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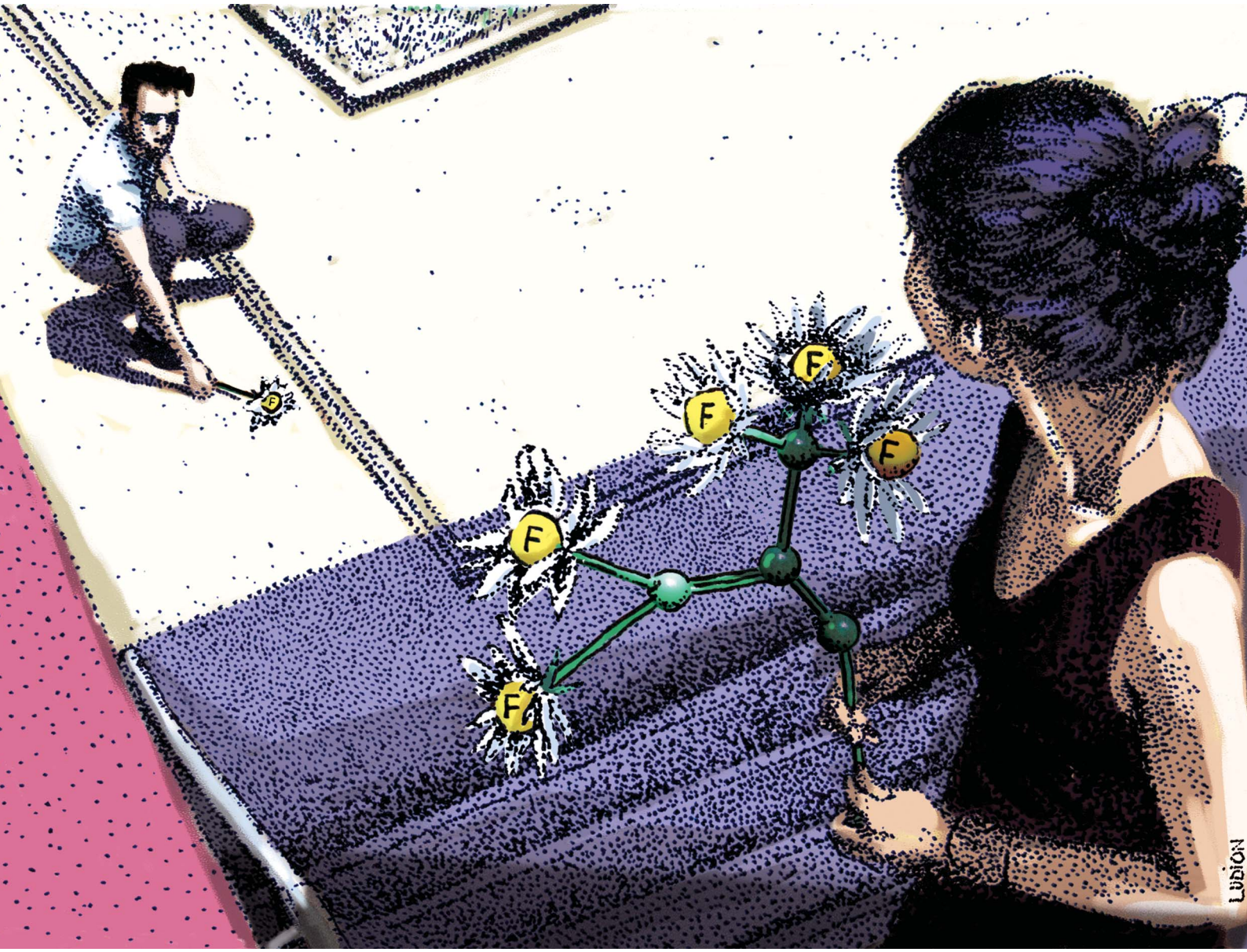

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EDGE ARTICLE

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Hexafluoroisobutylation of enolates through a tandem elimination/allylic shift/hydrofluorination reaction†

Aline Delamare,‡[a] Guillaume Naulet,‡[a] Brice Kauffmann,[b] Gilles Guichard *[a] and Guillaume Compain *[a]

The isobutyl side chain is a highly prevalent hydrophobic group in drugs, and it notably constitutes the side chain of leucine. Its replacement by a hexafluorinated version containing two CF_3 groups may endow the target compound with new and advantageous properties, yet this modification remains overlooked due to the absence of a general and practical synthetic methodology. Herein, we report the first general method to introduce the hexafluoroisobutyl group into ketoesters, malonates, 1,3-diketones, Schiff base esters and malononitrile. We demonstrated that the reaction occurs through an elimination/allylic shift/hydrofluorination cascade process which efficiently overcomes the usual fluoride β-elimination observed with α-CF_3-vinyl groups. We showed that with alkali metal bases, a pentafluorinated alkene is obtained predominantly, whereas the use of tetrabutylammonium fluoride (TBAF) allows hydrofluorination to occur. This tandem process represents a conceptually new pathway to synthesize bis-trifluoromethylated compounds. This methodology was applied to the multigram-scale synthesis of enantiopure (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine.

