New chemical and biological applications of fluorous technologies

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Since fluorous technology was first introduced by Horváth and Rábai in 1994, it has become well established in biphasic catalysis, high-throughput synthesis of small molecules and separation of biomolecules. In the last five years or so, this solution-phase technology has penetrated to other areas and shown great promise in organocatalysis, biocatalysis, microarray and microfluidic technologies. This *feature article* highlights the development of fluorous technologies in these new fields.

Introduction

Organic compounds can be rendered fluorous by the attachment of fluorocarbon chains. Attached fluorous compounds have unique characteristics such as temperature-dependent miscibility with organic phases, solvophobicity with aqueous and organic solvents, and fluorophilicity with fluorous media. These special properties have been exploited in the development of new interdisciplinary technologies across synthetic, analytical, separation, material and bioorganic sciences.[1,2]

Fluorous chemistry was first introduced by Horváth and Rábai in 1994 for biphasic catalysis.[3] Temperature-dependent miscibility of fluorous and organic systems was utilized to achieve homogeneous catalytic reaction and biphasic separation of fluorous catalysts. Since the middle 1990s, the Curran group and many other labs promoted the fluorous synthesis of small molecules,[4] natural product analogs,[5] and biomolecules including peptides,[6] oligosaccharine,[7] glycopeptides[8] and oligonucleotides.[9] Many of these works are related to "light fluorous" synthesis,[10] which is relied on fluorous solid-phase extraction (F-SPE) for the separation of reaction mixtures.[11] Fluorous biphasic catalysis[12] and fluorous synthesis of small molecules[10,13] and biomolecules[14] have been reviewed elsewhere and are not covered by this article. This article highlights several new and promising areas of fluorous technologies.

"Light fluorous" chemistry employs compounds containing few and short fluorocarbon ponytails. The attached molecules have reasonable solubilities in organic solvents and are generally compatible with common chemical and biological processes. Since "light fluorous" chemistry does not require fluorocarbon solvents for reactions and separations, it significantly reduces the environmental impact caused by the using of persistent perfluorocarbon chemicals. The good compatibility and improved green chemistry aspects of the "light fluorous" chemistry offer tremendous new opportunities for the development of fluorous-enhanced organocatalysis, biocatalysis, microarray and microfluidic technologies.

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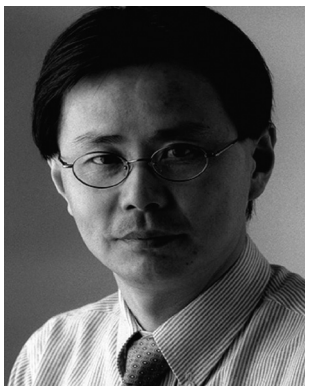

Wei Zhang

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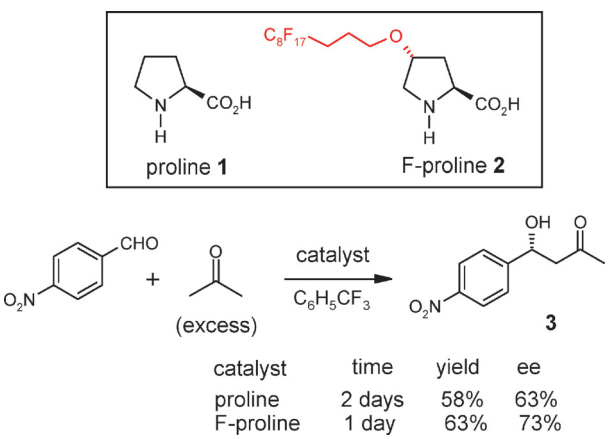
Fluorous organocatalysis

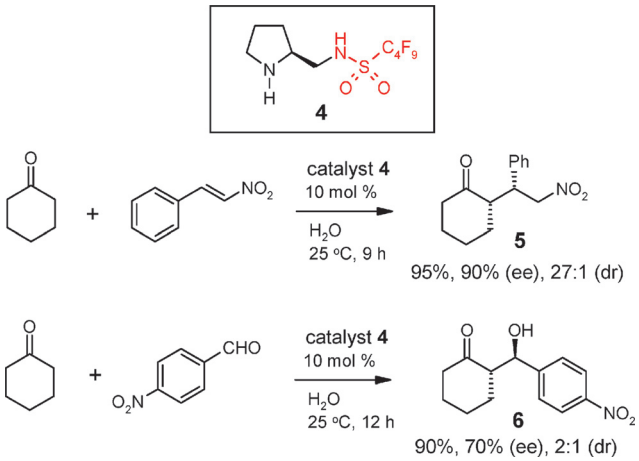
Metal-free organocatalysis has attracted a high level of current interest because of its novel activation mechanisms, mild reaction conditions, and environmentally friendly nature.[15] A series of organocatalysts for enantioselective reactions has been developed to cover a range of basic organic transformations such as Michael, aldol, Diels–Alder, Mannich and 1,3-dipolar cycloaddition reactions.[16] Since organocatalysis usually require a high (10–30 mol%) catalyst loading, without an appropriate catalyst recovery technique organocatalysis will have a cost concern when conducting large-scale reactions. The development of solid-phase supported organocatalysis provides a way to address the recovery issue.[17] However, reactions involving solid-supported catalysts are heterogeneous, and not all the active sites on the solid phase are accessible. Reactions could be slow and may require an extra amount of the catalyst. Fluorous organocatalysis holds a better promise since the reaction is in homogeneous solution-phase, and it also efficiently addresses the catalyst recovery issue.

