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Direct acyl-mono/-di/-tri-fluoromethylation of olefins: A review

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ABSTRACT

This review, which covers the literature from 2020 to 2025, aims to provide a thorough insight into the synthesis of β-mono-/di-/-tri-fluoromethylated carbonyl compounds *via* direct vicinal acyl-mono/-di/-tri-fluoromethylation of alkenes also highlighting their mechanistic accepts that may provide new insights into catalyst improvement and development.

1. Introduction

The introduction of fluorine or fluorinated groups into organic compounds is a critical aspect of drug discovery research, as these modifications often enhance physicochemical properties and pharmacokinetic profiles, thereby contributing to the development of innovative pharmaceutical agents [1-5].

Among the various fluorinated groups, mono-, di-, and tri-fluoromethyl substituents are particularly noteworthy due to their growing significance in pharmaceutical, agrochemical, and material sciences [6-10]. The influence of these substituents on drug development is evident from the steadily rising number of FDA-approved drugs containing CF3, CHF2, or CH2F groups (Scheme 1), as well as the increasing pipeline of drug candidates advancing into clinical trials [11-13]. Consequently, there remains a strong interest in devising novel and effective methodologies for incorporating these functional groups into target molecules.

The direct mono-, di-, and tri-fluoromethylative difunctionalization of carbon-carbon multiple bonds, enabling the simultaneous incorporation of CH2F, CHF2, or CF3 groups alongside another functional group, has emerged as a sustainable and versatile approach for constructing complex organofluorine compounds from simple precursors [14-20].

Among these strategies, the direct vicinal acyl-mono-, di-, or tri-fluoromethylation of readily available alkenes has recently gained attention as an efficient and atom-economical method for synthesizing valuable β-mono-, di-, or tri-fluoromethylated carbonyl compounds in a single step (Figure 1). This review aims to provide a comprehensive summary of the literature on the direct vicinal acyl-mono-, di-, or tri-fluoromethylation of alkene substrates, focusing on developments reported from 2019 to the present.

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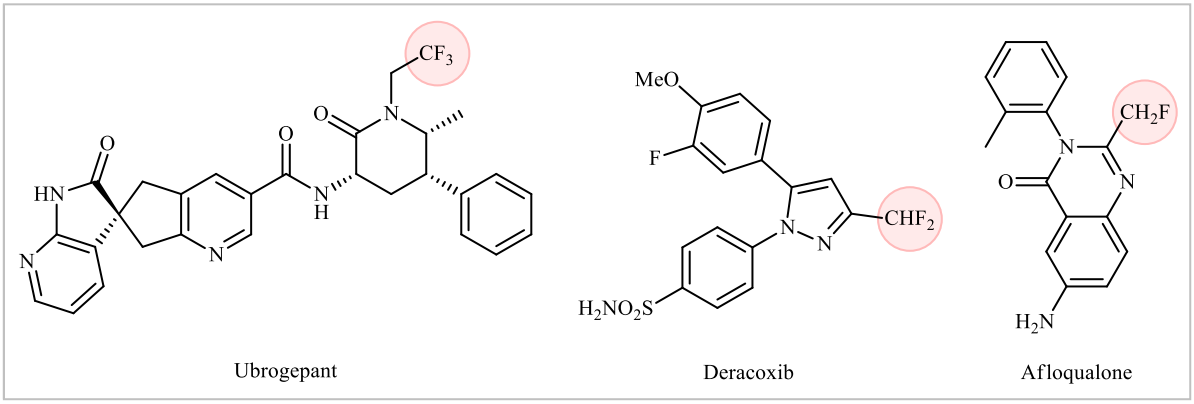


Scheme 1. Selection of FDA-approved drugs containing mono-, di-, and tri-fluoromethyl moieties.

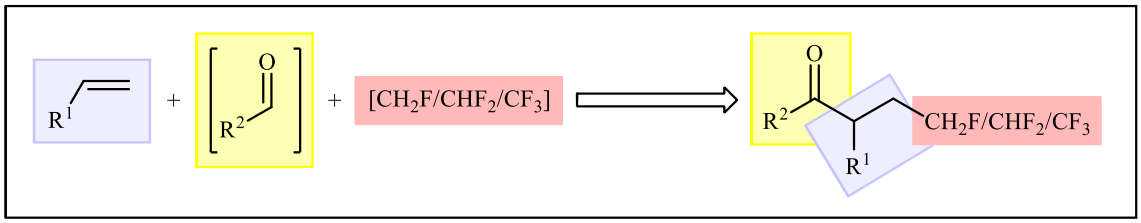


Fig. 1. Direct vicinal acyl-mono/-di/-tri-fluoromethylation of alkenes.

