Development of synthetic methods and expression of functions for organofluorine compounds by utilization of the properties of fluorine atoms

（フッ素原子の特性を活用する有機フッ素化合物の合成法開発と機能発現）

Ryunosuke Kani

2023

Preface

This research is carried out at the Department of Engineering, Graduate School of Engineering, Gifu University, under the supervision of Professor Kazumasa Funabiki from April 2018 to September 2023. In this thesis, synthetic studies of fluorine-containing compounds and characterization of fluorinated organic dyes were performed. The author would like to express my sincere gratitude to Professor Kazumasa Funabiki for his kind instruction, valuable suggestions, and encouragement in the laboratory. The author is also sincerely grateful to Professor Yohei Miwa for his useful advice and discussions during this research. The author is deeply grateful to Professor Shoichi Kutsumizu, Associate Professor Toshiyasu Inuzuka, and Assistant Professor Yasuhiro Kubota for their guidance and precious discussions. The author is thankful to Ms. Ayaka Hayakawa, Mr. Takaya Nakajima, Mr. Toshiya Gotoh, Mr. Hisaki Matsueda, Mr. Yuki Uehashi, and Mr. Yuta Arisawa for their valuable comments and kind technical assistance. The author also thanks all members of the Funabiki group for their encouragement and friendship. And generous support for research and living expenses by the Sasakawa Scientific Research Grant from The Japan Science Society, and Interdisciplinary Frontier Next-Generation Researcher Program of the Tokai Higher Education and Research System is gratefully acknowledged. Finally, the author's parents, Takashi and Yukako Kani, are most grateful for their financial support and understanding to his research activities.

Ryunosuke Kani

Department of Engineering Science

Graduate School of Engineering

Gifu university

Contents

General Introduction 1

Chapter 1. One-Pot Successive Turbo Grignard Reactions for the Facile Synthesis of α-Aryl-α-Trifluoromethyl Alcohols 8

Chapter 2. Synthesis of 1-Trifluoromethylated Propargyl Alcohols by Two Successive Reactions of Cyclopentylmagnesium Bromide in a One-Pot Manner 40

Chapter 3. Aromatic fluorine atom-induced highly amine-sensitive trimethine cyanine dye showing colorimetric and ratiometric fluorescence change 92

Chapter 4. Rapid and dual optical CO_2-responsive polydimethylsiloxane elastomer with fluorinated cyanine dye 123

General Conclusion 144

Publications List 148

Presentations List 149

General Introduction

The clever incorporation of fluorine atoms and fluorine substituents into organic compounds has attracted much attention because it is a powerful tool for giving unique physical, chemical, and biological properties in the field of functional materials such as medical and agrochemical products, polymers, and dyes.[1-3] In the field of pharmaceuticals and agrochemicals, 22% of all pharmaceuticals[4] and 16% of agrochemicals[5] currently on the market below 500 g/mol contain fluorine. The number has been increasing over the past decade and is expected to grow. Examples of significant fluorinated pharmaceuticals are shown in Fig. 1.

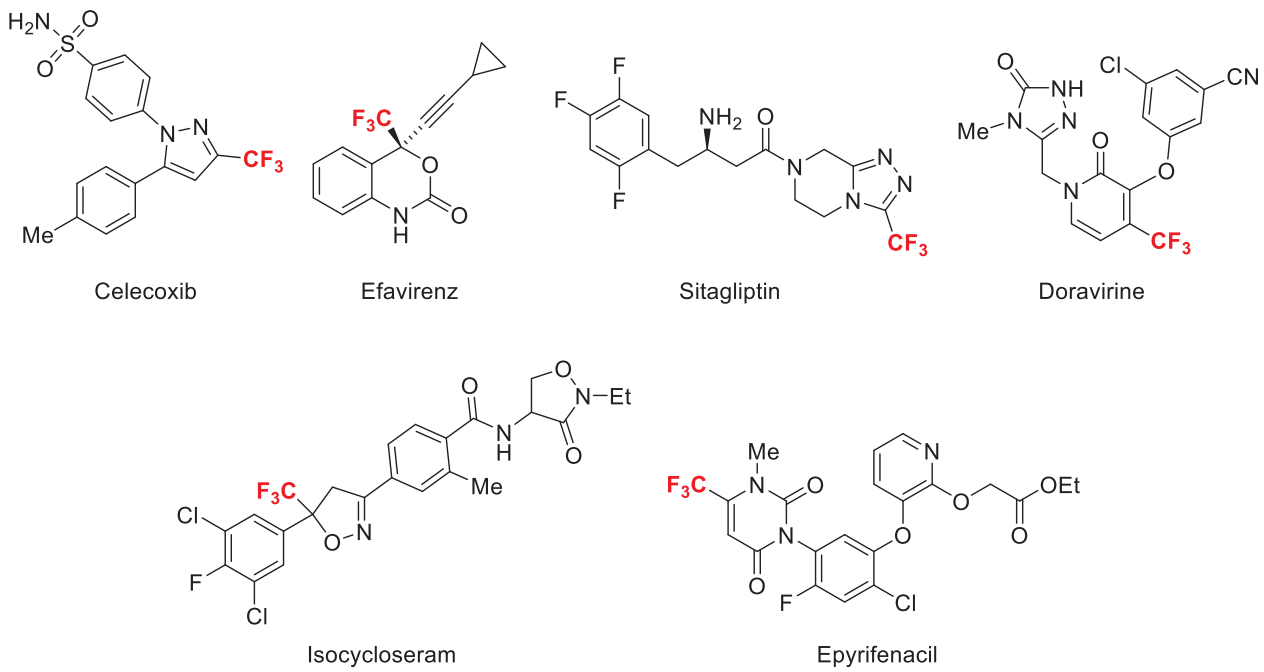


Fig. 1. Structures of significant trifluoromethylated compounds in the areas of pharmaceuticals and agrochemicals.

Fluorine atoms are valuable in pharmaceuticals for the following five reasons. 1) The mimic effect: The van der Waals radius of a fluorine atom (1.47 Å)[6] is close to that of a hydrogen atom (1.20 Å),

thus replacing some of the hydrogen atoms in existing pharmaceutical molecules with fluorine atoms will work in the same way. 2) Polarity effect: Fluorine has the highest electronegativity (4.0 in Pauling scale) among all atoms and introducing it into a molecule causes a large change in electron density. 3) Blocking effect; the C-F bond is strong (averages about 116 kcal/mol)[7] and is not readily oxidized in vivo, leading to sustain the drug effect. 4) The hydrophobic effect of fluorine substituent promotes transport and intracellular absorption of drug molecules. 5) Strong electron-withdrawing property of fluorine substituent (F: $\sigma_m = 0.34$, $\sigma_p = 0.06$) (CF_3: $\sigma_m = 0.43$, $\sigma_p = 0.54$)[8], which increases acidity and decreases basicity[9]. Hence, the combination of these unique properties of fluorine presumably exerts subtle effects on the absorption, distribution, metabolism, and excretion (ADME) of drug candidates[10-12] In the polymer field, fluorine-containing polymers have attracted great interest over the past few decades because of their attractive properties. Strong C-F bonds lead to high thermal and chemical stability and low surface energy of fluorine helps in oil-repellence resulting in increased resistance to wear and abrasion[13]. Moreover, in the development of solution-processed bulk heterojunction solar cells, fine-tuning the physical and chemical properties of conducting polymers by fluorination is a useful strategy for improving photoelectric conversion[14]. In a functional dye field, absorption and emission wavelengths and aggregation-induced emission properties are tunable with the position and number of fluorine atoms introduced into the dye backbone.[15-19] The fluorine substituents also decrease the electron density of the dye, which increases electrophilicity[20,21] and reduces reactivity with singlet oxygen, improving photostability [22-25]. Furthermore, changing to a counterion with multiple fluorine atoms greatly enhanced absorbance and dye solubility because of increasing hydrophobicity and inhibiting aggregation of dyes[26]. These methods are promising for further improvement and discoveries of the functions of organic dyes. In other functional materials, unique compounds such as perfluorocubane[27] and perfluorocycloparaphenylene[28] were synthesized for the first time, respectively, showing that the fluorine atom significantly changed their electronic properties. They are in the limelight as next-generation functional materials. In the synthesis of functional organic materials such

as pharmaceutical and agrochemical products, polymers, and dyes containing fluorine atoms, it is difficult to apply standard synthetic transformations for non-fluorinated compounds in many cases[29]. Therefore, it is essential to investigate the unique properties of fluorine substituents to establish a synthetic route to control the reaction. For example, the C-F bond is highly polarized, allowing the fluorine atom to provide a dipole-like stabilizing effect to the cation at the α-position. The σ*C-F bond is low energy and can interact with neighboring electrons. Therefore, the conformational gauche effect appears, and the reaction can be controlled[30]. Other unique reactivity of fluorinated compounds includes α, α-difluoroenolates, which behave as an electrophile because of the unusual induction effect of fluorine atom, reducing the electron density at the α-position. These results exhibit the opposite property of non-fluorinated enolates, acting as nucleophiles[31]. In addition, substituents such as the trifluoromethyl group cause negative inductive and hyperconjugation effects that can stabilize the anion at α-position[32]. Moreover, nucleophilic aromatic substitution (S_NAr) reactions are known to take place because the fluorine atom is a good leaving group. S_NAr reactions also occur with electron-withdrawing groups other than fluorine atoms (e.g., nitro and cyano groups). However, reactions which replace all fluorine atoms on the aromatic ring[33-35], are unique to fluorine atoms. As described above, fluorine atoms have specific properties not found in other atoms. Consequently, it is still challenging to develop new synthetic methods for organofluorine compounds and simple strategy to introduce fluorine atoms into existing compounds efficiently. Investigation of their exciting properties will be helpful in drug discovery and the development of functional materials. Accordingly, the purpose of this thesis is to assess the changes in molecular properties with fluorine atoms by exploring novel synthetic methods for organofluorine compounds and fluorine-containing functional materials.

In Chapter 1, the author describes a novel one-pot, facile synthetic method that involves two successive reactions of turbo Grignard reagent (*i*-PrMgCl·LiCl) for α-aryl-α-trifluoromethyl alcohols, valuable motifs as pharmaceutical molecules. The method showed tolerance to a wide

range of functional groups, including reducible substituents. The process utilizes three successive reactions in a one-pot manner: iodine/magnesium exchange reaction of iodoarenes or iodoheteroarenes with *i*-PrMgCl·LiCl and nucleophilic addition of the prepared aryl or heteroaryl magnesium reagents to 2,2,2-trifluoroethyl trifluoroacetate; and reduction of the aryl trifluoromethyl ketones formed in the system with *i*-PrMgCl·LiCl to afford the corresponding α-aryl or α-heteroaryl-trifluoromethyl alcohols with various substituents in good to excellent yield.

In Chapter 2, the author succeeded in a one-pot, functional-group-tolerant synthesis of various 3-substituted 1-trifluoromethylpropargyl alcohols using two reactions of cyclopentylmagnesium bromide (CpMgBr) with trifluoroacetic acid esters and terminal alkynes. This new synthetic method involves three successive reactions in a one-pot process: 1) deprotonation of terminal alkynes with cyclopentylmagnesium bromide, 2) reduction of 2,2,2-trifluoroethyl trifluoroacetate with cyclopentylmagnesium bromide, and 3) nucleophilic addition of in-situ generated alkynyl Grignard reagents to in-situ formed trifluoroacetaldehyde, leading to the corresponding 1-trifluoromethylated propargyl alcohols. This method can be applied to various fluorine-containing esters as well as terminal alkynes carrying alkyl or aryl groups to obtain 1-polyfluoroalkylated propargyl alcohols. Furthermore, the obtained 1-trifluoromethyl propargyl alcohol having aromatic substituents can be converted in good to excellent yields to 1,5-diaryl-3-trifluoromethyl dihydropyrazole, some of the most important motifs in pharmaceuticals for treating pain and inflammation associated with osteoarthritis in dogs.

In Chapter 3, the author discusses a powerful method for dramatically increasing sensitivity to amines by introducing fluorine atoms into the aromatic rings of trimethine cyanine dye. Ratiometric fluorescent properties afforded only by intramolecular additions were also available for reactions with intermolecular amines and other nucleophiles. Furthermore, the amine adduct

of this dye was also sensitive to CO_2. The presence of fluorine atoms reduced the lowest unoccupied orbital (LUMO) of the dye, increasing its reactivity to amines.

In Chapter 4, the author has developed a rapid CO_2 responsiveness elastomer prepared from polydimethylsiloxane (PDMS) with carboxy groups, an amine cross-linker, and fluorinated cyanine dye. This elastomer sheet reacted to CO_2 gas, with the color turning from colorless to red and the fluorescent color changing from blue to pink (within 1 min). Elastomer sheet using dye without fluorine atoms did not respond to CO_2, indicating that the CO_2 response of the amine adduct of fluorinated cyanine dye was improved by introducing fluorine atoms into the aromatic rings.

References

1. D. Cahard, V. Bizet, *Chem. Soc. Rev.* **2014**, *43*, 135-147.
2. T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470-477.
3. K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886.
4. M. Inoue, Y. Sumii, N, Shibata, *ACS Omega* **2020**, *5*, 10633-10640.
5. Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 9, 101467.
6. A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441-451.
7. C. Ni, M. Hu, J. Hu, *Chem. Rev.* **2015**, *115*, 765-825.
8. C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165-195.
9. B. E. Smart, *J. of Fluorine Chem.* **2001**, *109*, 3-11.
10. J. Han, L. Kiss, H. Mei, A. M. Remete, M. Ponikvar-Svet, D. M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki, V. A. Soloshonok, *Chem. Rev.* **2021**, *121*, 4678-4742.
11. M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2004**, *44*, 214-231.
12. H. J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander, M. Stahl, *Chembiochem* **2004**, *5*, 637-643.
13. M. G. Dhara, S. Banerjee, *Prog. Polym. Sci.* **2010**, *35*, 1022-1077.
14. F. Meyer, *Prog. Polym. Sci.* **2015**, *47*, 70-91.
15. M. Masato, S. Yamada, and T. Konno, *Molecules* **2021**, *26,* 8, 2274.
16. K. Funabiki, K. Yamada, H. Matsueda, Y. Arisawa, T. Agou,Y. Kubota, T. Inuzuka, and H. Wasada, *Eur. J. Org. Chem.* **2021**, 1344–1350.
17. I. Caivano, Z. Tošner, I. Císařová, D. Nečas, and M. Kotora, *ChemPlusChem* **2020**, *85*, 9, 2010-2016.
18. K. Funabiki, Y. Saito, T. Kikuchi, K. Yagi, Y. Kubota, T. Inuzuka, Y. Miwa, M. Yoshida, O. Sakurada, S. Kutsumizu, *J. Org. Chem.* **2019**, *84,* 7, 4372-4380.
19. M. A. Potopnyk, D. Volyniuk, M. Ceborska, P. Cmoch, I. Hladka, Y. Danyliv, and J. V. Gražulevičius, *J. Org. Chem.,* **2018**, *83*, 19, 12129–12142.

20. R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki, *RSC Adv.* **2022**, *12*, 25587-25592.
21. For a recent paper of dyes with trifluoroacetyl groups, see. J.-F. Lin, J. Kukkola, T. Sipola, D. Raut, A. Samikannu, J.-P. Mikkola, M. Mohl, G. Toth, W.-F. Su, T. Laurila, K. Kordas, *J. Mater. Chem. A* **2015**, *3*, 4687-4694.
22. Y. Sonoda, K. Kamada, *J. Fluorine Chem.* **2023**, *267*, 110110.
23. Y. Uehashi, S. Izawa, Y. Yamada, Y. Miwa, T. Inuzuka, Y. Kubota, M. Hiramoto, K. Funabiki, *ChemistrySelect* **2023**, *8*, e202300309.
24. Y. Arisawa, Y. Kubota, T. Inuzuka, K. Funabiki, *ChemistrySelect* **2022**, *7*, e202104213.
25. K. Funabiki, K. Yagi, M. Ueta, M. Nakajima, M. Horiuchi, Y. Kubota, M. Mastui, *Chem. - Eur. J.* **2016**, *22*, 12282-12285.
26. Y. Yang, C. Sun, S. Wang, K. Yan, M. Zhao, B. Wu, F. Zhang, *Angew. Chem. Int. Ed.* **2022**, *61,* e202117436.
27. M. Sugiyama, M. Akiyama, Y. Yonezawa, K. Komaguchi, M. Higashi, K. Nozaki, T. Okazoe, *Science* **2022**, *377*, 756-759.
28. H. Shudo, M. Kuwayama, M. Shimasaki, T. Nishihara, Y. Takeda, N. Mitoma, T. Kuwabara, A. Yagi, Y. Segawa, K. Itami, *Nat. Commun.* **2022**, *13*, 3713.
29. C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441-5454.
30. L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860-11871.
31. D. L. Orsi, R. A. Altman, *Chem. Commun.* **2017**, *53*, 7168-7181.
32. C. M. Volla, A. Das, I. Atodiresei, M. Rueping, *Chem. Commun.* **2014**, *50*, 7889-7892.
33. N. Shida, K. Ninomiya, N. Takigawa, K. Imato, Y. Ooyama, I. Tomita, S. Inagi, *Macromolecules* **2021**, *54*, 725-735.
34. K. Ninomiya, N. Shida, T. Nishikawa, T. Ishihara, H. Nishiyama, I. Tomita, S. Inagi, *ACS Macro Lett.* **2020**, *9*, 284-289.
35. W. J. Ong, T. M. Swager, *Nat. Chem.* **2018**, *10*, 1023-1030.

Chapter 1.

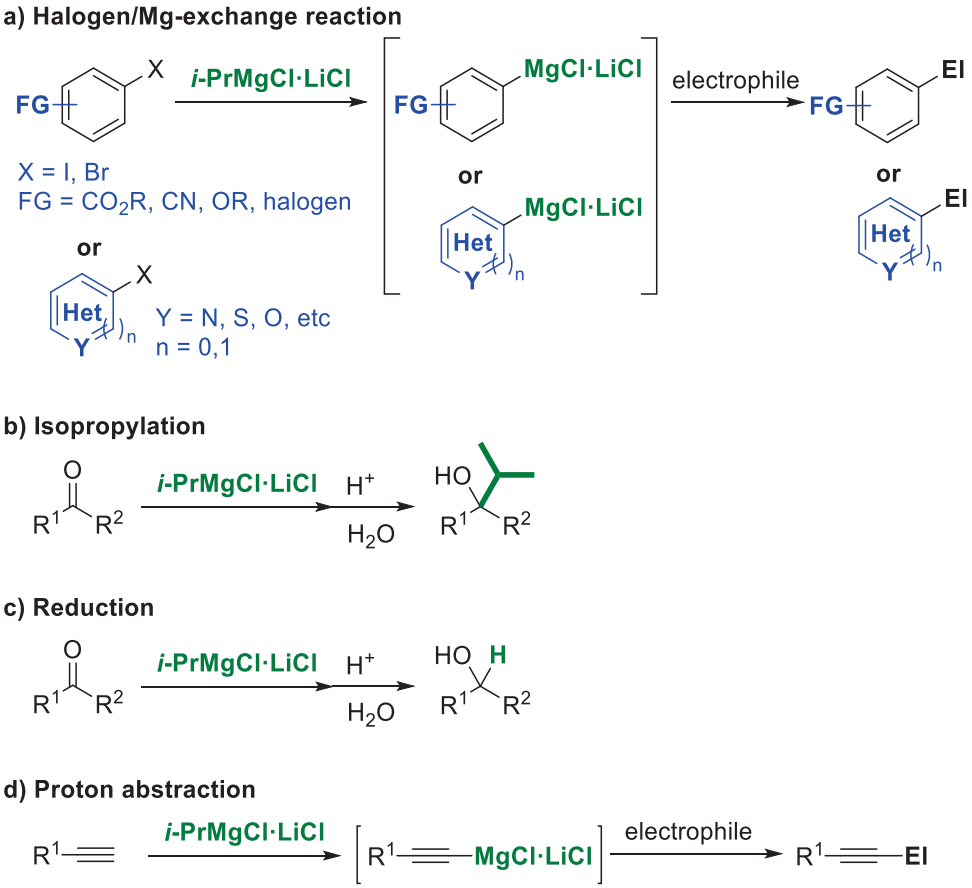
One-Pot Successive Turbo Grignard Reactions for the Facile Synthesis of α-Aryl-α-Trifluoromethyl Alcohols

Abstract

A novel straightforward one-pot methodology for two successive turbo Grignard reagent (*i*-PrMgCl·LiCl) reactions, was developed for a facile synthesis of α-aryl-α-trifluoromethyl alcohols, motifs of value in pharmaceutical molecules. The method displayed broad functional group tolerance, including reducible groups. Dual roles of *i*-PrMgCl·LiCl were exploited in the tandem reaction with commercially available iodoarenes or iodoheteroarenes and 2,2,2-trifluoroethyl trifluoroacetate. The process encompasses three successive reactions in a one-pot process: the *i*-PrMgCl·LiCl-mediated iodine/magnesium-exchange reaction of iodoarenes or iodoheteroarenes; nucleophilic addition of various generated aryl or heteroaryl magnesium reagents to 2,2,2-trifluoroethyl trifluoroacetate; and the reduction of in-situ generated aryl trifluoromethyl ketones with *i*-PrMgCl·LiCl, to produce the corresponding α-aryl or α-heteroaryl-α-trifluoromethyl alcohols bearing various substituents, including reducible functional groups in good to excellent yields.

Introduction

The Turbo Grignard reagent (*i*-PrMgCl·LiCl) introduced by Knochel in 2004, is among the most general and promising reagents for the preparation of polyfunctionalized aryl, heteroaryl, and alkenylmagnesium reagents by selective halogen/magnesium (Mg)-exchange reactions of various halo-arenes and -heteroarenes. It enables the synthesis of a variety of complex molecules at laboratory and industrial scale.[1-11] A significant advantage of the reagent is the tolerance of various functional groups, such as esters, nitriles, hydroxyl, and boronic esters in the halogen/Mg-exchange reaction, due to increased reactivity compared to the Mg metal or other Grignard reagents by the formation of a lithium chloride complex (Scheme 1a).



Scheme 1. Reactions of the turbo Grignard reagent.

Although *i*-PrMgCl·LiCl has been employed as a carbon nucleophile (Scheme 1b), a reducing agent (Scheme 1c), and a base (Scheme 1d) in addition to the halogen/Mg-exchange reaction, there are no reports of synthetic methodologies that utilize two or more of these reactions successively in a one-pot manner.

On the other hand, in recent years, α-aryl-α-trifluoromethyl alcohols have become more prominent in pharmaceutical molecules, for example in LP-533401 and LX1606/LX1033, which are tryptophan inhibitors used for the treatment of osteoporosis and of gastrointestinal symptoms related to the carcinoid syndrome (Fig. 1).[12-20]

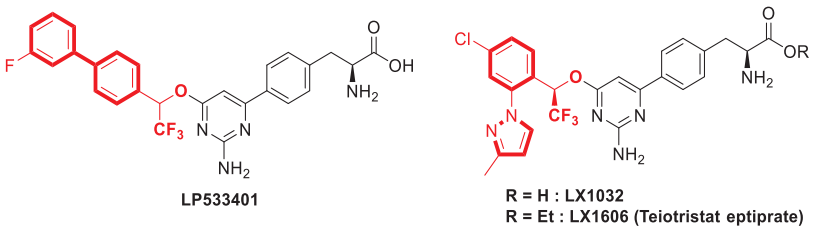
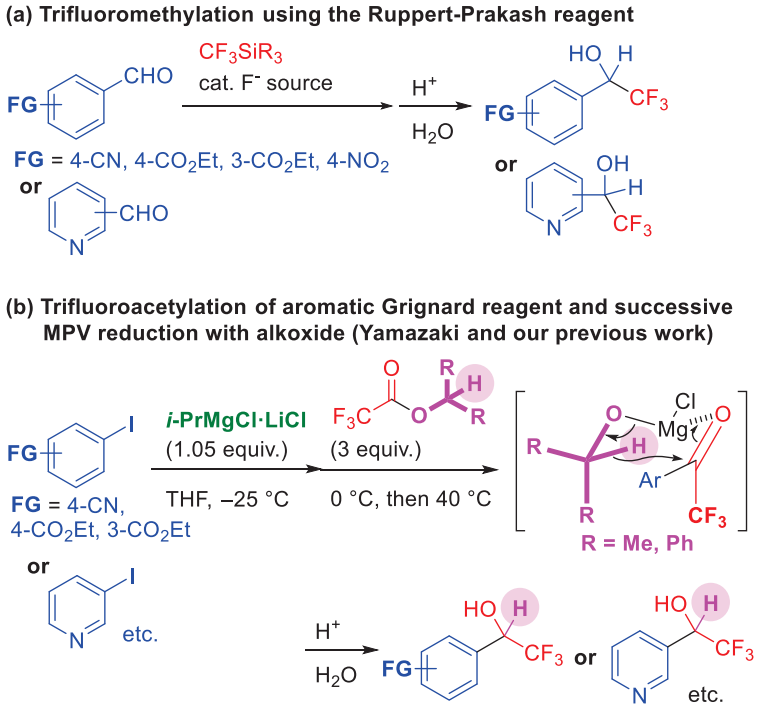


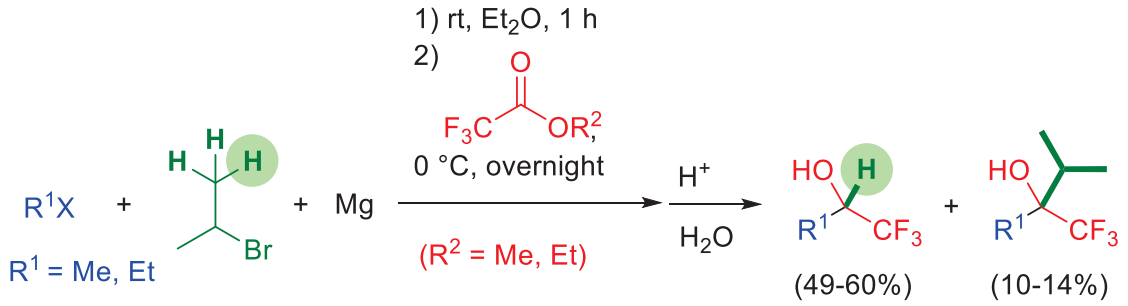
Fig. 1. Pharmaceutical molecules with an α-trifluoromethyl ether motif.

Although various synthetic approaches to α-aryl-α-trifluoromethyl alcohols have been developed, there are limited examples of syntheses that tolerate reducible functional groups. Examples include reactions with the Ruppert–Prakash reagent (Scheme 2a)[21-30] or the tandem iodine/Mg-exchange reaction, arylation of isopropyl or diphenylmethyl trifluoroacetate, and the Meerwein–Ponndorf–Verley type reduction of in-situ generated aryl trifluoromethyl ketones by isopropoxide or diphenylmethoxide (Scheme 2b).[31,32] However, the development of the methodologies for simple and efficient route to such compounds has still been desired.



Scheme 2. Previous work on the reducible functional group-tolerant syntheses of α-aryl-α-trifluoromethyl alcohols.

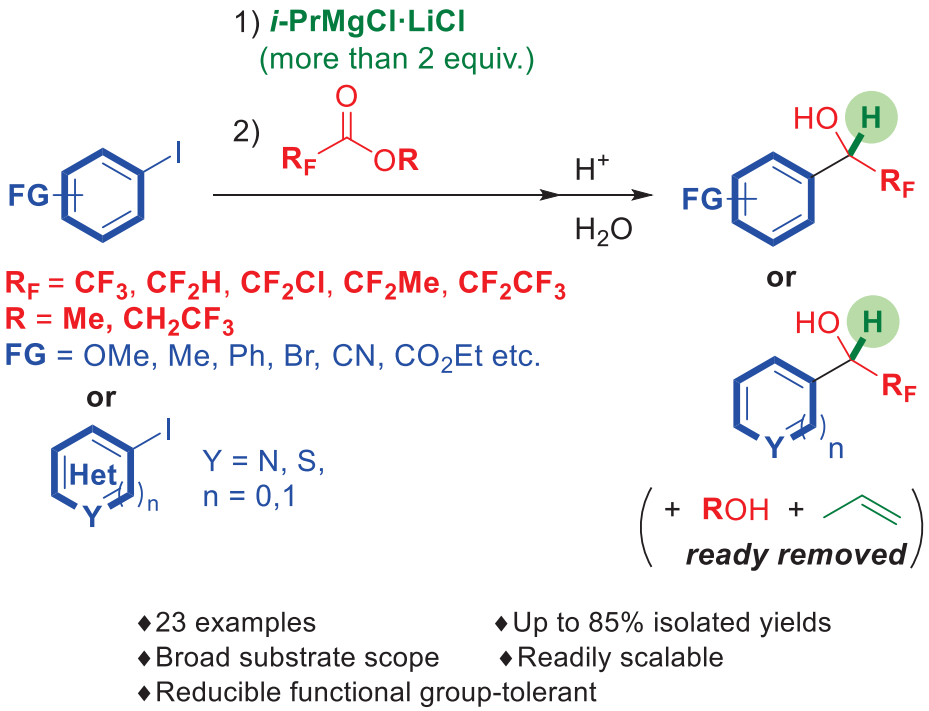
In 1953, McBee et al. reported that two types of Grignard reagents, including methyl- or ethyl-magnesium iodides and isopropylmagnesium bromide, were successfully employed for the successive alkylation and reduction of trifluoroacetic acid esters to afford the corresponding α-trifluoromethyl secondary alcohols in moderate yields (Scheme 3).[33]



Scheme 3. Previous work on the successive alkylation and reduction of trifluoroacetic acid esters with Grignard reagents.

However, this method suffers a significant disadvantage, which is the narrow scope of Grignard reagents, due to the difficulty of preparing aryl or heteroaryl Grignard reagents with various reducible functional groups from the corresponding haloarenes and haloheteroarenes and Mg metal.

We present herein the development of a novel and straightforward one-pot synthetic methodology entailing two distinct successive reactions with the turbo Grignard reagent (*i*-PrMgCl·LiCl), for the facile and reducible functional group-tolerant synthesis of α-aryl-α-trifluoromethyl alcohols from iodoarenes or iodeheteroarenes and 2,2,2-trifluoroethyl trifluoroacetate (Scheme 4). This approach entails three successive steps: 1) the in-situ formation of aryl Grignard reagents from iodo-arenes or -heteroarenes by the iodine/Mg-exchange reaction with *i*-PrMgCl·LiCl; 2) in-situ generation of aryl trifluoromethyl ketones by the reaction of the formed aryl Grignard reagents with the trifluoroacetic acid ester; and 3) the reduction of generated aryl trifluoromethyl ketones by *i*-PrMgCl·LiCl. (Scheme 4). Advantages of the protocol include tolerance of various reducible functional groups, and straightforward operation and removal of by-products.

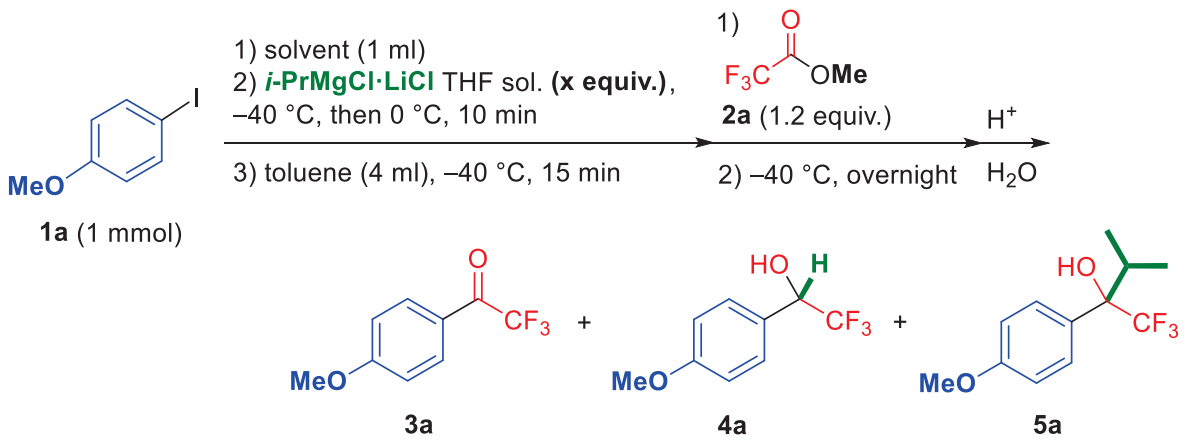


Scheme 4. This work.

Results and Discussion

When 1-iodo-4-methoxybenzene (**1a**) was added to 1 equiv. of *i*-PrMgCl·LiCl in THF at –40 °C, the iodine/Mg-exchange proceeded smoothly to give the corresponding arylmagnesium reagent, which readily reacted with 1.2 equiv. of methyl trifluoroacetate (**2a**). The reaction afforded the corresponding trifluoromethyl ketone, 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one (**3a**) and its equivalents, the hemiacetal and hydrate in a combined yield of 46 %, together with a 13 % yield of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) and a trace amount of an isopropylated adduct, 1,1,1-trifluoro-2-(4-methoxyphenyl)-3-methylbutan-2-ol (**5a**) (Table 1, entry 1).

Table 1. Optimization of reaction conditions using 1-iodo-4-methoxybenzene (**1a**)

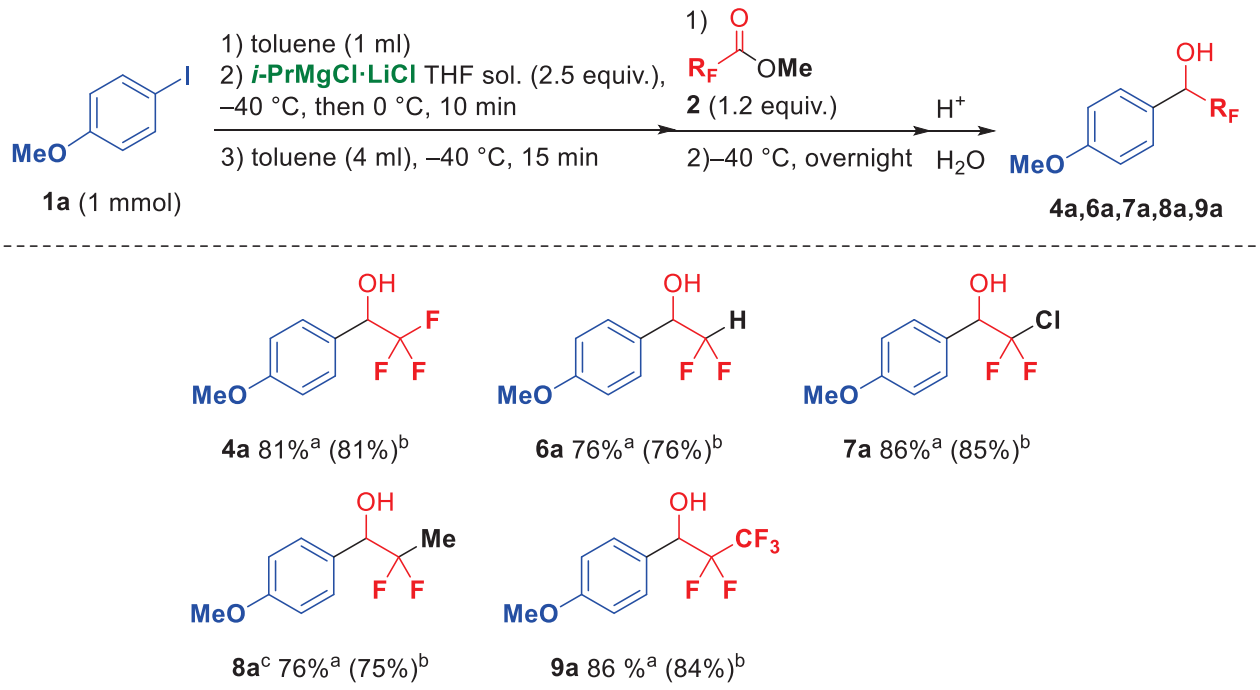


Entry	Solvent	*i*-PrMgCl·LiCl (equiv.)	^{19}F NMR yield (%) of Ketone **3a**, its hemiacetal, and hydrate	Alcohol **4a**	*i*-Pr-adduct **5a**
1	THF	1.0	46	13	trace
2	THF	2.5	8	72	trace
3	toluene	2.5	0	81 (81)[a]	trace

[a] Yields of isolated product.

Increasing *i*-PrMgCl·LiCl equivalents from 1 to 2.5 resulted in a significant increase in the yield of the secondary trifluoromethyl alcohol **4a** (72 %), while the combined yield of ketone **3a** and its equivalents decreased to 8 % (Entry 2). It should be noted that the use of toluene as a solvent led to the complete reduction of ketone **3a** to increase the yield (81 %) of the secondary trifluoromethyl alcohol **4a** (entry 3).

Next, other commercially available fluorine-containing esters **2** were evaluated in the tandem dual reaction under this optimized reaction conditions (Method A). (Scheme 5).

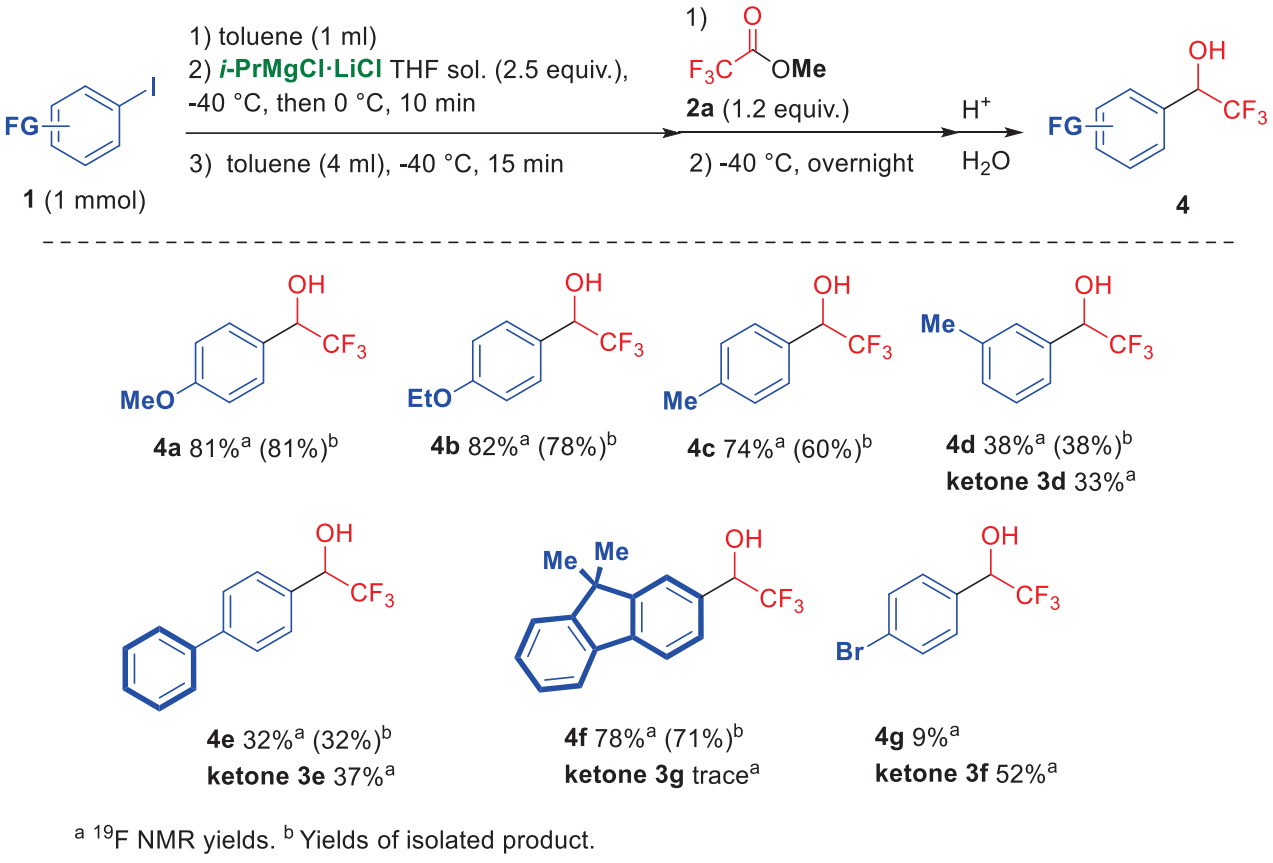


[a] ^{19}F NMR yields. [b] Yields of isolated product. [c] Ethyl ester for the synthesis of **8a** was used.

Scheme 5. Substrate scope of fluorine-containing esters **2** (Method A).

Hence, methyl 2,2-difluoroacetate, methyl 2-chloro-2,2-difluoroacetate, ethyl 2,2-difluoropropanoate, and methyl 2,2,3,3,3-pentafluoropropanoate (**2b**–**e**) were treated with 1-iodo-4-methoxybenzene (**1a**) and 2.5 equiv. of *i*-PrMgCl·LiCl under the above-described conditions to deliver the corresponding difluoromethylated, chlorodifluoromethylated, difluoroethylated, and pentafluoroethylated alcohols **6a**, **7a**, **8a**, and **9a** in good to excellent yields.

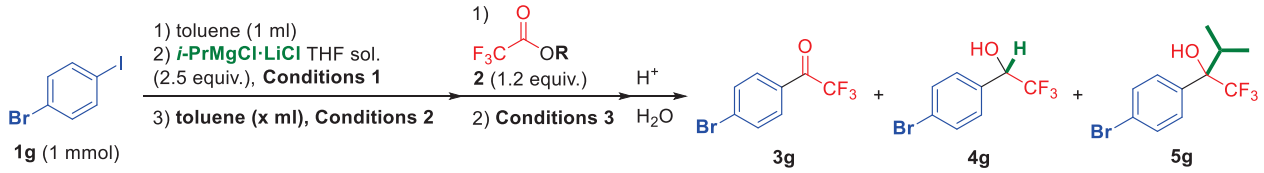
Other iodoarenes, such as 1-ethoxy-4-iodobenzene (**1b**) and 1-iodo-4-methylbenzene (**1c**), as well as 2-iodo-9,9-dimethyl-9*H*-fluorene (**1f**), also participated in the tandem dual reaction of *i*-PrMgCl·LiCl with methyl trifluoroacetate (**2a**) to give the corresponding trifluoromethyl alcohols **4b**, **4c**, and **4f** in high yields (Scheme 6).



Scheme 6. Substrate scope of iodoarenes **1** using methyl trifluoroacetate (**2a**) (Method A).

The use of 1-iodo-3-methylbenzene (**1d**) and 4-iodo-1,1'-biphenyl (**1e**) afforded the corresponding trifluoromethyl alcohols **4d** and **4e** in 38 % and 32 % yields, respectively, together with the corresponding trifluoromethyl ketones **3d** and **3e** in 33 % and 37 % yields, respectively. The reaction of 1-bromo-4-iodobenzene (**1g**) with 2.5 equiv. of *i*-PrMgCl·LiCl and 1.2 equiv. of methyl trifluoroacetate (**2a**) provided the corresponding trifluoromethyl alcohol **4g** in a poor yield of 9 % and trifluoromethyl ketone **3f** as the major product in 52 % yield. To improve the yield of alcohol **4g** bearing the 4-bromophenyl group, the reaction conditions were investigated in more detail, as shown in Table 2.

Table 2. Optimization of reaction conditions using 1-bromo-4-iodobenzene (**1g**)

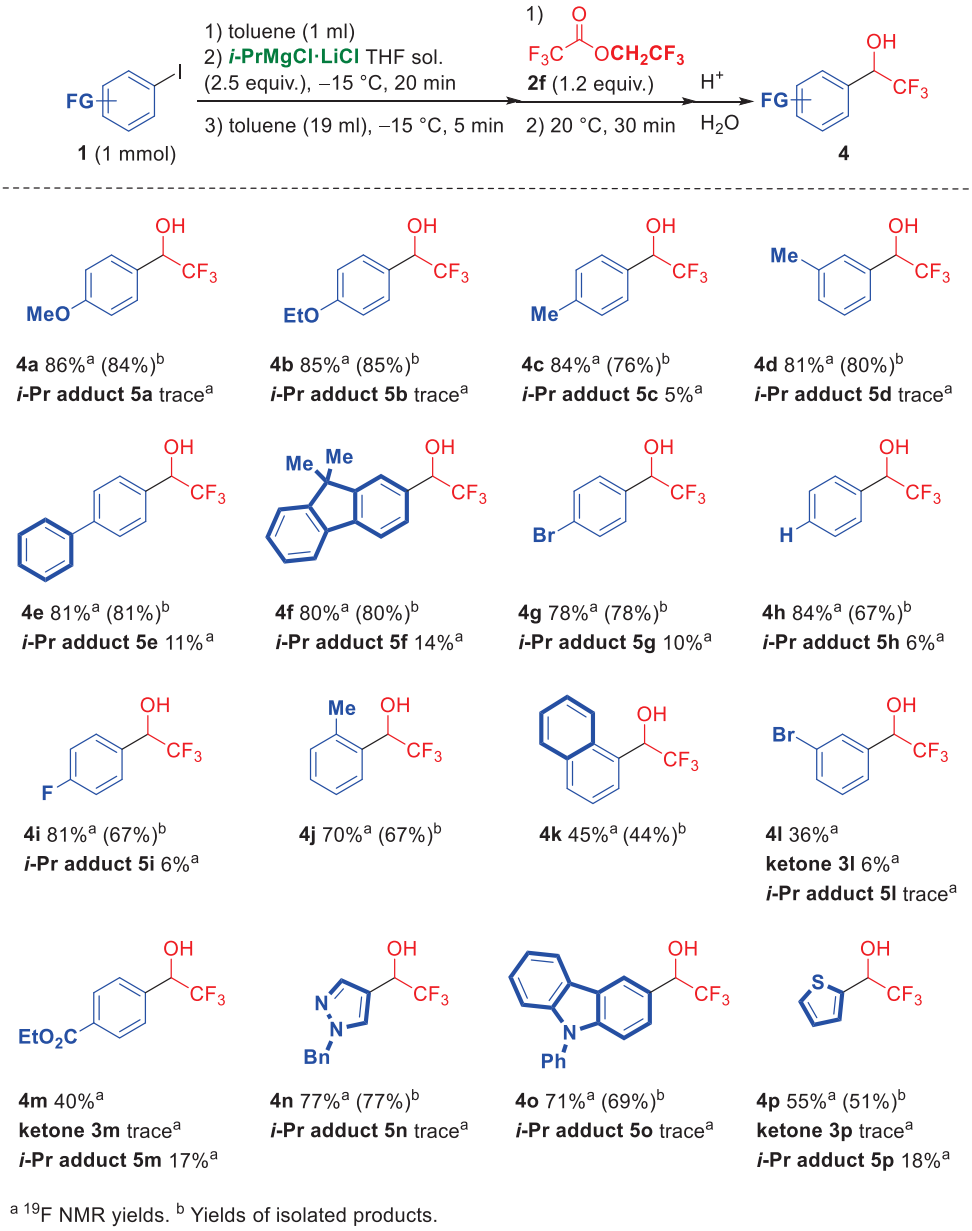


Entry	Ester **2**: **R**	Conditions 1	Additive toluene (ml)	Conditions 2	Conditions 3	^{19}F NMR yield (%) of Ketone **3g**, its hemiacetal and hydrate	Alcohol **4g**	*i*-Pr adduct **5g**
1	**2a: Me**	–40 °C, then 0 °C, 10 min	4	–40 °C, 15 min	–40 °C, overnight	52	9	trace
2	**2f: CH_2CF_3**	–40 °C, then 0 °C, 10 min	4	–40 °C, 15 min	–40 °C, overnight	trace	51	6
3	**2f: CH_2CF_3**	–15 °C, 20 min	4	–40 °C, 15 min	–40 °C, overnight	8	59	8
4	**2f: CH_2CF_3**	–15 °C, 20 min	19	–15 °C, 5 min	0 °C, 60 min	trace	65	9
5	**2f: CH_2CF_3**	–15 °C, 20 min	19	–15 °C, 5 min	20 °C, 30 min	trace	78 (78)[a]	10

[a] Yields of isolated product.

The use of commercially available 2,2,2-trifluoroethyl trifluoroacetate (**2f**) in place of methyl trifluoroacetate (**2a**) successfully improved the yields of alcohol **4g** from 9 % to 51 % (Table 2, entry 2). GC analysis revealed that the iodine/Mg-exchange with 1-bromo-4-iodobenzene (**1g**) proceeded efficiently at –15 °C for 20 min (Temp. 1 and conditions 1, entries 3–5). Then, the reaction conditions for the tandem nucleophilic addition of the in-situ generated 4-bromophenylmagnesium chloride and reduction of the in-situ generated trifluoromethyl ketone **3g** by *i*-PrMgCl·LiCl were examined. It was established that elevated reaction temperatures were beneficial for both the nucleophilic addition (–40 °C to –15 °C, entries 3 and 4), as well as the subsequent reduction of ketone **3g** (0 °C to 20 °C, entries 4 and 5). Furthermore, increasing the amount of added toluene from 4 mL to 19 mL (entries 3 and 4) was crucial for increasing the yields of **4g**, and it was obtained in 78 % yield, along with 10 % yield of isopropyl adduct **5g** (entry 5).

Scheme 7 illustrates the scope of iodoarenes **1** and iodoheteroarenes **1** under this optimized reaction conditions (Method B).



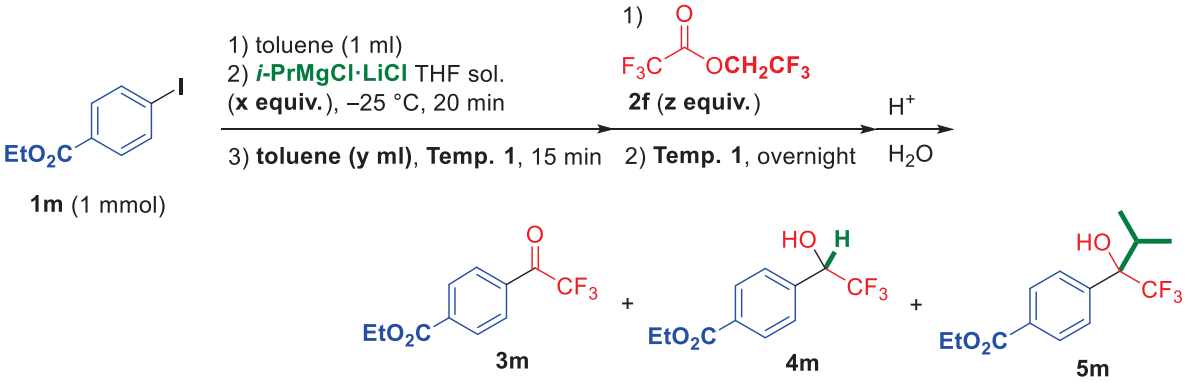
Scheme 7. Substrate scope of various iodo-arenes and -heteroarenes 1 using 2,2,2-trifluoroethyl trifluoroacetate (**2f**) (Method B).

Various iodoarenes **1a**–**e**,**g**–**i**, such as 1-iodo-4-methoxybenzene (**1a**), 1-ethoxy-4-iodobenzene (**1b**), 1-iodo-4-methylbenzene (**1c**), 1-iodo-3-methylbenzene (**1d**), 4-iodo-1,1'-biphenyl (**1e**), 1-bromo-4-iodobenzene (**1g**), iodobenzene (**1h**), and 1-fluoro-4-iodobenzene (**1i**), smoothly reacted with *i*-PrMgCl·LiCl to furnish the corresponding α-aryl-α-trifluoromethyl alcohols **4a**–**i** in good to excellent yields. Fused iodoarenes, such as 2-iodo-9,9-dimethyl-9*H*-fluorene (**1f**) and 1-

iodonaphthalene (**1k**), likewise reacted with *i*-PrMgCl·LiCl to give the corresponding α-aryl-α-trifluoromethyl alcohols **4f**, **4k** in good to excellent yields. Although the presence of a methyl group at the 2-position led to a decrease in the yield of **4j** compared with substrates bearing the methyl at 3- or 4-positions (81–84 %), 1-iodo-2-methylbenzene (**1j**) participated well in the reaction to give the α-aryl-α-trifluoromethyl alcohol **4j** in good yield. The reaction of iodoheteroarenes, such as 1-benzyl-4-iodo-1*H*-pyrazole (**1n**), 3-iodo-9-phenyl-9*H*-carbazole (**1o**), and 2-iodothiophene (**1p**) with *i*-PrMgCl·LiCl and 2,2,2-trifluoroethyl trifluoroacetate (**2f**) proceeded smoothly to give the corresponding α-trifluoromethyl alcohols **4n**, **4o**, and **4p** in good yields.

