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# Practical Synthesis of Fluorous Oxazolidinone Chiral Auxiliaries from α-Amino Acids

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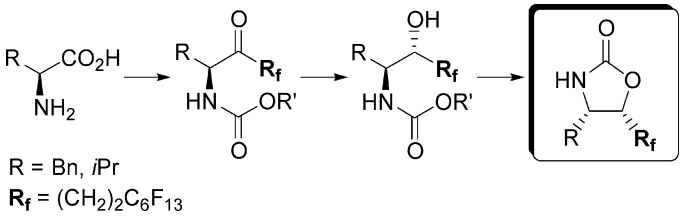


A series of new fluorous-supported oxazolidinone chiral auxiliaries has been prepared using a versatile and general five-step pathway, starting from readily available chiral α-amino acids. The key feature of this synthesis is the efficient generation of a suitably active perfluoroalkyllithium species. By use of this protocol, the auxiliaries can be obtained in high enantiomeric purity and on multigram scales from L-phenylalanine and L-valine with overall yields as high as 55%. The new methodology also incorporates fluorous solid-phase extraction on the large scale, allowing bulk quantities (up to 25 g) of fluorous compounds to be purified from the crude reaction mixture.

## Introduction

Fluorous techniques have been applied to many chemical transformations, offering a powerful alternative to standard polymer-supported methods.[1] Initially proposed as a method of separating catalysts from process streams,[2] fluorous chains have been developed as general supports for organic reagents and for synthesis by Curran et al.[1,3] In addition to their uses in organic synthesis, fluorous-tagged molecules have been employed by several researchers in proteomics,[4] nucleotide research,[5] chromatography,[6] and supercritical fluid chemistry.[7]

We identified the fluorous tag as the ideal support for applications in stoichiometric asymmetric synthesis. Polymer-supported chiral auxiliary systems have been created and successfully applied to several asymmetric transformations.[8,9] However, these examples cover a relatively narrow range of reaction conditions and substrates. Many polymer-supported auxiliaries have afforded inconsistent yields and/or levels of stereoselectivity compared to the analogous solution-phase reactions.[8,9b,c,f,10] These problems are the result of incompatibilities between the polymer support and the conditions applied, leading to side reactions or degradation of the polymer or difficulties in drying and purifying the polymer-bound materials.[9c,11]

In contrast, many fluorous supported compounds are soluble in typical organic reaction solvents, and the support itself is impervious to most common reagents. After a reaction is complete, selective recovery of supported material is usually easily accomplished by fluorous

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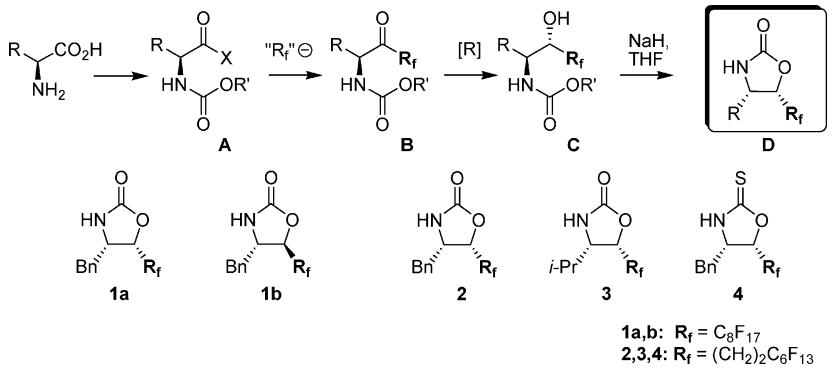
**SCHEME 1. General Pathway for the Synthesis of Fluorous Chiral Auxiliaries from α-Amino Acids**




solid-phase extraction (FSPE).[12] We have demonstrated that coupling fluorous synthesis with chiral auxiliary methods is both viable and broadly applicable in our published studies of model aldol reactions,[13] conjugate radical additions,[14] and 1,3-dipolar cycloadditions[15] using fluorous oxazolidinone chiral auxiliaries **1** and **2** derived from L-phenylalanine.

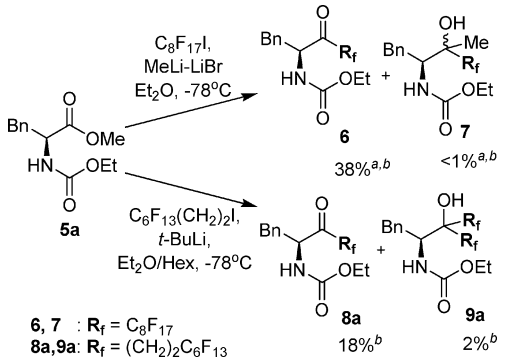
In this paper we report simple, efficient, and scaleable syntheses of a series of fluorous chiral auxiliaries **2**−**4**. Our procedure (Scheme 1) consists of five steps: *N*-protection and carbonyl activation of the parent α-amino acid producing **A**, perfluoroalkylation to give ketone **B**, diastereoselective reduction to selectively generate anti alcohol **C**, and finally cyclization to give oxazolidinone **D**. In our initial studies, we created diastereomers **1a** and **1b**, allowing us to determine that the cis geometry was necessary for an effective auxiliary.[13] We noted that the possibility of epimerization existed at each stage of the synthesis, a problem which obviously had to be avoided. We also recognized the particular challenges posed by the unique properties of highly fluorinated carbanions, which had proven troublesome in our initial synthesis of **1a** and **1b**.[13]

## Results and Discussion

L-Phenylalanine, L-valine, and D - and L-phenylglycine were selected as starting points for this study. We first required an appropriately activated *N*-carbamoyl electrophile (**A**), which could react with a perfluoroalkyl nucleophile. An ester group was the simplest option. Unlike the reaction of alkyl nucleophiles with esters, addition of perfluoroalkyl nucleophiles usually generates a stabilized, long-lived tetrahedral intermediate.[16] This intermediate does not undergo a second nucleophilic addition, and thus the corresponding ketone (**B**) can be obtained.

