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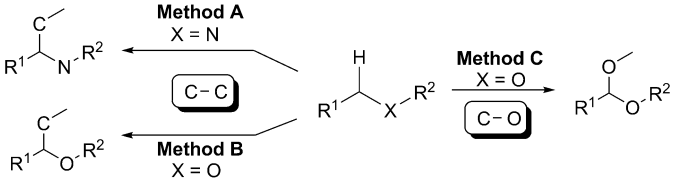
Copper-Catalyzed Formation of C–O Bonds by Direct α-C–H Bond Activation of Ethers Using Stoichiometric Amounts of Peroxide in Batch and Continuous-Flow Formats

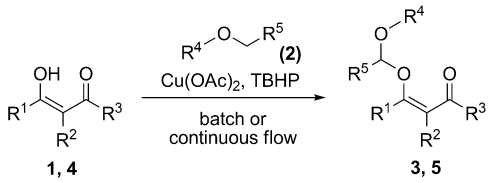
G. Sathish Kumar,[a] Bartholomäus Pieber,[b] K. Rajender Reddy,*[a] and C. Oliver Kappe*[b]

Numerous synthetic strategies for the transition-metal catalyzed formation of C–C as well as C–heteroatom bonds have been advanced during the last decades.[1] Apart from the well-established classical cross-coupling protocols involving prefunctionalized starting materials,[1] the direct functionalization of the C–H bond ("C–H activation") for the atom- and step-economical synthesis of functionalized molecules has attracted significant interest in the synthetic community.[2] Among the many C–H bond activation protocols which have been developed over the past few years, catalytic cross-dehydrogenative-coupling (CDC) reactions have been shown to be particularly useful,[3] and have been extensively utilized in various C–C bond forming protocols.[4] The α-functionalization of amines, for example, is a widely investigated method for the formation of C–C bonds using the CDC approach under oxidative conditions (Scheme 1, Method A).[5] In addition, several methods involving the concept of C–H bond activation for the construction of C–O bonds have appeared in the literature.[6–10] For example, the synthesis of 2,3-dihydrobenzofurans via intramolecular oxidative C–O coupling involving activation of an aromatic C–H bond was recently described.[6] Similarly, intermolecular C–O couplings have been reported for the acetoxylation of aromatic and aliphatic C–H bonds using transition-metal catalysts.[7] These and related methods for the α-functionalization of ethers via C–H bond activation have recently been reviewed.[8] In this context, CDC methods have demonstrated to be very efficient for the formation of C–C bonds (Scheme 1, Method B).[9] However, the α-functionalization of ethers toward the formation of a C–O bond has rarely been disclosed in the literature (Scheme 1, Method C).[10] The only known example involves the Bu_4NI-catalyzed formation of esters from carboxylic acids and ethers requiring 20 mol% of the catalyst, 2.2 equivalents of *tert*-butyl hydroperoxide (TBHP) as oxidant, and a typical reaction time of 12 h at 80 °C.[10]



Scheme 1. Cross-dehydrogenative-coupling (CDC) approaches for C–C and C–O bond formation via α-C–H bond activation.

Herein, we present a novel copper-catalyzed oxidative C–O bond formation protocol in which 2-carbonyl-substituted phenols and β-ketoesters are directly coupled with simple ethers to generate hitherto undisclosed unsymmetrical acetal scaffolds (Scheme 2). Under optimized conditions, catalyst amounts as low as 1 mol% of $Cu(OAc)_2$ can be employed, resulting in high product yields within 20–30 min in an elevated temperature regime. Since a key requirement to the success of this oxidative C–O bond forming protocol is the use of 2–3 equivalents of TBHP as oxidant, an obvious safety issue results from the combination of a peroxide with ethers at high temperatures. Therefore, the synthesis was successfully translated to a continuous-flow/microreactor protocol providing a means to safely scale this process to synthetically useful quantities of acetal products, and to best



Scheme 2. Copper-catalyzed oxidative cross-dehydrogenative-coupling of β-ketoesters or 2-carbonyl-substituted phenols with ethers.

