A Three-Pronged Approach to the Development of New Trifluoromethylation Reactions

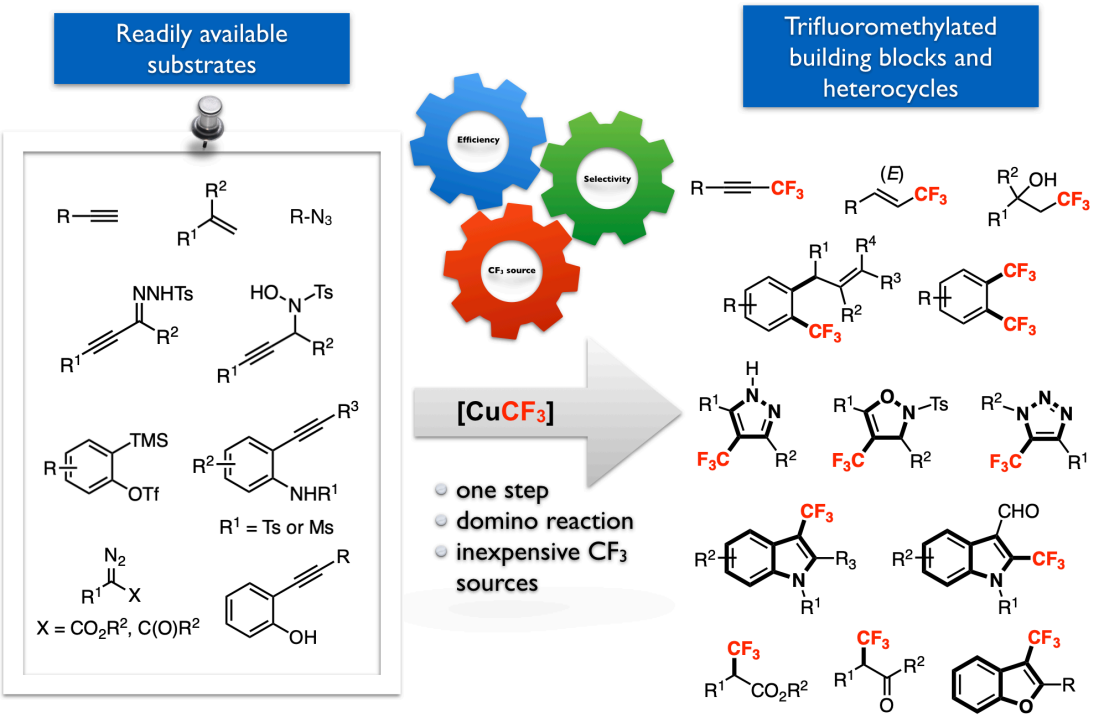
Fluorinated molecules continue to be of major interest for the applications in pharmaceuticals, agrochemicals and functional materials. To address the synthetic challenges in the area of trifluoromethylation reactions, a three-pronged approach is needed to solve the problems of *efficiency*, *selectivity* and *CF_3-source*. We have recently developed a series of novel trifluoromethylation methods using the fluoroform-derived $CuCF_3$ reagent. By employing common feedstocks such as terminal alkynes and simple alkenes, a variety of valuable CF_3-containing building blocks including the trifluoromethylated alkynes,[1] alkenes[2] and *β*-trifluoromethyl alcohols[3] can be synthesized in one step. These processes, namely trifluoromethylation, *hydro*trifluoromethylation and *hydroxy*trifluoromethylation, allow the distinctive construction of C(sp)-CF_3, C(sp^2)-CF_3 and C(sp^3)-CF_3 bonds, respectively. Furthermore, a three-component vicinal *trifluoromethylation-allylation* of arynes was realized where two carbon-carbon bonds (C-CF_3 and C-allyl) are formed in one pot to provide the trifluoromethylated allylarenes.[4] Even *1,2-bis(trifluoromethylation)* of arynes was made possible for the first time.[5] This reagent also enables the preparation of *α*-trifluoromethyl esters and ketones directly from *α*-diazo carbonyl compounds under mild conditions.[6] Overall, the ultimate CF_3 source in these versatile fluorinated molecules is the inexpensive industrial by-product *fluoroform* from Teflon manufacturing.

We have also investigated the synthesis of diverse trifluoromethylated heterocycles *via* domino strategies with copper. An interrupted click reaction, using CuI/phen as the catalyst and (trifluoromethyl)trimethylsilane ($TMSCF_3$) as the nucleophilic CF_3 source, has been developed to synthesize 5-trifluoromethyl 1,2,3-triazoles in one step from readily available terminal alkynes and azides.[7] The reaction shows complete regioselectivity, broad substrate scope and good functional group tolerability. Moreover, domino *5-endo-dig* cyclization/trifluoromethylation of *α,β*-alkynic tosylhydrazones and propargylic *N*-hydroxylamines allows convenient access to 4-(trifluoromethyl)pyrazoles[8] and 4-trifluoromethyl-4-isoxazolines,[9] respectively. These reactions are facilitated by the $Cu(OTf)_2$/$TMSCF_3$/KF combination. By employing easily accessible 2-alkynylanilines and the low-cost fluoroform-derived $CuCF_3$ reagent, both 2- and 3-(trifluoromethyl)indoles can be prepared in good yields with no ambiguity of the CF_3 position.[10-11] Analogous cyclization/trifluoromethylation of 2-alkynylphenols can afford 3-(trifluoromethyl)benzofurans and one of the compounds was identified as a promising antibacterial and antifungal agent.[12] Applications of the above methods in the expedient synthesis of trifluoromethylated drug analogues including rufinamide, celecoxib, bazedoxifene, melatonin, papaverine and estrone have also been successfully demonstrated.