On the contrary, the reactions of 1-bromo-3-iodobenzene (**1l**) and ethyl 4-iodobenzoate (**1m**) afforded lower yields (36 % and 40 %) of the alcohols **4l** and **4m**, respectively. Therefore, further optimization of the reaction conditions with regard to ethyl 4-iodobenzoate (**1m**) was performed, as shown in Table 3.

Table 3. Optimization of reaction conditions using ethyl 4-iodobenzoate (**1m**)

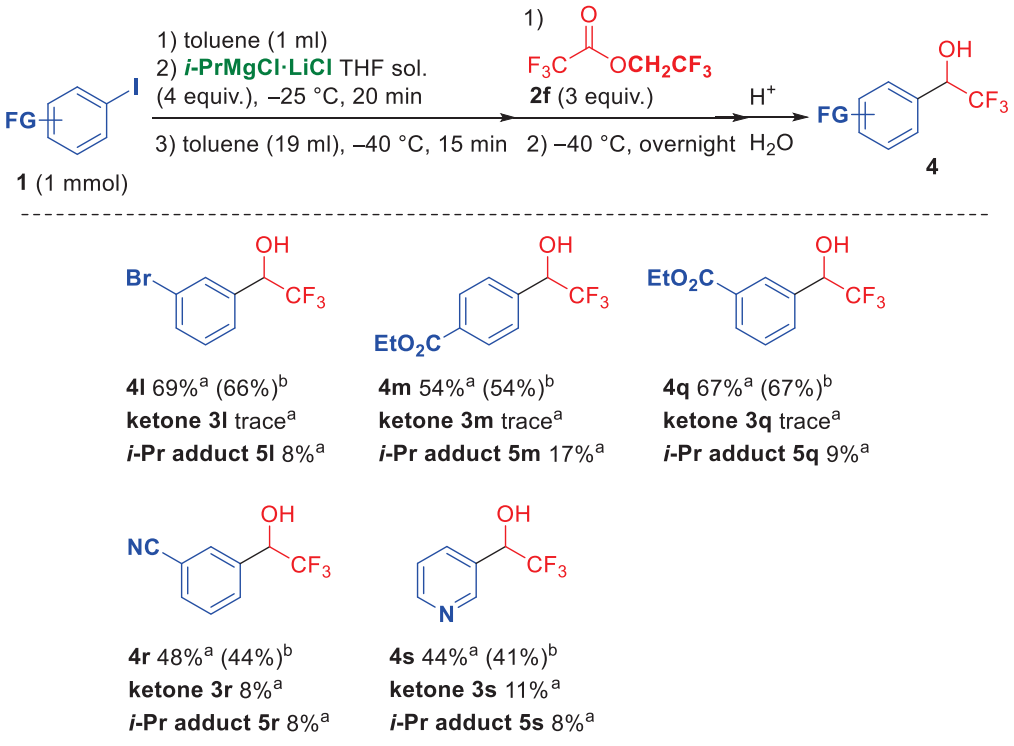


Entry	*i*-PrMgCl·LiCl (equiv.)	Additive toluene (ml)	Ester **2f** (equiv.)	Temp. 1 (°C)	^{19}F NMR yield (%) of Ketone **3m**, its hemiacetal and hydrate	Alcohol **4m**	*i*-Pr adduct **5m**
1	2.5	4	1.2	–20	trace	31	13
2	2.5	4	1.2	–40	trace	35	12
3	2.5	4	3.0	–40	29	30	8
4	2.5	19	3.0	–40	11	43	15
5	4.0	19	3.0	–40	trace	54 (54)[a]	17

[a] Yield of isolated product.

The reaction of ethyl 4-iodobenzoate (**1m**) with *i*-PrMgCl·LiCl was monitored by GC analysis, which indicated that conditions of –25 °C and 20 min were sufficient for the iodine/Mg-exchange reaction of **1m**. It was established that lowering the reaction temperature from –20 to –40 °C (entries 1 and 2), increasing the amount of *i*-PrMgCl·LiCl to 4 equiv. (entries 4 and 5), as well as that of the ester **2f** to 3 equiv. (entries 2 and 3), and the addition of a large amount (19 mL) of toluene (entries 3 and 4), resulted in efficient conversion from the ketone hemiacetal alkoxide to ketone **3m** and increased the yield of **4m** to 54 %.

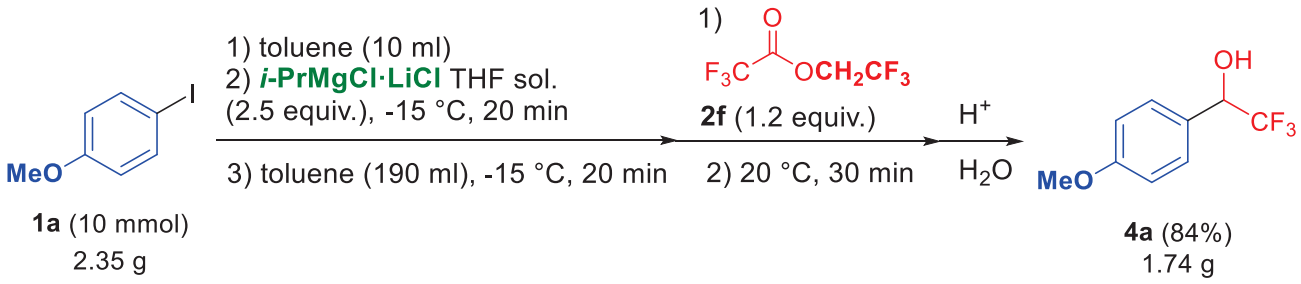
Under the optimized reaction conditions, not only the iodoarenes, such as 1-bromo-3-iodobenzene (**1l**), ethyl 4-iodobenzoate (**1m**), ethyl 3-iodobenzoate (**1q**), and 3-iodobenzonitrile (**1r**) but also 3-iodopyridine (**1s**), participated well in the tandem reactions with *i*-PrMgCl·LiCl and ester **2f** to give the corresponding alcohols **4l**, **m**, **q**, **r**, **s** in moderate to good yields, as shown in Scheme 8.



a ^{19}F NMR yields. b Yields of isolated product.

Scheme 8. Substrate scope of various iodo-arenes and -heteroarenes **1** using 2,2,2-trifluoroethyl trifluoroacetate (**2f**) (Method C)

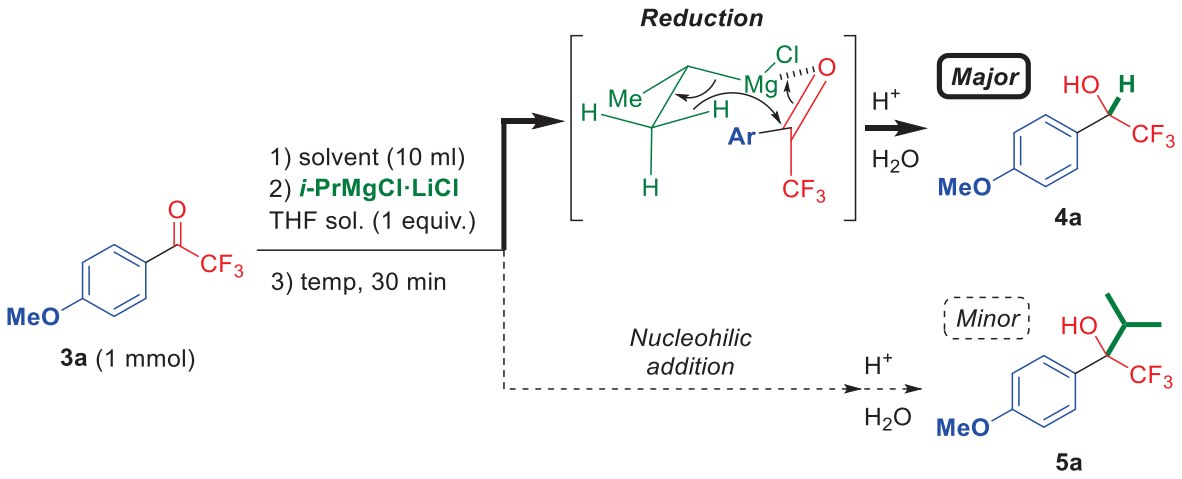
Finally, gram-scale synthesis of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) was performed by Method B using 1-iodo-4-methoxybenzene (**1a**), as shown in Scheme 9. Consequently, the reaction of 1-iodo-4-methoxybenzene (**1a**) with *i*-PrMgCl·LiCl proceeded smoothly to give 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) in 84 % yield, analogous to results from the 1 mmol scale. This result demonstrates that the operation is amenable to scale-up.



Scheme 9. Gram-scale synthesis (Method B)

To investigate the reaction mechanism, the reaction of trifluoromethyl ketone, 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one (**3a**), with *i*-PrMgCl·LiCl in THF at –78 °C was performed (Table 4, entry 1). Consequently, 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) was obtained in 86 % yield as the major product, together with 9 % of isopropylated adduct, 1,1,1-trifluoro-2-(4-methoxyphenyl)-3-methylbutan-2-ol (**5a**).

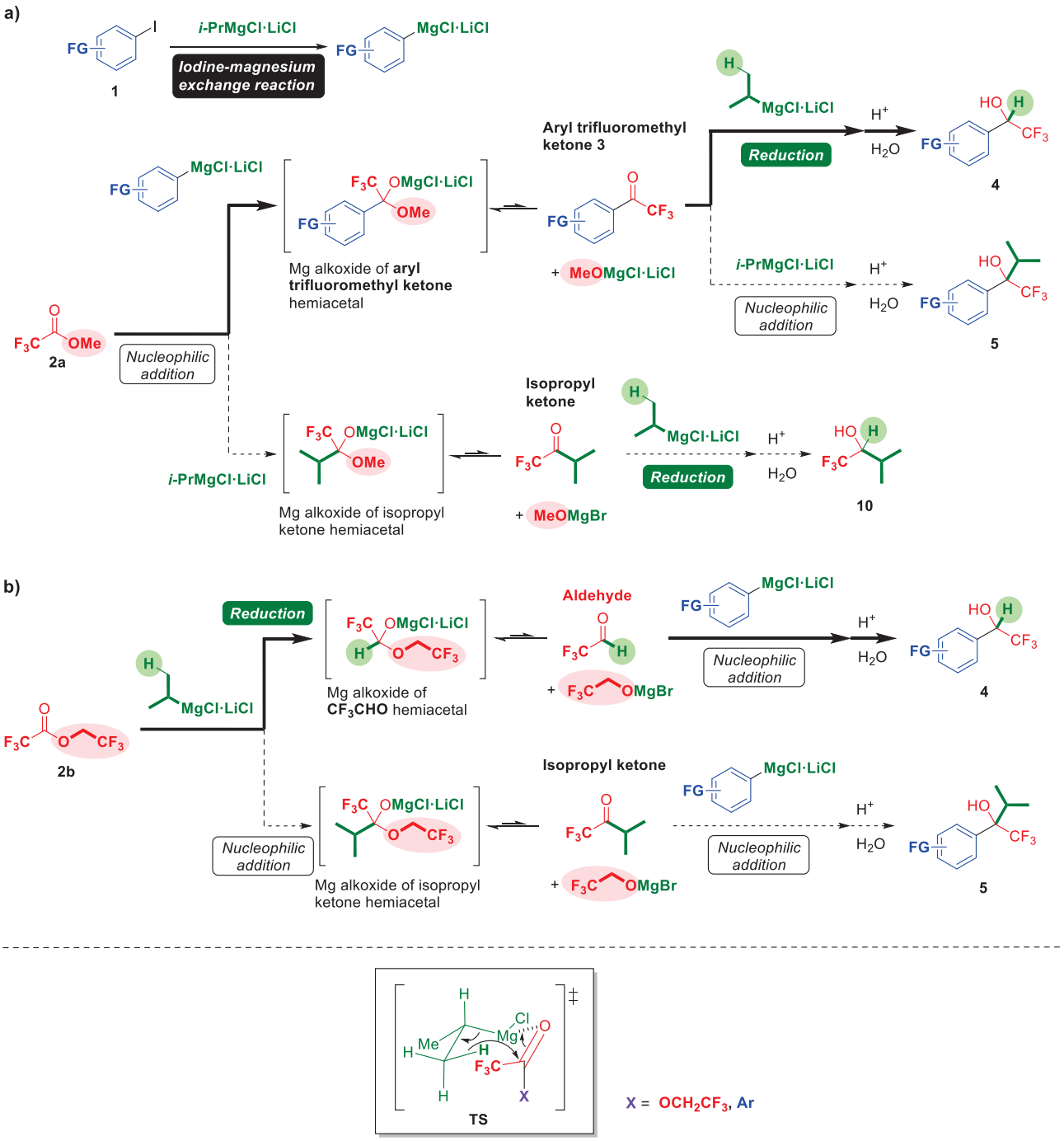
Table 4. Reduction of aryl trifluoromethyl ketone **3a** with turbo Grignard reagent



Entry	Solvent	Temp (°C)	^{19}F NMR yield (%) of Alcohol **4a**	*i*-Pr-adduct **5a**
1	THF	–78	86	9
2	THF-toluene (v/v=1/9)	–40	91	trace

The use of mixed solvents, namely THF and toluene (v/*v* = 1:9), proved effective for the suppression of the nucleophilic addition by the isopropyl to ketone **3a** and acceleration of the reduction to give alcohol **4a** in 92 % yield, even at an elevated reaction temperature (–40 °C) (entry 2).

The above-discussed results along with previous reports on the turbo Grignard reagent and McBee's studies, allow us to propose the following plausible reaction mechanism for the reaction of iodoarene **1**, *i*-PrMgCl·LiCl, and trifluoroacetic acid ester **2**, as shown in Scheme 10.



Scheme 10. Proposed reaction mechanism of the one-pot successive dual turbo Grignard reactions

First, the reaction of iodoarene **1** with *i*-PrMgCl·LiCl in THF occurred smoothly via an iodine/Mg-exchange reaction to give the corresponding arylmagnesium chloride under mild conditions. Then, the next reaction goes through two main routes, depending on the ester used (Scheme 10a and 10b). In scheme 10a, the addition of the in-situ generated arylmagnesium chloride to methyl trifluoroacetate **2a**

gave the corresponding aryl trifluoromethyl ketone hemiacetal alkoxide, which is stabilized by the existence of a strongly electron-withdrawing trifluoromethyl group. This was followed by the slow elimination of the alkoxide, leading to in-situ generated aryl trifluoromethyl ketone **3**, in equilibrium with the aryl trifluoromethyl ketone hemiacetal alkoxide. Notably, the iodine/Mg-exchange reaction and the nucleophilic addition of the generated arylmagnesium chloride are both faster than the nucleophilic addition of *i*-PrMgCl·LiCl to ester **2**. Next, the reduction of ketone **3** with *i*-PrMgCl·LiCl proceeded preferentially over the nucleophilic addition of the isopropyl group, to selectively afford α-aryl-α-trifluoromethyl alcohol **4**. The addition of toluene in place of THF may be beneficial for lowering the polarity of the solvents, which thereby suppresses the nucleophilic addition of the isopropyl group.[4] In the case of iodoarenes bearing electron-withdrawing groups, the use of trifluoroethyl ester **2f** can promote the elimination of the alkoxide from the trifluoromethyl ketone hemiacetal alkoxide, leading to efficient in-situ generation of aryl trifluoromethyl ketone in the reaction. Using 2,2,2-trifluoroethyl trifluoroacetate **2b** could increase the reaction yield because of the smooth nucleophilic addition of aryl magnesium chlorides to in-situ generated trifluoroacetaldehyde (CF_3CHO) by the reduction of the ester with *i*-PrMgCl·LiCl (Scheme 10b).

Conclusion

We have developed a novel synthetic one-pot methodology involving two distinct successive turbo Grignard reagent (*i*-PrMgCl·LiCl)-mediated transformations for the facile synthesis of α-aryl or α-heteroaryl-α-trifluoromethyl alcohols, which are important pharmaceutical motifs. The strategy exhibited a wide substrate scope and tunable reaction conditions. Tandem reactions using *i*-PrMgCl·LiCl with commercially available iodoarenes and 2,2,2-trifluoroethyl trifluoroacetate consist of three tandem reactions, namely, the iodine/Mg-exchange of iodo-arenes or -heteroarenes with *i*-PrMgCl·LiCl, nucleophilic addition of various aryl- or heteroaryl-magunesium reagents to 2,2,2-trifluoroethyl trifluoroacetate, and the reduction of in-situ generated aryl trifluoromethyl ketones by *i*-PrMgCl·LiCl in a one-pot process. This methodology can be applied to a variety of iodo-arenes or -heteroarenes, as well as fluorine-containing esters and has several advantages, such as tolerance of a variety of reducible functional groups on the aromatic rings, ease of operation, and readily removable side-products.

Experimental Section

Measurement.

^{1}H NMR spectra were measured at 392 or 400 MHz in deuterochloroform ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal standard using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. ^{13}C NMR spectra were obtained at 99 or 101 MHz in $CDCl_3$ or $(CD_3)_2CO$ solution with Me_4Si as an internal standard using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. ^{19}F NMR spectra were recorded at 369 or 376 MHz in $CDCl_3$ or $(CD_3)_2CO$ solutions using $CFCl_3$ as an external standard using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, br s = broad singlet, coupling constant(s), integration). Melting points were obtained on a Yanagimoto MP-S3 micro melting point apparatus and were uncorrected. Electrospray ionization mass spectroscopy (ESI-MS) analysis using MeOH was performed with a JEOL JMS-T100LP (Accu TOF LC-plus).

Materials.

A THF solution of turbo Grignard reagent (*i*-PrMgCl·LiCl complex) was purchased from Aldrich Co. THF was purchased from Kanto Chemical Co., and toluene was obtained from FUJIFILM Wako Pure Chemical Co. Pure products were isolated by column chromatography using Wakogel C-200 (100-200 mesh, Wako Pure Chemical Ind., Ltd.) or silica gel 60 (spherical, 40-50 μm, Kanto Chemical Co., Inc.). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F254 plates.

General procedure in Scheme 6 (Method A)

1-Iodo-4-methoxybenzene (**1a**) (0.236 g, 1 mmol) was dissolved in dry toluene (1 mL) and a THF solution of *i*-PrMgCl·LiCl (1.3 M) (2.5 mmol, 1.9 mL) was added at -40 ° C under an argon atmosphere. After the mixture was stirred at 0 °C for 10 min, dry toluene (4 mL) was added to the mixture, which was cooled at -40 °C for 15 min, and then methyl trifluoroacetate (**2a**) (0.155 g, 1.2 mmol) was added. The mixture was stirred at -40 °C overnight and then quenched with sat. NH_4Cl

aqueous solution (20 mL), extracted with dichloromethane (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum to give the crude residue. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by chromatography (hexane/dichloromethane = 1/1) to give 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) (0.167 g, 81%).

General procedure in Scheme 7 (Method B)

1-Bromo-4-iodobenzene (**1g**) (0.289 g, 1 mmol) was dissolved in dry toluene (1 mL) and a THF solution of *i*-PrMgCl·LiCl (1.3 M) (2.5 mmol, 1.9 mL) was added at -15 ° C under an argon atmosphere. After the mixture was stirred at -15 ° C for 20 min, dry toluene (19 mL) was added and the reaction was cooled at -15 °C for 5 min. Then, 2,2,2-trifluoroethyl trifluoroacetate (**2f**) (0.245 g, 1.2 mmol) was added and the mixture was stirred at 20 °C for 30 min. Thereafter it was quenched with sat. NH_4Cl aqueous solution (20 mL), extracted with dichloromethane (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum to give the crude product. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by chromatography (hexane/dichloromethane = 1/1) to give 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-ol (**4g**) (0.199 g, 78%).

General procedure in Scheme 8 (Method C)

Ethyl-4-iodobenzoate (**1m**) (0.282 g, 1 mmol) was dissolved in dry toluene (1 mL) and a THF solution of *i*-PrMgCl·LiCl (1.3 M) (2.5 mmol, 1.9 mL) was added at -25 ° C under an argon atmosphere. After the mixture was stirred at -25 °C for 20 min, dry toluene (19 mL) was added, and the solution was cooled at -40 °C for 15 min, then 2,2,2-trifluoroethyl trifluoroacetate (**2f**) (0.245 g, 1.2 mmol) was added and the reaction was stirred at -40 °C overnight. The resulting mixture was quenched with sat. NH_4Cl aqueous solution (20 mL), extracted with dichloromethane (30 mL × 3), dried over Na_2SO_4, and concentrated under vacuum to give the crude product. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by chromatography (hexane/dichloromethane = 1/1) to give ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (**4m**) (0.134 g, 54%).

Procedure for reduction of trifluoromethyl ketone 3a by turbo Grignard reagent

2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-one (**3a**) (0.204 g, 1 mmol) was dissolved in the mixture of super dehydrated toluene (9 ml) and super dehydrated THF (1 ml) and it was cooled at -78 ° C for 15 min under an argon atmosphere. A THF solution of *i*-PrMgCl·LiCl (1.3 M) (1 mmol, 0.8 ml) was added to the mixture and stirred at -78 °C for 30 min. The resulting mixture was quenched with NH_4Cl aq solution (20 ml), extracted with dichloromethane (30 ml X 3), dried over Na_2SO_4, and concentrated under vacuum to give the residue. After the yield of 2,2,2-trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4a**) were measured by ^{19}F NMR with benzotrifluoride (92% ^{19}F NMR yield).

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-ol (4a).[32]

Yield 84%; R_f 0.13 (hexane/dichloromethane = 1/1); IR (KBr) 3444 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 8.97 Hz, 2H, aryl H), 6.93 (d, J = 8.97 Hz, 2H, aryl H), 4.92-4.97 (m, 1H, CH), 3.82 (s, 3H, CH_3), 2.86 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 160.4 (s), 128.9 (s), 126.4 (s), 124.5 (q, J = 281.9 Hz), 114.1 (s), 72.4 (q, J = 31.9 Hz), 55.3 (s); ^{19}F NMR ($CDCl_3$) δ–78.5 (d, J = 7.6 Hz, 3F).

2,2,2-Trifluoro-1-(4-ethoxyphenyl)ethan-1-ol (4b).[34]

Yield 85%; R_f 0.15 (hexane/dichloromethane = 1/1); m.p. = 53.3 °C; IR (KBr) 3437 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (dd, J = 4.94 Hz, 0.90 Hz, 1H, aryl H), 7.37 (d, J = 8.52 Hz, 1H, aryl H), 6.91 (d, J = 8.52 Hz, 1H, aryl H), 4.91-4.97 (m, 1H, CH), 4.04 (q, J = 6.78 Hz, 2H, CH_2), 2.69 (s, 1H, OH), 1.42 (t, J = 6.85Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 159.8 (s), 128.9 (s), 126.2 (s), 124.5 (q, J = 282.2 Hz), 114.6 (s), 72.4 (q, J = 31.9 Hz), 63.7 (s), 14.7 (s); ^{19}F NMR ($CDCl_3$) δ –78.4 (d, J = 6.6 Hz, 3F).

2,2,2-Trifluoro-1-(*p*-tolyl)ethan-1-ol (4c).[35]

Yield 76%; R_f 0.19 (hexane/dichloromethane = 1/1); IR (KBr) 3399 (OH) cm^{-1};

^1H NMR ($CDCl_3$) δ 7.35 (d, J = 8.07 Hz, 2H, aryl H), 7.22 (d, J = 8.07 Hz, 2H, aryl H), 4.90-4.99 (m, 1H, CH), 3.01 (d, J = 3.59 Hz, 1H, OH), 2.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.7 (s), 131.2 (s), 129.4 (s), 127.5 (s), 124.4 (q, J = 282.7 Hz), 72.8 (q, J = 31.5 Hz), 21.2 (s); ^{19}F NMR ($CDCl_3$) δ –78.4

(d, J = 6.7 Hz, 3F).

2,2,2-Trifluoro-1-(*m*-tolyl)ethan-1-ol (4d).[35]

Yield 80%; R_f 0.18 (hexane/dichloromethane = 1/1); IR (KBr) 3429 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22-7.33 (m, 4H, aryl H), 4.96 (q, J = 6.6 Hz, 1H, CH), 2.82 (s, 1H, OH), 2.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.6 (s), 134.0 (s), 130.5 (s), 128.7 (s), 128.2 (s), 124.7 (s), 124.4 (q, J = 281.9 Hz), 73.0 (q, J = 32.5 Hz), 21.5 (s); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J = 6.6 Hz, 3F).

2,2,2-Trifluoro-1-(*m*-tolyl)ethan-1-one (3d).[36]

Yield 25%; R_f 0.83 (hexane/dichloromethane = 1/1); IR (KBr) 1716 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86-7.89 (m, 1H, aryl H), 7.53 (d, J = 7.18 Hz, 1H, aryl H), 7.43 (t, J = 8.08 Hz, 7.63 Hz, 1H, aryl H), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 180.8 (q, J = 34.8 Hz), 139.3 (s), 136.5 (s), 130.6 (s), 130.1 (s), 129.1 (s), 127.5 (s), 116.8 (q, J = 291.9 Hz), 21.4 (s); ^{19}F NMR ($CDCl_3$) δ −71.2 (s, 3F).

1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethan-1-ol (4e).[37]

Yield 81%; R_f 0.13 (hexane /dichloromethane = 1/1); m.p. = 116 °C; IR (KBr) 3394 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 8.08 Hz, 2H, aryl H), 7.60 (d, J = 8.08 Hz, 2H, aryl H), 7.56 (d, J = 8.08 Hz, 2H, aryl H), 7.46 (t, J = 7.41 Hz, 2H, aryl H), 7.38 (t, J = 7.41 Hz, 1H, aryl H), 5.05-5.12 (m, 1H, CH), 2.57 (d, J = 4.49 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 142.6 (s), 140.4 (s), 129.0 (s), 128.0 (s), 127.8 (s), 127.5 (s), 127.3 (s), 124.4 (q, J = 282.8 Hz), 72.8 (q, J = 31.9 Hz); ^{19}F NMR ($CDCl_3$) δ −78.3 (d, J = 6.6 Hz, 3F).

1-([1,1'-Biphenyl]-4-yl)-2,2,2-trifluoroethan-1-one (3e).[38]

Yield 37%; R_f 0.68 (hexane/ dichloromethane = 1/1); m.p. = 51.4 °C; IR (KBr) 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (d, J = 8.08 Hz, 2H, aryl H), 7.77 (d, J = 8.08 Hz, 2H, aryl H), 7.66 (d, J = 8.08 Hz, 2H, aryl H), 7.46-7.54 (m, 3H, aryl H); ^{13}C NMR ($CDCl_3$) δ 180.2 (q, J = 34.8 Hz), 130.9 (s), 129.2 (s), 129.0 (s), 128.7 (s), 127.7 (s), 127.5 (s), 116.9 (q, J = 291.3 Hz); ^{19}F NMR ($CDCl_3$) δ −71.4 (s, 3F).

2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-3-methylbutan-2-ol (5e).

Yield 11%; R_f 0.38 (hexane /dichloromethane = 1/1); m.p. = 96.8 ℃; IR (KBr) 3495 (OH) cm^{-1}; HRMS (ESI) found: m/z 295.1332. Calc. for $C_{17}H_{18}OF_3$: $[M+H]^+$, 295.1310; ^1H NMR ($CDCl_3$) δ 7.61-7.64 (m, 6H, aryl H), 7.46 (t, *J* = 7.63 Hz, 7.18 Hz, 2H, aryl H), 7.37 (d, *J* = 7.18 Hz, 1H, aryl H), 2.57 (sep, *J* = 6.73 Hz, CH), 2.44 (s, 1H, OH), 1.15 (dd, *J* = 6.73 Hz, 0.90 Hz, 3H, CH_3), 0.79 (d, *J* = 6.73 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.0 (s), 140.5 (s), 137.0 (s), 128.9 (s), 127.6 (s), 127.2 (s), 127.0 (s), 126.3 (s), 126.2 (q, *J* = 287.2 Hz), 79.8 (q, *J* = 27.3 Hz), 33.9 (s), 17.4 (s), 16.9 (s); ^{19}F NMR ($CDCl_3$) δ −73.7 (s, 3F).

1-(9,9-Dimethyl-9*H*-fluoren-2-yl)-2,2,2-trifluoroethan-1-ol (**4f**).

Yield 80%; R_f 0.21 (hexane /dichloromethane = 1/1); m.p. = 135 ℃; IR (KBr) 3414 (OH) cm^{-1}; HRMS (EI) found: m/z 292.1048. Calc. for $C_{17}H_{15}OF_3$: $[M]^+$, 292.1075; ^1H NMR ($CDCl_3$) δ 7.72-7.77 (m, 2H, aryl H), 7.56 (s, 1H, aryl H), 7.43-7.47 (m, 2H, aryl H), 7.34-7.39 (m, 2H, aryl H), 5.07-5.13 (m, 1H, CH), 2.71 (s, 1H, OH), 1.51 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.2 (s), 154.1 (s), 140.8 (s), 138.5 (s), 132.9 (s), 127.9 (s), 127.2 (s), 126.6 (s), 124.4 (q, *J* = 281.8 Hz), 122.8 (s), 121.9 (s), 120.5 (s), 120.2 (s), 73.3 (q, *J* = 31.9 Hz), 47.1 (s), 27.1 (s); ^{19}F NMR ($CDCl_3$) δ -78.1 (d, *J* = 5.7 Hz, 3F).

2-(9,9-Dimethyl-9*H*-fluoren-2-yl)-1,1,1-trifluoro-3-methylbutan-2-ol (5f).

Yield 14%; R_f 0.43 (hexane/dichloromethane = 1/1); IR (KBr) 3595 (OH) cm^{-1}; HRMS (ESI) found: m/z 335.1639. Calc. for $C_{20}H_{22}OF_3$: $[M+H]^+$, 335.1623; ^1H NMR ($CDCl_3$) δ 7.73 (d, *J* = 8.08 Hz, 1H, aryl H), 7.64 (s, 1H, aryl H), 7.52 (d, *J* = 8.08 Hz, 1H, aryl H), 7.43-7.47 (m, 1H, aryl H), 7.33-7.36 (m, 2H, aryl H), 2.59 (sep, *J* = 6.73 Hz, CH), 2.46 (s, 1H, OH), 1.51 (d, *J* = 2.69 Hz, $2CH_3$), 1.16 (d, *J* = 6.73 Hz, 3H, CH_3), 0.78 (d, *J* = 6.73 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.1 (s), 153.8 (s), 139.3 (s), 138.7 (s), 137.0 (s), 127.6 (s), 127.1 (s), 126.3 (q, *J* = 287.5 Hz), 124.6 (s), 122.8 (s), 120.3 (s), 120.2 (s), 119.7 (s), 80.1 (q, *J* = 26.3 Hz), 47.1 (s), 34.1 (s), 27.2 (s), 17.4 (s),16.9 (s); ^{19}F NMR ($CDCl_3$) δ −73.5 (s, 3F).

1-(4-Bromophenyl)-2,2,2-trifluoroethan-1-ol (**4g**).[38]

Yield 78%; R_f 0.16 (hexane/dichloromethane = 1/1); m.p. = 51.0 ℃; IR (KBr) 3390 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (d, J = 8.08 Hz, 2H, aryl H), 7.36 (d, J = 8.08 Hz, 2H, aryl H), 4.96-5.03 (m, 1H, CH), 2.66 (d, J = 4.49 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 132.9 (s), 131.9 (s), 129.2 (s), 124.0 (q, J = 282.8 Hz), 123.9 (s), 72.3 (q, J = 32.9 Hz); ^{19}F NMR ($CDCl_3$) δ −78.4 (d, J = 6.6 Hz, 3F).

1-(4-Bromophenyl)-2,2,2-trifluoroethan-1-one (3g).[39]

Yield 12%; R_f 0.58 (hexane/dichloromethane = 1/1); m.p. < 30 ℃; IR (KBr) 1724 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (d, J = 8.70 Hz, 2H, aryl H), 7.70 (d, J = 8.70 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 179.7 (q, J = 35.7 Hz), 132.6 (s), 131.43 (s), 131.41 (s), 128.6 (s), 116.5 (q, J = 291.3 Hz); ^{19}F NMR ($CDCl_3$) δ −71.4 (s, 3F).

2-(4-Bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol (5g).

Yield 10%; R_f 0.45 (hexane /dichloromethane = 1/1); IR (KBr) 3437 (OH) cm^{-1}; HRMS (ESI) found: m/z 318.9945. Calc. for $C_{11}H_{12}OF_3NaBr$: $[M+Na]^+$, 318.9921; ^1H NMR ($CDCl_3$) δ 7.52 (d, J = 8.47 Hz, 2H, aryl H), 7.42 (d, J = 8.47 Hz, 2H, aryl H), 2.47 (sep, J = 6.87 Hz, CH), 2.39 (s, 1H, OH), 1.11 (dd, J = 6.87 Hz, 1.37 Hz, 3H, CH_3), 0.71 (d, J = 6.87 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.1 (s), 131.5 (s), 127.7 (s), 125.9 (q, J = 287.5 Hz), 122.5 (s), 79.6 (q, J = 27.3 Hz), 33.8 (s), 17.3 (s), 16.8 (s); ^{19}F NMR ($CDCl_3$) δ −73.8 (s, 3F).

2,2,2-Trifluoro-1-phenylethan-1-ol (**4h**).[35]

Yield 67%; R_f 0.18 (hexane/dichloromethane = 1/1); IR (KBr) 3372 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46-7.48 (m, 2H, aryl H) 7.41-7.44 (m, 3H, aryl H), 4.95-5.01 (m, 1H, CH), 2.97 (d, J = 4.94 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 134.1 (s), 129.7 (s), 128.8 (s), 127.6 (s), 124.4 (q, J = 281.9 Hz), 72.9 (q, J = 32.0 Hz); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J = 7.1 Hz, 3F).

1-(4-Fluorophenyl)-2,2,2-trifluoroethan-1-ol (4i). [40]

Yield 67%; R_f 0.15 (hexane /dichloromethane = 1/1); IR (KBr) 3406 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (dd, *J* = 8.70 Hz, 3.21Hz, 2H, aryl H), 7.10 (t, *J* = 8.70 Hz, 2H, aryl H), 5.00 (q, *J* = 6.63 Hz, 1H, CH), 2.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 163.5 (d, *J* = 248.1) 129.8 (s), 129.5 (d, *J* = 8.49), 124.2 (q, *J* = 281.9 Hz), 115.8 (d, *J* = 21.6), 72.3 (q, *J* = 31.9 Hz); ^{19}F NMR ($CDCl_3$) δ −78.7 (d, *J* = 6.6 Hz, 3F), −112.1-−112.0 (m, 1F).

2,2,2-Trifluoro-1-(*o*-tolyl)ethan-1-ol (4j). [41]

Yield 67%; R_f 0.18 (hexane/dichloromethane = 1/1); IR (KBr) 3394 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, *J* = 7.79 Hz, 1H, aryl H), 7.13-7.20 (m, 2H, aryl H), 7.86 (d, *J* = 8.24 Hz, 1H, aryl H), 5.16 (q, *J* = 6.63 Hz, 1H, CH), 2.90 (s, 1H, OH), 2.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.7 (s), 132.6 (s), 130.8 (s), 129.4 (s), 127.1 (s), 126.5 (s), 124.8 (q, *J* = 281.8 Hz), 68.9 (q, *J* = 31.5 Hz), 19.3 (s),; ^{19}F NMR ($CDCl_3$) δ −77.6 (d, *J* = 6.6 Hz, 3F).

2,2,2-Trifluoro-1-(naphthalen-1-yl)ethan-1-ol (4k).[32]

Yield 44%; R_f 0.21 (hexane/dichloromethane = 1/1); IR (KBr) 3367 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01 (d, *J* = 8.53 Hz, 1H, aryl H), 7.91-7.91 (m, 2H, aryl H), 7.83 (d, *J* = 7.63 Hz, 1H, aryl H), 7.55-7.60 (m, 2H, aryl H), 7.52 (t, *J* = 7.86 Hz, 1H, aryl H), 5.81-5.87 (m, 1H, CH), 3.22 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 133.7 (s), 131.1 (s), 130.3 (s), 130.0 (s), 129.1 (s), 126.9 (s), 126.0 (s), 125.9 (s), 125.3 (s), 124.8 (s), 124.8 (q, *J* = 282.8 Hz), 122.8 (s), 68.9 (q, *J* = 32.0 Hz); ^{19}F NMR ($CDCl_3$) δ −76.8 (d, *J* = 6.6 Hz, 3F).

1-(3-Bromophenyl)-2,2,2-trifluoroethan-1-ol (4l).[41]

Yield 66%; R_f 0.20 (hexane/dichloromethane = 1/1); IR (KBr) 3394 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (s, 1H, aryl H), 7.44 (d, *J* = 8.08 Hz, 1H, aryl H), 7.29 (d, *J* = 7.63 Hz, 1H, aryl H), 7.17 (t, *J* = 8.08Hz, 7.63 Hz, 1H, aryl H), 4.84-4.90 (m, 1H, CH), 2.92 (d, *J* = 4.04 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$)

δ 136.0 (s), 132.8 (s), 130.6 (s), 130.3 (s), 126.2 (s), 124.0 (q, *J* = 282.2 Hz), 122.7 (s), 72.2 (q, *J* = 32.3 Hz); ^{19}F NMR ($CDCl_3$) δ −78.4 (d, *J* = 5.8 Hz, 3F).

Ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (**4m**).[32]

Yield 54%; R_f 0.15 (dichloromethane); m.p. = 70.8 °C; IR (KBr) 1713 (C=O), 3429 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, *J* = 8.47 Hz, 2H, aryl H), 7.55 (d, *J* = 8.47 Hz, 2H, aryl H), 5.10 (q, *J* = 6.63 Hz, 1H, CH), 4.38 (q, *J* = 7.14 Hz, 2H, CH_2),3.19 (br s, 1H, OH), 1.39 (t, *J* = 7.14 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.6 (s), 139.0 (s), 131.4 (s), 129.8 (s), 127.6 (s), 124.2 (q, *J* = 281.9 Hz), 72.5 (q, *J* = 32.9 Hz), 61.5 (s), 14.4 (s); ^{19}F NMR ($CDCl_3$) δ −78.0 (d, *J* = 6.63 Hz, 3F)

Ethyl 4-(1,1,1-trifluoro-2-hydroxy-3-methylbutan-2-yl)benzoate (5m).

Yield 17%; R_f 0.45 (dichloromethane); IR (KBr) 3452 (OH) cm^{-1}; HRMS (ESI) found: m/z 313.0999. Calc. for $C_{14}H_{17}O_3F_3Na$: $[M+Na]^+$, 313.1027; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, *J* = 8.47 Hz, 2H, aryl H), 7.63 (d, *J* = 8.47 Hz, 2H, aryl H), 4.39 (q, *J* = 7.33 Hz, CH_3), 2.55 (s, 1H, OH), 2.52 (sep, *J* = 6.87 Hz, CH), 1.40 (t, *J* = 7.33 Hz, CH_3), 1.13 (dd, *J* = 6.87 Hz, 1.37 Hz, 3H, CH_3), 0.69 (d, *J* = 6.87 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.5 (s), 143.1 (s), 130.4 (s), 129.6 (s), 125.9 (q, *J* = 287.5 Hz), 125.9 (s), 79.9 (q, *J* = 27.3 Hz), 61.3 (s), 33.9 (s), 17.2 (s), 16.8 (s), 14.4 (s); ^{19}F NMR ($CDCl_3$) δ −73.5 (s, 3F).

1-(1-Benzyl-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethan-1-ol (4n).

Yield 77%; R_f 0.28 (dichloromethane /diethyl ether = 1/1); IR (KBr) 3194 (OH) cm^{-1}; HRMS (ESI) found: m/z 257.0923. Calc. for $C_{12}H_{12}N_2OF_3$: $[M+H]^+$, 257.0902; ^{1}H NMR ($CDCl_3$) δ 7.37 (s, 1H, pyrazole H), 7.33 (s, 1H, pyrazole H), 7.20-7.22 (m, 3H, benzene H), 7.05-7.07 (m, 2H, benzene H), 4.79 (q, *J* = 7.00 Hz, 1H, CH), 5.09 (s, 2H, CH_2), 4.60 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 138.4(s), 135.7(s), 129.1 (s), 129.0 (s), 128.4 (s), 127.9 (s), 124.5 (q, *J* = 281.6 Hz), 116.5 (s), 65.8 (q, *J* = 33.2 Hz), 56.1 (s); ^{19}F NMR ($CDCl_3$) δ −79.3 (d, *J* = 7.0 Hz, 3F).

2,2,2-Trifluoro-1-(9-phenyl-9*H*-carbazol-3-yl)ethan-1-ol (4o).

Yield 69%; R_f 0.30 (hexane /dichloromethane = 1/1); IR (KBr) 3406 (OH) cm^{-1}; HRMS (ESI) found: m/z 342.1092. Calc. for $C_{20}H_{15}NOF_3$: $[M+H]^+$, 342.1106; ^1H NMR ($CDCl_3$) δ 82.8 (s, 1H, aryl H), 8.18 (t, *J* = 7.63 Hz, 1H, aryl H), 7.62 (t, *J* = 7.63 Hz, 2H, aryl H), 7.41-7.56 (m, 7H, aryl H), 7.32-7.36 (m, 1H, aryl H), 5.21 (q, *J* = 7.00 Hz, 1H, CH), 2.74 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 141.53 (s), 141.46 (s), 137.4 (s), 130.1 (s), 127.9 (s), 127.2 (s), 126.6 (s), 125.6 (s), 125.3 (s), 124.7 (q, *J* = 281.9 Hz), 123.5 (s), 123.1 (s), 120.6 (s), 120.4 (s), 119.8 (s), 110.1 (s), 110.0 (s), 73.4 (q, *J* = 32.6 Hz); ^{19}F NMR ($CDCl_3$) δ −78.3 (d, *J* = 7.0 Hz, 3F).

2,2,2-Trifluoro-1-(thiophen-2-yl)ethan-1-ol (4p).[42]

Yield 57%; R_f 0.16 (hexane/dichloromethane = 1/1); m.p. = 46.3 °C; IR (KBr) 3360 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (d, *J* = 4.94 Hz, 1H, aryl H), 7.21 (d, *J* = 3.59 Hz, 1H, aryl H), 7.06 (t, *J* = 4.49 Hz, 1H, aryl H), 5.29 (q, *J* = 6.28 Hz, 1H, CH), 2.68 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 136.1 (s), 127.7 (s), 127.3 (s), 127.2 (s), 123.8 (q, *J* = 281.9 Hz), 69.4 (q, *J* = 33.8 Hz); ^{19}F NMR ($CDCl_3$) δ −78.7 (d, *J* = 6.6 Hz, 3F).

1,1,1-Trifluoro-3-methyl-2-(thiophen-2-yl)butan-2-ol (5p).

Yield 12%; R_f 0.45 (hexane/dichloromethane = 1/1); IR (KBr) 3591 (OH) cm^{-1}; HRMS (ESI) found: m/z 247.0395. Calc. for $C_9H_{11}OF_3NaS$: $[M+Na]^+$, 247.0380; ^1H NMR ($CDCl_3$) δ 7.32 (dd, *J* = 5.04 Hz, 0.92 Hz, 1H, aryl H), 7.09 (d, *J* = 3.66 Hz, 1H, aryl H), 7.04 (dd, *J* = 5.04 Hz, 3.66 Hz, 1H, aryl H), 2.61 (s, 1H, OH), 2.43 (sep, *J* = 6.87 Hz, CH), 1.05 (dd, *J* = 6.87 Hz, 1.37 Hz, 3H, CH_3), 0.93 (d, *J* = 6.87 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 141.4 (s), 127.1 (s), 125.5 (s), 125.5 (q, *J* = 286.6 Hz), 125.1 (s), 79.8 (q, *J* = 28.8 Hz), 35.0 (s), 17.4 (s), 16.9 (s); ^{19}F NMR ($CDCl_3$) δ −75.9 (s, 3F).

Ethyl 3-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (4q).[32]

Yield 67%; R_f 0.18 (dichloromethane); IR (KBr) 1701 (C=O), 3445 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (s, 1H, aryl H), 8.07 (d, *J* = 7.63 Hz, 1H, aryl H), 7.69 (d, *J* = 7.63 Hz, 1H, aryl H), 7.49 (t, *J* =

7.63 Hz, 1H, aryl H), 5.10 (q, J = 6.68 Hz, 1H, CH), 4.38 (q, J = 7.18 Hz, 2H, CH_2),3.21 (br s, 1H, OH), 1.39 (t, J = 7.18 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.8 (s), 135.0 (s), 132.1 (s), 130.6 (s), 130.5 (s), 128.8 (s), 124.3 (q, J = 282.2 Hz), 72.3 (q, J = 31.6 Hz), 61.6 (s), 14.2 (s); ^{19}F NMR ($CDCl_3$) δ −78.0 (d, J = 6.7 Hz, 3F)

3-(2,2,2-Trifluoro-1-hydroxyethyl)benzonitrile (**4r**).

Yield 44%; R_f 0.15 (dichloromethane); IR (KBr) 2237 (C≡N), 3421 (OH) cm^{-1}; HRMS (ESI) found: m/z 224.0276. Calc. for $C_9H_6NOF_3Na$: $[M+Na]^+$, 224.0299; ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1H, aryl H), 7.74 (d, J = 7.79 Hz, 1H, aryl H), 7.67 (d, J = 7.79 Hz, 1H, aryl H), 7.67 (d, J = 7.79 Hz, 1H, aryl H), 7.53 (t, J = 7.79 Hz, 1H, aryl H), 5.09 (q, J = 6.17 Hz, 1H, CH), 3.58 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 135.9 (s), 133.0 (s), 132.2 (s), 131.3 (s), 129.5 (s), 124.0 (q, J = 281.8 Hz), 118.4 (s), 112.5 (s), 71.6 (q, J = 32.6 Hz); ^{19}F NMR ($CDCl_3$) δ −78.2 (d, J = 6.2 Hz)

2,2,2-Trifluoro-1-(pyridin-3-yl)ethan-1-ol (4s). [43]

Yield 44%; R_f 0.53 (dichloromethane/methanol = 10/1); IR 3074 (KBr) (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H, aryl H), 7.73 (d, J = 7.79 Hz, 1H, aryl H), 7.66 (d, J = 7.79 Hz, 1H, aryl H), 7.06 (t, J = 7.79 Hz, 1H, aryl H), 5.07 (q, J = 6.82 Hz, 1H, CH), 3.57 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 149.3 (s), 148.1 (s), 136.5 (s), 132.0 (s), 124.4 (q, J = 282.8 Hz), 124.1 (s), 70.2 (q, J = 32.6 Hz); ^{19}F NMR ($CDCl_3$) δ −78.4 (d, J = 6.8 Hz, 3F).

2,2,2-trifluoro-1-methoxy-1-(pyridin-3-yl)ethan-1-ol (3s). [44]

Yield trace; R_f 0.56 (dichloromethane /methanol = 10/1); IR (KBr) 3055 (OH) cm^{-1}; ^{1}H NMR (CD_3OD) δ 9.26 (d, J = 1.60 Hz, 1H, aryl H), 9.10 (dd, J = 4.82 Hz, 1.60 Hz, 1H, aryl H), 8.56 (d, J = 8.02 Hz, 1H, aryl H), 8.01 (dd, J = 8.02 Hz, 4.82 Hz, 1H, aryl H), 5.46 (br s, 1H, OH), 3.85 (s, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 150.9 (s), 149.9 (s), 138.3 (s), 132.9 (s), 124.9 (s), 124.1 (q, J = 287.5 Hz), 96.9 (q, J = 31.6 Hz), 49.8 (s); ^{19}F NMR ($CDCl_3$) δ −84.0 (s, 3F).

2,2-Difluoro-1-(4-methoxyphenyl)ethan-1-ol (**6a**). [45]

Yield 76%; R_f 0.25 (dichloromethane); IR (KBr) 3441 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (d, J = 8.53 Hz, 2H, aryl H), 6.91 (d, J = 8.53 Hz, 2H, aryl H), 5.73 (td, J = 56.28 Hz, 4.49 Hz, 1H, CF_2H), 4.67-4.74 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.12 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 160.1 (s), 128.6 (s), 128.2 (s), 116.0 (t, J = 244.3 Hz), 114.2 (s), 73.3 (t, J = 24.4 Hz), 55.4 (s); ^{19}F NMR ($CDCl_3$) δ –127.3 (dd, J = 56.3 Hz, 9.96 Hz, 2F).

2-Chloro-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-ol (**7a**). [46]

Yield 85%; R_f 0.11 (hexane/dichloromethane = 1/1); IR (KBr) 3441 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, J = 8.76 Hz, 2H, aryl H), 6.92 (d, J = 8.76 Hz, 2H, aryl H), 4.94-5.00 (m, 1H, CH), 3.81 (s, 3H, CH_3), 2.97 (d, J= 4.49 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 160.4 (s), 129.2 (s), 129.2 (t, J = 296.9 Hz), 126.6 (s), 113.9 (s), 77.0 (t, J = 27.3 Hz), 55.4 (s); ^{19}F NMR ($CDCl_3$) δ –64.9 (dd, J = 164.6 Hz, 8.4 Hz, 1F), –63.2 (dd, J = 164.6 Hz, 8.4 Hz, 1F).

2,2-Difluoro-1-(4-methoxyphenyl)propan-1-ol (**8a**). [47]

Yield 75%; R_f 0.18 (hexane/dichloromethane = 1/1); IR (KBr) 3441 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (d, J = 8.52 Hz, 2H, aryl H), 6.90 (d, J = 8.52 Hz, 2H, aryl H), 4.77 (td, J = 9.60 Hz, 3.00 Hz 1H, CH), 3.81 (s, 3H, CH_3), 2.75 (d, J= 3.00 Hz, 1H, OH), 1.50 (t, J= 18.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 159.8 (s), 129.1 (s), 128.6 (s), 123.5 (t, J = 242.9 Hz), 113.8 (s), 75.3 (t, J = 28.6 Hz), 55.3 (s), 19.0 (t, J = 26.3 Hz); ^{19}F NMR ($CDCl_3$) δ –101.2- –101.0 (m, 2F).

2,2,3,3,3-Pentafluoro-1-(4-methoxyphenyl)propan-1-ol (**9a**). [48]

Yield 84%; R_f 0.13 (hexane/dichloromethane = 1/1); m.p. = 63.0 °C; IR (KBr) 3390 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (d, J = 8.76 Hz, 2H, aryl H), 6.92 (d, J = 8.76 Hz, 2H, aryl H), 4.98-5.05 (m, 1H, CH), 3.80 (s, 3H, CH_3), 3.35 (d, J= 4.49 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 160.6 (s), 129.3 (s), 126.2 (s), 119.2 (qt, J = 286.6 Hz, 35.7 Hz), 114.1 (s), 113.2 (ddq, J = 259.3 Hz, 235.7 Hz, 34.8 Hz), 55.4 (s), 71.7 (dd, J = 22.6 Hz, 5.6 Hz); ^{19}F NMR ($CDCl_3$) δ -129.8 (dd, J = 274.5 Hz, 18.0 Hz, 1F), -121.1 (dd, J = 274.5 Hz, 7.1 Hz, 1F), -81.2 (s, 3F).

