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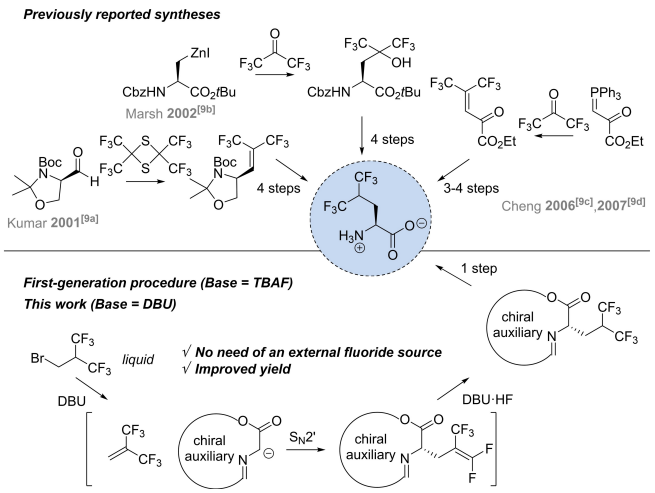
In Situ Generated DBU·HF Acts as a Fluorinating Agent in a Hexafluoroisobutylation Tandem Reaction: An Effective Route to 5,5,5,5′,5′,5′-Hexafluoroleucine

Guillaume Naulet[+],[a] Aline Delamare[+],[a] Gilles Guichard,*[a] and Guillaume Compain*[a]

We report the direct incorporation of the hexafluoroisobutyl group on a chiral glycine Schiff base complex mediated by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The fluoroalkylation involves 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane reagent, which generates *in situ* hexafluoroisobutylene (HFIB), and reacts then with the enolate through a tandem allylic shift/hydrofluorination process. We showed that the use of neutral organic base DBU generates *in situ* an original DBU·HF salt, which preserves the fluoride nucleophilicity and acts as a fluorinating agent. This fluoride salt promotes the hydrofluorination of the pentafluorinated alkene overcoming the usual fluoride β-elimination observed with α-CF_3-vinyl reagents. With alkali metal bases, by contrast, the hydrofluorination is disfavored and the pentafluorinated alkene intermediate is obtained predominantly. This study highlights the critical role of the fluoride counter ion to preserve its nucleophilicity. The protocol is amenable to multidecagram scale synthesis of enantiopure (*S*)- and (*R*)-5,5,5,5′,5′,5′-hexafluoroleucine and their N-Fmoc or N-Boc derivatives in good overall yield.

Introduction

Fluorinated amino acids in drug design and protein science are currently the focus of intensive research.[1] Fluorination influences many properties including hydrophobicity, conformational preferences, basicity/acidity and hydrogen bonding properties of amino acids and related peptides and proteins. Yet, the replacement of hydrogen atoms by fluorines in proteinogenic amino acids has only a small impact on the steric parameters providing amino acid derivatives with a morphology close to the parent compound.[1b] In this context, amino acids with polyfluorinated chains have recently emerged as promising building blocks to modulate the properties of biologically active peptides.[1e] This interest parallels the development of new methods to incorporate polyfluorinated groups in organic molecules to allow exploration of their potential benefits in drug discovery.[2,3] Moreover, fluorinated proteinogenic hydrophobic amino acids have proved to be useful tools to study the structure and function of peptides and proteins by ^{19}F NMR spectroscopy.[4] In particular, (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine (Hfl) is a key fluorinated amino acid.[1e,5] With six fluorine atoms, this highly fluorinated amino acid displays a significantly higher hydrophobicity than the corresponding canonical version,[5d,f,6] and the side chain possesses a relatively strong dipole moment (1.98 D),[7] higher than that of the CF_3 group (1.65 D).[8] Several syntheses giving access to enantiopure (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine have been previously reported.[9] The construction of the hexafluoroisobutyl side chain employs either hexafluoroacetone, a highly toxic gas requiring specific safety equipment – even though more manageable trihydrate form can also be used as reported by the Cheng's group[9d] – or the $[(CF_3)_2C]_2S_2$ reagent, currently costly or requiring the use of hexafluoropropene gas and sulfur to prepare it (Scheme 1, top).[10] Impor-



Scheme 1. Top, previously reported synthetic strategies to introduce the fluorinated side chain to synthesize (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine; Bottom, strategy reported here to incorporate the hexafluoroisobutyl side chain on a chiral glycine derivative using DBU as base.

