HETEROCYCLES, Vol. 103, No. 2, 2021, pp. 839 - 861. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 29th November, 2020, Accepted, 12th January, 2021, Published online, 1st March, 2021
DOI: 10.3987/COM-20-S(K)52

A FLUOROUS PROLINE CATALYST IMMOBILIZED ON TEFLON® FOR HIGHLY STEREOSELECTIVE ASYMMETRIC ALDOL REACTIONS

Kazuki Ishihara, Riho Obayashi, Mizuki Ohira, Yuki Kobayashi, Kotaro Ishihara, Yamato Kato, Narisa Takeuchi, Risa Mizuno, Takayuki Shioiri, and Masato Matsugi*

Faculty of Agriculture, Meijo University, 1-501 Shiogamaguchi, Tempaku-ku, Nagoya 468-8502, Japan

We would like to dedicate this article to Prof. Yasuyuki Kita on his 77th birthday.

Abstract – An immobilized fluorous-tagged proline catalyst and its application as a recycling system in highly stereoselective asymmetric aldol reactions are described. The introduction of acidic sulfonamide groups bearing multifluorous tags at the carboxy position proved to be more effective than the introduction of bulky substituents on the proline backbone to achieve high stereoselectivity. The Teflon®-immobilized proline catalyst could be recovered and reused at least five times while maintaining high levels of catalytic activity and stereoselectivity.

INTRODUCTION

In recent years, research on asymmetric organocatalysis has made rapid progress,[1] which was mainly driven by the development of natural proline as a catalyst for the intermolecular asymmetric aldol reaction in 2000 by List et al.[2] This report is the first example of the effectiveness of proline as a chiral catalyst in an intermolecular reaction. Since then, many proline-derived catalysts have been reported, partly owing to the advantages of L-proline in terms of natural abundance, ease of handling, and low cost.[3] In 2006, Hayashi et al.[4] reported that the introduction of a bulky substituent such as a *t*-butyldiphenylsilyl group at the 4-position of *trans*-4-hydroxy-L-proline improved the reactivity and stereoselectivity in the asymmetric aldol reaction in water.[5] It was also reported that the proton at the carboxy moiety of the proline catalyst plays an important role in the stereoselectivity and reactivity.[6] Moreover, proline derivatives with a sulfonamide structure instead of a carboxy group proved to be effective catalysts in the asymmetric aldol reaction.[7]

Recently, we successfully developed a recyclable catalytic ring closing metathesis reaction[8] system in which the catalyst can be recovered by fluorous solid-state adsorption, even though the catalyst is in homogeneous state during the reaction.[9] Utilizing this medium-fluorous strategy,[9] we have just reported a recyclable multifluorous-tagged proline catalyst for asymmetric aldol reactions that can be recycled by adsorption onto FluoroFlash®, which is composed of fluorous silica gel.[10] Herein, we report the results of a detailed study on an asymmetric aldol reaction system in which fluorous tags are introduced into a proline-derived catalyst to enable activation, recovery, and recycle of the catalyst, which is immobilized on Teflon®.

RESULTS AND DISCUSSION

First, a fluorous proline catalyst **1a** was synthesized by introducing a C_8F_{17} tag at the 4-position of the proline backbone using a propylene spacer, followed by conversion of the carboxylic acid moiety to 3,5-bis(trifluoromethyl)benzenesulfonamide (**Figure 1**). This catalyst was expected to exhibit high stereoselectivity for intermolecular asymmetric reaction due to the presence of a bulky and large hydrophobic fluorous tag at the 4-position[4] and an electron-withdrawing group (trifluoromethyl group) on the benzenesulfonamide moiety, which would increase the acidity of the amide proton.[7]

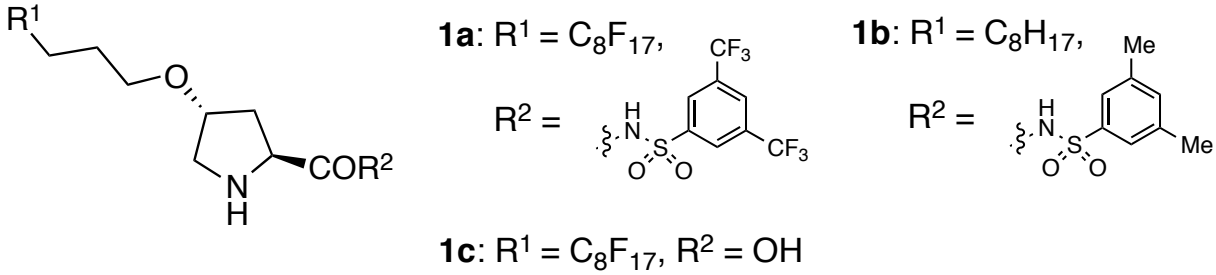
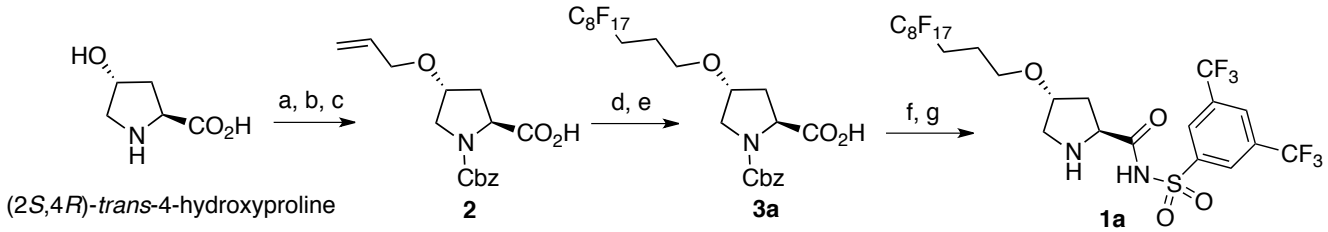


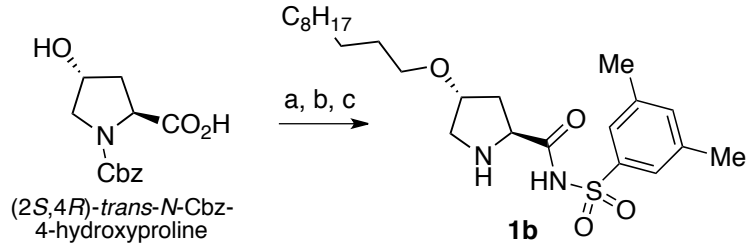
Figure 1. Fluorous proline catalyst **1a**, nonfluorous analog **1b**, and previously reported fluorous catalyst **1c**[11]

The synthetic route to catalyst **1a** is shown in **Scheme 1**. Using (2*S*,4*R*)-*trans*-4-hydroxy-L-proline as a substrate, **1a** was obtained by introducing a C_8F_{17} tag via a radical addition reaction. To provide comparison of the catalytic performance in the aldol reaction, a control catalyst **1b** (**Figure 1**), which is a nonfluorous analog of **1a**, was prepared as described in **Scheme 2**. In addition, proline catalyst **1c** bearing a C_8F_{17} tag at the 4-position (**Figure 1**), which was previously reported by Fache group,[1] was prepared following the reported method.[11]



a) Na_2CO_3 (2.5 eq.), Cbz-Cl (1.2 eq.), H_2O/acetone, rt, 21 h; b) NaH (2.5 eq.), allyl bromide (2.6 eq.), dry THF, 0 °C to rt, 41 h; c) NaOH (1.8 eq.), H_2O/MeOH, rt, 24 h, 68% (3 steps); d) AIBN (0.1 eq.), $C_8F_{17}I$ (1.0 eq.), 80 °C, 48 h; e) AIBN (0.1 eq.), H_3PO_2 (10 eq.), $NaHCO_3$ (12 eq.), EtOH, reflux, 4 h, 27% (2 steps); f) 3,5-bis(trifluoromethyl)benzenesulfonamide (1.5 eq.), EDCI (1.5 eq.), DMAP (0.25 eq.), HOBt (1.5 eq.), dry CH_2Cl_2/dry DMF, 0 °C to rt, 32 h; g) Pd/C (20 mol%), H_2, MeOH, rt, 17 h, 73% (2 steps).

Scheme 1. Synthetic route to fluorous proline catalyst **1a**

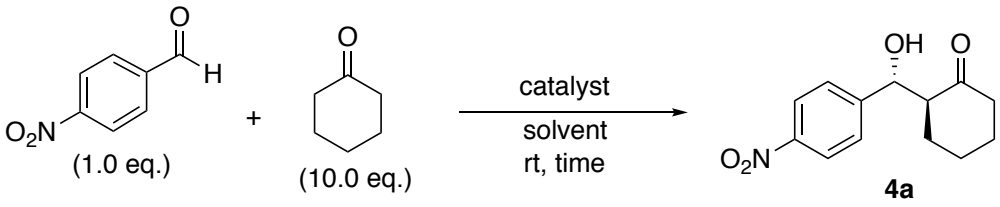


a) NaH (2.5 eq.), 1-bromoundecane (2.6 eq.), dry DMF, 0 °C to rt, 7 h; b) 3,5-dimethylbenzenesulfonamide (0.96 eq.), EDCI (2.5 eq.), DMAP (3.0 eq.), 1,2-dichloroethane/^{t}butyl alcohol, 0 °C to rt, 4 h; c) Pd/C (20 mol%), H_2, MeOH, rt, 16 h, 37% (3 steps).

Scheme 2. Synthetic route to nonfluorous proline catalyst **1b**

Initially, an extensive screening of reaction conditions was performed to evaluate the feasibility of **1a** to serve as an organocatalyst in the aldol reaction **(Table 1**). Using 4-nitrobenzaldehyde and cyclohexanone as model substrates, the aldol reaction was examined in various solvents.[12] It was found that the reaction proceeded successfully at room temperature when using THF, water, or toluene (**Table 1**, **entries 1**–**3**). The result in water was especially surprising, since the aldol products were obtained with complete stereoselectivity despite the high hydrophobicity and insolubility of **1a** in water (**Table 1**, **entry 2**). However, the reaction required long reaction time; therefore, no further investigation was conducted under aqueous conditions. Catalyst **1a** also worked effectively in toluene, which is relatively easy to handle and allows scaling up (**Table 1**, **entry 3**). The reactivity and stereoselectivity were reduced when the reactions were performed in various highly polar solvents such as MeCN, DMF, DMSO, and MeOH (**Table 1**, **entries 4**–**7**). Although the reaction time could be shortened by increasing the amount of catalyst from the starting 1 mol%, the *anti*/*syn* selectivity and enantiomeric excess (ee) (*anti*) were reduced when using 30 mol% of catalyst (**Table 1**, **entry 9**). Control catalyst **1b** exhibited much lower reactivity and stereoselectivity than **1a** (**Table 1**, **entry 10**). Furthermore, when fluorous catalyst **1c** was used, the reaction hardly proceeded, and the *anti*/*syn* selectivity was very low (**Table 1**, **entry 11**), principally due to the scarce solubility of **1c** in toluene.

