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Copper-Catalyzed Synthesis of Mixed Alkyl Aryl Phosphonates

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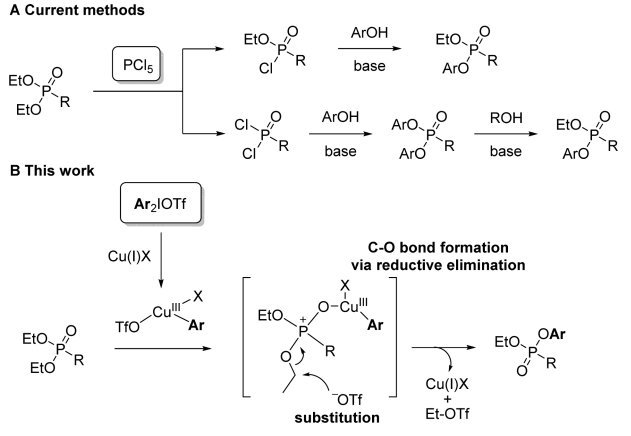
Supporting Information

ABSTRACT: Copper-catalysis allows the direct oxygen-arylation of dialkyl phosphonates with diaryliodonium salts. This novel methodology proceeds with a wide range of phosphonates and phosphoramidates under mild conditions and gives straightforward access to valuable mixed alkyl aryl phosphonates in very good yields and near perfect selectivity.

Organic phosphonates represent a highly important class of compounds with a wide range of applications in biology,[1] agriculture,[2] and synthetic organic chemistry.[3] In particular, mixed alkyl aryl phosphonate esters play a key role in nucleotide chemistry[4] and have been used as transition-state analogues in the study of catalytic antibodies.[5] Unsymmetrical phosphonate esters specifically bind to proteinase amino acid residues,[6] show a variety of important biological activities,[7] and are used in selective covalent immobilization of proteins to surfaces.[8]

While many methods are available for the synthesis of symmetrical phosphonate diesters,[9] Arbuzov[10] and Michaelis–Becker[11] reactions being the most common ones, the synthesis of mixed alkyl aryl phosphonates mainly relies on multistep processes based on the reaction of a phenol with an in situ formed alkyl phosphonochloridate[12] or involve the substitution of a diaryl phosphonate by a metal alkoxide[13] (Scheme 1A). In both cases the reactions are subject to selectivity problems due to the formation of varying amounts of phosphonic dichloride or dialkyl phosphonate esters or to instability of the intermediate phosphonochloridate. More importantly, these methods are associated with the use of phosphorus chlorides, which are hazardous and toxic reagents. Therefore, the development of alternative methods for the synthesis of mixed alkyl aryl phosphonate esters is highly desirable.

Scheme 1. Synthesis of Mixed Alkyl Aryl Phosphonate Esters



Since pioneering work by Stang and co-workers,[14] diaryliodonium salts, which are air- and moisture-stable, nontoxic, and easy to prepare compounds, have recently gained considerable attention as mild and selective arylating reagents in organic synthesis.[15−20] It is known that a Cu(I) catalyst can be oxidized in the presence of a diaryl iodonium salt to form a highly electrophilic aryl-Cu(III) intermediate.[17,21] We hypothesized that the Lewis-basic phosphoryl oxygen of a dialkyl phosphonate[22] could react under mild conditions with this aryl-Cu(III) species giving rise to a phosphonium-like intermediate,[23] which might evolve by substitution of one of the alkyl groups (Scheme 1B). Reductive elimination would form the new C(sp^2)−O bond, regenerate the Cu(I) catalyst, and lead to the formation of an alkyl aryl phosphonate ester. We report here the development of catalytic methodology for the synthesis of mixed alkyl aryl phosphonates from readily available dialkyl phosphonates and, to the best of our knowledge, the first catalytic oxygen-arylation of phosphonates with diaryliodonium salts.[24,25] The catalytic transformation operates under mild conditions and proceeds both with phosphonates and phosphoramidates and a variety of diaryliodonium salts.

