Chiral and Achiral Lithium Amides Having a Fluorous Ponytail: Preparation and Evaluation as a Recycling Reagent for Lithium Enolate Generation

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Abstract: Diisopropylamine derivatives bearing a perfluoroalkyl chain were prepared and converted to the corresponding lithium amides by treatment with n-butyllithium. The fluorous lithium amides reacted with ketones to efficiently produce lithium enolates. Asymmetric deprotonation of prochiral ketones was also studied using lithium amides derived from chiral fluorous amines, which gave optical yields comparable with the parent nonfluorous chiral lithium amides. These reusable fluorous amines can be easily recovered by liquid-liquid extraction or chromatographic separation.

Key words: fluorous, chiral amine, enolate, LDA, asymmetric deprotonation, recycling

Introduction

Since the pioneering work of Horváth and Rábai,1 the concept of the fluorous biphasic system (FBS) has been proposed in organic chemistry as an environmentally benign recycling process.2 This concept is based on the physical phenomena that highly fluorinated compounds (fluorous materials) are immiscible with organic solvents, while they exhibit a thermomorphic nature to give a homogeneous solution upon heating. Thus, a variety of organic compounds in which perfluorinated alkyl chains (fluorous ponytails) are introduced and used as reagents, are easily separable from organic products by extraction using perfluorinated solvents such as FC-72 (perfluorohexanes) or liquid/solid extraction using fluorous silica gel.3 Work in our laboratories in this area has been directed toward the design, synthesis, and application of novel environmentally benign fluororous reaction media as well as effective fluororous reagents and catalysts. To this end, our group has recently reported fluororous versions of diethyl ether and DMF that function as easily recyclable reaction media.4,5 Our group has also established phase-vanishing methods based on the use of fluororous solvents as a liquid membrane, which permits transport of reagents and regulates the reactions in triphasic and quadruphasic.6

Lithium diisopropylamide (LDA)7 and its analogues are frequently used for the generation of lithium enolates from corresponding carbonyl compounds by proton abstraction. Lithium enolates can be used in a variety of synthetic reactions including O- and C-alkylations, acylations, and transmetalations to other useful metal enolates.8 Since diisopropylamine is soluble in water, the workup procedure of the reaction of LDA involves treatment with water to remove diisopropylamine from organic solution generally without recovery. In pursuit of useful methods to prepare chiral compounds, the recent work surrounding lithium enolate chemistry focuses on chiral lithium amide reagents available for the enantioselective generation of lithium enolates,9,10 in which a precious chiral function is embedded by appropriate molecular design. This study reports on the preparation and testing of recyclable fluororous-tagged substitutes for chiral and achiral LDA-type reagents, whose concept is outlined in Scheme 1. Consequently we found that α-phenethyl amines having a fluororous ponytail on the benzene ring worked equally well with non-fluorous reagents and were easily recovered and recycled.

Scheme 1  Concept of recycling fluororous amines acting as fluororous LDA precursors by FBS

Results and Discussion

Preparation and Properties of Fluorous Amines: (5-Perfluorooctyl-2-pentyl)-2-propylamine (1) and 2-(4-Perfluoroalkylphenyl)ethyl-2-propylamine (2)

We started our fluorous LDA project by preparing the fluorous amine 1 where a perfluorooctyl chain is attached to a diisopropylamine core as a ponytail in order to acquire a light fluororous character. Fluorous amine 1 was synthesized according to the procedure outlined in Scheme 2. Thus, perfluoroctyl iodide was treated with but-3-en-2-ol under radical conditions to give 3-iodo-4-perfluoroctylbutan-2-ol (4) in 82%, whose iodine was removed by tin hydride reduction to give 4-perfluoroctylbutan-2-ol (5). Butanol 5 was then converted into the
corresponding tosylate 6 in 88% yield, which was subjected to an S_N2 reaction with isopropylamine in the presence of potassium carbonate in acetonitrile to afford the desired amine 1 in 63% yield. Fluorous amine 1 is a pale yellow, clear, and slightly viscous liquid with a boiling point of 65–65 °C at 5 mmHg. This compound is miscible with a wide range of organic solvents, such as hexane, benzene, diethyl ether, ethyl acetate, acetone, and ethanol, and is poorly soluble in water.

