Part I Transition metal-catalyzed
trifluoromethylation of olefins Part II
Biocompatible disulfide bridging reaction

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2018

Wu, L. (2018). Part I Transition metal-catalyzed trifluoromethylation of olefins Part II Biocompatible disulfide bridging reaction. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/88615>

<https://doi.org/10.32657/10220/47074>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**Part I: TRANSITION METAL-CATALYZED
TRIFLUOROMETHYLATION OF OLEFINS**

**Part II: BIOCOMPATIBLE DISULFIDE
BRIDGING REACTION**

WU LIUHAI

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2018

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TRIFLUOROMETHYLATION OF OLEFINS**

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BRIDGING REACTION**

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A thesis submitted to Nanyang Technological University in particular fulfillment of
the requirement for the degree of Doctor of Philosophy

2018

This thesis is dedicated to my beloved fiancée

Zhang Ye

ACKNOWLEDGEMENTS

First, I own my gratitude to my supervisor Professor Loh Teck Peng who has become my supervisor since I joined his research group as an undergraduate in 2012. His brilliant insight into chemistry and invaluable guidance have encouraged me to become a good researcher.

I would also like to express my gratitude to my labmates, Prof. Shen Zhi Liang, Mr Zhang Qiu Chi, Dr Shen, Liang, Dr Zhang Yong Hui, Dr Cheng Jun Kee, Dr Hu Xu Hong and Dr Zhao Kai for their kind help and valuable suggestions.

I also acknowledge the staffs in Nanyang Technological University, namely, Mrs Chen Xiaoping, Mrs Goh Ee Ling, Ms Ng Pei Fan, Florence, Mrs Zhu Wen Wei, Mr Wang Wee Jian.

I would like to express my great and sincere thankfulness to my parents and grandparents for their constant support, endless love and numerous sacrifices for me.

Finally, I would like to express my gratitude and deepest love to my fiancée Zhang Ye, the girl who I have fallen in love with since I was 15 years old. My dear, I still remember the old days, when the young boy met the young girl in the school bus. Thank you for being with me, your love and encouragement have brightened up my day.

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SUMMARY

This thesis contains two parts. Part I describes trifluoromethylation of olefins and Part II describes biocompatible disulfide bridging reactions

Chapter 1

In chapter 1, recent development in preparation of fluorinated compounds via fluoroalkylation and C–H bond functionalization of alkenes via radical intermediate were discussed.

Chapter 2

In chapter 2, copper-catalyzed trifluoromethylation of olefins with Langlois reagent was described. Excellent selectivity was achieved with styrene derivatives and mechanistic studies revealed the involvement of a radical process.

Chapter 3

In chapter 3, visible light-induced trifluoromethylation of fluorinated alkenes via $\text{C}(\text{sp}^2\&\text{sp}^3)\text{--F}$ bond functionalization using Langlois reagent as CF_3 source was discussed. The reactions proceeded efficiently via trifluoromethyl radical addition

followed by β -fluorine elimination process, providing a new entry to multifluorinated alkenes in moderate to good yields with excellent stereoselectivities.

Chapter 4

In chapter 4, a new class of site-specific reagents to effect disulfide bridging with thiol substrates under biocompatible conditions was described. Disulfide bridging of N-Ac-oxytocin with these reagents was successfully achieved in high yields.

LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
Ar	aryl
Asn	asparagine
Boc	tert-butyloxycarbonyl
bs	broad singlet
d	doublet
dd	doublets of doublet
dt	doublet of triplets
DCE	1,2-dichloroethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DTBP	di- <i>tert</i> -butyl peroxide
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate

EtOH	ethanol
EWG	electron-withdrawing group
Gln	glutamine
Gly	glycine
h	hour
$h\nu$	photoirradiation
HRMS	high resolution mass spectrometry
Hz	Hertz
Ile	isoleucine
<i>i</i> Pr	isopropyl
<i>i</i> PrOH	isopropanol
J	coupling constant
LED	light-emitting diode
Leu	leucine
m	multiplet
m.p.	melting point
MAP	mitogen-activated protein
MHz	megahertz
MTBE	methyl tert-butyl ether
<i>n</i> Pr	n-propyl
<i>n</i> Bu	n-butyl
<i>n</i> Hex	n-hexane

NFSI	N-fluorobenzenesulfonimide
NMI	1-methylimidazole
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
OAc	acetate
OTf	trifluoromethanesulfonate
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
PivOH	pivalic acid
Pro	proline
Py	pyridine
q	quartet
rt	room temperature
s	singlet
SET	single-electron-transfer
t	triplet
td	triplet of doublets
<i>t</i> Bu	<i>tert</i> -butyl
TBHP	<i>tert</i> -butyl hydroperoxide
NEt ₃	triethylamine
TBAB	tetra- <i>n</i> -butylammonium bromide
TFA	trifluoroacetate
TMS	trimethylsilyl

TLC	thin layer chromatography
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidine
Tyr	tyrosine

Chapter 1

General Introduction

1.1 Preparation of Fluorinated Organic Molecules

Fluorination chemistry has played an important role in organic synthesis, which could be trace back to 100 years ago.¹ However, owing to the unique properties of fluorine (high electronegativity etc.),² the development efficient and convenient methods to introduce fluorine into organic molecules is an important area in organic synthesis especially in medical and agricultural sciences. Therefore, over the last decades, fluorination chemistry has drawn increasing attention and various novel methodologies including monofluorination and multifluorination have been developed.

1.1.1 Fluorination

Direct carbon–fluorine bond formation is the most straightforward way to introduce fluoride into organic molecules. Generally, such protocol could be achieved by both electrophilic fluorination and nucleophilic fluorination with the necessary fluorinating reagents. The first transition metal-catalyzed electrophilic aromatic fluorination of C–H bond was reported by Sanford’s group (Scheme 1-1, a).³ Later in 2009, Yu also developed aromatic C–H bond fluorination in the presence of palladium complex (Scheme 1-1, b).⁴ In both these reactions, the coordinating groups are necessary, which limit the structural diversity of the substrates.

¹ a) Borodine, A. *Ann. Chem. Pharm.* 1863, 126, 58–62. b) Swarts, F. *Bull. Acad. R. Med. Belg.* **1898**, 35, 375–420.

² O’Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308–319.

³ K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, 128, 7134 – 7135.

⁴ Wang, X. Mei, T.-S. Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, 131, 7520–7521.

a. Sanford's group

b. Yu's group

Scheme 1-1. Palladium-catalyzed electrophilic fluorination of arenes

Over the latest 20 years, organocatalysis has been widely applied in the organic synthesis, which provides an alternative way to achieve asymmetric synthesis without transition metals. In 2005, Groups of Macmillan, Jørgensen and Barbas have simultaneously pioneered enantioselective α -fluorination of aldehydes/ketones through asymmetric organocatalysis (Scheme 1-2).⁵ In these processes, chiral enamine intermediates are induced in the presence of chiral amine catalysts, which then undergo chiral fluorination with electrophilic fluorinating reagents to give chiral α -fluorination products.

⁵ a) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828. b) Marigo, M.; Fielenbach, D. I.; Braunton, A.; Kjøersgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706. c) Steiner, D. D.; Mase, N.; Barbas, C. F.; *Angew. Chem. Int. Ed.* **2005**, *44*, 3706–3710.

a. MacMillan's group

catalyst =

b. Jørgensen's group

catalyst =

c. Barbas's group

catalyst =

Scheme 1-2. Organocatalytic enantioselective α -fluorination of aldehydes

Alternatively, nucleophilic fluorination provides an attractive approach to fluorinated compound owing to low-cost alkali-metal fluoride salts are commonly used in these protocols. At the same time, nucleophilic fluorination is still a challenge as fluorine is the most electronegative element and fluoride ion has low nucleophilicity. As Pd^{II} complex tends to form the fluoride-bridge dimer,⁶ which impeded the reductive elimination, palladium-catalyzed nucleophilic fluorination is more difficult, compared

⁶ Grushin, V. V.; Marshall, W. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4476–4479.

with nickel, copper etc. Buchwald first developed cross-coupling fluorination with cesium fluoride through palladium catalysis in 2009 (Scheme 1-3).⁷ In this transformation, bulky monodentate phosphine ligand (*t*BuBrettPhos) was used, which was essential to the C–F reductive elimination.

Scheme 1-3. Palladium-catalyzed nucleophilic fluorination

1.1.2 Mono-/di-/trifluoromethylation

In addition to direct fluorination, fluoroalkylation is also an alternative and convenient approach to introduce fluorinated group into molecules in organic synthesis. In 2009, Olah reported the nucleophilic fluoromethylation via introducing α -fluoro- α -nitro(phenylsulfonyl)methane into α,β -unsaturated ketones through organocatalysis. In this transformation, a chiral cinchona alkaloid derived catalyst was used for enantioselective addition through hydrogen bonding (Scheme 1-4).⁸

⁷ Watson, D. A.; Su, M. J.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, 325, 1661–1664.

⁸ Prakash, G. K. S.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *Proc. Natl. Acad. Sci. USA* **2009**, 106, 4090–4094.

Scheme 1-4. Asymmetric nucleophilic fluoromethylation through organocatalysis.

In addition to fluoromethylation, introduction of difluoromethyl and trifluoromethyl group into organic molecules through nucleophilic or electrophilic substitution reaction is another important strategy to give multifluorinated compounds. For the electrophilic difluoromethylation reactions, radical process is usually involved in the presence of oxidant. In 2012, Baran's group reported difluoromethylation of hetero-arenes with oxidant ($t\text{BuOOH}$) and $\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$ as novel difluoromethylating reagent (Scheme 1-5).⁹ In the reaction, the difluoromethyl radical was generated from single electron transfer (SET) and reacted with the electron-poor sites bearing a variety of hetero-arenes.

Scheme 1-5. Electrophilic difluoromethylation of hetero-arenes

⁹ Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497.

Later in 2012, the nucleophilic difluoromethylation of aryl and vinyl iodide has been developed by Hartwig's group. This difluoromethylation is mediated by copper salt, bearing both electron-poor and electron-rich substituent groups to give desired products in good yields (Scheme 1-6).¹⁰

Scheme 1-6. Nucleophilic difluoromethylation of aryl and vinyl iodide

Moreover, recently, Hu and Wang have independently reported transition metal-free difluoromethylation of diazo compounds (Scheme 1-7).¹¹ The reactions proceeded through nucleophilic addition of diazo compounds generated in situ from difluorocarbene along with elimination of N₂ to give the desired difluoromethylated compounds.

¹⁰ Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527.

¹¹ a) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14496–14501. b) Zhang, Z.; Yu, W.; Wu, C.; Wang, C.; Zhang, Y.; Wang, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 273–277.

Hu

Condition **A**: $TMSCF_3$ (2.4 equiv), NaI (2.2 equiv), THF, 60 °C, 5 h

Condition **B**: $TMSCF_2Br$ (1.5 equiv), $n-Bu_4NBr$ (4 mol%), THF, 80 °C, 12 h

Wang

Scheme 1-7. Difluoromethylation of diazo compounds with difluorocarbene

Compared to mono-/difluoromethylation, introducing trifluoromethyl group has drawn considerable interests in the past decade, owing to its lipophilicity and wide application in the pharmaceutical synthesis. Hence, various reagents and methodologies have been developed and selected examples will be introduced in the chapter 2.

1.1.3 Our group's work

Selective examples:

a.

Tian, P.; Feng, C. *Nat. Commun.* **2015**, 6, 7472

b.

Tian, P.; Wang, C.-Q.; Cai, S.-H.; Song, S.; Ye, Lu.; Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* **2016**, 138, 15869–15872

c.

Tang, H.-J.; Li, L.-Z.; Feng, C.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2017**, 56, 9872–9876

In recent years, our group has also achieved a series of novel and practical fluorinations/trifluoromethylations through C–F bond activation or F[−] addition to *gem*-difluoroalkenes, giving the corresponding fluorinated/trifluoromethylated products in good yields.

1.2 Radical Involved C–H Bond Functionalization of Alkenes

Scheme 1-8. Radical functionalization of alkenes

Substituted alkene is one of the most important structures in natural products, agrochemicals and pharmaceuticals.¹² Thus, functionalization of olefins has constantly drawn the attention of chemists in the past decades. Browsing through the various strategies reported, direct C–H bond functionalization has emerged as one of the most convenient approaches to introduce functional group into alkenes.¹³ Radical addition to unsaturated C=C bond is a well-known process which has been widely used in polymer chemistry.¹⁴ In addition to conventional transition metal-catalyzed cross-coupling alkenylation,¹⁵ radical involved C–H bond functionalization has gained increasing importance in view of its high reactivity and wide synthetically potential.¹⁶ Normally, the radical is generated from SET reduction or SET oxidation initiated by a transition metal, followed by radical addition to form radical adduct intermediate with carbon-centered radical.¹⁷ However, the subsequent elimination is usually impeded by coupling reaction with radical species (Scheme 1-8, path a)¹⁸ or reductive addition with nucleophile (Scheme 1-8, path b)¹⁹ to give the difunctional product. In past decade, a series of methodologies have been developed to achieve the C(sp²)–H bond functionalization with elimination step (Scheme 1-8, path c).¹⁶

1.2.1 Radical generated through SET reduction of organic halides

¹² Wang, J.; Chataigner, I. *Stereoselective alkene synthesis*, Springer Verlag, Heidelberg, New York, **2012**.

¹³ Oestreich, M. *The Mizoroki–Heck reaction*, Wiley, Hoboken, NJ, **2009**.

¹⁴ Tōgō, H. *Advanced free radical reactions for organic synthesis*, Elsevier, Amsterdam, Boston, 1st edn, **2004**.

¹⁵ a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–9652. b) Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Chem. Soc. Rev.* **2017**, *46*, 586–602.

¹⁶ Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753–764.

¹⁷ Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070–1082.

¹⁸ Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610.

¹⁹ a) Fumagalli, G.; Boyd, S.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4398–4401. b) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 2794–2800.

Scheme 1-9. Nickel or copper-catalyzed radical alkenyl C–H activation

Among radical processes of C–H bond functionalization, alkyl radicals can be readily generated via the single electron transfer between organic halides and transition metals. Since 2012, Lei's group has reported a series of nickel-catalyzed radical alkenyl C–H activation protocol which used alkyl bromide as coupling partner.²⁰ In the following year, Nishikata's and Lei's groups individually developed radical alkenylation with copper catalyst and tertiary alkyl bromide to form corresponding product as the *E* isomer.²¹ In these reactions, the alkyl radical is induced by SET reduction of alkyl bromide with nickel or copper catalyst. Such radical then undergoes radical addition to alkene and the resulting intermediate was oxidized and deprotonated

²⁰ a) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 3638–3641.
 b) Tang, S.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, 49, 2442–2444.

²¹ a) Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013**, *135*, 16372–16375. b) Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. *Org. Biomol. Chem.* **2014**, *12*, 6790–6793.

to give the title product (Scheme 1-9).

