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Fluorous technologies for solution-phase high-throughput organic synthesis

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Dedicated to Professor Dennis P. Curran on the occasion of his 50th birthday

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1. Introduction

The combination of compound library synthesis and high-throughput screening has become a powerful tool in today's drug discovery effort. Implementation of traditional solution-phase reactions in library synthesis, however, is hampered by the time-consuming step of product purification. The development of combinatorial synthesis on solid support has reduced the separation to be an easy wash and filtration process.[1] Large libraries can be prepared by split and pool of the beads. Compared to conventional solution-phase methods, solid-phase synthesis successfully addresses the separation issue, but sacrifices the reactivity of the supported substrates because of unfavorable heterogeneous reaction kinetics. In addition, time-consuming chemistry development and limitations on both the reaction scope and scale have slowed down further development of this technology. In drug discovery chemistry, with the recent paradigm shift from large libraries to relatively small and focused libraries, solution phase methods are making a comeback.[2] Several 'tag-based' solution-phase methods[3] including polymer-assisted synthesis,[4] soluble polymer-supported synthesis,[5] dendrimer-supported synthesis,[6] ring-opening metathesis polymerization (ROMP)-based synthesis,[7] precipitation-based synthesis,[9] ionizable tag-based synthesis,[8] and fluorous synthesis have been developed.

The development of fluorous technologies for high-throughput organic synthesis was pioneered by Curran[10] at the University of Pittsburgh from the mid 1990s and has been continuously developing at Fluorous Technologies, Inc. (FTI) since 2000.[11] Fluorous synthesis is a complementary type of liquid-phase synthesis that is similar to solid-phase synthesis in concept but very different in practice. Functionalized perfluoroalkyl groups, instead of beads, are employed as the 'phase tag'[10c] to facilitate the

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Table 1. Comparison of conventional solution-phase, solid-phase, and fluorous synthesis

	Solution phase	Solid phase	Fluorous
Literature methods used	✓		✓
Broad reaction scope	✓		✓
Standard lab equipment	✓		✓
Intermediate analysis	✓		✓
Ease of scale-up	✓		✓
Familiarity to chemists	✓	✓	
Ease of purification		✓	✓
Use of excess reagent		✓	✓
Mixture synthesis		✓	✓
Potential for automation		✓	✓

separation process. The fluorous chain can be attached to reagents, scavengers, and catalysts for parallel synthesis or attached to substrates for parallel and mixture synthesis. A comparison of conventional solution-phase, solid-phase, and fluorous synthesis is listed in Table 1 and some unique features of fluorous synthesis are outlined as follows:

1. The fluorous tags are inert to chemical reactions and have minimal effect on the reactivity of the attached molecules.
2. The solubility of the 'light fluorous' molecules in organic solvents is equal or even better than the untagged molecules because of the lipophilicity of the perfluoroalkyl chain.
3. Homogeneous reactions in organic solvents are much faster than polymer-bound heterogeneous reactions.
4. Large excess of fluorous reagents is not needed.
5. The reaction process can be monitored by conventional analytical methods such as TLC, HPLC, IR and NMR.
6. Both intermediates and final products can be purified by fluorous separations as well as by regular and reverse-phase chromatography.
7. Literature reaction conditions can be easily applied with little or no modification.
8. Scale up and automation are possible.
9. Accurate stoichiometric control on the input of fluorous compounds.

The goal of this Report is to summarize recent progress of fluorous technologies in high-throughput synthesis with the emphasis on 'light fluorous' chemistry and fluorous solvent-free separation processes. Solution-phase parallel synthesis using fluorous reagents, catalysts, scavengers, tags, and protecting groups are discussed. Fluorous tag strategy in mixture synthesis, peptide and oligosaccharide synthesis, and microwave-assisted fluorous synthesis are also described.

2. Fluorous separations

Early fluorous synthesis technologies relied on 'heavy fluorous' tags (60% or more fluorine by molecular weight) and liquid–liquid extraction with fluorous solvents to separate fluorous molecules from non-fluorous organics.[10,12] In the recently introduced 'light fluorous' synthesis (40% or less fluorine by molecular weight), shorter fluorous chains (C_3F_7 to $C_{10}F_{21}$) are used and liquid–liquid extraction is replaced by fluorous silica gel-based solid-phase extraction or HPLC.[13–15] Fluoro*Flash*™ silica gel has a bonded phase of C_8F_{17} perfluorohydrocarbon chains that has the capability to retain the fluorous molecules by strong fluorine–fluorine interactions. Since no fluorous solvents are required for reactions and separations, the 'light fluorous' method has quickly gained popularity in parallel and combinatorial synthesis.

2.1. Fluorous solid-phase extraction (F-SPE)

A mixture containing fluorous molecules with a Rf chain, such as C_6F_{13} or C_8F_{17}, can be easily separated from non-fluorous molecules by SPE with Fluoro*Flash*™ cartridges.[13,14] In a typical separation, a crude reaction mixture is loaded onto a cartridge with a minimum amount of solvent (less than 20% of silica gel volume), then the cartridge is eluted with a 'fluorophobic solvent' such as 80:20 MeOH–H_2O to remove the non-fluorous compounds. Final elution with a 'fluorophilic solvent' such as MeOH, acetone, acetonitrile, or THF provides fluorous compounds.[16] Depending on the chemistry, the desired product can be a non-fluorous compound in the first fraction (MeOH–H_2O) or a fluorous compound in the second fraction (MeOH). A demonstration with a mixture of non-fluorous (blue) and fluorous (orange) aminoanthraquinone dyes is shown in Figure 1. These two dyes can be separated on a HPLC column but not on the SPE cartridges charged normal or reverse-phase silica gel. The separation of these two dyes on a Fluoro*Flash*™ cartridge, however, is very straightforward: the non-fluorous blue dye is readily eluted with 80:20 MeOH–H_2O (Fig. 1, picture 1), while the fluorous dye is retained until it is washed out with 100% MeOH (Fig. 1, pictures 2 and 3). It is noteworthy that on a C18 reverse-phase HPLC column the elution order of these two dyes is reversed: the fluorous orange dye comes out first. This result demonstrates that F-SPE is a tag-based instead of a polarity-controlled separation process.

A typical loading for SPE is between 5–15% by weight. The cartridge can be regenerated by washing with strong solvents such as MeOH, THF or acetone. F-SPE has been widely used in the parallel separation of reaction mixtures involving fluorous reagents, catalysts, scavengers, tags, and protecting groups. Plate-to-plate F-SPE can further enhance its utility in high-throughput purification. This technique is currently under development at FTI.

2.2. Fluorous HPLC (F-HPLC)

Fluoro*Flash*™ silica gel packed in an HPLC column can be used for separation of mixtures of fluorous compounds based on their different fluorine content.[13,15] Molecules with longer fluorine chains (R_f) have longer retention times on the column. A typical mobile phase is a gradient of MeOH–H_2O with increasing MeOH up to 100%, which is similar to reverse-phase HPLC. Gradients of MeCN-H_2O or THF-H_2O can also be used. Figure 2 shows a tag-based separation of a 9-component mixture of isonipecotic acid derivatives with different fluorous tags (R_f).[15a] Eight fluorous compounds (R_f=C_3F_7 to $C_{10}F_{21}$) were nicely distributed in a 30 min time period, while the non-fluorous compound