Fache and Piva are pioneers in the development of fluorous organocatalysis.[18] They prepared a fluorous alcohol-attached proline derivative **2** and tested it side-by-side with an unmodified proline **1** for the aldol reaction of acetone and *p*-nitrobenzaldehyde to form β-hydroxyketone **3**. Under similar reaction conditions, the fluorous proline-catalyzed reaction proceeded at a high rate. It also gave a better yield and better enantioselectivity than the normal proline (Scheme 1). However, the catalyst recovery was not fully addressed for this particular reaction.

The development of fluorous pyrrolidine sulfonamides **4** for enantioselective Michael additions and aldol reactions has been performed by the Wang group.[19] The Michael reaction of cyclohexanone and *trans*-β-nitrostyrene under 10 mol% of the catalyst gave product **5** in 95% yield with a 90% ee and a 27 : 1 *syn* : *anti* ratio (Scheme 2). The reaction was carried out in water at room temperature. The catalyst was recovered by F-SPE and was subsequently reused six times without a significant loss of catalytic activity. Further extension of the utility of fluorous pyrrolidine sulfonamide catalyst **4** for the aldol reaction to prepare **6** has also been achieved.[20]



Scheme 1 Proline-catalyzed aldol reactions.

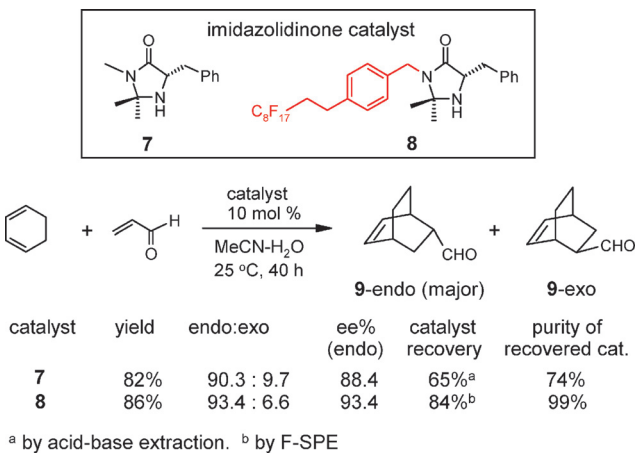


Scheme 2 Fluorous pyrrolidine sulfonamide for enantioselective Michael addition (top) and aldol reaction (bottom).

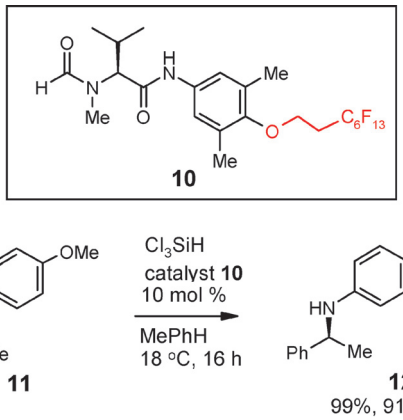
Imidazolidinone (MacMillan) catalyst **7** has a broad scope for catalysis of Diels–Alder, 1,3-dipolar cycloaddition, Michael and Friedel–Crafts reactions.[21] A fluorous version of imidazolidinone **8** has been prepared and tested for the asymmetric Diels–Alder reaction (Scheme 3).[22] Compared to the normal imidazolidinone catalyst **7**, fluorous imidazolidinone **8** gave cycloaddition product in a slightly higher yield (86%) and **9**-endo in a better enantioselectivity (93.4% ee). The catalyst was recovered by F-SPE in 84% yield with 99% purity. A catalyst with such a purity can be directly used for the next round of catalytic reaction. On the other hand, regular imidazolidinone catalyst **7** was recovered by acid–base worked up in 65% yield with only 74% purity. It needs further purification before it can be used for the next round of catalytic reaction.

