

平成28年度医療研究開発推進事業費補助金
(創薬等ライフサイエンス研究支援基盤事業) 補助事業成果報告書

I. 基本情報

事業名：創薬等ライフサイエンス研究支援基盤事業（創薬等支援技術基盤プラットフォーム事業）
Platform Project for Supporting Drug Discovery and Life Science Research
(Platform for Drug discovery, Informatics, and Structural life science)

補助事業課題名：（日本語）C-H 結合活性化を活用する独創的リード化合物高度化
（含フッ素化合物高度化）
（英語）Advancement of Lead Compounds in Drug Discovery by Utilizing C-H
Bond Activation (Advancement of Organofluorine Compounds in Drug
Discovery)

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実施期間：平成 28 年 4 月 1 日 ～ 平成 29 年 3 月 31 日

II. 成果の概要（総括研究報告）

補助事業期間最終年度にあたりますので、初年度から最終年度までの全補助事業期間における活動
総括概要を作成してください。

和文

含フッ素有機化合物の創薬開発における重要性は、市場に出ている医薬品の約 2 割から 3 割が含
フッ素医薬品であることから明白である。そのため、試行錯誤的要因の強い創薬開発において、フ
ッ素化合物のライブラリーにそのリードを求める方法は、医薬品開発を効率的にする手段のひとつ
である。しかしながら、フッ素有機化合物を合成することでは簡単でなく、如何にして効率良く含
フッ素有機化合物を合成するかが課題となっている。当該プロジェクトでは、外部研究者等から依

頼のあった化合物を元に含フッ素誘導体成し、生理活性増強を狙う「支援」研究と、既存法では合成困難なフッ素化やフッ素官能基化を行う新手法の開発を行う「高度化」の2つの側面から研究を展開してきた。その結果、支援としては、独自の高度化手法で合成した数多くの含フッ素化合物サンプルを合成・構造公開し、ライブラリーへ提供した。また、治療薬を目指したタンパク質間結合阻害低分子の開発支援にて含フッ素複素環化合物の多数の合成に成功・構造開示し提供した。他機関との共同（学生派遣）も実施し、創薬サンプルの合成に成功した。これらの成果を他機関と共同で特許出願した。また、この成果は、現在、論文投稿中である。また、最終年度にも新たな支援案件を開始し、化合物を他機関に提供した。

一方、高度化に関しては、様々な新手法の開発に成功した。まず、フッ素化合物合成の高度化技術を推進する試薬群を開発し、*JACS*, *AngewChemIntEd*, *Chemical Science*, *ACS Catalysis*, *GreenChem*, *ChemMedChem* など含むインパクトファクターの高い論文に多数発表した。その試薬には、トリフルオロメチル化試薬、ジフルオロメチル化試薬、トリフルオロメチルチオ化試薬、ジフルオロメチル化試薬、ペンタフルオロスルファニルフェニル化試薬およびペンタフルオロスルファニルピリジル化試薬が含まれる。高度化で発表した手法のいくつかは、メディア（新聞）でも取り上げられた。

また支援と高度化を融合させ、フッ素を導入したフルオロサリドマイド、フルオロドネペジルなどの生理活性物質の合成にも成功した。

英文

Fluorine is one of the most attractive elements in the drug development. As many as 20-30% of pharmaceuticals on the market contain fluorine(s) in the structures, Lipitor is an example of blockbuster. Thus, it is quite reasonable to find out the drug leads from the library of organofluorine compounds in order to minimize the try and errors. However, the synthesis of organofluorine compounds is not easy. Hence development of efficient synthetic methodologies for organofluorine compounds is of great importance in the medicinal chemistry research. This academia drug development project, "Advancement of Lead Compounds in Drug Discovery by Utilizing C-H Bond Activation (Advancement of Organofluorine Compounds in Drug Discovery)" had been carried out for 5 years, consisting of two major parts, i.e., drug candidate's support and development of novel methodology of fluorine-containing compounds. The former is the "advancement" of designing and synthetic supports of organofluorine compounds requested from external researchers within the whole project for drug discovery. The latter is the "advancement" of the new technique for fluorination and fluoro-functionalization reactions capable to synthesize potential biologically active organofluorine compounds which are currently hard to synthesize. As a result, as support, we had synthesized a wide variety of organofluorine compounds containing complex structures and provided them to a drug library. All the fluorinated compounds from us are completely original and new compounds thus some of them have been submitted to the patent. Two collaborative projects were carried out. Our group had much contribution to the projects based on the synthesis of a large number of fluorine-containing heterocyclic compounds. One of them went to the very good results which was submitted to the patent.

