C–H Activation

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Synthesis of Aryl Ethers from Benzoates through Carboxylate-Directed C–H-Activating Alkoxylation with Concomitant Protodecarboxylation**

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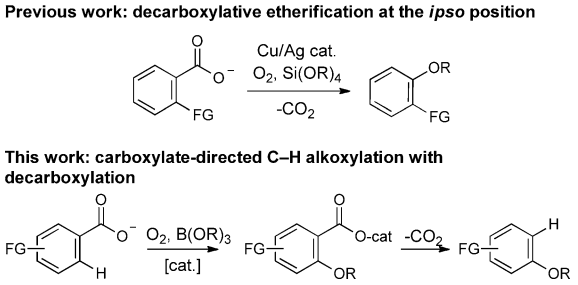
The aryl ether functionality is a common motif in many classes of biologically active compounds and functional materials.[1] Traditional methods to attach ether groups to aromatic rings require either activated substrates (S_NAr) or harsh reaction conditions (Ullmann-type condensation), and are therefore not ideal for the late-stage functionalization of complex molecules.[2]

In the last two decades, the need for reliable and atom-economic methods to access aryl ethers started a rapid development of new methodologies for C–O bond formation. Important advances include copper- and palladium-catalyzed couplings of aryl halides with alcohols or phenols,[3] and copper-mediated oxidative coupling of aryl borates with phenols.[4] These methods depend on the availability of starting materials with the desired substitution pattern, a limitation that may be overcome with C–H activating alkoxylation processes.[5] Several protocols for palladium-catalyzed regioselective alkoxylations of arenes were recently reported with the use of pyridyl,[6] *N*-methoxyimine,[7] *N*-methoxybenzamide,[8] cyano,[9] and anilide[10] directing groups. Copper-based systems have been used for similar transformations,[11] including oxygen atom transfer[12] or catalytic acetoxylation reactions,[13] but to the best of our knowledge, no copper-catalyzed C–H activating alkoxylations of arenes have been reported to date. However, the possibility of directed copper-mediated aryl ether formation is supported by two experimental findings: Yu et al. observed the coupling of 2-phenylpyridine with 4-cyanophenol,[13a] and Ribas and Stahl found that methoxylation of a benzene ring within a macrocyclic ligand scaffold takes place in the presence of copper.[14]

In our studies of decarboxylative coupling reactions,[15,16] we recently disclosed a decarboxylative etherification in which a C–O bond is formed at the original position of the carboxylate group of benzoates.[17] For a broad range of substrate combinations, the decarboxylative alkoxylation was found to proceed regiospecifically at the *ipso* position. Only for one substrate, we observed the formation of a by-product in which the C–O bond had formed in the *ortho* position of the extruded carboxylic group. This by-product, although obtained in only modest yield and using stoichiometric amounts of silver and copper, pointed to the principal feasibility of a second, complementary pathway for alkoxylations with decarboxylation, namely the carboxylate-directed *ortho* alkoxylation of benzoates through C–H activation,[18,19] followed by protodecarboxylation.[20] If further developed, such a reaction concept could give access to aryl ethers with a complementary product range to decarboxylative *ipso* alkoxylations: *meta*-substituted aryl ethers would arise from *para*- or *ortho*-substituted benzoates, and *para*-substituted aryl ethers from *meta*-substituted benzoates (Scheme 1).



Scheme 1. *Ipso*- versus *ortho*-directed decarboxylative alkoxylation. FG = functional group.

The viability of a reaction concept that combines an *ortho* alkoxylation with a concomitant decarboxylation is further supported by the documented ability of aromatic carboxylate groups to direct other types of C–H functionalization into their *ortho* position,[21] for example, as described by Yu et al.[22] Furthermore, Satoh, Miura, and Larrosa and their respective co-workers described C–H arylations of aromatic carboxylic acids with subsequent removal of the carboxylate directing group by in situ protodecarboxylation.[23]

Our mechanistic outline for an efficient decarboxylative *ortho* alkoxylation process of benzoates is shown in Scheme 2. It consists of a silver/copper-mediated oxidative *ortho* alkoxylation cycle of the benzoate linked with a decarboxylation cycle. In the alkoxylation cycle, a Cu^{II} benzoate species (**c**), which is formed by salt metathesis, undergoes C–H activation in the presence of another Cu^{II} salt, leading to a Cu^{III}–aryl species (**d**), as established by Ribas and Stahl.[14] Transfer of