[a] G. S. Kumar, Dr. K. R. Reddy
Inorganic and Physical Chemistry Division
Indian Institute of Chemical Technology
Tarnaka, Hyderabad-500 607 (India)
Fax: (+91) 40-27160921
E-mail: rajender@iict.res.in
rajenderkallu@yahoo.com

[b] B. Pieber, Prof. Dr. C. O. Kappe
Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
and Institute of Chemistry, Karl-Franzens-University Graz
Heinrichstrasse 28, 8010 Graz (Austria)
Fax: (+43) 316-380-9840
E-mail: oliver.kappe@uni-graz.at

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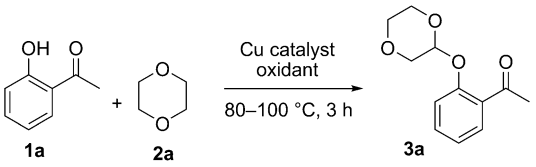
of our knowledge represents the first application of continuous-flow processing to C–H activation chemistry.[11]

Previous investigations from our laboratory on the copper-catalyzed CDC reaction of β-dicarbonyl derivatives or 2-carbonyl-substituted phenols with *N,N′*-disubstituted formamides mediated by stoichiometric amounts of TBHP have indicated that the carbonyl group adjacent to the hydroxy moiety acts as directing group, and therefore constitutes an essential functionality for efficient coupling reactions.[12] To explore the ability of these substrates in a putative CDC reaction with ethers, the coupling behavior of 2-hydroxyacetophenone (**1a**) and 1,4-dioxane (**2a**) under different conditions was evaluated (Table 1). Gratifyingly, the

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Catalyst [mol%]	Oxidant [equiv]	*T* [°C]	**3a** [%][b]
1	$Cu(OAc)_2$ (10)	TBHP in water (1.5)	80	29
2	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP in water (1.5)	80	24
3	$CuCl_2$ (10)	TBHP in water (1.5)	80	–
4	CuCl (10)	TBHP in water (1.5)	80	24
5	$Cu(OAc)_2$ (10)	H_2O_2 (1.5)	80	–
6	$Cu(OAc)_2$ (10)	NaOCl (1.5)	80	–
7	$Cu(OAc)_2$ (10)	DTBP[c] (1.5)	80	–
8	$Cu(OAc)_2$ (10)	TBHP in decane (1.5)	80	31
9	$Cu(OAc)_2$ (5)	TBHP in water (2.2)	100	69
10	$Cu(OAc)_2$ (5)	TBHP in decane (2.2)	100	81
11	–	TBHP in decane (2.2)	100	–
12	$Cu(OAc)_2$ (5)	–	100	–

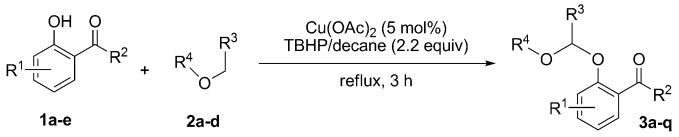
[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mL), 3 h, unless noted otherwise. [b] Yields isolated after chromatograhpy. [c] Di-*tert*-butyl hydroperoxide.

use of 10 mol% of $Cu(OAc)_2$ as catalyst in combination with aqueous (70%) TBHP at 80°C for 3 h did indeed afford the desired acetal (**3a**) in moderate yield (Table 1, entry 1). Surprisingly, all other tested Cu^{II} species, with the exception of $Cu(OAc)_2$ hydrate, were completely inactive (Table 1, entries 2 and 3, see also Table S1 in the Supporting Information), whereas several Cu^{I} catalysts showed moderate catalytic activity (Table 1, entry 4 and Table S1). The nature of the oxidant was also found to be a crucial factor in this transformation; no desired product was observed by replacing TBHP with a variety of other common oxidants (Table 1, entries 5–7, see also Table S1). Moving from aqueous TBHP to a commercially available solution of TBHP in decane (5–6 M), the product yield could be slightly increased (Table 1, entry 8) and further experiments at elevated temperature clearly demonstrated a reaction enhancement using the water-free variant (Table 1, entries 9 and 10). A systematic reaction optimization using both increased temperatures and higher amounts of oxidant in combination with a significantly reduced catalyst loading ultimately resulted in virtually full substrate conversion and a 81% isolated yield of the desired acetal **3a** (Table 1, entry 10, see also Table S1). The lack of product formation in control experiments without oxidant clearly underlines the importance of both metal catalyst and oxidant (Table 1, entries 11 and 12).

Encouraged by the results obtained in the optimization experiments described above, a number of analogous CDC transformations varying both reaction partners were studied (Table 2). Cyclic ethers such as 1,4-dioxane (**2a**) and THF (**2b**) reacted smoothly with different 2-carbonyl-substituted phenol derivatives (**1a–e**) to provide the corresponding acetal products (**3a–j**) in moderate to excellent yields. Linear, unsymmetrical ethers such as 1,2-dimethoxyethane (DME; **2c**) furnished a mixture of products resulting from competitive C–H activation of the internal methylene and the terminal methyl group, respectively (**3k–3n**). Methyl *tert*-butyl ether (MTBE; bp. 56°C) as well as simple Et_2O (bp. 35°C) remained completely unreactive under these reaction conditions operating at the reflux temperature of the solvent (**3p–3q**). Subsequently, without further reoptimization, the substrate scope was further extended to β-ketoesters **4a–h** (Scheme 3).