Introduction

Fluorine is highly prevalent in pharmaceuticals due to its potential beneficial effects.[1] The incorporation of one or several fluorine atoms is a well-established approach to improve the physical properties, stability and/or biological activity of a lead compound.[2,3] This approach was highly successful as shown by the large number of approved fluorinated drugs on the market,[1c,4] and many of them are polyfluorinated.[5] Therefore, there is a growing interest in developing methods to introduce emerging polyfluorinated groups.[6] In this context, we were interested in incorporating a hexafluoroisobutyl group, a fluorinated analogue of the leucine side chain. The isobutyl group is found in many peptide therapeutics and numerous other medicinal compounds (Chart 1). Replacing this hydrophobic side chain in such bioactive compounds by its hexafluorinated counterpart could enhance/modulate their biological properties (Fig. 1, top). With a dipole moment of 1.98 D,[7] it is more polar than a single CF_3 group (1.65 D),[8] and could promote dipolar interactions with a biological target. More importantly, the presence of two CF_3 groups significantly increases the hydrophobicity of the molecule while preserving the morphology of the parent compound.[9] This could favor the affinity for a biological target and/or the membrane permeability. Additionally, polyfluorinated versions of proteinogenic hydrophobic amino acids have proved particularly well suited to studying the structure and function of proteins as they provide additional sensitivity in ^{19}F NMR experiments and can be incorporated into proteins/peptides by either synthetic or biosynthetic methods.[10] In these respects, 5,5,5,5′,5′,5′-hexafluoroleucine which bears six fluorine atoms is a key fluorinated amino acid.[9b,c,11]

However, as there is no general synthetic method reported so far to incorporate this fluoroalkyl group, we seek to work out an efficient and practical protocol. Ideally, the side chain should be introduced in one step. The hexafluoroisobutene reagent would be a suitable reagent to perform such fluoroalkylation on enolates as it is highly electrophilic due to the presence of both CF_3 groups. However, α-CF_3-vinyl reagents usually react with nucleophiles through the S_N2' mechanism leading to β-fluoride eliminations (Fig. 1, middle). This reaction mechanism has often been considered as an opportunity to synthesize *gem*-difluoroalkenes for several decades.[12–15] Nevertheless, this elimination reaction remains the main obstacle for effective synthesis of

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^1H, ^{13}C, and ^{19}F NMR and HRMS) for all compounds; additional experiments to support the proposed mechanism including *in situ* NMR spectra; crystallographic data for compounds **11e**, **24b**, (*S*,*S*)-**25c** and (*S*,*S*)-**25b**. CCDC 2144790 (**11e**), 2144789 (**24b**), 1998317 ((*S*,*S*)-**25b**), 1998318 ((*S*,*S*)-**25c**). For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2sc02871a

‡ These authors contributed equally to this work.

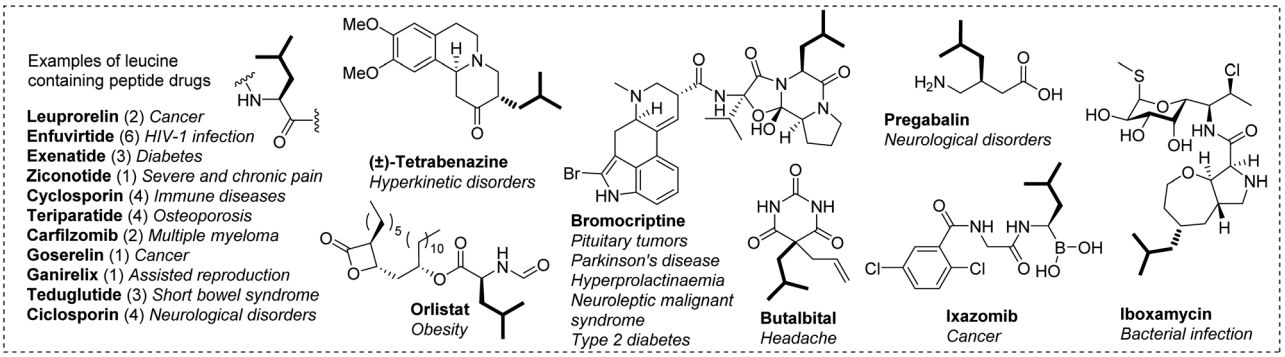


Chart 1 Selected drugs bearing the isobutyl side chain and their medical applications. For peptides, the number under brackets refers to the number of leucine residues.