[a] Dr. G. Naulet,[+] A. Delamare,[+] Dr. G. Guichard, Dr. G. Compain
Univ. Bordeaux, CNRS, Bordeaux INP, CBMN, UMR 5248, IECB, 33600 Pessac, France
E-mail: g.guichard@iecb.u-bordeaux.fr
g.compain@iecb.u-bordeaux.fr

[+] These authors contributed equally to this work.

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tantly, the fluorinated side chain is generally incorporated at an early stage in the synthetic pathway starting from either enantiopure (Kumar and Marsh groups) or achiral (Cheng group) substrates, and three to four additional steps are still needed to access the unprotected amino acid. Therefore, the amount of fluorinated reagent needed to produce a large quantity of the final compound is substantially higher compared to a strategy where the fluorinated side chain would be incorporated at a later stage.

Recently, we described an alternative method to introduce the fluorinated side chain by using the 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane reagent, a liquid at room temperature, and TBAF, as base and fluoride source.[11] This methodology was subsequently applied to the synthesis of 5,5,5,5′,5′,5′-hexafluoroleucine by using a chiral nickel complex of glycine Schiff base allowing installation of the hexafluoroisobutyl group at the penultimate stage of the amino acid synthesis. Chiral nickel complexes are particularly well-suited for the synthesis of non-proteinogenic amino acids including also fluorinated amino acids as exemplified by the Soloshonok[12–14] and more recently the Koksch[15] groups. We showed that the brominated reagent undergoes an *in situ* elimination of HBr to produce HFIB which acts as the electrophile. Then, HFIB reacts with the enolate through a S_N2' mechanism to provide a pentafluorinated alkene. This intermediate is then fully converted to the hexafluorinated compound thanks to the excess of fluoride ions in the media. Notably, this procedure allows to overcome the usual β-fluoride elimination (S_N2' mechanism) observed when α-CF_3-vinyl groups react with nucleophiles leading to *gem*-difluoroalkenes.[16–21] However, we found that the efficiency of this cascade reaction was strongly dependent on the quantity of fluoride source. The use of 5 equiv. of tetrabutylammonium fluoride (TBAF) instead of 10 considerably lengthens the reaction time and provides the desired compound with a significantly lower yield. TBAF is well-known for its hygroscopic properties and the presence of water strongly reduces the fluoride nucleophilicity which results in a relatively weak fluorinating agent. However, the generation of dry TBAF is possible but requires to implement a cumbersome procedure.[22] We thus envisioned to improve the fluoroalkylation procedure to *i*) avoid the use of TBAF and *ii*) increase the yield.

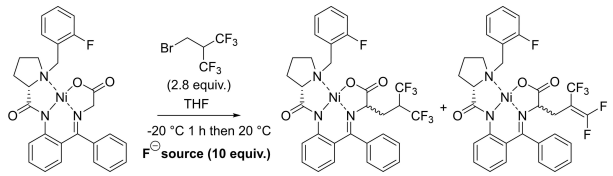
Herein, we report an optimized procedure using DBU as a strong organic base, which does not require an external fluoride source and provide the desired compound in higher yield. This procedure involves a soluble DBU·HF salt generated *in situ* during the S_N2' process, which acts as an original fluorinating agent, allowing the formation of the hexafluorinated compound. This novel procedure is compatible with multidecagram scale and represents an easy synthetic route for the synthesis of both the L- and the D-amino acid in zwitterionic form as well as their N-Fmoc and N-Boc protected derivatives.