**Perfluoroalkyl Addition to *N*-Carbamoyl Esters.** The most commonly applied nucleophilic perfluororganometallic reagents are alkyl cuprates, alkyllithiums, alkyl zinc species, and Grignards.[17] Perfluoroalkyl cuprates and zinc reagents have afforded only modest yields in addition reactions with esters.[17,18] We therefore concentrated on the lithium and Grignard derivatives derived from $C_8F_{17}I$.

**SCHEME 2. Nucleophilic Perfluoroalkyl Addition[a]**




[a] Results from ref 13. [b]Percent conversion from **5a**.

We rapidly discovered that these organometallic species could be difficult to prepare and handle. Ultimately, the perfluoroalkyllithium reagent emerged as the best option (Scheme 2), provided that reactions were conducted with stringent control of addition rates, temperature and reagent concentrations. Because the lithiated species rapidly decomposed, even at low temperatures,[16a] the transmetalation had to be carried out in situ through addition of MeLi−LiBr to a solution of $C_8F_{17}I$ and ester **5a**.[13] By use of the method, we were able to obtain 38% of the required ketone **6**, with only minimal amounts of tertiary alcohol **7** formed by initial reaction of **5a** with MeLi, followed by perfluoroalkylation of the resulting methyl ketone. The low yield reflected a combination of degradation of the perfluoroalkyllithium reagent via $\beta$-elimination,[16a] and competitive Wurtz-type coupling with the iodide starting material.[19] After considerable experimentation, we concluded that we could not suppress this Wurtz coupling. By the use of larger excesses of $C_8F_{17}I$, we were able to improve the conversion to **6** marginally; however, generation of tertiary alcohol **7** was also enhanced under these conditions. The two fluorous

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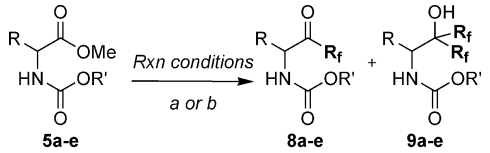
**TABLE 1. Perfluoroalkyl Addition to *N*-Protected Amino Esters**




5a-e 8a-e 9a-e

$R_f = (CH_2)_2C_6F_{13}$

| entry | s.m. | R | R′ | reaction | $R_fI$ equiv | yield (**8**:**9**)[c] |
|---|---|---|---|---|---|---|
| 1 | **5a** | Bn (*S*) | Et | A | 3.0 | 42:36 |
| 2 | **5a** | Bn (*S*) | Et | B | 2.0 | 18:2 |
| 3 | **5b** | Bn (*S*) | *i*pr | A | 3.0 | 30:17 |
| 4 | **5b** | Bn (*S*) | *i*pr | B | 1.5 | 39:19 |
| 5 | **5b** | Bn (*S*) | *i*pr | B | 2.0 | 47:32 |
| 6 | **5b** | Bn (*S*) | *i*pr | B | 3.0 | 12:68 |
| 7 | **5c** | Bn (*S*) | Bn | A | 3.0 | 15:5 |
| 8 | **5c** | Bn (*S*) | Bn | B | 2.0 | 10:0 |
| 9 | **5d** | $^i$Pr (*S*) | *t*Bu | B | 1.5 | 42:21 |
| 10 | **5e** | Ph (*R*) | Et | B | 1.5 | 35:34 |

[a] Mg powder, $C_6F_{13}(CH_2)_2I$, $Et_2O$. [b] *t*-BuLi, $C_6F_{13}(CH_2)_2I$, 3:2 Hex:Ether, −78 °C → rt. [c] Percent conversion from the corresponding electrophile.

materials **6** and **7** could be separated by column chromatography on silica, but these disappointing results led us to change our fluorous nucleophile.

Fluoroalkyllithium species containing an ethylene spacer, such as $C_6F_{13}(CH_2)_2Li$, behave much more like typical organometallic reagents.[1,20] The alkyl portion of these compounds helps to insulate the reactive site, allowing the resulting carbanion to be more nucleophilic and less prone to $\beta$-elimination. A series of *N*-protected amino esters **5a**−**e** (Table 1) were synthesized via literature procedures[21] and subjected to perfluoroalkylation with both the lithiated and Grignard derivatives of $C_6F_{13}(CH_2)_2I$.

The Grignard protocol required a 3-fold excess of the fluorous iodide to give adequate conversion to the fluorous products (Table 1, entries 1 and 3). In contrast, the lithium reagent gave moderate to good yields of fluorous materials for most of the esters tested using only 1.5−2.0 equiv. The solvent in which the perfluoroalkyllithium species was generated and used proved to be critical. Reactions of $C_6F_{13}(CH_2)_2Li$ with esters **5** in pure ether at −78 °C afforded <10% yields of perfluoroalkyl adducts, along with corresponding amounts of unreacted ester. By use of a mixed ether/hydrocarbon solvent system analogous to the conditions reported by Legros et al.,[22] we were able to improve the conversion to the desired perfluoroalkyl derivatives substantially. We assayed a series of hexane:ether and pentane:ether mixtures ranging from 1:1 to 5:1 (v/v) for both the generation and reaction of $C_6F_{13}(CH_2)_2Li$ and found that 3:2 hexane:ether gave the optimal results shown in Table 1.

The data in Table 1 show that the best overall yields of perfluoroalkyl adducts were obtained using ester **5b**. This reflected two factors. First, it was quite simple to remove alcohol contamination from the ethyl and isopropyl carbamates **5a** and **5b** on multigram scales, whereas it was much harder to remove traces of benzyl alcohol from the benzyl carbamate **5c**. The use of highly purified esters led to more efficient perfluoroalkylation. A problem with solubility also affected the yields in some cases. The ethyl carbamate **5a** was only partly soluble in ether−hexane mixtures at −78 °C (Table 1, entry 2). In contrast, phenylglycine-derived ester **5e** was quite soluble under these conditions, and it reacted with $R_fLi$ in good net yield. Overall, the shorter alkyl carbamates were more practical, with the isopropyl carbamate **5b** giving the best results.