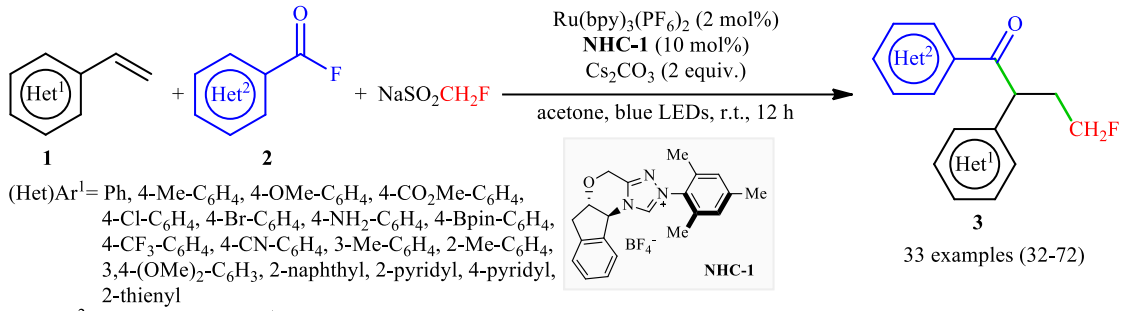
2. Acyl-monofluoromethylation

In 2023, Wang and colleagues introduced the first direct acylative monofluoromethylation of alkenes, enabling the synthesis of β-monofluoromethylated ketones [21]. This innovative approach involved treating various styrene derivatives (1) with (hetero)aroyl fluorides (2) as acylating agents and utilizing sodium monofluorosulfite ($NaSO_2CH_2F$) as a cost-effective and bench-stable source of the CH2F radical. The reaction was catalyzed by a combination of Ru(bpy)3(PF6)2 and triazolylidene-derived N-heterocyclic carbene (NHC-1), along with Cs_2CO_3, under 30 W blue LED irradiation. This method successfully yielded monofluoromethylated alkyl aryl ketones (3) in synthetically useful yields ranging from 32% to 72% (Scheme 2). The procedure demonstrated broad applicability, as styrene derivatives bearing electron-donating groups such as Me, OMe, and NH_2, as well as electron-withdrawing groups like CF_3, CN, and Cl at the phenyl ring periphery, effectively underwent the reaction. Various electron-rich and electron-deficient (hetero)aroyl fluorides demonstrated effective applications under standard reaction conditions [1]. Importantly, this difunctionalization approach proved valuable for the late-stage modification of pharmaceutical and bioactive molecules, including olefinic derivatives of indomethacin, oseltamivir, dihydroartemisinin, estrone, ibuprofen, and febuxostat, as well as acyl fluoride derivatives of probenecid and mefenamic acid [2].

However, the study revealed certain limitations of this protocol when applied to substrates such as aliphatic alkenes, internal aryl alkenes, 1,1-disubstituted styrene derivatives, and aliphatic acyl fluorides under identical conditions [3]. In these cases, the desired products were obtained in negligible yields or were not formed at all. The authors proposed that the difunctionalization reaction operates via two interconnected catalytic cycles, as illustrated in Scheme 3 [4]. Initially, the ground-state photocatalyst Ru^{II} undergoes photoexcitation under blue LED irradiation to generate the excited state $[Ru^{II}]^*$. This excited species then oxidizes $NaSO_2CH_2F$ through a single-electron transfer (SET) process, resulting in the formation of a CH_2F radical and Ru^{I} [5]. Following the initial radical addition of styrene 1 by the CH2F radical, the benzylic radical intermediate E is formed. Concurrently, acyl fluoride 2 interacts with Cs_2CO_3 to produce the bisacyl carbonate intermediate A, which subsequently acylates the NHC catalyst NHC-1, yielding the acyl azolium ion B. The reduction of this intermediate B by Ru^{I} generates the ketyl radical C, thereby completing the photoredox catalytic cycle. Ultimately, the intermolecular radical-radical cross-coupling between the ketyl radical C and the benzylic radical E results in the formation of the NHC-bound intermediate D. Upon fragmentation, this intermediate leads to the formation of the observed ketone product 3, while simultaneously regenerating the NHC catalyst NHC-1 [1]. Recently, the Sun-Zheng laboratory introduced a dual organocatalytic approach to the aforementioned reaction [22]. This method was conducted under a nitrogen atmosphere in MeCN, employing only 1.5 mol% of the carbazole-based photocatalyst (4CzIPN), 15 mol% of the triazolylidene-based NHC catalyst (NHC-2), and 2 equivalents of Cs_2CO_3 as the base at 30 °C. Under optimized conditions, the acylative

monofluoromethylation of various styrene derivatives 4, featuring electron-donating or electron-withdrawing groups at the para, meta, or ortho positions of the phenyl ring, along with a broad range of (hetero)aroyl fluorides 5, yielded the corresponding α-aryl-β-monofluoromethyl ketones 6 with yields ranging from poor to excellent (Scheme 4).

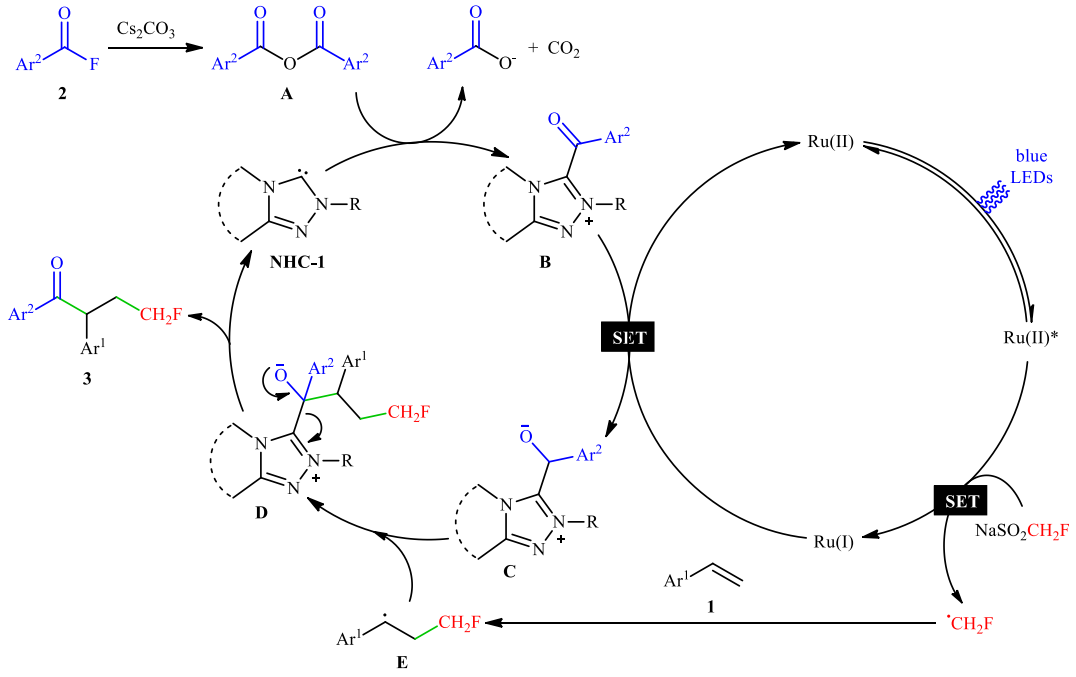
Furthermore, the authors extended this transformation to include the acyl-monofluoromethylation of a Michael alkene, resulting in the desired product with a low yield (23%). However, non-activated aliphatic olefins—whether terminal, internal, or cyclic—and aliphatic acyl fluorides proved to be ineffective substrates for this reaction



