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Development of Pentafluoroethylation Methods

Yihan Tang,[a] Tao Dong[a] and Gavin Chit Tsui[a,b]*

[a]Department of Chemical Synthesis, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

*Email: gctsui@cuhk.edu.hk

Abstract:
Compared to the smallest perfluoroalkyl group, *i.e.* trifluoromethyl (CF_3), the pentafluoroethyl group (C_2F_5) has rather been overlooked in terms of synthetic methods and applications in pharmaceuticals/agrochemicals. However, this situation has changed in the last decade or so where more reports have appeared in the literature describing the reagents and reactions that can allow the efficient preparation of C_2F_5-containing compounds. This review summarizes the methods of pentafluoroethylation for the period of *ca.* 2015-2025 organized by reagents including transition metal-based reagents, perfluoroalkyl silanes, gaseous reagents, hypervalent iodine, sulfonium ylide and sulfoximine reagents, and miscellaneous reagents. These methods have significantly advanced our access to structurally diverse pentafluoroethylated compounds and will have a major impact on their potential applications in medicinal chemistry as drug candidates and in organic synthesis as building blocks.

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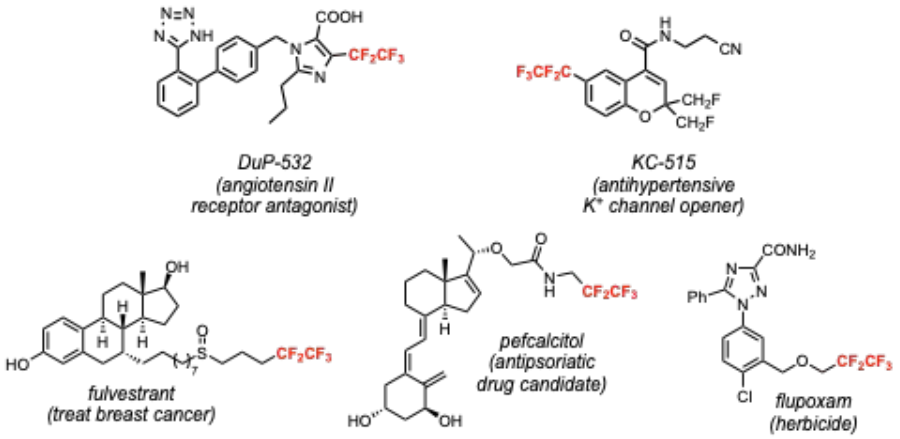
1. Introduction

Method development for introducing perfluoroalkyl groups into organic molecules has become increasingly important,[1] owing to the desirable biological and chemophysical properties exhibited by perfluoroalkylated compounds which are prevalent in marketed drugs.[2] The smallest perfluoroalkyl group CF_3 has been shown to be crucial in drug discovery and its installation, *i.e.* trifluoromethylation, has been extensively studied and reached certain level of maturity.[3] In contrast, the pentafluoroethyl group (C_2F_5), a homolog of CF_3, has been largely overlooked in the literature until recently. Although C_2F_5 belongs to the broader family of perfluoroalkyl groups, its installation is not simply an extension of the trifluoromethylation methodology. In practice, the limited availability and different reactivities of C_2F_5-containing reagents have made pentafluoroethylation a more specialized and less developed transformation. According to a SciFinder® search, during the period of 2000-2022, there were over 3000 references on the topic of "trifluoromethylation" versus less than 100 references on "pentafluoroethylation". That being said, bioactive compounds containing the C_2F_5 group are well-documented including angiotensin II receptor antagonist DuP-532, antihypertensive potassium channel opener KC-515 and fulvestrant for treating breast cancer (Scheme 1.1).[4] The number of pentafluoroethylated drug molecules, however, is significantly lower than that of the trifluoromethylated ones, despite some evidence pointing to the superior biological activities of the pentafluoroethylated congeners.[5] Thus, new tools for pentafluoroethylation will have impact on the application of C_2F_5-containing compounds as therapeutic agents in the future.



Scheme 1.1. Bioactive compounds containing the C_2F_5 group.

Review articles containing pentafluoroethylation reactions are limited and often include various kinds of perfluoroalkylation reactions.[6] However, in this review, we focus solely on the development of pentafluoroethylation methodology and related reagents in the past decade (*ca.* 2015-2025). The content is categorized by reagents: (1) transition metal-based reagents; (2) perfluoroalkyl silanes; (3) gaseous reagents; (4) hypervalent iodine, sulfonium ylide and sulfoximine reagents; and (5) miscellaneous reagents. The shorthand "C_2F_5" or "CF_2CF_3" for the pentafluoroethyl group is used interchangeably throughout this review.

2. Transition metal-mediated pentafluoroethylation

2.1 CuC_2F_5 reagent (as a solution in DMF) generated from pentafluoroethane (C_2F_5H)

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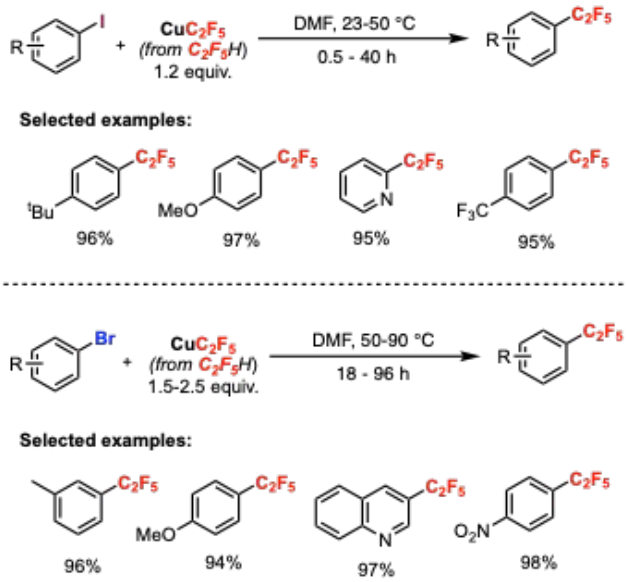
Transition metals played an important part in pentafluoroethylation and *copper* was among the most used metals for this development. In 2013, Grushin's group disclosed a landmark report on the cupration of pentafluoroethane (C_2F_5H) for the preparation of a novel CuC_2F_5 reagent.[7] Pentafluoroethane is an inexpensive and readily available gas that is used as a refrigerant and fire suppression agent. It is a potent greenhouse gas yet non-ozone depleting. Following their previous protocol for the preparation of $CuCF_3$ from fluoroform (CF_3H),[8] Grushin and co-workers demonstrated that a "CuC_2F_5" species could be formed using CuCl, KO^{t}Bu and pentafluoroethane in DMF (Scheme 2.1). The *in situ* generated [K(DMF)][(^{t}BuO)$_2$Cu] reacted with C_2F_5H smoothly at room temperature and atmospheric pressure to give "CuC_2F_5" quantitatively, which was structurally characterized to be [K(DMF)$_2$][(^{t}BuO)Cu(C_2F_5)] by X-ray crystallography. Surprisingly, only CF_3H and C_2F_5H could be cuprated, other higher *H*-perfluoroalkanes were found to be unreactive under identical conditions.

R_f-H	Yield of "Cu-R_f" (%)
CF_3H	>90
CF_3CF_2H	**>95**
$H(CF_2)_6H$	not observed
$CF_3(CF_2)_nH$ (n = 2,5,7)	not observed
$(CF_3)_2CFH$	not observed

Scheme 2.1. Cupration of pentafluoroethane to generate "CuC_2F_5". {"CuC_2F_5" = [K(DMF)$_2$][(^{t}BuO)Cu(C_2F_5)]}

Grushin's CuC_2F_5 complex was found to be much more thermally stable than the previous $CuCF_3$ complex from fluoroform. Its stability allowed efficient pentafluoroethylation of not only (hetero)aryl iodides but also less reactive *bromides* (Scheme 2.2). Moreover, the CuC_2F_5 reagent could also react with other types of substrates including benzylic/vinylic halides,[9] arylboronic acids and terminal alkynes.



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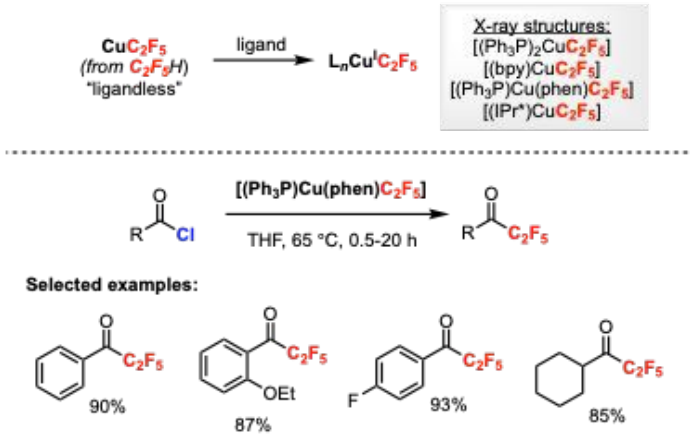
Scheme 2.2. Pentafluoroethylation of (hetero)aryl iodides/bromides using CuC_2F_5 generated from C_2F_5H.

Subsequently, Grushin and co-workers prepared four new well-defined $L_nCu^IC_2F_5$ complexes using the "ligandless" CuC_2F_5 generated from pentafluoroethane by adding ligands (L).[10] These complexes, including $[(Ph_3P)_2CuC_2F_5]$, $[(bpy)CuC_2F_5]$, $[(Ph_3P)Cu(phen)C_2F_5]$ and $[(IPr^*)CuC_2F_5]$, were structurally verified by X-ray crystallography. In particular, the $[(Ph_3P)Cu(phen)C_2F_5]$ complex was shown to be an efficient pentafluoroethylating reagent for acid chlorides to synthesize pentafluoroethyl ketones (Scheme 2.3).



Scheme 2.3. Well-defined $L_nCu^IC_2F_5$ complexes and pentafluoroethylation of acid chlorides for the synthesis of pentafluoroethyl ketones using $[(Ph_3P)Cu(phen)C_2F_5]$.

Since 2020, Tsui's group has investigated new reactivities of the CuC_2F_5 reagent generated from pentafluoroethane. Prior to their works, the majority of the applications of this reagent were in cross-coupling type pentafluoroethylation based on Cu(I) reaction pathways. Tsui and co-workers found that *unactivated* alkenes could be pentafluoroethylated with CuC_2F_5 under *aerobic* conditions to form novel allylic CF_2CF_3 compounds with excellent *E*-selectivity and functional group tolerance (Scheme 2.4).[11] The use of *air*, an ideal green oxidant, was the key to this reaction. The allylic CF_2CF_3 product could be further transformed to diverse pentafluoroethylated compounds through reactions at the double bond. Mechanistic studies strongly suggested the involvement of *C_2F_5 radical*. Initially, $Cu^IC_2F_5$ is oxidized by molecular oxygen to $Cu^{II}C_2F_5$, which undergoes Cu–C bond homolysis to release the C_2F_5 radical. Addition of the C_2F_5 radical to the alkene generates the carbon radical **A**. Intermediate **A** may combine with Cu(II) to form an alkyl–Cu(III) intermediate **C**, which undergoes *β*-hydride elimination to furnish the product. Alternatively, **A** may undergo single-electron oxidation by Cu(II) to afford carbocation **B**, followed by deprotonation under basic conditions to yield the same product. Thus, Tsui and co-workers have unlocked an unprecedented radical pathway of the CuC_2F_5 reagent generated from pentafluoroethane where CuC_2F_5 could act as a source of C_2F_5 radical under air at room temperature.

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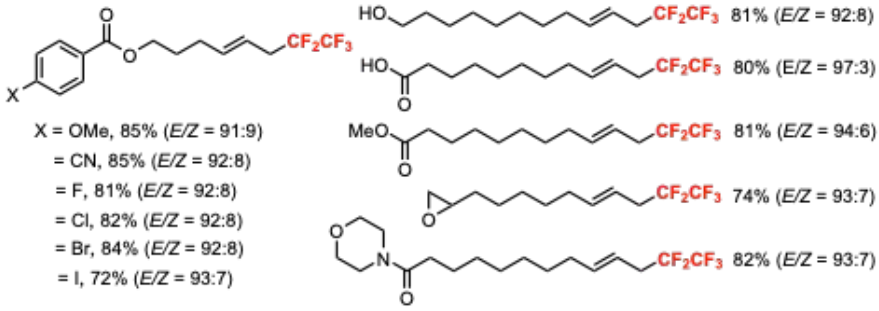
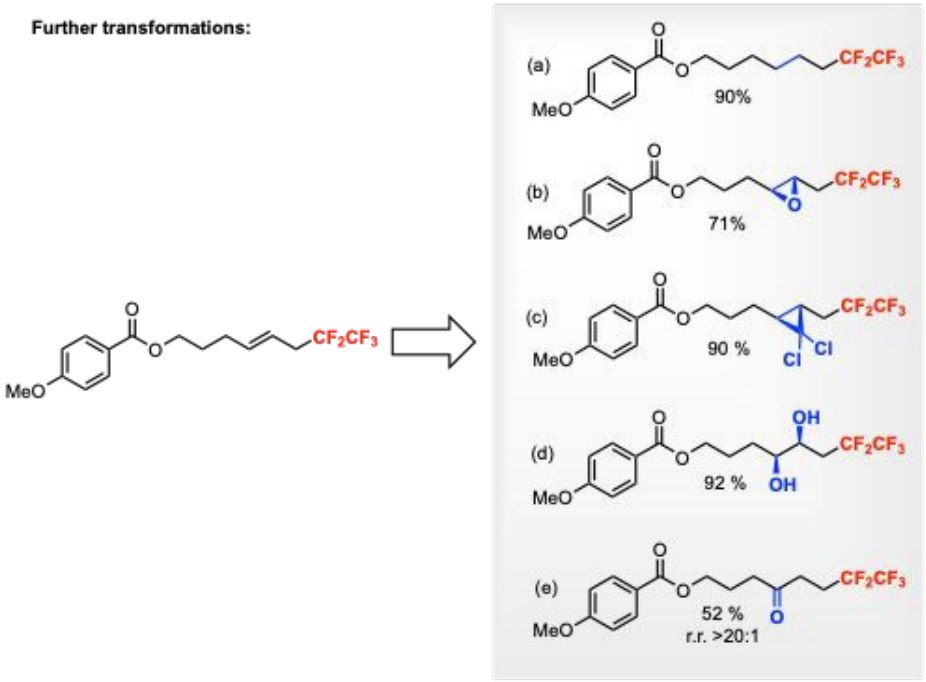
Selected examples:

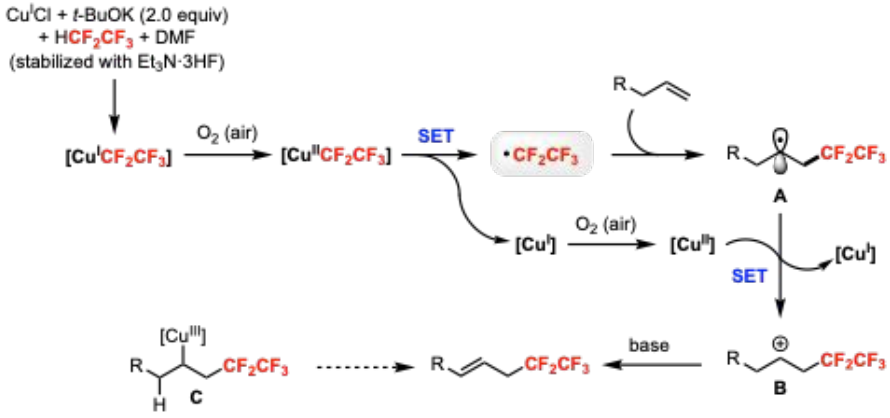


Further transformations:



Conditions:
(a) Pd/C (10 mol%), H_2 balloon, MeOH, rt, 12 h; (b) *m*-CPBA (2.4 equiv), $CHCl_3$, rt, 12 h; (c) TBAB (5 mol%), aq. NaOH, $CHCl_3$, rt, 12 h; (d) AD-mix-α, $CH_3SO_2NH_2$ (1.0 equiv), *t*-BuOH/H_2O, rt, 24 h; (e) $Pd(OAc)_2$ (7.5 mol%), aq. HBF_4 (1.4 equiv), 1,4-benzoquinone (1.0 equiv), CH_3CN/H_2O, 40 °C, 24 h.