References

1. For a first report, see. A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, 43, 3333-3336.
2. For recent reviews, see. H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Lett.* **2006**, *35*, 2–7.
3. H. Ila, O. Baron, A. J. Wagner, P. Knochel, *Chem. Commun.* **2006**, 583–593.
4. F. Mongin, A. Harrison-Marchand, *Chem. Rev.* **2013**, *113*, 7563–7727.
5. D. Tilly, F. Chevallier, F. Mongin, P. C. Gros, *Chem. Rev.* **2014**, *114*, 1207–1257.
6. C. T. O'Hara, *Organomet. Chem.* **2011**, *37*, 1–26.
7. T. Klatt, J. T. Markiewicz, C. Sämann, P. Knochel, *J. Org. Chem.* **2014**, *79*, 4253–4269.
8. Y. Liu, Y. Fang, L. Zhang, X. Jin, R. Li, S. Zhu, H. Gao, J. Fang, Q. Xia, Chin. *J. Org. Chem.* **2014**, *34*, 1523–1541.
9. N. M. Barl, V. Werner, C. Sämann, P. Knochel, *Heterocycles* **2014**, *88*, 827–844.
10. R. L. -Y. Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 6884-6990.
11. D. S. Ziegler, B. Wei, P. Knochel, *Chem. Eur. J.* **2019**, *25*, 2695-2703.
12. J. Y. Gauthier, M. Belley, D. Deschenes, J. -F. Fournier, S. Gagne, Y. Gareau, M. Hamel, M. Henault, H. Hyjazie, S. Kargman, G. Lavallee, J. -F. Levesque, L. Li, Y. Mamane, J. Mancini, N. Morin, E. Mulrooney, J. Robichaud, M. Therien, G. Tranmer, Z. Wang, J. Wu, W. C. Black, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2836-2839.
13. K. A. Lyseng-Williamson, *Drugs* **2018**, *78*, 941-950.
14. D. Pawlak, B. Znorko, B. Kalaska, T. Domaniewski, R. Zawadzki, P. Lipowicz, M. Doroszko, U, Łebkowska, P. Grabowski, K. Pawlak, *Bone* **2018**, *113*, 124-136.
15. G. M. G. Lima, B. J. M. Corazza, R. M. Moraes, F. E. de Oliveira, L. D. de Oliveira, G. C. N. Franco, D. S. Perrien, F. Elefteriou, A. L. Anbinder, *J. Periodontal Res.* **2016**, *51*, 661-668.
16. D. R. Goldberg, S. De Lombaert, R. Aiello, P. Bourassa, N. Barucci, Q. Zhang, V. Paralkar, J. Valentine, W. Zavadoski, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1124-1129.

17. C. -M. Oh, J. Namkung, Y. Go, K. E. Shong, K. Kim, H. Kim, B. -Y. Park, H. W. Lee, Y. H. Jeon, J. Song, M. Shong, V. K. Yadav, G. Karsenty, S. Kajimura, I. -K. Lee, S. Park, H. Kim, *Nat. Commun.* **2015**, *6*, 6794.
18. J. J. Kim, H. Wang, J. D. Terc, B. Zambrowicz, Q. M. Yang, W. I. Khan, *Am. J. Physiol.* **2015**, *309*, G455–G465.
19. V. Yadav, S. Balaji, P. S. Suresh, X. S. Liu, X. Lu, Z. Li, X. E. Guo, J. J. Mann, Anil. K. Balapure, M. D. Gershon, R. Medhamurthy, M. Vidal, G. Karsenty, P. Ducy, *Nat. Med.* **2010**, *16*, 308-312.
20. K. G. Margolis, K. Stevanovic, Z. Li, Q. M. Yang, T. Oravecz, B. Zambrowicz, K. G. Jhaver, A. Diacou, M. D. Gershon, *Gut.* **2014**, *63*, 928-937.
21. With $TMSCF_3$: (a) D. X. Ngo, W. W. Kramer, B. J. McNicholas, H. B. Gray, B. J. Brennan, *Inorg. Chem.* **2019**, *58*, 737–746.
22. K. Mishra, K. C. Bharadwaj, R. M. Singh, *Tetrahedron Lett.* **2018**, *59*, 3439-3442.
23. V. A. Pistritto, J. M. Paolillo, K. A. Bisset, N. E. Leadbeater, *Org. Biomol. Chem.* **2018**, *16*, 4715-4719.
24. S. Okusu, K. Hirano, Y. Yasuda, E. Tokunaga, N. Shibata, *RSC Adv.* **2016**, *86*, 82716-82720.
25. J. Sun, X. Peng, H. Guo, *Tetrahedron Lett.* **2015**, *56*, 797-800.
26. H. Cheng, Y. Pei, F. Leng, J. Li, A. Liang, D. Zou, Y. Wu, Y. Wu, *Tetrahedron Lett.* **2013**, *54*, 4483-4486.
27. C. B. Kelly, M. A. Mercadante, T. A. Hamlin, M. H. Fletcher, N. E. Leadbeater, *J. Org. Chem.* **2012**, *77*, 8131-8141.
28. M. Baumann, I. R. Baxendale, L. J. Martin, S. V. Ley, *Tetrahedron* **2009**, *65*, 6611-6625.
29. J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2005**, *7*, 2193-2193.
30. J. B. Geri, M. M. W. Wade, N. K. Szymczak, *Angew. Chem. Int. Ed.* **2018**, *57*, 1381-1385.
31. T. Yamazaki, T. Terajima, T. Kawasaki, *Tetrahedron* **2008**, *64*, 2419–2424.

32. K. Funabiki, A. Hayakawa, R. Kani, T. Inuzuka, Y. Kubota, *Eur. J. Org. Chem.* **2019**, 5978-5984.

33. O. R. Pierce, J. C. Siegle, E, T. McBee, *J. Am. Chem. Soc.* **1953**, 75, 6324-6325.

34. R. Stewart, K. C. Teo, *Can. J. Chem.* **1980**, *58*, 2491-2496.

35. F. Brüning, H. Nagae, D. Käch, K. Mashima, A. Togni, *Chem. Eur. J.* **2019**, *25*, 10818-10822.

36. W. Wu, Q. Tian, T. Chen, Z. Weng, *Chem. Eur. J.* **2016**, *22*, 16455-16458.

37. A. B. Frost, M. Brambilla, R. M. Exner, *Angew. Chem. Int. Ed.* **2019**, *58*, 472-476.

38. S. T. Keaveney, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2018**, *57*, 4073-4077.

39. F. Scheidt, J. Neufeld, M. Schäfer, C. Thiehoff, R. Gilmour, *Org. Lett.* **2018**, *20*, 8073-8076.

40. K. Aikawa, W. Toya, Y. Nakamura, K. Mikami, *Org. Lett.* **2015**, *17*, 4996-4999.

41. M. Brambilla, M. Tredwell, Angew. *Chem. Int. Ed.* **2017**, *56*, 11981-11985.

42. S. Crotti, N. D. Iorio, A. Mazzanti, P. Righi, G. Bencivenni, *J. Org. Chem.* **2018**, *83*, 12440-12448.

43. O. V. Kucher, A. O. Kolodiazhnaya, O. B. Smolii, D. V. Prisuazhnyk, K. A. Tolmacheva, O. A. Zaporozhets, Y. S. Moroz, P. K. Mykhailiuk, A. A. Tolmachev, *Eur. J. Org. Chem.* **2014**, *34*, 7692-7698.

44. Z. Han, S. Chen, Y. Tu, X. Lian, G. Li, *Eur. J. Org. Chem.* **2019**, *29*, 4658-4661.

45. S. Krishnamoorthy, S. Kar, J. Kothandaraman, G. K. S. Prakash, *J. Fluor. Chem.* **2018**, *208*, 10-14.

46. L. I. Panferova, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Chem. Commun.* **2019**, *55*, 1314-1317.

47. Z. Deng, C. Liu, X. Zeng, J. Lin, J. Xiao, *J. Org. Chem.* **2016**, *81*, 12084-12090.

48. M. Kuroboshi, T. Hiyama, *Chem. Lett.* **1990**, *9*, 1607-1610.

Chapter 2.

Synthesis of 1-Trifluoromethylated Propargyl Alcohols by Two Successive Reactions of Cyclopentylmagnesium Bromide in a One-Pot Manner

Abstract

We have developed a functional-group-tolerant one-pot route to various 3-substituted 1-trifluoromethylpropargyl alcohols utilizing two reactions of cyclopentylmagnesium bromide with trifluoroacetic acid esters and terminal alkynes. This new synthetic method involves three successive reactions in a one-pot process: 1) deprotonation of terminal alkynes with cyclopentylmagnesium bromide, 2) reduction of 2,2,2-trifluoroethyl trifluoroacetate with cyclopentylmagnesium bromide, and 3) nucleophilic addition of in-situ-generated alkynyl Grignard reagents to in-situ-formed trifluoroacetaldehyde, leading to the corresponding 3-substituted 1-trifluoromethylated propargyl alcohols. This method can be applied to various fluorine-containing esters as well as terminal alkynes bearing alkyl and aryl groups to give 1-polyfluoroalkylated propargyl alcohols. The obtained 1-trifluoromethylpropargyl alcohols with aromatic groups can be converted in good to excellent yields to 1,5-diaryl-3-trifluoromethyl-dihydropyrazoles, some of the most important motifs in medicine for the treatment of pain and inflammation associated with osteoarthritis in dogs.

Introduction

The introduction of fluorinated substituents, especially trifluoromethyl groups, into organic molecules is one of the most effective methods for achieving molecules and macromolecules with desirable chemical and physical properties owing to the inherent characteristics of the fluorine atom, such as its small size and high electronegativity.[1,2] Especially, much attention has been paid to trifluoromethylated nitrogen-containing heterocycles in the pharmaceutical[3-8] and agrochemical[9] industries, with examples shown in Fig. 1.

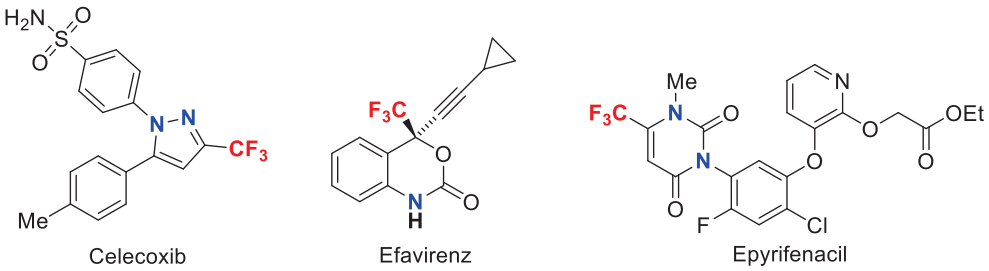
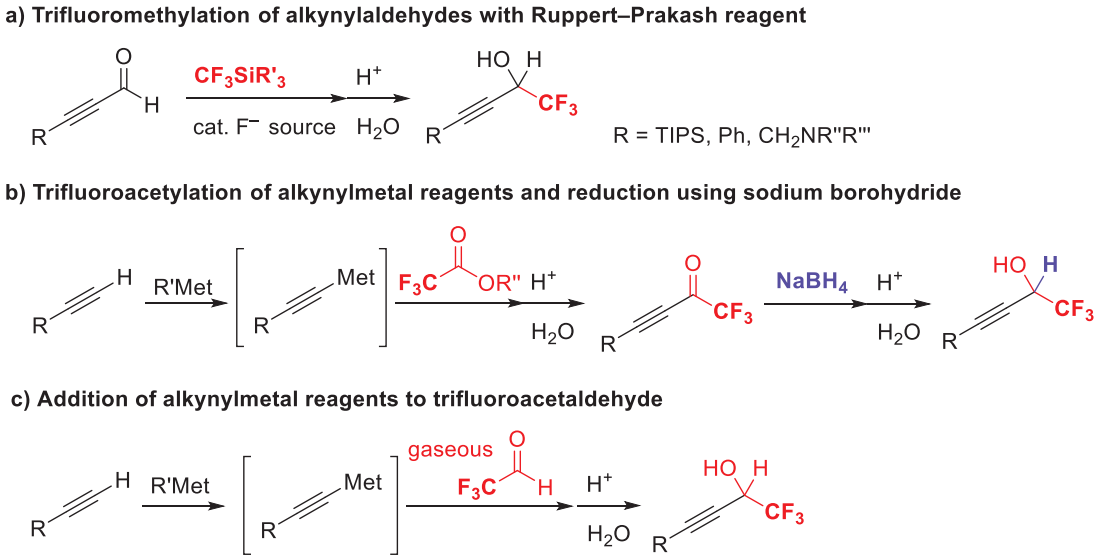


Fig. 1. Structures of significant trifluoromethylated nitrogen-containing heterocycles in the areas of pharmaceuticals and agrochemicals.

There are two methods for synthesizing trifluoromethylated heterocycles: the direct trifluoromethylation method[10-15] and the building block method using trifluoromethylated molecules.[16-22] Excellent methods for the direct trifluoromethylation of organic molecules have recently been developed. The building block methods are also promising for further progress due to their many advantages, such as high regioselectivity, convenience, flexibility, and ease of scalability.[23,24]

Secondary[25-31] and tertiary[32,33] propargyl alcohols carrying trifluoromethyl groups can also serve as useful building blocks to introduce not only a trifluoromethyl moiety but also alkynyl or

alkenyl groups into various organic molecules. Many efforts have been made to synthesize trifluoromethylated secondary and tertiary propargyl alcohols. In terms of secondary 1-trifluoromethylated propargyl alcohols, three types of reactions are available, although it is difficult to obtain and handle some of the starting substrates with certain functional groups: 1) trifluoromethylation of alkynyl aldehydes with Ruppert-Prakash reagent (Scheme 1a),[34,35] 2) reduction of alkynyl trifluoromethyl ketones derived from alkynylmetal reagents and trifluoroacetic acid esters (Scheme 1b),[36-38] and 3) addition of alkynylmetal reagents to gaseous trifluoroacetaldehyde (CF_3CHO) (Scheme 1c).[39-41]

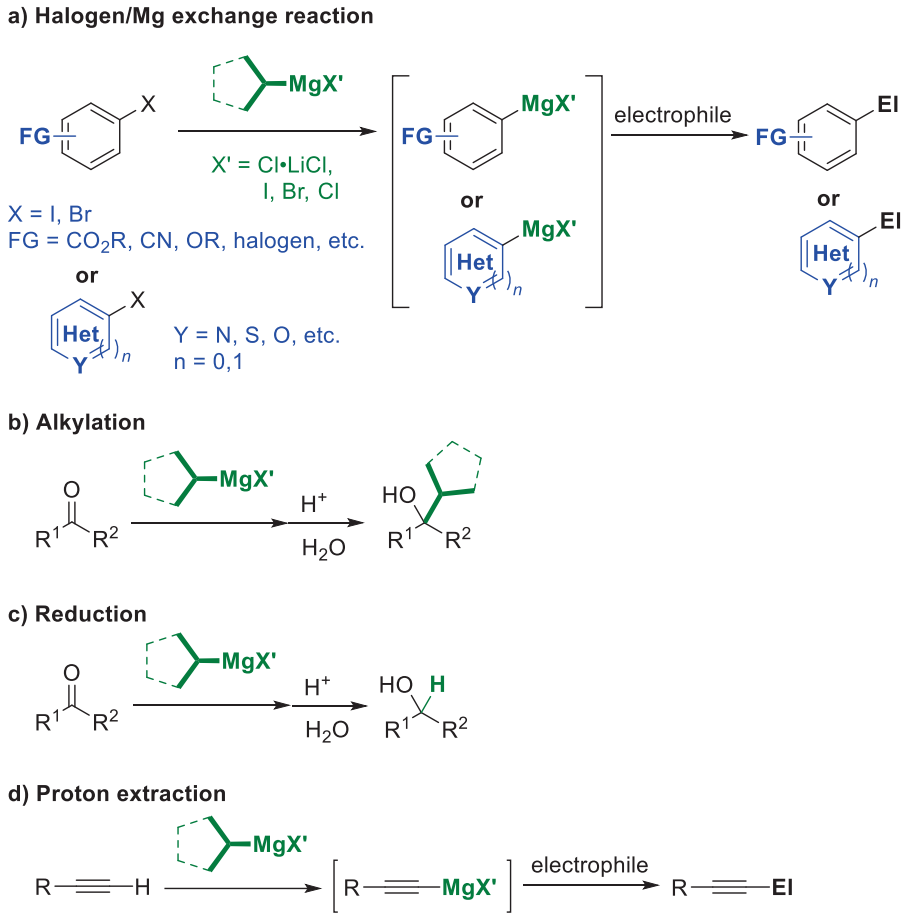


Scheme 1. Previous synthetic routes to secondary 1-trifluoromethylated propargyl alcohols.

Therefore, a more straightforward, easily scalable, functional-group-tolerant, and novel tandem reaction using commercially available chemicals in a one-pot manner for the synthesis of secondary 1-trifluoromethylated propargyl alcohols under mild conditions is still required.

Grignard reagents are some of the oldest and most valuable organometallic reagents for creating new carbon-carbon and carbon-heteroatom bonds.[42] The isopropylmagnesium chloride-lithium chloride complex (*i*-PrMgCl·LiCl), a secondary alkylmagnesium halide called the turbo Grignard

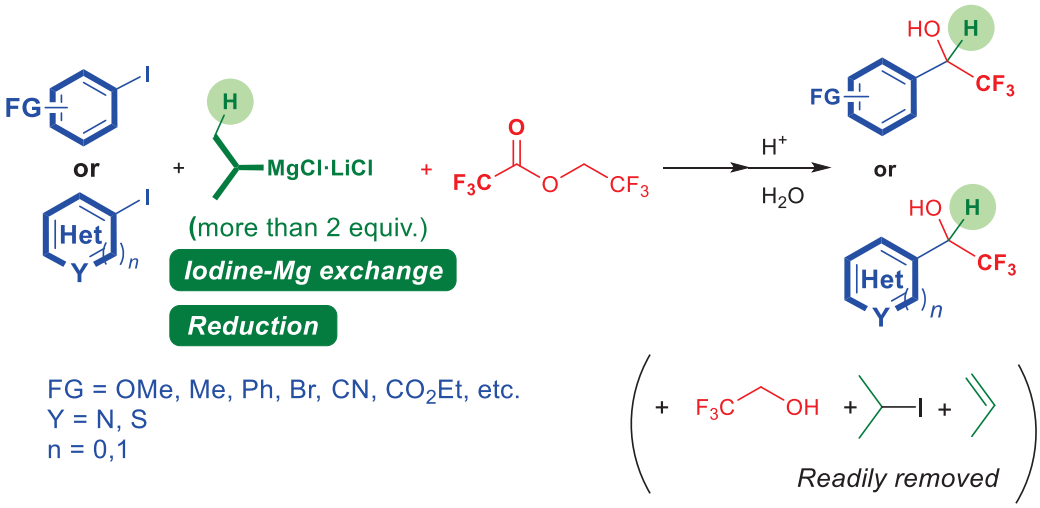
reagent, is one of the most useful Grignard reagents and has been widely used in organic syntheses as a halogen-magnesium exchange agent (Scheme 2a), carbon nucleophile (Scheme 2b),[43-45] reducing reagent (Scheme 2c),[46] and deprotonating reagent (Scheme 2d).[47]



Scheme 2. Typical reactions of secondary Grignard reagents.

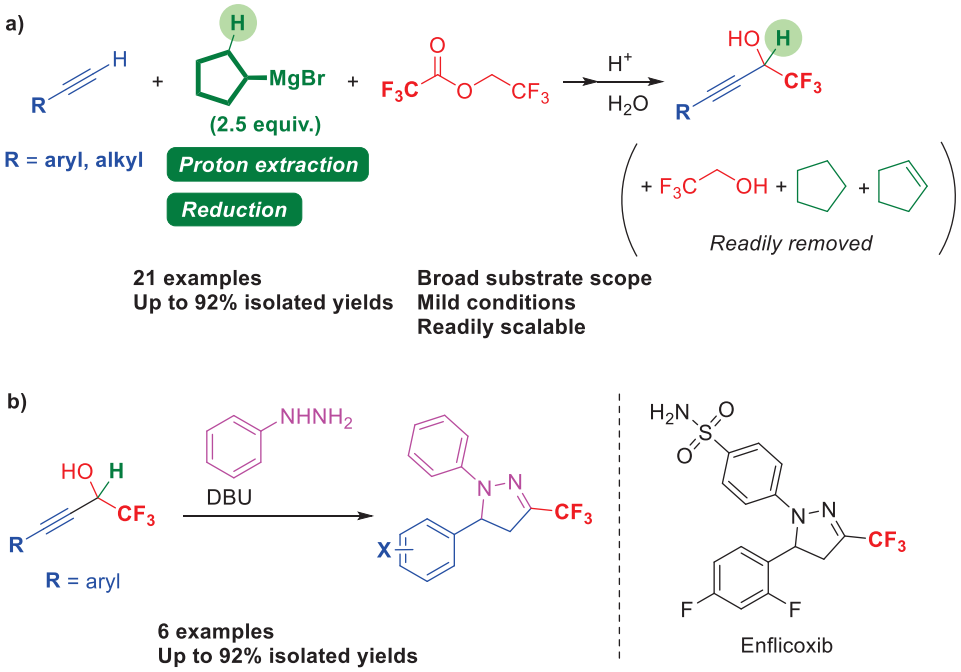
However, to the best of our knowledge, highly functional-group-tolerant organic synthetic methods utilizing two or more of these Grignard reagent reactions in a one-pot manner are very rare.[48-53]

We previously reported a new, straightforward, and functional-group-tolerant synthesis for α-aryl- or heteroaryl-α-trifluoromethyl alcohols utilizing two different turbo Grignard reactions in a one- pot process: halogen-magnesium exchange and reduction (Scheme 3).[54]



Scheme 3. Our previous work.

As part of our research on concise and efficient syntheses using two Grignard reactions in a one-pot manner, we report herein the convenient, functional-group-tolerant, easily scalable, one-pot synthesis of various 1-trifluoromethylated propargyl alcohols using tandem reactions of cyclopentylmagnesium bromide (CpMgBr) with commercially available 2,2,2-trifluoroethyl trifluoroacetate and terminal alkynes (Scheme 4a). This synthetic method involves three successive one-pot reactions: 1) reduction of 2,2,2-trifluoroethyl trifluoroacetate with CpMgBr, 2) deprotonation of terminal alkynes with CpMgBr, and 3) nucleophilic addition of in-situ-generated alkynyl Grignard reagents to in-situ-generated trifluoroacetaldehyde, leading to the corresponding 1-trifluoromethylated propargyl alcohols. This method has advantages including its one-pot nature, tolerance of functional groups, suppression of bis-propargyl adduct formation, high product yields, use of commercially available chemicals, and ease of scalability.



Scheme 4. This work.

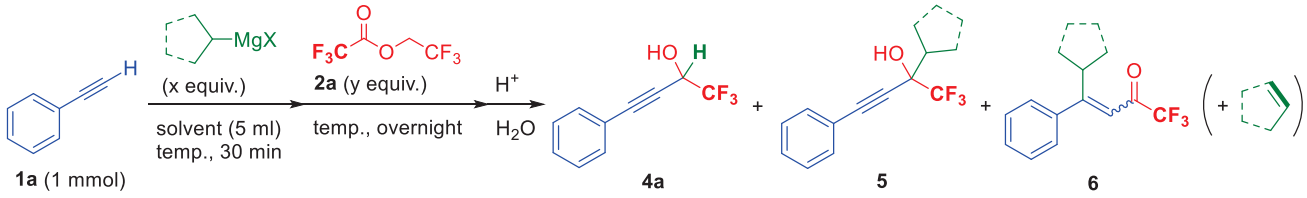
Furthermore, we also describe how the obtained 1-trifluoromethylpropargyl alcohols carrying aromatic groups can serve as promising trifluoromethylated building blocks for the new regioselective synthesis of 1,5-diaryl-3-trifluoromethyl-dihydropyrazoles, some of the most important motifs in the medicine Enflicoxib used to treat pain and inflammation associated with osteoarthritis in dogs (Scheme 4b).

Results and Discussion

The reaction of ethynylbenzene (**1a**) with 2.5 equiv. of *i*-PrMgCl·LiCl and 1.2 equiv. of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) in toluene at −40 °C smoothly proceeded to give the secondary alcohol 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4a**) in 59% yield, tertiary alcohol 4-methyl-1-phenyl-3-(trifluoromethyl)pent-1-yn-3-ol (**5**) in 24% yield, and α, β-unsaturated ketone 1,1,1-trifluoro-5-methyl-4-phenylhex-3-en-2-one (**6**) in 6% yield (Table 1, entry 1). 1,1,1-Trifluoro-4-

phenylbut-3-yn-2-one (**3a**) was hardly obtained.

Table 1. Optimization of the reaction conditions using ethynylbenzene (**1a**) and 2,2,2-trifluoroethyl trifluoroacetate (**2a**).



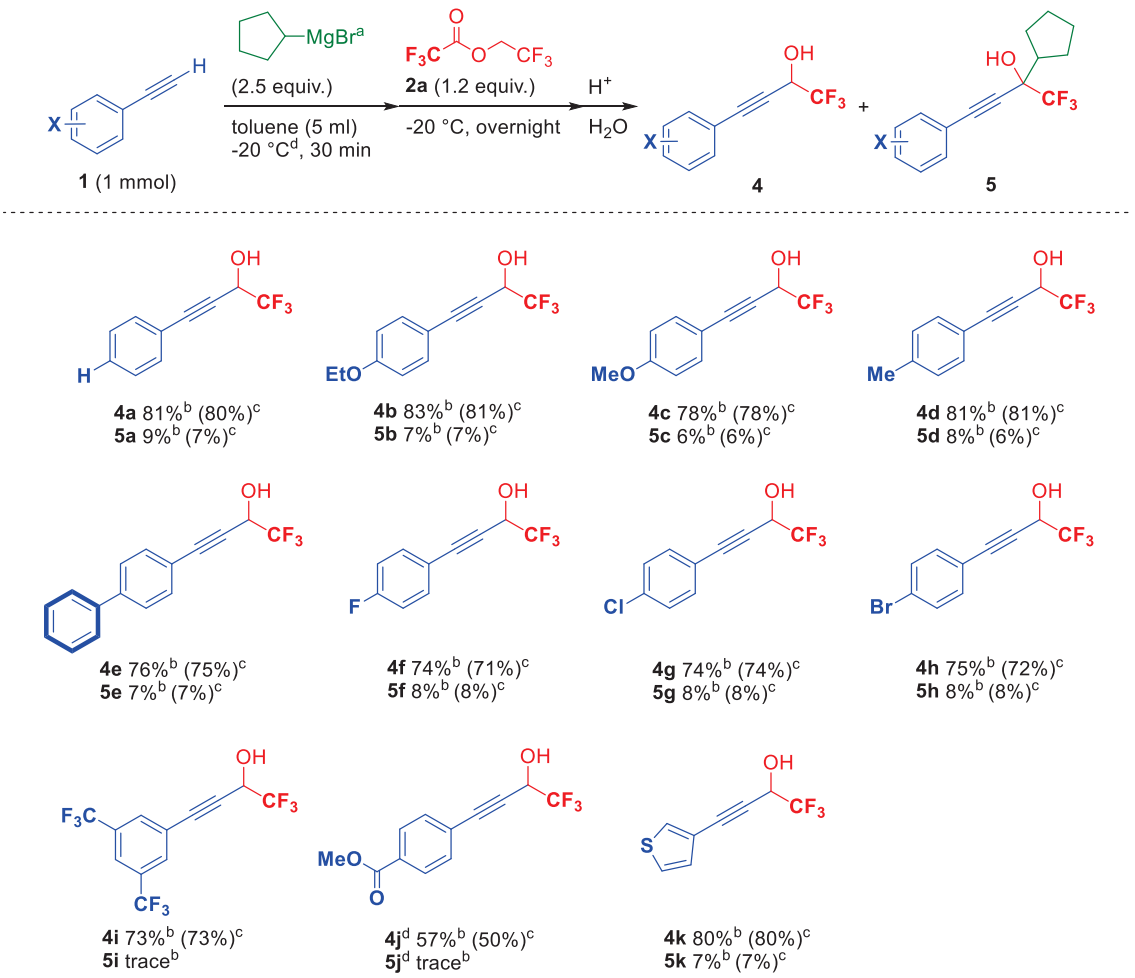
Entry	Solvent	Grignard reagent (x equiv.)	Ester **2a** (y equiv.)	Temp. (°C)	^{19}F NMR yield of **4a** (%)	**5** (%)	**6** (%)
1	Toluene	*i*-PrMgCl·LiCl[a] (2.5)	1.2	-40	59 (54)[d]	24 (21)[d]	6 (trace)[d]
2	Toluene	*i*-PrMgCl[b] (2.5)	1.2	-40	68	19	trace
3	Toluene	CPMgBr[c] (2.5)	1.2	-40	71	8	trace
4	Toluene	CPMgBr[c] (2.5)	1.2	-20	81 (80)[d]	9 (7)[d]	trace
5	Toluene	CPMgBr[c] (2.5)	2.0	-20	73	8	trace
6	Toluene	CPMgBr[c] (3.0)	1.2	-20	70	6	trace
7	THF	CPMgBr[c] (2.5)	1.2	-20	69	8	trace

[a] A THF solution of *i*-PrMgCl·LiCl (1.3 M) was used.[b] A THF solution of *i*-PrMgCl (2.0 M) was used.
[c] A THF solution of CpMgBr (1.0 M) was used. [d] Yields of isolated products.

By using *i*-PrMgCl instead of *i*-PrMgCl·LiCl, the yield of secondary alcohol **4a** improved to 68%, and tertiary alcohol **5** as a byproduct was obtained in 19% yield (Entry 2). The use of CpMgBr at −20 °C afforded the best results, giving secondary alcohol **4a** in better yield (81%) and byproduct 2-cyclopentyl-1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**5a**) in lower yield (9%) (Entry 4). The cyclopentyl group (steric effect (*Es*)=0.51) is bulkier than the isopropyl group (*Es*)=0.47), which may have inhibited alkylation and allowed the reduction to proceed.[55] Increasing the added equivalents of not only ester **2a** from 1.2 to 2.0 but also CpMgBr from 2.5 to 3.0 did not have a significant effect on the yield of alcohol **4a** (Entries 5 and 6). When THF was used as the solvent in place of toluene, the yield of alcohol **4** a slightly decreased to 69% (Entry 7).

As shown in Scheme 5, other ethynylbenzene derivatives **1**, such as 1-ethoxy-4-ethynylbenzene (**1b**), 1-ethynyl-4-methoxybenzene (**1c**), 1-ethynyl-4-methylbenzene (**1d**), 4-ethynyl-1,1'-biphenyl (**1e**), 1-ethynyl-4-fluorobenzene (**1f**), 1-chloro-4-ethynylbenzene (**1g**), and 1-ethynyl-

3,5-bis(trifluoromethyl)benzene (**1i**), also participated in successive reactions of CpMgBr with 2,2,2-trifluoroethyl trifluoroacetate (**2a**) to give the corresponding 1-trifluoromethylated propargyl alcohols **4** in good yields under the optimized conditions, as well as a small amount of cyclopentylated adducts **5** as byproducts.



[a] A THF solution of CpMgBr (1.0 M) was used. [b] ^{19}F NMR yields. [c] Yields of isolated products.
[d] After the addition of Grignard reagent, the reaction was carried out at -40 °C, 30 min.

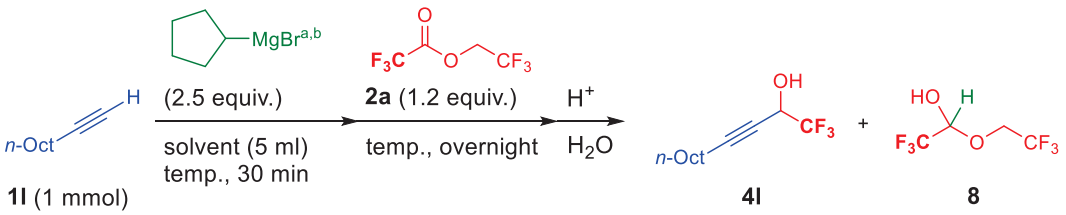
Scheme 5. Substrate scope of the aromatic terminal alkynes **1**.

It should be noted that in the case of ethynylbenzene **1 h** with a bromine atom on the phenyl ring, no bromine-Mg exchange reaction with CpMgBr occurred, and only secondary alcohol **4h** as the desired product with a small amount of cyclopentylated adduct **5h** were obtained. Notably, the

tandem reactions of ethynylbenzene derivative **1j**, which has a reducible ester group on the phenyl ring, smoothly proceeded to give corresponding 1-trifluoromethylated propargyl alcohol **4j** in moderate yield (50%). The use of ethynyl heteroarene 3-ethynylthiophene (**1k**) also gave a good yield of 80%. In terms of the substrate scope of ethynyl arenes **1**, the yields tended to be higher for ethynyl arenes with electron-donating substituents on not only the phenyl group but also the thienyl group.

Next, the reaction of 1-decyne (**1l**) as an aliphatic terminal alkyne was carried out under the same reaction conditions as the aromatic alkynes. Treatment of 1-decyne (**1l**) with 2.5 equiv. of CpMgBr in THF and 1.2 equiv. of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) in toluene at −20 °C gave 1,1,1-trifluorododec-3-yn-2-ol (**4l**) in only 41% yield, along with 9% yield of the trifluoroethyl hemiacetal of CF_3CHO **8** [56] which was produced by the reduction of ester **2a** with CpMgBr (Table 2, entry 1).

Table 2. Optimization of reaction conditions using 1-decyne (**1l**) and 2,2,2-trifluoroethyl trifluoroacetate (**2a**).

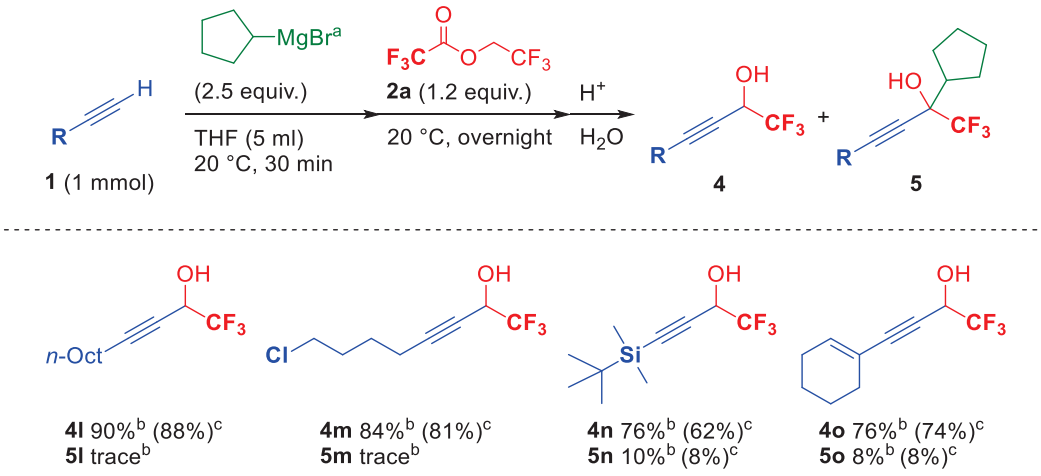


Entry	Temp. (°C)	Solvent	^{19}F NMR yield of **4l** (%)	**8** (%)
1[a]	-20	Toluene	41	9
2[a]	20	Toluene	78	trace
3[a]	20	THF	84	trace
4[b]	-20	Toluene	trace	57
5[b]	20	Toluene	81	trace
6[b]	20	THF	90 (88)[c]	trace

[a] A THF solution of CpMgBr (1.0 M) was used.
[b] An Et_2O solution of CpMgBr (2.0 M) was used.
[c] Yield of isolated product.

Increasing the reaction temperature from −20 to 20 °C resulted in a dramatic improvement in

the yield of alcohol **4l** from 41% to 78% (Entry 2). THF could also be used to give slightly higher yields of alcohol **4l** (Entries 2 and 3). When a commercially available diethyl ether solution of CpMgBr was used in place of the THF solution, CF_3CHO hemiacetal **8** was the main product at −20 °C, which was confirmed by ^1H, ^{19}F NMR, and HRMS analyses of the crude reaction mixture (see Supporting Figures and Tables), whereas alcohol **4l** was hardly obtained (Entry 4). The reaction with a diethyl ether solution of CpMgBr at 20 °C in THF proceeded smoothly to give the best yield of alcohol **4l** (Entry 6). Under the optimized reaction conditions listed in Table 2, a range of aliphatic alkynes including 1-decyne (**1l**), 6-chlorohex-1-yne (**1m**), tert-butyl(ethynyl) dimethyl silane (**1n**), and 1-ethynylcyclohex-1-ene (**1o**) participated well in the successive Grignard reactions of CpMgBr with 2,2,2-trifluoroethyl trifluoroacetate (**2a**) to produce the corresponding 1-trifluoromethylated propargyl alcohols **4** in good to high yields. Some substrates also gave a small amount of cyclopentylated byproducts **5** (Scheme 6). It should be noted that the reactions exhibited a tolerance to chlorine atoms and silyl groups.

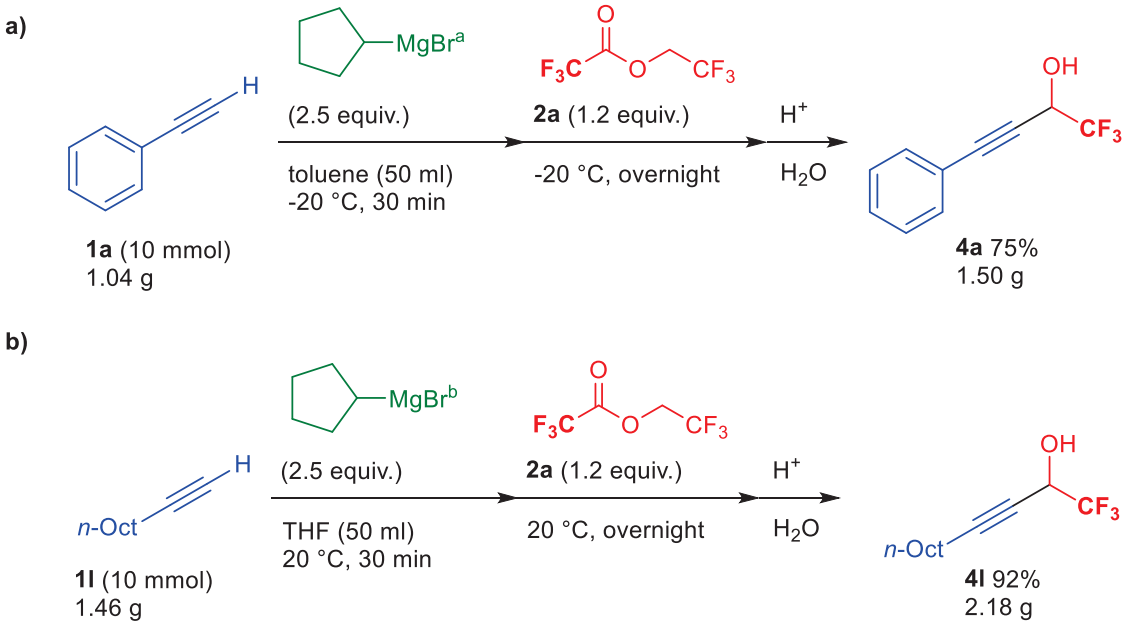


[a] An Et_2O solution of CpMgBr (2.0 M) was used. [b] ^{19}F NMR yields. [c] Yields of isolated products.

Scheme 6. Substrate scope of aliphatic terminal alkynes **1**.

These successive Grignard reactions of CpMgBr with 2,2,2-trifluoroethyl trifluoroacetate (**2a**)

can be applied to gram-scale syntheses, as shown in Scheme 7. The reaction of ethynylbenzene (**1a**) with 2.5 equiv. of CpMgBr in THF and 1.2 equiv. of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) in toluene proceeded smoothly, even on a gram scale, to obtain 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4a**) in 75% yield (Scheme 7a). Similarly, the reaction using 1-decyne (**1l**) with 2.5 equiv. of CpMgBr in Et_2O and 1.2 equiv. of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) in THF also succeeded in the gram-scale production of 1,1,1-trifluorododec-3-yn-2-ol (**4l**) in 92% yield (Scheme 7b). These results demonstrate that the operation of the successive Grignard reactions of CpMgBr with 2,2,2-trifluoroethyl trifluoroacetate (**2a**) and terminal alkynes is amenable to scaling.

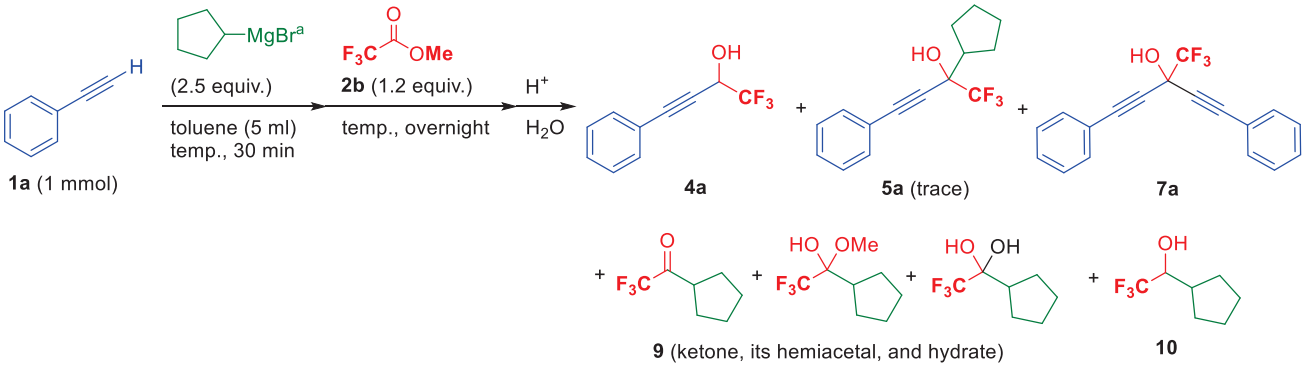


[a] A THF solution of CpMgBr (1.0 M) was used.
[b] An Et_2O solution of CpMgBr (2.0 M) was used.

Scheme 7. Gram-scale syntheses.

Commercially available methyl trifluoroacetate (**2b**) was then used instead of 2,2,2-trifluoroethyl trifluoroacetate (**2a**), and the conditions shown in Table 3 were used to perform the successive Grignard reactions of CpMgBr with the aromatic alkyne ethynylbenzene (**1a**).

Table 3. Optimization of reaction conditions using methyl trifluoroacetate (**2b**) and ethynylbenzene (**1a**).

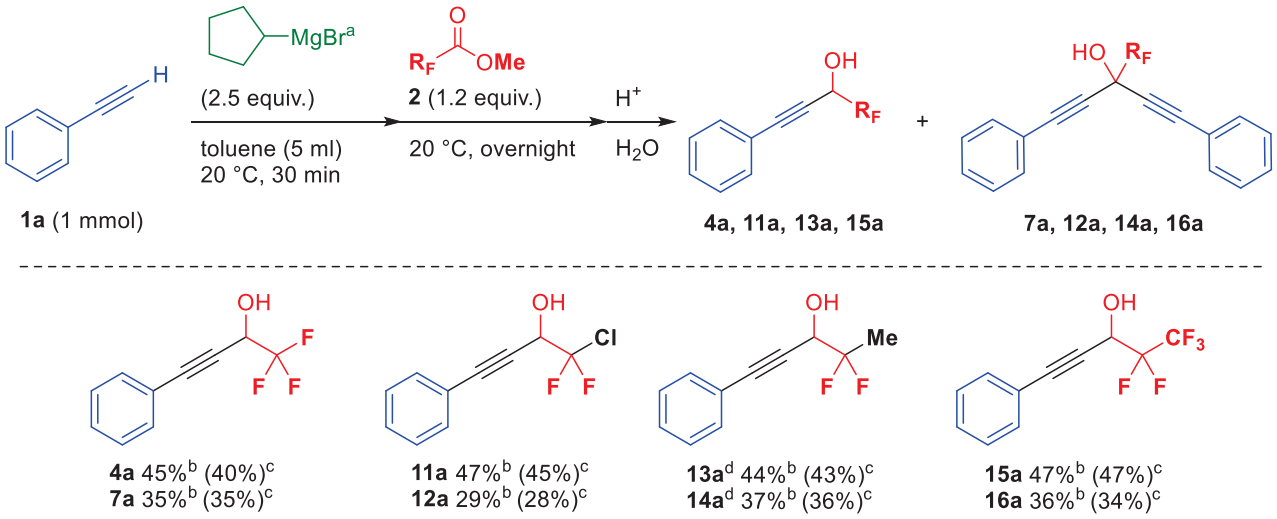


		^{19}F NMR yield of			
Entry	Temp. (°C)	**4a** (%)	**7a** (%)	**9**, its hemiacetal, and hydrate (%)	**10** (%)
1	-20	24	14	31	34
2	0	42	19	trace	29
3	20	45 (40)[b]	35 (35)[b]	trace	30

[a] A THF solution of CpMgBr (1.0 M) was used. [b] Yields of isolated products.

The reaction of methyl trifluoroacetate (**2b**) with ethynylbenzene (**1a**) and CpMgBr under the same reaction conditions gave only 24% yield of 1-trifluoromethylated propargyl alcohol **4 a**; 14% yield of bis-adduct 1,5-diphenyl-3-(trifluoromethyl)penta-1,4-diyn-3-ol (**7a**); 31% yield of a mixture of 1-cyclopentyl-2,2,2-trifluoroethan-1-one (**9**), its hemiacetal, and its hydrate; and 34% yield of 1-cyclopentyl-2,2,2-trifluoroethan-1-ol (**10**) (Table 3, entry 1). An elevated temperature (20 °C) gave alcohol **4** a in 45% yield and bis-adduct **7a** in 35% yield (Entry 3).

As shown in Scheme 8, other commercially available fluorine-containing methyl esters **2**, such as methyl 2-chloro-2,2-difluoroacetate, ethyl 2,2-difluoropropanoate, and methyl 2,2,3,3-pentafluoropropanoate, also participated in the successive Grignard reactions of CpMgBr with ethynylbenzene (**1a**) to give the corresponding 1-chlorodifluoromethyl, 2,2-difluoroethyl, pentafluoroethyl propargyl alcohols **4a**, **11a**, **13a**, and **15a**, respectively, in 40–47% isolated yields, along with bis-adducts **7a**, **12a**, **14a**, and **16a**, respectively, carrying two phenylethynyl groups in 28–36% isolated yields.

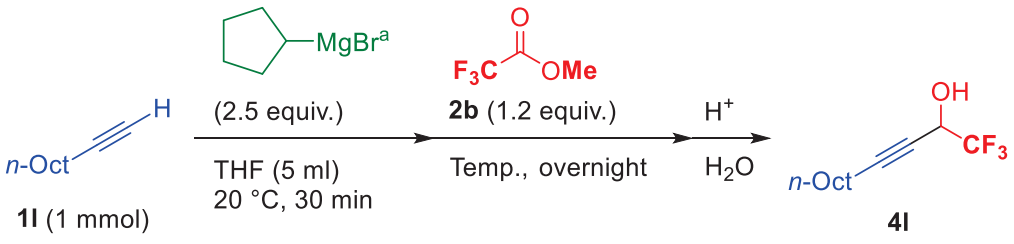


[a] A THF solution of CpMgBr (1.0 M) was used. [b] ^{19}F NMR yields. [c] Yields of isolated products.
[d] $MeCF_2CO_2Et$ **2** was used.

Scheme 8. Substrate scope of methyl esters **2** carrying various fluoroalkyl groups with ethynylbenzene (**1a**).

When the reaction of methyl ester **2b** was carried out with the aliphatic alkyne 1-decyne (**1l**) under the same conditions as in Scheme 6, alcohol **4l** was obtained in 72% yield (Table 4, entry 1). Elevating the temperature from 20 to 40 °C after the addition of 1.2 equiv. of methyl trifluoroacetate (**2b**) improved the yield of alcohol **4l** to 79% (Entry 2).

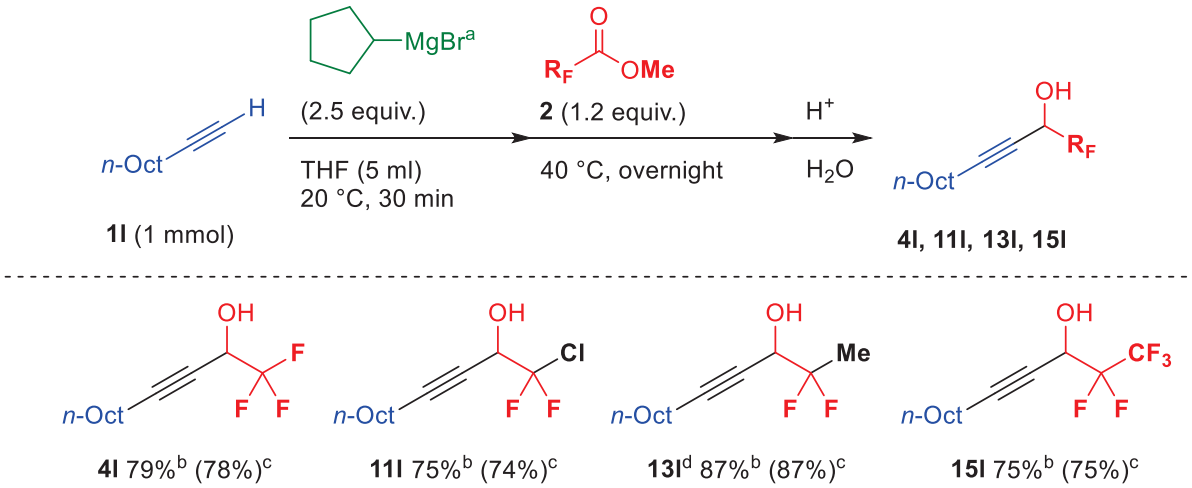
Table 4. Optimization of reaction conditions using methyl trifluoroacetate (**2b**) and 1-decyne (**1l**).



Entry	Temp. (°C)	^{19}F NMR yield of **4l** (%)
1	20	72
2	40	79 (78)[b]

[a] An Et_2O solution of CpMgBr (2.0 M) was used.
[b] Yield of isolated product.

Other commercially available fluorine-containing methyl esters **2**, such as methyl 2-chloro-2,2-difluoroacetate, ethyl 2,2-difluoropropanoate, and methyl 2,2,3,3-pentafluoropropanoate, also participated in the successive Grignard reactions of CpMgBr with 1-decyne (**1l**) in THF to afford alcohols **4l**, **11l**, **13l**, and **15l**, respectively, in good to high yields (Scheme 9).

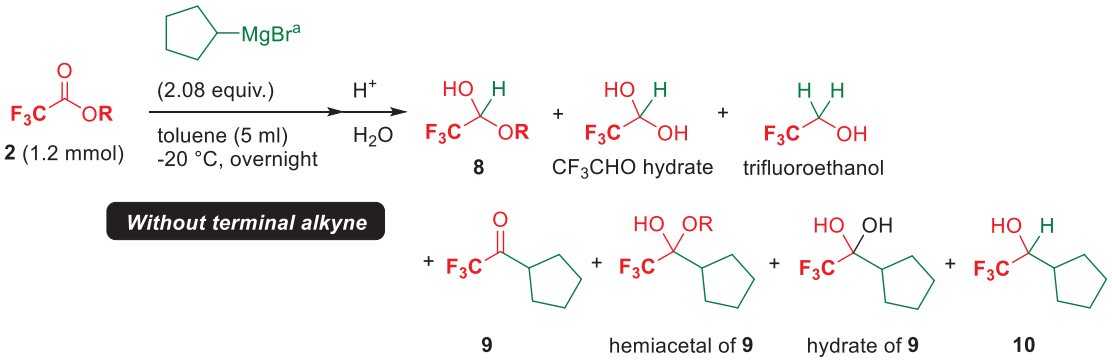


[a] An Et_2O solution of CpMgBr (2.0 M) was used. [b] ^{19}F NMR yields. [c] Yields of isolated products. [d] $MeCF_2CO_2Et$ **2** was used.

Scheme 9. Substrate scope of methyl esters **2** carrying various fluoroalkyl groups with 1-decyne (**1l**).

To investigate the reaction mechanism in detail, the reaction of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) with CpMgBr was carried out without terminal alkyne **1** under the conditions shown in Scheme 5, and the results are summarized in Table 5.

Table 5. Reactions of 2,2,2-trifluoroethyl trifluoroacetate (**2a**) or methyl trifluoroacetate (**2b**) with CpMgBr without terminal alkynes.