In addition to the "support" above mentioned, we had much effort on the "advancement" of the new technique for fluorination and fluoro-functionalization reactions. A variety of novel fluoro-functionalization reagents had been reported such as trifluoromethylation, difluoromethylation, trifluoromethylthiolation, difluoromethylthiolation, pentafluorosulfanyl-phenylation and pentafluorosulfanyl-pyridylation. All the

reagents are very powerful tools for the synthesis of fluorine containing organic compounds. Some of them are going to be discussed for commercialization in near future. These research had been published in high quality journals such as *JACS*, *AngewChemIntEd*, *Chemical Science*, *ACS Catalysis*, *GreenChem*, *ChemMedChem* and so on. Selected works were also announced by advancement, even the media (newspaper) was taken up.

In addition to the development of fluoro-functionalized reagents, “advancement” drug candidates had been developed such as fluoro-thalidomide for cancer and fluoro-donepezil for Alzheimer diseases.

III. 成果の外部への発表

(1) 学会誌・雑誌等における論文一覧（国内誌 3 件、国際誌 58 件）

1. Hiroyuki Kawai, Zhe Yuan, Etsuko Tokunaga, Norio Shibata. Regioselective Synthesis of Pyrazole Triflones Based on Triflyl Alkyne Cycloadditions. *Organic Letters*. 2012, 14(20), 5330-3.
2. Norio Shibata, Kazunobu Fukushi, Tatsuya Furukawa, Satoru Suzuki, Etsuko Tokunaga, Dominique Cahard. Decarboxylative Allylation of Trifluoroethyl Sulfones and Approach to Difluoromethyl Compounds. *Organic Letters*. 2012, 14 (20), 5366-9.
3. Yu-Dong Yang, Kanji Iwamoto, Etsuko Tokunaga, Norio Shibata. Transition-metal-free oxidative trifluoromethylation of unsymmetrical biaryls with trifluoromethanesulfinate. *Chemical Communications*. 2013, 49(48), 5510-2.
4. Yu-Dong Yang, Ayaka Azuma, Etsuko Tokunaga, Mikio Yamasaki, Motoo Shiro, Norio Shibata. Trifluoromethanesulfonyl Hypervalent Iodonium Ylide for Copper-Catalyzed Trifluoromethylthiolation of Enamines, Indoles, and β -Keto Esters. *Journal of the American Chemical Society*. 2013, 135(24), 8782-5.
5. Kohei Matsuzaki, Tatsuya Furukawa, Etsuko Tokunaga, Takashi Matsumoto, Motoo Shiro, Norio Shibata. Highly Enantioselective Monofluoromethylation of C2-Arylindoles Using FBSM under Chiral Phase-Transfer Catalysis. *Organic Letters*. 2013, 15(13), 3282-5.
6. Hiroyuki Kawai, Satoshi Okusu, Etsuko Tokunaga, Norio Shibata. Enantioselective Synthesis of 5-Trifluoromethyl-2-isoxazolines and Their N-Oxides. *European Journal of Organic Chemistry*. 2013, 2013(29), 6506-9.
7. Hai Ma, Kohei Matsuzaki, Yu-Dong Yang, Etsuko Tokunaga, Daisuke Nakane, Tomohiro Ozawa, Hideki Masuda, Norio Shibata. Enantioselective monofluoromethylation of aldehydes with 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide catalyzed by a bifunctional cinchona alkaloid-derived thiourea-titanium complex. *Chemical Communications*. 2013, 49(95), 11206-8.
8. Xiu-Hua Xu, Misaki Taniguchi, Xin Wang, Etsuko Tokunaga, Tomohiro Ozawa, Hideki Masuda, Norio Shibata. Stereoselective Synthesis of Vinyl Triflones and Heteroaryl Triflones via Anionic $O \rightarrow C_{\text{vinyl}}$ and $N \rightarrow C_{\text{vinyl}}$ Trifluoromethanesulfonyl Migration Reactions. *Angewandte Chemie International Edition*. 2013, 52(48), 12628-31.

