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著者	Matsubara Hiroshi, Maeda Louis, Sugiyama Hiroyuki, Ryu Ilhyong
journal or publication title	Synthesis
volume	2007
number	18
page range	2901-2912
year	2007-09
権利	(C) 2007 Georg Thieme Verlag
その他のタイトル	フルオラス鎖を有するキラルおよびアキラルなリチウムアミド類 : 再利用可能なリチウムエノラート発生剤の合成と利用
URL	http://hdl.handle.net/10466/14995

doi: 10.1055/s-2007-983877

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-butyl lithium. 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 non-fluorous chiral lithium amides. These reusable fluorous amines can be easily recovered by liquid-liquid extraction or chromatographic separation.

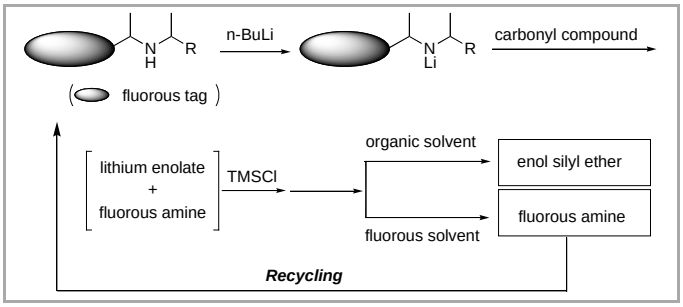
Key words: fluorous, chiral amine, enolate, LDA, asymmetric deprotonation, recycling

1 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 pony tails) 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 fluorous reaction media as well as effective fluorous reagents and catalysts. To this end, our group recently reported fluorous versions of ether and DMF that function as easily recyclable reaction media.[4,5] This group has also established phase-vanishing methods based on the use of fluorous solvents as a liquid membrane, which permits transport of reagents and regulates the reactions in triphasic and quadraphasic.[6]

Needless to say, lithium diisopropylamide (LDA)[7] and its analogs 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 transmetallations 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 diisopopylamine 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 fluorous-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 fluorous ponytail on the benzene ring worked equally well with non-fluorous reagents and were easily recovered and recycled.



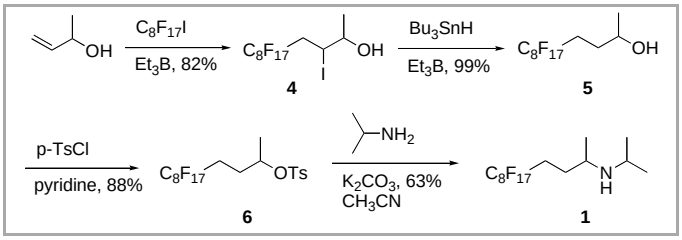
Scheme 1 Concept of recycling fluorous amines acting as fluorous LDA precursors by FBS

2 Results and Discussion

2.1 Preparation and properties of fluorous amines: (5-perfluorooctyl-2-pentyl)-2-propylamine

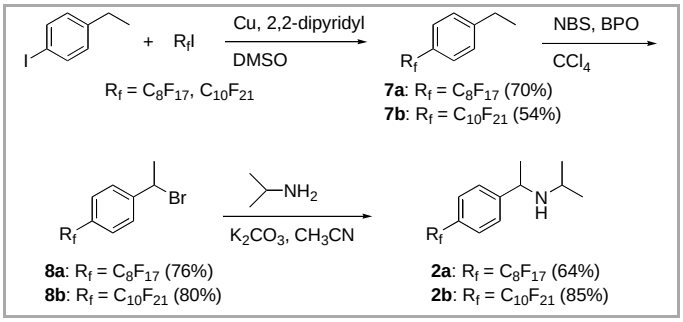
(1) and 2-(4-perfluoroalkylphenyl)ethyl-2-propylamine (2)

We started our fluorous LDA project by preparing fluorous amine **1** where a perfluorooctyl chain is attached to a diisopropylamine core as a ponytail in order to acquire a light fluorous character. Fluorous amine **1** was synthesized according to the procedure outlined in Scheme 2. Thus, perfluorooctyl iodide was treated with 3-buten-2-ol under radical conditions to give 3-iodo-4-perfluorooctyl-2-butanol (**4**) in 82 %, whose iodine was removed by tin hydride reduction to give 4-perfluorooctyl-2-butanol (**5**). Butanol **5** was then converted to 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[11] 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.



Scheme 2

We also prepared α-phenethyl type fluorous amines **2a** and **2b**, whose synthetic pathway is shown in Scheme 3. Perfluorooctyl iodide was treated with 4-iodoethylbenzene in the presence of copper[12] to give 4-perfluorooctyl-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 fluorous amine **2a** in 64% yield. Fluorous amine **2a** is a pale yellow, viscous liquid with a boiling point of 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.