We also prepared α-phenethyl type fluorous amines 2a and 2b, whose synthetic pathway is shown in Scheme 3. Perfluoroocetyl iodide was treated with 4-iodoethylbenzene in the presence of copper to give 4-perfluoroocetyl-ethylbenzene (7a) in 70% yield, which was converted to α-phenethyl bromide 8a by NBS bromination in 76% yield. The bromide was treated with isopropylamine to afford fluoruous amine 2a in 64% yield. Fluorous amine 2a is a pale yellow, viscous liquid with a boiling point of

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**Biographical Sketches**

**Hiroshi Matsubara** was born in Shiga, Japan in 1963. He received his PhD from Osaka University in 1991 under the supervision of Professor Shigetoshi Takahashi. He was appointed as a Research Associate at Osaka Prefecture University in 1991 and was a visiting researcher at the University of Melbourne in the research group of Professor Carl H. Schiesser from 2002 to 2003. He was promoted to Lecturer in 2002 and to Associate Professor in the Graduate School of Science, Osaka Prefecture University, in 2005. His research interests include development of synthetic methodologies utilizing fluorous chemistry and computational investigations into radical reactions.

**Louis Maeda** was born in Hyogo, Japan in 1980 and studied chemistry at Osaka Prefecture University. He received his MSc in 2006 under the guidance of Professor Ilhyong Ryu. Since April 2006, he has been working as a research chemist at Osaka Organic Chemical Industry, Ltd., Japan.

**Hiroyuki Sugiyama** was born in Shizuoka, Japan in 1979 and studied chemistry at Osaka Prefecture University. He received his MSc in 2004 under the guidance of Professor Ilhyong Ryu. Since April 2004, he has been working as a research chemist at Tsutsunaka Plastic Industry Co., Ltd., Japan (2004–2007) and Sumitomo Bakelite Co., Ltd., Japan (2007–).

**Ilhyong Ryu** received his BSc from Nagoya University in 1973. He then moved to the Graduate School of Osaka University, where he received his PhD in 1978 under the direction of Professors Noboru Sonoda and Shinji Murai. After serving as a JSPS Postdoctoral Fellow and a Research Associate at Osaka University, he was appointed Assistant Professor at Osaka University in 1988 and promoted to Associate Professor in 1995. He also had the experience of working with Professor Howard Alper (1991–1992) at the University of Ottawa as a Visiting Scientist. In 2000, he moved to Osaka Prefecture University as a Full Professor. He has been the recipient of the Progress Award in Synthetic Organic Chemistry, Japan (1990), and the Chemical Society of Japan Award for Creative Work (2004). His research interests include new synthetic methodologies based on radical reactions, new catalytic transformations, the utilization of green reaction media, and microwaves in organic synthesis.
100–105 °C at 3 mmHg. Fluorous amine 2b bearing a perfluorodecyl chain was synthesized by a similar three-step procedure, which started with the use of perfluorodecyl iodide. Fluorous amine 2b is a white solid with a melting point of 48.0–49.0 °C.

Fluorous compounds having perfluoroctyl or perfluorodecyl chains are called light fluorous compounds. Approximate partition coefficients of light fluorous amines prepared in this study were determined by the Curran’s method13 and listed in Table 1. Table 1 also lists partition coefficients of chiral fluorous amines, (R,S)-3 and (S,S)-3, the preparation of which is referred below.

When fluorous amine 1 was treated with a 1:1 mixture of FC-72 and cyclohexane, some 80% of fluorous amine 1 was distributed in FC-72 phase, indicating that the amine can be recovered from the reaction mixture through repeated biphasic treatment. Bearing a benzene ring, amine 2a became less fluorous than 1, whereas the introduction of a longer perfluorodecyl group increased distribution of the resulting amine 2b in the fluorous phase. Interestingly, as more polar solvent, such as acetone, methanol, and acetonitrile, was used, a greater amount of fluorous amine was distributed in the FC-72 phase. This tendency is similar to that of fluoruous ether, F-626.4 As expected, chiral fluorous amines 3, which have two phenyl rings, are less fluoruous than 2b; however, the amine (R,S)-3 and the diastereomer (S,S)-3 are distributed mainly in the fluorous phase when acetonitrile is used in the organic phase. Little difference in the partition coefficient is observed between these two diastereomers. It is generally perceived that more than 60% of the fluorine (in weight) is required to show fluorous character.14 However, the results from Table 1 show that by choosing polar organic solvent, fluorous amines 2 and 3 can be recovered from the FC-72 layer.

