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LEWIS ACID PROMOTED PRINS CYCLIZATION USING NON-CONJUGATED DIENE ALCOHOL: SEQUENTIAL REACTIONS TERMINATED BY FLUORIDE ION

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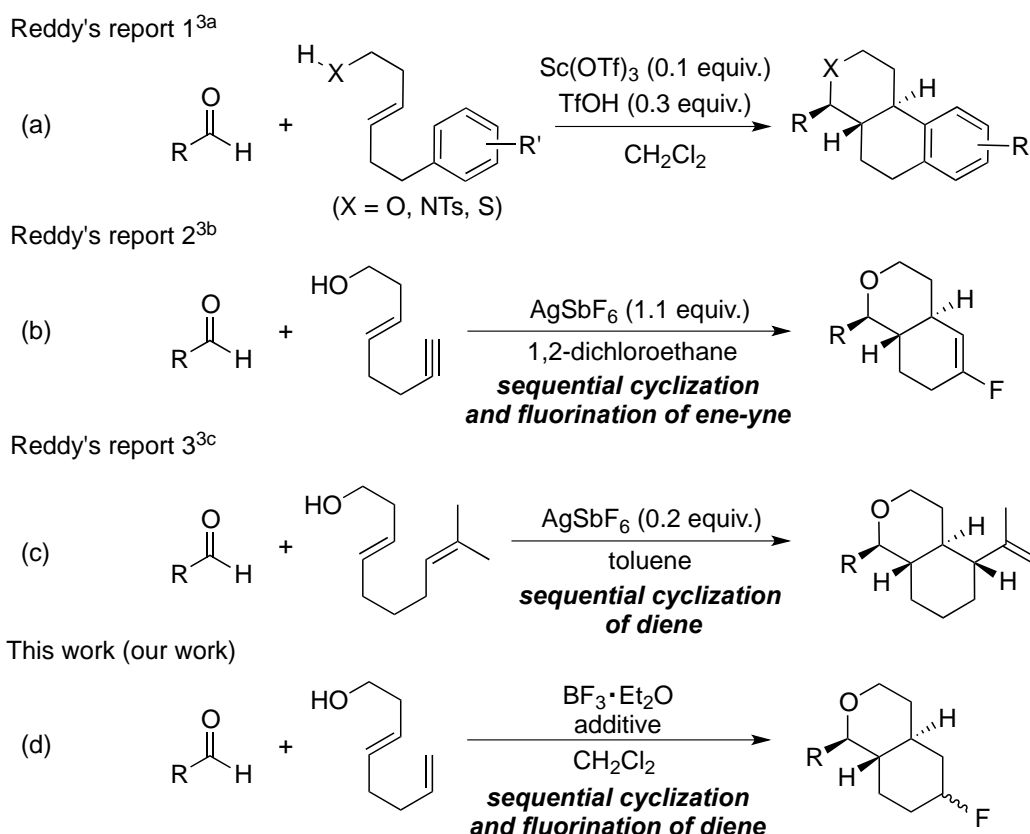
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Abstract – The sequential cyclization involving Prins cyclization was successfully demonstrated, in which the various aldehydes bearing the alkyl or aromatic substituent were reacted with the alcohol bearing the non-conjugated diene moiety in the presence of 2 equiv. of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and 4 mol% of TMSCl at $-40\text{ }^\circ\text{C}$ to afford the corresponding fluorinated bicyclic compounds in moderate to good yields.

Prins cyclization is one of the powerful methods to construct the tetrahydropyran units stereoselectively, and the extensive studies have been still devoted in this field.^{1,2} Especially, the reaction integration involving Prins cyclization is attractive in the viewpoint of the synthesis of complicated cyclic molecules, which sometimes shortens the reaction steps. For example, Reddy and co-workers reported that Prins cyclization of aldehydes with homoallylic alcohols, amines, and thiols bearing aromatic rings produced the corresponding tricyclic compounds (Scheme 1 (a)).^{3a} In this case, the intramolecular Friedel-Crafts reaction was involved to terminate the reactions. They have also developed the use of (*E*)-oct-3-en-7-yn-1-ol as a nucleophile to demonstrate the sequential cyclization and fluorination of ene-yne alcohol using AgSbF_6 , in which Prins cyclization occurred, and the generated carbocation can be trapped by the nucleophilic moieties such as carbon-carbon triple bonds (Scheme 1 (b)).^{3b} AgSbF_6 also served as the fluoride ion source in the final step. In addition, the use of (*E*)-8-methylnona-3,7-dien-1-ol