Table 1. Asymmetric aldol reaction using fluorous catalysts **1a** and **1c** and control catalyst **1b**



entry	cat. (mol%)	solvent	time(h)	yield(%) [a]	*anti* : *syn* [b]	ee(%) of *anti* [c]
1	**1a** (1)	THF	96	87	100 : 0	>99
2	**1a** (1)	H_2O	168	81	100 : 0	>99
3	**1a** (1)	toluene	120	92	97 : 3	>99
4	**1a** (1)	MeCN	24	3 [d]	82 : 18	88
5	**1a** (1)	DMF	24	31 [d]	97 : 3	85
6	**1a** (1)	DMSO	24	9 [d]	86 : 14	79
7	**1a** (1)	MeOH	24	10 [d]	87 : 13	83
8	**1a** (10)	toluene	24	94	97 : 3	>99
9	**1a** (30)	toluene	23	100	94 : 6	97
10	**1b** (10)	toluene	24	56	82 : 18	84
11	**1c** (10)	toluene	24	3 [d]	53 : 47	85

[a] isolated yield.
[b] determined by ^{1}H NMR of the crude product.
[c] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[d] conversion yield determined by ^{1}H NMR of the crude product.

From these results, it can be concluded that THF and toluene were suitable as reaction solvents, and the aldol reaction could be conducted at room temperature. By comparing the performance of the three catalysts, it was found that the presence of an electron-withdrawing benzenesulfonamide moiety in the proline catalyst was essential for the reaction.

Motivated by the results summarized in **Table 1**, we decided to further optimize the catalytic structure. Namely, we planned to improve the stereoselectivity in the aldol reaction by optimizing the substituent structure at the 4-position of the proline molecule and elongating the fluorous tag on the aromatic ring of the benzenesulfonamide structure. First, to optimize the substituents at the 4-position of the proline framework, catalysts **1d**–**h** (**Figure 2**) having 3,5-bis(trifluoromethyl)benzenesulfonamide as the carbonyl moiety and different substituents at the 4-position were prepared, and their catalytic performance was evaluated. The multistep synthetic route to catalysts **1d**–**h** is shown in **Schemes 3** and **4**, in which

(2*S*,4*R*)-*trans*-*N*-Cbz-4-hydroxy-L-proline and *N*-Cbz-L-proline were used as substrates for **1d**–**g** and **1h**[13], respectively.

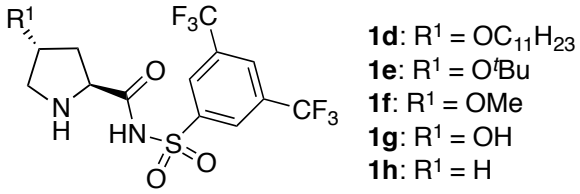
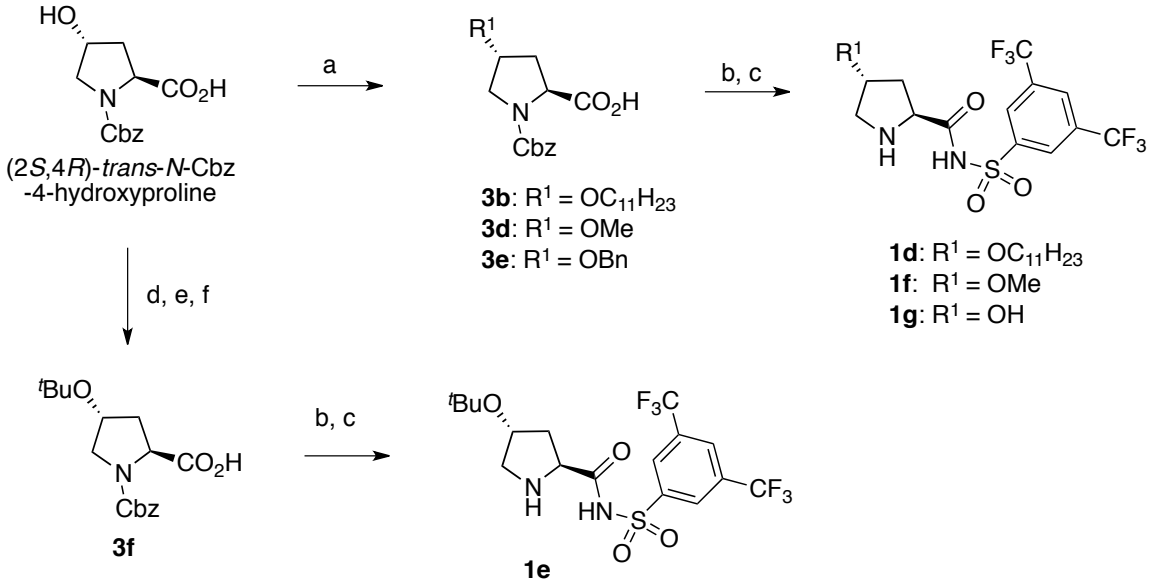
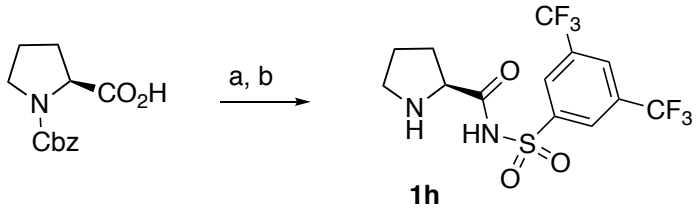


Figure 2. Control catalysts **1d**–**h**



a) NaH (2-2.5 eq.), Alkyl halide (2-2.6 eq.), dry THF or dry DMF, 0 °C to rt, 7-18 h, 78-99%; b) 3,5-bis(trifluoromethyl)benzenesulfonamide (0.90-0.96 eq.), EDCI (2.0-2.5 eq.), DMAP (3.0-4.1 eq.), 1,2-dichloroethane/*t*butyl alcohol, 0 °C to rt, 12-24 h, 56-99%; c) Pd/C or $Pd(OH)_2$ (20 mol%), H_2, MeOH, rt, 2-24 h, 54-97%; d) MeI (5.0 eq.), K_2CO_3 (2.0 eq.), dry DMF, rt, 16 h, 88%; e) $(Boc)_2O$ (3.0 eq.), $Mg(ClO_4)_2$ (0.5 eq.), CH_2Cl_2, reflux, 46 h, 58%; f) $LiOH \cdot H_2O$ (1.4 eq.), H_2O/THF, rt, 6 h, quant.

Scheme 3. Synthetic route to control catalysts **1d**–**g**



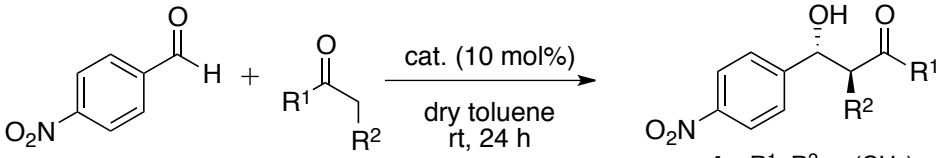
a) 3,5-bis(trifluoromethyl)benzenesulfonamide (0.95 eq.), EDCI (2.0 eq.), DMAP (3.0 eq.), 1,2-dichloroethane/*t*butyl alcohol, 0 °C to rt, 72 h, 94%; b) Pd/C (20 mol%), H_2, MeOH, rt, 7 h, 92%.

Scheme 4. Synthetic route to control catalyst **1h**

The aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using catalysts **1d**–**h** gave good results, with little difference in terms of reactivity and stereoselectivity between catalysts (**Table 2**, **entries 1**–**6**). We therefore examined the aldol reaction of 4-nitrobenzaldehyde with acetone, which is less reactive than

cyclohexanone.[4] Both reactivity and stereoselectivity were high when using **1a** bearing a C_8F_{17} tag and **1d** with a long alkyl chain (**Table 2**, **entries 7** and **8**), whereas catalysts **1f**–**h** having less-bulky substituents showed good reactivity but lower stereoselectivity (40%–70% ee; **Table 2**, **entries 10**–**12**). Contrary to expectations, the stereoselectivity was as low as 78% when using catalyst **1e** bearing a bulky ^{t}Bu group (**Table 2**, **entry 9**).

Table 2. Asymmetric aldol reaction using fluorous catalyst **1a** or control catalysts **1d-h**



4a: R^1, R^2 = -$(CH_2)_4$-
4b: R^1= Me, R^2= H

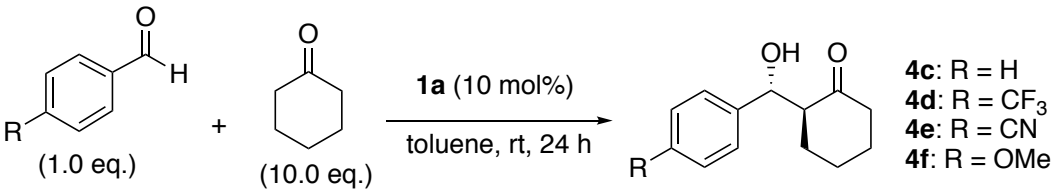
entry	cat.	R^1, R^2 [a]	conv. (%) [b]	*anti* : *syn* [b]	ee(%) of *anti*
1	**1a**	-$(CH_2)_4$-	100 (94)[c]	97 : 3	>99 [d]
2	**1d**	-$(CH_2)_4$-	99	98 : 2	>99 [d]
3	**1e**	-$(CH_2)_4$-	94	99 : 1	>99 [d]
4	**1f**	-$(CH_2)_4$-	98	97 : 3	>99 [d]
5	**1g**	-$(CH_2)_4$-	98	96 : 4	99 [d]
6	**1h**	-$(CH_2)_4$-	97	95 : 5	97 [d]
7	**1a**	Me, H	95	-	92 [e]
8	**1d**	Me, H	93	-	95 [e]
9	**1e**	Me, H	95	-	78 [e]
10	**1f**	Me, H	99	-	40 [e]
11	**1g**	Me, H	94	-	70 [e]
12	**1h**	Me, H	98	-	54 [e]

[a] cyclohexanone 10 eq, acetone 27 eq
[b] determined by ^{1}H NMR of the crude product.
[c] isolated yield.
[d] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[e] determined by chiral HPLC (Daicel Chiralcel OJ-3 column, hex : ^{i}PrOH = 80 : 20, 0.8 mL/min).