**Generation of Lithium Enolates with Lithium Amides Derived from Fluorous Amine 1 and 2**

Using fluorous amine 1, our group attempted to generate lithium enolate 9 from cyclohexanone using fluoruous lithium amide 10 (Scheme 4). Fluorous amine 1 was treated with n-butyllithium at −78 °C in THF giving fluoruous lithium amide 10. Cyclohexanone was added to the lithium amide solution at −78 °C. After quenching the reaction mixture with chlorotrimethylsilane, the resulting mixture was subjected to aqueous workup using hexane and aqueous NaHCO₃. After drying and concentration of the hexane phase, biphasic treatment of the crude mixture with benzene and perfluorohexane (FC-72) was carried out. The product, 1-trimethylsiloxyxycyclohexene (11), was obtained in 49% yield from the benzene solution, whereas 88% of fluoruous amine 1 was recovered from the FC-72 solution. We found that the 1H NMR spectrum of the recovered fluoruous amine contained small signals assigned to olefinic protons bearing spin coupling with fluorine (δ = 5.69, and double-triplet, J_H,F(trans) = 33.9 Hz and J_C,H = 8.0 Hz), suggesting the occurrence of an intramolecular proton abstraction pathway under the reaction conditions (Scheme 4).
The observation of a partial decomposition of 1 led to the use of fluorous amines 2a and 2b in which a benzene ring had been inserted between the perfluoroctyl chain and the amine moiety to eliminate a self-decomposition pathway. When fluorous amine 2b was exposed to the same reaction conditions as fluorous amine 1, we obtained the desired enol silyl ether 11 in 92% yield from the cyclohexane phase (Scheme 5, Procedure A). Quantitative recovery of 2b from the FC-72 phase was also achieved. We also examined separation using silica gel chromatography (Procedure B), which also worked well. The results of the synthesis of enol silyl ethers from a variety of cyclic ketones using fluorous amine 2a and 2b are summarized in Table 2.

Both 2a and 2b were found to serve as effective fluorous lithium amide precursors, which effectively generated lithium enolates from ketones. Quenching the enolates with chlorotrimethylsilane gave enol silyl ethers 11–16 in good to high yields. Due to the less fluorous character, the organic/fluorous biphasic treatment (Procedure A) for recovery of fluorous amine 2a from the product was not necessarily satisfactory (92%, Table 2, entry 1). However, the use of column chromatography on silica gel (Procedure B) resulted in nearly quantitative recovery of 2a (entry 2). On the other hand, fluorous amine 2b bearing a perfluorodecyl chain gave satisfactory results both in yield of the product and in the recovery of the amine even for the liquid/liquid workup (entries 3 and 4). Reaction with 2-methylcyclohexanone gave the kinetically formed enolate (entry 9) exclusively, demonstrating that fluorous

<table>
<thead>
<tr>
<th>Fluorous amine</th>
<th>FC-72/cyclohexane</th>
<th>FC-72/C₆H₆</th>
<th>FC-72/acetone</th>
<th>FC-72/MeOH</th>
<th>FC-72/MeCN</th>
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<tr>
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<td>57/43</td>
<td>58/42</td>
<td>67/33</td>
<td>93/7</td>
<td>56</td>
</tr>
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<td>66/34</td>
<td>80/20</td>
<td>90/10</td>
<td>97/3</td>
<td>59</td>
</tr>
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<td>–c</td>
<td>–c</td>
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</table>

\( ^{a} \) Measured at 23 ± 3 °C. Average of two runs. To a biphasic mixture of organic solvent (3 mL) and FC-72 (3 mL) was added fluorous amine (300 mg), and the mixture was stirred vigorously for 30 min. After standing for 5 min, the two layers were separated and evaporated, then weighed.

\( ^{b} \) Percent fluorine by molecular weight.

\( ^{c} \) Not determined.
lithium amide generated from amine 2b has the same selectivity as LDA.15 As shown in Table 2, a variety of enol silyl ethers were prepared in excellent yields using lithium amide derived from fluorous amine 2b and n-butyllithium, with excellent recovery of 2b in an essentially pure form.

Scheme 6 outlines the model recycling study. After obtaining 14 (entry 9), fluorous amine 2b recovered by Procedure B was dried under reduced pressure for six hours and subjected to use for the next reaction. The second reaction afforded enol silyl ether 14 in 88% yield after isolation by silica gel column chromatography (entry 10). The amine 2b was recovered in 97% yield from the reaction mixture of the second run. In summary, fluorous lithium amide derived from perfluorodecyl substituted amine 2b and n-butyllithium is a useful substitute for LDA in the generation of lithium enolates; also, it can be recovered easily and reused for the next reaction.