The Malkov group employed fluorous amino acid-derived formamide **10** to catalyze the asymmetric reduction of imine **11** with trichlorosilane to form amine **12** (Scheme 4).[23] The reaction gave good yield and enantioselectivity. The catalyst recovered by F-SPE can be reused four–five times without a significant loss of catalytic activity.

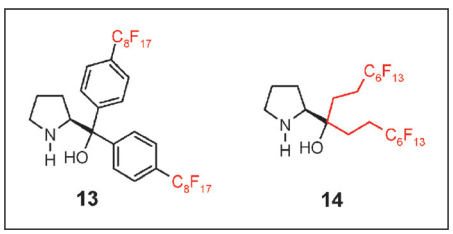
Preparations and catalytic applications of fluorous dialkyl and diaryl-substituted prolinols (**13** and **14**) have been



Scheme 3 Imidazolidinone-catalyzed asymmetric Diels–Alder reactions.



Scheme 4 Fluorous amino acid-derived formamide for asymmetric reduction.



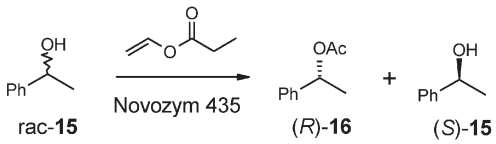
Scheme 5 Dialkyl and diaryl-substituted prolinols.

reported by several research groups (Scheme 5). These two kinds of compounds have been used as precatalysts for CBS asymmetric reductions of ketones,[24] for enantioselective epoxidations of α,β-enones[25] and for Michael addition reactions of aldehydes and nitroolefins.[26]

Fluorous biocatalysis

Biocatalysis represents a powerful tool for the synthesis of enantiomerically pure compounds. Different from the asymmetrical chemical reactions described in the previous section, enzymatic reactions are highly substrate specific; enzymes are very sensitive to environmental change; and the reactions are usually carried out in the aqueous phase at a low substrate concentration. Since the product is also presented in a low concentration in the reaction mixture, product separation and disposal of a large amount of waste solvent are the challenging tasks in enzyme-catalyzed synthesis.[27] Fluorous technologies have a potential to enhance the biocatalysis from the following three approaches: (1) using fluorinated solvents to improve enzyme activities; (2) using the fluorous tagging strategy to facilitate product separation; and (3) using fluorous-immobilized enzymes for continuous flow reactors and large-scale productions. So far preliminary works related to the first two approaches have been reported in literature.

Recent works on solvent engineering have extended the scope of enzyme-catalyzed reactions in nonaqueous media including organic solvents,[28] supercritical fluidics,[29] and ionic liquids.[30] For example, hexane was found to be able to increase lipase-catalyzed transesterifications.[31] It helps the enzyme to retain "essential water" hydrated on its surface and hold the protein in a catalytically active form; to prevent the enzyme from being attacked by the polar solvent; and to be



solvent	t (h)	conv. (%)	ee (*R*)-**16** (%)	ee (*S*)-**15** (%)
R-32	5	50	>99	>99
R-227ea	3.5	49	96	>99
R-134a	4	49	96	>99
hexane	8	46	85	>99
MTBE	35	49	96	>99

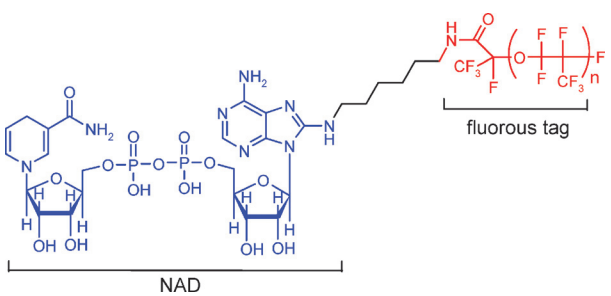
difluoromethane (R-32)
1,1,1,2-tetrafluoroethane (R-134a)
1,1,1,2,3,3,3-heptafluoropropane (R-227ea)

Scheme 6 Lipase-catalyzed kinetic resolution of racemic 1-phenylethanol.

