EurJOC
European Journal of Organic Chemistry

Communication
doi.org/10.1002/ejoc.202000820

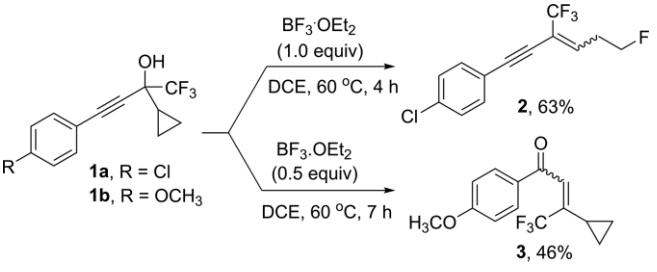
Ring-Opening Reactions

Dehydrative Ring-Opening of *gem*-Difluorocyclopropyl Carbinols to Allylic Trifluoromethyl and Difluorohalomethyl Derivatives Promated by Titanium Tetrahalide

Manickavasakam Ramasamy,[a] Sheng-Chu Kuo,[a,b,c] and Min-Tsang Hsieh*[a,b,c,d]

Abstract: We report herein the titanium tetrahalide-promoted dehydrative ring-opening of *gem*-difluorocyclopropyl carbinols as a novel method for the synthesis of (*E*)-allylic CF_3, (*E*)-allylic CF_2Cl, and (*E*)-allylic CF_2Br compounds. This TiF_4-promoted reaction appears to proceed via a concerted S_N2' mechanism. A control experiment revealed that the $TiCl_4$-promoted ring-opening initially proceeds by conversion of the *gem*-difluorocyclopropyl carbinol into a *gem*-difluorocyclopropyl chloride intermediate.

Fluorinated molecules have figured prominently in chemistry due to their unique medicinal properties, structural novelty, and rich chemistry.[1] Over the past two decades, more than 40 % of blockbuster drugs have incorporated fluorinated functional groups.[2] Fluorine substitution is a valuable strategy for enhancing target selectivity, drug potency, and achieving a favorable physicochemical/pharmacokinetic profile at the lead-to-candidate optimization stage of drug discovery.[3] Numerous investigations have cumulated in the development of improved general methods for the synthesis of fluorinated compounds. Previously, we developed a practical BF_3•OEt_2-catalyzed Meyer–Schuster rearrangement for the preparation of β-fluoroalkyl-α,β-enones,[4] which are versatile compounds for the synthesis of trifluoroalkyl-containing cyclic compounds.[5] During the course of our synthetic studies toward trifluoromethyl-substituted compounds, we observed that treatment of cyclopropyl-substituted propargylic alcohol **1a** with BF_3•OEt_2 did not afford the expected rearrangement product, rather, the dehydrative ring-opening product **2** was obtained instead. Further studies revealed substitution group-controlled selectivity, as evidenced by an experiment in which the *p*-methoxy-substituted compound **1b** preferred to rearrange rather than ring-open under similar reaction conditions to those used to prepare **2** (Scheme 1).



Scheme 1. Reactions of propargylic alcohols with BF_3•OEt_2.

We then reasoned that an electron-withdrawing group positioned on the benzene ring would hinder the rearrangement of the adjacent propargylic alcohol skeleton and facilitate ring-opening, while BF_3•OEt_2 would serve as an effective agent to promote the dehydrative ring-opening of cyclopropyl carbinols toward the allylic fluoride products. Based on strain energies calculated by G2 theory, *gem*-dimethyl substitution lowers the ring strain of the cyclopropane, whereas *gem*-difluoro substitution destabilizes the cyclopropane ring by increasing the strain energy by 12–14 kcal/mol.[6] The energetic nature of the *gem*-difluoro-substituted cyclopropane renders it more reactive to nucleophilic substitution than an unsubstituted cyclopropane. Brønsted acids, such as hydrobromic acid and the acetic acid/*p*-TSA system,[7] have been documented to promote the ring-opening of *gem*-difluorocyclopropyl carbinols towards the β,β-difluorohomoallyl and α,α-difluorohomoallyl derivatives. Xiao et al. reported that BF_3•OEt_2 promoted the ring-opening of *gem*-difluorocyclopropyl ketones to give β-trifluoromethyl ketones.[8] The method is not restricted to BF_3•OEt_2, as BCl_3 and BBr_3 both effectively facilitated the ring-opening of the *gem*-difluorocyclopropyl ketone. The same group also reported that the treatment of *gem*-difluorocyclopropyl ketones with nitriles in the presence of triflic acid afforded 2-fluoropyrroles.[9] In addi-