We started our studies by investigating the reaction between diethyl 1-butylphosphonate **1a** and diphenyliodonium triflate **2a** (Table 1). The initial experiments were carried out using $Cu(OTf)_2$ as a catalyst[26] in dichloroethane at 70 °C. Although the conversion was moderate, the reaction led to the formation of the mixed phosphonate **3a** and a small amount (4%) of diarylated product **4a** (entry 1). The use of a hindered non-nucleophilic base such as 2,6-di-*tert*-butylpyridine (dtbpy)[27] had a beneficial effect on both conversion and selectivity, exclusively leading to the formation of the monoarylated phosphonate (entry 2).[28] A screening of copper complexes (see Supporting Information, Table S1) revealed that $Cu(OTf)_2$ and CuCl are the most efficient catalysts for this transformation, the latter giving slightly higher conversion (entries 2 and 3). The use of 1.5 equiv of **2a** gave almost full conversion, but a small amount of diphenyl phosphonate **4a** was found (entry 4). Total selectivity could be restored by carrying out the reaction at a lower temperature (entry 5). The nature of the solvent has also an important role in the reaction outcome (entries 5−7). By using dichloromethane as solvent, full conversion was achieved, and ethyl phenyl phosphonate **3a** was isolated in 90% yield with >99% selectivity[29] (entry 7). The reaction also proceeds at room temperature, but incomplete conversion is observed, probably due to competing decomposition[21a,b] of **2a** (entry 8). Finally, no reaction was

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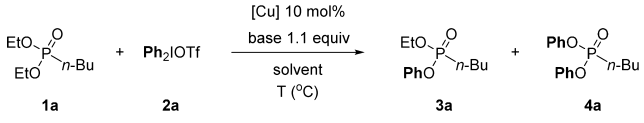
Table 1. Screening of Reaction Conditions



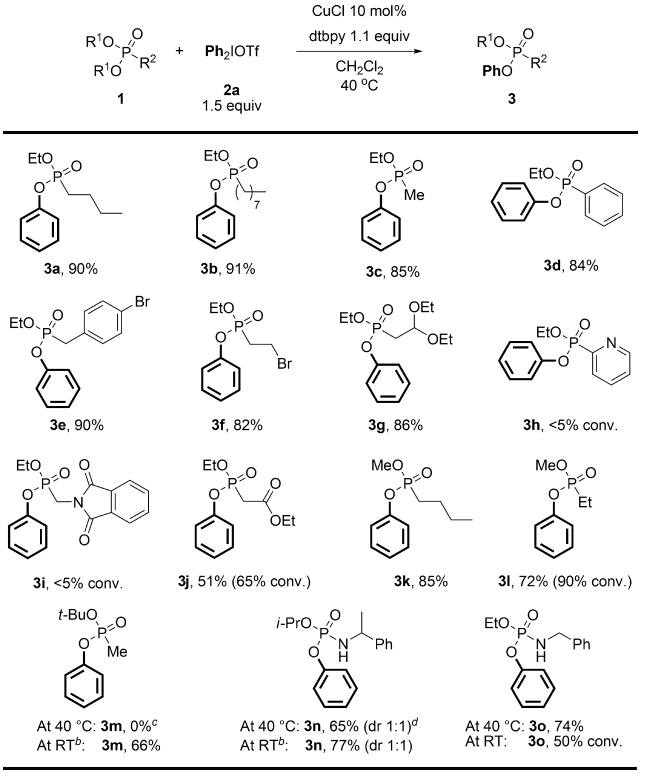
entry[a]	[Cu]	2a equiv	base	solvent	T (°C)	conv (%)[b,c]
1	$Cu(OTf)_2$	1		DCE	70	66[d]
2	$Cu(OTf)_2$	1	dtbpy	DCE	70	76
3	CuCl	1	dtbpy	DCE	70	80
4	CuCl	1.5	dtbpy	DCE	70	98[e]
5	CuCl	1.5	dtbpy	DCE	40	96
6	CuCl	1.5	dtbpy	toluene	40	85
7	CuCl	1.5	dtbpy	CH_2Cl_2	40	full (90)
8	CuCl	1.5	dtbpy	CH_2Cl_2	rt	76
9		1.5	dtbpy	CH_2Cl_2	40	0
10	CuCl	1.5		CH_2Cl_2	40	83