Proposed mechanism:



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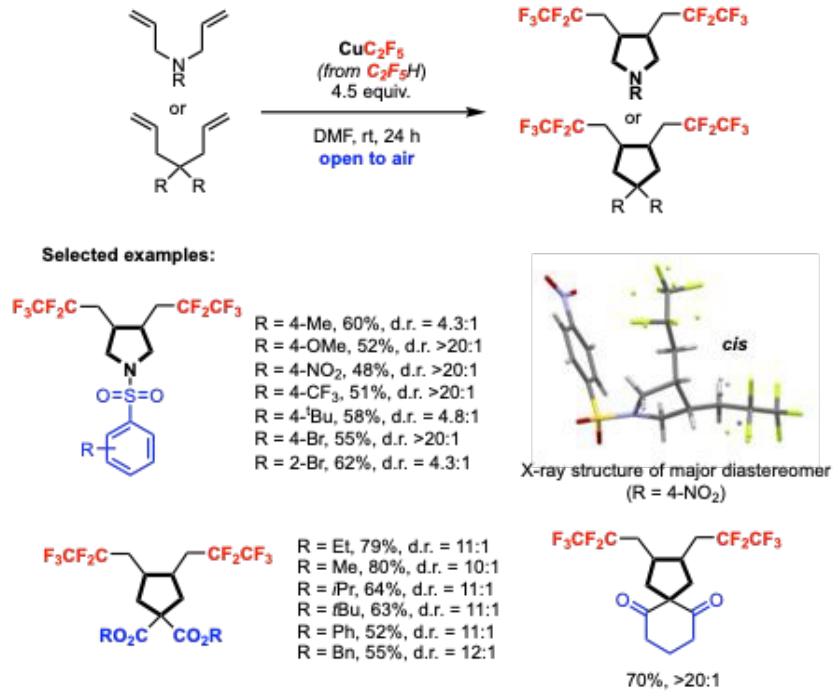
Scheme 2.4. Pentafluoroethylation of unactivated alkenes using CuC_2F_5 generated from C_2F_5H to synthesize allylic C_2F_5 compounds.

Pyrrolidines and cyclopentanes are prevalent structural motifs in pharmaceuticals and natural products. Domino radical cyclization of 1,n-dienes represents a highly efficient and atom-economical strategy for constructing such five-membered hetero- and carbocycles. Building on the observation of pentafluoroethyl radical from the CuC_2F_5 reagent under aerobic conditions, Tsui and co-workers subsequently developed a domino radical cyclization/bis(pentafluoroethylation) of 1,6-dienes to synthesize fluoroalkylated pyrrolidine and cyclopentane scaffolds containing two C_2F_5 units (Scheme 2.5).[12] The reactions proceeded smoothly at room temperature open to air affording the desired pyrrolidines (up to 7.7:1 d.r.) and cyclopentanes (up to 12:1 d.r.). Upon column chromatography, the major diastereomers could be isolated with d.r. >20:1. The relative *cis* configuration of the two –$CH_2C_2F_5$ groups was confirmed by X-ray crystallography. Overall, three bonds were formed and ten fluorine atoms were introduced in this transformation in one step.



Scheme 2.5. Domino radical cyclization/bis(pentafluoroethylation) of 1,6-dienes using CuC_2F_5 generated from C_2F_5H to construct pentafluoroethylated pyrrolidine and cyclopentane scaffolds.

Tsui's group also reported that when applying the CuC_2F_5 reagent to *styrene* derivatives, instead of unactivated alkenes, a variety of pentafluoroethylated products could be obtained depending on the substrates and conditions (Scheme 2.6).[13]The

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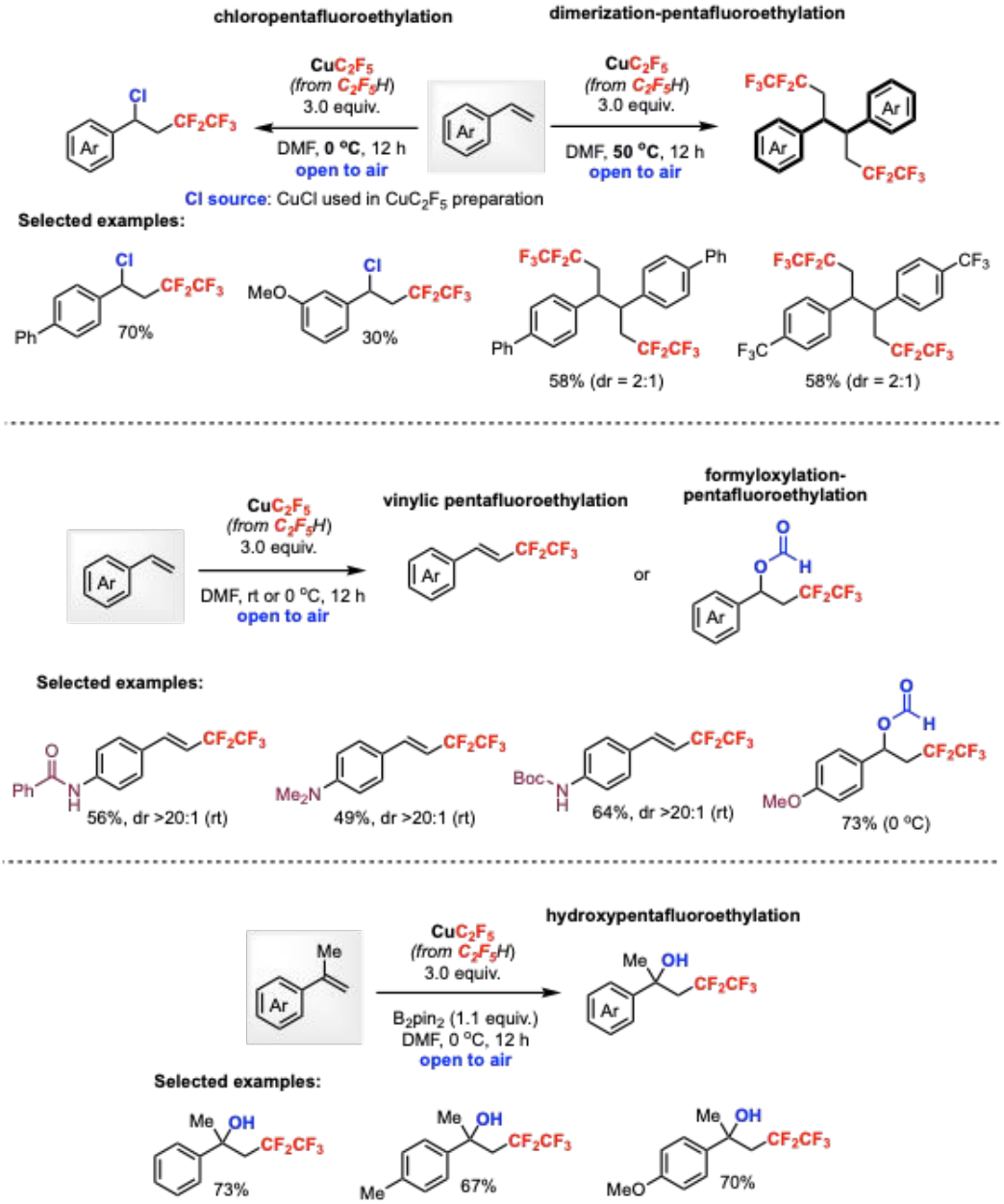
chloropentafluoroethylated products predominated at 0 °C whereas bis-pentafluoroethylated dimers were favoured at 50 °C. Vinyl C_2F_5 products were obtained with substrates containing *para* amino groups at room temperature. Formyloxylated products were formed with substrates containing *para* methoxy groups at 0 °C. With *α*-methylstyrenes, hydroxypentafluoroethylated products were obtained using B_2Pin_2 as an additive.[14] Overall, a single reagent allowed access to diverse pentafluoroethylated products from styrene derivatives.



Scheme 2.6. Divergent pentafluoroethylation of styrene derivatives using CuC_2F_5 generated from C_2F_5H.

Tsui and co-workers reported the gram-scale synthesis of TEMPO-C_2F_5 by capturing the C_2F_5 radical generated from the CuC_2F_5 reagent (Scheme 2.7).[15] A series of TEMPO derivatives were employed to prepare novel *pentafluoroethoxyamines* which were well-

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characterized including X-ray structural analysis. An unexpected application of the TEMPO-C_2F_5 compound was found when it was heated in *acetonitrile* at 40 °C with alcohols. Trifluoroacetylation of alcohols occurred smoothly to afford the corresponding trifluoroacetates up to 94% yield. This transformation featured a broad substrate scope tolerating both alcohols and amines, and proceeded under mild and base-free conditions. Kinetic analyses revealed that both the thermal decomposition of TEMPO-C_2F_5 in MeCN and its reactions with nucleophiles followed first-order kinetics with respect to TEMPO-C_2F_5, whereas the latter processes exhibited zero-order dependence on the nucleophile concentration. These results, together with DFT calculations, support a mechanistic pathway involving N–O bond *heterolysis* through a Stieglitz-type rearrangement, forming a pentafluoroethoxy anion that undergoes *α*-fluoride elimination to generate trifluoroacetyl fluoride, which is subsequently trapped by nucleophiles. The computed energy profile further corroborated this mechanistic proposal and rationalized the solvent and substituent effects observed experimentally.

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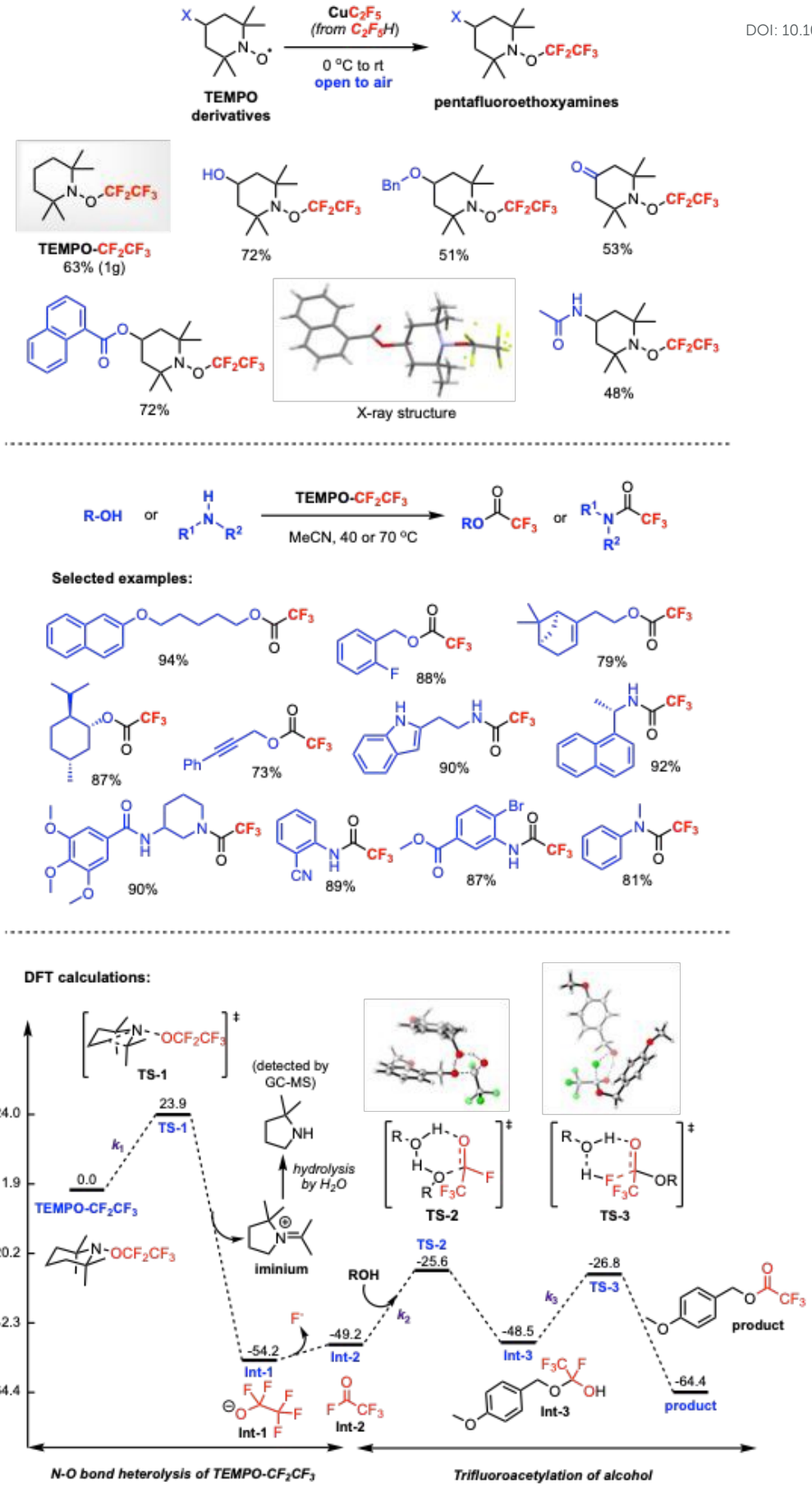

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Scheme 2.7. Preparation of TEMPO-C_2F_5 using CuC_2F_5 generated from C_2F_5H and its applications in trifluoroacetylation of alcohols and amines.

Another useful application of the CuC_2F_5 reagent generated from C_2F_5H was in the synthesis of pentafluoroethylated heterocycles. Click chemistry, particularly the Cu-catalyzed azide–alkyne cycloaddition (CuAAC) for constructing 1,2,3-triazoles, represents one of the most powerful and reliable transformations in modern synthetic chemistry. Tsui and co-workers have described a copper-mediated interrupted click reaction that enabled the synthesis of 5-pentafluoroethyl-substituted 1,2,3-triazoles in a single step using the CuC_2F_5 reagent (Scheme 2.8).[16] The reaction proceeded under mild conditions and exhibited a broad substrate scope compatible with both aryl and alkyl alkynes to deliver the desired triazoles in good to excellent yields. Moreover, this methodology was successfully applied to the synthesis of a 5-pentafluoroethyl analogue of the antiepileptic drug rufinamide, highlighting its potential in medicinal chemistry for precise incorporation of fluorinated motifs into bioactive frameworks.[17]

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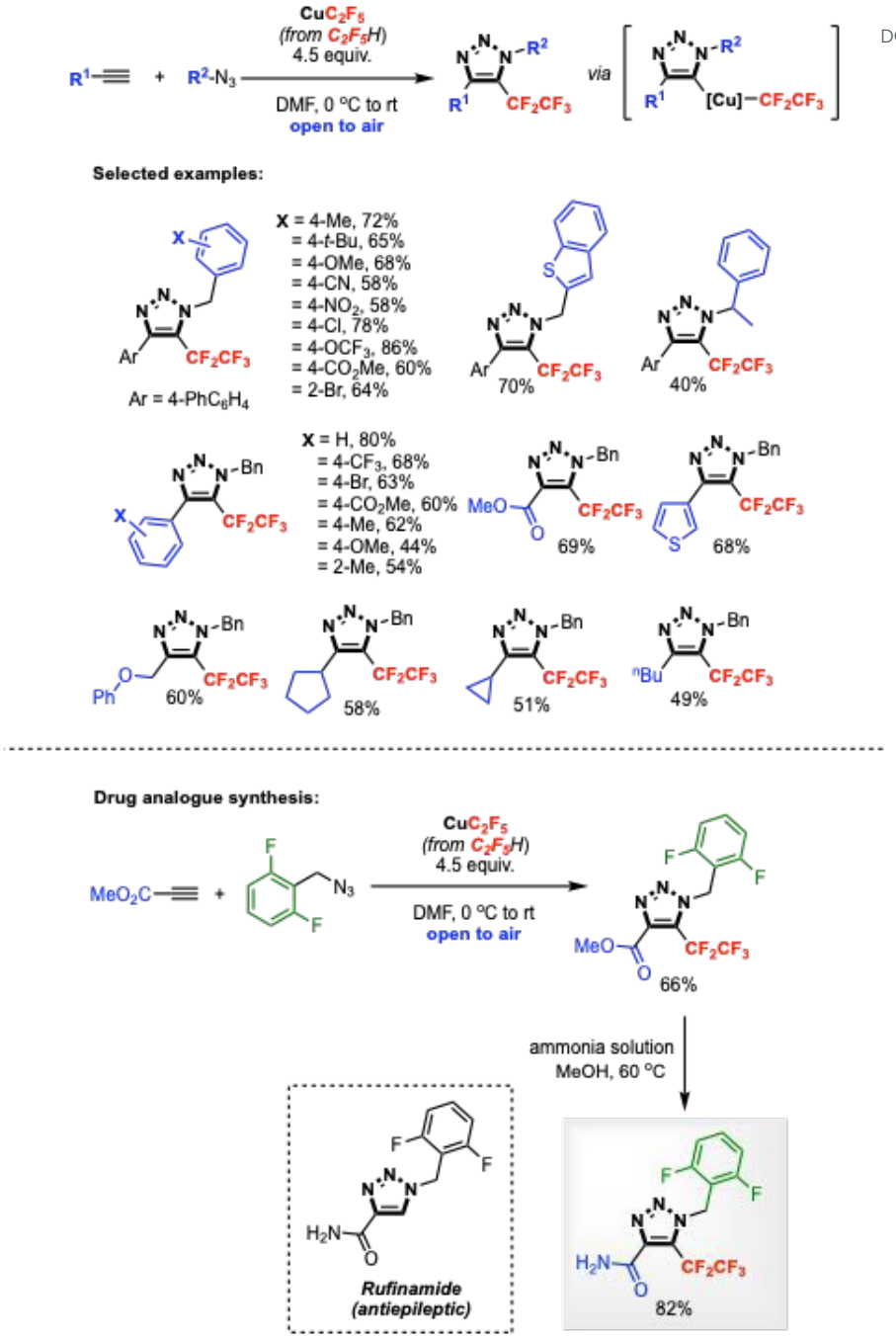

Scheme 2.8. Interrupted click reaction using CuC_2F_5 generated from C_2F_5H for the synthesis of pentafluoroethylated 1,2,3-triazoles.