The use of a spacer in the fluorous nucleophile increased the net conversion, but as is evident from the data in Table 1 it also led to the formation of tertiary alcohols. The ketone:alcohol ratio could be controlled to some extent by adjusting the amount of the perfluoroalkyllithium reagent applied. The tertiary alcohols **9** predominated when a 3-fold excess of the perfluoroalkyl species was employed (Table 1, entry 6, cf. entries 4 and 5). Unfortunately, it was not possible to favor the ketones **8** by using smaller amounts of the nucleophile without sacrificing the overall conversion of the reaction.

The installation of the fluorous tag permitted us to use FSPE to purify the products of these reactions. The quenched reactions were evaporated, and the crude residues were applied as concentrated solutions to short pads of FluoroFlash.[23] We found that not only could we separate fluorous from nonfluorous (organic and inorganic) materials but we could also separate products of differing fluorine content simply by adjusting the polarity of the eluting solvent. By use of this technique, (perfluoroalkyl)ketones **8a**−**e** and bis(perfluoroalkyl)alcohols **9a**−**e** could easily be purified and separated using only three washes of the FSPE pad: 70:30 MeOH:$H_2O$ removed organic and inorganic byproducts, 85:15 MeOH:$H_2O$ removed ketones **8**, and finally 100% MeOH released the tertiary alcohols **9**.

**Perfluoroalkyl Addition to *N*-Carbamoyl Weinreb Amides.** To obtain the ketone selectively we turned to Weinreb amides **10a**−**e**, which were prepared using a modification of the reported procedures. To form the amides, the *N*-carbamoyl amino acids first had to be activated. In preliminary experiments, carboxyl activation using mixed anhydride methods[24] or CDMT[25] led to racemic products. This could be suppressed by stringent temperature control at ≤−20 °C. However, under these conditions the Weinreb amides could not be obtained in sufficient purity for our purposes, necessitating further purification by chromatography on silica.

We found that TBTU was the best coupling reagent, promoting Weinreb amide formation at 0 °C without epimerization. By use of this method, we have prepared Weinreb amides **10a**, **c**, **d**, and **e** on multigram scales with no need for any further purification after simply

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(23) FluoroFlash perfluorooctylethylsilyl ($C_8F_{17}CH_2CH_2Si$) silica gel was provided by Fluorous Technologies, Inc.

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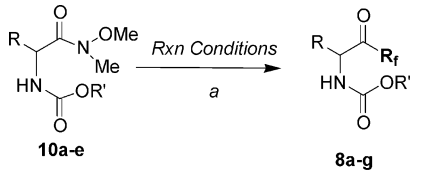
**TABLE 2. Perfluoroalkyl Addition to *N*-Protected Weinreb Amides**




| entry | s.m. | R | R′ | $R_fI$ equiv | yield[b] |
|---|---|---|---|---|---|
| 1 | **10a** | Bn (*S*) | Et | 1.5 | 48% |
| 2 | **10b** | Bn (*S*) | Bn | 1.5 | 30% |
| 3 | **10a** | Bn (*S*) | Et | 3.5 | 61% |
| 4[c] | **10a** | Bn (*S*) | Et | 1.5 | 68% |
| 5[d] | **10a** | Bn (*S*) | Et | 1.5 | 75% |
| 6[d] | **10c** | *i*Pr (*S*) | *t*Bu | 1.5 | 55% |
| 7[d] | **10d** | Ph (*R*) | *t*Bu | 1.5 | 45% |
| 8[d] | **10e** | Ph (*S*) | *t*Bu | 1.5 | 35% |

[a] *t*-BuLi, $C_6F_{13}(CH_2)_2I$, Ether:Hex, −78 °C → rt. [b] Percent conversion from corresponding Weinreb amide. [c] *n*-BuLi used as sacrificial base. [d] *t*-BuLi used as sacrificial base.

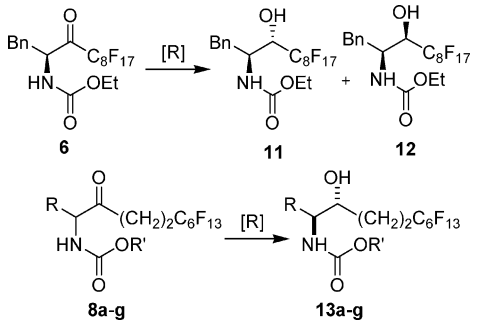
extracting the products from the quenched reaction mixtures with ether.

As we observed with esters **5**, the Weinreb amides bearing smaller carbamate groups (Table 2, entries 1 vs 2) gave better results in the perfluoroalkylation reactions. It was possible to obtain ketones **8a**−**g** as the sole perfluoroalkylated products, but an excess of the fluorous iodide was still required to obtain acceptable yields (Table 2, entries 1 and 2 vs 3). This was unacceptable in our overall plan, because the fluorous material was the most expensive component of our synthesis. Nucleophilic addition to *N*-carbamoyl Weinreb amides of α-amino acids reportedly can be improved by employing sacrificial bases to deprotonate the carbamate N−H prior to introducing the desired nucleophile.[26] By pretreating Weinreb amide **10a** with *n*-BuLi or *t*-BuLi (Table 2, entries 4 and 5), we increased the yield of perfluoroketone **6c** to 68 and 75% respectively, using only 1.5 equiv of perfluoroalkyl iodide.

Similar results were obtained using L-valine-derived Weinreb amide **10c**, leading to ketone **8d**. The reactions of D - and L-phenylglycine-derived **10d** and **10e** (Table 2, entries 7 and 8) afforded ketones **8f** and **8g** having optical rotations near zero. This stood in marked contrast to the results of entries 1−6 (Table 2), in which the products showed significant optical activity. Determining the enantiomeric purity of our products was thus our next task.

