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Fluorous tagging strategy for solution-phase synthesis of small molecules, peptides and oligosaccharides

Wei Zhang

Abstract

The purification of reaction mixtures is a slow process in organic synthesis, especially during the production of large numbers of analogs and compound libraries. Phase-tag methods such as solid-phase synthesis and fluorous synthesis, provide efficient ways of addressing the separation issue. Fluorous synthesis employs functionalized perfluoroalkyl groups attached to substrates or reagents. The separation of the resulting fluorous molecules can be achieved using strong and selective fluorous liquid-liquid extraction, fluorous silica gel-based solid-phase extraction or high-performance liquid chromatography. Fluorous technology is a novel solution-phase method, which has the advantages of fast reaction times in homogeneous environments, being readily adaptable to literature conditions, having easy intermediate analysis, and having flexibility in reaction scale and scope. In principle, any synthetic methods that use a solid-support could be conducted in solution-phase by replacing the polymer linker with a corresponding fluorous tag. This review summarizes the progress of fluorous tags in solution-phase synthesis of small molecules, peptides and oligosaccharides.

Abbreviations

μW Microwave; Boc tert-Butoxycarbonyl; BTF Benzotrifluoride; Cbz Benzyloxycarbonyl; DIC Diisopropylcarbodiimide; DMAP 4-Dimethylaminopyridine; FC-72 Perfluorohexane; F-LLE Fluorous liquid-liquid extraction; Fmoc 9-Fluorenylmethoxycarbonyl; F-SPE Fluorous solid-phase extraction; HPLC High-performance liquid chromatography; PMB 4-Methoxybenzyl; Rf Perfluoroalkyl group

Introduction

Phase tagging is a useful strategy for the purification of reaction mixtures [1•], and has been successfully employed in solid-phase peptide synthesis. Further application of solid-phase synthesis for small molecules, however, has not yet fulfilled the high expectations of chemists. Small-molecule synthesis has a much broader scope than peptide synthesis, and the solid-phase approach for small molecules is limited by unfavorable heterogeneous reaction kinetics, longer development times and difficulties in analyzing resin-bound intermediates. With a paradigm shift away from the synthesis of libraries containing millions of compounds toward much smaller libraries, solution-phase methods, such as polymer-assisted synthesis [2] and fluorous synthesis [3••,4•,5•], have gained popularity in recent years.

Fluorous synthesis employs functionalized perfluoroalkyl groups (Rf) as phase tags [6••]. This technology has inherited the characteristics of solution-phase synthesis, ie, fast reaction times in a homogeneous environment, adaptability to literature conditions, easy analysis of intermediates and flexibility in reaction scale and scope. Fluorous tags are usually attached to the parent molecules via a $(CH_2)_m$ segment to insulate the reactive site from the electron-

Address Fluorous Technologies Inc, University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, USA, Email: w.zhang@fluorous.com.

withdrawing fluorine atoms (a fluorous alkyl chain C_nF_{2n+1}-$(CH_2)_m$ can be abbreviated as Rf_nH_m). In fluorous synthesis, the functional group of the fluorous molecules controls the reaction, while the fluorous tag dominates the separation. Fluorous tags can be categorized as 'heavy' or 'light'. Heavy tags contain multiple Rf chains and have a fluorine content greater than 60% of the molecular weight, while light tags contain only one or two Rf chains with significantly fewer fluorine atoms. Fluorous separation is based on strong and selective fluorine-fluorine interactions between the fluorous molecules and the fluorous separation media [7•]. Liquid-liquid extraction (LLE) with fluorous and organic solvents has been used for the separation of heavy fluorous molecules, while silica gel-based fluorous solid-phase extraction (F-SPE) and high-performance liquid chromatography (HPLC) have been used for the separation of light fluorous molecules.

A broad technology platform of fluorous chemistry has been available since the early 1990s. The original fluorous tagging strategy for catalyst recycling [8] has been extended to substrate tagging and reagent/scavenger tagging. Fluorous molecules have been applied to many areas of organic synthesis [9], including biphasic catalyses, thermomorphic catalyses, triphasic reactions, mixture syntheses [10•], multicomponent reactions, microwave (μW) reactions, ion reactions and solid-phase liquid reactions, supercritical CO_2 reactions. This review discusses a substrate-tagging strategy for the parallel synthesis of small molecules, peptides and oligosaccharides.

Fluorous tags are the derivatives of protecting groups such as *tert*-butoxycarbonyl (Boc), 4-methoxybenzyl (PMB), benzyloxycarbonyl (Cbz) and silyl groups, or Wang, Rink and Marshall linkers. Some representative fluorous tags for 'catch and release' of substrates are listed in Table 1.

Fluorous silyl

Studer and Curran reported the synthesis of isoxazolines **4** (Scheme 1A) and isoxazoles **7** (Scheme 1B) by cycloaddition of nitrile oxides **1** with fluorous silyl-protected allyl and propargyl alcohols (compounds **2** and **5**, respectively; Scheme 1) [11]. An excess amount of nitrile oxides **1** were used to drive the cycloaddition reaction to completion.

Unreacted nitrile oxides were isolated by fluorous liquid-liquid extraction (F-LLE) with perfluorohexane (FC-72)/benzene/water. Following desilylation with hydrogen fluoride and pyridine, final products **4** and **7** were purified by a second liquid extraction with FC-72, dichloromethane and aqueous ammonium chloride.

The combination of fluorous and solid-phase technologies for small-molecule synthesis has been reported by Wipf and co-workers [101]. Resin-bound intermediates **8** (Scheme 2), prepared by several steps of solid-phase synthesis, were attached to a fluorous silyl group (*tert*-butyl-phenyl-((2-perfluorooctyl)ethyl) silyl (BPFOS)), and the resulting fluorous molecule **9**, along with untagged byproducts accumulated from previous steps, were cleaved from the polymer support to provide the fluorous tagged product **10** (Scheme 2). Fluorous product **10** was isolated by F-SPE and subjected to further reactions to afford oxazole and thioazole analogs of curacin (compounds **11**; Scheme 2).

The Wipf and Curran research groups also conducted a multicomponent Biginelli reaction using fluorous urea **12** (Scheme 3) as the limiting agent, while other components such as β-ketone ester **13** and aldehyde **14** were used in excess with a mixture of tetrahydrofuran (THF) and benzotrifluoride (BTF) [28]. The condensed fluorous dihydropyrimidine intermediates (not shown) were isolated by FC-84 extraction, and the cleaved fluorous tag was removed from the reaction mixture by a second FC-84 extraction to produce pyrimidine-2-one derivative **15** (Scheme 3).

Fluorous *tert*-butoxycarbonyl

Fluorous Boc (F-Boc) has been employed as an amino protecting group in the parallel synthesis of a small library of isonipecotic acid derivatives **20** (Scheme 4) [14]. Fluorous intermediate **17** was coupled with a number of different amines to provide amides **18**. Following deprotection with trifluoroacetic acid (TFA), the resulting piperidine amide compounds **19** were further reacted with an array of halide compounds, resulting in a 96-compound library. All of the reaction mixtures containing fluorous components were purified by F-SPE.

The synthetic efficiency of an Ugi reaction/de-Boc/cyclization method, originally developed by the Hulme research group, has been improved by the application of fluorous and •W technologies [29]. In the synthesis of quinoxalinone **26** and benzimidazole **29** (Scheme 5A and 5B, respectively) using F-Boc protected aniline **22**, the time for the Ugi reaction was reduced from 36 to 48 h to less than 20 min under μW irradiation. The removal of excess aldehydes and unreacted acids from the reaction mixture was accomplished using F-SPE instead of double-scavenging with polymer-supported tosylhydrazide and *N*,*N*-diisopro-pylethylamine (DIPEA). The deprotection of the F-Boc group with TFA and purification of the final product were also benefited by a faster μW reaction and easy F-SPE separation.

Fluorous benzyloxycarbonyl

Schwinn and Bannwarth employed fluorous Cbz (F-Cbz)-protected anilines in the synthesis of quinazoline-2,4-diones **33** (Scheme 6) [30]. Amidation of F-Cbz-protected acids **31**, followed by cyclative deprotection of furans **32** in an FC-72 layer, led to the formation of products **33**, which were extracted into an ethyl acetate layer and purified by F-LLE.

This chemistry has since been improved by the same research group through absorption of the fluorous molecules onto fluorous silica gel via strong fluorine-fluorine interactions to eliminate the requirement for fluorous solvents in both the reaction and separation steps [31].

Fluorous alcohols

Wipf and Methot accomplished the synthesis of dihydropyridazinone **40** (Scheme 7) using fluorous alcohol-protected carboxylic acid **36** (Scheme 7) [20]. The δ-keto ester **38** was treated with hydrazine to form a dihydro-pyridazinone ring (Scheme 7). The fluorous tag was cleaved during the cyclization, and the resulting product **39** was separated from the reaction mixture by F-LLE with FC-72 and methanol.