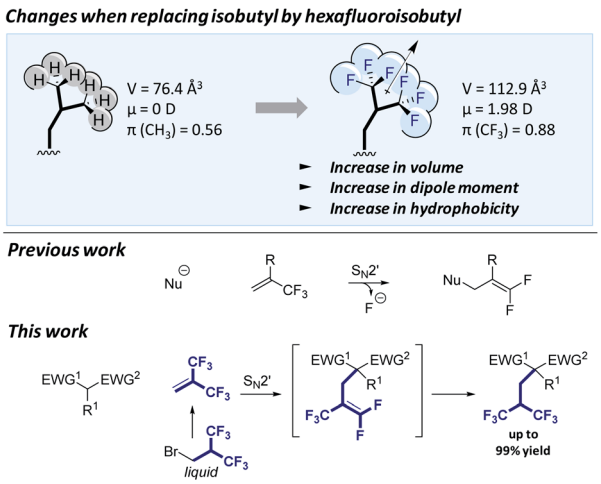


Fig. 1 Top: Changes in physical properties when replacing the isobutyl group by its hexafluorinated counterpart. π corresponds to the hydrophobic substituent constant.[9d] Middle: S_N2' mechanism previously described on α-CF_3-vinyl derivatives.[12–17] Bottom: The reaction reported in this work.

trifluoromethylated compounds using α-CF_3-vinyl groups or more generally α-CF_3 carbanion chemistry (Fig. 1, top).[16,17] Another disadvantage is that hexafluoroisobutene is a gas at room temperature[18] and applying this method would require specific safety equipment and make the measurement of small quantities inaccurate.

Herein, we report the first general synthetic method to introduce this fluorinated side chain in enolates based on an α,α-bis-CF_3-vinyl electrophile. The reaction requires the use of a non-gaseous simple fluorinated reagent generating *in situ* the α,α-bis-CF_3-vinyl electrophile. Furthermore, instead of avoiding fluoride elimination, the reaction involves a tandem allylic shift/hydrofluorination process (Fig. 1, bottom), overcoming the usual S_N2' undesired mechanism. Remarkably, the reaction occurs through a well-controlled cascade process under optimized conditions. This method was successfully applied to the synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine.

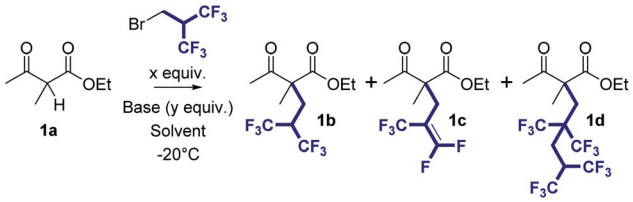
Results and discussion

Optimization of the reaction conditions

To incorporate the hexafluorinated side chain, we thought to use commercially available 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane. With a boiling point of 78 °C, this reagent is a liquid at room temperature, thus facilitating handling. We started this study by evaluating the alkylation reaction on ketoester **1a** using NaOH powder in THF at −20 °C (Table 1, entry 1). The reaction reached a maximum of conversion after 2 h. Unfortunately, the desired product **1b** was formed with a very low yield (12%, entry 1) and the pentafluoroalkenylated compound **1c** was obtained as the predominant product (45% yield). Despite the successful alkylation of **1a**, an elimination of fluoride is thus taking place at some point in the process. With LiOH, the elimination product was obtained with a better yield (51%) but compound **1b** was still the minor compound (14%). As the pentafluoroalkene moiety should be quite electrophilic due to the presence of five electron-withdrawing fluorine atoms, we tested whether the elimination could be reversed by using a source of fluoride as a base.[19] To our delight, TBAF alone was found to be effective in promoting the reaction. Disappointingly, with 4 equiv. of tetrabutylammonium fluoride (TBAF), **1c** was again obtained as the predominant product and the yield was even higher (69%). Only a trace amount of **1b** was observed in the crude mixture. In contrast, compound **1b** was successfully isolated with a good 63% yield when a larger quantity of TBAF (10 equiv.) was employed (entry 4). It is noteworthy that under these conditions, no elimination product **1c** was formed after 1 h of reaction. Additionally, an unexpected byproduct, compound **1d**, was also isolated as a minor compound formed during the reaction (9% yield). This compound is the result of two consecutive fluoroalkylations of **1a** with a close polarity to that of **1b**. At that stage, it was necessary to further improve the selectivity for the desired mono(hexafluoroalkylated) compound not only to increase the yield, but also to simplify the purification step.

Therefore, we next focused our effort on the optimization of the reaction conditions by changing the concentration, the

Table 1 Optimization of reaction conditions for hexafluoroisobutylation of **1a**



Entry	Base	y	Solvent	Conc. [mM]	x	t [h]	Yield 1b	Yield 1c	Yield 1d	1b/1c/1d[a]
1	NaOH	4	THF	33	2.0	2.0	12%	45%	—	1/4.3/0[b]
2	LiOH	4	THF	33	2.0	2.0	14%	51%	—	1/4.8/0[b]
3	TBAF	4	THF	33	2.0	1.0	Trace	69%	—	1/15.1/0
4	TBAF	10	THF	33	2.0	1.0	63%	—	9%	1/0/0.23
5	TBAF	10	THF	17	2.0	1.0	65%	—	8%	—[c]
6[d]	TBAF	10	THF	17	2.0	1.0	Trace	16%	Trace	1/7.2/0.28
7[e]	TBAF	10	THF	17	2.0	2.0	17%	19%	11%	1/1.8/0.67
8	TBAF	10	Toluene	33	2.0	5.0	2%	—	—	1/0/0
9[f]	TBAF	10	CH_2Cl_2	33	2.0	5.0	27%	11%	—	1/0.44/0
10	TBAF	10	AcOEt	33	2.0	1.5	32%	—	—	1/0/0
11	TBAF	10	CH_3CN	33	2.0	1.5	61%	—	—	1/0/0
12	TBAF	10	DMF	33	2.0	1.5	8%	—	—	—[c]
13	**TBAF**	**10**	**CH_3CN**	**33**	**1.1**	**1.0**	**71%**	**—**	**—**	**1/0/0**
14	TBAF	10	THF	33	1.1	1.0	48%	—	—	—[c]
15[g]	TBAF	10	CH_3CN	33	1.1	1.0	16%	—	—	—[c]
16	TBAF	10	CH_3CN	100	1.1	1.0	47%	—	—	1/0/0