Scheme 3

Table 1 Partition Coefficient of Fluorous Amines Prepared for this Study[a]

	FC-72/cyclohexane	FC-72/C_6H_6	FC-72/acetone	FC-72/MeOH	FC-72/CH_3CN	% F [b]
1	87 : 13	82 : 18	— [c]	— [c]	— [c]	61
2a	59 : 41	47 : 43	58 : 42	67 : 33	93 : 7	56
2b	77 : 23	66 : 34	80 : 20	90 : 10	97 : 3	59
3-RS	47 : 53	— [c]	— [c]	63 : 37	86 : 14	54
3-SS	40 : 60	— [c]	— [c]	66 : 34	73 : 27	54

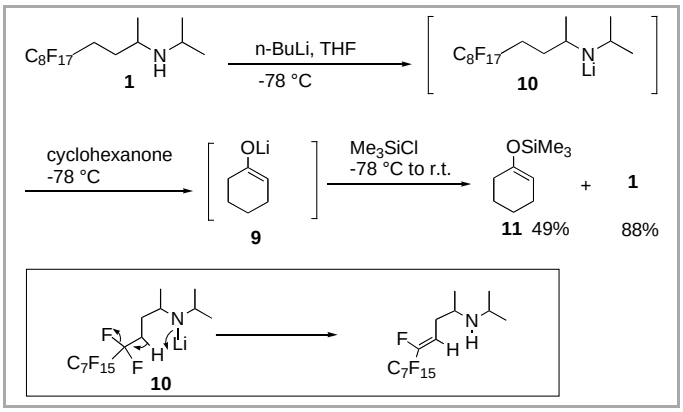
[a] Measured at 23 ± 3 °C. Average of two runs. To a biphasic mixture of organic solvent (3 mL) and FC-72 (3 mL), fluorous amine (300 mg) was added, and the mixture was stirred vigorously for 30 min. After standing for 5 min, the two layers were separated and evaporated, then weighed. [b] Percent fluorine by molecular weight. [c] Not determined.

Fluorous compounds having perfluorooctyl 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 method[13] and listed in Table 1. Table 1 also lists partition coefficients of chiral fluorous amines, **3-RS** and **3-SS**, the preparation of which is referred to in Section 2.3.

When fluorous amine **1** was treated with a 1: 1 mixture of FC-72 and cyclohexane, some 80% of fuorous 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 fluorous ether, F-626.[4] As expected, chiral fluorous amines **3**, which have two phenyl rings, are less fluorous than **2b**; however, the amine **3-RS** and the diastereomer **3-SS** 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 of Table 1 show that by choosing polar organic solvent, fluorous amines **2** and **3** can be recovered from the FC-72 layer.

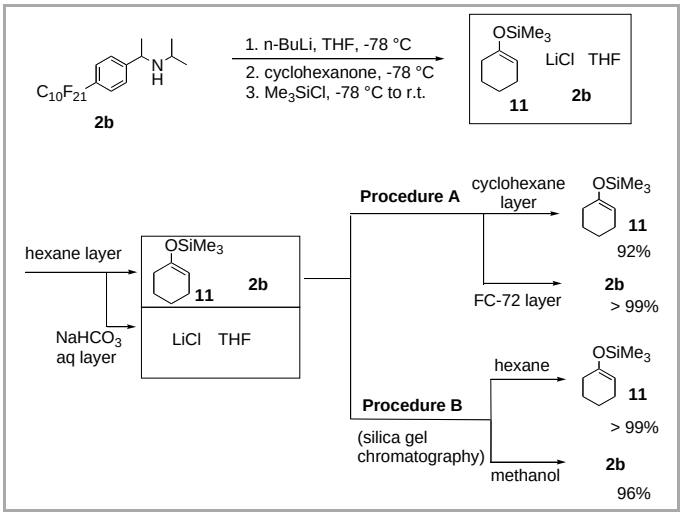
2.2 Generation of lithium enolates with lithium amides derived from fluorous amine 1 and 2

Using fluorous amine **1**, our group attempted to generate lithium enolate **9** from cyclohexanone using fluorous lithium amide **10** (Scheme 4). Fluorous amine **1** was treated with n-butyl lithium at -78 °C in THF giving fluorous 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 $NaHCO_3$. After drying and concentration in the hexane phase, biphasic treatment of the crude mixture with benzene and perfluorohexane (FC-72) was carried out. The product, 1-trimethylsiloxycyclohexene (**11**), was obtained in 49% yield from the benzene solution, whereas 88% of fluorous amine **1** was recovered from the FC-72 solution. We found that the ^{1}H-NMR spectrum of the recovered fluorous 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).



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 perfluorooctyl 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.