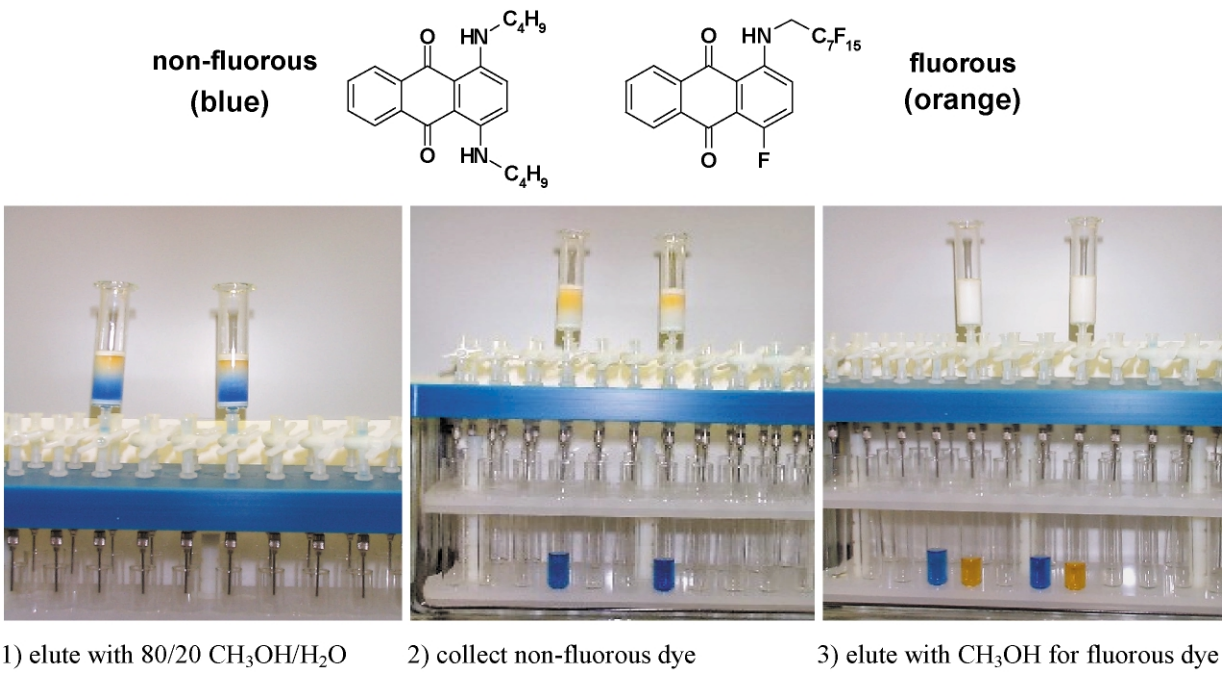


Figure 1. F-SPE separation of non-fluorous (blue) and fluorous (orange) dye. (1) Elute with 80/20 CH_3OH/H_2O; (2) collect non-fluorous dye; (3) elute with CH_3OH for fluorous dye.

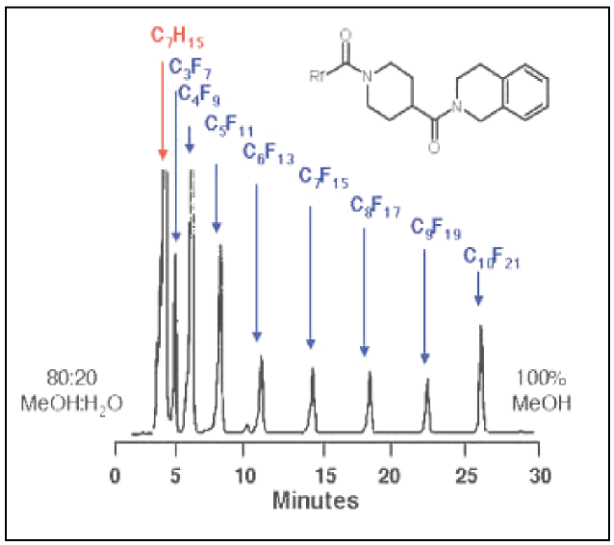


Figure 2. Tag-based F-HPLC separation of eight fluorous homologs.

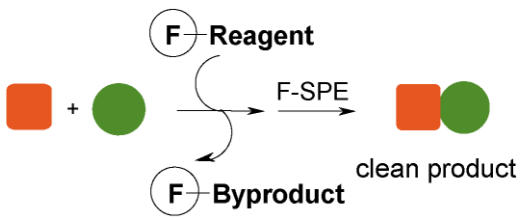
(R_f=C_7H_{15}) was eluted out with the solvent front because of its low affinity with the fluorous stationary phase. F-HPLC analysis and demixing have played a key role in fluorous mixture synthesis (Section 4).

3. Fluorous parallel synthesis

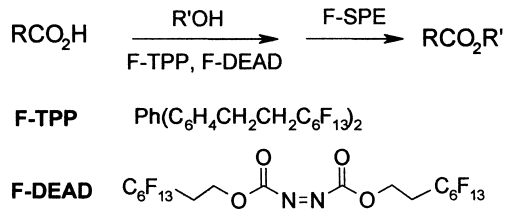
Light fluorous tags such as C_6F_{13} or C_8F_{17} chains are sufficient for F-SPE separations. There are no restrictions on the selection of reaction solvents because light fluorous compounds usually have similar or even better solubility than their un-tagged counterparts in organic solvents. Fluorous parallel synthesis can be performed either with fluorous reagents, catalysts, and scavengers for single-step reactions or with fluorous tags and protecting groups for multi-step synthesis. In both cases, the reaction mixtures can be purified by F-SPE.

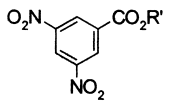
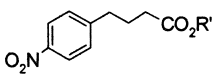
3.1. Using fluorous reagents

One current trend in solution-phase parallel synthesis is the use of polymer-bound reagents.[3] Polymer-assisted solution-phase reactions are heterogeneous, but no attachment and cleavage steps are required compared to solid-phase synthesis. In addition, excess polymer-bound reagents can be used to push the reactions to completion. Unreacted reagents and their derivatives can be easily removed by filtration of the reaction mixtures. Numerous polymer-bound reagents and catalysts are now commercially available. A similar concept is being adapted to fluorous reagents (Scheme 1), where reactions can be performed in a homogeneous environment. Fluorous triphenylphosphine and diethyl azodicarboxylate (DEAD), for example, have been developed by Dandapani and Curran and used for the Mitsunobu reaction (Scheme 2).[17] Fluorous triphenylphosphines have also been employed by Bannwarth and co-workers[18a] for the Aza-Wittig reaction and by Lindsley and co-workers for the Staudinger reaction (Scheme 3).[18b] Normally problematic phosphine oxide species can be

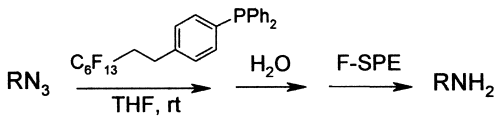


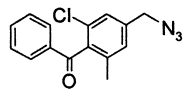
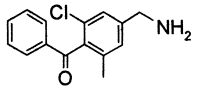
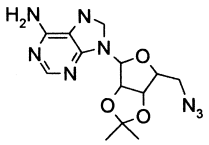
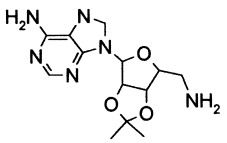
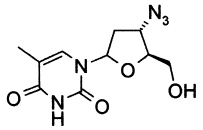
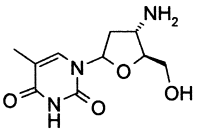
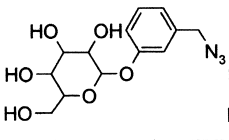
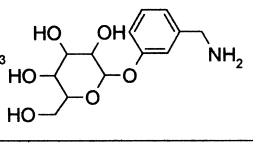
Scheme 1. Reaction using fluorous reagent.



Product	R'	yield (purity) (%)
	CH_3	93(100)
	$CH_2CH{=}CH_2$	85(100)
	p-$FC_6H_4CH_2$	75(91)
	CH_3	93(100)
	$CH_2CH{=}CH_2$	78(100)
	p-$FC_6H_4CH_2$	88(100)

Scheme 2. Fluorous Mitsunobu reaction.



Azide	Amine	yield (%)*
		88
		88
		82
		80

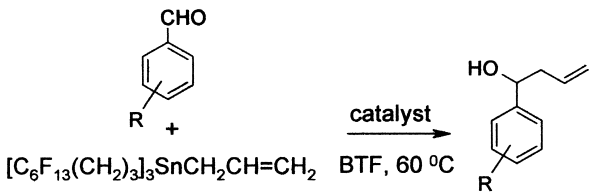
*Purities ≥ 95% by LCMS-214 nm

Scheme 3. Fluorous Staudinger reaction.

separated easily by F-SPE either on individual reactions or in parallel. The non-fluorous products are collected in the first fraction eluted with MeOH–H_2O. The fluorous reagent derivatives are retained on the cartridge. Many fluorous reagents including organotin compounds,[14a,19] coupling agents, oxidation[20] and reduction agents are known and new ones are appearing regularly.[21,22]

3.2. Using fluorous ligands and catalysts

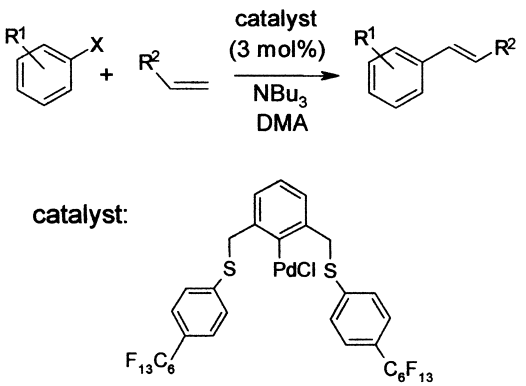
The development of fluorous biphasic synthesis was pioneered by Horvath and Rabai in early 1990s.[12a,b] In a fluorous biphasic catalytic reaction, a fluorous phase containing a fluorous catalyst is mixed with an organic phase containing organic reagents. The mixture is heated up until it becomes a homogenous system to allow the catalytic reaction take place. When the reaction is over, cooling down the reaction mixture renders it a fluorous and organic biphasic system. The fluorous catalyst is recovered in the fluorous phase and the product is separated from the organic phase. Heavy fluorous ligands are usually required for efficient recovery of fluorous catalysts by the fluorous-organic liquid extraction. Conducting the fluorous catalytic reaction in an organic solvent followed by the F-SPE separation eliminates the use of expensive fluorous solvents



catalyst: $Cl_2Pt[(PPh\text{-}p\text{-}CH_2CH_2C_6F_{13})_2]_2$
BTF: benzyltrifluoride