Results and Discussion

We started our investigation by evaluating the ability of fluoride salts other than TBAF (Table 1), – such as KF, KHF_2, CsF and tetramethylammonium fluoride (TMAF) – to promote the reaction and we compared their efficiency with our previously reported procedure using TBAF (which afforded compound **2** with 66% yield). Unfortunately, after 25 h none of them afforded compound **2**. No conversion of starting material **1** was observed with TMAF and KHF_2. Only elimination product **3** was observed with CsF and KF with a **1**/**3** ratio of 7:3 and 49:1 respectively. The difference in reactivity of these salts compared to TBAF is presumably due to their low solubility in THF.

Then, we tested alkali metal bases (Table 2). However, compound **3** was always isolated as the predominant product

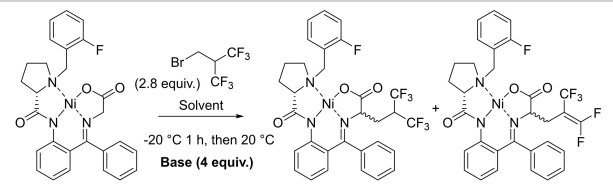
Table 1. Influence of the fluoride ion source.



Entry	F^- source	Reaction time (h)	**1**/**2**/**3** ratio[a]	Yield **2**
1	TBAF	3	0/1/0	66 [%][b]
2	KF	25	49/0/1	–
3	KHF_2	25	1/0/0	–
4	CsF	25	7/0/3	–
5	TMAF	25	1/0/0	–

[a] Determined by ^{19}F NMR. [b] Compounds **2** was obtained as a mixture of diastereoisomers ((*S*,*S*)-**2**:(*S*,*R*)-**2**: 90:10).

Table 2. Influence of the alkali metal base.



Entry	Base	Solvent	Reaction Time [h]	Yield **1**	**2**[a]	**3**[a]
1	NaOH	THF	4	20%	6%	55%
2	LiOH	THF	4	40%	15%	38%
3	KOH	THF	4	32%	6%	44%
4	*t*BuOK	THF	4	20%	13%	47%
5[b,c]	NaOH	DMF	4	nd	–	23%
6[b]	LiOH	DMF	4	–	–	53%
7[b,d]	*t*BuOK	DMF	5.5	nd	–	52%
8[b]	CsOH	DMF	4	–	23%	35%
9[e]	NaOH	THF	4	25%	Trace	61%

[a] Compounds **2** and **3** were obtained as a mixture of diastereoisomers, the diastereoisomeric ratio ((*S*,*S*):(*S*,*R*)) determined by ^{19}F NMR was between 88:12 and 93:7 for all tested conditions. [b] At the end of the indicated time, the solvent was evaporated under high vacuum. [c] **1**/**2**/**3** ratio: 68:1:31, determined by ^{19}F NMR. [d] 1 equiv. of 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was added after 4.5 h of reaction at 20 °C; **1**/**2**/**3** ratio: 25:0:75, determined by ^{19}F NMR. [e] 5 equiv. of 15-crown-5 were added.

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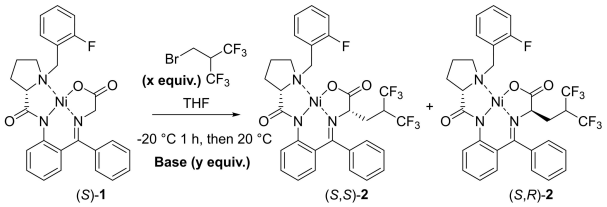
(38 to 55% yield) when using NaOH, LiOH, KOH or *t*BuOK (Table 2, Entries 1–4). The desired hexafluorinated compound **2** was obtained with low ≤15% yields. In these conditions, a significant amount of the starting material was left unreacted and no evolution of the reaction was observed after the indicated time, presumably because the fluorinated reagent is not stable over time with these bases. We also tested alkali metal bases in DMF to see if a more polar solvent could favour the formation of the hexafluorinated compound (Table 2, Entries 5–8). However, compound **2** was not observed with NaOH, LiOH and tBuOK. In contrast, CsOH tends to favour the formation of compound **2** (23% yield) and lower the yield of compound **3**. These observations indicate the crucial role of the fluoride counter ion by dictating the solubility of the salt. The fluoride released during the reaction (1 equiv.) is trapped by alkali metals (*i.e.* LiF, NaF, KF) to form insoluble fluoride salts precluding further reaction. With CsOH, the resulting fluoride salt is more soluble and the hydrofluorination of **3** is thus more favoured. To see whether the addition of a crown ether could capture the metal and preserve the nucleophilicity of the fluoride, we tested the combination of 15-crown-6 with NaOH (Table 2, entry 9).[23] Surprisingly, this condition favoured the formation of the elimination product **3**, which was obtained in a yield higher than without the crown ether (61% versus 55% respectively). In these conditions, only trace amount of **2** could be detected in the crude NMR compared to 6% yield obtained without crown ether.

