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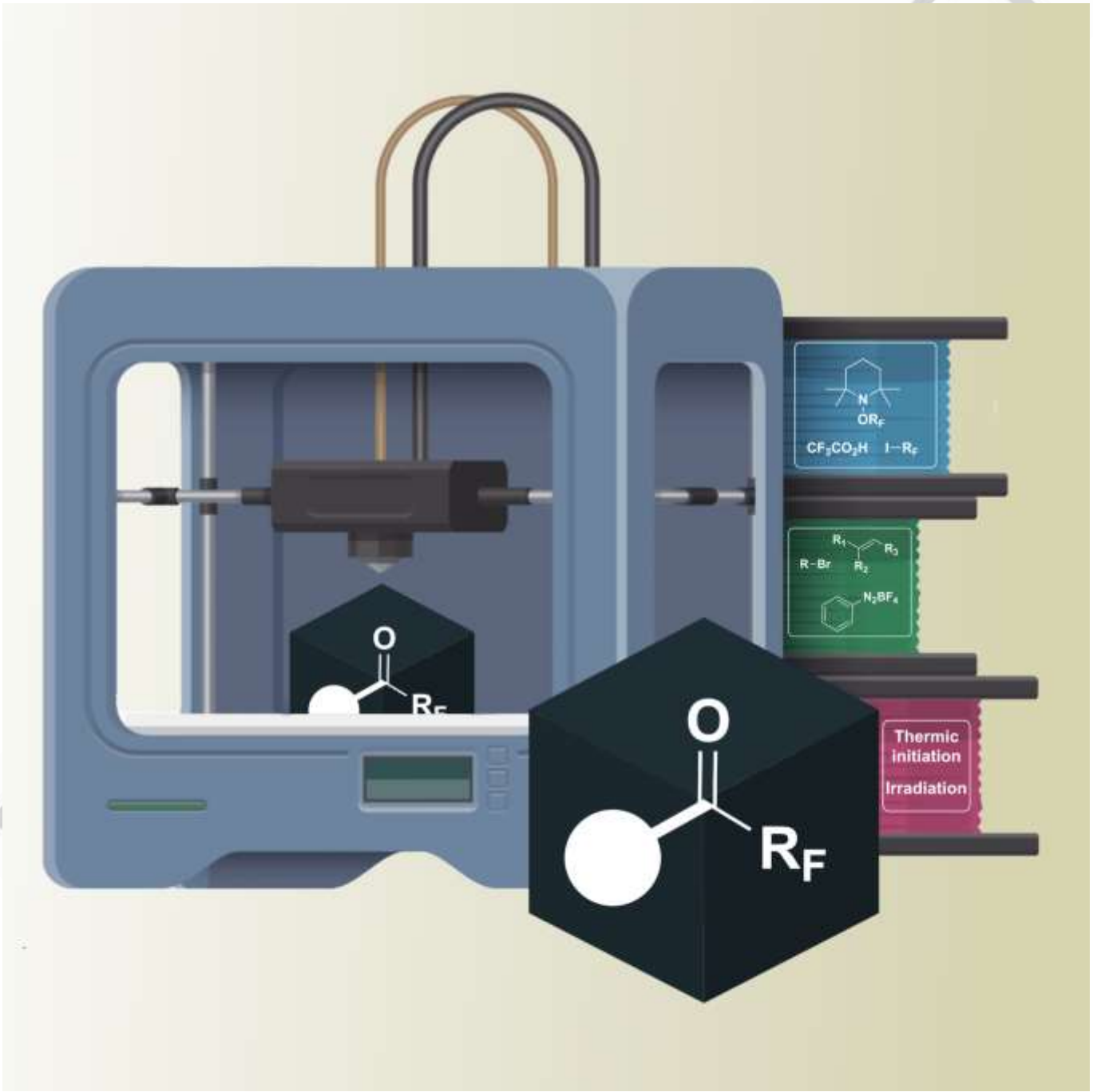
REVIEW

Direct Introduction of Perfluoroacyl (-COR_F) Groups into Organic Substrates

Sebastian Barata-Vallejo,*[a,b] Damian E. Yerien,[a] Agustin A. Zottola,[a] and Al Postigo*[a]



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REVIEW

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Abstract: The direct addition of perfluoroacyl (-COR_F) groups to organic frameworks has seen a resurgence in interest due to the benefits of these groups in late-stage modification of pro-drugs and biologically active compounds, helping to identify new active leads. The presence of -COR_F groups positively impacts the structure-activity relationships of these compounds. In that sense, both polar methods and radical protocols have been developed for the direct syntheses of trifluoromethyl and perfluoroalkyl ketones. In particular, methodologies to tame the unstable trifluoroacyl radical, which could be a key intermediate in the late-stage syntheses of trifluoroacyl-substituted compounds, has allowed much progress in this area. In the next sections, the direct incorporation of perfluoroacyl groups into (hetero)aromatic compounds, -COR_F substitutions at C_{sp^3}-H, alkyl halides, alkenes, amides, and N-atoms will be discussed in detail, suggesting the future directions and perspectives in the field. These known reactions are summarized in Table 1.

1. Introduction

Fluorine-containing compounds are prevalent in pharmaceuticals, agrochemicals, and materials sciences because of their enhanced physicochemical properties, including high thermal and chemical stability, lipophilicity, and strong electronegativity, which contribute to increased biological activity.[1] Among them, trifluoromethyl or perfluoroalkyl ketones constitute a significant class of fluorine-containing functional groups commonly found in bioactive targets.[2] Recent studies indicate that these modified derivatives exhibit potential as enzyme inhibitors targeting Herpesvirus protease,[3] Histone deacetylase,[4] SARS-CoV 3CL protease,[5,6] and also serve as precursors for clinically utilized glucocorticoid receptor agonists, among other medicinal uses (Figure 1).[7]

The notable properties of the trifluoromethyl ketone group in bioactive compounds result from the strong electron-withdrawing nature and large hydrophobic domain of the CF_3 group, combined with the ketone's tendency to form hydrates and other tetrahedral adducts.

Furthermore, they serve as potent and selective coupling reagents, enabling the incorporation of trifluoromethyl or perfluoroalkyl groups into a broad array of substrates.[8] In that line, trifluoromethyl ketones undergo various transformations such as reduction[9] and nucleophilic addition,[10] making them valuable tools in advancing new synthetic methodologies and creating a new chemical space.

Trifluoromethyl or perfluoroalkyl ketones[11] could be accessed through two different methodologies, *i*) either from a carbonyl source and a separate fluorine source, indirect methods; or *ii*) through direct routes, which employ reagents which bear the carbonyl and the fluoroalkyl moiety in their scaffolds.

Indirect methods to obtain perfluoroacyl -substituted compounds (R-COR_F or Ar-COR_F) rely on the perfluoroalkylation of ketones. Li`s group reported an example of oxidative trifluoromethylation of aldehydes through (bpy)Cu-$(CF_3)_3$ in the presence of the Prakash reagent.[12]

Prakash and co-workers developed in 2021 a Cu-mediated trifluoromethylation of carboxylic acids by *in situ* generation of acyloxyphosphonium electrophiles with PPh_3.[13]

On the other hand, direct methods that contemplate the introduction of the -COR_F group by radical routes (i.e.: the perfluoroacyl radical)[14] are challenging due to decomposition of the radical precursor into CO and the fluoroalkyl radical.[15] An ideal precursor of trifluoroacyl radical is trifluoroacetic anhydride (TFAA).[16] There have been studies relying on the use of TFAA as trifluoromethylating reagent,[17] purporting to the instability of the trifluoroacyl radical. Other trifluoroacetylating reagents, such as ethyl trifluoropyruvate,[18] 2-(trifluoromethyl)-1,3-dioxolane-2-carboxylic acid (a masked trifluoroacetyl reagent),[19a] trifluoroacetic acid,[20] or TEMPO-C_2F_5,[21] have been proposed as trifluoroacetylating reagents.

In the early 1990s, Balenkova and colleagues[22] described a method involving the activation of TFAA using a freshly generated BF_3(gas)/Me_2S complex at around - 60 °C. This method enables direct olefinic trifluoroacetylation, presumably through an electrophilic pathway. TFAA was also employed[23] for the site-selective trifluoroacetylation of dimethylamino-substituted pyridines in refluxing benzene. However, these methods employed harsh reaction conditions or unfriendly solvent systems. There is a recent review article on trifluoroacetylation and hydroxytrifluoroethylation[24] reactions; however, this latter review only treats three examples and is limited to trifluoroacylation reactions of alkenes[25,26] and alkyl bromides.[27]

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We herein study the direct introduction of -COR_F groups (R_F = C_nF_{2n+1}, n≥1), into (hetero)aromatic compounds, substitutions at $C_{sp}{}^3$-H, alkyl halides, alkenes, amides, and the trifluoroacetylation of *N* atoms. Also, some miscellaneous reactions are contemplated. In doing so, it will become apparent that direct methods for introducing -COR_F motifs are gaining advantages over indirect methodologies, as far as late-stage strategies are concerned and friendlier reaction conditions. These reactions are summarized in Table 1.