[a] *M. Ramasamy, Prof. S.-C. Kuo, Prof. M.-T. Hsieh*
School of Pharmacy, China Medical University,
Taichung 40402, Taiwan
E-mail: t21917@mail.cmu.edu.tw
http://webap.cmu.edu.tw/TchEportfolio/index_1/t21917
[b] *Prof. S.-C. Kuo, Prof. M.-T. Hsieh*
Chinese Medicine Research Center, China Medical University,
Taichung 40402, Taiwan
[c] *Prof. S.-C. Kuo, Prof. M.-T. Hsieh*
Research Center for Chinese Herbal Medicine, China Medical University,
Taichung 40402, Taiwan
[d] *Prof. M.-T. Hsieh*
Chinese Medicinal Research and Development Center, China Medical
University Hospital, Taiwan
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202000820.

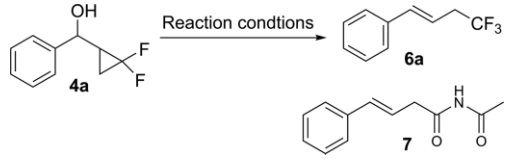
tion, MgI_2[10] strong bases,[11] thiol nucleophiles,[12] and the *N*-pentylpyridinium bromide/triflic acid system[13] showed substantial abilities to promote the ring-opening of *gem*-difluorocyclopropyl ketones. Recently, the synthesis of 3-fluorofurans from the *gem*-difluorocyclopropyl ketones was realized with two equivalents of triflic acid.[14]

With this background in mind, we became interested in the dehydrative ring-opening of *gem*-difluorocyclopropyl carbinols for the synthesis of allylic CF_3 compounds.[15] In this communication, we report the titanium tetrahalide-promoted dehydrative ring-opening of *gem*-difluorocyclopropyl carbinols for the synthesis of allylic CF_3, allylic CF_2Cl,[16] and allylic CF_2Br compounds,[7] which are useful fluorine-containing synthetic building blocks.

All *gem*-difluorocyclopropyl carbinols used in the current study were prepared by the direct reduction of the corresponding *gem*-difluorocyclopropyl ketones[8] or in four-step sequences comprising acetal protection of a chalcone followed by *gem*-difluorocyclopropanation and acid hydrolysis of the resulting 1,3-dioxolane, followed by reduction of the obtained *gem*-difluorocyclopropyl chalcone analog[17] (see SI for more details). At the onset of the study, difluorocyclopropyl carbinol **4a** was used as the model compound. The abilities of $BF_3{\cdot}OEt_2$ and metal fluorides, including AlF_3, TiF_4, CuF_2, and AgF, to effect the ring-opening reaction were examined, the results of which are summarized in Table 1. Carbinol **4a** was treated with one equivalent of $BF_3{\cdot}OEt_2$ in 1,2-DCE to give the thermodynamically more stable (*E*)-allyl CF_3 product **6a** in moderate-to-good yields. The (*E*)-geometry of **6a** was determined by the vicinal ^1H NMR coupling constant of the olefinic moiety, which is typical for *trans*-oriented protons. AgF and CuF_2, which are mildly Lewis acidic, did not promote the reaction, and AlF_3 appears not to be the reagent of choice due to the very low yield of **6a** obtained. The use of TiF_4 proved to be fruitful for producing **6a** in good yield (76 %, entry 5). The reagent loading can also be reduced to 0.5 equivalents without significant loss of reaction efficiency or yield (entry 6). The reaction displayed significant solvent dependence; low yields were obtained with three solvents, namely 1,4-dioxane (entry 8), THF (entry 9), and toluene (entry 10). The imide **7** was unexpectedly formed when acetonitrile was employed as the solvent (entry 11). The formation of **7** is possibly ascribable to a defluorinative hydrolysis process, in which the nitrile rather than the fluoride ion is involved in the initial nucleophilic ring-opening of the *gem*-difluoromethyl group to form an unstable intermediate which, in turn, undergoes facile hydrolysis of its difluoromethyl and nitrile moieties.[18] Therefore, we conclude that the conditions shown in entry 6 are optimal and were subsequently used in the general procedure.