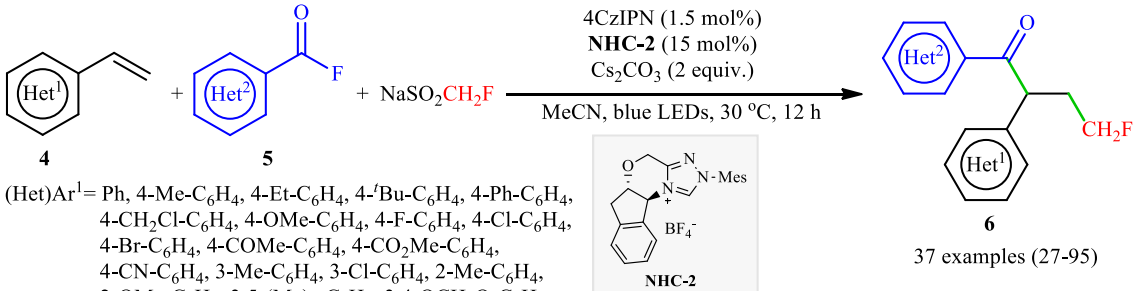
(Het)Ar^1= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-CO_2Me-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NH_2-C_6H_4, 4-Bpin-C_6H_4, 4-CF_3-C_6H_4, 4-CN-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 3,4-$(OMe)_2$-C_6H_3, 2-naphthyl, 2-pyridyl, 4-pyridyl, 2-thienyl

(Het)Ar^2= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-CF_3-C_6H_4, 4-OCF_3-C_6H_4, 4-COMe-C_6H_4, 4-Br-C_6H_4, 4-I-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 3,4-OCH_2O-C_6H_3, 2-naphthyl, 2-benzofuryl

Scheme 2. Dual NHC/photoredox-catalyzed acylmonofluoromethylation of alkenes 1, developed by Tian *et al*.



Scheme 3. Proposed mechanism for the reaction in Scheme 2.



(Het)Ar^1= Ph, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-CH_2Cl-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-COMe-C_6H_4, 4-CO_2Me-C_6H_4, 4-CN-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4, 2-Me-C_6H_4, 2-OMe-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 3,4-OCH_2O-C_6H_4, 2-naphthyl, 2-anthracenyl, 6-quinolinyl, 3-dibenzo[*b*,*d*]furyl, 5-benzofuryl, 5-(NTs)-indolyl

(Het)Ar^2= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OCF_3-C_6H_4, 4-CN-C_6H_4, 3-Me-C_6H_4, 3-F-C_6H_4, 2-OMe-C_6H_4, 3,5-$(Me)_2$-C_6H_3, 2-naphthyl, 2-thienyl

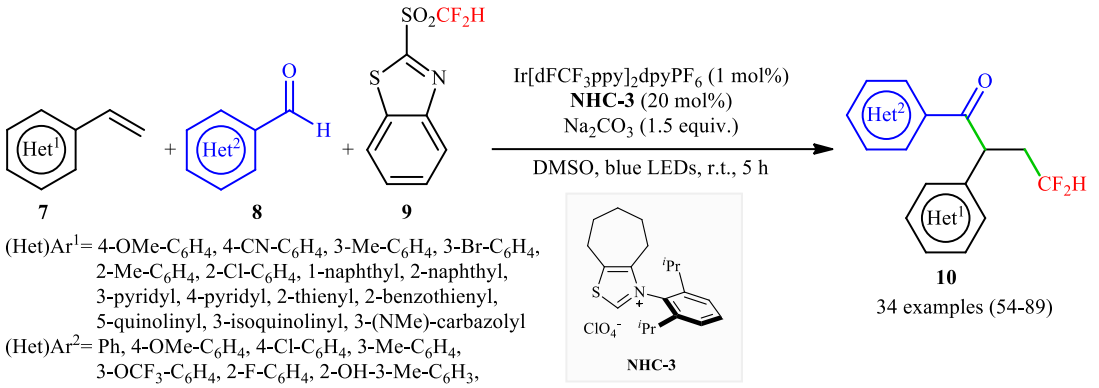
Scheme 4. Sun-Zheng's acylmonofluoromethylation of styrene derivatives 4.

