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13. The charged PMMA surface was covered with a drop (30 μl) of deionized water (resistance: 10 megohms) for 3 min for the first experiment (not shown), followed by another 30 min for the second experiment. Before characterizing the charge patterns, we dried the surface of the PMMA under a stream of dry nitrogen.
14. The corona discharge occurs at the front of the electrostatic gun (Zerostat, Aldrich) between two electrodes. A slow release of the trigger, lasting about 2 s, emits a stream of negatively ionized air {mainly CO_3^- [(*1*), p. 30]}. The positively charged PMMA was neutralized by releasing the handle 10 times, with the gun placed 1 cm above the surface.
15. The chip was heated for 10 min at 130°C on a hot-plate at ambient pressure and humidity. The glass transition temperature of PMMA is 105°C [D. R. Lide, *Handbook of Chemistry and Physics* (CRC, Boca Raton, FL, ed. 80, 2000), p. 13-6].
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17. When the surfaces are contaminated with dust particles, and the weight of the stamp provides insufficient pressure to deform around these particles, external pressure can become necessary to establish contact.
18. Oriented dipoles and trapped charges in electrets have been used to generate shorter wavelength light from a longer wavelength source [see (*19–21*), and references therein].
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26. We assume that trapped charge inside or on the surface of the PMMA film will attract mobile charge carriers inside the Si substrate. This displacement of charge carriers will result in the formation of a double layer. For a double layer separated by a distinct distance d, the charge density σ can be calculated with $\sigma = \varepsilon \Delta V/d$, where ε is the permittivity, and ΔV is the voltage drop across the layer (*16*). For $\varepsilon = 8 \times 10^{-12}$ C/Vm (permittivity of PMMA), $\Delta V = 2$ V (measured potential change), and $d = 100$ nm (assumed intermediate distance between the counter charges), we obtain a first-order estimate of the effective charge density of $\sigma_{eff} = 100$ elementary charges per surface area of 100^2 nm^2. The exact number depends on the actual distribution of the charges inside the PMMA film and the Si substrate; we presently have no information on this distribution.
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Fluorous Mixture Synthesis: A Fluorous-Tagging Strategy for the Synthesis and Separation of Mixtures of Organic Compounds

Zhiyong Luo,[1,2] Qisheng Zhang,[1] Yoji Oderaotoshi,[1] Dennis P. Curran[1]*

The solution-phase synthesis of organic compounds as mixtures rather than in individual pure form offers efficiency advantages that are negated by the difficulty in separating and identifying the components of the final mixture. Here, a strategy for mixture synthesis that addresses these separation and identification problems is presented. A series of organic substrates was tagged with a series of fluorous tags of increasing fluorine content. The compounds were then mixed, and multistep reactions were conducted to make enantiomers or analogs of the natural product mappicine. The resulting tagged products were then demixed by fluorous chromatography (eluting in order of increasing fluorine content) to provide the individual pure components of the mixture, which were detagged to release the final products.

We introduce a technique for the synthesis of mixtures of organic compounds that simultaneously solves both the separation and identification problems heretofore inherent in solution-phase mixture synthesis. The technique, called fluorous mixture synthesis (FMS), follows from early fluorous techniques such as fluorous biphasic catalysis (*1–3*) and solution-phase synthesis of small organic molecules by fluorous tagging (*4, 5*) (sometimes called "fluorous synthesis"). We envision a broad range of applications for FMS techniques, and here we introduce two applications: quasiracemic synthesis and parallel library synthesis. Both are illustrated in the context of the natural product mappicine (*6, 7*).

The synthesis of small organic molecules can be conducted either in solution or on the solid phase (*8*). When a single product or a few products are targeted, solution-phase synthesis is almost always used. When larger numbers of products are targeted, the options include solution-phase parallel synthesis, solid-phase parallel synthesis, and solid-phase mixture (split-mix) synthesis (*9–11*). Solution-phase synthesis allows for diverse and homogeneous reaction conditions, and products are readily analyzed and identified, but purifications are time-consuming and keeping all samples spatially separate is inefficient. Solid-phase synthesis renders separation of excess or spent reagents and reactants easy, and the efficiency of mixture methods allows more compounds to be made without a proportional increase in effort. But the scope of reactions that succeed on the solid phase is still limited, as are methods for purification, analysis, and identification of resin-bound products.