[a] Crude ratio determined by ^{19}F NMR. [b] Other side products were observed in the crude NMR spectra. [c] The ratio could not be determined due to signal overlaps with other side products. [d] Reaction conducted at −50 °C for 1 h. [e] Reaction conducted at −50 °C for 1 h and then at RT for 1 h. [f] Reaction conducted at −20 °C for 1 h and then at RT for 4 h; no evolution of the reaction mixture after 4 h. [g] Reaction conducted at 0 °C.

temperature and the solvent. The concentration was reduced two-fold to see whether it could improve the selectivity, but similar yield and selectivity were observed (entry 5). Then, when running the reaction at −50 °C for 1 h, the conversion was dramatically reduced and the compound distribution was unsatisfactory (entry 6), even if the mixture was run at RT for one more hour (entry 7). Next, we tested different solvents (entries 8–12). When using toluene, a less polar solvent than THF, we observed almost no conversion after 5 hours of reaction (entry 8). In dichloromethane, the reaction provided only 27% of the desired compound **1b** and 11% of **1c** was also recovered. Pleasingly, the use of ethyl acetate and acetonitrile favored the selective formation of **1b** with no trace of **1c** or **1d** observed in the NMR spectra of the crude product (entries 10 and 11 respectively). Notably, the yield was twice as high in acetonitrile as it was in ethyl acetate, respectively at 61% *versus* 32%. Finally, the use of the more polar solvent DMF resulted in a complex mixture and compound **1b** was isolated with only 8% yield (entry 12). We thus selected acetonitrile to pursue our investigation. To our delight, when using only 1.1 equiv. of the fluorinated electrophile instead of 2.0 equiv. (entry 13 *versus* 11), the yield of compound **1b** was increased substantially (71%). However, changing back acetonitrile to THF (entry 14), increasing the temperature to 0 °C (entry 15) or increasing the concentration (entry 16) drastically reduced the yield of **1b**.

Scope of the hexafluoroisobutylation reaction

With our optimized conditions in hand (Table 1, entry 13), we examined the substrate scope of this reaction for a series of ketoesters (Fig. 2) with various substitutions at R^1, EWG^1 and EWG^2 positions, *i.e.* alkyl, cycloalkyl and aromatic groups. Overall, all substrates tested provided the desired compounds with high selectivity, *i.e.* no other side product was observed in the NMR spectra of the crude product. The reaction was found to be very effective with ethyl and benzyl groups positioned at the central carbon (R^1 group) leading to compounds **2b** and **3b** with 84% and 95% yield respectively. However, a lower yield was obtained when using a more hindered substrate such as **4a** bearing an isopropyl group which gave **4b** with a moderate yield (44%). Replacing the CH_3 group at the EWG^1 position by an aromatic substituent was found to be well tolerated (compounds **5–7b**) leading to the desired hexafluorinated products with good yields (60 to 78%). Then cyclic substrates were tested (compounds **8–11a**). The size of the ring was found to be critical. While with cyclopentanone **8a**, the resulting product **8b** was isolated with only 15% yield, cyclohexanone **9a** and cycloheptanone **10a** provided the hexafluorinated products with high yields, 84% and 87% respectively.

Finally, the lactone **11a** was found to be a special case. The expected compound **11b** was successfully isolated but with a moderate yield of 38%, and the reaction provided the