3. Acyl-difluoromethylation

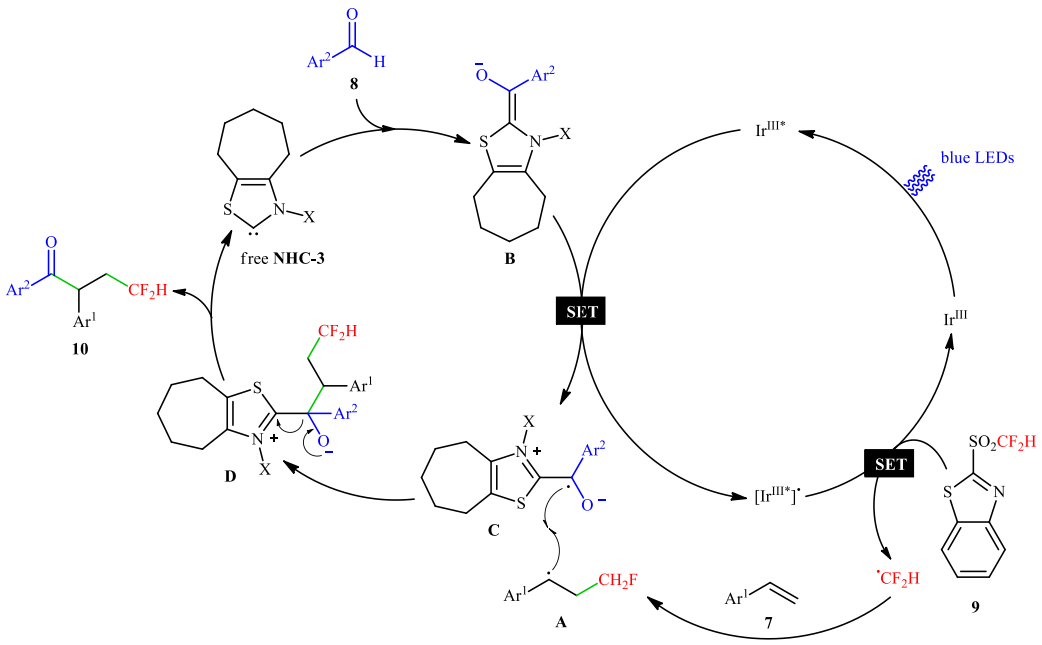
The vicinal acylative difluoromethylation of alkenes has been minimally explored, with only two examples documented in the literature to date. In 2022, Zhang and Wang introduced a groundbreaking method for synthesizing β-difluoromethylated ketones via the direct acyl-difluoromethylation of alkenes [23]. Their study demonstrated that treating terminal (hetero)aromatic alkenes 7 with (hetero)aromatic aldehydes 8 and 2-((difluoromethyl)sulfonyl)benzo[d]-thiazole 9, serving as acyl and difluoromethyl sources respectively, in the presence of catalytic amounts of Ir-[dFCF3ppy]2dpyPF6 and thiazole-based NHC (NHC-3) in DMSO under visible-light irradiation led to the formation of β-difluoromethylated ketones 10 in moderate to high yields (Scheme 5).

Importantly, both the photocatalyst and the organocatalyst were integral to the success of this reaction, as no product formation occurred in their absence. The findings highlighted the critical role of the solvent in facilitating this transformation. Substituting DMSO with alternative solvents such as NMP, DMPU, MeCN, DCM, DME, or MeOH resulted in a complete cessation of the reaction [1].

Regarding substrate scope, the reaction demonstrated minimal sensitivity to the electronic and steric properties of substituents on the phenyl rings of styrenes and benzaldehydes. Both electron-donating and electron-withdrawing groups at various positions on these components were effectively accommodated by this methodology [2]. Nonetheless, the approach proved ineffective for alkyl aldehydes, cinnamaldehyde, and alkynaldehyde, and the use of aliphatic alkenes as starting materials was not explored in this investigation [3]. The proposed mechanism for this reaction sequence, illustrated in Scheme 6, aligns with the pathway described by Wang and colleagues for the acyl-monofluoromethylation of alkenes using aroyl fluorides and $NaSO_2CH_2F$ [4].



Scheme 5. Zhang-Wang's synthesis of β-difluoromethylated ketones 10.



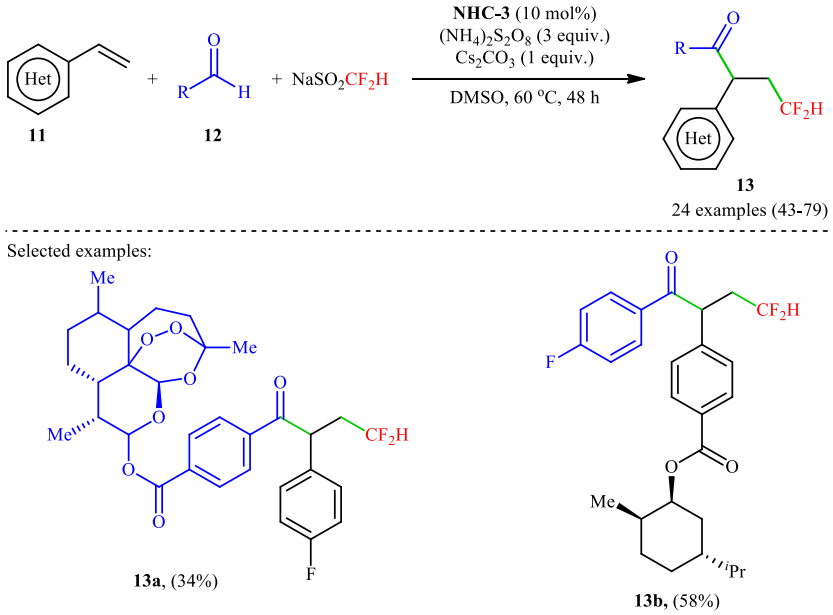
Scheme 6. Proposed mechanism for the formation of β-difluoromethylated ketones 10.

She et al. later introduced an enhanced approach to this reaction by utilizing sodium difluoromethanesulfinate ($NaSO_2CF_2H$) as the CF_2H source in conjunction with a catalytic system consisting of NHC-3, $(NH_4)_2S_2O_8$, and Cs_2CO_3 [24]. Under the influence of this catalytic system in DMSO, a variety of styrene derivatives 11 reacted with different aldehydes 12, including aliphatic, aromatic, and heteroaromatic types, alongside $NaSO_2CF_2H$. This process occurred gradually and resulted in the formation of acyl-difluoromethylated products 13 with yields ranging from modest to good (Scheme 7). Mechanistic investigations indicated that the reaction follows a radical pathway analogous to the mechanism proposed by Zhang and Wang.