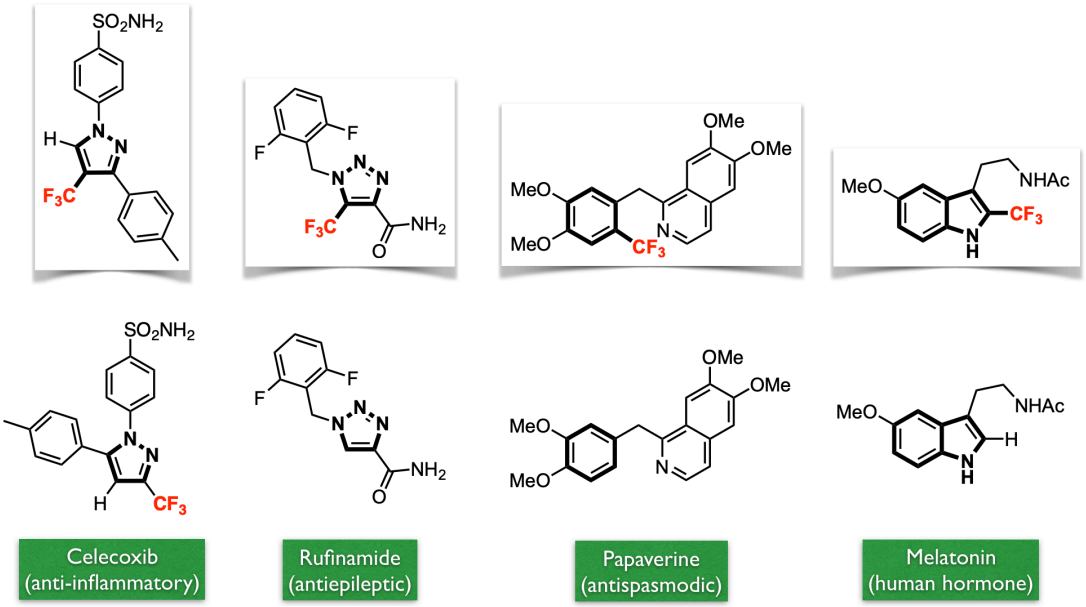
References:

(1) He, L.; Tsui, G. C. *Org. Lett.* **2016**, *18*, 2800-2803. (2) He, L.; Yang, X.; Tsui, G. C. *J. Org. Chem.* **2017**, *82*, 6192-6201. (3) Yang, X.; He, L.; Tsui, G. C. *Org. Lett.* **2017**, *19*, 2446-2449. (4) Yang, X.; Tsui, G. C. *Org. Lett.* **2018**, *20,* 1179-1182. (5) Yang, X.; Tsui, G. C. *Chem. Sci.* **2018**, *9*, 8871-8875. (6) Ma, Q.; Tsui, G. C. *Org. Chem. Front.* **2019**, *6*, 27-31. (7) Cheung, K. P. S.; Tsui, G. C. *Org. Lett.* **2017**, *19*, 2881-2884. (8) Wang, Q.; He, L.; Li, K. K.; Tsui, G. C. *Org. Lett.* **2017**, *19*, 658-661. (9) Wang, Q.; Tsui, G. C. *J. Org. Chem.* **2018**, *83*, 2971-2979. (10) Ye, Y.; Cheung, K. P. S.; He, L.; Tsui, G. C. *Org. Lett.* **2018**, *20,* 1676-1679. (11) Ye, Y.; Cheung, K. P. S.; He, L.; Tsui, G. C. *Org. Chem. Front.* **2018**, *5,* 1511-1515. (12) Li, M.; Ye, Y.; He, L.; Hui, M.; Ng, T. B.; Wong, J. H.; Tsui, G. C. *Asian J. Org. Chem.* **2019**, *8,* 702-709.

Gavin Chit Tsui 徐哲. University of Toronto (Ph.D, 2013, with Prof. Mark Lautens). Max-Planck-Institut für Kohlenforschung (Postdoc, 2015, with Prof. Benjamin List). The Chinese University of Hong Kong (Assistant Professor, 2015-present). [Field of research] organofluorine chemistry, metal-mediated reactions, homogeneous catalysis, ligand/catalyst design, medicinal chemistry.
E-mail: gctsui@cuhk.edu.hk
Website: http://www.cuhk.edu.hk/research/gctsui



Trifluoromethylated Drug Analogues



Celecoxib (anti-inflammatory)

Rufinamide (antiepileptic)

Papaverine (antispasmodic)

Melatonin (human hormone)