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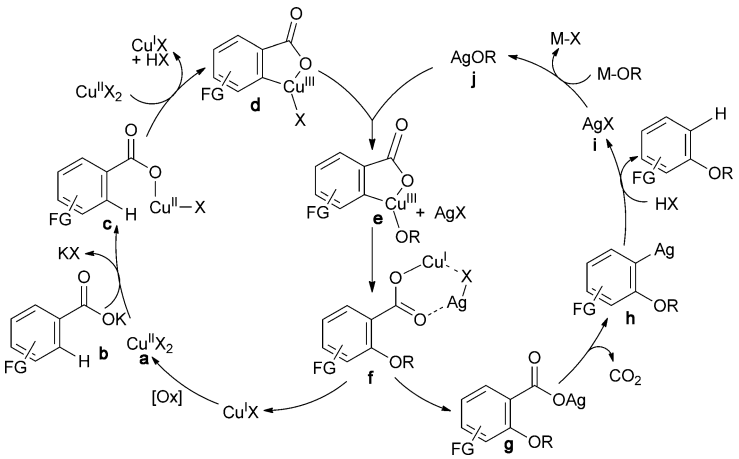


Scheme 2. Suggested mechanism for a decarboxylative alkoxylation.

an alkoxide to the Cu^{III} center and reductive alkoxyarene elimination give rise to a Cu^{I} *ortho* alkoxybenzoate. The carboxylate ion is likely to be directly transferred to the silver co-catalyst (**f**, **g**), and the catalytic cycle is closed by reoxidation of the copper center (**a**). The choice of silver as a decarboxylation co-catalyst is decisive. In contrast to copper, silver effectively promotes the decarboxylation specifically of *ortho*-alkoxybenzoic acids already at 120 °C, while it does not decarboxylate benzoic acids without σ-electron-withdrawing groups in the *ortho* position.[24] As long as the substrates do not contain such groups, competing decarboxylative *ipso* substitution would thus effectively be suppressed. In contrast, a silver *ortho*-alkoxybenzoate would, once it is formed, swiftly decarboxylate, thereby precluding double alkoxylation.

We started our search for a suitable protocol by evaluating alkoxide sources as well as alkoxylation and decarboxylation catalysts, using the methoxylation of potassium 4-anisate as a model reaction (Tables 1 and S1 in the Supporting Information). The reaction temperature was set to 150 °C, well below the temperature required for a copper-mediated protodecarboxylation of this substrate, but sufficient for a silver-mediated decarboxylation of *ortho* alkoxybenzoates. In the presence of stoichiometric amounts of both $Cu(OAc)_2$ and Ag_2CO_3 and using tetramethoxysilane, the alkoxide source of choice for *ipso* alkoxylations, the desired product **3aa** was indeed obtained, while the *ipso* product was not detected (entry 1).

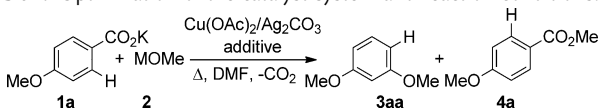
The key modification to achieve higher yields was the use of trimethylborate, whereas other methoxide sources were not effective (entry 2). Reducing the loading of copper(II) acetate to 25 mol% improved the yield, while the competing esterification to **4a** was slowed down (entries 2 and 3). Performing the reaction under O_2 atmosphere and lowering the reaction temperature to 140 °C further improved the yield to 84% (entries 4 and 5).

Additional studies confirmed that copper acetate and silver carbonate are the most effective metal precursors (see the Supporting Information). Control experiments showed that without either Ag_2CO_3 or $Cu(OAc)_2$, the reaction does not proceed (entries 6 and 7). In agreement with the proposed mechanism, the presence of silver carbonate was crucial, not only for the decarboxylation, but also for the methoxylation process. Neither *ortho*-alkoxylated anisic acid nor anisole were formed in its absence.