To move this potentially hazardous coupling protocol involving a peroxide/ether mixture to a safe and scalable continuous-flow regime,[13] we first attempted to reduce the initially optimized reaction time of 3 h under reflux conditions (Table 1) to something more suitable for a continuous processing approach (<30 min). Therefore the CDC of 2-hy-

Table 2. Substrate scope in the $Cu(OAc)_2$-catalyzed coupling of 2-carbonyl-substituted phenols with ethers.[a]



1a-e **2a-d** **3a-q**

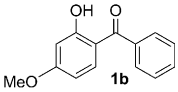
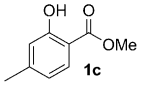
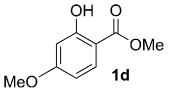
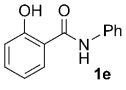
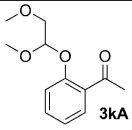
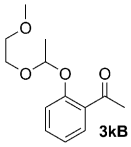
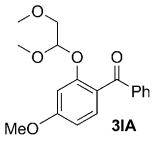
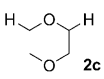
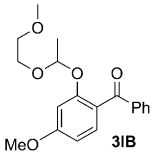
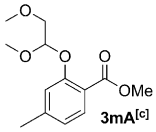
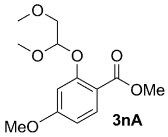
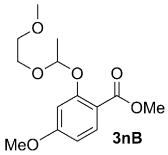
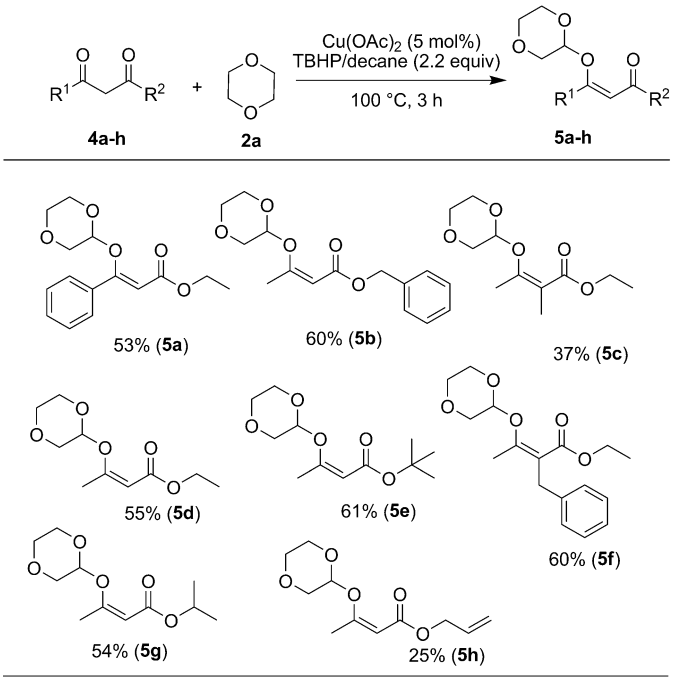
Entry	**1**	**2**	Product	Yield [%][b]
1	 **1a**		**3a**	79
2	 **1b**		**3b**	80
3	 **1c**	 **2a**	**3c**	55
4	 **1d**		**3d**	85
5	 **1e**		**3e**	28
6	**1a**		**3f**	74
7	**1b**	 **2b**	**3g**	66
8	**1c**		**3h**	39
9	**1d**		**3i**	82
10	**1e**		**3j**	45

Table 2. (Continued)

Entry	1	2	Product	Yield [%][b]
11	**1a**		 **3kA**	65
			 **3kB**	12
12	**1b**		 **3lA**	41
		 **2c**	 **3lB**	18
13	**1c**		 **3mA**[c]	35
			 **3nA**	64
14	**1d**		 **3nB**	20
15	**1a**	 **2d**	**3o**	76
16	**1a**	 **2e**	**3p**	–
17	**1a**	 **2f**	**3q**	–

[a] Reaction conditions: **1a–e** (1 mmol), **2a–d** (2 mL), reflux temperature of the respective ether. [b] Yields isolated after chromatography. [c] Amount of terminal coupling product too low for isolation.