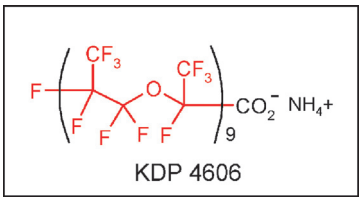
able to increase the temperature for enzymes operation. The use of supercritical fluids and ionic liquids as the alternatives to the volatile organic solvents is an important step towards the direction of "green chemistry". Fluoroform (CHF_3) is a CO_2 alternative for supercritical enzymatic reactions. The dielectric constants (ε) of supercritical fluoroform can be controlled from 1 to 7, while the ε values of supercritical CO_2 is in a narrow range of 0.1–0.3. The advantage of supercritical fluoroform has been demonstrated in many kinds of biocatalysis reactions.[29b]

Fluorous biocatalysis has also been carried out under non-supercritical conditions. The Micklefield group tested three low boiling point fluorocarbon solvents for a kinetic resolution of racemic 1-phenylethanol (*rac*-**15**) using Novozym 435 as a catalyst (Scheme 6).[32] Compared to similar reactions carried out in hexane and methyl *tert*-butyl ether (MTBE), reactions in fluorinated solvents were faster and gave better yields. The enhanced performance is attributed to the low viscosity of fluorinated solvents that increased the solute diffusivity. The Goto group reported the lipase-catalyzed alcoholysis between vinyl cinnamate and alcohol in perfluorohexanes (FC-72).[33] In a fluorous solvent, the poly(ethylene glycol) (PEG)–lipase PL complex from *Alcaligence* sp was found 16 times more reactive than that of the native lipase powder.

The Beckman group reported that the perfluoropolyether-attached coenzyme nicotinamide adenine dinucleotide (F-NAD) could form micelles when dissolved in a fluorinated solvent such as methoxynonafluorobutane and liquid carbon dioxide (Scheme 7).[34] In these micelles, the enzyme horse liver alcohol dehydrogenase (HLADH) was found active in



Scheme 7 Fluorous coenzyme nicotinamide adenine dinucleotide (F-NAD).



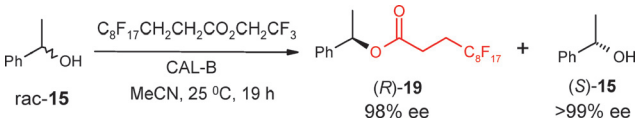
Scheme 8 Perfluoropolyether carboxylate surfactant.

catalyzing oxidation/reduction reactions. The activity of F-NAD is greater than that of unmodified NAD.

Thomas and co-workers introduced a hydrophobic ion pairing technique for enzymatic catalysis. In this work, α-chymotrypsin (CMT) was paired with perfluoropolyether carboxylate surfactant KDP 4606 to form protein–surfactant complexes (Scheme 8).[35] The KDP–CMT complexes have shown catalytic activity in the extraction of proteins from an aqueous solution into perfluoromethylcyclohexane (PFMC). The enzyme can be solubilized up to 20 mg (protein) mL^{-1} in PFMC. The homogeneous enzyme reaction of KDP–CMT ion pairs gave enhanced catalytic activity compared to that of the native enzyme. The KDP–CMT complexes in the fluorous biphasic system could be recycled for four times without a significant loss of enzyme activity.

In addition to the solvent engineering technique described above that involve the use of fluorocarbon liquids or additives to improve the performance of enzymes, another important approach relying on fluorous tags for facile product separation has been developed. Beier and O'Hagan employed lipase from *Canadida rugosa* (*CRL*) for enzymatic transesterifications of racemic 2-methylpentanoic acid (*rac*-**15**) with a fluorous alcohol. The reactions and separations were carried out in a 1 : 1 hexane–perfluorohexanes (PFH) solvent system (Scheme 9).[36] The monophasic enzymatic reaction took place at 40 °C, and the biphasic separation was performed at 0 °C. Fluorous (*S*)-**18** ester was isolated from the perfluorohexanes phase and unreacted methylpentanoic acid (*R*)-**17** was isolated from the hexane phase. Isolated fluorous (*S*)-**18** ester was hydrolyzed to (*S*)-2-methylpentanoic acid through chemical or biocatalytical methods. This reaction and separation process can be conducted on a gram scale.

The Theil group reported the lipase-mediated kinetic resolution of secondary racemic alcohols by transesterification reaction with fluorous esters.[37] Lipase B from *Candida antarctica* (CAL-B) in acetonitrile promoted the transesterification and resolved the enantiomers of *rac*-**15** into (*R*)-**19** and (*S*)-**15** in 19 h at room temperature (Scheme 10). The separation of fluorous ester and unreacted alcohol was accomplished by a biphasic partition between MeOH and *n*-perfluorohexane. A reverse process to resolve the racemic fluorous ester to (*R*)-alcohol and fluorous (*S*)-ester was also conducted in the same enzymatic reaction and separation system.

