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Direct and Chemoselective Synthesis of Tertiary Difluoroketones via Weinreb Amide Homologation with a CHF_2-Carbene Equivalent

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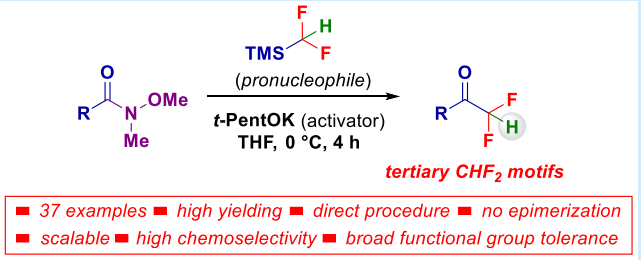
Supporting Information

ABSTRACT: The homologation of Weinreb amides into difluoromethylketones with a formal nucleophilic CHF_2 transfer agent is reported. Activating $TMSCHF_2$ with potassium *tert*-amylate enables a convenient access to the difluorinated homologation reagent, which adds to the acylating partners. The high chemoselectivity showcased in the presence of variously multifunctionalized Weinreb amides, jointly with uniformly high yields, enables the strategy of general applicability without requiring any stabilization element for the putative carbanion.



Embodying a difluoromethyl unit into an organic array profoundly tunes the chemico-physical properties of the resulting scaffold.[1] In more detail, the weakly acidic CHF_2 motif represents a rare example of a methinic carbon capable of establishing hydrogen-bonding interactions[2] to improve the binding selectivity of pharmaceuticals.[3] Thus, valuable optimization processes in drug design can be realized by introducing the CHF_2 unit acting as a competent more lipophilic isostere of widespread functionalities such as hydroxyl, mercapto, hydroxamic, or amidic species.[3a,4] Placing the CHF_2 fragment at the vicinal position of a ketone carbonyl results in the simultaneous modulation of the reactivity profile of both moieties: the carbonyl and the difluorinated C−H group (Scheme 1).[5] Evidently, the electron-withdrawing effect exerted by CHF_2 guarantees a significant increase of the electrophilicity of the carbonyl carbon, whereas it causes a remarkable inertness of the corresponding enolates.[6] However, the remarkable significance of difluoroketones in the general context of the chemical sciences is somehow counterbalanced by the lack of a general tactic to access them.[7] Accordingly, the most common logical approaches to the motif can be summarized as follows: (1) progressive introduction of fluorine through C−F bond formation operations (Scheme 1a) and (2) transfer of the difluorinated building block onto a proper acceptor, thus formally constituting a C−C bond formation event (Scheme 1b). Techniques belonging to the first tactic (e.g., use of enolate-like materials, alkynes, etc.) are often plagued by important concerns on the regioselectivity of the transformation observed during the fluorination under electrophilic regime, also manifesting a strong dependence on the structure of the nucleophilic scaffold (mainly in the presence of different enolization centers).[7a,8] A breakthrough in the field has been introduced by Pattison through the homologative ester difluorination coupling with lithiated bis(boron) species: accordingly, *quaternary* difluoromethyl ketones can be prepared under full regio- and chemocontrol.[9] As a common feature, these strategies are valuable platforms for accessing fully substituted difluoroketones, but unfortunately, the flexibility and adaptability to prepare *tertiary* α-CHF_2 analogues appear limited. A conceptually different disconnection would suggest adopting an intuitive C−C bond formation strategy by transferring the formal CHF_2-containing nucleophile onto an electrophilic partner.[10] To be productive, the tactic should overcome the inherent high instability of putative CHF_2-type carbanions.[11] In this context, the installation of stabilizing electron-withdrawing elements on them emerged as an effective solution to tackle the challenge; however, the requirement of unnecessary extra steps (installation and removal of these stability enhancing factors under forcing conditions) undoubtedly decreases the overall synthetic efficiency as, for example, evidenced in recent work by Kuhakarn.[12] In 2011, Hu and co-workers introduced Me_3SiCF_2H (**I**) as a valid equivalent of the CF_2H carbanion, pointing out some remarkable characteristics of the reagent:[1g,13] unlike the similar Ruppert−Prakash reagent (Me_3SiCF_3),[14] **I** requires proper activation to be synthetically useful as a consequence of the very strong Si−C bond it possesses.[13] We reasoned a homologation event carried out with a formal CHF_2 nucleophile, i.e., presenting the exact degree of substitution as the targeted structures, on a Weinreb amide acting as the electrophilic acylating partner[15] would represent an effective solution to the problem of preparing tertiary difluoromethylketones. As documented in recent work