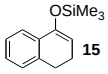
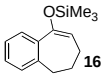


Scheme 5

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%, 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 per-

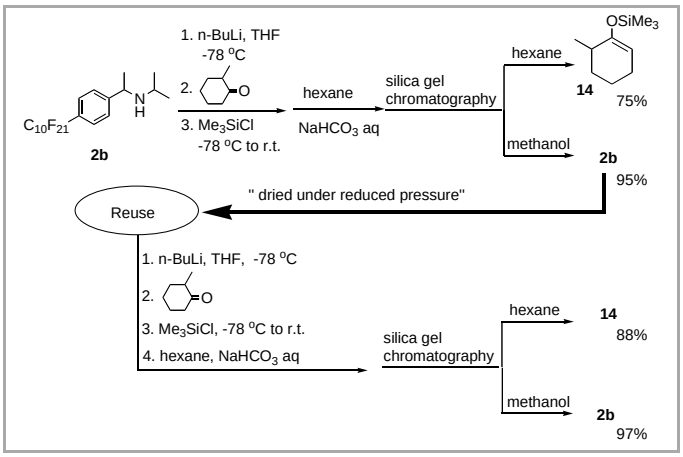
fluorodecyl chain gave satisfactory results both in yield of the product and in the recovery of the amine even for the liquid/liquid workup (entries 3 and 4). Reaction with 2-methylcyclohexanone gave the kinetically formed enolate (entry 9) exclusively, demonstrating that fluorous lithium amide generated 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-butyl lithium, with excellent recovery of **2b** in an essentially pure form.

Table 2 Preparation of Enol Silyl Ethers Using Fluorous Lithium Amide

Entry	Substrate	Amine	Workup[a]	Product	Yield (%)	Recovery of amine (%)
1		**2a**	A	 **11**	89[b]	92
2		**2a**	B		71	98
3		**2b**	A		92	>99
4		**2b**	B		>99	96
5		**2a**	B	 **12**	76	>99
6		**2b**	A		99	>99
7		**2b**	B		>99	>99
8		**2b**	B	 **13**	96	>99
9		**2b**	B	 **14**	75[c]	95
10[d]		**2b**	B		88[c]	97
10		**2b**	A	 **15**	>99	>99
11		**2b**	B		>99	97
12		**2b**	C		96	>99
13		**2b**	A	 **16**	92	99
14		**2b**	B		>99	>99
15		**2b**	C		89	97

[a]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 fluorous amine. Procedure C: biphasic workup using acetonitrile as the organic solvent. [b]Deteremined by 1H-NMR. [c]1-Trimethylsiloxy-2-methyl-1-cyclohexene (thermodynamically stable enolate) was obtained in less than 1% yield. [d]2nd run of entry 9 using recovered amine **2b**.

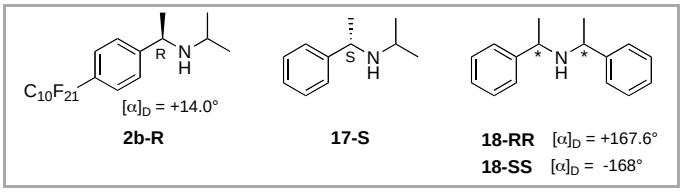
Scheme 6 outlined the model recycling study. After obtaining **14** (entry 9), fluorous amine **2b** recovered by Procedure B was dried under reduced pressure for six hours and subjected to use for the next reaction. The second reaction afforded enol silyl ether **14** in 88% yield after isolation by 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-butyl lithium is a useful substitute for LDA in the generation of lithium enolates;also, it can be recovered easily and reused for the next reaction.



Scheme 6

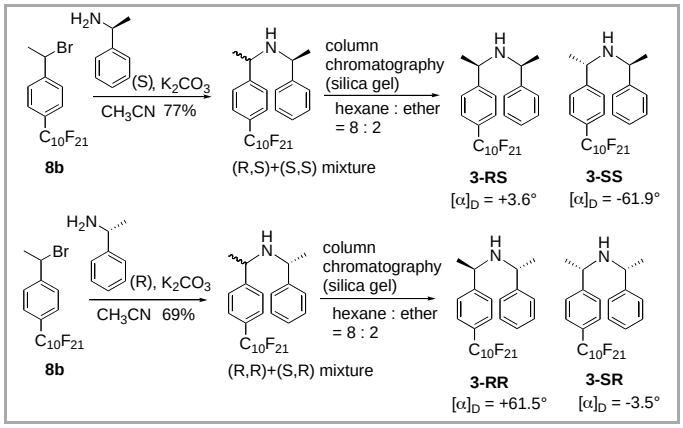
2.3 Preparation of chiral fluorous amines: (R)-2-(4-perfluorodecylphenyl)ethyl-2-propylamine (2b-R) and [1-(4-perfluorodecylphenyl)ethyl](1-phenethyl)amine (3)