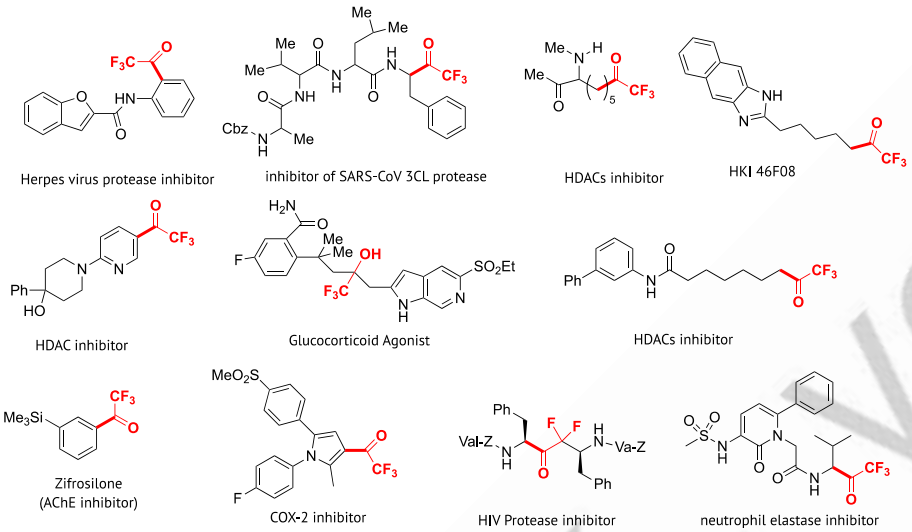
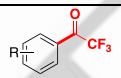
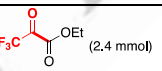
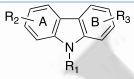
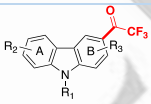
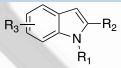
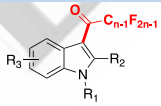
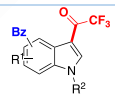
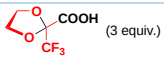
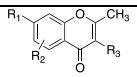
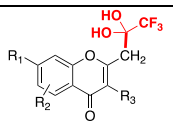
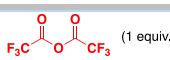
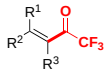
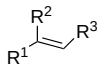
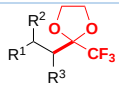
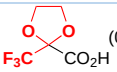
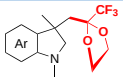
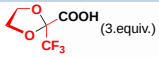
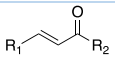
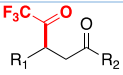
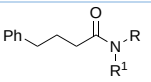
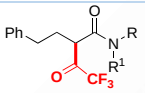
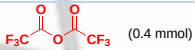
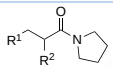
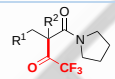
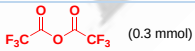
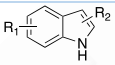
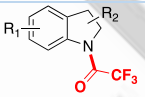
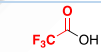
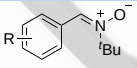
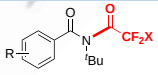
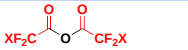


Figure 1. Selected examples for trifluoroacetyl-containing bioactive structures (HDACs inhibitor: Histone deacetylase inhibitor; HKI 46F08: a novel potent HDAC inhibitor).

Table 1. Direct trifluoroacetylation reactions of (hetero)arenes, C(sp^3)-H, alkyl bromides, alkenes, amides, and the trifluoroacetylation of *N* atoms.

Entry	Substrate	Product	Reaction conditions	Reference
1			 (2.4 mmol) Cu_2O (25 mol%) CH_2Cl_2 : DMSO 17: 1 (2.12 mL) r.t., 16 h	[18]
2			$(CF_3CO)_2O$ (10 equiv.) CF_3COOH (10 equiv.) DCE, 100 °C air 10- 24 h	[28]
3			$C_nF_{2n+1}I$ (3 equiv.) $Na_2S_2O_4$ (3 equiv.) DMSO:CH_3CN:H_2O (1:2:1), 1 mL 100 °C, 4 h	[29a]
4			$(CF_3CO)_2O$ (0.375 mmol) PhCOCl (0.5 mmol) $FeCl_3$ (40 mol%) DCE (2 mL), 80 °C, 4 h	[30]
5	Het-H		 (3 equiv.) $PhI(OCOMe)_2$ (3 equiv.) MeCN (2 mL) 70 °C, Ar, 24 h	[19a]
6			1) $(CF_3CO)_2O$ (1.5 mL) CF_3COOK (1 equiv.) reflux, 16 - 24 h 2) H_2O (excess)	[31]

7	**R–Br**		 (1 equiv.) Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$ (2 mol%) Ph_3SiH (4 equiv.) 2,6-di-*n*-propoxypyridine (1 equiv.) K_2HPO_4 (0.3 equiv.) *tert*-butyl methyl ether, 0.33 M N_2, rt, Blue LEDs (30 W), 12 h	[25]
8			$Ir(ppy)_3$ (1 mol%), TFAA (2.0 equiv) blue LEDs EtOAc (2.0 M) 12h	[27]
9			 (0.22 mmol) 4CzIPN (2 mol%) Cs_2CO_3 (1.2 equiv.), DMF (2 mL, 0.1 M) 456 nm Kessil, r.t., 15 h	[26]
10			 (3.equiv.) $PhI(OCOMe)_2$ (3 equiv.) THF (2 mL) 30 °C, Ar, 24 h	[19a]
11			1) **CF_3CO_2Et** (10 equiv.); TMSCl (5 equiv.); Mg (4 equiv.) 2) *p*-TsOH (10 mmol); THF (3 mL), 50 °C, 4 h	[32]
12			 (0.4 mmol) 2,4,6-colidine DCE, rt, 24h	[33]
13			 (0.3 mmol) 2,4,6-colidine DCE, rt, 24h	[33]
14			 (24 equiv.) $(CH_3)_3N$-BH_3 (0.5 equiv.) CH_3CN (2 mL) 100 °C, air, 3 h	[20]
15			TEMPO-CF_2CF_3 (0.3 mmol) MeCN (2 mL), 40 °C, 12 h	[21]
16			 (0.60 mmol) X = F, H THF (5 mL) 25 °C, 1 h	[34]

Sebastián Barata-Vallejo was born in General Villegas (Argentina) and holds degrees in Pharmacy (2007) and Biochemistry (2010). He obtained his Ph.D.degree (2012) at the University of Buenos Aires, studying radical reactions in aqueous and microheterogeneous media under the supervision of Prof. A. Postigo. He has been a research fellow and held several postdoctoral positions at the Istituto per la Sintesi Organica e la Fotoreattività (ISOF), Consiglio Nazionale delle Ricerche (CNR), Bologna, Italia, under the supervision of Dr. C. Chatgilialoglu, studying biomimetic radical reactions and their mechanisms. He is currently a researcher at the National Council for Scientific and Technical Investigation, CONICET (Argentina), research associate at ISOF-CNR, Bologna, Italy, and assistant professor at the Chemical Sciences Department, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. His research activities focus on radical organic chemistry, in particular carbon- and sulfur-centered radicals reactivity, fluoroalkylation reactions by radical pathways and photocatalysis.

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Damian E. Yerien was born in Argentina and obtained his Biochemistry degree from University of Buenos Aires in 2014. He obtained his Ph.D. degree (2019) at the University of Buenos Aires studying synthetic and mechanistic aspects of radical perfluoroalkylation reactions through photoredox catalysis, under the direction of Prof. Dr. Al Postigo. He is currently a National Argentine Research Council research member and a Teaching Assistant at the Department of Chemical Sciences, Faculty of Pharmacy and Biochemistry, University of Buenos Aires.

Agustin A. Zottola was born in Buenos Aires, Argentina. He earned a degree as a Chemical Technician from Technical School No. 27 "Hipólito Yrigoyen" (CABA, Argentina) and is currently completing his Pharmacy studies at the University of Buenos Aires. Since 2018, he has been a Laboratory Teaching Assistant in the Chemical Sciences Department, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. In 2022, he began an internship as a Research Assistant, focusing on radical reactions applied to the fluoroalkylation of organic substrates under the supervision of Dr. Sebastián Barata-Vallejo and Dr. Al Postigo.

Al Postigo was born in Argentina and obtained his M.Sc. degree from the University of Buenos Aires in 1986. He moved to Canada in 1990, and obtained his Ph.D. from McMaster University in 1994, under the direction of Prof. Dr. W. J. Leigh. After postdoctoral positions in Canada, he returned to Argentina and worked with Prof. Dr. R. Rossi at the University of Córdoba in the area of radical ion reactions. He held assistant and associate professorship positions at the University of Córdoba, University of Buenos Aires, and University of Belgrano. He is currently full professor of Organic Chemistry at the Department of Chemical Sciences, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. His interests are in the areas of radical chemistry, both carbon-centered radicals and metal-centered radicals. He is devoted to studying radical reactions of these species in water and non-conventional media.

2. Introduction of -COR$_F$ into (Hetero)aromatic Compounds

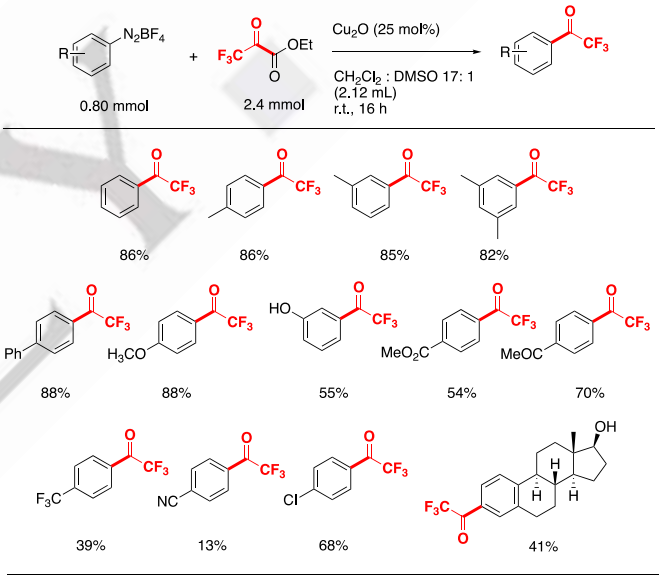
(Hetero)aromatic backbones substituted with trifluoroacyl groups have found relevant applications in medicinal chemistry, such as inhibitors of Herpes virus protease, histone deacetylase, or COX-2 inhibitors (see Figure 1); consequently, research in the late synthesis of these compounds is becoming an increasingly active area of study.