**Diastereoselective Reduction and MTPA Derivatives.** Hoffmann et al.[27] have shown that α-amino ketones can be reduced diastereoselectively to give the corresponding anti amino alcohols using a strongly chelating reducing agent such as $LiAlH(OtBu)_3$. Reduction of perfluoroalkyl ketone **6** using this reagent afforded mixtures of the syn and anti diastereomers **11** and **12**, with only a slight preference for the chelation-controlled pathway (Table 3, entries 1 vs 2). In contrast, ketones

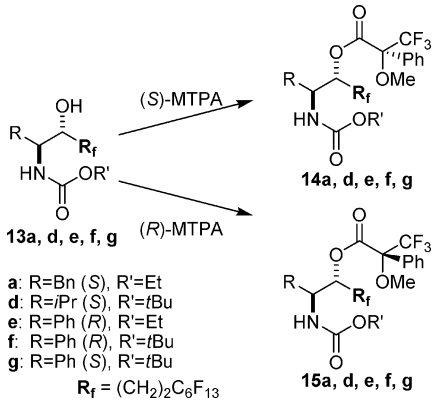
**TABLE 3. Diastereoselective Reduction via Chelation Control**




| entry | s.m. | R | R′ | yield | anti:syn |
|---|---|---|---|---|---|
| 1[a,c] | **6** | Bn (S) | Et | 98% | 3:1 |
| 2[b,c] | **6** | Bn (S) | Et | 98% | 5:1 |
| 3[b] | **8a** | Bn (S) | Et | 95% | >99:1 |
| 4[b] | **8b** | Bn (S) | *i*Pr | 99% | >99:1 |
| 5[b] | **8c** | Bn (S) | Bn | 97% | >99:1 |
| 6[b] | **8d** | *i*Pr (S) | *t*Bu | 97% | >99:1 |
| 7[b] | **8e** | Ph (R) | Et | 95% | >99:1 |
| 8[b] | **8f** | Ph (R) | *t*Bu | 90% | >99:1 |
| 9[b] | **8g** | Ph (S) | *t*Bu | 96% | >99:1 |

[a] $NaBH_4$, EtOH, −78 °C → rt. [b] $LiAl(OtBu)_3$, EtOH, −78 °C → rt. [c] Results from ref 13.

**SCHEME 3. Esterification of (Perfluoroalkyl)Alcohols with (*R*)- and (*S*)-MTPA[a]**




[a] Reaction conditions: MTPA, DCC, DMAP, $Et_2O$, rt, 24 h.

**8a**−**f** were reduced with excellent anti stereoselectivity (Table 3). Clearly, the fully fluorinated ketone **6** was able to react with $LiAlH(OtBu)_3$ by both chelated and nonchelated pathways, leading to the observed product mixture. We attribute this to weak Lewis basicity of the carbonyl in **6** due to the strong electron-withdrawing effects of the $C_8F_{17}$ group directly bonded to it. The ethylene spacer separating the fluorocarbon moiety from the carbonyl of ketones **8a**−**f** attenuates this effect. It should also be noted that the nature of the carbamate group had no effect on the selectivity of the reduction, indicating that steric bulk in this position does not interfere with the required chelated transition state.

The enantiomeric excesses of alcohols **13a**, **d**, **e**, **f**, and **g** were determined by conversion to the corresponding (*S*)- and (*R*)-MTPA esters (Scheme 3). The $^1H$ and $^{19}F$ NMR spectra of the products clearly indicated that alcohols **13a** and **d**, synthesized from L-phenylalanine and L-valine, contained a single enantiomer (∼99%

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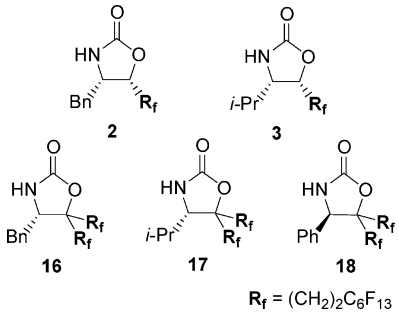
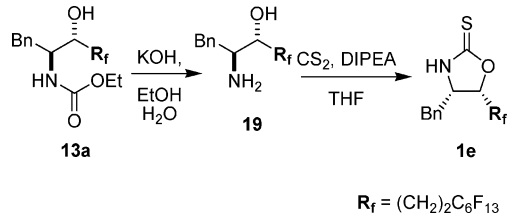



**FIGURE 1.** (Perfluoroalkyl) oxazolidinones.

**SCHEME 4. Synthesis of Oxazolidinethione 1e**




enantiomeric excess (ee)). In contrast, alcohols **13e**−**g** (derived from D- or L-phenylglycine) proved to have very low enantiomeric purities (37, ∼0, and ∼0% ee, respectively). This was consistent with the low optical rotations observed for their fluoroketone precursors **8e**−**g**. Clearly, the α center in these compounds had epimerized, suggesting that the α position of phenylglycine is too acidic to tolerate the conditions of the fluoroalkylation. These phenylglycine-derived compounds prepared by this route were clearly not of sufficient stereochemical purity to be of use as chiral auxiliaries.

**Synthesis and Application of the Fluorous Oxazolidinones.** Hydroxycarbamates **13a**−**g** were treated with NaH in THF to give the corresponding mono(perfluoroalkyl) oxazolidinones **2** and **3** (Figure 1). Treating the bis(perfluoroalkyl) alcohols **9a**−**e** under similar conditions generated the disubstituted oxazolidinones **16**, **17**, and **18** (Figure 1). Alcohols **13a**−**d** derived from L-phenylalanine and L-valine produced diastereomerically and enantiomerically pure oxazolidinones **2** and **3**. The syn geometry at C4 and C5 in these oxazolidinones was evident from the vicinal H4−H5 coupling constants, which were found to be 7.2 and 7.0 Hz in **2** and **3**, respectively. Nuclear Overhauser effect experiments further established the syn geometry: anti oxazolidinone **1b** showed <1% NOE between H4 and H5, whereas in **1a**, **2**, and **3**, ∼5% NOE was observed between these protons.