as the non-conjugated diene in Prins cyclization has realized the sequential cyclization reactions (Scheme 1 (c)).^{3c} In this report, the termination is the intramolecular attack of dimethyl-substituted carbon-carbon double bond to generate the tertiary carbocation intermediate,^{4,5} which releases H⁺ to form the final product. Thus, the integrated Prins cyclization is one of the attractive method to construct complicated cyclic molecules.^{6,7} However, to our knowledge, there is no report of Prins cyclization followed by the fluorination using the alcohol bearing the non-conjugated diene of no-substituted carbon-carbon double bond in the terminal moiety (Scheme 1 (d)).

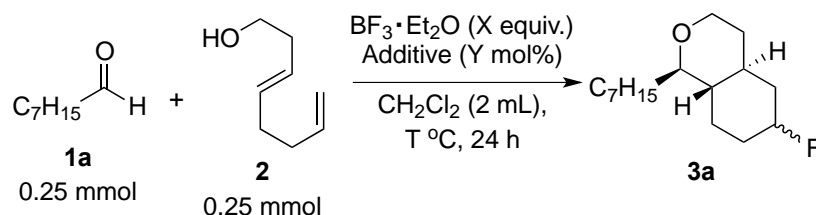
We envisioned that the reaction of aldehydes with (*E*)-octa-3,7-dien-1-ol in the presence of the suitable chemical reagents and the fluoride ion source affords the corresponding fluorinated bicyclic products (Scheme 1 (d)). In addition, the introduction of a fluorine atom into organic molecules attracts much attention because of the change of the biological activity.⁸ Herein, we wish to report the first example of the sequential cyclization using the simple diene alcohol involving Prins cyclization, followed by the fluorination by using BF₃·Et₂O.



Scheme 1. The sequential reactions involving Prins cyclization: (a)-(c) Reddy's reports 1-3, and (d) our work

First, we have carried out the reaction optimization. The reaction condition and work-up procedures used here were based on the report from Liu et al. (Table 1).^{9,10} The typical reaction procedure is as follows. The reactions of octanal (**1a**, 0.25 mmol) and (*E*)-octa-3,7-dien-1-ol (**2**, 0.25 mmol)¹¹ in the presence of the additive (5-15 mol%)¹² and BF₃·Et₂O (X, 2-4 equiv.) in CH₂Cl₂ (2 mL) were performed at T °C for 24 h. The reaction was evaluated by the product yield, according to the usual work up procedures and the purification. The reactions using aluminum(III) chloride (AlCl₃) at room temperature and 0 °C did not give the desired product **3a** at all (entries 1 and 2). However, the low reaction temperature such as -40 and -78 °C afforded the corresponding **3a** in the moderate yields (entries 3 and 4). Interestingly, the product contained the fluorine atom in the molecules. The reactions also proceeded at -40 °C without AlCl₃ (entries 5 and 6). In order to increase the product yield, we examined the various additives such as trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), *p*-toluenesulfonic acid (*p*-TSA), zinc chloride (ZnCl₂) and trimethylsilyl chloride (TMSCl), and the use of TMSCl results in slightly better yields (entries 7-11).^{13,14} In the case of the use of TMSCl, the initial stage might generate TMS-protected alcohol and HCl (vide infra). The ratio of **1a** and **2** did not dramatically affect reaction yields, and the product was obtained around 70% yields (entries 12-14). In order to obtain the better yields in the studies of the scope and limitations section, the condition of 2 equiv. of **1a** based on **2** at -40 °C was decided as the optimized condition (entry 13).