Ideal solution-phase synthesis methods would retain the reaction, identification, and analysis features of traditional solution-phase synthesis while capturing the separation and mixture advantages of solid-phase synthesis. Although there has been much work recently

[1]Department of Chemistry and Center for Combinatorial Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA. [2]Fluorous Technologies, U-PARC, 970 William Pitt Way, Pittsburgh, PA 15238, USA.

*To whom correspondence should be addressed.

to increase the separation efficiency of solution-phase methods (*12–15*), there is as yet no solution-phase synthesis technique that allows for operation on mixtures of compounds during a synthesis yet still provides for the orchestrated separation and identification of the final products (*16–21*).

In FMS, we capitalize on the ability of fluorous solid phases to separate molecules by fluorine content (*5*) in a process termed "fluorous chromatography." The concept of FMS is shown schematically in Fig. 1 and involves five stages: tagging, mixing, synthesis, demixing, and detagging. Members of a series of "*n*" organic substrates (S) are tagged with a corresponding number of fluorous tags (F). These tags bear the same basic functionality but contain increasing numbers of fluorine atoms. The tagged compounds (F–S) are then mixed and taken through a series of steps to make a mixture of fluorous-tagged products (F–P). During this stage of the synthesis, the numerical benefits of mixture synthesis are reaped because the number of operations needed relative to serial or parallel synthesis is reduced by a factor equal to the number of tags *n*.

At the end of the synthetic sequence, the mixture is separated by fluorous chromatography over silica gel with a fluorocarbon bonded phase, whereupon the pure products (F–P) elute from the column in order of increasing fluorine content. The order of separation can be predicted in advance by the original tag/substrate pairings. We call this orchestrated process of separation and identification "demixing" because it provides the individual final products in a step that can be loosely considered as the reverse of the original mixing. In essence, the substrates are "compressed" at the mixing stage for synthetic efficiency and then "decompressed" at the demixing stage to produce individual products. Finally, the tags are removed to give the individual pure target products (P).

The simplest possible mixture synthesis has two components, and we introduce FMS with the new technique of "quasiracemic synthesis" (*22–24*), where the two components are enantiomers. This technique captures the inherent efficiency of traditional racemic synthesis (two products made in one synthesis), yet it provides both enantiomers of the final product in enantiopure form without the need for a separation on a chiral support.

We have recently described a synthesis of (*S*)-mappicine by solution-phase methods, and this was used as the basis for the quasiracemic synthesis shown in Fig. 2 (*25–27*). Keto-pyridine **1** was individually reduced with both enantiomers of DIP-chloride [*B*-chlorodiisopinocampheylborane] to give a pair of enantiomeric alcohols [>98% enantiomeric excess (ee)]. The (R)-enantiomer was tagged with a silyl protecting group bearing a C_6F_{13} chain to give (R)-**2**, and the (S)-enantiomer was tagged with a group bearing a C_8F_{17} chain to give (S)-**2**. These two products were then mixed in equimolar portions to make the first quasiracemic mixture (M)-**2**, and the remaining steps of the synthesis were carried out. Exchange of iodine for a trimethylsilyl group (ICl) followed by demethylation (BBr_3) provides pyridone (M)-**3**. N-Propargylation under standard conditions gave radical precursor (M)-**4**, which in turn was reacted with phenyl isonitrile under cascade radical annulation conditions to provide the quasiracemic mixture of protected mappicine enantiomers (M)-**5**.

The sequence of reactions was carried out as in a normal racemic synthesis. Reactions were followed by thin-layer chromatography, worked up, and purified by flash chromatography. Yields were calculated on the basis of the average molecular weight of the mixture. Products were characterized by ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. In no case was any separation of the quasienantiomers evident, and both ^1H and ^{13}C NMR (without ^{19}F decoupling) spectra were single sets of resonances with no doubling.