[a]Reactions performed on a 0.1 mmol scale. **3a**:**4a** ratio >99:1 unless otherwise noted. [b]Determined by GC analysis. [c]Yield of isolated product showed in parentheses. [d]4% of **4a** formed. [e]5% of **4a** formed. DCE = 1,2-dichloroethane.

observed in the absence of copper complex at 40 °C (entry 9), while the absence of dtbpy leads to a lower conversion (entry 10). The use of diphenyliodonium salts bearing halide counteranions did not result in any arylated phosphonate, while the use of salts displaying other noncoordinating anions led to lower conversions (see Supporting Information, Table S2).

Having established the optimized conditions (Table 1, entry 7), we set out to investigate the scope of the reaction. First, we explored this new transformation by using different dialkyl phosphonates **1** (Table 2). The reaction proved to be very efficient, with both diethyl alkyl (**1a**−**c**) and diethyl aryl phosphonates (**1d**) providing in all cases very good yields. Functionalized benzyl (**1e**) and alkyl (**1f**) diethyl phosphonates and acetal-protected aldehyde **1g** also worked well and led to the corresponding ethyl phenyl phosphonates **3e**, **3f**, and **3g** in high yields without any traces of side products. Substrates bearing a pyridyl group (**1h**) and a phthalimide (**1i**) did not give any conversion. We propose that in these cases a stronger coordination from the pyridine or phthalimide to the aryl-Cu(III) intermediate might block the reaction. On the other hand triethyl phosphonoacetate (**1j**) reacted under these catalytic conditions and led to the mixed phosphonate **3j**, although no full conversion was achieved This new methodology is also applicable to dimethyl phosphonates as illustrated by the synthesis of products **3k** and **3l**. Interestingly, di-*tert*-butyl phosphonates, albeit more reactive,[30] are also suitable substrates for this transformation. High selectivity and full conversion was reached for the arylation of **1m** at room temperature, providing product **3m** in 66% yield.[31] Phosphoramidates (**1n** and **1o**) also undergo this copper-catalyzed arylation with a similar trend in reactivity. When the reaction with di-isopropyl phosphoramidate **1n** was carried out at 40 °C a mixture of mono- and diarylated products was found. Again, total selectivity toward the monoarylation could be restored by performing the reaction at room temperature while using a lower amount of phenyl-iodonium triflate. Using these conditions isopropyl phenyl phosphoramidate **3n** was obtained in 77% yield as a 1:1 mixture of diastereoisomers. In contrast, diethyl phosphoramidate **1o** led exclusively to monoarylated product **3o** at 40 °C, although the reaction stopped at 50% conversion when it was carried out at room temperature.

Table 2. Scope of Dialkyl Phosphonates[a]



[a]Reactions performed on a 0.2 mmol scale. **3**:**4** ratio >99:1 unless otherwise noted. Yields refer to isolated pure products. [b]1 equiv of **2a** was used. [c]**4m** was obtained in 32% yield. [d]**4n** was obtained in 21% yield.