Crimmins et al. have found that oxazolidinethiones offered some advantages over oxazolidinone chiral auxiliaries in particular applications.[28] We therefore submitted **13a** to alkaline hydrolysis to produce amino alcohol **19** (Scheme 4), which was then treated with $CS_2$ in the presence of DIPEA, generating **1e** (80%). We also briefly examined the conversion of **19** to the corresponding thiazolidinethione using a reported procedure (refluxing $CS_2$ in aqueous KOH),[29] but this only afforded **1e** in very low yield, with no sign of the thiazolidinethione. We are continuing to pursue this transformation, although we note that to obtain the required syn geometry by this process requires the use of the syn diastereomer of amino alcohol **19**.

We have already reported the use of fluorous oxazolidinone **2** in several asymmetric transformations including aldol reactions, 1,3-dipolar cycloadditions, and radical conjugate additions.[13,14,15] The new supported chiral auxiliary reacted under standard solution phase conditions, affording yields and stereoselectivities comparable to those reported for corresponding nonfluorous oxazolidinones.

The greatest advantage of the fluorous oxazolidinones lies in the use of FSPE, allowing us to recover fluorous materials rapidly and efficiently. The auxiliaries were easily acylated and employed in asymmetric transformations, each time using FSPE to obtain the desired products from crude reaction mixtures. Because of this characteristic, it was trivial to recover and reuse the oxazolidinone following cleavage of the newly formed exocyclic chiral material. In our study of 1,3-dipolar cycloadditions we have demonstrated that auxiliary **2** could be recycled no fewer than five times with no deleterious effect on the reactions.[15] This also suggests their potential use in multistep supported syntheses.

## Conclusions

Our detailed experiments have led to an efficient five-step sequence (presented in the Experimental Section) requiring no conventional chromatography to produce fluorous oxazolidinone and oxazolidinethione chiral auxiliaries from common α-amino acids. This route is distinguished by: TBTU-promoted formation of an *N*-carbamoyl amino acyl Weinreb amide to avoid epimerization; perfluoroalkylation in hexane:ether mixtures, in the presence of a sacrificial base, to install a *spacer-linked* fluorous chain; chelation-controlled stereoselective reduction of the resulting ketone; and facile conversion to either oxazolidinone or oxazolidinethione final products. Purification consists of silica and fluorous solid-phase extractions, with only two recrystallizations required. We have performed the complete sequence on various scales, up to the formation of 25 g of the target oxazolidinone in a single batch.[30] The process on these scales requires no equipment other than typical laboratory glassware. These fluorous auxiliaries are truly powerful tools for drug discovery and high-throughput chemistry and are viable alternatives to the standard supported or nonsupported auxiliaries.

## Experimental Procedures

**General Protocol for Large-Scale Purification of Fluorous Materials Using FSPE: Purification and Separation of 2(*S*)-(Ethoxycarbonylamino)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-one (8a) and 2(*S*)-(Ethoxycarbonylamino)-3,3-bis(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-1-pheny l-propan-3-ol (9a).** The crude material obtained after concentrating the reaction under vacuum (∼43 g) was thinned with a minimum volume of $Et_2O$ and applied to a pad of dry Fluoroflash (4−6 × crude weight) in a fritted glass funnel. The oily material was driven onto the solid phase using compressed air. The pad was blown dry until no evidence of the loading solvent remained and then washed with 70%

(28) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66,* 894−902.
(29) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604−6607.

methanol in water (1.5−2.0 L) to remove organic and inorganic impurities. Ketone **8a** was selectively eluted from the solid phase with 85% methanol in water (1−1.5 L). The solid phase was then eluted with MeOH to obtain **9a**.

**Representative Procedure for the Synthesis of *N*-Carbamoyl Weinreb Amides Using Isobutyl Chloroformate: 2(*S*)-*N*-(Ethoxycarbonyl)-*N*′-methoxy-*N*′-methylphenylalaninamide (10a).** 2(*S*)-*N*-(Ethoxycarbonyl) phenylalanine (21.00 g, 89 mmol) was dissolved in $CH_2Cl_2$ (250 mL) and cooled to −30 °C. DIPEA (16.96 mL, 97 mmol) was added dropwise, and the solution was allowed to stir at −30 °C for 15 min. Isobutyl chloroformate (12.79 mL, 97 mmol) was added dropwise while monitoring the reaction temperature with a digital thermometer. The addition rate was carefully controlled to keep the internal temperature between −30 and −25 °C. Upon completion of the addition, stirring was continued at −30 °C for an additional 15 min, at which time DIPEA (20.81 mL, 119 mmol) was added dropwise. Solid *N,O*-dimethylhydroxylamine hydrochloride (11.66 g, 119 mmol) was added in one portion, followed by DMF (10 mL). The reaction was allowed to warm to room temperature (rt) over 3 h and was then quenched with 1 M HCl and diluted with $CH_2Cl_2$. The layers were separated, and the organic layer was washed successively with 1 M HCl, $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residual oil was eluted through a pad of silica gel (4:1 hexanes/ethyl acetate) to produce **10a** (22.12 g, 79 mmol, 89% yield) as a clear oil.

