EDGE ARTICLE
Gilles Guichard, Guillaume Compain et al.
Hexafluoroisobutylation of enolates through a tandem elimination/allylic shift/hydrofluorination reaction
Hexafluoroisobutylolation of enolates through a tandem elimination/allylic shift/hydrofluorination reaction†

Aline Delamare,‡a Guillaume Naulet,‡a Brice Kauffmann, b Gilles Guichard †b 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 CF₃ 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-CF₃-vinyl groups. We showed that with alkali metal bases, a pentafluoromethylated 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'-hexafluoroisoleucine.

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,⁴⁻⁶ and many of them are polyfluorinated.⁵ Therefore, there is a growing interest in developing methods to introduce emerging polyfluorinated groups.⁵ In this context, we were interested in incorporating a hexafluoroisobutylic 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 CF₃ group (1.65 D),⁸ and could promote dipolar interactions with a biological target. More importantly, the presence of two CF₃ 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 ¹⁹F NMR experiments and can be incorporated into proteins/peptides by either synthetic or biosynthetic methods.¹⁰ In these respects, 5,5,5,5',5'-hexafluoroisoleucine which bears six fluorine atoms is a key fluorinated amino acid.¹⁰⁻¹²

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 CF₃ groups. However, α-CF₃-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.¹²⁻¹⁸ Nevertheless, this elimination reaction remains the main obstacle for effective synthesis of
triﬂuoromethylated compounds using $\alpha$-CF$_3$-vinyl groups or more generally $\alpha$-CF$_3$ carbanion chemistry (Fig. 1, top). Another disadvantage is that hexaﬂuoroisobutene is a gas at room temperature 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 $\alpha$,$\alpha$-bis-CF$_3$-vinyl electrophile. The reaction requires the use of a non-gaseous simple ﬂuorinated reagent generating in situ the $\alpha$,$\alpha$-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 $\text{S}_2^\text{O}$ 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 0 °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, a 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 our source of ﬂuoride as a base. 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 (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. To our delight, TBAF alone was found to be effective in promoting the reaction. Disappointingly, with 4 equiv. of tetrabutylammonium ﬂuoride (TBAF), 1e 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(hexam ﬂuoroalkylated) 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
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 R1, EWG1 and EWG2 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 (R1 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 CH3 group at the EWG1 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

---

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

| Entry | Base   | y | Solvent | Conc. [mM] | x | t [h] | Yield |
|-------|--------|---|---------|------------|---|------|-------|
| 1     | NaOH   | 4 | THF     | 33         | 2.0 | 2.0  | 12% 45%  — 1/4.3/0    |
| 2     | LiOH   | 4 | THF     | 33         | 2.0 | 1.0  | 14% 51%  — 1/4.8/0    |
| 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%  1/0.23      |
| 5     | TBAF   | 10| THF     | 17         | 2.0 | 1.0  | 65% — 8%  —           |
| 6     | TBAF   | 10| THF     | 17         | 2.0 | 1.0  | Trace 16% Trace 1/7.2/0.28 |
| 7     | TBAF   | 10| Toluene | 33         | 2.0 | 5.0  | 17% 19%  11% 1/1.8/0.67 |
| 8     | TBAF   | 10| CH2Cl2 | 33         | 2.0 | 5.0  | 2% — — 1/0/0          |
| 9     | TBAF   | 10| CH2CN  | 33         | 2.0 | 1.5  | 27% 11% — 1/0.4/0     |
| 10    | TBAF   | 10| AcOEt  | 33         | 2.0 | 1.5  | 32% — — 1/0/0         |
| 11    | TBAF   | 10| CH3CN  | 33         | 2.0 | 1.5  | 61% — — 1/0/0         |
| 12    | TBAF   | 10| DMF    | 33         | 2.0 | 1.5  | 8% — — —              |
| 13    | TBAF   | 10| CH2CN  | 33         | 1.1 | 1.0  | 71% — — 1/0/0         |
| 14    | TBAF   | 10| THF    | 33         | 1.1 | 1.0  | 48% — — —              |
| 15    | TBAF   | 10| CH2CN  | 33         | 1.1 | 1.0  | 16% — — —              |
| 16    | TBAF   | 10| CH2CN  | 100        | 1.1 | 1.0  | 47% — — 1/0/0         |