These results indicate that long-chain fluorous tags or alkyl groups are appropriate substituents to be introduced at the 4-position of the proline framework. In particular, catalyst **1a** bearing a long-chain fluorous tag can be considered as a "medium-fluorous molecule" with a fluorous content of 50.4%, and therefore, it can be expected to be recyclable by the medium-fluorous strategy.[10] Thus, no elongation of the fluorous tag on the substituted benzenesulfonamide would be required.

The substrate scope of the aldol reaction using catalyst **1a** and cyclohexanone was then investigated with various benzaldehydes (**Table 3**).[12,14] Good stereoselectivities were observed for all the benzaldehydes, with ee's ranging from 93% to 99% (**Table 3**, **entries 1–4**). However, the use of aldehydes with electron-donating groups decreased the yield (**Table 3**, **entry 4**).

Table 3. Asymmetric aldol reaction using various benzaldehydes and cyclohexanone



entry	R	yield(%) [a]	*anti* : *syn*	ee(%) of *anti* [b]
1	H	40	89 : 11 [b]	98
2	CF_3	38	95 : 5 [b]	93
3	CN	100	98 : 2 [c]	>99
4	OMe	15	87 : 13 [c]	>99

[a] isolated yield.
[b] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[c] determined by ^{1}H NMR.

Next, we investigated the feasibility of the separation and recovery of fluorous catalyst **1a** using our previously reported medium-fluorous strategy.[8] Following the procedure shown in **Figures 3** and **4**, the adsorption of catalyst **1a** onto a fluorous solid-phase support (Teflon®[15] or FluoroFlash®[16]) was examined by adding water to the reaction system. After the reaction in toluene, FluoroFlash® (30 times the amount of catalyst **1a**) and an equivalent amount of water to that of toluene was added. The catalyst was effectively immobilized on FluoroFlash® and could be easily separated by filtration. The filtrate was subjected to a ninhydrin test,[17] demonstrating no catalyst leakage. In contrast, catalyst leakage was observed when Teflon® was used as the solid-phase support under the same conditions.

It is noteworthy that toluene, which is not miscible with water, was a better solvent for the recovery of the catalyst than other hydrophilic solvents such as MeOH, THF, and DMSO. Interestingly, when the same amount of water as that of toluene was added to the system in the presence of FluoroFlash®, the reaction system was suspended, and the interface between the toluene and the water layers disappeared.

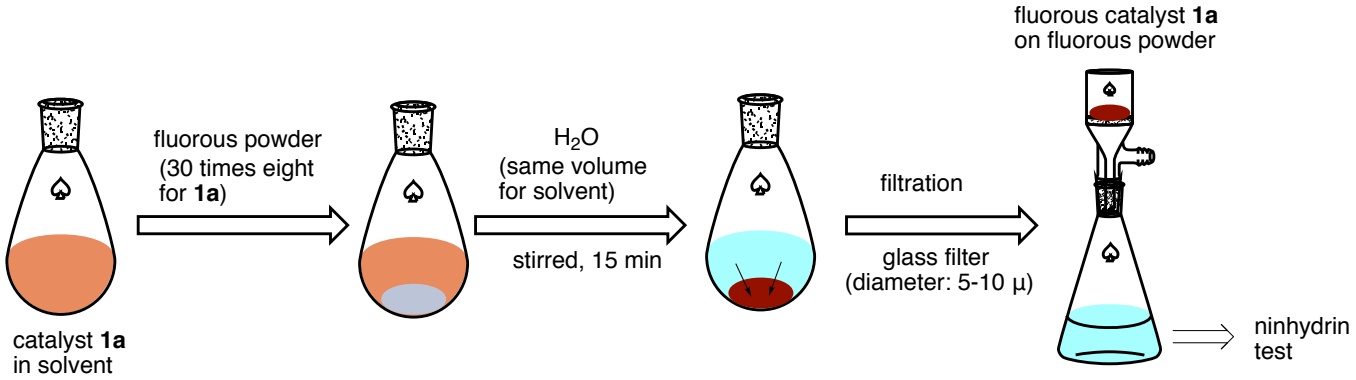


Figure 3. Separation procedure by medium-fluorous strategy using FluoroFlash®

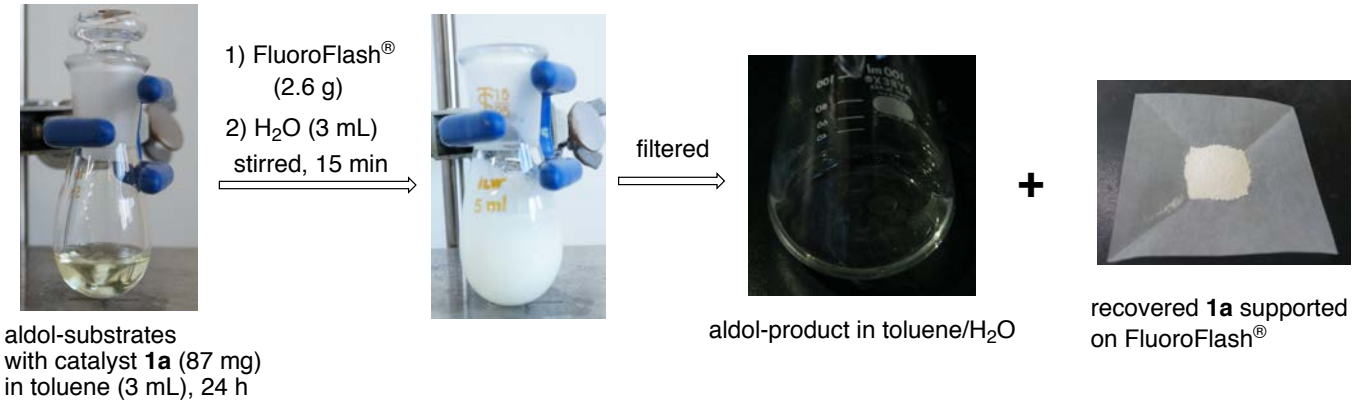
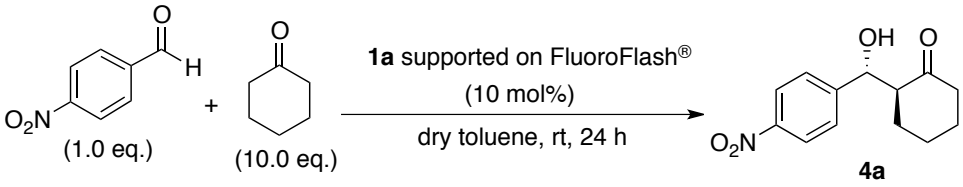


Figure 4. Photographs of the first separation cycle of **1a**

The recyclability of catalyst **1a** was evaluated by performing a series of aldol reactions of nitrobenzaldehyde with cyclohexanone. The results are shown in **Table 4**. In this experiment, the reaction was stirred in toluene (3 mL) in the presence of 87 mg (10 mol%) of catalyst **1a**, 151 mg (1 mmol) of nitrobenzaldehyde, and 1.0 mL (10 mmol) of cyclohexanone for 24 h at room temperature. FluoroFlash® (2.6 g, 30 times the weight of the catalyst) and 3 mL of water (an equivalent volume to that of toluene) were then added, and the mixture was stirred for 15 min. The reaction mixture was then filtered, and catalyst **1a** was recovered as a solid-phase catalyst supported on FluoroFlash®. Furthermore, a ninhydrin test performed on the filtrate confirmed that the catalyst did not leak. The filtrate was extracted with ethyl acetate and then purified by column chromatography to obtain the product in 94% yield. Catalyst **1a** supported on FluoroFlash® was hydrophobic and dried fast, which renders it easy to handle. The recovered solid-phase catalyst **1a** was used directly in the next cycle. The amount of substrate and solvent was adjusted appropriately to maintain a catalyst ratio of 10 mol%. The process was repeated six times, and the catalyst recovery was high (96%–100%) in all the cycles, giving the corresponding product in 34%–100% yields. However, a decrease in both yield and stereoselectivity was observed as the number of cycles increased (**Table 4**, **cycles 1–6**). After the sixth cycle, the FluoroFlash®-supported catalyst **1a** was drained from the FluoroFlash® system and analyzed by ^{1}H NMR. We found that the recovered catalyst

was not pure and was somewhat degraded. Therefore, catalyst **1a** was not completely stable under the reaction conditions and its catalytic activity gradually decreased; however, a high level of stereoselectivity (97%–99% ee) was maintained up to the fifth cycle.

Table 4. Reuse of FluoroFlash®-supported **1a** in the aldol reaction



cycle	conv.(%)	*anti* : *syn* [a]	ee(%) of *anti* [b]	recovered catalyst(%)
1	100 (94) [c]	97 : 3	>99	100
2	79	98 : 2	>99	100
3	61	96 : 4	98	98
4	41	95 : 5	97	96
5	34	94 : 6	97	99
6 [d]	68	89 : 11	93	99

[a] determined by ^{1}H NMR.
[b] determined by chiral HPLC (Daicel Chiralpak IB + OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[c] isolated yield.
[d] 48 h.

The gradual decrease in the reactivity and stereoselectivity of the solid-phase catalyst **1a** could be attributed to the acidity of FluoroFlash®, which could cause degradation of the catalyst. Therefore, we decided to investigate neutral Teflon® as the fluorous support. Additionally, Teflon® is cheaper than FluoroFlash®, which is desirable from an environmental standpoint.

First, we planned to increase the fluorine content by introducing a long fluorous tag on the aromatic ring of the benzenesulfonamide moiety containing a C_8F_{17}-tagged proline at 4-position, which could be immobilized on Teflon® to develop a recoverable solid-phase catalyst. To investigate the optimum fluorine content for a successful immobilization on Teflon®, we synthesized catalysts **1i**–**k** having different fluorous tags in the benzenesulfonamide ring (**Figure 5**).