2.2 Well-defined CuC_2F_5 complexes generated by other methods

Besides Grushin's CuC_2F_5 reagent from pentafluoroethane, other well-defined CuC_2F_5 complexes have also been described in the literature. In 2011, Daugulis *et al.* documented the synthesis of $[K(DMPU)_3]^+[(CF_2CF_3)CuCl]^-$ from CuCl, KF and $TMSCF_3$ in DMPU/THF in 14% yield, which was characterized by NMR spectroscopy and X-ray crystallography (Scheme 2.9a).[18] This anionic complex was a temperature and moisture sensitive solid that decomposed at room temperature under argon over few hours. In 2012, Hartwig *et al.* reported the preparation of $[(phen)CuC_2F_5]$ from $[Cu(Mesityl)]_5$, *t*-BuOH, 1,10-phenanthroline (phen) and $TMSCF_2CF_3$ in 78% yield (Scheme 2.9b).[19]

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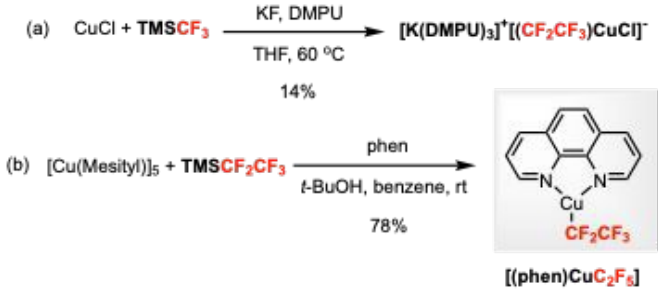
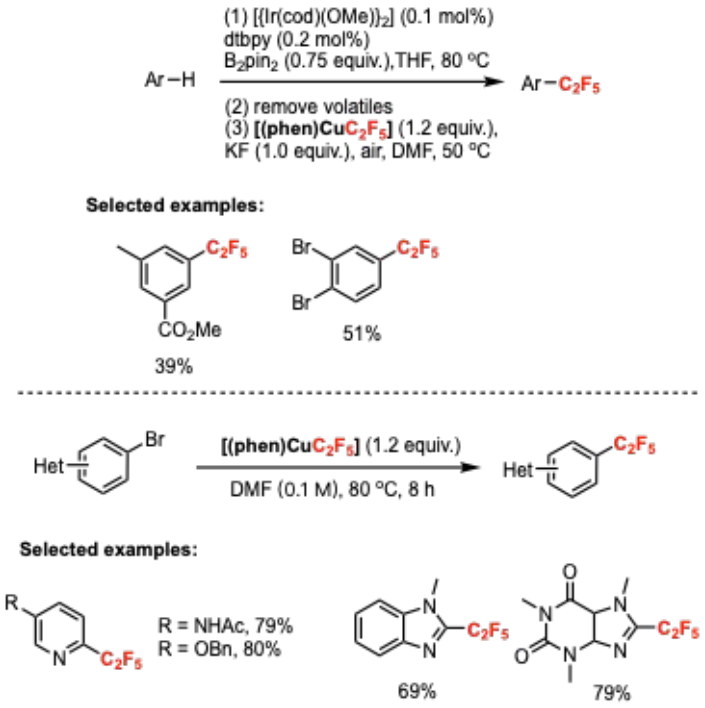


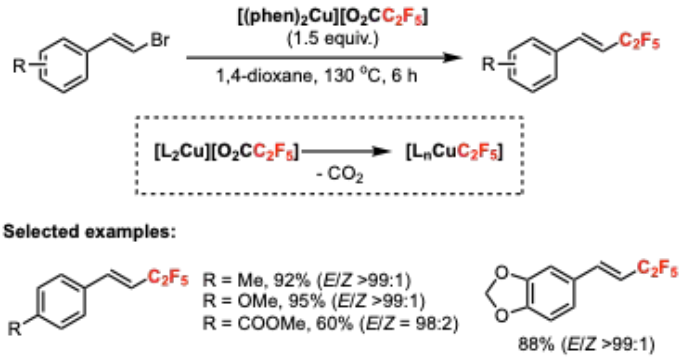
Scheme 2.9. Daugulis' and Hartwig's methods for preparing CuC_2F_5 complexes.

The [(phen)CuC_2F_5] complex was utilized for constructing C(sp^2)–C_2F_5 bonds under mild cross-coupling conditions (Scheme 2.10). The combination of Ir-catalyzed C–H borylation with Cu-mediated pentafluoroethylation enabled the direct transformation of simple arenes into pentafluoroethylated arenes. It was demonstrated that the [(phen)CuC_2F_5] complex could undergo oxidative addition and reductive elimination analogous to [(phen)$CuCF_3$]. The same group further extended the cross-coupling to heteroaryl bromides.[20]Compared to [(phen)$CuCF_3$], these pentafluoroethylation reactions gave higher yields and broader substrate scope, tolerating both electron-rich and electron-deficient heterocycles. A later mechanistic investigation by the same group provided insights into the reactivity and electronic structure of the copper(I) pentafluoroethyl complexes.[21] The study revealed that oxidative addition of aryl halides to copper(I) pentafluoroethyl complexes proceeds most efficiently with electron-poor ligands, showing an inverse relationship between ligand donor strength and reactivity. This counterintuitive trend was attributed to the higher electrophilicity and lower activation barrier of less electron-rich Cu(I) centres.



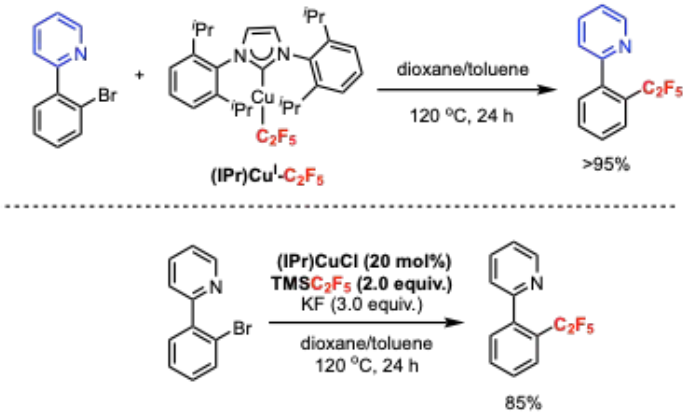
Scheme 2.10. Pentafluoroethylation of arenes and heteroaryl bromides using [(phen)CuC$_2$F$_5$].

Weng/Zhang and co-workers employed the copper(I) pentafluorocarboxylate complex [(phen)$_2$Cu][O$_2$CC$_2$F$_5$] for the decarboxylative pentafluoroethylation of vinyl bromides (Scheme 2.11).[22] The *E/Z* configuration of the products corresponded to the starting alkenes.



Scheme 2.11. Pentafluoroethylation of vinyl bromides using [(phen)$_2$Cu][O$_2$CC$_2$F$_5$].

Sanford's group developed a NHC-copper(I) pentafluoroethyl complex (IPr)Cu^{I}–C$_2$F$_5$ for the pentafluoroethylation of aryl halides bearing *ortho*-directing groups (Scheme 2.12).[23] It was shown that pyridine, pyrazole, oxazoline, imine and ester directing groups could dramatically enhance the reactivity of aryl bromides/chlorides with this complex. Moreover, a catalytic version was also demonstrated using 20 mol% of (IPr)CuCl and TMSC$_2$F$_5$.



Scheme 2.12. Pentafluoroethylation of aryl bromides using (IPr)Cu^{I}–C$_2$F$_5$ enabled by directing groups.

In 2024, Tsui/Shen and co-workers reported the preparation of a bispentafluoroethylated organocuprate [Ph$_4$P]$^+$[Cu(CF$_2$CF$_3$)$_2$]$^-$ complex (Scheme 2.13).[24] This

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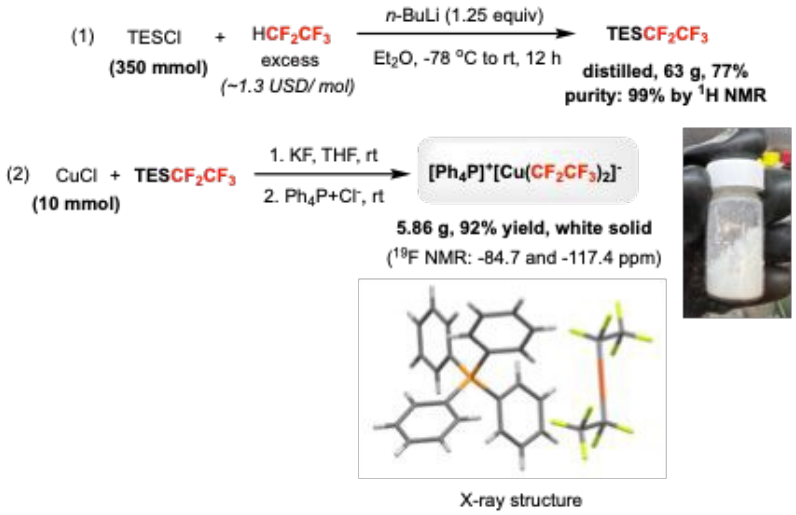
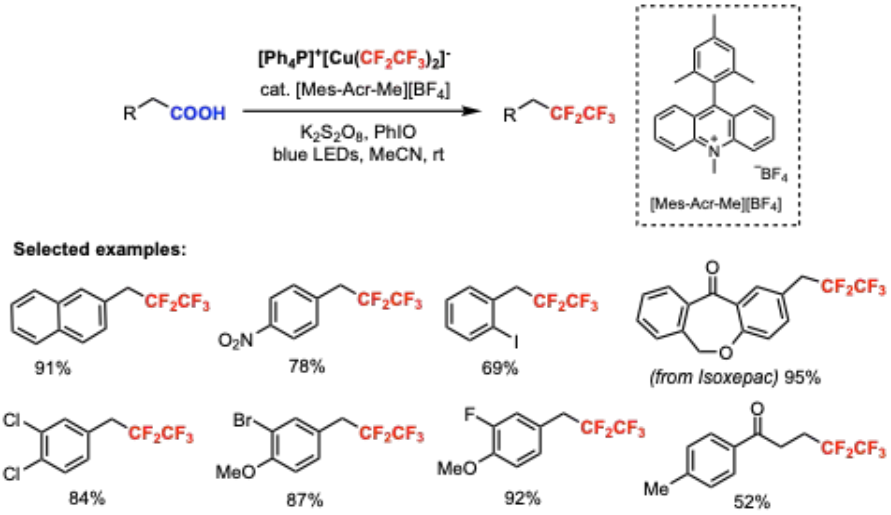
complex was synthesized from $TMSC_2F_5$ (ultimately from HC_2F_5) on gram-scale as a stable white solid.



Scheme 2.13. Preparation of $[Ph_4P]^+[Cu(CF_2CF_3)_2]^-$ complex.

Using this copper complex, the authors were able to achieve an unprecedented *decarboxylative* pentafluoroethylation of readily available carboxylic acids under photocatalytic conditions (Scheme 2.14).



Scheme 2.14. Photocatalytic decarboxylative pentafluoroethylation using $[Ph_4P]^+[Cu(CF_2CF_3)_2]^-$.

Furthermore, the $[Ph_4P]^+[Cu(CF_2CF_3)_2]^-$ complex exhibited a range of reactivities towards diazonium salts, organic halides, boronic esters, terminal alkynes and (hetero)arenes as a versatile pentafluoroethylating reagent (Scheme 2.15). Thus, a single reagent allowed the construction of $C(sp^3)$-/$C(sp^2)$-/C(sp)-CF_2CF_3 bonds.

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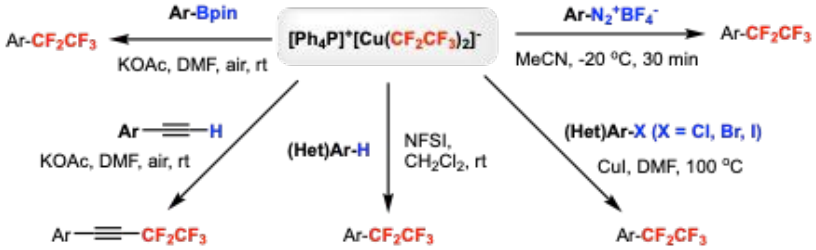

Scheme 2.15. $[Ph_4P]^+[Cu(CF_2CF_3)_2]^-$ complex as a versatile pentafluoroethylation reagent.

2.3 ZnC_2F_5 reagents

Besides CuC_2F_5 species, pentafluoroethylzinc reagents were also among the first to be prepared and characterized. In 2011, Daugulis' group reported the formation and structural confirmation (X-ray) of $(DMPU)_2Zn(C_2F_5)_2$ from TMP_2Zn and HC_2F_5 (Scheme 2.16a).[18] Mikami's group subsequently reported the preparation of this reagent from C_2F_5I and used it for the pentafluoroethylation of aryl iodides with catalytic CuI.[25] Fan and co-workers employed $(DMPU)_2Zn(C_2F_5)_2$ in a Cu-catalyzed pentafluoroethylation of allyl phosphates for the construction of $C(sp^3)–C_2F_5$ bonds (Scheme 2.16b).[26] The $Cu(acac)_2$/phenanthroline catalytic system promoted efficient coupling of allyl phosphates with $(DMPU)_2Zn(C_2F_5)_2$ to afford allyl C_2F_5 products in high yields and excellent regio- and stereoselectivities. Mechanistic studies supported the formation of π-allyl-Cu(III) intermediate indicating transmetalation of $Zn(C_2F_5)_2$ to copper followed by oxidative addition and reductive elimination. Furthermore, the reaction conditions could be applied to the introduction of CF_2H, C_3F_7, C_4F_9 and C_6F_{13} groups. Liu/Cao and co-workers developed a copper-catalyzed, chloroamide-directed benzylic C-H bond pentafluoroethylation using the $(DMPU)_2Zn(C_2F_5)_2$ reagent (Scheme 2.16c).[27] Mechanistic studies suggested the formation of benzylic radicals via intramolecular C-H bond activation, followed by copper-mediated transfer of the C_2F_5 group to the benzylic radicals. Zeng's group described a copper-catalyzed cross-coupling of propargyl *gem*-dichlorides with $(DMPU)_2Zn(C_2F_5)_2$ to synthesize chloro-substituted pentafluoroethyl allenes (Scheme 2.16d).[28] Mechanistic studies suggested transmetalation between $Zn(C_2F_5)_2$ and Cu(I) to form an active $[Cu^IC_2F_5]$ species followed by a possible S_N2' substitution.

