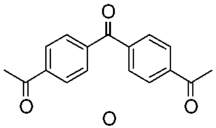
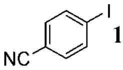
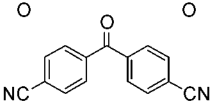
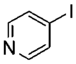
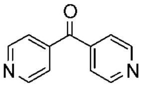
Scheme 1. Synthesis of Diaryl Ketones Employing Aryl Iodides



1a-j **2a-j**

The preparative carbonylation reactions were conducted on a 0.6 mmol scale under air in sealed microwave transparent vessels using a commercially available batch reactor[13] for heating. With less than 10 s of directed irradiation, all starting **1a**−**j** underwent complete conversion and afforded useful to excellent isolated yields of products **2a**−**j** (57−97%).[14] The results are summarized in Table 1. Notably, the coupling with parent **1e** was further optimized down to 6 s with consistent yield (entry 5). Using the 10 s standard condition, only electron-rich **1a** and sterically hindered **1b** produced unsatisfying yields, mainly due to competing dehalogenation (entries 1 and 2). The heteroaromatic sulfur-containing **1d** proved to be a very efficient coupling partner (entry 4) while coupling with **1k** was unsuccessful. As expected, chemoselective coupling of **1g** was facile due to the reluctance of aryl chlorides to undergo cobalt-mediated activation.[15] Employing **1j** furnished a satisfying preparative outcome, despite the well-known capacity of nitriles to substitute carbon monoxide and to form stable complexes with the metal center (entry 10).[16,17] In general, entries 1−7 provided small quantities of benzil side products while the electron-poor **1h**, **1i**, and **1j** furnished trace amounts of homocoupled biaryls. No conversion occurs in the absence of heating regardless of reaction time.

Table 1. Ultrafast Generation of Benzophenones under Air in Sealed Vessels

entry	aryl iodide		product		yield (%)[a]
1		**1a**		**2a**	57
2		**1b**		**2b**	60
3		**1c**		**2c**	91
4		**1d**		**2d**	96
5		**1e**		**2e**	78 76[b] 75[c]
6		**1f**		**2f**	97
7		**1g**		**2g**	87
8		**1h**		**2h**	97
9		**1i**		**2i**	91
10		**1j**		**2j**	88
11		**1k**		**2k**	<5[d]

[a] Isolated yield based on **1** (>95% purity of **2** by GC−MS). [b] 6 s of microwave irradiation. [c] Performed with a preheated oil bath (oil temperature 140 °C) for 2 min using an open reaction vessel. [d] Not isolated, less than 5% according to GC−MS.

The carbonylative coupling of the more sluggish aryl bromides was also examined with $Co_2(CO)_8$. Despite employing different irradiation times, temperatures, and amounts of $Co_2(CO)_8$, a smooth and general protocol to exploit aryl bromides was not identified. At present, incomplete conversions and varying reaction times plague the methodology. For example, ketones **2e** and **2i** were both synthesized in moderate yields (64% and 43%), but very different heating times were required in the two cases (Scheme 2).

In an attempt to explore the possibility to perform cobalt-catalyzed carbonylative couplings, nonstoichiometric amounts of $Co_2(CO)_8$ were investigated in the reaction with **1f**. Two conclusions were made from these experiments. First, the reaction is catalytic with more than one turnover in cobalt

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(12) Brunet, J. J.; Taillefer, M. *J. Organomet. Chem.* **1990**, *384*, 193−197.

(13) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630.

(14) The aryl iodide (0.60 mmol), $Co_2(CO)_8$ (0.40 mmol, 137 mg), and 2,3-dimethylnaphthalene (0.15 mmol, 23 mg) as internal standard and 2.5 mL of dry acetonitrile were mixed in a septum-capped tube (a Smith process vial). The microwave synthesizer was set to 250 °C and the heating time to 10 s. After 10 s, the temperature was ca. 130 °C. After cooling, the reaction mixture was filtered through Celite, concentrated, and purified with silica chromatography.

(15) Brunet, J. J.; Demontauzon, D.; Taillefer, M. *Organometallics* **1991**, *10*, 341−346.

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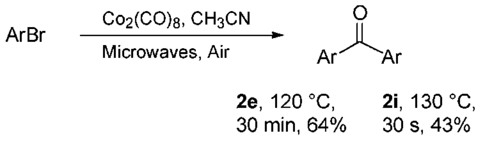
Scheme 2. Synthesis of Diaryl Ketones Employing Aryl Bromides



since 0.35 equiv of $Co_2(CO)_8$ affords more than 95% conversion and high yield of **2f** (91%). Second, a further reduction of $Co_2(CO)_8$ to 0.3 equiv results in an incomplete reaction, most likely as a consequence of an insufficient amount of available carbon monoxide. In Table 1, an excess of $Co_2(CO)_8$ (0.66 equiv) was utilized to improve the scope of the reaction with regard to different aryl iodides.

The importance of the carbon monoxide buildup in sealed vessels was investigated by preparing the diaryl ketone **2e** under conditions with open vessels using traditional oil-bath heating (oil temperature 140 °C, 2 min), but otherwise using the standard method from Table 1. A somewhat larger amount of dicarbonylated benzil byproduct accompanied this protocol, although the result suggests that this in situ carbonylation route can be performed also without a dedicated microwave synthesizer.