Preparation of Chiral Fluorous Amines: (R)-2-(4-Perfluorodecylphenyl)ethyl-2-propylamine [(R)-2b] and [1-(4-Perfluorodecylphenyl)ethyl](1-phenethyl)amine (3)

Based on the pioneering efforts of two research groups, Koga16 and Simpkins, 17 asymmetric deprotonation of prochiral ketones using chiral lithium amide bases has been pursued by many researchers.9,10 Having successful results with achiral fluorous lithium amides derived from 2a and 2b, our group advanced our fluorous LDA chemistry to synthesize chiral fluorous amine (R)-2b, the R-
enantiomer of 2b, with the hope of using the amine in the enantioselective formation of lithium enolates. (R)-2b was prepared by the fractional crystallization of a racemic mixture of amine 2b with (R)-tartaric acid. (R)-Tartaric acid salt of the racemic amine 2b was recrystallized three times from ethanol to give pure (R)-2b (>99% ee). The absolute configuration of (R)-2b was determined to be R by comparison of its CD spectrum with that of chiral phenethylamine.18 R-Configuration of amine (R)-2b was also supported by its specific rotation: reported S-enantiomer of 2-phenethyl-2-propylamine (S)-17 (Figure 1), the parent compound of fluorous amine (R)-2b, showed a specific rotation of −59.7 (levorotatory),19 while the chiral amine (R)-2b provided a specific rotation of +14.0 (dextrorotatory).

A set of fluorous chiral amines 3 bearing two chiral centers were prepared to provide a larger asymmetric environment than amine (R)-2b. Fluorous amines (R)-2b and 3 are fluoruous derivatives of chiral amines 17 and 18 (Figure 1), respectively. These ‘parent’ amines, made popular by Simpkins,17b are still important chiral bases for enantioselective deprotonation of ketones. The synthetic pathway toward chiral fluoruous amines 3 is summarized in Scheme 7. 1-(4-Perfluorodecylphenyl)ethyl bromide (8b)

### Table 2 Preparation of Enol Silyl Ethers Using Fluorous Lithium Amide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Amine</th>
<th>Workup</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Recovery of amine (%)</th>
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<td>C</td>
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</table>

*Procedure A: biphasic workup using cyclohexane as the organic solvent. Procedure B: silica gel column chromatography using hexane to give the products, then using methanol to recover fluoruous amine. Procedure C: biphasic workup using acetonitrile as the organic solvent.*

b Determined by 1H NMR spectroscopy.

c 1-Trimethylsiloxy-2-methylcyclohex-1-ene (thermodynamically stable enolate) was obtained in less than 1% yield.

d Second run of entry 9 using recovered amine 2b.

![Figure 1](image-url)  Chiral amines (R)-2b, (S)-17, (R,R)-18, and (S,S)-18
was treated with (S)-phenethylamine to give an R,S- and S,S-mixture of amine 3, which was separated by column chromatography on silica gel, affording (R,S)-3 and (S,S)-3. The fluorous amines, (R,R)-3 and (S,R)-3, were prepared by a similar procedure starting from 8b and (R)-phenethylamine.

The absolute configurations of chiral amines 3 were determined by comparison of their specific rotations relative to those of the parent amines. Parent amines 18 with R,R or S,S configuration have specific rotations of +167.6 (dextrorotatory) or –168 (levorotatory), respectively, while R,S-amine shows no optical activity, since the amine is a meso compound. Since the perfluoroalkyl chain of the fluorous amines 3 is located far from the chiral center, it was expected that the fluorous ponytail attached to the para position of the benzene ring might exert a bit of influence on the specific rotations. Chiral amines with very small rotations were assigned to meso-related compounds, (R,S)-3 and (S,R)-3. Chiral fluorous amine with a specific rotation of +61.5 was derived from (R)-phenethylamine, and was determined to be (R,R)-3. That with –61.9 of rotation was derived from (S)-phenethylamine, and was determined to be (S,S)-3. As mentioned above, the parent amine 18 with R,R-configuration was dextrorotatory, while that with S,S-configuration was levorotatory. Thus, we concluded that the prepared fluorous amines with specific rotations of +3.6, –61.9, +61.5, and –3.5 can be assigned the R,S-, S,S-, R,R-, and S,R-configurations, respectively.

Because of a single fluoruous chain, C2 symmetry was lost and therefore two geometries are available in the lithiation step for chiral lithium amides derived from (R,R)-3. Our group constructed a model of transition states for the stereoselective lithiation. Predicted molecular structures of the transition states for generating S-lithium enolate of 4-methylcyclohexane are shown in Figure 2. The remote fluoruous group would have essentially no effect on the stereoselectivity of the lithiations involving the chiral amines, affording the same configuration of lithium enolate in either case.

