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Copper-Mediated Oxidative Cross-Coupling Reaction of Terminal Alkynes with α-Silyldifluoromethylphosphonates: An Efficient Method for α,α-Difluoropropargylphosphonates

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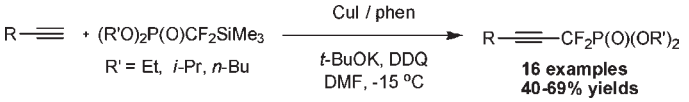
ABSTRACT



A copper-mediated oxidative cross-coupling reaction of terminal alkynes with readily available α-silyldifluoromethylphosphonates under mild conditions has been developed. This method allows for an efficient synthesis of a series of synthetically useful α,α-difluoropropargylphosphonates with excellent functional group compatibility.

Phosphonates are of great importance by virtue of their similarity to phosphates.[1] In recent years, there has been an increasing interest in the development of fluorinated phosphonates[2] due to the unique properties that fluorine imparts on organic molecules.[3] Among them, difluorophosphonates have gained special attention because of their potential as analogues of biologically important phosphate esters and utilization in the design and development of new drugs.[4]

Generally, difluorophosphonates can be prepared by direct electrophilic fluorination of phosphonate carbanions[5] or DAST-promoted nucleophilic fluorination of α-oxophosphonates.[6] The addition of a phosphonodifluoromethyl radical onto alkenes, alkynes, and unsaturated ketones has also been developed.[7] Furthermore, the nucleophilic displacement,[8] nucleophilic addition,[9] or transtion-metal-mediated cross-coupling reaction[10] of metalated difluoromethylphosphonates ($(EtO)_2P(O)CF_2M$; M = Li, ZnBr, MgCl, CdBr) has been extensively investigated. Although these methods have been widely used in

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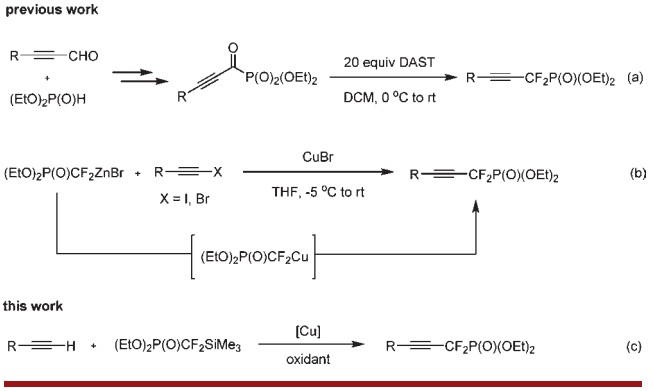
the preparation of a variety of difluorophosphonates, they are limited by some combination of expensive reagents, the incompatibility of functional groups, and restricted synthetic applications. The current synthetic methods have been applied mainly for the preparation of alkyldifluorophosphonates and aryldifluorophosphonates. A method for the construction of functionalized difluorophosphonate derivatives such as α,α-difluoropropargylphosphonates has not been well developed.

α,α-Difluoropropargylphosphonates were originally recognized as a new type of difluorophosphonate by Hammond in 1996.[6c] These compounds would be highly useful as versatile synthetic intermediates to various biologically important difluorophosphonates through conversion of the triple bond into other functional groups.[6c,d,10d,e] Hammond first reported the preparation of α,α-difluoropropargylphosphonates *via* nucleophilic fluorination of α-ketophosphonates, but this method required the use of limitedly stable α-ketophosphonates and a large excess of the fluorinating reagent (Scheme 1a).[6c,d] Later, Burton and co-workers developed a copper-mediated cross-coupling reaction of propargyl halides and $(EtO)_2P(O)CF_2ZnBr$, providing an alternative method for the preparation of these compounds (Scheme 1b).[10d,e] A pathway involving $(EtO)_2P(O)CF_2Cu$ species generated in situ was proposed for this copper-mediated cross-coupling reaction. This method is useful and practical but requires prefunctionalized alkynyl substrates and metalated difluoromethylphosphonates. Therefore, the development of direct and efficient methods for the preparation of α,α-difluoropropargylphosphonates is still highly desirable.

Scheme 1. Preparation of α,α-Difluoropropargylphosphonates



Fluoroalkyl cross-coupling has been proven to be an efficient strategy to introduce the fluoroalkyl moiety into organic molecules. Recently, the copper-mediated oxidative trifluoromethylation developed by our group has facilitated the direct and efficient synthesis of a wide range of trifluoromethylated compounds.[11] Specifically, this protocol allows the direct installation of a trifluoromethyl group in place of C−H bonds without the need for prefunctionalized substrates.[11a,c,e] Encouraged by these results, we anticipated that a similar copper-mediated C−H oxidation protocol might allow for the preparation of difluorophosphonate analogues. Herein, we describe the first example of a copper-mediated oxidative cross-coupling reaction of teminal alkynes with α-silyldifluoromethylphosphonates (Scheme 1c). This reaction provides a novel and direct methodology for the preparation of α,α-difluoropropargylphosphonates bearing a wide range of functional groups by employing readily available α-silyldifluoromethylphosphonates.