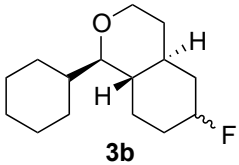
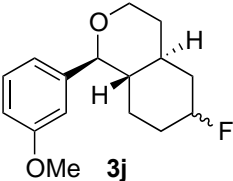
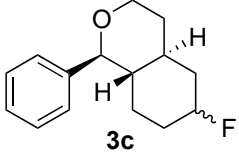
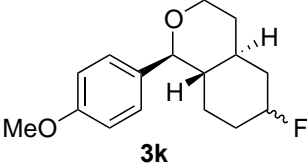
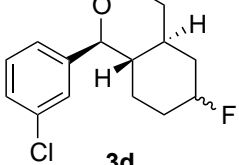
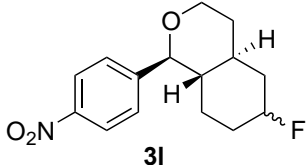
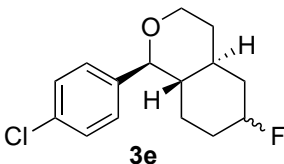
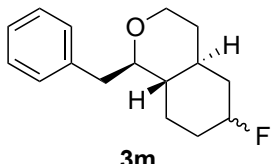
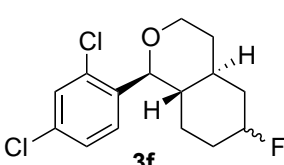
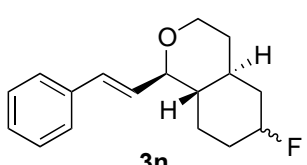
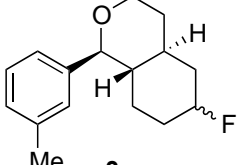
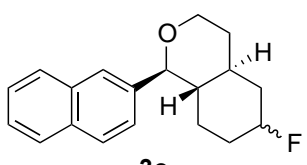
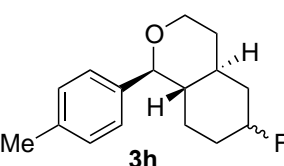
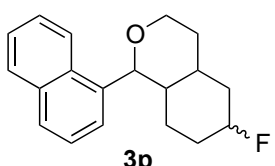
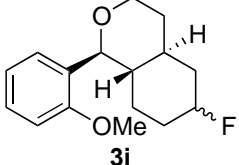
With the optimized reaction condition in hand, the scope and limitations of the sequential cyclizations were investigated (Table 2).¹⁵ The aldehydes bearing the substituents such as cyclohexyl, phenyl, *m*-ClC₆H₄-, *p*-ClC₆H₄-, *m,p*-Cl₂C₆H₃-, *m*-MeC₆H₄-, *p*-MeC₆H₄-, *o*-MeOC₆H₄-, *m*-MeOC₆H₄-, *p*-MeOC₆H₄-, and *p*-NO₂C₆H₄- could be utilized as the substrates to yield the corresponding bicyclic compounds **3b-3l** in moderate to good yields (entries 1-11). The reaction of phenylacetaldehyde with **2** in the same reaction condition afforded **3m** in 56% yield (entry 12). Interestingly, the cinnamaldehyde bearing the carbon-carbon double bond was also effective in this reaction to give **3n** in 54% yield (entry 13). The reaction of 2-naphthaldehyde with **2** led to the formation of **3o** in 66% yield (entry 14). The same reaction using 1-naphthaldehyde did not give the corresponding product **3p** at all (entry 15), although 1-naphthaldehyde as the starting material was consumed and the unidentified product was obtained.

Table 1. Reaction optimization^a

Entry	T °C	BF ₃ ·Et ₂ O (X equiv.)	Additive (Y mol%)	% Yield ^b	Ratio of diastereomers ^c a : b : g
1 ^d	rt	2	AlCl ₃ (5)	n.d. ^e	—
2	0	2	AlCl ₃ (10)	n.d. ^e	—
3	-40	2	AlCl ₃ (9)	54	0.46 : 0.45 : 0.09
4	-78	2	AlCl ₃ (9)	45 ^f	0.46 : 0.42 : 0.12
5	-40	2	—	54	0.49 : 0.40 : 0.11
6	-40	4	—	59	0.48 : 0.41 : 0.11
7	-40	2	TFA (8)	57 ^f	0.47 : 0.42 : 0.11
8	-40	2	TfOH (8)	56	0.46 : 0.43 : 0.11
9 ^g	-40	2	<i>p</i> -TSA (15)	56	0.49 : 0.43 : 0.08
10	-40	2	ZnCl ₂ (6)	70	0.46 : 0.42 : 0.12
11	-40	2	TMSCl (5)	70 ^f	0.49 : 0.40 : 0.11
12 ^h	-40	2	TMSCl (5)	65	0.45 : 0.43 : 0.12
13 ⁱ	-40	2	TMSCl (5)	71 ^f	0.48 : 0.44 : 0.08
14 ^{i,j}	-40	2	TMSCl (5)	68	0.48 : 0.41 : 0.11