**Enantioselective Generation of Lithium Enolates with Lithium Amides Derived from Chiral Fluorous Amines**

Generation of chiral lithium enolate of 4-tert-butylcyclohexane using fluoruous amines (R)-2b and 3 has been accomplished. The conditions employed for (R)-2b were similar to those for the reaction using fluoruous amine 2. Since chiral fluorous amines 3 precipitated below –50 °C in THF, the fluorous lithium amides had to be prepared from 3 and n-butyllithium at –40 °C, then the resulting amide solution was cooled to –78 °C, and reacted with ketones. The results of the enantioselective reaction involving fluorous amine (R)-2b and 3 are listed in Table 3. With the exception of entry 5, which employed a reaction temperature of –94 °C, all reactions for generating chiral lithium enolate using chiral fluorous amines were carried out at –78 °C. Quenching the generated chiral enolates with chlorotrimethylsilane at –78 °C gave the corresponding enol silyl ethers, with enantioselectivities determined by GC equipped with a chiral column (J & W CYCLOSILB).

Fluorous amine (R)-2b gave (S)-19 in approximately 60% ee (Table 3, entries 1 and 2). On the other hand, amine (S,S)-3 gave (R)-19 with much higher enantioselectivity (up to 86% ee) (entries 3 and 4). In each case, the fluorous amines used could be recovered in 92–99% yield using either of two procedures (A: biphasic workup with FC-72 and acetonitrile; B: silica gel chromatography with hex-
ane and EtOAc). Although there was little difference in the recovery efficiency of 3 between these two procedures, a rather tedious extraction with FC-72 had to be repeated five times when procedure A was employed. Lowering the reaction temperature to –94 °C did not improve enantioselectivity of the product (entry 5). As expected, fluorous amine (R,R)-3 afforded S-enolate as the major product (entry 6), while the ‘meso-type’ amine (R,S)-3 and (S,R)-3 gave R- and S-enolate, respectively, in much lower enantioselectivity (entries 7 and 8). Table 3 also demonstrates that lithium enolates of cyclohexanone derivatives with various substituents at the 4-position were prepared by a similar protocol (entries 9–11). These results are comparable to those reported in the previous work, in which (R,R)-18 was used to obtain (S)-19 in 87% ee.16b

Table 3 Enantioselective Silylation Using Chiral Fluorous Amine

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Amine</th>
<th>Workup&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Configuration of product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Recovery of amine (%)</th>
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<td>B</td>
<td>S</td>
<td>86</td>
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<td>74</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>(S,S)-3</td>
<td>B</td>
<td>R</td>
<td>75</td>
<td>76</td>
<td>99</td>
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<tr>
<td>11</td>
<td>Ph</td>
<td>(S,S)-3</td>
<td>B</td>
<td>R</td>
<td>86</td>
<td>90</td>
<td>99</td>
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</tbody>
</table>

<sup>a</sup>Procedure A: biphasic workup using acetonitrile as the organic solvent. Procedure B: silica gel column chromatography using hexane to give the products, then using ethyl acetate to recover fluorous amine.

<sup>b</sup>Determined by comparison of specific rotations with the reported data.16b

<sup>c</sup>Determined by GC attached with a J & W CYCLOSILB chiral column.

<sup>d</sup>Carried out at –94 °C.
Our group performed the preparation of lithium enolate using recovered fluorous chiral amines \((R)-2b\) and \((S,S)-3\). Recycling of the amine was carried out using procedure B (silica gel, hexane and ethyl acetate). As shown in Table 4, the yields and enantioselectivities of reactions using recovered amines were almost identical to those of the first run, indicating that fluorous amine \((R)-2b\) and \((S,S)-3\) can be recycled without any loss of the ability to form enantioselective enolates.

### Conclusions

A series of diisopropylamine derivatives bearing a perfluorooctyl or perfluorodecyl chain (fluorous ponytail) were prepared and considered for use in the generation of lithium enolates. Although fluorous amine 1, in which a perfluorooctyloctyl chain is attached to a diisopropylamine core, suffers from decomposition of the corresponding lithium amide 10 at \(-78^\circ C\), the fluorous-tagged \(\alpha\)-phenylethylamines 2a and 2b can nevertheless be used for the efficient generation of lithium enolates. These amines can be recovered almost quantitatively by liquid/liquid (organic/fluous) or liquid/solid (organic/SiO\(_2\)) extraction, and reused for the next reaction. Chiral fluorous amines \((R)-2b\), \((S,S)-3\), and \((R,R)-3\) were prepared and used for asymmetric deprotonation of ketones. These amines afford similar performance in asymmetric reactions as non-fluous mother compounds. Again, the fluorous chiral amines can be separated effectively by the two kinds of workup procedures and reused without any loss of both optical and isolated yields of enol silyl ethers. It was demonstrated that fluorous ponytails attached to the benzene ring can survive under strong basic conditions using \(n\)-butyllithium at \(-78^\circ C\). Thus, fluorous substitutes of secondary amines have proven useful even for lithium enolate formation.