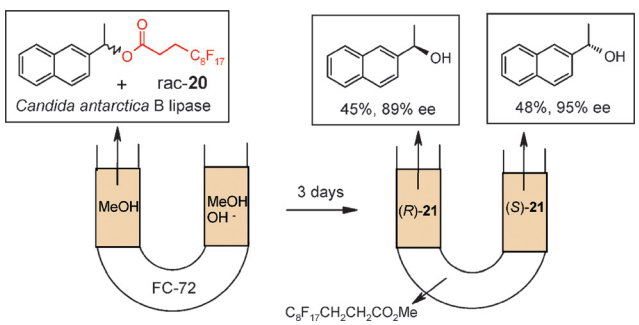


Scheme 10 Lipase-catalyzed transesterification of racemic 1-phenylethanol.

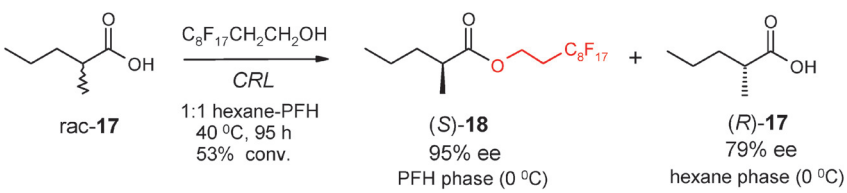
In addition to the research work described above, the Theil and Curran groups jointly designed a U-tube triphasic system to integrate the resolution and detagging processes into a single operation (Scheme 11).[38] The U-tube has a resource phase for the enzymatic deacylation of (*R*)-**20** to form (*R*)-**21** and a receiving phase for the cleavage of fluorous (*S*)-**20** ester to form (*S*)-**21** alcohol. These two phases were separated by a fluorous phase (FC-72) in the middle, which served as a reservoir to keep the cleaved fluorous acid in methyl ester form and as a membrane to selectively transfer fluorous (*S*)-**20** ester from the resource phase to the receiving phase. At the end of the three-day kinetic resolution, (*R*)-**21** alcohol was in the resource phase in 45% yield and 89% ee, and (*S*)-**21** alcohol was in the receiving phase in 48% yield and 95% ee.

Kinetic resolution has a major limitation since the maximum yield of the desired enantiomer cannot exceed 50% of the racemate. The "dynamic kinetic resolution" technique combines the kinetic resolution and the racemization of undesired isomers to offer potentially 100% yield of the desired stereoisomer. The Jaenicke group modified Theil's work of lipase CAL-B catalyzed kinetic resolution of phenylethanol (*rac*-**15**) by coupling it with Zeolite Zr-beta-catalyzed racemization for the secondary alcohol (Scheme 12).[39] Up to 95% conversion was achieved in this dynamic kinetic resolution. However, the enantiomeric excess was only about 70%, which needs further optimization.

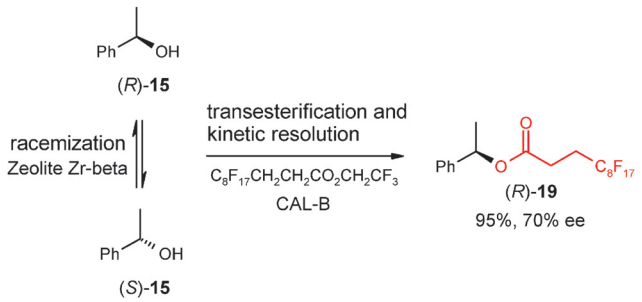
The Hatanaka group introduced a fluorous alcohol-attached lactoside primer **22** into muse B16 cells for an *in vivo* glycosylation to produce GM3-type oligosaccharide **23** (Scheme 13).[40] The product was isolated by fluorous liquid–liquid extraction. The fluorous tag was found to be



Scheme 11 Triphasic resolution of fluorous racemic ester **20**.



Scheme 9 Lipase-catalyzed transesterification of racemic 2-methylpentanoic acid.



Scheme 12 Dynamic kinetic resolution of phenylethanol *rac*-**15**.

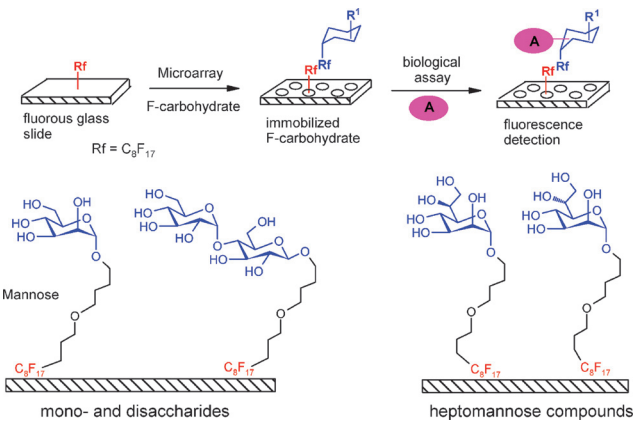
non-cytotoxic and with increased hydrophobicity and membrane permeability of the primer. This unique cellular enzymatic approach is simple and also environmentally friendly since much less reaction solvent is involved in the production process.