Fluorous amino acids have been used in the parallel synthesis of a hydantoin/thiohydantoin library **45** (Scheme 8) [21]. Two fluorous-tagged amino acids **41** (Scheme 8) having different R_1 groups underwent reductive amination with six different aldehydes **42**. Each of the 12 intermediates **43** were reacted with ten aryl isocyanates/aryl isothiocyanates. The resulting ureas/thioureas **44** were spontaneously cyclized to displace the fluorous tag and form heterocyclic products **45**.

Fluorous amino acids have also been employed in the synthesis of an N-alkylated dihydropteridinone library **54** (Scheme 9) [32]. 4,6-Dichloro-5-nitropyrimidine (**46**) was first displaced with fluorous amino acids **47**, and then displaced with secondary amines **49** (Scheme 9). The reduction of the nitro group of nitropyrimidines **50** was conducted by hydrogenation using Pd/C as a catalyst, and this was followed by a cyclization reaction of aminopyrimi-dines **51**, promoted by μW irradiation. The N-alkylation reaction of fused heterocyclic compounds **52** with benzyl halides **53** (Scheme 9) gave mono products **54** in high selectivity, using 1.0 equivalent of a base and 1.0 equivalent of benzyl halides **53** in the present of lithium bromide.

Fluorous amino esters **57** (Scheme 10) have been used in the synthesis of proline analogs via three-component reactions [Zhang W, Lu Y, Chen C-T, unpublished results]. 1,3-Dipolar cycloaddition of pyrrolidine diones **55**, benzaldehydes **56** and amino ester **57**, gave fused heterocycle **58** as a single diastereomer, which was purified by F-SPE. Adducts **58** have been used as key intermediates in the construction of novel tricyclic compounds, such as compounds **59** and **60** (Scheme 10).

Fluorous diols

The utility of fluorous diols as carbonyl group protecting agents has been demonstrated by Read and Zhang in the synthesis of 4-phenyl-pyridine derivative **68** (Scheme 11) [Read R, Zhang C, personal communications]. One of the carbonyl groups of 1,4-benzodialdehyde (**61**) was protected with fluorous diol **62**. The resulting protected compound **63** underwent condensation, cycloaddition and oxidation reactions, and was finally deprotected with hydrochloric acid to afford substituted pyridine **68**.

Fluorous thiols

A fluorous thiol group has been used as a nucleophilic tag to anchor 2,4-dichloropyrimidine **69** (Scheme 12) [22]. The tagged substrate **71** was further displaced with 3-(trifluoromethyl) pyrazole (**72**) to give pyrazolylpyrimidine **73** (Scheme 12). The thiol tag was then activated by oxidation to sulfone **74** and displaced by a set of nucleophiles (Nu) to afford disubstituted pyrimidines **75** (Scheme 12).

FluoMar™

FluoMar™ (**77**; Scheme 13) is a fluorous version of the Marshall resin, and has been used as a catch and release tag in the parallel synthesis of amides **81** (Scheme 13) [24]. FluoMar™ was attached to carboxylic acids **76** under general coupling conditions with diisopropylcarbodiimide (DIC) and dimethylaminopyridine (DMAP). The tagged compound **78** (Scheme 13) underwent Boc deprotection and acylation to give amide **80**. The fluorous tag was then displaced with a set of amines to give diamides **81**.

Fluorous benzophenone imines

Herr and co-workers employed fluorous benzophenone imine 82 (Scheme 14) to tag aryl halides 83 or triflates and converted them to corresponding amines 85 by hydrolysis of *N*-aryl benzophenone imines 84 (Scheme 14) [26]. Fluorous benzophenone was recovered by F-SPE for the regeneration of 82.

Fluorous sulfonyls

The perfluorooctylsulfonyl group has been used to tag phenols, with the resulting F-sulfonates having similar reactivity to triflates, which have been used in cross-coupling reactions to form aryl C-C [23], C-S [33] and C-H [34] bonds. Such cross-coupling reactions have been accelerated by μW irradiation.

The fluorous sulfonyl tag has been employed in multistep syntheses, for example, the fluorous benzaldehyde **86** (Scheme 15A) underwent a reductive amination to form compound **88**, which was then reacted with an isocyanate **89** (Scheme 15B) to form substituted hydantoin **90** or with a benzoyl chloride **93** to form amide **94**. F-SPE-purified

F-sulfonates **90** and **94** were used for palladium-catalyzed cross-couplings to form the corresponding biaryl **92** [23] and aryl sulfide **96** [33] compounds, respectively. In the multistep synthesis, the fluorous sulfonyl tag facilitated the intermediate purification, and also served as

a hydroxyl-protecting group during the early steps of the reaction and activated the hydroxyl group for the coupling reaction at the last step.

μW and fluorous technologies have been employed in the solution-phase parallel synthesis of a substituted 3-aminoimidazo[1,2-*a*]pyridine and 3-aminoimidazo[1,2-*a*]pyrazine library (compounds **101**; Scheme 16) [35]. Multicomponent reactions of perfluorooctylsulfonyl-tagged benzaldehydes **97** with isonitriles **98** and 2-amino-pyridines/2-aminopyrazines **99** produced compounds **100** (Scheme 16). The condensation products were subjected to Pd-catalyzed cross-coupling reactions with boronic acids or thiols to form imidazopyridines or imidazopyrazines **101** (Scheme 16).

Fluorous benzaldehyde

Ladlow and co-workers recently developed an acid-labile fluorous benzaldehyde protecting group **102** to facilitate the parallel synthesis of sulfonamides **107** (Scheme 17) [27]. All intermediates and the final products were purified by F-SPE.

Peptide synthesis

The application of fluorous tags to solid-phase peptide synthesis was first reported by van Boom and co-workers [36]. In a 9-fluorenylmethoxycarbonyl (Fmoc)-based amino acid synthesis, the unreacted free amines were capped with the acetyl group after each condensation step (Scheme 18) [36]. After the desired number of iterations, the deprotection of the final Fmoc group was followed by tagging with an F-Cbz moiety. A mixture containing the desired F-tagged product and acetyl-capped byproducts were separated by HPLC with a fluorous column. Using this method, the van Boom research group was able to purify peptide oligomers containing seven to 22 amino acids. Recently, Overkleeft and co-workers introduced a base-labile fluorous methylsulfonylethoxycarbonyl (F-Msc) moiety as an alternative protecting group for Fmoc-based peptide synthesis [37].

Inazu and co-workers applied a Rink-type protecting group with a fluorous support containing six perfluorooctyl groups (Hfb), ie, compound **108** (Scheme 19), to peptide synthesis [38]. An excess amount of an amino acid derivative was used in each coupling step. The unreacted reagent and coupling agents were removed by extraction with methanol from the FC-72 layer. The product **109** was extracted into an FC-72 layer and was deprotected and purified to give pure tripeptide **110**. The Mizuno research group recently reported a new PMB-type protecting group also using a fluorous Hfa support for peptide synthesis [39].

Recently, Kumar an co-workers developed a trivalent iodonium compound **112** and used it as a capping reagent to remove deletion sequences up to 21 residues in length (Scheme 20) [40]. The fluorous byproducts were separated by reverse-phase chromatography or by precipitation following the addition of water to the reaction mixture.

Oligosaccharide synthesis

A fluorous tagging strategy has also been applied to the synthesis of oligosaccharides. Curran and co-workers employed fluorous benzyl (F-Bn) to protect hydroxyl groups in the synthesis of disaccharide **118** (Scheme 21) [41]. Tribenzyl tagged D-glucal **114** was coupled with excess diacetone galactose **115**, under standard reaction conditions and in BTF, to give pure fluorous disaccharide **116** (Scheme 21) after triphasic extraction. Fluorous compound **116** was then debenzylated by catalytic hydrogenation with H_2 and palladium(II) hydroxide in FC-72. After the triphasic extraction, product **117** was acylated in the organic phase to give disaccharide **118** (Scheme 21) in a methanol layer.

Inazu and co-workers employed a fluorous bisperfluorooctyl acid tag (Bfp; Scheme 22) to protect the hydroxyl groups of a mannose derivative [42,43]. The triphenylmethyl (Trt) group of mannose derivative **119** was selectively removed by treatment with 10-camphorsulfonic acid (CSA). The deprotected hydroxyl group was then coupled to galactose derivative **120** to give fluorous disaccharide **121** (Scheme 22). Deprotection of both the acetyl and Bfp groups, followed by FC-72/methanol extraction gave disaccharide **122** in the methanol layer. The Bfp protecting group was recovered from the FC-72 layer as a methyl ester.

Jing and Huang developed fluorous thiol **123** (Scheme 22) and used it to displace the bromo group of a tetraacetyl-α-glucosyl bromide **124** [44]. After removal of the acetate, the thiolglucoside **125** was subjected to benzoylation and glycosylation to give disaccharide **127** (Scheme 23) in good yield and high purity following F-SPE. The fluorous thiol **123** could be recycled.