**Representative Procedure for the Synthesis of *N*-Carbamoyl Weinreb Amides Using TBTU: 2(*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*′-methoxy-*N*′-methyl-valinamide (10c).** Solid (*S*)-*N*-(*tert*-butoxycarbonyl)-valinate (1.50 g, 6.90 mmol), *N,O*-dimethoxyhydroxylamine hydrochloride (1.010 g, 10.36 mmol), and TBTU (3.33 g, 10.36 mmol) were combined. Dry $CH_3CN$ (25 mL) was added, and the mixture was cooled to 0 °C. The solution was stirred at 0 °C for 10 min, and then DIPEA (3.61 mL, 20.71 mmol) was added dropwise. The solution turned yellow and quickly became opaque. The reaction was allowed to warm to rt over 3 h. After this time, the reaction was concentrated under vacuum, and the residue was taken up in $Et_2O$. The mixture was washed sequentially with 1 M HCl, 1 M $NaHCO_3$, and brine. The organic fraction was dried with $MgSO_4$ and evaporated to dryness. The resulting crude yellow oil was applied to a 10-cm pad of silica gel and eluted with 4:1 hexanes/ethyl acetate, providing **10c** (0.102 g, 0.346 mmol, 87% yield) as a clear oil.

**Representative Procedure for the Application of a Sacrificial Base in the Perfluoroalkylation of *N*-Carbamoyl Weinreb Amides Using Perfluoroalkyllithium Reagents: 2(*S*)-(Ethoxycarbonylamino)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-one (8a).** 1*H*,1*H*,2*H*,2*H*-Perfluorooctyl iodide (26.6 mL, 112 mmol) was dissolved in ether:hexane (3:2, 500 mL) and cooled to −78 °C. *t*-BuLi (70.5 mL, 120 mmol) was added dropwise via cannula, taking care to keep the reaction temperature below −60 °C. In a separate flask **10a** (21 g, 74.9 mmol) was dissolved in dry $Et_2O$, and the solution was cooled to −78 °C. *t*-BuLi (48.5 mL, 82 mmol) was then added to this solution, again adjusting the addition rate to maintain a temperature below −60 °C. This solution was then transferred via a cannula into the perfluoroalkyllithium solution. The reaction was then stirred at −78 °C for ∼15 min and was then allowed to warm to rt over 4 h. The reaction was quenched with dilute aqueous $NH_4Cl$, and the solution was extracted with $Et_2O$. The combined ether extracts were washed with brine, dried with $MgSO_4$, and evaporated to dryness. The crude material was then purified by FSPE according to the general procedure to give 8a (28.88 g, 51.1 mmol, 68.2% yield).

**2(*S*)-(Ethoxycarbonylamino)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-one (8a).** $R_f$ 0.3 (9:1 hexanes/ethyl acetate); mp = 57−60 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.31−7.14 (m, 5H), 5.4 (br d, 1H, $^3J$ = 7.0 Hz), 4.58 (ddd, 1H, $^3J_1$ = 7.5 Hz, $^3J_2$ = 7.0 Hz,$^3J_3$ = 7.0 Hz), 4.09 (q, 2H, $^3J$ = 7.0 Hz), 3.04 (dd, 1H, $^3J_1$ = 13.8 Hz, $^3J_2$ = 7.0 Hz), 3.04 (dd, 1H, $^3J_1$ = 13.8 Hz, $^3J_2$ = 7.5 Hz), 2.75−2.69 (m, 1H, −C*H*HCH$_2$C$_6$F$_{13}$), 2.60−2.53 (m, 1H, −CH*H*CH$_2$C$_6$F$_{13}$), 2.43−2.23 (m, 2H, −CH$_2$C*H*$_2$C$_6$F$_{13}$), 1.20 (t, 3H, $^3J$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.4 (−OCH$_2$*C*H$_3$), 24.9 (−CH$_2$*C*H$_2$-C$_6$F$_{13}$), 31.8 (−*C*H$_2$CH$_2$C$_6$F$_{13}$), 37.8 (Ph*C*H$_2$−), 60.5 (Bn*C*HN−), 61.4 (−O*C*H$_2$CH$_3$), 127.4, 128.9, 129.0, 135.6 (−C$_6$H$_5$), 156.1 (−NH*C*OOEt), 206.4 (−*C*OCH$_2$CH$_2$C$_6$F$_{13}$); $^{19}$F NMR (282 MHz,-$CDCl_3$) $\delta$ −81.25, −114.93, −122.36, −123.32, −123.93, −126.58; [$\alpha$]$^{25}_D$ +15.0° (*c* 1.00, $CHCl_3$). Anal. Calcd for formula $C_{20}H_{18}F_{13}NO_3$: C, 42.34; H, 3.20; N, 2.47. Found: C, 42.44; H, 3.43; N, 2.34.

**2(*S*)-(*tert*-Butoxycarbonylamino)-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluoro-2-methyl-dodecan-4-one (8d).** $R_f$ 0.4 (9:1 hexanes/ethyl acetate); mp = 36−37 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.05 (d, 1H, $^3J$ = 8.2 Hz), 4.25 (dd, 1H, $^3J_1$ = 8.2 Hz, $^3J_2$ = 4.6 Hz, *i*PrC*H*−), 2.90−2.72 (m, 2H, −C*H*$_2$-CH$_2$C$_6$F$_{13}$), 2.51−2.33 (m, 2H, −CH$_2$C*H*$_2$C$_6$F$_{13}$), 2.24−2.29 (m, 1H, (CH$_3$)$_2$C*H*−), 1.43 (s, 9H, (C*H*$_3$)$_3$C−), 1.01 (d, 3H, $^3J$ = 7.1 Hz, C*H*$_3$CHCH$_3$), 0.82 (d, 3H, $^3J$ = 7.0 Hz, CH$_3$CHC*H*$_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 16.9 (*C*H$_3$CHCH$_3$), 19.7 (CH$_3$CHC*H*$_3$), 25.0 (−CH$_2$*C*H$_2$C$_6$F$_{13}$), 28.3 ((*C*H$_3$)$_3$C−), 30.0 ((CH$_3$)$_2$*C*H−), 31.5 (−*C*H$_2$CH$_2$C$_6$F$_{13}$), 64.3 (*i*Pr*C*HN−), 80.03 ((CH$_3$)$_3$*C*−), 156.4 (−NH*C*OOEt), 206.6 (−*C*OCH$_2$CH$_2$C$_6$F$_{13}$); $^{19}$F NMR (282 MHz,-$CDCl_3$) $\delta$ −81.29, −114.69, −122.36, −123.34, −123.94, −126.61; [$\alpha$]$^{25}_D$ +17.0° (*c* 1.06, $CHCl_3$). Anal. Calcd for formula $C_{18}H_{22}F_{13}NO_3$: C, 39.50; H, 4.05; N, 2.56. Found: C, 39.64; H, 3.89; N, 2.55.