9. Satoshi Okusu, Yutaka Sugita, Etsuko Tokunaga, Norio Shibata. Regioselective 1,4-Trifluoromethylation of α , β -Unsaturated Ketones via a S-(trifluoromethyl)diphenylsulfonium salts/Copper System. *Beilstein Journal of Organic Chemistry*. 2013, 9, 2189-93.
10. 柴田哲男, 杉田豊, 河合洋幸. フッ素化学の錬金術: フッ素樹脂副産物フルオロホルムの医薬品原料・液晶材料への活用. *ファインケミカル*. 2013, 42(11), 48-55.
11. Xiu-Hua Xu, Norio Shibata. New Approaches to the Regioselective Synthesis of Heteroaryl Triflones. *有機合成化学協会誌*. 2013, 71(11), 1195-201.
12. Xin Wang, Guokai Liu, Xiu-Hua Xu, Naoyuki Shibata, Etsuko Tokunaga, Norio Shibata. S-((Phenylsulfonyl)difluoromethyl)thiophenium Salts: Carbon-Selective Electrophilic Difluoromethylation of beta-Ketoesters, beta-Diketones, and Dicyanoalkylidenes. *Angewandte Chemie International Edition*. 2013, 53(7), 1827-31
13. Norio Shibata, Satoru Mori, Masamichi Hayashi, Masashi Umeda, Etsuko Tokunaga, Motoo Shiro, Hiroyasu Sato, Tomonori Hoshi, Nagao Kobayashi. A phthalocyanine-subphthalocyanine heterodinuclear dimer: comparison of spectroscopic properties with those of homodinuclear dimers of constituting units. *Chemical Communications*. 2014, 50(23), 3040-3.
14. Hiroyuki Kawai, Yutaka Sugita, Etsuko Tokunaga, Hiroyasu Sato, Motoo Shiro, Norio Shibata. Diastereoselective Additive Trifluoromethylation/Halogenation of Isoxazole Triflones: Synthesis of All-carbon Functionalized Trifluoromethyl Isoxazoline Triflones. *ChemistryOpen*. 2013, 3(1), 14-8.
15. Yu-Dong Yang, Etsuko Tokunaga, Hidehiko Akiyama Norimichi Saito, Norio Shibata. Bis(pentafluorosulfanyl)phenyl Azide as an Expeditious Tool for Click Chemistry toward Antitumor Pharmaceuticals. *ChemMedChem*. 2013, 9(5), 913-7.
16. Satoru Suzuki, Tomohiro Kamo, Kazunobu Fukushi, Takaaki Hiramatsu, Etsuko Tokunaga, Toshifumi Dohi, Yasuyuki Kita, Norio Shibata. Iodoarene-catalyzed fluorination and aminofluorination by Ar-I/HF•pyridine/mCPBA system. *Chemical Science*. 2013, 5(7), 2754-60.
17. Satoshi Okusu, Hiroyuki Kawai, Yoshimasa Yasuda, Yutaka Sugita, Takashi Kitayama, Etsuko Tokunaga, Norio Shibata. Asymmetric Synthesis of Efavirenz via Organocatalyzed Enantioselective Trifluoromethylation. *Asian Journal of Organic Chemistry*. 2014, 3(4), 449-52.
18. Hiroyuki Kawai, Norio Shibata. Asymmetric Synthesis of Agrochemically Attractive Trifluoromethylated Dihydroazoles and Related Compounds under Organocatalysis. *The Chemical Record*. 2014, 14(6), 1024-40.
19. Xiu-Hua Xu, Kohei Matsuzaki, Norio Shibata. Synthetic Methods for Compounds Having CF₃-S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chemical Reviews*. 2014, 115(2), 731-64.
20. Norihito Iida, Etsuko Tokunaga, Norimichi Saito, Norio Shibata. Pentafluorosulfanyl (SF₅) in dyes: C3-Regioselective synthesis of α -mono-substituted subphthalocyanine with SF₅-phenyl group. *Journal of Fluorine Chemistry*. 2014, 171, 120-3.
21. Kohei Matsuzaki, Kenta Okuyama, Etsuko Tokunaga, Motoo Shiro, Norio Shibata. Sterically Demanding Unsymmetrical Diaryl- λ 3-iodanes for Electrophilic Pentafluorophenylation and an Approach to α -Pentafluorophenyl Carbonyl Compounds with an All-Carbon Stereocenter. *ChemistryOpen*. 2014, 3(6), 233-7.