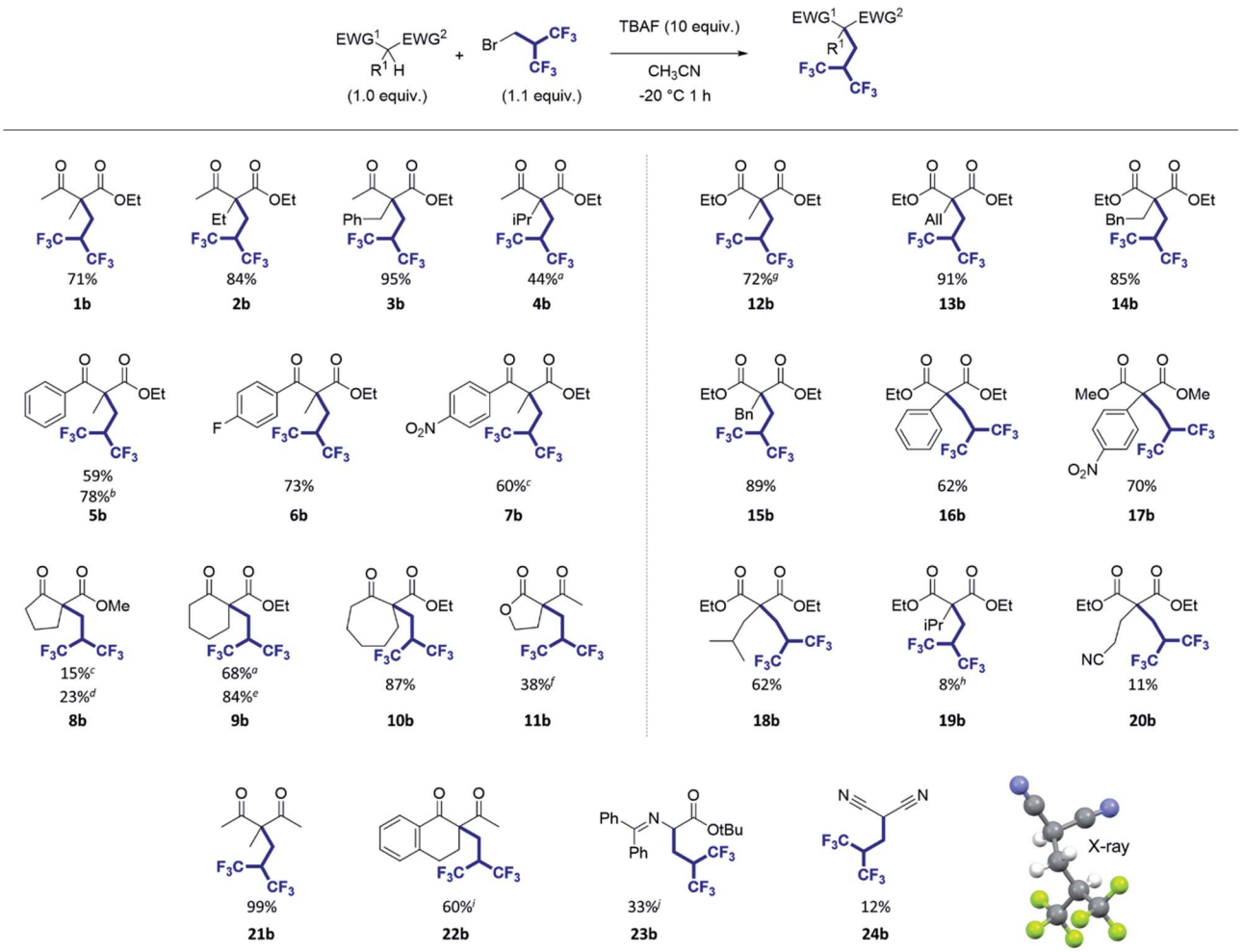
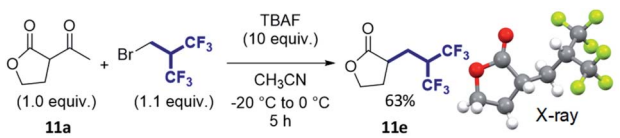


Fig. 2 Scope of the hexafluoroisobutylation reaction. [a]1.5 h of reaction time; [b]THF was used instead of CH_3CN; [c]2 h of reaction time; [d]THF was used instead of CH_3CN, 1.5 h of reaction time; [e]THF was used instead of CH_3CN with 2 equiv. of the electrophile; [f]the deacetylated product **11e** was obtained with 39% yield (see Scheme 1); [g]2 h of reaction time; [h]2.5 h of reaction time, 35% of the starting materials were recovered; [i]2 h of reaction time; [j]this compound was found unstable on silica gel and could not be separated from benzophenone, its decomposition product. The yield was estimated using the NMR ratio of the two products.



Scheme 1 Hexafluoroisobutylation/deacetylation domino reaction.[20]

deacetylated product **11e** as well with 39% yield. The structure of **11e** was confirmed by X-ray structure analysis. Notably, we thought that promoting the deacetylation reaction would be of special interest since it could provide the hexafluoroalkylated ester in one step. The reaction was carried out for a longer time and at higher temperature to see whether **11b** could be converted to **11e**. Pleasantly, this cascade reaction exclusively afforded **11e**, isolated with 63% yield which is a remarkable yield for such a multi-reaction process, and this reaction allows direct access to a substituted ester (Scheme 1).

Next, we explored the reactivity of malonate derivatives (Fig. 2, right) bearing saturated, unsaturated and aromatic substituents. Gratifyingly, this reaction is quite compatible with these substrates. Good to excellent yields were obtained for compounds **12–18b**, having methyl, allyl, benzyl, homobenzyl, phenyl, *p*-nitrophenyl and isobutyl groups. Interestingly, compound **13b** could be used as a potential precursor of the fluorinated analogue of butalbital (see Chart 1). Nonetheless, the reaction afforded a lower yield with an isopropyl group (substrate **19a**), even lower than that for substrate **4a** in the ketoester series, which seems to confirm the sensitivity of the reaction to steric effects. A low yield was also obtained for the compound **20b** bearing a nitrile functional group.