The finding that only caesium hydroxide gave compound **2** in DMF, in contrast with other alkali metal bases, suggests that the nature of the base could change the outcome of the reaction. By using a strong neutral organic base, the deprotonation of (*S*)-**1**, would give a cationic protonated base which would act as the fluoride counter ion. We assumed that the organic salt could potentially be soluble enough in the solvent of the reaction, thus preserving the nucleophilicity of the fluoride ion. Based on this hypothesis, we tested 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 3, entry 1). To our delight, the reaction provided compound **2** with an overall yield of 84%, corresponding to a substantial improvement compared to the condition with TBAF (Table 1, entry 1). The reaction proceeded with very good diastereoselectivity and the two diastereoisomers (*S*,*S*)-**2** and (*S*,*R*)-**2** were successfully separated by flash chromatography affording pure (*S*,*S*)-**2** with 76% yield and (*S*,*R*)-**2** with 8% yield. We also tested other nitrogenous bases (Table 3, entries 2 and 3). However, Et_3N is not basic enough[24] to efficiently induce the reaction. The use of the more basic triazabicyclodecene (TBD) was also unsuitable for the reaction probably because of its poor solubility in THF. Next, we wanted to further optimize the reaction conditions when using DBU. We tested the reaction with a reduced amount of the brominated electrophile. A similar yield was obtained with 2 equiv. (Table 3, entry 4), but the use of 1.5 equiv. reduced the yield by ~20 p.p. (Table 3, entry 5). With 2 equiv. of DBU instead of 4 (entry 6), the reaction is slower and the yield is also substantially reduced. If 1.1 equiv. of DBU is used (entry 7), only 22% yield was obtained for the diastereoisomeric mixture of **2** and a few amounts of **3** was observed (4%). Even after 21 h of reaction, 68% of the starting material was recovered. Finally, when the reaction was performed at 20 °C, lower yields were obtained (entry 8).

Table 3. Investigating the hexafluoroisobutylation reaction with neutral organic bases.



Entry	Base (y)	x	Reaction time [h]	Yield **1**	(*S*,*S*)-**2**[a]	(*S*,*R*)-**2**[a]	**3**
1	DBU (4)	2.8	3	–	76%	8%	–
2	Et_3N (4)	2.8	23	>95%	Trace	–	–
3[b]	TBD (4)	2.8	23	74%	18%	5%	–
4	DBU (4)	2.0	3	–	76%	5%	–
5	DBU (4)	1.5	3	–	57%	5%	–
6	DBU (2)	2.0	21	–	54%	3%	–
7	DBU (1.1)	2.0	21	68%	22%		4%
8[c]	DBU (4)	2.8	1	–	68%	7%	–

[a] Diastereoisomers (*S*,*S*)-**2** and (*S*,*R*)-**2** were separated by flash chromatography using CH_2Cl_2/Et_2O as eluent, excepted when low yields were obtained. [b] TBD was poorly soluble in THF. [c] Reaction performed at 20 °C.