---

The yields are expressed as a ratio of the desired compound to other products observed in the crude product. The ratio was determined by 1H NMR. Other side products were observed in the crude NMR spectra. The reaction conducted at –50 °C for 1 h. The reaction conducted at –50 °C for 1 h and then at RT for 1 h. The reaction conducted at –20 °C for 1 h and then at RT for 4 h; no evolution of the reaction mixture after 4 h.
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'-hexafluoroisoleucine**

Then, we sought to apply this methodology to the synthesis of (S)-5,5,5',5',5'-hexafluoroisoleucine whose potential use is still limited by its synthetic accessibility. Although several enantioselective syntheses of this fluorinated amino acid have been reported, the incorporation of the hexafluorosobutyl group essentially relies on the use of either hexafluoroacetone, a highly toxic gas requiring specific safety equipment, or the expensive [(CF₃)₂C]₂S₂ reagent. Moreover, several steps are still necessary after the installation of the fluorinated moiety to access the desired fluoroacyl 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). The stereoselective homologation of Ni(II) chiral complexes is a robust synthesis approach to access non-canonical amino acids, which has been efficiently employed for the synthesis of various fluorinated amino acids. 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 CH₂Cl₂ 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).

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 hexafluoroisoleucine ([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†). 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 ¹9F NMR (Fig. 3A) and ¹H 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 CF₃ groups which extensively contribute to enhancing the acidity of the central C–H bond. 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†).

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

| Entry | Solvent | Reaction timeb | Yield 25b | ([S,S]-25b : [S,R]-25b) |
|-------|---------|----------------|-----------|-------------------------|
| 1     | CH₃CN   | 21 h           | 63%       | 92 : 8                  |
| 2     | CH₂Cl₂  | 21 h           | 39%       | 93 : 7                  |
| 3     | DMF     | 1.5 h          | 36%       | 92 : 8                  |
| 4     | THF     | 3 h            | 66%       | 90 : 10                 |
| 5      | THF     | 21 h           | 53%       | n.d.                    |

* 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 ¹9F NMR. d 5 equiv. of TBAF were used. e 19% of 25a was recovered after flash chromatography.
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_{N}2 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 SN2 mechanism affording the corresponding pentfluorinated 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 hexafluoroisobutylation 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′-hexafluoroleucine thanks to diastereoselective fluorooalkylation 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 base chiral nickel complex. Hydrolysis of the nickel complex readily affords the fluorinated amino acid in one step with high enantiopurity.

Notes and references

1 (a) N. A. Meanwell, J. Med. Chem., 2018, 61, 5822–5880; (b) E. P. Gillis, K. J. Eastman, M. D. Hill and D. J. Donnelly, J. Med. Chem., 2015, 58, 8315–8359; (c) A. C. Flick, C. A. Leverett, H. X. Ding, E. McInturff, S. J. Fink, C. J. Helal and C. J. O’Donnell, J. Med. Chem., 2019, 62, 7340–7382.

2 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, Chem. Rev., 2016, 116, 422–518.

3 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Chem. Soc. Rev., 2008, 37, 320–330.

4 (a) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, Chem.–Eur. J., 2019, 25, 11797–11819; (b) M. Inoue, Y. Sunii and N. Shibata, ACS Omega, 2020, 5, 10633–10640.

5 (a) M. Bassetto, S. Ferla and F. Pertusati, Future Med. Chem., 2015, 7, 527–546; (b) F. Pertusati, M. Serpi and E. Pileggi, Polfluorinated Scaffolds in Drug Discovery, in Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals, Elsevier, 2019, pp. 141–180.

6 (a) D. Cahard and J. Ma, in Emerging Fluorinated Motifs: Synthesis, Properties, and Applications, Wiley, 1st edn, 2020; (b) S. Meyer, J. Häfliger and R. Gilmour, Chem. Sci., 2021, 12, 10686–10695; (c) Q. Wang, Q. Tao, H. Dong, C. Ni, X. Xie and J. Hu, Angew. Chem. Int. Ed., 2021, 60, 27318–27323; Angew. Chem., 2021, 133, 27524–27529.

