Diazo Compounds

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Copper Salt-Controlled Divergent Reactivity of $[Cu]CF_2PO(OEt)_2$ with α-Diazocarbonyl Derivatives

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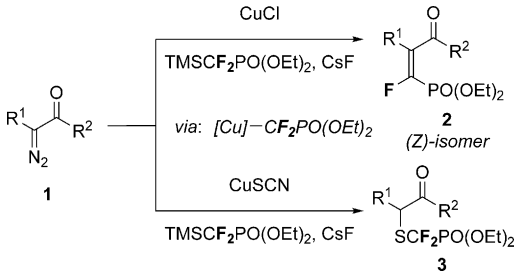
Abstract: *Herein, we report a copper salt-controlled divergent reactivity toward α-diazocarbonyl compounds. By a simple change of the copper counteranion under identical reaction conditions, the reported method allowed an easy access to either (Z)-α-fluorovinylphosphonate or alkyl-$SCF_2PO(OEt)_2$ derivatives in good yields. Mechanistic studies were performed and suggested two different pathways to explain the formation of these products.*

The control of selectivity is a longstanding goal in organic chemistry.[1] Indeed, for decades, scientists devoted considerable efforts to control the chemo-, regio-, diastereo- and enantioselectivity of chemical reactions. In that purpose, the creativity of organic chemists gave birth to many innovative transformations.[2] An interesting strategy toward the control of selectivity is the control of the product distribution. Indeed, the formation of different products by using identical reagents with a sole modification of the mediator or the catalyst is a powerful and convenient strategy to access a plethora of compounds.[2] In that context, α-diazocarbonyl compounds proved to be versatile reaction partners in metal-dependent processes. By a subtle change of the metal catalyst or the ligand, this class of compounds revealed a high potential to develop divergent reactions with identical starting materials.[3]

Besides, organofluorine chemistry is a blossoming research area. Its recent and rapid expansion culminated in the development of innovative and elegant transformations over the last five years.[4] This impressive growth is readily explained by the impact that fluorinated molecules have in the development of novel and more efficient pharmaceuticals and agrochemicals.[5] In fact, the incorporation of fluorine atoms in a molecule results in an alteration of its physical and biological properties.[6] Another important feature of the fluorinated groups is their role as metabolically stable bioisosters.[7] Among them, α-fluorinated phosphonates (mono- or di-) appeared as excellent mimics of the phosphate residue. This paradigm, introduced by Blackburn et al. more than thirty years ago,[8] led to plenty of bioactive compounds with interesting bioactivity and good metabolic resistance against the in vivo hydrolysis. As part of our ongoing investigations dedicated to the development of new synthetic methods to access α-fluorinated phosphonates as phosphate mimics,[9] we studied the reactivity of $[Cu]CF_2PO(OEt)_2$ with α-diazocarbonyl compounds. This strategy, already successfully applied to the copper-mediated introduction of the CF_3[10a] and SCF_3 groups,[10b–f] has never been used to incorporate other fluorinated residues, despite the high interest of the resulting fluorinated molecules as valuable building blocks.

Herein, we report the remarkable impact of the nature of the copper salt on the outcome of the reaction (Scheme 1). By a simple change of the copper(I) counteranion (Cl vs. SCN), the reaction could either furnish the tetrasubstituted (*Z*)-α-fluorovinylphosphonate **2** or the alkyl-$SCF_2PO(OEt)_2$ derivative **3** under identical reaction conditions. α-Fluorovinylphosphonates were already recognized as phosphate mimics.[11] Usual accesses to this class of compounds relied on an olefination reaction,[12a–c] a cross-coupling reaction,[11c,12d] the fluorination of vinylphosphates[11b] or after a fluoride elimination,[12e–f] usually with moderate stereocontrol. In contrast, thiodifluoromethyl phosphonate derivatives remain underexplored despite the potential of this emerging fluorinated group, and the access to this motif is poorly documented so far.[13]



Scheme 1. Copper salt-mediated divergent reactivity.