To get more insights into the reaction mechanism, the reaction was monitored by ^{19}F NMR and ^{1}H NMR when using DBU as a base (Figure S1). The elimination product **3** was formed rapidly prior to conversion to hexafluorinated compound **2** over time as observed previously with TBAF.[11] This result supports our hypothesis that DBU·HF promotes the fluorination of the double bond on **3**. To further confirm this reactivity, alkene **3** was treated with 1 equiv. of DBU·HF prepared from DBU and NH_4F by following the reported previously procedure (See SI),[25] and the reaction was monitored by ^{19}F NMR (Figure 1 and Figure S2). The formation of compound **2** was successfully observed and **3** was gradually consumed until full conversion. Surprisingly, the ^{19}F NMR signal from DBU·HF was not observed in [D_8]THF, possibly due to hydrogen bond exchange with THF broadening the peak (Figure S2).[26] These NMR experiments confirm that the reaction proceeds through a tandem allylic shift/hydrofluorination process and shows that only 1 equiv. of the fluoride is necessary to drive the reaction to completion. Based on these data, we propose the following mechanism (Scheme 2). After the deprotonation of the nickel complex, the enolate reacts with HFIB through an allylic shift to give **3**, generating *in situ* the DBU·HF salt. The solubility of this organic salt preserves the nucleophilicity of the fluoride which can efficiently react with **3** to give compound **2**. In contrast, the use of alkali metal bases leads to insoluble fluoride salts and **3** is obtained predominantly. The efficiency of the reaction when using DBU was remarkable since only 1 equiv. of fluoride is released in the reaction medium while previously 10 equiv. of TBAF were necessary to reach completion. Whereas with TBAF, the fluoride is highly hydrated

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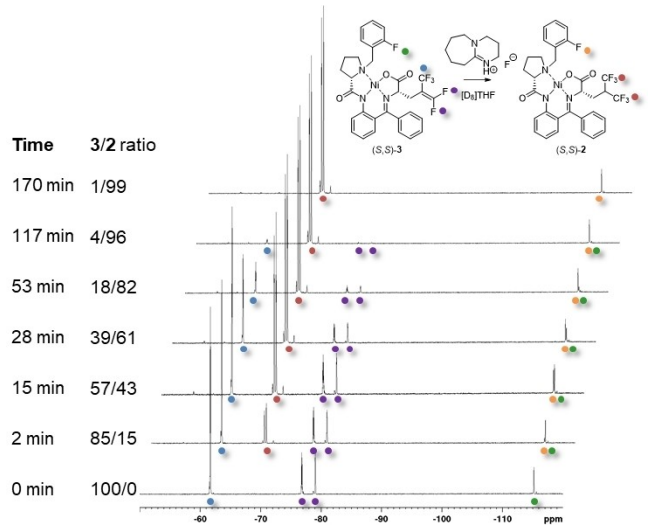
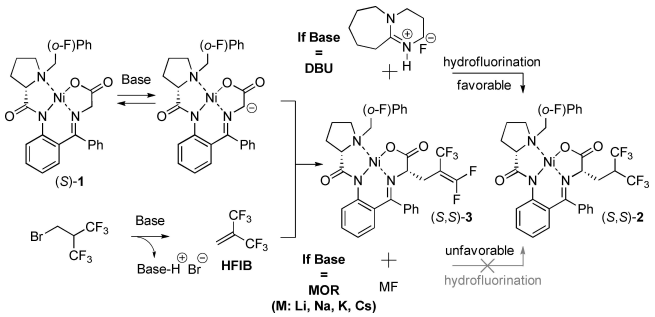


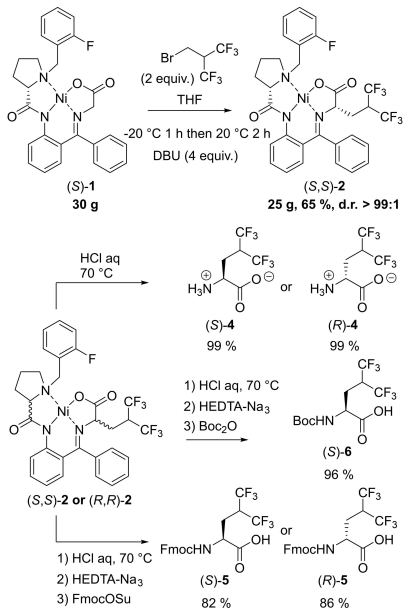
Figure 1. *In situ* ^{19}F NMR spectra of the reaction of alkene (*S*,*S*)-**3** with DBU·HF (1 equiv.).