Based on the pioneering efforts of two research groups, Koga[16] 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 **2b-R**, R-enantiomer of **2b**, with the hope of using the amine in the enantioselective formation of lithium enolates. **2b-R** 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 **2b-R** (> 99% ee). The absolute configuration of **2b-R** was determined to be (R) by comparison of its CD spectrum to that of chiral phenethylamine.[18] R-configuration of amine **2b-R** was also supported by its specific rotation: reported (S)-enantiomer of 2-phenethyl-2-propylamine (**17-S**), the parent compound of fluorous amine **2b-R**, showing a specific rotation of -59.7°: levorotatory,[19] while the chiral amine **2b-R** provided 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 **2b-R**. Fluorous amines **2b-R** and **3** are fluorous derivatives of chiral amines **17** and **18**, respectively. These "parent" amines, made popular by Simpkins,[17b] are still important chiral bases for enanti-

oselective deprotonation of ketones. The synthetic pathway toward chiral fluorous amines **3** is summarized in Scheme 7. 1-(4-Perfluorodecylphenyl)ethyl bromide (**8b**) was treated with (S)-phenethylamine to give an (R,S) and (S,S) mixture of amine **3**, which was separated with column chromatography on silica gel, affording (R,S)-fluorous-amine **3-RS** and (S,S)-fluorous-amine **3-SS**. (R,R)-fluorous-amine **3-RR** and (S,R)-fluorous-amine **3-SR** were prepared by a similar procedure started from **8b** with (R)-phenethylamine.



Scheme 7

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[20] or -168°: levorotatory,[21] respectively, while (R,S)-amine shows no optical activity,[22] since the amine is a meso compound. Since the perfluoroalkyl chain of the fluorous amines **3** locates 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, **3-RS** and **3-SR**. Chiral fluorous amine with a specific rotation of +61.5° was derived from (R)-phenethylamine, and was determined to be **3-RR**, That with -61.9° of rotation was derived from (S)-phenethylamine, and was determined to be **3-SS**. 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 prepared chiral fluorous amines with specific rotations of +3.6°, -61.9°, +61.5°, and -3.5° were assigned to (R,S)-, (S,S)-, (R,R)-, and (S,R)-configurations, respectively.

Because of a single fluorous chain, *C2* symmetry was lost and therefore two geometries are available in the lithiation step for chiral lithium amides derived from **3-RR**. Our group constructed a model of transition states for the stereoselective lithiation. Predicted molecular structures[23] of the transition states for generating (S)-lithium enolate of 4-methylcyclohexanone are shown in Figure 1. The remote fluorous 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.

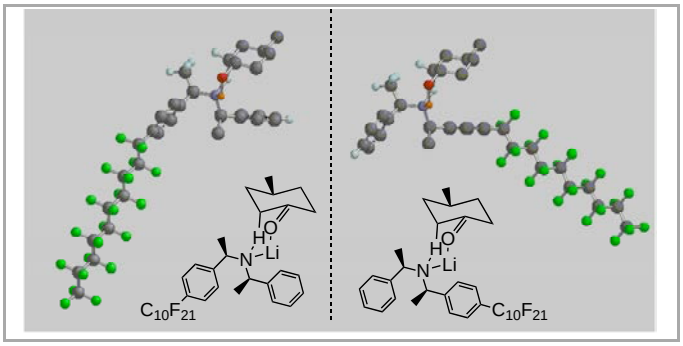


Figure 1 Two possible transition states leading to (S)-lithium enolate of 4-methylcyclohexanone with **3-RR**

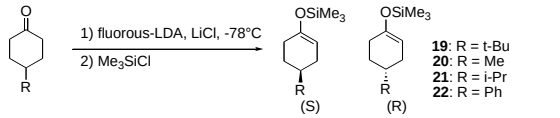
2.4 Enantioselective generation of lithium enolates with lithium amides derived from chiral fluorous amines

Generation of chiral lithium enolate of 4-t-butylcyclohexanone using chiral fluorous amines **2b-R** and **3** was accomplished.[16b] The conditions employed for **2b-R** were similar to those for the reaction using fluorous 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-butyl lithium 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 **2b-R** 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 **2b-R** gave (S)-**19** in approximately 60% ee (entries 1 and 2). On the other hand, amine **3-SS** 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 hexane and AcOEt). 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 **3-RR** afforded (S)-enolate as the major product (entry 6), while the "meso-type" amine **3-RS** and **3-SR** 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 **18-RR** was used to obtain (S)-**19** in 87% ee.[16b]

Table 3 Enantioselective Silylation Using Chiral Fluorous Amine

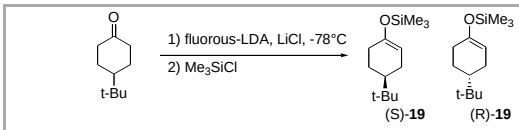


Entry	R	Amine	Workup procedure[a]	Configuration of product[b]	Yield (%)	ee (%)[c]	Recovery of amine (%)
1	t-Bu	**2b-R**	A	S	93	57	99
2	t-Bu	**2b-R**	B	S	86	60	98
3	t-Bu	**3-SS**	A	R	73	83	92
4	t-Bu	**3-SS**	B	R	82	86	95
5[d]	t-Bu	**3-SS**	B	R	66	85	94
6	t-Bu	**3-RR**	B	S	81	83	99
7	t-Bu	**3-RS**	B	R	78	21	95
8	t-Bu	**3-SR**	B	S	70	25	99
9	Me	**3-SS**	B	R	74	85	99
10	i-Pr	**3-SS**	B	R	75	76	99
11	Ph	**3-SS**	B	R	86	90	99

[a]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. [b]Determined by comparison of specific rotations to literature**16b**. [c]Determined by GC attached a J&W CYCLOSILB chiral column. [d]Carried out at -94°C.