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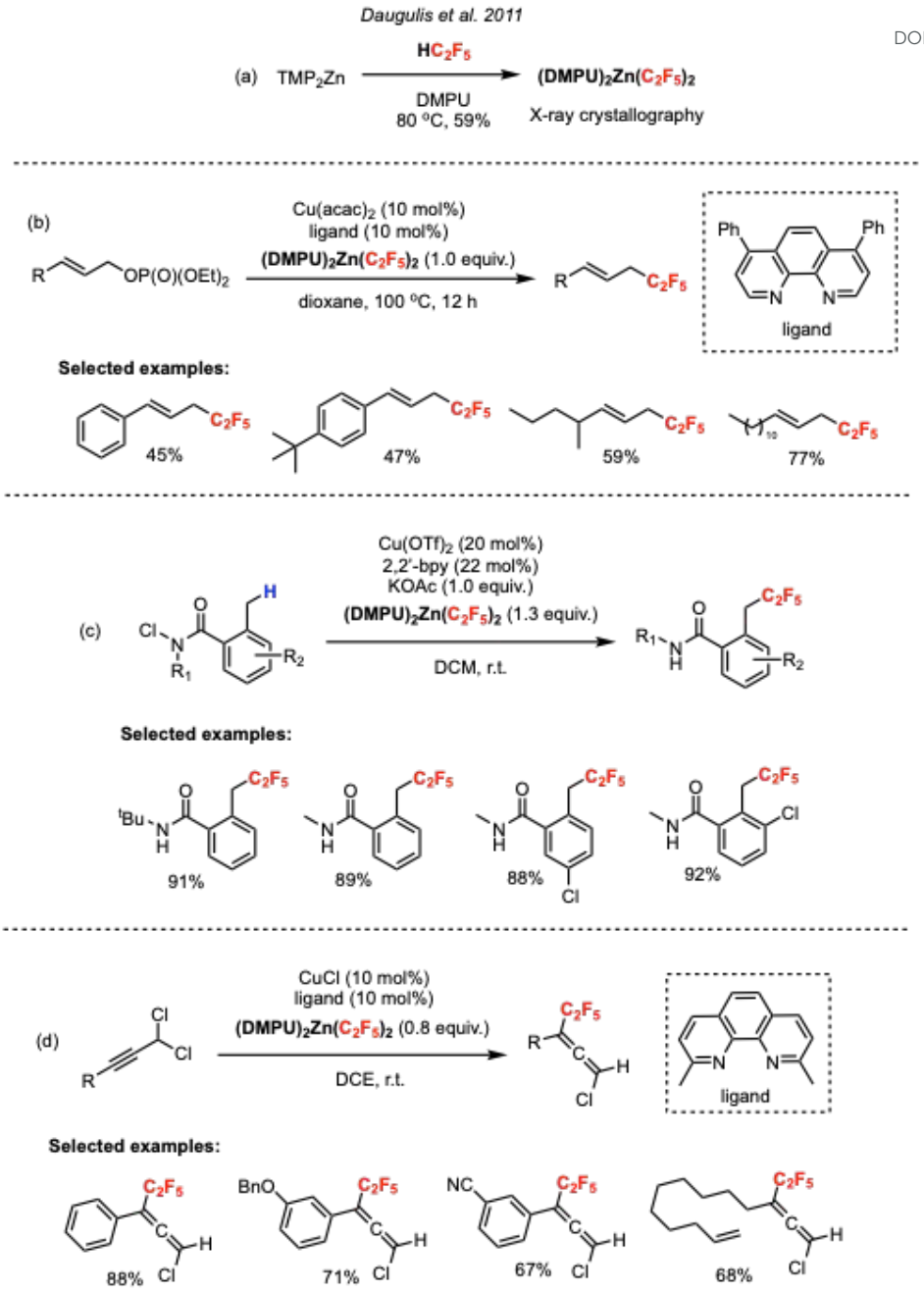
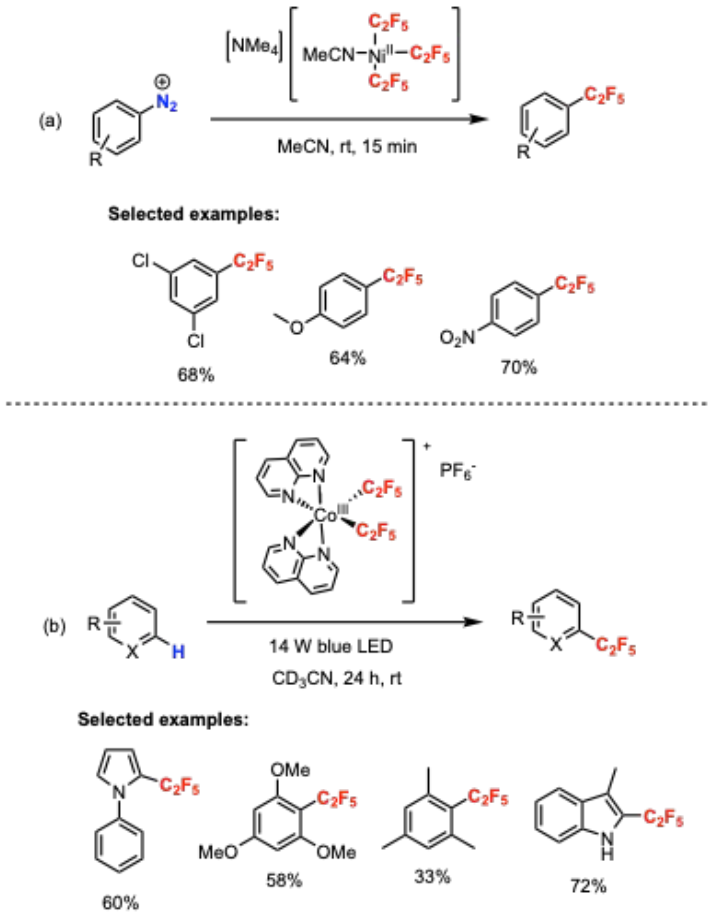


Scheme 2.16. Preparation of the $(DMPU)_2Zn(C_2F_5)_2$ reagent and its applications in pentafluoroethylation of allyl phosphates, benzylic C-H bonds and propargyl *gem*-dichlorides.

2.4 Other metal-C_2F_5 complexes

Nickel and cobalt complexes have also been explored for metal-mediated pentafluoroethylation. Vicic's group reported the preparation of a solvated $Ni^{II}(C_2F_5)_3$ complex from $[(dme)NiBr_2]$, $TMSC_2F_5$ and AgF in acetonitrile solvent in the presence of $[NMe_4]Cl$ (Scheme 2.17a).[29] This Ni(II) complex could undergo single-electron oxidation to release C_2F_5 radical enabling stoichiometric pentafluoroethylation of aryl diazonium salts under mild conditions. Khusnutdinova's group developed a photoactive cobalt(III)

pentafluoroethyl complex with naphthyridine ligands, which could undergo visible-light-induced Co–C_2F_5 bond homolysis to generate C_2F_5 radical (Scheme 2.17b).[30] This complex enabled stoichiometric and preliminary catalytic pentafluoroethylation (with Togni reagent) of electron-rich arenes and heteroarenes via C-H bond transformations.



Scheme 2.17. Pentafluoroethylation using Ni- and Co-C_2F_5 complexes.

Overall, transition metal-based reagents have provided one of the most established platforms for pentafluoroethylation. Well-defined metal–C_2F_5 complexes can offer predictable reactivity and broad applicability in C(sp)–C_2F_5, C(sp^2)–C_2F_5 and C(sp^3)–C_2F_5 bond formation. Thus, structurally diverse pentafluoroethylated products can be accessed. However, many of these methods still require pre-formation and stoichiometric use of organometallic C_2F_5 species. Their operational practicality may be limited by the reagent stability under air and moisture as well as functional group tolerability of the substrates.

3. Pentafluoroethylation using perfluoroalkyl silanes

3.1 Trifluoromethyl silanes

The Ruppert-Prakash reagent ($TMSCF_3$) is one of the most popular reagents for *trifluoromethylation* reactions.[31] In 2018, Hu's group revealed a remarkable usage of $TMSCF_3$ in pentafluoroethylation.[32] The so-called "C_1 to C_2" process relied on the formation of $CuCF_3$

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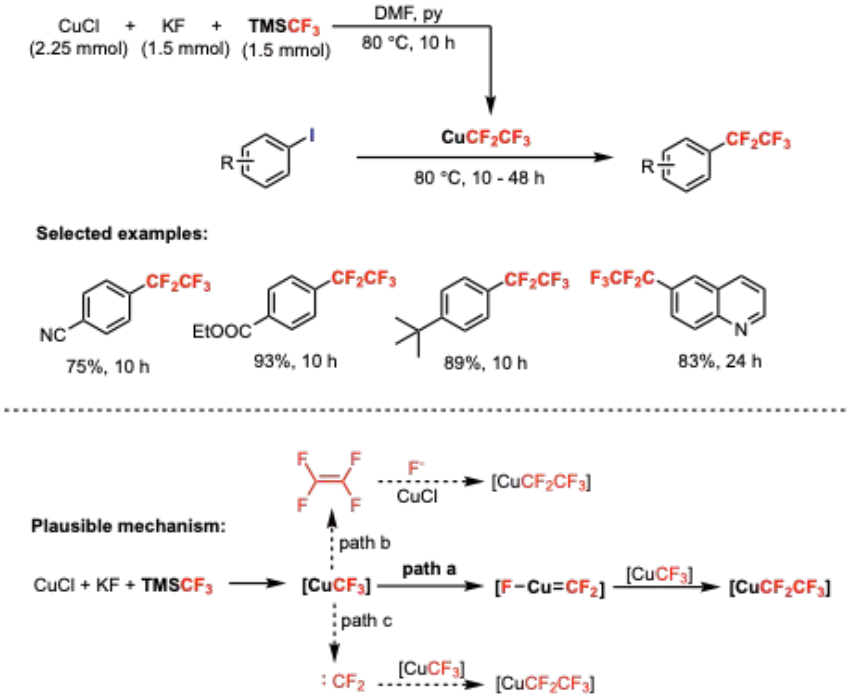
from $TMSCF_3$ followed by spontaneous transformation into CuC_2F_5 (Scheme 3.1). By mixing CuCl, KF, and $TMSCF_3$ (1.5:1:1) in DMF at room temperature, CuC_2F_5 was formed in 75% yield with minimal formation of $CuCF_3$. Aryl iodides were efficiently pentafluoroethylated with the *in situ* generated CuC_2F_5. Three plausible pathways (a-c) for the formation of CuC_2F_5 from $CuCF_3$ were suggested by the authors. Path b was refuted due to the absence of *tetrafluoroethylene* (TFE) in the reaction system. Electron-rich alkenes, phenols and thiophenols were tolerated and did not afford difluoromethylation products, suggesting that free difluorocarbene species were not formed, thus path c was also not likely. Since metal-CF_3 complexes are known to be precursors of metal difluorocarbenes ($M{=}CF_2$), the authors argued that the $Cu{=}CF_2$ species could be formed as a possible intermediate for CuC_2F_5 (*i.e.* path a).



Scheme 3.1. The use of $TMSCF_3$ for pentafluoroethylation of aryl iodides via *in situ* generated CuC_2F_5.

The $TMSCF_3$-derived $CuCF_2CF_3$ was also successfully applied in the pentafluoroethylation of organoboronates and terminal alkynes under *aerobic* conditions by Hu and co-workers (Scheme 3.2).[33] The ligand 1,10-phenanthroline was found to be essential for the pentafluoroethylation of organoboronates but was not required for terminal alkynes. Aromatic and alkenyl organoboronates gave moderate to high yields while alkyl ones failed. A variety of aromatic terminal alkynes were converted to the corresponding pentafluoroethyl alkynes and alkyl substrates were also tolerated. An analogous approach for the generation of the "ligandless" CuC_2F_5 from $TMSCF_3$ was reported by Boutureira and co-workers.[34] The authors demonstrated pentafluoroethylation of unactivated $C(sp^2)$-X bonds (X = I, Br) including late-stage introduction of C_2F_5 group into glycals, nucleosides and nucleobases. Detailed and insightful studies such as ^{19}F NMR and ESI-MS analyses were carried out to probe the nature of the reagent in solution. A pathway of insertion of $[Cu{=}CF_2]$ to $[Cu^ICF_3]$ was suggested for the formation of $[Cu^IC_2F_5]$.

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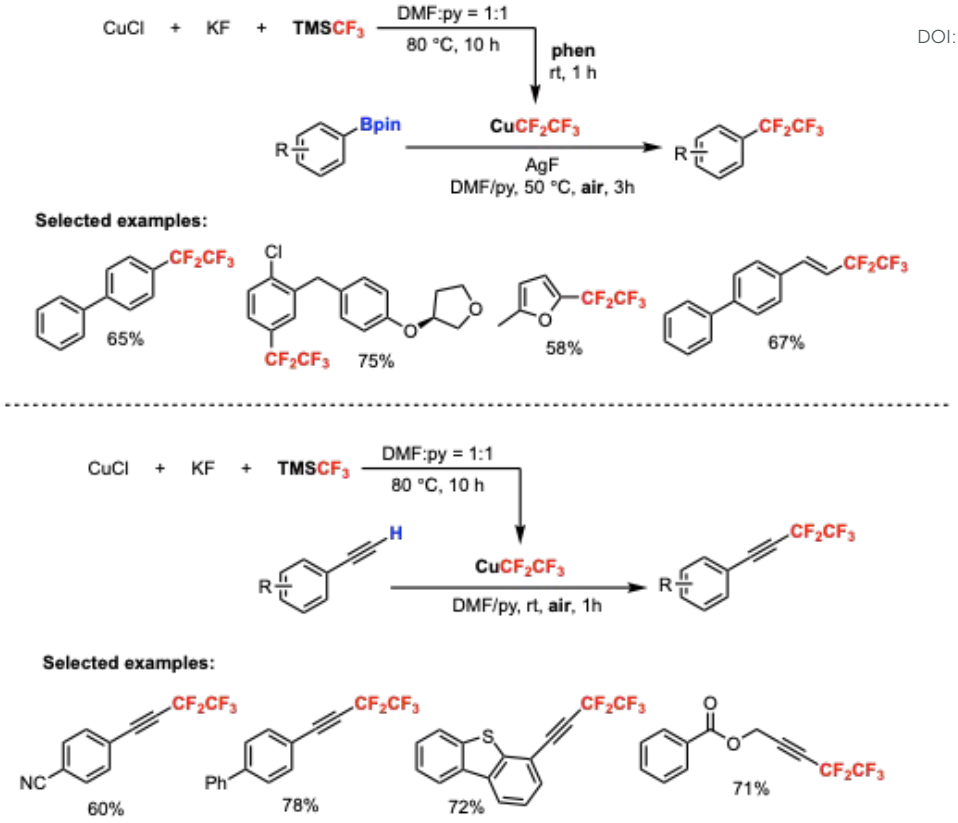
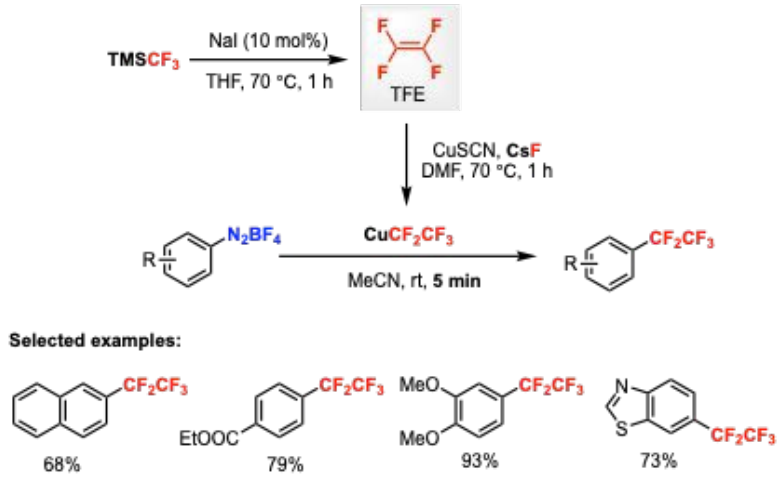


Scheme 3.2. Pentafluoroethylation of organoboronates and terminal alkynes under aerobic conditions using $TMSCF_3$-derived $CuCF_2CF_3$.