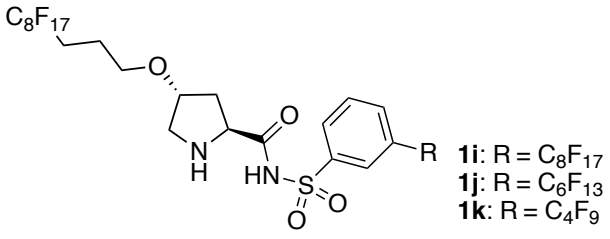
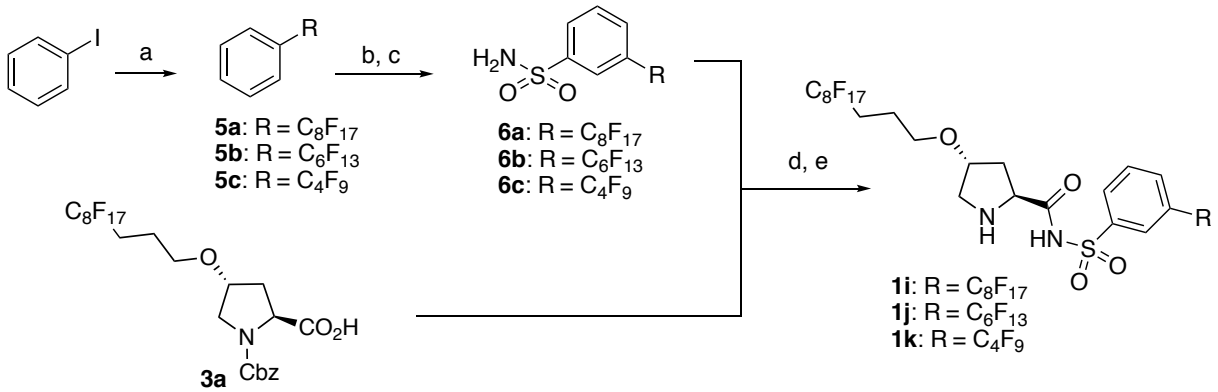


Figure 5. Fluorous proline catalysts **1i-k**

The starting sulfonamides **6a**–**c** were synthesized from iodobenzene as a substrate.[18,19] Then, fluorous proline catalysts **1i**–**k** were prepared via condensation reaction of proline intermediate **3a** with sulfonamides **6a**–**c** and subsequent deprotection of the Cbz group (**Scheme 5**).

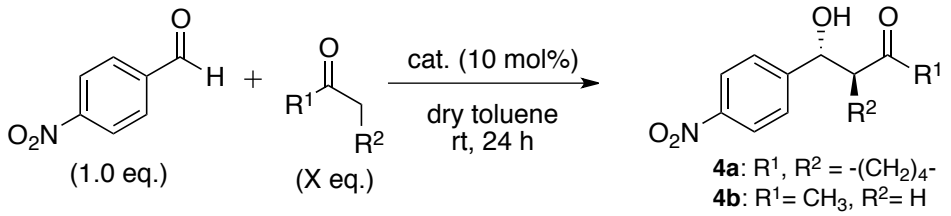


a) perfluoroalkyl iodide (1.5-3.0 eq.), Cu (8.0-16.0 eq.), DMSO, 120 °C, 14-9 h, 28-83%; b) HSO_3Cl (15.0 eq.), 120 °C, 2-3 h, 45-76%; c) 25% NH_3 aq (10.0-20.0 eq.), THF, reflux, 12-19 h, 80%-quant; d) **6a-c** (0.72-2.0 eq.), EDCI (2.0-3.0 eq.), DMAP (2.0-3.0 eq.), 1,2-dichloroethane/^{t}butyl alcohol, 0 °C to rt, 5-24 h, 63-81%; e) Pd/C (20 mol%), H_2, MeOH, rt, 20-24 h, 8-71%.

Scheme 5. Synthetic route to fluorous proline catalysts **1i**–**k**

The performance of the prepared catalysts **1i**–**k** in the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone was evaluated (**Table 5**). Catalyst **1i** showed a high stereoselectivity (99% ee) but a low yield of 15%, and the *anti*/*syn* selectivity was lower than that of catalyst **1a** (**Table 5**, **entry 1**). The lower reactivity of **1i** could be due to its very high fluorine content, which rendered it virtually insoluble in toluene. Increasing the amount of cyclohexanone to 30 equivalents did not improve the yield, and the stereoselectivity decreased to 89% ee (**Table 5**, **entry 2**). When catalysts **1j**–**k** were used, the reaction proceeded in a homogeneous manner, and the products were obtained in high yields. However, the reactivity and stereoselectivity were not as good as those of catalyst **1a** (**Table 5**, **entries 3**–**4**). The aldol reaction of acetone with 4-nitrobenzaldehyde was also performed using catalyst **1i**, which showed the highest stereoselectivity; however, the stereoselectivity was low (66% ee) (**Table 5**, **entry 5**). Catalysts **1i**–**k** have only one electron-withdrawing substituent on the aromatic ring of the benzenesulfonamide, which may result in lower acidity of the amide proton and reduced stereoselectivity compared with that of catalyst **1a**.

Table 5. Asymmetric aldol reaction using fluorous catalysts **1i–k**



entry	cat.	R^1, R^2	X (eq.)	yield (%) [a]	*anti* : *syn* [b]	ee(%) of *anti*
1	**1i**	$-(CH_2)_4-$	10	15	91 : 9	>99 [c]
2	**1i**	$-(CH_2)_4-$	30	11	93 : 7	89 [c]
3	**1j**	$-(CH_2)_4-$	10	83	95 : 5	94 [c]
4	**1k**	$-(CH_2)_4-$	10	84	89 : 11	76 [c]
5	**1i**	Me, H	27	49	-	66 [d]

[a] isolated yield.
[b] determined by ^{1}H NMR of the crude product.
[c] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[d] determined by chiral HPLC (Daicel Chiralcel OJ-3 column, hex : ^{i}PrOH = 80 : 20, 0.8 mL/min).

We then decided to synthesize catalyst **1l** bearing a 3,5-bis(trifluoromethyl)benzenesulfonamide and an elongated fluorous tag at the 4-position (**Figure 6**). Catalyst **1l** has higher fluorine content than catalyst **1a**, and the high acidity of the amide proton is maintained. Therefore, the immobilization of **1l** on Teflon® was not expected to cause a decrease in stereoselectivity.

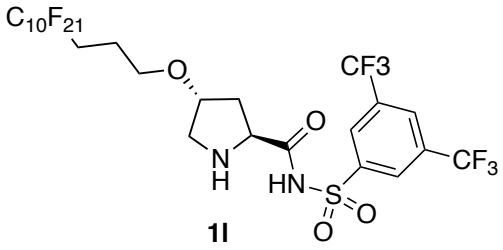
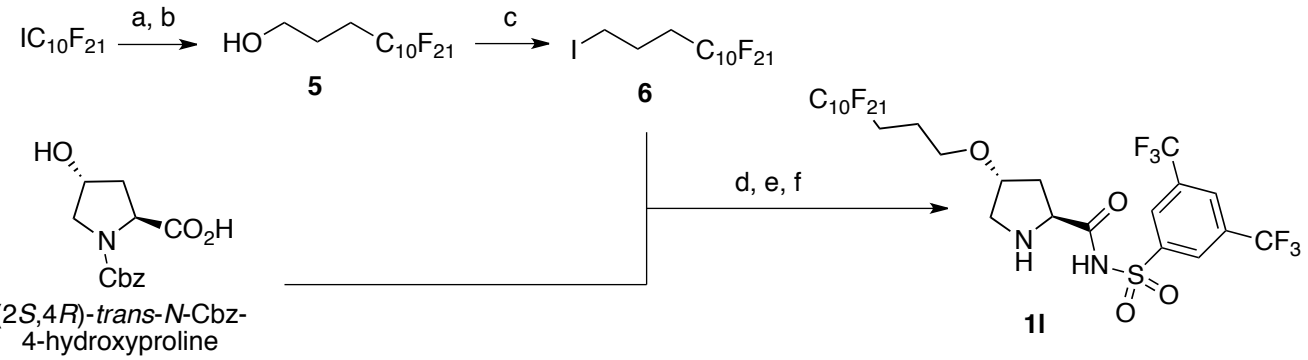


Figure 6. Fluorous proline catalysts **1l**

We attempted to synthesize **1l** following the same procedure as that used for catalyst **1a**; however, the radical addition of perfluorodecyl iodide[20] to intermediate **2** did not proceed. Consequently, we decided to introduce the $C_{10}F_{21}$ tag by the nucleophilic substitution reaction of $C_{10}F_{21}$-tagged iodopropane **8**[20] with (2*S*,4*R*)-*trans*-*N*-Cbz-4-hydroxy-L-proline. The synthetic route shown in **Scheme 6** afforded $C_{10}F_{21}$-tagged iodopropane **8** in three steps, which was then used to prepare the $C_{10}F_{21}$-tagged fluorous catalyst **1l**.

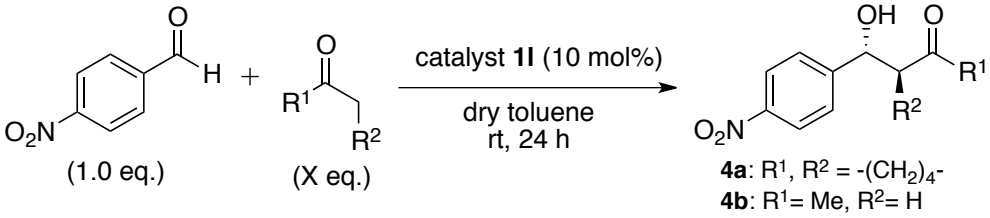


a) allyl alcohol (4.0 eq.), AIBN (0.1 eq.), 90 °C, 19 h, 64%; b) AIBN (0.1 eq.), Bn_3SnH (1.2 eq.), toluene, 90 °C, 19 h, 90%; c) I_2 (2.0 eq.), PPh_3 (1.8 eq.),Et_2O/MeCN, 0 °C to rt, 5 h, 98%; d) NaH (2.5 eq.), **6** (1.1 eq.), dry DMF/dry THF, 0 °C to rt, 24 h, 45%; e) 3,5-bis(trifluoromethyl)benzenesulfonamide (1.20 eq.), EDCI (2.0 eq.), DMAP (3.0 eq.), 1,2-dichloroethane/^{t}butyl alcohol, 0 °C to rt, 12 h, 76%; f) Pd/C (20 mol%), H_2, MeOH, rt, 2 h, 92%.