With an effective catalyst system in hand, we next investigated the scope of the new transformation. As shown by the examples in Scheme 3, both for primary and secondary alkoxides, the alkyl aryl ethers were obtained in good yields (**3aa**–**3ag**). Chiral alkoxides were transferred with retention of configuration (**3ah**). The reaction is also broadly applicable with regard to the aromatic carboxylic acids. Benzoates with electron-donating or electron-withdrawing groups were smoothly converted, and a broad range of functional groups, including keto, cyano, nitro, sulfonyl, N-heterocyclic, and even bromo substituents are tolerated. When starting from *meta*-substituted benzoates, the coupling occurs selectively in the position *para* to the substituent (**3ka**–**3na**), with only one notable exception: for 3-nitro-4-methoxybenzoate the alkoxylation takes place in *ortho* position (**3oa**), presumably because of chelate assistance by the nitro group. *Meta*-substituted ethers are obtained from *para*-substituted carboxylates (**3ci**–**3ea** and **3ga**–**3jb**) and from *ortho*-alkyl benzoates (**3pa, 3qi**). The anthraquinone **3ra** and flurenone **3sa** are not known to be accessible through Ullmann-type couplings. Competing decarboxylative *ipso* alkoxylation was only observed for substrates with σ-electron-withdrawing substituents, for example, alkoxy groups in *ortho* position to the carboxylate group. Neither double alkoxylation nor non-decarboxylative alkoxylation was observed, confirming the high efficiency of the decarboxylation step following alkoxylation.

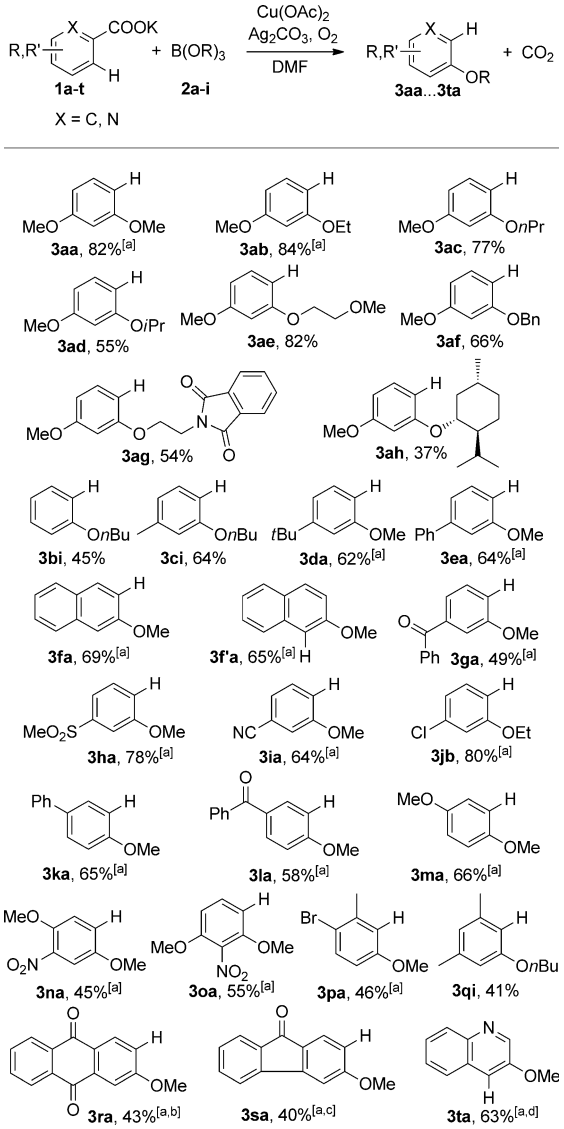
The synthesis of the borate ester reagent can be combined with the decarboxylative alkoxylation in a one-pot procedure (Scheme 4). The alcohol is first treated with an equivalent amount of pinacol borane, and when gas evolution ceases, the carboxylate salt and catalyst are added and the decarboxylative coupling is performed as usual. This variant is

Table 1: Optimization of the catalyst system and reaction conditions.[a]