In 2002, Oshima et al. developed a cobalt-catalyzed cross-coupling reaction between alkyl halide and styrene.²² A further mechanistic study demonstrated this reaction proceeds with a single electron transfer process (Scheme 1-10). The alkyl radical is generated through SET reduction along with oxidation of Co^0 to Co^{I} . Then, benzyl radical adds to styrene with formation of an alkyl radical. After that, such radical species is captured by Co^{I} complex to form C-Co^{II} followed by β -Hydride elimination. Finally, Co^0 is regenerated by reductive elimination. In addition to traditional Heck reaction, the radical process was also proposed to be involved in the palladium catalysis. In 2014, Alexanian and Zhou simultaneously demonstrated radical coupling reactions between alkenes and alkyl iodide with good functional group tolerance. In the proposed mechanism, a single electron transfer process is involved, which is similar to cobalt catalytic cycle (Scheme 1-10).

Nowadays, various novel radical alkenyl functionalization reactions with SET reduction have been explored. In addition to conventional transition metal catalysis, photocatalysis and organocatalysis have been successfully introduced in this reaction protocols.²³

²² Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514–6515.

²³ a) Maity S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9562–9566. b) Sun, C.-L.; Gu, Y.-F.; Wang, B.; Shi, Z.-J. *Chem. – Eur. J.* **2011**, *17*, 10844–10847. c) Shirakawa, E.; Zhang, X.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 4671–4674.

Scheme 1-10. Cobalt or palladium-catalyzed radical alkenyl C–H functionalization

1.2.2 Radical generated through SET oxidation

Alternatively, alkyl radical could also be furnished from organoboron compounds or directly from aliphatic C–H bond through single electron transfer oxidation. In 2013, Lei's group achieved nickel-catalyzed oxidative coupling reaction between arylboronic acids and styrenes through single electron transfer oxidation, while TEMPO was employed as oxidant (Scheme 1-11).²⁴ In the same year, such oxidative protocol was also achieved by Chemler and co-workers while copper complex was served as catalyst along with MnO₂ as oxidant (Scheme 1-11).²⁵ The further ring expansion reaction of 1-phenylvinylcyclopropane, carried out by Chemler's group, strongly supported the

²⁴ Liu, D.; Liu, C.; Lei, A. *Pure Appl. Chem.* **2014**, *86*, 321–328.

²⁵ Liwosz, T. W.; Chemler, S. R. *Org. Lett.* **2013**, *15*, 3034–3037.

radical mechanism.²⁵

Scheme 1-11. Nickel or copper-catalyzed radical alkenyl C–H functionalization with organoboron compounds

Aside from oxidation of organoboron compounds, the direct oxidation of aliphatic C–H bond to generate alkyl radical supply a more atom-economic and environmentally friendly pathway to functionalize alkenes. In 2014, Lei's group reported a copper-catalyzed direct alkenylation of ether derivatives. In this transformation, DTBP was used as oxidant and various ether derivatives were applicable (Scheme 1-12, a).²⁶ Simultaneously, Wei's group also demonstrated an oxidative alkenylation of unactivated alkanes in the presence of copper catalyst and DTBP (Scheme 1-12, b).²⁷ The radical process was involved in proposed mechanism. In this reaction protocol, alkyl radical is directly initiated from oxidation of C–H bond with *tert*-butoxyl radical. The adduct intermediate is generated through radical addition, followed by the oxidative elimination to obtain the desired alkenylated product. The copper catalyst in this transformation plays an important role to mediate the generated of *tert*-butoxyl radical.

²⁶ Liu, D.; Liu, C.; Li, H.; Lei, A. *Chem. Commun.* **2014**, 50, 3623–3626.

²⁷ Zhu, Y.; Wei, Y. *Chem. Sci.* **2014**, 5, 2379–2382.

a. Lei's work:

b. Wei's work:

Scheme 1-12. Copper-catalyzed radical alkenylation through direct aliphatic C–H bond oxidation

In addition to aliphatic C–H bond, aldehyde, amide, sulfonate and etc., which are capable to generate corresponding radicals through SET oxidation, have been also applied to radical C–H bond functionalization of alkenes in recent years.²⁸

²⁸ a) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, 52, 2256–2259. b) Liwosz, T. W.; Chemler, S. R. *Chem.–Eur. J.* **2013**, 19, 12771–12777. c) Taniguchi, N. *Synlett*, **2011**, 1308–1312.

Chapter 2

Copper-catalyzed Trifluoromethylation of Olefins with $\text{CF}_3\text{SO}_2\text{Na}$

2.1 Introduction

Organic molecules containing trifluoromethyl groups have played a very important role in pharmaceuticals, agrochemicals, and organic materials, mainly owing to their unique electron-withdrawing character, metabolic stability, and lipophilicity.²⁹ Hence, developing efficient and reliable methodologies for the generation of C-CF₃ bond is highly sought after. In the last decade, various strategies for copper- and palladium-catalyzed trifluoromethylation of aromatic compounds have been well developed.³⁰ Typically, a general method for the trifluoromethylation of aryl chlorides has been developed by Buchwald and co-workers.^{30a} Moreover, the groups of Yu,^{30b} Bräse,^{30c} and Zhang^{30d} have individually reported efficient strategies for the direct trifluoromethylation of aryl C-H bonds in proximity to directing groups.

Scheme 2-1. Trifluoromethylating reagents

²⁹ For selected reviews, see: a) Hiyama, T. *Fluorine Compounds: Chemistry and Applications*; Springer: Berlin, **2000**. b) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, UK, **2006**. c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

³⁰ For selected reviews of aromatic trifluoromethylation, see: a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679–1681. b) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649. c) Hafner, A.; Bräse, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3713–3715. d) Shen, C.; Xu, J.; Ying, B.; Zhang, P. *ChemCatChem* **2016**, *8*, 3560–3564. e) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464–5467. f) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4521. g) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477. h) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 5048–5050. i) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948–11951. j) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298–1304. k) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95–99. l) Li, Y.; Wu, L.; Neumann, H.; Beller, M. *Chem. Commun.* **2013**, *49*, 2628–2630. m) O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11868–11871. n) Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2016**, *138*, 5809–5812.

Recently, introducing trifluoromethyl groups into alkenes has drawn increasing attention from the synthetic community, owing to the unique bioactivity and wide application of trifluoromethylated alkenes in the biochemistry and chemical synthesis.³¹ There are various novel and efficient methods having been developed to achieve trifluoromethylation of both pre-functionalized and terminal alkenes with nucleophilic or electrophilic trifluoromethylation reagents.

2.1.1 Trifluoromethylation of pre-functionalized alkenes

In 2011, Buchwald's group first achieved palladium-catalyzed trifluoromethylation of vinyl sulfonates. Commercially available TMSCF₃ and TESCF₃ were served as nucleophilic CF₃⁻ source in the presence of fluoride salt (Scheme 2-2).³² This reaction prefers six-membered substrates while smaller or larger rings demonstrated low yields.

Scheme 2-2. palladium-catalyzed trifluoromethylation of vinyl sulfonates

³¹ a) Xiao, J.; Weisblum, B.; Wipf, P. *J. Am. Chem. Soc.* **2005**, *127*, 5742–5743; b) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157.

³² Cho, E. J.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 6552–6555.

Simultaneously, Bräse and co-workers, on the other hand, reported a trifluoromethylation of vinyl halides by employing a stoichiometric quantity of copper iodide to *in situ* generate CuCF_3 species (Scheme 2-3).³³ Both activated and non-activated vinyl halides were compatible to this reaction, giving the corresponding products in moderate to excellent yields. Notably, *E/Z* ratio of products are highly depending on the *E/Z* ratio of starting materials, single product would be given with single isomer while *E/Z* mixtures only give non-stereospecific products.³⁴

Scheme 2-3. Copper-mediated trifluoromethylation of vinyl halides

Not only nucleophilic trifluoromethylation reagents, but also electrophilic reagent, for example, Togni's reagent, has been widely applied to the vinyl trifluoromethylation.³⁵ In 2012, Buchwald's group demonstrated an iron(II)-catalyzed trifluoromethylation of vinyl borates with Togni's reagent as CF_3 source (Scheme 2-4).³⁶ The reaction proceeds under mild reaction conditions and is amenable to various vinyl borates, including styrene and aliphatic vinyl derivatives, giving the corresponding products with good to excellent stereoselectivity. The authors suggested that a

³³ Hafner, A.; Bräse, S. *Adv. Synth. Catal.* **2011**, 353, 3044–3048.

³⁴ a) Zhang, X.; Qing, F.-L.; Yu, Y. *J. Org. Chem.* **2000**, 65, 7075–7082. b) Nowak, I.; Robins, M. J. *J. Org. Chem.* **2007**, 72, 2678–2681.

³⁵ a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, 12, 2579–2586. b) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem. Int. Ed.* **2009**, 48, 4332–4336. c) Koller, R.; Huchet, Q.; Battaglia, P.; Welch, J. M.; Togni, A. *Chem. Commun.* **2009**, 0, 5993–5995. d) Fantasia, S.; Welch, J. M.; Togni, A. *J. Org. Chem.* **2010**, 75, 1779–1782.

³⁶ Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012**, 51, 2947–2950.

carbocationic intermediate is involved in the process while FeCl₂ is served as a Lewis acid.

Scheme 2-4. Iron(II)-catalyzed trifluoromethylation of vinyl borates

Carboxylic acids play an important role in organic synthesis, which was widely used for decarboxylative C–C bond formation. In 2012, Hu's group reported a copper-catalyzed decarboxylative trifluoromethylation of α , β -unsaturated carboxylic acids with Togni's reagent (Scheme 2-5).³⁷ A series of substrates with both electron-withdrawing and electron-donating groups were successfully subjected to this reaction with high *E/Z* ratio. Meanwhile, other Togni-type electrophilic fluoroalkylating reagents were tested, furnishing the corresponding products as well.

Scheme 2-5. Copper-catalyzed decarboxylative trifluoromethylation of α,β -unsaturated

³⁷ He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3944–3947.

carboxylic acids

In 2015, a similar work was then disclosed by Cai's group. They extended the work to achieve metal-free trifluoromethylation of α,β -unsaturated carboxylic acids, using Togni's reagent as CF_3 source (Scheme 2-6).³⁸ Controlled experiment was carried out and the reaction was shut down in the presence of radical scavengers TEMPO, which indicated a radical process was likely involved in this transformation. In this case, a plausible radical mechanism was proposed, in which CF_3 radical is supposed to be induced from homolytic cleavage of Togni's reagent under heating. The radical species then undergoes radical addition to α,β -unsaturated carboxylic acid to generate intermediate, followed by facile release of CO_2 , leading to the desired trifluoromethylated product in good yield with single *E* isomer.

Scheme 2-6. Metal-free decarboxylative trifluoromethylation of α,β -unsaturated carboxylic acids

³⁸ Ma, J.-J.; Yi, W.-b.; Lu, G.-P.; Cai, C. *Adv. Synth. Catal.* **2015**, 357, 3447–3452.

In addition to generation of CF_3 radical from Togni's reagent, Beller's group has employed a stable and less expensive reagent, $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois reagent), as CF_3 source to achieve copper-catalyzed trifluoromethylation of vinyl boronic acid in the presence of TBHP served as oxidant (Scheme 2-7).³⁰¹ Two mechanistic paths were proposed in this reaction. Initially, CF_3 radical is induced from oxidation of $\text{CF}_3\text{SO}_2\text{Na}$ with TBHP along with release of SO_2 . CF_3 radical then reacts with copper complex in the presence of vinyl boronic acid to give intermediate $\text{vinylCu(III)CF}_3\text{Ln}$ through path A³⁹ or path B⁴⁰. Trifluoromethylated alkene is obtained by reductive elimination, followed by release of Cu(I)Ln . Finally, Cu(I)Ln is oxidized to recover initial Cu(II)Ln . Notably, this reaction protocol is robust and works under mild reaction conditions, which gives the desired vinyl products in excellent *E/Z* selectivity.

³⁹ Chen, C.; Xie, Y.; Chu, L.; Wang, R.-W.; Zhang, X.; Qing, F.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2492–2495.

⁴⁰ Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298–1304.

Scheme 2-7. Copper-catalyzed trifluoromethylation of vinyl boronic acid with $\text{CF}_3\text{SO}_2\text{Na}$

2.1.2 Trifluoromethylation of terminal alkenes

Although trifluoromethylation of pre-functionalized alkenes shows good reactivity and regioselectivity, but it is not economical (in terms of both cost and atom) in view that multistep synthesis is required to prepare the pre-functionalized substrates. Thus, in the viewpoint of cost and atom economy, developing new methods for direct trifluoromethylation of vinyl C-H bonds is desirable.^[4] Notably, several seminal works for the direct trifluoromethylation of terminal alkenes by employing various trifluoromethyl reagents (e.g., trifluoroalkyl halide, Togni's reagent, and Umemoto's reagent) in the presence of transition metal catalysis have been developed.

In 2012, Cho and co-workers achieved trifluoromethylation of unactivated alkenes through photocatalysis (Scheme 2-8).⁴¹ The key step involves generation of CF_3 radical from volatile CF_3I via visible light-induced single electron transfer, followed by radical addition to double bond.⁴² Finally, the authors proposed the final *E*-isomer product is likely generated through E2 elimination.

⁴¹ Iqbal, N.; Choi, S.; Kim, E.; Cho, E. *J. Org. Chem.* **2012**, 77, 11383–11387.

⁴² a) Tokel-Takvoryan, N. E.; Hemingway, R. E.; Bard, A. J. *J. Am. Chem. Soc.* **1973**, 95, 6582–6589. b) Onesi, S. M.; Erra-Balsells, R. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1583–1595.

Scheme 2-8. Photocatalyzed trifluoromethylation of terminal alkenes

Cho's work supplies a novel approach to trifluoromethylation of terminal alkenes. However, the use of gaseous CF_3I limited the application of this methodology, owing to the toxicity and volatility associated with CF_3I . In 2013, Xiao's group demonstrate an alternative approach to access trifluoromethylation of terminal alkenes in the presence of copper catalyst and Togni's reagent (Scheme 2-9).⁴³ The controlled experiment with TEMPO reveals that a radical process is involved in this transformation. Initially, the reaction between copper and Togni's reagent generated a radical intermediate, releasing trifluoromethyl radical via homolytic ruptures of C–I bond. The CF_3 radical is then trapped by alkene, leading to trifluoromethylated secondary carbon radical. Subsequently, the radical adduct is oxidized and undergoes elimination in the presence of base to form the desired *E*-isomer product. In 2016, a similar work was disclosed by Noël's group, in which Ir(ppy)_3 and CF_3I was employed to achieve trifluoromethylation of styrene derivatives in good yields.⁴⁴

⁴³ Wang, X.-P.; Lin, J.-H.; Zhang, C.-P.; Xiao, J.-C.; Zheng, X. *Beilstein J. Org. Chem.* **2013**, *9*, 2635–2640.