Instead of tagging the substrates, Seeberger and co-workers employed fluorous silyl protecting groups to cap the hydroxyl group of the undesired sequences [45]. Since the desired oligomeric species were non-fluorous, they could be separated from the fluorous byproducts by HPLC and no detagging step was required.

Manzoni recently reported the use of fluorous silyl reagent **129** (Scheme 24) to protect the anomeric position of sugar acceptors in saccharide synthesis. The tagged substrates **130** were purified by F-SPE [46].

Conclusion

Fluorous synthesis has favorable solution-phase reaction kinetics and overcomes some of the disadvantages of solid-phase synthesis. This new high-throughput technology also has the characteristics of easy reaction monitoring and a broad synthetic scope. The linker strategy developed for solid-phase synthesis can be applied to solution-phase fluorous synthesis by simply replacing the polymer support with a fluorous tag. With the increasing availability of fluorous tagging agents, organic chemists should find additional applications of fluorous technologies in the preparation of small molecules, peptides and oligosaccharides.

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•• of outstanding interest

• of special interest

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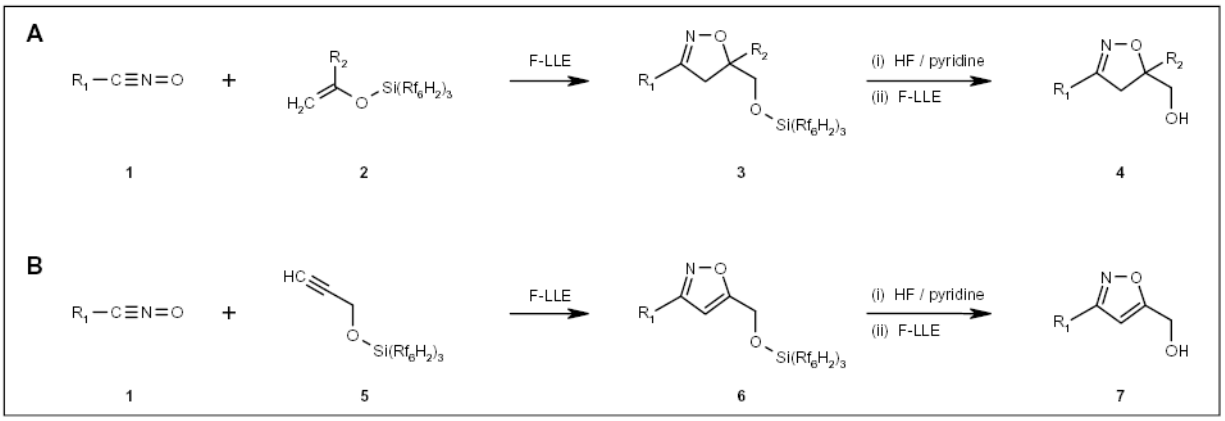
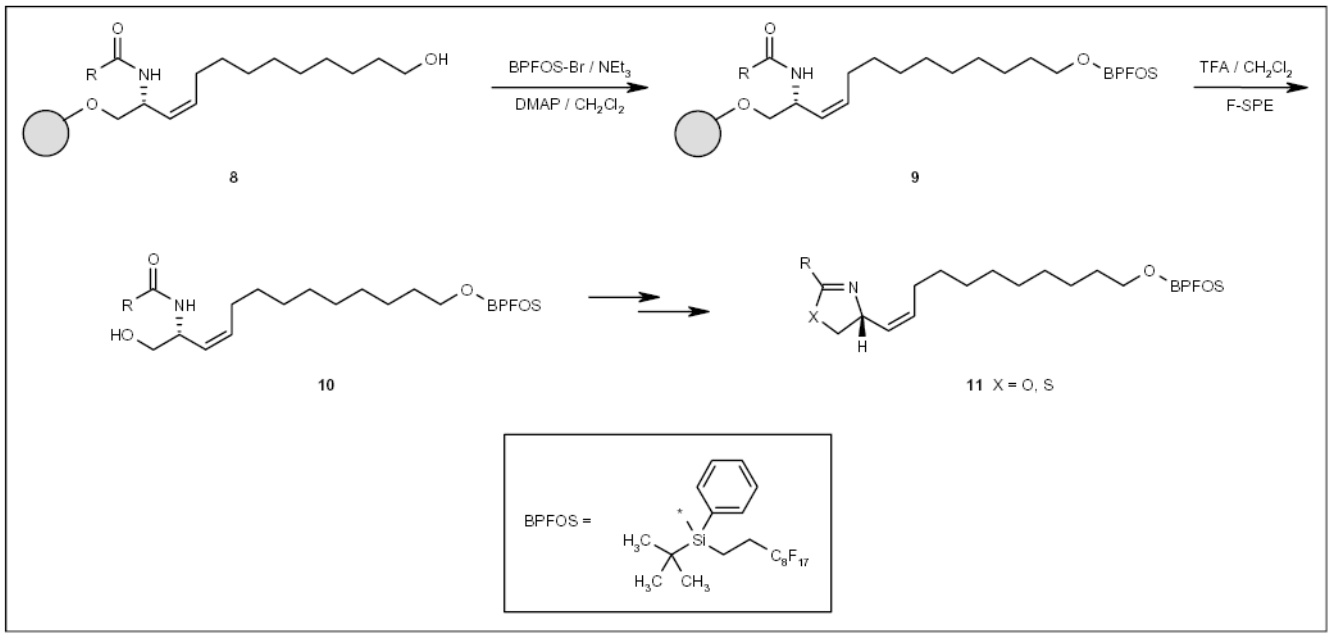
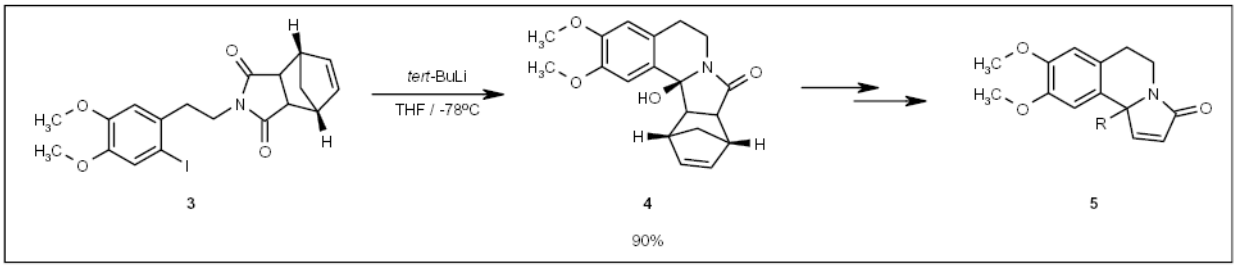


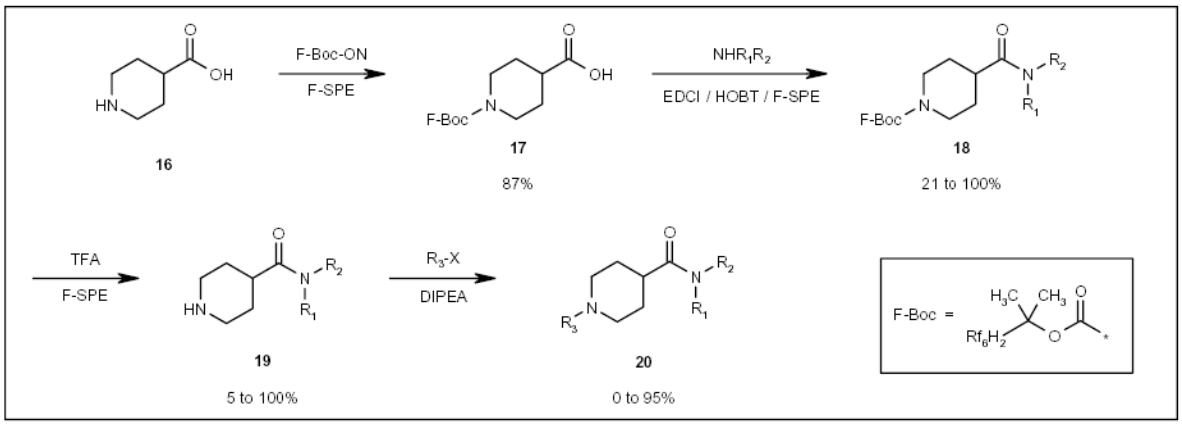
Scheme 1.
The application of a fluorous silyl tag for isoxazole and isoxazoline synthesis.



Scheme 2.
The application of a fluorous silyl tag for oxazole and thioazole synthesis.

