Frontier Chemistry Center
フロンティア化学教育研究センター

講演会

演 題：**A Three-Pronged Approach to the Development of New Trifluoromethylation Reactions**

講 師：**Prof. Gavin Chit Tsui**

Chinese University of Hong Kong

日 時：2019 年 9 月 30 日（月）16:30~18:00

場 所：理学部本館 N-308 講義室

要 旨：

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, alkenes and *β*-trifluoromethyl alcohols 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. Even *1,2-bis(trifluoromethylation)* of arynes was made possible for the first time. This reagent also enables the preparation of α-trifluoromethyl esters and ketones directly from α-diazo carbonyl compounds under mild conditions. 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. The reaction shows complete regioselectivity, broad substrate scope and good functional group tolerability. Moreover, domino 5-*endo-dig* cyclization/trifluoro-methylation of *α,β*-alkynic tosylhydrazones and propargylic *N*-hydroxylamines allows convenient access to 4-(trifluoromethyl)pyrazoles and 4-trifluoromethyl-4-isoxazolines, 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. 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. 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.

本講演は、大学院総合化学院『化学研究先端講義（修士課程選択科目／総合化学特別研究第二（博士後期課程選択科目）』の一部として認定されています。

協　賛：公益社団法人 有機合成化学協会 SSOCJ - The Society of Synthetic Organic Chemistry, Japan　有機合成化学協会北海道支部

連絡先：理学研究院化学部門　鈴木孝洋（内線：2703）

フロンティア化学教育研究センター