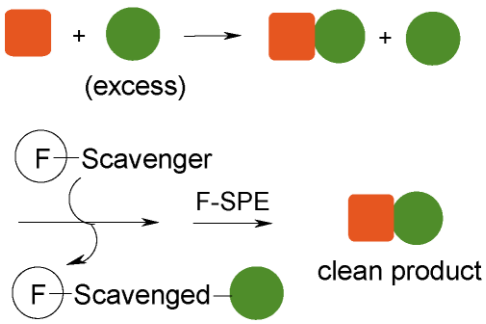
R	NMR yield (%)	GC-MS purity (%)
2,4-dinitro	100	100
2,4-dichloro	56	100
2-chloro-5-nitro	67	100
2-nitro	98	100
4-trifluoromethyl	66	100
2-bromo	60	100
3-bromo	71	100

Scheme 4. Fluorous platinum-catalyzed allylation reaction.



R^1	X	R^2	T(°C)	Yield (%)
MeO	I	MeOCO	140	89
CN	Br	MeOCO	140	84
MeCO	OTf	MeOCO	140	87
H	I	Ph	140	82
MeO	I	Ph	140	76
MeCO	Br	Ph	140	92

Scheme 5. Fluorous palladium-catalyzed Heck reaction.

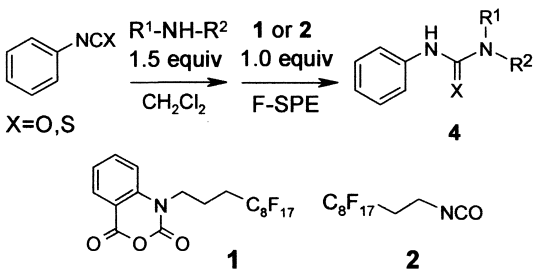


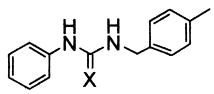
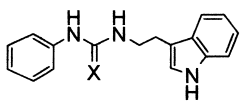
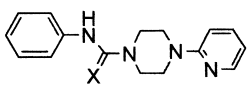
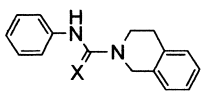
Scheme 6. Fluorous scavenging reaction.

and to use of light fluorous ligands.[23] A parallel platinum-catalyzed allylation of aldehydes with fluorous allyl stannanes developed by the Curran group illustrates the utility of the fluorous arylphosphines in small-scale synthesis (Scheme 4).[24a] In another case, a fluorous palladium catalyst was used in the Heck reaction (Scheme 5).[24b] Other fluorous ligands such as BINOL and BINAP and their chiral versions have great potential in fluorous-solvent-free organic synthesis.[25] Since reactions require very small amount of catalysts, existing 'heavy fluorous' ligands can be used to enhance the efficiency of F-SPE without significant increase of cost compared to use of light ligands.

3.3. Using fluorous scavengers

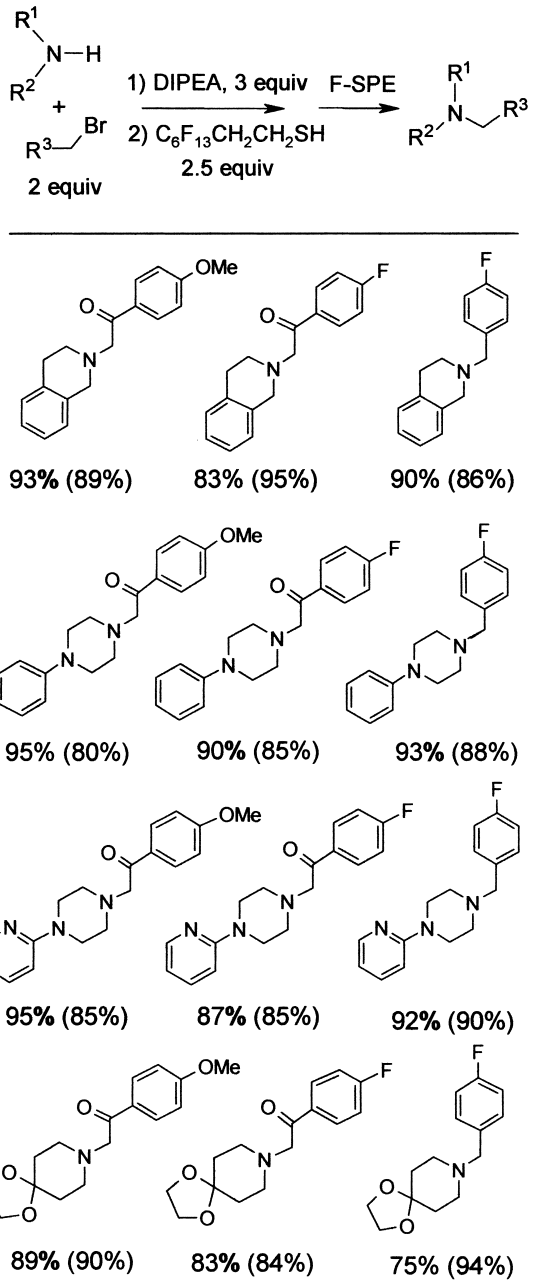
Scavengers are now widely applied in solution-phase parallel synthesis to selectively remove unwanted species from a reaction mixture.[4] The scavengers can either be polymer-supported or fluorous molecules (Scheme 6). Following up on the early work by Curran and Wipf in the heavy fluorous area,[26] FTI and the Lindsley group at



scavenger	product	X	yield (%)*
1		O	100
1		S	72
2		O	100
2		S	80
1		O	100
1		S	95
2		O	100
2		S	34
1		O	100
1		S	100
2		O	100
2		S	68
1		O	100
1		S	100
2		O	100
2		S	96

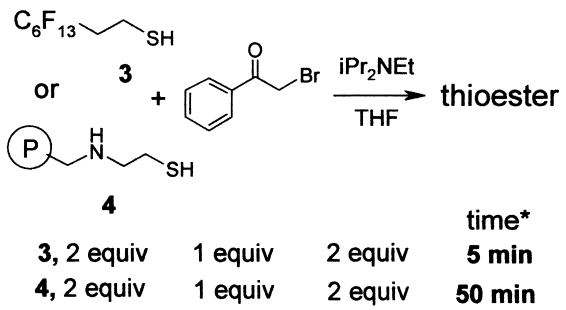
*Purities ≥ 95% by H NMR

Scheme 7. Use of electrophilic scavengers in the synthesis of ureas and thioureas.



Number in the parenthesis shows the purity by HPLC-245 nm

Scheme 8. Use of fluorous thiol scavenger in the synthesis of tertiary amines.



Scheme 9. Fluorous vs polymer-supported thiol quenching.