Scheme 2. Proposed mechanism for the hexafluoroisobutylation reaction.

which lowers its nucleophilicity, with DBU in dry THF, the fluoride is generated *in situ* to form an anhydrous DBU·HF salt.

This methodology is compatible with a multidecagram scale procedure as shown in Scheme 3, giving (*S*,*S*)-**2** with a diastereoisomeric ratio higher than 99% after purification. Although chromatography on silica was used to isolate (*S*,*S*)-**2**, we subsequently found, that recrystallization was also well suited to isolate enantiopure **2** on small scale and thus could potentially be more advantageous for a larger scale synthesis. The hydrolysis of the alkylated complex (*S*,*S*)-**2** afforded hexafluoroleucine (*S*)-**4** with an almost quantitative yield (Scheme 3). The N-Fmoc or N-Boc protected derivatives (respectively (*S*)-**5** and (*S*)-**6**) can be obtained using FmocOSu or Boc_2O respectively, directly after hydrolysis of the alkylated nickel complex without intermediate purification. Also, hexafluoroleucine derivatives (*R*)-**4** and (*R*)-**5** have been synthesised with this strategy starting from nickel complex (*R*)-**1**. After the hydrolysis of complexes (*S*,*S*)-**2** or (*R*,*R*)-**2**, the chiral ligand derived from proline can be recovered quantitatively and reused to synthesise the Ni(II) complex (*S*)-**1** or (*R*)-**1**, respectively (See experimental section and SI). To confirm the high enantiopurity of the resulting fluorinated amino acids, the enantiomeric excess



Scheme 3. Large scale hexafluoroisobutylation of complex (*S*)-**1** (top), hydrolysis of alkylated nickel (II) complexes (*S*,*S*)-**2** and (*R*,*R*)-**2** and Fmoc and Boc protection of the amine (bottom).

was determined using Marfey's derivatization method (see SI).[27] An excellent enantiomeric ratio $>99:1$ was found for (*S*)-**4** and (*R*)-**4**.

Conclusion

In summary, we report a hexafluoroisobutylation cascade reaction mediated by DBU for the synthesis of enantiopure (*S*)- or (*R*)-5,5,5,5′,5′,5′-hexafluoroleucine. 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. HFIB reacts first with the deprotonated Schiff base complex through a S_N2' mechanism promoting a fluoride β-elimination affording a fluoroalkene group, as observed with other reactions involving α-CF_3-vinyl derivatives. We showed that the use of DBU preserves the nucleophilicity of the fluoride ion released *in situ*, and allows the hydrofluorination of the pentafluorinated intermediate affording the hexafluoroisobutyl side chain. In contrast, the use of alkali metal bases (LiOH, NaOH, KOH, tBuOK CsOH) does not efficiently convert this intermediate to the hexafluorinated compound, because fluoride salts generated from alkali metal bases (*i.e.* LiF, NaF, KF or CsF) are hardly soluble in organic solvents. When using DBU as a base, the hexafluoroalkylated product was exclusively formed and was isolated with an excellent yield and high diastereoselectivity. Remarkably, this procedure does not require the use of a large excess of fluoride salt to convert the pentafluoroalkene intermediate to the hexafluorinated compound. *In situ* NMR experiments provided evidence of a tandem allylic shift/hydrofluorination process and that DBU·HF salt reacts with the pentafluoroalkene. Both (*S*)- and (*R*)- config-

urations were easily synthesised depending on whether L- or D-proline was employed in the chiral nickel complex. Hydrolysis of the nickel complex readily affords the fluorinated amino acid, as well as N-Boc and Fmoc-protected derivatives with high enantiopurity.

This study demonstrates the pivotal role of the nature of the base to generate the hexafluorinated side chain. To the best of our knowledge, this study reports for the first time that the DBU·HF salt, generated *in situ*, can react as an effective fluorinating agent. It can be anticipated that this reagent will find useful applications in organofluorine chemistry for nucleophilic fluorination. Finally, the finding that the whole procedure is amenable to multi-decagram-scale synthesis bodes well for a broader use of this polyfluorinated leucine analogue to engineer peptides and proteins for applications in medicinal chemistry and chemical biology.

