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Catalytic enantioselective cyclopropanation of allylic alcohols using recyclable fluorous disulfonamide ligand

Tsuyoshi Miura, Keisuke Itoh, Yumi Yasaku, Naka Koyata, Yasuoki Murakami, Nobuyuki Imai *

Faculty of Pharmaceutical Sciences, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

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The authors dedicate this article to the 80th birthday of Professor E. J. Corey at Harvard University.

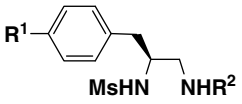
ABSTRACT

Cyclopropanation of allylic alcohols with Et_2Zn and CH_2I_2 in the presence of a catalytic amount of fluorous disulfonamide **3** afforded the corresponding cyclopropylmethanols in 69–96% yield with 49–83% ee. The fluorous ligand **3** was readily recovered from the reaction mixture by the fluorous solid-phase extraction (FSPE) and could be reused without a significant loss of the catalytic activity and enantioselectivity.

Development of a catalytic enantioselective cyclopropanation is an attractive research field because cyclopropane derivatives show various kinds of bioactivities.[1] Since Kobayashi developed the first enantioselective Simmons–Smith cyclopropanation, some effective methods have been reported.[2] We have also reported enantioselective Simmons–Smith cyclopropanation catalyzed by chiral disulfonamides (**1** and **2**) derived from L-phenylalanine, which afforded the corresponding cyclopropylmethanols in 82–100% yield with 39–86% ee.[3] However, recovery and reuse of the expensive chiral ligands are generally difficult. The separation of the expensive ligand from the product after cyclopropanation reaction and its recycling are highly desirable. Furthermore, fluorous recovering technique has been developed initially in the field of catalytic chemistry by Horváth and Rabái,[4] and Curran has elaborated the fluorous solid-phase extraction (FSPE) methodology using fluorous silica gel.[5] Recently, asymmetric reactions by FSPE concept for recovery and reuse of the expensive chiral ligands have been reported.[6]

To recover and reuse the valuable ligands such as **1** and **2** for enantioselective Simons–Smith cyclopropanation, we have attempted the development of a novel chiral ligand with fluorous tag and designed the fluorous disulfonamide **3**. We guess that a fluorous chain should be introduced into a distant position from the two sulfonamides, which are important for the enantioselectivity.[3c] In this Letter, we describe a catalytic enantioselective cyclopropanation using flurous disulfonamide **3**, which can be recovered and reused.

The fluorous disulfonamide **3** was prepared as a novel recyclable chiral ligand (see Scheme 1). The amino group of tyrosinol **4** was protected by *t*-butoxycarbonyl (Boc) group to give the corresponding alcohol **5** in 98% yield. The reaction of **5** with the fluorous tosylate **6**[7] in the presence of potassium carbonate in acetonitrile provided the fluorous alcohol **7** in 87% yield. The Boc group of **7** was removed by treatment with hydrogen chloride in ethyl acetate, followed by the reaction with methanesufonyl chloride (MsCl) in tetrahydrofuran (THF) to afford 78% yield of the corresponding mesylate **8** in two steps. The azide **9** was obtained in 88% yield by the reaction of **8** with sodium azide in *N*,*N*-dimethylformamide (DMF). The azide **9** was hydrogenated on Pd/C in 1,4-dioxane, followed by the reaction of *p*-toluenesulfonyl chloride (TsCl) in pyridine to provide 93% yield of the desired fluorous disulfonamide **3**[8] in two steps. We optimized the reaction conditions for enantioselective cyclopropanation as shown in Table 1. The various reaction temperatures from −23 °C to 10 °C were examined in the presence of the fluorous disulfonamide **3** (0.1 equiv) in anhydrous dichloromethane (entries 1–6). The more suitable reaction temperature was 0 °C as indicated in entry 4. The cyclopropanation was carried out with 0.2 and 0.3 equiv of the fluorous disulfonamide **3** to afford 78% and 79% ee, respectively (entries 7 and 8).



1: R^1 = H, R^2 = $SO_2C_6H_4$-*p*-NO_2
2: R^1 = H, R^2 = Ts
3: R^1 = $OCH_2CH_2CH_2C_8F_{17}$, R^2 = Ts

Next, the results of enantioselective cyclopropanation of various allylic alcohols **10a**–**j** in the presence of 0.2 equiv of **3** are shown in Table 2.[9] We selected methoxy and methyl substituents as representative electron-donating groups (entries 2 and 3, respectively),

* Corresponding author. Tel./fax: +81 479 30 4610.
E-mail address: nimai@cis.ac.jp (N. Imai).