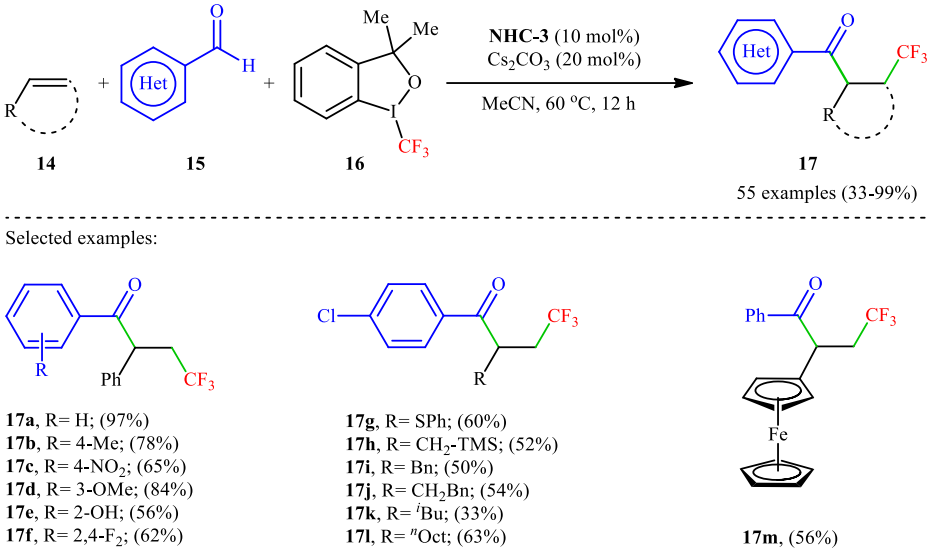
4. Acyl-trifluoromethylation

In 2020, Han, Li, and their team explored the synthesis of β-trifluoromethylated ketones via direct vicinal acyl-trifluoromethylation of alkenes [25]. Using styrene and benzaldehyde as model substrates, they conducted extensive screening of trifluoromethylating reagents, catalysts, bases, and solvents. Ultimately, they identified the NHC-3/Cs_2CO_3 combination as the most effective catalytic system, selected Togni I reagent as the optimal trifluoromethylating agent, and determined DMSO to be the best solvent. Under these optimized conditions, thirty-one aromatic and aliphatic alkenes 14—including 1,1-disubstituted, 1,2-disubstituted, and terminal alkenes—successfully underwent selective acyl-trifluoromethylation with various (hetero)aromatic aldehydes 15 and Togni I reagent 16, yielding the desired β-trifluoromethylated ketones 17 in fair to nearly quantitative yields (Scheme 8). Notably, when N-methyl indoles were subjected to these reaction conditions, highly diastereoselective trifluoromethylated indolinyl ketones were obtained through dearomatizative difunctionalization. A diverse array of significant functional groups (e.g., F, Cl, Br, CF_3, OAc, OMe, CO_2H, OH, NO_2, TMS, SPh) demonstrated excellent compatibility with this reaction, underscoring its wide-ranging applicability. The proposed mechanism for the acyltrifluoromethylation process is illustrated in Scheme 9. It begins with the formation of the deprotonated Breslow intermediate A, which arises from the reaction between the NHC catalyst and aldehyde 15 in the presence of a base. This step is followed by the single-electron reduction of the Togni I reagent 16 by the electron-rich intermediate A, generating both a trifluoromethyl radical and a persistent ketyl radical B. Subsequently, the trifluoromethyl radical undergoes addition to the styrene substrate 14, leading to the formation of a benzylic radical C. The recombination of radical C with radical B via a radical−radical cross-coupling pathway results in intermediate D. Finally, fragmentation of intermediate D yields the desired product 17 along with regeneration of the NHC catalyst.

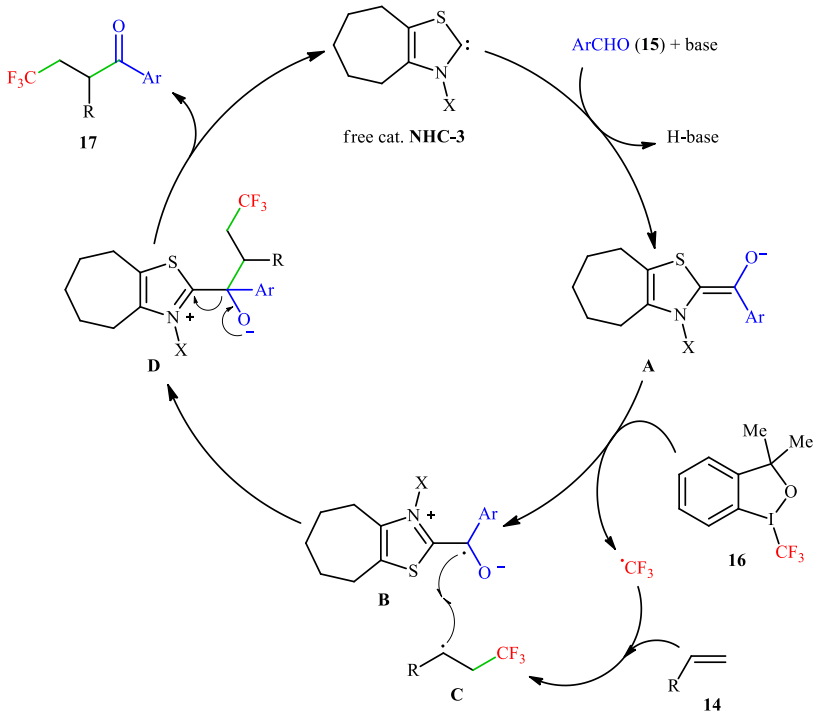
Wang and colleagues later demonstrated an additional method for synthesizing β-trifluoromethyl-α-substituted ketones 20 using alkenes 18, aldehydes 19, and the Togni I reagent 16. This process was conducted in a binary solvent system comprising DCM/H_2O and utilized Han-Li's catalytic system [26]. The reactions were performed under ambient conditions, showcasing compatibility with both aromatic and aliphatic alkenes, and yielded the desired difunctionalized products 20 in varying efficiencies, ranging from poor to excellent yields (Scheme 10). The relative reaction rates of different alkene substrates under these conditions followed the order: aromatic alkenes ≥ heteroaromatic alkenes > aliphatic alkenes > benzylic alkenes



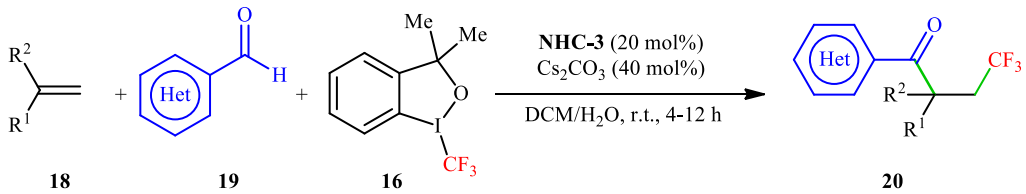
Scheme 7. Acylative difluoromethylation of alkenes 11 with aldehydes 12 and $NaSO_2CF_2H$ catalyzed by NHC-13.