We finally tested a set of other pronucleophiles including 1,3-diketones, iminoester, and malononitrile (Fig. 2, bottom). The reaction was found to be compatible with 1,3-diketones **21a** and **22a**. Notably, a quantitative yield was obtained for compound **21b**. The reaction on iminoester **23a** provided the desired fluorinated compound with 33% yield. It is worth

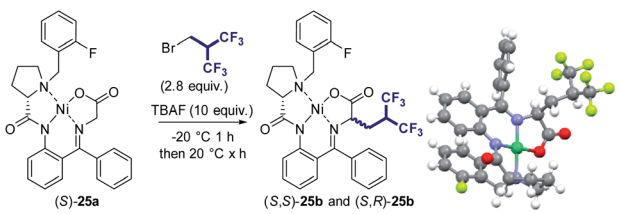
noting that the presence of a second acidic proton on the molecule did not provide a dialkylated compound. Finally, only 12% yield was obtained for the compound **24b** starting from malononitrile.

Synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine

Then, we sought to apply this methodology to the synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine whose potential use is still limited by its synthetic accessibility. Although several enantiopure syntheses of this fluorinated amino acid have been reported,[21] the incorporation of the hexafluoroisobutyl group essentially relies on the use of either hexafluoroacetone, a highly toxic gas requiring specific safety equipment, or the expensive $[(CF_3)_2C]_2S_2$ reagent. Moreover, several steps are still necessary after the installation of the fluorinated moiety to access the desired fluoroalkyl amino acid and cognate amino acid. We tested our methodology starting from the Ni(II) chiral complex of the glycine Schiff base (*S*)-**25a** (Table 2).[22–24] The stereoselective homologation of Ni(II) chiral complexes is a robust synthesis approach to access non-canonical amino acids,[25] which has been efficiently employed for the synthesis of various fluorinated amino acids.[26] To our delight, the use of our optimized procedure provided the desired mono(hexafluoroalkylated) compound **25b** with 63% yield (Table 2, entry 1). The compound was obtained with a very good diastereoselectivity ((*S*,*S*)-**25b**/(*S*,*R*)-**25b**: 92/8). The major diastereoisomer was readily crystallizing and its structure was confirmed by X-ray analysis.

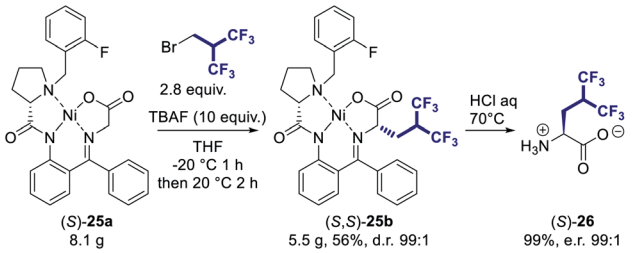
However, the reaction was found to be much slower compared to the previous substrates, requiring 1 h at −20 °C and then 20 h at room temperature to reach a full conversion. This is probably due to the increased steric hindrance of the nucleophile. Less polar solvents CH_2Cl_2 gave **25b** in 39% yield (entries 2). In DMF, 36% yield was obtained (entry 3) which is significantly higher than the yield attained with **1a** (8%). In contrast, when using THF (entry 4), the yield was improved (66%) and the reaction was found to proceed much faster than in acetonitrile (3 h *versus* 21 h). If only 5 equiv. of TBAF were used, the reaction was slowed down and provided **25b** with a lower yield confirming that 10 equiv. of TBAF are necessary (entry 5).

Table 2 Optimization of hexafluoroisobutylation on nickel complex **25a**



Entry	Solvent	Reaction time[a]	Yield **25b**[b]	(*S*,*S*)-**25b** : (*S*,*R*)-**25b**[c]
1	CH_3CN	21 h	63%	92 : 8
2	CH_2Cl_2	21 h	39%	93 : 7
3	DMF	1.5 h	36%	92 : 8
4	THF	3 h	66%	90 : 10
5[d,e]	THF	21 h	53%	n.d.

[a] The reaction time corresponds to 1 + *x*. [b] The isolated yield refers to the isolation of the mixture of diastereoisomers (*S*,*S*)-**25** and (*S*,*R*)-**25**. [c] Determined by ^{19}F NMR. [d] 5 equiv. of TBAF were used. [e] 19% of **25a** was recovered after flash chromatography.



Scheme 2 Hexafluoroisobutylation scale-up procedure on nickel complex (*S*)-**25a** and hydrolysis of alkylated complexes (*S*,*S*)-**25b** to provide enantiomerically pure amino acid (*S*)-**26**.