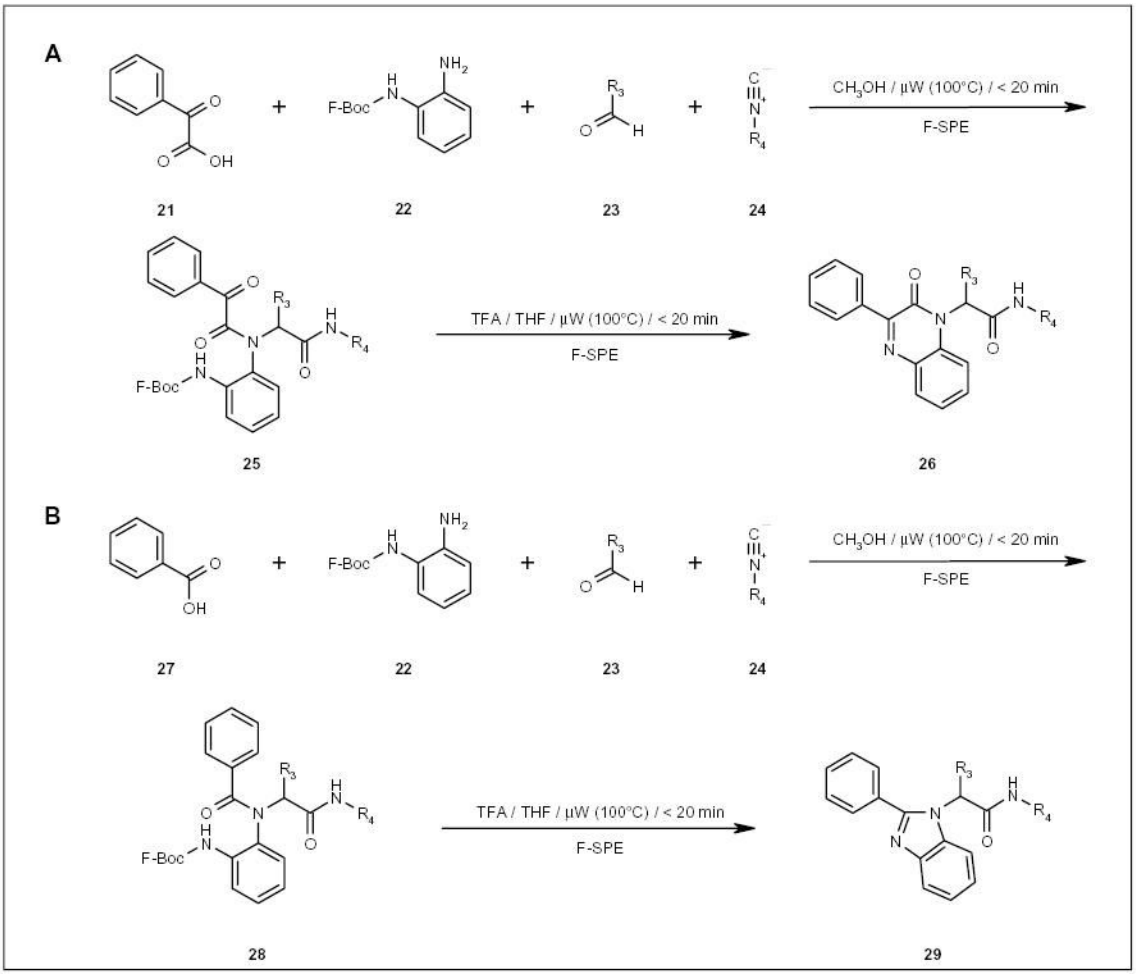


Scheme 3.
The application of a fluorous silyl tag in a Biginelli reaction.

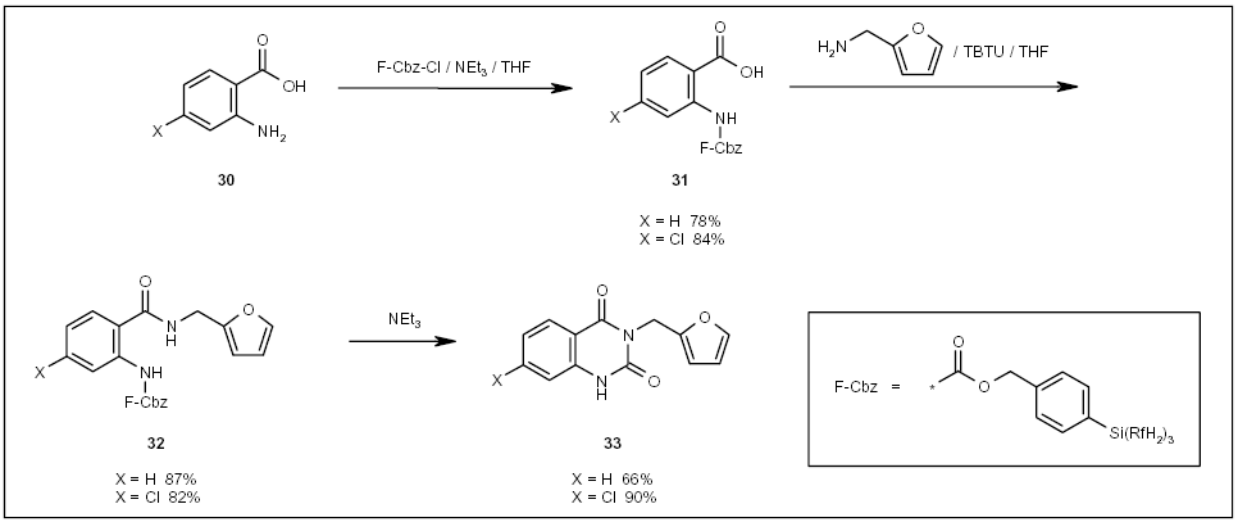


Scheme 4.

The application of an F-Boc protecting group for the synthesis of isonipecotic acid derivatives. **EDCI 1**-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, **HOBT** 1-hydroxybenzotriazole, **DIPEA** *N*,*N*-diisopropylethylamine.

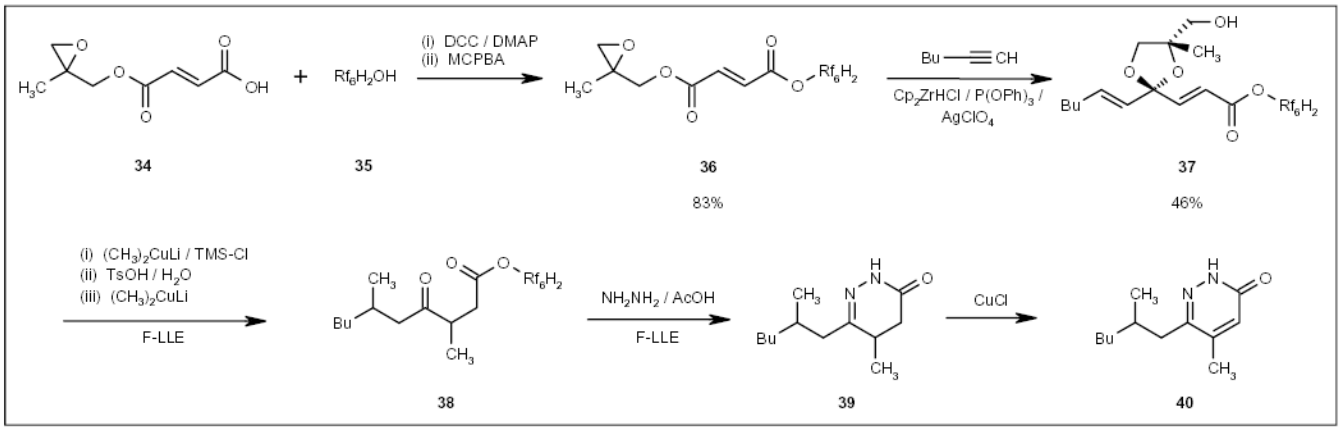


Scheme 5.
The μW-assisted fluorous synthesis of quinoxalinones and benzimidazoles.



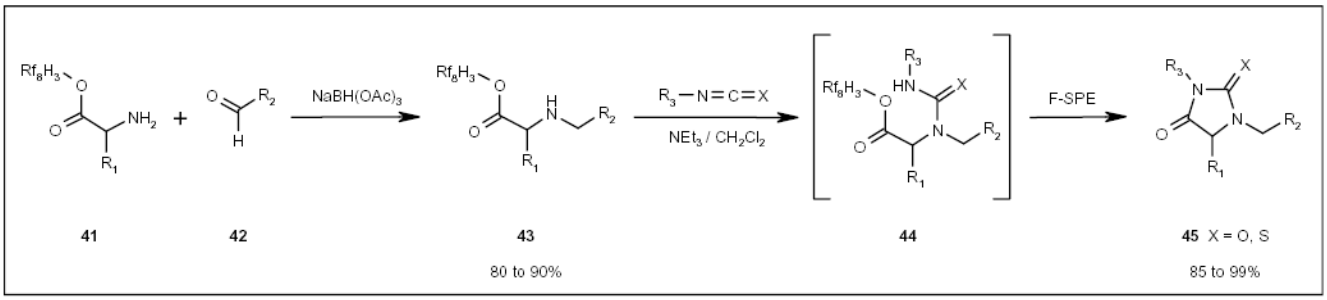
Scheme 6.