In 2017, Hu and co-workers realized that $TMSCF_3$ could serve as a source of *tetrafluoroethylene* (TFE) by dimerization of difluorocarbene generated *in situ* in a two-chamber system from $TMSCF_3$/NaI in THF.[35] The TFE could react with CsF, CuI and phen leading to the formation of (phen)CuC_2F_5 which facilitated pentafluoroethylation of iodoarenes. Later on, this method was applied to the efficient (5 min) pentafluoroethylation of arenediazonium salts in the Sandmeyer-type reaction by the same group (Scheme 3.3).[36] The *in situ* generated TFE was reacted with CuSCN and CsF to form the CuC_2F_5 reagent.



Scheme 3.3. Pentafluoroethylation of arenediazonium salts via *in situ* generated TFE from $TMSCF_3$/NaI.

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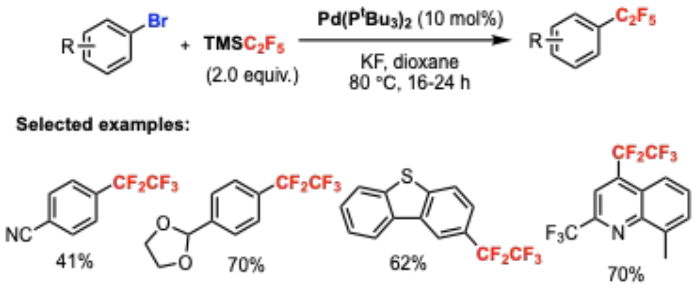
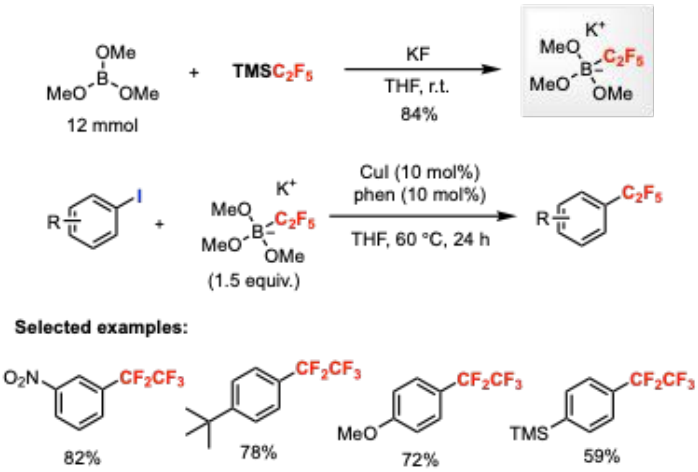
3.2 Pentafluoroethyl silanes

Compared to $TMSCF_3$, the *pentafluoroethyl* silane $TMSC_2F_5$ is a more direct pentafluoroethylation reagent albeit at a higher cost from current commercial suppliers. Transition metal-catalyzed cross-coupling type pentafluoroethylation using $R_3SiC_2F_5$ has been described. In 2017, Sanford's group reported a *palladium*-catalyzed pentafluoroethylation of aryl bromides using $TMSCF_2CF_3$ (Scheme 3.4).[37] The reactivity of $(P^tBu_3)Pd^{II}(Ph)(R_F)$ type complex was investigated through experimental and computational studies. DFT calculations showed that the α-fluoride elimination of the CF_2CF_3 derivative ($\Delta G^{\ddagger}$ = 34.7 kcal/mol) was *less* likely than the CF_3 derivative ($\Delta G^{\ddagger}$ = 20.8 kcal/mol). The P^tBu_3 ligand was crucial for the reaction and potassium fluoride was used as an activator.



Scheme 3.4. Palladium-catalyzed pentafluoroethylation of aryl bromides using $TMSCF_2CF_3$.

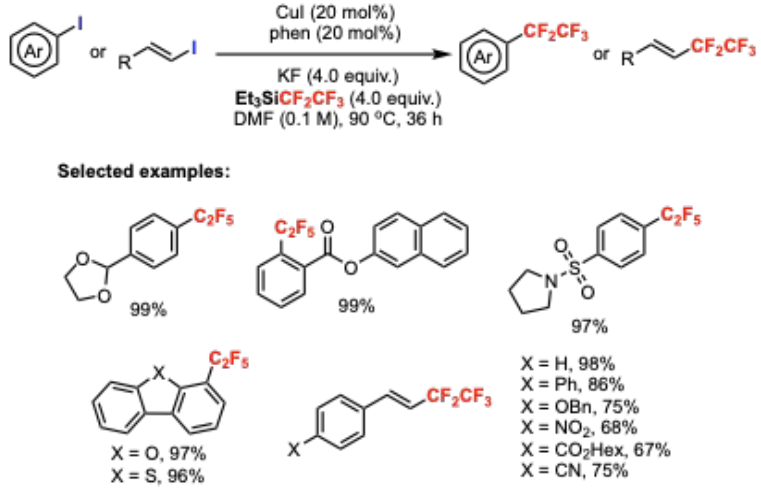
In the same year, Amii and co-workers reported a *copper*-catalyzed pentafluoroethylation of aryl iodides using potassium (pentafluoroethyl)trimethoxyborate (Scheme 3.5).[38] This reagent was prepared from $TMSCF_2CF_3$ and trimethylborate in the presence of potassium fluoride, which enabled the transformation under base-free conditions. Interestingly, one example of the pentafluoroethylation of 1-iodo-3-nitrobenzene using $TMSCF_2CF_3$ (56% ^{19}F NMR yield) was mentioned in this paper.



Scheme 3.5. Copper-catalyzed pentafluoroethylation of aryl iodides using potassium (pentafluoroethyl)trimethoxyborate prepared from $TMSCF_2CF_3$.

The direct use of pentafluoroethyl silanes in the cross-coupling reactions would be more efficient and atom-economical. To this end, Tsui's group developed a protocol to use $Et_3SiCF_2CF_3$ in the Cu-catalyzed pentafluoroethylation of aryl and alkenyl halides (Scheme 3.6).[39] The reagent $Et_3SiCF_2CF_3$ was prepared on a 200 mmol scale from low-cost materials

chlorotriethylsilane and *pentafluoroethane*. By using CuI/phen (1,10-phenanthroline) as the catalyst, KF as the activator and $Et_3SiCF_2CF_3$ as the reagent, aryl or alkenyl iodides were smoothly converted into pentafluoroethyl arenes and alkenes in good yields. This method featured broad substrate scope and excellent functional group compatibility, offering a simple and practical approach to access pentafluoroethylated compounds.



Scheme 3.6. Copper-catalyzed pentafluoroethylation of aryl/alkenyl iodides using $Et_3SiC_2F_5$.

MacMillan's group developed a metallaphotoredox pentafluoroethylation of organobromides in 2020.[40] This copper-catalyzed process allowed nucleophilic pentafluoroethylation of aryl, heteroaryl and even *alkyl* bromides using $TMSC_2F_5$ as a convenient nucleophile (Scheme 3.7). The key strategy in this reaction is a silyl radical-mediated halogen abstraction–radical capture (HARC) pathway, where the silyl radical abstracts the bromide to generate a carbon radical followed by combination of the pentafluoroethyl copper complex. This strategy circumvents the need of substrates to undergo challenging Cu-mediated oxidative additions thus significantly broadens the reaction scope to include alkyl substrates. The method provided a mild, general, and efficient approach to install perfluoroalkyl groups including CF_3, C_2F_5 and C_3F_7, which was also utilized in late-stage functionalization of drug analogues.

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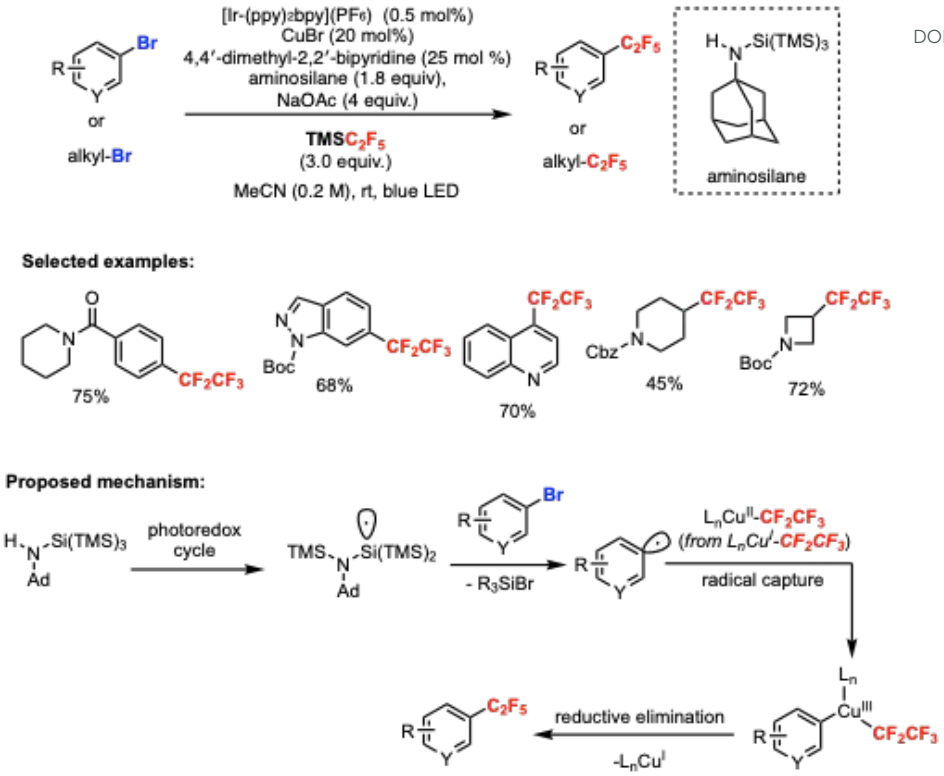
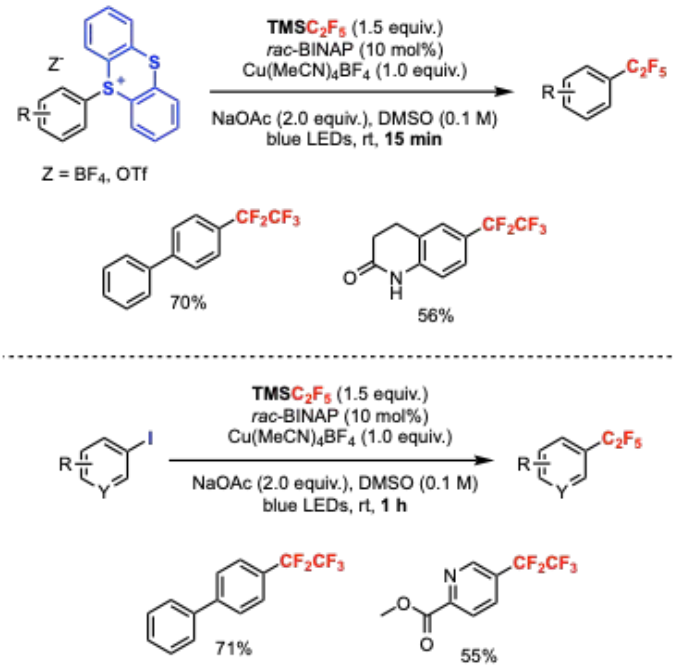


Scheme 3.7. Metallaphotoredox pentafluoroethylation of (hetero)aryl and alkyl bromides using $TMSCF_2CF_3$.

Wei/Shang/Wang and co-workers reported a copper-mediated photochemical late-stage pentafluoroethylation of arylthianthrenium salts using the *in situ* generated CuC_2F_5 from $TMSC_2F_5$ (Scheme 3.8).[41] The reaction could be significantly accelerated by adding a catalytic amount of *rac*-BINAP, which completed in only 15 minutes. The same group also applied the reaction to aryl iodides finishing in one hour.[42]



Scheme 3.8. Copper-mediated BINAP-accelerated pentafluoroethylation of arylthianthrenium salts and aryl iodides using $TMSC_2F_5$.

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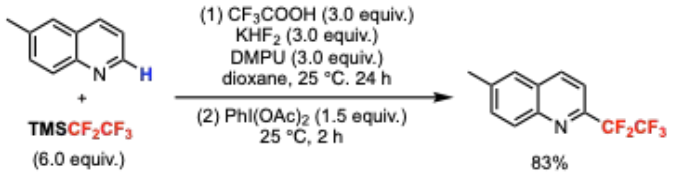
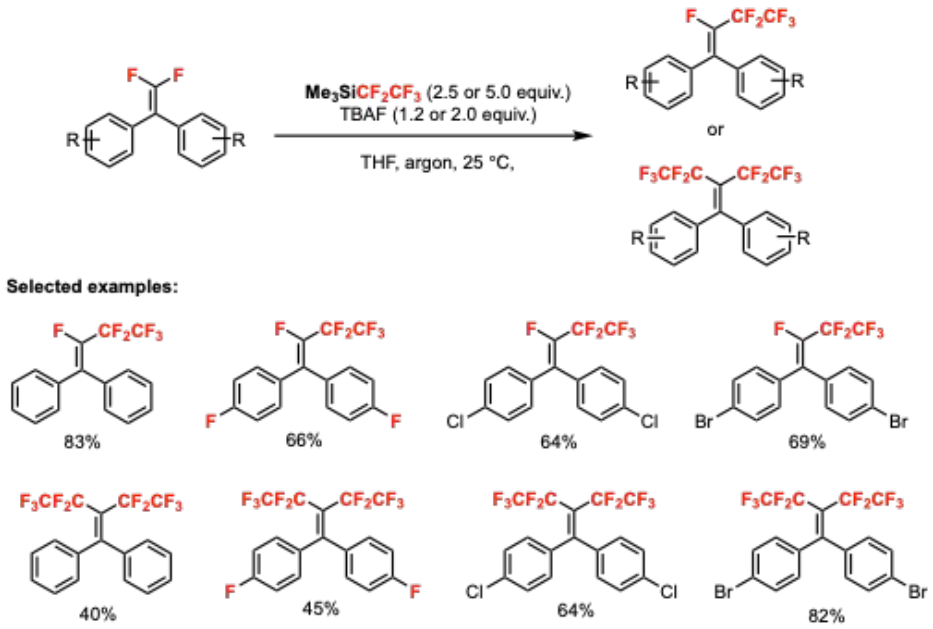
Expanding on the utility of transition metal-free perfluoroalkylation, Kuninobu/Kanai and co-workers developed a 2-position-selective C–H functionalization of quinolines using perfluoroalkyltrimethylsilanes (Scheme 3.9).[43] This catalyst-free protocol relied on the dual activation of the substrate and the silane reagent through an *in situ* generated hydrogen fluoride source (CF_3COOH and KHF_2) and the additive DMPU. While the study primarily focused on trifluoromethylation, the methodology was successfully extended to pentafluoroethylation, as demonstrated by the reaction of 6-methylquinoline with $TMSC_2F_5$ to furnish the corresponding 2-pentafluoroethylated product in 83% yield and excellent regioselectivity.



Scheme 3.9. 2-Position selective pentafluoroethylation of C-H bond of a quinoline derivative using $TMSC_2F_5$.

Cao's group reported a transition metal-free pentafluoroethylation of *gem*-difluoroalkenes (1,1-diaryl-2,2-difluoroethenes) using $TMSC_2F_5$ in the presence of TBAF (Scheme 3.10).[44] This simple protocol allowed the selective synthesis of both mono- and bis-pentafluoroethylated alkenes.



Scheme 3.10. Pentafluoroethylation of *gem*-difluoroalkenes using $TMSC_2F_5$.