The substrate scope and generality of the TiF_4-promoted ring-opening reaction were next examined for *gem*-difluorocyclopropyl carbinols **4b**–**l** (Table 2). Compounds **4b**–**f** bearing electron-donating groups, including *p*-methyl, *p*-methoxy, *m*-methoxy, *p*-phenoxy, and *m*-dimethoxy, were amenable to the optimized reactions and furnished the corresponding (*E*)-allylic CF_3 compounds **6b**–**f** in moderate-to-good yields (55–80 %). Electron-withdrawing groups, such as *p*-chloro, *p*-bromo, *p*-iodo, and *p*-nitro appeared to retard the reaction and extended reaction times (≈ 2 h) were required to produce **6g**–**i**. The reactions of *gem*-difluorocyclopropyl carbinols substituted with 3-chloro-4-methoxyphenyl and naphthyl groups proceeded well to yield **6k** (79 %) and **6l** (67 %), respectively. The effect of phenyl substitution at the vicinal position of the *gem*-difluoromethylene carbon was then examined. The reactions of **5a** and **5b** with TiF_4 provided the corresponding trifluorinated compounds **8a** and **8b** instead of the allylic trifluoromethylated compounds, suggesting that the benzylic carbon is more elec-

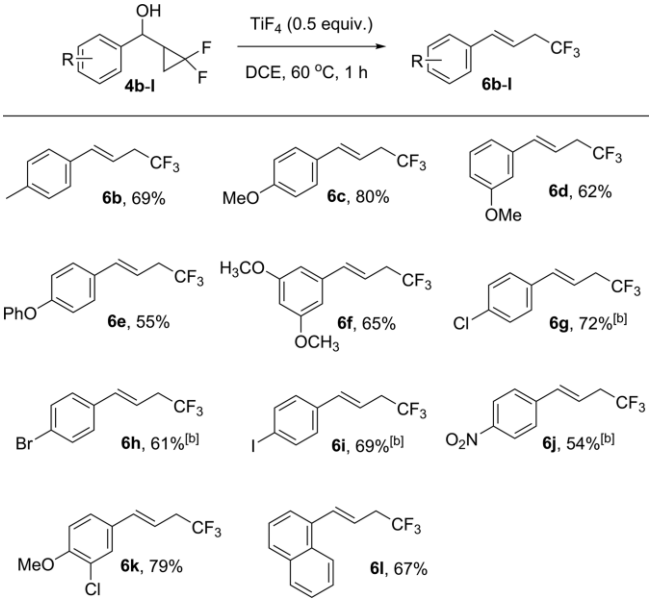
Table 1. Optimizing the reaction conditions.[a]



Entry	Regent	Solvent/Temp	Time [h]	Yield [%][b]
1	$BF_3{\cdot}OEt_2$ (1.0 equiv.)	1,2-DCE/60 °C	0.5	58
2	AlF_3 (1.0 equiv.)	1,2-DCE/60 °C	3.0	< 5
3	AgF (1.0 equiv.)	1,2-DCE/60 °C	4.0	0
4	CuF_2 (1.0 equiv.)	1,2-DCE/60 °C	4.0	0
5	TiF_4 (1.0 equiv.)	1,2-DCE/60 °C	0.5	76
6	TiF_4 (0.5 equiv.)	1,2-DCE/60 °C	0.5	75
7	TiF_4 (0.25 equiv.)	1,2-DCE/60 °C	2.0	39[c]
8	TiF_4 (0.5 equiv.)	1,4-dioxane/60 °C	1.0	26
9	TiF_4 (0.5 equiv.)	THF/60 °C	2.0	23
10	TiF_4 (0.5 equiv.)	Toluene/60 °C	2.0	19
11	TiF_4 (0.5 equiv.)	Acetonitrile/40 °C	0.5	**7** (44 %)[d]