22. Norihito Iida, Etsuko Tokunaga, Norimichi Saito, Norio Shibata. Synthesis and property of novel phthalocyanine having a 3,5-bis-pentafluorosulfanylphenyl group on the α -peripheral position . Journal of Fluorine Chemistry. 2014, 168, 93-8.
23. Satoru Mori, Naoya Ogawa, Etsuko Tokunaga, Norio Shibata. Synthesis and optical properties of trifluoroethoxysubstituted double-decker phthalocyanines. Journal of Porphyrins and Phthalocyanines. 2014, 18(10n11), 1034-41.
24. Xin Wang, Etsuko Tokunaga, Norio Shibata. Direct nucleophilic difluoromethylation of aromatic isoxazoles activated by electron-withdrawing groups using (difluoromethyl)trimethylsilane. ScienceOpen Research–Section: SOR-CHEM. 2014, on line
25. Mayaka Maeno, Etsuko Tokunaga, Takeshi Yamamoto, Toshiya Suzuki, Yoshiyuki Ogino, Emi Ito, Motoo Shiro, Toru Asahi, Norio Shibata. Self-disproportionation of Enantiomers of Thalidomide and its Fluorinated Analogue via Gravity-driven Achiral Chromatography: Mechanistic Rationale and Implications. Chemical Science. 2015, 6(2), 1043-8.
26. Satoru Mori, Hideyuki Yoshiyama, Etsuko Tokunaga, Norihito Iida, Masamichi Hayashi, Tohru Obata, Motohiro Tanaka, Norio Shibata. Design, synthesis, spectral investigations and biological activity of fluorinated phthalocyanine conjugated with galactose and comparison to its non-fluorinated counterpart. Journal of Fluorine Chemistry. 2015, 174, 137-41.
27. Norihito Iida, Kenta Tanaka, Etsuko Tokunaga, Hiromi Takahashi, Norio Shibata. Regioisomer-Free C₄h β -Tetrakis(tert-butyl)metallo-phthalocyanines: Regioselective Synthesis and Spectral Investigations. ChemistryOpen. 2015, 4(2), 102-6.
28. Zhongyan Huang, Yu-Dong Yang, Etsuko Tokunaga, Norio Shibata. Copper-Catalyzed Regioselective Trifluoromethylthiolation of Pyrroles by Trifluoromethanesulfonyl Hypervalent Iodonium Ylide. Organic Letters. 2015, 17(5), 1094-7.
29. Sadayuki Arimori, Masahiro Takada, Norio Shibata. Trifluoromethylthiolation of Allylsilanes and Silyl Enol Ethers with Trifluoromethanesulfonyl Hypervalent Iodonium Ylide under Copper Catalysis. Organic Letters. 2015, 17(5), 1063-5.
30. Yi-Yong Huang, Xing Yang, Zhuo Chen, Francis Verpoort, Norio Shibata. Catalytic Asymmetric Synthesis of Enantioenriched Heterocycles Bearing a C CF₃ Stereogenic Center. Chemistry - A European Journal. 2015, 21(24), 8664-884.
31. Sadayuki Arimori, Norio Shibata. Catalytic Trifluoromethylation of Aryl- and Vinylboronic Acids by 2-Cyclopropyl-1-(trifluoromethyl)benzo[b]thiophenium Triflate. Organic Letters. 2015, 17(7), 1632-1635.
32. Kohei Matsuzaki, Kenta Okuyama, Etsuko Tokunaga, Norimichi Saito, Motoo Shiro, Norio Shibata. Synthesis of Diaryliodonium Salts Having Pentafluorosulfanylarenes and Their Application to Electrophilic Pentafluorosulfanylarylation of C-, O-, N-, and S-Nucleophiles. Organic Letters. 2015, 17(12), 3038-41.
33. Ibrayim Saidalimu, Etsuko Tokunaga, Norio Shibata. Carbene-Induced Intra- vs Intermolecular Transfer-Fluoromethylation of Aryl Fluoromethylthio Compounds under Rhodium Catalysis. ACS Catalysis. 2015, 5(8), 4668-72.