Reported direct methods for the trifluoroacetylation of aromatics rely on the use of $CoCl_2$ catalyst, TFAA as $COCF_3$ source, using TFA as solvent, at 100 °C, for 15 days.[35] Other protocols involve Friedel Crafts acylations,[36] Grignard reactions,[37] *ortho*-lithiation,[38] or Wittig reactions with trifluoroacetamides.[39] Trifluoroacetylation of (hetero)aromatics has also been achieved with TFAA and $MgCl_2$ as catalyst.[40] The palladium-catalyzed cross coupling reaction of aryl trifluoroacetate with aryl boronic acids at 80 °C in the presence of P^{n}Bu$_3$ in NMP as solvent afforded trifluoroacetylated aryl derivatives in yields ranging from 17 to 80%.[41]

The electrophilic perfluoroalkylacylation of indoles has been achieved in 2016 by the use of perfluoroalkanoic acids at 100 °C for 2 – 10 h.[42]

Notably, these extreme reaction conditions led scientists to explore environmentally friendlier and more direct ways to achieve such substitutions.

In 2016, Wu, Weng and colleagues[18] reported the trifluoroacetylation of arenediazonium salts with ethyl trifluoropyruvate. The reaction entailed the use of a diazonium (tetrafluoroborate salt), trifluoropyruvate, Cu_2O as catalyst in CH_2Cl_2: DMSO 17: 1, at r.t. for 16 h. The scope of the transformation is illustrated in Scheme 1.



Scheme 1. Selected examples for the trifluoroacetylation of benzene diazonium salts.

The authors[18] also explored the usefulness of the reaction onto a complex structure such as that of an estradiol derivative (Scheme 1), affording good yield of substitution. The authors[18] also investigated the reaction mechanism. In the presence of radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) substrate 4-methylbenzene diazonium salt afforded a very low yield of the respective trifluoroacetylated product under the reaction conditions. The intervention of radical clock 2-propenyloxy-benzene diazonium tetrafluoroborate salt did not afford product. However, ring closure and reduced products were observed (Scheme 2A). A mechanistic proposal was developed by the authors[18] as illustrated in Scheme 2B.

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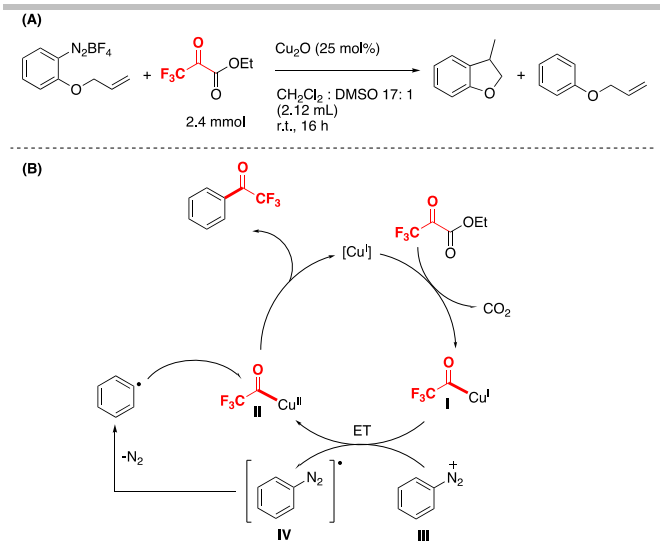
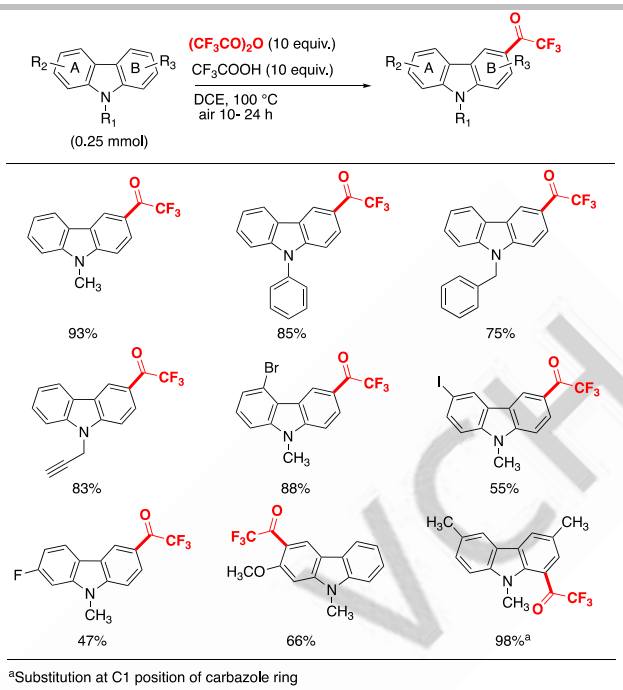


Scheme 2. (**A**) Ring closure and reduced products observed; (**B**) Proposed reaction mechanism.

In the mechanism proposed (Scheme 2B) decarboxylation of trifluoromethylpyruvate by Cu^I species affords intermediate **I**, which suffers electron transfer (ET) with benzene diazonium **III** to form a diazo radical intermediate **IV** and Cu^{II} species **II**. Diazo radical **IV** releases nitrogen to afford an aryl radical that reacts with **II** to form the final product and regenerate Cu^I species.

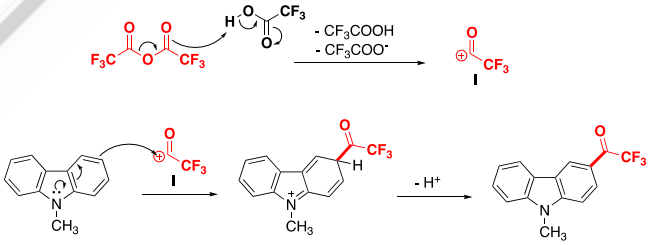
Jian and collaborators[28] reported on the synthesis of fluoroacylated carbazoles via Friedel-Crafts acylation. Optimized reaction conditions were achieved when carbazole derivatives were treated with trifluoroacetic anhydride (10 equiv.) and trifluoroacetic acid (10 equiv.) in 1,2-dichloroethane (DCE) as solvent, under air atmosphere at 100 °C for 10 - 24 h (Scheme 3). Regarding the substrate scope, the reaction performed well with carbazoles bearing different substituents such as alkyl, phenyl, propargyl and benzyl group at the *N*-9 position (Scheme 3). Conversely, acetyl group substitution on carbazole *N*-9 position afforded no reaction product probably due to the marked electron withdrawing properties of this group. Substituents including phenyl, bromine, fluorine and iodide on the A ring of carbazole provided the corresponding B-ring 3-trifluoroacetylated product in yields ranging from moderate to very good (Scheme 3). Particularly, carbazole substituted with an electron donating group such as -OCH_3 on ring A afforded the 3-trifluoroacetylated product. Notably, 3,6-disubstituted carbazoles, which have the most nucleophilic C-3 and C-6 positions occupied, yielded the 1-trifluoroacetylated products in excellent yields (Scheme 3). Other fluoroacylating reagents, such as mixtures of chlorodifluoroacetic acid and chlorodifluoroacetic anhydride or pentafluoropropionic acid and pentafluoropropionic anhydride, were also successfully employed as fluoroacylating agents affording the corresponding fluoroacetylated products in good to excellent yields.



[a]Substitution at C1 position of carbazole ring

Scheme 3. Selected examples for the fluoroacylation of carbazoles via Friedel-Crafts acylation.

Regarding some mechanistic aspects for the C-3 trifluoroacetylation of carbazoles, the authors[28] proposed the initial generation of acylium cation **I** (Scheme 4) from trifluoroacetic anhydride catalyzed by trifluoroacetic acid. Then, acylium cation **I** reacts with the corresponding carbazole via an electrophilic aromatic substitution mechanism to yield, upon proton loss, the trifluoroacetylated carbazole product (Scheme 4).



Scheme 4. Proposed reaction mechanism for the fluoroacylation of carbazoles via Friedel-Crafts acylation.

A direct *one-pot* tandem perfluoroalkylation-defluorination reaction towards the synthesis of perfluoroacyl 1*H*-indole derivatives[29b] was achieved by Leng and co-workers[29a] This approach provides a simple synthetic alternative for a fluoroacylation reaction because it employs commercially available, easy to handle and store perfluoroalkyl iodides along with $Na_2S_2O_4$ in aqueous media. Although this method does not utilize an -COR_F reagent *per se*, this one-pot procedure merits discussion as a direct strategy. Optimum reaction conditions were stablished when using 3 equiv. of perfluoroalkyl iodides, 3 equiv. $Na_2S_2O_4$ in DMSO: CH_3CN: H_2O (1:2:1) solvent mixture at 100 °C for 4 h. Several substituted indoles proved to be useful substrates for this reaction, though some substituents on the indole ring affected the reaction yield to some extent (Scheme 5). For instance, indoles substituted with methyl group at 2-position

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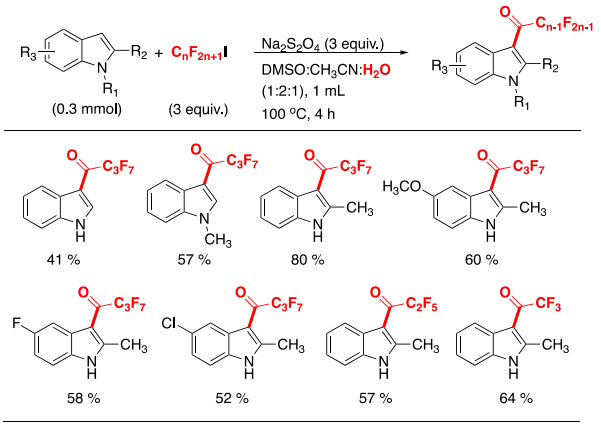
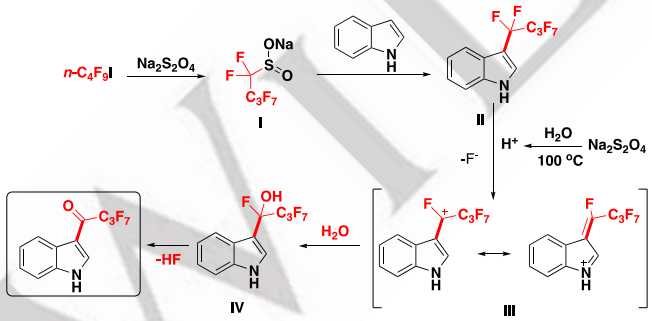
doubled the yield when compared with non-substituted indole. The reaction tolerated the presence of halide substituents; however stronger electron-withdrawing groups such as cyano or nitro afforded very low yields of products. Regarding the perfluoroalkyl iodide reagent, the reaction proceeded smoothly when perfluorobutyl, perfluoropropyl and perfluoroethyl iodides were employed (Scheme 5).