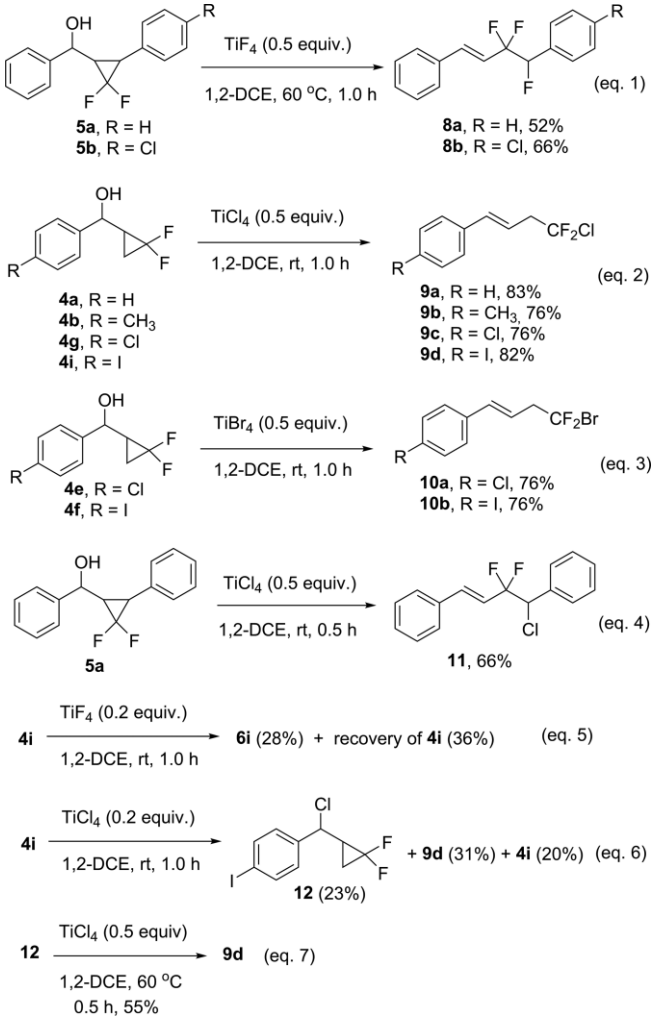
[a] All reactions were performed using alcohol **4a** (0.27 mmol) in 1 mL of anhydrous solvent as indicated above. [b] Yields are for isolated, chromatographically pure products. [c] **4a** was recovered in 30 % yield. [d] Imide **7** was obtained instead of the expected **6a**.

Table 2. Reaction scope of the TiF_4-promoted dehydrative ring-opening.[a]



[a] Isolated yields after silica gel chromatography. [b] 2 h reaction time is required for these cases.

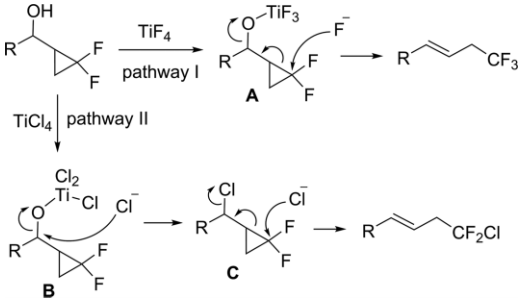
trophilic than the *gem*-difluoromethylene carbon toward fluoride addition (eq. 1, Scheme 2). Subsequently, $TiCl_4$ and $TiBr_4$, which are both more Lewis acidic than TiF_4, were used to promote the dehydrative ring-opening reaction. Using slightly modified reaction temperatures and times, the $TiCl_4$-promoted reactions of **4a**–**b**, **4g**, and **4i** smoothly provided the corresponding (*E*)-allyl CF_2Cl compounds **9a**–**d** in good yields (76–83 %, eq. 2). Similar results were obtained in the $TiBr_4$-mediated reactions, which smoothly produced the (*E*)-allyl CF_2Br compounds **10a** and **10b** (eq. 3). In addition, treatment of **5a** with $TiCl_4$ gave the *gem*-difluorodichloromethane **11** (eq. 4), confirming again that **5a** prefers to be nucleophilically attacked at the benzylic position.