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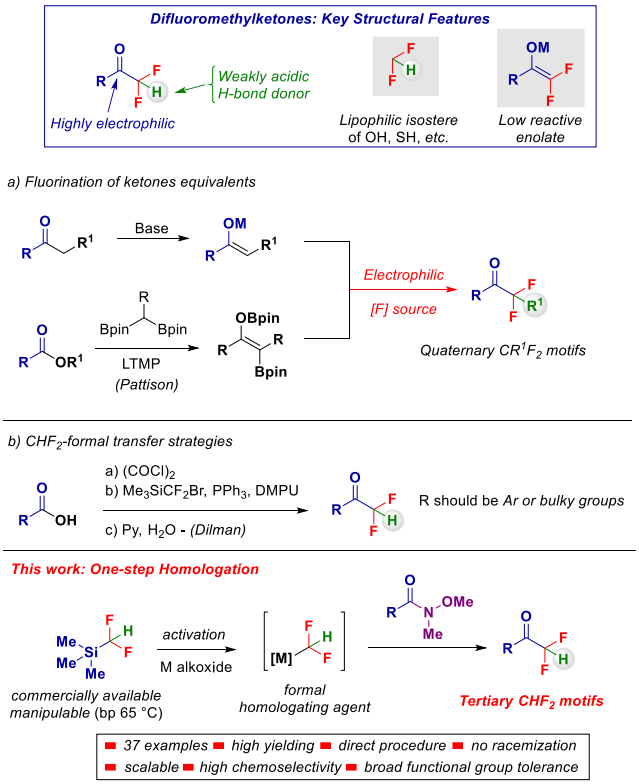
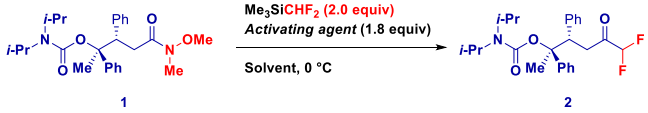
Scheme 1. Difluoromethyl Ketones: State of the Art



by our group, these amides act as highly competent acylating agents for α-substituted methyl-type carbanions,[16] including the unprecedented lithium *mono*fluoromethyl nucleophile ($LiCH_2F$).[17] Additionally, structural limitations, e.g., needing aromatic or bulky groups, pointed out by Dilman in the case of using difluorinated phosphorus ylides could be advantageously circumvented.[18]

We selected the optically active Weinreb amide **1**[19] as the model substrate for gaining insight into both chemical reactivity and preservation of the stereochemical information (Table 1). Cognizant of the requirement of activating $TMSCHF_2$, we screened a set of conditions for generating the formal CHF_2-transfer nucleophilic agent. Nonoptimal efficiency was noticed by using TBAT (tetrabutylammonium difluorotriphenylsilicate) or an alkaline metal fluoride in DMF, accompanied by minor but still noticeable racemization (entries 1−3). Moreover, the use of the amidic solvent DMF is responsible for self-difluoromethylation phenomena, as indicated by ^{1}H NMR analysis of reaction crudes. The process manifested a strong solvent-activating agent dependence, as deducted by the complete lack of reactivity when switching—*coeteris paribus*—from DMF to THF (entry 4). Activating the pronucleophile Me_3SiCHF_2 with a stoichiometric amount of a low nucleophilic alkoxide in THF (potassium *tert*-butoxide) allowed us to produce in satisfying yield the desired difluoroketone **2**, albeit with minor epimerization (entry 5). Changing to a commercially available THF solution of *t*-BuOK had a positive effect on the yield, although epimerization could not be fully avoided (entry 6). Pleasingly, the activation of $TMSCHF_2$ with a commercially available solution of the more sterically hindered potassium *tert*-pentoxide (i.e., amylate, 0.9 M in cyclohexane)[20] resulted in an excellent 91% yield of the targeted ketone with full preservation of the optical purity (entry 7). Some additional points merits mention: (a) Despite

Table 1. Model Reaction: Optimization.[a]