Scheme 5. Selected examples for the *one-pot* tandem perfluoroalkylation-defluorination reaction towards the synthesis of perfluoroalkyloylated indole derivatives.

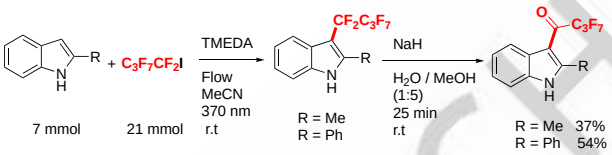
Based on some mechanistic studies, the authors[29a] proposed a reaction mechanism such as that shown in Scheme 6 for the perfluorobutanoylation of indole. Initially $Na_2S_2O_4$ reacts with *n*-C_4F_9I affording sodium perfluorobutylsulfinate **I** (Scheme 6) which reacts with indole affording perfluorobutyl indole **II** (Scheme 6). **II** further reacts with H^+, generated by thermal decomposition of $Na_2S_2O_4$ in the aqueous environment, to give carbocation intermediate **III** (Scheme 6) that reacts with water producing alcohol **IV** (Scheme 6) which upon HF loss yields the perfluoroacylated reaction product.



Scheme 6. Proposed reaction mechanism for the *one-pot* tandem perfluoroalkylation-defluorination reaction towards the synthesis of perfluoroalkyloylated indole derivatives.

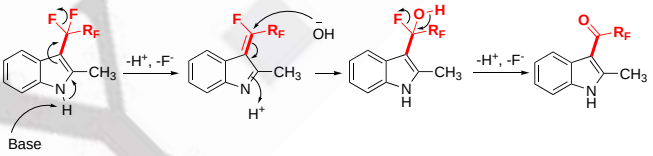
This latter methodology[29a] for obtaining 3-perfluoroalkylacyl-substituted 1*H*-indoles seems to be only feasible for the syntheses of 3-perfluoroalkyl-substituted indoles, since other perfluoroalkyl-substituted (hetero)aromatic compounds were not reported to undergo such transformations.

An alternative methodology was developed by Tallarek and colleagues[43] for indirectly activating the C-F bond of the fluorinated chain in the β-position of 1*H*-indoles using nucleophile species. Initially, they synthesized the corresponding 3-perfluorobutyl-1*H*-indole derivatives by activating a photoactive EDA complex between perfluorobutyl iodide and *N,N,N`,N`*-tetramethylethylenediamine, TMEDA, in MeCN as the solvent, under 370 nm LED irradiation in a flow chemistry setup. The subsequent step could be conducted without purifying the synthetic intermediate. Under basic conditions, in the presence of an H_2O : MeOH solvent mixture, the corresponding perfluorobutyl heteroaryl ketone was obtained in moderate yields (Scheme 7).



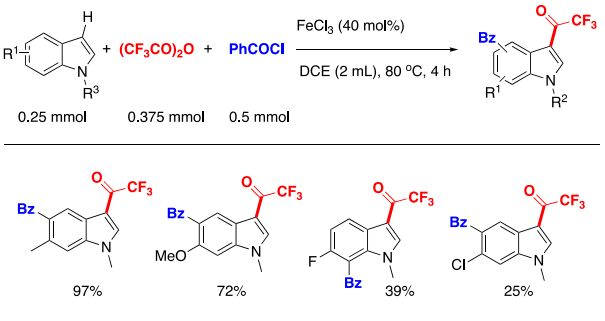
Scheme 7. Perfluoroalkylation of 1*H*-indoles followed by nucleophilic activation of the C-F bond in the fluorinated chain.

A proposed mechanism is depicted in Scheme 8, where loss of fluoride anion under basic conditions, and ulterior hydration and proton/fluoride eliminations produces the perfluoroalkyl acylated derivative.



Scheme 8. Activation of the C-F bond in the fluorinated chain: Proposed reaction mechanism.

In 2024, Wu, Wei, Liang and colleagues[30] reported the trifluoroacetylation of indole derivatives though the use of TFAA as trifluoroacetylating reagent, benzoyl chloride, $FeCl_3$ as catalyst, in DCE as solvent. A brief scope of the transformation is illustrated in Scheme 9.



Scheme 9. Selected examples for the trifluoroacetylation of indoles.

The proposed reaction mechanism is illustrated in Scheme 10. In the mechanism proposed (Scheme 10) the trifluoroacetylated indole derivative undergoes electrophilic substitution with benzoyl cation (**I**) produced from the $FeCl_3$-induced ET-reduction of benzoyl chloride to produce intermediate II which suffers re-aromatization to product.

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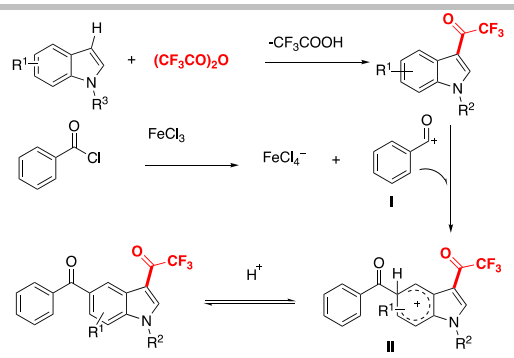
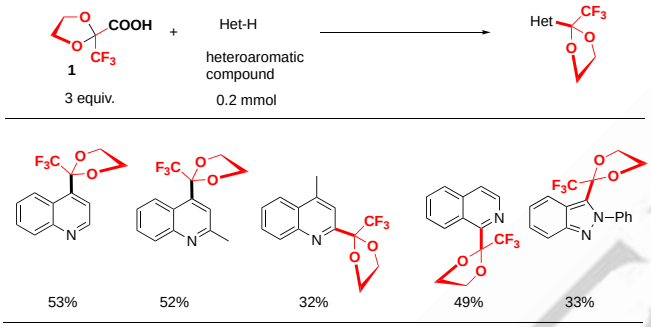


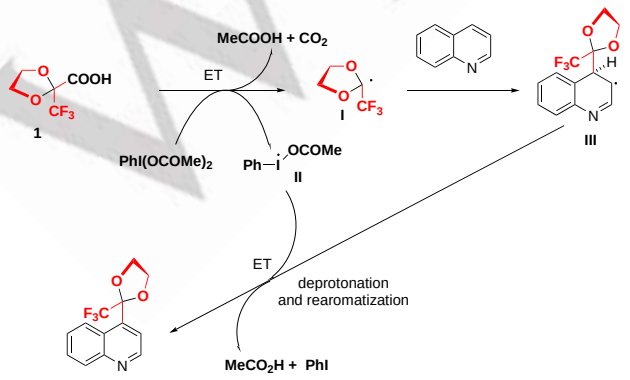
Scheme 10. Proposed reaction mechanism.

In 2024, Ye, Chen, Yang and colleagues[19a] developed a strategy for the trifluoroacetylation of (hetero)aromatic compounds[19b] by using a masked trifluoroacetyl reagent **1** in the presence of $PhI(OCOMe)_2$ as oxidant in MeCN as solvent, according to Scheme 11.



Scheme 11. Selected examples for the trifluoroacetylation of heteroaromatics with masked **1**.

The protected trifluoroacetal derivatives were deprotected by using BBr_3 in DCM at 0 °C in good yields. The authors[19a] investigated the reaction mechanism by using *N*-methyl-*N*-phenylmethacrylamide as an acceptor of the trifluoroacetal group in probe experiments in the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) (3 equiv.) or butylated hydroxytoluene (3 equiv.) affording traces of trifluoroacetylated derivative, suggesting a radical pathway. A proposed mechanism is given in Scheme 12.

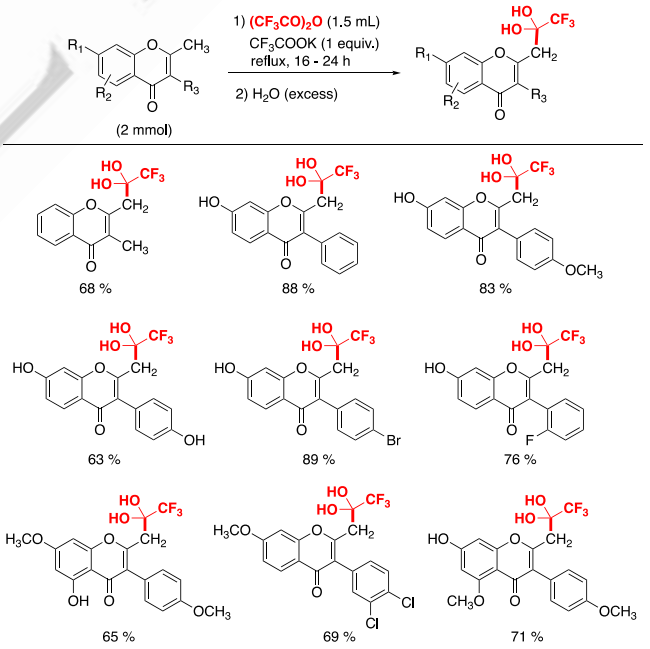


Scheme 12. Proposed reaction mechanism.

In the mechanism proposed (Scheme 12) an electron transfer (ET) between **1** and $PhI(OCOMe)_2$ takes place, affording intermediates **I** and **II**. Radical **I**, which is more resistant to decomposition than the trifluoroacetyl radical due to its longer lifetime,[44] substitutes the heteroaromatic C_{sp^2}-H bond to afford radical intermediate **III**, which undergoes an oxidative ET with **II** and ulterior deprotonation to afford the final product.