⁴⁴ Straathof, N. J. W.; Cramer, S. E.; Hessel, V.; Noël, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 15549–15553.

Scheme 2-9. Copper-catalyzed trifluoromethylation of terminal alkenes

In addition to *E*-isomers obtained from trifluoromethylation of terminal alkenes, Qing's group has achieved selective controlment of *E/Z* products by choosing different trifluoromethylation reagents and catalysts via photocatalysis (Scheme 2-10).⁴⁵ By employing Togni's reagent and styrene in the presence of Ru(bpy)₃Cl₂•6H₂O as photocatalyst, single *E*-product was attained through single electron transfer. Alternatively, Umemoto's reagent resulted in major *Z*-product by employing Ir(ppy)₃. In the second protocol, single electron transfer followed by energy transfer⁴⁶ were proposed to be involved, which successfully control the configuration of the final

⁴⁵ Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2014**, 79, 10434–10446.

⁴⁶ Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, 113, 5322–5363.

product, leading to less stable *Z*-isomers as major products.

Scheme 2-10. Visible light-mediated stereoselective trifluoromethylation of styrene derivatives

Palladium complexes are widely used in organic coupling reactions normally through oxidative addition and reductive elimination path. However, the palladium-catalyzed reactions involved radical process were less explored.⁴⁷ In 2015, Zhang's group first reported a palladium-catalyzed trifluoromethylation of alkenes by using CF_3I as reagent (Scheme 2-11).⁴⁸ Unlike conventional coupling reaction, in this case, initial step of this reaction involves single electron transfer with the participation of palladium complex to give CF_3 radical. The trifluoromethyl radical undergoes radical addition to alkene, giving a radical adduct which was trapped by $\text{XPd}^{\text{I}}\text{Ln}$ to form the key intermediate. Subsequent β -hydride elimination provides the desired product with single isomer.

⁴⁷ Liu, Q.; Dong, X.; Li, J.; Xiao, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, 5, 6111–6137.

⁴⁸ Feng, Z.; Min, Q.-Q.; Zhao, H.-Y.; Gu, J.-W.; Zhang, X. *Angew. Chem. Int. Ed.* **2015**, 54, 1270–1274.

Scheme 2-11. Palladium-catalyzed trifluoromethylation of terminal alkenes

In recent years, our group has also paid attention to trifluoromethylation of terminal enamides and alkenes, and several strategies have been investigated by our group members. In 2012, our group achieved copper-catalyzed trifluoromethylation of enamides via direct C–H functionalization with Togni’s reagent (Scheme 2-12).⁴⁹ The reaction is carried out under mild reaction conditions with excellent stereoselectivity and yields. Control experiments indicated that a radical process is involved in this transformation.

⁴⁹ Chao, F.; Loh, T.-P. *Chem. Sci.* **2012**, 3, 3458–3462.

Scheme 2-12. copper-catalyzed trifluoromethylation of terminal enamides

Scheme 2-13. Copper-catalyzed direct trifluoromethylation of acrylate-type derivatives

Later, our group further explored copper-catalyzed direct trifluoromethylation of other electron-deficient olefins (Scheme 2-13).⁵⁰ In this protocol, amide group in the olefin serves as a directing group, in which nitrogen atom could react with copper

⁵⁰ Feng, C.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2013**, 52, 12414–12417.

catalyst. Then, Cu^I undergoes oxidative addition to Togni's reagent to form Cu^{III}-CF₃ intermediate, followed by single electron transfer and cyclization to give the intermediate bearing carbocation in α -position. Subsequently, reductive elimination, following hydride elimination affords the trifluoromethylated acrylate-type products.

However, to the best of our knowledge, direct trifluoromethylation of olefins, especially styrene derivatives with a cheap and stable reagent, is still proven to be a challenge. Herein, we report a copper-catalyzed direct trifluoromethylation of vinyl C-H bonds of olefins with CF₃SO₂Na (Langlois reagent).⁵¹

⁵¹ Zhang, C. *Adv. Synth. Catal.* **2014**, 356, 2895–2906.

2.2 Results and discussion

Table 2-1. Optimization of Reaction Conditions

$\text{Ph}_2\text{C=CH}_2$ (**1a**) + $\text{CF}_3\text{SO}_2\text{Na}$ (**2**) $\xrightarrow[\text{Solvent (1 mL), 12 h}]{\text{Cat. (10 mol\%), Ligand (15 mol\%), Oxidant (2 equiv)}}$ $\text{Ph}_2\text{C=CH-CF}_3$ (**3a**)

Entry	Catalyst	Ligand	Oxidant	Solvent	T (°C)	Yield (%) ^b
1	CuI	--	TBHP	DCE	80	19
2	Co(OAc) ₂	--	TBHP	DCE	80	17
3	CuI	--	TBHP	DCE	rt	0
4	CuI	--	TBHP	DCE	120	29
5	CuI	--	K ₂ S ₂ O ₈	DCE	80	6
6	CuI	--	DTBP	DCE	80	0
7	CuI	--	DTBP	DCE	120	18
8	CuI	NMI	DTBP	DCE	120	75(64) ^c
9	CuI	NMI	TBHP	DCE	120	19
10	CuI	NMI	DTBP	toluene	120	20
11	CuI	NMI	DTBP	dioxane	120	32
12	CuI	NMI	DTBP	DCE	120	80(69) ^{c,d}
13	CuI	NMI	DTBP	DCE	120	81(73) ^{c,e}
14	--	NMI	DTBP	DCE	120	30 ^e

^aReaction conditions: **1a** (0.20 mmol), **2** (0.3 mmol), catalyst (0.02 mmol), oxidant (0.4 mmol), ligand (0.03 mmol), solvent (1 mL). ^bDetermined by ¹H NMR using 1,4-dinitrobenzene as an internal standard.

^cIsolated yield. ^d**2** (0.48 mmol). ^e**2** (0.48 mmol), ⁿBu₄NI (0.04 mmol).

At the beginning of our investigation, 1,1-diphenylethylene (**1a**) was chosen as a model substrate to react with CF₃SO₂Na for the optimization of reaction conditions (Table 2-1). Based on previous reports,³⁹ ^tBuOOH (TBHP) was used as an oxidant in the presence of metal catalysts. To our delight, the desired product **3a** was obtained by using either CuI or Co(OAc)₂ as catalyst, albeit in low yield (entries 1 and 2). Considering the comparatively lower cost and higher reaction efficiency, CuI was selected as catalyst to continue the optimization studies. Different oxidants and

temperatures were surveyed and it was found that product yield was increased to 29% yield by employing TBHP at 120 °C (entries 3-6). Interestingly, it was observed that the use of di-*tert*-butyl peroxide (DTBP) as oxidant could also provide product **3a** in 18% yield at 120 °C (entry 7). In comparison, no reaction occurred at 80 °C when other parameters remained the same (entry 6 vs entry 7).^{17,52} To further improve the yields of this reaction by using DTBP as oxidant, we tried to add 1-methylimidazole (NMI) as additive to the reaction system. Gratifyingly, the yield was significantly increased to 75% in the presence of 1-methylimidazole, which possibly served as a ligand to coordinate with copper (entry 8).⁵³ Subsequently, diverse solvents were screened, but all led to low yields except 1,2-dichloroethane (DCE) (entries 10 and 11). Increasing the ratio of Langlois reagent improved the yield to 80% (entry 12). Finally, it was observed that the addition of tetrabutylammonium iodide (TBAI) as additive could also deliver the product in a slightly higher yield (81%) along with 73% isolated yield (entry 13).

Table 2-2. Reaction Scope of 1,1-Diphenyl Derivative

⁵² Liu, D.; Liu, C.; Li, H.; Lei, A. *Chem. Commun.* **2014**, 50, 3623–3626.

⁵³ Citek, C.; Lyons, C. T.; Wasinger, E. C.; Stack, T. D. P. *Nat. Chem.* **2012**, 4, 317–322.

3a, 73%

3b, 83%

3c, 77%

3d, 84%
E/Z = 2 : 1

3e, 82%
E/Z = 2 : 1

3f, 72%

3g, 65%

3h, 68%
E/Z = 1 : 1

3i, 83%
E/Z = 1 : 3

3j, 75%
E/Z = 6 : 1

3k, 74%
E/Z = 1 : 1

3l, 76%
E/Z = 3 : 1

^aReaction conditions: **1** (0.2 mmol), **2** (0.48 mmol), DTBP (0.40 mmol), CuI (0.02 mmol), 1-methylimidazole (0.03 mmol), ⁿBu₄NI (0.04 mmol), DCE (1 mL). Yields of isolated products are given. *E/Z* ratio was determined by crude ¹⁹F NMR.

Table 2-3. Reaction Scope of Styrene Derivatives

^aReaction conditions: **4** (0.2 mmol), **2** (0.48 mmol), DTBP (0.40 mmol), CuI (0.02 mmol), 1-methylimidazole (0.03 mmol), ⁿBu₄NI (0.04 mmol), DCE (1 mL). Yields of isolated products are given.

With the optimized protocol in hand, the substrate scope of the present transformation was investigated and the results are listed in Table 2-2. 1,1-Diphenylethene derivatives containing electron-donating groups underwent the trifluoromethylation to give the corresponding products **3b-e** in good yields. Substrates containing halogen could also be well tolerated in this reaction, leading to the target

products **3f-i** in 65-83% yields. Notably, as for substrate bearing both electron-withdrawing and electron-donating substituents, was found to proceed smoothly to deliver the expected product **3j** in good yield. Moreover, both naphthalene-substituted and heteroaryl-substituted alkenes are also amenable to the standard reaction conditions, providing the anticipated products **3k-l** in good yields.

Encouraged by the results of trifluoromethylation with 1,1-diphenylethene derivatives, we further explored the applicability of various styrene derivatives and other conjugated alkenes with Langlois reagent in this transformation (Table 2-3). Styrene derivatives possessing electron-donating substituents underwent the trifluoromethylation smoothly to afford the desired products in moderate to good yields (**5a-h**). In particular, methylthio and N-containing substituents could survive in this reaction (**5g** and **5h**). Especially noteworthy is that reaction involving conjugated dienes could also proceed smoothly (**5i** and **5j**). However, substrates bearing electron-withdrawing groups were not suitable for this reaction. It should be noted that the trifluoromethylation of styrene derivatives proceeded with excellent stereoselectivity and only (*E*) isomer was observed during this transformation.

To gain mechanistic insight into this trifluoromethylation, a radical trapping reagent was introduced into the reaction system. When the reaction mixture of **1a** and **2** were treated with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard reaction conditions, the trifluoromethylation reaction was completely suppressed (Scheme 2-14a). This result suggested that a radical process is likely involved in this

transformation.⁵³ In order to further clarify that fluoroalkyl radical was generated in the reaction, a radical-clock experiment was conducted (Scheme 2-14b). When substrate **1m** was treated with **2** under standard reaction conditions, compound **6** was obtained in 21% yield, while no routine product **3m** was detected. Such result demonstrated that an alkyl radical species **A** was generated, which participated in the following radical rearrangement to form the cyclohexene product **6**.⁵⁴

Scheme 2-14. Controlled Experiments

Based on the experimental results, a plausible reaction mechanism was proposed (Figure 2-1). Initially, DTBP undergoes homolysis to generate 'BuO' radical under heating,⁵⁵ which then reacts with copper(I) species and CF_3SO_2^- to form copper(II)

⁵⁴ a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699–5707. b) Ogawa, A.; Ogawa, I.; Sonoda, N. *J. Org. Chem.* **2000**, *65*, 7682–7685. c) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197–1212. d) Shirakawa, E.; Zhang, X.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 4671–4674. e) Liwosz, T. W.; Chemler, S. R. *Org. Lett.* **2013**, *15*, 3034–3037.

⁵⁵ Zhao, J.; Fang, H.; Han, J.; Pan, Y.; Li, G. *Adv. Synth. Catal.* **2014**, *356*, 2719–2724.

complex and $\text{CF}_3\text{SO}_2^\bullet$ radical. Trifluoromethyl radical ($\text{CF}_3^\bullet$) is generated from the homolysis of $\text{CF}_3\text{SO}_2^\bullet$ along with the concomitant release of sulfur dioxide,^{30l} followed by addition across alkene **1** or **4** to afford an alkyl radical species **D** (based on Scheme 2b). Subsequently, the reaction of **D** and copper(II) complex should afford the intermediate **E**. Finally, elimination occurs in the presence of strong base ($^t\text{BuO}^-$) to furnish the desired product **3** or **5**, accompanied by the releasing of copper(I) complex.

Figure 2-1. Proposed Reaction Mechanism

2.3 Conclusion

In conclusion, we have developed a copper(I)-catalyzed trifluoromethylation of terminal alkenes by using stable and less expensive Langlois reagent. Various olefins were proven to be appropriate candidates for the reaction under the mild reaction conditions, leading to the corresponding trifluoromethylated alkenes in good yields.

Notably, styrene derivatives underwent the present trifluoromethylation with excellent stereoselectivity. Mechanistic studies reveal that this reaction probably proceeds through a radical pathway.

2.4 Experimental Section

General Information

Unless otherwise noted, all reagents and solvents were purchased from the commercial sources and used as received. The di-*tert*-butyl peroxide and 1-methylimidazole were purchased from Alfa-Aesar, copper(I) iodide was purchased from Stream. Thin layer chromatography was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on Spectroline Model ENF-24061/F 254 nm. Other visualization method was staining with a basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating. Flash column chromatography was performed using Merck silica gel 60 with analytical grade solvents as eluents. ¹H NMR, ¹³C NMR, ¹⁹F NMR and NOESY spectra were recorded on Bruker Avance 300 MHz spectrometers and Bruker Avance 400 MHz spectrometers. Corresponding chemical shifts are reported in ppm downfield relative to TMS and were referenced to the signal of chloroform-d (δ =7.26, singlet). Multiplicities were given as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd=doublets of doublet, dq=doublets of quartet. Values of coupling constant are reported as *J* in Hz. HRMS spectra were recorded on a Waters Q-Tof Premier Spectrometer

General procedures for the synthesis of olefins.

1a was commercially available, **1b** – **1l**¹ and **1m**² were prepared following the reported procedure.

4a – 4h², **4i**¹ and **4j**² were prepared following the reported procedure.

General procedures for the trifluoromethylation of olefins

To a 8 mL vial, charged with CuI (3.8 mg, 0.02 mmol, 10 mol%), ⁿBu₄NI (14.8 mg, 0.04 mmol, 20 mol%) and CF₃SO₂Na (75.0 mg, 0.48 mmol, 2.4 equiv.) in 1.0 mL 1,2-dichloroethane, 1-methylimidazole (2.5 mg, 0.03 mmol, 15 mol%), DTBP (58.5 mg, 0.4 mmol, 2 equiv.) and olefin (0.2 mmol, 1 equiv.) were added under nitrogen atmosphere at room temperature. The vial was sealed with screw cap and stirred at 120 °C for 12 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (5 mL), filtered through filter paper and concentrated *in vacuum*. Purification by silica gel column chromatograph affords the target product.