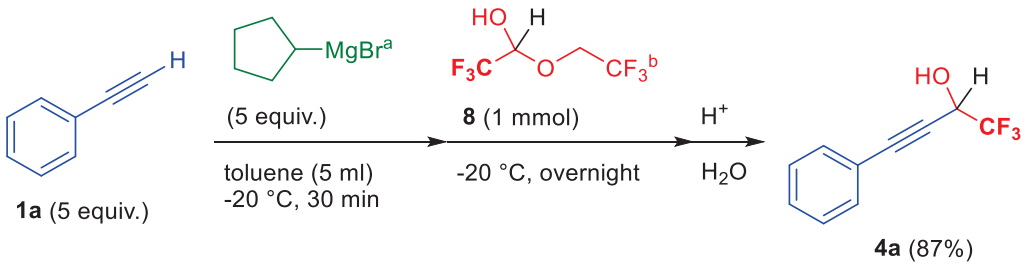


Entry	R	**8** (%)	CF_3CHO hydrate (%)	^{19}F NMR yield of Trifluoroethanol (%)	**9**, its hemiacetal, and hydrate (%)	**10** (%)
1	CH_2CF_3	24	18	89	trace	8
2	CH_3	trace	0	0	15	53

[a] A THF solution of CpMgBr (1.0 M) was used.

The reaction of trifluoroethyl ester **2a** with CpMgBr without terminal alkyne **1** gave CF_3CHO hemiacetal 8 in 24% yield, its hydrate in 18% yield, and trifluoroethanol in 89% yield (table 5, entry 1). On the other hand, the reaction of methyl ester **2b** in place of trifluoroethyl ester **2a** without terminal alkyne **1** gave cyclopentyl ketone **9** in 15% yield and cyclopentyl trifluoroethanol 10 in 53% yield (Entry 2). Not only the lower LUMO (−1.21 eV) of the ester **2a** than those of the methyl ester **2b** (−0.84 eV) (see Supporting Figures and Tables) but also the bigger size of the trifluoroethyl group than the methyl group should favor the reduction rather than the addition of the Grignard reagent. The hemiacetal of CF_3CHO **8**, its hydrate, cyclopentyl ketone **9**, and cyclopentyl trifluoroethanol **10** were detected by HRMS (see Supporting Figures and Tables).

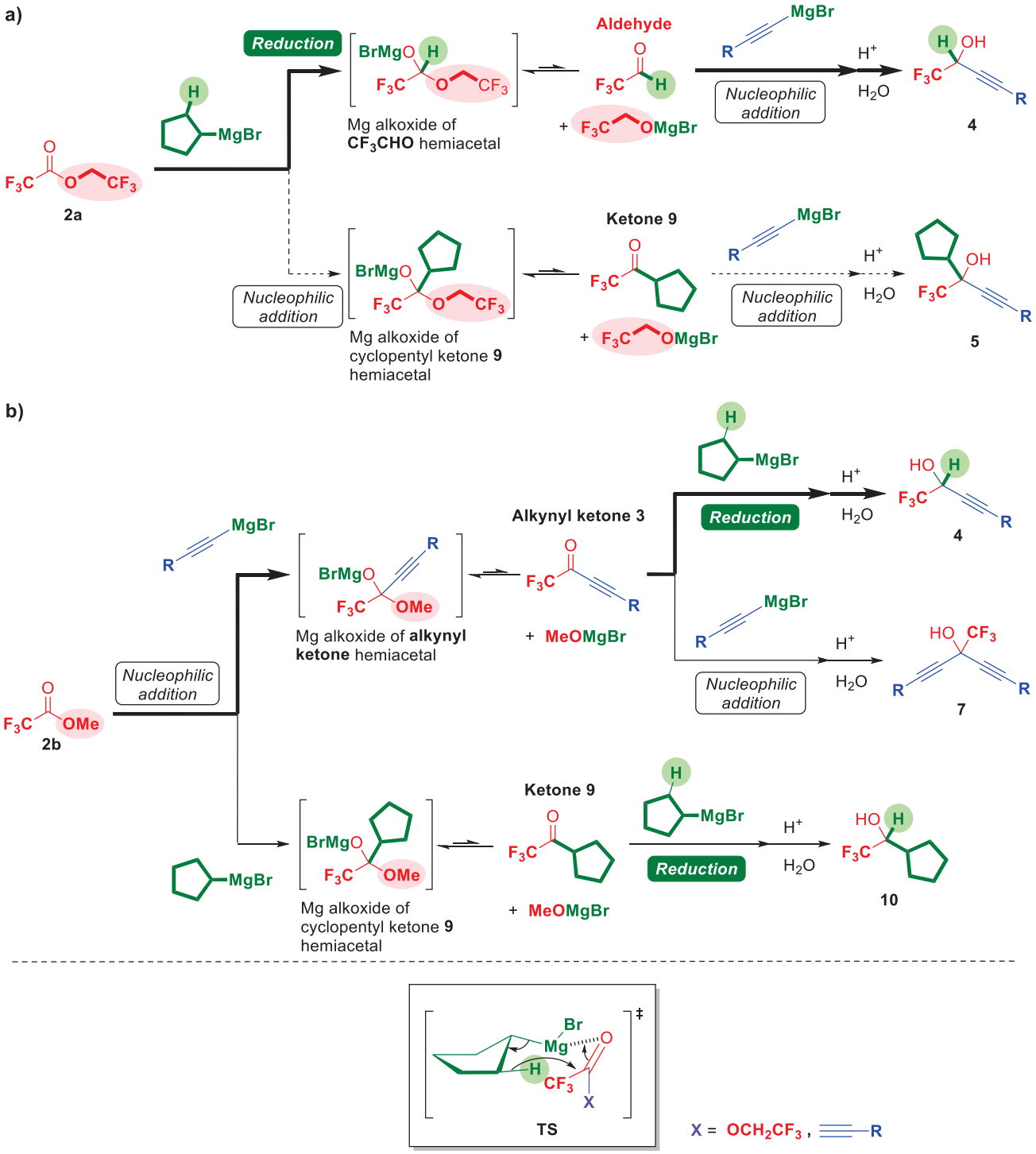
In addition, the reaction of the trifluoroethyl hemiacetal of CF_3CHO **8** with alkynyl Grignard reactants was also studied, as illustrated in Scheme 10. A large excess of alkynyl Grignard reagent carrying a phenyl group was reacted with the hemiacetal **8** at −20 °C overnight to give the corresponding propargyl alcohol **4a** in 87% yield.



[a] A THF solution of CpMgBr (1.0 M) was used.
[b] A trifluoroethanol solution of the hemiacetal of CF_3CHO **8** (61 wt%) was used.

Scheme 10. The reaction of the trifluoroethyl hemiacetal of CF_3CHO **8** with alkynyl Grignard reagent.

Based on these results, the reaction mechanism of the successive Grignard reactions of CpMgBr with 2,2,2-trifluoroethyl trifluoroacetate (**2a**) and terminal alkynes can be considered to follow the steps shown in Scheme 11a.



Scheme 11. Proposed reaction mechanism for one-pot synthesis of 1-trifluoromethylated propargyl alcohols 4 using 2,2,2-trifluoroethyl trifluoroacetate (**2a**) or methyl trifluoroacetate (**2b**).

The reduction of trifluoroethyl ester **2a**[52] with CpMgBr proceeds mainly via TS,[48, 57] as shown in Scheme 11, to give the Mg alkoxide trifluoroethyl hemiacetal of CF_3CHO, followed by elimination to

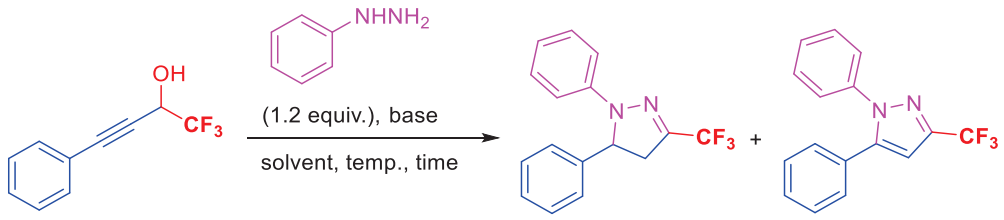
produce highly reactive CF_3CHO in-situ. Nucleophilic addition of the alkynyl Grignard reagents to the in-situ-generated CF_3CHO followed by protonation results in the formation of propargyl alcohols **4**. On the other hand, because of the poor reactivity of methyl trifluoroacetate (**2b**) compared with that of trifluoroethyl ester **2a**, the reduction of methyl trifluoroacetate (**2b**) with CpMgBr does not occur. Instead, the nucleophilic addition of CpMgBr or the alkynyl Grignard reagent generated by deprotonation of the terminal alkyne proceeds predominantly to produce the Mg alkoxides of the hemiacetal of the alkynyl trifluoromethyl ketone. This is followed by elimination of the methoxide from the Mg alkoxide, leading to alkynyl trifluoromethyl ketone **3** or cyclopentyl ketone **9**, as shown in Scheme 11b.This is followed by elimination of the methoxide from the Mg alkoxide, leading to alkynyl trifluoromethyl ketone **3** or reduction of the generated alkynyl ketone **3** with CpMgBr via TS or the addition of another molecular equivalent of alkynyl Grignard reagent to ketone **3** gave trifluoromethylated propargyl alcohol **4** or bis-adduct **7**, respectively. The reduction of cyclopentyl ketone **9** with CpMgBr gave alcohol **10**.

Finally, 1-trifluoromethylated propargyl alcohols **4** were evaluated as trifluoromethylated building blocks for the synthesis of 1,5-diaryl-3-(trifluoromethyl)-4,5-dihydro-*1H*-pyrazole,[58, 59] an important skeleton of Enflicoxib,[60] which is used for the treatment of pain and inflammation associated with osteoarthritis in dogs, as shown in Scheme 4b.

The reaction conditions were optimized based on the results of the reactions of non-fluorinated propargyl alcohols with phenylhydrazine, and the results are summarized in Table 6.[61, 62] Upon treating 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4a**) with 1.2 equiv. of phenylhydrazine and 20 mol % of *t*-BuOK in toluene under reflux for 4 h, the reaction proceeded via the redox isomerization of 1-trifluoromethylated propargyl alcohols to α, β-unsaturated carbonyl compounds,[63,64] giving 1,5-diphenyl-3-(trifluoromethyl)-4,5-dihydro-*1H*-pyrazole (**17a**) in only 6% yield, together with 73% recovery of starting material **4a** (Table 6, entry 1). The use of 1 equiv. of DBU instead of *t*-BuOK gave 3-(trifluoromethyl)-4,5-dihydro-*1H*-pyrazole **17a** in 35% yield, together with 56% recovery of starting

alcohol **4a** (Entry 2). By Increasing the concentration of the reaction solution and prolonging the reaction time from 4 to 24 h, the yield of product **17a** was improved to 90% (Entry 3). DMF was found to be an unsuitable solvent for the synthesis of product **17a**, giving only 62% yield, together with 10% yield of 1,5-diphenyl-3-(trifluoromethyl)-*1H*-pyrazole (**18a**) (Entry 4). At present, the oxidation process from the **17a** to the **18a** is not clear.

Table 6. Optimization of reaction conditions for the synthesis of 1,5-diphenyl-3-trifluoromethyl-dihydropyrazole (**17a**).

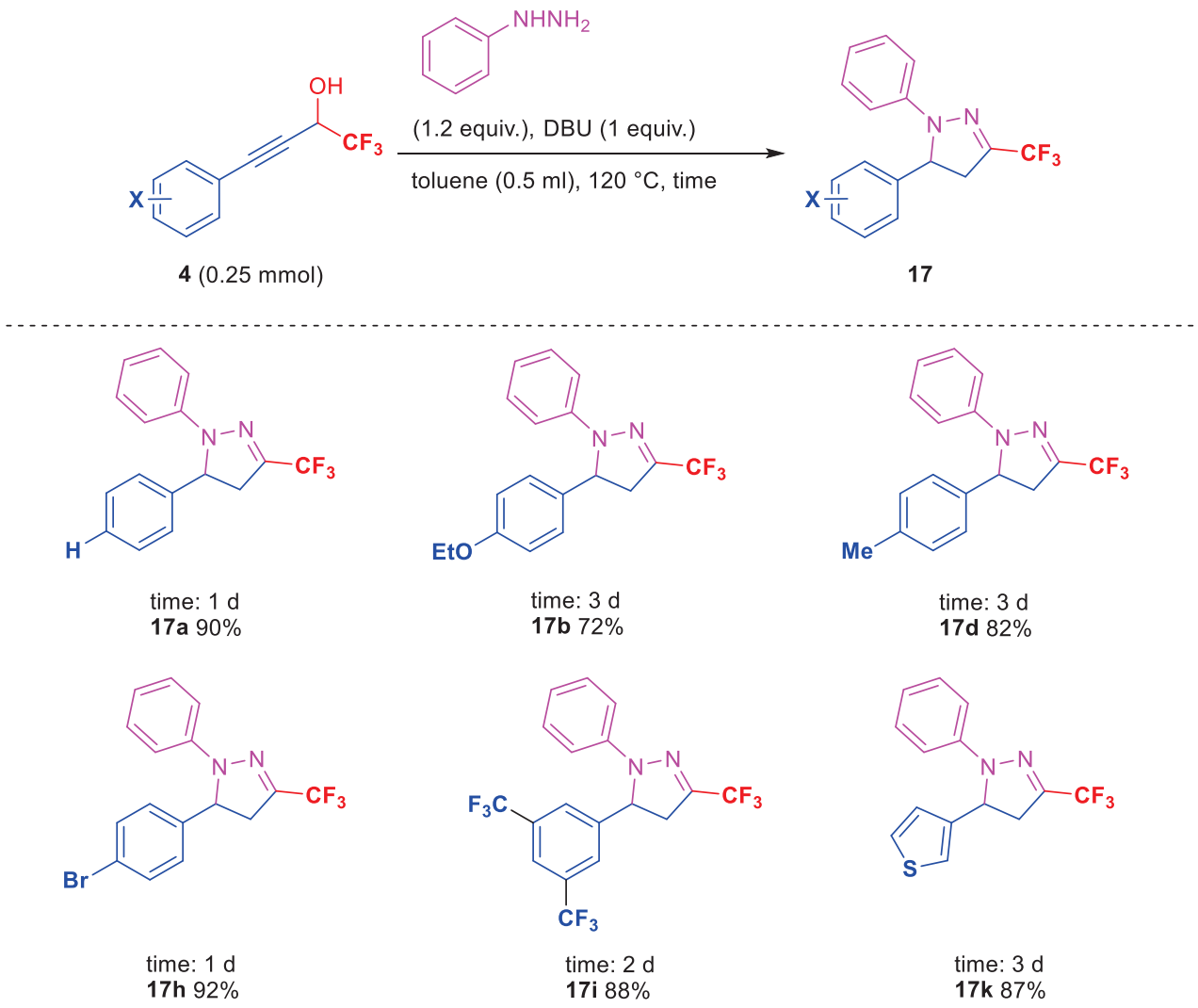


4a (0.25 mmol) **17a** **18a**

Entry	Solvent (ml)	Base	Temp. (°C)	Time (h)	^{19}F NMR yield of Dihydropyrazole **17a** (%)	Pyrazole **18a** (%)	Recovery of **4a** (%)
1	Toluene (1.0)	*t*-BuOK (20 mol%)	reflux	4	6	-	73
2	Toluene (1.0)	DBU (1 equiv.)	reflux	4	35	-	56
3	Toluene (0.5)	DBU (1 equiv.)	reflux	24	90 (90)[a]	-	0
4	DMF (0.5)	DBU (1 equiv.)	120	24	62 (56)[a]	10 (10)[a]	0

[a] Yields of isolated products.

Other 1-trifluoromethylpropargyl alcohols **4** carrying various substituent groups on not only the phenyl ring but also the thienyl group, including 4-(4-ethoxyphenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4b**), 1,1,1-trifluoro-4-(p-tolyl)but-3-yn-2-ol (4 d), 4-(4-bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4h**), 4-(3,5-bis(trifluoromethyl)phenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4i**), and 1,1,1-trifluoro-4-(thiophen-3-yl)but-3-yn-2-ol (**4k**), also participated well in the reactions with phenylhydrazine to give the corresponding trifluoromethylated 1,5-diaryldihydropyrazoles **17** in good to excellent yields (Scheme 12).



Scheme 12. Substrate scope for the synthesis of 1,5-diaryl-3-trifluoromethyldihydropyrazoles **17**.

However, for aliphatic propargyl alcohol 1,1,1-trifluorododec-3-yn-2-ol (**4l**), the reaction under the same conditions did not proceed smoothly. Instead, 90% of starting alcohol **4l** was recovered, together with a trace amount of the desired 5-alkyl-3-trifluoromethyldihydropyrazole **17l**.

Conclusion

We have developed a straightforward, functional-group-tolerant, one-pot synthesis for various 3-aryl-1-trifluoromethylpropargyl alcohols based on two reactions of cyclopentylmagnesium bromide (CpMgBr) with commercially available 2,2,2-trifluoroethyl trifluoroacetate and terminal alkynes. This synthetic method involves three successive one-pot reactions: 1) reduction of 2,2,2-trifluoroethyl trifluoroacetate with CpMgBr, 2) deprotonation of terminal alkynes with CpMgBr, and 3) nucleophilic addition of in-situ-generated alkynyl Grignard reagents to in-situ-generated CF_3CHO, leading to the corresponding 3-substituted 1-trifluoromethylated propargyl alcohols. This method has some advantages, such as its one-pot nature, tolerance of functional groups, suppression of bis-propargyl adduct formation, high product yields (up to 92%), use of commercially available chemicals, ease of scalability, and product diversity. Furthermore, the obtained aromatic 1-trifluoromethyl propargyl alcohols reacted smoothly with phenylhydrazine in the presence of DBU in toluene to give good to excellent yields of 1,5-diaryl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazoles, important skeletons of Enflicoxib, a drug used for the treatment of pain and inflammation associated with osteoarthritis in dogs.

Experimental Section

Measurements.

^{1}H NMR spectra were measured at 392 or 400 MHz, ^{13}C NMR spectra were measured at 99 or 101 MHz, and ^{19}F NMR spectra were measured at 369 or 376 MHz. All samples were dissolved in deuterochloroform ($CDCl_3$) and measured on a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. Benzotrifluoride was used as an external standard for the ^{19}F NMR measurements. The data are reported as follows: (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sep = septet, m = multiplet, br s = broad singlet, coupling constant(s), integration). Melting points were obtained on a Yanagimoto MP-S3 micro melting point apparatus and are uncorrected. Electrospray ionization mass spectroscopy (ESI-MS) analysis using MeOH was performed using a JEOL JMS-T100LP (Accu TOF LC-plus) instrument.

Materials.

Et_2O and THF solutions of cyclopentylmagnesium bromide (CpMgBr) were purchased from Aldrich Co. and FUJIFILM Wako Pure Chemical Co., respectively. Dehydrated THF and dehydrated toluene were purchased from Kanto Chemical Co. and FUJIFILM Wako Pure Chemical Co., respectively. Trifluoroacetaldehyde trifluoroethyl hemiacetal was obtained from Central Glass Co. The pure products were isolated by column chromatography using silica gel (Wakogel C-200, 100–200 mesh, Wako Pure Chemical Ind., Ltd. or silica gel 60, spherical, 40–50 mm, Kanto Chemical Co., Inc.). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F254 plates.

Typical procedure using ethynylarenes 1 with 2,2,2-trifluoroethyl trifluoroacetate (2a)

Ethynylbenzene (**1a**) (0.104 g, 1 mmol) was dissolved in dehydrated toluene (5 ml) and cooled to −20 °C under an argon atmosphere. A THF solution of CpMgBr (2.5 ml, 2.5 mmol, 1.0 M) was added to the mixture and stirred at −20 °C for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (**2a**) (0.245 g, 1.2 mmol) was then added, and the solution was stirred overnight. The resulting mixture was quenched

with a saturated aqueous NH_4Cl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, and concentrated under vacuum to obtain the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride as the standard, the residue was purified by chromatography (hexane/dichloromethane=1/1) to give 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4 a**) (0.160 g, 80%).

1,1,1-Trifluoro-4-phenylbut-3-yn-2-ol (**4 a**). [26]

Yield 80%; R_f 0.20 (hexane/dichloromethane=1/1); m.p. <30 °C; IR (KBr) 3360 (OH), 2245 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.48 (m, 2H, aryl H), 7.40–7.31 (m, 3H, aryl H), 4.96–4.91 (m, 1H, CH), 3.11 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 132.2, 129.6, 128.6, 122.9 (q, *J*=282.2 Hz), 121.0, 88.1, 80.5, 63.0 (q, *J*=36.3 Hz).

2-Cyclopentyl-1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**5a**).

Yield 7%; R_f 0.31 (hexane/dichloromethane=1/1); IR (KBr) 3580 (OH), 2252 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 291.0994. Calcd for $C_{15}H_{15}OF_3Na$: $[M+Na]^+$, 291.0973; ^1H NMR ($CDCl_3$) δ 7.48–7.46 (m, 2H, aryl H), 7.40–7.32 (m, 3H, aryl H), 2.64 (br s, 1H, OH), 2.45 (quin, 1H, *J*=8.97 Hz, CH), 2.00–1.57 (m, 8H, CH_2×4); ^{19}F NMR ($CDCl_3$) δ −78.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 132.1, 129.4, 128.5, 124.5 (q, *J*=285.6 Hz), 121.4, 87.6, 83.3, 75.1 (q, *J*=30.7 Hz), 44.5, 28.5, 27.9, 25.9, 25.4.

4-Methyl-1-phenyl-3-(trifluoromethyl)pent-1-yn-3-ol (**5**). [25]

Yield 21%; R_f 0.43 (hexane/dichloromethane=1/1); IR (KBr) 3441 (OH), 2234 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.48 (m, 2H, aryl H), 7.40–7.32 (m, 3H, aryl H), 2.72 (s, 1H, OH), 2.27 (sep, 1H, *J*=6.87 Hz, CH), 1.20 (d, 3H, *J*=6.87 Hz, CH_3), 1.16 (dd, 3H, *J*=6.87 Hz, 1.37 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −77.0 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 132.1, 129.4, 128.5, 124.6 (q, *J*=286.6 Hz), 121.4, 88.0, 82.8, 75.8 (q, *J*=30.1 Hz), 33.8, 17.9, 17.6.

1,1,1-Trifluoro-5-methyl-4-phenylhex-3-en-2-one (**6**).

Yield trace; R_f 0.75 (hexane/dichloromethane=1/1); IR (KBr) 1728 (C=O), 1597 (C=C) cm^{-1}; HRMS (ESI) found: *m/z* 265.0842. Calcd for $C_{13}H_{13}OF_3Na$: $[M+Na]^+$, 265.0816; ^1H NMR ($CDCl_3$) δ 7.42–7.38 (m, 3H, aryl H), 7.13–7.10 (m, 2H, aryl H), 6.46 (s, 1H, vinyl H), 2.79 (sepd, 1H, *J*=6.73 Hz, 0.90 Hz, CH), 1.17–1.15 (d, *J*=6.73 Hz, 6H, CH_3×2); ^{19}F NMR ($CDCl_3$) δ −78.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 179.1 (q, *J*=33.8 Hz), 175.3,139.1, 128.4, 128.3, 126.8, 116.2 (q, *J*=292.2 Hz), 114.1, 38.6, 21.0.

4-(4-Ethoxyphenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4b**).

Yield 81%; R_f 0.15 (hexane/dichloromethane=1/1); m.p.=76.1 °C; IR (KBr) 3391 (OH), 2225 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (d, 2H, *J*=8.93 Hz, aryl H), 6.82 (d, 2H, *J*=8.93 Hz, aryl H), 4.92–4.86 (m, 1H, CH), 4.01 (q, 2H, *J*=6.87 Hz, CH_2), 2.98 (d, 1H, *J*=8.24 Hz, OH), 1.40 (t, 3H, *J*=6.87 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F, *J*=5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 159.9, 133.7, 122.9 (q, *J*=281.8 Hz), 114.7, 112.8, 88.3, 79.2, 63.8, 63.1 (q, *J*=36.4 Hz), 14.7.

2-Cyclopentyl-4-(4-ethoxyphenyl)-1,1,1-trifluorobut-3-yn-2-ol (**5b**).

Yield 7%; R_f 0.23 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2303 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 313.1414. Calcd for $C_{17}H_{20}O_2F_3$: $[M+H]^+$, 313.1415; ^1H NMR ($CDCl_3$) δ 7.38 (d, 2H, *J*=8.76 Hz, aryl H), 6.84 (d, 2H, *J*=8.76 Hz, aryl H), 4.04 (q, 1H, *J*=6.81 Hz, CH_2CH_3), 2.60 (br s, 1H, OH), 2.43 (quin, 1H, *J*=8.98 Hz, CH), 2.00–1.57 (m, 8H, CH_2×4), 1.42 (t, 3H, *J*=6.81 Hz, CH_2CH_3); ^{19}F NMR ($CDCl_3$) δ −79.0 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 159.8, 133.7, 124.5 (q, *J*=285.6 Hz), 114.7, 113.2, 87.8, 82.0, 75.1 (q, *J*=30.7 Hz), 63.7, 44.5, 28.5, 27.9, 25.9, 25.4, 14.8.

1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (**4c**). [26]

Yield 78%; R_f 0.44 (dichloromethane); m.p.=42.6 °C; IR (KBr) 3414 (OH), 2226 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, 2H, *J*=8.70 Hz, aryl H), 6.85 (d, 2H, *J*=8.70 Hz, aryl H), 4.95–4.89 (m, 1H, CH), 3.81 (s, 3H, CH_3), 3.40 (d, 1H, *J*=8.24 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −79.3 (d, 3F, *J*=5.8 Hz); ^{13}C

NMR ($CDCl_3$) δ 160.4, 133.7, 123.0 (q, *J*=281.8 Hz), 114.2, 113.1, 88.1, 79.3, 63.0 (q, *J*=36.4 Hz), 55.4.

2-Cyclopentyl-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-ol (**5c**).

Yield 6%; R_f 0.23 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 299.1275. Calcd for $C_{16}H_{18}O_2F_3$: $[M+H]^+$, 299.1259; ^1H NMR ($CDCl_3$) δ 7.40 (d, 2H, *J*=8.53 Hz, aryl H), 6.85 (d, 2H, *J*=8.53 Hz, aryl H), 3.81 (s, 3H, CH_3), 2.69 (br s, 1H, OH), 2.43 (quin, 1H, *J*=8.53 Hz, CH), 1.94–1.58 (m, 8H, CH_2×4); ^{19}F NMR ($CDCl_3$) δ −78.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 160.4, 133.7, 124.5 (q, *J*=285.6 Hz), 114.2, 113.4, 87.7, 82.1, 75.1 (q, *J*=30.1 Hz), 55.5, 44.5, 28.5, 27.9, 25.9, 25.4.

1,1,1-Trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (**4d**). [26]

Yield 81%; R_f 0.18 (hexane/dichloromethane=1/1); m.p.=69.8 °C; IR (KBr) 3302 (OH), 2230 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, 2H, *J*=8.24 Hz, aryl H), 7.15 (d, 2H, *J*=8.24 Hz, aryl H), 4.97–4.91 (m, 1H, CH), 3.13 (d, 1H, *J*=8.24 Hz, OH), 2.37 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ −79.4 (d, 3F, *J*=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 140.0, 132.1, 129.3, 122.9 (q, *J*=281.9 Hz), 117.9, 88.4, 79.8, 63.1 (q, *J*=36.6 Hz), 21.6.

2-Cyclopentyl-1,1,1-trifluoro-4-(*p*-tolyl)but-3-yn-2-ol (**5d**).

Yield 7%; R_f 0.36 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 305.1111. Calcd for $C_{16}H_{17}OF_3Na$: $[M+Na]^+$, 305.1129; ^1H NMR ($CDCl_3$) δ 7.36 (d, 2H, *J*=8.31 Hz, aryl H), 7.14 (d, 2H, *J*=8.31 Hz, aryl H), 2.63 (br s, 1H, OH), 2.45 (quin, 1H, *J*=8.53 Hz, CH), 2.36 (s, 3H, CH_3), 1.96–1.58 (m, 8H, CH_2×4); ^{19}F NMR ($CDCl_3$) δ −78.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 139.7 (s), 132.0 (s), 129.3 (s), 124.5 (q, *J*=288.5 Hz), 118.3 (s), 87.8 (s), 82.7 (s), 75.1 (q, *J*=31.0 Hz), 44.5 (s), 28.5 (s), 27.9 (s), 25.9 (s), 25.4 (s), 21.7 (s).

4-(1,1′-Biphenyl]-4-yl)-1,1,1-trifluorobut-3-yn-2-ol (**4e**).

Yield 75%; R_f 0.16 (hexane/dichloromethane=1/1); m.p.=106.2 °C; IR (KBr) 3352 (OH), 2230 (C ≡ C) cm^{-1}; HRMS (ESI) found: *m/z* 277.0860. Calcd for $C_{16}H_{12}OF_3$: $[M+H]^+$, 277.0840; ^1H NMR ($CDCl_3$) δ 7.61–7.56 (m, 6H, aryl H), 7.48 (t, *J*=7.22 Hz, 2H, aryl H), 7.41 (t, 1H, *J*=7.22 Hz, aryl H), 4.99–4.97 (m, 1H, CH), 2.86 (d, 1H, *J*=6.87 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −79.1 (d, 3F, *J*=5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 142.4, 140.1, 132.6, 129.0, 128.0, 127.2, 122.9 (q, *J*=281.8 Hz), 119.8, 88.1, 81.0, 63.1 (q, *J*=36.4 Hz).

4-([1,1′-Biphenyl]-4-yl)-2-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (**5e**).

Yield 8%; R_f 0.30 (hexane/dichloromethane=1/1); m.p.=74.0 °C; IR (KBr) 3576 (OH), 2307 (C ≡ C) cm^{-1}; HRMS (ESI) found: *m/z* 345.1493. Calcd for $C_{21}H_{20}OF_3$: $[M+H]^+$, 345.1466; ^1H NMR ($CDCl_3$) δ 7.60–7.53 (m, 6H, aryl H), 7.46 (t, 2H, *J*=7.33 Hz, aryl H), 7.38 (t, 1H, *J*=7.33 Hz, aryl H), 2.67 (br s, 1H, OH), 2.47 (quin, 1H, *J*=9.62 Hz, CH), 1.96–1.60 (m, 8H, CH_2×4); ^{19}F NMR ($CDCl_3$) δ −78.8 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 142.2, 140.2, 132.6, 129.1, 128.0, 127.2, 124.5 (q, *J*=285.6 Hz), 120.2, 87.5, 83.9, 75.2 (q, *J*=30.7 Hz), 44.5, 28.5, 27.9, 25.9, 25.4.

1,1,1-Trifluoro-4-(4-fluorophenyl)but-3-yn-2-ol (**4f**).

Yield 71%; R_f 0.20 (hexane/dichloromethane=1/1); m.p.=45.3 °C; IR (KBr) 3352 (OH), 2252 (C ≡ C) cm^{-1}; HRMS (ESI) found: *m/z* 241.0233. Calcd for $C_{10}H_6OF_4Na$: $[M+Na]^+$, 241.0252; ^1H NMR ($CDCl_3$) δ 7.46 (dd, 2H, *J*=8.71 Hz, 5.50 Hz, aryl H), 7.02 (t, 2H, *J*=8.71 Hz, aryl H), 4.96–4.88 (m, 1H, CH), 3.10–3.02 (m, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F, *J*=5.8 Hz), −108.66–−108.73 (m, 1F); ^{13}C NMR ($CDCl_3$) δ 163.3 (d, *J*=251.1 Hz), 134.2 (d, *J*=8.6 Hz), 122.9 (q, *J*=280.8 Hz), 117.1 (d, *J*=3.8 Hz), 115.9 (d, *J*=22.2 Hz), 87.1, 80.2, 63.0 (q, *J*=36.4 Hz).

2-Cyclopentyl-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-yn-2-ol (**5f**).

Yield 8%; R_f 0.34 (hexane/dichloromethane=1/1); IR (KBr): 3576 (OH), 2303 (C ≡ C) cm^{-1}; HRMS (ESI) found: *m/z* 287.1036. Calcd for $C_{15}H_{15}OF_4$: $[M+H]^+$, 287.1059; ^1H NMR ($CDCl_3$) δ 7.45–7.42

(m, 2H, aryl H), 7.04–7.00 (m, 2H, aryl H), 2.68 (br s, 1H, OH), 2.43 (quin, 1H, *J*=8.70 Hz, CH), 1.94–1.83 (m, 2H, CH_2), 1.80–1.55 (m, 6H, CH_2×3); ^{19}F NMR ($CDCl_3$) δ −78.9 (s, 3F), −109.1–−109.0 (m, 1F); ^{13}C NMR ($CDCl_3$) δ 163.2 (d, *J*=250.9 Hz), 134.2 (d, *J*=8.5 Hz), 124.4 (q, *J*=285.6 Hz), 117.5 (d, *J*=3.8 Hz), 115.9 (d, *J*=22.6 Hz), 86.6, 83.2, 75.1 (q, *J*=31.0 Hz), 44.5, 28.5, 27.8, 25.9, 25.4.

4-(4-Chlorophenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4g**). [27]

Yield 74%; R_f 0.16 (hexane/dichloromethane=1/1); m.p.=55.8 °C; IR (KBr) 3352 (OH), 2234 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (d, 2H, *J*=8.24 Hz, aryl H), 7.30 (d, 2H, *J*=8.24 Hz, aryl H), 4.95–4.92 (m, 1H, CH), 3.16 (d, 1H, *J*=7.33 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −79.1 (d, 3F, *J*=5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 135.9 (s), 133.4 (s), 128.9 (s), 122.8 (q, *J*=281.8 Hz), 119.4 (s), 87.0 (s), 81.3 (s), 63.0 (q, *J*=36.4 Hz).

4-(4-Chlorophenyl)-2-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (**5g**).

Yield 8%; R_f 0.36 (hexane/dichloromethane=1/1); IR (KBr) 3572 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 303.0756. Calcd for $C_{15}H_{15}OF_3Cl$: $[M+H]^+$, 303.0764; ^1H NMR ($CDCl_3$) δ 7.39 (d, 2H, *J*=8.53 Hz, aryl H), 7.32 (d, 2H, *J*=8.53 Hz, aryl H), 2.64 (br s, 1H, OH), 2.44 (quin, 1H, *J*=8.53 Hz, CH), 1.94–1.60 (m, 8H, CH_2×4); ^{19}F NMR ($CDCl_3$) δ −78.8 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 135.4, 133.2, 128.8, 124.3 (q, *J*=285.6 Hz), 119.7, 86.3, 84.2, 75.0 (q, *J*=30.1 Hz), 44.3, 28.3, 27.7, 25.7, 25.2.

4-(4-Bromophenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4h**). [26]

Yield 72%; R_f 0.21 (hexane/dichloromethane=1/1); m.p.=63.3 °C; IR (KBr) 3364 (OH), 2249 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, 2H, *J*=8.70 Hz, aryl H), 7.31 (d, 2H, *J*=8.70 Hz, aryl H), 4.96–4.90 (m, 1H, CH), 3.21 (d, 1H, *J*=7.79 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −79.2 (d, 3F, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 133.5, 131.9, 124.2, 122.8 (q, *J*=281.9 Hz), 119.8, 87.1, 81.4, 63.0 (q, *J*=36.6 Hz)

4-(4-Bromophenyl)-2-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (**5h**).

Yield 8%; R_f 0.33 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 347.0240. Calcd for $C_{15}H_{15}OF_3Br$: $[M+H]^+$, 347.0258; ^1H NMR ($CDCl_3$) δ 7.48 (d, 2H, *J*=8.53 Hz, aryl H), 7.32 (d, 2H, *J*=8.53 Hz, aryl H), 2.69 (br s, 1H, OH), 2.44 (quin, 1H, *J*=8.98 Hz, CH), 1.93–1.60 (m, 8H, $CH_{2\times}4$); ^{19}F NMR ($CDCl_3$) δ −78.8 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 133.5, 131.9, 124.4 (q, *J*=285.6 Hz), 123.8, 120.3, 86.5, 84.5, 75.1 (q, *J*=31.0 Hz), 44.5, 28.5, 27.8, 25.9, 25.4.

4-(3,5-Bis(trifluoromethyl)phenyl)-1,1,1-trifluorobut-3-yn-2-ol (**4i**).

Yield 73%; R_f 0.24 (hexane/dichloromethane=1/1); m.p.=68.0 °C; IR (KBr) 3448 (OH), 2260 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 337.0297. Calcd for $C_{12}H_6OF_9$: $[M+H]^+$, 337.0275; ^1H NMR ($CDCl_3$) δ 7.92 (s, 2H, aryl H), 7.88 (s, 1H, aryl H), 4.99–4.93 (m, 1H, CH), 2.75 (d, *J*=8.24 Hz, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −63.2 (s, 6F), −79.0 (d, 3F, *J*=5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 132.6 (q, *J*=34.5 Hz), 132.15, 132.12, 123.3, 123.2 (m), 122.9 (q, *J*=273.2 Hz), 122.7 (q, *J*=281.8 Hz), 84.9, 83.8, 63.0 (q, *J*=36.4 Hz).

Methyl 4-(4,4,4-trifluoro-3-hydroxybut-1-yn-1-yl)benzoate (**4j**).

Yield 50%; R_f 0.16 (dichloromethane); m.p.=69.4 °C; IR (KBr) 3406 (OH), 2306 (C≡C), 1713 (C=O) cm^{-1}; HRMS (ESI) found: *m/z* 259.0598. Calcd for $C_{12}H_{10}O_3F_3$: $[M+H]^+$, 259.0582; ^1H NMR ($CDCl_3$) δ 7.97 (d, 2H, *J*=8.08 Hz, aryl H), 7.47 (d, 2H, *J*=8.08 Hz, aryl H), 4.96–4.93 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.46 (d, 1H, *J*=5.83 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −79.0 (d, 3F, *J*=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 132.1, 130.5, 129.6, 125.8, 122.9 (q, *J*=281.9 Hz), 86.7, 83.5, 63.0 (t, *J*=36.6 Hz), 52.6.

1,1,1-Trifluoro-4-(thiophen-3-yl)but-3-yn-2-ol (**4k**).

Yield 80%; R_f 0.18 (hexane/dichloromethane=1/1); IR (KBr) 3333 (OH), 2230 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 207.0110. Calcd for $C_9H_6OF_3S$: $[M+H]^+$, 207.0091; ^1H NMR ($CDCl_3$) δ 7.56 (d, 1H, *J*=2.92 Hz, aryl H), 7.29 (dd, 1H, *J*=4.94 Hz, 2.92 Hz, aryl H), 7.15 (d, 1H, *J*=4.94 Hz, aryl H),

4.91 (q, 1H, *J*=5.82 Hz, CH), 2.80 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −79.1 (d, *J*=5.8 Hz, 3F); ^{13}C NMR ($CDCl_3$) δ 131.0, 129.9, 125.9, 122.9 (q, *J*=281.9 Hz), 120.0, 83.5, 80.2, 63.1 (q, *J*=35.7 Hz).

2-Cyclopentyl-1,1,1-trifluoro-4-(thiophen-3-yl)but-3-yn-2-ol (**5k**).

Yield 7%; R_f 0.28 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 297.0508. Calcd for $C_{13}H_{13}OF_3NaS$: $[M+Na]^+$, 297.0537; ^{1}H NMR ($CDCl_3$) δ 7.53 (dd, 2H, *J*=2.92 Hz, 1.35 Hz, aryl H), 7.29 (dd, 2H, *J*=4.94 Hz, 2.92 Hz, aryl H), 7.13 (dd, 2H, *J*=4.94 Hz, 1.35 Hz, aryl H), 2.65 (br s, 1H, OH), 2.43 (quin, 1H, *J*=8.98 Hz, CH), 1.95–1.56 (m, 8H, CH_2 x 4); ^{19}F NMR ($CDCl_3$) δ −78.8 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 130.5, 130.0, 125.8, 124.4 (q, *J*=285.6 Hz), 120.5, 83.1, 82.8, 75.1 (q, *J*=30.1 Hz), 44.5, 28.5, 27.8, 25.9, 25.3

Typical procedure using aliphatic terminal alkynes 1 with 2,2,2-trifluoroethyl trifluoroacetate (2a)

1-Decyne (**1 l**) (0.146 g, 1 mmol) was dissolved in dry THF (5 ml) and cooled to 0 °C under an argon atmosphere. An Et_2O solution of CpMgBr (1.3 ml, 2.5 mmol, 2.0 M) was added to the mixture and stirred at 20 °C for 30 min and then at 0 °C for 5 min. 2,2,2-Trifluoroethyl trifluoroacetate (**2 a**) (0.245 g, 1.2 mmol) was then added, and the solution was stirred at 20 °C overnight. The resulting mixture was quenched with a saturated aqueous NH_4Cl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, and concentrated under vacuum to obtain the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride as the standard, the residue was purified by chromatography (hexane/dichloromethane=2/1) to give 1,1,1-trifluorododec-3-yn-2-ol (**4 l**) (0.21 g, 88%).

1,1,1-Trifluorododec-3-yn-2-ol (**4l**).

Yield 88%; R_f 0.23 (hexane/dichloromethane=2/1); IR (KBr) 3426 (OH), 2245 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 237.1474. Calcd for $C_{12}H_{20}OF_3$: $[M+H]^+$, 237.1466; ^{1}H NMR ($CDCl_3$) δ 4.67–4.62 (m, 1H, CH), 2.43 (br s, 1H, OH), 2.24 (td, 2H, *J*=7.33 Hz, 1.83 Hz, C≡C*CH*$_2$CH$_2$), 1.53 (quin,

2H, *J*=7.33 Hz, C≡CCH$_2$*CH$_2$*), 1.40–1.34 (m, 2H, CH$_2$), 1.32–1.22 (m, 8H, CH$_2\times$4), 0.88 (t, 3H, *J*=6.87 Hz, CH$_3$); ^{19}F NMR (CDCl$_3$) δ −79.8 (d, 3F, *J*=5.7 Hz); ^{13}C NMR (CDCl$_3$) δ 123.0 (q, *J*=280.9 Hz), 89.8 (s), 72.2 (s), 62.6 (q, *J*=35.7 Hz), 31.9 (s), 29.3 (s), 29.1 (s), 28.9 (s), 28.2 (s), 22.8 (s), 18.6 (s), 14.1 (s).

8-Chloro-1,1,1-trifluorooct-3-yn-2-ol (**4m**).

Yield 81%; *R$_f$* 0.20 (hexane/dichloromethane=1/1); IR (KBr) 3437 (OH), 2245 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 215.0434. Calcd for C$_8$H$_{11}$OF$_3$Cl: [M+H]$^+$, 215.0451; ^{1}H NMR (CDCl$_3$) δ 4.67–4.62 (m, 1H, CH), 3.55 (t, 2H, *J*=6.64 Hz, CH$_2$*CH$_2$*Cl), 2.92 (br s, 1H, OH), 2.29 (td, 2H, *J*=6.87 Hz, 1.83 Hz, C≡C*CH$_2$*CH$_2$), 1.87 (quin, 2H, *J*=6.98 Hz, CH$_2$*CH$_2$*CH$_2$), 1.68 (quin, 2H, *J*=7.33 Hz, CH$_2$*CH$_2$*CH$_2$); ^{19}F NMR (CDCl$_3$) δ −79.8 (d, 3F, *J*=5.8 Hz); ^{13}C NMR (CDCl$_3$) δ 122.9 (q, *J*=281.8 Hz), 88.6, 72.8, 62.4 (q, *J*=36.1 Hz), 44.5, 31.4, 25.2, 17.9.

4-(*Tert*-butyldimethylsilyl)-1,1,1-trifluorobut-3-yn-2-ol (**4n**).

Yield 62%; *R$_f$* 0.35 (hexane/dichloromethane=1/1); IR (KBr) 3356 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 239.1070. Calcd for C$_{10}$H$_{18}$OF$_3$Si: [M+H]$^+$, 239.1079; ^{1}H NMR (CDCl$_3$) δ 4.66 (q, 2H, *J*=5.64 Hz, CH), 2.68 (br s, 1H, OH), 0.94 (s, 9H, CH$_3\times$3), 0.14 (s, 6H, CH$_3\times$2); ^{19}F NMR (CDCl$_3$) δ −79.4 (d, 3F, *J*=5.6 Hz); ^{13}C NMR (CDCl$_3$) δ 122.8 (q, *J*=280.9 Hz), 97.0, 92.9, 62.8 (q, *J*=36.6 Hz), 26.0, 16.6, −4.98.

4-(*Tert*-butyldimethylsilyl)-2-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (**5n**).

Yield 8%; *R$_f$* 0.50 (hexane/dichloromethane=1/1); IR (KBr) 3576 (OH), 2307 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 307.1676. Calcd for C$_{15}$H$_{26}$OF$_3$Si: [M+H]$^+$, 307.1705; ^{1}H NMR (CDCl$_3$) δ 2.56 (br s, 1H, OH), 2.34 (quin, *J*=8.24 Hz, 1H, CH), 1.90–1.51 (m, 8H, CH$_2\times$4), 0.94 (s, 9H, CH$_3\times$3), 0.13 (s, 6H, CH$_3\times$2); ^{19}F NMR (CDCl$_3$) δ −79.0 (s, 3F); ^{13}C NMR (CDCl$_3$) δ 124.3 (q, *J*=285.6 Hz), 99.9, 92.0, 74.8 (q, *J*=30.1 Hz), 44.2, 28.4, 27.8, 26.03, 25.95, 25.4, 16.6, −4.80, −4.84.

4-(Cyclohex-1-en-1-yl)-1,1,1-trifluorobut-3-yn-2-ol (**4o**).

Yield 74%; R_f 0.25 (hexane/dichloromethane=1/1); IR (KBr) 3333 (OH), 2230 (C≡C), 1678 (C=C) cm^{-1}; HRMS (ESI) found: *m/z* 205.0827. Calcd for $C_{10}H_{12}OF_3$: $[M+H]^+$, 205.0840; ^1H NMR ($CDCl_3$) δ 6.23–6.21 (m, 1H, C=CH), 4.78 (q, 1H, *J*=5.87 Hz, CF_3CH), 3.02 (br s, 1H, OH), 2.13–2.06 (m, 4H, $CH_2\times2$), 1.66–1.56 (m, 4H, $CH_2\times2$); ^{19}F NMR ($CDCl_3$) δ −79.6 (d, 3F, *J*=5.9 Hz); ^{13}C NMR ($CDCl_3$) δ 138.1, 123.0 (q, *J*=281.9 Hz), 119.2, 89.8, 77.9, 62.9 (q, *J*=36.6 Hz), 28.6, 25.7, 22.1, 21.4.

4-(Cyclohex-1-en-1-yl)-2-cyclopentyl-1,1,1-trifluorobut-3-yn-2-ol (**5o**).

Yield 8%; R_f 0.28 (hexane/dichloromethane=1/1); IR (KBr) 3410 (OH), 2307 (C≡C), 1678 (C=C) cm^{-1}; HRMS (ESI) found: *m/z* 273.1495. Calcd for $C_{15}H_{20}OF_3$: $[M+H]^+$, 273.1466; ^1H NMR ($CDCl_3$) δ 6.20–6.18 (m, 1H, C=CH), 2.54 (br s, 1H, OH), 2.36 (quin, 1H, *J*=8.24 Hz, CH_2CHCH_2), 2.13–2.08 (m, 4H, $CH_2\times2$), 1.89–1.54 (m, 12H, $CH_2\times6$); ^{19}F NMR ($CDCl_3$) δ −79.1 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 137.5, 124.5 (q, *J*=285.6 Hz), 119.4, 89.5, 80.6, 75.0 (q, *J*=30.1 Hz), 44.4, 28.9, 28.4, 27.8, 25.9, 25.7, 25.3, 22.2, 21.4.

2,2,2-Trifluoro-1-(2,2,2-trifluoroethoxy)ethan-1-ol (**8**) [55]

HRMS (ESI) found: *m/z* 199.0170. Calcd for $C_4H_5O_2F_6$: $[M+H]^+$, 199.0194; ^1H NMR ($CDCl_3$) δ 5.03 (q, 1H, *J*=3.70 Hz, CH), 4.16 (q, 2H, *J*=8.53 Hz, CH_2); ^{19}F NMR ($CDCl_3$) δ −74.2 (t, 3F, *J*=8.5 Hz), −83.3 (d, 3F, *J*=3.7 Hz).

1-Cyclopentyl-2,2,2-trifluoroethan-1-ol (**10**)

R_f 0.38 (hexane/dichloromethane=1/1); IR (KBr) 3391 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 167.0680. Calcd for $C_7H_{10}OF_3$: $[M-H]^-$, 167.0684; ^1H NMR ($CDCl_3$) δ 3.85–3.77 (m, 1H, CF_3CH), 2.46 (d, 1H, *J*=5.95 Hz, OH), 2.20–2.10 (m, 1H, CH), 1.87–1.76 (m, 2H, CH_2), 1.71–1.36 (m, 6H, $CH_2\times3$); ^{19}F NMR ($CDCl_3$) δ −77.5 (d, 3F, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 125.5 (q, *J*=282.8 Hz), 73.5 (q, *J*=29.7 Hz), 40.1, 29.1, 27.8, 25.4, 25.1.

Typical procedure using ethynylbenzene (1a) with fluorine-containing carboxylic acid esters 2

Ethynylbenzene (**1a**) (0.104 g, 1 mmol) was dissolved in dehydrated toluene (5 ml) and cooled under an argon atmosphere at 0 °C. A THF solution of CpMgBr (2.5 ml, 2.5 mmol, 1.0 M) was added and stirred at 0 °C for 30 min; methyl trifluoroacetate (**2 b**) (0.157 g, 1.2 mmol) was then added and stirred overnight. The resulting mixture was quenched with a saturated aqueous NH_4Cl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, and concentrated under vacuum to obtain the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride as the standard, the residue was purified by chromatography (hexane/dichloromethane=1/1) to give 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4 a**) (0.080 g, 40%).

1,5-Diphenyl-3-(trifluoromethyl)penta-1,4-diyn-3-ol (**7a**).

Yield 35%; R_f 0.23 (hexane/dichloromethane=1/1); IR (KBr) 3418 (OH), 2237 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 299.0685. Calcd for $C_{18}H_{10}OF_3$: $[M-H]^-$, 299.0684; ^1H NMR ($CDCl_3$) δ 7.55–7.53 (m, 4H, aryl H), 7.43–7.34 (m, 6H, aryl H), 3.29 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −81.2 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 132.3, 129.8, 128.5, 122.3 (q, *J*=284.7 Hz), 120.8, 86.6, 81.5, 65.6 (q, *J*=36.6 Hz).

1-Chloro-1,1-difluoro-4-phenylbut-3-yn-2-ol (**11a**). [65]

Yield 45%; R_f 0.20 (hexane/dichloromethane=1/1); IR (KBr): 3572 (OH), 2253 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.48 (m, 2H, aryl H), 7.41–7.31 (m, 3H, aryl H), 4.95 (q, 1H, *J*=6.70 Hz, CH), 3.03 (d, 1H, *J*=6.70 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −64.8 (dd, 1F, *J*=162.3 Hz, 6.7 Hz), −64.9 (dd, 1F, *J*=162.3 Hz, 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 132.1, 129.6, 128.6, 127.5 (t, *J*=296.9 Hz), 121.0, 88.3, 81.3, 67.9 (t, *J*=32.0 Hz).

3-(Chlorodifluoromethyl)-1,5-diphenylpenta-1,4-diyn-3-ol (**12a**).

Yield 28%; R_f 0.28 (hexane/dichloromethane=1/1); IR (KBr) 3541 (OH), 2237 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 339.0345. Calcd for $C_{18}H_{11}OF_2NaCl$: $[M+Na]^+$, 339.0364; ^1H NMR ($CDCl_3$) δ 7.55–7.53 (m, 4H, aryl H), 7.43–7.34 (m, 6H, aryl H), 3.30 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −66.3 (s,

2F); ^{13}C NMR ($CDCl_3$) δ 132.3, 129.8, 128.6, 127.7 (t, *J*=301.6 Hz), 120.8, 86.9, 82.1, 69.8 (t, *J*=31.0 Hz).