Scheme 8. Han-Li's synthesis of β-trifluoromethylated ketones 17.



Scheme 9. Plausible mechanism for the reaction in Scheme 8.



R^1= 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-CN-C_6H_4, 3-Cl-C_6H_4, 2-Me-C_6H_4, 2-Cl-C_6H_4, 2-Br-C_6H_4, 1-naphthyl, 2-naphthyl, 2-pyridyl, 4-pyridyl, 3-thienyl, 9-carbazolyl, NHAc, OAc, OMe, SPh, Bn, $CH_2{}^t$Bu, 4-(CO-4-$OCMe_2CO_2{}^i$Pr-C_6H_4)-C_6H_4

R^2= H, Me

(Het)Ar= Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-CF_3-C_6H_4, 3-Me-C_6H_4, 3-NO_2-C_6H_4, 2-CN-C_6H_4, 3,4-OCH_2CH_2O-C_6H_3, 3,4-F_2-C_6H_3, 2-naphthyl, 3-pyridyl, 3-(NTs)-pyrrolyl, 3-furyl, 3-thienyl, 2-furyl, 2-thienyl, 2-benzofuryl, 2-benzothienyl, 2-quinolinyl, 3-quinolinyl, 6-quinolinyl, 4-(1-Me)-imidazolyl

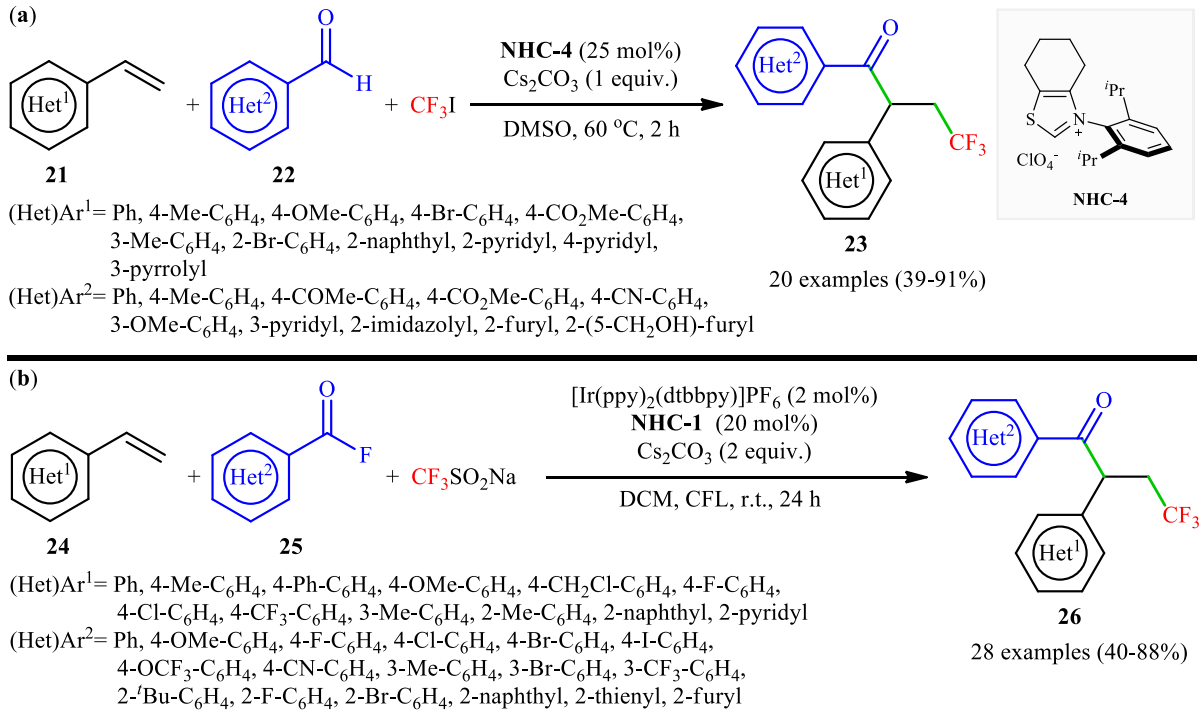
Scheme 10. Wang's synthesis of β-trifluoromethyl-α-substituted ketones 20.

In the same year, Yang and Wu, along with their collaborators, developed a novel synthetic approach for the direct acylative trifluoromethylation of alkenes 21. This method utilized trifluoroiodomethane (CF_3I) as the source of trifluoromethyl radicals and aldehydes 22 as acylating agents, facilitated by the NHC-4/Cs_2CO_3/DMSO catalytic system. The procedure enabled the efficient synthesis of various β-trifluoromethyl-α-aryl ketone derivatives 23 in modest to high yields within a short reaction time of 2 hours (Scheme 11a) [27]. While this protocol exhibited good compatibility with aromatic (electron-rich and electron-poor) and heteroaromatic alkenes, it was found to be ineffective for simple aliphatic alkenes. Notably, NHC-3 was also identified as an effective catalyst for this difunctionalization reaction but resulted in lower product yields. Concurrently, Studer and his research team demonstrated that direct acyltrifluoromethylation of alkenes could be achieved using the Langlois reagent (CF_3SO_2Na), an inexpensive and easily manageable solid source of CF_3, along with aroyl fluorides as acyl group donors under a dual catalytic system involving NHC and photocatalysis [28]. This approach facilitated the synthesis of 28 β-trifluoromethyl-α-aryl ketones 26 in moderate to high yields from the corresponding (hetero)aromatic terminal alkenes 24 and (hetero)aroyl fluorides 25 (Scheme 11b). Additionally, the authors successfully applied this methodology to two aliphatic alkenes, though the resulting ketones were obtained in poor yields (15-20%). Mechanistically, this reaction follows a pathway closely resembling that of acyl-monofluoromethylation under the same catalytic system, as illustrated in Scheme 3.