Experimental Section

General procedure for the synthesis of (*S*,*S*)-2 and (*S*,*R*)-2. In a double neck round bottom flask, under argon, nickel complex (*S*)-**1** (100 mg, 516.20 g mol^{-1}, 0.19 mmol) was dissolved in anhydrous THF (1.5 mL). The solution was cooled to −20 °C and DBU (0.11 mL, 1.86 g, 152.24 g mol^{-1}, 0.76 mmol, 1.02 g mL^{-1}) was added. The reaction mixture was stirred for 10 minutes at −20 °C. Then, the 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was introduced dropwise (70 µL, 128 mg, 244.96 g mol^{-1}, 0.52 mmol, 1.83 g mL^{-1}). The mixture was stirred under argon at −20 °C for 1 h and at 20 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 to change the solution to a one neck round bottom flask and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel with Et_2O, and then with Et_2O/MeOH: 98/2. Compound (*S*,*S*)-**2** eluted first (100 mg, 680.25 g mol^{-1}, 1.47 mmol, 78%) followed by (*S*,*R*)-**2** (11 mg, 680.25 g mol^{-1}, 16 µmol, 9%). Both (*S*,*S*)-**2** and (*S*,*R*)-**2** were obtained as a red solid. Monocrystals of (*S*,*S*)-**2** and of (*S*,*R*)-**2** for X-ray analysis were obtained in a mixture of CH_2Cl_2/hexane.

Multi-decagram scale synthesis of (*S*,*S*)-2. In a dry 1 L triple neck round bottom flask, under argon, nickel complex (*S*)-**1** (30.0 g, 516.20 g mol^{-1}, 58.1 mmol) was dissolved in anhydrous THF (29 mL). The solution was cooled to −20 °C and DBU (34.8 mL, 35.5 g, 152.24 g mol^{-1}, 233 mmol, 1.02 g mL^{-1}) was added over a period of 5 minutes. The reaction mixture was stirred for 10 minutes at −20 °C. Then, the 2-(bromomethyl)-1,1,1,3,3,3-hexafluoropropane was added (15.4 mL, 28.5 g, 244.96 g mol^{-1}, 116 mmol, 1.83 g mL^{-1}). The mixture was stirred under argon at −20 °C for 1 h and at 20 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2, transfer to a one neck round bottom flask, and then the solution was concentrated under reduced pressure to evaporate THF. Water was added to the crude and the solution was extracted three times with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crude was purified by automatic flash column chromatography on silica gel using first Et_2O as eluent, and then Et_2O/MeOH: 98/2. Compound (*S*,*S*)-**2** eluted first followed by (*S*,*R*)-**2**. Pure fractions were isolated and mixed fractions were combined and recrystallized in a mixture of CH_2Cl_2/heptane: 3/5 (16 mL/g) to get pure compound (*S*,*S*)-**2** (25.6 g, 680.25 g mol^{-1}, 37.6 mmol, 65%).

Determination of the enantiomeric excess of (*S*)- and (*R*)-5,5,5,5′,5′,5′-hexafluoroleucine (Marfey's derivatization method).[27] In a vial were introduced the amino acid (1.2 mg, 5 µmol), then 200 µL of a solution Marfey's reagent (3 mg, 272.19 g mol^{-1}, 11 µmol) dissolved in acetone (300 µL) and 40 µL of an aqueous solution of $NaHCO_3$ 1 M. The reaction mixture was heated at 40 °C during 1 h. An aqueous solution of HCl 2 M was added (20 µL) and the mixture was filtered and diluted with water. Then, the solution was analyzed by reversed phase HPLC with a 25 minutes run using a gradient of 15 to 60% MeCN in water.

Preparation of DBU·HF. DBU·HF was prepared using the reported procedure[25] and the adapted procedure performed for this work is described in the SI.

The synthesis of nickel (II) complex (*S*)-**1** was performed by using the reported procedures.[12–14]

All other synthetic procedures and analytical data are described in the SI.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: fluoroalkylation · fluorination · amino acids · stereoselective synthesis · synthetic methods

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