Mechanism study

I. Controlled reaction with TEMPO

General procedure: To a 8 mL vial, charged with CuI (3.8 mg, 0.02 mmol, 10 mol%), $n\text{Bu}_4\text{NI}$ (14.8 mg, 0.04 mmol, 20 mol%) and $\text{CF}_3\text{SO}_2\text{Na}$ (75.0 mg, 0.48 mmol, 2.4 equiv.) in 1.0 mL 1,2-dichloroethane, 1-methylimidazole (2.5 mg, 0.03 mmol, 15 mol%), DTBP (58.5 mg, 0.4 mmol, 2 equiv.), olefin (0.2 mmol, 1 equiv.) and TEMPO (78.1 mg, 0.5 mmol, 2.5 equiv.) were added under nitrogen atmosphere at room temperature. The vial was sealed with screw cap and stirred at 120 °C for 12 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (5 mL), filtered through filter paper and concentrated *in vacuum*. Based on NMR analysis, no desired trifluoromethylated product was observed.

II. Controlled reaction with radical clock.

General procedure: To a 8 mL vial, charged with CuI (3.8 mg, 0.02 mmol, 10 mol%), $n\text{Bu}_4\text{NI}$ (14.8 mg, 0.04 mmol, 20 mol%) and $\text{CF}_3\text{SO}_2\text{Na}$ (75.0 mg, 0.48 mmol, 2.4 equiv.) in 1.0 mL 1,2-dichloroethane, 1-methylimidazole (2.5 mg, 0.03 mmol, 15 mol%), DTBP (58.5 mg, 0.4 mmol, 2 equiv.) and olefin (0.2 mmol, 1 equiv.) were added under

nitrogen atmosphere at room temperature. The vial was sealed with screw cap and stirred at 120 °C for 12 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (5 mL), filtered through filter paper and concentrated *in vacuum*. Purification by silica gel column chromatograph affords the target product.

Characterization data for the trifluoromethylated olefins

3a (3,3,3-trifluoroprop-1-ene-1,1-diyl)dibenzene

Colorless oil.

Yield = 73%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.41 – 7.37 (m, 3H), 7.36 – 7.30 (m, 3H), 7.27 – 7.22 (m, 4H), 6.12 (q, J = 8.4 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 152.4 (q, J = 6 Hz), 140.1, 137.2, 129.4, 129.1 (q, J = 2 Hz), 128.5, 128.4, 128.0, 127.9, 123.1 (q, J = 269 Hz), 115.4 (q, J = 34 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -55.6 (d, J = 8.4 Hz).

HRMS (ESI, m/z): calcd for C₁₅H₁₂F₃⁺ [M+H]⁺ 249.0891, found: 249.0900.

3b 4,4'-(3,3,3-trifluoroprop-1-ene-1,1-diyl)bis(methylbenzene)

Colorless oil.

Yield = 83%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.22 – 7.16 (m, 2H), 7.16 – 7.08 (m, 6H), 6.06 (q, J = 8.4 Hz, 1H), 2.39 (s, 3H), 2.35 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 152.4 (q, J = 6 Hz), 139.5, 138.3, 137.6, 134.5, 129.1, 129.1 (q, J = 2 Hz), 128.7, 127.9, 123.3 (q, J = 268 Hz), 114.3 (q, J = 34 Hz), 21.3, 21.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -55.3 (d, J = 8.4 Hz).

HRMS (ESI, m/z): calcd for C₁₇H₁₆F₃⁺ [M+H]⁺ 277.1204, found: 277.1194.

3c 4,4'-(3,3,3-trifluoroprop-1-ene-1,1-diyl)bis(methoxybenzene)

Light yellow oil.

Yield = 77%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.22 – 7.14 (m, 4H), 6.94 – 6.88 (m, 2H), 6.88 – 6.82 (m, 2H), 5.99 (q, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 160.6, 159.8, 151.8 (q, J = 6 Hz), 133.0, 130.6 (q, J = 2 Hz), 129.8, 129.5, 123.4 (q, J = 268 Hz), 113.7, 113.4, 113.1 (q, J = 34 Hz), 56.3, 56.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -55.0 (d, J = 8.4 Hz).

HRMS (ESI, m/z): calcd for C₁₇H₁₆F₃O₂⁺ [M+H]⁺ 309.1102, found: 309.1102.

3d (*E/Z*)-1-methoxy-4-(3,3,3-trifluoro-1-phenylprop-1-enyl)benzene

Colorless oil.

Yield = 84%, *E/Z* = 2:1.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.41 – 7.32 (m, 3H, mixture), 7.27 – 7.21 (m, 2H, mixture), 7.20 – 7.15 (m, 2H, mixture), 6.94 – 6.89 (m, 2H, minor), 6.87 – 6.82 (m, 2H, major), 6.06 (q, J = 8.4 Hz, 1H, major), 6.04 (q, J = 8.4 Hz, 1H, minor), 3.85 (s, 3H, minor), 3.81 (s, 1H, major).

¹³C NMR of the *E/Z* mixture (100 MHz, CDCl₃) δ (ppm): 160.7, 159.8, 152.4 (q, J = 5 Hz), 151.8 (q, J = 5 Hz), 140.7, 137.5, 132.4, 130.6 (q, J = 2 Hz), 129.6, 129.3, 129.3, 129.1 (q, J = 2 Hz), 128.4, 128.3, 128.2, 128.0, 123.3 (q, J = 269 Hz), 123.2 (q, J = 269 Hz), 114.9 (q, J = 33 Hz), 114.0, 113.5 (q, J = 33 Hz), 113.4, 55.3, 55.2.

¹⁹F NMR of the *E*-mixture (376 MHz, CDCl₃) δ (ppm): -55.2 (d, J = 8.3 Hz).

¹⁹F NMR of the *Z*-mixture (376 MHz, CDCl₃) δ (ppm): -55.5 (d, J = 8.3 Hz).

HRMS (ESI, m/z): calcd for C₁₆H₁₄F₃O⁺ [M+H]⁺ 279.0997, found: 279.0993.

3e (*E/Z*)-1-(benzyloxy)-4-(3,3,3-trifluoro-1-phenylprop-1-enyl)benzene

White solid.

Yield = 82%, *E/Z* = 2 : 1.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.46 – 7.30 (m, 8H, mixture), 7.25 – 7.21 (m, 2H, mixture), 7.19 – 7.15 (m, 2H, mixture), 7.00 – 6.96 (m, 2H, minor), 6.93 – 6.88 (m, 2H, major), 6.05 (q, J = 8.4 Hz, 1H, major), 6.04 (q, J = 8.4 Hz, 1H, minor), 5.08 (s, 2H, minor), 5.06 (s, 1H, major).

¹³C NMR of the *E/Z* mixture (100 MHz, CDCl₃) δ (ppm): 159.8, 159.1, 152.3 (q, J = 5 Hz), 151.8 (q, J = 5 Hz), 140.7, 137.4, 136.7, 136.5, 132.6, 130.7 (q, J = 2 Hz), 129.8, 129.3, 129.3, 129.1 (q, J = 2 Hz), 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.6, 127.4, 123.3 (q, J = 268 Hz), 123.2 (q, J = 268 Hz), 115.0 (q, J = 33 Hz), 114.7,

114.3, 113.6 (q, $J = 33$ Hz), 70.1.

^{19}F NMR of the *E*-mixture (376 MHz, CDCl_3) δ (ppm): -55.1 (d, $J = 7.9$ Hz).

^{19}F NMR of the *Z*-mixture (376 MHz, CDCl_3) δ (ppm): -55.4 (d, $J = 8.3$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{O}^+ [\text{M}+\text{H}]^+$ 355.1310, found: 355.1299.

3f 4,4'-(3,3,3-trifluoroprop-1-ene-1,1-diyl)bis(fluorobenzene)

Colorless oil.

Yield = 72%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.25 – 7.18 (m, 4H), 7.12 – 7.00 (m, 4H), 6.08 (q, $J = 8.4$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 164.5 (d, $J = 62$ Hz), 162.0 (d, $J = 62$ Hz), 150.4 (q, $J = 6$ Hz), 136.1 (d, $J = 3$ Hz), 133.0 (d, $J = 4$ Hz), 131.0 (dq, $J_1 = 9$ Hz, $J_2 = 2$ Hz), 129.8 (d, $J = 8$ Hz), 122.9 (q, $J = 269$ Hz), 115.6 (q, $J = 33$ Hz), 115.6 (d, $J = 22$ Hz), 115.3 (d, $J = 22$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -55.6 (d, $J = 8.4$ Hz), -111.4 (m), -112.6 (m).

HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{10}\text{F}_3^+ [\text{M}+\text{H}]^+$ 285.0703, found: 285.0689.

3g 4,4'-(3,3,3-trifluoroprop-1-ene-1,1-diyl)bis(chlorobenzene)

Colorless oil.

Yield = 65%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 2H), 7.21 – 7.11 (m, 4H), 6.12 (q, $J = 8.4$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 150.2 (q, $J = 6$ Hz), 138.1, 135.9, 135.2, 135.0, 130.4 (q, $J = 2$ Hz), 129.2, 128.8, 128.5, 122.7 (q, $J = 269$ Hz), 116.3 (q, $J = 34$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -55.7 (d, $J = 7.9$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{F}_3^+ [\text{M}+\text{H}]^+$ 317.0112, found: 317.0096.

3h (*E/Z*)-1-chloro-4-(3,3,3-trifluoro-1-phenylprop-1-enyl)benzene

Light yellow oil.

Yield = 68%, *E/Z* = 1 : 1.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.42 – 7.28 (m, 5H, mixture), 7.25 – 7.15 (m, 4H, mixture), 6.14 (q, *J* = 8.4 Hz, 1H), 6.11 (q, *J* = 8.4 Hz, 1H).

¹³C NMR of the *E/Z* mixture (100 MHz, CDCl₃) δ (ppm): 151.3 (q, *J* = 5 Hz), 151.3 (q, *J* = 5 Hz), 139.6, 138.6, 136.8, 135.7, 135.6, 134.7, 130.5 (q, *J* = 2 Hz), 129.6, 129.2, 129.0 (q, *J* = 2 Hz), 128.7, 128.7, 128.6, 128.4, 128.2, 127.9, 122.9 (q, *J* = 269 Hz), 122.9 (q, *J* = 269 Hz), 116.3 (q, *J* = 33 Hz), 116.1 (q, *J* = 33 Hz).

¹⁹F NMR of the *E/Z* mixture (376 MHz, CDCl₃) δ (ppm): -55.6 (d, *J* = 8.4 Hz), -55.7 (d, *J* = 8.4 Hz).

HRMS (ESI, *m/z*): calcd for C₁₅H₁₁ClF₃⁺ [*M*+*H*]⁺ 283.0501, found: 283.0492.

3i (*E/Z*)-1-bromo-4-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-enyl)benzene

Colorless oil.

Yield = 83%, *E/Z* = 1 : 3.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.55 – 7.50 (m, 2H, major), 7.48 – 7.44 (m, 2H, minor), 7.18 – 7.09 (m, 4H, mixture), 6.94 – 6.89 (m, 2H, minor), 6.87 – 6.82 (m, 2H, major), 6.07 (q, *J* = 8.4 Hz, 1H, major), 6.02 (q, *J* = 8.4 Hz, 1H, minor), 3.85 (s, 3H, minor), 3.82 (s, 1H, major).

¹³C NMR of the *E/Z* mixture (100 MHz, CDCl₃) δ (ppm): 160.8, 160.1, 151.3 (q, *J* = 5 Hz), 150.6 (q, *J* = 5 Hz), 139.7, 136.4, 131.8, 131.6, 130.8 (q, *J* = 2 Hz), 130.6 (q, *J* = 2 Hz), 129.7, 129.3, 129.0, 123.8, 122.8 (q, *J* = 269 Hz), 123.0 (q, *J* = 269 Hz), 122.7, 115.2 (q, *J* = 34 Hz), 113.9, 113.9 (q, *J* = 34 Hz), 113.6, 55.4, 55.2.

¹⁹F NMR of the *E*-mixture (376 MHz, CDCl₃) δ (ppm): -55.7 (d, *J* = 8.3 Hz).

¹⁹F NMR of the *Z*-mixture (376 MHz, CDCl₃) δ (ppm): -55.1 (d, *J* = 8.3 Hz).

HRMS (ESI, *m/z*): calcd for C₁₆H₁₃BrF₃O⁺ [*M*+*H*]⁺ 357.0102, found: 357.0091.

3j (E/Z)-1-methoxy-4-(3,3,3-trifluoro-1-(4-(trifluoromethyl)phenyl)prop-1-enyl)benzene

Colorless oil.

Yield = 75%, *E/Z* = 6 : 1.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.69 – 7.63 (m, 2H, major), 7.61 – 7.57 (m, 2H, minor), 7.39 – 7.27 (m, 2H, mixture), 7.18 – 7.05 (m, 2H, mixture), 6.95 – 6.90 (m, 2H, minor), 6.89 – 6.83 (m, 2H, major), 6.14 (q, *J* = 8.4 Hz, 1H, major), 6.07 (q, *J* = 8.4 Hz, 1H, minor), 3.85 (s, 3H, minor), 3.82 (s, 1H, major).

¹³C NMR of the *E*-isomer (100 MHz, CDCl₃) δ (ppm): 160.9, 150.4 (q, *J* = 5 Hz), 141.2, 131.4, 130.6 (q, *J* = 32 Hz), 129.5 (q, *J* = 2 Hz), 129.2, 125.0 (q, *J* = 4 Hz), 124.0 (q, *J* = 271 Hz), 123.0 (q, *J* = 268 Hz), 114.4 (q, *J* = 34 Hz), 114.0, 55.4.

¹⁹F NMR of the *E*-mixture (376 MHz, CDCl₃) δ (ppm): -55.2 (d, *J* = 8.3 Hz), -62.6.

¹⁹F NMR of the *Z*-mixture (376 MHz, CDCl₃) δ (ppm): -55.9 (d, *J* = 8.3 Hz), -62.8.

HRMS (ESI, *m/z*): calcd for C₁₇H₁₃F₆O⁺ [*M*+*H*]⁺ 347.0871, found: 347.0876.

3k (E/Z)-2-(3,3,3-trifluoro-1-phenylprop-1-enyl)naphthalene

White solid.

Yield = 74%, *E/Z* = 1 : 1.

¹H NMR of the *E/Z* mixture (400 MHz, CDCl₃) δ (ppm): 7.90 – 7.62 (m, 4H, mixture), 7.57 – 7.47 (m, 2H, mixture), 7.57 – 7.47 (m, 2H, mixture), 7.39 – 7.27 (m, 4H, mixture), 6.27 (q, *J* = 8.4 Hz, 1H), 6.22 (q, *J* = 8.4 Hz, 1H).