Merck developed several light fluorous nucleophilic and electrophilic scavengers.[27–29]

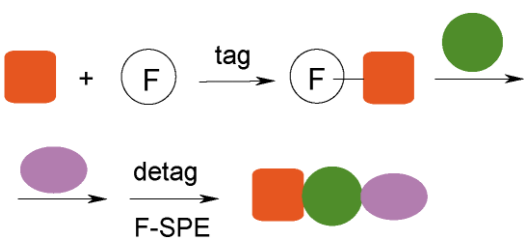
Scheme 7 demonstrates the use of isatoic anhydride **1** and isocyanate **2** as electrophilic scavengers to remove primary and secondary amines in the synthesis of urea, thiourea, and β-hydroxyamine analogs,[27] while Scheme 8 outlines the utility of fluorous thiol ($C_6F_{13}CH_2CH_2SH$) as a nucleophilic scavenger to remove unreacted halides in the parallel synthesis of a small tertiary amine library.[28,29]

Because fluorous scavengers are used under homogeneous solution-phase conditions, the quenching process is fast and does not require large excess of scavengers. A comparison experiment revealed that fluorous thiol scavenging is about 10 times faster than that of a polymer-supported analog (Scheme 9).[28]

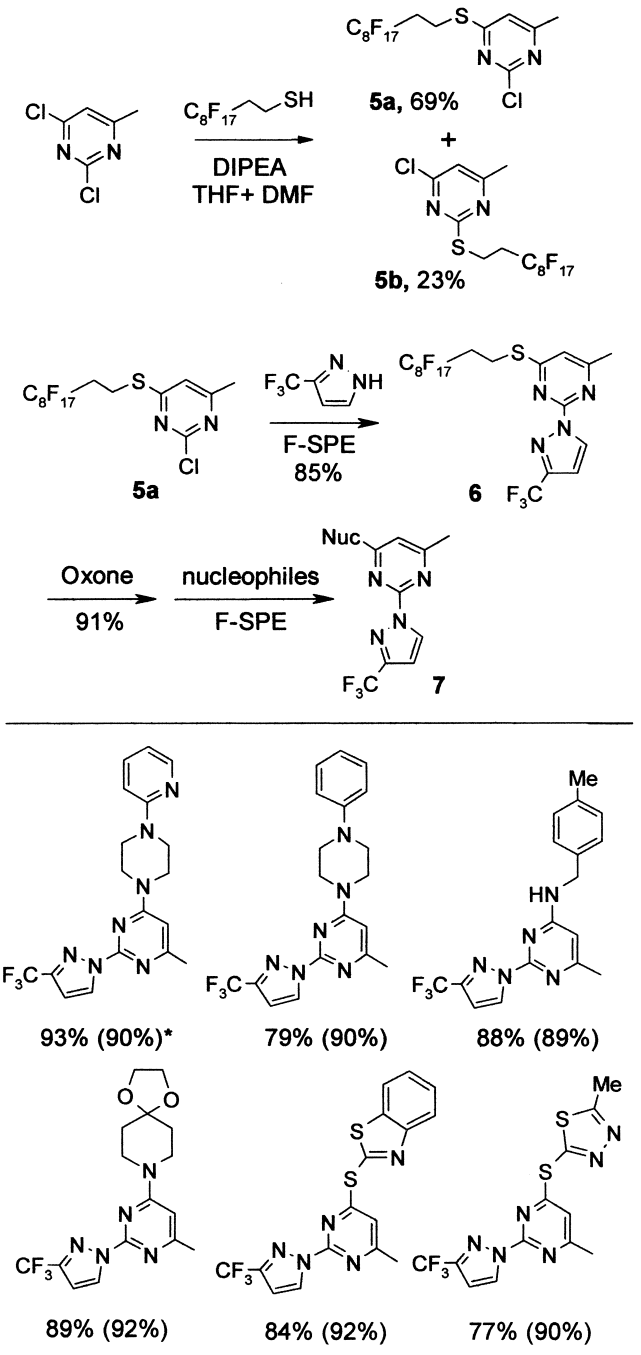
3.4. Using fluorous tags

Similar to the linkers used in solid-phase synthesis, functionalized fluorous chains can be attached to substrates as tags and applied in multi-step synthesis (Scheme 10).

The use of a fluorous thiol tag in the synthesis of disubstituted pyrimidines has been recently reported by FTI (Scheme 11).[30] In this work, 1,3-dichloro-5-methyl-pyrimidine was first attached to the thiol tag by a nucleophilic substitution. Two regioisomers, **5a** and **5b** were generated in a ratio of 3:1 by HPLC analysis. If polymeric tags were used, then regioisomers like **5a** and **5b** could not have been separated. Fluorous compound **5a** was readily separated from **5b** by flash column chromatography on normal silica gel based on their polarity difference. The major isomer **5a** was used for further nucleophilic substitution with 3-(trifluoromethyl)-pyrazole to give **6**.



Scheme 10. Synthesis with fluorous tags.



*** Number in the parenthesis is purity by HPLC-245 nm**

Scheme 11. Synthesis of disubstituted pyrimidines with a fluorous thiol tag.

The thiol tag was then activated by oxidation to the sulfone and displaced by nucleophiles to afford disubstituted pyrimidine analogs. Both the intermediates and the final products were purified by F-SPE (Fig. 3). The fluorous intermediate **6** was collected in the MeOH fraction, while the final product was collected in the MeOH/H_2O fraction. The purities after F-SPE were usually greater than 90%.

The Marshall resin as a carbonate and carbamate linker has been widely used in solid-phase synthesis. We recently developed FluoMar™ as a fluorous version of the Marshall

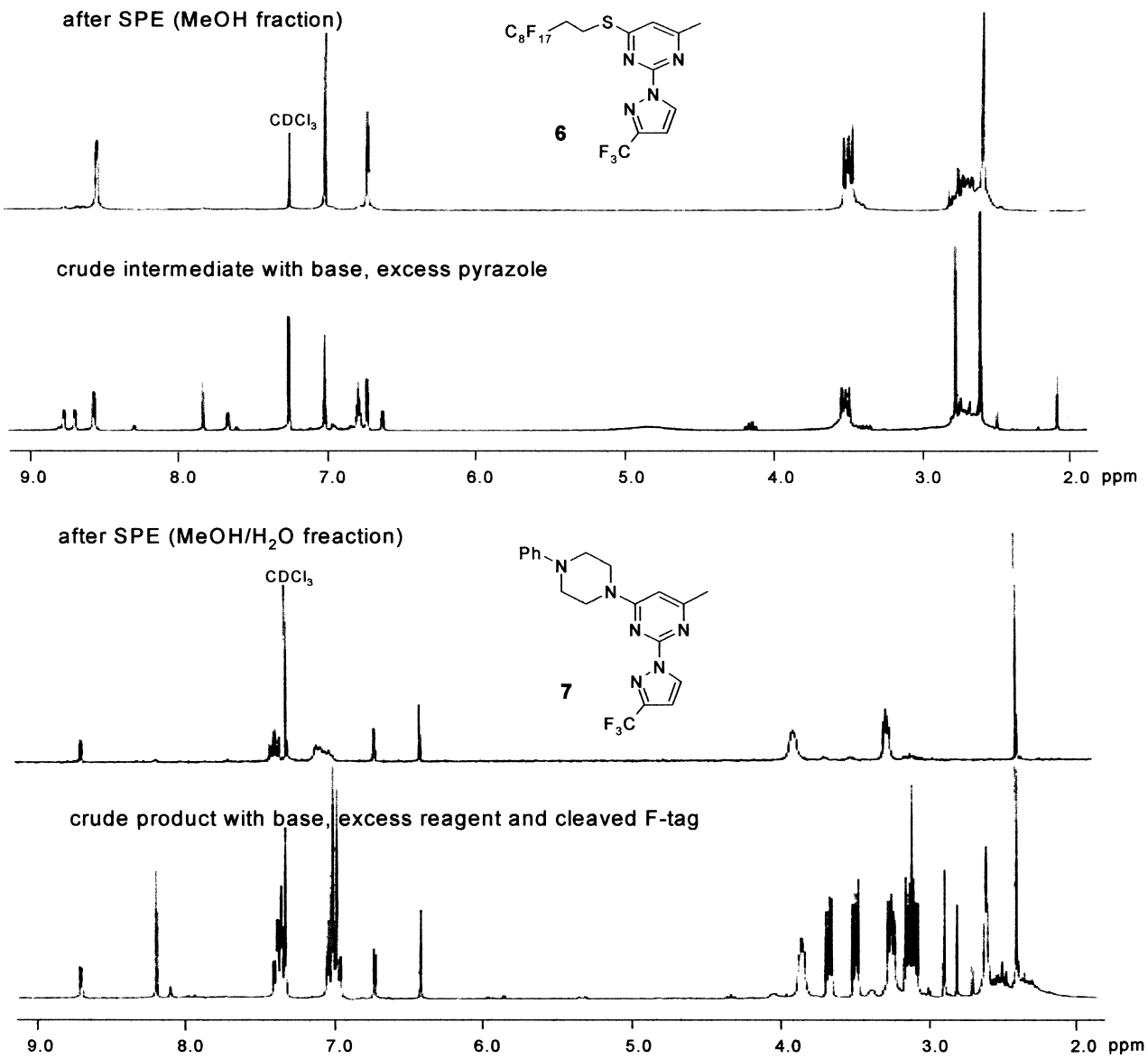


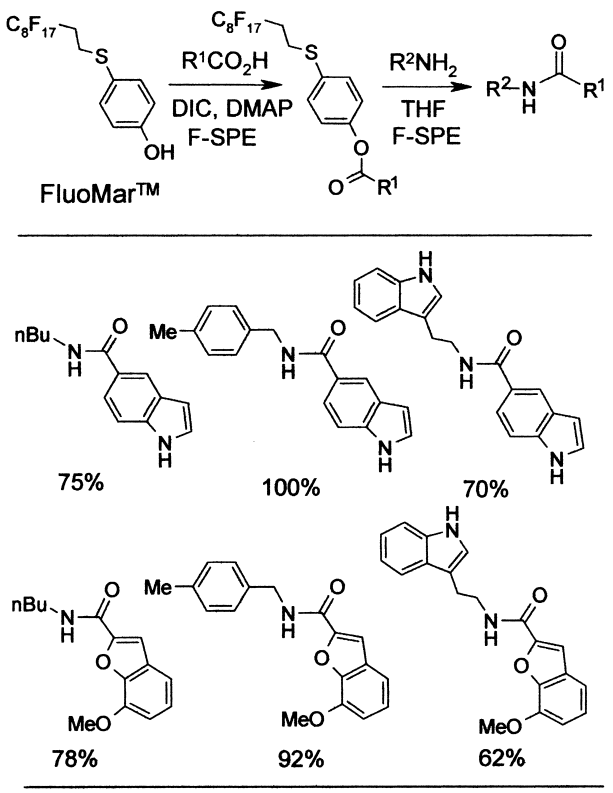
Figure 3. ^{1}H NMR spectra of intermediate **6** and a product **7** before and after F-SPE.