4,4-Difluoro-1-phenylpent-1-yn-3-ol (**13a**).

Yield 43%; R_f 0.15 (hexane/dichloromethane=1/1); IR (KBr) 3426 (OH), 2230 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 195.0617. Calcd for $C_{11}H_9OF_2$: $[M+H]^+$, 195.0621; ^{1}H NMR ($CDCl_3$) δ 7.50–7.47 (m, 2H, aryl H), 7.39–7.30 (m, 3H, aryl H), 4.77–4.72 (m, 1H, CH), 2.88 (d, 1H, *J*=6.87 Hz, OH), 1.80 (t, 3H, *J*=18.6 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −101.9 (dqd, 1F, *J* =243.9 Hz, 18.6 Hz, 8.1 Hz), −102.3 (dqd, 1F, *J*=243.9 Hz, 18.6 Hz, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 132.0, 129.2, 128.5, 121.9 (t, *J*=244.3 Hz), 121.6, 87.1, 83.6, 66.0 (t, *J*=32.9 Hz), 19.2 (t, *J*=26.3 Hz).

3-(1,1-Difluoroethyl)-1,5-diphenylpenta-1,4-diyn-3-ol (**14a**).

Yield 36%; R_f 0.20 (hexane/dichloromethane=1/1); IR (KBr) 3557 (OH), 2234 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 319.0929. Calcd for $C_{19}H_{14}OF_2Na$: $[M+Na]^+$, 319.0910; ^{1}H NMR ($CDCl_3$) δ 7.54–7.51 (m, 4H, aryl H), 7.40–7.32 (m, 6H, aryl H), 3.05 (br s, 1H, OH), 1.98 (t, 3H, *J*=18.0 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −103.6 (q, 2F, *J*=18.0 Hz); ^{13}C NMR ($CDCl_3$) δ 132.2, 129.4, 128.5, 121.8 (t, *J*=251.3 Hz), 121.4, 85.8, 84.1, 68.0 (t, *J*=32.0 Hz), 19.2 (t, *J*=25.4 Hz).

4,4,5,5,5-Pentafluoro-1-phenylpent-1-yn-3-ol (**15a**).

Yield 47%; R_f 0.28 (hexane/dichloromethane=1/1); m.p. <30 °C; IR (KBr) 3576 (OH), 2241 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 273.0292. Calcd for $C_{11}H_7OF_5Na$: $[M+Na]^+$, 273.0315; ^{1}H NMR ($CDCl_3$) δ 7.51–7.48 (m, 2H, aryl H), 7.42–7.33 (m, 3H, aryl H), 5.09–5.02 (m, 1H, CH), 2.78 (d, 1H, *J*=8.24 Hz, OH); ^{19}F NMR ($CDCl_3$) δ −81.0 (s, 3F), −123.3 (dd, 1F, *J*=271.0 Hz, 10.1 Hz), −127.3 (dd, 1F, *J*=271.0 Hz, 10.1 Hz); ^{13}C NMR ($CDCl_3$) δ 132.1, 129.7, 128.6, 121.0, 118.9 (qt, *J*=273.2 Hz, 35.5 Hz), 112.0 (tq, *J*=273.2 Hz, 35.5 Hz), 89.1, 80.0, 62.4 (t, *J*=28.8 Hz).

3-(Perfluoroethyl)-1,5-diphenylpenta-1,4-diyn-3-ol (**16a**).

Yield 34%; R_f 0.29 (hexane/dichloromethane=1/1); IR (KBr) 3557 (OH), 2237 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 373.0604. Calcd for $C_{19}H_{11}OF_5Na$: $[M+Na]^+$, 373.0628; ^1H NMR ($CDCl_3$) δ 7.55–7.52 (m, 4H, aryl H), 7.43–7.34 (m, 6H, aryl H), 3.24 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$) δ −77.6 (s, 3F), −121.3 (s, 2F); ^{13}C NMR ($CDCl_3$) δ 132.2, 129.9, 128.6, 120.8, 118.8 (qt, *J*=258.9 Hz, 35.2 Hz), 111.7 (tq, *J*=258.9 Hz, 35.2 Hz), 87.5, 81.3, 65.6 (t, *J*=29.1 Hz).

Typical procedure using 1-decyne (1l) with fluorine-containing carboxylic acid esters 2.

1-Decyne (**1l**) (0.146 g, 1 mmol) was dissolved in dry THF (5 ml) and cooled to 0 °C under an argon atmosphere. An Et_2O solution of CpMgBr (1.3 ml, 2.5 mmol, 2.0 M) was added to the mixture and stirred at 20 °C for 30 min and then at 0 °C for 5 min. Methyl trifluoroacetate (**2b**) (0.157 g, 1.2 mmol) was then added, and the solution was stirred at 40 °C overnight. The resulting mixture was quenched with a saturated aqueous NH_4Cl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, and concentrated under vacuum to obtain the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride as the standard, the residue was purified by chromatography (hexane/dichloromethane=2/1) to give 1,1,1-trifluorododec-3-yn-2-ol (**4 l**) (0.18 g, 78%).

1-Chloro-1,1-difluorododec-3-yn-2-ol (**11l**).

Yield 74%; R_f 0.19 (hexane/dichloromethane=2/1); IR (KBr) 3576 (OH), 2245 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 275.1008. Calcd for $C_{12}H_{19}OF_2NaCl$: $[M+Na]^+$, 275.0990; ^1H NMR ($CDCl_3$) δ 4.69–4.65 (m, 1H, CH), 2.88 (br s, 1H, OH), 2.23 (td, 2H, *J*=7.10 Hz, 1.83 Hz, C≡C$CH_2$$CH_2$), 1.53 (quin, 2H, *J*=7.10 Hz, C≡CC$H_2$$CH_2$), 1.41–1.34 (m, 2H, CH_2), 1.31–1.25 (m, 8H, CH_2), 0.87 (t, 3H, *J*=6.87 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −65.2 (dd, 1F, *J*=161.3 Hz, 5.7 Hz), −65.3 (dd, 1F, *J*=161.3 Hz, 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 127.7 (t, *J*=296.2 Hz), 89.9, 73.0, 67.5 (t, *J*=31.6 Hz), 31.9, 29.3, 29.1, 28.8, 28.2, 22.8, 18.7, 14.2.

2,2-Difluorotridec-4-yn-3-ol (**13l**).

Yield 87%; R_f 0.14 (hexane/dichloromethane=2/1); IR (KBr) 3414 (OH), 2237 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 233.1695. Calcd for $C_{13}H_{23}OF_2$: $[M+H]^+$, 233.1717; ^1H NMR ($CDCl_3$) δ 4.48–4.42 (m, 1H, CH), 2.52 (br s, 1H, OH), 2.23 (td, 2H, *J*=7.18 Hz, 2.24 Hz, C≡C*CH*$_2$CH$_2$), 1.69 (t, 3H, *J*=18.3 Hz, CF_2CH_3), 1.51 (quin, 2H, *J*=7.18 Hz, C≡CCH$_2$*CH*$_2$), 1.39–1.33 (m, 2H, CH_2), 1.31–1.22 (m, 8H, CH_2×4), 0.87 (t, 3H, *J*=7.18 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −102.3 (dqd, 1F, *J*=243.4 Hz, 18.3 Hz, 8.1 Hz), −103.0 (dqd, 1F, *J*=243.4 Hz, 18.3 Hz, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 122.1 (t, *J*=244.2 Hz), 88.4, 75.0, 65.6 (t, *J*=32.9 Hz), 31.9, 29.3, 29.1, 28.9, 28.4, 22.7, 19.0 (t, *J*=26.3 Hz), 18.7, 14.2.

1,1,1,2,2-Pentafluorotridec-4-yn-3-ol (**15l**).

Yield 75%; R_f 0.30 (hexane/dichloromethane=2/1); IR (KBr) 3395 (OH), 2245 (C≡C) cm^{-1}; HRMS (ESI) found: *m/z* 287.1457. Calcd for $C_{13}H_{20}OF_5$: $[M+H]^+$, 287.1434; ^1H NMR ($CDCl_3$) δ 4.79–4.74 (m, 1H, CH), 2.75 (br s, 1H, OH), 2.24 (td, 2H, *J*=7.10 Hz, 2.29 Hz, C≡C*CH*$_2$CH$_2$), 1.52 (quin, 2H, *J*=7.10 Hz, C≡CCH$_2$*CH*$_2$), 1.40–1.33 (m, 2H, CH_2), 1.32–1.24 (m, 8H, CH_2), 0.88 (t, 3H, *J*=6.87 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ −81.2 (s, 3F), −123.8 (dd, 1F, *J*=270.2, 10.9 Hz), −127.8 (dd, 1F, *J*=270.2 Hz, 10.9 Hz); ^{13}C NMR ($CDCl_3$) δ 118.9 (qt, *J*=273.4 Hz, 35.2 Hz), 110.7 (tq, *J*=273.4 Hz, 35.2 Hz), 90.8, 71.7, 62.0 (t, *J*=27.3 Hz), 32.0, 29.3, 29.2, 28.9, 28.2, 22.8, 18.7, 14.1.

The procedure using the trifluoroethyl hemiacetal of CF_3CHO 8 with alkynyl Grignard reagent

Ethynylbenzene (**1 a**) (0.520 g, 5 mmol) was dissolved in dehydrated toluene (5 ml) and cooled to −20 °C under an argon atmosphere. A THF solution of CpMgBr (5.0 ml, 5 mmol, 1.0 M) was added to the mixture and stirred at −20 °C for 30 min. Trifluoroacetaldehyde 2,2,2-trifluoroethyl hemiacetal (**8**) (0.3252 g, 1 mmol, 61 wt %) was then added, and the solution was stirred overnight. The resulting mixture was quenched with a saturated aqueous NH_4Cl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, and concentrated under vacuum to obtain the residue. After the yield was measured by ^{19}F NMR with benzotrifluoride as the standard, the residue was

purified by chromatography (hexane/dichloromethane=1/1) to give 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol (**4a**) (0.174 g, 87%).

Typical procedure using propargyl alcohols 4 with phenylhydrazine

1,1,1-Trifluoro-4-phenylbut-3-yn-2-ol (**4a**) (0.050 g, 0.25 mmol) was dissolved in dehydrated toluene (0.5 ml) under an argon atmosphere. After phenylhydrazine (0.033 g, 0.3 mmol) and DBU (0.038 g, 0.25 mmol) were added to the mixture at room temperature, it was stirred at 120 °C for more than 1 d until the reaction was complete. The resulting mixture was quenched with a saturated aqueous NaCl solution (20 ml), extracted with dichloromethane (30 ml×3) dried over Na_2SO_4, concentrated under vacuum, and purified by chromatography (hexane/dichloromethane=4/1) to give 1,5-diphenyl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17 a**) (0.065 g, 90%).

1,5-Diphenyl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17a**). [66]

Yield 90%; R_f 0.44 (hexane/dichloromethane=4/1); m.p.=90.0 °C; IR (KBr) 1597 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 291.1089. Calcd for $C_{16}H_{14}N_2F_3$: $[M+H]^+$, 291.1109 ; ^1H NMR ($CDCl_3$) δ 7.41–7.28 (m, 5H, aryl H), 7.23–7.19 (m, 2H, aryl H), 7.04 (d, 2H, *J*=8.08 Hz, aryl H), 6.90 (t, 1H, *J*=7.63 Hz, aryl H), 5.38 (dd, 1H, *J*=13.01 Hz, 8.08 Hz, CH), 3.72–3.63 (m, 1H, CH_AH_B), 3.00 (ddq, 1H, *J*=17.95 Hz, 8.08 Hz, 1.80 Hz, CH_AH_B); ^{19}F NMR ($CDCl_3$) −65.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 143.4, 141.0, 136.3 (q, *J*=38.3 Hz), 129.5, 129.1, 128.3, 125.9, 121.1 (q, *J*=269.3 Hz), 121.1, 114.2, 65.6, 41.2.

1,5-Diphenyl-3-(trifluoromethyl)-1*H*-pyrazole (**18a**). [67]

Yield 10%; R_f 0.21 (hexane/dichloromethane=4/1); m.p.=90.9 °C; IR (KBr) 1597 (N=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.30 (m, 8H, aryl H), 7.24–7.21 (m, 2H, aryl H), 6.76 (s, 1H, aryl H); ^{19}F NMR ($CDCl_3$) δ −62.1 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 144.8, 143.3 (q, *J*=38.5 Hz), 139.4, 129.34, 129.25, 129.1, 128.9, 128.8, 128.6, 125.6, 121.4 (q, *J*=268.7 Hz), 105.7.

5-(4-Ethoxyphenyl)-1-phenyl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17b**).

Yield 72%; R_f 0.32 (hexane/dichloromethane=4/1); m.p.=82.1 °C; IR (KBr) 1597 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 335.1356. Calcd for $C_{18}H_{18}N_2OF_3$: $[M+H]^+$, 335.1371 ; ^1H NMR ($CDCl_3$) δ 7.21–7.17 (m, 4H, aryl H), 7.03 (d, 2H, *J*=7.63 Hz, aryl H), 6.89–6.86 (m, 3H, aryl H), 5.32 (dd, 1H, *J*=12.79 Hz, 7.86 Hz, CH), 4.02 (d, 3H, *J*=6.96 Hz, CH_2CH_3), 3.63 (ddq, 1H, *J*=17.95 Hz, 12.79 Hz, 1.80 Hz, CH_AH_B), 2.96 (ddq, 1H, *J*=17.95 Hz, 7.86 Hz, 1.80 Hz, CH_AH_B), 1.42 (t, 3H, *J*=6.96 Hz, CH_2CH_3); ^{19}F NMR ($CDCl_3$) δ −65.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 158.9, 143.5, 136.2 (q, *J*=38.5 Hz), 132.9, 129.1, 127.1, 121.1 (q, *J*=268.7 Hz), 121.0, 115.3, 114.3, 65.2, 63.6, 41.3, 14.9.

1-Phenyl-5-(*p*-tolyl)-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17d**).

Yield 82%; R_f 0.40 (hexane/dichloromethane=4/1); m.p.=86.7 °C; IR (KBr): 1597 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 305.1276. Calcd for $C_{17}H_{16}N_2F_3$: $[M+H]^+$, 305.1266 ; ^1H NMR ($CDCl_3$) δ 7.22–7.16 (m, 6H, aryl H), 7.06–7.03 (m, 2H, aryl H), 6.89 (td, 1H, *J*=7.63 Hz, 0.9 Hz, aryl H), 5.35 (dd, 1H, *J*=13.01 Hz, 7.86 Hz, CH), 3.65 (ddq, 1H, *J*=17.95 Hz, 13.01 Hz, 1.80 Hz, CH_AH_B), 2.98 (ddq, 1H, *J*=17.95 Hz, 7.86 Hz, 1.80 Hz, CH_AH_B), 2.36 (s, 1H, CH_3); ^{19}F NMR ($CDCl_3$) δ −65.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 143.5, 138.0, 136.2 (q, *J*=38.5 Hz), 130.2, 129.1, 125.8, 121.1 (q, *J*=268.7 Hz), 121.0, 114.2, 65.4, 41.3, 21.2.

5-(4-Bromophenyl)-1-phenyl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17h**).

Yield 92%; R_f 0.50 (hexane/dichloromethane=4/1); m.p.=75.1 °C; IR (KBr) 1597 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 369.0207. Calcd for $C_{16}H_{13}N_2F_3Br$: $[M+H]^+$, 369.0214 ; ^1H NMR ($CDCl_3$) δ 7.50 (d, 2H, *J*=8.53 Hz, aryl H), 7.24–7.18 (m, 2H, aryl H), 7.16 (d, 2H, *J*=8.53 Hz, aryl H), 7.00 (d, 2H, *J*=7.63 Hz, aryl H), 6.91 (t, 1H, *J*=7.18 Hz, aryl H), 5.34 (dd, 1H, *J*=12.57 Hz, 7.86 Hz, CH), 3.66 (ddq, 1H, *J*=17.95 Hz, 12.57 Hz, 1.80 Hz, CH_AH_B), 2.95 (ddq, 1H, *J*=17.95 Hz, 7.86 Hz, 1.80 Hz, CH_AH_B); ^{19}F NMR ($CDCl_3$) δ −65.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 143.1, 139.9, 136.3 (q, *J*=38.5 Hz), 132.7, 129.2, 127.6, 122.2, 121.3, 120.9 (q, *J*=268.7 Hz), 114.2, 64.9, 41.1.

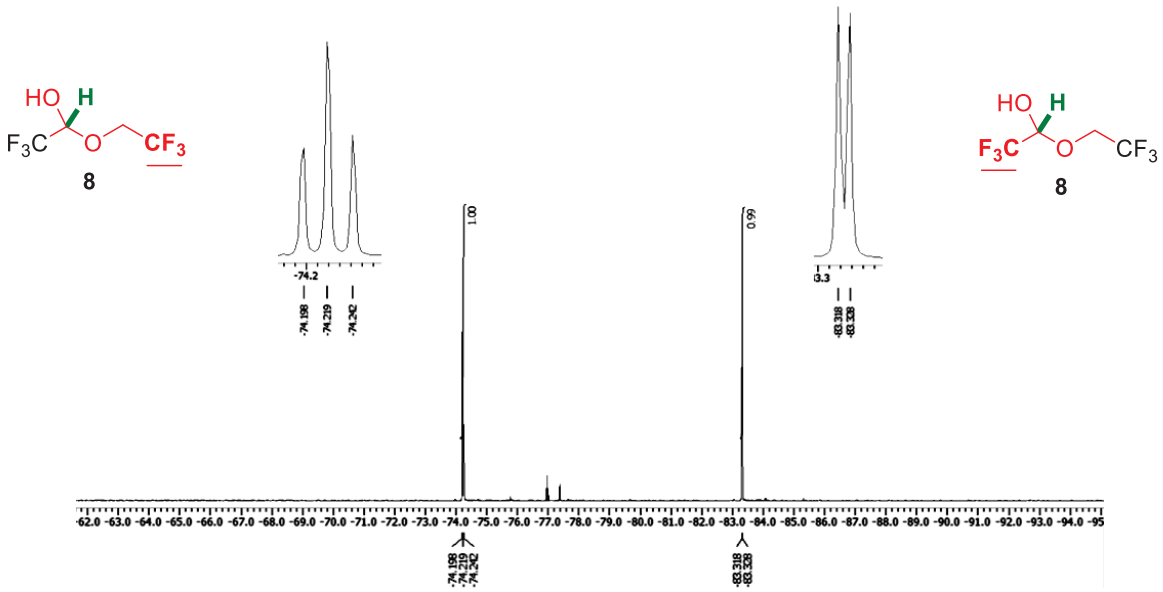
5-(3,5-Bis(trifluoromethyl)phenyl)-1-phenyl-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17i**). Yield 88%; R_f 0.45 (hexane/dichloromethane=4/1); m.p.=83.7 °C; IR (KBr) 1601 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 427.0843. Calcd for $C_{18}H_{12}N_2F_9$: $[M+H]^+$, 427.0857; ^1H NMR ($CDCl_3$) δ 7.86 (s, 1H, aryl H), 7.75 (s, 2H, aryl H), 7.25–7.21 (m, 2H, aryl H), 6.97–6.93 (m, 3H, aryl H), 5.49 (dd, 1H, *J*=13.01 Hz, 8.08 Hz, CH), 3.77 (ddq, 1H, *J*=17.95 Hz, 13.01 Hz, 1.80 Hz, CH_AH_B), 2.98 (ddq, 1H, *J*=17.95 Hz, 8.08 Hz, 1.80 Hz, CH_AH_B); ^{19}F NMR ($CDCl_3$) δ −62.8 (s, 6F), −66.1 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 143.7, 143.0, 136.9 (q, *J*=38.5 Hz), 133.1 (q, *J*=32.9 Hz), 129.5, 126.2, 123.1 (q, *J*=273.4 Hz), 122.6 (t, *J*=3.3 Hz), 122.5–122.8 (m), 120.7 (q, *J*=268.7 Hz), 114.3, 65.0, 41.2.

1-Phenyl-5-(thiophen-3-yl)-3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole (**17k**).
Yield 87%; R_f 0.33 (hexane/dichloromethane=4/1); m.p.=64.3 °C; IR (KBr) 1597 (N=C) cm^{-1}; HRMS (ESI) found: *m/z* 297.0683. Calcd for $C_{14}H_{12}N_2F_3S$: $[M+H]^+$, 297.0673 ; ^1H NMR ($CDCl_3$) δ 7.33 (dd, 1H, *J*=4.94 Hz, 3.14 Hz, aryl H), 7.22 (dd, 2H, *J*=8.53 Hz, 7.63 Hz, aryl H), 7.17–7.16 (m, 1H, aryl H), 7.07 (dd, 2H, *J*=8.98 Hz, 0.90 Hz, aryl H), 6.99 (dd, 1H, *J*=4.94 Hz, 1.35 Hz, aryl H), 6.93–6.89 (m, 1H, aryl H), 5.49 (dd, 1H, *J*=12.79 Hz, 7.63 Hz, CH), 3.60 (ddq, 1H, *J*=17.50 Hz, 12.79 Hz, 1.80 Hz, CH_AH_B), 3.02 (ddq, 1H, *J*=17.50 Hz, 7.63 Hz, 1.80 Hz, CH_AH_B); ^{19}F NMR ($CDCl_3$) δ −65.9 (s, 3F); ^{13}C NMR ($CDCl_3$) δ 143.5, 141.7, 136.6 (q, *J*=37.6 Hz), 129.1, 127.8, 125.2, 121.8, 121.2, 121.0 (q, *J*=269.7 Hz), 114.3, 61.5, 40.3.

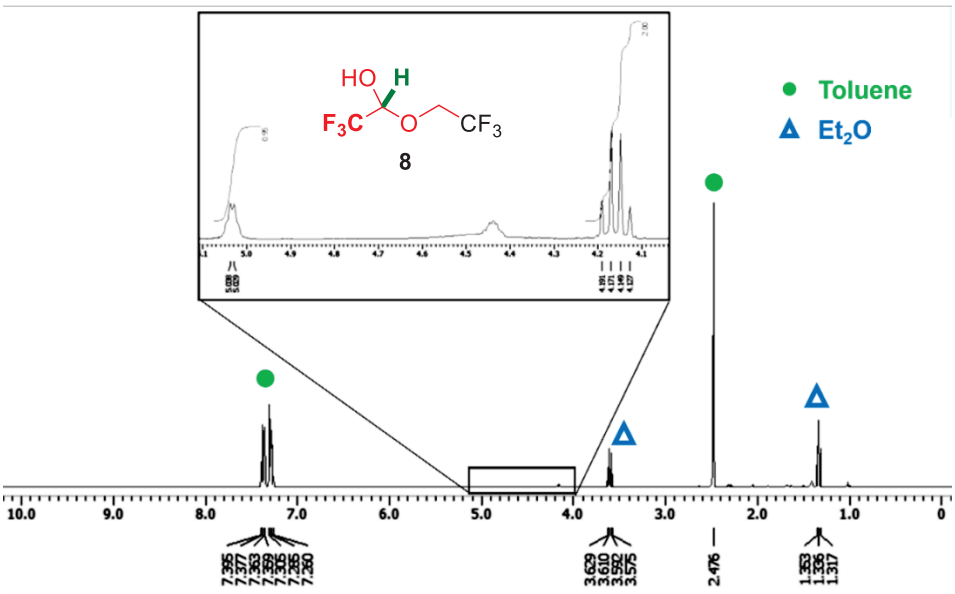
Supporting Figures and tables

Crude ^{19}F NMR, ^{1}H NMR, and HRMS (ESI) results for Table 2, entry 4.

Crude ^{19}F NMR



Crude ^{1}H NMR

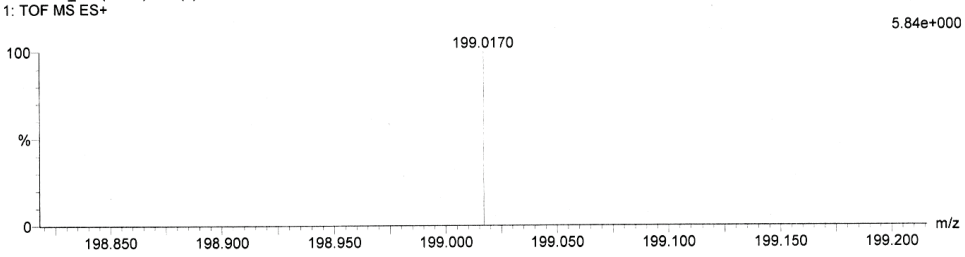


Found **2,2,2-trifluoro-1-(2,2,2-trifluoroethoxy)ethan-1-ol (8)**: m/z 199.0170. Calcd for $C_4H_5O_2F_6$: $[M+H]^+$, 199.0194.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

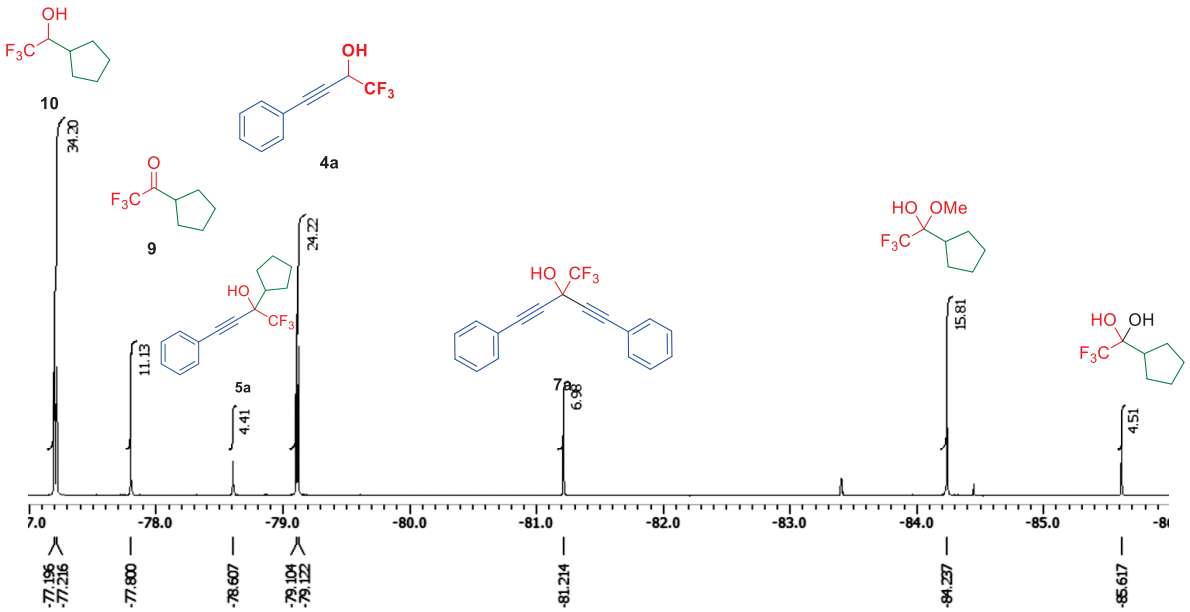
Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 5 best isotopic matches for each mass)
Elements Used:
C: 4-4 H: 0-5 O: 1-2 F: 3-6 Na: 0-1
20210126_1 2 (0.079) Cm (2)
1: TOF MS ES+



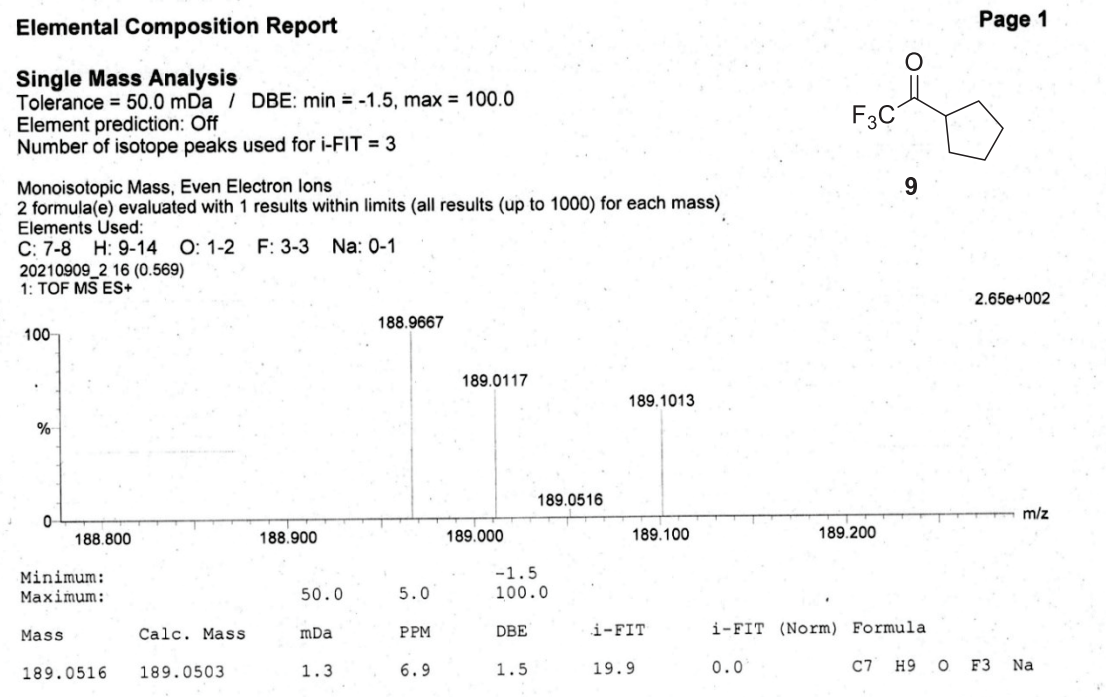
Minimum:				-1.5					
Maximum:		5.0	3.0	50.0					
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula		
199.0170	199.0194	-2.4	-12.1	-0.5	11.5	0.0	C4	H5	O2 F6

Crude ^{19}F NMR and HRMS (ESI) results for Table 3, entry 1.

Crude ^{19}F NMR



Found **1-cyclopentyl-2,2,2-trifluoroethan-1-one (9)**: m/z 189.0516. Calcd for $C_7H_9OF_3Na$: $[M+Na]^+$, 189.0503.



Elemental Composition Report Page 1

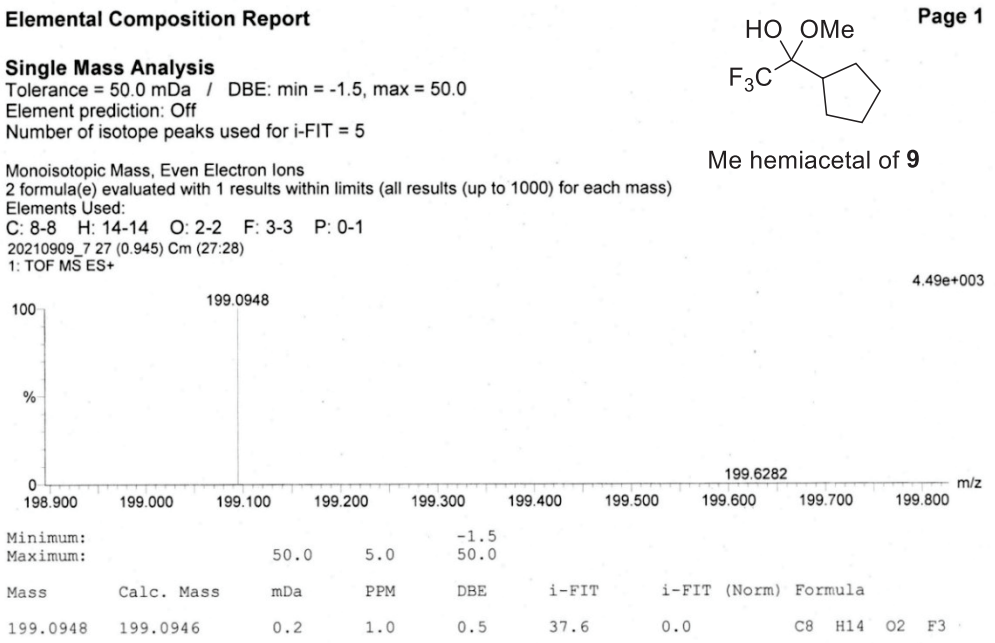
Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 7-8 H: 9-14 O: 1-2 F: 3-3 Na: 0-1
20210909_2 16 (0.569)
1: TOF MS ES+

2.65e+002

Minimum:				-1.5						
Maximum:		50.0	5.0	100.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
189.0516	189.0503	1.3	6.9	1.5	19.9	0.0	C7	H9	O	F3 Na

Found **1-cyclopentyl-2,2,2-trifluoro-1-methoxyethan-1-ol**: m/z 199.0948. Calcd for $C_8H_{14}O_2F_3$: $[M+H]^+$, 199.0946.



Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 5

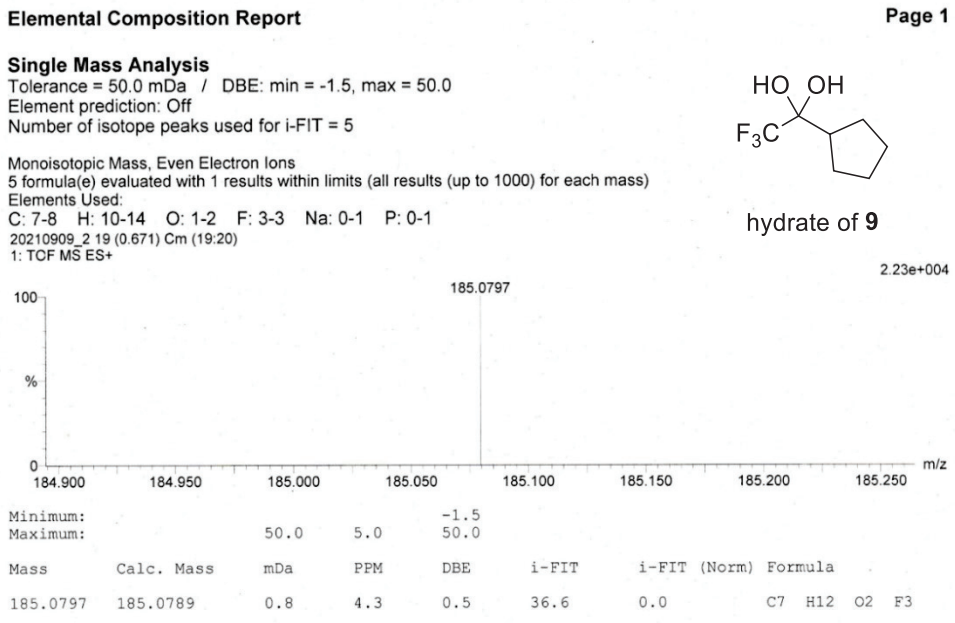
Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 8-8 H: 14-14 O: 2-2 F: 3-3 P: 0-1
20210909_7 27 (0.945) Cm (27:28)
1: TOF MS ES+

Me hemiacetal of **9**

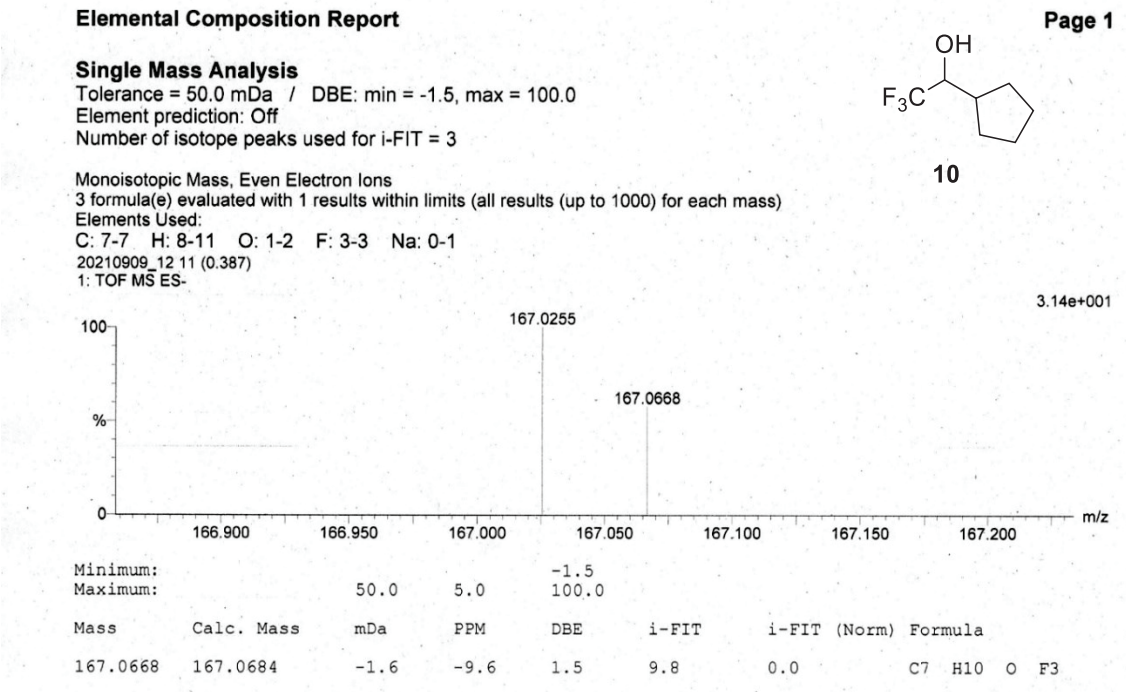
4.49e+003

Minimum:				-1.5						
Maximum:		50.0	5.0	50.0						
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula			
199.0948	199.0946	0.2	1.0	0.5	37.6	0.0	C8	H14	O2	F3

Found **1-cyclopentyl-2,2,2-trifluoroethane-1,1-diol**: m/z 185.0797. Calcd for $C_7H_{12}O_2F_3$: $[M+H]^+$, 185.0789.



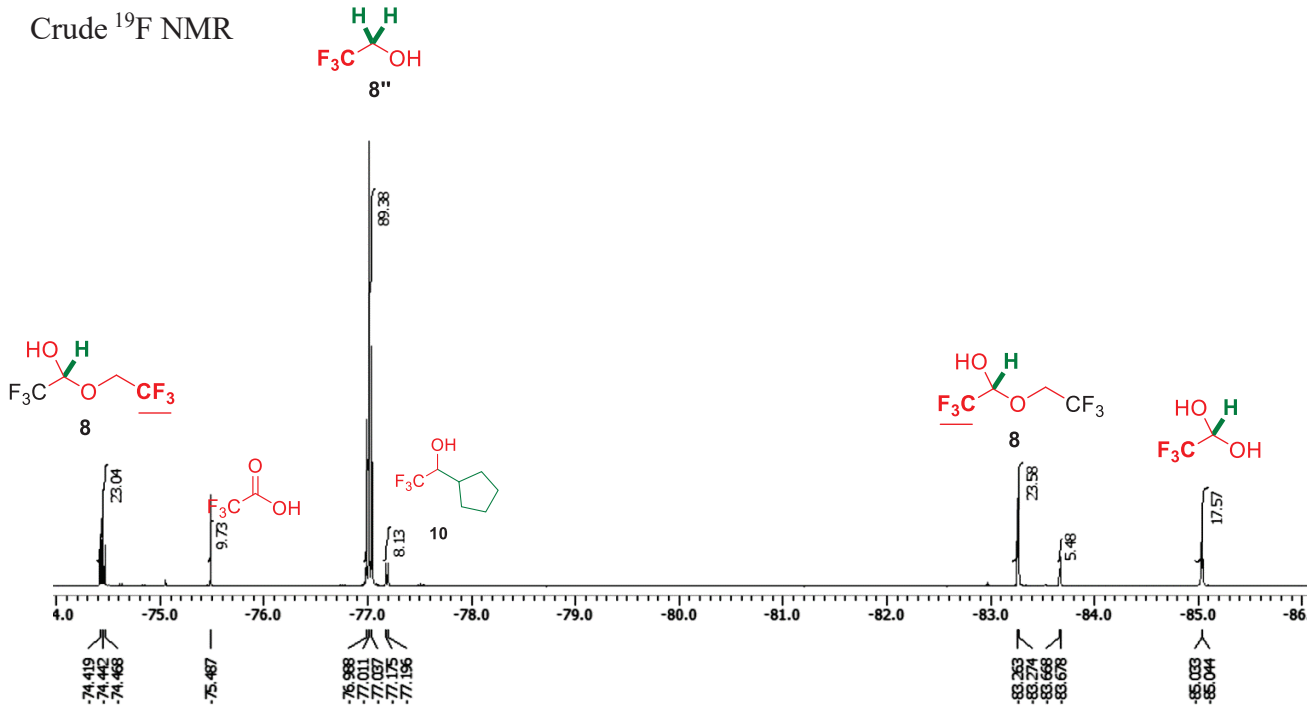
Found **1-cyclopentyl-2,2,2-trifluoroethan-1-ol (10)**: m/z 167.0668. Calcd for $C_7H_{10}OF_3$: $[M-H]^-$, 167.0684.



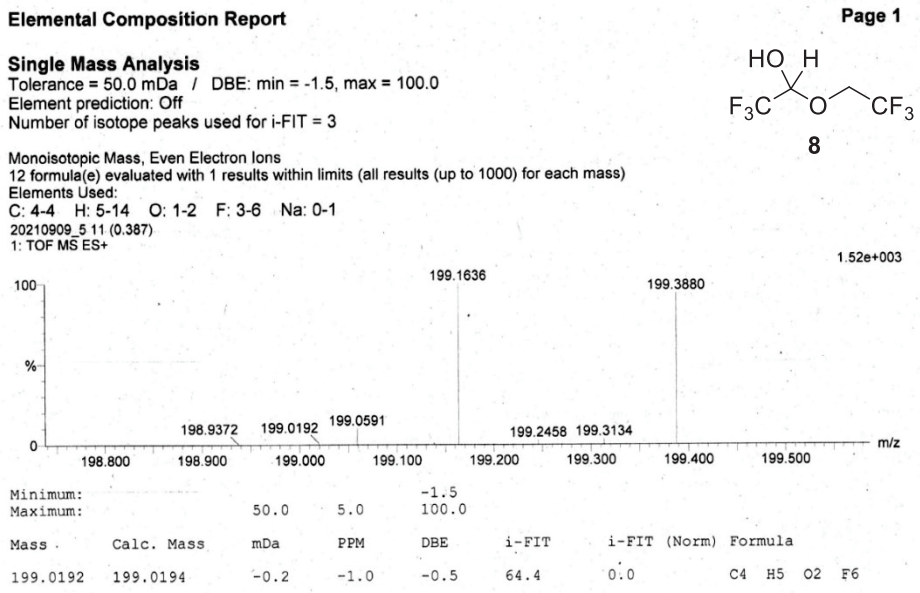
Crude ^{19}F NMR and HRMS (ESI) result for Table 5.

Table 5, entry 1

Crude ^{19}F NMR



Found **2,2,2-trifluoro-1-(2,2,2-trifluoroethoxy)ethan-1-ol (8)**: m/z 199.0192. Calcd for $C_4H_5O_2F_6$: $[M+H]^+$, 199.0194.



Found **2,2,2-trifluoroethane-1,1-diol**: m/z 115.0009. Calcd for $C_2H_2O_2F_3$: $[M-H]^-$, 115.0007.

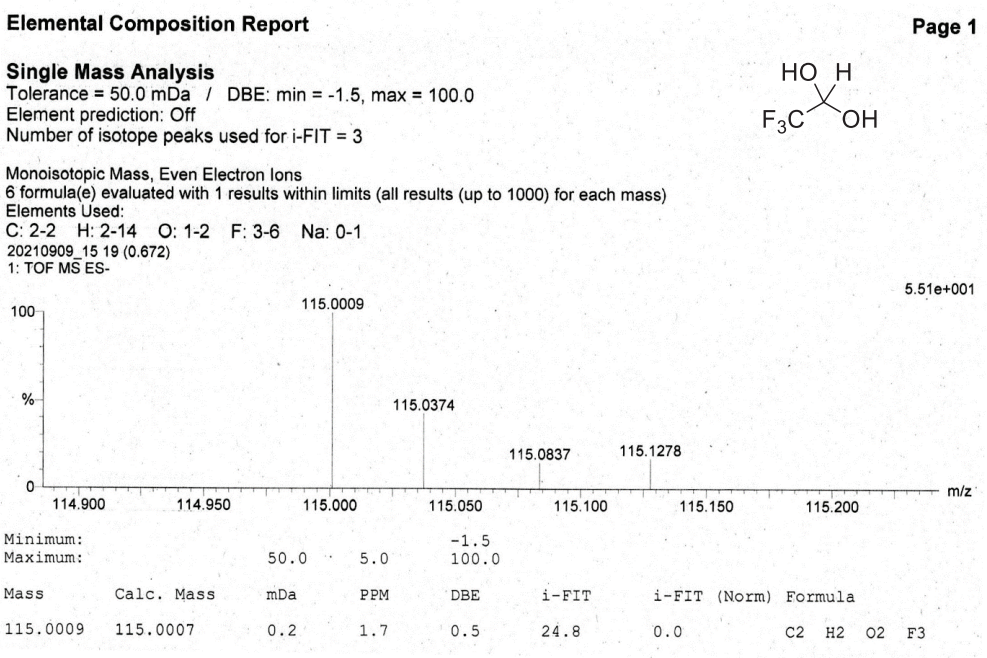
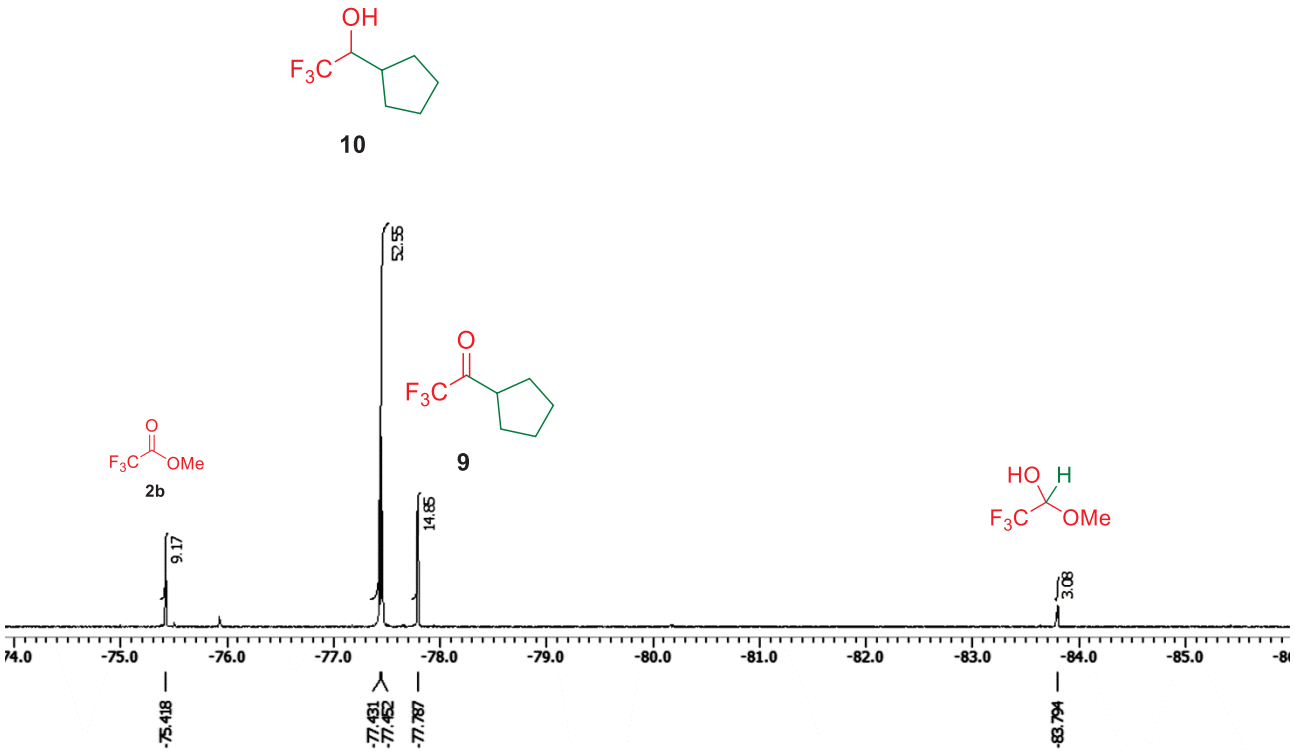
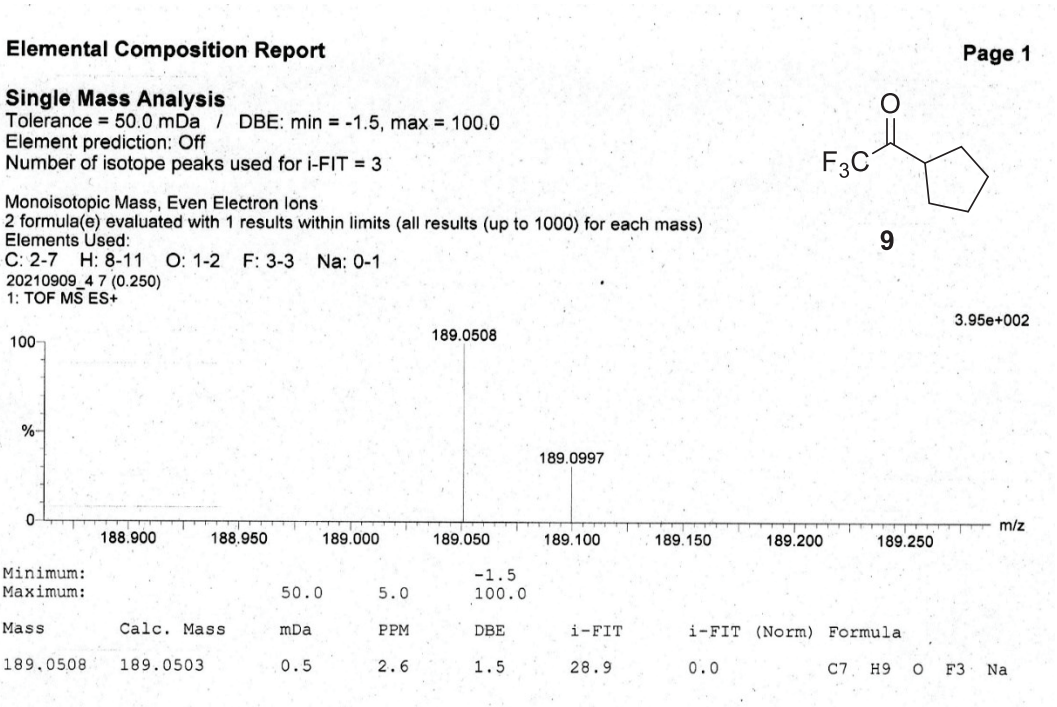


Table 5, entry 2

Crude ^{19}F NMR



Found **1-cyclopentyl-2,2,2-trifluoroethan-1-one (9)**: m/z 189.0508. Calcd for $C_7H_9OF_3Na$: $[M+Na]^+$, 189.0503.