¹³C NMR of the *E/Z* mixture (100 MHz, CDCl₃) δ (ppm): 152.4, 152.3, 140.1, 137.4, 137.2, 134.7, 133.6, 133.1, 132.9, 132.8, 129.4, 129.2 (q, *J* = 2 Hz), 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 127.7, 127.7, 127.6, 127.0, 126.8, 126.8, 126.6, 126.6, 126.4, 124.8, 123.1 (q, *J* = 269 Hz), 123.1 (q, *J* = 269 Hz), 122.9 (q, *J* = 269 Hz), 115.8 (q, *J* = 33 Hz).

¹⁹F NMR of the *E/Z* mixture (376 MHz, CDCl₃) δ (ppm): -55.4 (d, *J* = 8.3 Hz), -55.5 (d, *J* = 8.3 Hz).

HRMS (ESI, *m/z*): calcd for C₁₉H₁₄F₃⁺ [*M*+*H*]⁺ 299.1048, found: 299.1053.

3I (*E/Z*)-2-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-enyl)thiophene

Yellow solid.

Yield = 68%, *E/Z* = 3 : 1.

¹H NMR of the *E*-isomer (400 MHz, CDCl₃) δ (ppm): 7.33 (dd, *J*₁ = 5.2 Hz, *J*₂ = 1.2 Hz, 1H), 7.26 – 7.23 (m, 2H), 6.98 – 6.95 (m, 1H), 6.95 – 6.90 (m, 2H), 6.85 – 6.82 (m, 1H), 6.13 (q, *J* = 8.4 Hz, 1H), 3.85 (s, 3H).

¹H NMR of the *Z*-isomer (400 MHz, CDCl₃) δ (ppm): 7.45 (dd, *J*₁ = 5.2 Hz, *J*₂ = 1.2 Hz, 1H), 7.28 – 7.26 (m, 2H), 7.22 – 7.20 (m, 1H), 7.09 – 7.06 (m, 1H), 6.88 – 6.85 (m, 2H), 5.95 (q, *J* = 8.4 Hz, 1H), 3.82 (s, 3H).

¹³C NMR of the *E*-isomer (100 MHz, CDCl₃) δ (ppm): 160.9, 145.4 (q, *J* = 5 Hz), 144.3, 130.2 (q, *J* = 2 Hz), 129.6, 129.2, 127.8, 127.7, 123.1 (q, *J* = 269 Hz), 113.4, 112.7 (q, *J* = 34 Hz), 55.2.

¹³C NMR of the *Z*-isomer (100 MHz, CDCl₃) δ (ppm): 160.0, 145.1 (q, *J* = 5 Hz), 138.1, 132.9, 129.8 (q, *J* = 2 Hz), 128.6, 128.0, 126.8, 123.0 (q, *J* = 269 Hz), 114.9 (q, *J* = 33 Hz), 113.7, 55.4.

¹⁹F NMR of the *E*-mixture (376 MHz, CDCl₃) δ (ppm): -55.0 (d, *J* = 8.6 Hz).

¹⁹F NMR of the *Z*-mixture (376 MHz, CDCl₃) δ (ppm): -55.6 (d, *J* = 7.9 Hz).

HRMS (ESI, *m/z*): calcd for C₁₄H₁₂F₃OS⁺ [*M*+H]⁺ 285.0561, found: 285.0566.

5a (*E*)-1-methoxy-4-(3,3,3-trifluoroprop-1-enyl)benzene

Colorless oil.

Yield = 69%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.44 – 7.35 (m, 2H), 7.09 (dq, *J*₁ = 16.0 Hz, *J*₂ = 2.4 Hz, 1H), 6.95 – 6.86 (m, 1H), 6.06 (dq, *J*₁ = 16.0 Hz, *J*₂ = 6.4 Hz, 1H), 3.84 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 161.0, 137.1 (q, *J* = 7 Hz), 129.0, 126.1, 123.9 (q, *J* = 267 Hz), 114.3, 113.4 (q, *J* = 34 Hz), 55.3.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -62.8 (dd, *J*₁ = 6.4 Hz, *J*₂ = 2.4 Hz).

HRMS (ESI, *m/z*): calcd for C₁₀H₁₀F₃O⁺ [*M*+H]⁺ 203.0684, found: 203.0687.

5b (*E*)-1-isopropoxy-4-(3,3,3-trifluoroprop-1-enyl)benzene

Colorless oil.

Yield = 53%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 (d, *J* = 8.4 Hz, 1H) 7.08 (dq, *J*₁ = 16.0 Hz,

$J_2 = 2.4$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 6.05 (dq, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 4.64 – 4.53 (m, 1H), 1.36 (d, $J = 6.0$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 159.5, 137.1 (q, $J = 6$ Hz), 129.0, 125.7, 124.0 (q, $J = 267$ Hz), 116.0, 113.2 (q, $J = 34$ Hz), 70.0, 22.0.

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -62.8 (dd, $J_1 = 6.4$ Hz, $J_2 = 2.4$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{14}\text{F}_3\text{O}^+$ $[\text{M}+\text{H}]^+$ 231.0997, found: 231.1003.

5c (*E*)-1-(benzyloxy)-4-(3,3,3-trifluoroprop-1-enyl)benzene

White solid (m.p. = 59 – 63 °C)

Yield = 62%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.46 – 7.37 (m, 6H) 7.37 – 7.32 (m, 1H), 7.08 (dq, $J_1 = 16.0$ Hz, $J_2 = 2.4$ Hz, 1H), 7.01 – 6.94 (m, 2H), 6.07 (dq, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 5.10 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 160.2, 137.0 (q, $J = 7$ Hz), 136.4, 129.0, 128.6, 128.1, 127.4, 126.3, 123.9 (q, $J = 267$ Hz), 115.2, 113.5 (q, $J = 33$ Hz), 70.0.

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -62.8 (dd, $J_1 = 6.4$ Hz, $J_2 = 2.4$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{14}\text{F}_3\text{O}^+$ $[\text{M}+\text{H}]^+$ 279.0997, found: 279.0988.

5d (*E*)-1,2-dimethoxy-4-(3,3,3-trifluoroprop-1-enyl)benzene

Light yellow oil.

Yield = 74%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.08 (dq, $J_1 = 16.0$ Hz, $J_2 = 2.4$ Hz, 1H), 7.02 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 6.99 – 6.95 (m, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.07 (dq, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 150.7, 149.2, 137.4 (q, $J = 7$ Hz), 126.3, 123.8 (q, $J = 267$ Hz), 121.6, 113.6 (q, $J = 34$ Hz), 111.1, 109.3, 55.9, 55.9.

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -62.8 (dd, $J_1 = 6.4$ Hz, $J_2 = 2.4$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_{12}\text{F}_3\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 233.0789, found: 233.0791.

5e (*E*)-1,2,3-trimethoxy-5-(3,3,3-trifluoroprop-1-enyl)benzene

White solid (m.p. = 104 – 106 °C).

Yield = 67%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.07 (dq, $J_1 = 16.0$ Hz, $J_2 = 2.4$ Hz, 1H), 6.67 (s, 1H), 6.11 (dq, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 3.88 (s, 6H), 3.82 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 153.5, 139.8, 137.6 (q, *J* = 7 Hz), 128.9, 123.6 (q, *J* = 267 Hz), 115.2 (q, *J* = 34 Hz), 104.7, 60.9, 56.1.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -63.1 (dd, *J*₁ = 6.4 Hz, *J*₂ = 2.4 Hz).

HRMS (ESI, m/z): calcd for C₁₂H₁₄F₃O₃⁺ [M+H]⁺ 263.0895, found: 263.0903.

5f (*E*)-5-(3,3,3-trifluoroprop-1-enyl)benzo[d][1,3]dioxole

Colorless oil

Yield = 65%

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.04 (dq, *J*₁ = 16.0 Hz, *J*₂ = 2.4 Hz, 1H), 6.97 - 6.89 (m, 2H), 6.84 - 6.77 (m, 1H), 6.08 - 5.95 (m, 1H), 6.01 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 149.2, 148.4, 137.2 (q, *J* = 7 Hz), 127.7, 123.8 (q, *J* = 267 Hz), 123.4, 113.9 (q, *J* = 33 Hz), 108.5, 106.2, 101.5.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -62.9 (d, *J* = 6.4 Hz).

HRMS (ESI, m/z): calcd for C₁₀H₈F₃O₂⁺ [M+H]⁺ 217.0476, found: 217.0466.

5g (*E*)-methyl(4-(3,3,3-trifluoroprop-1-enyl)phenyl)sulfane

White solid (59 - 60 °C).

Yield = 62%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.39 - 7.34 (m, 2H), 7.26 - 7.21 (m, 2H), 7.09 (dq, *J*₁ = 16.0 Hz, *J*₂ = 2.4 Hz, 1H), 6.15 (dq, *J*₁ = 16.0 Hz, *J*₂ = 6.4 Hz, 1H), 2.50 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 141.4, 137.0 (q, *J* = 7 Hz), 129.9, 127.8, 126.1, 123.7 (q, *J* = 267 Hz), 114.8 (q, *J* = 34 Hz), 15.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -63.1 (dd, *J*₁ = 6.4 Hz, *J*₂ = 2.4 Hz).

HRMS (ESI, m/z): calcd for C₁₀H₁₀F₃S⁺ [M+H]⁺ 219.0455, found: 219.0459.

5h (*E*)-N-methyl-N-phenyl-4-(3,3,3-trifluoroprop-1-enyl)aniline

Light yellow solid (m.p. = 65 - 68 °C).

Yield = 51%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.40 - 7.33 (m, 2H), 7.33 - 7.28 (m, 2H), 7.20 - 7.11 (m, 3H), 7.05 (dq, *J*₁ = 16.0 Hz, *J*₂ = 2.4 Hz, 1H), 6.88 - 6.81 (m, 2H), 6.00 (dq, *J*₁ = 16.0 Hz, *J*₂ = 2=6.4 Hz, 1H), 3.35 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 150.4, 148.0, 137.3 (q, *J* = 7 Hz), 129.6, 128.6, 124.5, 124.3, 124.2 (q, *J* = 267 Hz), 123.9, 116.2, 111.9 (q, *J* = 34 Hz), 40.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -62.4 (dd, *J*₁ = 6.4 Hz, *J*₂ = 2.4 Hz).

HRMS (ESI, *m/z*): calcd for C₁₆H₁₅F₃N⁺ [M+H]⁺ 278.1157, found: 278.1164.

5i (*E*)-(5,5,5-trifluoropenta-1,3-diene-1,1-diyl)dibenzene

Colorless oil

Yield = 59%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.46 – 7.40 (m, 3H), 7.35 – 7.28 (m, 5H), 7.23 – 7.18 (m, 2H), 5.92 – 5.80 (m, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 149.9, 141.2, 138.4, 135.1 (q, *J* = 7 Hz), 130.2, 128.6, 128.4, 128.3, 128.2, 128.0, 123.8, 123.5 (q, *J* = 267 Hz), 119.2 (q, *J* = 34 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -63.0 (d, *J* = 6.4 Hz).

HRMS (ESI, *m/z*): calcd for C₁₇H₁₄F₃⁺ [M+H]⁺ 275.1048, found: 275.1053.

5j 1-methoxy-4-((1*E*,3*E*)-5,5,5-trifluoropenta-1,3-dienyl)benzene

Light yellow solid (m.p. = 72 – 74 °C).

Yield = 33%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.42 – 7.35 (m, 2H), 6.93 – 6.83 (m, 3H), 6.80 – 6.72 (m, 1H), 6.68 – 6.60 (m, 1H), 5.80 – 5.68 (m, 1H), 3.83 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 160.3, 138.9, 137.8 (q, *J* = 7 Hz), 128.6, 128.4, 123.6 (q, *J* = 267 Hz), 122.8, 117.1 (q, *J* = 33 Hz), 114.3, 55.3.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -62.9 (d, *J* = 6.4 Hz).

HRMS (ESI, *m/z*): calcd for C₁₂H₁₂F₃O⁺ [M+H]⁺ 229.0840, found: 229.0834.

6 4-(2,2,2-trifluoroethyl)-1,2-dihydronaphthalene

Colorless oil

Yield = 21%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.25 – 7.10 (m, 4H) 7.26 – 7.21 (m, 2H), 6.14 (t, *J* = 4.8 Hz, 1H), 3.24 (qd, *J*₁ = 10.8 Hz, *J*₂ = 1.2 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.37 – 2.29 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 136.3, 133.7, 132.0, 127.8, 127.3, 126.7 (q, *J* = 3 Hz), 126.4, 126.0 (q, *J* = 275 Hz), 122.7, 36.8 (q, *J* = 29 Hz), 27.9, 23.2.

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -64.5 (t, J = 11.3 Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3^+$ $[\text{M}+\text{H}]^+$ 213.0891, found: 213.0894.

Reference

1. T. Wang, Y. Hu, S. Zhang, *Org. Biomol. Chem.* **2010**, 8, 2312.
2. A. J. Perkowski, W. You, D. A. Nicewicz, *J. Am. Chem. Soc.* **2015**, 137, 7580.

Chapter 3

***VISIBLE LIGHT-INDUCED TRIFLUOROMETHYLATION OF
FLUORINATED ALKENES VIA C(sp² & sp³)-F BOND
FUNCTIONALIZATION***

3.1 Introduction

3.1.1 Conventional Functionalization of C–F Bond

Fluorinated organic compounds play a very important role in numerous fields such as pharmaceutical, agrichemical and material science, which is often employed as versatile building blocks to access synthetic molecules with unique chemical and physical properties.⁵⁶ The conventional methods to construct fluorinated compounds mainly focused on trifluoromethylation or new C–F bond formation. Alternatively, defluorinative functionalization of multifluorinated alkenes via C–F bond cleavage also provided efficient access to functionalized fluorinated molecules. Thus, developing new approaches to achieve C–F bond functionalization has drawn increasing attention in recent years.

Generally, the C–F bond could be activated by cross-coupling reaction of fluorinated molecules with functional reagents. The process normally involves transition metal-mediated (for example palladium, nickel, platinum etc.) oxidative addition, followed by transmetallation and reductive elimination to give the functionalized fluorinated compounds (Scheme 3-1, a).⁵⁷ Such reactions could be highly regioselective in the presence of adjacent directing group.

Alternatively, the nucleophile such as Grignard reagent, lithium reagent, etc. could proceed nucleophilic addition to fluorine-containing unsaturated carbon–carbon bond

⁵⁶ a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. d) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev.* **2012**, *41*, 31–42.