Apart from carbon-C_2F_5 bond formations, pentafluoroethyl silanes have also been employed to construct *heteroatom*-C_2F_5 bonds. Qing's group reported a silver triflate (AgOTf)-mediated oxidative pentafluoroethylation of alkyl alcohols and phenols with $TMSC_2F_5$ (Scheme 3.11).[45] Selectfluor was used as a key oxidant. Various pentafluoroethyl *ethers* were obtained and the method could be extended to the oxidative heptafluoropropylation and ethoxycarbonyldifluoromethylation as well. The reaction presumably proceeds via Ag(I)CF_2CF_3 generated from AgOTf, KF and $TMSC_2F_5$, which may

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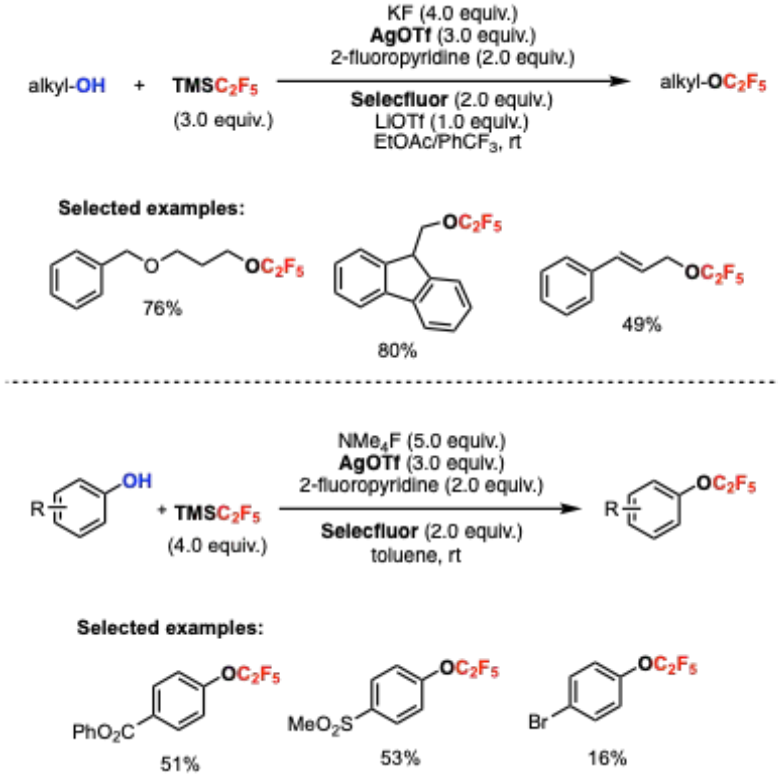
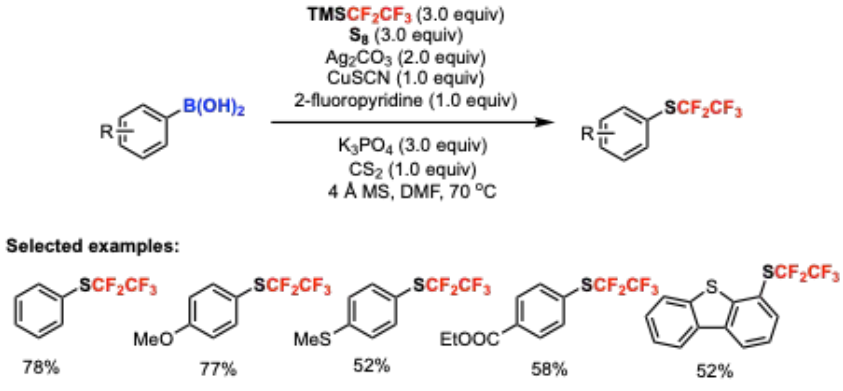
undergo oxidative addition to the O-H bond forming a Ag(III) species in the presence of an oxidant, subsequent reductive elimination leads to the formation of O-C_2F_5 bond in the pentafluoroethyl ether product.



Scheme 3.11. Silver-mediated oxidative pentafluoroethylation of alkyl alcohols and phenols for the synthesis of pentafluoroethyl ethers using $TMSC_2F_5$.

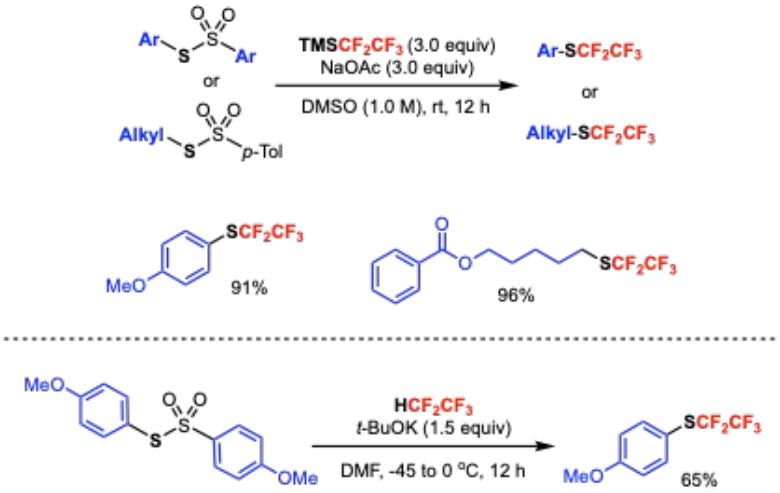
The same group developed a copper-mediated oxidative *pentafluoroethylthiolation* of aryl boronic acids, utilizing $TMSC_2F_5$ and elemental sulfur as the source of the pentafluoroethylthio group (Scheme 3.12).[46] This reaction employed 2-fluoropyridine as ligand, enabling the transformation of aryl and heteroaryl boronic acids into the corresponding pentafluoroethyl sulfides.



Scheme 3.12. Copper-mediated oxidative pentafluoroethylthiolation of aryl boronic acids using $TMSC_2F_5$ and elemental sulfur.

Tsui and co-workers described a practical synthesis of pentafluoroethyl sulfides by using *thiosulfonates* as electrophiles and $TMSC_2F_5$ as a nucleophile (Scheme 3.13).[47] This

method allowed access to *both* aryl and alkyl pentafluoroethyl sulfides in high yields. Moreover, pentafluoroethane could be employed directly in the presence of a base to react with thiosulfonate. Thus, challenging S-C_2F_5 bond formation was achieved in this simple protocol without the need of transition metals.



Scheme 3.13. Transition metal-free pentafluoroethylation of aryl and alkyl thiosulfonates for the synthesis of pentafluoroethyl sulfides using $TMSC_2F_5$.

Compared to pre-formed metal-C_2F_5 complexes, pentafluoroethyl silanes are generally more convenient and versatile C_2F_5 sources, particularly because they can be handled as bench-stable reagents and used in conjunction with transition metal and photoredox catalysis. On the other hand, the high cost and limited availability of some C_2F_5-silanes, together with the need for activators such as fluoride salts may hinder their applications.

4. Pentafluoroethylation using gaseous reagents

4.1 Pentafluoroethane (C_2F_5H)

The use of gaseous pentafluoroethane for generating well-defined CuC_2F_5 complexes and their applications in pentafluoroethylation reactions have been described above (*cf.* Section 2.1). There are also reports of using this gas directly to introduce C_2F_5 groups with or without transition metals. Daugulis and co-workers described the CuCl/phen-catalyzed pentafluoroethylation of 2-iodobenzoate with pentafluoroethane in the presence of TMP_2Zn and DMPU (Scheme 4.1a).[18] The *in situ* formation of $(C_2F_5)_2Zn(DMPU)_2$ was proven to be crucial. Shibata and co-workers reported the use of pentafluoroethane as a nucleophile in addition reactions to aldehydes, ketones and esters (Scheme 4.1b).[48] The use of potassium bases with triglyme or tetraglyme as a solvent for the encapsulation of the K cation with glymes was the key to success.

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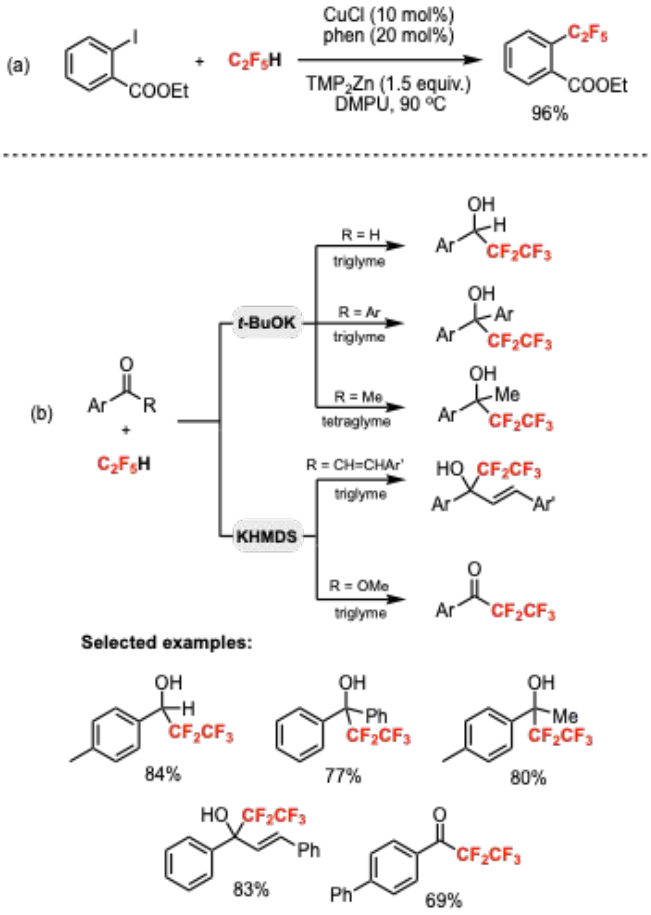
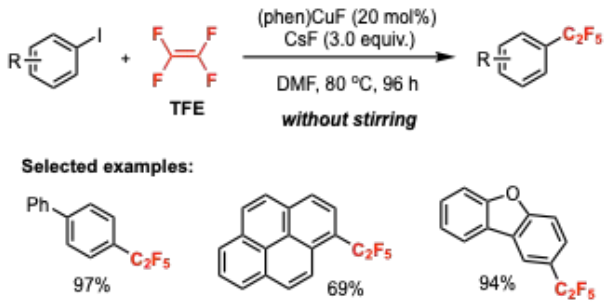


Scheme 4.1. Pentafluoroethylation of an aryl iodide and carbonyl compounds using pentafluoroethane with or without transition metals.

4.2 Tetrafluoroethylene (TFE)

Ogoshi/Ohashi and co-workers have demonstrated that tetrafluoroethylene (TFE) could also be employed as a starting material for the preparation of pentafluoroethylated aromatic compounds (Scheme 4.2).[49] The reaction design relied on the fluorocupration of TFE with (phen)CuF and CsF to generate the active species (phen)Cu(C_2F_5) *in situ*, which was isolated and confirmed by X-ray crystallography. The key to suppressing the competing oligomerization of TFE was to refrain from stirring the reaction mixture.



Scheme 4.2. Cu-catalyzed pentafluoroethylation of aryl iodides using tetrafluoroethylene (TFE).

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5. Pentafluoroethylation using hypervalent iodine, sulfonium ylide and sulfoximine reagents

5.1 Pentafluoroethyl hypervalent iodine reagents

The application of hypervalent iodine chemistry to perfluoroalkylation has significantly advanced the synthesis of perfluoroalkyl compounds. Following the success of the famous Togni reagents for electrophilic trifluoromethylation,[50] researchers began to design analogous pentafluoroethylating reagents including the early development of Yagupolskii and Umemoto's pentafluoroethyliodonium salts.[51] In 2016, Shen's group reported an improved method for the preparation of pentafluoroethyl benziodoxole (BIX-C_2F_5) as an electrophilic pentafluoroethylating reagent (Scheme 5.1a).[52] The BIX-C_2F_5 reagent was synthesized from BIX-F with $TMSC_2F_5$ in anhydrous CH_3CN at room temperature. It is a crystalline white solid and the structure was confirmed by X-ray crystallography. By using a weak base such as DBU or K_2CO_3, BIX-C_2F_5 could react with *β*-ketoesters in good yields. Moreover, copper-catalyzed pentafluoroethylation of (hetero)aryl boronic acids was also achieved using this reagent.

Later on, Vallribera/Granados and co-workers developed an *asymmetric* pentafluoroethylation using BIX-C_2F_5 (Scheme 5.1b).[53] The authors achieved the asymmetric *α*-pentafluoroethylation of alkyl 1-indanone-2-carboxylates using $La(OTf)_3$/(*S*,*R*)-indanyl-pybox as a chiral Lewis acid catalytic system. A quaternary *α*-pentafluoroethyl centre could be constructed with up to 89% ee. Chen's group also used BIX-C_2F_5 to accomplish the ring-opening pentafluoroethylation of cycloalkanols in a dual photoredox/copper-catalyzed protocol (one example).[54]

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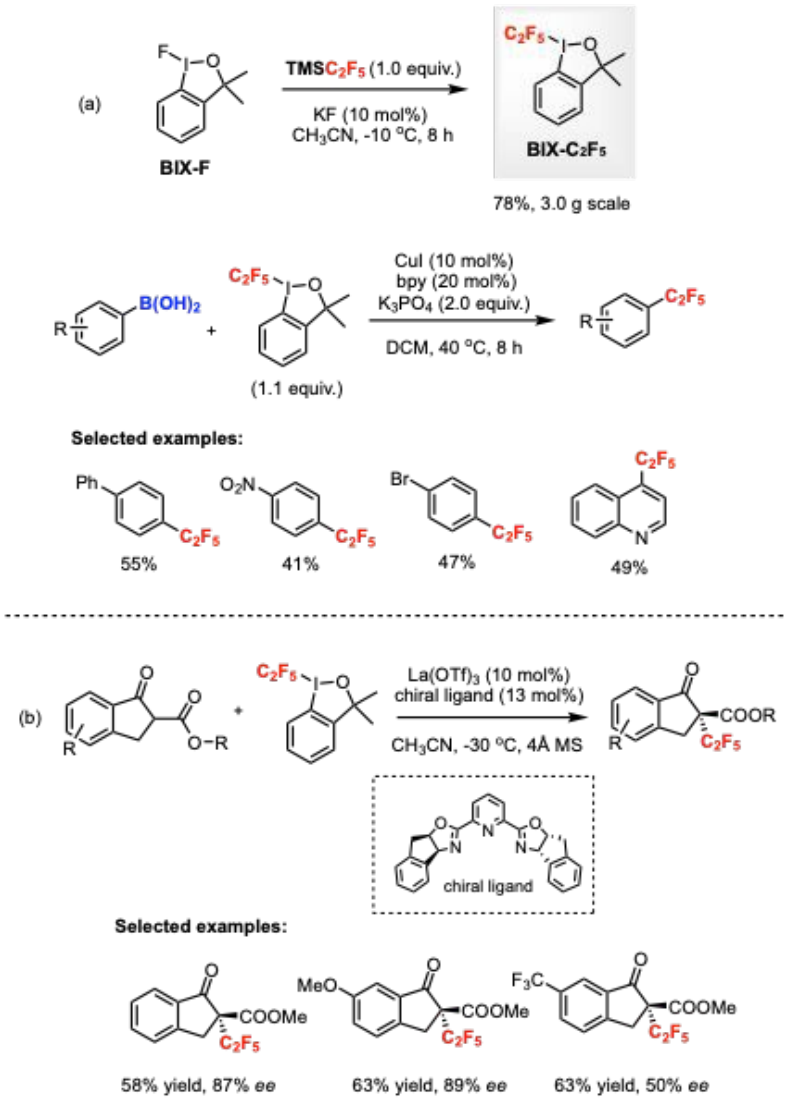

Scheme 5.1. Synthesis of the BIX-C_2F_5 reagent and its applications in copper-catalyzed pentafluoroethylation of (hetero)aryl boronic acids and asymmetric pentafluoroethylation.