Scheme 2. Ring-opening of *gem*-difluorocyclopropyl carbinols.

Insight into the ring-opening reaction was gained through control studies in which reduced amounts of titanium reagents and mild conditions were used. The reaction of **4i** with TiF_4 (0.2 equiv.) at ambient temperature led only to **6i** and recovery of starting carbinol, with no trace of a possible intermediate detected (eq. 5). Apart from (*E*)-allylic **9d**, the $TiCl_4$-promoted reaction of **4i** (eq. 6) afforded chloro compound **12**, which is a possible reaction intermediate. This presumption was then verified in a reprocessing experiment (eq. 7); **9d** was obtained in 55 % yield when **12** was heated with $TiCl_4$ (0.5 equiv.).

A plausible mechanism for this chemistry is shown in Scheme 3. Dehydrative ring-opening of a *gem*-difluorocyclopropyl carbinol can occur via two S_N2'-type pathways. In pathway I, the reaction of the carbinol with TiF_4 produces the TiF_3-carbinol complex **A**, which undergoes fluoride addition and ring-opening with concurrent elimination of $TiOHF_3$ in a concerted fashion. In pathway II, treatment of the carbinol with $TiCl_4$ gives the $TiCl_3$-carbinol complex **B**, which quickly rearranges to form the intermediate chloride **C**; this intermediate then undergoes an addition/ring-opening/elimination sequence to yield the allylic CF_2Cl product. However, the possibility that the $TiCl_4$-promoted ring-opening of a *gem*-difluorocyclopropyl carbinol proceeds via a pathway I-like concerted mechanism still exists.



Scheme 3. The plausible mechanism.

In summary, we established an effective reaction system for inducing the dehydrative ring-opening of *gem*-difluorocyclopropyl carbinols, leading to the corresponding (*E*)-allylic CF_3, (*E*)-allylic CF_2Cl, and (*E*)-allylic CF_2Br derivatives in moderate-to-high yields. The current methodology, which uses readily accessible TiF_4, $TiBr_4$, and $TiCl_4$, is operationally simple. We are currently synthesizing challenging allylic CF_3 compounds in our laboratory by extending these reactions.

Acknowledgments

This research project was funded by Ministry of Science and Technology, Taiwan (MOST 106-2113-M-039-005) and "Chinese Medicine Research Center, China Medical University" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-6).

Keywords: Cyclopropanes · Fluorinated compounds · Ring-opening reactions · Synthetic methods · Titanium

[1] a) M. T. Hsieh, S. C. Kuo, H. C. Lin, *Adv. Synth. Catal.* **2015**, *357*, 683; b) C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441; c) H. X. Song, Q. Y. Han, C. L. Zhao, C. P. Zhang, *Green Chem.* **2018**, *20*, 1662; d) M. T. Hsieh, K. H. Lee, S. C. Kuo, H. C. Lin, *Adv. Synth. Catal.* **2018**, *360*, 1605; e) M. Cheng, C. Guo, M. Gross, *Angew. Chem. Int. Ed.* **2020**, *59*, 5880; *Angew. Chem.* **2020**, *132*, 5932.
[2] a) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. AceÇa, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Solo-

shonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432; c) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev.* **2018**, *118*, 3887; d) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi, V. A. Soloshonok, *Chem. Eur. J.* **2019**, *25*, 11797.

[3] a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315; b) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822.

[4] M. Ramasamy, H. C. Lin, S. C. Kuo, M. T. Hsieh, *Synlett* **2019**, *30*, 356.

[5] a) J. Congmon, M. A. Tius, *Eur. J. Org. Chem.* **2003**, *2003*, 2853; b) Y. Li, H. Wang, Y. Su, R. Li, C. Li, L. Liu, J. Zhang, *Org. Lett.* **2018**, *20*, 6444.

[6] R. D. Bach, O. Dmitrenko, *J. Org. Chem.* **2002**, *67*, 2588.