Purification of (M)-**5** was conducted first by standard chromatography to give the pure quasiracemate, which was then resolved into its two components, (R)-**5** and (S)-**5**, by high-performance liquid chromatography (HPLC) separation over fluorous reverse-phase silica gel (Fluofix column, Keystone Scientific, Bellefonte, Pennsylvania). The quasienantiomers were widely separated, with (R)-**5** bearing the smaller tag, eluting well before (S)-**5** (18 versus 26 min, respectively). Detagging then gave both individual enantiomers

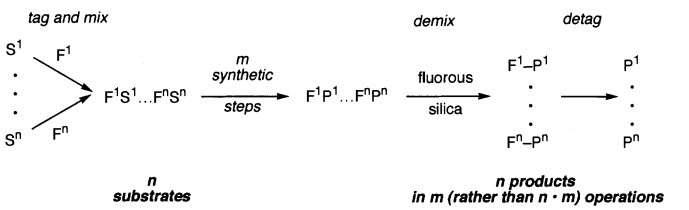

Fig. 1. Fluorous mixture synthesis. A series of "*n*" substrates (S) is tagged with *n* different fluorous tags (F), and the tagged compounds (F–S) are mixed. The mixture is then taken together through a series of "*m*" synthetic steps to provide *n* products (F–P) in *m* (rather than *n*·*m*) operations. The final mixtures are demixed by fluorous chromatography and tagged products elute in order of increasing fluorine content of the original tag. The individual tagged products are detagged to give the pure target products (P).

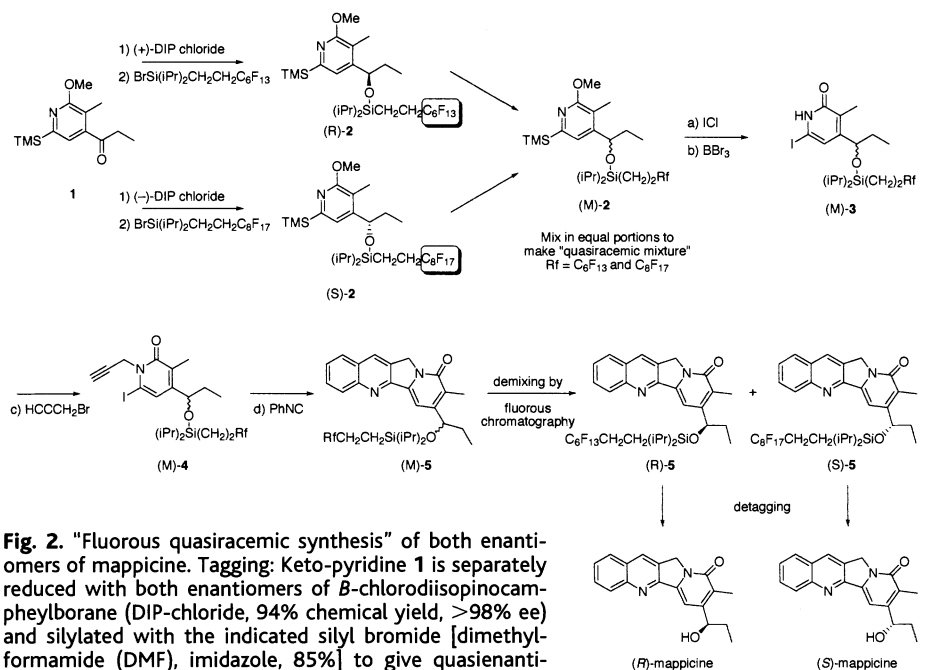

Fig. 2. "Fluorous quasiracemic synthesis" of both enantiomers of mappicine. Tagging: Keto-pyridine **1** is separately reduced with both enantiomers of *B*-chlorodiisopinocampheylborane (DIP-chloride, 94% chemical yield, >98% ee) and silylated with the indicated silyl bromide [dimethylformamide (DMF), imidazole, 85%] to give quasienantiomers **2**. Mixture synthesis: a) ICl, CH_2Cl_2, CCl_4; b) BBr_3, $CHCl_3$, 48% overall yield for steps a and b; c) propargyl bromide, NaH, LiCl, DMF, 61%; and d) C_6H_5NC, $Me_3SnSnMe_3$, sunlamp irradiation, 67%. Demixing: Fluorous chromatography over a Fluofix 120E column with the following gradient: 0 to 20 min, 90% MeOH/H_2O up to 100% MeOH; 20 to 30 min, 100% MeOH. Detagging: Tetrabutylammonium fluoride, tetrahydrofuran (THF), 71%.