The Ikeda group employed 2-(perfluorohexyl)ethoxymethyl (F-MOM) tag-attached *N*-acetyl-D-mannosamine **24** for chemoenzymatic synthesis of sialidase inhibitor 2-deoxy-2,3-didehydrosialic acid **27** (Scheme 14).[41] Neu5Ac aldolase-catalyzed reaction of **24** afforded compound **25** which was then converted to the final product **27** through sequential esterification, AcCl treatment, and tag cleavage.

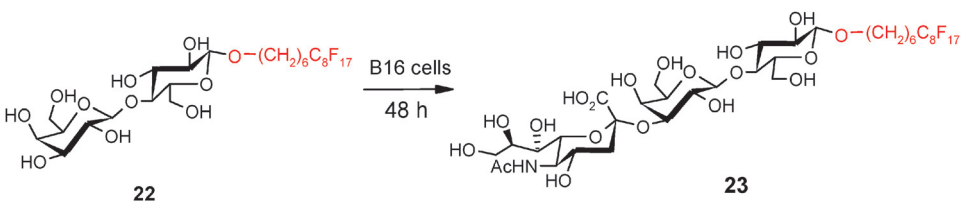
Fluorous microarray

The microarray of small molecules and biomolecules represents a new tool for high-throughput screening.[42] This array platform originates from the SPOT-synthesis of peptides on cellulose supports.[43] Expanding this technique beyond peptidic systems into the realm of complex small molecules and carbohydrates was challenged by the lack of general protocols for specific attachment to the array surface. The covalent attachment is an available technique, but the additional reaction step for small molecule immobilization requires good functional group selectivity and tolerance, which is not always compatible with complicated substrates. Alternative techniques for noncovalent immobilization have also been explored.[44] The Pohl group introduced the concept of fluorous microarray, a noncovalent attachment technique for carbohydrates.[45a] In this work, a series of fluorous alcohol-attached monosaccharides were synthesized and spotted on glass microscope slides whose surface had been pretreated with a fluorous silane. The fluorous affinity interaction was strong enough to hold the substrates on the slide even against a wash with a detergent. The microarray printed slides were then screened with fluorescent carbohydrate-binding proteins (Scheme 15). The initial work was then extended for the microarray of disaccharides and charged sugars and screened with plant lectins.[45b] The fluorous tag not only provides a unique way for the microarray of carbohydrates, but also facilitates the purification of intermediates in automated glycosylation–deprotection cycles required for the construction of disaccharides and oligosaccharides.

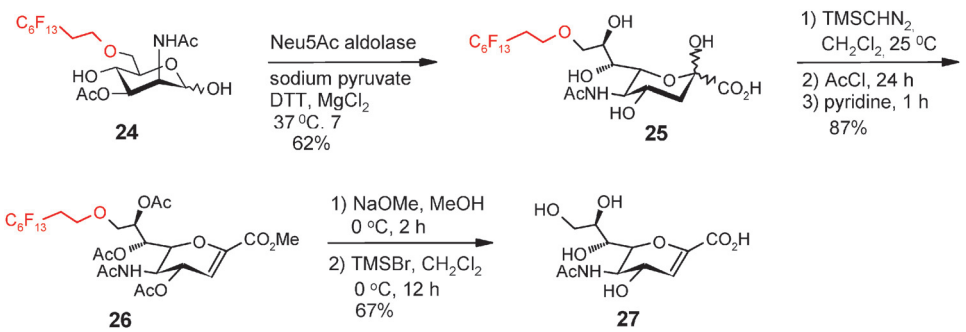
The Pohl group also reported the quantitative fluorous microarray screening of α-linked mannose and α-linked manno-heptose against plant lectin concanavalin A (Scheme 15).[46]



Scheme 15 Microarray screening of carbohydrates.



Scheme 13 Synthesis of fluorous GM3-type oligosaccharide **23**.

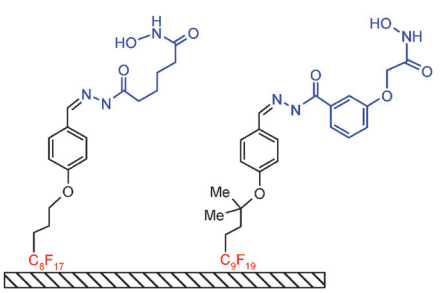


Scheme 14 Chemoenzymatic synthesis of 2-deoxy-2,3-didehydrosialic acid.