This methodology is compatible with a multi-gram scale procedure as shown in Scheme 2. The two diastereoisomers (*S*,*S*)-**25b** and (*S*,*R*)-**25b** were successfully separated by flash chromatography affording pure (*S*,*S*)-**25b** with a diastereomeric ratio of 99 : 1. The hydrolysis of the alkylated complex (*S*,*S*)-**25b** afforded hexafluoroleucine (*S*)-**26** with an almost quantitative yield. To confirm the high enantiopurity of the resulting fluorinated amino acid, the enantiomeric excess was determined using the Marfey's derivatization method (see ESI†),[27] and an enantiomeric ratio of 99 : 1 ((*S*)-**26** : (*R*)-**26**) was obtained.

Mechanistic study

To get insights into the reaction mechanism, the reactivity of the fluorinated electrophile was studied in the presence of TBAF and the reaction was followed by ^{19}F NMR (Fig. 3A) and ^{1}H NMR (Fig. S1†). After only 2 minutes, the brominated reagent undergoes an elimination of HBr to produce HFIB, and the latter one is relatively stable in the reaction medium beyond 3 h. Indeed, this reaction is favored due to the presence of two CF_3 groups which extensively contribute to enhancing the acidity of the central C–H bond.[28] Consequently, the alkylating reagent in the reaction is unlikely to be the bromo derivative but rather the alkene instead. Interestingly, we did not observe HF addition to the alkene by NMR despite the high content of TBAF. To get additional insights on the reaction mechanism, we performed several experiments with **25a**, with which the reaction was found to be slower than with other substrates. As observed with **1a**, the pentafluoroalkene product **25c** was formed predominantly when using NaOH as the base (55% yield). The structure of compound **25c** was confirmed by X-ray diffraction analysis (Fig. 4). Aside from **25c**, compound **25b** was recovered only in 6% yield together with 20% of the starting material (see the ESI†). Interestingly, when monitoring the reaction performed with TBAF by TLC (Table 2, entry 5), the pentafluorinated elimination product **25c** was observed first and then converted into the hexafluorinated compound **25b** (Fig. S2†). We also

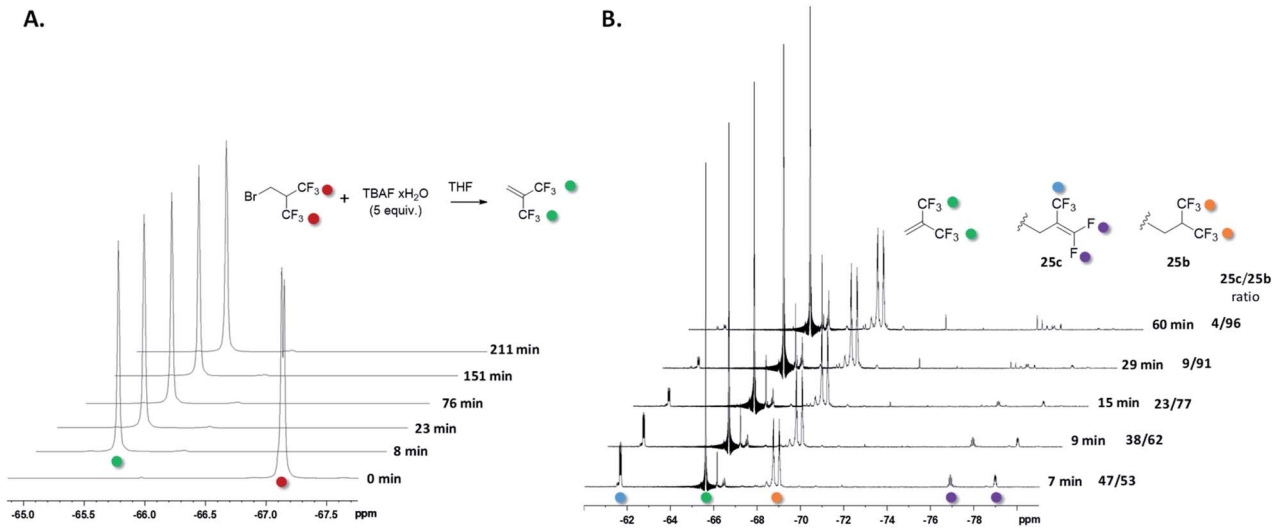


Fig. 3 (A) *In situ* ^{19}F NMR spectra of the reaction of 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane and TBAF in THF-d_8. (B) *In situ* ^{19}F NMR spectra of the reaction of **25a**, 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane and TBAF (10 equiv.) in THF-d_8.