34. Satoru Mori, Naoya Ogawa, Etsuko Tokunaga, Norio Shibata. Synthesis and optical properties of subphthalocyanine homo- and heterodimers axially connected via a hydroquinone linker. Dalton Transactions. 2015, 44(45), 19451-5.
35. Satoshi Okusu, Etsuko Tokunaga, Norio Shibata. Difluoromethylation of Terminal Alkynes by Fluoroform. Organic Letter. 2015, 17(15), 3802-5.
36. Sadayuki Arimori, Masahiro Takada, Norio Shibata. Reactions of allyl alcohols and boronic acids with trifluoromethanesulfonyl hypervalent iodonium ylide under copper-catalysis. Dalton Transactions. 2015, 44(45), 19456-9.
37. Norihito Iida, Kenta Tanaka, Etsuko Tokunaga, Satoru Mori, Norimichi Saito, Norio Shibata. Synthesis of Phthalocyanines with a Pentafluorosulfonyl Substituent at Peripheral Positions. ChemistryOpen. 2015, 4(6), 698-702.
38. Satoshi Okusu, Kazuki Hirano, Etsuko Tokunaga, Norio Shibata. Organocatalyzed Trifluoromethylation of Ketones and Sulfonyl Fluorides by Fluoroform under a Superbase System. ChemistryOpen. 2015, 4(5), 581-5.
39. Takayuki Nishimine, Hiromi Taira, Etsuko Tokunaga, Motoo Shiro, Norio Shibata. Enantioselective Trichloromethylation of MBH-Fluorides with Chloroform Based on Silicon-assisted C-F Activation and Carbanion Exchange Induced by Ruppert–Prakash Reagent. Angewandte Chemie International Edition. 2015, 55(1), 359-63.
40. Zhongyan Huang, Chen Wang, Etsuko Tokunaga, Yuji Sumii, Norio Shibata. Stereoselective Synthesis of β -Lactam-triflones under Catalyst-Free Conditions. Organic Letter. 2015, 17(22), 5610-3.
41. Kazunobu Fukushi, Satoru Suzuki, Tomohiro Kamo, Etsuko Tokunaga, Yuji Sumii, Takumi Kagawa, Kosuke Kawada, Norio Shibata. Methyl NFSI: Atom-economical alternative to NFSI shows higher fluorination reactivity under Lewis acid-catalysis and non-catalysis. Green Chemistry. 2015, 18(7), 1864-8.
42. Satoru Mori, Naoya Ogawa, Etsuko Tokunaga, Seiji Tsuzuki, Norio Shibata. Design, synthesis and optical properties of unsymmetrical subphthalocyanine trimer connected by phloroglucinol via axial positions. Dalton Transactions. 2016, 45(3), 908-12.
43. Ibrayim Saidalimu, Shugo Suzuki, Etsuko Tokunaga, Norio Shibata. Successive C-C bond cleavage, fluorination, trifluoromethylthio- or pentafluorophenylthiolation under metal-free conditions to provide compounds with dual fluoro-functionalization. Chemical Science. 2016, 7(3), 2106-10.
44. Zhongyan Huang, Kenta Okuyama, Chen Wang, Etsuko Tokunaga, Xiaorui Li, Norio Shibata. 2-Diazo-1-phenyl-2-((trifluoromethyl)sulfonyl)ethan-1-one: Another Utility for Electrophilic Trifluoromethylthiolation Reactions. ChemistryOpen. 2016, 5(3), 188-91.
45. 森悟, 柴田哲男. トリフルオロエトキシ化フタロシアニンおよびサブフタロシアニン類の開発とその展開. 有機合成化学協会誌. 2016, 74(2), 154-66.
46. Kazunobu Fukushi, Etsuko Tokunaga, Yuji Sumii, Takumi Kagawa, Noritaka Nagasaki, Norio Shibata. Lewis Acid-Catalyzed Selective Mono-fluorination of Malonates Using Me-NFSI. Fluorine notes. 2016, 2(105).