resin and applied it in solution-phase synthesis of amide analogs (Scheme 12).[31] In the preparation of a small demonstration library, carboxylic acids were coupled with FluoMar™ under standard conditions using diisopropylcarbodiimide (DIC) and dimethylaminopyridine (DMAP). The fluorous tag was then displaced with a set of amines in parallel to give a small compound library.

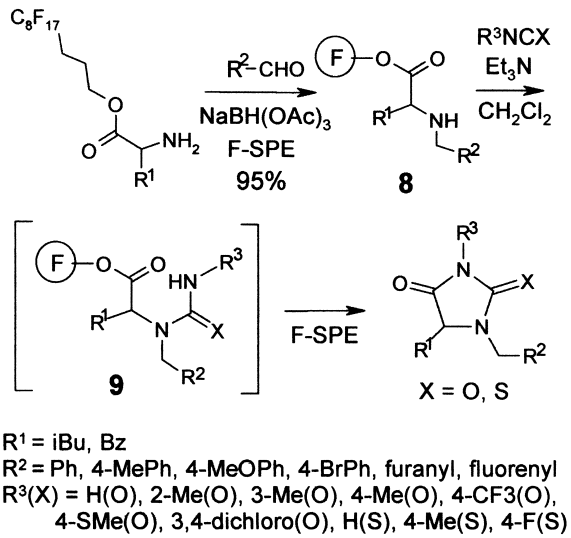
We recently prepared a 120-membered substituted hydantoin and thiohydantoin library using fluorous amino esters as the starting material (Scheme 13).[32] Two fluorous amino esters (R^1=*i*-Bu and Bz) were each reacted with six aldehydes under standard reductive amination conditions. The so-formed twelve intermediates **8** were then each reacted with 10 aryl isocyanates or aryl isothiocyanates in parallel. The resulting ureas or thioureas **9** were cyclized in situ to displace the fluorous tag to form the heterocyclic ring. All intermediates and products in this project were purified by F-SPE. LC-MS analysis of 120-membered library revealed that 88% of products had purities greater than 90%, and about 90% products had yields greater than 50%.

3.5. Using fluorous protecting groups

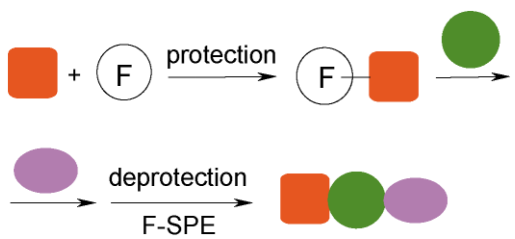
The use of fluorous protecting groups is a 'hits two birds with one stone' strategy that protects the desired functional group and at the same time introduces the 'phase tag' for fluorous separation (Scheme 14).[33] Both protection and deprotection can be achieved by using traditional reaction conditions. Fluorous protecting agents such as silanes, Cbz, Boc, PMB, Fmoc for O and N protections are now commercially available (Scheme 15). Curran and collaborators have demonstrated the utility of F-Boc in the multistep synthesis of a 96-membered library of isonipecotic acid derivatives (Scheme 16).[34] In this chemistry, the amino group of the isonipecotic acid was first protected by F-Boc. The carboxylic group was then coupled with eight amines (R^1NHR^2) in parallel to give eight amides **10**. After deprotection of F-Boc with TFA, the resulting compounds



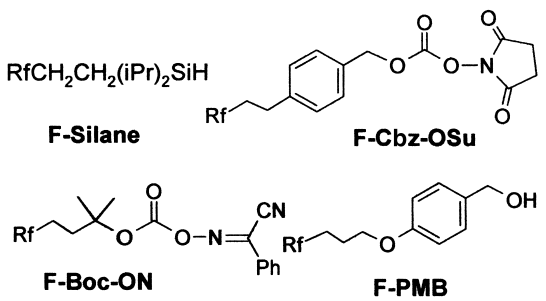
Scheme 12. Use of FluoMar™ tag in the synthesis of amides.



Scheme 13. Synthesis of a substituted hydantoin and thiohydantoin library.



Scheme 14. Synthesis with fluorous protecting groups.

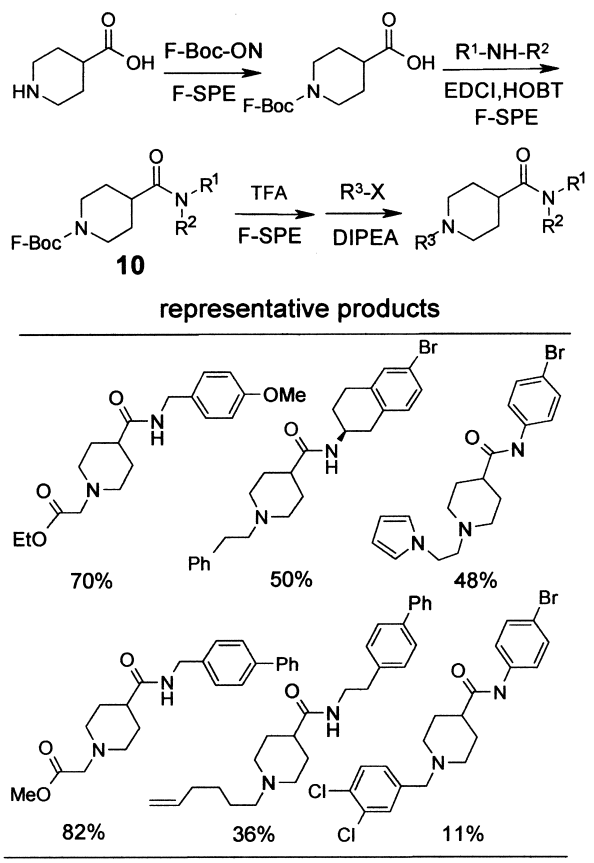


Scheme 15. Fluorous protecting groups.

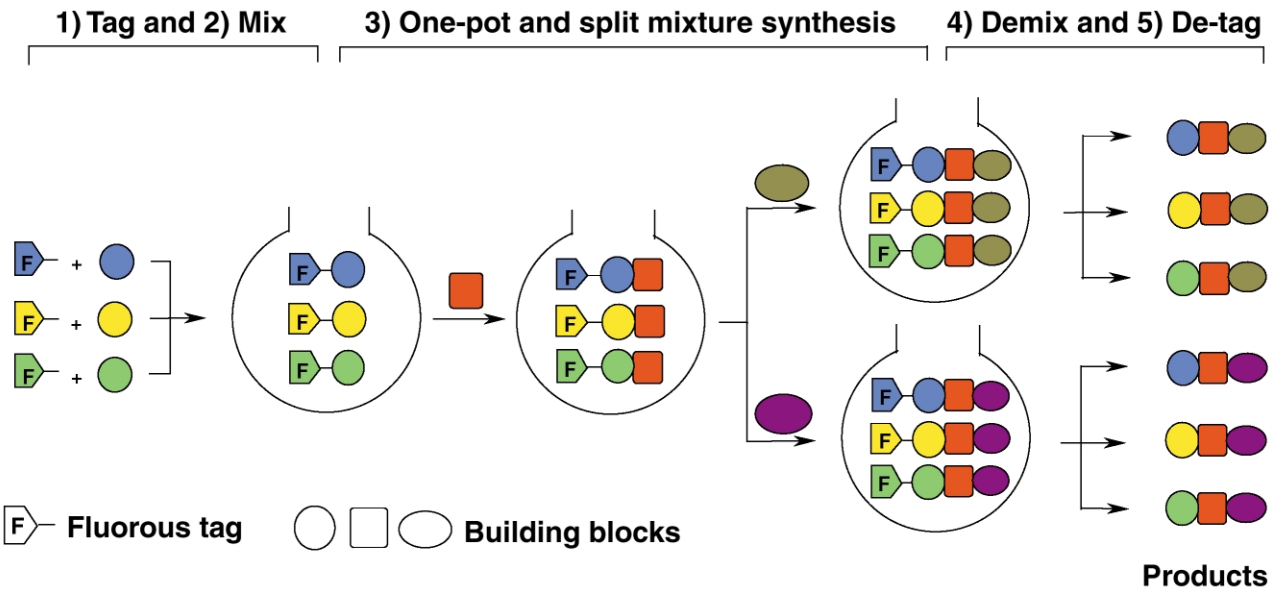
were each reacted with twelve electrophiles (R^3X) to give a 96-compound library. Other examples for the use of fluorous protecting groups in fluorous mixture synthesis will be discussed in Section 4.

