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New Trifluoromethylation Reactions with Fluoroform-Derived CuCF$_3$
and Domino Synthesis of Trifluoromethylated Heterocycles

Fluorinated molecules continue to be of major interest for the applications in pharmaceuticals, agrochemicals and functional materials. The constant search for more efficient, selective and convenient trifluoromethylation methods is an important yet challenging priority. We herein present the recent development of novel trifluoromethylation methods using the fluoroform(CF$_3$H)-derived CuCF$_3$. 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 6-trifluoromethyl alcohols$^3$ can be synthesized in one step. These processes, namely trifluoromethylation, hydrotrifluoromethylation and hydroxytrifluoromethylation, allow the distinctive construction of C(sp$_3$)-CF$_3$, C(sp$^2$)-CF$_3$ and C(sp$^3$)-CF$_3$ bonds, respectively. Furthermore, we have developed an unprecedented three-component vicinal trifluoromethylation-allylation of arynes where two carbon-carbon bonds (C-CF$_3$ and C-allyl) are formed in one pot to provide the trifluoromethylated allylarenes.$^4$ 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.$^5$ 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$^6$ and 4-trifluoromethyl-4-isoxazolines,$^7$ respectively. These reactions are facilitated by the Cu(OTf)$_2$/TMSCF$_3$/KF combination. By employing easily accessible 2-alkynylalines 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.$^8,9$ Applications of the above methods in the expedient synthesis of CF$_3$-containing drug analogues such as rufinamide, celecoxib, bazedoxifene and melatonin have also been successfully demonstrated.

References:

Date: 14th August 2018 (Tuesday)
Time: 11:00am – 12:30pm
Venue: SPMS Research & Graduate Studies Office Conference Room
Host: Professor Tamio Hayashi