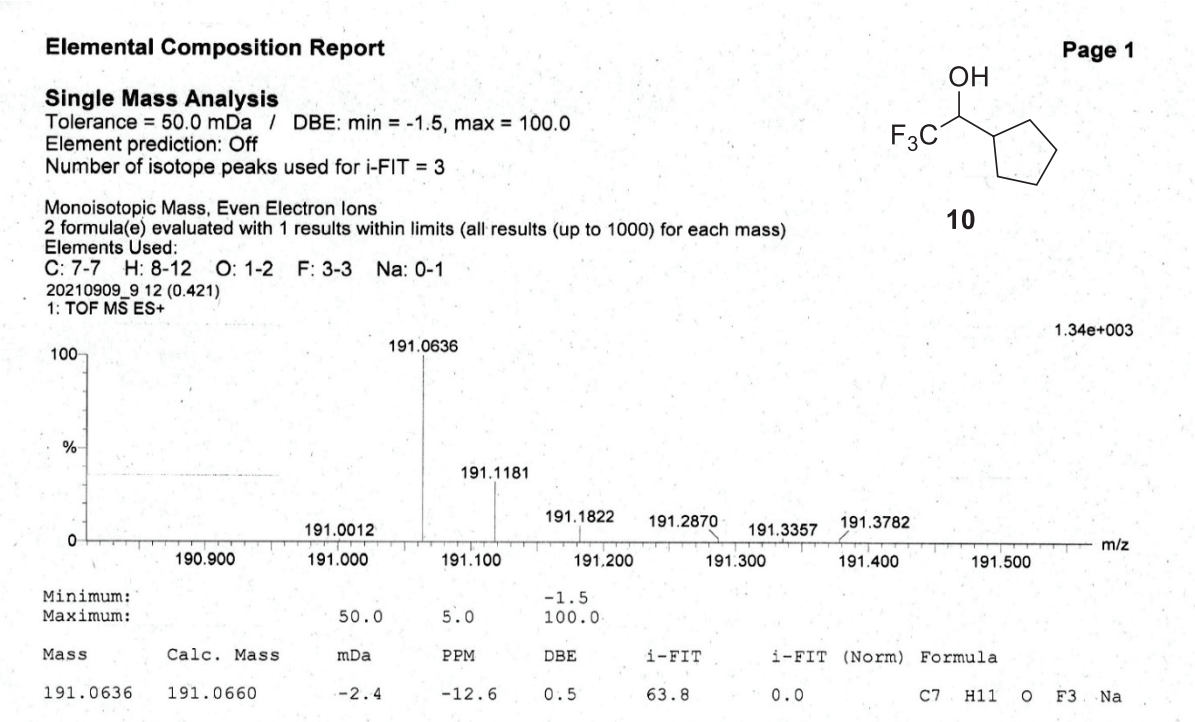
Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 2-7 H: 8-11 O: 1-2 F: 3-3 Na: 0-1
20210909_4 7 (0.250)
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		50.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
189.0508	189.0503	0.5	2.6	1.5	28.9	0.0	C7 H9 O F3 Na

Found **1-cyclopentyl-2,2,2-trifluoroethan-1-ol (10)**: m/z 167.0668. Calcd for $C_7H_{10}OF_3$: $[M+Na]^+$, 167.0684.



Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 7-7 H: 8-12 O: 1-2 F: 3-3 Na: 0-1
20210909_9 12 (0.421)
1: TOF MS ES+

Minimum:				-1.5			
Maximum:		50.0	5.0	100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
191.0636	191.0660	-2.4	-12.6	0.5	63.8	0.0	C7 H11 O F3 Na

Computational Details.

All calculations were performed using the computational chemistry software package Gaussian 16 ver. C.01 [68]. Computational resources in the form of super computers were provided by Research Center for Computational Science, Okazaki, Japan.

Ground state geometries of compound **2a**, **2b** were calculated by DFT at the RB3LYP/6-31G(d,p) level for HOMO and LUMO level.

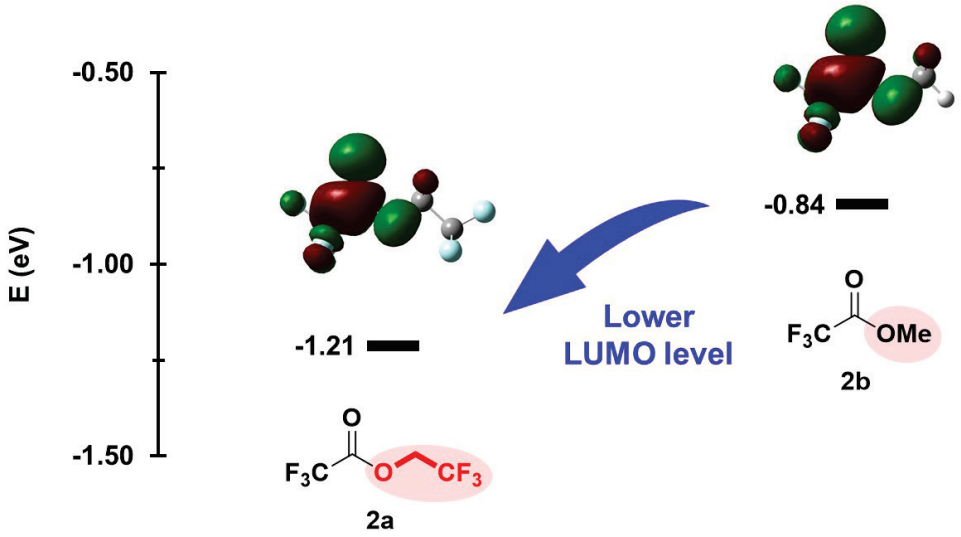
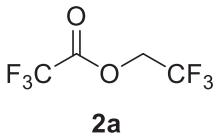


Fig. S1. Computed LUMO level of compound **2a** and **2b**.

At the optimized structures, no imaginary frequency was found through the frequency analysis. All coordinates are reported as XYZ Cartesian coordinates. And computed E (RB3LYP), HOMO, and LUMO level of optimized structures are shown.

2a



E (RB3LYP) = -903.127516 a.u.

Imaginary Frequency = 0

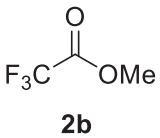
LUMO -0.04450 a.u. = -1.21 eV

HOMO -0.31974 a.u. = -8.70 eV

Table S2. Cartesian coordinates of the optimized **2a**.

	Coordinates (Angstroms)		
Atom	X	Y	Z
C	-1.302587	0.296696	-0.178903
C	-1.135813	1.262569	-0.641161
O	-0.310731	-0.534105	0.184597
O	-0.611245	-1.509123	0.563213
C	-2.741576	-0.074322	-0.051169
H	-3.409253	0.81211	0.731417
H	-3.363575	-0.06148	-1.255068
F	-2.931427	-1.299724	0.485802
F	1.138025	-0.343567	0.097905
F	1.78638	0.920585	0.0353
C	1.938209	-1.50268	0.082948
F	3.185277	0.961545	-0.096029
F	3.319188	-1.451404	-0.049823
F	1.441513	-2.466475	0.159551

2b



2b

E (RB3LYP) = -566.097428 a.u.

Imaginary Frequency = 0

LUMO -0.03097 a.u. = -0.84 eV

HOMO -0.30572 a.u. = -8.32 eV

Table S3. Cartesian coordinates of the optimized **2b**.

	Coordinates (Angstroms)		
Atom	X	Y	Z
C	1.634034	1.331993	0.003333
C	3.013006	1.173791	0.003847
O	3.581625	-0.112016	0.005282
O	2.71563	-1.224291	0.006147
C	1.341029	-1.05231	0.005088
H	0.759567	0.230452	0.003425
H	1.218112	2.336325	0.000208
H	3.660371	2.04686	0.006834
F	3.13551	-2.226959	0.011321
F	0.707424	-1.934054	0.002741
F	4.95713	-0.285437	0.059699

References

1. Trifluoromethylation reactions of hydrocarbon derivative for books, see. P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications,* Wiley-VCH, Weinheim, Germany **2013**.
2. K. Uneyama, *Organofluorine Chemistry*, Blackwell Publishing, Oxford, United Kingdom **2006**.
3. For recent reviews, see. M. Inoue, Y. Sumii, N, Shibata, *ACS Omega* **2020**, *5*, 10633-10640.
4. G. Haufe, F. Leroux, *Fluorine in Life Sciences. Pharmaceuticals, Medicinal Diagnostics and Agrochemicals*, Academic Press, San Diego, United States of America **2019**.
5. Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 2, 422-518.
6. J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Org. Biomol. Chem.* **2015**, *13*, 11153-11183.
7. X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744−1754.
8. O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 8, 4475-4521.
9. For recent reviews, see. Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 9, 101467.
10. For recent reviews, see. S. Barata-Vallejo, A. Postigo, *Chem. Eur. J.* **2020**, *26*, 49, 11065-11084.
11. C. Alonso, E. M. de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847-1935.
12. J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 2, 650-682.
13. S. Barata-Vallejo, S. M. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2015**, *13*, 11153-11183.
14. X.-F. Wu, H. Neumann, M. Beller, *Chem. -Asian J.* **2012**, *7*, 1744−1754.
15. O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 8, 4475-4521.
16. For recent reviews, see. X. Wang, J. Lei, Y. Liu, Y. Ye, J. Li, K. Sun, *Org. Chem. Front.* **2021**, *8*, 2079-2109.
17. Z. Chen, S. Hu, X.-F. Wu, *Org. Chem. Front.* **2020**, *7*, 223-254.
18. P. K. Mykhailiuk, *Chem. Rev.* **2020**, *120*, 12718-12755.

19. A. Y. Rulev, *Eur. J. Org. Chem.* **2018**, 3609-3617.
20. F. Meyer, *Chem. Commun.* **2016**, *52*, 3077-3094.
21. A. Y. Rulev, A. R. Romanov, *RSC Adv.* **2016**, *6*, 1984-1998.
22. F. Aribi, E. Schmitt, A. Panossian, J.-P. Vors, S. Pazenok, F. R. Leroux, *Org. Chem. Front.* **2016**, *3*, 1392-1415.
23. For recent examples, see. Y. Li, M. Hao, M. Xia, N. Sun, C.-L. Zhang, W.-Q. Zhu, *React. Chem. Eng.* **2020**, *5*, 961-966,
24. V. M. Muzalevskiy, A. Y. Rulev, A. R. Romanov, E. V. Kondrashov, I. A. Ushakov, V. A. Chertkov, V. G. Nenajdenko, *J. Org. Chem.* **2017**, *82*, 14, 7200-7214.
25. For recent examples, see. a) C. Liu, G. P. A. Yap, C. A. Rowland, M. A. Tius, *Org. Lett.* **2020**, *22*, 7208-7212.
26. F. Noël, V. D. Vukovic, J. Yi, E. Richmond, P. Kravljanac, J. Moran, *J. Org. Chem.* **2019**, *84*, 15926-15947.
27. S. K. Nursahedova, A. V. Zerov, I. A. Boyarskaya, E. V. Grinenko, V. G. Nenajdenko, A. V. Vasilyev, *Org. Biomol. Chem.* **2019**, *17*, 1215-1224.
28. M. Ramasamy, H.-C. Lin, S.-C. Kuo, M.-T. Hsieh, *Synlett* **2019**, *30*, 356-360.
29. A. Boreux, A. Lambion, D. Campeau, M. Sanita, R. Coronel, O. Riant, F. Gagosz, *Tetrahedron* **2018**, *74*, 5232-5239.
30. A. Boreux, G. H. Lonca, O. Riant, F. Gagosz, *Org, Lett.* **2016**, *18,* 5162-5165.
31. For a review of fluorine-free propargyl alcohols, see. R. Roy, S. Saha, *RSC Adv.* **2018**, *8*, 31129.
32. For a review of α-trifluoromethyl propargyl alcohols, see. H. Noda, N. Kumagai, M. Shibasaki, *Asian J. Org. Chem.* **2018**, *7*, 4, 599-612.
33. For a recent review of fluorine-free propargyl alcohols, see. H. Qian, D. Huang, Y. Bi, G. Yan, *Adv. Synth. Catal.* **2019**, *361*, 14, 3240-3280.
34. M. Zhou, J. Zhang, X. G. Zhang, X. Zhang, *Org. Lett.* **2019**, *21*, 3, 671-674.
35. M. Ishizaki, D. Suzuki, O. Hoshino, *J. Fluor. Chem.* **2001**, *111*, 1, 81-90.
36. L. An, F. F. Tong, S. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 27, 11884-11892.

37. Y. M. Zhang, M. L. Yuan, W. P. Liu, J. H. Xie, Q. L. Zhou, *Org. Lett.* **2018**, *20*, 15, 4486-4489.
38. R. J. Linderman, M. S. Lonikar, *J. Org. Chem.* **1988**, *53*, 26, 6013-6022.
39. R. J. Linderman, D. M. Graves, *J. Org. Chem.* **1989**, *54*, 3, 661-668.
40. R. J. Linderman, D. M. Graves, *Tetrahedron Lett.* **1987**, *28*, 4259-4262.
41. N. Ishikawa, M. G. Koh, T. Kitazume, S. K. Choi, *J. Fluor. Chem.* **1984**, *24*, 419-430.
42. For a recent review, see. D. S. Ziegler, B. Wei, P. Knochel, *Chem. Eur. J.* **2019**, *25*, 11, 2695-2703, and references cited therein.
43. S. R. Sahoo, D. Sarkar, *Tetrahedron Lett.* **2020**, *61*, 12, 151646.
44. V. S. Shinde, M. V. Mane, L. Cavallo, M. Rueping, *Chem. Eur. J.* **2020**, *26*, 37, 8308-8313,
45. W. Dong, H. Yang, W. Yang, W. Zhao, *Org. Lett.* **2020**, *22*, 4, 1265-1269.
46. S. Roy, A. Sharma, S. Mula, S. Chattopadhyay, *Chem. Eur. J.* **2009**, *15*, 7, 1713-1722.
47. A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 30, 5010-5014.
48. S. P. Chavan, H. S. Khatod, *Synthesis* **2017**, *49*, 1410-1418.
49. S. P. Chavan, H. S. Khatod, T. Das, K. Vanka, *RSC Adv.* **2016**, *6*, 50721-50725.
50. E. Torres, R. Fernández, S. Miquet, M. Font-Bardia, E. Vanderlinden, L. Naesens, S. Vázquez, *ACS Med. Chem. Lett.* **2012**, *3*, 12, 1065-1069.
51. H. Ooi, N. Ishibashi, Y. Iwabuchi, J. Ishihara, S. Hatakeyama, *J. Org. Chem.* **2004**, *69*, 22, 7765-7768.
52. O. R. Pierce, J. C. Siegle, E. T. McBee, *J. Am. Chem. Soc.* **1953**, *75*, 6324-6325.
53. R. N. Haszeldine, *J. Chem. Soc.* **1953**, 1748-1757.
54. R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki, *Eur. J. Org. Chem.* **2020**, *29*, 4487-4493.
55. J. A. MacPhee, A. Panaye, J.-E. Dubois, *Tetrahedron* **1978**, *34*, 3553-3562.
56. J. Kim, S. Kim, D. Kim, S. Chang, *J. Org. Chem.* **2019**, *84*, 20, 13150-13158.
57. A. Tuulmets, M. Sassian, *J. Organomet. Chem.* **1999**, *586*, 2, 145-149.
58. For recent papers, see. V. M. Muzalevskiy, Z. A. Sizova, V. V. Panyushkin, V. A. Chertkov, V. N. Khrustalev, V. G. Nenajdenko, *J. Org. Chem.* **2021**, *86*, 3, 2385-2405.

59. C. J. Thomson, D. M. Barber, D. J. Dixon, *Angew. Chem. Int. Ed.* **2019**, *58*, 2469-2473; *Angew. Chem.* **2019**, *131*, 2491-2495.

60. R. F. Reinoso, R. Farran, T. Moragon, A. Garcia-Soret, L. Martinez, *Biopharm. Drug. Dispos.* **2001**, *22*, 6, 231-242.

61. X. Wang, Y. M. Pan, X. C. Huang, Z. Y. Mao, H. S. Wang, *Org. Biomol. Chem.* **2014**, *12*, 2028-2032.

62. T. J. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem. Int. Ed.* **2000**, *39*,1253-1256.

63. Redox isomerization of 1-trifluoromethylated propargyl alcohols to α, β-unsaturated ketones have hardly been studied, although that of 3-trifluoromethylated propargyl alcohols have been well investigated, see. Y. Watanabe, T. Yamazaki, *J. Org. Chem.* **2011**, *76*, 6, 1957-1960,

64. T. Yamazaki, T. Kawasaki-Takasuka, A. Furuta, S. Sakamoto, *Tetrahedron* **2009**, *65*, 31, 5945-5959.

65. S. J. Ko, J. Y. Lim, N. Y. Jeon, K. Won, D. C. Ha, B. T. Kim, H. Lee, *Tetrahedron: Asymmetry* **2009**, *20*, 10, 1109-1114.

66. T. Kiyoshi, I. Tohru, M. Seiji, M. Keiryo, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 9, 2689-2690.

67. M. A. Topchiy, D. A. Zharkova, A. F. Asachenko, V. M. Muzalevskiy, V. A. Chertkov, V. G. Nenajdenko, M. S. Nechaev, *Eur. J. Org. Chem.* **2018**, 3750-3755.

68. Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2019**.

Chapter 3.

Aromatic fluorine atom-induced highly amine-sensitive trimethine cyanine dye showing colorimetric and ratiometric fluorescence change

Abstract

Herein, introducing multiple fluorine atoms into aromatic rings of trimethine cyanine dye is proposed as a powerful method for dramatically increasing sensitivity to amines. The highly sensitive ratiometric fluorescence properties previously available only by intramolecular addition can be exploited in reactions with intermolecular amines or other nucleophiles. In addition, the amine adduct of fluorinated cyanine dye responded to CO_2 and restored the original optical properties.

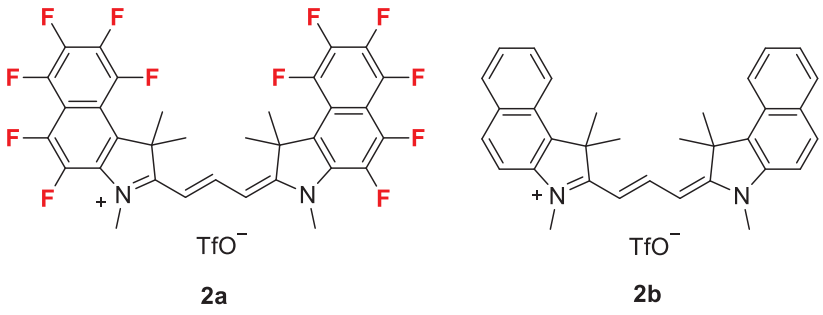
Introduction

Ratiometric fluorescence, a method wherein the ratio of fluorescence intensities at two or more wavelengths are used, has attracted much attention in analytical sensing and optical imaging because it can reduce the effects of many factors such as dye concentration, surrounding pH, polarity, and changes in environmental temperature compared to when single fluorescence intensity is measured.[1-4]

Amines could cause serious damage in public health and the environment owing to their toxic nature, so, simple, fast, low-cost, and accurate amine monitoring systems are becoming highly urgent.[5] The detection of amines using ratiometric fluorescence through utilized intramolecular charge transfer (ICT),[6-17] twisted ICT,[18] aggregation-induced emission,[19–23] and excited state intramolecular proton transfer[24] has been reported.

Polymethine cyanine dyes have several features such as good fluorescence quantum yield and the ability to easily prepare the fluorescence wavelength by changing the methine chain length.[25-27] However, they lack reactivity with amines, and the reported examples are limited to reactions with intramolecular amines.[28-34]

Herein, we report that the prepared ring-perfluorinated trimethine cyanine dye **2a** (Fig. 1) has a significantly higher response to *n*-hexylamine than the non-fluorinated dye **2b**. The dye **2a** exhibited a dual change in the solution and fluorescence color at widely shifted wavelengths, visible to the naked eye. Moreover, in order to explore further possibilities for the high amine responsiveness of dye **2a**, the CO_2 responsiveness of the amine adduct of dye **2a** was evaluated, inspired by reported cases in which the CO_2 responsiveness of dyes were activated by injecting base.[35-39]



2a **2b**

Fig. 1. Structure of trimethine cyanine dyes **2a** and **2b**.

Furthermore, dye **2a** adsorbed on the filter paper could be repeatedly used because the orange emission was instantly converted into blue by the amine vapor and returned to its original color after drying rapidly in the air. These results are the first example of the highly sensitive ratiometric fluorescence properties of polymethine cyanine dyes with intermolecular amines and advance the development of rapid and reversible vapochromic response materials to amines with two changes in papers and emission color.

Results and discussion

The responsivity of the ring-perfluorinated trimethine cyanine dyes **2a** and **2b** to *n*-hexylamine in tetrahydrofuran (THF) stored overnight in the dark at 25 °C were investigated; the results are summarized in Fig. 2 and Table 1. *n*-Hexylamine was used as a representative example of a primary aliphatic amine because it is not easily volatilized. As the amount of *n*-hexylamine gradually increased, the orange fluorescence at 596 nm from dye **2a** decreased, and the blue emission at 404 nm increased at an excitation of 257 nm. This phenomenon led to the disappearance of the solution color and a shift in the fluorescence color from orange through pink to blue, according to the CIE color system. Thus, dye **2a** was highly sensitive, completing the reaction with only 2 equiv. of the amine. For dye **2b**, the red fluorescence at 612 nm diminished, and the blue fluorescence at 380 nm increased significantly at an excitation of 250 nm, although 6400 equiv. of the amine was

required to complete the reaction with the non-fluorinated dye **2b**. These results suggest that replacing all the hydrogen atoms with fluorine on the aromatic rings dramatically improved the sensitivity of trimethine cyanine dye to the amine.

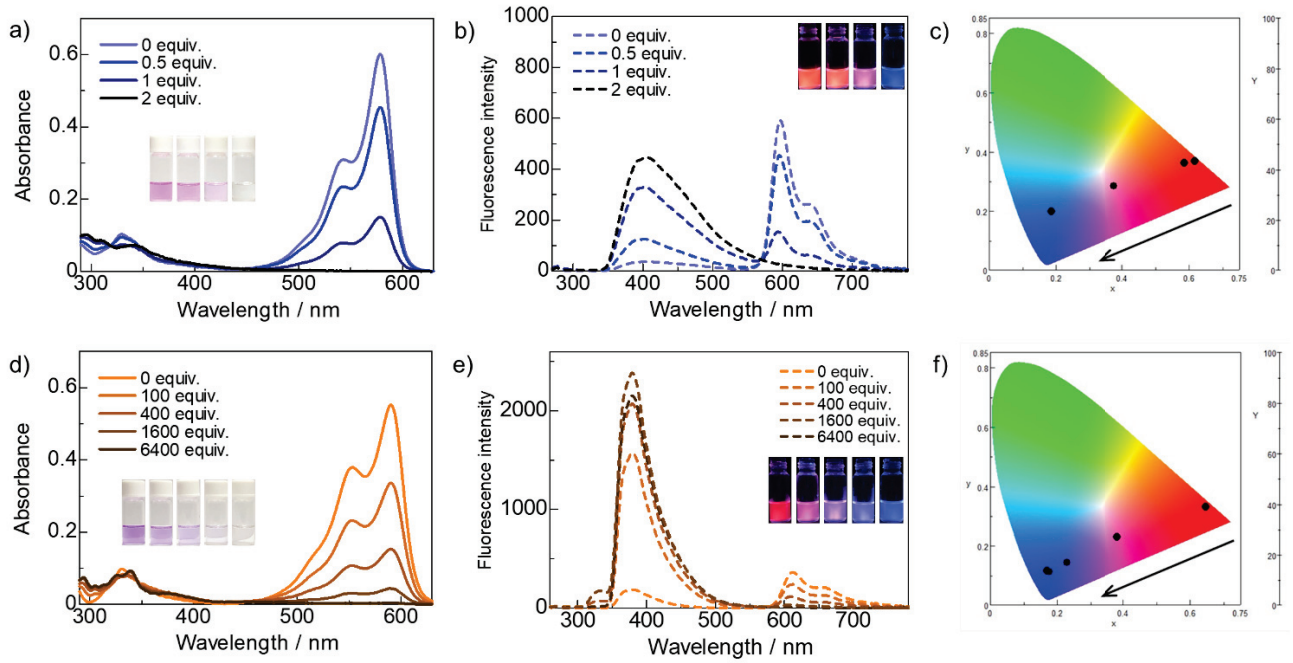


Fig. 2. (a) Ultraviolet-visible (UV-vis), (b) fluorescence spectra, and (c) CIE color systems of dye **2a** (5×10^{-6} M) in THF stored overnight in the dark at 25 °C after adding *n*-hexylamine. (d) UV-vis, (e) fluorescence spectra, and (f) CIE color systems of dye **2b** under similar conditions. The excitation wavelengths were determined by the excitation spectra (Fig. S1) and were as follows: 257 nm (dye **2a**), 250 nm (dye **2b**), and 365 nm (CIE color systems). Inset photos were obtained under white LED light and UV light (λ = 365 nm), and the order of amine concentration is left to right.

Table 1. Optical properties of dyes **2a** and **2b** in THF with *n*-hexylamine

Dye	*n*-hexylamine (equiv.)	λ_{max} (nm) (ε ($M^{-1}cm^{-1}$))	λ_{ex} (nm)	F_{max} (nm)[b]	Φ_f[c]	τ_s (ns)[e]
2a	0	579 (120000)	580	596	0.14	0.7
	0.5	579 (91000)	-	-	-	-
	1	579 (30000)	-	-	-	-
	2	579 (200)	257	404	0.04[d]	6.1
2b	0	591 (110000)	591	612	0.10	0.5
	6400	254	250	380	0.24[d]	12.5

[a] Measured dye **2** (5 x 10^{-6} M) in THF stored overnight in the dark at 25 °C after the addition of *n*-hexylamine.
[b] Measured by using excitation wavelengh (λ_{ex}) at low sensitivity.
[c] Measured using an integrating sphere method excited at λ_{ex}.
[d] Measured by excitation at 290 nm. [e] Measured using a single-photon-counting method.

The fluorescence quantum yields for dyes **2a** and **2b** were 14 and 10%, respectively. When the dyes reacted with the amine, the maximum excitation wavelength overlapped with the absorption band of THF; therefore, excluding this band, the dyes were excited at 290 nm, with fluorescence quantum yields of 4 and 24%, respectively. Furthermore, a calibration curve for the fluorescence intensity ratio of dye **2a** ($I_{404\ nm}/I_{596\ nm}$) versus the concentration of *n*-hexylamine demonstrated good linearity (R^2 = 0.988), while the estimated detection limit (3σ/slope) was 17 nM, as shown in Fig. 3. The obtained value shows sensitivity as high as that of an activated ester and aldehydes.[8,10,11]

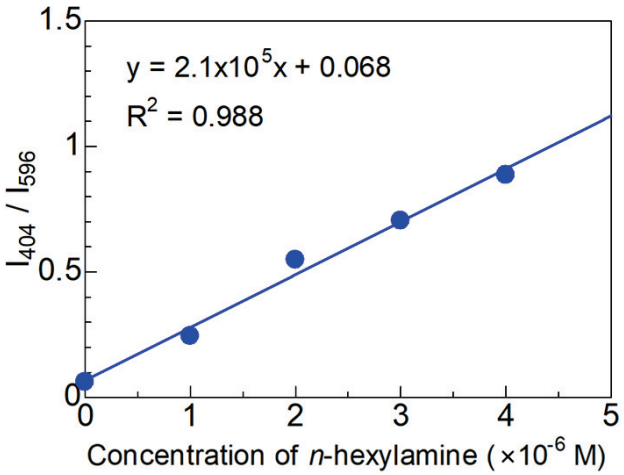


Fig. 3. Calibration curve for the fluorescence intensity ratio ($I_{404\ nm}/I_{596\ nm}$) of dye **2a** vs. the concentration of *n*-hexylamine (0–4×10^{-6} M).

Next, absorbance changes in various solvents were followed to examine the sensitivity of dye **2a** to *n*-hexylamine (Fig. 4). The results revealed that this reaction was primarily promoted by THF, followed by other solvents in the order dimethyl sulfoxide (DMSO), methyl alcohol (MeOH), acetone, chloroform, and dichloromethane (DCM). The large difference in the reactivity was related to the Gutmann donor number (DN) and acceptor number (AN) of solvent molecules, which are the empirical measures of the nucleophilic and electrophilic properties of the solvents.[40,41]

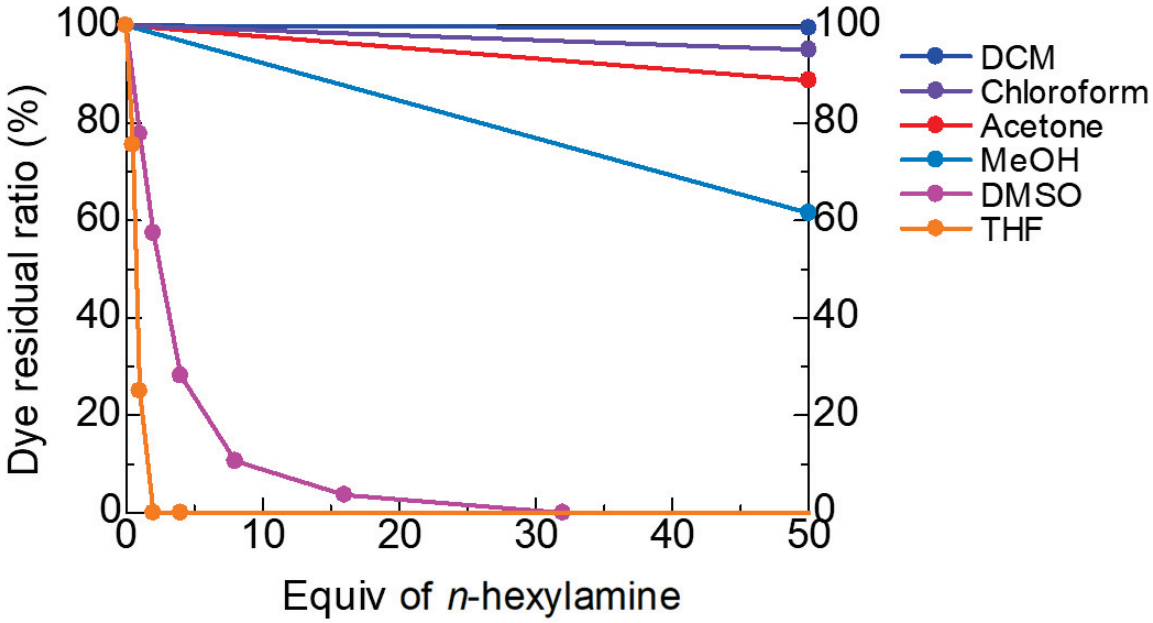


Fig. 4. Dye residual ratio calculated from molar absorption coefficient (ε) at 579 nm of dye **2a** solusion (5×10^{-6} M) in adding *n*-hexylamine.

Solvents with high DN can stabilize cations,[42] while an opposite phenomenon is observed for AN. Therefore, the reaction of the dye with the amine is more likely to proceed in THF and DMSO, which have larger DN and/or smaller AN than acetone, MeOH, chloroform, and DCM, because the cationic dye is most involved in this system. The DN and AN of these solvents are listed in Table S1.

Other analytes, such as not only other amines (aniline, triethylamine, and diethylamine) but also anions (perchlorate, acetate, bromide, chloride, and fluoride) in THF were also examined. The results are summarized in Fig. 5. The reactions of dye **2a** with 2 equiv. of amines such as triethylamine and diethylamine occurred smoothly, and the color of the fluorescent changed from orange to blue, as in the case of *n*-hexylamine, as illustrated in Fig. 5c. Although, accurate measurement for aniline was not possible due to its fluorescence, the dye-derived maximum absorption was slightly reduced.

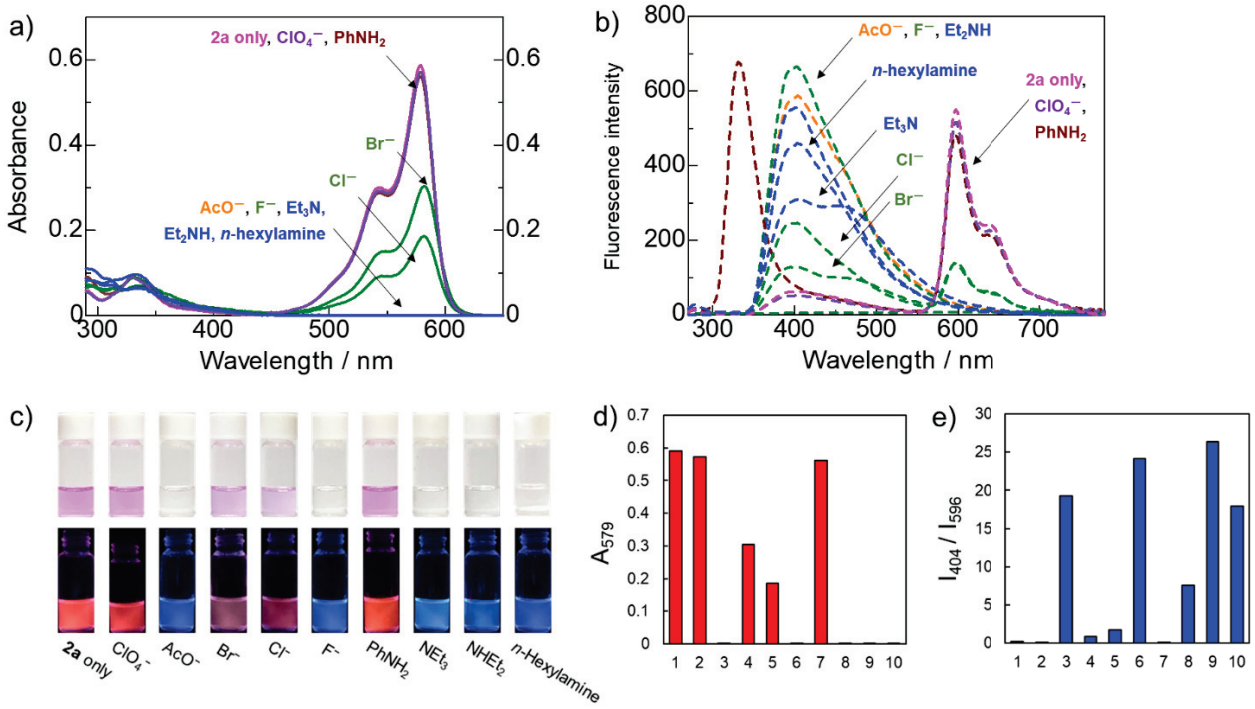


Fig. 5. (a) UV-vis, (b) fluorescence spectra, and (c) the photos of dye **2a** (5×10^{-6} M) in THF stored overnight in the dark at 25 °C after adding various analytes (2 equiv.). The excitation wavelength was 257 nm. (d) Absorbance at 579 nm and (e) fluorescence intensity ratio ($I_{404\ nm}/I_{596\ nm}$) were calculated from the UV-vis and fluorescence spectra, respectively. Analytes are as follows: (1) **2a** only, (2) ClO_4^-, (3) AcO^-, (4) Br^-, (5) Cl^-, (6) F^-, (7) $PhNH_2$, (8) NEt_3, (9) $NHEt_2$, and (10) *n*-hexylamine. Photos were captured under white LED light and UV light (λ = 365 nm) with various analytes. The counter cations of these anionic species are all Bu_4N^+.

Using 2 equiv. of a couple of anions, such as acetate and fluoride,[43] also resulted in observation to change the fluorescent color from orange to blue, as in the case of *n*-hexylamine, as illustrated in Fig. 5c. The detection of other anionic species, such as bromide and chloride, demonstrated only moderate changes in the fluorescent color and reacted slightly with perchlorate.

To observe the difference in the detection of these neutral and anionic nucleophiles, UV-vis and fluorescence spectra of dye **2a** were measured in detail in THF with different equiv. of not only diethylamine and triethylamine but also acetate and fluoride anions, were carried out. The results are summarized in Fig. 6. It was found that the highly nucleophilic anion, such as acetate and fluoride are more reactive than *n*-hexylamine. Detection of diethylamine appears to be similar

to that of *n*-hexylamine, but somewhat lower for the tertiary triethylamine.

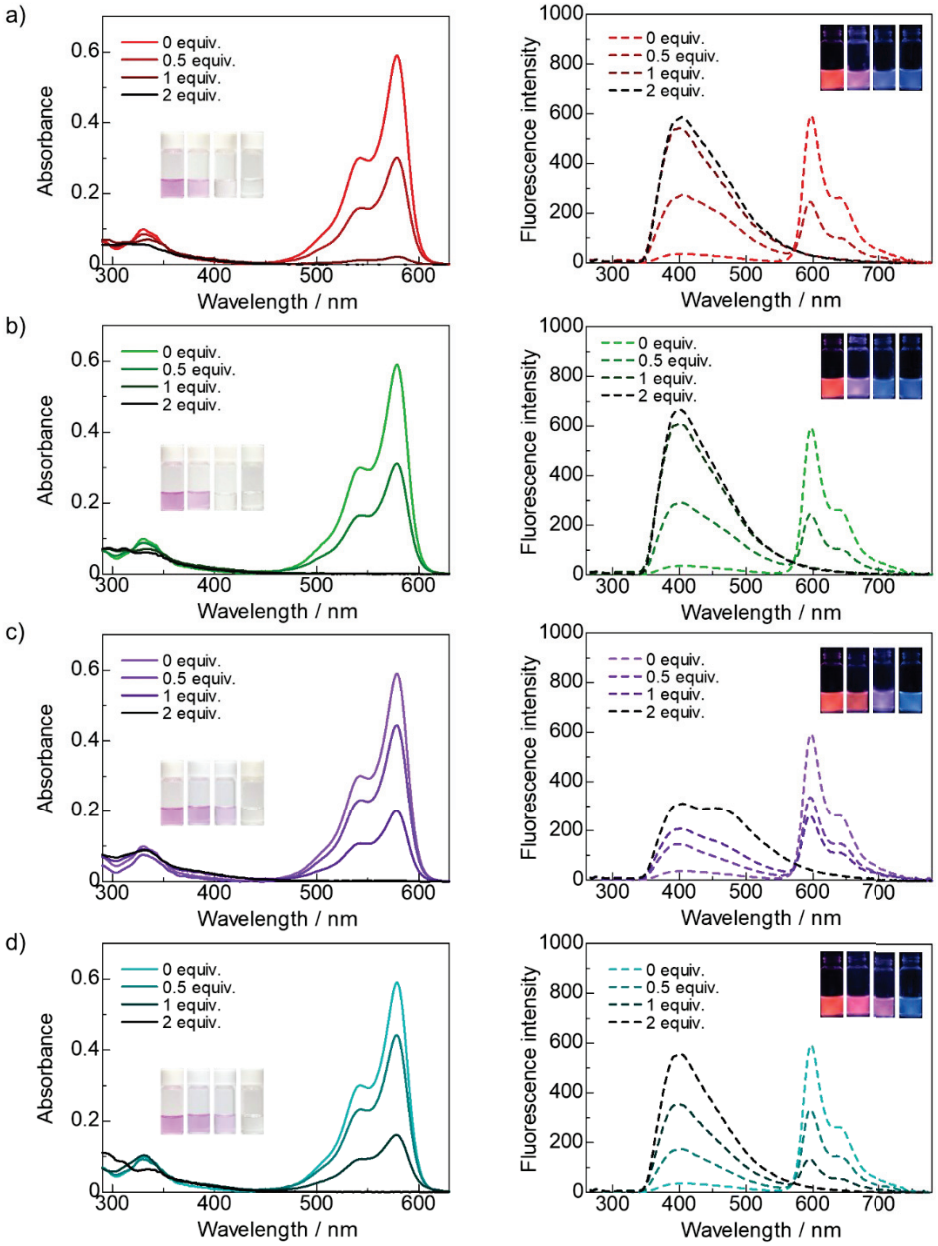


Fig. 6. UV-vis and fluorescence spectra of dye **2a** (5×10^{-6} M) in THF stored overnight in the dark at 25 °C after adding analytes which are as follows: (a) AcO^{-}, (b) F^{-}, (c) NEt_3, and (d) $NHEt_2$. The counter cations of these anionic species are all Bu_4N^{+}.

Importantly, the ring-perfluorinated trimethine cyanine dye **2a** has a significantly higher response to very small amounts of neutral amines than the non-fluorinated dye **2b** and underwent a dual change in the solution and fluorescent. The reason can seem to be that the introduction of

fluorine atoms into the aromatic rings significantly lowers the LUMO of trimethine cyanine dye **2a** and promotes the addition reaction of even neutral amines, as shown in Fig. 7.[44]

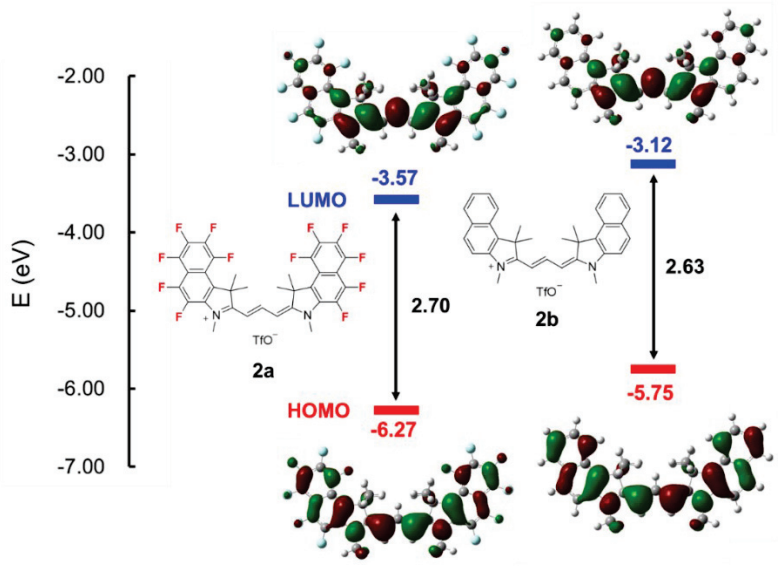


Fig. 7. Energy diagrams and molecular orbitals of the cationic parts of dyes obtained using DFT calculations at the B3LYP/6-31+G(d,p) level.

In order to investigate the reaction product, the results of nuclear magnetic resonance (NMR) and high-resolution mass spectrometry illustrated in Fig. 8 and S2 suggest the 1,2-addition of *n*-hexylamine to the iminium carbon of dye **2a**. In particular, ^{1}H NMR confirmed that the doublet signal split in two and the triplet signal changed to a double doublet, along with an up-field shift in all signals regarding the methine chain protons. Furthermore, the amine-added dyes **2a** and **2b** were characterized by MS analysis (Fig. S2), where peaks at m/z 774.2719 (calculated = 774.2718, $[C_{39}H_{36}F_{12}N_3]^+$) and m/z 558.3849 (calculated = 558.3848, $[C_{39}H_{48}N_3]^+$) were detected, respectively. Although it was difficult to measure the non-fluorinated dye **2b** by NMR owing to its poor reactivity with amines, it is expected to react with amines in the manner similar to that as the fluorinated dye **2a** because of its very similar structure and the MS result.

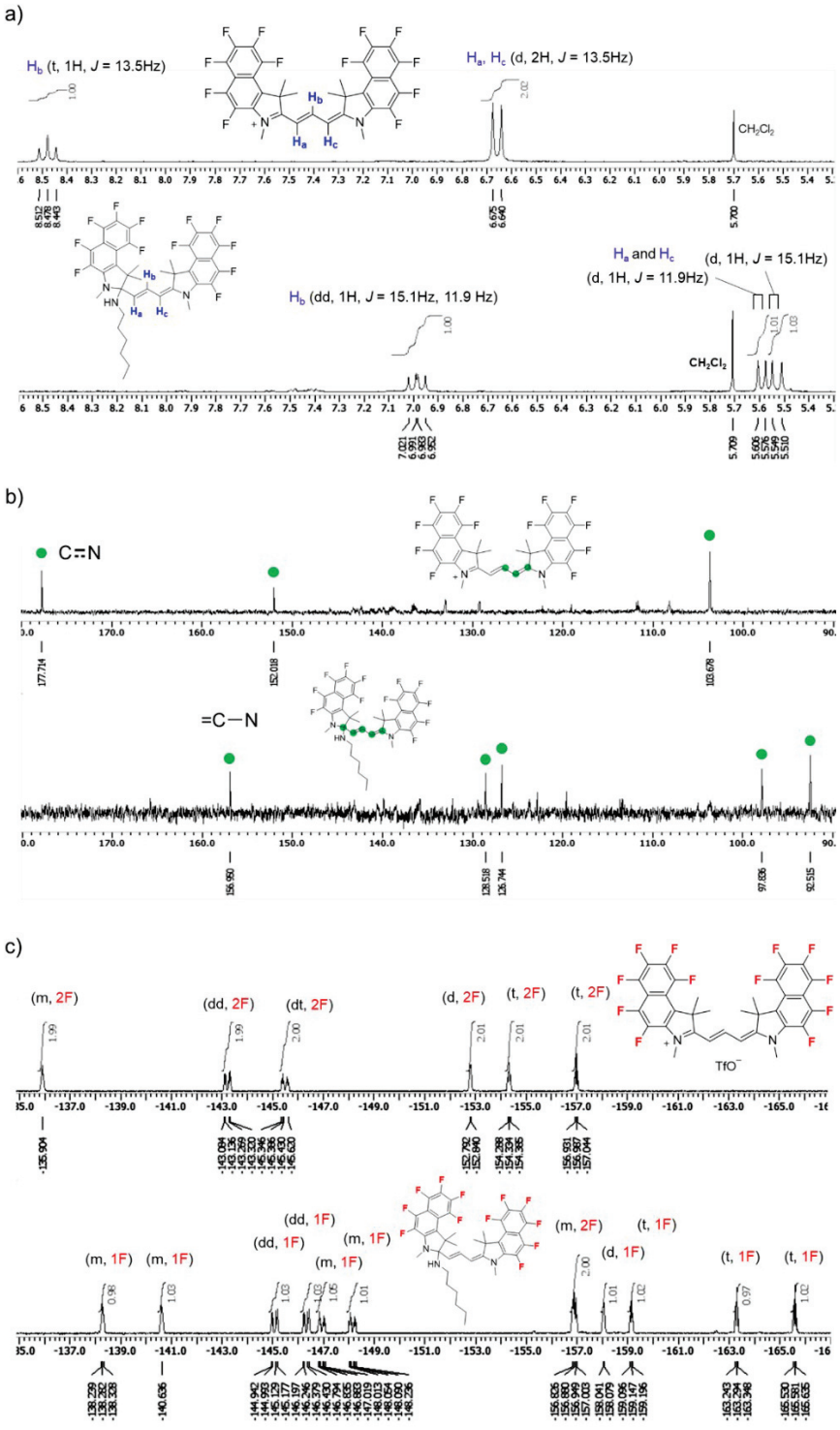


Fig. 8. a) ^{1}H, b) ^{13}C, and c) ^{19}F NMR analysis for the reaction of dye **2a** (1×10^{-5} mol) with *n*-hexylamine (20 equiv.) in DMSO-d_6.

To assess the versatility of application, the repeatability of dye **2a** was investigated using filter paper, as shown in Fig. 9.

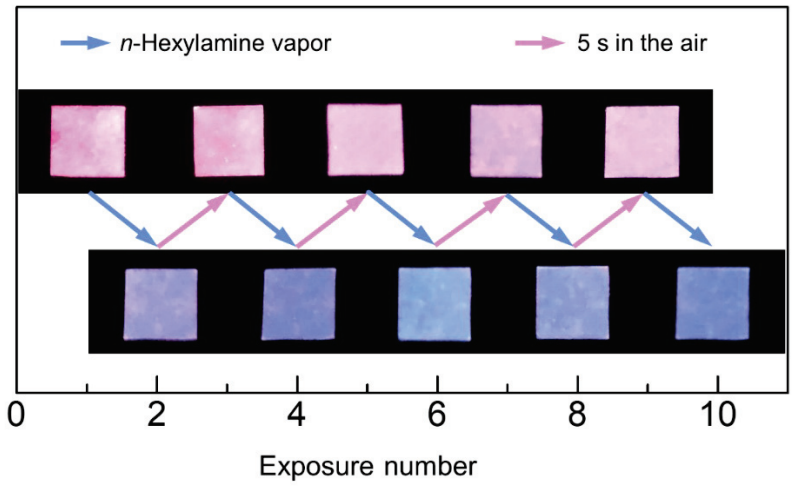


Fig. 9. Repeatability of fluorescence using filter paper adsorbed with dye **2a** upon alternative exposure to *n*-hexylamine vapor and drying in the air. The inset photos were captured under UV light (λ = 365 nm).

The filter paper for dye adsorption was fabricated by soaking a white filter paper overnight in the DCM solution of dye **2a** (5×10^{-4} M) and then drying in the dark for 1 h at 25 °C. Exposure to *n*-hexylamine vapor resulted in rapid disappearance of the pink of the filter paper and change in the fluorescence from orange to blue. Subsequently, drying in the air caused the pink of the filter paper to return to pink and emit orange fluorescence. This reversible change in fluorescent color was particularly pronounced, with the blue fluorescence reverting to orange in only 5 s when kept in the air after exposure to the amine.

Finally, we evaluated the CO_2 responsiveness of the reaction mixture of the dye with hexylamine. Unfortunately, a THF solution previously prepared from dye **2a** with 2 equiv. of hexylamine did not react with CO_2. Therefore, it did not affect the absorption and fluorescence spectra (Figures 10a and 10b). In contrast, a DMSO solution of the dye with hexylamine recovered 60% of its fluorescence intensity after 20 mL of CO_2 bubbling, indicating moderate CO_2 reactivity (Figures 10c and 10d).

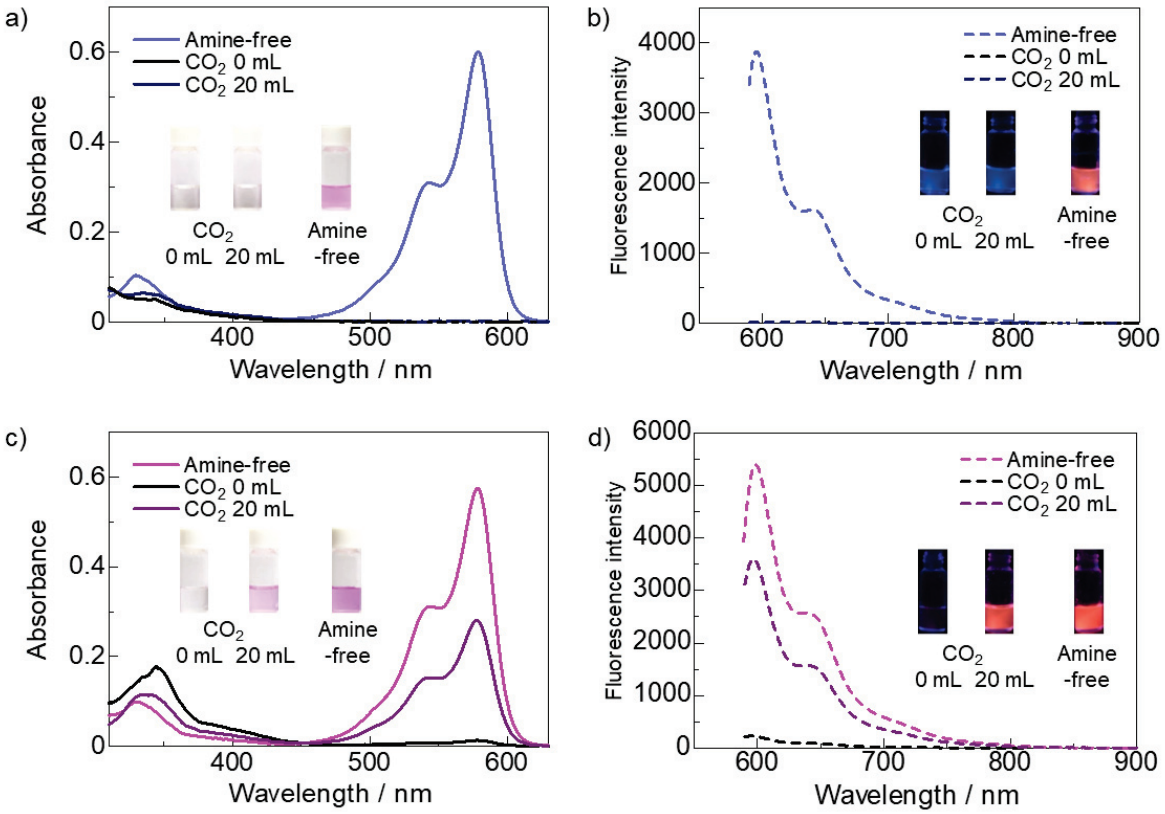


Fig. 10. a) UV-vis and b) fluorescence spectra of a solution (3.3 mL) prepared from fluorinated dye **2a** (5×10^{-6} M) and 2 equiv. of *n*-hexylamine in THF obtained after a specific volume of CO_2 (0, 20 mL) was allowed to bubble through the solution. c) UV-vis and d) fluorescence spectra of a DMSO solution obtained after a specific volume of CO_2 was allowed to bubble through the solution. Solutions of fluorinated cyanine dye **2a** (5×10^{-6} M) were used for the spectra under amine-free conditions. Insert photographs were obtained under white LED and UV light (λ = 365 nm).