3. Trifluoroacetylation of C_{sp^3}-H bonds

Frasinyuk and co-workers[31] developed a methodology towards the trifluoroacetylation of 2-methylchromone derivatives. Optimized reaction conditions were achieved by refluxing the substrate for 16-24 h in the presence of an excess of trifluoroacetic anhydride and potassium trifluoroacetate (employed as base) under neat conditions followed by the treatment with water. The authors proved that the reaction proceeded with exceptional regioselectivity in the 2-methyl group as observed when a 2,3-dimethylchromone was employed as substrate (Scheme 13). The reaction exhibited broad functional group tolerance as demonstrated when performed on isoflavones bearing hydroxy, methoxy, halides and alkyl substituents (Scheme 13). Interestingly, compounds were isolated in the *gem*-diol form resulting from the favored addition of water to the C=O group bearing a CF_3 electron withdrawing substituent (Scheme 13).[31] This example constitutes the only reported substitution at C(sp^3)-H by the trifluoroacyl group.



Scheme 13. Selected examples for the trifluoroacetylation of 2-methylchromone derivatives. Compounds isolated in the gem-diol form.

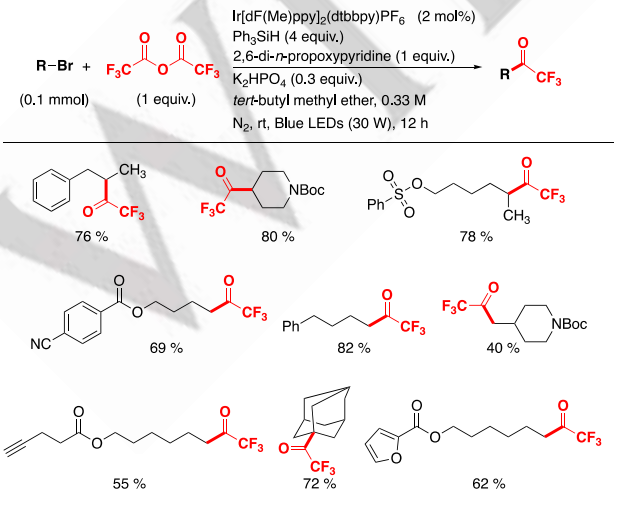
4. Trifluoroacetylation of Alkyl Bromides

Trifluoroacetic anhydride, TFAA, exhibiting a discernible reduction onset at approximately 1.2 V (vs. SCE), undergoes an

irreversible, exergonic, and reductive electron transfer (ET) process in the presence of a photocatalyst operating under oxidative quenching conditions. This process is expected to lead to the formation of the corresponding radical ion species. Subsequent fragmentation of the (O)C=O bond would likely favor the CF_3CO radical species (ΔG = -20.1 kJ mol^{-1} in favor of the trifluoroacyl radical) and trifluoroacetate anion. The reactive trifluoroacyl radical intermediate could then react *in situ* with an alkene substrate, ultimately forming trifluoroacylated adducts (see section 5). However, due to the limited lifetime of the liberated $CF_3(CO)$ radical and its tendency to fragment into CF_3 and CO,[44] the overall process requires carefully controlled reaction conditions. The utilization of an Ir photoredox catalyst was found to be effective, given the sufficiently low reduction potential of its excited state.

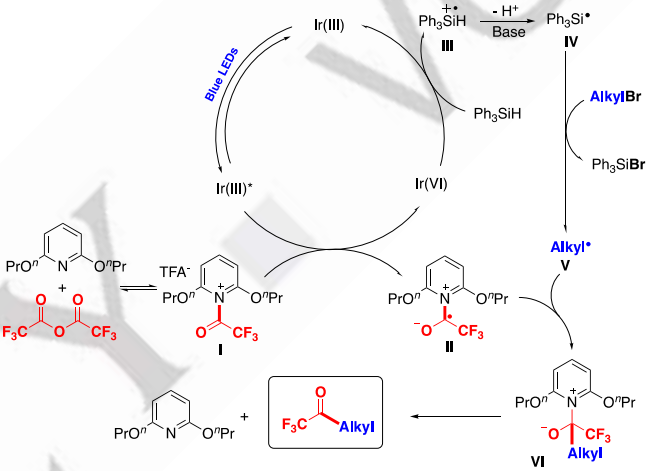
Shu and colleagues[25] developed a synthetic strategy for accessing trifluoromethylketones from alkyl bromides and TFAA by photocatalysis. This methodology highlights the use of TFAA as a precursor of trifluoroacetyl radicals, which are prone to undergo decarbonylation to trifluoromethyl radicals, by using 2,6-di-*n*-propoxypyridine as additive. Indeed, catalytic approaches for the direct synthesis of aliphatic trifluoromethyl ketones are highly sought after but still largely underexplored, mainly due to the instability of the trifluoroacetyl radical. Previous investigations have profited from the above mentioned decarbonylation process for generating trifluoromethyl radicals that have been trapped by alkenes or arenes to yield the corresponding trifluoromethylated products.[45]

The authors[25] conceived a novel approach to improve the stability of the trifluoroacetyl radical, facilitating a subsequent trifluoroacetylation process. After a careful analysis, optimum reaction conditions were established when employing $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$ as photocatalyst, Ph_3SiH as halogen atom transfer reagent, K_2HPO_4 as base, 2,6-di-*n*-propoxypyridine as additive in *tert*-butyl methyl ether as solvent and under blue LEDs (30 W) irradiation (Scheme 14). This methodology showed compatibility with a wide range of functional groups and various substitution patterns with respect to alkyl bromides (Scheme 14).



Scheme 14. Selected examples for the synthesis of trifluoromethylketones by photozatalyzed trifluoroacetylation of alkyl bromides.

Drawing on experimental results and existing literature, the authors[25] proposed the reaction mechanism illustrated in Scheme 15. Initially, trifluoroacetic anhydride and 2,6-di-*n*-propoxypyridine form adduct **I** (Scheme 15) which undergoes a single electron transfer with the excited photocatalyst Ir^{III}* to produce radical zwitterionic intermediate **II** (Scheme 15) and Ir^{IV}. Then, Ir^{IV} oxidizes triphenyl silane, regenerating Ir^{III} and forming radical cation **III** (Scheme 15). Deprotonation of **III** (Scheme 15) yields silicon-centered radical **IV**. A halogen atom transfer between the alkyl bromide substrate and **IV** (Scheme 15) generates triphenyl silane bromide and alkyl radical **V** which cross-couples with **II** to form zwitterionic intermediate **VI** (Scheme 15). Finally, the release of 2,6-di-*n*-propoxypyridine from **VI** (Scheme 15) yields the alkyl trifluoromethyl ketone reaction product.



Scheme 15. Proposed reaction mechanism for the synthesis of trifluoromethylketones by photozatalyzed trifluoroacetylation of alkyl bromides.

5. Trifluoroacetylation of Carbon-Carbon Double Bonds

The trifluoroacetylation of terminal dienes was accomplished by TFAA under Co-catalysis ($Na[Co(CO)_4]$).[46a] However, this was an isolated example, and the reaction conditions required careful temperature control and stepwise addition of reagents.

Katayev and colleagues[27] have developed a photocatalytic protocol to achieve direct chemo- and regio-selective trifluoroacetylation of alkenes. Optimization studies showed that the best yields were obtained using tris(2-phenylpyridine)iridium [$Ir(ppy)_3$] as the photocatalyst, trifluoroacetic anhydride (TFAA) as the radical source, and ethyl acetate as the solvent under blue light irradiation conditions.

Scheme 16 illustrates selected examples of the scope of this transformation. A wide range of commercially available alkenes yielded the desired α,β-unsaturated trifluoromethyl ketones in good to excellent yields. Aryl-substituted alkenes[46b] with both electron-withdrawing and electron-donating groups in *ortho*, *meta*, and *para* positions produced the corresponding products in yields ranging from 40% to 90%. Notably, this methodology is tolerant of halogen and ester groups, which remain unmodified.

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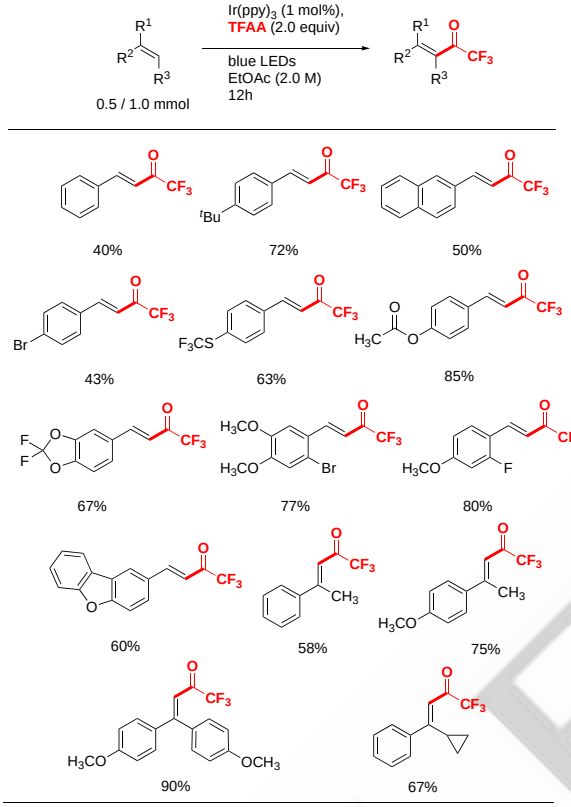
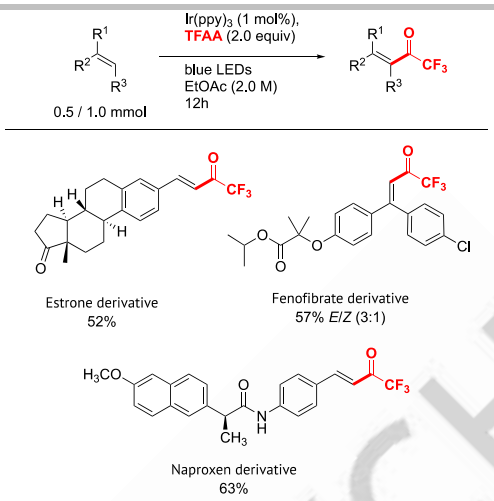
The authors also demonstrated the versatility of the methodology by trifluoroacetylating several complex and biologically relevant molecules, as depicted in Scheme 17. A fenofibrate derivative was functionalized with a 57% yield and good stereoselectivity. A derivative of the anti-inflammatory drug naproxen was trifluoroacetylated with a 63% yield, showing the reaction's tolerance of the amide functionality. The reaction was also tested on a steroid analogue, yielding 52% of the desired product.