⁵⁷ Selected examples: a) Saeki, T.; Takashima, Y.; Tamao, K. *Synlett* **2005**, 1771–1174. b) Schaub, T.; Fischer, P.; Steffen, A.; Braun, T.; Radius, U.; Mix, A. *J. Am. Chem. Soc.* **2008**, *130*, 9304–9317. c) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 3256–3259.

to generate the adduct intermediate. Then defluorination is incorporated in the reaction to give the functionalized product (Scheme 3-1, b).⁵⁸

a. transition metal-catalyzed C-F bond functionalization

b. nucleophile involved C-F bond functionalization

c. radical involved C-F bond functionalization

Scheme 3-1. Conventional C–F bond functionalization

Compared to the nucleophilic addition, radical involved addition has also been widely employed in the functionalization of fluorinated molecules, which allowed introduction of various carbon-centered radicals into the corresponding compound. Normally, the process involves radical addition and single electron transfer (SET) followed by β -fluorine elimination (Scheme 3-1, c). Especially, such method has drawn much attention in the field of carbon–fluorine bond functionalization via photocatalysis.

⁵⁸ Selected examples: a) Pasumansky, L.; Hernandez, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **2004**, 45, 6417–6420. b) Guiu, E.; Claver, C.; Benet-Buchholz, J.; Castillon, S. *Tetrahedron: Asymm.* **2004**, 15, 3365–3373. c) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, 109, 2119–2183.

3.1.2 Visible Light-Mediated C–F Bond Functionalization

In recent decades, photocatalysis has been regarded as one of the most powerful tools in organic synthesis and various visible-light-mediated reactions have been developed by researchers.^{47,59} The photocatalyst excited by visible light can act as both oxidant and reductant under mild reaction conditions, providing a convenient access to reactions involving redox processes. In the conventional C–F functionalization, harsh reaction conditions or stoichiometric organometallic reagents are normally required, which limit the scope of substrates and applications. Hence, merging photocatalysis with C–F functionalization providing a facile and versatile access to functionalized fluoro-containing molecules is of great importance.

3.1.2.1 Aromatic C(sp²)–F bond functionalization

Dates back to 2014, Weaver's group firstly reported photocatalytic hydrodefluorination to access polyfluorinated arenes (Scheme 3-2).⁶⁰ Compared to traditional hydrodefluorinations, in which extremely fluorophilic reductants such as expensive Si-hydrides or Al-hydrides are normally used,⁶¹ this visible light-mediated reaction involving amine-based reductant is milder, safer and less expensive. In this reaction, the authors speculated Ir photocatalyst facilitates single electron transfer and results in C–F bond cleavage to generate the product via abstraction of H-atom from

⁵⁹ a) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898–6926. b) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 52. c) Kärkäs, M. D.; Porco, J. A., Jr.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683–9747.

⁶⁰ Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002–3005.

⁶¹ Reade, S. P.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2009**, *131*, 1847–1861.

amine.

Scheme 3-2. Photocatalytic hydrodefluorination

In succession, based on the previous work mentioned above (Scheme 3-2), Weaver's group further developed photocatalytic C–F alkylation to access multifluorinated arenes.⁶² In this transformation perfluoroaryl radical was generated by single electron transfer followed by C–C bond formation through radical addition rather than H-atom abstraction to give alkylated multifluorinated arenes (Scheme 3-3).

Scheme 3-3. Photocatalytic C–F alkylation

Later in 2016, photocatalytic dual C–F, C(sp²)–H functionalization was reported by Weaver et al (Scheme 3-4).⁶³ Multifluorinated arene and arene–H could be accommodated in this transformation to give multifluorinated biaryls in good yields. Unlike the previous carbon–carbon alkylation (Scheme 3-3), oxidation and

⁶² Singh, A.; Kubik, J. J.; Weaver, J. D. *Chem. Sci.* **2015**, *6*, 7206–7212.

⁶³ Senaweera, S.; Weaver, J. D. *J. Am. Chem. Soc.* **2016**, *138*, 2520–2523.

rearomatization is following after addition of perfluoroaryl radical to electron-rich π systems.

Scheme 3-4. Photocatalytic dual C–F, C(sp²)–H functionalization

In 2017, Hashmi's group has achieved defluorinated coupling reaction between C(sp²)–F and C(sp³)–H, using N-aryl amine instead of Arene-H as coupling partner, (Scheme 3-5).⁶⁴ In this case, N-aryl amine was oxidized by visible light-activated ^{*}Ir^{III} through single electron transfer to produce amino radical cation, which delivers α -amino radical by deprotonation. Subsequently, multifluoroarene is reduced by Ir^{II} species to give multifluoroaryl radical species. A radical coupling process occurs between α -amino radical and multifluoroaryl radical species to give the functionalized product. Interestingly, by controlling equivalence of substrates, mono-multifluoroarylation and di-multifluoroarylation of N-aryl amine is well controlled in this reaction.

⁶⁴ Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, F. S. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 7266–7270.

Scheme 3-5. Photocatalytic C–F bond functionalization with amine

3.1.2.2 Alkenyl C(sp²)–F bond functionalization

In addition to aromatic C(sp²)–F bond functionalization, introducing functional group into molecules through fragmentation of alkenyl C(sp²)–F bond has also provided an alternative access to (mono)fluorinated compounds.

In 2016, Hashmi's group communicated a photocatalytic monofluoroalkenylation of dimethylamino compounds via C(sp²)–F bond cleavage (Scheme 3-6).⁶⁵ In this reaction protocol, instead of radical addition, the radical-radical coupling process between fluoroalkenyl radical and α -aminoalkyl radical species was proposed by authors. This reaction provides a mild and convenient approach to monofluoroalkenyl compound. However, owing to radical process involved in the transformation,

⁶⁵ Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2016**, 55, 9416–9421.

stereoselectivity is poorly controlled.

Scheme 3-6. Photocatalytic monofluoroalkenylation of dimethylamino compounds

In 2017, photocatalytic monofluoroalkenylation of α -amino acids with difluoroalkenes was then reported by Fu's group (Scheme 3-7).⁶⁶ Different from Hashmi's work (Scheme 3-6), α -aminoalkyl radical is generated from decarboxylative process in this reaction. After that, radical-radical coupling proceeds to give desired product, which still lacks stereoselectivity.

Scheme 3-7. Photocatalytic decarboxylative monofluoroalkenylation.

3.1.2.3 C(sp³)-F bond functionalization

⁶⁶ Li, J.; Lefebvre, Q.; Yang, H.; Zhao, Y.; Fu, H. *Chem. Commun.* **2017**, 53, 10299–10302.

Scheme 3-8. Photocatalytic decarboxylative/defluorinative reaction

In addition to C(sp²)-F bond functionalization, the photocatalytic activation of C(sp³)-F bond to give 1,1-difluoroalkenes has been developed in recent years. In 2016, Zhou's group reported a novel photocatalytic decarboxylative/defluorinative reaction to prepare gem-difluoroalkenes (Scheme 3-8).⁶⁷ Mechanistic study, illustrated by the authors, delineates the initial oxidative decarboxylation of the substrate by visible light-excited *Ir^{III} to generate α -amino/carbonyl radical. The radical addition reaction to α -trifluoromethyl olefins, followed by reduction of Ir^{II}, forms the α -trifluoromethyl alkyl anion intermediate. Then, such anion species undergoes β -fluoride elimination to give functionalized gem-difluoroalkenes.

In 2017, Molander's group employed a similar strategy to achieve C(sp³)-F bond functionalization (Scheme 3-9).⁶⁸ The initial radical species is generated through

⁶⁷ Xiao, T.; Li, L.; Zhou, L. *J. Org. Chem.* **2016**, *81*, 7908–7916.

⁶⁸ Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 15073–15077.

desilylative fragmentation with single electron transfer (SET) followed by similar addition/elimination process (Scheme 3-8) to give the desired product.

Scheme 3-9. Photocatalytic desilylative/defluorinative reaction

Notably, remarkable progress was achieved by König's group in 2017.⁶⁹ They first reported direct C(sp³)–F bond activation of trifluoromethyl arenes through photocatalysis, coordinating with Lewis acid (Scheme 3-10). The controlled experiment indicated radical species was generated in this reaction. In author's proposed mechanism, visible light-excited *Ir^{III} is reductively quenched by TMP to afford Ir^{II}, which reduces ArCF₃ to the corresponding radical anion **B**. The Lewis acid, produced from protonated TMP and HBpin, abstracts F[–] through C(sp³)–F cleavage from **B** to generate aryldifluoromethyl radical species **D**. The following radical addition, cyclization and oxidation give the final product.

⁶⁹ Chen, K.; Berg, N.; Gschwind, R.; König, B. *J. Am. Chem. Soc.* **2017**, *139*, 18444–18447.

Scheme 3-10. Direct C(sp³)-F bond activation of trifluoromethyl arenes via photocatalysis merged with Lewis acid

3.2 Results and discussion

Scheme 3-11. Scope of photocatalysts

Table 3-1. Optimization of visible light-mediated defluorinative trifluoromethylation of **7a**^a

Entry	Catalyst (2 mol%)	Solvent (1 mL)	Yield (%) ^b
1	PC1	DMSO	22
2	PC1	CH ₃ CN	21
3	PC1	acetone	15
4	PC2	DMSO	mess

5	PC3	DMSO	68
6	PC4	DMSO	37
7	PC3	DMF	68
8	PC4	DMF	71
9	PC4	DMA	90
10 ^c	PC4	DMA	83
11	--	DMA	0
12 ^d	PC4	DMA	0

^aReaction conditions: photocatalyst (0.004 mmol), **7a** (0.2 mmol), **2** (0.3 mmol), blue LEDs, solvent (1 mL), rt, 12 hours. ^bIsolated yield. ^cPhotocatalyst (0.002 mmol). ^dWithout light.

Initially, α -trifluoromethyl styrene (**7a**) and CF₃SO₂Na (**2**) were selected as the model compound to explore the optimum reaction conditions under the irradiation of blue LEDs (Table 3-1). To our delight, in the presence of **PC1** in DMSO, the corresponding trifluoromethylated product was obtained in 22% yield (entry 1). We then processed on with screening of different solvents. Among different solvents investigated in the presence of **PC1**, the use of CH₃CN and acetone led to poor product yields (entries 2 and 3). Subsequent optimization of photocatalysts showed that **PC3** and **PC4** was more efficient, which might be rationalized by **PC3**'s and **PC4**'s higher oxidizing excited state, as compared with **PC1**, while **PC2** led to messy products (entries 4-6). Encouragely, reaction in DMF with **PC4** resulted in 71% yield and a further survey of solvents showed that DMA was the solvent of choice, producing **8a** in 90% yield (entries 7-9). Notably, halving the catalyst loading reduced the product yield (entry 10), and control experiments demonstrated that both photocatalyst and visible light are necessary in this reaction (entries 11 and 12).

Table 3-2. Defluorinative trifluoromethylation of α -trifluoromethyl alkenes^a

^aReaction conditions: **PC2** (0.004 mmol), **7** (0.2 mmol), **2** (0.3 mmol), blue LEDs, DMA (1 mL), rt, 12 hours. Yields of isolated products are given.

With the optimized reaction conditions (Table 3-1, entry 9), we then investigated the substrate scope of the present transformation (Table 3-2). Substrates bearing electron-withdrawing, the substrates bearing halide in *para* position and electron-

donating groups in *ortho*, *meta* or *para* position were amenable to the reaction conditions to give products **8b-l** in 62-89% yields. It was noteworthy that a substrate bearing a silyl group, which is a versatile building block, underwent the reaction smoothly, even in the presence of F⁻, leading to **8m** in excellent yield. Moreover, the reaction was compatible to both naphthalene-substituted and heteroaryl-substituted substrates, giving rise to **8n** and **8o** in moderate to good yields. Especially noteworthy is that a protected aldehyde and ketone (**8p** and **8q**) also proved to be appropriate candidates for this defluorinative reaction. Furthermore, enynyl substrate, 2-trifluoromethyl-1,3-enyne, was also capable of undergoing the present trifluoromethylation smoothly to produce the corresponding **8r** in 53% yield.

Table 3-3. α -trifluoromethyl alkenes failed to undergo defluorinative trifluoromethylation

$ \begin{array}{c} \text{CF}_3 \\ \\ \text{R}-\text{C}=\text{CH}_2 \\ \mathbf{7} \end{array} + \text{CF}_3\text{SO}_2\text{Na} \xrightarrow[\text{blue LEDs, DMA, rt, 12 h}]{[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6 \text{ (PC4)}} \begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad \diagup \\ \text{R}-\text{C}=\text{CH}-\text{CF}_3 \\ \mathbf{8} \end{array} $
<p>7s</p>	<ul style="list-style-type: none"> • messy products • trace amount of desired product
<p>7t</p>	<ul style="list-style-type: none"> • messy products • trace amount of desired product
<p>7u</p>	<ul style="list-style-type: none"> • messy products • trace amount of desired product
<p>7v</p>	<ul style="list-style-type: none"> • messy products

Moreover, several other substituted α -trifluoromethyl alkenes were tested under

basic conditions (Table 3-3). The substrates with another alkenyl or aldehyde group (**7s** and **7t**) only led to messy products with trace amount of desired products, possibly owing to the instability of both alkenyl and aldehyde groups in the presence of radical species. Meanwhile, alkyl substrate **7u** was also proved not suitable for this reaction and only trace amount of trifluoromethylated corresponding product was formed, which could be attributed to a lack of capacity of alkyl substituent to stabilize the α -trifluoromethyl anion intermediate. Internal alkene **7v** also gave no desired product and only messy byproducts was obtained.

Table 3-4. Optimization of visible light-mediated defluorinative trifluoromethylation of **9a**^a

Entry	Catalyst	Additive	Solvent	Yield [%] ^b	Z/E ^c
1	PC4	--	DMA	15	50:50
2	PC4	--	DMSO	22	50:50
3	PC4	--	THF	trace	--
4	PC4	--	CH ₃ CN	trace	--
5	PC4	--	NMP	15	67:33

^aReaction conditions: photocatalyst (0.004 mmol), **9a** (0.2 mmol), **2** (0.4 mmol), additive (0.3 mmol), blue LEDs, solvent (1 mL), rt, 12 hours. ^bIsolated yield. ^cThe Z/E ratio was confirmed by crude ¹⁹F NMR.

Inspired by the result of trifluoromethylation via defluorination of α -trifluoromethyl alkenes, we further explored the defluorinative trifluoromethylation of *gem*-difluoroalkenes in this transformation (Table 3-4). Unfortunately, under the afore-

mentioned reaction conditions, the reaction involving *gem*-difluorostyrene **9a** only provided the desired product **10a** in low yield with extremely poor stereoselectivity (entries 1). We then explored solvent effect in this reaction and found DMSO could slightly improve the yield to 22% (entry 2). Reaction in acetonitrile or THF only gave trace of desired product whereas that in NMP slightly increased *Z/E* selectivity to 67:33 (entries 3-5).