**Representative Procedure for Diastereoselective Reductions of (Perfluoroalkyl)ketones: (2*S*,3*R*)-2-(Ethoxycarbonylamino)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-ol (13a).** A solution of ketone **8a** (21.0 g, 35.3 mmol) in anhydrous ethanol (2.0 L) at −78 °C was treated with powdered LiAlH(OtBu)$_3$ (26.9 g, 106 mmol). The reaction was allowed to warm to rt over 16 h. It was then quenched by gradual addition of 1 M HCl, and the solution was stirred until it became translucent. The solution was then concentrated under vacuum, and the crude residue was taken up in distilled water and extracted with $Et_2O$. The combined ether extracts were dried with $MgSO_4$ and evaporated to dryness to give 13a (20 g, 33.5 mmol, 95% yield) as a white powder. This material was used without further purification.

**(2*S*,3*R*)-2-(Ethoxycarbonylamino)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-ol (13a).** $R_f$ 0.37 (9:1 hexanes/ethyl acetate); mp = 116−120 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34−7.17 (m, 5H), 4.67 (br d, 1H, $^3J$ = 7.4 Hz), 4.10−4.01 (m, 2H), 3.96−3.88 (m, 1H), 3.75−3.70 (m, 1H), 3.24 (br s, 1H), 2.91 (dd, 1H, $^3J_1$ = 14.3 Hz, $^3J_2$ = 5.2 Hz), 2.77 (dd, 1H, $^3J_1$ = 14.3 Hz, $^3J_2$ = 9.5 Hz), 2.55−2.36 (m, 1H), 2.22−2.00 (m, 1H), 1.86−1.67 (m, 2H), 1.19 (t, 3H, $^3J_2$ = 7.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.4, 23.5, 27.8, 36.0, 57.4, 61.4, 73.0, 126.8, 128.7, 129.0, 137.3, 157.4; $^{19}$F (282 MHz, $CDCl_3$) $\delta$ −81.27, −114.95, −122.38, −123.38, −124.01, −126.60; [$\alpha$]$^{25}_D$ −6.5° (*c* 1.00, $CHCl_3$). Anal. Calcd for formula $C_{20}H_{20}F_{13}NO_3$: C, 42.19; H, 3.54; N, 2.46. Found: C, 42.59; H, 3.14; N, 2.65.

**(3*S*,4*R*)-3-(*tert*-Butoxycarbonylamino)-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluoro-2-methyl-dodecan-4-ol (13d).** $R_f$ 0.32 (9:1 hexanes/ethyl acetate); mp = 101−107 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.54 (d, 1H, $^3J$ = 9.0 Hz), 3.64−3.57 (m, 1H), 3.53−3.46 (m, 1H), 2.57−2.36 (m, 1H), 2.20−1.98 (m, 1H), 1.90 (dqq, 1H, $^3J_1$ = 7.1 Hz, $^3J_2$ = 7.1 Hz, $^3J_3$ = 7.0 Hz), 1.79−1.55 (m, 2H), 1.42 (s, 9H), 0.93 (d, 3H, $^3J$ = 7.1 Hz), 0.89 (d, 3H, $^3J$ = 7.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$)

(30) We have made one attempt to perform the reaction sequence using 200 g of C$_6$F$_{13}$(CH$_2$)$_2$I and 100 g of Weinreb amide **10a**. A significant exotherm occurred during the metalation of the perfluoroalkyl iodide, leading to decomposition of the perfluoroalkyllithium reagent. On this occasion we were unable to control the exotherm, but this difficulty can probably be overcome with the use of specialized reaction vessels able to dissipate the heat more efficiently than can standard round-bottom flasks.

δ 17.6, 18.2, 23.2, 27.6, 28.1, 28.4, 60.5, 71.4, 80.0, 157.2; $^{19}$F (282 MHz, $CDCl_3$) δ −81.49, −114.98, −122.54, −123.50, −124.08, −126.80; $[\alpha]^{25}_D$ −3.2° (*c* 0.760 $CHCl_3$). Anal. Calcd for formula $C_{18}H_{24}F_{13}NO_3$: C, 39.35; H, 4.40; N, 2.55. Found: C, 38.94; H, 3.99; N, 2.38.

**Representative Procedure for Cyclization of Mono- and Bis(perfluoroalkyl)alcohols: (4*S*,5*R*)-4-Benzyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinone (2).** To a stirred solution of **13a** (20.00 g, 35.1 mmol) in THF (250 mL) was added NaH (4.21 g, 105.3 mmol). The reaction was stirred at rt for 12 h and then quenched (1M HCl) with vigorous stirring. The solution was then evaporated to yield a crude product (∼21 g). FSPE afforded **2** (17.12 g, 32.7 mmol, 93% yield) as a white crystalline solid.