Scheme 6. Synthetic route to fluorous proline catalyst **1l**

The aldol reaction of 4-nitrobenzaldehyde with cyclohexanone using **1l** was performed, and the results on the reactivity and stereoselectivity are summarized in **Table 6**. The reaction proceeded successfully with high levels of *anti/syn* selectivity and ee (*anti*) (**Table 6**, **entry 1**). Even when acetone and 4-nitrobenzaldehyde were used as substrates, the product was obtained in a high yield of 80% and a high stereoselectivity of 90% ee (**Table 6**, **entry 2**).

Table 6. Asymmetric aldol reaction using fluorous catalyst **1l**



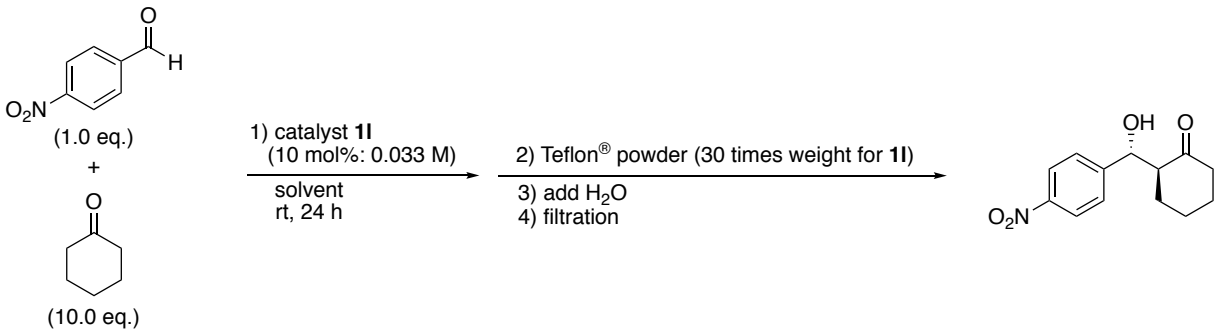
entry	R^1, R^2	X (eq.)	conv. (%)[a]	*anti* : *syn* [a]	ee(%) of *anti*
1	$-(CH_2)_4-$	10	94	98 : 2	98 [b]
2	Me, H	27	80	-	90 [c]

[a] determined by ^{1}H NMR of the crude product.
[b] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex : ^{i}PrOH = 96 : 4, 1.0 mL/min).
[c] determined by chiral HPLC (Daicel Chiralcel OJ-3 column, hex : ^{i}PrOH = 80 : 20, 0.8 mL/min).

Next, fluorous catalyst **1l** was immobilized on Teflon® to investigate its recoverability. First, the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was carried out, followed by addition of Teflon® (30 times the amount of Teflon® to that of **1l**) and water. In this reaction, catalyst **1l** was used at a concentration of 0.033 M to account for the addition of Teflon®. In addition, to promote the catalyst adsorption on Teflon®, the amount of water was increased compared with that used for the

FluoroFlash®-based recycling system, reaching a water content of 70%. However, the catalyst was not completely immobilized on Teflon®, and a leakage equivalent to 5% was observed (**Table 7**, **entry 1**).

Table 7. Asymmetric aldol reaction using various solvents



entry	solvent	water content (%)	catalyst leakage (%)[a]	conv. (%)[a]	*anti* : *syn* [a]	ee of *anti* (%)[b]
1	toluene	70	5	24	98 : 2	98
2	THF	70	26	97	98 : 2	>99
3 [c]	MeOH	50	0	10	89 : 11	91

[a] determined by ^{1}H NMR.
[b] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex:^{i}PrOH = 96:4, 1.0 mL/min).
[c] 12 h.

The aldol reaction using Teflon®-immobilized **1l** was examined with various solvents (**Table 7**). On the one hand, we found that the reaction in THF proceeded in high yield and with high stereoselectivity (**Table 7**, **entry 2**). On the other hand, MeOH proved to be a suitable solvent for the immobilization of **1l** on Teflon® (**Table 7**, **entry 3**). Therefore, we attempted to construct a recycling system that combined the advantages of both solvents. Thus, after performing the aldol reaction with catalyst **1l** in THF, the reaction solvent was removed, and the residue was dissolved in MeOH, followed by addition of Teflon® and then water. The catalyst was thereby immobilized on Teflon® and recovered (**Figure 7**).

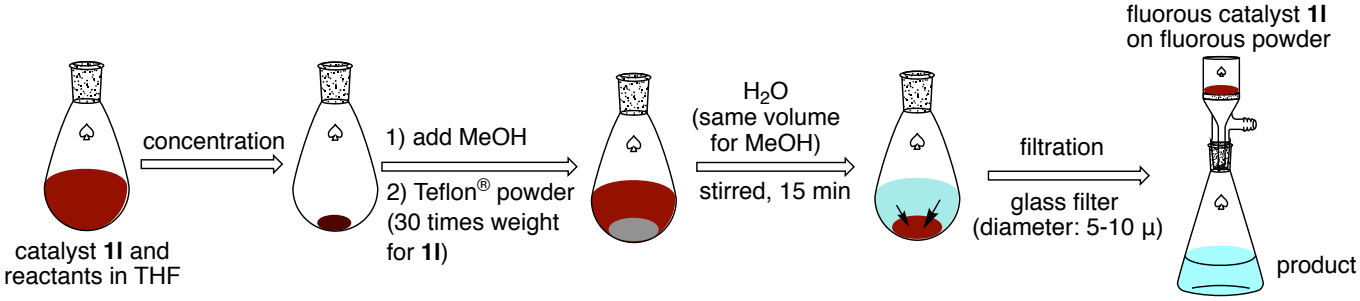


Figure 7. Separation procedure by medium-fluorous strategy using Teflon®

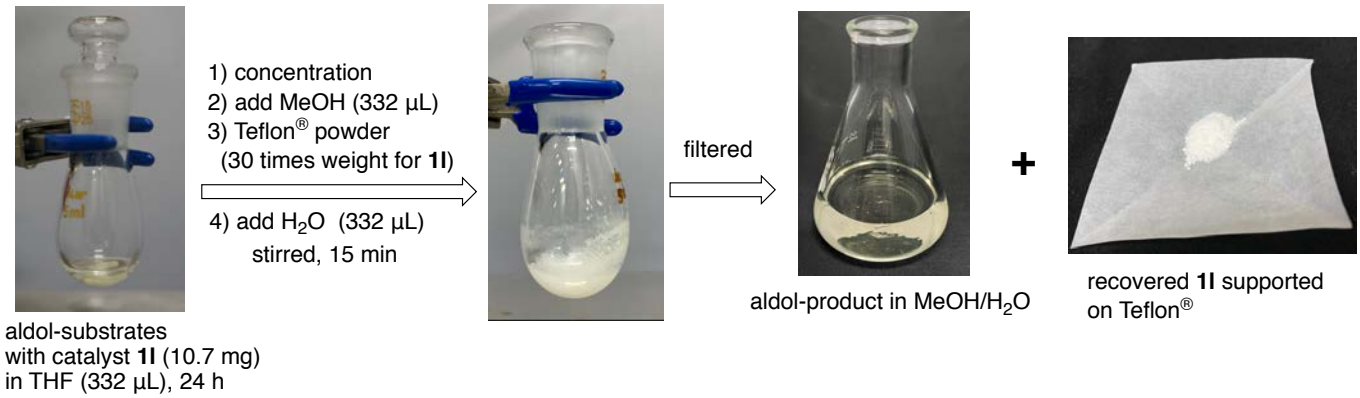


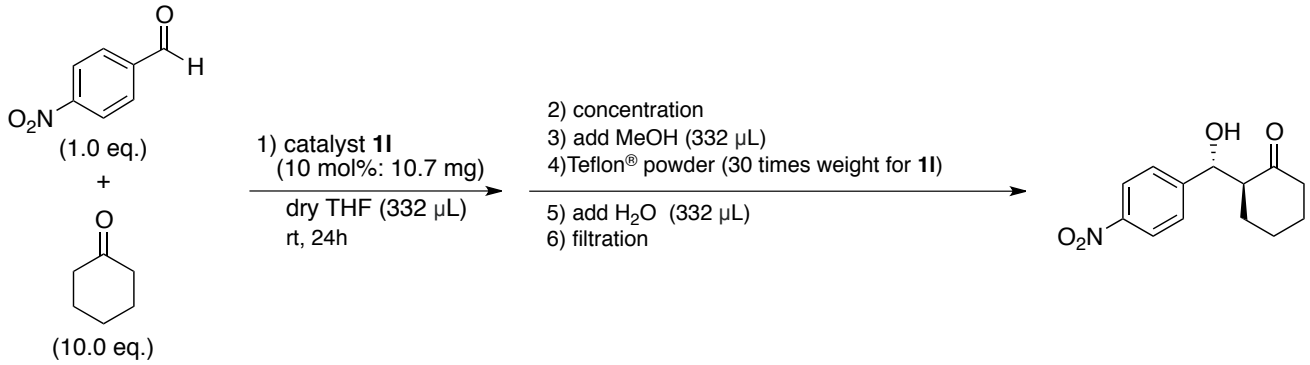
Figure 8. Photographs of the first separation cycle of **1l**

This procedure was performed as follows: 10.7 mg (10 mol%) of catalyst **1l**, 16.7 mg (0.111 mmol) of 4-nitrobenzaldehyde, and 115 μL (1.107 mmol) of cyclohexanone were stirred in THF (332 μL) for 24 h at room temperature. The reaction solvent was then removed, and the residue was dissolved in MeOH (332 μL). Teflon® (321 mg, 30 times the weight of the catalyst) was added, followed by 332 μL of water (the same volume as that of MeOH). The reaction mixture was stirred for 15 min and then filtered. Catalyst **1l** was thereby recovered as a solid catalyst supported on Teflon® (**Figure 8**). Similarly to **1a**, solid catalyst **1l** was hydrophobic and dried fast.