Our group performed the preparation of lithium enolate using recovered fluorous chiral amines **2b-R** and **3-SS**. 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 **2b-R** and **3-SS** can be recycled without any loss of the ability to form enantioselective enolates.

Table 4 Enantioselective Silylation with Recycling Chiral Fluorous Amine[a]



Entry	Amine	Run	Configuration of product[b]	Yield (%)	ee (%)[c]	Recovery of amine (%)
1	**2b-R**	1st	S	86	60	98
2	**2b-R**	2nd	S	85	65	95
3	**3-SS**	1st	R	75	82	99
4	**3-SS**	2nd	R	76	84	99
5	**3-SS**	3rd	R	76	84	99

[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 to literature**16b**. [c]Determined by GC attached a J&W CYCLOSILB chiral column.

3 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 perfuluorooctyl chain is attached to a diisopropylamine core, suffers from decomposition of the corresponding lithium amide **10** at -78 °C, the fluorous-tagged α-phenetylamines **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/fluorous) or liquid/solid (organic/SiO_2) extraction, and reused for the next reaction. Chiral fluorous amines **2b-R**, **3-SS** and **3-RR** were prepared and used for asymmetric deprotonation of ketones. These amines afford similar performance in asymmetric reactions as non-fluorous 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-butyl lithium at -78 °C. Thus, fluorous substitutes of secondary amines have proven useful even for lithium enolate formation.

4 Experimental Section

General

Melting points were obtained with a Yanako micro melting point apparatus and not corrected. Products were purified by flash chromatography on silica gel (Kanto

Chemical Co., Inc., Silica Gel 60N, 70-230 mesh). ^{1}H 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_6D_6. Chemical shifts were reported in parts per million (δ) downfield from internal TMS at 0.00. ^{13}C NMR spectra were recorded with either a JEOL JMN ECP-500 (125 MHz) or a EX-270 (68 MHz) spectrometer in $CDCl_3$ and referenced to the solvent peak at 77.00 ppm. ^{19}F NMR spectra were recorded with a JEOL JMN ECP-500 (471 MHz) spectrometer and referenced to external $CFCl_3$ at 0.00 ppm. Coupling constants, *J*, are reported in Hertz(Hz), and splitting patterns are designated as s(singlet), d(doublet), t(triplet), q(quartet), sept(septet), dd(double doublet), and m(multiplet). Infrared 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 μm) and N_2 (100 kPa). Determination of diasteromeric purity and product purity was accomplished by analytical GC using a SHIMADZU GC-18A; column: J&W DB-1 (ID: 0.32 mm, Length: 30 m, Film: 1 μm), N_2 (700 kPa); 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. All enol silyl ethers prepared in this study are known compounds: **11**[24], **12**[25], **13**[25], **14**[26], **15**[27], **16**[28] and **19** – **21**[29]; their spectral data are in agreement with the literature.

Isopropyl(4-perfluoro-2-butyl)amine (1)

Bp 60 - 65 °C (5 mmHg); IR (KBr): 3300, 2950, 2860, 1450, 1375, 1365, 1320, 1240, 1200, 1140, 1105, 1060, 990, 880, 710, 700, 650 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.03-1.11 (m, 9H, CH_3), 1.29 (bs, 1H, NH), 1.60 - 1.84 (m, 2H, $C\underline{H}_2CH_2C_8F_{17}$), 2.04 - 2.42 (m, 2H, $CH_2C_8F_{17}$), 2.79 (m, 1H, $C\underline{H}(CH_3)_2$), 2.92 (m, 1H, $C\underline{H}CH_3$); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.81, 23.13, 23.73, 27.45 (t, $J_{C\text{-}F}$ = 22.4 Hz, $\underline{C}H_2C_8F_{17}$), 27.62, 45.37, 49.01, 110.65-119.19 (C_8F_{17}); HRMS-EI: $[M\text{-}H]^+$ m/z calcd for $C_{15}H_{16}F_{17}N$: 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'-dipyridyl (0.93 g, 5.94 mmol) and DMSO (50 mL), was heated to 120 °C under N_2 for 2 days. After cooling to room temperature, water and ether were added, then the mixture was filtered through a pad of Celite. The insoluble solid on the pad was washed with ether. The organic layer of the filtrate was separated, washed with water, dried over $MgSO_4$, then 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 = 47.0 - 48.0 °C; IR (KBr): 2970, 2930, 1620, 1375, 1245, 1200, 1150, 1115, 1090, 1055, 880, 830, 650, 640, 555, 530 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 2.71 (q, *J* = 7.5 Hz, 2H, CH_2), 7.33 (d, *J* = 8.2 Hz, 2H, ArH), 7.50 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.00, 28.70, 105 - 120 ($C_{10}F_{21}$), 126.44, 126.84, 128.08, 148.35; HRMS-EI: $[M]^+$ m/z calcd for $C_{18}H_9F_{21}$ 624.0369; found: 624.0352.