7 A. R. H. Goodwin and J. B. Mehl, Int. J. Thermophys., 1997, 18, 795–806.

8 D. O’Hagan, Chem. Soc. Rev., 2008, 37, 308–319.

9 (a) B. Linclau, Z. Wang, G. Compain, V. Paumelle, C. Q. Fontenelle, N. Wells and A. Weymouth-Wilson, Angew. Chem. Int. Ed., 2016, 55, 674–678; Angew. Chem., 2016, 128, 684–688; (b) S. Huhmann, A.-K. Stegemann, K. Follmert, D. Klemczak, J. Moschner, M. Kubé and B. Koksch, Beilstein J. Org. Chem., 2017, 13, 2869–2882; (c) E. N. G. Marsh, Acc. Chem. Res., 2014, 47, 2878–2886; (d) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikitani and E. J. Lien, J. Med. Chem., 1973, 16, 1207–1216.

10 (a) M. A. Miller and E. M. Sletten, ChemBioChem, 2020, 21, 3451–3462; (b) E. N. G. Marsh and Y. Suzuki, ACS Chem. Biol., 2014, 9, 1242–1250.

11 (a) H. Mei, J. Han, K. D. Klika, K. Izawa, T. Sato, N. A. Meanwell and V. A. Soloshonok, Eur. J. Med. Chem., 2020, 186, 111826; (b) H. Meng and K. Kumar, J. Am. Chem. Soc., 2007, 129, 15615–15622; (c) L. M. Gottler, H.-Y. Lee, C. E. Shelburne, A. Ramamoorthy and E. N. G. Marsh, ChemBioChem, 2008, 9, 370–373; (d) H. Meng,
S. T. Krishnaji, M. Beinborn and K. Kumar, *J. Med. Chem.*, 2008, 51, 7303–7307; (e) S. Huhmann and B. Koksch, *Eur. J. Org. Chem.*, 2018, 2018, 3667–3679.

12 (a) X. Zhang and S. Cao, *Tetrahedron Lett.*, 2017, 58, 375–379; (b) G. Chelucci, *Chem. Rev.*, 2012, 112, 1344–1462; (c) F. Tian, G. Yan and J. Yu, *Chem. Commun.*, 2019, 55, 13486–13505.

13 (a) T. Fuchikami, Y. Shibata and Y. Suzuki, *Tetrahedron Lett.*, 1986, 27, 3173–3176; (b) T. Kitazume and T. Ohnogi, *Synthesis*, 1988, 1988, 614–615; (c) T. Kitazume, T. Ohnogi, H. Miyauchi, T. Yamazaki and S. Watanabe, *J. Org. Chem.*, 1989, 54, 5630–5632; (d) S. Watanabe, K. Sugahara, T. Fujita, M. Sakamoto and T. Kitazume, *J. Fluorine Chem.*, 1993, 62, 201–206; (e) H. M. Park, T. Uegaki, T. Konno, T. Ishihara and H. Yamanaka, *Tetrahedron Lett.*, 1999, 40, 2985–2988; (f) K. Funabiki, K. Sawa, K. Shibata and M. Matsui, *Synlett*, 2002, 2002, 1134–1136; (g) W. Dai, Y. Lin, Y. Wan and S. Cao, *Org. Chem. Front.*, 2018, 5, 55–58.

14 (a) V. Martin, H. Molines and C. Wakselman, *J. Org. Chem.*, 1992, 57, 5530–5532; (b) J. Ichikawa, H. Fukui and Y. Ishibashi, *J. Org. Chem.*, 2003, 68, 7800–7805; (c) J.-P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Tetrahedron Lett.*, 1995, 36, 5003–5006; (d) J.-P. Bégué, B.-D. Delpon and M. H. Rock, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1409–1413; (e) J. Ichikawa, Y. Ishibashi and H. Fukui, *Tetrahedron Lett.*, 2003, 44, 707–710; (f) J. Ichikawa, H. Miyazaki, K. Sakoda and Y. Wada, *J. Fluorine Chem.*, 2004, 125, 585–593; (g) J. Ichikawa, M. Yokota, T. Kudo and S. Umezaki, *Angew. Chem. Int. Ed.*, 2008, 47, 4870–4873; *Angew. Chem.*, 2008, 120, 4948–4951; (h) K. Fuchibe, M. Takahashi and J. Ichikawa, *Angew. Chem. Int. Ed.*, 2012, 51, 12059–12062; *Angew. Chem.*, 2012, 24, 12225–12228.