To test our hypothesis, the initial investigation focused on the reaction of phenylacetylene **1a** with $(EtO)_2P(O)CF_2SiMe_3$[12a] **2a** under the optmized conditions of copper-mediated trifluoromethylation of terminal alkynes.[11a] However, when the reaction was run using stoichiometric amounts of CuI, 1,10-phenthroline, and KF under air none of the desired product, **3a**, was observed. Instead dimer **4a** and $(EtO)_2P(O)CF_2H$ **5a** were obtained (Table 1, entry 1). Lowering the reaction temperature did not inhibit the decomposition of $(EtO)_2P(O)CF_2SiMe_3$ **2a** and the formation of homocoupling product **4a** (entry 1).

To achieve this transformation, we evaluated a series of oxidants and found that a significant amount of the desired product **3a** was observed when the reaction was carried out with $PhI(OAc)_2$ (entries 2−5). Since the base is known to have a profound effect on transmetalations and cross-coupling reactions, we investigated the influence of the base. It was found that *t*-BuOK gave the highest yield of product **3a** (entries 6−10). Switching to other bases such as K_2CO_3, K_3PO_4, or *t*-BuONa led to a dramatic decrease in yield (entries 6−10). Various copper salts were found to mediate this transformation, while CuI proved to be better than other copper salts (entries 11−14). Considering the effectiveness of $PhI(OAc)_2$ as the oxidant, a series of other hypervalent iodine reagents such as $PhI(OPiv)_2$ and

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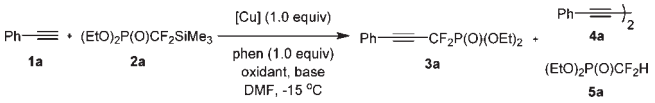
Table 1. Optimization of the Reaction Conditions[a]



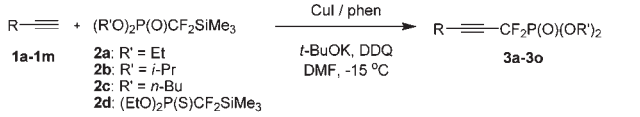
entry	[Cu]	base	oxidant	yield (%)[b]
1[c]	CuI	KF	air	none
2	CuI	KF	DDQ	trace
3	CuI	KF	Ag_2CO_3	trace
4	CuI	KF	$Cu(OAc)_2$	trace
5	CuI	KF	$PhI(OAc)_2$	22
6	CuI	K_3PO_4	$PhI(OAc)_2$	none
7	CuI	K_2CO_3	$PhI(OAc)_2$	none
8	CuI	*t*-BuOLi	$PhI(OAc)_2$	trace
9	CuI	*t*-BuONa	$PhI(OAc)_2$	36
10	CuI	*t*-BuOK	$PhI(OAc)_2$	71
11	$[Cu(OTf)]_2 \cdot C_6H_6$	*t*-BuOK	$PhI(OAc)_2$	53
12	CuCl	*t*-BuOK	$PhI(OAc)_2$	60
13	CuBr	*t*-BuOK	$PhI(OAc)_2$	68
14	$Cu(OAc)_2$	*t*-BuOK	$PhI(OAc)_2$	44
15	CuI	*t*-BuOK	$PhI(OPiv)_2$	54
16	CuI	*t*-BuOK	$PhI(O_2CCF_3)_2$	11
17	CuI	*t*-BuOK	DDQ	98
18[d]	**CuI**	***t*-BuOK**	**DDQ**	**97**
19[e]	CuI	*t*-BuOK	DDQ	19
20	/	*t*-BuOK	DDQ	none
21[f]	CuI	*t*-BuOK	DDQ	none
22[g]	CuI	*t*-BuOK	DDQ	none

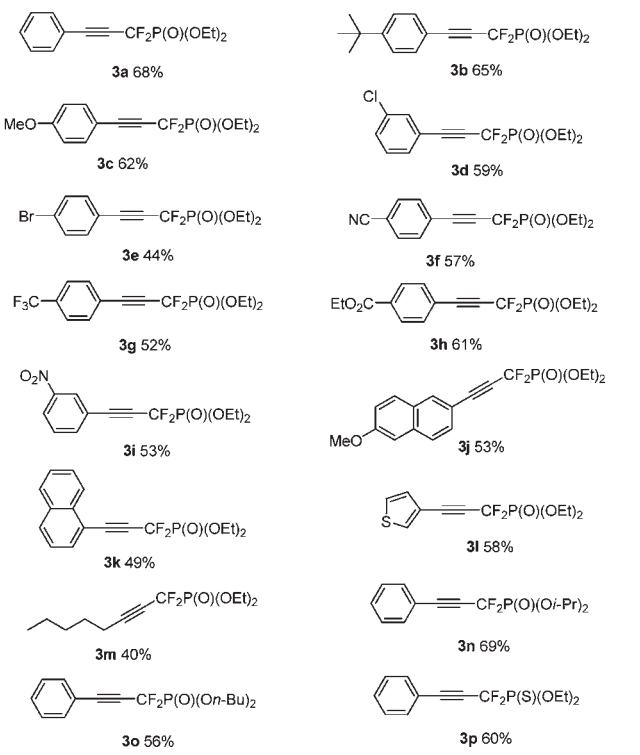
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (3.0 equiv), copper salt (1.0 equiv), phen (1.0 equiv), base (4.0 equiv), oxidant (2.0 equiv), DMF (1.0 mL), ethanol-ice bath (−15 °C). [b] Yield was determined by ^{19}F NMR using fluorobenzene as an internal standard. [c] The reaction was conducted at 80 °C or −15 °C. [d] 1.5 equiv of DDQ. [e] In the absence of 1,10-phenanthroline. [f] All reagents were mixed simultaneouly. [g] **1a** was premixed with CuI, 1,10-phenanthroline, and *t*-BuOK followed by addition of **2a** and DDQ