Table 3-5. Optimization of visible light-mediated defluorinative trifluoromethylation of **9a**^a

Entry	Catalyst	Additive	Solvent	Yield [%] ^b	<i>Z/E</i> ^c
1	PC1	--	DMSO	15	55:45
2	PC3	--	DMSO	28	94:6
3	PC3	--	dioxane	6	99:1
4	PC3	--	MeOH	5	99:1
5	PC3	--	CH ₃ CN	33	99:1
6	PC3	--	acetone	37	99:1

^aReaction conditions: photocatalyst (0.004 mmol), **9a** (0.2 mmol), **2** (0.4 mmol), additive (0.3 mmol), blue LEDs, solvent (1 mL), rt, 12 hours. ^bIsolated yield. ^cThe *Z/E* ratio was confirmed by crude ¹⁹F NMR.

The different photocatalysts were investigated in DMSO (Table 3-5). **PC1** could slightly increase the stereoselectivity but decreased the yield. To our delight, switching the catalyst to **PC3** whose reduced Ir^{II} state has higher reduction potential ($E_{1/2}^{\text{III/II}} = -$

1.07 V vs Fc/Fc+),⁷⁰ as compared to the reduced state of **PC1** and **PC4**, led to good stereoselectivity (*Z/E* = 94:6) with slightly higher yield (entry 2). Various solvents including dioxane, methanol and acetonitrile were then surveyed again in the presence of **PC3** and we found acetone could result in higher yield with excellent stereoselectivity (entries 3-6). Hence, we continued the optimization study by employing **PC3** as catalyst and acetone as solvent.

Table 3-6. Optimization of visible light-mediated defluorinative trifluoromethylation of **9a**^a

Entry	Catalyst	Additive	Solvent	Yield [%] ^b	<i>Z/E</i> ^c
1	PC3	NaOAc	acetone	10	99:1
2	PC3	TFA	acetone	0	--
3	PC3	--	acetone	43 ^d	99:1
4	PC3	Li ₂ CO ₃	acetone	45 ^d	99:1
5	PC3	LiClO₄	acetone	52^e	99:1
6	PC5	--	acetone	43 ^d	36:64

^aReaction conditions: photocatalyst (0.004 mmol), **9a** (0.2 mmol), **2** (0.4 mmol), additive (0.3 mmol), blue LEDs, solvent (1 mL), rt, 12 hours. ^bIsolated yield. ^cThe *Z/E* ratio was confirmed by crude ¹⁹F NMR. ^dPhotocatalyst (0.006 mmol). ^ePhotocatalyst (0.006 mmol), 36 hours.

With the excellent stereoselectivity, we continued to search additives and modify other reaction conditions to improve the reaction yield (Table 3-6). Adding base such

⁷⁰ a) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, 539, 268–271. b) Zhu, Q.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, 140, 741–747.

as sodium acetate to the reaction reduced the yield and trifluoroacetic acid (TFA) shut down the reaction (entries 1 and 2). A further study revealed that **PC3** in combination with LiClO₄⁷¹ as additive in acetone was identified as the best choice to afford the product **10a** in 52% yield with excellent stereoselectivity (*Z/E* = 99:1, entry 5). This result is in agreement with the reported calculation result,^{72a} where *Z* isomer displayed thermodynamically higher stability and kinetically lower energy barrier in the transition state. Meanwhile, compared to fluoride, trifluoromethyl group is bulkier and thus it prefers to attack the C=C bond via an orientation trans to sterically hindered aryl group, thereby giving a less hindered *Z* isomer (Scheme 3-12).⁷² Interestingly, we found that **PC5** served as photocatalyst in this transformation would reverse the *E/Z* value and *E* isomer would be the major product in spite of low stereoselectivity (entry 6).

Scheme 3-12. Transition state

⁷¹ Bergeron, M.; Johnson, T.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2011**, 50, 11112–11116.

⁷² a) Nenajdenko, V. G.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *Russ. Chem. Bull.* **2004**, 53, 1034–1064. b) Goldberg, A. A.; Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Nenajdenko, V. G. *J. Fluor. Chem.* **2010**, 131, 384–388; c) Li, Y.; Tu, D.-H.; Gu, Y.-J.; Wang, B.; Wang, Y.-Y.; Liu, Z.-T.; Liu, Z.-W.; Lu, J. *Eur. J. Org. Chem.* **2015**, 4340–4343.

Table 3-7. Defluorinative trifluoromethylation of *gem*-difluoroalkenes^a

^aReaction conditions: **PC3** (0.006 mmol), **9** (0.2 mmol), **2** (0.4 mmol), LiClO₄ (0.3 mmol), blue LEDs, acetone (1 mL), rt, 36 hours. Isolated yields are given. *Z/E* ratio was confirmed by crude ¹⁹F NMR.

Next, the substrate scope and limitations with *gem*-difluoroalkene derivatives were investigated (Table 3-7). In this transformation, electron-withdrawing groups substituted compounds reacted smoothly to deliver the corresponding products **10a-f** in moderate yields. Notably, the *gem*-difluoroalkenes bearing cyanide, ester, organophosphate, and amide, for example were amenable to this transformation with excellent stereoselectivity (up to 99:1 *Z/E*).

Table 3-8. *gem*-Difluoroalkenes failed to undergo defluorinative trifluoromethylation

However, substrates containing electron-donating groups or other conjugate systems such as naphthalene or conjugated diene (**9g-9i**) were not suitable in this reaction, which was possibly ascribed to its low reactivity or the instability of the formed α -trifluoromethylcarbanion intermediate during the course of the transformation. Possibly owing to the instability of nitro group under the reaction conditions involving radical species, nitro-substituted substrates **9j** only gave the messy product (Table 3-8).

Scheme 3-12. Controlled experiments.

To further explore the mechanism of defluorinative trifluoromethylation, radical trapping experiments were performed. When TEMPO was added to the reaction mixture of **7a/9a** and **2** under corresponding reaction conditions, the defluorinative trifluoromethylation was completely suppressed (Scheme 3-12a and 3-12b). This result implied that radical species is regarded to be involved in this process. In order to further explore possible isomerization mechanism of **10**, *E/Z*-**10a** was employed in the reaction under standard reaction conditions. However, the *E/Z* ratio remained the same after reaction, suggesting that isomerization was not likely induced through energy transfer process.⁷³

Based on the experiment results, a plausible reaction mechanism was proposed (Figure 3-1). Initially, NaSO₂CF₃ is oxidized by visible light-excited ^{*}Ir^{III} via a single electron transfer (SET) process to generate trifluoromethyl radical (CF₃[•]), along with the generation of reduced Ir^{II}. Next, CF₃[•] undergoes a radical addition to alkene **1** or **4**

⁷³ a) Singh, A.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275–5278. b) Singh, A.; Fennell, C. J.; Weaver, J. D. *Chem. Sci.* **2016**, *7*, 6796–6802.

to deliver a transient α -trifluoromethyl radical **A** or **A'**, which subsequently undergoes a SET reduction by Ir^{II}, providing an α -trifluoromethyl anion **B** or **B'** with the concomitant regeneration of photocatalyst Ir^{III}. Finally, β -fluoride elimination readily occurs to furnish the desired product **8** or **10**.

Figure 3-1. Proposed mechanism

3.3 Conclusion

In summary, an efficient defluorinative trifluoromethylation of α -trifluoromethyl alkenes and *gem*-difluoroalkenes via Ir photoredox C–F bond cleavage has been developed. The reaction has provided a convenient and competent approach to

construct substituted difluoroalkenes, which is compatible to various functional groups. Meanwhile, the reaction exhibits excellent stereoselectivity with *gem*-difluoroalkenes, which provides potential for further applications in pharmaceutical and agrochemical research.

3.4 Experimental section

General Information

The NaSO₂CF₃ was commercially available from Alfa-Aesar, LiClO₄ was purchased from Strem. LED irradiation was accomplished using the 8 W blue LED strip. ¹H NMR and ¹³C NMR spectra were carried out on a Bruker Advance 400 NMR spectrometer. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard. Coupling constants, *J*, are reported in Hertz. *E/Z* isomer ratio was confirmed via NMR spectra analysis of the crude product. HRMS was carried out on Waters Q-ToF Mass spectrometer.

General procedures for the synthesis of photocatalysts, α -trifluoromethyl alkenes and *gem*-difluoroalkenes

PC1¹, PC2², PC3³, 7a – r⁴ and 9a – f⁵ were prepared following the reported procedures.

General procedures for the defluorinative trifluoromethylation of α -trifluoromethyl alkenes

To an 8 mL sample vial, charged with [Ir(dF(CF₃)ppy)₂dtbpy]PF₆ (PC2) (0.004 mmol, 2 mol%), and CF₃SO₂Na (0.3 mmol, 1.5 equiv) in dimethylacetamide (1 mL) was

sequentially added α -trifluoromethyl alkene (0.2 mmol, 1 equiv) under nitrogen atmosphere at ambient temperature. The vial was sealed and kept at ambient temperature under blue LEDs for 12 hours. EtOAc (10 mL) was added to the reaction mixture, washed with water (2×20 mL), brine (20 mL), and concentrated under vacuum. Purification by column chromatograph with DCM and hexane as eluent affords the target product.

General procedures for the defluorinative trifluoromethylation of *gem*-difluoroalkenes

To an 8 mL sample vial, charged with [Ir(dF(CF₃)ppy)₂(5,5'-d(CF₃)bpy)]PF₆ (**PC3**) (0.006 mmol, 3 mol%), LiClO₄ (0.3 mmol, 1.5 equiv) and CF₃SO₂Na (0.4 mmol, 2.0 equiv) in acetone (1 mL) was sequentially added *gem*-difluoroalkene (0.2 mmol, 1 equiv) under nitrogen atmosphere at ambient temperature. The vial was sealed and kept at ambient temperature under blue LEDs for 36 hours. EtOAc (10 mL) was added to the reaction mixture, filtered through filter paper and concentrated under vacuum. Purification by column chromatograph with DCM and hexane as eluent affords the target product.

Characterization data for the products

4-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)-1,1'-biphenyl (**8a**)

Colorless sticky oil.

Yield = 90%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.67 – 7.55 (m, 4H), 7.49 – 7.32 (m, 5H), 3.22 (qt, *J*₁ = 12.0 Hz, *J*₂ = 1.6 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.6 (t, *J* = 292 Hz), 140.8, 140.3, 130.9 (t, *J* = 3 Hz), 128.8, 128.5 (t, *J* = 3 Hz), 127.6, 127.3, 127.0, 125.5 (qt, *J*₁ = 276 Hz, *J*₂ = 4 Hz), 84.3 (tq, *J*₁ = 20 Hz, *J*₂ = 3 Hz), 33.3 (td, *J*₁ = 31 Hz, *J*₂ = 2 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (qdd, *J*₁ = 11.3 Hz, *J*₂ = 5.3 Hz, *J*₃ = 1.1 Hz, 3F), -85.5 – -85.7 (m, 1F), -85.7 – -85.8 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₆H₁₂F₅⁺ [M+H]⁺ 299.0859, found: 299.0860.

1-(*tert*-Butyl)-4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzene (**8b**)

Colorless oil.

Yield = 66%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.42 – 7.37 (m, 2H), 7.28 – 7.22 (m, 2H), 3.18 (qt, *J*₁ = 10.1 Hz, *J*₂ = 2.1 Hz, 2H), 1.32 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.5 (t, *J* = 290 Hz), 151.0, 129.0 (t, *J* = 3 Hz), 127.8 (t, *J* = 3 Hz), 125.6, 125.5 (qt, *J*₁ = 276 Hz, *J*₂ = 4 Hz), 84.3 (tq, *J*₁ = 20 Hz, *J*₂ = 3 Hz), 34.6, 33.4 (qd, *J*₁ = 31 Hz, *J*₂ = 2 Hz), 31.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (qd, *J*₁ = 11.3 Hz, *J*₂ = 4.9 Hz, 3F), -86.2 – -86.4 (m, 1F), -86.4 – -86.5 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₄H₁₆F₅⁺ [M+H]⁺ 279.1172, found: 279.1181.

1,3-di-*tert*-Butyl-5-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzene (**8c**)

Colorless oil.

Yield = 72%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 (t, J = 1.8 Hz, 1H), 7.14 (s, 2H), 3.19 (qt, J_1 = 10.2 Hz, J_2 = 2.1 Hz, 2H), 1.33 (s, 18H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.5 (t, J = 290 Hz), 151.0, 131.3 (t, J = 3 Hz), 125.6 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 122.5 (t, J = 3 Hz), 122.0, 85.2 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 34.9, 33.8 (qd, J_1 = 31 Hz, J_2 = 2 Hz), 31.4.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -64.8 (qd, J_1 = 10.1 Hz, J_2 = 5.3 Hz, 3F), -86.3 – -86.4 (m, 1F), -86.6 – -86.8 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₈H₂₄F₅⁺ [M+H]⁺ 327.1172, found: 327.1180.

4-Methoxy-2-methyl-1-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzene (**8d**)

Light yellow oil.

Yield = 62%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.15 – 7.05 (m, 2H), 6.82 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.15 (qt, J_1 = 10.1 Hz, J_2 = 2.1 Hz, 2H), 2.23 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 157.4, 155.3 (t, J = 290 Hz), 130.4 (t, J = 3 Hz), 127.0, 126.8 (t, J = 3 Hz), 125.5 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 123.7 (t, J = 3 Hz), 109.9, 84.1 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 55.3, 33.6 (qd, J_1 = 30 Hz, J_2 = 2 Hz), 16.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (qd, J_1 = 9.8 Hz, J_2 = 4.5 Hz, 3F), -87.3 – -87.5 (m, 1F), -87.5 – -87.6 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₂H₁₂F₅O⁺ [M+H]⁺ 267.0808, found: 267.0811.

1,2-Dimethoxy-4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzene (**8e**)

Light yellow oil.

Yield = 74%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.87 (d, J = 1.1 Hz, 2H), 6.82 (q, J = 1.2 Hz,

1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.16 (qt, $J_1 = 10.1$ Hz, $J_2 = 2.1$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 155.4 (t, $J = 290$ Hz), 148.9, 148.8, 125.4 (qt, $J_1 = 276$ Hz, $J_2 = 4$ Hz), 124.5 (t, $J = 3$ Hz), 120.8 (t, $J = 3$ Hz), 111.6, 111.2, 84.3 (tq, $J_1 = 20$ Hz, $J_2 = 3$ Hz), 55.9, 55.8, 33.6 (qd, $J_1 = 31$ Hz, $J_2 = 2$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -65.0 (qd, $J_1 = 9.8$ Hz, $J_2 = 4.9$ Hz, 3F), -86.5 – -86.6 (m, 1F), -86.9 – -87.0 (m, 1F).

HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_{12}\text{F}_5\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 283.0757, found: 283.0765.

1-(1,1,4,4,4-pentafluorobut-1-en-2-yl)-4-phenoxybenzene (8f)

Colorless oil.