Scheme 16. Visible-light promoted trifluoroacetylation of alkenes: selected examples.

The scalability of the reaction conditions was demonstrated by performing a gram-scale reaction of *p-tert*-butylstyrene under standard conditions, which yielded 2.6 g (67%) of the corresponding fluorinated compound.

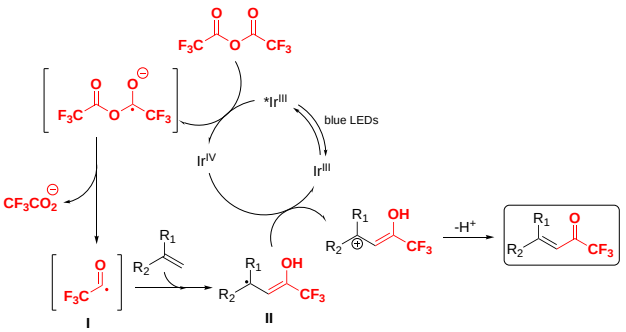


Scheme 17. Visible-light promoted trifluoroacetylation of alkenes: selected examples of complex and biological relevant molecules.

To elucidate the mechanism involved, several studies and determinations were conducted, including Stern-Volmer quenching experiments, photocyclovoltammetric measurements, kinetic isotope effects, and theoretical investigations. Scheme 18 illustrates the proposed catalytic cycle for the visible light-promoted trifluoroacetylation of alkenes. The cycle begins with a single electron transfer between the highly reducing species $*Ir^{III}$ [$E_0(Ir^{IV}/*Ir^{III})$ = -1.73 vs. SCE] and TFAA, resulting in the oxidized form Ir^{IV} and the trifluoromethylacyl radical **I**. The addition of radical **I** to the alkene forms the radical adduct **II**, which can then be oxidized by Ir^{IV}, yielding the α,β-unsaturated trifluoromethyl ketone and regenerating Ir^{III}, thus completing the photocatalytic cycle.

Kim and colleagues[26] employed an alternative strategy to achieve the trifluoroacetylation of double bonds by using a masked (protected) trifluoroacetyl group **1**, such as that illustrated in Scheme 19.

The reaction employed 2,4,5,6-*tetrakis*(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as photocatalyst under blue LED irradiation in the presence of radical precursor **1**, olefin and Cs_2CO_3 in DMF solution. Trifluoroacyl radical precursor **1** is a much more resistant radical that cannot undergo decarbonylation.



Scheme 18. Proposed catalytic cycle for the visible-light promoted trifluoroacetylation of alkenes.

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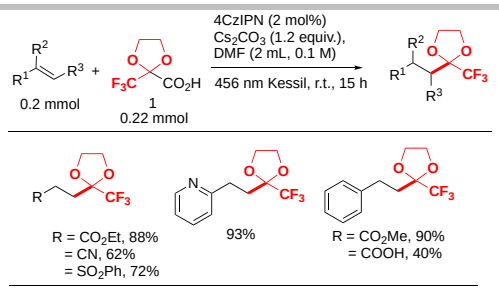
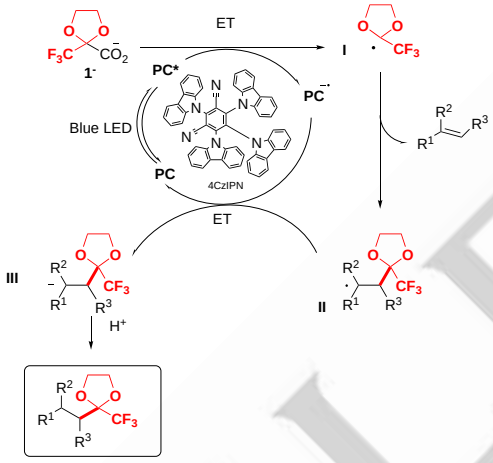


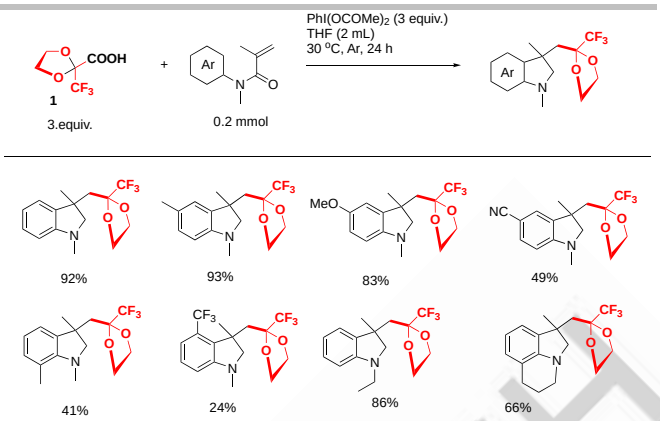
Scheme 19. Selected examples for the use of masked **1** as trifluoroacetylating reagent.

The radical mechanism of the reaction is quite similar to that shown in Scheme 12 (*vide supra*), with the proviso that the photocatalyst (i.e., 4CzIPN) undergoes a reductive quenching cycle after ET-oxidation of the deprotonated precursor **1** to CO_2 and 2-(trifluoromethyl)-1,3-dioxolanyl radical (**I**, Scheme 20). This latter radical (i.e.: **I**) adds to the double bond, to afford a radical intermediate **II**, which undergoes reduction by the lower oxidation state of the photocatalyst ($PC^{\bullet-}$), to afford carbanion **III** which is protonated in the reaction medium (Scheme 20).



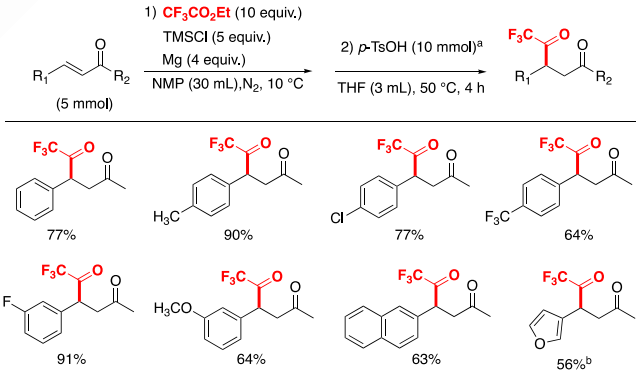
Scheme 20. Proposed reaction mechanism.

In 2024, Ye, Chen, Yang, and colleagues[19a] developed an alternative of the work of Kim[26] where an oxidative decarboxylation of the masked trifluoroacetyl precursor **1** was employed in the presence of $PhI(OCOMe)_2$ as oxidant. The scope of the reaction is illustrated in Scheme 21.



Scheme 21. Selected examples for the use of masked **1** as trifluoroacetylating reagent under oxidative conditions.

Maekawa and colleagues[32] reported on a two-step protocol for obtaining 1,1,1-trifluoro-2,5-diketones from benzalacetones in good to excellent yields by means of a magnesium-promoted reductive trifluoroacetylation followed by an acid-mediated deacetalization process. Optimized reaction conditions were established when dibenzalacetone was allowed to react with ethyl trifluoroacetate in the presence of chlorotrimethylsilane (TMSCl) and magnesium powder in *N*-methylpyrrolidone (NMP) as solvent. The corresponding acetal formed is then deacetalized without further purification in a subsequent step by treatment with *p*-TsOH in THF (Scheme 22). The reaction exhibits a broad substrate scope and substituents such as methyl and methoxy groups, as well halogen atoms and trifluoromethyl groups on the benzene ring are well tolerated (Scheme 22). Moreover, enones containing aromatic rings like the 2-naphthyl group and 3-furyl group yielded the corresponding products in good yields (Scheme 22).

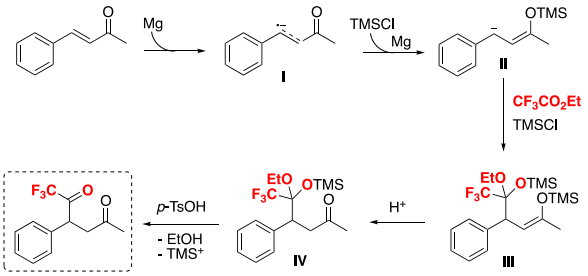


[a] One-fifth of crude acetal by weight from the first step.
[b] Step 2: concentrated H_2SO_4 (0.3 mL), THF (5 mL), 25 °C, 24 h.

Scheme 22. Selected examples for the synthesis of 1,1,1-trifluoro-2,5-diketones from benzalacetones by reductive trifluoroacetylation.

The authors[32] proposed a reaction mechanism shown in Scheme 23. Initially benzalacetone is reduced by Mg to yield radical anion **I** (Scheme 23) which is attacked by TMSCl, followed by a second electron transfer from Mg, to yield carbanion **II** (Scheme 23). Carbanion **II** further reacts with ethyl trifluoroacetate and TMSCl to afford reaction intermediate **III** (Scheme 23) which upon

hydrolysis at the quenching step yields acetal **IV** (Scheme 23). Upon treatment with *p*-TsOH in THF, acetal **IV** is transformed in the 1,1,1-trifluoro-2,5-diketone product (Scheme 23).