The filtrate was subjected to ^{1}H NMR analysis, and no peaks corresponding to the catalyst were detected. The filtrate was extracted with ethyl acetate and purified by column chromatography to obtain the product in high yield and high optical purity (**Table 8**, **cycle 1**). Since the catalyst was successfully immobilized in Teflon® in this reaction system and could be easily separated by filtration, a recycling experiment was conducted using the recovered solid-phase catalyst **1l**. The amount of substrate and solvent was appropriately adjusted to maintain a catalyst ratio of 10 mol%. The process was repeated five times, and high catalyst recoveries (90%–96%) were observed in all cases. Moreover, the products were obtained in 96%–98% yields with 98%–99% ee (**Table 8**, **cycles 1–5**). The yield and stereoselectivity did not decrease significantly until the fifth cycle (**Table 8**, **cycles 1–5**); however, a slight leakage of catalyst **1l**

was observed in the fifth cycle. Overall, the catalyst **1l** could be reused in this reaction system for at least five cycles while maintaining high levels of reactivity and stereoselectivity, thereby circumventing the gradual decrease in the reactivity and stereoselectivity observed for the FluoroFlash®-supported catalyst **1a**.[10]

Table 8. Reuse of **1l** supported on Teflon® in the aldol reaction



cycle	conv. (%)[a]	*anti* : *syn* [a]	ee of *anti* (%)[b]	recovered catalyst (%)	catalyst leakage (%)[a]
1	98	98 : 2	99	96	0
2	98	98 : 2	99	95	0
3	98	98 : 2	99	95	0
4	99	97 : 3	98	93	0
5	96	98 : 2	98	90	5

[a] determined by ^{1}H NMR.
[b] determined by chiral HPLC (Daicel Chiralpak IB+OD-3 column, hex:^{i}PrOH = 96:4, 1.0 mL/min).

In summary, we have shown that fluorous-tagged proline catalyst **1l** can be successfully immobilized on Teflon® to provide an effective and reusable catalytic system for the intermolecular asymmetric aldol reaction. In this reaction system, the catalyst could be reused up to five times while maintaining high levels of reactivity and stereoselectivity. The present medium-fluorous strategy for recycling catalysts could be applicable to a variety of catalysts apart from the proline catalysts described here.

EXPERIMENTAL

All the laboratory chemicals were purchased from Tokyo Chemical Industry Co., Ltd., FUJIFILM Wako Pure Chemical Corporation, Sigma-Aldrich Co. LLC, and Kanto Chemical Co., Inc. used without further purification unless otherwise stated. FluoroFlash® was purchased from Boron Specialties LLC. Solvents were removed by rotary evaporation under reduced pressure using a 40-50 ºC water bath. Non-volatile compounds were dried in vacuo at 0.01 mbar. All reactions were stirred magnetically and reaction was

monitored by thin layer chromatography (TLC) using silica gel plates. Purification by chromatography was performed on silica gel 60 N (spherical, neutral, 63–210 μm, Kanto Chemical Co., Inc.). Melting points were determined in open-ended capillaries using a Bibby Scientific Ltd. Stuart® SMP-30 instrument or ATM-01 of AS ONE Corporation and are uncorrected. All nuclear magnetic resonance (NMR) spectra were recorded with JNM EX270 (^{1}H: 270 MHz), JNM ECZ-400 (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F: 376 MHz) and JNM ECA-500 (^{1}H: 500 MHz, ^{13}C: 125 MHz, ^{19}F: 466 MHz) spectrometers. Chemical shifts (δ) are given in units of ppm, and coupling constants (*J*) are given in Hz. Abbreviations for multiplicity are as follows: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (double doublet), *brs* (broad). High-performance liquid chromatography (HPLC) analyses were performed by Daicel Chiralpak IB columns and Daicel Chiralpak OD-3 columns with UV Detector L2400 or SPD-20A. High-resolution mass spectra (HRMS) was performed by Exactive™ Plus Orbitrap (Thermo Fisher SCIENTIFIC). The spectra were calibrated with Pierce™ LTQ Velos ESI Positive Ion Calibration Solution prior to data acquisition.

General Procedures for Aldol Reaction in Table 1-3, 5;

To a solution of catalyst in solvent was added ketone and aldehyde (1 M). After being stirred at room temperature for 24 h, the mixture was concentrated. Conversion and diastereoselectivity (*anti : syn*) were determined by ^{1}H NMR of the crude product. Ee of the *anti* aldol product was determined *via* HPLC of the crude product.

General Procedures for Aldol Reaction Using 1l in Table 6;

To a solution of catalyst in solvent was added ketone and aldehyde (1 M). After being stirred at room temperature for 24 h. EtOAc was added to reaction mixture and organic layer was washed with brine. Aqueous layer was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated. Conversion and diastereoselectivity (*anti : syn*) was determined by ^{1}H NMR of the crude product. Ee of the *anti* aldol product was determined *via* HPLC of the crude product.

Reuse of catalyst 1l on Teflon® in the aldol reaction;

To a solution of **1l** (10.7 mg, 0.0111 mmol) in dry THF (332 μL) was added cyclohexanone (115 μL, 1.107 mmol) and 4-nitrobenzaldehyde (16.7 mg, 0.111 mmol). After being stirred at room temperature for 24 h. The reaction solvent was then removed, and the residue was dissolved in MeOH (332 μL). Teflon® (321 mg, 30 times the weight of the catalyst) was added, followed by of water (332 μL, the same volume as that of MeOH). The reaction mixture was stirred for 15 min and then filtered. The resulting mixture was filtered through a glass filter 3G4 (diameter : 5-10 μ) and washed with MeOH/H_2O (1 : 1 v/v). The filtrate was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The recovered catalyst **1l** was dried and used directly in the next cycle.

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (4a)[10]**;** White solid; mp 97.7-98.8 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 8.9 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 4.90 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 4.07 (d, *J* = 3.0 Hz, 1H), 2.64-2.31 (m, 3H), 2.17-2.09 (m, 1H), 1.86-1.35 (m, 5H).

(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (4b) [4]**;**

White solid; mp 58-59 °C; ^{1}H NMR (270 MHz, CDCl3) δ = 8.21 (d, *J* = 8.4 Hz, 2H), 8.54 (d, *J* = 8.9 Hz, 2H), 5.29-5.25 (m, 1H), 5.60 (s, 1H), 2.92-2.78 (m, 2H), 2.23 (s, 3H).

(*S*)-2-((*R*)-Hydroxy(phenyl)methyl)cyclohexan-1-one (4c) [10]**;** Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.38-7.29 (m, 5H), 4.79 (dd, *J* = 8.9 Hz, 2.4 Hz, 1H), 3.96 (d, *J* = 2.4 Hz, 1H), 2.67-2.30 (m, 3H), 2.13-2.04 (m, 1H), 1.82-1.22 (m, 5H).

(*S*)-2-((*R*)-Hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (4d) [10]**;** White solid; mp 91.9-92.7 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 4.85 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 4.06 (d, *J* = 2.7 Hz, 1H), 2.65-2.31 (m, 4H), 2.18-2.05 (m, 1H), 1.84-1.26 (m, 4H).

4-((*R*)-Hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile (4e) [10]**;** Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 1H), 2.62-2.30 (m, 3H), 2.16-2.05 (m, 1H), 1.86-1.47 (m, 5H).

Catalyst (1a) [10]**:** White solid; mp 103.8-104.9 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.35 (s, 2H), 7.99 (s, 1H), 4.55-4.48 (m, 1H), 4.20 (s, 1H), 3.62-3.46 (m, 4H), 2.59-2.51 (m, 1H), 2.18-2.02 (m, 3H), 1.85-1.75 (m, 2H).

Catalyst (1b) [10]**:** Yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.51 (s, 2H), 7.09 (s, 1H), 4.43-4.37 (m, 1H), 4.05 (brs, 1H) 3.69-3.63 (m, 1H), 3.44-3.31 (m, 3H), 2.58-2.46 (m, 1H), 2.34 (s, 6H), 1.99-1.88 (m, 1H), 1.52-1.44 (m, 2H), 1.21 (s, 16H), 0.88 (t, *J* = 6.8 Hz, 3H).

Catalyst (1c) [11]**:** Yellow solid; mp 128.8-131.3 °C; ^{1}H NMR (270 MHz, CD_3OD) δ = 4.16-4.14 (m, 1H), 3.80-3.65 (m, 1H), 3.56-3.26 (m, 2H), 2.93-2.88 (m, 2H), 2.53-2.38 (m, 1H), 2.30-2.05 (m, 3H), 1.92-1.82 (m, 2H).

Catalyst (1h) [13]**:** White solid; mp 186.4-186.8 °C; ^{1}H NMR (500 MHz, CD_3OD) δ = 8.38 (s, 2H), 8.03 (s, 1H), 3.93-3.90 (m, 1H), 3.25-3.09 (m, 4H), 2.25-2.18 (m, 1H), 1.96-1.76 (m, 3H).

Typical Procedure for the Preparation of Products 1d-g;

(2*S*,4*R*)-*N*-((3,5-Bis(trifluoromethyl)phenyl)sulfonyl)-4-(undecyloxy)pyrrolidine-2-carboxamide (1d): 3b (102 mg, 0.24 mmol), DMAP (118.8 mg, 0.98 mmol) and WSCD·HCl (93.3 mg, 0.49 mmol) in *t*-butyl alcohol/1,2-dichloroethane (4.8 mL, 2.4 mL/2.4 mL v/v) was stirred at 0 °C for 10 min. 3,5-Bis(trifluoromethyl)benzenesulfonamide (67.4 mg, 0.23 mmol) in *t*-butyl alcohol/1,2-dichloroethane (5.0 mL, 2.5 mL/2.5 mL v/v) was added dropwise to the reaction mixture, and then the mixture was stirred at room temperature for 12 h. 1N HCl was added to reaction mixture until pH = 1-2. The mixture

was extracted with EtOAc. The organic layer was washed with 1N HCl, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The crude was purified by silica gel chromatography (EtOAc : *n*-hexane = 1 : 3) to give desired product (117.8 mg, 74%).

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.50, (s, 2H), 8.09, (s, 1H), 7.34-7.26 (m, 5H), 5.19-5.05 (m, 2H), 4.41 (s, 1H), 4.23-4.00 (s, 1H), 3.73-3.33 (m, 4H), 2.44-2.07 (m, 2H), 1.46-1.24 (m, 23H), 0.89-0.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.79, 157.31, 142.61, 135.67, 128.63, 128.43, 127.97, 127.79, 126.65, 123.93, 121.21, 77.31, 76.66, 69.60, 68.38, 60.65, 52.14, 33.76, 31.98, 29.78, 29.67, 29.63, 29.48, 29.39, 26.13, 22.75, 14.16; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.80; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{32}H_{40}F_6N_2O_6S$ 695.2590, found: 659.2589.