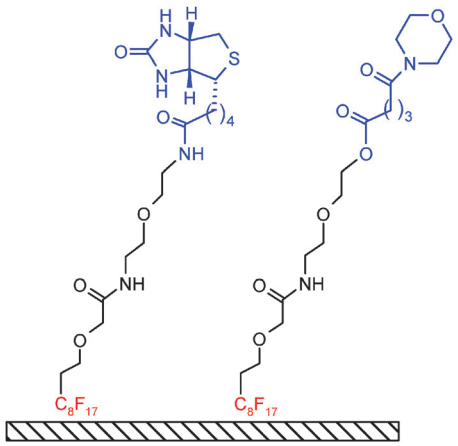
Fluorous β-D-mannose exhibited a robust fluorescent response indicating protein binding. This experiment shows for the first time that concanavalin A can recognize seven-carbon mannose analogues as ligands. Substitution by a hydroxymethyl group at one of the hydrogen atoms in the C-6 position of d-mannopyranose does not demolish the carbohydrate–protein binding. This result is different from what has been reported previously in the literature.

Fluorous microarray is not only limited to hydrophilic species such as carbohydrates. The Schreiber group reported the microarray of more hydrophobic drug-like small molecules and screened them against *histone deacetylases* (HDAC).[47] Histone deacetylases are a class of enzymes that remove acetyl groups from an ε-*N*-acetyl lysine amino acids of histone proteins. The identification of novel HDAC inhibitors could lead to the discovery of new drugs for the treatment of cancer, fibroproliferative disorders, neurodegenerative diseases and inflammatory diseases. In this work, a total of twenty fluorous modified HDAC inhibitors were synthesized (Scheme 16). They are varied in linker lengths, metal chelating groups, and fluoroaffinity to the slides. Fluorous immobilization was found to tolerate the removal of unbound HDAC from the slide, subsequent incubation with antibodies, and rinses before the quantitative fluorescent scanning. The control experiment using solution-based biochemical assays and surface plasmon resonance-based screening has revealed a strong correlation with the fluorous microarray-based screening for HDAC inhibitors. In addition, the authors reported that fluorous microarray-based approach has the advantages of allowing for controlled molecular display of inhibitory functionality, low uniform background signals, and excellent signal-to-noise ratios.

Another work related to the fluorous microarray of small molecules was reported by the Spring group.[48] Fluorous-tagged biotin molecules were immobilized onto the fluorous glass slide and screened against dye-labeled avidin. In the screening of a collection of fluorous biotins and nonbiotin compounds (Scheme 17), only the biotin compounds showed strong fluorescent spots on the slide indicating binding with avidin. Two different fluorous biotins and untagged biotins were tested. It was found that the high fluorine-content C_8F_{17}-attached biotin had better spot morphology and gave more consistent screening results than the shorter C_6F_{17}-tagged analogs. The untagged biotin compound showed visible bleed between array spots on the fluorous surface, which demonstrated that the simple hydrophobic effect is not sufficient.



Scheme 16 Representative structures of immobilized HDAC inhibitors.



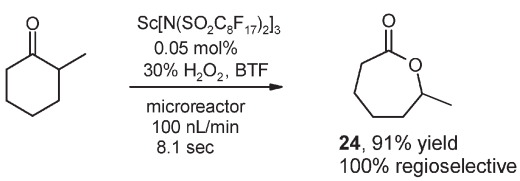
Scheme 17 Structures of immobilized biotin (left) and nonbiotin (right) compounds.

Noncovalent fluorophilic interaction is critical in obtaining discrete spots for microarray screening. Authors also demonstrated that fluorous immobilization is reversible. The fluorous slides can be cleaned for reuse by washing sequentially with methanol and dichloromethane. The reused slides had a weak fluorescence background and nonspecific interactions between avidin and other compounds, but were not related to fluorous biotin.