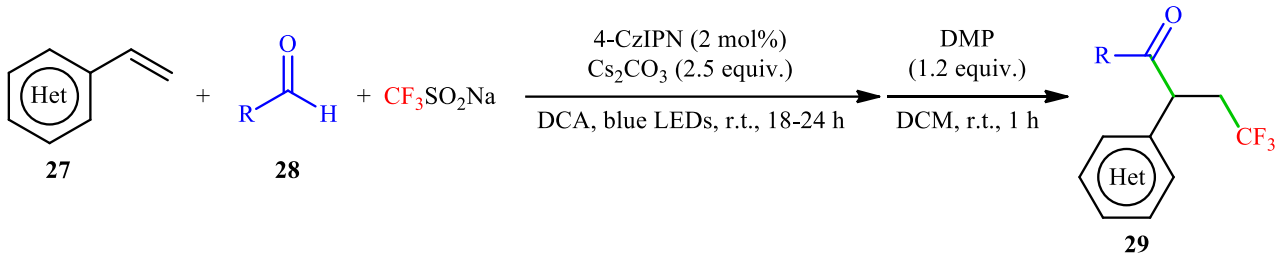
Zhu-Feng and collaborators conducted a study focusing on the synthesis of various β-trifluoromethylated ketones 29 via a three-component reaction involving styrene derivatives 27, aldehydes 28, and the Langlois reagent. This process employed 4-CzIPN as a photocatalyst under blue LED irradiation, followed by the oxidation of in situ-formed γ-trifluoromethylated alcohols using Dess-Martin periodinane (DMP) at ambient temperature (Scheme 12) [29]. Notably, the reaction demonstrated broad compatibility with both aliphatic and aromatic aldehydes. However, it appears to be restricted to aromatic terminal alkenes.

Wu and collaborators made a notable advancement in this area by developing a sophisticated Cu-catalyzed carbonylative trifluoromethylation of olefinic double bonds. This reaction involves unactivated alkenes 30, amines 31, and the Togni II reagent 32, employing CuCl2 as the catalyst and 1,10-phen as the ligand under a pressurized carbon monoxide atmosphere of 40 bar [30]. The reaction is conducted in DMAc at 60 °C, yielding β-trifluoromethyl amides 33 with moderate to high efficiency, ranging from 45% to 81% (Scheme 13).

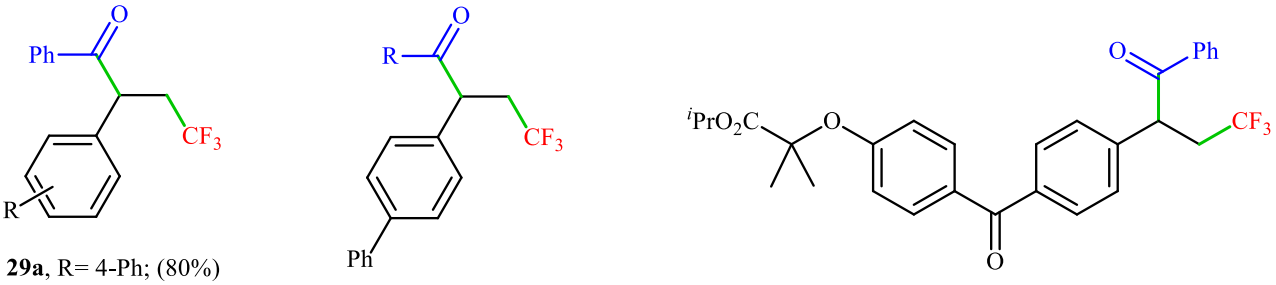
This methodology demonstrates a wide substrate scope, accommodating both aromatic and aliphatic amines (primary and secondary), as well as diverse unactivated terminal alkenes. Remarkably, ethylene gas was also successfully utilized as a substrate under identical conditions.



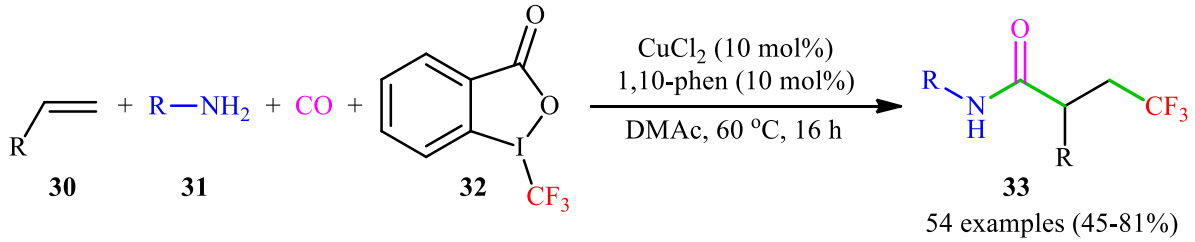
Scheme 11. (a) Yang-Wu's synthesis of β-trifluoromethyl-α-aryl ketones 23; (b) Studer's synthesis of β-trifluoromethyl-α-aryl ketones 26.