The carbonylation described appears, after a starting thermally induced homolytic cleavage of $Co_2(CO)_8$ into $Co(CO)_4^{\bullet}$, to occur via a radical pathway,[16,18] since the reaction is completely inhibited by 1.3 equiv of the radical scavenger nitrobenzene.[19,20] Furthermore, addition of 1.5 equiv radical inhibiting TEMPO afforded less than 10% yield.[21] The suggested radical pathway is also supported by Pályi et al. reporting on the importance of nitrile solvents in dicobalt octacarbonyl radical processes.[16] Regarding the radical initiation step, we see no reason to suggest a nonthermal microwave-promoted process.

The initial microwave power and the corresponding temperature response are illustrated in Figure 1 for a preparative 10 s reaction (entry 5, Table 1) using the standard amount of $Co_2(CO)_8$ (0.66 equiv). A first powerful 2.5 s microwave pulse (300 W) starts the coupling reaction before the IR-temperature feedback system temporarily cuts off the irradiation. After a real-time, computer-controlled calibration, the next heating period brings the reaction mixture up to the final temperature of 130 °C. The magnetron is thereafter turned off and the automatic air-cooling starts. The pressure never exceeds 12 bar.

Note that the response of the IR-thermometer lags behind and that the actual reaction temperature is higher than indicated in the figures. This is a consequence of measuring the temperature remotely using IR pyrometry,[22] though substantial differences exist between the surface of the reaction vessel and the higher internal temperature. The deviation is particularly true at short irradiation times and high microwave power. In fact, the measured temperature maximum with the IR-sensor is detected after the irradiation power is turned off, during the cooling period.

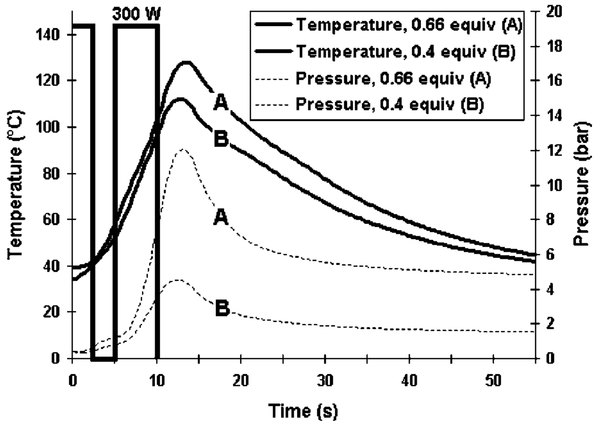


Figure 1. Temperature, pressure, and power profiles for the synthesis of **2e** with 0.66 equiv (A) (Table 1, entry 5) and 0.4 equiv (B) of $Co_2(CO)_8$.

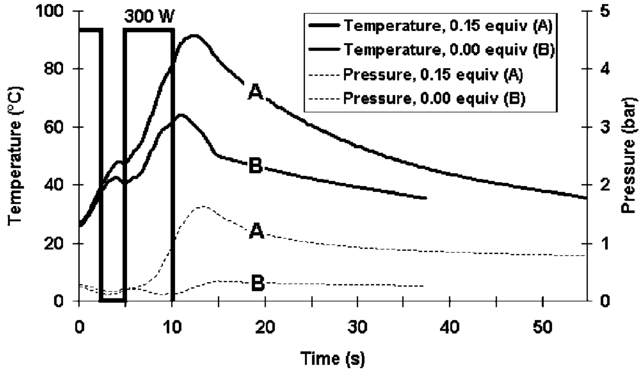


Figure 2. Temperature, pressure, and power profiles for the synthesis of **2e** with 0.15 equiv (A) and 0.00 equiv (B) of $Co_2(CO)_8$. No temperature or pressure measurements were performed below 40 °C.

Interestingly the maximum temperature depends on the added amount of $Co_2(CO)_8$. Figure 2 visualizes the temperature profile for the synthesis of **2e** in the presence of only 0.15 equiv of $Co_2(CO)_8$ (ca. 50% conversion of **1e**). The reaction mixture was only heated to 91 °C despite an identical output power from the magnetron, compared to 112 °C at 0.4 equiv (Figure 1B) and 130 °C at 0.66 equiv $Co_2(CO)_8$, (Figure 1A). We speculate that this difference might be a consequence of the initial $Co(CO)_4^{\cdot}$ generation; either it is a

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[18] Sisak, A.; Ungvary, F.; Marko, L. *Organometallics* **1986**, *5*, 1019−1023.

[19] Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1965**, *87*, 4520−4528.

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[21] Reynolds, M. A.; Guzei, I. A.; Angelici, R. J. *Organometallics* **2001**, *20*, 1071−1078.

[22] Whittaker, A. G.; Mingos, D. M. P. *J. Microwave Power Electromagn. Energy* **1994**, *29*, 195−219.

highly exothermic process or, alternatively, a more efficient microwave heating is obtained by a change of the dielectric properties of the mixture.[23]

Although we have made no analysis determining the gas composition during the reaction, the remaining pressure after cooling indicates that substantial amounts of carbon monoxide is released. The low-pressure detected in absence of $Co_2(CO)_8$ (Figure 2, B) supports this suggestion.

Spurred by the desire to discover ultrafast organic chemistry, a cobalt-mediated and microwave-heated carbonylation method to prepare benzophenones from aryl iodides has been developed. Compared to the previously reported methods for diaryl ketone generation from aryl iodides,[12] this method does not need either an external source of carbon monoxide gas,[12] nor strong base[12] or an oxidating agent.[24] In addition, the reported method affords both higher yields and is faster by order of magnitudes (seconds instead of hours).

Acknowledgment. This work was supported by the Swedish Research Council and by the Knut and Alice Wallenberg Foundation. We thank Johan Wannberg for helpful discussions and Anna Baumgarten and Johan Edin for laboratory assistance. We thank Personal Chemistry for providing the Smith microwave synthesizer.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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