Similarly, bubbling 8 mL of CO2 into the dye with the amine in MeOH immediately changed the color and recovered both absorbance and fluorescence intensity. They reached more than 91% compared to the amine-free situation (Fig. 11) (Table 2) to exhibit high CO_2 responsiveness in MeOH.

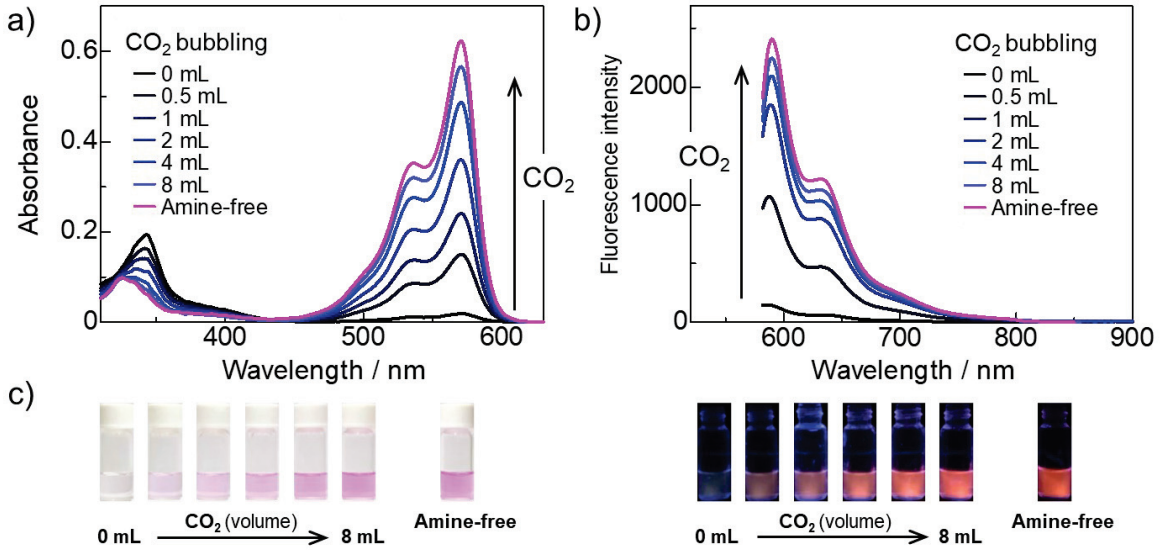


Fig. 11. a) UV-vis and b) fluorescence spectra of a solution (3.3 mL) prepared from fluorinated dye **2a** (5×10^{-6} M) and 5000 equiv. of *n*-hexylamine in methanol obtained after a specific volume of CO_2 (0–8 mL) was allowed to bubble through the solution. A methanol solution of fluorinated dye **2a** (5×10^{-6} M) was used for the spectra under amine-free conditions. c) The photographs were obtained under white LED and UV light (λ = 365 nm).

Table 2. Optical properties of amine adduct responding to CO_2.

CO_2 (mL)	λ_{max} (nm) (ε ($M^{-1}cm^{-1}$))	λ_{ex} (nm)	F_{max} (nm)[b]	Φ_f[c]	τ_s (ns)[d]
0	572 (4000)	571	587		
0.5	571 (30000)		587		
1	571 (48000)		589		
2	571 (72000)		589		
4	571 (97000)		590		
8	571 (110000)		590		
Amine-free	571 (130000)		590	0.07	0.38

[a] Measured immediately after CO_2 was allowed to bubble through a solution comprising dye **2a** (5×10^{-6} M) in MeOH that had been stored for 1 h in the dark at 25 °C after adding *n*-hexylamine (2.5×10^{-2} M). [b] The fluorescence spectrum was obtained by using excitation wavelength (λ_{ex}). [c] Measured using an integrating sphere method. [d] Measured using a single photon-counting method.

The above results suggested a reversible reaction mechanism: 1) dye **2a** reacts with hexylamine to form the amine adduct of the dye, and 2) CO_2 removes amines from the amine adduct, as illustrated in Fig. 12.

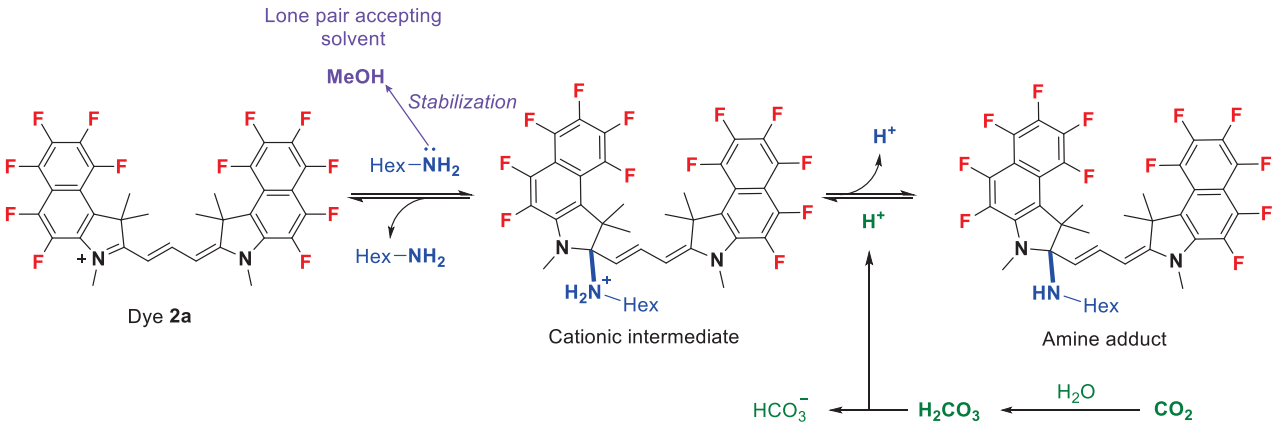


Fig. 12. Estimated reversible reaction mechanism in which dye **2a** reacts with amines and CO_2 removes amines from the dye.

In amine responsiveness, hexylamine first performs a nucleophilic attack on the iminium moiety of the dye, giving a cationic intermediate. Next, deprotonation proceeds to form the amine adduct. In the reverse reaction, Carbonic acid protonates the amine adduct. ^{13}C NMR confirmed that carbonic acid is made from CO_2 with a small amount of water in MeOH (Fig. S3). Finally, the elimination of amine from the amine adduct leads to the recovery of the dye skeleton. This reaction proceeds reversibly. The main reason why CO_2 responsiveness was affected by solvent is the DN and AN of the solvents listed in Table S1. In other words, we assumed that CO_2 responsiveness was enhanced in solvents with large AN value, such as MeOH, because solvents with large AN can stabilize the lone pair of the amine and favor acid-induced amine elimination, in contrast to solvents with large DN, which promote the addition of amines to the dye.

Conclusion

We reported that the ring-perfluorinated trimethine cyanine dye **2a** was highly sensitive to *n*-hexylamine and underwent a dual change in the solution and fluorescent color with a large shift. The methodology of introducing many fluorine atoms proved valuable for efficiently enhancing the sensitivity of the dye to amines. In addition, the fluorinated dye **2a** adsorbed on the filter paper exhibited reversible ratiometric fluorescence properties, such that the orange emission was instantly changed to blue by the amine vapor and returned to its original color when dried in the air for 5 seconds. Furthermore, the amine adduct of fluorinated cyanine dye responded to CO_2 and recovered up to 90% of the original optical properties.

Experimental Section

Materials. Acetone, methanol, and ethyl acetate were purchased from Kanto Chemical Industry Co., Inc. Tetrahydrofuran (THF; stabilizers not included), dimethyl sulfoxide, chloroform, triethylamine, aniline, and tetrabutylammonium chloride were purchased from FUJIFILM Wako Pure Chemical Co. *n*-Hexylamine, diethylamine, tetrabutylammonium fluoride, and tetrabutylammonium acetate were purchased from TCI Co., Ltd. Tetrabutylammonium bromide was purchased from Sigma-Aldrich. Tetrabutylammonium perchlorate and dichloromethane were purchased from Nacalai Tesque Inc. Dyes **2a** and **2b** were synthesized by our method.[45]

Measurement. ^{1}H nuclear magnetic resonance (NMR) spectra were measured at 392 or 400 MHz in hexadeuterodimethyl sulfoxide ($(CD_3)_2SO$) solutions with residual solvents as internal standards using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. ^{13}C NMR spectra were obtained at 99 or 101 MHz in $(CD_3)_2SO$ solution with residual solvents as internal standards using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. ^{19}F NMR spectra were recorded at 369 or 376 MHz in $(CD_3)_2SO$ solutions using a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. The data were reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, coupling constant(s), integration). Electrospray ionization mass spectroscopy (ESI-MS) analysis using MeOH was performed with a JEOL JMS-T100LP (AccuTOF LC-plus). Ultraviolet-visible absorption spectra were obtained using a Hitachi U-4100. The fluorescence spectra were acquired using a Jasco FP-8600 spectrofluorometer. The absolute fluorescence quantum yields were obtained on Hamamatsu Quantaurus-QY C11347-01. The fluorescence lifetimes were measured using Hamamatsu Quantaurus-Tau compact fluorescence lifetime spectrometer C11367-01.

Determination of limit of detection (LOD)

The fluorescence intensity ratio at 404 nm and 596 nm of the ring-perfluorinated dye **2a** in THF was collected 10 times to obtain the background noise σ. The fluorescence intensity ratios were measured overnight after adding different concentrations of *n*-hexylamine. LOD (3σ/slope) was calculated as three times the background noise σ divided by the slope of the fluorescence intensity ratio fitted to a calibration curve as a function of the amine concentration.

Supporting Figures and Tables

Table S1. DN and AN value of solvents.

Solvent	AN	DN (kcal mol^{-1})
DCM	20	1
Chloroform	23	4
Acetone	13	17
MeOH	42	19
DMSO	19	30
THF	8	20

[a] Gutmann Acceptor number (AN) and Donor number (DN).

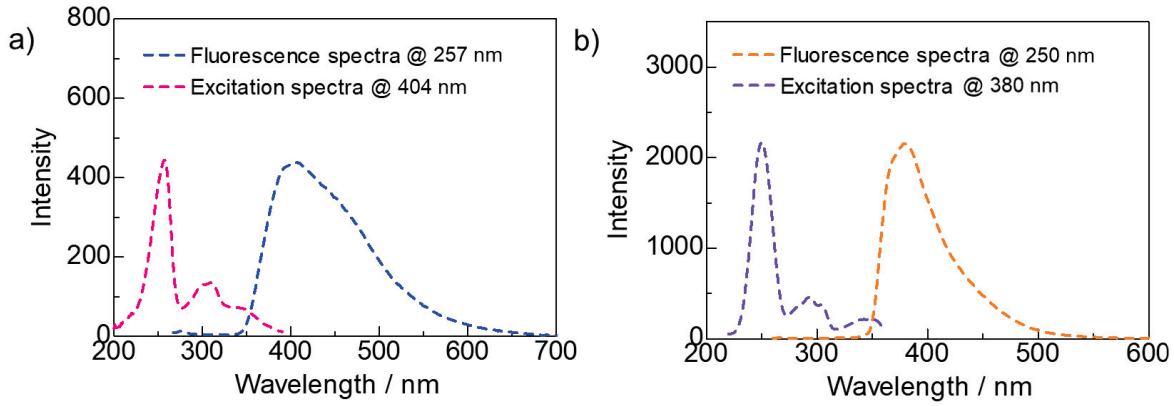
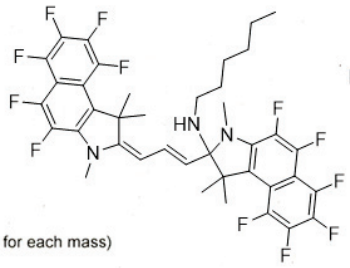


Fig. S1. a) Fluorescence and excitation spectra of dye **2a** and b) **2b** (5×10^{-6} M) in THF completely reacted with *n*-hexylamine.

a)

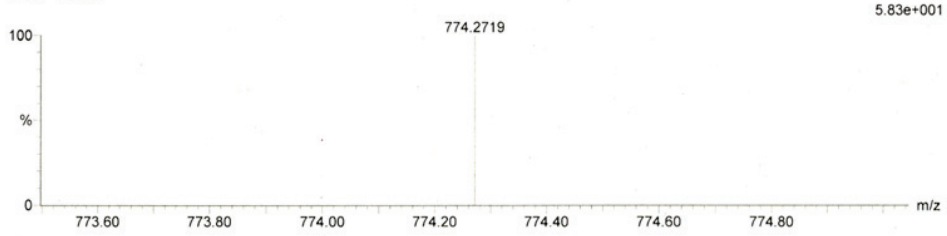


Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

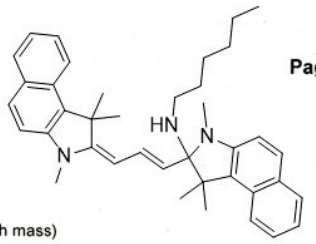
Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 33-39 H: 21-36 N: 2-3 F: 11-12
20210716_2 18 (0.637)
1: TOF MS ES+

5.83e+001



Minimum:		50.0	5.0	-1.5			
Maximum:				100.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
774.2719	774.2718	0.1	0.1	17.5	17.7	0.0	C39 H36 N3 F12

b)

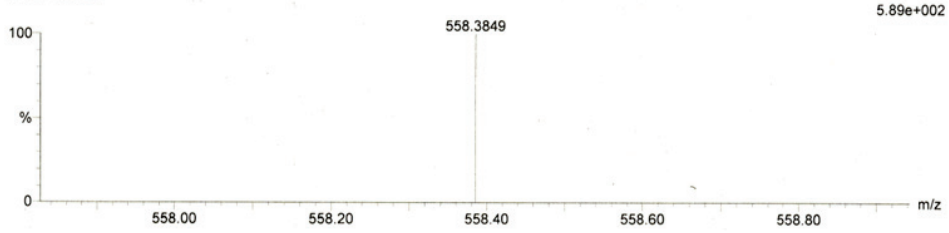


Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 39-39 H: 48-48 N: 3-3 Na: 0-1
20220214_2 22 (0.774)
1: TOF MS ES+

5.89e+002



Minimum:		5.0	10.0	-1.5			
Maximum:				50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
558.3849	558.3848	0.1	0.2	17.5	23.7	0.0	C39 H48 N3

Fig. S2. a) MS analysis for amine-added dyes **2a** and b) **2b**.

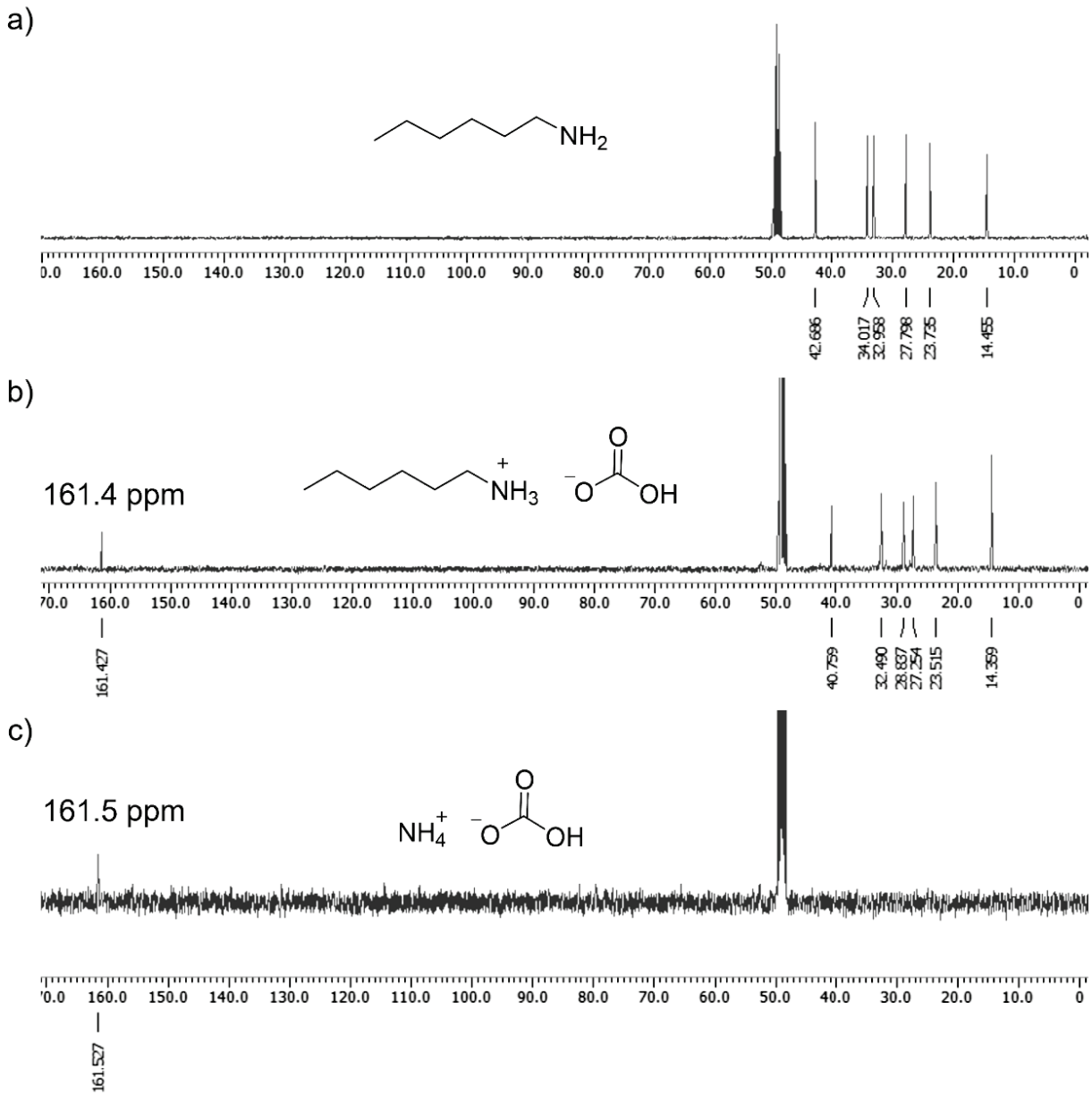


Fig. S3. a) ^{13}C NMR results of *n*-hexylamine, b) *n*-hexylamine with CO_2 bubbling for 1 min, and c) Saturated ammonium bicarbonate in MeOH-d_4.

Computational Details.

All calculations were performed using the computational chemistry software package Gaussian 16 ver. C.01 [46]. Computational resources in the form of super computers were provided by Research Center for Computational Science, Okazaki, Japan.

Ground state geometries of compound **2a**, **2b** were calculated by DFT at the RB3LYP/6-31+G(d,p) scrf=(solvent=dichloromethane) level.

At the optimized structures, no imaginary frequency was found through the frequency analysis. All coordinates are reported as XYZ Cartesian coordinates. And computed E (RB3LYP) and sum of electronic and thermal Energies of optimized structures are shown.

2a

E (RB3LYP) = -2577.625224 a.u.

Sum of electronic and thermal Energies= -2577.105643 a.u.

Imaginary Frequency = 0

Table S2. Cartesian coordinates of the optimized **2a**.

	Coordinates (Angstroms)		
Atom	X	Y	Z
C	-4.774293	1.679121	0.113635
C	-4.470385	0.326227	0.028708
C	-7.129699	1.214178	0.096221
C	-6.109535	2.128579	0.145227

C	-7.717549	-2.467815	-0.114018
C	-6.39228	-2.934096	-0.14786
C	-7.955656	-1.119263	-0.03362
C	-5.517185	-0.64266	-0.019877
C	-6.892559	-0.180418	0.015315
C	-5.340403	-2.052482	-0.102301
N	-3.603706	2.453804	0.147685
F	-4.107832	-2.601618	-0.138989
F	-6.169158	-4.253266	-0.224546
F	-8.72643	-3.347827	-0.159563
F	-9.23736	-0.713067	-0.001876
F	-8.385876	1.691996	0.124729
F	-6.43154	3.436279	0.215262
C	-2.940127	0.194919	-0.002834
C	-2.449846	-0.41239	-1.345305
H	-2.818832	0.177788	-2.188852
H	-1.35994	-0.421335	-1.391677
H	-2.799661	-1.436685	-1.458139
C	-2.407165	-0.556135	1.248391
H	-2.739138	-0.057855	2.1634
H	-2.765246	-1.58366	1.263404
H	-1.316505	-0.581564	1.254173
C	-2.503949	1.663284	0.069525
C	-1.220919	2.214996	0.049669
H	-1.156294	3.297585	0.070494

C	-3.538674	3.917438	0.256423
H	-3.104668	4.337972	-0.654453
H	-4.534484	4.319885	0.394101
H	-2.923325	4.189931	1.116578
C	4.774294	1.679122	-0.113637
C	4.470386	0.326228	-0.02871
C	7.1297	1.214178	-0.096234
C	6.109536	2.12858	-0.145234
C	7.717546	-2.467817	0.114009
C	6.392276	-2.934095	0.147862
C	7.955655	-1.119265	0.033605
C	5.517186	-0.642658	0.019873
C	6.89256	-0.180418	-0.015327
C	5.3404	-2.052479	0.102305
N	3.603706	2.453803	-0.147679
F	4.107828	-2.601609	0.139009
F	6.169152	-4.253264	0.224556
F	8.726425	-3.34783	0.159551
F	9.237361	-0.713072	0.001853
F	8.385877	1.691996	-0.124746
F	6.431541	3.436279	-0.215266
C	2.94013	0.194917	0.002839
C	2.449864	-0.412407	1.345308
H	2.818846	0.17777	2.188858
H	1.359958	-0.421368	1.391686

H	2.799693	-1.436699	1.458133
C	2.407165	-0.556131	-1.248388
H	2.739126	-0.057842	-2.163395
H	2.765255	-1.583654	-1.263411
H	1.316505	-0.58157	-1.254161
C	2.50395	1.663282	-0.069508
C	3.538672	3.917437	-0.256418
H	3.104717	4.337977	0.65448
H	4.534475	4.319881	-0.394155
H	2.923276	4.189928	-1.11654
C	0	1.533904	0.000011
H	-0.000001	0.452585	0.000002
C	1.220919	2.214995	-0.049639
H	1.156296	3.297585	-0.07045

2b

E (RB3LYP) = -1386.857547 a.u.

Sum of electronic and thermal Energies= -1386.250611 a.u.

Imaginary Frequency = 0

Table S3. Cartesian coordinates of the optimized **2b**.

	Coordinates (Angstroms)		
Atom	X	Y	Z

C	4.789846	1.298894	-0.072853
C	4.451362	-0.041172	-0.009714
C	7.124263	0.81666	-0.063018
C	6.122905	1.761442	-0.099119
C	7.627154	-2.881807	0.096161
C	6.284639	-3.333637	0.124224
C	7.892986	-1.531113	0.034932
C	5.471224	-1.031601	0.027173
C	6.839779	-0.576295	-0.001204
C	5.237192	-2.437193	0.091056
N	3.615191	2.084655	-0.101136
C	2.929019	-0.162516	0.010734
C	2.437767	-0.809493	1.331719
H	2.797733	-0.245401	2.196623
H	1.34751	-0.843293	1.376574
H	2.808566	-1.832679	1.416098
C	2.411509	-0.9215	-1.239199
H	2.743836	-0.428653	-2.156985
H	2.79223	-1.944532	-1.247403
H	1.32099	-0.971085	-1.253474
C	2.503744	1.314039	-0.046215
C	1.224542	1.879063	-0.034018
H	1.170765	2.963316	-0.048685
C	3.602645	3.543591	-0.173531
H	3.182193	3.967429	0.742964

H	4.618345	3.910238	-0.29548
H	3.01029	3.871391	-1.031537
C	-4.789838	1.298902	0.072879
C	-4.451363	-0.041162	0.009658
C	-7.124255	0.816655	0.063607
C	-6.122893	1.761443	0.099469
C	-7.627165	-2.881814	-0.095435
C	-6.284654	-3.333638	-0.123818
C	-7.892989	-1.531121	-0.03415
C	-5.471229	-1.031596	-0.026977
C	-6.839779	-0.576298	0.001728
C	-5.237204	-2.437188	-0.090908
N	-3.61518	2.084666	0.100939
C	-2.929025	-0.162497	-0.011216
C	-2.43814	-0.809315	-1.332416
H	-2.798328	-0.245107	-2.197151
H	-1.347898	-0.843134	-1.377571
H	-2.808979	-1.832484	-1.416827
C	-2.411153	-0.921625	1.238478
H	-2.743197	-0.428875	2.156418
H	-2.791887	-1.944653	1.24668
H	-1.320626	-0.971222	1.252414
C	-2.503742	1.314054	0.045805
C	-3.602624	3.543599	0.17342
H	-3.182386	3.967495	-0.743147

H	-4.618296	3.910234	0.295627
H	-3.010071	3.871347	1.031307
C	-0.000001	1.204482	-0.000246
H	-0.000008	0.122533	-0.000235
C	-1.224538	1.879072	0.033561
H	-1.170752	2.963324	0.048294
H	-6.366361	2.816072	0.143152
H	-8.162635	1.134134	0.081268
H	-8.918752	-1.172839	-0.012154
H	-8.440561	-3.600269	-0.122147
H	-6.077392	-4.398532	-0.172135
H	-4.223698	-2.817248	-0.114365
H	4.223683	-2.817258	0.114276
H	6.077371	-4.398532	0.172499
H	8.440547	-3.600258	0.123074
H	8.918752	-1.172825	0.013182
H	8.162646	1.134143	-0.080425
H	6.366378	2.816073	-0.142729

References

1. R. Gui, H. Jin, X. Bu, Y. Fu, Z. Wang and Q. Liu, *Coord. Chem. Rev.* **2019**, *383*, 82–103.
2. M. H. Lee, J. S. Kim and J. L. Sessler, *Chem. Soc. Rev.* **2015**, *44*, 4185–4191.
3. J. Fan, M. Hu, P. Zhan and X. Peng, *Chem. Soc. Rev.* **2013**, *42*, 29–43.
4. T. Doussineau, A. Schulz, A. Lapresta-Fernandez, A. Moro, S. Korsten, S. Trupp and G. J. Mohr, *Chem. - Eur. J.* **2010**, *16*, 10290–10299.
5. L. Wang, X. Ran, H. Tang and D. Cao, *Dyes Pigm.* **2021**, *194*, 109634.
6. S. Zhang, Z. Li, B. Zhang, F. Dong, B. Han, J. Lv, Y. Sun, H. Lu, Y. Yang and H. Ma, *New J. Chem.* **2021**, *45*, 20441–20446.
7. Z. Quan, H. He, H. Zhou, Y. Liang, L. Wang, S. Tian, H. Zhu and S. Wang, *Sens. Actuators B: Chem.* **2021**, *333*, 129535.
8. S. Sawminathan, S. Munusamy, D. Jothi and S. K. Iyer, *ChemistrySelect* **2021**, *6*, 858–864.
9. H. Nawaz, J. Zhang, W. Tian, K. Jin, R. Jia, T. Yang and J. Zhang, *J. Hazard. Mater.* **2020**, *387*, 121719.
10. M. Saravanakumar, B. Umamahesh, R. Selvakumar, J. Dhanapal, S. K. A. Kumar and K. I. Sathiyanarayanan, *Dyes Pigm*. **2020**, *178*, 108347.
11. S. Jeon, T.-I. Kim, H. Jin, U. Lee, J. Bae, J. Bouffard and Y. Kim, *J. Am. Chem. Soc.* **2020**, *142*, 9231–9239.
12. R. Jia, W. Tian, H. Bai, J. Zhang, S. Wang and J. Zhang, *Nat. Commun.* **2019**, *10*, 795.
13. D. Kim, S. W. Cho, Y. W. Jun and K. H. Ahn, *Bull. Korean Chem. Soc.* **2017**, *38*, 995–996.
14. S. Mallick, F. Chandra and A. L. Koner, *Analyst* **2016**, *141*, 827–831.
15. D. Meng, S. Yang, D. Sun, Y. Zeng, J. Sun, Y. Li, S. Yan, Y. Huang, C. W. Bielawski and J. Geng, *Chem. Sci.* **2014**, *5*, 3130–3134.
16. J.-T. Hou, K. Li, B.-Y. Liu, Y.-X. Liao and X.-Q. Yu, *Tetrahedron* **2013**, *69*, 2118–2123.
17. S.-i. Sasaki, Y. Kotegawa and H. Tamiaki, *Tetrahedron Lett.* **2006**, *47*, 4849–4852.
18. T. Han, W. Wei, J. Yuan, Y. Duan, Y. Li, L. Hu and Y. Dong, *Talanta* **2016**, *150*, 104–112.
19. M. Kataria, J. Hwang, H. D. Chau, N. Y. Kwon, D. W. Lee, T. Kim, K. Lee, Y. Kim, S. Park and D. H. Choi, *Sens. Actuators B: Chem.* **2021**, *343*, 130110.

20. R. Roy, N. R. Sajeev, V. Sharma and A. L. Koner, *ACS Appl. Mater. Interfaces* **2019**, *11*, 47207–47217.
21. S. Pramanik, H. Deol, V. Bhalla and M. Kumar, *ACS Appl. Mater. Interfaces* **2018**, *10*, 12112–12123.
22. S. Lohar, D. A. Safin, A. Sengupta, A. Chattopadhyay, J. S. Matalobos, M. G. Babashkina, K. Robeyns, M. P. Mitoraj, P. Kubisiak, Y. Garcia and D. Das, *Chem. Commun.* **2015**, *51*, 8536–8539.
23. A. Ghosh, A. Sengupta, A. Chattopadhyay and D. Das, *Chem. Commun.* **2015**, *51*, 11455–11458.
24. S. Zheng, Y. Fang, Y. Chen, Q. Kong, F. Wang and X. Chen, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.* **2022**, *267*, 120616.
25. K. Ilina and M. Henary, *Chem. - Eur. J.* **2021**, *27*, 4230–4248.
26. W. Sun, S. Guo, C. Hu, J. Fan and X. Peng, *Chem. Rev.* **2016**, *116*, 7768–7817.
27. A. Mishra, R. K. Behera, P. K. Behera, B. K. Mishra and G. B. Behera, *Chem. Rev.* **2000**, *100*, 1973–2012.
28. A. Mukherjee, P. C. Saha, R. S. Das, T. Bera and S. Guha, *ACS Sens.* **2021**, *6*, 2141–2146.
29. H. Mu, K. Miki, H. Harada, K. Tanaka, K. Nogita and K. Ohe, *ACS Sens.* **2021**, *6*, 123–129.
30. M. Oe, K. Miki, K. Ohe, *Org. Biomol. Chem.* **2020**, *18*, 8620–8624.
31. M. Oe, K. Miki, H. Mu, H. Harada, A. Morinibu and K. Ohe, *Tetrahedron Lett.* **2018**, *59*, 3317–3321.
32. H. Mu, K. Miki, Y. Takahashi, N. Teshima, M. Oe, K. Kojima and K. Ohe, *Chem. Lett.* **2018**, *47*, 1147–1150.
33. K. Miki, K. Kojima, K. Oride, H. Harada, A. Morinibu and K. Ohe, *Chem. Commun.* **2017**, *53*, 7792–7795.
34. L. He, W. Lin, Q. Xu, M. Ren, H. Wei and J.-Y. Wang, *Chem. Sci.* **2015**, *6*, 4530–4536.
35. C. Pati, R. Raza, K. Ghosh, *Spectrochim Acta A Mol. Biomol. Spectrosc.* **2020**, *229*, 117910.
36. D. Pfeifer, I. Klimant, S. M. Borisov, *Chem. - Eur. J.* **2018**, *24*, 10711-10720.
37. G. Xia, Y. Liu, B. Ye, J. Sun, H. Wang, *Chem. Commun.* **2015**, *51*, 13802-13805.
38. X. Zhang, S. Lee, Y. Liu, M. Lee, J. Yin, J. L. Sessler, J. Yoon, *Sci. Rep.* **2014**, *4*, 4593.

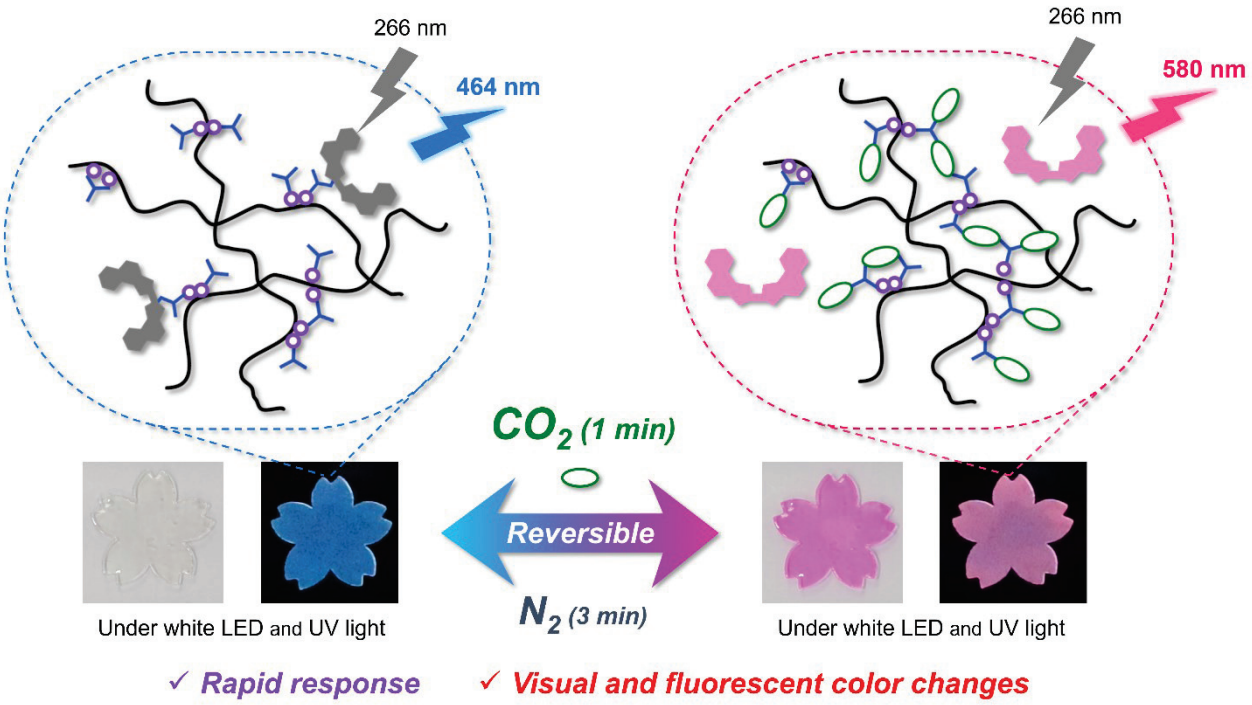
39. M. Ishida, P. Kim, J. Choi, J. Yoon, D. Kim, J. L. Sessler, *Chem. Commun.* **2013**, *49*, 6950-6952.
40. E. V. Vetrova, N. I. Makarova, N. I. Omelichkin, L. G. Minyaeva, V. V. Chernyavina, R. N. Borisenko and A. V. Metelitsa, *J. Photochem. Photobiol. A: Chem.* **2019**, *370*, 127–134.
41. V. Gutmann, *The Donor-Acceptor Approach to Molecular Interactions*, Springer, New York, **1978**.
42. E. A. Ribeiro, T. Sidooski, L. G. Nandi and V. G. Machado, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.* **2011**, *81*, 745–753.
43. There is a report where an anionic fluoride ion can be detected via addition to non-fluorinated cyanine dye, see. Y. Wang, S.-Y. Gwon, Y.-A. Son, S.-H. Kim, *Mol. Cryst. Liq. Cryst.* **2012**, *566*, 61-62.
44. Introduction CN groups also effective for detection of amines via addition to the fluorescent dyes, see. Z. Li, R. Toivola, J. Yang, P.-N. Lai, T. Howie, S.-H. Jang, B. D. Flinn, A. K.-Y. Jen, *Adv. Mater.* **2016**, *28*, 6592–6597.
45. K. Funabiki, Y. Saito, T. Kikuchi, K. Yagi, Y. Kubota, T. Inuzuka, Y. Miwa, M. Yoshida, O. Sakurada and S. Kutsumizu, *J. Org. Chem.* **2019**, *84*, 4372–4380.
46. Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2019**.

Chapter 4.

Rapid and dual optical CO_2-responsive polydimethylsiloxane elastomer with fluorinated cyanine dye

Abstract

A polydimethylsiloxane elastomer doped with a fluorinated cyanine dye and containing excess amines exhibits a rapid and pronounced optical response (within 1 min) comprising a visual color change from colorless to pink and a fluorescent shift from blue to pink in a CO_2 gas stream.



Introduction

Carbon dioxide (CO_2), which is a greenhouse gas, is the major cause of climate change and related environmental problems. Therefore, technologies concerning CO_2, such as the separation,[1,2] capture,[3–5] utilization,[6–8] and detection of CO_2 gas, are very important. Consequently, CO_2-responsive polymers that change their properties in the presence of CO_2 gas are promising materials.[9–11] In particular, optically CO_2-responsive polymeric materials that can detect, monitor, and quantify CO_2 gas via a visual color change make it possible to sense CO_2 gas without any special equipment.[12,13]

In such materials, CO_2-responsive dyes are usually introduced to polymers via blending,[14,15] bonding,[10,16] or encapsulation.[17] Polydimethylsiloxane (PDMS) is frequently used as a polymer matrix because it is optically transparent in the wavelength range 240–1100 nm,[18] and is highly permeable with regard to gases.[19,20] For example, PDMS elastomer films have been doped with classical pH indicators as CO_2-responsive dyes.[17,21–24] Such dyes change color or fluoresce in the presence of CO_2, but their response basically requires water. Therefore, these optically CO_2-responsive PDMS films cannot be used continuously in dry gaseous conditions. Polymer films that exhibit dual visual and fluorescent responses to the presence of CO_2 gas have been reported by Pfeifer et al.[25] and Ali et al.[26] These polymer films sensitively indicate the presence of CO_2 via fluorescent and visible color changes. However, the optical responses of these materials take more than 10 min, and the materials also require the presence of water for the color change.

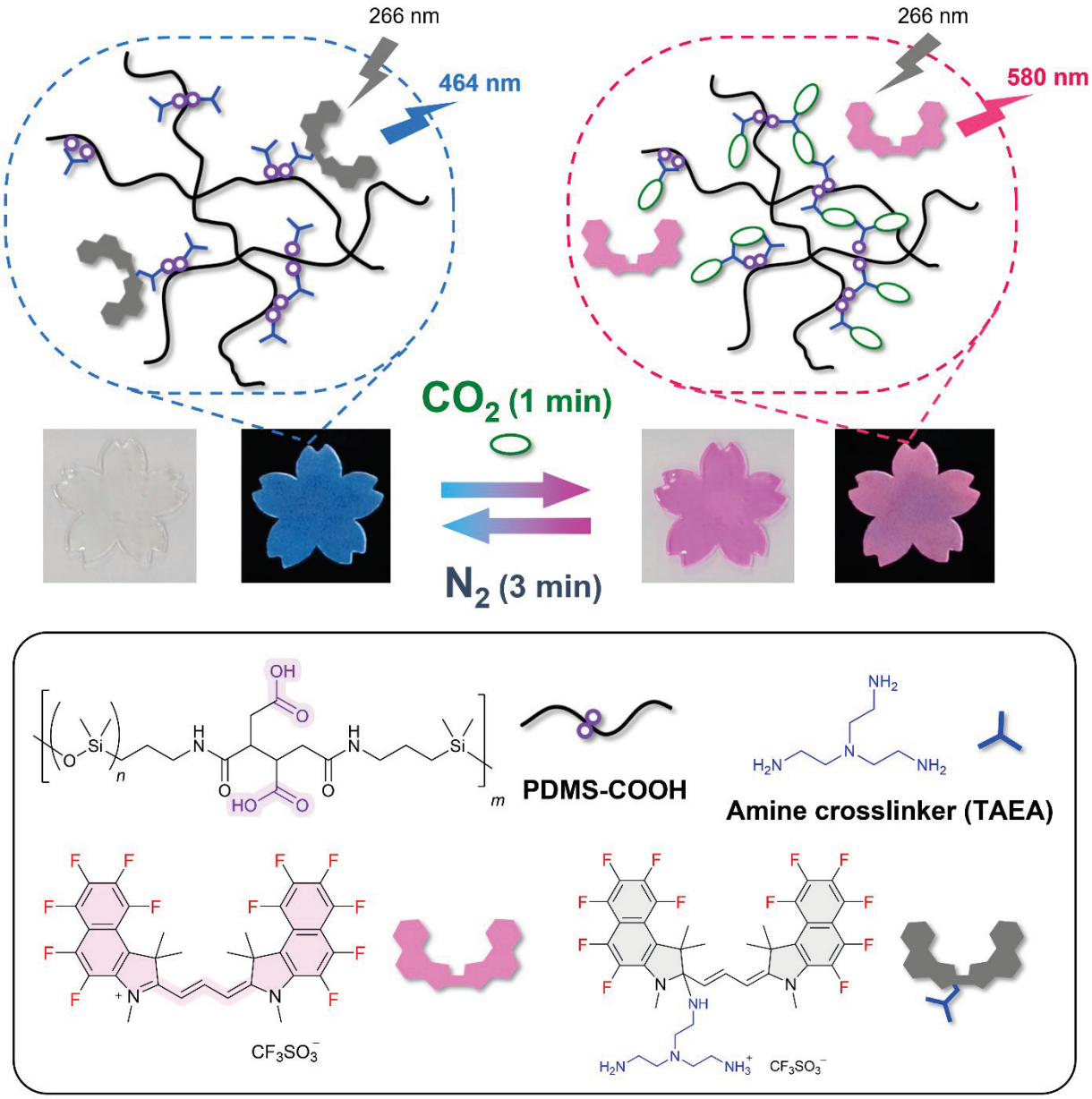


Fig. 1. Chemical structures of the carboxy PDMS and fluorinated cyanine dye **2a**, and schematic illustration of the optical change of the PDMS(**2a**) in the presence of CO_2. The photographs of PDMS(**2a**) with and without CO_2 are shown under white LED and UV light (365 nm). (PDMS = polydimethylsiloxane; LED = light-emitting diode).

Herein, we report the first study of a CO_2-responsive PDMS elastomer that contains fluorinated cyanine dye **2a**. Both the visible and fluorescent colors of the dye rapidly (within 1 min) and obviously change when the elastomer comes into contact with CO_2 gas, even under dry gaseous conditions (Fig. 1). Cyanine dyes have attracted considerable attention among researchers owing to their advantageous optical properties, such as high absorption coefficients and high fluorescence quantum yields. The absorption and emission spectra of these dyes can be tuned via extension of the chromophore. For example, the insertion of a vinylene moiety results in a red shift of approximately 100 nm.[27] Recently, we reported that the visible and fluorescent colors of a solution of cyanine dye **2a** (Fig. 1), which contains fluorine atoms in its aromatic rings, sensitively and reversibly responds to the presence of hexylamine in the solution.[28] In a previous study, we examined the amine detection ability of cyanine dye **2a**. More recently, we found that when CO_2 is bubbled through a methanol solution of the quenched amine adduct of fluorinated cyanine dye **2a**, it recovers its visible and fluorescent colors (Fig. S1 and Table S1). This demonstrated that a solution of the amine adduct of fluorinated cyanine dye **2a** is capable of CO_2 detection. However, from the perspective of practical handling, dry, solid, and moldable polymeric materials are more desirable for CO_2 detection. Therefore, in the present study we developed an optically CO_2-responsive PDMS elastomer that contains dye **2a**. To impart CO_2 responsiveness, mechanical stability, and remoldability to the elastomer, we ionically crosslinked a carboxy PDMS (PDMS-COOH, Fig. 1) with a tri-functional amine (tris(2-aminoethyl)amine (TAEA), Fig. 1). The amine is neutralized by the carboxy groups and enhances the mechanical strength of the elastomer via ionic crosslinking of the polymer chains,[29,30] while the free amine interacts with the dye. It is well known that non-covalent crosslinking techniques impart certain advantages, such as remoldability, toughness, and self-healing capability, to elastomers.[31] Our PDMS elastomer is mechanically elastic at room temperature (Fig. S2), whereas it has excellent remoldability at 100 °C owing to the non-

covalent crosslinking with ionic bonds (Fig. S3). A sheet of the elastomer also exhibits excellent responsiveness with regard to the presence of CO_2 gas: both the visible (colorless in N_2 ↔ red in CO_2) and fluorescent (blue in N_2 ↔ pink in CO_2) colors are rapidly and reversibly changed (Fig. 1). Moreover, in contrast to conventional optically CO_2-responsive polymeric materials, our elastomer functions in totally dry gaseous conditions (Fig. S4).

Results and Discussion

We dissolved fluorinated cyanine dye **2a** (0.534 mg), PDMS-COOH (0.353 g, carrying 1.30×10^{-4} mol carboxy groups, Fig. S5, Fig. S6, and Fig. S7), and an amine crosslinker (TAEA, 15.8 mg) in a mixture of dichloromethane (4 mL) and methanol (0.7 mL), and dried the resulting solution at 40 °C on a Teflon Petri dish. The resultant polymer sheet was dried at 40 °C for 2 days in vacuum. The number-average molecular weight and polydispersity index of the PDMS-COOH were 34,700 and 2.75, respectively. The resulting elastomer sheet, which we shall hereafter refer to as PDMS(**2a**), was almost colorless and transparent. The sheet was approximately 0.36 mm thick. The mixing ratio of the groups in PDMS(**2a**) was 200 equivalents of carboxy groups to 500 equivalents of NH_2 groups compared with the dye.

The UV-vis and fluorescence spectra of the PDMS(**2a**) sheet, obtained in N_2 and CO_2 atmospheres, are shown in Fig. 2a and Fig. 2b, respectively. As a control experiment, we also obtained the spectra of the PDMS elastomer without the dye, as shown in Fig. 2a and Fig. 2b. The PDMS elastomer sheet was optically transparent, although it did emit a very faint blue fluorescence. The characteristics of the spectra are provided in Table 1. Upon the addition of CO_2, the PDMS(**2a**) exhibited a significant increase in absorption at 580 nm and a slight decrease in absorption at 350 nm. The fluorescence spectra exhibited ratiometric fluorescent characteristics, with a large increase in the intensity of the peak at 599 nm and a decrease in intensity near 460 nm. These changes in the UV-vis and fluorescence

spectra corresponded to the visible (colorless in N_2 ↔ red in CO_2) and fluorescent (blue in N_2 ↔ pink in CO_2) colors as the gases were switched. PDMS(**2a**) switched color rapidly and reversibly. The absorbance at the maximum absorption wavelength (580 nm) was monitored during CO_2 and N_2 switching, and the results are shown in Fig. 2c. The changes in the optical signals produced by the PDMS(**2a**) sheet were rapid and repeatable, and persisted for at least 20 times as the gas was switched. Notably, the color of the PDMS(**2a**) sheet changed within 1 min in a CO_2 gas stream. This color switching of the PDMS(**2a**) sheet was much faster than in other CO_2-responsive polymeric materials with dual optical switching,[25,26] even though the PDMS(**2a**) sheet was relatively thick (approximately 0.36 mm). We also confirmed that CO_2 gas did not affect the mechanical strength of the PDMS(**2a**) sheet (Fig. S8). In contrast to polyimide membranes plasticized with CO_2 gas,[32] our PDMS(**2a**) sheet is mechanically stable, even in CO_2 gas. Furthermore, our PDMS(**2a**) sheet is capable of visually detecting dilute CO_2 gas (5%) within 1 min.

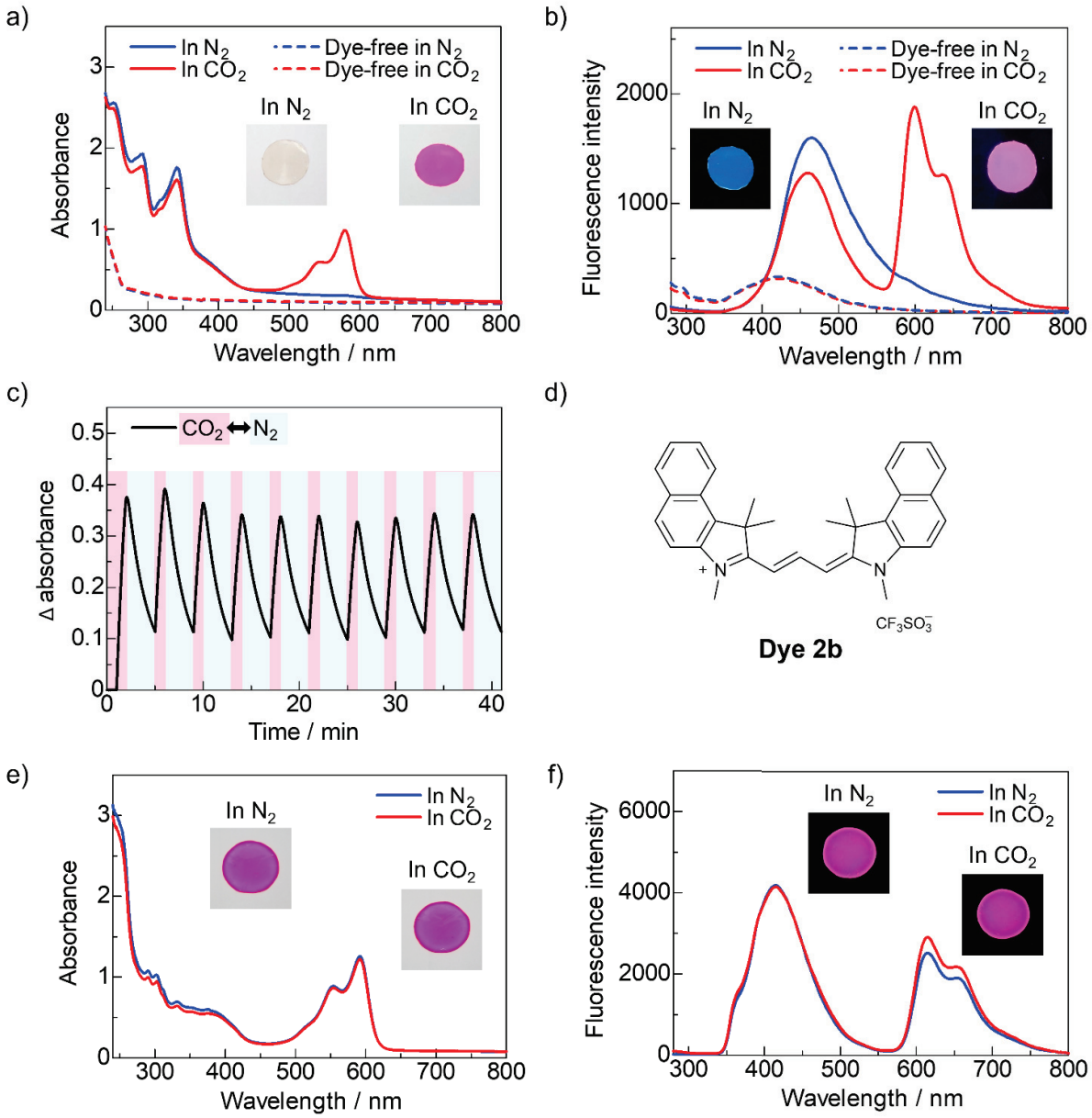


Fig. 2. a) Ultraviolet-visible (UV-vis) and b) fluorescence spectra of the PDMS(**2a**) sheet exposed to N_2 or CO_2 gas supplied at a flow rate of 1.5 L min^{-1} for 3 min. The inset photographs were obtained in white LED light and UV light (λ = 365 nm). The UV-vis and fluorescence spectra of a dye-free PDMS elastomer sheet, which functioned as a control, are also included. The excitation wavelength was 268 nm, as referred to by the excitation spectra (Fig. S9). c) Time-dependent response of the PDMS(**2a**) sheet monitored according to the absorption of 580 nm radiation by dye **2a** alternately exposed to CO_2 gas for 1 min and N_2 gas for 3 min at a flow rate of 1.5 L min^{-1}. d) Chemical structure of dye **2b**. e) UV-vis and f) fluorescence spectra of the PDMS(**2b**) sheet exposed to N_2 or CO_2 gas at a flow rate of 1.5 L min^{-1} for 3 min. (PDMS = polydimethylsiloxane; LED = light-emitting diode).