1 2

entry	solvent	base	reaction time (h)	yield of **2**[a] (%)	er of **2**
1	DMF	TBAT	8	traces	
2	DMF	KF/18-crown-6	8	27	95:5
3	DMF	CsF	8	15	96:4
4	THF	KF/18-crown-6	8	traces	
5[b]	THF	*t*-BuOK	4	63	96:4
6[c]	THF	*t*-BuOK	4	75	96:4
7	***THF***	***t*-PentOK**	**4**	**91**	***99:1***
8	Et_2O	*t*-PentOK	8	52	97:3
9	toluene	*t*-BuOK	8	75	98:2
10[d]	THF	*t*-PentOK	8	77	99:1
11[e]	THF	*t*-PentOK	4	36	98:2
12[f]	THF	*t*-PentOK	4	<10	

[a]Otherwise stated reactions were run at 0 °C with *t*-PentOK 1 M solution in cyclohexane under Barbier-type conditions. [b]*t*-BuOK solid. [c]*t*-BuOK 1.0 M in THF. [d]Me_3SiCHF_2 (1.5 equiv) and *t*-PentOK (1.4 equiv) were used. [e]Reaction run at rt (23 °C). [f]Non-Barbier-type conditions (e.g., CHF_2-transfer agent generated from Me_3SiCHF_2 (2.0 equiv) and *t*-PentOK (1.8 equiv)) and then Weinreb amide **1** was added.

the existence of an enolization site at the α-position of the starting Weinreb amide, no deleterious effect was evidenced, thus making the reaction productive. This is a particularly remarkable result compared to the elusive attitude of similar enolizable ketones to undergo difluoromethylation observed by Hu.[13] (b) THF represented the ideal solvent for the transformation as indicated by compared with diethyl ether and toluene even after prolonged reaction times (entries 8 and 9). (c) Decreasing the nucleophile loading to 1.4 equiv was detrimental for the yield (entry 10). (d) By increasing the temperature up to rt, a dramatic lost of efficiency was observed, presumably as a consequence of the nucleophile thermal stability (entry 11). It is worth mentioning that the use of Barbier-type conditions not only compromised the chemoselectivity but also constituted a *conditio sine qua non* to enable reactivity, in analogy to the highly unstable monofluoromethylating agent $LiCH_2F$ we introduced in 2017.[17] In fact, when the nucleophile was generated prior to the acylation event (3 min, i.e., non-Barbier conditions) compound **2** was formed in only <10% yield.

With the optimized conditions in hand, we then studied the scope of the reaction (Scheme 2). Unsaturated Weinreb amides smoothly undergo the homologative difluoromethylation, providing the resulting ketones (**3**−**8**) in excellent yields (>91%). Interestingly, substitution across the cinnamoyl core (both on the aromatic ring—with functionalities of diverse electronic behavior—or on the exocyclic olefin) are perfectly tolerated, thus affording interesting products, including the unprecedented ketone **6** presenting two different fluorine-containing substituents (sp^2 C−F) and (sp^3 CHF_2) at the α and α'-position, respectively. Moreover, incorporating a triple bond into the Weinreb amide core maintains untouched the efficiency (**9**). The excellent yields observed in the case of aromatic Weinreb amides, delivering difluoroketones (**10**−**33**), accounts for the robustness and versatility of the process. Substitution on the aromatic nuclei is uniformly permitted