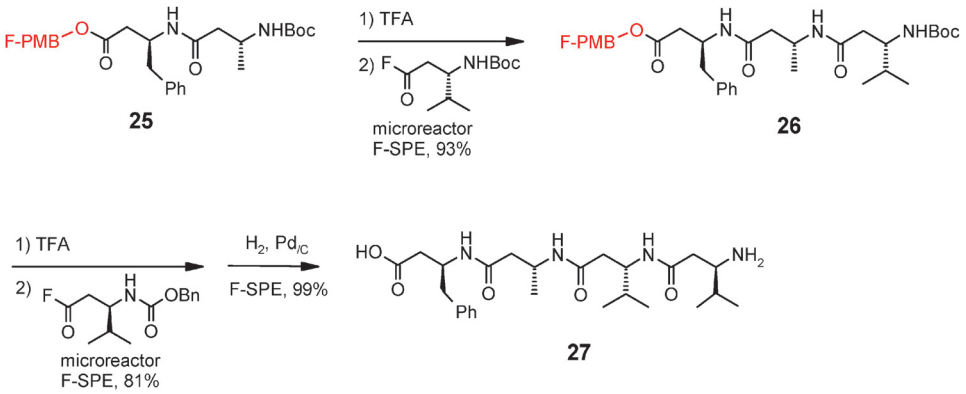
Microfluidic technology

Chemical microfluidic devices provide the advantages of fast sample delivery and heat transfer, favorable reaction kinetics, quick online detection, easy automation, low energy consumption and a small amount of waste disposal. Design and development of miniaturized lab-on-a-chip devices to integrate the reaction, analytical, separation and even bioscreening process is a very active research area.[49]

The Mikami group developed fluorous nanoflow microreactors.[50] One of the objectives of their work was to find a pump system suitable for the delivery of non-polar fluorous solvents at micro- to nano-order levels. A commercial available nanofeeder DiNaS having the capability of controlling tunable flow of solution from 1 to 200 000 nL min^{-1} was used for the Baeyer–Villiger oxidation of cyclic ketones.[50b] The reactions were carried out using 30% H_2O_2 in the presence of low concentrations of a fluorous lanthanide catalyst $Sc[N(SO_2C_8F_{17})_2]_3$ in benzotrifluoride as a solvent. The flow rate was continuously controlled at 100 nL min^{-1} for the liquid phase containing the substrate and the catalyst in benzotrifluoride, and also for the phase of 30% H_2O_2. It took only 8.1 s for the Baeyer–Villiger reaction to convert 2-methylcyclohexanone to corresponding lactone **24** and gave 91% yield in 100% regioselectivity (Scheme 18), whereas the similar reaction in a



Scheme 18 Fluorous Baeyer–Villiger reaction in a nanoflow microreactor.



Scheme 19 Fluorous microreactor synthesis of β-peptide tetramer **27**.

batch system took 5 h to give only 28% yield in 69 : 31 regioselectivity. This work clearly demonstrates that the Baeyer–Villiger reaction conducted in a nanoflow reactor has significant advantages over the corresponding batch reaction in product yields, regioselectivity and reaction rate.

The synthesis of β-peptides on traditional solid supports is a difficult task due to the formation of secondary structures. Seeberger and coworkers successfully prepared β-peptide tetramer **27** by conducting solution-phase synthesis in a continuous flow microreactor using fluorous PMB protected β-peptide dimer **25** as the starting material (Scheme 19).[51] In the microreactor, a variety of reaction conditions were quickly tested using a very small amount of materials. The optimized conditions were applied to microreactor synthesis and the obtained result was compared to that obtained by a nonfluorous method. Although different protocols provided the tetramer **27** in comparable yields, the fluorous-attached peptides were found much easier to purify. The combination of the microreactor reaction and the F-SPE separation provides a new and efficient method for the synthesis of β-peptides.

The Li group implemented the F-SPE technique into a microfluidic chip and tested its feasibility for separation of fluorous amino acids from a mixture containing untagged components.[52] To achieve the desired result, a poly(dimethylsiloxane) (PDMS) microfluidic F-SPE device containing a retaining chamber containing 5 μm fluorous silica gel in a microchannel was produced. Through the use of electrokinetic pumping, a mixture of fluorous Cbz-protected L-proline was carried into the F-SPE chamber and successfully separated. The extraction efficiency of the eluted fluorous-tagged amino acid was evaluated by MS detection. The F-SPE microchips showed good reproducibility and efficiency, yielding an average extraction efficiency of 55% with an RSD of 10.6% under the typical experimental conditions. This work demonstrates that F-SPE can be integrated into a microfluidic device for a facile separation. Different from the work described above which used a fluorous silica gel for microfluidic F-SPE, Jensen and co-workers employed a fluoropolymer membrane for continuous microfluidic liquid–liquid extraction for organic, aqueous and fluorous systems.[53]

Conclusions

Fluorous chemistry represents a new technology platform. In addition to well-established biphasic catalysis and synthesis of small molecules and biomolecules, fluorous chemistry has made significant advances in organocatalysis, biocatalysis, microarray and microfluidic technologies, which are highlighted in this article. Fluorous chemistry has also been explored in the areas of proteomics,[54] nanomaterials,[55] radiolabeling,[56] mass spectrometry enzymatic assay,[57] ionic liquids,[58] natural product separation,[59] green chemistry,[60] and analytical chemistry.[61] There is no doubt that we will continuously witness the development of more fluorous enabling and enhanced technologies for life science applications.

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