Benzyl (2*S*,4*R*)-2-(((3,5-bis(trifluoromethyl)phenyl)sulfonyl)carbamoyl)-4-(undecyloxy)pyrrolidine-1-carboxylate (89.0 mg, 0.13 mmol) and Pd/C (54.5 mg, 0.026 mmol) in MeOH (2.6 mL) was stirred at room temperature for 2 h under H_2 balloon. The Pd/C was removed by filtration through a pad of celite with MeOH. The filtrate was concentrated. The crude was purified by silica gel chromatography (CH_2Cl_2: MeOH = 10 : 1) to give **1d** (45.4 mg, 63%).

Colorless Oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.99 (s, 1H), 4.52-4.46 (m, 1H), 4.16 (s, 1H), 3.68-3.54 (m, 2H), 3.37 (t, *J* = 67.5 Hz, 2H), 2.56-2.49 (m, 1H), 2.04-1.95 (m, 1H), 1.47-1.45 (m, 2H), 1.19 (s, 20H), 0.87 (t, *J* = 62.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.09, 145.61, 127.00, 125.15, 124.14, 121.41, 77.30, 69.71, 69.46, 62.19, 51.82, 35.90, 33.97, 31.90, 29.58, 29.52, 29.45, 29.33, 25.89, 22.68, 14.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.73; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{24}H_{34}F_6N_2O_4S$ 561.2222, found: 561.2222.

Typical Procedure for the Preparation of Products 5a-c;

(Perfluorooctyl)benzene 5a[21]**:** To a suspension of iodobenzene (546 μL, 4.90 mmol) and Cu powder (2.49 g, 39.21 mmol) in dry DMSO (7.0 ml) was added perfluorooctyl iodide (1.95 mL, 7.35 mmol) under N_2 atmosphere at 120 °C and stirred for 14 h. After the addition of water, Cu powder was removed by filtration through a pad of celite and washed with Et_2O. The filtrate was extracted with Et_2O. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, filtered, and the s concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane) to give **5a** (2022.9 mg, 83%).

Colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 7.61-7.48 (m, 5H).

Typical Procedure for the Preparation of Products 6a-c;

3-(Perfluorooctyl)benzenesulfonamide 6a[22]**: 5a** (500 mg, 1.01 mmol) was added to chlorosulfonamide (1.0 mL, 15.12 mmol) at room temperature. The mixture was stirred at 120 °C for 2 h, and then cooled to room temperature was pippeted cautiously onto ice. The aqueous layer was extracted with EtOAc. The

organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane) to give desired product (456.0 mg, 76%).[23]

Colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 8.31-8.28 (m, 2H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H).

In a 50 mL round bottom flask equipped with a magnetic stirring bar and a condenser coil, 3-(perfluorooctyl)benzenesulfonyl chloride (446.3 mg, 0.75 mmol) was dissolved in THF. This solution was treated with 25% ammonia solution (1.12 mL, 15.0 mmol) and was refluxed for 12 h. Excess water was separated as the toluene azeotrope. After the addition of 1N HCl, the suspension was purified by filtration to give **6a** (488.5 g, quant.).

Yellow solid; mp 145.4-146.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.16 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.88 (t, *J* = 8.4 Hz, 1H), 7.63 (s, 2H).

Typical Procedure for the Preparation of Products 1i-k;

(2*S*,4*R*)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoroundecyl)oxy)-*N*-((3-(perfluorooctyl)-phenyl)sulfonyl)pyrrolidine-2-carboxamide 1i: 3a[10] (192 mg, 0.28 mmol), DMAP (102.2 mg, 0.83 mmol) and WSCD·HCl (105.9 mg, 0.55 mmol) in *t*-butyl alcohol/1,2-dichloroethane (1.4 mL, 0.7 mL/0.7 mL v/v) was stirred at 0 °C for 10 min. **6a** (141.7 mg, 0.25 mmol) in *t*-butyl alcohol/1,2-dichloroethane (1.4 mL, 0.7 mL/0.7 mL v/v) was added dropwise to the reaction mixture, and then the mixture was stirred at room temperature for 15 h. 1N HCl was added to reaction mixture until pH = 1-2. The mixture was extracted with EtOAc. The organic layer was washed with 1N HCl, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The crude was purified by silica gel chromatography (EtOAc : *n*-hexane = 1 : 3) to give desired product (252.3 mg, 74%).

White Solid; mp 28.9-29.6 °C; ^{1}H NMR (270 MHz, CD_3OD) δ = 8.28-8.20 (m, 2H), 7.90-7.65 (m, 2H), 7.30-7.16 (m, 5H), 5.10-4.75 (m, 2H), 4.33-4.24 (m, 1H), 4.05 (brs, 1H), 3.64-3.30 (m, 2H), 2.39-2.09 (m, 3H), 2.01-1.80 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ = 173.81, 154.93, 140.57, 136.70, 131.48, 131.06, 129.70, 128.14, 127.78, 127.44, 126.91, 126.12, 123.11, 118.57, 118.41, 118.27, 115.81, 113.97, 113.272, 112.08, 110.80, 110.37, 108.66, 77.37, 76.58, 66.93, 60.19, 51.92, 36.37, 29.40, 13.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -80.75, -110.70, -114.31, -121.28, -121.88, -122.69, -123.39, -126.08; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{38}H_{24}F_{34}N_2O_6S$ 1283.0890, found: 1283.0897.

Benzyl (2*S*,4*R*)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecyl)oxy)-2-(((3-(perfluorooctyl)phenyl)sulfonyl)carbamoyl)pyrrolidine-1-carboxylate (197.0 mg, 0.15 mmol) and Pd/C (65.4 mg, 0.03 mmol) in MeOH (4.5 mL) was stirred at room temperature for 19.5 h under H_2 balloon. The Pd/C was removed by filtration through a pad of celite with MeOH. The filtrate was concentrated. The crude was purified by recyclization (MeOH) to give **1i** (14.4 mg, 8%).

White solid; mp 69-70 °C; ^{1}H NMR (400 MHz, CD_3OD+Hexfluoroisopropanol) δ = 8.17-8.10 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 4.11 (brs, 1H), 4.07-4.03 (m, 1H), 3.54-3.40 (m, 2H), 2.54-2.47 (m, 1H), 2.22-2.10 (m, 2H), 1.87-1.82 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD+Hexafluoroisopropanol) δ = 174.03, 143.66, 130.27, 129.78, 129.54, 128.89, 125.23, 124.47, 122.46, 121.56, 121.43, 118.66, 118.52, 115.99, 115.70, 115.42, 114.11, 112.45, 110.88, 110.79, 110.51, 108.57, 108.47, 78.19, 67.14, 61.14, 51.10, 35.26, 27.45, 20.61; ^{19}F NMR (376 MHz, CD_3OD+Hexafluoroisopropanol) δ = -82.73, -111.98, -115.75, -122.26, -122.67, -122.86, -123.06, -123.89, -124.73, -127.52; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{30}H_{18}F_{34}N_2O_4S$ 1149.0523, found: 1149.0521.

Procedure for the Preparation of Products 1l;

(2*S*,4*R*)-*N*-((3,5-Bis(trifluoromethyl)phenyl)sulfonyl)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-henicosafluorotridecyl)oxy)pyrrolidine-2-carboxamide (1l): Under N_2 atmosphere, a solution of (*2S*,*4R*)-*trans*-*N*-Cbz-4-hydroxyproline (208.8 mg, 0.787 mmol) in dry THF (10 mL) was stirred at 0 °C, then sodium hydride (60% dispersion in oil, 94.5 mg, 2.36 mmol) was added. The reaction mixture was warmed to room temperature and then stirred for 10 min. Solution of **8** (595.8 mg, 0.866 mmol) in dry THF/dry DMF (1 mL, 0.5 mL/0.5 mL v/v) was added dropwise to the reaction mixture. After stirred at room temperature for 24 h, the reaction mixture was quenched with H_2O and added 1N HCl until pH = 1-2. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude was purified by silica gel chromatography (EtOAc : *n*-hexane = 1 : 1) to give desired product (292.5 mg, 45%).

White solid; mp 61-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.29 (m, 5H), 5.19-5.08 (m, 2H), 4.53-4.44 (m, 1H), 4.08-4.06 (m, 1H), 3.71-3.44 (m, 4H), 2.45-2.08 (m, 4H), 1.86-1.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.79, 176.03, 155.95, 154.61, 136.30, 136.15, 128.60, 128.48, 128.01, 121.16, 118.56, 115.74, 113.71, 110.81, 108.12, 77.16, 67.83, 67.72, 67.47, 58.15, 57.64, 51.85, 51.67, 36.70, 35.06, 27.90, 20.96; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -80.69, -114.20, -121.63, -122.61, -123.31, -126.03; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{26}H_{18}F_{26}N_2O_4S$ 826.1084, found: 826.1082.

(2*S*,4*R*)-1-((Benzyloxy)carbonyl)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-henicosafluorotridecyl)oxy)pyrrolidine-2-carboxylic acid (292.5 mg, 0.354 mmol), DMAP (129.9 mg, 1.063 mmol) and EDCI (125 μL, 0.709 mmol) in 1,2-dichloroethane / ^{t}BuOH (2 mL, 1 mL/1 mL v/v) was stirred at 0 °C for 10 min. 3,5-Bis(trifluoromethyl)benzenesulfonamide (260.1 mg, 0.425 mmol) in 1,2-dichloroethane 2 / ^{t}BuOH (2 mL, 1 mL/1 mL v/v) was added dropwise to the reaction mixture, and then the mixture was stirred at room temperature for 12 h. 1N HCl was added to reaction mixture until pH = 1-2. The mixture was extracted with EtOAc. The organic layer was washed with 1N HCl, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The crude was purified by silica gel

chromatography (EtOAc : *n*-hexane = 1 : 3) to give desired product (295.5 mg, 76%).

White solid; mp 41-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (s, 2H), 8.09 (s, 1H), 7.34 (s, 5H), 5.23-5.13 (m, 2H), 4.40-4.36 (m, 1H), 4.03-4.00 (m, 1H), 3.60-3.41 (m, 4H), 2.50-2.46 (m, 1H), 2.14-2.01 (m, 3H), 1.83-1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.19, 157.29, 141.86, 135.54, 132.77, 128.67, 128.56, 128.09, 127.24, 125.81, 123.62, 121.43, 120.54, 119.24, 118.50, 118.34, 116.45, 116.02, 113.42, 113.16, 110.91, 110.53, 110.26, 108.62, 108.35, 68.58, 67.77, 59.91, 51.85, 32.79, 27.84, 20.92; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.80, -80.59, -114.15, -121.58, -122.56, -123.28, -125.95; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{26}H_{18}F_{26}N_2O_4S$ 1101.0924, found: 1101.0917.