47. Ibrayim Saidalimu, Shugo Suzuki, Etsuko Tokunaga, [Norio Shibata](#). Activation of Trifluoromethylthio Moiety by Appending Iodonium Ylide under Copper Catalysis for Electrophilic Trifluoromethylation Reaction. *Chinese Journal of Chemistry*. 2016, 34(5), 485-9.
48. Satoshi Okusu, Hiroki Okazaki, Etsuko Tokunaga, Vadim A. Soloshonok, [Norio Shibata](#). Organocatalytic Enantioselective Nucleophilic Alkynylation of Allyl Fluorides Affording Chiral Skipped Ene-ynes. *Angewandte Chemie International Edition*. 2016, 55(23), 6744-8.
49. Hélène Chachignon, Mayaka Maeno, Hiroya Kondo, [Norio Shibata](#), Dominique Cahard. Novel Use of $\text{CF}_3\text{SO}_2\text{Cl}$ for the Metal-Free Electrophilic Trifluoromethylthiolation. *Organic Letters*. 2016, 18(10), 2467-70.
50. Sadayuki Arimori, Okiya Matsubara, Masahiro Takada, Motoo Shiro, [Norio Shibata](#). Difluoromethanesulfonyl hypervalent iodonium ylides for electrophilic difluoromethylthiolation reactions under copper catalysis. *ROYAL SOCIETY OPEN SCIENCE*. 2016, 3(5), 160102.
51. Junko Tanaka, Satoru Suzuki, Etsuko Tokunaga, Günter Haufe, [Norio Shibata](#). Asymmetric Desymmetrization via Metal-Free C–F Bond Activation: Synthesis of 3,5-Diaryl-5-fluoromethyloxazolidin-2-ones with Quaternary Carbon Centers. *Angewandte Chemie International Edition*. 2016, 55(32), 9432-6.
52. Ibrayim Saidalimu, Ming Guo, Etsuko Tokunaga, [Norio Shibata](#). Direct Fluoro-aminosulfonylation of Active Methylenes by Dialkylaminosulfur Trifluorides under Catalyst-Free Conditions. *Asian Journal of Organic Chemistry*. 2016, 5(10), 1208-12.
53. Mikhail Kosobokov, Benqiang Cui, Andrii Balia, Kohei Matsuzaki, Etsuko Tokunaga, Norimichi Saito, [Norio Shibata](#). Importance of a Fluorine Substituent for the Preparation of meta- and para-Pentafluoro- λ 6-sulfanyl-Substituted Pyridines. *Angewandte Chemie International Edition*. 2016, 55(36), 10781-5.
54. [Norio Shibata](#). Development of Shelf-Stable Reagents for Fluoro-Functionalization Reactions. *Bulletin of the Chemical Society of Japan*. 2016, 89(11), 1307-20.
55. Satoshi Okusu, Kazuki Hirano, Etsuko Tokunaga, [Norio Shibata](#). Flow trifluoromethylation of carbonyl compounds by Ruppert-Prakash reagent and its application for pharmaceuticals, Efavirenz and HSD-016. *RSC Advances*. 2016, 6(86), 82716-20.
56. Mayaka Maeno, Hiroya Kondo, Etsuko Tokunaga, [Norio Shibata](#). Synthesis of fluorinated donepezil by palladium-catalyzed decarboxylative allylation of α -fluoro- β -keto ester with tri-substituted heterocyclic alkene and the self-disproportionation of its enantiomers. *RSC Advances*. 2016, 6(88), 85058-62.
57. Satoshi Okusu, Kazuki Hirano, Yoshimasa Yasuda, Junko Tanaka, Etsuko Tokunaga, Haruhiko Fukaya, [Norio Shibata](#). Alkynyl Cinchona Catalysts affect Enantioselective Trifluoromethylation for Efavirenz under Metal-Free Conditions. *Organic Letters*. 2016, 18(21), 5568-71.
58. Ibrayim Saidalimu, Shugo Suzuki, Takuya Yoshioka, Etsuko Tokunaga, [Norio Shibata](#). Perfluoroalkyl Analogues of Diethylaminosulfur Trifluoride: Reagents for Perfluoroalkylthiolation of Active Methylene Compounds under Mild Conditions. *Organic Letters*. 2016, 18(24), 6404-7.
59. Takayuki Nishimine, Hiromi Taira, Satoru Mori, Okiya Matsubara, Etsuko Tokunaga, Hidehiko Akiyama, Vadim Soloshonok, [Norio Shibata](#). Synthesis of chiral (tetrazolyl)methyl-containing acrylates via silicon-induced organocatalytic kinetic resolution of Morita-Baylis-Hillman fluorides. *Chemical Communications*. 2016, 53(6), 1128-31.

60. Zhongyan Huang, Okiya Matsubara, Shichong Jia, Etsuko Tokunaga, Norio Shibata. Difluoromethylthiolation of Phenols and Related Compounds with a $\text{HF}_2\text{CSO}_2\text{Na}/\text{Ph}_2\text{PCI}/\text{Me}_3\text{SiCl}$ System. *Organic Letters*. 2017, 19(4), 934-7.
61. Ibrayim Saidalimu, Shugo Suzuki, Jiandong Wang, Etsuko Tokunaga, Norio Shibata. Construction of Fluorinated Benzoxathiin Skeleton by Successive Perfluorophenylthiolation/Cyclization of Activated α -Methylene Ketones by Perfluorophenyl Diethylaminosulfur Difluoride. *Organic Letters*. 2017, 19(5), 1012-5.