1-Ethyl-4-perfluorooctylbenzene (7a)

1-Ethyl-4-perfluorooctylbenzene(**7a**) 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}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.3 Hz, 3H, CH_3), 2.72 (q, *J* = 7.3 Hz, 2H, CH_2), 7.33 (d, *J* = 8.2 Hz, 2H, ArH), 7.50 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.08, 28.74, 108-118 (C_8F_{17}), 126.32, 126.86, 128.11, 148.56; HRMS-EI: $[M]^+$ m/z calcd for $C_{16}H_9F_{17}$: 524.0433; found: 524.0449.

1-(1-Bromoethyl)-4-perfluorodecylbenzene (8b)

A mixture of **8b** (14.33 g, 23.0 mmol), *N*-bromosuccinimide (3.88 g, 21.8 mmol), benzoyl peroxide (0.20 g) and carbon tetrachloride (60 mL) was heated under reflux. After 12 h, the hot mixture was filtered using a Büchner funnel with suction. The solid on the funnel was washed with hot carbon tetrachloride. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: hexane) to yield **8b** (15.7 g, 97%) as white crystals.

Mp = 65.8 - 67.0 °C; IR (KBr): 2980, 2925, 2865, 1615, 1445, 1420, 1375, 1340, 1310, 1285, 1245, 1205, 1150, 1110, 1095, 1055, 1020, 975, 880, 835, 770, 655, 640, 555, 530 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06 (d, *J* = 6.8 Hz, 3H, CH_3), 5.20 (q, *J* = 6.8 Hz, 1H, CHBr), 7.56 (m, 4H. ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.47, 47.33, 105 - 120 ($C_{10}F_{21}$), 127.18, 127.41, 129.12, 147.47; HRMS-EI: $[M]^+$ m/z calcd for $C_{18}H_8BrF_{21}$: 701.9474; found: 701.9433.

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

1-(1-Bromoethyl)-4-perfluorooctylbenzene (**8a**) was prepared in a manner similar to that described for 1-(1-Bromoethyl)-4-perfluorodecylbenzene (**8b**).

Colorless oil: IR (KBr): 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, $CDCl_3$): δ = 2.06 (d, *J* = 6.8 Hz, 3H, CH_3), 5.21 (q, *J* = 6.8 Hz, 1H, CHBr), 7.54 - 7.61 (m, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.45, 47.24, 108 – 119 (C_8F_{17}), 127.20, 127.41, 129.11, 147.52;HRMS-EI: $[M]^+$ m/z calcd for $C_{16}H_8BrF_{17}$: 601.9538; found: 601.9555.

[1-(4-Perfluorodecylphenyl)ethyl]isopropylamine (2b)

A magnetic stirring bar, **8b** (14.1 g, 20.0 mmol), isopropylamine (3.76 g, 64.0 mmol), potassium carbonate (2.77 g, 20.0 mmol) and acetonitrile (200 mL) were placed in a 500 mL stainless steel autoclave. The autoclave was closed and heated at 80 ℃ for 4 days. After cooling, the reaction mixture was diluted with ether and filtered. Water (500 mL) was then added to the filtrate. The aqueous layer was separated and extracted with ether. The combined organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. The residue was distilled under reduced pressure (110 °C at 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): t_R(**2b-S**) = 37.9 min, t_R (**2b-R**) = 38.8 min.

Fractional crystallization of fluorous-amine 2b

Racemic fluorous amine **2b** (3.70 g, 5.43 mmol) and (R)-tartaric acid (818 mg, 5.43 mmol) were dissolved in ethanol under reflux, then let stand at room temperature for 12 h. A white solid separate was collected by filtration and subjected to a second recrystallization. After a third recrystallization, the solid was dissolved in 10%-NaOHaq (20 mL) and ether (20 mL). The aqueous layer was separated and then extracted with ether. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to yield (R)-enantiomer of **2b**: **2b-R** (296 mg, 99%ee).

(R)-[1-(4-perfluorodecylphenyl)ethyl]isopropylamine (2b-R)

Mp = 48.0 - 49.0 °C; $[\alpha]_D^{28}$ = +14.0 (c 5.5, $CHCl_3$); IR (KBr): 640, 770, 840, 880, 980, 1020, 1060, 1200, 1340, 1380, 1620, 2980 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.4 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.33 (d, *J* = 6.5 Hz, 3H, $CHC\underline{H}_3$), 2.61 (sept, *J* = 6.4 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.96 (q, *J* = 6.5 Hz, 1H, $C\underline{H}CH_3$), 7.43 (d, *J* = 8.3 Hz, 2H, ArH), 7.52 (d, *J* = 8.3 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.12, 23.80, 24.68, 45.94, 55.01, 105－120 ($C_{10}F_{21}$), 126.73, 126.98, 127.57, 150.97; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -125.99, -122.59, -121.78, -121.63, -121.17, -110.25, -80.62; HRMS-EI: $[M]^+$ m/z calcd for $C_{21}H_{16}F_{21}N$: 681.0947; found: 681.0917.