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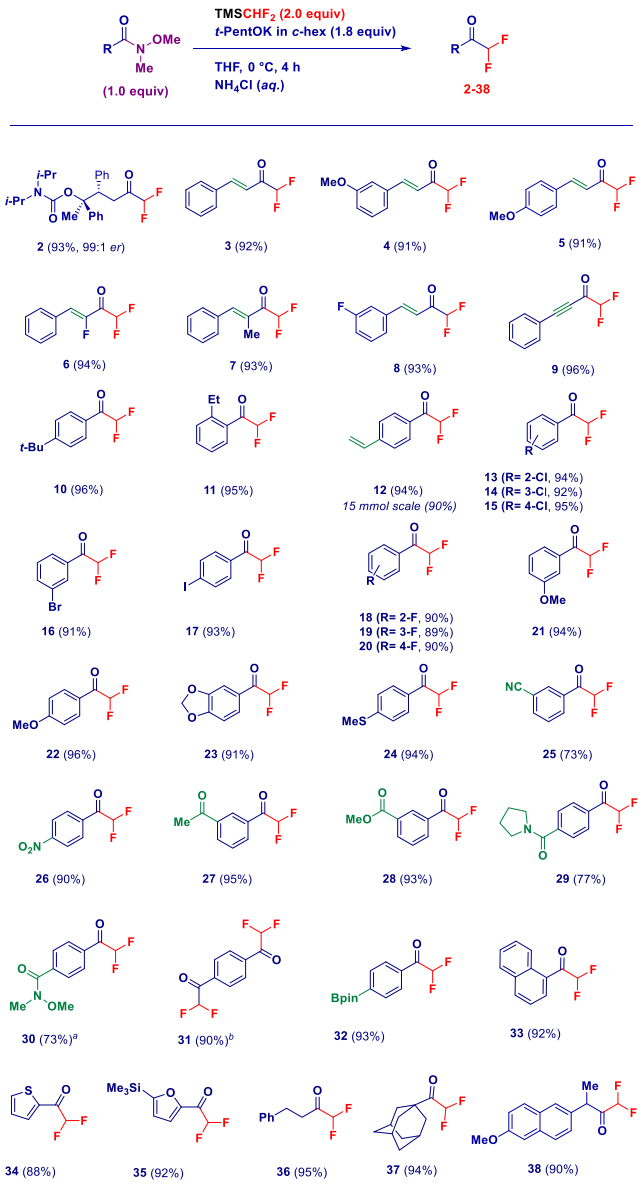
Scheme 2. Scope of the Reaction: Synthesis of Difluoromethylketones



with both electron-donating (**10**, **11**, **21**−**24**) and electron-withdrawing substituents (**13**−**20**). Significantly, positioning the substituent on delicate sites (*ortho*, **11**, **13**) does not influence the yield. In analogy to the compatibility of the reaction conditions with the presence of unsaturated C−C bonds seen above, a vinyl fragment (**12**) does not suffer any modification during the generation of the carbene-like species. Scaling-up the process (15 mmol, compound **12**) resulted in comparable efficiency, thus making it of potential interest for nonacademic audiences. We anticipate these mild conditions enable further elaboration of the scaffold upon tuning of the difluoromethylation methodology en route to difluorocyclopropanes (vide infra). The whole set of halogens (**13**−**20**) can be placed on the aromatic ring as well as ether (**21**, **22**), acetal (**23**), or thioether (**24**) functionalities, thus adding reliability to the technique. The compatibility of the procedure with highly sensitive groups to the nucleophilic environment is undoubtedly one of the main advantages of the methodology.[21] In fact, susceptible electrophilic decorating elements such as nitrile (**25**), nitro (**26**), ketone (**27**), ester (**28**), or a pyrrolidinyl amide (**29**) remain completely untouched during the transformation, presumably due to the excellent performance of Weinreb amides in reaction with α-functionalized carbanions. Additionally, a bis-Weinreb amide is amenable for mono- or bis-difluoromethylation by simply tuning the stoichiometry: in the case of using 1.0 equiv of nucleophile and cooling the mixture at −20 °C, it is possible to introduce a single CHF_2 group, leaving untouched the remaining Weinreb amide site (**30**). Alternatively, by increasing the nucleophile loading up to 3.0 equiv, both Weinreb amides undergo the difluoromethylation, affording the symmetric bis-difluoroketone **31** in an excellent 90% yield through a single operation. A synthetically useful boronate ester—a benchmark for further chemistry—is analogously tolerated (**32**), pointing out the unique characteristics of the CHF_2 nucleophile compared to different $CHHal_2$ carbenoids whose addition to boronate esters follows a Matteson-type homologation pathway.[22] Moreover, polyaromatic (**33**) or thiophene (**34**) Weinreb amides can be employed, further highlighting the stability of a sensitive TMS group on the furan ring (**35**). Finally, additional aliphatic Weinreb amides including the highly sterically demanding adamantyl substituted (**37**) or the one generated from the nonsteroidal anti-inflammatory drug naproxen could be conveniently employed for preparing the targeted scaffolds in very high yield.