**(4*S*,5*R*)-4-Benzyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinone (2).** Mp = 100−101 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.39−7.17 (m, 5H), 4.93 (br s, 1H), 4.69 (ddd, 1H, $^3J_1$ = 7.2 Hz, $^3J_2$ = 7.2 Hz, $^3J_3$ = 7.2 Hz), 4.05 (ddd, 1H, $^3J_1$ = 7.2 Hz, $^3J_2$ = 7.2 Hz, $^3J_3$ = 7.2 Hz), 2.89 (dd, 1H, $^3J_1$ = 14.1 Hz, $^3J_2$ = 4.3 Hz), 2.71 (dd, 1H, $^3J_1$ = 14.1 Hz, $^3J_2$ = 7.9 Hz), 2.62−2.43 (m, 1H), 2.30−2.08 (m, 2H), 2.06−1.94 (m, 1H); $^{13}$C (75 MHz, $CDCl_3$) δ 21.1, 28.0, 36.3, 56.6, 78.3, 127.3, 128.9, 129.1, 136.1, 158.0; $^{19}$F (282 MHz, $CDCl_3$) δ −81.32, −115.18, −122.34, −123.23, −124.18, −126.91; $[\alpha]_D$ = −30.0° (*c* = 1.0, $CHCl_3$). Anal. Calcd for formula $C_{18}H_{14}F_{13}NO_2$: C, 41.31; H, 2.70; N, 2.68. Found: C, 41.34; H, 2.64; N, 2.69.

**(4*S*,5*R*)-4-*iso*-Propyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinone (3).** Mp = 96−99 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.90 (br s, 1H), 4.58 (ddd, 1H, $^3J_1$ = 10.6 Hz, $^3J_2$ = 7.5 Hz, $^3J_3$ = 2.6 Hz), 3.6 (dd, 1H, $^3J_1$ = 7.5 Hz, $^3J_2$ = 7.5 Hz), 2.58−2.37 (m, 1H), 2.28−1.97 (m, 2H), 1.94−1.80 (m, 2H), 1.01 (d, 3H, $^3J$ = 6.4 Hz), 0.93 (d, 3H, $^3J$ = 6.4 Hz); $^{13}$C (75 MHz, $CDCl_3$) δ 19.0, 19.7, 20.2, 27.7, 27.7, 28.2, 62.0, 78.7, 159.8; $^{19}$F (282 MHz, $CDCl_3$) δ −81.12, −115.56, −122.12, −123.34, −124.23, −126.83; $[\alpha]_D$ = −46.0° (*c* = 0.43, $CHCl_3$). Anal. Calcd for formula $C_{14}H_{14}F_{13}NO_2$: C, 35.38; H, 2.97; N, 2.95. Found: C, 35.12; H, 2.73; N, 2.68.

**(2*S*,3*R*)-2-Amino-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluoro-1-phenyl-undecan-3-ol (19).** KOH (28.4 g, 506 mmol) and **13a** (4.80 g, 8.43 mmol) were suspended in 60% EtOH in water (500 mL) and stirred at rt until the solids dissolved. The reaction was then heated to reflux for 4 h. The solution was cooled, and 1 M NaOH was added until the mixture became cloudy. The solution was extracted with $Et_2O$, and the combined organic fractions were dried ($MgSO_4$) and evaporated to dryness to yield **19** (4.05 g, 8.14 mmol, 97% yield) as a flaky solid. This material was used without further purification. $R_f$ 0.33 (4:1 hexanes/ethyl acetate); mp = 72−80 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.35−7.17 (m, 5H), 3.60−3.56 (br m, 1H), 3.14−3.08 (br m, 1H), 2.87 (dd, 1H, $^3J_1$ = 13.7 Hz, $^3J_2$ = 3.1 Hz), 2.49 (dd, 1H, $^3J_1$ = 13.7 Hz, $^3J_2$ = 10.0 Hz), 2.58−2.41 (m, 1H), 2.22−1.98 (br m, 4H), 1.85−1.70 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.6, 27.9, 38.4, 56.8, 72.7, 126.6, 128.8, 129.1, 138.6; $^{19}$F (282 MHz, $CDCl_3$) δ −81.3, −114.7, −123.0, −123.3, −123.9, −126.6; $[\alpha]^{25}_D$ −3.0 (*c* 1.01, $CHCl_3$). Anal. Calcd for formula $C_{17}H_{16}F_{13}NO$: C, 41.06; H, 3.24; N, 2.82. Found: C, 41.48; H, 2.96; N, 2.88.

**(4*S*,5*R*)-4-Benzyl-5-(1′*H*,1′*H*,2′*H*,2′*H*-perfluorooctyl)-2-oxazolidinethione (1e).** Carbon disulfide (0.995 mL, 16.50 mmol) and **19** (5.47 g, 11.00 mmol) were dissolved in $CH_2Cl_2$ (500 mL) and cooled to 0 °C. DIPEA (3.83 mL, 22.00 mmol) was added dropwise over 10 min. The reaction was allowed to warm to rt overnight. A second charge of carbon disulfide (0.199 mL, 3.30 mmol) was added, and the reaction was stirred for an additional 24 h. After this time, the reaction appeared complete by TLC. It quenched with saturated aqueous $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$, and the organic fractions were pooled, dried ($MgSO_4$), and concentrated under vacuum. The crude material was then purified by FSPE to give **1e** (4.76 g, 8.83 mmol, 80% yield) as a yellow solid. $R_f$ 0.54 (2:1 hexanes/ethyl acetate); mp = 124−130 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.40−7.16 (m, 5H), 6.94 (br s, 1H), 4.94 (dd, 1H,$^3J_1$ = 7.9 Hz, $^3J_2$ = 7.8 Hz), 4.28−4.21 (br m, 1H), 2.92 (dd, 1H, $^3J_1$ = 13.5 Hz, $^3J_2$ = 3.4 Hz), 2.77 (dd, 1H, $^3J_1$ = 13.5 Hz, $^3J_2$ = 11.5 Hz), 2.65−2.48 (br m, 1H), 2.33−2.13 (br m, 2H), 2.09−1.98 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.7, 28.3, 35.6, 60.2, 84.0, 127.7, 128.9, 129.6, 135.2, 188.6; $^{19}$F (282 MHz, $CDCl_3$) δ −81.2, −114.9, −122.3, −123.3, −123.8, −126.5; $[\alpha]^{25}_D$ −40.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for formula $C_{18}H_{14}F_{13}NOS$: C, 40.08; H, 2.62; N, 2.60. Found: C, 40.40; H, 2.40; N, 2.73.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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