At the beginning of the project, we investigated the reaction of $[Cu]CF_2PO(OEt)_2$ with ethyl α-diazophenylacetate **1a** as a model substrate (Table 1). We found that $[Cu]CF_2PO(OEt)_2$ prepared from CuCl and $TMSCF_2PO(OEt)_2$ reacted smoothly with **1a**, in the presence of H_2O as an additive,[14] in a MeCN/*N*-methylpyrrolidone (NMP) mixture. The corresponding (*Z*)-α-fluorovinylphosphonate **2a** was obtained in 99% isolated yield as a single stereoisomer (entry 1).[15] The replacement of CuCl by $CuPF_6{\cdot}(MeCN)_4$

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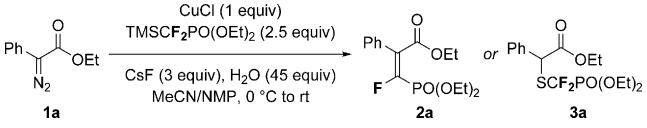
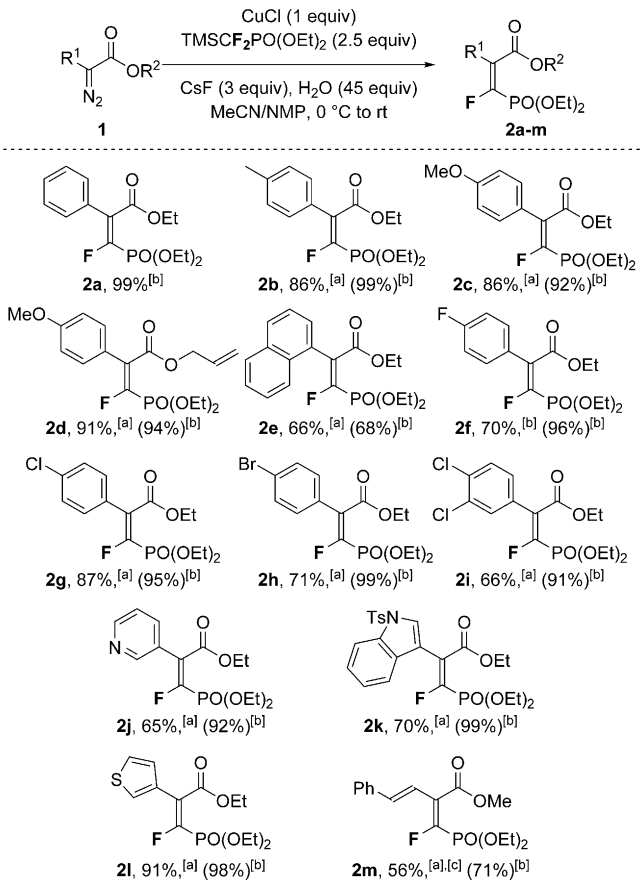
Table 1: Reaction of ethyl α-diazophenylacetate **1a** with $[Cu]CF_2PO(OEt)_2$.



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

Entry	Variation from standard conditions	**2a** Yield [%][a]	**3a** Yield [%][a]
1	none	99[b]	0
2	$CuPF_6{\cdot}(MeCN)_4$ instead of CuCl	99	0
3	CuOTf instead of CuCl	NR[c]	
4	No H_2O	75	0
5	CuSCN instead of CuCl	0	83 (52)[b]
6	CuSCN instead of CuCl and DMF instead of NMP	0	52
7	CuSCN instead of CuCl and MeCN instead of NMP	0	28
8	CuSCN instead of CuCl and MeOH instead of H_2O	0	22
9	CuSCN instead of CuCl No H_2O	NR[c]	

[a] Yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Isolated yields. [c] NR = no reaction, starting material **1a** was recovered. All reactions were performed on a 0.5 mmol scale.