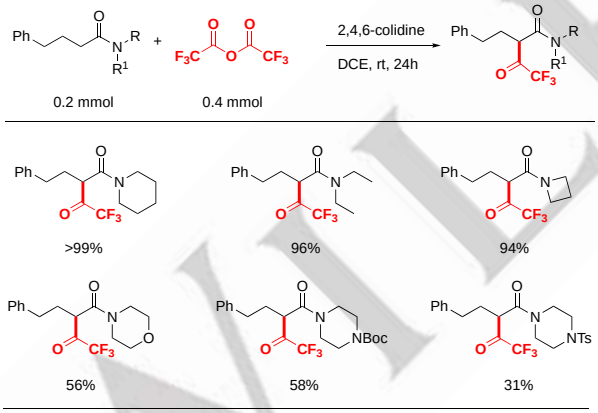


Scheme 23. Proposed reaction mechanism for the synthesis of 1,1,1-trifluoro-2,5-diketones from benzalacetones by reductive trifluoroacetylation.

6. Trifluoroacylation of Amides

Although there have been unprecedented advances in chemo-selective activation of amides,[47,48] amide-selective α-functionalization remains challenging. Enolate formation via deprotonation by a strong base and a subsequent reaction with electrophiles is the standard protocol for α-functionalization of amides.

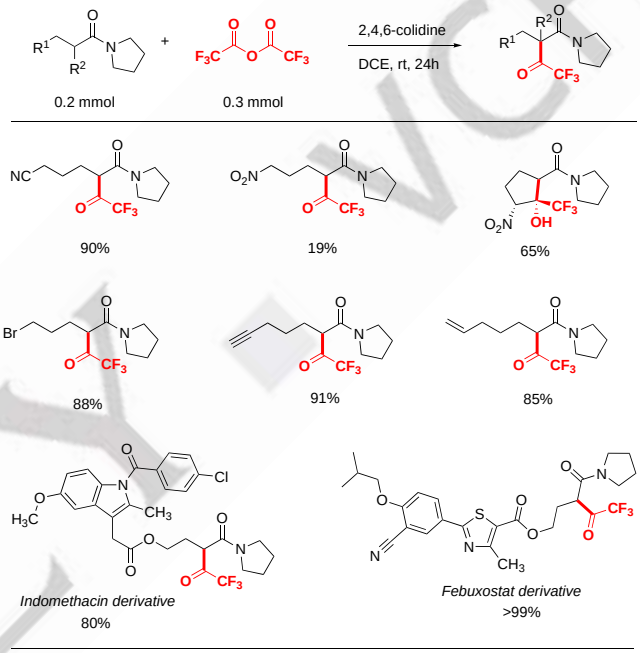
In 2023, Morita, Nakamura and co-workers[33] reported a method for accomplishing the α-trifluoroacetylation of tertiary amides. The optimized reaction conditions employed TFAA as a trifluoroacyl moiety source, 2,4,6-colidine as base, in DCE as solvent at room temperature.



Scheme 24. α-Trifluoroacetylation of tertiary amides: scope of the amine moiety in the amide substrate.

The authors[33] investigated the scope and limitations of the amine rest in the amide substrate (Scheme 24). For substrates derived from cyclic amines, such as piperidine and azetidine, the corresponding products were obtained with excellent yields. Also, very good yields were observed for reactions involving acyclic amines. However, lower yields were obtained for reactions with substrates derived from morpholine, Boc- and Ts-protected piperazine groups. The authors suggested that the electron-donating effect of the nitrogen atom in the amide is crucial for the activation of these substrates in the presence of trifluoroacetic anhydride.

Additionally, the scope of the transformation regarding to chemoselectivity was examined. As shown in Scheme 25, the reaction conditions were very well tolerated by several functional groups, including nitrile, alkene, alkyne, ester, nitro, and halide. However, with the nitro group, this substituent promoted the intramolecular cyclization of the α-trifluoroacetyl compound, resulting in only a 19% yield of the desired product. The protocol was also applied to the functionalization of bioactive compounds, such as indomethacin and febuxostat derivatives, achieving excellent yields. DFT calculations performed suggested the formation of an enamine as intermediate which played an important role in the chemoselectivity of the reaction pathway.



Scheme 25. α-Trifluoroacetylation of tertiary amides: amide scope.

7. Trifluoroacetylation of N Atoms from Amines and Nitrones

Relevant biological active compounds do exist containing the functionality N-COCF$_3$. Among them (Figure 2), isoxazole derivatives used as plant disease control agents,[49] pyrazole-3-carboxamides that exhibit microbicides for agriculture and horticulture,[50] or piperidinyl-substituted amides used for treatment of asthma, allergic disease, or inflammation.[51]

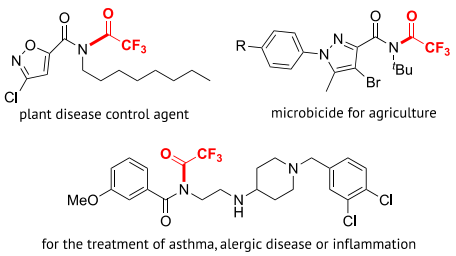


Figure 2. Biological active trifluoroacetylated amides

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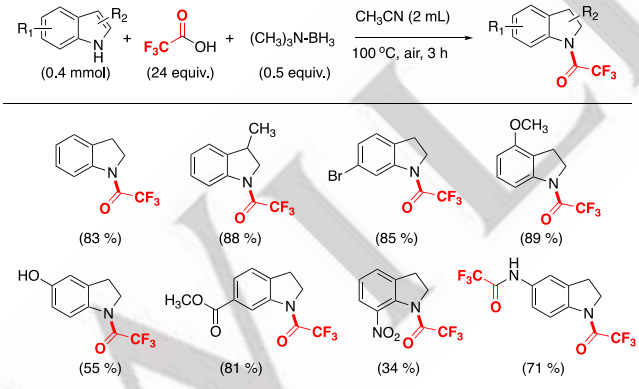
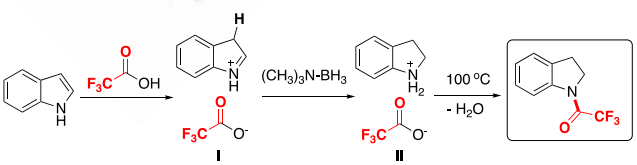
The trifluoroacetylation of amines or amides is generally accomplished by TFA under various conditions.[52] Trifluoroacetyl triflate was also employed as trifluoroacetylating agent for pyridine N atoms.[53] Methyl trifluoroacetate was also used to trifluoroacetylate N atoms from amines, but this reagent failed to trifluoroacetylate 1*H*-indoles.[54a] Trifluoropyruvate was also employed to trifluoroacetylate aniline derivatives.[54b]

Wang, Guo and collaborators[20] reported on the synthesis of *N*-trifluoroacetylated indolines from indoles employing low-cost, commercially available and bench stable trifluoroacetic acid (TFA) and trimethylamine borane as reagents. Optimized reaction conditions were achieved when employing 24 equiv. of TFA, 0.5 equiv. of trimethylamine borane in acetonitrile as solvent at 100 °C for 3 h and under air atmosphere. The reaction showed a broad substrate scope being compatible with indoles bearing electron-donating or electron-withdrawing groups at different positions (Scheme 26); for indoles bearing an amino group *bis*-trifluoroacetylated products were obtained (Scheme 26). Regarding the mechanistic aspects of the reaction, indole undergoes initial protonation by TFA to yield the iminium cation intermediate **I** (Scheme 27) that suffers hydrogenation by trimethylamine borane affording indolinium trifluoroacetate intermediate **II** which upon dehydration at 100 °C yields the *N*-trifluoroacetylated indoline final product (Scheme 27).[20] An interesting aspect of this transformation is that product outcome can be shifted, by increasing the amount of reducing agent trimethylamine borane to 8 equiv. and employing toluene as solvent at 50 °C, to yield exclusively the *N*-trifluoroethylated (i.e.: N-CH_2CF_3) indoline instead of the *N*-trifluoroacetylated indoline (N-$COCF_3$).[20]

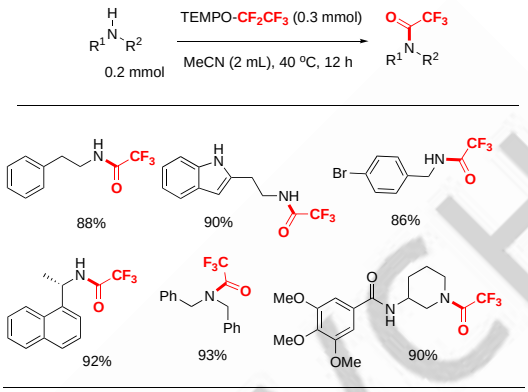


Scheme 26. Selected examples of the catalyst free *N*-trifluoroacetylation of indoles with trifluoroacetic acid and trimethylamine borane to yield *N*-trifluoroacetylated indolines.



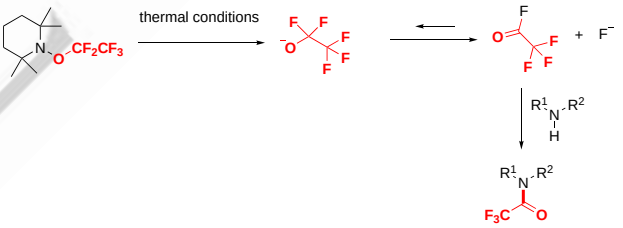
Scheme 27. Proposed reaction mechanism for the *N*-trifluoroacetylation of indoles with trifluoroacetic acid and trimethylamine borane to yield *N*-trifluoroacetylated indolines.

Dong, Tsui and colleagues[21] have recently accomplished the trifluoroacetylation of amines under very mild reaction conditions employing the adduct TEMPO-CF_2CF_3, in MeCN at 40 °C. The scope of the reaction is illustrated in Scheme 28.



Scheme 28. Selected examples for the trifluoroacetylation of amines with TEMPO-CF_2CF_3 adduct.

The mechanism of the reaction is quite interesting, in the sense that the authors report an O-N heterolysis of the TEMPO-CF_2CF_3 adduct under thermal conditions, affording pentafluoroethoxy anion, which undergoes fluoride elimination to generate a trifluoroacetyl fluoride intermediate which couples with the nucleophile (Scheme 29).



Scheme 29. Postulated reaction mechanism.