Different diaryliodonium salts were also used for this arylation of phosphonates. As previously shown by Gaunt, Sanford, and others,[16,17] unsymmetrical diaryliodonium salts bearing one bulky mesityl ligand allow the selective transfer of the other aryl group. This approach is attractive from a practical point of view as only 1 equiv of the desired transferring aryl group is required. Furthermore, these diaryliodonium salts are easily prepared from commercially available reagents in one-pot operations.[32] To our delight, diaryliodonium salts **2b**−**g** bearing *ortho*-, *meta*- and *para*-substituents all worked well in this copper-catalyzed transformation independently of the electronic properties of the substituent (Table 3). The corresponding alkyl aryl phosphonates **3p**−**w** were obtained with perfect selectivity and good to excellent yields in all cases. Noteworthy is the reaction with 4-nitrophenyl(mesityl)iodonium triflate **2d**, which gives access to alkyl 4-nitrophenyl phosphonates in a very straightforward manner. Phosphonates of this type react selectively with a range of esterase enzymes and are commonly used in the study of biological processes.[5,8,12] The synthetic utility of the new method was demonstrated by the reaction between **1a** and **2c** on a gram scale (4 mmol), which led to **3r** (1.22 g) in an excellent 97% yield using only 5 mol % of CuCl. It is also important to note that mesityl iodide was obtained quantitatively and 2,6-di-*tert*-butylpyridine could be recovered as a triflic salt (see Supporting Information for further details), adding to the practicality of the process.

On the basis of our experimental observations and some preliminary mechanistic investigations (Scheme 2 and Supporting Information, Schemes S1−S3), we propose the following mechanism for the copper-catalyzed oxygen-arylation of

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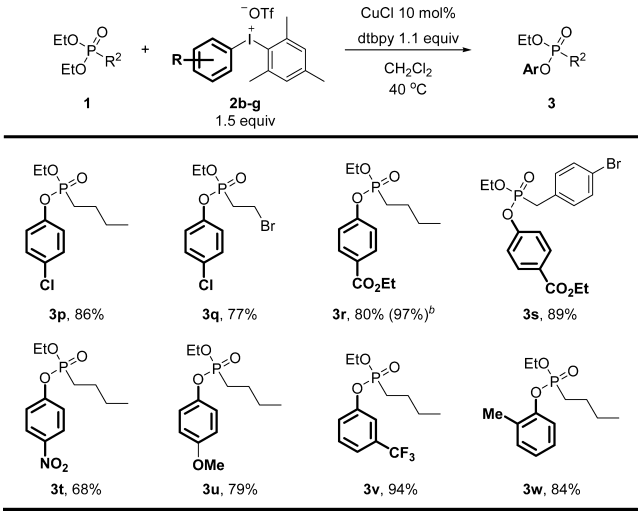
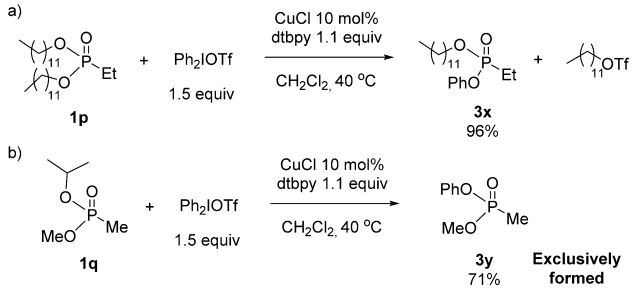
Table 3. Scope of the Diaryliodonium Salts[a]



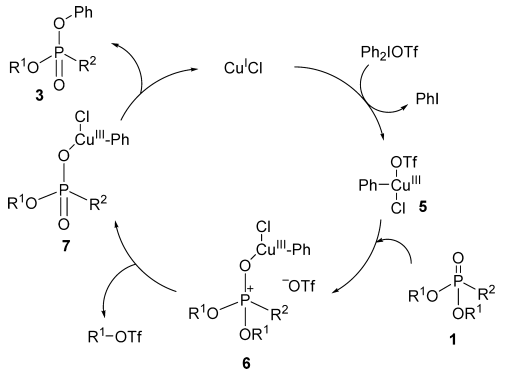
[a]Reactions performed on a 0.2 mmol scale. **3:4** ratio >99:1 in all cases. Yields refer to isolated pure products. [b]Yield in brackets refers to the reaction run on a 4 mmol scale using 5 mol % of CuCl.