of mappicine in enantiopure form (>98% ee). Quasiracemic synthesis should find general use in the simultaneous preparation of both enantiomers of a compound for structure assignment or comparative assaying.

The efficiency of mixture synthesis increases as more compounds are mixed. However, when the mixed compounds are not enantiomeric or even isomeric, will the tag be able to dominate over the tagged product in the final fluorous separation? To address this question, we made 100 analogs of the natural product mappicine by the cascade radical annulation route, as shown in Fig. 3. This annulation has been used to make mappicine and analogs by both traditional (*26*) and solution-phase parallel synthesis (*27*). Recently, we also attempted (without success) to translate this route to the solid phase for split-mix synthesis by attaching the secondary hydroxyl group to various polymers (*28*). This effort was abandoned because high-yielding reaction conditions could not be identified for either the N-propargylation or the radical annulation, despite extensive effort.

We conducted the four-step sequence shown in Fig. 3 to make the small library of 100 tagged mappicines. The experiment started with a mixture of four (racemic) tagged compounds (M)-**6**, where each R^1 group was coded with a different Rf group. There were no intermediate purifications. This mixture of compounds was subjected to iodinative desilylation and demethylation to give (M)-**7**. The mixture was divided into five portions for N-propargylation, and the resulting five mixtures (M)-**8** were divided again by five and reacted with different isonitriles in a combinatorial fashion to give 25 tagged mappicine mixtures (M)-**9**, each containing four components.

These final product mixtures (M)-**9** were then demixed under analytical conditions. Authentic mappicine bearing a $CF(CF_3)_2(^iC_3F_7)$ tag (*i*, iso) was added to each mixture as an internal standard, and the mixtures were analyzed by HPLC on a Fluofix column with both ultraviolet (for yield and purity) and mass spectrometric (for identification and purity) detection. This analysis identified 99 out of the expected 100 products, with each one emerging in the expected order of elution, based on the fluorine content of the tag. The average four-step overall yield with no intermediate purifications was 11%. This yield is comparable to similar reactions done serially (*27*). Preparative demixing (see below) was not conducted on all of these samples; however, the LC analysis showed that 87 of the 99 products could readily be isolated in pure form. Two typical-mixture HPLC chromatograms are shown in Fig. 4. The chromatogram in Fig. 4A shows a fully separable mixture; the first peak is the standard mappicine with the $^iC_3F_7$ tag, and the four subsequent peaks are the products with C_4F_9, C_6F_{13}, C_8F_{17}, and $C_{10}F_{21}$ tags, respectively. The chromatogram in Fig. 4B shows a mixture in which one of the four products (with the C_4F_9 tag) could not (readily) be isolated in pure form on preparative demixing. [A table of yields and retention times of all 99 products is available as supplemental material (*29*).]

FMS experiments can be conducted on typical-solution synthesis scales; the mixtures in Figs. 2 and 3 were made on the scale of 0.1 to 2.0 g, but larger scales are possible. Preparative demixing is currently limited by the size of commercial fluorous HPLC columns. We have conducted demixing experiments on scales of 7 to 10 mg, and we isolate the tagged products in pure form and in yields comparable to those expected by HPLC analysis.

These results (87 out of 100 pure final products, based on demixing only) are highly satisfactory, considering that there was no purification over four steps and that the reactions do not proceed in quantitative yield; indeed, both the iodinative desilylation and the radical annulation typically occur in only 40 to 50% each (*25, 26*). However, we postulated that the library quality could be improved by intermediate mixture purification, and we made a new 20-compound library to test this postulate. Intermediate purification is not an option in solid-phase synthesis because compounds would have to be removed from beads.