Wang and Weng[34] reported in 2019 the trifluoroacetylation and difluoroacetylation of nitrones, employing TFAA and DFAA (difluoroacetic acid anhydride). A brief scope of the transformation is summarized in Scheme 30.

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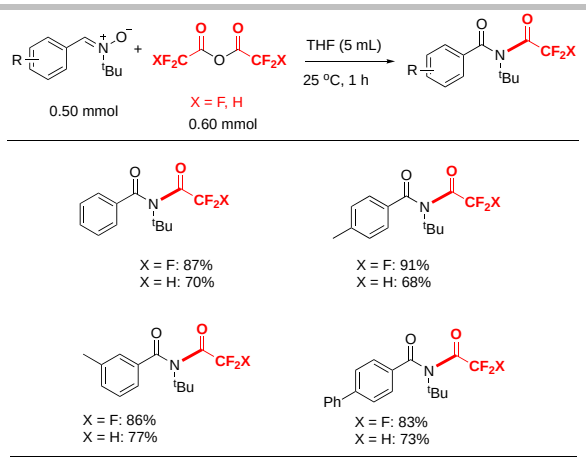
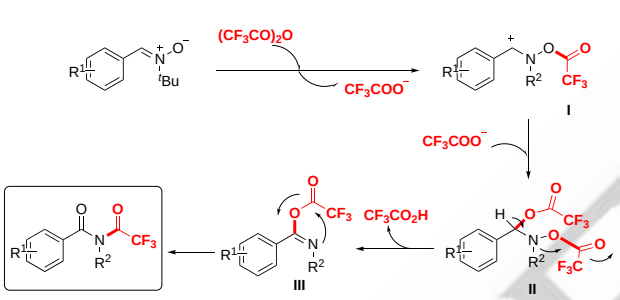


Scheme 30. Selected examples for the trifluoroacetylation and dilfuoroacetylation of nitrones.

The authors[34] postulated a reaction mechanism, according to probe experiments performed, as shown in Scheme 31.

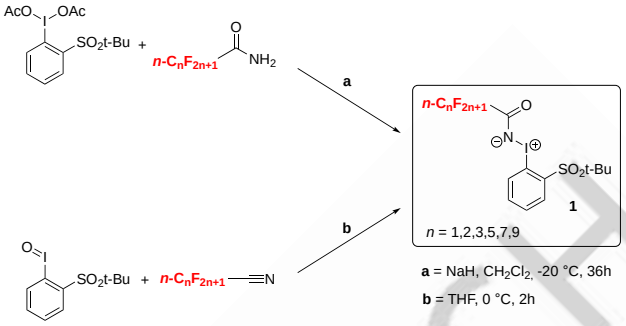


Scheme 31. Postulated reaction mechanism.

In the mechanism proposed (Scheme 31) the authors[34] hypothesized that the trifluoroacetylation of nitrone oxygen with TFAA will produce the carbocation intermediate **I**. This intermediate **I** undergoes nucleophilic attack by the trifluoroacetate anion, affording intermediate **II**, which suffers elimination to form intermediate **III**. Following an intramolecular substitution of intermediate **III**, the formation of *N*-trifluoroacetyl amide ensues.

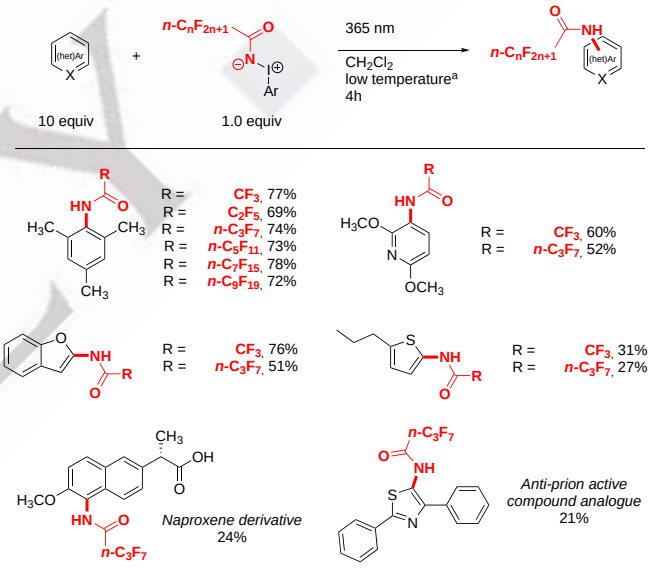
8. Miscellaneous Reactions

Kimura, Takemoto, Kobayashi, and colleagues[55] have developed a synthetic protocol for preparing *N*-perfluoroacylimino-λ^3-iodanes with fluoroalkyl chains of several lengths via a metathesis reaction between iodosoarenes and perfluoroalkanenitriles. As shown in Scheme 32, the authors used two different pathways to achieve the preparation of this reagent. For shorter fluoroalkyl chains (CF_3, C_2F_5, and C_3F_7), the reaction between iodosoarenes and perfluoroalkylamides proceeded smoothly under basic conditions and at low temperatures (pathway a). However, this protocol afforded low yields with longer fluoroalkyl chains. Therefore, an alternative strategy was employed (pathway b) using perfluoroalkylnitriles and iodosoarenes at 0 °C in THF.



Scheme 32. Preparation of *N*-perfluoroacylimino-I^3-iodanes.

The authors examined the direct introduction of the *N*-perfluoroacyl group in the (hetero)aromatic C-H bonds under irradiation conditions (Scheme 33).



[a] for CF_3, C_2F_5 and n-C_3F_7 -78 °C was used; for C_5F_{11}, C_7F_{15} and n-C_9F_{19} 0 °C was used.

Scheme 33. Perfluoroacylamination of (hetero)arenes, selected examples.

The perfluoroacylamination of mesitylene was achieved with moderate to good yields. Additionally, to benzene rings, heterocyclic compounds like pyridine, benzofuran, and thiophene were functionalized yielding 27% to 76% of the corresponding mono-functionalized regioisomers, respectively. The late-stage functionalization of biologically active compounds was also attempted, resulting in a 24% yield from a Naproxene derivative and a 21% from the reaction of an anti-prion drug analogue.

9. Summary and Outlook

The direct perfluoroacylations of (hetero)aromatics, olefins, and substitutions at C_{sp}^3-H, alkyl bromides, amides and N-atoms from amines and nitrones with the -COR_F moiety have been analyzed

in this perspective. The convenience of the direct introduction of the -COR_F group into organic scaffolds is both strategic and necessary in the case of structure-activity relationship studies and search for new pharmaceutical leads.

The direct reagents proposed for trifluoroacetylation (or perfluoroalkylacylation) reactions entail the use of trifluoropyruvate (under Cu^I catalysis), perfluoroalkyl iodides (with $Na_2S_2O_4$ or reducing basic conditions), or the versatile trifluoroacetic acid anhydride, TFAA, under various polar or radical protocols. Also, trifluoroacetic acid, TFA, has been proposed as trifluoroacetylating agent for N atoms derived from indoles. To the extent of our knowledge, an iodonium trifluoroacetylating reagent has not been reported as was the case for the perfluoroacylamination of (hetero)aromatics with *N*-perfluoroacylimino-λ^3-iodanes. A reagent that could possibly transfer the -$COCF_3$ group directly would invariably be highly regarded and convenient in the area of trifluoroacetylating reagents.

In the realm of direct radical trifluoroacetylation reactions, the use of TFAA is the reagent of choice. Much progress has been witnessed in avoiding the instability of intermediate trifluoroacyl radicals (from decomposition of TFAA radical anion intermediate) towards fragmentation into trifluoromethyl radical and CO, in radical trifluoroacetylation reactions. This has been attained through the use of photocatalysts and carefully controlled reaction conditions. Another approach was recently cited in the employment of masked (protected) trifluoroacetyl group as in **1** (Schemes 11 & 19), which proved much more resistant to fragmentation. These TFAA photocatalytic protocols, however, have not been applied to (hetero)aromatic compounds, or unsaturated substrates such as alkynes, enamines, etc. to obtain the respective trifluoroacetylated products substituted with the COR_F group, constituting a vacant research area. The extension of photocatalytic techniques such as that used with TFAA to other anhydrides derived from long-chain perfluoroalkanoic acids to corroborate the versatility of the methodology to obtain perfluoroalkanoyl radicals would wake intensive research in the field.

Numerous families of organic compounds remain yet to be substituted in the late-stage substitution with -COR_F, such as sugars, peptides, proteins, and oligonucleotides. Stereospecific direct introduction of perfluoroacyl groups into organic substrates has not yet been achieved, making this an understudied area that requires investigation. Notably, substitutions at C(sp^3) with -COR_F are rare, except for a recent study on trifluoroacetylation of the 2-methyl group as observed in 2,3-dimethylchromones. This vacant area of research, i.e.: substitutions at C(sp^3), remains to be fully explored.

We envision high prospects of development in the area of radical perfluoroalkylacylation reactions under milder conditions, employing visible light photocatalysis and environmentally friendly solvent systems. Also, the application of flow systems to the -COR_F substitution of organic substrates could bring forward an active area of research, especially under photocatalysis.

Acknowledgements

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Keywords: perfluoroacylation • trifluoroacetylation • perfluoroalkyl ketones • catalysis • perfluoroalkyl (hetero)aryl ketones

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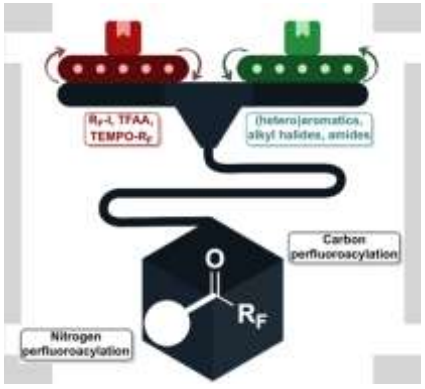

Direct strategies towards the incorporation of perfluoroacyl (-COR_F) groups into (hetero)aromatic compounds, -COR_F substitutions at C_{sp^3}-H, alkyl halides, alkenes, amides, and N-atoms are discussed in detail. Future directions and perspectives in the field are suggested.