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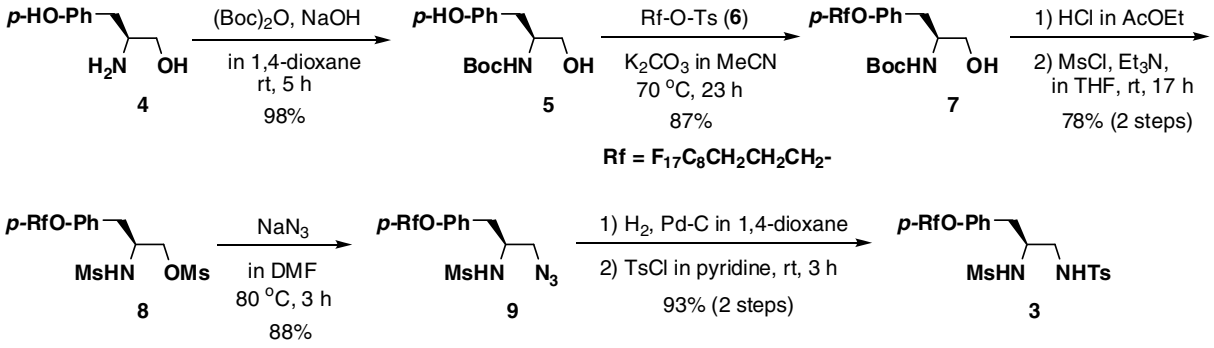
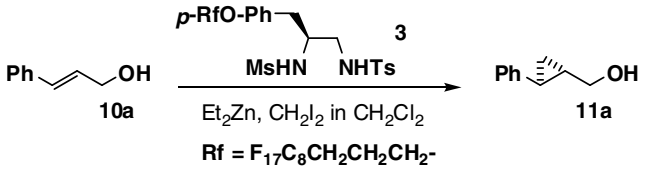


Scheme 1. Preparation of fluorous disulfonamide **3**.

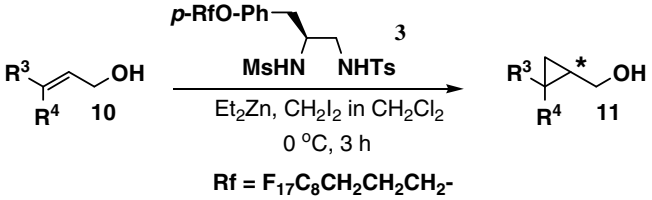
Table 1
Optimaization of reaction conditions[a]



Entry	Temperature (°C)	Compound **3** (equiv)	Time (h)	Yield (%)	ee (%)[b]
1	−23	0.1	23	88	63
2	−10	0.1	3	95	69
3	−5	0.1	3	95	68
4	0	0.1	2.5	97	74
5	5	0.1	2.5	97	66
6	10	0.1	2.5	95	66
7	0	0.2	2.5	93	78
8	0	0.3	2.5	97	79

[a] All reactions were carried out with 1 equiv of cinnamyl alcohol **10a**, 2 equiv of Et_2Zn, and 3 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined by HPLC analysis using Chiralcel OD.

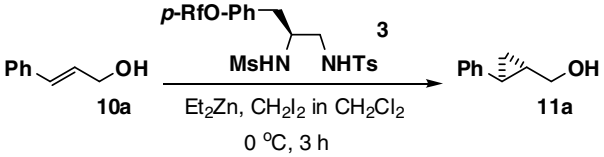
Table 2
Cyclopropanation of various allylic alcohols **10a–j** in the presence of **3**[a]



Entry	Compound **10**	R^3	R^4	Yield (%)	ee (%)
1	**10a**	Ph	H	93	78[b]
2	**10b**	4-$MeOC_6H_4$	H	94	77[b]
3	**10c**	4-MeC_6H_4	H	96	70[b]
4	**10d**	4-$CF_3C_6H_4$	H	90	83[c]
5	**10e**	4-ClC_6H_4	H	89	72[c]
6	**10f**	$PhMe_2Si$	H	95	74[b]
7	**10g**	$PhCH_2CH_2$	H	95	67[d]
8	**10h**	$TrOCH_2$	H	91	70[b]
9	**10i**	H	$TrOCH_2$	69	49[b]
10	**10j**	Ph	Ph	88	71[b]

[a] All reactions were carried out with 1 equiv of allylic alcohol **10**, 0.2 equiv of **3**, 2 equiv of Et_2Zn, and 3 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined byHPLC analysis using Chiralcel OD.
[c] Determined by HPLC analysis using Chiralcel AD after acetylation.
[d] Determined by HPLC analysis using Chiralcel AD.