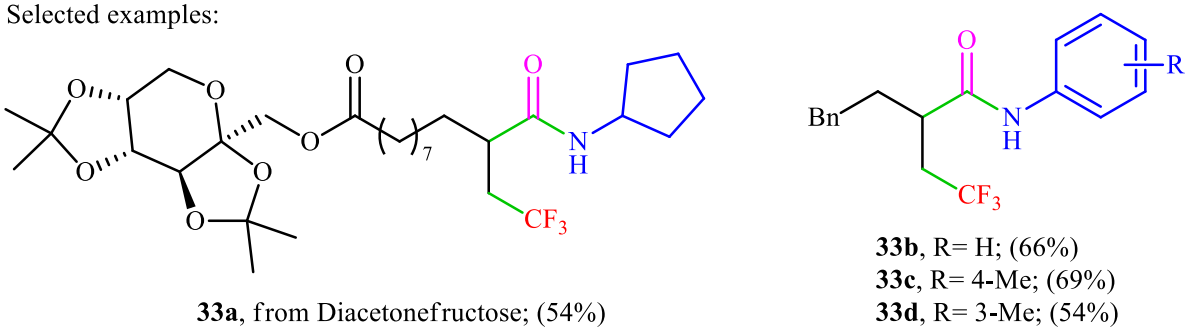
Selected examples:



Scheme 12. Zhu-Feng's synthesis of β-trifluoromethylated ketones 29.



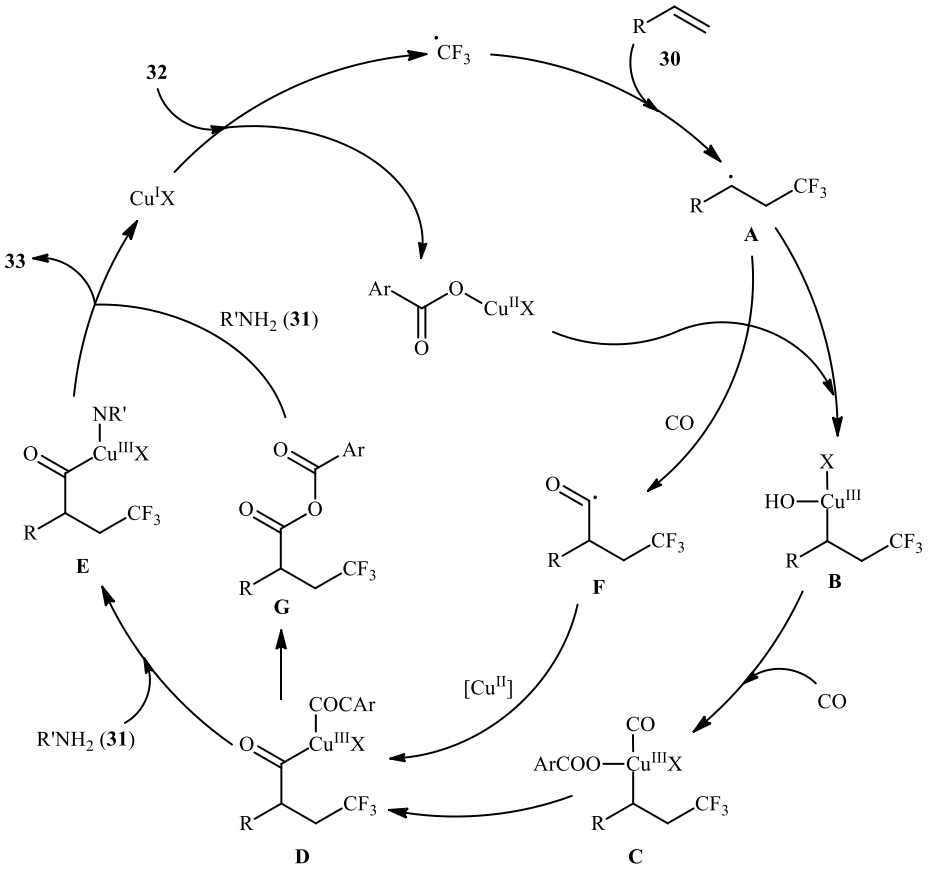
Selected examples:



Scheme 13. Wu's synthesis of β-trifluoromethyl amides 33.

Furthermore, the scope of nucleophiles was extended beyond amines to include alcohols, which produced the corresponding β-trifluoromethyl esters in excellent yields. According to the mechanistic cycle proposed by the authors (Scheme 14), the difunctionalization reaction begins with the formation of CF_3 radicals and an $ArCO_2Cu(II)$ species, facilitated by the interaction of Togni II reagent 32 with CuX.

The CF3 radical then adds across the unactivated alkene 30, generating alkyl radical intermediate A. This intermediate undergoes reduction by the $ArCO_2Cu(II)$ species to form Cu^{III} intermediate B. Following this, coordination of CO to the metal center in intermediate B results in the formation of a new Cu^{III} intermediate C, which undergoes CO insertion into the Cu–C bond to yield acyl-copper intermediate D. Alternatively, radical A may directly react with CO to produce acyl radical F, which subsequently interacts with the ArCO2Cu(II) species to generate acyl-copper intermediate D. This intermediate D then reacts with amine 31, forming intermediate E. Finally, reductive elimination of intermediate E yields the desired β-trifluoromethyl amide product 33 and regenerates Cu^I, thereby completing the catalytic cycle.



Scheme 14. Mechanism that accounts for the formation of β-trifluoromethyl amides 4.

5. Conclusion

Organofluorine chemistry currently plays a significant role in medicinal chemistry and drug discovery research. Notably, about 20% of new pharmaceutical drugs entering the market bear fluorine atoms or fluorinated moieties within their structures. Mono-, di-, and tri-fluoromethyl substituents are particularly interesting fluorinated moieties as they found in a number of FDA-approved drugs such as celecoxib, fluoxetine, ubrogepant, alpelisib, deracoxib and afloqualone. In this class of compounds, β-mono-/di-/-tri-fluoromethylated carbonyl compounds have recently attracted strong interest in medicinal chemistry owing to their wide range of notable biological activities. As illustrated, the direct vicinal acyl-mono/-di/-tri-fluoromethylation of easily accessible alkene substrates has recently arisen as an efficient and straightforward route to β-mono-/di-/-tri-fluoromethylated carbonyl compounds. Although there have been recent advancements, this area of research is still in its infancy and additional studies and enhancements are necessary to reach maturity.

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