The availability of a highly efficient preparative procedure for tertiary difluoroketones spurred us to undertake a survey on their use in chemical synthesis. By simply selecting the reaction conditions, high chemoselective processes with strong nucleophiles can be designed (Scheme 3). The Feringa Pd-catalyzed cross-coupling of *p*-iodoketone **17** with PhLi gave the corresponding *p*-phenyl derivative **39** in very high yield without touching the sensitive difluorocarbonyl unit.[23] Also, a selective Wittig reaction on the ketone functionality of **24** conducted to the difluoroallyl compound **40**. The carbonyl of **23** undergoes the attack of the carbenoid iodomethyllithium ($LiCH_2I$)[24] to prepare in a single operation the extremely rare α-difluoromethyl epoxide core[25] (**41**). Moreover, the pendant vinyl substituent of **12** could be used to construct a difluoromethyl cyclopropane,[26] furnishing the unknown ketone **42**, featuring contemporaneously two different difluoromethyl fragments. Finally, the tetrahedral hemiaminal generated by the addition of the CHF_2 unit to a Weinreb amide could be trapped and fully characterized according to our previous established procedure.[27] It is worth noting that analogous stable tetrahedral adducts derived from difluoromethyl ketones are relevant for enzymatic inhibition studies of potential pharmacological interest.[7a]

In summary, we have disclosed a conceptually intuitive and smooth access to difluoromethyl ketones via the straightforward homologation with a formal CHF_2-type carbanion equivalent of variously functionalized Weinreb amides. The methodology paves on the activation of the commercially available reagent $TMSCHF_2$ in the presence of potassium *tert*-amylate in THF. Particularly attractive characteristics of this uniformly high-yielding and general methodology are (1) the excellent tolerance of sensitive functionalities (including challenging ketone, ester, amide, nitro, nitrile groups, inter alia), (2) the perfect flexibility to Weinreb amides of diverse electronic behavior; (3) the negligible effect of sterically demanding elements positioned on the acylating partner; and

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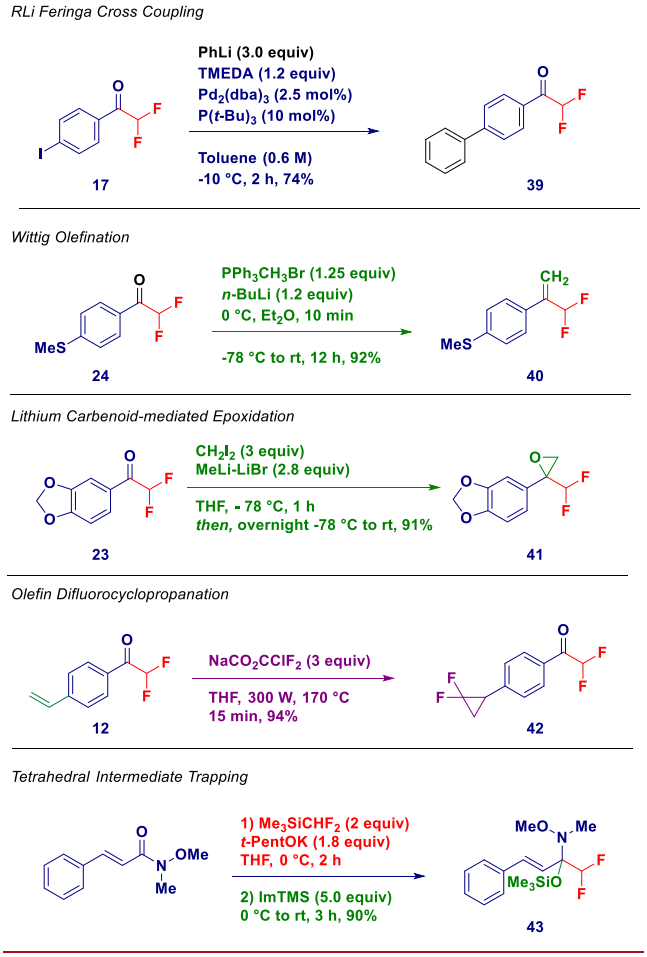
Scheme 3. Synthetic Versatility of α,α-Difluoromethylketones



(4) the complete retention of the stereochemical information contained in an optically active Weinreb amide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03024.

Experimental procedure, NMR spectra, HPLC traces, and analytical data for all the compounds (PDF)

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§M.M. and A.C contributed equally.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Norbert Haider in the occasion of his retirement.

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