Melting points were obtained with a Yanako micro melting point apparatus and are not corrected. Products were purified by flash chromatography on silica gel (Kanto Chemical Co., Inc., Silica Gel 60N, 70–230 mesh). \(^1H\) NMR spectra were recorded with either a JEOL JMN ECP-500 (500 MHz) or an EX-270 (270 MHz) spectrometer in CDCl\(_3\) or C\(_6\)D\(_6\). Chemical shifts were reported in parts per million (\(\delta\) downfield from internal TMS at 0.00 ppm). \(^13C\) NMR spectra were recorded with either a JEOL JMN ECP-500 (125 MHz) or an EX-270 (68 MHz) spectrometer in CDCl\(_3\), and referenced to the solvent peak at 77.00 ppm. \(^19F\) NMR spectra were recorded with a JEOL JMN ECP-500 (471 MHz) spectrometer and referenced to external CFCl\(_3\) at 0.00 ppm. IR spectra were obtained on a JASCO FT/IR 4100 spectrometer; absorptions are reported in reciprocal centimeters. Both conventional and high-resolution mass spectra were recorded with a JEOL MS-700 spectrometer. Determination of enantiomeric purity was accomplished by analytical GC using a SHIMADZU GC-14A; column: J & W CYCLOSILB (ID: 0.25 mm, length: 30 m, film: 0.25 \(\mu\)m), temperature program: 60 °C for 6 min, then 60 °C to 250 °C at 20 °C/min. Optical rotations were measured with a JASCO DIP-370 polarimeter. All enol silyl ethers prepared in this study are known compounds: 11, 12, 13, 14, 15, 16, 17, 18, 19, 20; their spectral data are in agreement with the literature.

### Table 4 Enantioselective Silylation with Recycling Chiral Fluorous Amine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Run</th>
<th>Configuration of product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Recovery of amine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>((R)-2b)</td>
<td>1st</td>
<td>(S)</td>
<td>86</td>
<td>60</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>((R)-2b)</td>
<td>2nd</td>
<td>(S)</td>
<td>85</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>((S,S)-3)</td>
<td>1st</td>
<td>(R)</td>
<td>75</td>
<td>82</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>((S,S)-3)</td>
<td>2nd</td>
<td>(R)</td>
<td>76</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>((S,S)-3)</td>
<td>3rd</td>
<td>(R)</td>
<td>76</td>
<td>84</td>
<td>99</td>
</tr>
</tbody>
</table>

\(^a\) Workup procedure: silica gel column chromatography using hexane to give the products, then using ethyl acetate to recover fluorous amine.

\(^b\) Determined by comparison of specific rotations with the reported data. 16

\(^c\) Determined by GC attached with a J & W CYCLOSILB chiral column.
1H NMR (270 MHz, CDCl3): \(\delta = 1.03 - 1.11\) (m, 9 H, 3 CH3), 1.29 (br s, 1 H, NH), 1.60 – 1.84 (m, 2 H, CH2CH2CF3), 2.04 – 2.42 (m, 2 H, CH2CH2CF3), 2.79 [m, 1 H, CH(CH3)2], 2.92 (1 H, CHCH3).

13C NMR (68 MHz, CDCl3): \(\delta = 20.81, 23.13, 23.73, 27.45\), \(I_{298} = 22.4\) Hz, CH2CH2CF3), 27.62, 45.37, 49.01, 110.65 – 119.19 (CF2CF3).

HRMS-EI: \(m/z\) calcld for C14H17F23N [M – H]⁺: 532.0933; found: 532.0905.

**1-Ethyl-4-perfluorodecylbenzene (7b)**

A mixture of 1-ethyl-4-iodobenzene (6.90 g, 29.7 mmol), perfluorodecyl iodide (21.1 g, 32.7 mmol), copper powder (300 mesh, 6.23 g, 98.0 mmol), 2,2′-dipyrindil (0.93 g, 5.94 mmol), and DMSO (50 mL) was heated to 120 °C under N2 for 2 days. After cooling to r.t., H2O (100 mL) and Et2O (100 mL) were added, and the mixture was filtered through a pad of Celite. The insoluble solid on the pad was washed with Et2O (150 mL). The organic layer of the filtrate was separated, washed with H2O (2 × 100 mL), dried (MgSO4), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane) to yield 7b (14.3 g, 77%) as white crystals; mp 65.8 – 67.0 °C.