^a Aldehyde (0.25 mmol) and alcohol (0.25 mmol) were used in CH₂Cl₂ (2 mL). **3a** is drawn as the estimated form for major two diastereomers **α** and **β**. ^b Isolated yields after column chromatography and/or preparative gel permeation chromatography. ^c Ratio of diastereomers of isolated products by ¹H NMR analysis. Judging from ¹H NMR analysis, there is the possibility that the purified product might contain the third diastereomer **γ**, which is a small amount but cannot be sure at present. The order of ratio of diastereomers means **α** : **β** : **γ**. The plausible structures of **α** and **β** are described in Figure 1 (vide infra). ^d The reaction time was 27 h. ^e n.d. = no detection. ^f The product contained a small amount of impurity. ^g Ratio of diastereomers was calculated based on the two separated fractions after the purification procedure. ^h Aldehyde (0.25 mmol) and alcohol (0.5 mmol) were used. ⁱ Aldehyde (0.5 mmol) and alcohol (0.25 mmol) were used. ^j The reaction time was 12 h.

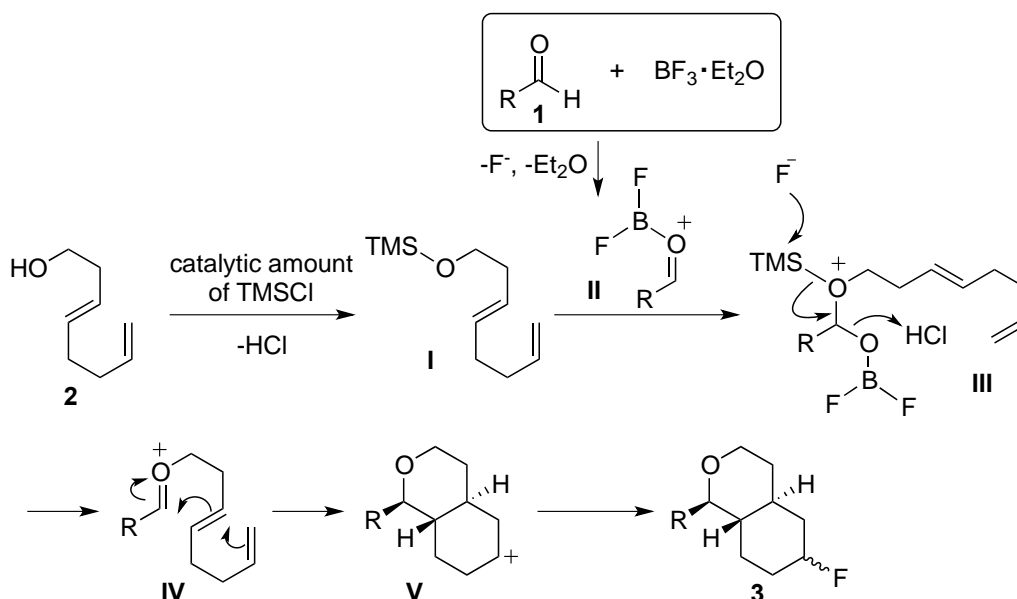
Table 2. Scope and limitations^a

Entry	Product	% Yield ^b	Entry	Product	% Yield ^b
1		81 (0.47 : 0.43 : 0.10) ^c	9		77 (0.72 : 0.24 : 0.04) ^c
2		67 (0.50 : 0.39 : 0.11) ^{c,d}	10		45 (0.56 : 0.35 : 0.09) ^{c,d}
3		65 (0.52 : 0.48) ^c	11		63 (0.72 : 0.28) ^{c,d}
4		78 (0.59 : 0.33 : 0.08) ^c	12		56 (0.52 : 0.38 : 0.10) ^{c,d}
5		61 ^{d,e}	13		54 (0.58 : 0.42) ^c
6		74 (0.76 : 0.21 : 0.03) ^c	14		66 (0.57 : 0.34 : 0.09) ^{c,d}
7		76 (0.50 : 0.39 : 0.11) ^c	15		n.d. ^f
8		56 ^e			