4. Fluorous mixture synthesis (FMS)

FMS has high efficiency in the production of large libraries. This is the first technique that takes advantage of solution-phase synthesis yet still allows the reliable separation of individual pure final products.[35,36] A typical FMS consists of five steps (Scheme 17): (1) a set of substrates is individually tagged with a corresponding set of homologous fluorous tags with increasing fluorine content; (2) the tagged substrates are mixed together; (3) the mixed components taken through a multi-step synthesis which can be a



Scheme 16. Use of F-Boc in the synthesis of a 96-member amide library.

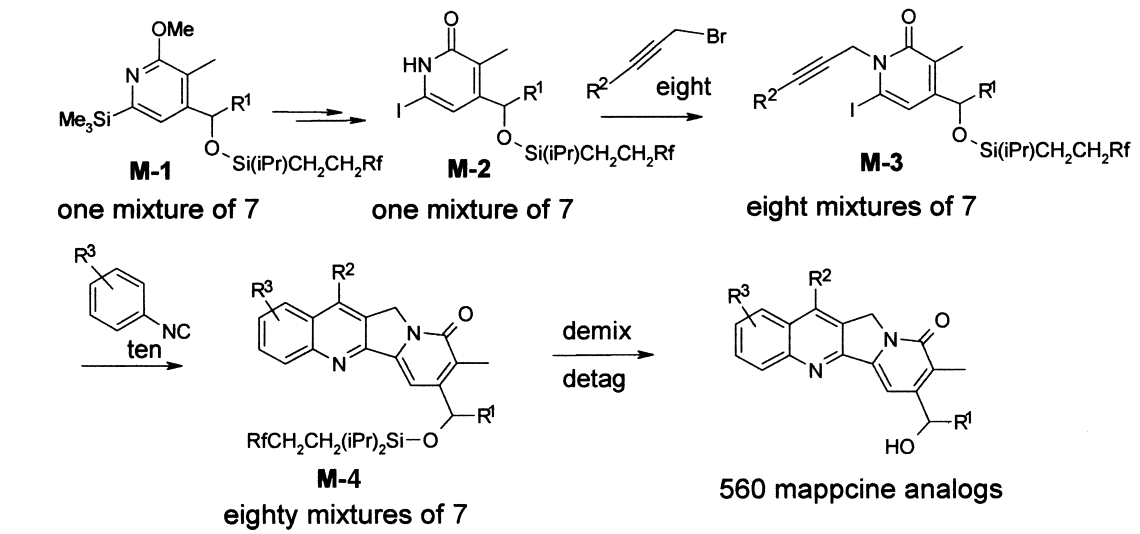


Scheme 17. Schematic diagram of the concept of FMS.

combination of one-pot reactions or split-parallel reactions; (4) the mixture of tagged products is demixed by F-HPLC to give individually pure tagged-products; and (5) detagging is conducted to release the final products. The efficiency of FMS is directly proportional to the number of components mixed and steps of the mixture synthesis. The split-parallel synthesis at the 3rd step is the key to incorporate new diversity points and increase the size of the library.

4.1. Library or analog synthesis

We have demonstrated the power of FMS by the preparation of a 560-member library of mappicine analogs (Scheme 18).[36] A mixture of seven pyridines **M-1** (7 different R^1 groups) was taken through a 4-step reaction sequence. The mixture **M-1** underwent iodo exchange and demethylation steps to give **M-2**. The mixture **M-2** was then split into 8 portions at the N-propargylation (8 different R^2



Rf	R^1	R^2	R^3
{1} C_3F_7 {5} C_8F_{17}	{1} Me {5} *i*-Pr	{1} H {5} Pr	{1} H {6} *p*-Cl
{2} C_4F_9 {6} C_9F_{19}	{2} Pr {6} *c*-C_6H_{11}	{2} *m*-MeOPh {6} Bu	{2} *p*-F {7} *p*-OCF_3
{3} C_6F_{13} {7} $C_{10}F_{21}$	{3} Et {7} C_2H_4-*c*-C_6H_{11}	{3} Me {7} C_5H_{11}	{3} *p*-OMe {8} *o*-F
{4} C_7F_{15}	{4} *s*-Bu	{4} Et {8} Ph	{4} *p*-CF_3 {9} *p*-Me
			{5} *p*-Et {10} *p*-SMe

Scheme 18. 7-Component FMS of a 560-membere mappicine.

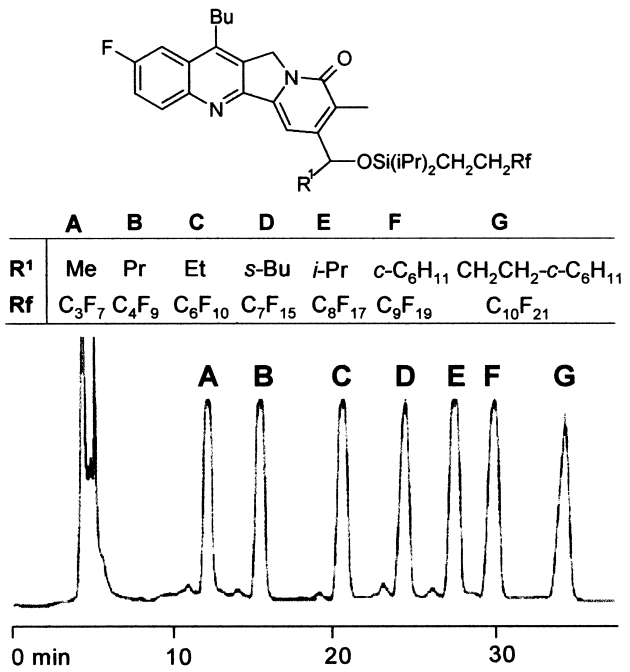


Figure 4. A typical tag-based demix of 7-component mixtures by F-HPLC.

groups) step and each of the 8 mixtures **M-3** was further split to 10 at the radical annulation with isonitriles (10 different R^3 groups). The resulting eighty mixtures **M-4** each containing seven tagged-products were demixed by F-HPLC based on their different fluorine content and then detagged by HF–pyridine to give a 560-member mappicine library (Fig. 4).

At each reaction step, unreacted species and byproducts were removed by standard silica gel flash column chromatography in a mixed mode. In other words, the mixed components were purified without being demixed. Figure 5 shows the purification effort at the alkylation step. A mixture of N-alkylation and O-alkylation products (each has 7-components) in a ratio of 10:1 was observed. A set of 7 O-alkylation byproducts **M-5** was separated from a set of seven desired N-alkylation products **M-3** by normal flash column chromatography. Standard silica gel separation is based on the polarity difference of the O- and N-alkylated compounds, which is not sensitive to the fluorous tags. The polarity difference of the N- and O-alkylation mixtures also helps the F-HPLC analysis, which showed two set of peaks with slightly different retention times. The synthesis of this 560-membered library was accomplished in 90 reactions (not including the detagging step), compared to 630 for a corresponding parallel synthesis. The overall separations required only 90 chromatography steps, whereas 630 would have been needed with the parallel synthesis.