$PhI(O_2CCF_3)_2$ were examined (entries 15−16). However, when the reactions were conducted with $PhI(OPiv)_2$ or $PhI(O_2CCF_3)_2$ much lower yields were obtained compared to when $PhI(OAc)_2$ was used (entries 10, 15−16). Interestingly, the best yield of **3a** was obtained when *t*-BuOK and DDQ were employed as the base and oxidant (entry 17). This result was surprising to us because DDQ was found to be completely ineffective when used in combination with KF (entry 2). Decreasing the quantity of DDQ from 2.0 to 1.5 equiv had no significant effect on the yield of product **3a** (entry 18). Both copper salts and ligands were essential for this transformation (entries 19−20).

The mode of addition of reagents was critical to achieving a high yield of product **3a**: $(EtO)_2P(O)CF_2SiMe_3$ **2a** should be injected into the mixture of CuI, 1,10-phenanthroline, *t*-BuOK, and DMF at −15 °C, followed by the addition of phenylacetylene **1a** and DDQ (entries 17−18). When all of the reagents were mixed simultaneously, no product was observed (entry 21). Moreover, no detectable amount of products was formed when phenylacetylene was added to the mixture of CuI, 1,10-phenanthroline, *t*-BuOK, and

Scheme 2. Copper-Mediated Oxidative Cross-Coupling Reaction of Terminal Alkynes with α-Silyldifluoromethylphosphonates[a]





[a] Reaction was conducted on a 0.4 mmol scale under the optimal conditions of entry 18 in Table 1. Isolated yield.

DMF at −15 °C followed by the addition of $(EtO)_2P(O)CF_2SiMe_3$ **2a** and DDQ (entry 22). These results prompted us to hypothesize that $(EtO)_2P(O)CF_2Cu$ species might be involved in this process. $(EtO)_2P(O)CF_2Cu$ species, which is most commonly generated from $(EtO)_2P(O)CF_2ZnBr$, has been generally suggested as the key intermediate in the copper-mediated cross-coupling reaction of metalated difluoromethylphosphonates.[10] However, to the best of our knowledge, the use of $(EtO)_2P(O)CF_2SiMe_3$ as the precursor to the $(EtO)_2P(O)CF_2Cu$ species has not been reported, despite the availability, stability, convenience of handling, and wide applications of α-silyldifluorophosphonates as equivalents of difluorinated carbonions.[12] Further studies will be needed to support the possibility of $(EtO)_2P(O)CF_2Cu$ intermediates.

With the optimal reaction conditions in hand, we next examined the substrate scope of the oxidative cross-coupling

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reaction between terminal alkynes **1** and α-silyldifluoromethylphosphonates **2** (Scheme 2). A variety of aryl alkynes bearing electron-donating and electron-withdrawing groups can be transformed into the desired products in moderate yields (**3b**−**3j**). Many functional groups, including cyano, ester, and nitro, were well-tolerated in the reaction (**3f**, **3h**−**3i**). Notably, chloro or bromo containing substrates were compatible with the reaction, enabling further transformations via transition-metal-catalyzed cross-coupling reactions (**3d**−**3e**). The heterocyclic alkyne as well as the aliphatic alkyne was also effective in this reaction, producing the desired products in moderate yields (**3l**−**3m**).

The reaction scope was also investigated with respect to the α-silyldifluoromethylphosphonate coupling partner under the optimized conditions (Scheme 2). A series of different α-silyldifluoromethylphosphonates, including diisopropyl difluoro(trimethylsilyl)methylphosphonate **2b**, dibutyl difluoro(trimethylsilyl)methylphosphonates **2c**, and *O*,*O*-diethyl difluoro(trimethylsilyl)methylphosphonothioate **2d**, are effective, and all reactions afforded the corresponding products in moderate yields (**3n**−**3p**).

In summary, a copper-mediated oxidative cross-coupling reaction between terminal alkynes and α-silyldifluoromethylphosphonates was developed, affording a series of synthetically useful α,α-difluoropropargylphosphonates in moderate yields. Due to the high functional group tolerance and mild conditions of our methodology, and the potential of difluorophosphonates as biologically active agents, we expect this procedure will be useful for the synthesis of this class of compounds.

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Supporting Information Available. Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.