IR (KBr): 2980, 2925, 2865, 1615, 1445, 1420, 1370, 1340, 1310, 1285, 1245, 1205, 1150, 1110, 1095, 1055, 1020, 975, 880, 835, 770, 655, 555, 530 cm⁻¹.

HRMS-EI: \(m/z\) calcld for C14H17F23N [M – H]⁺: 532.0933; found: 532.0905.

**1-Ethyl-4-perfluorooctylbenzene (7a)**

1-Ethyl-4-perfluoroethylbenzene was prepared in a manner similar to that described for 1-ethyl-4-perfluorodecylbenzene (7b); colorless oil.

IR (neat): 2930, 2855, 1620, 1515, 1460, 1420, 1370, 1300, 1245, 1210, 1150, 1115, 1090, 1050, 1030, 1015, 960, 940, 920, 870, 835, 725, 705, 655 cm⁻¹.

1H NMR (500 MHz, CDCl3): \(\delta = 1.26\) (t, J = 7.5 Hz, 3 H, CH3), 2.71 (q, J = 7.5 Hz, 2 H, CH2), 7.33 (d, J = 8.2 Hz, 2 H, ArH), 7.50 (d, J = 8.2 Hz, 2 H, ArH).

13C NMR (125 MHz, CDCl3): \(\delta = 15.00, 28.70, 105–120\) (CF2CF3).

HRMS-EI: \(m/z\) calcld for C14H17F23N [M – H]⁺: 524.0369; found: 524.0352.

**1-(Bromoethyl)-4-perfluorooctylbenzene (8a)**

The title compound 8a was prepared in a manner similar to that described for 8b; colorless oil.

IR (neat): 2990, 2920, 2855, 1615, 1510, 1445, 1420, 1370, 1330, 1300, 1200, 1150, 1115, 1090, 1040, 960, 945, 845, 820, 705, 680, 660, 595, 560, 530 cm⁻¹.

1H NMR (500 MHz, CDCl3): \(\delta = 2.06\) (d, J = 6.8 Hz, 3 H, CH3), 5.21 (q, J = 6.8 Hz, 1 H, CHBr), 7.54–7.61 (m, 4 H, ArH).

13C NMR (125 MHz, CDCl3): \(\delta = 26.45, 47.24, 108–119\) (CF2CF3).


**1-(4-Perfluorodecylphenyl)ethylisopropylamine (2b)**

Compound 2b (14.1 g, 20.0 mmol), i-PrNH2 (3.76 g, 64.0 mmol), K2CO3 (2.77 g, 20.0 mmol), and MeCN (200 mL) were placed in a 500 mL stainless steel autoclave together with a magnetic stirring bar. The autoclave was closed and heated at 80 °C for 4 days. After cooling, the mixture was diluted with Et2O (300 mL) and filtered. H2O (500 mL) was then added to the filtrate. The aqueous layer was separated and extracted with Et2O (3 × 200 mL). The combined organic layers were dried (MgSO4) and evaporated under reduced pressure. The residue was distilled under reduced pressure (110 °C/2 mmHg) to yield racemic fluorous amine 2b (10.9 g, 64%) as white crystals. Retention time \(t_R\) in the GC-14A with the chiral column (130 °C isothermal); (S): \(t_R = 37.9\) min, (R): \(t_R = 38.8\) min.

**Fractional Crystallization of Fluorous Amine 2b**

Racemic fluorous amine 2b (3.70 g, 5.43 mmol) and \((R)-\)tartric acid (818 mg, 5.43 mmol) were dissolved in EtOH (40 mL) under reflux, then allowed to stand at r.t. for 12 h. The separated white solid was collected by filtration and subjected to a second recrystallization. After a third recrystallization, the solid was partitioned between 10%aq NaOH (20 mL) and Et2O (20 mL). The aqueous layer was separated and extracted with Et2O (3 × 20 mL). The combined organic layers were dried (MgSO4) and evaporated under reduced pressure to yield \((R)-2b\), the \((R)-\)enantiomer of 2b (296 mg, 99% ee).

\[(R)-1-(4-Perfluorodecylphenyl)ethylisopropylamine [(R)-2b] \]

Mp 48.0–49.0 °C; [\(\alpha\)D]20 +14.0 (c 5.5, CHCl3).

IR (KBr): 640, 770, 840, 880, 980, 1020, 1060, 1200, 1340, 1380, 1620, 2980 cm⁻¹.

1H NMR (500 MHz, CDCl3): \(\delta = 1.00\) (d, J = 6.4 Hz, 6 H, CH(CH3)2), 1.33 (d, J = 6.5 Hz, 3 H, CHCH3), 2.61 (sept, J = 6.4 Hz, 1 H, CH(CH3)2), 3.96 (q, J = 6.5 Hz, 1 H, CH2CH3), 7.43 (d, J = 8.3 Hz, 2 H, ArH), 7.52 (d, J = 8.3 Hz, 2 H, ArH).