The application of an F-Cbz protecting group in the synthesis of quinazoline-2,4-diones. **TBTU** *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

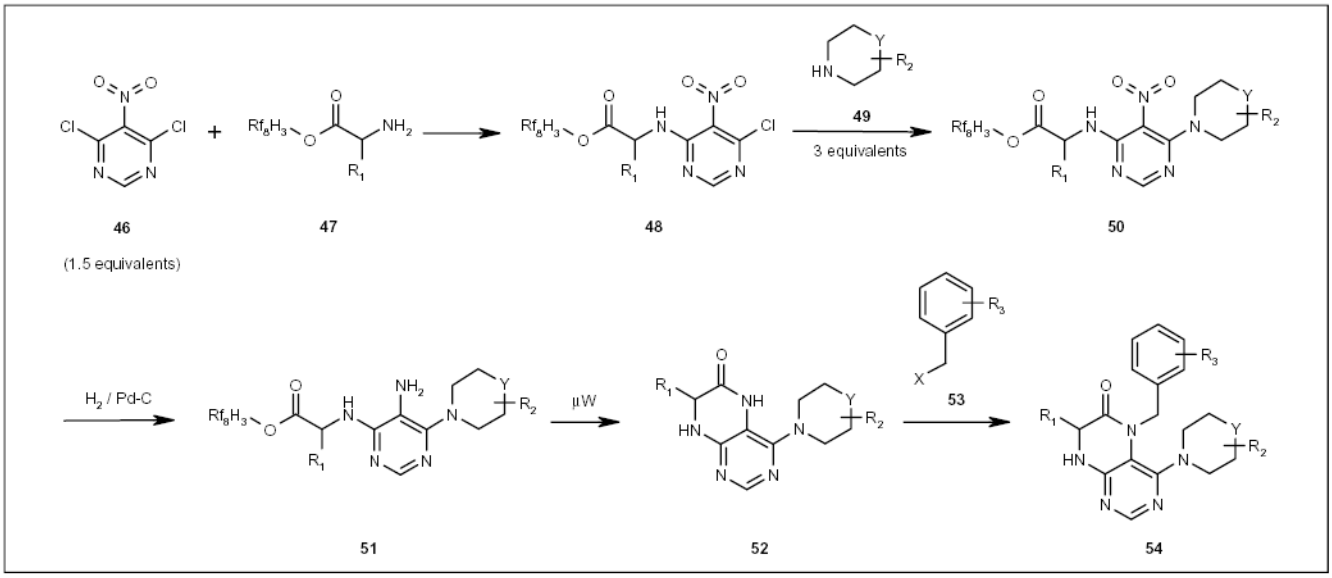


Scheme 7.

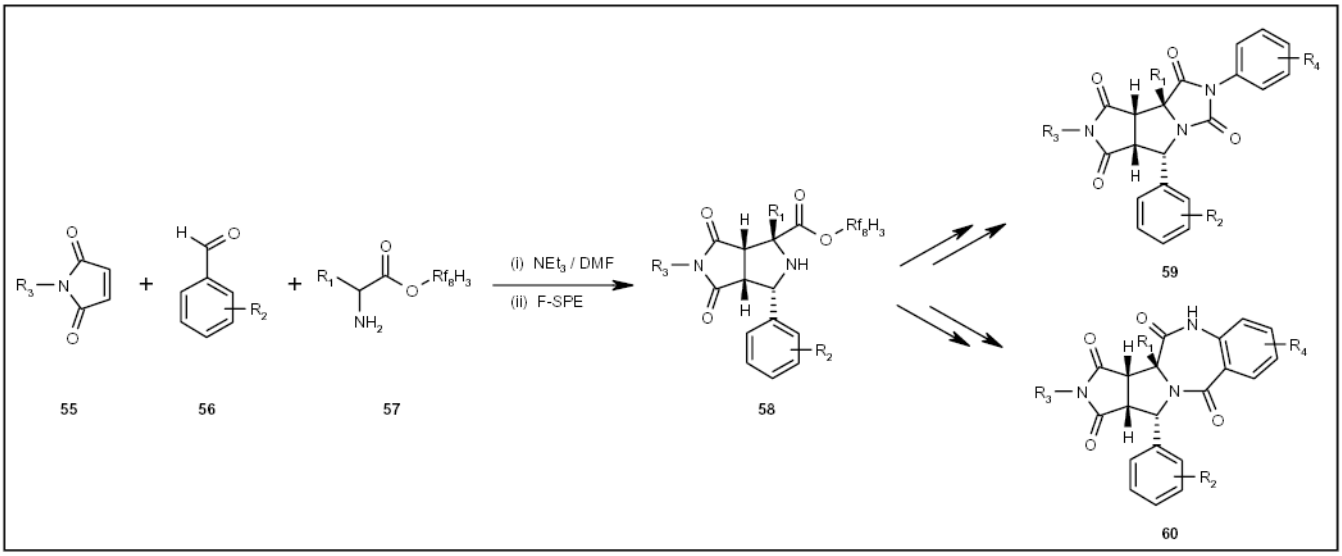
The fluorous alcohol-protected synthesis of a dihydropyridazinone. DCC Dicyclohexylcarbodiimide, DMAP dimethylaminopyridine, MCPBA 3-chloroperoxybenzoic acid, TMS trimethylsilyl.



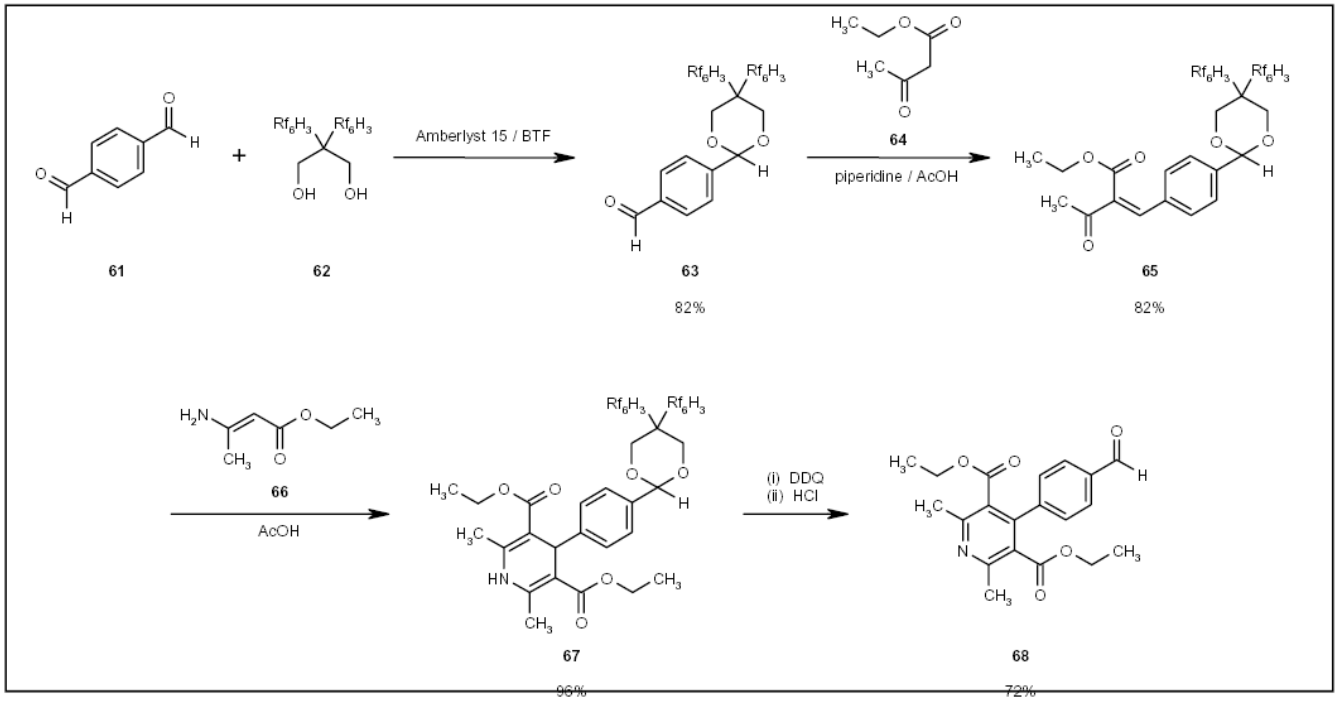
Scheme 8.
The fluorous synthesis of a substituted hydantoin/thiohydantoin library.