Scheme 2. CuCl-mediated formation of α-fluorovinylphosphonates **2**. [a] Isolated yields. [b] NMR yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c] Diasteroisomeric ratio (2*Z*,3*E*: 2*E*,3*E*) = 3:1, the major isomer was represented. All reactions were performed on a 0.5 mmol scale.

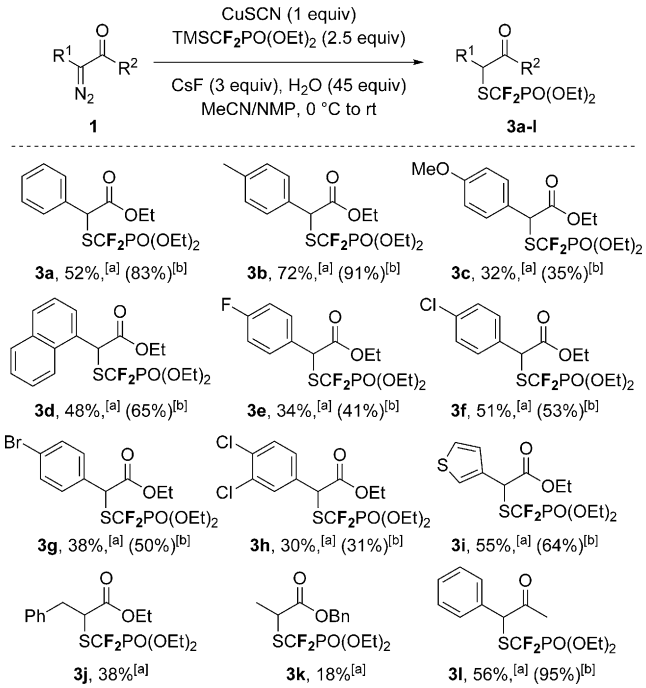
furnished **2a** in a similar yield (entry 2), while CuOTf was ineffective (entry 3). The addition of water as an additive was important since a lower yield was obtained in its absence (entry 4). Quite surprisingly, we observed that the replacement of CuCl by CuSCN, under the same reaction conditions, did not provide the expected compound **2a** but the thiodifluoromethyl phosphonate **3a** in 52% yield, offering a divergent pathway driven by the nature of the copper salt (entry 5). The replacement of NMP by *N*,*N*-dimethylformamide (DMF) or MeCN did not improve the reaction yield (entries 6 and 7). The replacement of H_2O by MeOH as an additive provided a lower yield (entry 8) while no reaction was observed in the absence of H_2O (entry 9), showcasing its crucial role for the formation of **3a**.

With these two divergent processes in hand, we first examined the scope of the reaction providing the (*Z*)-α-fluorovinylphosphonates **2** (Scheme 2). First, we tested α-aryl-substituted diazo esters bearing an electron-donating group. Methyl- and methoxy-substituted ones afforded the corresponding fluorinated olefins **2b** and **2c** in excellent yields. The allyl ester (**1d**) was compatible under our reaction conditions. Halogen substituents such as fluorine, chlorine and bromine atoms were tolerated and the corresponding products **2f–i** were isolated in good to excellent yields (66–87%). Interestingly, α-heteroaryldiazoacetates were suitable substrates in this transformation. Pleasingly, pyridine derivative **2j** was readily obtained in 65% yield, while indole derivative **2k** was isolated in 70% yield. Thiophene-substituted α-diazo acetate **1l** was readily converted into the α-fluorovinylphosphonate **2l** in 91% yield. Then we turned our attention to vinyl-substituted diazoacetate derivative **1m**, and the resulting fluorinated diene **2m** was isolated in 56% yield as a 3:1 mixture of isomers.[16]

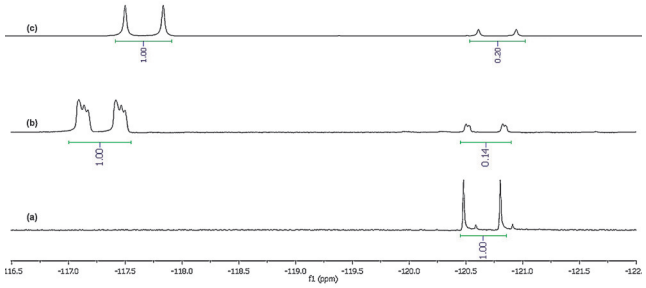
Then we sought to extend the scope of the reaction providing the thiodifluoromethylated phosphonates **3**, using CuSCN as the copper source (Scheme 3).