[7] Y. Kobayashi, T. Morikawa, T. Taguchi, *Chem. Pharm. Bull.* **1983**, *31*, 2616.

[8] T. P. Yang, Q. Li, J. H. Lin, J. C. Xiao, *Chem. Commun.* **2014**, *50*, 1077.

[9] T. P. Yang, J. H. Lin, Q. Y. Chen, J. C. Xiao, *Chem. Commun.* **2013**, *49*, 9833.

[10] W. Xu, I. Ghiviriga, Q. Y. Chen, W. R. Dolbier, *J. Fluorine Chem.* **2010**, *131*, 958.

[11] Y. Kobayashi, T. Taguchi, T. Morikawa, T. Takase, H. Takanashi, *Tetrahedron Lett.* **1980**, *21*, 1047.

[12] Y. Kobayashi, T. Taguchi, T. Morikawa, T. Takase, H. Takanashi, *J. Org. Chem.* **1982**, *47*, 3232.

[13] W. Xu, W. R. Dolbier, J. Salazar, *J. Org. Chem.* **2008**, *73*, 3535.

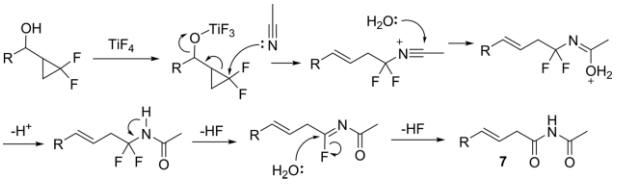
[14] T. Sugiishi, C. Matsumura, H. Amii, *Org. Biomol. Chem.* **2020**, *18*, 3459.

[15] For recent synthesis of allylic CF_3 compounds, see a) A. T. Parsons, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9120; *Angew. Chem.* **2011**, *123*, 9286; b) Y. Miyake, S. Ota, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 13255; c) B. R. Ambler, R. A. Altman, *Org. Lett.* **2013**, *15*, 5578; d) J. M. Larsson, S. R. Pathipati, K. J. Szabó, *J. Org. Chem.* **2013**, *78*, 7330; e) J. Li, P. Wang, F. F. Xie, X. G. Yang, X. N. Song, W. D. Chen, J. Ren, B. B. Zeng, *Eur. J. Org. Chem.* **2015**, *2015*, 3568; f) F. de Azambuja, S. M. Lovrien, P. Ross, B. R. Ambler, R. A. Altman, *J. Org. Chem.* **2019**, *84*, 2061.

[16] S. Kawamura, C. J. Henderson, Y. Aoki, D. Sekine, S. Kobayashi, M. Sodeoka, *Chem. Commun.* **2018**, *54*, 11276.

[17] W. Xu, Q. Y. Chen, *Org. Biomol. Chem.* **2003**, *1*, 1151.

[18] The proposed mechanism for the formation of imide **7** is represented schematically as follows. The hydrolysis of the σ-difluoro acetamide intermediate into the imide product was recently reported by Selander's lab. For reference, see: Z. Zheng, A. van der Werf, M. Deliaval, N. Selander, *Org. Lett.* **2020**, *22*, 2791.

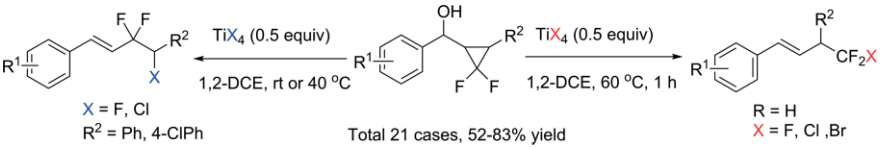


Received: June 9, 2020

Communication
doi.org/10.1002/ejoc.202000820

Chemistry Europe
European Chemical Societies Publishing

Ring-Opening Reactions



An effective approach to (*E*)-allylic CF_3, (*E*)-allylic CF_2Cl, (*E*)-allylic CF_2Br derivatives, 1-chloro-2,2-difluoromethylene, and polyfluorinated compounds has been developed, based on a titanium tetrahalide-promoted dehydrative ring-opening of *gem*-difluorocyclopropyl carbinols.

doi.org/10.1002/ejoc.202000820