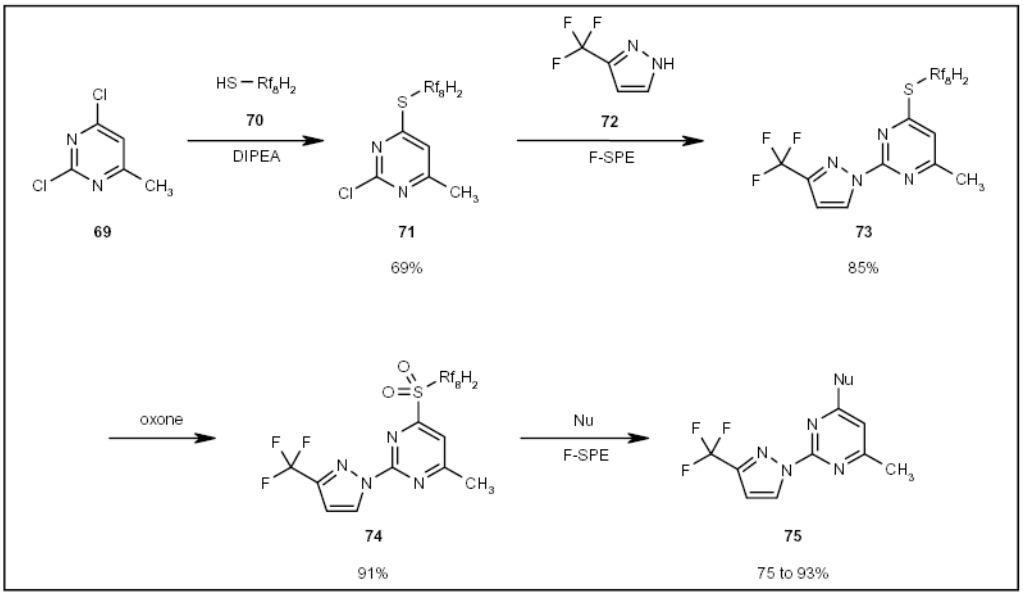
Scheme 9.
The fluorous synthesis of dihydropteridinone derivatives.



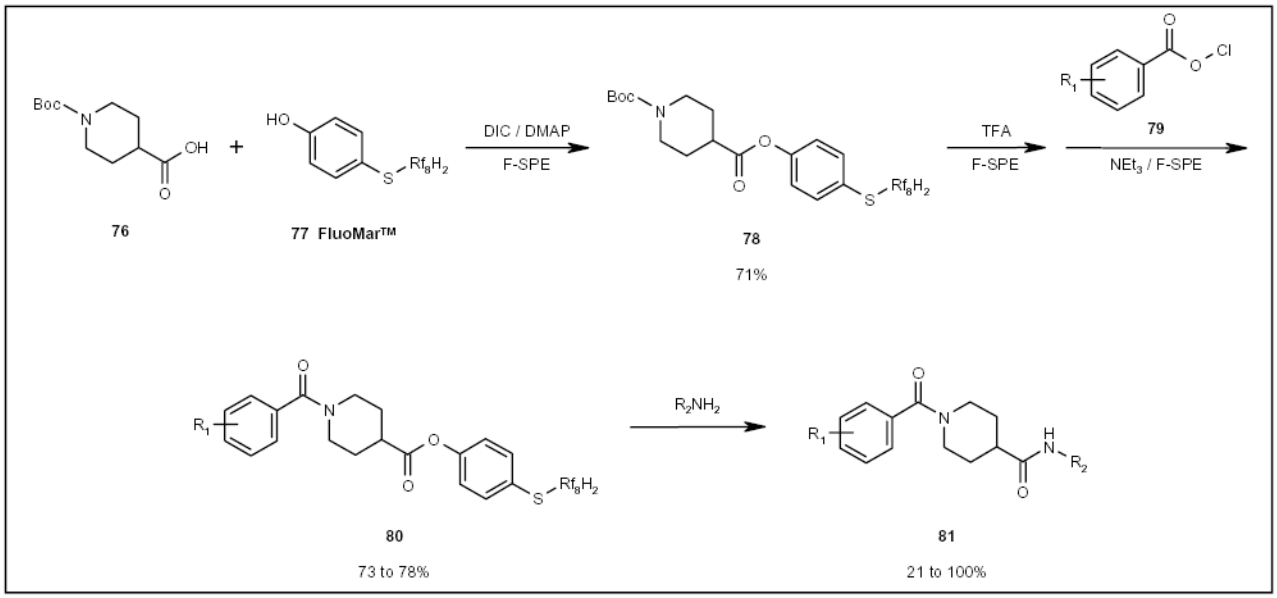
Scheme 10.
The fluorous synthesis of novel heterocyclic systems.



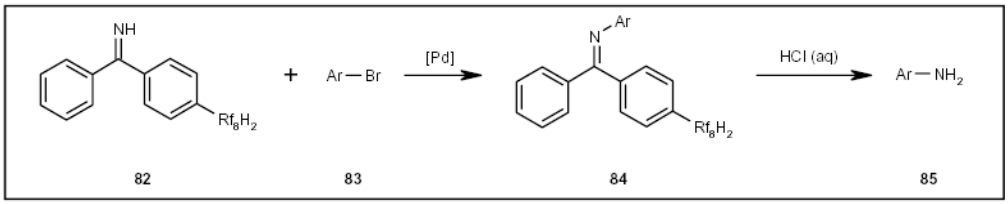
Scheme 11.
The fluorous synthesis of a substituted pyridine.
DDQ Dichlorodicyanoquinone.



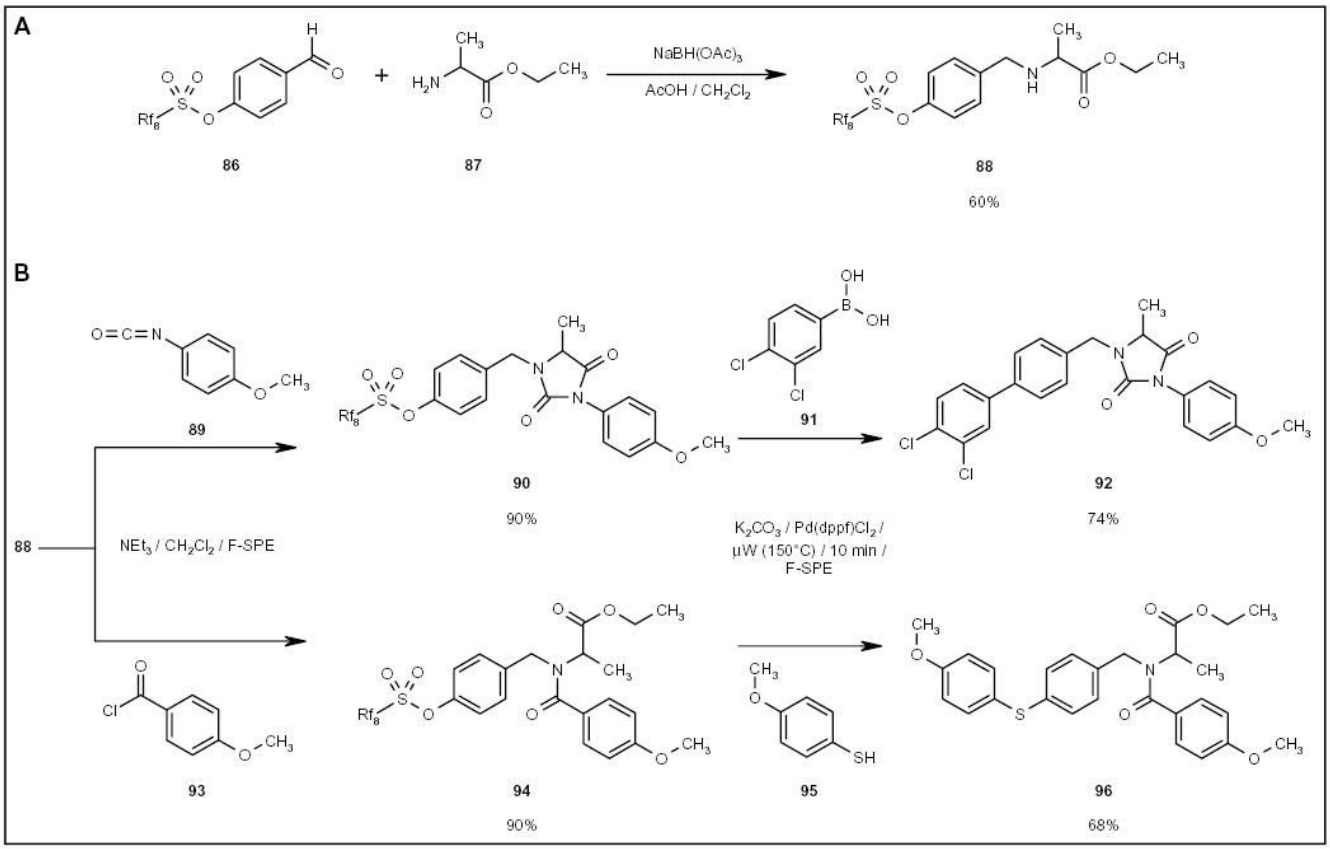
Scheme 12.
The application of a fluorous thiol tag for the synthesis of a disubstituted pyrimidine analog.