Benzyl (2*S*,4*R*)-2-(((3,5-bis(trifluoromethyl)phenyl)sulfonyl)carbamoyl)-4-((4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-henicosafluorotridecyl)oxy)pyrrolidine-1-carboxylate (295.5 mg, 0.268 mmol) and Pd/C (114.3 mg, 0.054 mmol) in MeOH (9 mL) was stirred at room temperature for 2 h under H_2 balloon. The Pd/C was removed by filtration through a pad of celite with MeOH. The filtrate was concentrated. The crude was purified by silica gel chromatography ($CHCl_3$: MeOH = 10 : 1) to give **1l** (238.1 mg, 92%).

White solid; mp 137-139 °C; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.44 (s, 2H), 8.10 (s, 1H), 4.21 (s, 1H), 4.13-4.09 (m, 1H), 3.59-3.47 (m, 2H), 3.33 (d, *J* = 2.4 Hz, 2H), 2.57-2.52 (m, 1H), 2.32-2.18 (m, 2H), 1.97-1.81 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD+Hexfluoroisopropanol) δ = 173.45, 144.96, 132.33, 127.26, 124.93, 124.00, 121.29, 119.62, 113.95, 113.63, 113.36, 113. 22, 111.17, 110.87, 110.55, 110.22, 108.62, 108.22, 107.84, 107.52, 77.77, 67.26, 61.11, 51.09, 34.79, 27.40, 20.26; ^{19}F NMR (376 MHz, CD_3OD) δ = -64.29, -82.25, -115.29, -122.60, -123.58, -124.31, 127.16; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{26}H_{18}F_{26}N_2O_4S$ 967.0556, found: 967.0565.

Catalyst (1e): White solid; mp 42.2-43.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 2H), 7.98 (s, 2H), 4.51 (m, 1H), 4.35 (brs, 1H), 3.69 (dd, *J* = 12Hz, *J* = 4.8 Hz, 1H), 3.33 (d, *J* =12 Hz, 1H,), 2.35-2.29 (m, 1H), 2.11-2.04 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 174.15, 145.60, 132.32, 131.99, 127.04, 125.19, 121.47, 77.30, 75.01, 62.27, 53.78, 38.36, 28.01; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{17}H_{20}F_6N_2O_4S$ 463.1126, found: 463.1122.

Catalyst (1f): White solid; mp 46.6-46.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 2H), 8.00 (s, 1H), 4.53-4.49 (m, 1H), 4.09 (s, 1H), 3.64 (s, 2H), 3.30 (s, 3H), 2.59-2.54 (m, 1H), 2.02-1.95 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.94, 145.45, 132.34, 132.01, 127.12, 125.29, 124.17, 121.38, 118.73, 115.05, 79.24, 77.29, 62.14, 56.68, 51.67, 35.35; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.78; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{14}H_{14}F_6N_2O_4S$ 421.0657, found: 421.0653.

Catalyst (1g): White solid; mp 36.5-37.3 °C; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 (s, 2H), 8.03 (s, 1H), 4.39 (d, *J* = 4.0 Hz, 1H), 4.15-4.10 (m, 1H), 3.24-3.20 (m, 1H), 3.10-3.07 (m, 1H), 2.31-2.26 (m, 1H), 1.91-1.84 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ = 173.53, 146.47, 131.25, 127.79, 124.56, 121.71,

69.77, 61.09, 53.32, 38.43; ^{19}F NMR (376 MHz, CD_3OD δ = -64.10; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{13}H_{12}F_6N_2O_4S$ 407.0500, found: 407.0495.

Catalyst (1j): White solid; mp 89-90 °C; ^{1}H NMR (500 MHz, CD_3OD) δ = 8.13-8.11 (m, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 4.11 (brs, 1H), 4.03-3.99 (m, 1H), 3.50-3.40 (m, 2H), 3.25-3.21 (m, 2H), 2.48-2.43 (m, 1H), 2.23-2.12 (m, 2H), 1.91-1.75 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ = 172.84, 144.76, 130.99, 129.64, 128.78, 128.61, 125.63, 121.53, 119.58, 118.86, 118.42, 117.65, 117.09, 115.76, 114.72, 113.38, 110.55, 108.23, 107.34, 106.59, 78.02, 67.12, 61.03, 50.82, 35.02, 27.47, 20.55; ^{19}F NMR (466 MHz, CD_3OD) δ = -82.32, -111.50, -115.26, -122.30, -122.49, -122.61, -122.80, -123.68, -124.33, 127.18; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{28}H_{18}F_{30}N_2O_4S$ 1049.0586, found: 1049.0568.

Catalyst (1k): White solid; mp 28.8-29.6 °C; ^{1}H NMR (500 MHz, CD_3OD) δ = 8.20-8.18 (m, 2H), 7.76 (d, *J* = 10.5 Hz, 1H), 7.68 (t, *J* = 10.0 Hz, 1H), 4.20 (d, *J* = 2.5 Hz, 1H), 4.13-4.09 (m, 1H), 3.58-3.47 (m, 2H), 3.34-3.28 (m, 4H), 2.54 (dd, *J* = 18.0 Hz, *J* = 10.0 Hz, 1H), 2.31-2.18 (m, 2H), 1.96-1.78 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ = 172.86, 144.73, 130.96, 129.29, 128.98, 128.42, 125.59, 121.35, 121.08, 118.85, 118.58, 116.05, 115.72, 115.55, 113.33, 113.18, 111.19, 110.89, 110.61, 108.47, 108.28, 108.00, 77.91, 67.12, 61.10, 50.88, 35.12, 27.48, 20.54; ^{19}F NMR (466 MHz, CD_3OD) δ = -82.29, -82.56, -111.73, -115.29, -122.61, -122.79, -123.50, -123.63, -124.31, -126.62, -127.17; HRMS-DART (*m/z*):$[M+H]^+$ calcd for $C_{26}H_{18}F_{26}N_2O_4S$ 949.0650, found: 949.0659.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grunt Number JP19K07006, Takahashi Industrial and Economic Research Foundation (public interest incorporated foundation No.10-003-181), and Professor Y. Uozumi's JST-ACCEL program (JPMJAC1401).

REFERENCES AND NOTES

1. J. Liu and L. Wang, *Synthesis*, 2017, **49**, 960.
2. B. List, R. A. Lerner, and C. F. Barbas, *J. Am. Chem. Soc*., 2000, **122**, 2395.
3. G. D. Yadav, Deepa, and S. Singh, *ChemistrySelect*, 2019, **4**, 5591.
4. Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, and M. Shoji, *Angew. Chem. Int. Ed.*, 2006, **45**, 958.
5. Y. Wang, S. Wei, and J. Sun, *Synlett*, 2006, **19**, 3319; N. Mase, N. Noshiro, A. Mokuya, and K. Takabe, *Adv. Synth. Catal.*, 2009, **351**, 2791; M. Bhati, S. Upadhyay, and S. Easwar, *Eur. J. Org. Chem.*, 2017, 1788.
6. Z. Li, X. Li, X. Ni, and J.-P. Cheng, *Org. Lett.*, 2015, **17**, 1196.
7. A. Berkessel, B. Koch, and J. Lex, *Adv. Synth. Catal.*, 2004, **346**, 1141.
8. J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999,

121, 791.

9. Y. Kobayashi, S. Inukai, N. Kondo, T. Watanabe, Y. Sugiyama, H. Hamamoto, T. Shioiri, and M. Matsugi, *Tetrahedron Lett.*, 2015, **56**, 1363.
10. K. Ishihara, R. Obayashi, M. Gotoh, Y. Watanabe, Y. Kobayashi, K. Ishihara, T. Shioiri, and M. Matsugi, *Tetrahedron Lett*., 2020, **61**, 151657.
11. F. Fache and O. Piva, *Tetrahedron: Asymmetry*, 2003, **14**, 139.
12. Y. Wu, Y. Zhang, M. Yu, G. Zhao, and S. Wang, *Org. lett.*, 2006, **8**, 4417.
13. M. Kinsella, P. G. Duggan, and C. M. Lennon, *Tetrahedron: Asymmetry*, 2011, **22**, 1423.
14. K. M. Ruíz-Pérez, B. Quiroz-García, and M. Hernández-Rodríguez, *Eur. J. Org. Chem.*, 2018, 5763.
15. This material is commercially available from SANPRATEC corp. (average particle size: 25 μm).
16. The FluoroFlash® is commercially available from Boron Specialties LLC Sigma-Aldrich® (average particle size: 40 μm).
17. S. Ruhemann, *J. Chem. Soc.*, 1910, **97**, 2025; M. Friedman, *J. Agric. Food Chem.*, 2004, **52**, 385.
18. G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, and S. Quici, *Eur. J. Org. Chem.*, 1999, 1947; T. Mathivet, E. Monflierb, Y. Castanet, A. Mortreux, and J. L. Couturier, *Tetrahedron Lett.*, 1998, **39**, 9411.
19. A. D. Worthy, M. M. Gagnon, M. T. Dombrowski, and K. L. Tan, *Org. Lett*., 2009, **11**, 2764.
20. K. Chiba, K. Kurogi, K. Monde, M. Hashimoto, M. Yoshida, H. Mayama, and K. Tsujii, *Colloids Surf. A Physicochem. Eng. Asp.*, 2010, **354**, 234; B. Menczinger, A. Nemes, C. Szíjjártó, and J. Rábai, *J. Fluorine Chem.*, 2018, **210**, 70.
21. S. Zhang, N. Rotta-Loria, F. Weniger, J. Rabeah, H. Neumann, C. Taeschler, and M. Beller, *Chem. Commun.*, 2019, **55**, 6723.
22. S. Cerezo, J. Corte`s, D. Galvan, E. Lago, C. Marchi, E. Molins, M. Moreno-Manas, R. Pleixats, J. Torrejon, and A. Vallribera, *Eur. J. Org. Chem.*, 2001, **2**, 329.
23. T. Kasahara and Y. Kondo, *Chem. Commun.*, 2006, **8**, 891.