(2) 学会・シンポジウム等における口頭・ポスター発表

1. Enantioselective Synthesis of Epoxides having a Tetrasubstituted Trifluoromethylated Carbon Center by Methylhydrazine-induced Non-metallic Aerobic Epoxidation of β,β -Disubstituted Enones, 口頭 (招待講演), Norio Shibata, 1st International Conference & 6th Symposium on Organocatalysis, Prince Hotel Otsu (Otsu, Japan), 2013/5/27-28, 国内 (国際会議).
2. A Sterically Demanding Organo-superbase Avoids Decomposition of a Naked Trifluoromethyl Carbanion Directly Generated from Fluoroform, 口頭 (招待講演), Norio Shibata, 10th International Symposium on Carbanion Chemistry (ISCC-10), Doshisha University (Kyoto, Japan), 2013/9/23-26, 国内 (国際会議).
3. Kinetic Resolution of Allylic Fluorides by Enantioselective Allylic Trifluoromethylation based on Silicon-assisted C-F Bond Cleavage, 口頭 (招待講演), Norio Shibata, ZING Conference (Asymmetric Synthesis Conference), Parador de Nerja (Nerja, Spain), 2014/2/25-28, 国外.
4. Thalidomide and Its Chirality: Towards Paradox, 口頭 (招待講演), Norio Shibata, Pharmacy –a journey from Edo times to modern pharmaceuticals and health economics 19. Japanese-German Symposium, Erlangen-Nürnberg University (Germany), 2014/5/23-24, 国外.
5. サリドマイドとキラリティー:パラドックスへの返答, 口頭 (招待講演), 柴田哲男, シンポジウム モレキュラー・キラリティー2014, 仙台国際センター (仙台), 2014/6/6-7, 国内.
6. サリドマイドとフッ素:パラドックスへの挑戦, 口頭 (招待講演), 柴田哲男, 第4回フッ素化学若手の会, 浜名湖かんざんじ温泉「開華亭」, 浜松, 2014/8/7-8, 国内.
7. Trifluoromethanesulfonyl iodonium ylide for trifluoromethylthiolation, 口頭 (招待講演), Norio Shibata, 248th ACS National Meeting & Exposition, San Francisco Moscone Center (San Francisco, USA), 2014/8/10-14, 国外.
8. Trifluoromethanesulfonyl Hypervalent Iodonium Ylide for Trifluoromethylthiolation, 口頭 (招待講演), Norio Shibata, Molecular Complexity in Modern Chemistry (MCMC-2014), Zelinsky Institute of Organic Chemistry (Moscow, Russia), 2014/9/13-19, 国外.
9. Novel Reagents for Electrophilic Pentafluorosulfanylphenylation of C, O, S and N - Nucleophiles, 口頭 (招待講演), Norio Shibata, Japan/Russian Conference on Fluorine Chemistry and Friends 2014, Department of Nanopharmaceutical Sciences Nagoya Institute of Technology (Nagoya, Japan), 2014/12/8-10, 国内 (国際会議).