15 (a) B. M. Kraft and W. D. Jones, *J. Am. Chem. Soc.*, 2002, 124, 8681–8689; (b) Y. Huang and T. Hayashi, *J. Am. Chem. Soc.*, 2016, 138, 12340–12343; (c) Y. Liu, Y. Zhou, Y. Zhao and J. Qu, *Org. Lett.*, 2017, 19, 946–949; (d) M. Wang, X. Pu, Y. Zhao, P. Wang, Z. Li, C. Zhu and Z. Shi, *J. Am. Chem. Soc.*, 2018, 140, 9061–9065.

16 C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, 45, 5441–5454.

17 K. Burger and B. Helmreich, *J. Chem. Soc., Chem. Commun.*, 1992, 348–349.

18 P. M. Murphy, *J. Fluorine Chem.*, 2013, 156, 345–362.

19 For some examples of the use of TBAF as a base, see: (a) S. Liu, X. Chen, Y. Hu, L. Yuan, S. Chen, P. Wu, W. Wang, S. Zhang and W. Zhang, *Adv. Synth. Catal.*, 2015, 357, 553–560; (b) G. V. M. Sharma, V. G. Chander, A. S. Reddy and K. R. Reddy, *Tetrahedron: Asymmetry*, 2002, 13, 21–24; (c) J. H. Clark, *Chem. Rev.*, 1980, 80, 429–452.

20 J. J. Ritter and T. J. Kaniecki, *J. Org. Chem.*, 1962, 27, 622–623.

21 (a) Y. Tang and D. A. Tirrell, *J. Am. Chem. Soc.*, 2001, 123, 11089–11090; (b) X. Xing, A. Fichera and K. Kumar, *Org. Lett.*, 2001, 3, 1285–1286; (c) J. T. Anderson, P. L. Toogood and E. N. G. Marsh, *Org. Lett.*, 2002, 4, 4281–4283; (d) H.-P. Chiu and R. P. Cheng, *Org. Lett.*, 2007, 9, 5517–5520; (e) H.-P. Chiu, Y. Suzuki, D. Gullickson, R. Ahmad, B. Kokona, R. Fairman and R. P. Cheng, *J. Am. Chem. Soc.*, 2006, 128, 15556–15557.

22 H. Mei, T. Hiramatsu, R. Takeda, H. Moriwaki, H. Abe, J. Han and V. A. Soloshonok, *Org. Process Res. Dev.*, 2019, 23, 629–634.

23 F. Drouet, A. F. M. Noisier, C. S. Harris, D. P. Furkert and M. A. A. Brimble, *Eur. J. Org. Chem.*, 2014, 2014, 1195–1201.

24 (a) A. S. Saghyan, A. S. Dadayan, S. A. Dadayan, A. F. Mkrtchyan, A. V. Geolchanyan, L. L. Manasyan, H. R. Ajvazyan, V. N. Khristalev, H. H. Hambardzumyan and V. I. Maleev, *Tetrahedron: Asymmetry*, 2010, 21, 2956–2965; (b) J. Wang, D. Lin, S. Zhou, X. Ding, V. A. Soloshonok and H. Liu, *J. Org. Chem.*, 2011, 76, 684–687; (c) The Ni(u) complex can be easily synthesized in four steps. Please see the ESI.†

25 Y. Wang, X. Song, J. Wang, H. Moriwaki, V. A. Soloshonok and H. Liu, *Amino Acids*, 2017, 49, 1487–1520.

26 J. L. Aceña, A. E. Sorochinsky, H. Moriwaki, T. Sato and V. A. Soloshonok, *J. Fluorine Chem.*, 2013, 155, 21–38.

27 R. Bhushan and H. Brückner, *Amino Acids*, 2004, 27, 231–247.

28 R. N. Haszeldine, *J. Chem. Soc.*, 1953, 3565–3572.