Table 1. Optical properties of elastomer sheets in N_2 and CO_2.

	λ_{max} (nm)	Δabs.	λ_{ex} (nm)	F_{max} (nm)[a]
PDMS(**2a**) in N_2			266	464
PDMS(**2a**) in CO_2	580	0.797	266	464, 598, 635
Dye-free PDMS elastomer in N_2			266	433
Dye-free PDMS elastomer in CO_2			266	433
PDMS(**2b**) in N_2	592	0.00	259	415, 614, 653
PDMS(**2b**) in CO_2	592		259	416, 615, 653

[a] Maximum absorption wavelength. [b] Absorption difference between N_2 and CO_2 gases at λ_{max}. [c] Maximum excitation wavelength. [d] Maximum fluorescence wavelength measured using excitation wavelengh (λ_{ex}). (PDMS = polydimethylsiloxane).

The fluorination of the dye is crucial for optical CO_2-responsiveness. In fact, the PDMS elastomer sheet containing dye **2b** without fluorine atoms (Fig. 2d) was red even in N_2 gas, and its UV-vis and fluorescence spectra remained almost unchanged in the presence of CO_2 gas (Fig. 2e and Fig. 2f; Table 1, entries 5 and 6). This result was as expected because the energy of the lowest unoccupied molecular orbital (LUMO) of fluorinated dye **2a** is greatly reduced by the electron-withdrawing property of fluorine atoms, and can readily form a CO_2-sensitive amine adduct. In contrast, dye **2b**, which has no fluorine atoms, does not readily form an amine adduct. Both the fluorinated cyanine dye and the high permeability of the PDMS with regard to CO_2 are important for the design of our material. As a control, we prepared an approximately 0.32 mm thick poly(methyl methacrylate) (PMMA) sheet doped with dye **2a** (Fig. 3). The concentrations of the fluorinated dye **2a** and the TAEA were 1.55×10^{-6} mol g^{-1} and 2.58×10^{-4} mol g^{-1}, respectively. The PMMA sheet exhibited little color change over the course of a few minutes. Even after 1 day of CO_2 exposure, only a slight color change was visible (Fig. 3). The slow response of the PMMA sheet to CO_2 gas was owing to the much lower CO_2 permeability of PMMA (6×10^{-11} m^2 s^{-1} at 6 MPa)[33] compared with that of PDMS (2×10^{-9} m^2 s^{-1} at 0.1 MPa).[19]

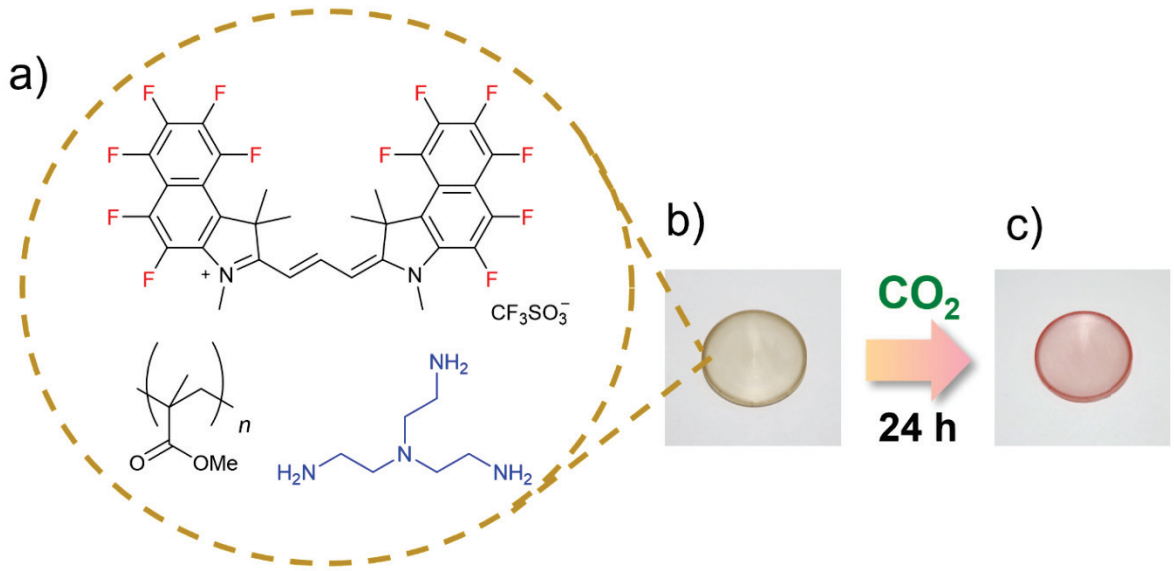


Fig. 3. a) Contents of the PMMA sheet doped with fluorinated dye **2a**. Photographs of the polymer sheet under white LED light b) in N_2 and c) in CO_2 after exposure for 24 h. (PMMA = poly(methyl methacrylate); LED = light-emitting diode).

On the basis of the behavior of dye **2a** in the polymers, as described above, we speculate that the consumption of free amines via the formation of carbamates with CO_2 molecules is the trigger for the optical switching of PDMS(**2a**) in the presence of CO_2 gas. The expected mechanism of the reaction with CO_2 is schematically illustrated in Scheme 1. In the first step, free amines react with CO_2 molecules to form carbamates. The formation of carbamates was confirmed by the presence of vibration bands attributable to them in the infrared spectrum (Fig. S10),[34–36] and the weight increase due to the reaction with CO_2 (Fig. S4). In the second step, the ammonium salts protonate the amine adduct of dye **2a**, thereby recovering the conjugation of the dye and causing a color change.

Conclusion

We designed an optically CO_2-responsive PDMS elastomer that rapidly and reversibly undergoes both visible and fluorescent color changes in the presence of CO_2 gas. In contrast to conventional optically CO_2-responsive polymeric materials, our elastomer functions in totally dry gaseous conditions. The visible color (colorless in N_2 ↔ red in CO_2) and fluorescence (blue in N_2 ↔ pink in CO_2) of the elastomer sheet change after only 1 min of exposure to CO_2. The sheet also exhibits excellent repeatability in terms of color switching following exposure to CO_2 or N_2 gas, which persists for at least 20 times.

Experimental Section

Materials

All reagents were purchased from appropriate commercial suppliers (Sigma-Aldrich, Tokyo Kasei Kogyo, Wako Pure Chemical Industries, and Kanto Chemical) and used as received unless otherwise noted. The reactive amino-functional polydimethylsiloxane (FM-3321) was provided by JNC Corporation. The PMMA was obtained from Sigma-Aldrich. Dyes **2a** and **2b** were synthesized according to the methods described in the literature.[37]

Measurements

The UV-visible absorption spectra were obtained in solution using a Hitachi U-4100 system and in sheet form using a PerkinElmer LAMBDA 950 system. The fluorescence spectra were obtained using a JASCO FP-8600 spectrofluorometer (JASCO, Tokyo, Japan). The absolute fluorescence quantum yields were determined by using a Hamamatsu Quantaurus-QY C11347-01 system. The fluorescence lifetimes were calculated using a C11367-01 Hamamatsu Quantaurus-Tau compact fluorescence lifetime spectrometer. The thermogravimetric measurements were performed using a TG-DSC NEXTA STA 300 system manufactured by Hitachi High-Tech Co. (Tokyo, Japan). The Fourier-transform infrared (FT-IR) spectra were obtained using a JASCO FT/IR6600 spectrometer. The proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained at 392 or 400 MHz in deuterochloroform ($CDCl_3$) using the residual solvent peak as an internal standard on a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. The carbon 13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 99 or 101 MHz in $CDCl_3$ using the residual solvent peak as an internal standard on a JEOL ECS-400 or ECX-400P FT-NMR spectrometer. The molecular weights and the polydispersity indices of the polymers were determined by gel permeation chromatography (GPC) using an EXTREMA HPLC system (JASCO Co.) equipped with a polystyrene gel column (Shodex GPC LF-804) and calibrated with polystyrene standards. The dynamic mechanical analysis (DMA) measurements were obtained

on a DMA MCR702 system manufactured by Anton Paar Co. A tensile force of 0.05 N was applied to a rectangular sample sheet (5.20 mm × 7.09 mm × 0.418 mm) at 1 Hz and 25 °C. A dumbbell-shaped sample sheet with dimensions of 30 mm × 4.0 mm × 0.3 mm was stretched using an AND force tester MCT-2150 at 27 °C under dry nitrogen.

Synthesis of PDMS-COOH

FM-3321 (46.7 g; 1.78×10^{-2} mol primary amino groups) and 50 mL of dry tetrahydrofuran (THF) were added to a 500 mL three-necked flask under an argon atmosphere and stirred at 25 °C. Next, as much as possible of 1,2,3,4-butane tetracarboxylic dianhydride (1.76 g, 8.89×10^{-3} mol, 1 equiv.) was dissolved in 300 mL of THF and injected into the flask. The reaction mixture was stirred overnight at room temperature to complete the reaction. The polymer was then reprecipitated and purified using 2 L of MeOH. Next, the polymer was transferred to a Teflon petri dish and vacuum-dried at 40 °C for 4 days to produce PDMS-COOH (34.5 g, 71% yield). The number-average molecular weight and polydispersity index were M_n = 34700 and M_w/M_n = 2.75, respectively (Fig. S7). The polymer was identified by nuclear magnetic resonance. ^{1}H NMR (392 MHz, $CDCl_3$) δ = 3.72–3.45 (m, 2H, CH_2NH), 3.29–2.44 (m, 8H), 1.80–1.41 (m, 4H, CH_2CH_2NH), 0.59–0.44 (m, 4H, CH_2Si), 0.06 (s, $(CH_3)_2$Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0–171.1 (multiple peaks), 175.2, 171.1, 42.8, 42.1, 40.5-32.3 (multiple peaks), 23.5, 21.8, 15.6, 1.2 (Fig. S5 and Fig. S6).

Preparation of PDMS(2) sheet

PDMS-COOH (0.353 g, carboxy groups 1.30×10^{-4} mol) and dye **2** (6.49×10^{-7} mol) were added to a 10 mL beaker using 4 mL of CH_2Cl_2. The polymer and dye were dissolved at room temperature, and a mixture of amine crosslinker (TAEA) (15.8 mg, 1.08×10^{-4} mol) and 0.7 mL of MeOH was added. The resulting mixture was cast on a Teflon petri dish (Φ = 30 mm). The solution was allowed to stand overnight at 40 °C, then vacuum depressurized for 2 days.

Preparation of dye 2a-doped PMMA sheet

A solution of PMMA (0.418 g) and dye **2a** (6.49×10^{-7} mol) in CH_2Cl_2 (4 mL) was added to a Teflon petri dish (Φ = 30 mm) at room temperature. Next, a solution of amine (TAEA) (15.8 mg, 1.08×10^{-4} mol) in MeOH (0.7 mL) was added and the mixture was stirred well. The solution was allowed to stand overnight at 25 °C, then vacuum depressurized at 40 °C for 2 days.

Supporting Figures and tables

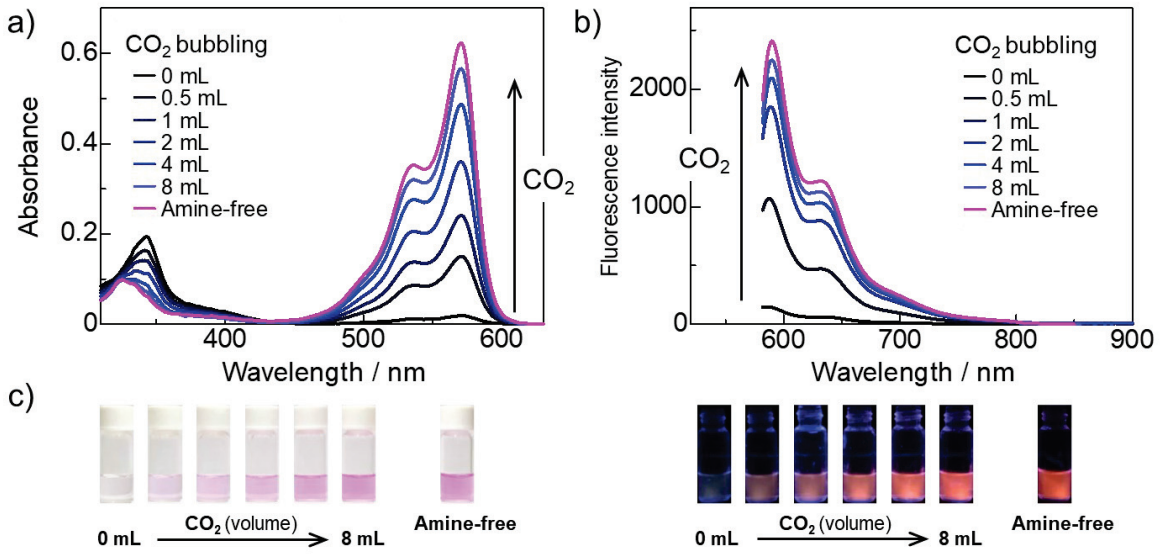


Fig. S1. a) UV-vis and b) fluorescence spectra of a solution (3.3 mL) prepared from fluorinated dye **2a** (5×10^{-6} M) and 5000 equiv. of *n*-hexylamine in methanol obtained after a specific volume of CO_2 (0–8 mL) was allowed to bubble through the solution. A methanol solution of fluorinated dye **2a** (5×10^{-6} M) was used for the spectra under amine-free conditions. c) The photographs were obtained under white LED and UV light (λ = 365 nm). (UV = ultraviolet; LED = light-emitting diode).

Table S1. Optical properties of amine adduct responding to CO_2.

CO_2 (mL)	λ_{max} (nm) (ε ($M^{-1}cm^{-1}$))	λ_{ex} (nm)	F_{max} (nm)[b]	Φ_f[c]	τ_s (ns)[d]
0	572 (4000)	571	587		
0.5	571 (30000)		587		
1	571 (48000)		589		
2	571 (72000)		589		
4	571 (97000)		590		
8	571 (110000)		590		
Amine-free	571 (130000)		590	0.07	0.38

[a] Measured immediately after CO_2 was allowed to bubble through a solution comprising dye **2a** (5×10^{-6} M) in MeOH that had been stored for 1 h in the dark at 25 °C after adding *n*-hexylamine (2.5×10^{-2} M). [b] The fluorescence spectrum was obtained by using excitation wavelength (λ_{ex}). [c] Measured using an integrating sphere method. [d] Measured using a single photon-counting method.

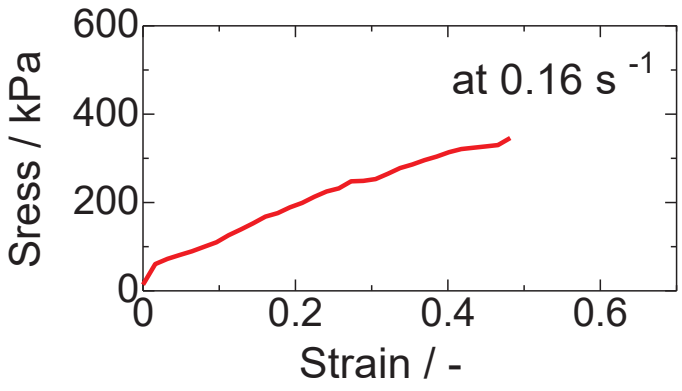


Fig. S2. Stress–strain curve of the PDMS(**2a**) sheet. (PDMS = polydimethylsiloxane).

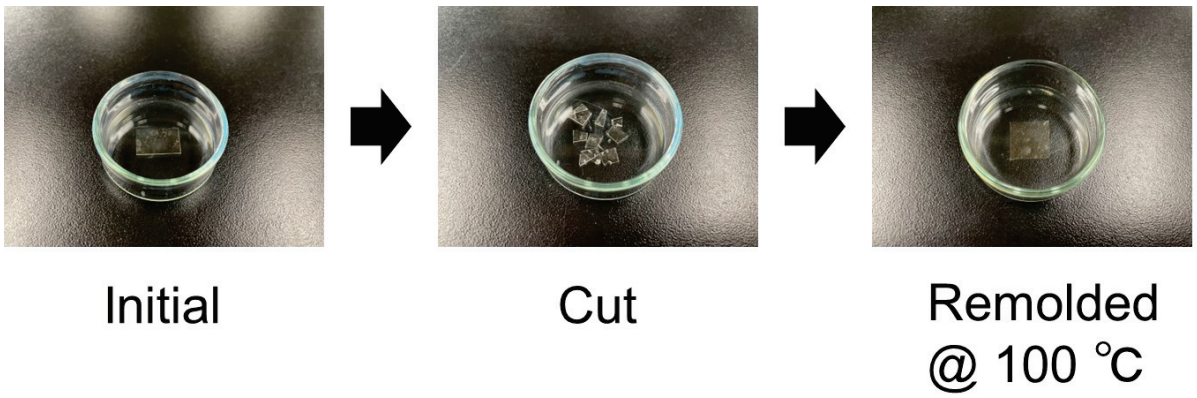


Fig. S3. Photographs of the remoldable PDMS(**2a**) sheet. (PDMS = polydimethylsiloxane).

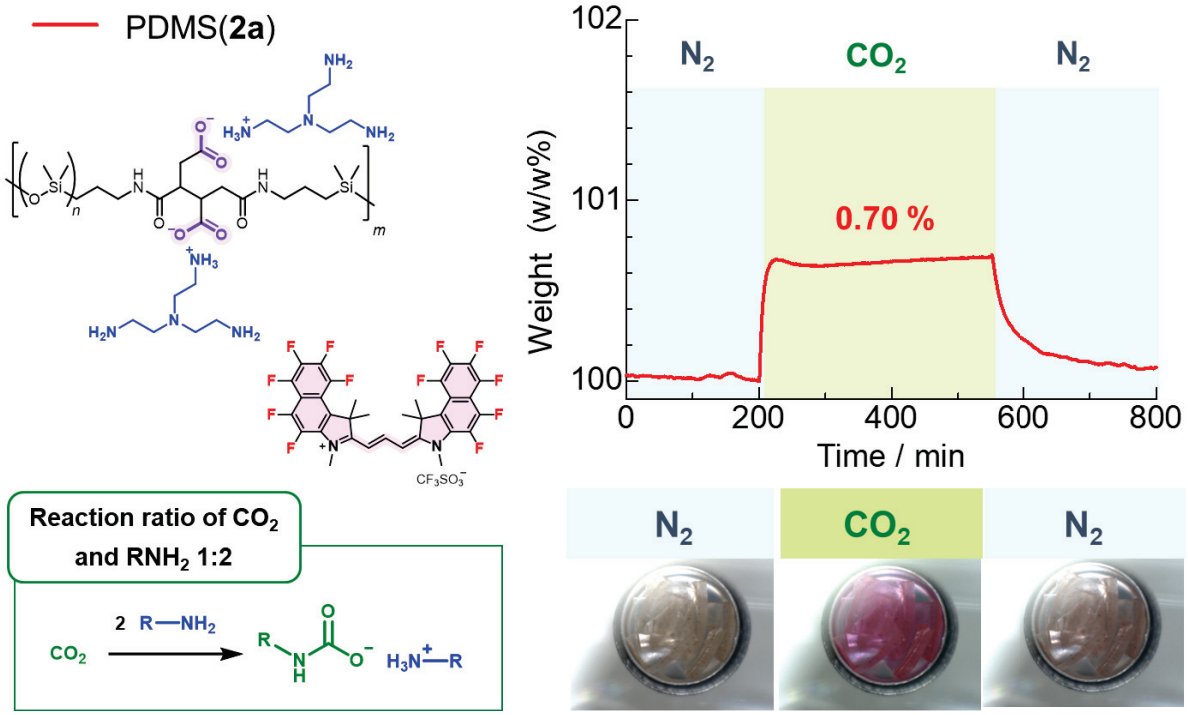


Fig. S4. Gravimetric measurement of PDMS(**2a**) exposed to N_2 or CO_2 gas at a flow rate of 100 mL min^{-1} at 27 °C, and real time photographs obtained under white LED light during the measurements. The elastomer was dried in N_2 at 40 °C, returned to 27 °C, and then CO_2 was pumped through it, switching to N_2 as soon as the weight gain was complete. (PDMS = polydimethylsiloxane; LED = light-emitting diode).

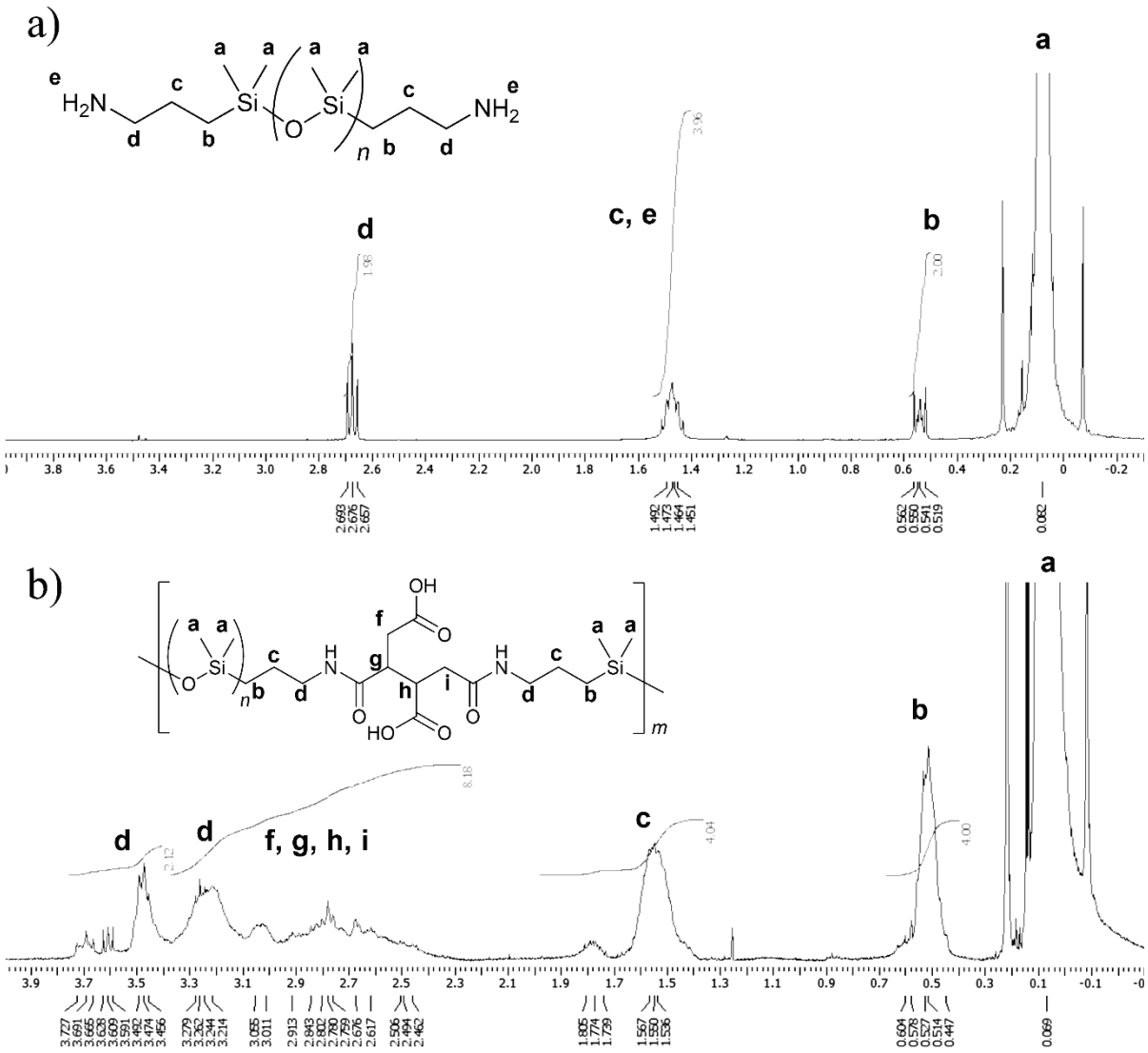


Fig. S5. ^{1}H NMR spectra produced by a) FM-3321 and b) PDMS-COOH. (^{1}H NMR = proton nuclear magnetic resonance; FM-3321 = a reactive amino-functional polydimethylsiloxane; PDMS = polydimethylsiloxane).

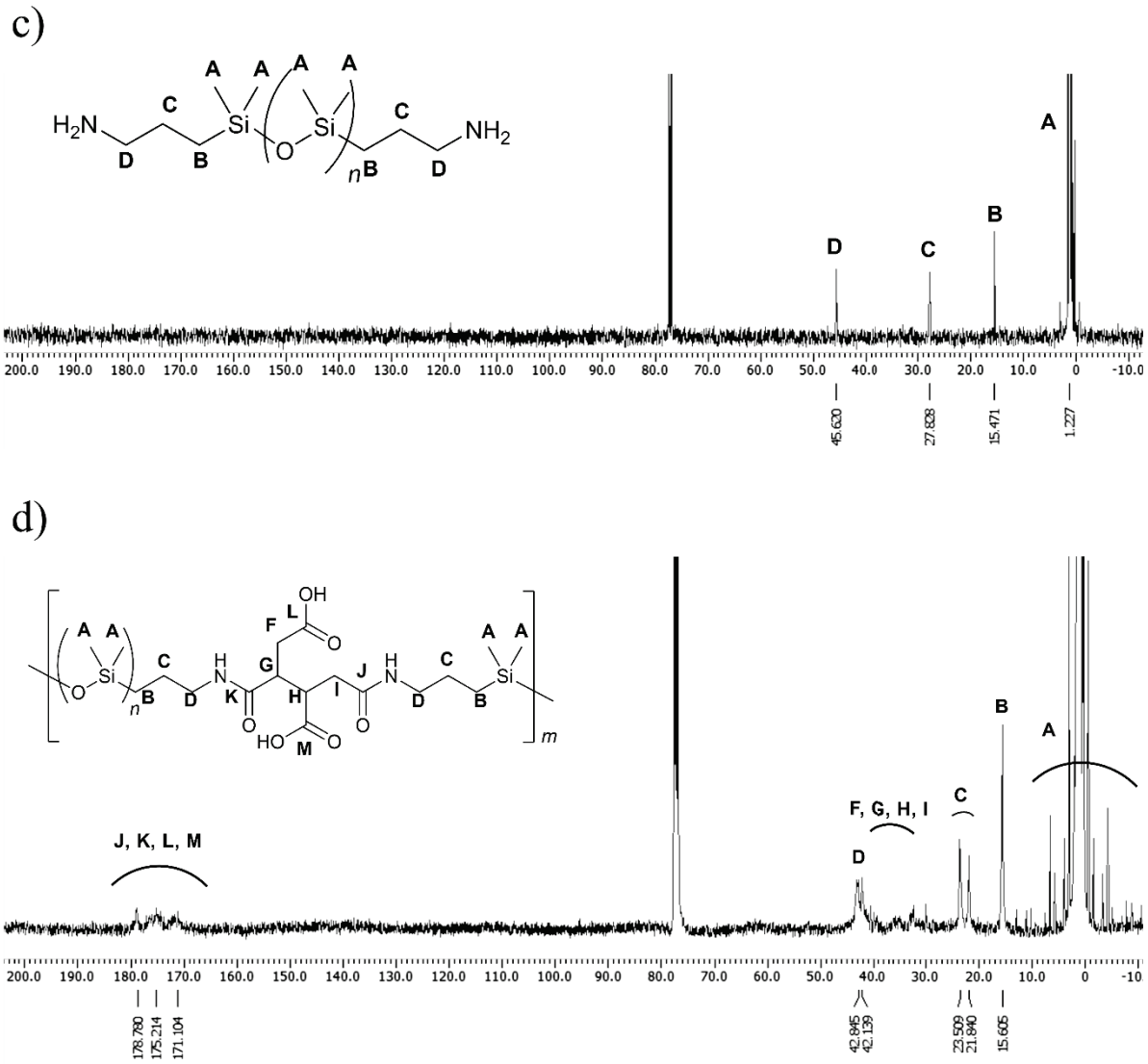


Fig. S6. ^{13}C NMR spectra produced by a) FM-3321 and b) PDMS-COOH. (^{13}C NMR = carbon 13 nuclear magnetic resonance; FM-3321 = a reactive amino-functional polydimethylsiloxane; PDMS = polydimethylsiloxane).

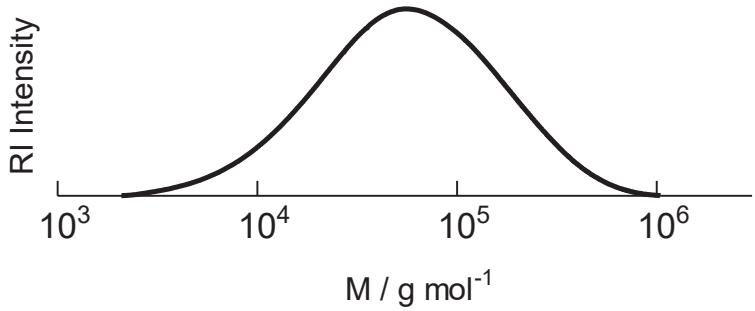


Fig. S7. Molecular weight distribution of PDMS(**2a**) determined by GPC. (PDMS = polydimethylsiloxane; GPC = gel permeation chromatography).

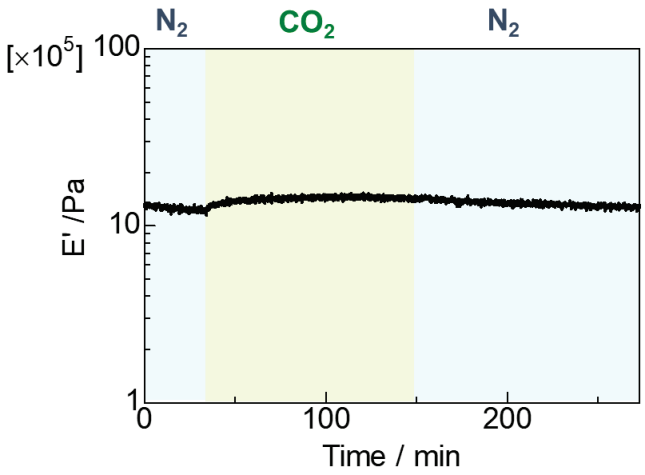


Fig. S8. DMA of the PDMS(**2a**) sheet by force dispersion measurement was performed after drying the sheet overnight in N_2 at 25 °C, then exposing it to a stream of CO_2 for 120 min, and switching to N_2. (DMA = dynamic mechanical analysis; PDMS = polydimethylsiloxane).

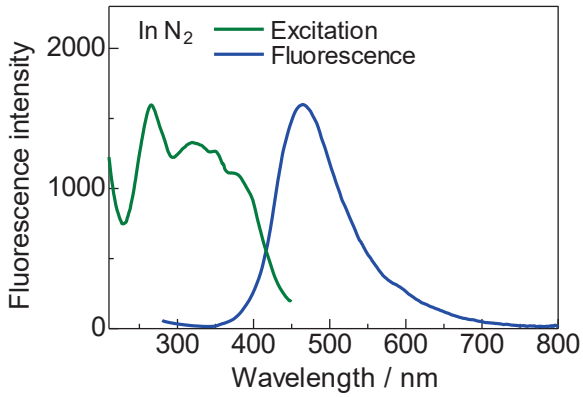


Fig. S9. Excitation spectrum obtained at 464 nm fluorescence and fluorescence spectrum obtained using an excitation wavelength of 266 nm of a PDMS(**2a**) sheet in N_2. (PDMS = polydimethylsiloxane).

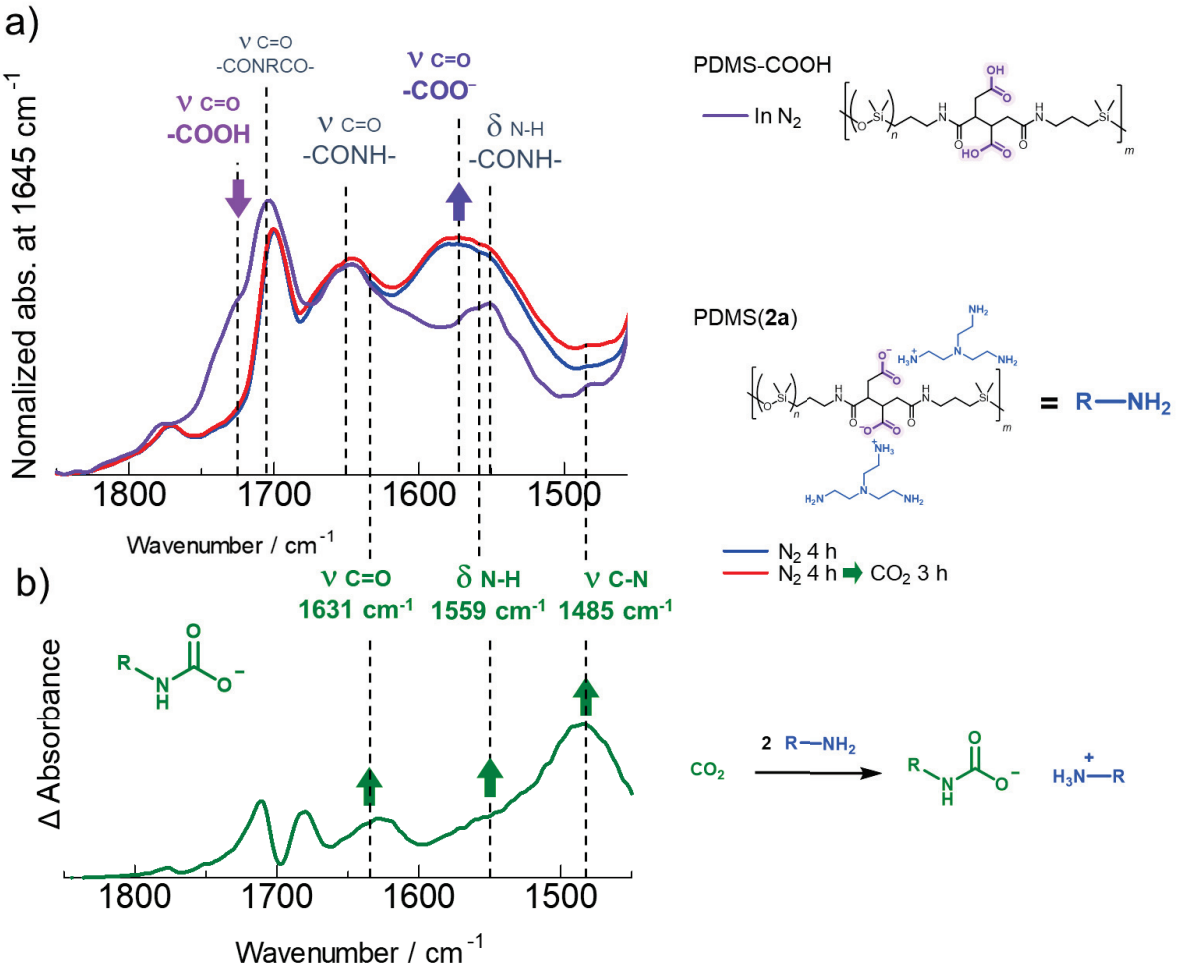


Fig. S10. a) IR spectra of PDMS-COOH and PDMS(**2a**) in N_2 or CO_2. The polymers films were cast on KBr plates from THF and from a mixture of CH_2Cl_2 and MeOH (4/1 ratio), respectively. Measurements were obtained after exposure to a stream of N_2 gas for 4 h, followed by another 3 h after switching to CO_2. b) Differential IR spectra of a PDMS(**2a**) cast film in CO_2 and in N_2. (IR = infrared; PDMS = polydimethylsiloxane; THF = tetrahydrofuran).

References

1. Y. Wang, S. Yang, J. Zhang, Z. Chen, B. Zhu, J. Li, S. Liang, Y. Bai, J. Xu, D. Rao, L. Dong, C. Zhang, X. Yang, *Nat. Commun.* **2023**, *14*, 1108.
2. J. Li, Z. Chen, A. Umar, Y. Liu, Y. Shang, X. Zhang, Y. Wang, *Sci. Rep.* **2017**, *7*, 40082.
3. A. A. Tourzani, F. Hormozi, M. Asadollahzadeh, R. Torkaman, *Sci. Rep.* **2023**, *13*, 6173.
4. D. M. D'Alessandro, B. Smit, J. R. Long, *Angew. Chem. Int. Ed.* **2010**, *49*, 6058-6082.
5. E. D. Bates, R. D. Mayton, I. Ntai, J. H. Davis, *J. Am. Chem. Soc.* **2002**, *124*, 926–927.
6. L. Zhang, E.-Q. Gao, *Coord. Chem. Rev.* **2023**, *486*, 215138.
7. Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933.
8. A. Otto, T. Grube, S. Schiebahn, D. Stolten, *Energy Environ. Sci.* **2015**, *8*, 3283-3297.
9. M. F. Cunningham, P. G. Jessop, *Macromol. React. Eng.* **2022**, *16*, 2200031.
10. M. F. Cunningham, P. G. Jessop, *Macromolecules* **2019**, *52*, 6801-6816.
11. H. Liu, S. Lin, Y. Feng, P. Theato, *Polym. Chem.* **2017**, *8*, 12-23.
12. X. Zhang, Y. Song, M. Liu, H. Li, H. Sun, M. Sun, H. Yu, *Dyes Pigm.* **2019**, *160*, 799-805.
13. Q. Zhu, R. C. Aller, *Limnol. Oceanogr.: Methods* **2010**, *8*, 326-336.
14. E. Fritzsche, P. Gruber, S. Schutting, J. P. Fischer, M. Strobl, J. D. Müller, S. M. Borisov, I. Klimant, *Anal. Methods* **2017**, *9*, 55-65.
15. S. Schutting, T. Jokic, M. Strobl, S. M. Borisov, D. d. Beer, I. Klimant, *J. Mater. Chem. C* **2015**, *3*, 5474-5483.
16. F. Khakzad, A. R. Mahdavian, H. Salehi-Mobarakeh, A. Rezaee Shirin-Abadi, M. Cunningham, *Polymer* **2016**, *101*, 274-283.
17. S. M. Borisov, M. C. Waldhier, I. Klimant, O. S. Wolfbeis, *Chem. Mater.* **2007**, *19*, 6187-6194.
18. M. P. Wolf, G. B. Salieb-Beugelaar, P. Hunziker, *Prog. Polym. Sci.* **2018**, *83*, 97-134.

19. T. C. Merkel, V. I. Bondar, K. Nagai, B. D. Freeman, I. Pinnau, *J. Polym. Sci, Part B: Polym. Phys.* **2000**, *38*, 415-434.
20. P. Mazurek, S. Vudayagiri, A. L. Skov, *Chem. Soc. Rev.* **2019**, *48*, 1448-1464.
21. M. Cajlakovic, A. Bizzarri, V. Ribitsch, *Anal. Chim. Acta.* **2006**, *573-574*, 57-64.
22. X. Ge, Y. Kostov, G. Rao, *Biosens. Bioelectron.* **2003**, *18*, 857-865.
23. Q. Chang, L. Randers-Eichhorn, J. R. Lakowicz, G. Rao, *Biotechnol. Prog.* **1998**, *14*, 326-331.
24. B. H. Weigl, O. S. Wolfbeis, *Anal. Chim. Acta* **1995**, *302*, 249-254.
25. D. Pfeifer, I. Klimant, S. M. Borisov, *Chem. - Eur. J.* **2018**, *24*, 10711-10720.
26. R. Ali, T. Lang, S. M. Saleh, R. J. Meier, O. S. Wolfbeis, *Anal. Chem.* **2011**, *83*, 2846-2851.
27. W. Sun, S. Guo, C. Hu, J. Fan, X. Peng, *Chem. Rev.* **2016**, *116*, 7768-7817.
28. R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki, *RSC. Adv.* **2022**, *12*, 25587-25592.
29. D. Wang, H. Zhang, B. Cheng, Z. Qian, W. Liu, N. Zhao, J. Xu, *J. Polym. Sci., Part A: Polym. Chem.* **2016**, *54*, 1357-1366.
30. J. Mo, X. Chen, Y. Fu, R. Li, Y. Lin, A. Zhang, *Polymer* **2021**, *228*, 123903.
31. R. J. Wojtecki, M. A. Meador, S. J. Rowan, *Nat. Mater.* **2011**, *10*, 14-27.
32. M. R. Coleman, W. J. Koros, *Macromolecules* **1999**, *32*, 3106-3113.
33. R. Li, N. Ye, V. Shaayegan, T. Fang, *J. Supercrit. Fluids* **2018**, *135*, 180-187.
34. D. Nagai, A. Suzuki, Y. Maki, H. Takeno, *Chem. Commun.* **2011**, *47*, 8856-8858.
35. T. Yu, K. Wakuda, D. L. Blair, R. G. Weiss, *J. Phys. Chem. C* **2009**, *113*, 11546–11553.
36. M. G. a. R. G. Weiss, *J. Am. Chem. Soc.* **2001**, *123*, 10393–10394.
37. K. Funabiki, Y. Saito, T. Kikuchi, K. Yagi, Y. Kubota, T. Inuzuka, Y. Miwa, M. Yoshida, O. Sakurada and S. Kutsumizu, *J. Org. Chem.*, 2019, **84**, 4372-4380.

General Conclusion

In this thesis, the author explored new synthetic methods for α-aryl-α-trifluoromethyl alcohols and 1-trifluoromethylpropargyl alcohols and evaluated the stimuli responsiveness of ring-perfluorinated trimethine cyanine dye.

In Chapter 1, the author presented a novel one-pot strategy using two successive conversions by turbo Grignard reagent (*i*-PrMgCl·LiCl) for the facile synthesis of α-aryl or α-heteroaryl-α-trifluoromethyl alcohols, which are important motifs in pharmaceuticals. This strategy exhibits a wide substrate range and tunable reaction conditions. Tandem reactions using *i*-PrMgCl·LiCl with commercially available iodoarenes and 2,2,2-trifluoroethyl trifluoroacetate consist of three tandem reactions, namely, the iodine/Mg-exchange of iodo-arenes or -heteroarenes with *i*-PrMgCl·LiCl, nucleophilic addition of various aryl- or heteroaryl-magunesium reagents to 2,2,2-trifluoroethyl trifluoroacetate, and the reduction of in-situ generated aryl trifluoromethyl ketones by *i*-PrMgCl·LiCl in a one-pot process. This methodology applies to various iodoarenes, heteroarenes, and fluorinated esters. Advantages include resistance to various reducible functional groups on aromatic rings, ease of operation, and readily removable byproducts.

In Chapter 2, the author mentioned the development of a simple, one-pot synthesis of various 3-aryl-1-trifluoromethyl propargyl alcohols based on the reaction of cyclopentylmagnesium bromide (CpMgBr) with two commercially available reagents, 2,2,2-trifluoroethyl trifluoroacetate, and terminal alkynes. This synthetic method involves three consecutive one-pot reactions: 1) reduction of 2,2,2-trifluoroethyl trifluoroacetate by CpMgBr, 2) deprotonation of the terminal alkyne by CpMgBr, 3) nucleophilic addition of the in-situ generated alkynyl Grignard reagent and in-situ formed CF_3CHO, leading to 1-trifluoromethylpropargyl alcohols substituted at

the 3-position. This method has several advantages: one-pot nature, functional group tolerance, suppression of bis-propargyl adduct formation, high product yields (up to 92%), use of commercially available chemicals, ease of scalability, and diversity of products. Furthermore, the resulting aromatic 1-trifluoromethylpropargyl alcohol reacts smoothly with phenylhydrazine in the presence of DBU in toluene to form 1,5-diaryl 3-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole in good to excellent yields.

In Chapter 3, the author described how ring-perfluorinated trimethine cyanine dye is highly sensitive to *n*-hexylamine and undergoes a dual change with a large shift in solution and fluorescent color. Furthermore, the dye was multi-responsive to various analytes other than amines. The methodology of introducing several fluorine atoms proved to be effective in increasing the sensitivity of the dye to amines and other nucleophiles. The fluorinated dye adsorbed on the filter paper displayed reversible ratiometric fluorescence properties, instantly changing from orange emission to blue emission upon amine vapor and returning to the original state after drying in the air for 5 seconds. Furthermore, the amine adduct of the dye reacted with CO_2 in the solution and returned to the conjugated system of the dye.

In Chapter 4, the author found that our optically CO_2-responsive PDMS elastomer rapidly and reversibly underwent both visible and fluorescent color changes in the presence of CO_2 gas. Unlike conventional optically CO_2-responsive polymeric materials, it functions in totally dry gaseous conditions. The visible color and fluorescence of the elastomer sheet change after only 1 min of exposure to CO_2, and the sheet exhibits excellent repeatability in terms of color switching that persists for at least 20 times.

The author introduces 1) the development of a new simple synthetic method for organofluorine compounds and 2) the evaluation of fluorine-containing functional dyes, which resulted in the following insights regarding fluorine atoms.

1) In the synthesis of α-aryl-α-trifluoromethyl alcohols, owing to the electron-withdrawing property of the fluorine atom, the trifluoroacetate ester is highly electrophilic, and the nucleophilic addition proceeded rapidly by the in-situ generated aryl Grignard reagent. The reduction with the turbo Grignard reagent favored low-polarity solvents such as toluene. Furthermore, the bulkiness of the trifluoromethyl group suppresses the formation of *i*-Pr adduct byproducts and promotes the reduction with Grignard reagents. In the case of methyl groups without fluorine atoms, the proton withdrawal and nucleophilic addition to the carbonyl carbon by Grignard reagents compete with the reduction, making an efficient reaction very difficult.
   In the synthesis of 1-trifluoromethylpropergyl alcohols, interestingly, the target compounds were obtained by different reaction mechanisms despite similar reactions. Namely, the reaction of cyclopentylmagnesium bromide (CpMgBr) with 2,2,2-trifluoroethyl trifluoroacetate was performed in the presence of alkynyl Grignard reagent. Because of the electron-withdrawing effect of fluorine atoms in the alcohol portion of the ester, CpMgBr reduces the ester, and addition of trifluoroacetaldehyde with alkynyl Grignard reagent proceeded. The different reaction mechanisms were probably due to the lower nucleophilicity of the alkynyl Grignard reagent compared to the reducing properties of the alkyl Grignard reagent.
2) In the evaluation of the stimuli responsiveness of trimethine cyanine dye, introducing fluorine atoms into the aromatic rings decreased LUMO of the dye, leading to a 3000-fold increase in amine responsiveness and demonstrating excellent reversibility. Moreover, the amine adduct of the dye responded to CO_2 in the solution, resulting in the elimination of the amine from the dye. An elastomer sheet with fluorinated cyanine dye also changes its visual and fluorescent colors against CO_2. Forming ammonium carbamate from the reaction of amines with CO_2

causes color changes. The CO_2 responsiveness is affected by the polymer structure, its polarity, its gas permeability, and other factors. The strategy to improve the stimuli-responsive property by introducing fluorine substituents is effective for various organic dyes.

Publication List

1. K. Funabiki, A. Hayakawa, R. Kani, T. Inuzuka, Y. Kubota, “One-Pot and Reducible-Functional-Group-Tolerant Synthesis of α-Aryl- and α-Heteroaryl-α-Trifluoromethyl Alcohols via Tandem Trifluoroacetylation and MPV Type Reduction”, *Eur. J. Org. Chem.* **2019**, *34*, 5978-5984.
2. R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki, "One-Pot Successive Turbo Grignard Reactions for the Facile Synthesis of α-Aryl-α-Trifluoromethyl Alcohols", *Eur. J. Org. Chem.* **2020**, *29*, 4487-4493. (Chapter 1)
3. K. Funabiki, T. Gotoh, R. Kani, T. Inuzuka, Y. Kubota, “Highly Diastereo- and Enantioselective Organocatalytic Synthesis of Trifluoromethylated Erythitols Based on the in-situ Generation of Unstable Trifluoroacetaldehyde”, *Org. Biomol. Chem.* **2021**, *19*, 1296-1304.
4. R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki, "Synthesis of 1-Trifluoromethylated Propargyl Alcohols by Two Successive Reactions of Cyclopentylmagnesium Bromide in a One-Pot Manner", *Asian J. Org. Chem.* **2022**, *11*, e202100700. (Chapter 2)
5. R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki, "Aromatic Fluorine Atom-induced Highly Amine-sensitive Trimethine Cyanine Dye Showing Colorimetric and Ratiometric Fluorescence Change", *RSC Adv.* **2022***,12,* 25587-25592. (Chapter 3)
6. R. Kani, Y. Miwa, Y. Kubota, T. Inuzuka, S. Kutsumizu, and K. Funabiki " Rapid and dual optical CO_2-responsive polydimethylsiloxane elastomer with fluorinated cyanine dye”, *Chem. - Asian J.* to be submitted. (Chapter 4)

Presentations List

1. CO_2 Responsivity of Silicone Elastomers Doped with Ring-Perfluorinated Dye and Their Optical Properties
   R. Kani, Y. Miwa, Y. Kubota, T. Inuzuka, S. Kutsumizu, K. Funabiki,
   72nd SPSJ Annual Meeting, 1G21, Gunma, Japan, May 2023
   (Oral presentation)
2. Amine and CO_2 Responsiveness of Ring-Perfluorinated Dye and Its Optical Properties
   R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,
   The 103rd CSJ Annual Meeting, K206-2pm-01, Chiba, Japan, March 2023
   (English oral presentation)
3. Fluorescence Properties of Ring-Perfluorinated Dye in Response to Amines and CO_2
   R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki
   the 95th JSCM Anniversary Conference, 2B15, Tokyo, Japan, October 2022
   (Oral presentation)
4. The Ratiometric Fluorescence Properties of Amine-Responsive Trimethine Cyanine Dye
   R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,
   The 102nd CSJ Annual Meeting, C205-1vn-09, Online, March 2022
   (Oral presentation)
5. Solvent-Dependent Colorimetric Properties of Ring-Perfluorinated Dye in Response to a Primary Amine
   R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki
   The 44th Fluorine Conference of Japan, P12, Online, November 2021
   (Poster Presentation)
6. Facile Synthesis of 1-trifluoromethyl Alcohols by One-pot Utilization of the Dual Reaction of Grignard Reagents

R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,

Synthetic Organic Chemistry Hokuriku Seminar 2021, OC-08, Online, October 2021

7. Facile Synthesis of Fluorine-containing 1,4-Dihydro-2*H*-benzo[*d*][1,3]oxazin-2-ones Carrying Various Substituents.

   R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,

   The 101st CSJ Annual Meeting, C205-1vn-09, Online, March 2021

   (Oral presentation)

8. New One-pot Synthesis of α-Alkynyl-α-Trifluoromethyl Alcohols Using Dual Reactions of Turbo Grignard Reagent

   R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,

   The 100th CSJ Annual Meeting, 1B5-50, Not held, March 2020

   (Oral presentation)

9. In-Situ Generation of Aryl Trifluoromethyl Ketones from Iodoarenes and Tandem Reduction Using the Dual Reactions of Turbo Grignard Reagent

   R. Kani, Y. Kubota, T. Inuzuka, K. Funabiki

   The 42nd Fluorine Conference of Japan, P14, Hyogo, Japan, November 2019

   (Poster Presentation, Best Poster Award)

10. Synthesis of α-Aryl-α-Fluoroalkyl Alcohols Using the Dual Reaction of Turbo Grignard Reagents

    R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,

    9th Fluorine Chemistry Young Researchers' Conference, Fukui, Japan, September 2019

    (Poster Presentation)

11. In Situ Generation of Aryl Trifluoromethyl Ketones from Iodoarenes and Successive Reduction by the Use of Turbo Grignard Reagent

    R. Kani, T. Inuzuka, Y. Kubota, K. Funabiki,

    The 99th CSJ Annual Meeting, 1F2-10, Hyogo, Japan, March 2019

    (Oral presentation)

12. Facile Synthesis of α-Aryl-α-Trifluoromethyl Alcohols Using Aromatic Grignard Reagents with Electron-Donating Substituents

R. Kani, T. Inuzuka, K. Funabiki,

8th Fluorine Chemistry Young Researchers' Conference, Ibaraki, Japan, August 2018

(Poster Presentation)