[1-(4-perfluoroocthylphenyl)ethyl]isopropylamine (**2a**) was prepared in a manner similar to that described for [1-(4-perfluorodecylphenyl)ethyl]isopropylamine (**2b**).

[1-(4-perfluorooctylphenyl)ethyl]isopropylamine (2a)

Bp = 100 – 105 °C (3 mmHg); IR (neat): 1200, 1510, 2860, 2925, 2950, 3310 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, J = 5.9 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.23-1.34 (d, J = 6.2 Hz, 3H, $CHC\underline{H}_3$), 2.60-2.62 (m, 1H, $C\underline{H}(CH_3)_2$), 3.97 (q, J = 6.2 Hz, 1H, $C\underline{H}CH_3$), 7.44-7.46 (m, 2H, ArH), 7.53-7.55 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.37, 23.94, 24.37, 45.86, 54.90, 108.58-118.30 (C_8F_{17}), 126.73-126.97 (Ar), 150.81; MS (EI, 70 eV), m/z (%) 581 (M^+, 5), 566($[M\text{-}CH_3]^+$, 100), 523($[M\text{-}NHCH(CH_3)_2]^+$, 33); HRMS (EI): m/z = $[M]^+$ calcd for $C_{19}H_{16}F_{17}N$: 581.1011; found: 581.1037.

Preparation of fluorous amine 3

A mixture of **8b** (15.7 g, 22.4 mmol), (S)-(-)-1-phenylethylamine (2.74 g, 22.6 mmol), potassium carbonate (3.09 g, 22.4 mmol) and acetonitrile (80 mL) was heated under reflux for 1 day. The reaction mixture evaporated under reduced pressure. Ether and water were added to the residue and the aqueous layer was separated and then extracted with ether. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to yield the crude mixture. The crude mixture was purified by column chromatography on silica gel (eluent: hexane to ethyl acetate) to yield a (S,S) and (R,S) mixture of fluorous amine **3** (12.9 g, 77%). Separation of (S,S) and (R,S) fluorous amine **3** was achieved by column chromatography on silica gel (eluent: hexane/ether = 8/2) affording (R,S)-amine **3-RS** (1.96 g, 98%ee) and (S,S)-amine **3-SS** (1.78 g, 99%ee).

Retention time (t_R) in the GC-18A: t_R (**3-RS**)= 16.16 min, t_R (**3-SS**) = 16.03 min.

(R)-1-(4-perfluorodecylphenyl)ethyl-(S)-1-phenethylamine (3-RS)

Mp = 36.5 - 37.1 ℃; $[\alpha]_D^{26}$ = +3.6 (c 5.2, $CHCl_3$); IR (KBr): 669, 701, 759, 835, 884, 928, 973, 1019, 1089, 1108, 1154, 1216, 1244, 1616, 2869, 2929, 2970, 3020, 3429 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, 3H, *J* = 6.4 Hz, CH_3), 1.36 (d, 3H, *J* = 6.8 Hz, CH_3 (fluorous tail side)), 3.78 (q, 1H, *J* = 6.4 Hz, CH), 3.82 (q, *J* = 6.8 Hz, 1H, CH (fluorous tail side)), 7.15 (m, 1H), 7.23 - 7.25 (m, 4H, ArH), 7.37 (d, *J* = 8.2 Hz, 2H, ArH), 7.48 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.41, 23.43, 55.03, 55.53, 108 - 118 ($C_{10}F_{21}$), 126.61, 126.89, 127.53 (t, $J_{C\text{-}F}$ = 23.9 Hz, $\underline{C}$(Ar)-CF_2), 128.45, 145.64, 150.51; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -126.55, -123.03, -122.19, -122.00, -121.86, -121.46, -110.60, -81.40; HRMS-EI: $[M]^+$ m/z calcd for $C_{26}H_{18}F_{21}N$: 743.1104; found: 743.1066.

(S)-1-(4-perfluorodecylphenyl)ethyl-(S)-1-phenethylamine (3-SS)

Mp = 40.5 - 41.2 ℃; $[\alpha]_D^{26}$ = -61.9 (c 5.0, $CHCl_3$); IR (KBr): 441, 481, 669, 759, 929, 1019, 1057, 1154, 1216, 1243, 1526, 1639, 2400, 2927, 2976, 3020, 3423 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.8 Hz, 3H, CH_3), 1.29 (d, *J* = 6.4 Hz, 3H, CH_3 (fluorous tail side)), 3.46 (q, *J* = 6.8 Hz, 1H, CH), 3.59 (q, *J* = 6.4 Hz , 1H, CH (fluorous tail side)), 7.18 (d, *J* = 7.4 Hz, 2H, ArH), 7.22-7.26 (m, 1H, ArH), 7.31-7.36 (m, 4H, ArH), 7.54 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.79, 54.90, 55.40, 108-118 ($C_{10}F_{21}$), 126.54, 126.95, 127.52 (t, J_{C-F} = 23.9 Hz, C-CF_2), 128.54, 145.42, 150.30; ^{19}F NMR (471 MHz, $CDCl_3$): δ = -126.36, -122.88, 122.08, -121.90, -121.78, -121.39, -110.43, -81.11; HRMS-EI: $[M]^+$ m/z calcd for $C_{26}H_{18}F_{21}N$: 743.1104; found: 743.1147.