Khaskin's group reported a "ligand-free" nickel-catalyzed pentafluoroethylation of (hetero)arenes using pentafluoroethyl Togni reagent (Scheme 5.2a).[55] The $[(MeCN)_2Ni^{II}(C_2F_5)_2]$ catalyst was prepared from $TMSC_2F_5$ and could efficiently functionalize (hetero)arene C-H bonds including natural products, drug analogues and peptides containing an aromatic unit. A radical mechanism was proposed based on preliminary studies. Subsequently, the same group described the synthesis of a cyclometalated $(CH_3CN)_2Ni(C_4F_8)$ complex for C-H bond pentafluoroethylation including chemoselective modification of tryptophan residues demonstrating potential for late-stage peptide derivatization (Scheme 5.2b).[56]

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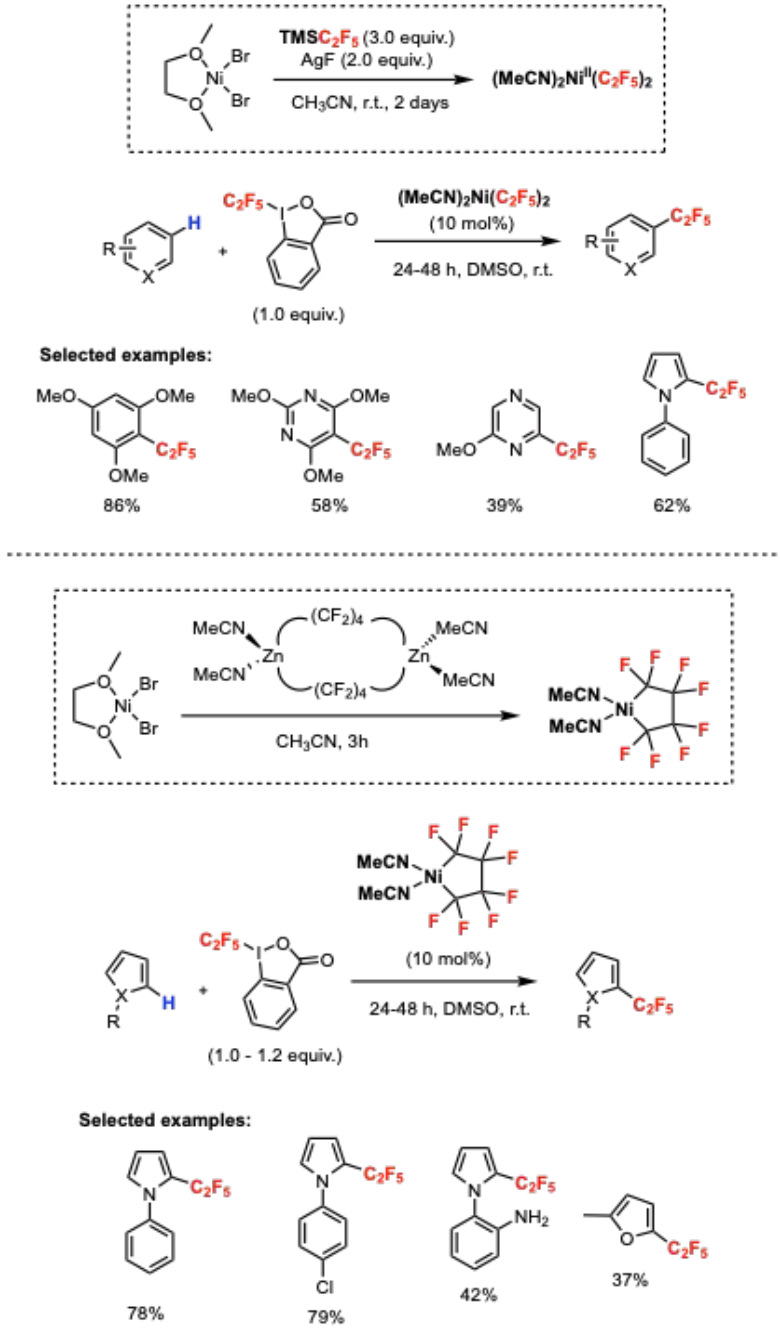

Scheme 5.2. Nickel-catalyzed pentafluoroethylation of (hetero)arenes using the C_2F_5–Togni reagent.

Hong/Choi and co-workers employed the C_2F_5–Togni reagent in a copper-catalyzed alkyne cyclization to synthesize pentafluoroethylated thiazoles (Scheme 5.3a).[57] The starting materials were aryl or alkyl-substituted thioureas containing a terminal alkyne. Liu/Li and co-workers described a copper-catalyzed radical cyanopentafluoroethylation of isocyanides using the same reagent (one example) (Scheme 5.3b).[58]

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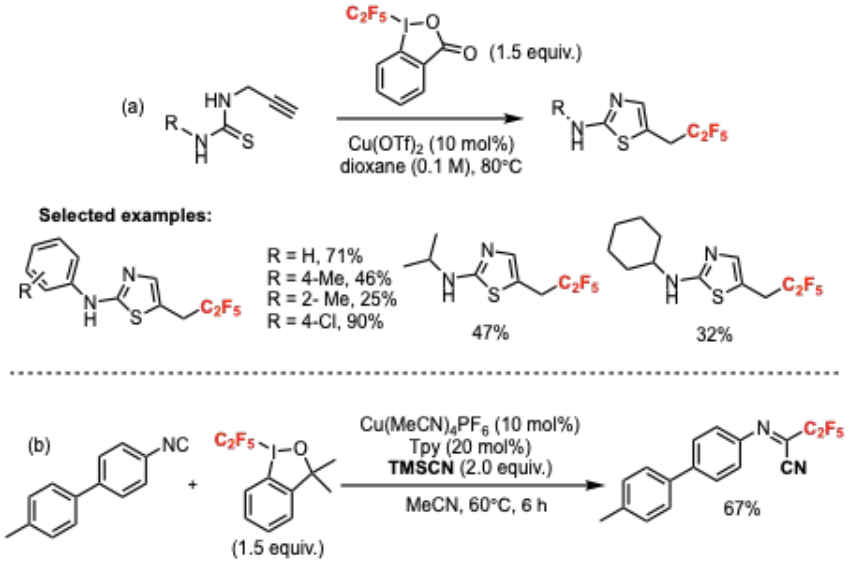
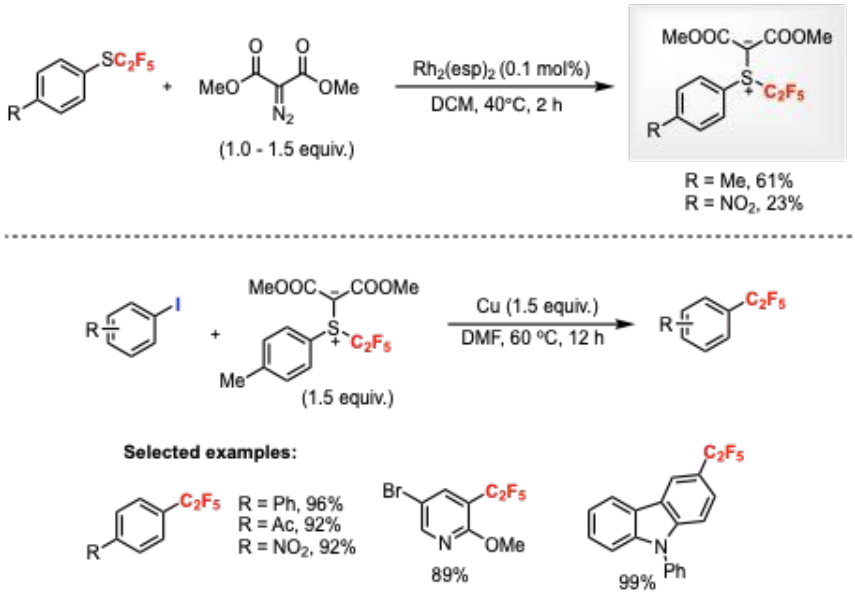


Scheme 5.3. Copper-catalyzed alkyne cyclization and cyanopentafluoroethylation of isocyanides using the C_2F_5–Togni reagent.

5.2 Sulfur-based pentafluoroethylating reagents

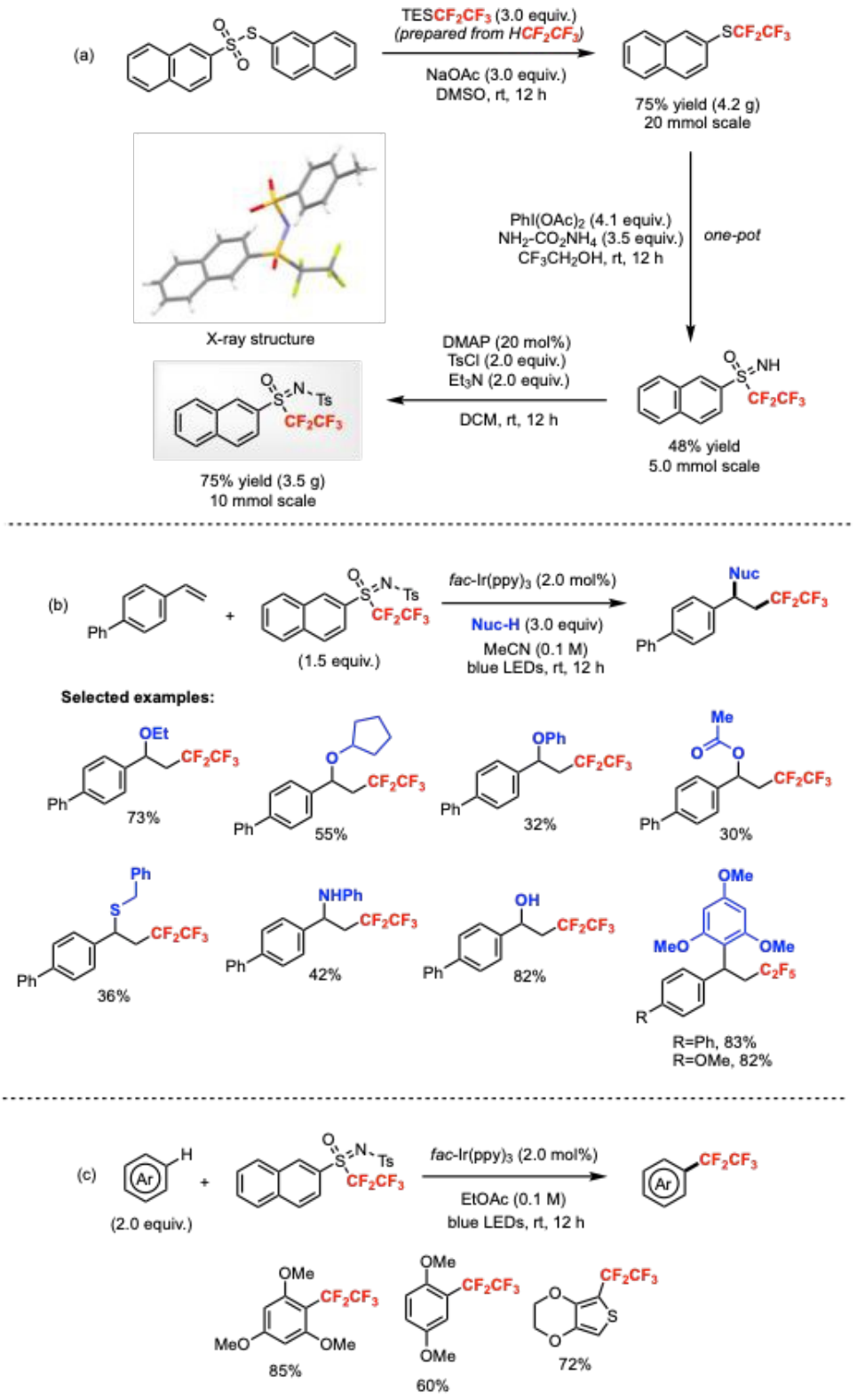
Shen/Lu and co-workers developed pentafluoroethyl-substituted *sulfonium ylides* as electrophilic pentafluoroethylating reagents (Scheme 5.4).[59] They were prepared by the cross-coupling of phenyl pentafluoroethyl thioether with dimethyl diazomalonate using rhodium catalyst. Efficient pentafluoroethylation of *β*-ketoesters, electron-rich heteroarenes and aryl iodides was achieved using these reagents.



Scheme 5.4. Preparation of pentafluoroethyl sulfonium ylides and application in copper-mediated pentafluoroethylation of aryl iodides.

Tsui/Magnier and co-workers developed a pentafluoroethyl *sulfoximine* reagent for the photocatalytic pentafluoroethylation-difunctionalization of styrene derivatives (Scheme 5.5a).[60] The reagent was prepared from a pentafluoroethyl sulfide which was synthesized according to a previously reported protocol.[47] Under mild photocatalytic conditions, the sulfoximine reagent could react with styrene derivatives tolerating various nucleophiles such as alcohol, water, thiol, carboxylic acid, amine and arene, leading to the difunctionalized

pentafluoroethylated products (Scheme 5.5b). Moreover, the challenging C-H bond pentafluoroethylation of arenes was also achieved photocatalytically (Scheme 5.5c).



Scheme 5.5. Synthesis of a pentafluoroethyl sulfoximine reagent and applications in photocatalytic pentafluoroethylation-difunctionalization of styrene derivatives and C-H bond pentafluoroethylation of arenes.

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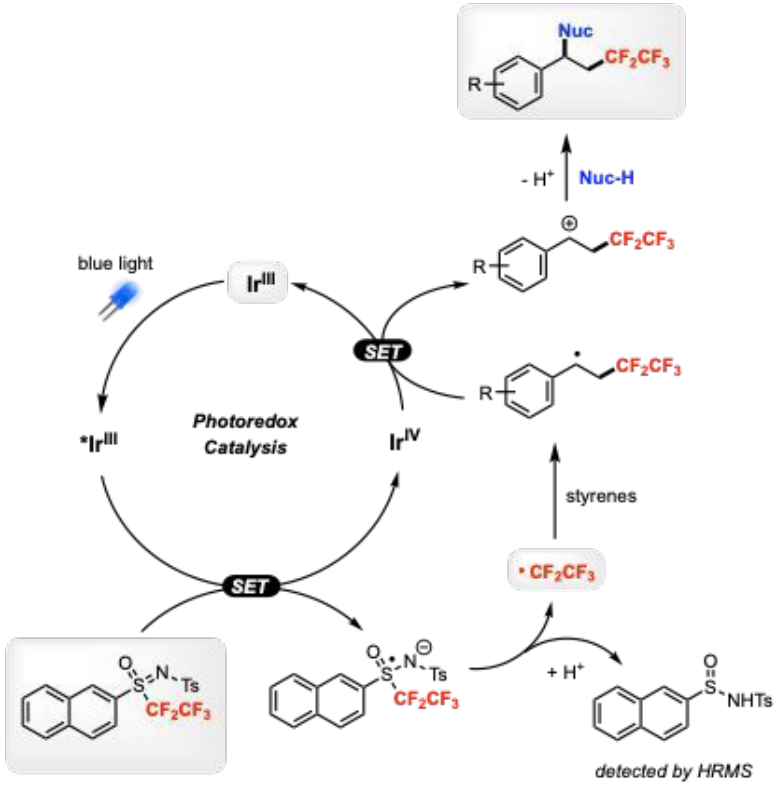
The mechanism involves the release of C_2F_5 radical from sulfoximine in the photoredox cycle, which then adds to styrene leading to the formation of a carbocation trapped by nucleophile (Scheme 5.6). This pathway would be a more efficient and green method for the generation of C_2F_5 radical compared to the copper-based methods (*c.f.* Section 2.1).