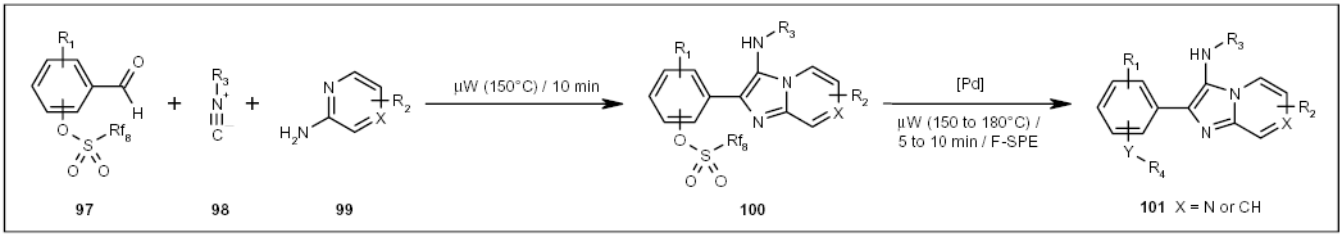
Scheme 13.
The application of a FluoMar^{TM} tag in the parallel synthesis of diamides.



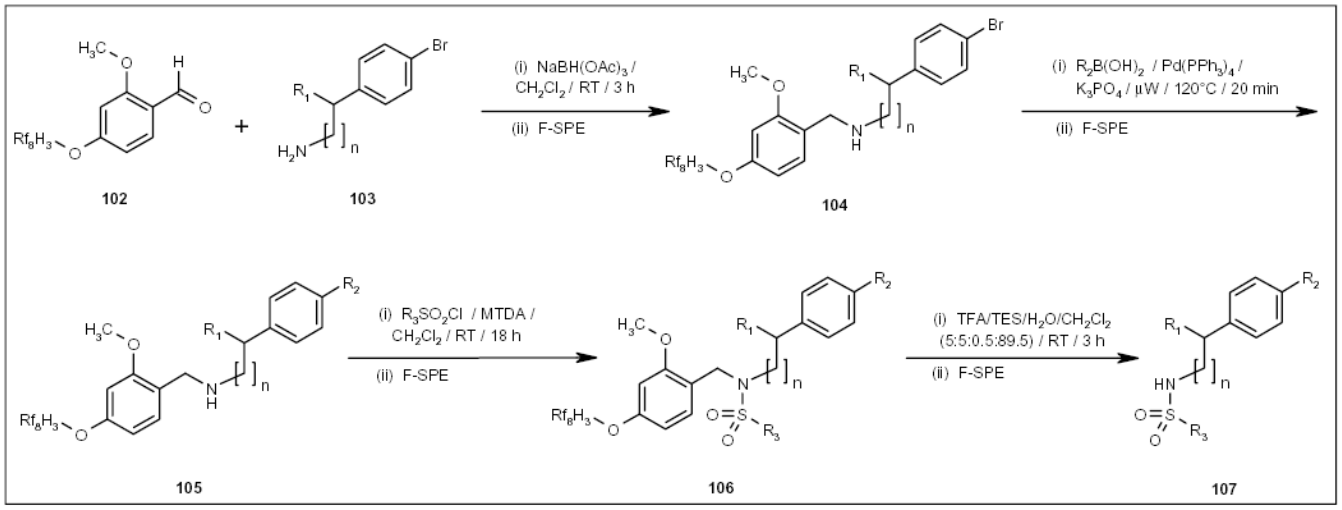
Scheme 14.
The fluorous synthesis of anilines.



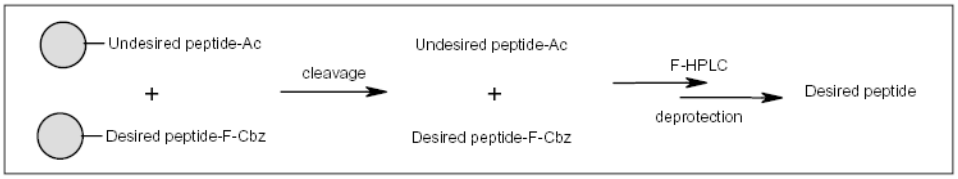
Scheme 15.
The application of an F-sulfonyl tag for multistep synthesis.



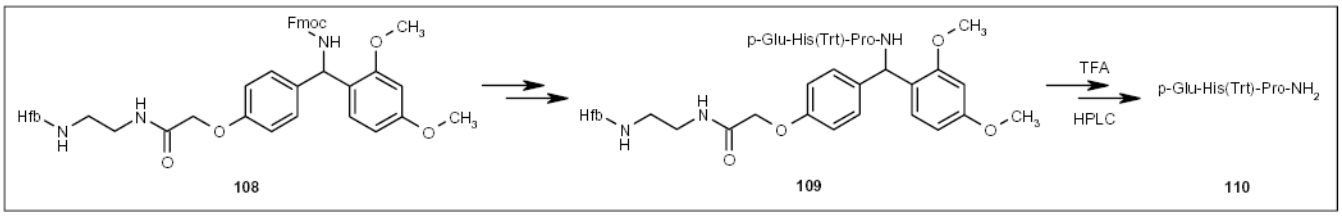
Scheme 16.
The application of an F-sulfonyl tag for multicomponent and subsequential cross-coupling reactions.



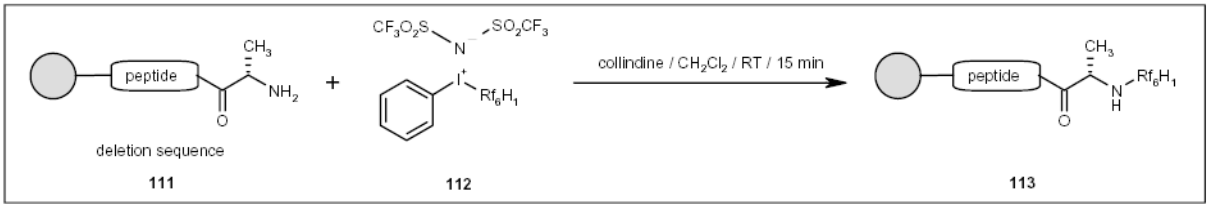
Scheme 17.
The fluorous synthesis of sulfonamides.
MTDA Methyl trimethylsilyl dimethylketene acetal, **TES** triethylsilyl.



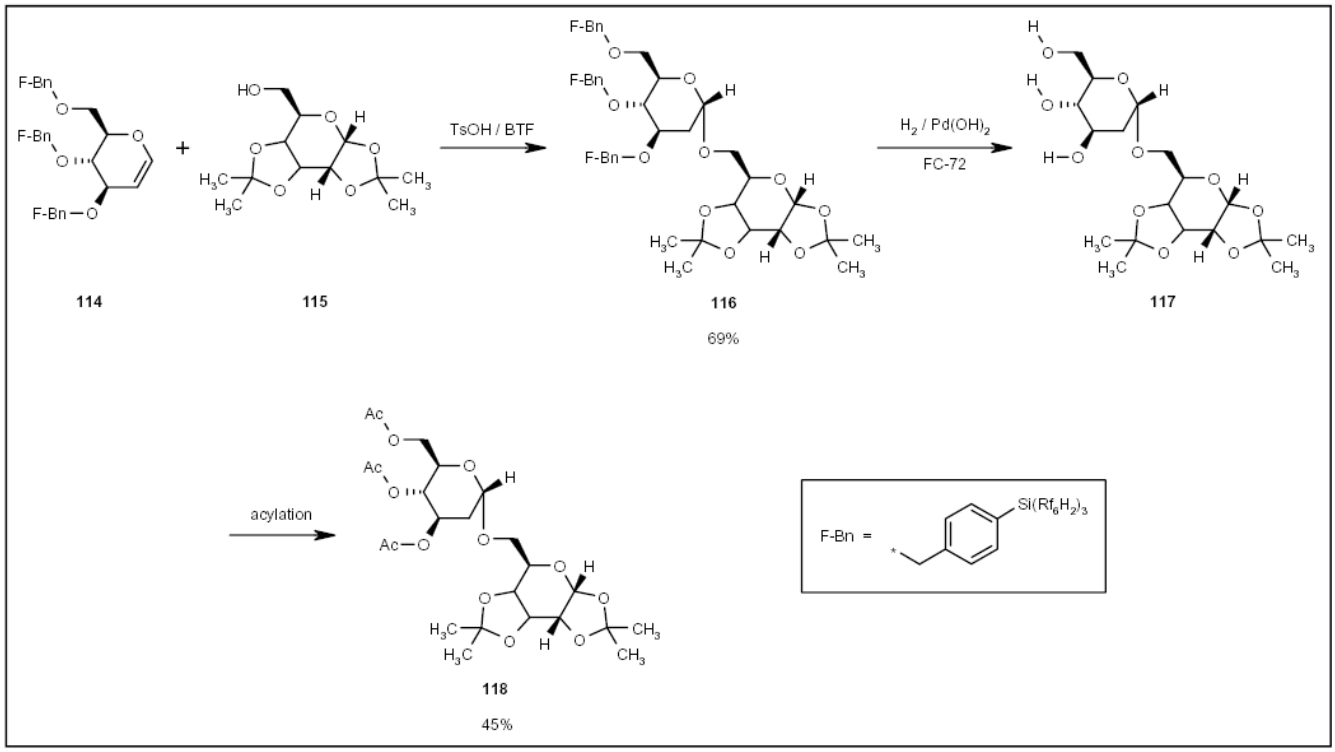
Scheme 18.
The application of F-Cbz for peptide synthesis.