Table 3
Recycling and reuse of the fluorous ligand **3** by FSPE methodology[a]



Entry	Yield (%)	ee (%)[b]
Initial	93	78
1st reuse	93	78
2nd reuse	94	77

[a] All reactions were carried out with 1 equiv of allylic alcohol **10a**, the recovered **3** (ca. 0.2 equiv), 2 equiv of Et_2Zn, and 3 equiv of CH_2I_2 in anhydrous CH_2Cl_2 at the 1st and 2 nd reuses.
[b] Determined by HPLC analysis using Chiralcel OD.

then trifluoromethyl and chloro substituents as electron-withdrawing groups (entries 4 and 5, respectively) on the benzene ring. The reaction of **10d** substituted trifluoromethyl group afforded higher enantioselectivity (83% ee) than those of other allylic alcohols **10a–c**, and **10e** (see entries 1–5). The other trans-oriented allylic alcohols **10f–h** were converted to the corresponding derivatives in excellent yields with 67–74% ee. A low enantioselectivity (49% ee) was obtained in the reaction of the cis-oriented allylic alcohol **10i** (entry 9). The reaction of 3,3-diphenyl-2-propen-1-ol **10j** afforded 71% ee.

The fluorous ligand makes it possible to recover itself using fluorous silica gel based on solid-phase extraction. The fluorous disulfonamide **3** was cleanly recovered (>92%) from the reaction mixture by FSPE and the ligand **3** can be reused repeatedly. The recovered and reused ligand **3** without further purification retains a similar catalytic activity and enantioselectivity at least for two times of the cyclopropanation as indicated in Table 3.

In summary, a novel fluorous disulfonamide **3** efficiently works as a ligand in the Simmons–Smith reaction of various allylic alcohols to give the corresponding cyclopropane derivatives with good enantioselectivities. It was observed that the enantioselectivities of the reaction of allylic alcohols with the ligand **3** were nearly equal to those with the original ligands (**1** and **2**).[3] The ligand **3** with the fluorous tag was readily recovered only by simple solid-phase extraction using fluorous silica gel after reaction, and can be reused without further purification. The catalytic activity and enantioselectivity of **3** used repeatedly are not reduced. Further application to the synthesis of bioactive compounds and novel reactions is now in progress.

Acknowledgements

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8. *Fluorous disulfonamide* **3**: Colorless amorphous solid; $[\alpha]_D^{20}$ −16.6 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (m, 2H), 2.29 (m, 2H), 2.41 (s, 3H), 2.47 (s, 3H), 2.71 (dd, *J* = 8.9, 14.0 Hz, 1H), 2.83 (dd, *J* = 5.5, 14.0 Hz, 1H), 3.00 (m, 1H), 3.09 (m, 1H), 3.60 (m, 1H), 3.98 (t, *J* = 5.9 Hz, 2H), 5.22 (d, *J* = 8.4 Hz, 1H), 5.70 (t, *J* = 6.4 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.63 (br s), 21.53, 27.99 (t, $^2J_{C-F}$ = 22.3 Hz), 38.39, 40.77, 47.38, 56.30, 66.42, 105.60-121.80 (complex signals of $-CF_2-$ and $-CF_3$), 114.80, 127.23, 129.85, 129.92, 130.76, 136.67, 143.74, 157.75; HRMS (ESI-TOF): calcd for $C_{28}H_{27}F_{17}N_2O_5S_2Na$ $(M+Na)^+$: 881.0982, found: 881.0981.
9. *A typical procedure of the cyclopropanation using* **3** *and* **10a** *is as follows*: To a colorless solution of **10a** (67.0 mg, 0.500 mmol) and the fluorous disulfonamide **3** (85.9 mg, 0.100 mmol) in 7.5 mL of dry dichloromethane were added dropwise 1.00 mL (1.00 mmol) of a 1.00 M solution of Et_2Zn in hexane and CH_2I_2 (121 μL, 1.50 mmol) at −40 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 2.5 h, and quenched with 0.3 mL of triethylamine. The reaction mixture was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was chromatographed on fluorous silica gel with 70% methanol to afford 71.0 mg of a crude product. Then, the fluorous silica gel was eluted with a 1:1 mixture of methanol and ethyl acetate, and the fraction was evaporated to recover the fluorous ligand **3** (81.7 mg, 95%). The crude product was purified by column chromatography on silica gel with a 2:1 mixture of hexane and ethyl acetate to afford the pure **11a** (68.9 mg, 93%) as a colorless oil.