^a Aldehyde (0.5 mmol) and alcohol (0.25 mmol) were used in the presence of TMSCl (4 mol%) and BF₃·Et₂O (2 equiv.) in CH₂Cl₂ (2 mL) at -40 °C for 24 h. **3** is drawn as the estimated form for major two diastereomers α and β . ^b Isolated yields after preparative gel permeation chromatography of crude materials. ^c Ratio of diastereomers of isolated products by ¹H NMR analysis. Judging from ¹H NMR analysis, there is the possibility that the purified product might contain the third diastereomer γ ,

which is a small amount but cannot be sure at present. The order of ratio of diastereomers means α : β : γ . The plausible structures of α and β are described in Figure 1 (vide infra). In the case of two diastereomers α and β , third diastereomer γ might be none, trace or due to the overlapping of ^1H NMR analysis.^d The product contained a small amount of impurity.^e Ratio of diastereomers could not be calculated because of the overlapping of ^1H NMR analysis.^f n.d. = no detection.

The effect of the use of a catalytic amount of TMSCl might be explained as follows (Scheme 2). The reaction of **2** and a catalytic amount of TMSCl generates TMS-protected alcohol **I** and HCl. The activated aldehyde **II** from **1** and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ can be reacted with **I** to form the intermediate **III**. Then, TMS group in **III** is attacked by F^- in the presence of HCl to give the alkoxy-carbenium ion intermediate **IV** and HOBF_2 . The sequential cyclization of **IV** gives the secondary carbocation **V**, which reacts with fluoride ion to afford the final product **3**.¹⁰ Thus, a catalytic amount of TMSCl might promote the initial stage of the reaction. After the consumption of a catalytic amount of TMSCl, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ might play an important role for this reactions as Lewis acid and the fluoride ion source. On the cyclization from **IV** to **V**, there seem to be difficult to clarify the concerted or stepwise mechanism at present.



Scheme 2. The plausible reaction mechanism using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and a catalytic amount of TMSCl, which shows the initial stage of reactions

As for the ratio of diastereomers of **3a**, it seems that there are at least three diastereomers by ^1H NMR analysis of the purified product, shown in Table 1. The main two diastereomers α and β of **3a** seem to be derived from carbon-fluorine bond shown in Figure 1. Judging from ^1H NMR analysis, there is the possibility that the purified product might contain the third diastereomer γ . The third diastereomer γ is a

small amount but cannot be sure at present. In addition, the possibility of the fourth diastereomer cannot be ruled out, because of the possibility of the overlapping of ^1H NMR (Table 1). Similarly, the entries of Table 2 indicate the existence of two or three diastereomers in each entry. In the case of two diastereomers α and β , third diastereomer γ might be none, trace or due to the overlapping of ^1H NMR. The same might be true of the possibility of the fourth diastereomer.

In order to investigate the stereochemistry of the main two diastereomers in which α and β are drawn as estimated forms (Figure 1), the extensive separation of **31** was carried out by column chromatography. The estimated α ($\text{R} = p\text{-NO}_2\text{C}_6\text{H}_4$) was successfully isolated as the single isomer. Although the extensive NMR measurement was examined, the stereochemistry of internal carbons of connected two rings in **31** (α , $\text{R} = p\text{-NO}_2\text{C}_6\text{H}_4$) was not determined, because of the overlapping of ^1H NMR.¹⁶

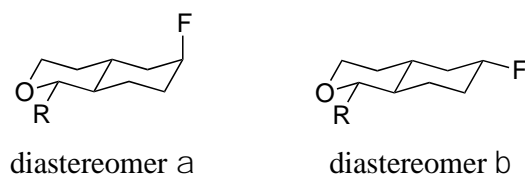


Figure 1. The plausible stereochemistry of main two diastereomers (α and β are drawn as the estimated forms.)

