

Copper Mediated Difluoromethylation Reactions

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Fluorinated molecules are of great interest in pharmaceutical and agrochemical research. As a result, the design of straightforward methodologies to access to these targets remains a challenge.¹

Among the fluorinated motifs, our research group was interested in the introduction of the CF₂CO₂Et residue by means of direct C-H bond functionalization.² Our process based on the use of inexpensive copper catalyst and the commercially available BrCF₂CO₂Et was applied to a broad range of substrates *eg.* glycals,^{3a} enamides,^{3b} furans/benzofurans^{3c} and electron-rich aryls derivatives.^{3d} Mechanistic studies pointed out a plausible Cu(I)/Cu(III) catalytic cycle involved in these reactions pathways.

In a second part, our effort to develop a straightforward method to introduce the CF₂PO(OEt)₂ group will be disclosed. Indeed, due to the importance of this phosphate bioisoster,⁴ the need to develop efficient access is of prime importance in medicinal chemistry. The use of the CuCF₂PO(OEt)₂ reagent to introduce this motif will be depicted as well as the discovery of a Cu-salt controlled product distribution.^{5,6}

¹ For selected reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.(b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (c) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 4000. (d) For a special issue on fluorine chemistry, see: *Chem. Rev.* **2015**, *115*, 563–1306.

² For reviews, see: (a) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2015**, *21*, 12836. (b) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, *20*, 16830.

³ (a) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 3428. (b) Caillot, G.; Dufour, J.; Belhomme, M.-C.; Poisson, T.; Grimaud, L.; Pannecoucke, X.; Gillaizeau, I. *Chem. Commun.* **2014**, *50*, 5887. (c) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 7205. (d) Belhomme, M.-C.; Bayle, A.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2015**, 1719.

⁴ Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Chem. Eur. J.* **2016**, *22*, 10284.

⁵ Ivanova, M. V.; Bayle, A.; Besset, T.; Poisson, T.; Pannecoucke, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 13406.

⁶ Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 14141.