13C NMR (125 MHz, CDCl3): \(\delta = 22.12, 23.80, 24.68, 45.94, 55.01, 105–120\) (CF2CF3).


**1-(4-Perfluorooctylphenyl)ethylisopropylamine (2a)**

The title compound 2a was prepared in a manner similar to that described for 2b.

Bp 100–105 °C/3 mmHg.

IR (neat): 1200, 1510, 2860, 2925, 2950, 3310 cm⁻¹.
1H NMR (500 MHz, CDCl3): δ = 1.03 [d, J = 5.9 Hz, 6 H, CH(CH3)2], 1.23–1.34 (d, J = 6.2 Hz, 3 H, CH2CH3), 2.60–2.62 [m, 1 H, CHCH3], 3.97 [q, J = 6.2 Hz, 1 H, CH2CH3], 7.44–7.46 (m, 2 H, ArH), 7.53–7.55 (m, 2 H, ArH).

13C NMR (125 MHz, CDCl3): δ = 21.37, 23.94, 24.37, 45.86, 54.90, 108.88–110.30 (CF3), 126.73–126.97 (Ar), 150.81.


HRMS-EI: \[ (M+) = 581.00, 566.86, 523.46, 508.40, 493.40. \]

HRMS-EI: \[ (M+) = 743.1066. \]

A mixture of 8b (15.7 g, 22.4 mmol), (S)-(−)-1-phenylethylamine (2.74 g, 22.6 mmol), K2CO3 (3.09 g, 22.4 mmol), and MeCN (80 mL) was heated under reflux for 1 day. The mixture was evaporated under reduced pressure. Et2O (80 mL) and hexane (80 mL) were added to the residue and the azeotropic layer was separated and then extracted with Et2O (3 × 80 mL). The combined organic layers were dried with MgSO4 and evaporated under reduced pressure to yield the crude mixture. The crude mixture was purified by column chromatography on silica gel (hexane to EtOAc) to afford an 89:1 mixture. The crude mixture was purified by column chromatography on silica gel (hexane:Et2O:O2, 8:2:2) affording (R,S)-3 (1.96 g, 98% ee) and (S,S)-3 (1.78 g, 99% ee); retention time (tR) in the GC-18A; (R,S)-3: tR = 16.16 min, (S,S)-3: tR = 16.03 min.

Fluorous Amines

A mixture of 3 (5.6 g, 22.4 mmol), (S)-(−)-1-phenylethylamine in a manner similar to that described for (R,S)-3 and (S,S)-3.

Isolation of Silyl Enol Ether 20 by Column Chromatography; Typical Procedure

To a solution of amine (825 mg, 92% recovery), while the MeCN layer was diluted with MeCN (20 mL), and perfluorohexanes (FC-72, 20 mL) were added; the aqueous layer was separated and extracted with hexane (2 × 30 mL). The combined organic layers were dried (MgSO4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluents: hexane:EtOAc) to yield (R)-4-methyl-1-trifluoromethylbicyclohexene (20): 136 mg, 74%, 85%ee) and the fluoruous amine (S,S)-3 (884.2 mg, 99% recovery).

Preparation of Enol Silyl Ether 19 Using Organic/Fluorous Biphasic Workup; Typical Procedure

To a solution of amine (S,S)-3 (898.9 mg, 1.21 mmol) and LiCl (26.5 mg, 0.63 mmol) in anhyd THF (15 mL) was added n-BuLi (0.95 mL, 1.50 mmol, 1.60 M in hexane) dropwise under N2 at –40 °C. The resulting yellowish solution was then cooled to –78 °C and 4-methylcyclohexanone (112.2 mg, 1.00 mmol) in anhyd THF (5 mL) was added dropwise. After 30 min, chlorotrimethylsilane (133.5 mg, 1.23 mmol) was added dropwise and the mixture was warmed slowly to r.t. Then, sat. aq NaHCO3 (20 mL) and hexane (30 mL) were added; the aqueous layer was separated and extracted with hexane (2 × 30 mL). The combined organic layers were dried (MgSO4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluents: hexane:EtOAc) to yield (R)-4-methyl-1-trifluoromethylbicyclohexene (20): 136 mg, 74%, 85%ee) and the fluoruous amine (S,S)-3 (884.2 mg, 99% recovery).

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References

(20) These structures were optimized by MIMM using Spartan 04 with freezing geometries around lithium.