In conclusion, we have demonstrated the sequential reactions involving Prins cyclization from an aldehyde and the non-conjugated diene alcohol using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and a catalytic amount of TMSCl . The products obtained here had bicyclic structures and fluorine atom. The conduction at low temperature such as $-40\text{ }^\circ\text{C}$ might lead to the success of the desired reaction. The reaction was applicable for various aldehydes as the starting materials. Further synthetic studies are in progress in our laboratory.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

- Selected reviews of Prins cyclization: (a) C. Olier, M. Kaafarani, S. Gastaldi, and M. P. Bertrand, *Tetrahedron*, 2010, **66**, 413; (b) X. Han, G. Peh, and P. E. Floreancig, *Eur. J. Org. Chem.*, 2013, 1193; (c) I. M. Pastor and M. Yus, *Curr. Org. Chem.*, 2012, **16**, 1277; (d) C. Díez-Poza and A. Barbero, *Eur. J. Org. Chem.*, 2017, 4651; (e) B. V. S. Reddy, P. N. Nair, A. Antony, and N.

- Srivastava, [Eur. J. Org. Chem., 2017, 5484](#); (f) S. J. Greco, R. G. Fiorot, V. Lacerda, and R. B. dos Santos, *Aldrichimica Acta*, 2013, **46**, 59.
- Recent some examples of Prins cyclization: (a) R.-Q. Li, Y. He, Y. Ding, C.-K. Ang, J.-S. Tian, and T.-P. Loh, [Chem. Commun., 2018, 54, 3150](#); (b) J. Scoccia, S. J. Pérez, V. Sinka, D. A. Cruz, J. M. López-Soria, I. Fernández, V. S. Martín, P. O. Miranda, and J. I. Padrón, [Org. Lett., 2017, 19, 4834](#); (c) Y. Xie, G.-J. Cheng, S. Lee, P. S. J. Kaib, W. Thiel, and B. List, [J. Am. Chem. Soc., 2016, 138, 14538](#); (d) L. Liu, P. S. J. Kaib, A. Tap, and B. List, [J. Am. Chem. Soc., 2016, 138, 10822](#); (e) S. Dubbu and Y. D. Vankar, [Eur. J. Org. Chem., 2017, 5986](#); (f) S. Slater, P. B. Lasonkar, S. Haider, M. J. Alqahtani, A. G. Chittiboyina, and I. A. Khan, [Tetrahedron Lett., 2018, 59, 807](#); (g) J. S. Yadav, M. A. Rahman, N. M. Reddy, and A. R. Prasad, [Tetrahedron Lett., 2015, 56, 365](#).
 - (a) B. V. S. Reddy, P. Borkar, J. S. Yadav, B. Sridhar, and R. Grée, [J. Org. Chem., 2011, 76, 7677](#); (b) A. Venkateswarlu, M. Kanakaraju, A. C. Kunwar, Y. V. R. Reddy, and B. V. S. Reddy, [Eur. J. Org. Chem., 2015, 5389](#); (c) B. V. S. Reddy, A. Venkateswarlu, B. Sridevi, K. Marumudi, A. C. Kunwar, and G. Gayatri, [Org. Biomol. Chem., 2015, 13, 2669](#).
 - 'Carbocation Chemistry', ed. by G. A. Olah and G. K. S. Prakash, Wiley, 2004.
 - For some literatures of the reactivity of cations: (a) H. Mayr and A. R. Ofial, [Angew. Chem. Int. Ed., 2006, 45, 1844](#); (b) M. Hofmann, N. Hampel, T. Kanzian, and H. Mayr, [Angew. Chem. Int. Ed., 2004, 43, 5402](#).
 - Some examples of the other integrated and sequential reactions involving Prins cyclization: (a) L. M. Reddy, V. V. Reddy, V. Sateyyanaidu, J. K. Lakshmi, C. K. Reddy, and B. V. S. Reddy, [Tetrahedron Lett., 2018, 59, 1084](#); (b) M. R. Reddy, G. R. Kumar, S. Yarlagaadda, C. R. Reddy, J. S. Yadav, B. Sridhar, and B. V. S. Reddy, [RSC Adv., 2016, 6, 113390](#); (c) A. Barbero, A. Diez-Varga, M. Herrero, and F. J. Pulido, [J. Org. Chem., 2016, 81, 2704](#); (d) H. Abas, S. M. Linsdall, M. Mamboury, H. S. Rzepa, and A. C. Spivey, [Org. Lett., 2017, 19, 2486](#); (e) B. V. S. Reddy, A. Venkateswarlu, P. Borkar, J. S. Yadav, M. Kanakaraju, A. C. Kunwar, and B. Sridhar, [J. Org. Chem., 2013, 78, 6303](#); (f) B. V. S. Reddy, A. Venkateswarlu, P. Borkar, J. S. Yadav, B. Sridhar, and R. Grée, [J. Org. Chem., 2014, 79, 2716](#); (g) A. Venkateswarlu, M. Kanakaraju, A. C. Kunwar, and B. V. S. Reddy, [Org. Biomol. Chem., 2015, 13, 10212](#). See also, ref. 1 (d).
 - Review of the reaction integration. See: (a) J. Yoshida, A. Shimizu, Y. Ashikari, T. Morofuji, R. Hayashi, T. Nokami, and A. Nagaki, [Bull. Chem. Soc. Jpn., 2015, 88, 763](#); (b) J. Yoshida, K. Saito, T. Nokami, and A. Nagaki, [Synlett, 2011, 1189](#).
 - Selected examples for the fluorinated tetrahydropyrans via Prins cyclizations: (a) S. Bondalapati, U. C. Reddy, D. S. Kundu, and A. K. Saikia, [J. Fluorine Chem., 2010, 131, 320](#); (b) A. P. Dobbs, L. Pivnevi, M. J. Penny, S. Martinović, J. N. Iley, and P. T. Stephenson, [Chem. Commun., 2006, 3134](#);