Mixture (M)-**6** was first reacted under the standard iodinative desilylation conditions, followed by standard silica gel flash chromatographic purification. HPLC analysis [see supplemental material for chromatograms (*29*)] of this mixture now with fluorous silica showed eight peaks in four alternating pairs with the larger, faster elut-

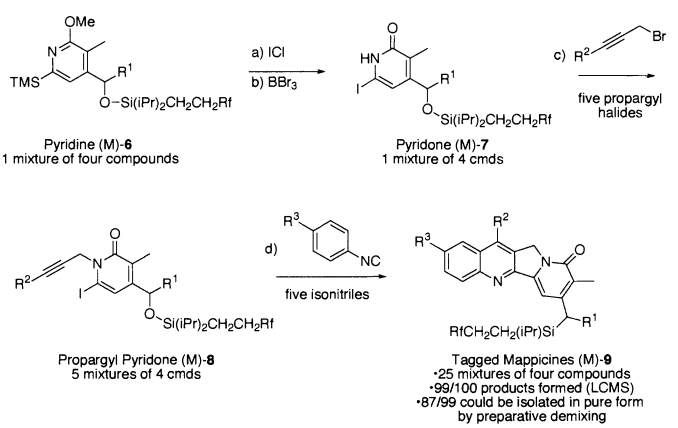

Fig. 3. Synthesis of 100 mappicine analogs by FMS. Reactants: Coding scheme for (M)-**6** (R, Rf); Pr, C_4F_9; Et, C_6F_{13}; *i*-Pr, C_8F_{17}; $CH_2CH_2C_6H_{11}$, $C_{10}F_{21}$; propargyl bromides, R^2 = H, Me, Et, C_5H_{11}, Si(*i*-Pr)Me_2; and isonitriles, R^3 = H, F, Me, OMe, CF_3. Tagging and mixing: The tags and the alcohols were attached under the same conditions as shown in Fig. 2 with the indicated coding scheme to give a mixture of four products **6**. Mixture synthesis: The reaction conditions are the same as in Fig. 2. The mixture of four compounds **6** was converted to a mixture of four compounds **7**, which was then split and reacted with the indicated five propargyl halides. The resulting five mixtures **8** were split and reacted with five isonitriles to give 25 mixtures, each containing four mappicines **9**. Demixing was conducted on a Waters high-performance liquid chromatograph by fluorous chromatography over a Fluofix 120E column with the following gradient: 0 to 30 min, 80% MeOH/H_2O up to 100% MeOH; 30 to 40 min, 100% MeOH up to 90% MeOH/10% THF.

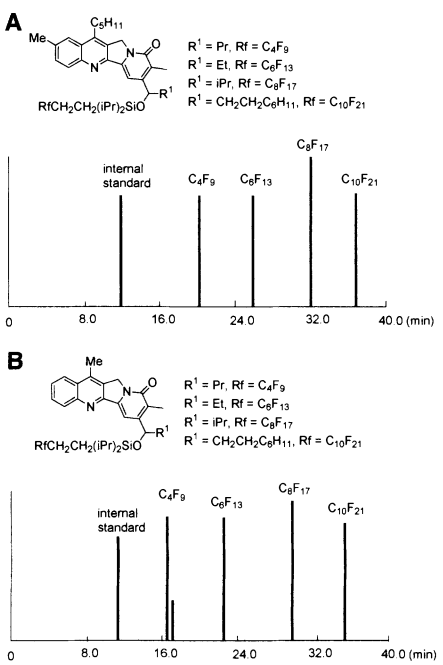

Fig. 4. HPLC chromatograms of two mixtures (M)-**9**. The first peak is the internal standard mappicine tagged with a $-Si(i\text{-}Pr)_2CH_2CH_2CF(CF_3)_2$ group. Demixing conditions are given in Fig. 3, and the original chromatograms are reproduced in the supplemental material (*29*). (**A**) A representative chromatogram of a mixture where all four compounds can be isolated in pure form by preparative demixing. (**B**) A representative chromatogram where three of the products can be isolated in pure form, but the fourth (C_4F_9 tag) is impure and must be chromatographed after detagging.