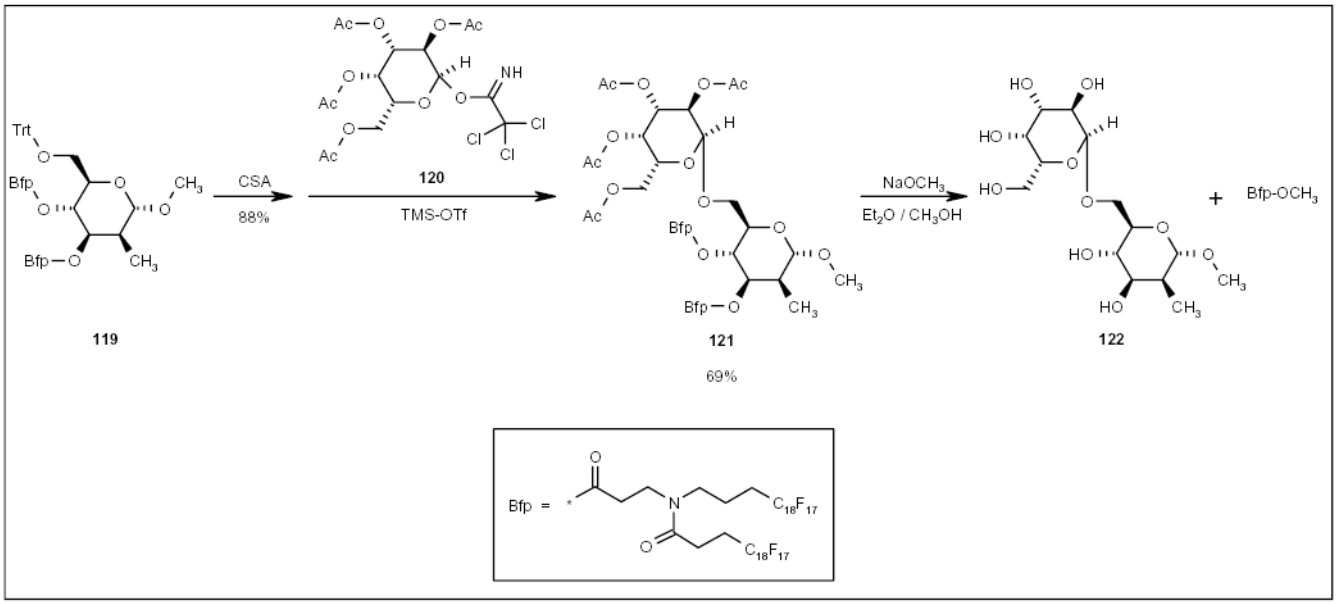
Scheme 19.
The application of a fluorous Rink-type tag for peptide synthesis.
Trt Triphenylmethyl.



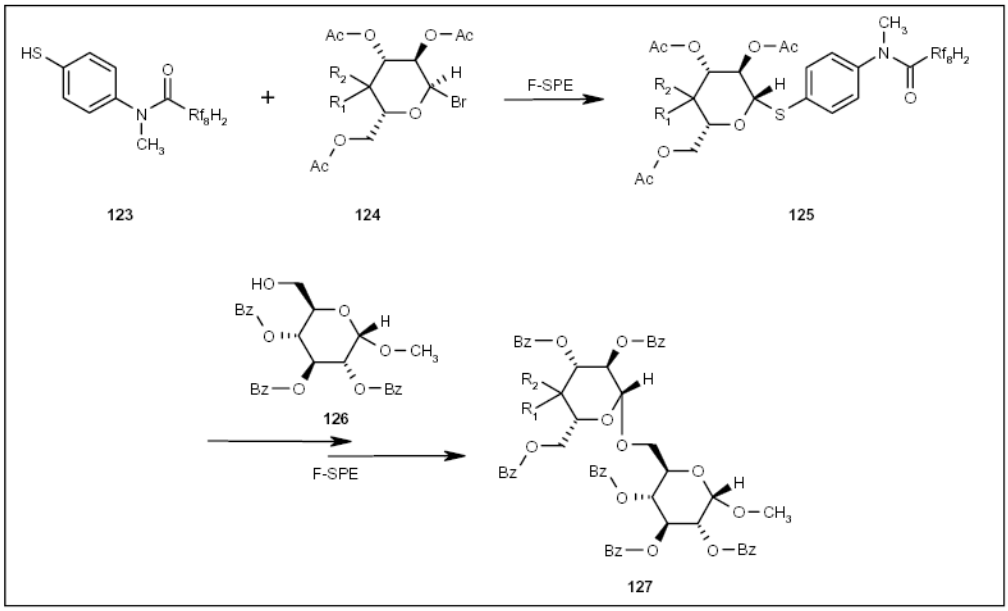
Scheme 20.
The application of a fluorous capping reagent for peptide synthesis.



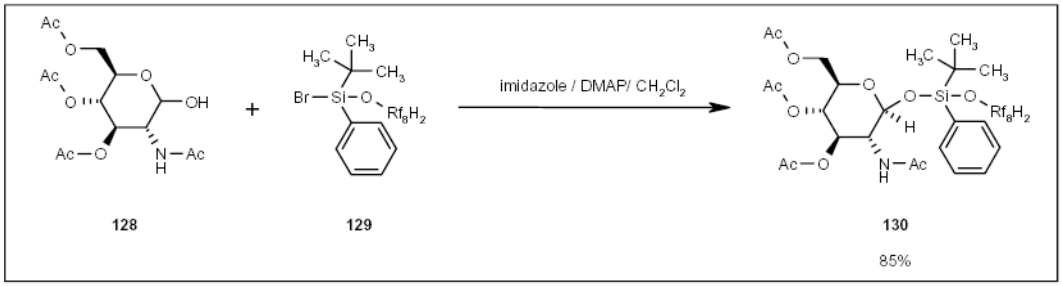
Scheme 21.
The application of an F-Bn tag for disaccharide synthesis.



Scheme 22.
The application of a fluorous Bfp tag for disaccharide synthesis.
TMS-OTf Trimethylsilyl triflate.



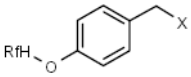
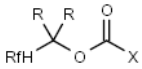
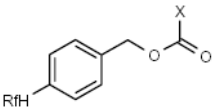
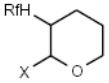
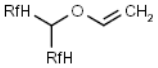
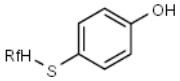
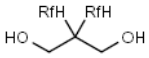
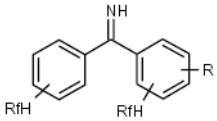
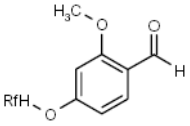
Scheme 23.
The application of a fluorous thiol tag to disaccharide synthesis.



Scheme 24.
The application of a fluorous silyl tag for saccharide synthesis.

Table 1

Representative catch and release fluorous tags.

Abbreviation	Tag	Tagged substrate/reagent	Reference
F-Silyl		Alcohols	[11,12]
F-PMB (Wang-type)		Alcohols	[13]
F-Boc		Amines	[14]
F-Cbz		Amines	[15,16]
F-THP		Alcohols	[17]
F-Alkoxyethene		Alcohols, amines	[18]
F-*tert*-Butanol		Carboxylic acids	[19]
F-Alcohol		Carboxylic (amino) acids	[20,21]
F-Thiol		Activated halides	[22]
F-Sulfonyl		Phenols	[23]
FluoMar (Marshall-type)		Carboxylic acids	[24]
F-Diol		Ketones, aldehydes	[25]
F-Benzophenone imine		Halides	[26]
F-Benzaldehyde		Amines	[27]

X Leaving group.