First, α-diazo acetates bearing an electron-rich aromatic ring were evaluated. The reaction proceeded smoothly with methyl-substituted aryl derivative **1b** and the desired thiodifluoromethylated phosphonates **3b** was isolated in good yields (72%). The methoxy-substituted diazo derivative **1c** furnished the corresponding product **3c** in lower yield, while the α-naphtyl-substituted diazoacetate gave **3d** in 48% yield. Electron-withdrawing halogen substituents on the aromatic ring were tolerated as shown by the formation of the corresponding thiodifluoromethylated phosphonates (**3e–h**), albeit in lower yields (30–51% yields). Interestingly, α-thienyldiazo acetate was a suitable substrate and the resulting product **3i** was obtained in 55% yield. The reaction was extended to α-alkyldiazo acetates and the products **3j** and **3k** were isolated in moderate yields, 38% and 18%, respectively. Finally, we have been able to extend the methodology to α-phenyl-diazo ketone and the corresponding product **3l** was isolated in a decent 56% yield.

Then to gain insight regarding the difference of reactivity between the $[Cu]CF_2PO(OEt)_2$ reagent prepared either from



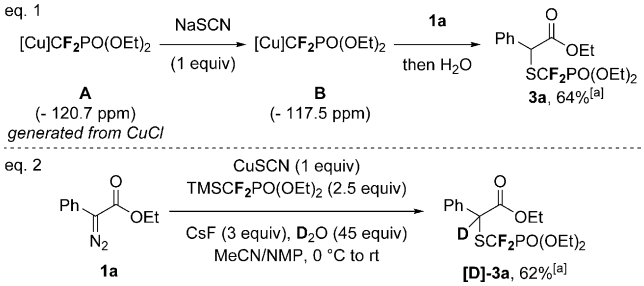
Scheme 3. CuSCN-mediated synthesis of alkyl-$SCF_2PO(OEt)_2$ derivatives **3**. [a] Isolated yields. [b] NMR yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. All reactions were performed on a 0.5 mmol scale.



Scheme 4. ^{19}F NMR measurement of the $[Cu]CF_2PO(OEt)_2$ species generated from $TMSCF_2PO(OEt)_2$ with CuCl or CuSCN. All chemical shifts were determined relative to $HCF_2PO(OEt)_2$ at −136.8 ppm. a) $CuCF_2PO(OEt)_2$ prepared from CuCl. b) $CuCF_2PO(OEt)_2$ prepared from CuSCN. c) $CuCF_2PO(OEt)_2$ prepared from CuSCN in the presence of water (45 equiv).

CuCl or CuSCN, ^{19}F NMR studies were performed (Scheme 4).

First, the ^{19}F NMR spectra of the Cu species prepared from CuCl (**A**, Scheme 4a) revealed a single Cu species at −120.7 ppm ($^2J_{F\text{-}P} = 91.3$ Hz), whereas the one prepared from CuSCN (Scheme 4b) showed two different fluorinated species at −117.5 ppm (**B**, $^2J_{F\text{-}P} = 92.0$ Hz) and −120.7 ppm (**A**, $^2J_{F\text{-}P} = 91.3$ Hz), respectively, assuming the existence of two different Cu species.[17] We presumed that the Cu species at −120.7 ppm was the reactive one since the addition of **1a** to this intermediate led to the formation of **2a** in 75% NMR yield (Table 1, entry 4).[18,19] Indeed, without the addition of water to the $[Cu]CF_2PO(OEt)_2$ reagent **B**, generated from CuSCN, no reaction occurred with **1a** and the latter was almost fully recovered after 16 h reaction time (Table 1, entry 9). To ascertain the impact of the additive toward the formation of **3** (Table 1, entry 5), the addition of H_2O to the species **B**, pointed out a slight increase of the reactive species **A** at −120.7 ppm, albeit in lower concentration with respect to the species **B** (Scheme 4c).[20] This observation led us to postulate the existence of a "ligandless Cu species" ("SCN free") at −120.7 ppm (**A**) and a coordinated Cu species at −117.5 ppm (**B**).[21] To ensure this hypothesis, control experiments were performed (Scheme 5). First, subsequently to the