ing member of each pair identified as the desired iodide and smaller, slower member identified as the silyl pyridone starting material. Demethylation gave a pyridone mixture (M)-**7**, which resolved into two components on preparative separation over regular silica gel. Liquid chromatography–mass spectrometry analysis of the less polar fraction showed only four peaks, which were the four desired iodopyridones (M)-**7**. The more polar impurity fraction was not analyzed but is evidently a mixture of four products resulting from failure of trimethylsilyl/iodine exchange followed by successful demethylation.

The purified mixture was then reacted with one propargyl halide [R^2 = $Si(Me_2)CH{=}CH_2$]. This mixture (M)-**8** was purified again by silica gel flash chromatography. The purified mixture (M)-**8** was divided into five portions, and each was reacted with the five isonitriles in Fig. 3 to give five mixtures of four compounds each [(M)-**5**, R^2 = H]. The mixtures were then demixed as above after addition of the mappicine standard. Each mixture showed only the expected four peaks (20 out of 20 products formed, no impurities) in the expected order. The average four-step overall yield with two intermediate purifications was 6% [see the supplemental material for a table of all yields and retention times (*29*)]. In the experiment, all 20 products could be isolated in pure form by preparative demixing, which illustrates the potential benefits of intermediate mixture purification when nonquantitative reactions are involved.

Techniques like fluorous quasiracemic synthesis, which focus on a single mixture, can be used to leverage traditional synthetic research (such as natural product synthesis) by providing more than one product at the end. When used in a parallel synthesis like that of mappicine, fluorous mixture methods allow the synthesis of multiple complex scaffolds made as mixtures. These scaffold mixtures are then leveraged in the parallel synthesis stage by providing multiple products per vessel or well in good yield and excellent purity after demixing. Although this work describes only four-compound mixtures, the internal yield standard has a fifth tag, so it is already certain that five-compound mixtures can be made. On the basis of the steep gradient used and the peak separations in the HPLC library experiments, we think that expansion to at least 8- and possibly 10-compound mixtures should be straightforward.

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Reversible Surface Morphology Changes of a Photochromic Diarylethene Single Crystal by Photoirradiation

Masahiro Irie,* Seiya Kobatake, Masashi Horichi

The surface morphology of a diarylethene single crystal [1,2-bis(2,4-dimethyl-5-phenyl-3-thienyl)perfluorocyclopentene] determined by atomic force microscopy changed reversibly upon photoirradiation. The crystal underwent a thermally irreversible but photochemically reversible color change (colorless to blue) upon alternate irradiation with ultraviolet (wavelength λ = 366 nm) and visible (λ > 500 nm) light that drove reversible photocyclization reactions. Upon irradiation with 366-nm light, new steps appeared on the (100) single-crystalline surface that disappeared upon irradiation with visible light (λ > 500 nm). The step height, about 1 nm, corresponds to one molecular layer. Irradiation with 366-nm light formed valleys on the (010) surface that also disappeared by bleaching upon irradiation with visible light (λ > 500 nm). The surface morphological changes can be explained by the molecular structural changes of diarylethenes regularly packed in the single crystal. These crystals could potentially be used as photodriven nanometer-scale actuators.

Photochromism is the reversible transformation by photoirradiation of a chemical species between two forms that have different absorption spectra (*1, 2*). Among various photochromic materials, photochromic single crystals are of particular interest because of their potential usefulness for holographic and three-dimensional memories (*3–6*). Although various kinds of photochromic crystals have been developed (*3, 7–9*), crystals that undergo thermally irreversible photochromic reactions (*10*) are very rare. Recently, we have developed thermally irreversible and fatigue-resistant photochromic diarylethene crystals (*11–21*). The photoinduced coloration-decoloration cycles of the crystals can be repeated more than 10^4 times while maintaining the shape of the single crystals, and the photogenerated colored states are stable even at 100°C. During our studies of the single-crystalline photochromism, we found