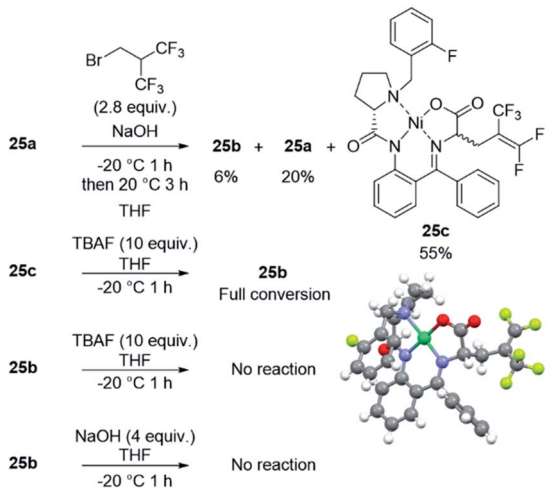
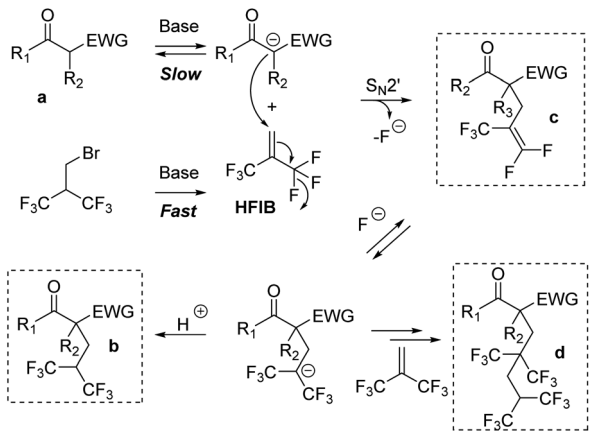


Fig. 4 Reactions of nickel complex **25a** with NaOH, **25c** with TBAF, **25b** with TBAF and NaOH. The X-ray structure of compound (*S*,*S*)-**25c**.



Scheme 3 Proposed mechanism for the formation of compounds **b**, **c** and **d** through cascade reactions.

performed *in situ* NMR experiments to monitor the reaction of **25a** at 0 °C (Fig. 3B). The formation of both compounds **25b** and **25c** was rapidly observed (after only 7 minutes). Then, the proportion of compound **25c** started to decrease progressively over time with a concomitant increase in the intensity of the signal corresponding to compound **25b**. These observations indicate that compound **25c** is formed first and then converted into compound **25b**, thus suggesting that TBAF promotes the addition of HF to the alkene. To confirm this mechanism, alkene **25c** was treated with 10 equiv. of TBAF, and under these conditions, the compound was fully converted into **25b** within 1 h. To see whether the hexafluorinated compound is in equilibrium with the alkene, **25b** was treated with both TBAF (10 equiv.) and NaOH (4 equiv.) for 1 h at 0 °C. Under these conditions, **25b** was found to be very stable with no trace of **25c** being observed (Fig. 4 and S3†).

Based on the overall results, we propose the mechanisms shown in Scheme 3. The brominated reagent rapidly undergoes an elimination of HBr under basic conditions to provide HFIB. In parallel, the deprotonation of the substrate **a** leads to the formation of enolate, which then reacts with HFIB through an S_N2' mechanism. This provides the elimination product **c**. Then, the difluoroalkene undergoes a fluoride addition to give an anionic intermediate. The latter one can either react with a proton to provide **b** or with HFIB leading to **d**. It is noteworthy that despite the complexity of the multiple cascade processes, the optimized procedure allows the selective and efficient formation of compound **b**.

Conclusions

In summary, we report the first general method to incorporate the hexafluoroisobutyl group into enolates, including ketoesters, malonates, Schiff base esters, diketones, and malononitrile.

The reaction is based on the nucleophilic attack on HFIB, rapidly formed under basic conditions from 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane, as revealed by NMR. This method is highly practical since the brominated reagent is liquid at room temperature, unlike HFIB. The reaction first promotes the β-elimination of a fluoride through an S_N2' mechanism affording the corresponding pentafluorinated alkene. Unfortunately, when using alkali metal bases, the reaction predominantly provides this undesired alkene. However, we found that the use of TBAF as a base allows the efficient and selective formation of the hexafluoroisobutylated compounds by promoting the addition of HF to the alkene. *In situ* NMR data and other experiments support the tandem elimination/allylic shift/hydrofluorination mechanism. This methodology was successfully applied to the synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine thanks to diastereoselective fluoroalkylation of a Schiff base chiral nickel complex. Hydrolysis of the nickel complex readily affords the fluorinated amino acid in one step with high enantiopurity. The ease to manipulate the brominated reagent, liquid at room temperature, makes the synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine much more simple and practical than the previously reported syntheses allowing its preparation on a multi-gram scale. This hexafluoroisobutylation reaction is the first example of a tandem allylic shift/hydrofluorination process and provides a conceptually new pathway to perform fluoroalkylation reactions. This methodology affords an easy protocol to incorporate hexafluoroisobutyl groups to engineer bioactive compounds, for applications in medicinal chemistry and chemical biology.

Data availability

The data that support the findings of this study are available in the ESI† and in the CIF files for crystallographic data.

Author contributions

A. D., G. N., and G. C. performed the experiments, optimized the reaction conditions, developed substrate scope, synthesized (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine and conducted detailed mechanistic studies. B. K. performed the X-ray diffraction analysis of the compounds. G. C. and G. G. conceived the idea, designed the research, and wrote the manuscript. All the authors commented on the draft of the manuscript and contributed to the analysis and interpretation of the data.

Conflicts of interest

The authors declare no conflict of interest.

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