- (c) Y. Kishi, H. Nagura, S. Inagi, and T. Fuchigami, *Chem. Commun.*, 2008, 3876; (d) G. G. Launay, A. M. Z. Slawin, and D. O'Hagan, *Beilstein J. Org. Chem.*, 2010, 6, No. 41; (e) Y. Liu and Y.-Y. Yeung, *Org. Biomol. Chem.*, 2017, 15, 6478; (f) K. Damera, B. Yu, and B. Wang, *J. Org. Chem.*, 2015, 80, 5457; (g) J. Yoshida, Y. Ishichi, and S. Isoe, *J. Am. Chem. Soc.*, 1992, 114, 7594; (h) Y. Kishi, S. Inagi, and T. Fuchigami, *Eur. J. Org. Chem.*, 2009, 103; (i) J. Yoshida, M. Sugawara, M. Tatsumi, and N. Kise, *J. Org. Chem.*, 1998, 63, 5950; (j) K. Matsumoto, S. Fujie, K. Ueoka, S. Suga, and J. Yoshida, *Angew. Chem. Int. Ed.*, 2008, 47, 2506.
9. G.-Q. Liu, B. Cui, R. Xu, and Y.-M. Li, *J. Org. Chem.*, 2016, 81, 5144.
10. Selected examples using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the fluorine source: (a) J. Wölfling, É. Frank, E. Mernyák, G. Bunkóczi, J. A. C. Seijo, and G. Schneider, *Tetrahedron*, 2002, 58, 6851; (b) M.-C. P. Yeh, C.-J. Liang, T.-L. Huang, H.-J. Hsu, and Y.-S. Tsau, *J. Org. Chem.*, 2013, 78, 5521; (c) J. Cui, Q. Jia, R.-Z. Feng, S.-S. Liu, T. He, and C. Zhang, *Org. Lett.*, 2014, 16, 1442; See also, (d) A. J. Cresswell, S. G. Davies, P. M. Roberts, and J. E. Thomson, *Chem. Rev.*, 2015, 115, 566.
11. (*E*)-Octa-3,7-dien-1-ol (**2**) was synthesized as follows. The reflux of 3-iodopropan-1-ol with PPh_3 in MeCN gave the corresponding phosphonium salt after removal of the solvent. It was then allowed to react with *n*-BuLi (0 °C) in THF, followed by commercially available pent-4-enal to give octa-3,7-dien-1-ol as the mixture of *E* and *Z* isomers, after the usual work up and the column chromatography. The mixture of *E* and *Z* isomers thus obtained was separated and purified by gel permeation chromatography (GPC), which was carried out on Japan Analytical Industry LC-9201 or LC-9210NEXT equipped with JAIGEL-1H and 2H using CHCl_3 as eluent, to obtain (*E*)-octa-3,7-dien-1-ol (**2**). The stereochemistry of *E* isomer was determined by the coupling constant of ^1H NMR analysis. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (br s, 1H), 2.14 (t, $J = 3.2$ Hz, 4H), 2.27 (dt, $J = 6.8, 6.0$ Hz, 2H), 3.62 (td, $J = 6.0, 4.8$ Hz, 2H), 4.97 (d, $J = 10.8$ Hz, 1H), 5.01 (d, $J = 18.8$ Hz, 1H), 5.40 (dt, $J = 15.6, 6.8$ Hz, 1H), 5.55 (br d, $J = 14.8$ Hz, 1H), 5.73-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 32.0, 33.6, 35.9, 61.8, 114.8, 126.4, 133.4, 138.3; HRMS (APCI) calcd for $\text{C}_8\text{H}_{15}\text{O}$ (MH^+): 127.1117, found: 127.1115.
12. Because it was difficult to take exactly a small amount of weight of additive in the reaction, the amount of additive used in the reactions in Table 1 was distributed from 5 mol% to 15 mol%.
13. The procedure of the reaction of octanal (**1a**) and (*E*)-octa-3,7-dien-1-ol (**2**) using TMSCl and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Table 1, entry 11): To a solution of TMSCl (ca. 1.6 μL , $d = 0.86$, ca. 0.013 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (65 μL , $d = 1.11$, ca. 0.51 mmol) in CH_2Cl_2 (2 mL), octanal (**1a**, 32.2 mg, 0.25 mmol) and (*E*)-octa-3,7-dien-1-ol (**2**, 31.4 mg, 0.25 mmol) was added at -40 °C. After 24 h, additional CH_2Cl_2 (10 mL) and H_2O (10 mL) was added and separated.^{8d,9} The organic layer was dried over MgSO_4 .