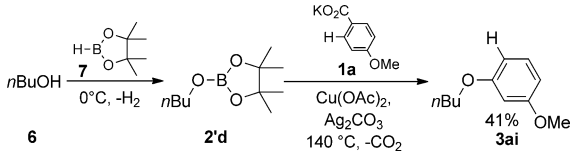


Entry	MOMe	Cu [equiv]	Additive	*T* [°C]	**3aa** [%]	**4a** [%]
1	$Si(OMe)_4$	1	–	150	12	0
2	$B(OMe)_3$	1	–	150	51	35
3	$B(OMe)_3$	0.25	–	150	73	12
4	$B(OMe)_3$	0.25	O_2	150	83	8
5	$B(OMe)_3$	0.25	O_2	140	84	trace
6[b]	$B(OMe)_3$	0	O_2	140	0	trace
7[b,c]	$B(OMe)_3$	0.25	O_2	140	0	0

[a] Reaction conditions: 0.3 mmol potassium 4-methoxybenzoate, 5 equiv MOMe, $Cu(OAc)_2$, 1 equiv Ag_2CO_3, 2 mL DMF, 36 h. Yields determined by GC using *n*-tetradecane as internal standard. [b] Near-quantitative recovery of **1a**. [c] No Ag_2CO_3.



Scheme 3. Scope of the directed etherification of aromatic carboxylates. Reaction conditions: 1.00 mmol **1a–t**, 1.20 mmol **2a–i**, 0.25 mmol $Cu(OAc)_2$, 1.00 mmol Ag_2CO_3, 1 atm. O_2, 5 mL DMF, 140°C, 36 h. [a] With 5 mmol $B(OR)_3$. [b] With 10% methylester. [c] With 12% methylester. [d] With 19% quinoline.

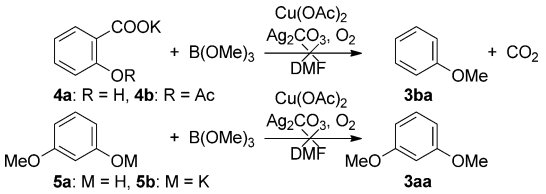


Scheme 4. Alkoxylation with a trialkoxyborate that was generated in situ.

particularly advantageous if the alcohol is too precious to be used in excess.

A series of experiments were performed to shed more light on the reaction mechanism. In the reaction of potassium benzoate with trimethylborate, a kinetic isotope effect of 2.8 was observed (see Scheme S1 in the Supporting Information). This suggests that the breaking of the C–H bond is rate-limiting, which is consistent with the proposed mechanism, but less so with other conceivable reaction pathways, that is, single-electron-transfer (SET) mechanisms or an attack of copper-coordinated oxide or peroxide onto the arene ring.[12,25]

The intermediacy of phenols as well as the involvement of acetoxylation pathways were excluded, because no etherification of the phenoxy group was observed when potassium salicylate, 3-methoxyphenol, potassium 3-methoxyphenolate, or potassium acetyl salicylate were subjected to the reaction conditions (Scheme 5). This observation confirms that the C–O bond is formed between the alkoxide and a metalated arene and not through an attack of (per)oxo–copper species onto the arene ring.[12]



Scheme 5. Evidence against the formation of (acetyl)phenols as intermediates.

In conclusion, a regiospecific *ortho* alkoxylation of aromatic carboxylates with concomitant decarboxylation has been developed. It gives access to the important substrate class of aromatic ethers from widely available carboxylic acids. This process, in which the carboxylate substituent serves as a cleavable directing group,[26] represents a rare example of an aromatic substitution reaction in which the original substitution pattern is altered in a defined way. Ongoing work is directed toward the development of reaction variants that start directly from alcohols.

Experimental Section

General procedure for the aryl ether synthesis: A 70 mL Schlenk tube was charged with the potassium carboxylate (**1a–t**; 1.00 mmol), copper(II) acetate (0.25 mmol), silver carbonate (1 mmol), and the trialkylborate (**2a–i**; 1.2 mmol). Anhydrous DMF (5 mL) was added, and the mixture was stirred at 140°C for 36 h under an oxygen atmosphere. After cooling, the reaction mixture was diluted with diethyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL), the organic layers were washed with water, 5 N HCl, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by column chromatography on SiO_2 with an *n*-hexane/ethyl acetate gradient to give the corresponding alkyl aryl ether.

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