10. Trifluoromethylthio Compounds for Electrophilic Trifluoromethylation under Rhodium Catalysis, 口頭 (招待講演), Norio Shibata, 22nd Winter Fluorine Conference, TradeWinds Island Grand Beach Resort, St. Pete Beach (Florida, USA), 2015/1/11-16, 国外.
11. Recent Progress in the Synthesis of Aryl Triflones, 口頭 (招待講演), Norio Shibata, 249th ACS National Meeting & Exposition, The Colorado Convention Center (Denver, USA), 2015/3/22-26, 国外.
12. 試薬開発に力点を置いたフッ素化合物の精密合成, 口頭 (招待講演), 柴田哲男, 日本化学会 第95 春季年会 (2015), 日本大学 (船橋), 2015/3/26-29, 国内.
13. Synthesis and Property of Novel Phthalocyanine Having Pentafluorosulfanyl (SF₅) Group on the Peripheral Positions, 口頭 (招待講演), Norio Shibata, 227th ECS Meeting, The Hilton Chicago (Chicago, USA), 2015/5/24-28, 国外.
14. Organocatalyzed trifluoromethylation of ketones and sulfonyl fluorides by fluoroform under superbase system, 口頭 (招待講演), Norio Shibata, 16th Tetrahedron Symposium Asia Edition, Shanghai Institute of Organic Chemistry (Shanghai, China), 2015/11/10-13, 国内.
15. 忘れ去られた原子団 SF₅ 基を持つ合成ツールの開発, 口頭 (招待講演), 柴田哲男, 第10 回プロセス化学ラウンジ, 和光純薬工業株式会社湯河原研修所 (熱海), 2015/12/4-5, 国内.
16. Carbene-induced intra- vs intermolecular transfer-trifluoromethylation of aryl trifluoromethylthio-compounds under rhodium catalysis, 口頭 (招待講演), Norio Shibata, The International Chemical Congress of Pacific Basin Societies 2015(Pacificchem 2015), Hawaii Convention Center(Honolulu, Hawaii, USA), 2015/12/15-20, 国外.
17. Asymmetric synthesis of efavirenz via organocatalyzed enantioselective trifluoromethylation, 口頭 (招待講演), Norio Shibata, The International Chemical Congress of Pacific Basin Societies 2015(Pacificchem 2015), Hawaii Convention Center(Honolulu, Hawaii, USA), 2015/12/15-20, 国外.
18. フロン 23 (フルオロホルム) を用いたフッ素化合物の合成, 口頭 (招待講演), 柴田哲男, 有機合成のニュートレンド 2016, 大阪科学技術センター (大阪), 2016/2/2-3, 国内.
19. Enantioselective Trichloromethylation of MBH-Fluorides with Chloroform Based on Silicon-assisted C-F Activation and Carbanion Exchange Process Induced by Ruppert-Prakash Reagent, 口頭, Norio Shibata, Molecular Chirality Asia 2016, Knowledge Capital Congrès Convention Center (Osaka, Japan), 2016/4/20-22, 国内 (国際会議).
20. Difluoromethanesulfonyl Hypervalent Iodonium Ylides for Electrophilic Difluoromethylthiolation Reactions under Copper Catalysis, 口頭 (招待講演), Norio Shibata, 5th International Symposium on Organofluorine Compounds in Biomedical, Materials and Agriculture Sciences ("Bremen Fluorine Days"), Jacobs University Bremen Campus Center (Bremen, Germany), 2016/7/3-7, 国外.
21. 製造コストの大幅削減を可能にするエイズ治療薬中間体の革新的合成, 口頭, 柴田哲男, 研究交流クラブ第177 回定例会 共同研究推進事業成果発表会, 名古屋銀行協会(名古屋), 2016/7/26, 国内.
22. Enantioselective Trichloromethylation of MBH-Fluorides with Chloroform Based on Silicon-assisted C-F Activation, 口頭 (招待講演), Norio Shibata, 18th European Symposium on Fluorine Chemistry, Hotel Ramada Encore (Kyiv, Ukraine), 2016/8/7-12, 国外.
23. C-F and C-H Bond Activations under Organocatalysis: Enantioselective trichloromethylation and Alkenylation of MBH-fluorides based on silicon-assisted C-F activation, 口頭 (招待講演), Norio

Shibata, International Symposium on Pure & Applied Chemistry (ISPAC) 2016, Borneo Convention Center Kuching (Kuching, Malaysia), 2016/8/15-18, 国外.

24. C-F and C-H Bond Activations under Organocatalysis: Enantioselective trichloromethylation and Alkenylation of MBH-fluorides based on silicon-assisted C-F activation, 口頭 (招待講演), Norio Shibata, 6th Korea-Japan-China Joint Seminar on Fluorine Chemistry, International Hotel Changwon (Changwon, Korea), 2016/9/7-9, 国外.
25. 炭素-フッ素結合の活性化を基軸とするフッ素化合物の不斉合成, 口頭 (招待講演), 柴田哲男, 第9回有機触媒シンポジウム, 名古屋大学 ES ホール (名古屋), 2016/12/1-2, 国内
26. Preparation of meta- and para-SF₅-substituted pyridines, 口頭 (招待講演), Norio Shibata, 23th Winter Fluorine Conference, Hilton Clearwater Beach (Florida, USA), 2017/1/15-20, 国外.
27. Asymmetric desymmetrization via non-metallic C-F bond activation: Synthesis of 3,5-diaryl-5-fluoromethyl-oxazolidin-2-ones with quaternary carbon center, 口頭 (招待講演), Norio Shibata, 253rd American Chemical Society National Meeting & Exposition, The Moscone Center (San Francisco, USA), 2017/4/2-6, 国外.

(3) 「国民との科学・技術対話社会」に対する取り組み
なし

(4) 特許出願

特願 2012-174671 号

特願 2013-101853 号

特願 2013-115430 号

特願 2013-115436 号

特願 2013-117554 号

特願 2013-117946 号

PCT/JP2013/070772

PCT/JP2013/070771

特願 2013-199758 号

特願 2013-208757 号

特願 2013-208766 号

特願 2013-223811 号

特願 2014-034045 号

PCT/JP2014/064817

特願 2014-153692 号

特願 2014-157623 号

特願 2014-164814 号

特願 2014-216164 号

特願 2014-235779 号

特願 2015-007675 号

特願 2015-008256 号