After removal of the solvent, the resulting crude material was purified by GPC to obtain 6-fluoro-1-heptyloctahydro-1*H*-isochromene (**3a**, 44.6 mg, 0.174 mmol, 70%).

14. Selected spectroscopic data: 6-fluoro-1-heptyloctahydro-1*H*-isochromene (**3a**). ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, *J* = 6.8 Hz, 3H), 0.91-1.17 (m, 1H), 1.13-1.82 (m, 19H), 1.92-2.23 (m, 2H), 2.90 (td, *J* = 8.4, 2.8 Hz, 1H, diastereomer **β**), 2.99 (td, *J* = 8.4, 2.4 Hz, 1H, diastereomer **α**), 3.42 (td, *J* = 11.6, 3.6 Hz, 1H, diastereomer **β**), 3.49 (td, *J* = 11.6, 2.8 Hz, 1H, diastereomer **α**), 4.00 (ddd, *J* = 11.6, 4.4, 1.6 Hz, 1H), 4.49 (d hep, *J* = 44.9, 6.0 Hz, 1H, diastereomer **β**), 4.87 (d, *J* = 48.8 Hz, 1H, diastereomer **α**), 4.93 (d, *J* = 47.6 Hz, 1H, diastereomer **γ**); ¹³C NMR (100 MHz, CDCl₃) diastereomer **α**: δ 14.1, 21.8, 22.7, 25.2, 29.3, 29.8, 30.6 (d, *J* = 20.9 Hz), 31.9, 32.7, 33.3, 34.2, 37.5 (d, *J* = 21.0 Hz), 45.6, 68.1, 81.2, 88.4 (d, *J* = 165.9 Hz), and diastereomer **β** (selected): δ 25.1, 25.6, 32.4, 33.0, 33.5, 38.4 (d, *J* = 10.5 Hz), 39.2 (d, *J* = 17.1 Hz), 45.1, 67.9, 81.3, 91.5 (d, *J* = 171.6 Hz); LRMS (EI) *m/z* 255 (M⁺-H), 157 (M⁺-C₇H₁₅); HRMS (EI) calcd for C₁₆H₂₈FO (M⁺-H): 255.2124, found: 255.2121.
15. TMSCl (4 mol%) was used in order to avoid the possibility that Cl⁻ derived from TMSCl attacks the cyclized carbocation intermediates.
16. Thus, the stereochemistry of purified products of **3a-3p** in Tables 1 and 2 is not clear at present. In particular, the determination of the stereochemistry of the internal carbons of connected two rings is difficult. Therefore, the structures are drawn as the estimated forms in Tables 1 and 2. As for this point, we will plan the X-ray analysis to clear the detail of the stereochemistry, when we obtain the solid and crystal products. The results will be reported elsewhere including the additional synthetic studies as the full paper.