(S)-1-(4-perfluorodecylphenyl)ethyl-(R)-1-phenethylamine (**3-SR**) and (R)-1-(4-perfluorodecylphenyl)ethyl-(R)-1-phenethylamine (**3-RR**) were prepared in a manner similar to that described for (R)-1-(4-perfluorodecylphenyl)ethyl- (S)-1-phenethylamine (**3-RS**) and (S)-1-(4-perfluorodecylphenyl)ethyl- (S)-1-phenethylamine (**3-SS**).

(S)-1-(4-perfluorodecylphenyl)ethyl-(R)-1-phenethylamine (3-SR)

$[\alpha]_D^{23}$ = -3.5 (c 5.6, $CHCl_3$); HRMS-EI: $[M]^+$ m/z calcd for $C_{26}H_{18}F_{21}N$: 743.1104; found: 743.1102.

(R)-1-(4-perfluorodecylphenyl)ethyl-(R)-1-phenethylamine (3-RR)

$[\alpha]_D^{17}$ = 61.5 (c 5.2, $CHCl_3$); HRMS-EI: $[M]^+$ m/z calcd for $C_{26}H_{18}F_{21}N$: 743.1104; found: 743.1134.

Determination of partition coefficients of fluorous amine

Partition coefficients were determined according to the procedure reported by the Curran group.[13] To a biphasic mixture of organic solvent (3 mL) and FC-72 (3 mL), F-Amine (300 mg) was added, and stirred vigorously for 30 min. After standing for 5 min, the two layers were separated and evaporated to dryness, then weighed.

Experimental procedure for preparation of silyl enolate using column chromatography: Typical Procedure

To a solution of amine **3-SS** (887.1 mg, 1.20 mmol) and lithium chloride (25.5 mg, 0.60 mmol) in dry THF (15 mL), *n*-BuLi (0.95 mL, 1.50 mmol, 1.60 M in hexane) was added dropwise under N_2 at -40 ℃. The resulting yellowish solution was then cooled to -78 ℃, 4-methylcyclohexanone (112.2 mg, 1.00 mmol) in dry THF (5 mL) was added dropwise. After 30 min, chlorotrimethylsilane (133.5 mg, 1.23 mmol) was added dropwise and the reaction mixture was warmed slowly to room temperature. Then, sat. $NaHCO_3$ aq (20 mL) and hexane(30 mL) were added; the aqueous layer was separated and extracted with hexane (2 x 30 mL). The organic layer was collected and dried over Mg_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane to ethyl acetate) to yield (R)-4-methyl-1-trimethylsiloxycyclohexene (**20**, 136 mg, 74%, 85%ee) and the amine (884.2 mg, 99% recovery).

Experimental procedure for preparation of enol silyl ether using organic/fluorous biphasic workup: Typical procedure

To a solution of amine **3-SS** (898 mg, 1.21 mmol) and lithium chloride (26.5 mg, 0.63 mmol) in dry THF (15 mL), *n*-BuLi (0.95 mL, 1.50 mmol, 1.60 M in hexane) was added dropwise under N_2 at -40 °C. The resulting yellowish solution was then cooled at -78 °C, and 4-*t*-butylcyclohexanone (155 mg, 1.00 mmol) in dry THF (5 mL) was added dropwise. After 30 min, chlorotrimethylsilane(132 mg, 1.21 mmol) was added dropwise and the reaction mixture was warmed slowly to room temperature. Then, sat. $NaHCO_3$ aq (20 mL) and hexane(30 mL) were added; the aqueous layer was separated and extracted with hexane (2 x 30 mL). The organic layer was collected and dried over Mg_2SO_4 and evaporated under reduced pressure. The residue was diluted with acetonitrile (20 mL), and perfluorohexanes (FC-72, 20 mL) were added to the solution. The FC-72 layer was separated, and the acetonitrile layer was extracted with FC-72 (4 x 20 mL). The combined FC-72 layer was evaporated under reduced pressure to yield the amine (825 mg, 92% recovery), while the acetonitrile layer was evaporated under reduced pressure to yield (R)-4-t-butyl-1-trimethylsiloxycyclohexene (**19**, 161 mg, 73%, 83%ee).

Acknowledgement

We gratefully acknowledge a Grant-in-Aid for Scientific Research from MEXT Japan and JSPS for funding. We also thank the Noguchi Foundation for partial financial support.

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