Scheme 5.6. Proposed mechanism for the photocatalytic pentafluoroethylation-difunctionalization of styrene derivatives using the pentafluoroethyl sulfoximine reagent

6. Miscellaneous pentafluoroethylating reagents

Pentafluoropropionic acid, pentafluoropropionic anhydride (PFPA), and pentafluoropropionate are readily available pentafluoroethylated compounds. The direct introduction of C_2F_5 groups into (hetero)aromatic rings using these reagents would be attractive. However, the oxidation of perfluoroalkylacetates is challenging due to their high redox potentials, which are beyond the accessible potential range of most photocatalysts. To address this issue, Stephenson and co-workers in 2016 developed a photoredox system using pyridine *N*-oxides as reagents for the decarboxylation of TFAA and PFPA as perfluoroalkyl sources (Scheme 6.1).[61] This protocol operated under mild conditions and could be scaled up to even kilogram quantities in flow, demonstrating its practicality for preparative and industrial applications. The presence of EDA complexes was evidenced by visible absorption and characteristically linear relationship between their charge-transfer absorbance energy. Upon photoexcitation, these EDA complexes undergo electron transfer leading to the

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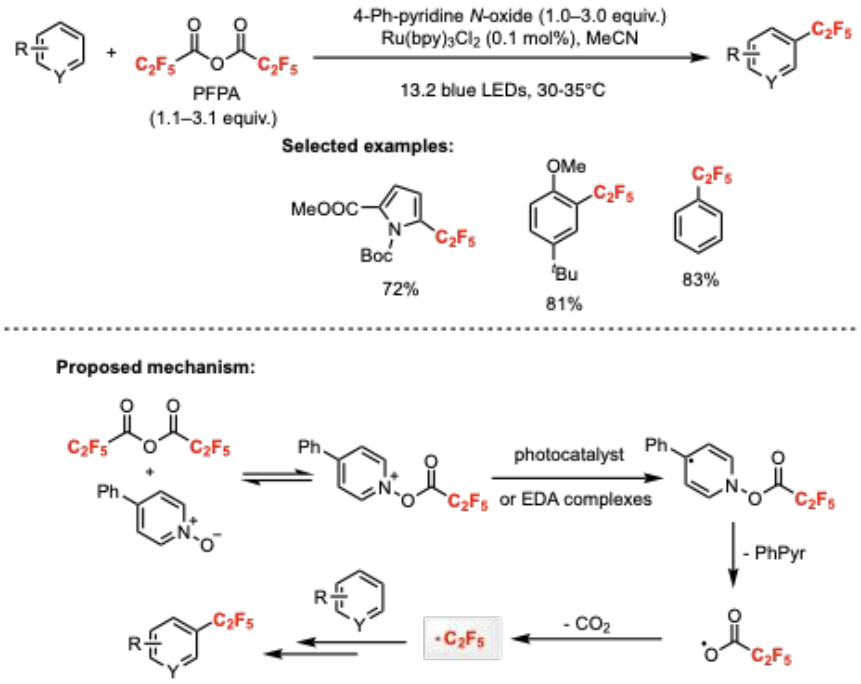
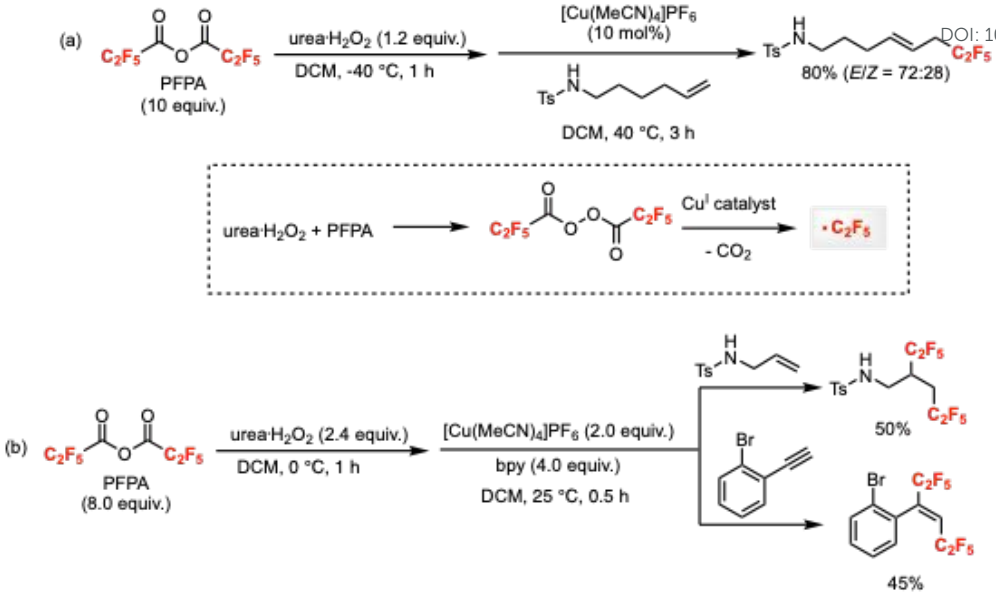
fragmentation of the acylated pyridine *N*-oxide to generate the C_2F_5 radical, which subsequently adds to electron-rich arenes followed by re-aromatization to give the pentafluoroethylated products. Su and co-workers later on discovered an acid-triggered reactivity umpolung of acetoxime esters, enabling direct generation of fluoroalkyl radicals from readily available fluoroalkyl anhydrides under visible light.[62] This mechanistically distinct strategy eliminated the need for preformed *N*-oxide adducts and extended the scope to include electron-deficient (hetero)arenes and various fluoroalkyl groups.



Scheme 6.1. Photochemical pentafluoroethylation of (hetero)arenes using pyridine *N*-oxides and pentafluoropropionic anhydride (PFPA).

In addition to photo-induced pentafluoroethylation using PFPA, copper was also found to be an efficient catalyst. Sodeoka and co-worker reported a perfluoroalkylation of unactivated alkenes using acid anhydrides including PFPA (Scheme 6.2a).[63] In their reaction system, PFPA reacts with urea·H_2O_2 to generate a diacyl peroxide, which undergoes Cu^{I}-catalyzed decarboxylation to afford a pentafluoroethyl radical. The radical then adds to the unactivated alkene eventually leading to the desired pentafluoroethylated product. In their subsequent work, the authors extended this strategy to achieve Cu-mediated 1,2-bis-pentafluoroethylation of alkenes and alkynes (Scheme 6.2b).[64] Notably, the addition of bpy ligand significantly improved the reaction yields.



Scheme 6.2. Copper-catalyzed/-mediated pentafluoroethylation of unactivated alkenes and alkynes using pentafluoropropionic anhydride (PFPA).

Pentafluoropropionate has been shown as an economical C_2F_5 source in the preparation of a pentafluoroethyl copper reagent. Mikami and co-workers employed ethyl pentafluoropropionate to obtain CuC_2F_5 in virtually quantitative yield (Scheme 6.3).[65] The CuC_2F_5 reagent prepared was successfully applied to the pentafluoroethylation of aryl bromides and aryl boronic acids.

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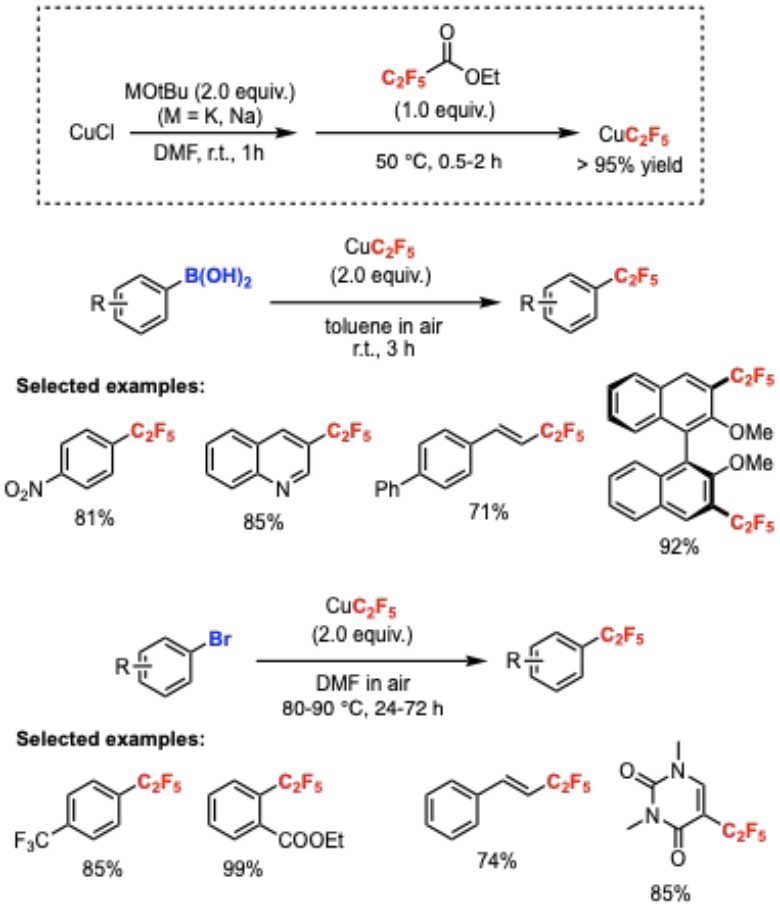

Scheme 6.3. Copper-mediated pentafluoroethylation using ethyl pentafluoropropionate as the C_2F_5 source.

More recently, Nocera and co-workers developed an electrophotocatalytic perfluoroalkylation that directly generates perfluoroalkyl radicals from native perfluoroalkyl carboxylates via Ag(II)-mediated LMCT excitation under visible light (Scheme 6.4).[66] This preactivation-free and redox-economical strategy differed fundamentally from previous systems thus achieving radical formation without *N*-oxide adducts or acid-induced umpolung chemistry. Other perfluoroalkyl groups such as CF_3 and C_3F_7 could also be installed by this method.

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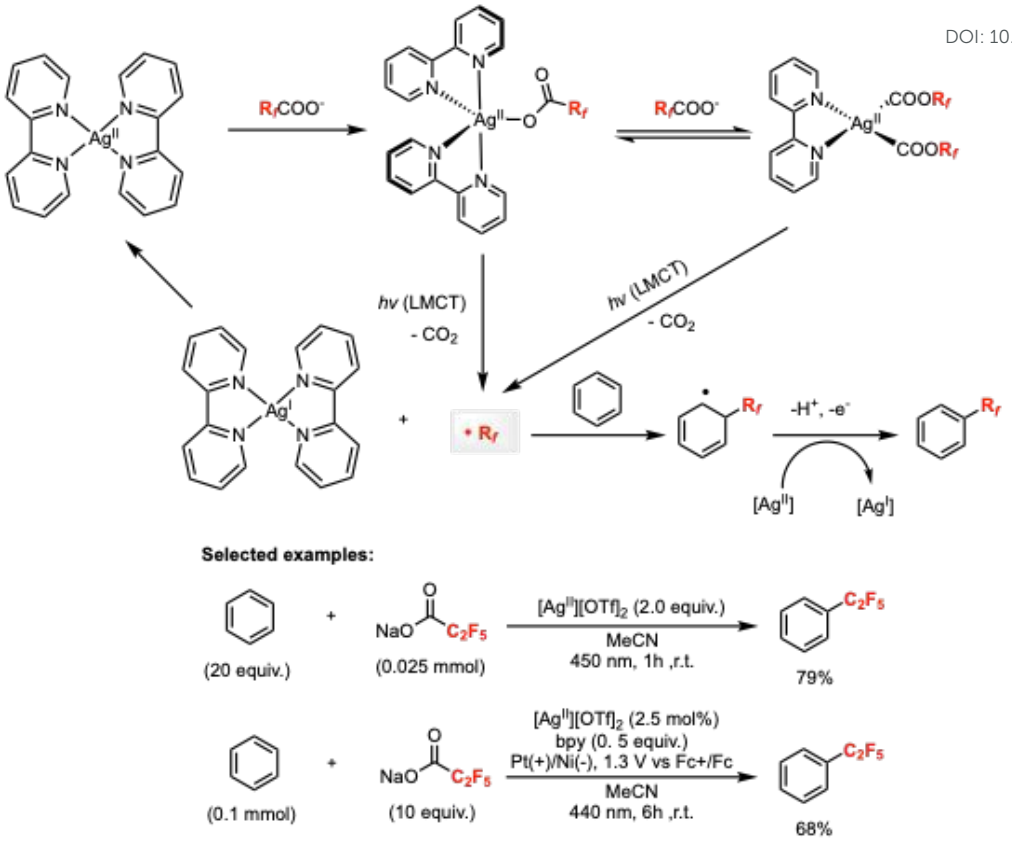

Scheme 6.4. Electrophotocatalytic pentafluoroethylation by LMCT excitation of Ag(II) pentafluoroethyl carboxylates.

Weng and co-workers reported a catalyst-free [3+2] cycloaddition for the synthesis of pentafluoroethylated heterocycles (Scheme 6.5).[67] A standout feature of this methodology was the utilization of chloropentafluoroethane (R115), a regulated byproduct of refrigerant production, as the pentafluoroethyl source. The authors successfully converted R115 into pentafluoropropanal O-(2,4-dinitrophenyl) oxime, which served as a stable precursor for pentafluoropropanenitrile. Upon treatment with triethylamine, the nitrile could be generated at room temperature almost quantitatively. Under transition-metal-free conditions, the *in situ* generated pentafluoropropanenitrile acted as a highly reactive electrophile in [3+2] cycloaddition reactions. Various dipole classes were demonstrated affording the pentafluoroethylated heterocycles in moderate to good yields.

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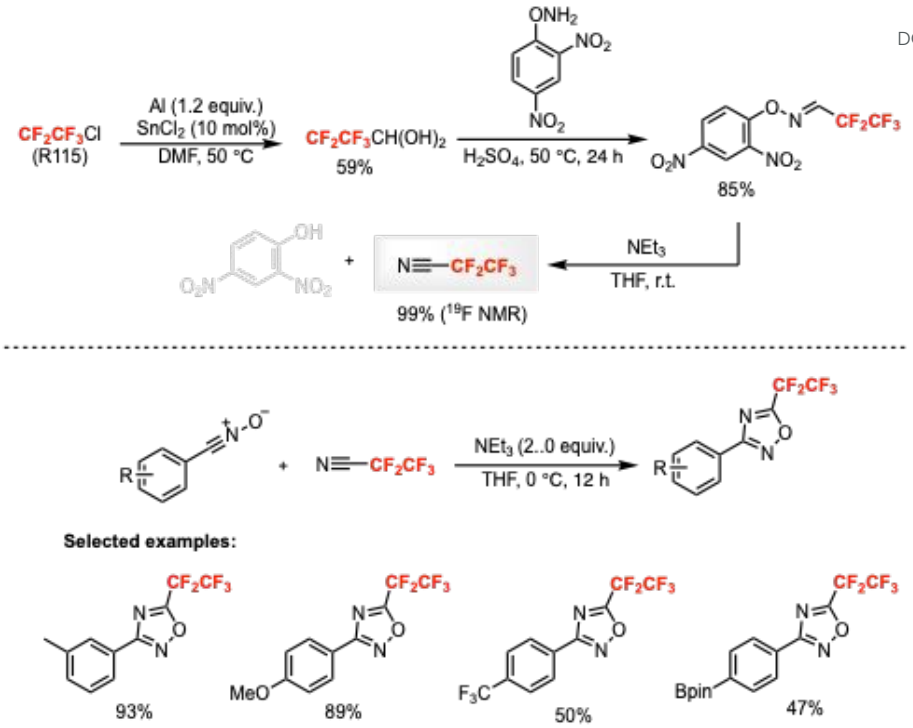

Scheme 6.5. Synthesis of pentafluoroethylated heterocycles via cycloaddition of pentafluoropropanenitrile derived from chloropentafluoroethane (R115).

7. Conclusion

In summary, the past decade has witnessed a tremendous progress in the development of reagents and methods for the synthesis of pentafluoroethylated compounds. From earlier transition metal-based [MC_2F_5] reagents and the use of C_2F_5H gas to the latest silicon-, iodine- and sulfur-based pentafluoroethylating reagents, chemists now have a much more complete toolbox for preparing structurally diverse compounds containing the C_2F_5 groups. These efforts will certainly have an impact on the future applications of pentafluoroethylated molecules in drug discovery. Furthermore, the pentafluoroethyl group can serve as synthetic handle for other emerging fluorinated motifs through C-F bond activation. Tsui and co-workers have demonstrated that pentafluoroethylated alkenes can serve as useful building blocks for synthesizing polyfluorinated alkenes containing a unique F- and CF_3-substituted sp^2-carbon (Scheme 7.1).[68] Their methods adopted a "defluorinative functionalization" strategy,[69] including rhodium-catalyzed defluoroarylation, [68a] copper-catalyzed defluoroborylation[68b] and defluorosilylation, [68c] and palladium-catalyzed defluorofunctionalization,[68d] for constructing carbon-carbon and carbon-heteroatom bonds in the products. More importantly, the reactions exhibited excellent levels of stereoselectivities.

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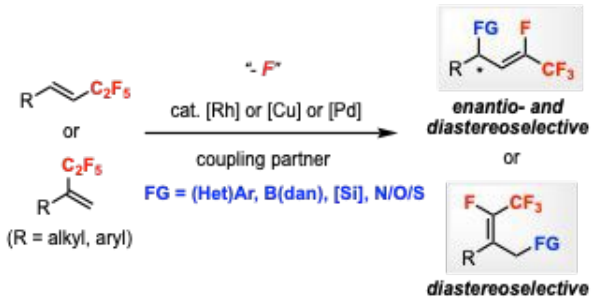
Thus, future works in this direction can be pursued where one or more C-F bonds in the C_2F_5 group is activated and functionalized selectively resulting in novel fluorinated compounds.



Scheme 7.1. Transition metal-catalyzed stereoselective defluorinative functionalization of pentafluoroethylated alkenes.

Author contributions

Yihan Tang: Conceptualization, Writing – original draft. Tao Dong: Conceptualization, Writing – original draft. Gavin Chit Tsui: Conceptualization, Supervision, Writing – review & editing, Funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Acknowledgements

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.