Scheme 3. Substrate scope in the $Cu(OAc)_2$-catalyzed coupling of ß-ketoesters with dioxane.

droxyacetophenone (**1a**) and 1,4-dioxane (**2a**) was reevaluated more closely under sealed-vessel microwave conditions paying particular attention to the reaction time.[14] An initial temperature screen using accurate internal temperature monitoring[15] indicated that the optimum temperature window for the oxidative coupling is between 120 and 135 °C. At lower, as well as higher temperatures, a drop in conversion was observed (see Table S2 and Figure S1 in the Supporting Information). We presume that the decomposition of TBHP is faster than the desired CDC reaction at higher temperatures.[16] However, further optimization at 135 °C showed almost full conversion within only 15 min when the amount of TBHP oxidant was increased to 3 equivalents, and was added portionwise (3×1 equiv).[16] In addition, under these intensified conditions it was possible to decrease the amount of $Cu(OAc)_2$ catalyst to 1 mol % at the expense of a 30 min reaction time. Ultimately, keeping the desire of throughput in the flow process in mind, a catalyst loading of 2.5 mol % and a reaction time of 20 min were chosen.[16] Under these high-temperature conditions in the sealed microwave vial, substrate **1a** was also successfully coupled not only with THF (**2b**) providing a 96 % isolated yield of acetal **3b**, but also with MTBE (**2e**) and diethyl ether (**2f**), furnishing the desired target molecules **3p** and **3q** in moderate yields (Table S5 in the Supporting Information).

The optimized microwave batch protocols were then translated to a continuous-flow regime ("microwave-to-flow" paradigm)[17] in a Uniqsis FlowSyn reactor equipped with a 20 mL internal volume stainless steel coil (i.d. = 1.0 mm) operating at 130 °C coil temperature.[18] To avoid large volumes of ether/peroxide mixtures, a two-feed strategy as shown in Figure 1 was devised. Therefore, a solution of the Cu catalyst and 2-hydroxyacetophenone substrate (**1a**) in 1,4-dioxane (*Feed A*, flow rate: 0.8 mL min^{-1}), and commercially available TBHP in decane (*Feed B*, flow rate 0.2 mL min^{-1}) were passed through a glass static mixer (M) and subsequently heated in the above-mentioned coil reactor (RC). Within the 20 min residence time of this flow experiment, conversion/yields similar to those obtained under microwave batch conditions were obtained, considering that

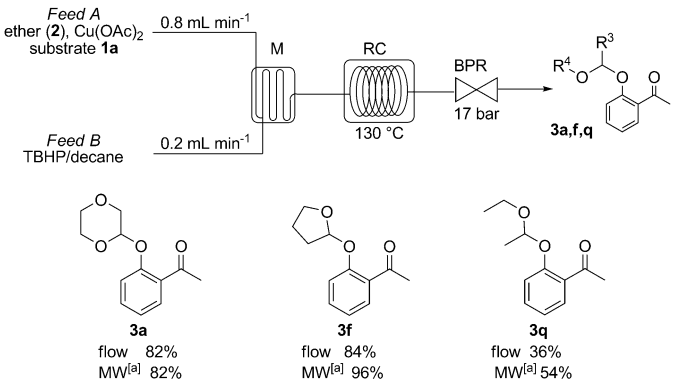


Figure 1. Schematic diagram for the two-feed continuous-flow oxidative C–O coupling of 2-hydroxyacetophenone **1a**. For more details, see the Supporting Information.[a] TBHP was added portionwise in the batch experiments, explaining the higher yields, see also Tables S7 and S8 in the Supporting Information.

multiple additions of oxidant were possible in the batch experiment.[16]

In summary, we have demonstrated the efficient construction of C–O bonds via α-C–H bond activation of simple ethers using an inexpensive copper catalyst in combination with a commercially available decane solution of TBHP as stoichiometric oxidant. This protocol allows the generation of unsymmetrical acetal scaffolds not easily available by other methods. To make this potentially hazardous synthetic protocol scalable, a two-feed high-temperature/pressure microreactor approach was developed that provided the desired acetals in yields similar to those obtained in the batch protocols.

Experimental Section

General procedure for the acetal synthesis (3a–3o) in a standard oil bath: (Table 2 and Scheme 3). A solution of 2-carbonyl-substituted phenol (**1a–e**) or β-keto ester (**4a–h**) (1.0 mmol), $Cu(OAc)_2$ (9 mg, 5 mol%) in 2 mL of the respective ether **2** was stirred at room temperature. To the same solution, a 5–6 M TBHP solution in decane (2.2 mmol) was added dropwise before the mixture was heated at the reflux temperature of the respective ether (oil bath) for 3 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by preparative column chromatography on silica gel (hexane/ethyl acetate = 9:1).

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Keywords: C–H activation · continuous-flow reactions · copper · ethers · oxidative coupling

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