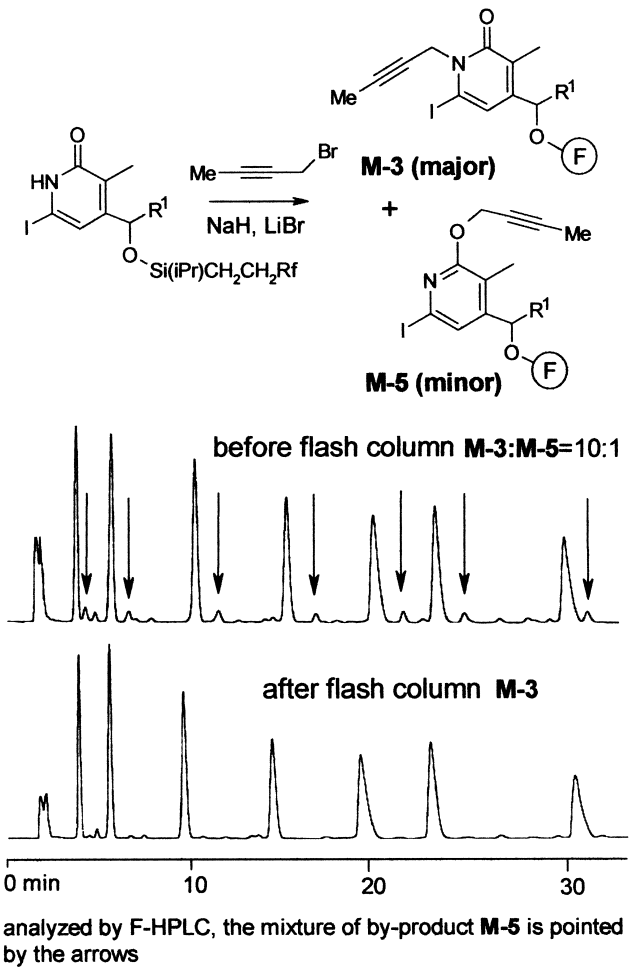
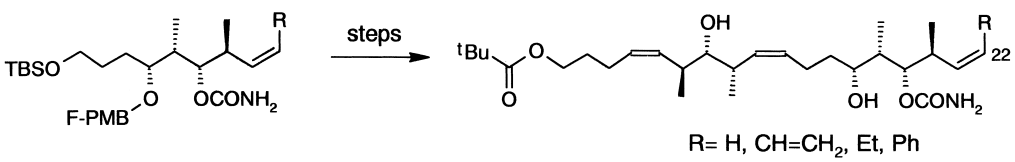


Figure 5. Purification of a propardylation mixture by standard flash column chromatography.

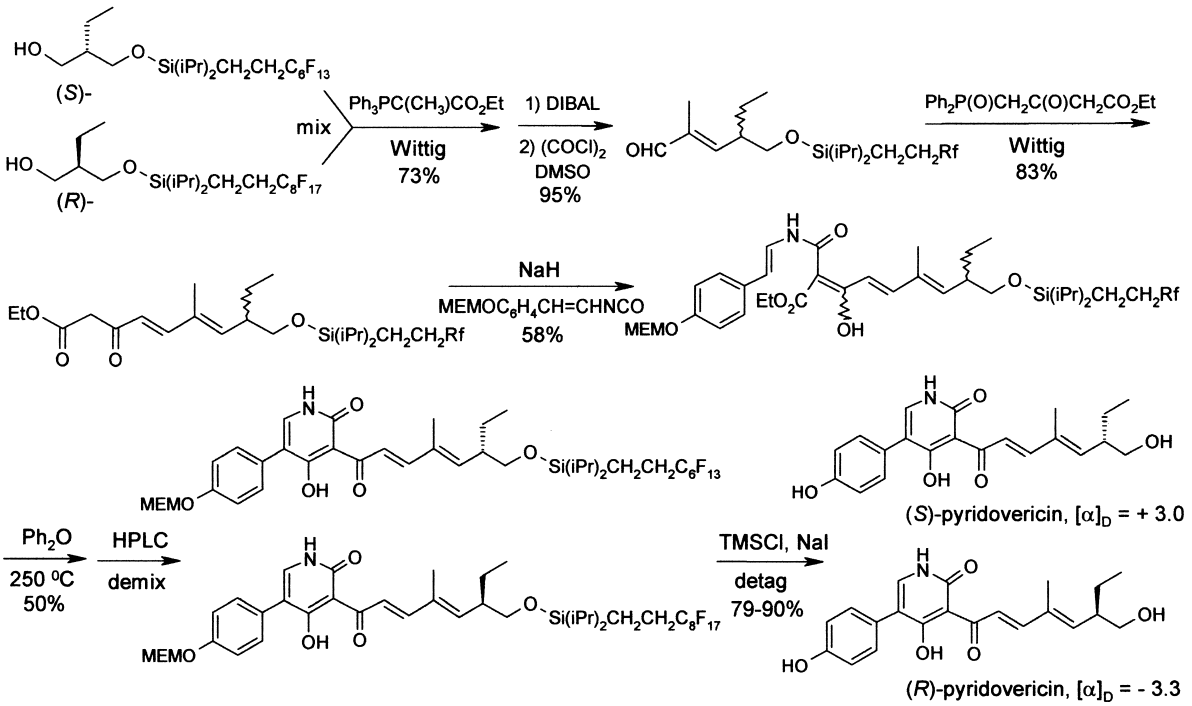
Synthesis of 4 truncated analogs of natural product (+)-discodermolide at the C22 position is another example from Curran and Furukawa which illustrates the utility of FMS (Scheme 19).[37] Four starting materials with different R (H, CH=CH_2, Et, Ph) were protected with the corresponding fluorous PMB group (R_f=C_4F_9, C_6F_{13}, C_8F_{17}, $C_{10}F_{21}$) and combined as a 4-component mixture for FMS to produce 4 truncated analogs of discodermolide.

4.2. Quasiracemic synthesis of enantiomers

Asymmetric synthesis and racemic synthesis/resolution are two general methods for the preparation of enantiopure (or enantioenriched) organic molecules. FMS provides a third option, quasiracemic synthesis, to produce two enantiomeric products in a mixture synthesis. The quasiracemic synthesis is exemplified by Zhang, Rivkin, and by Curran's



Scheme 19. (+)-Discodermolide and truncated analogs at C22.

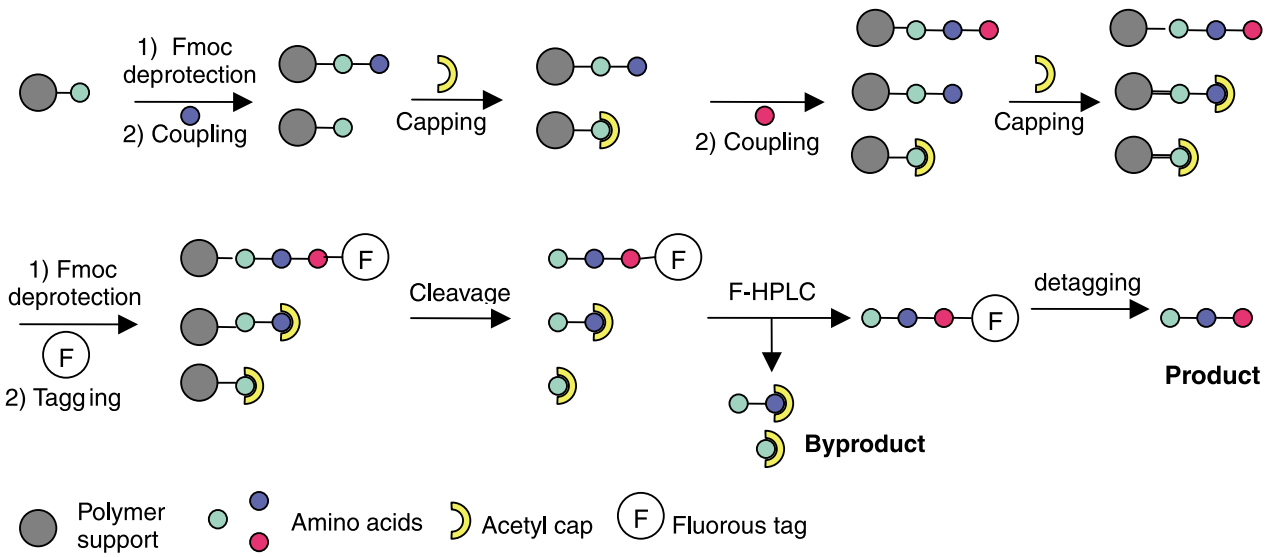


Scheme 20. Quasiracemic synthesis of (*S*)- and (*R*)-pyridovericins.

work on the preparation of two enantiomers of pyridovericin (Scheme 20).[38] The (*S*)- and (*R*)-enantiomers of the starting materials were attached to two different fluorous silanes (R_f=C_6F_{13} and C_8F_{17}) and combined together to make a quasienantiomeric mixture. The mixture was then taken through a multi-step synthesis to make a final tagged product mixture. F-HPLC was employed to demix the two quasienantiomers. The tags were then removed to release the (*S*)- and (*R*)-enantiomers of pyridovericin. Quasiracemic synthesis can be considered as the simplest version of FMS with only two mixture components, and only one-pot reactions, no split-parallel reactions, were used in the quasiracemic synthesis.