Scheme 2. Mechanistic Investigations



phosphonates with diaryliodonium salts (Scheme 3). Initially, the diaryliodonium salt **2** oxidizes the Cu(I) catalyst giving rise to

Scheme 3. Proposed Mechanism for the Copper-Catalyzed Oxygen-Arylation of Phosphonates



aryl-Cu(III) species **5**.[21] Then, the phosphoryl group of phosphonate **1** can attack this electrophilic intermediate, forming the phosphonium complex **6**.[33] In analogy to the Arbuzov reaction, this copper intermediate would undergo a substitution reaction[34] of one of its alkyl groups to afford phosphonate complex **7**. Accordingly, the copper-catalyzed arylation of didodecyl phosphonate **1p** provided dodecyl triflate as a major product (^{1}H, ^{19}F NMR) (Scheme 2a). This suggests the triflate anion as the nucleophile in this substitution.[35] Taking into account its low nucleophilicity and the observed reactivity trend for the different alkoxy groups (Table 1), we propose that this substitution might follow an S_N1-type mechanism.[36] The result obtained with phosphonate **1q** (Scheme 2b), in which only the isopropyl group was substituted, supports such pathway, although we cannot discard different alternatives.[37] Although the exact role of dtbpy is not entirely clear,[38] it could facilitate the substitution step by scavenging protic impurities and/or stabilization of the emerging carbocation[31] as reported for living carbocationic polymerizations.[39,40] Finally, a reductive elimination would regenerate the Cu(I) catalyst and afford alkyl aryl phosphonate **3**.

In summary, we have developed an efficient copper-catalyzed oxygen-arylation of dialkyl phosphonates and phosphoramidates with diaryliodonium salts based on the formation of high valent aryl-copper(III) species. The reaction proceeds under mild conditions, avoids the use of toxic reagents, and affords the monoarylated alkyl aryl phosphonates in high yields with near perfect selectivity.

■ ASSOCIATED CONTENT

Supporting Information

Optimization tables, mechanistic investigations, experimental procedures, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(28) The use of stronger bases or less hindered pyridines was detrimental for the conversion of the reaction. See Supporting Information, Table S3.
(29) In a crossover experiment, a 1:1 mixture of **1a** and **3a** was reacted with **2a**, leading only to the formation of monoarylated phosphonate and showing that no arylation of the mixed phosphonate takes place under these conditions.
(30) Reaction with **1m** turned out to be very fast at 40 °C, and only a small amount of diphenyl methylphosphonate **4m** was obtained in that case. It is probable that the corresponding *tert*-butyl phenyl methylphosphonate **3m** is thermally unstable, as reported for other *tert*-butyl phosphonates: Mark, V.; van Wazer, J. R. *J. Org. Chem.* **1964**, *29*, 1006−1008.
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(33) See Supporting Information, Schemes S1 and S2.
(34) As expected for a substitution mechanism, no arylation occurred in the reaction between diphenyl butylphosphonate and diaryliodonium salt **2b** (Supporting Information, Scheme S3).
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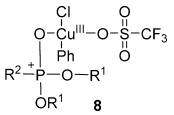
(37) An intramolecular trapping involving intermediate **8** cannot be ruled out.



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(38) A weak interaction between dtbpy and copper cannot be ruled out; however, when catalytic amounts of dtbpy were used, incomplete conversion was observed (see Supporting Information, Table S4).
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(40) A different mechanism (see ref 37) might apply for the arylation of dimethyl phosphonates **1k** and **1l**. However, in these cases the presence of dtbpy had a dramatic effect in the conversion. See, e.g., 90% conversion vs 48% conversion without dtbpy in the arylation of **1l**.