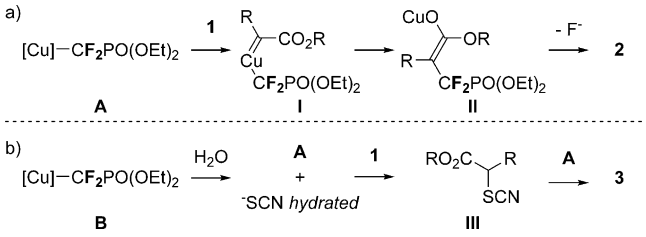


Scheme 5. Control experiments. [a] NMR yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

generation of the Cu species from CuCl (**A**), NaSCN (1 equiv) was added [Eq. (1)]. The ^{19}F NMR analysis of the mixture revealed a clear shift of the signal from −120.7 ppm to −117.5 ppm, showcasing the formation of the coordinated Cu species **B**.[19] After the addition of **1a** and water to the reaction mixture, the thiodifluoromethylated compound **3a** was obtained in 64% NMR yield. This result demonstrated the coordination of the SCN anion on the Cu species **A**, resulting in the formation of species **B**, and its involvement in the formation of **3a** by reaction with **1a** in the presence of H_2O. Finally, the standard reaction was performed using D_2O and a complete incorporation of D atom was observed, assuming the protonation by water [Eq. (2)].

Based on these findings, we proposed the following plausible mechanisms for the formation of α-fluorovinylphosphonates **2** and thiodifluoromethylated phosphonates **3**. Regarding the formation of **2**, the reactive Cu species **A**, generated from CuCl, reacted with **1a** to form a phosphonodifluoromethylcopper carbene **I**, which collapsed into the Cu enolate **II**. Then, the latter underwent fast fluoride elimination (E1cB) rather than a protonation reaction with H_2O to deliver the fluorinated olefin **2** (Scheme 6a). With respect to the formation of **3**, we proposed the initial water-promoted formation of reactive species **A** through the formation of hydrated SCN anion. Then, we presumed the fastest formation of the thiocyanate species **III** after reaction of **1a** with the hydrated SCN anion over the reaction with $[Cu]CF_2PO(OEt)_2$ **A**.[22] Then, a final Langlois-type nucleophilic substitution[23] at the sulfur center by $[Cu]CF_2PO(OEt)_2$ (species **A**) led to the formation of **3** (Scheme 6b).

In conclusion, we reported herein the remarkable effect of the copper salt on the reactivity of $[Cu]CF_2PO(OEt)_2$ with α-diazocarbonyl compounds. This change of reactivity, driven



Scheme 6. Proposed mechanisms.

by the nature of the copper salt, offered an interesting control of the products distribution. The use of CuCl to form the difluoromethylated copper complex led selectively to the stereocontrolled formation of (*Z*)-α-fluorovinylphosphonates, while CuSCN promoted the formation of the $SCF_2PO(OEt)_2$-containing derivatives. Both reactions furnished the corresponding fluorinated products in moderate to excellent yields under mild conditions. Mechanistic studies suggested the existence of two different copper species, depending on the Cu salt. The intervention of a copper carbene in the formation of α-fluorovinylphosphonate is presumed whereas an in situ formed isothiocyanate species could be involved in the formation of the thiodifluoromethylated phophonate species.

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[19] See supporting information for details.
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