5. Peptide and oligosaccharide synthesis

Combination of solid-phase synthesis with fluorous synthesis was first explored by Wipf.[39] Recently van Boom group reported the use of fluorous tags in the solid-phase peptide synthesis.[40a] The general concept of this chemistry is outlined in Scheme 21. Fmoc based solid-phase synthesis was used to build up the amino acid chain. At each condensation step the unreacted free amines were capped with acetyl (Ac) groups. After the desired number of iterations, the deprotection of the final Fmoc group was followed by tagging with a fluorous Cbz group. The cleavage of oligomers from the resin provided a mixture



Scheme 21. Schematic diagram of fluorous tag strategy in peptide synthesis.

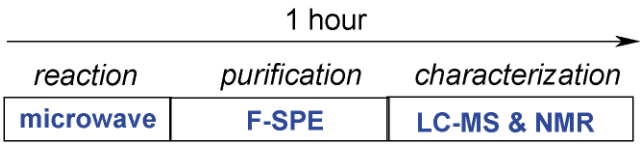
of desired F-tagged product and Ac-capped truncated sequences. The Cbz-tagged product was then easily separated from the Ac-capped material by F-HPLC. The fluorous Cbz containing a C_8F_{17} chain was found to have enough affinity on the F-HPLC column for the separate peptides with 7–22 amino acids (molecular weight up to 3000). Final detagging provided the desired oligomer.

A similar strategy has been developed in the synthesis of oligosaccharides in both Seeberger and Inazu groups.[40b,c] In Seeberger's case, the fluorous portion is a 'cap-tag', while the desired oligomeric species is non-fluorous. (Heptadecafluorodecyl)diisopropylsilyl triflate [$TfOSi(iPr)_2(CH_2CH_2C_6F_{13})_3$] was used to tag the hydroxyl group of unreacted monosaccharides. F-HPLC was again used for the separation of the desired oligosaccharide from the fluorous byproduct. Since the final product is the untagged species, no detagging step is required.

6. Microwave-assisted fluorous synthesis

Microwave-assisted organic synthesis has attracted a substantial amount of attention in recent years.[41] Compared to traditional oil bath heating, microwave irradiation can significantly reduce the reaction times from hours to minutes. However, this technology does not directly address the separation issue, which is usually the bottleneck of high-throughput synthesis. Microwave heating can be used to accelerate solid-phase synthesis,[42] but the physical integrity of the polymer under heating becomes a new issue that imposes limitations. Because of the thermostability and solution-phase character of fluorous tags, microwave-assisted fluorous synthesis is ideal to speed up both the reaction and purification processes (Fig. 6). Chemists can easily finish a synthesis including reaction, purification, and product characterization in less than 1 h (Scheme 22). The speed advantage for compound production or reaction optimization is tremendous. In a high-throughput synthesis set up, reactions can be run in parallel in a multimode microwave cavity or in sequence with automation in a monomode microwave cavity. The product purification can be done by plate-to-plate F-SPE.

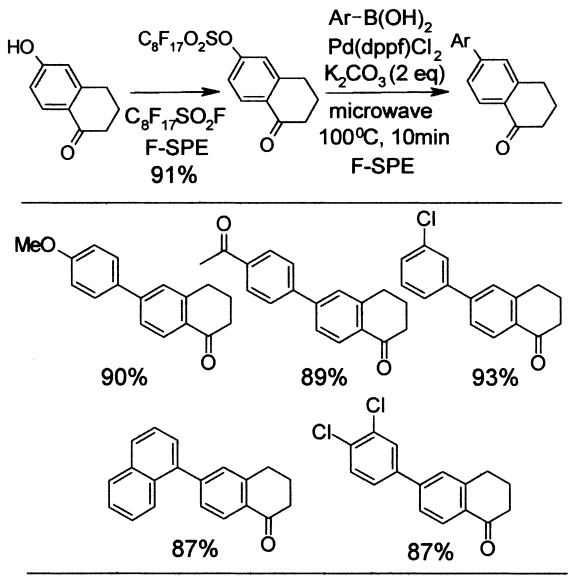
Figure 6. Fluorous synthesis with a microwave cavity (top) and an F-SPE manifold (bottom).



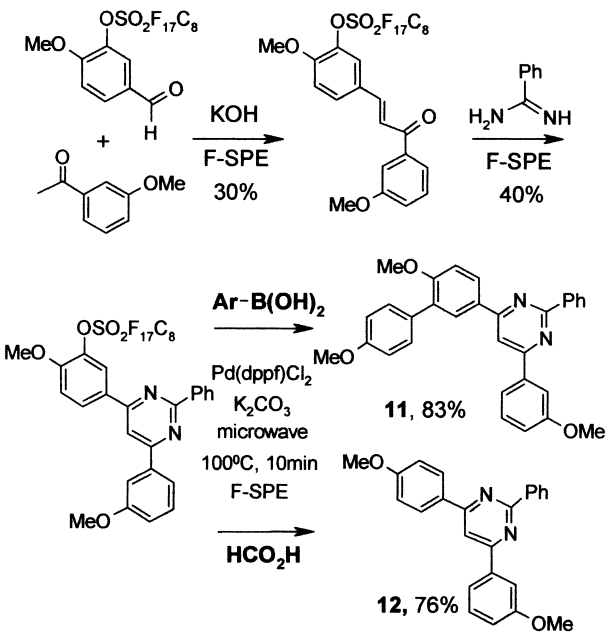
Scheme 22. One-hour turn around of microwave-assisted fluorous synthesis.

Following up on the early work by Larhed, Hallberg and Curran in the heavy fluorous area,[43,44] we recently explored the microwave-assisted light fluorous synthesis. Scheme 23 shows a Suzuki coupling reaction of fluorous sulfonates combined with the F-SPE product purification.[45] A commercially available phenol was converted to a sulfonate by reacting with C_8F_{17} perfluorosulfonyl fluoride. Similar conditions[46] for traditional thermo Suzuki coupling were applied to microwave reactions except the reaction temperature was higher (100°C) and reaction time was much shorter (10 min).[47] F-SPE was employed to separate the coupling product from the cleaved fluorous tag.

The benefit of the F-SPE has been magnified by designing a multi-step synthesis. The tagged substrate was taken through two additional transformations before it was reacted



Scheme 23. Microwave-assisted Suzuki coupling of F-sulfonates.



Scheme 24. Multi-step synthesis with F-sulfonate tag.

with boronic acids to generate the C–C bond of biaryl compounds **11** or reacted with HCO_2H to give traceless detagging product **12** (Scheme 24).[45] At each step of aldol condensation, cycloaddition, and Suzuki coupling, new diversity points can be introduced by running parallel reactions.

7. Conclusions

Fluorous synthesis has the characters of solution-phase reactivity and solid-phase like separation. Fluorous reactions coupled with microwave heating and fluorous silica gel-base separation have great potential to speed up both the chemistry development and library production process. Recent progress on fluorous technologies have demonstrated their broad applications in solution-phase parallel and mixture synthesis. Increasing interests from academic and industrial chemists combined with the strong commercialization effort from FTI will make fluorous technologies become powerful tools in organic synthesis and drug discovery.

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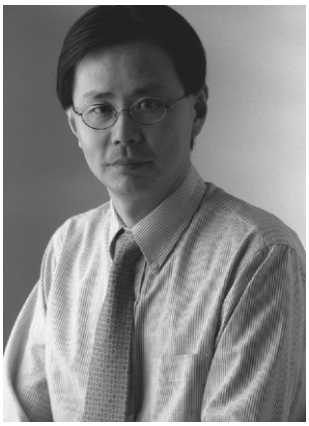
47. The reactions are performed under the license of US patent 6,136,157.

Biographical sketch



Dr Wei Zhang received his PhD from the University of Pittsburgh under the direction of the late Professor Paul Dowd. After a two-year stay at the same University as a Research Assistant Professor, he joined DuPont in 1995. Since 2001 he is a Senior Scientist and Head of Combinatorial Chemistry at Fluorous Technologies, Inc. in Pittsburgh. He leads the effort on research and development of fluorous technologies for solution-phase high-throughput synthesis and separations. Over the years, Dr Zhang has gained extensive experience in both industrial and academic research. His professional areas of interests are lead generation and optimization, free radical chemistry, heterocyclic chemistry, fluorous high-throughput synthesis, and microwave-assisted organic synthesis. He has 5 patents and patent applications, published more than 40 peer-reviewed papers including 2 book chapters and 4 review articles. In the last two years he has delivered many invited lectures and conference presentations on fluorous technologies.