Yield = 82%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.38 – 7.31 (m, 2H), 7.29 – 7.23 (m, 2H), 7.13 (td, $J_1 = 7.4$ Hz, $J_2 = 1.1$ Hz, 1H), 7.06 – 6.97 (m, 4H), 3.16 (qt, $J_1 = 10.0$ Hz, $J_2 = 2.1$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 157.3, 156.6, 155.5 (t, $J = 290$ Hz), 129.9, 129.7 (t, $J = 3$ Hz), 126.6 (t, $J = 3$ Hz), 125.5 (qt, $J_1 = 276$ Hz, $J_2 = 4$ Hz), 123.8, 119.4, 118.5, 84.1 (tq, $J_1 = 20$ Hz, $J_2 = 3$ Hz), 33.5 (qd, $J_1 = 32$ Hz, $J_2 = 2$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -65.0 (tdd, $J_1 = 10.1$ Hz, $J_2 = 2.6$ Hz, $J_3 = 1.9$ Hz, 3F), -86.4 – -86.6 (m, 2F).

HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{12}\text{F}_5\text{O}^+$ $[\text{M}+\text{H}]^+$ 315.0808, found: 315.0815.

Methyl(4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)phenyl)sulfane (8g)

Colorless oil.

Yield = 89%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.27 – 7.20 (m, 4H), 3.16 (qt, $J_1 = 10.0$ Hz, $J_2 = 2.1$ Hz, 2H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 155.4 (t, $J = 290$ Hz), 138.7, 128.5 (t, $J = 3$ Hz), 128.5, 126.4, 125.4 (qt, $J_1 = 276$ Hz, $J_2 = 4$ Hz), 84.1 (tq, $J_1 = 20$ Hz, $J_2 = 3$ Hz), 33.3 (qd, $J_1 = 32$ Hz, $J_2 = 2$ Hz), 15.4.

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -65.0 (tt, $J_1 = 10.1$ Hz, $J_2 = 2.6$ Hz, 3F), -86.0

– -86.1 (m, 2F).

HRMS (ESI, m/z): calcd for $C_{11}H_{10}F_5S^+$ $[M+H]^+$ 269.0423, found: 269.0432.

Methyl 4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzoate (**8h**)

Light yellow sticky oil.

Yield = 70%

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.11 – 8.03 (m, 2H), 7.43 (d, J = 8.1 Hz, 2H), 3.95 (s, 3H), 3.25 (qt, J_1 = 9.9 Hz, J_2 = 2.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.4, 155.7 (t, J = 290 Hz), 136.7 (t, J = 3 Hz), 129.9, 129.7, 128.2 (t, J = 3 Hz), 125.2 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 84.3 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 52.2, 33.3 (qd, J_1 = 31 Hz, J_2 = 2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -65.1 (td, J_1 = 9.8 Hz, J_2 = 4.6 Hz, 3F), -84.0 – -84.2 (m, 1F), -84.2 – -84.3 (m, 1F).

HRMS (ESI, m/z): calcd for $C_{12}H_{10}F_5O_2^+$ $[M+H]^+$ 281.0601, found: 281.0591.

Methyl 3-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzoate (**8i**)

Light yellow oil.

Yield = 83%

1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 – 7.97 (m, 2H), 7.55 – 7.43 (m, 2H), 3.93 (s, 3H), 3.22 (qt, J_1 = 10.0 Hz, J_2 = 2.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 166.5, 155.7 (t, J = 290 Hz), 132.7 (t, J = 3 Hz), 132.4, 130.8, 129.3 (t, J = 3 Hz), 129.2, 128.8, 125.3 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 84.1 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 52.2, 33.4 (qd, J_1 = 32 Hz, J_2 = 2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -65.1 (tt, J_1 = 9.9 Hz, J_2 = 2.8 Hz, 3F), -85.4 – -85.5 (m, 2F).

HRMS (ESI, m/z): calcd for $C_{12}H_{10}F_5O_2^+$ $[M+H]^+$ 281.0601, found: 281.0598.

1-(4-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)phenyl)ethan-1-one (**8j**)

Light yellow oil.

Yield = 76%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.00 – 7.94 (m, 2H), 7.47 – 7.41 (m, 2H), 3.23 (qt, J_1 = 10.0 Hz, J_2 = 2.1 Hz, 2H), 2.61 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 197.3, 155.7 (t, J = 290 Hz), 136.8 (t, J = 3 Hz), 136.5, 128.6, 128.4 (t, J = 3 Hz), 125.2 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 84.3 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 33.1 (qd, J_1 = 32 Hz, J_2 = 2 Hz), 26.6.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.1 (td, J_1 = 9.9 Hz, J_2 = 4.7 Hz, 3F), -83.8 – -83.9 (m, 1F), -84.0 – -84.1 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₂H₁₀F₅O⁺ [M+H]⁺ 265.0652, found: 265.0665.

4-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)benzonitrile (**8k**)

Light yellow oil.

Yield = 65%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.71 – 7.66 (m, 2H), 7.48 – 7.43 (m, 2H), 3.22 (qt, J_1 = 9.9 Hz, J_2 = 2.1 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.8 (t, J = 290 Hz), 136.8 (t, J = 3 Hz), 132.4, 128.9 (t, J = 3 Hz), 125.1 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 118.1, 112.0, 84.0 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 33.0 (qd, J_1 = 32 Hz, J_2 = 2 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.1 (td, J_1 = 9.8 Hz, J_2 = 4.9 Hz, 3F), -82.7 – -82.8 (m, 1F), -83.1 – -83.2 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₁H₇F₅N⁺ [M+H]⁺ 248.0499, found: 248.0497.

1-Chloro-4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)benzene (**8l**)

Light yellow oil.

Yield = 87%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 – 7.34 (m, 2H), 7.27 – 7.24 (m, 2H), 3.16 (qt, J_1 = 10.0 Hz, J_2 = 2.1 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.5 (t, J = 290 Hz), 134.0, 130.5 (t, J = 3 Hz), 129.5 (t, J = 3 Hz), 128.9, 125.3 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 83.9 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 33.4 (qd, J_1 = 31 Hz, J_2 = 2 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (tdd, J_1 = 9.4 Hz, J_2 = 3.4 Hz, J_3 = 2.2 Hz, 3F), -85.3 – -85.5 (m, 2F).

HRMS (ESI, m/z): calcd for C₁₀H₇F₅Cl⁺ [M+H]⁺ 257.0156, found: 257.0147.

Trimethyl(4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)phenyl)silane (**8m**)

Colorless oil.

Yield = 90%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.57 – 7.52 (m, 2H), 7.35 – 7.29 (m, 2H), 3.20 (qt, J_1 = 10.1 Hz, J_2 = 2.1 Hz, 2H), 0.29 (s, 9H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.5 (t, J = 290 Hz), 140.5, 133.6, 132.4 (t, J = 3 Hz), 127.3 (t, J = 3 Hz), 128.9, 125.4 (qt, J_1 = 276 Hz, J_2 = 4 Hz), 84.6 (tq, J_1 = 20 Hz, J_2 = 3 Hz), 33.3 (qd, J_1 = 31 Hz, J_2 = 2 Hz), -1.2.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (td, J_1 = 10.0 Hz, J_2 = 4.9 Hz, 3F), -85.71 – -85.87 (m, 1F), -85.9 – -86.0 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₃H₁₆F₅Si⁺ [M+H]⁺ 295.0941, found: 295.0946.

2-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)naphthalene (**8n**)

Light yellow oil.

Yield = 64%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.89 – 7.77 (m, 4H), 7.55 – 7.48 (m, 2H), 7.43

(dt, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, 1H), 3.30 (qt, $J_1 = 10.1$ Hz, $J_2 = 2.1$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 155.7 (t, $J = 290$ Hz), 133.2, 132.7, 129.4 (t, $J = 3$ Hz), 128.4, 128.0, 127.6 (t, $J = 3$ Hz), 126.6, 126.5, 125.6 (t, $J = 3$ Hz), 125.5 (qt, $J_1 = 276$ Hz, $J_2 = 4$ Hz), 84.7 (tq, $J_1 = 20$ Hz, $J_2 = 3$ Hz), 33.6 (qd, $J_1 = 32$ Hz, $J_2 = 2$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -65.0 (td, $J_1 = 9.9$ Hz, $J_2 = 4.6$ Hz, 3F), -85.6 – -85.8 (m, 1F), -85.9 – -86.0 (m, 1F).

HRMS (ESI, m/z): calcd for $\text{C}_{14}\text{H}_{10}\text{F}_5^+$ $[\text{M}+\text{H}]^+$ 273.0703, found: 273.0709.

3-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)quinoline (**8o**)

White solid.

Yield = 85%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.88 (t, $J = 2.0$ Hz, 1H), 8.15 – 8.07 (m, 2H), 7.82 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.4$ Hz, 1H), 7.75 (ddd, $J_1 = 8.4$ Hz, $J_2 = 6.9$ Hz, $J_3 = 1.5$ Hz, 1H), 7.58 (ddd, $J_1 = 8.1$ Hz, $J_2 = 6.9$ Hz, $J_3 = 1.2$ Hz, 1H), 3.31 (qt, $J_1 = 9.9$ Hz, $J_2 = 2.0$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 156.1 (t, $J = 290$ Hz), 149.6 (t, $J = 3$ Hz), 147.4, 135.2 (t, $J = 3$ Hz), 130.1, 129.3, 127.8, 127.4, 127.3, 125.3 (t, $J = 3$ Hz), 125.2 (qt, $J_1 = 276$ Hz, $J_2 = 4$ Hz), 82.3 (tq, $J_1 = 21$ Hz, $J_2 = 3$ Hz), 33.3 (qd, $J_1 = 32$ Hz, $J_2 = 2$ Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -64.9 (td, $J_1 = 9.9$ Hz, $J_2 = 4.6$ Hz, 3F), -83.6 – -83.8 (m, 1F), -84.2 – -84.4 (m, 1F).

HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_9\text{F}_5\text{N}^+$ $[\text{M}+\text{H}]^+$ 274.0655, found: 274.0657.

2-(4-(1,1,4,4,4-Pentafluorobut-1-en-2-yl)phenyl)-1,3-dioxolane (**8p**)

White solid.

Yield = 50%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.54 – 7.45 (m, 2H), 7.38 – 7.30 (m, 2H), 5.82 (s, 1H), 4.17 – 4.01 (m, 4H), 3.19 (qt, $J_1 = 9.9$ Hz, $J_2 = 2.0$ Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.6 (t, *J* = 290 Hz), 137.8, 132.9, 128.2 (t, *J* = 3 Hz), 126.8, 125.3 (qt, *J*₁ = 276 Hz, *J*₂ = 4 Hz), 103.2, 84.4 (tq, *J*₁ = 21 Hz, *J*₂ = 3 Hz), 65.3, 33.4 (qd, *J*₁ = 32 Hz, *J*₂ = 2 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (tdd, *J*₁ = 10.1 Hz, *J*₂ = 3.4 Hz, *J*₃ = 2.6 Hz, 3F), -85.6 – -85.9 (m, 2F).

HRMS (ESI, m/z): calcd for C₁₃H₁₂F₅O₂⁺ [M+H]⁺ 295.0757, found: 295.0764.

2-Methyl-2-(4-(1,1,4,4,4-pentafluorobut-1-en-2-yl)phenyl)-1,3-dioxolane (**8q**)

White solid.

Yield = 78%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.52 – 7.48 (m, 2H), 7.32 – 7.28 (m, 2H), 4.09 – 3.99 (m, 2H), 3.84 – 3.74 (m, 2H), 3.19 (qt, *J*₁ = 10.0 Hz, *J*₂ = 2.1 Hz, 2H), 1.66 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 155.5 (t, *J* = 290 Hz), 143.3, 131.5 (t, *J* = 3 Hz), 128.0 (t, *J* = 3 Hz), 125.6, 125.4 (qt, *J*₁ = 276 Hz, *J*₂ = 4 Hz), 108.6, 84.3 (tq, *J*₁ = 20 Hz, *J*₂ = 3 Hz), 64.5, 33.4 (qd, *J*₁ = 32 Hz, *J*₂ = 2 Hz), 27.5.

¹⁹F NMR (376 MHz, CDCl₃) δ (ppm): -65.0 (tdd, *J*₁ = 10.2 Hz, *J*₂ = 4.5 Hz, *J*₃ = 1.1 Hz, 3F), -85.8 – -85.9 (m, 1F), -85.9 – -86.0 (m, 1F).

HRMS (ESI, m/z): calcd for C₁₄H₁₄F₅O₂⁺ [M+H]⁺ 309.0914, found: 309.0908.

(3-(Difluoromethylene)-5,5,5-trifluoropent-1-yn-1-yl)benzene (**8r**)

Light yellow oil.

Yield = 53%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.49 – 7.41 (m, 2H), 7.37 – 7.29 (m, 3H), 2.97 (qt, *J*₁ = 9.8 Hz, *J*₂ = 1.9 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 160.45 (t, *J* = 297 Hz), 131.5, 128.8, 128.4, 125.0 (qt, *J*₁ = 275 Hz, *J*₂ = 4 Hz), 122.3, 94.4 (t, *J* = 4 Hz), 79.0 (dd, *J*₁ = 7 Hz, *J*₂ = 4 Hz), 70.9 (tq, *J*₁ = 27 Hz, *J*₂ = 4 Hz), 33.0 (q, *J* = 32 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ (ppm): -65.9 (td, $J_1 = 10.0$ Hz, $J_2 = 3.3$ Hz, 3F), -74.9 – -75.1 (m, 1F), -80.7 – -81 (m, 1F).

HRMS (ESI, m/z): calcd for $\text{C}_{12}\text{H}_8\text{F}_5^+$ $[\text{M}+\text{H}]^+$ 247.0546, found: 247.0550.

Methyl (Z)-4-(2,3,3,3-tetrafluoroprop-1-en-1-yl)benzoate (**10a**)

White solid.

Yield = 52%, E/Z = 1 : 99

^1H NMR of the Z-isomer (400 MHz, CDCl_3) δ (ppm): 8.14 – 8.01 (m, 2H), 7.68 – 7.58 (m, 2H), 6.41 (d, $J = 35.1$ Hz, 1H), 3.94 (s, 3H).

^{13}C NMR of the Z-isomer (100 MHz, CDCl_3) δ (ppm): 166.3, 146.2 (dq, $J_1 = 269$ Hz, $J_2 = 38$ Hz), 133.9 (d, $J = 4$ Hz), 130.9 (d, $J = 3$ Hz), 130.0, 129.6 (d, $J = 7$ Hz), 118.6 (qd, $J_1 = 270$ Hz, $J_2 = 41$ Hz), 110.6 (dq, $J_1 = 4$ Hz, $J_2 = 3$ Hz), 52.3.

^{19}F NMR of the Z-isomer (376 MHz, CDCl_3) δ (ppm): -72.2 (d, $J = 10.9$ Hz), -128.8 (dq, $J_1 = 35.2$ Hz, $J_2 = 10.9$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_9\text{F}_4\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 249.0539, found: 249.0546.

Methyl (Z)-2-(2,3,3,3-tetrafluoroprop-1-en-1-yl)benzoate (**10b**)

Yellow oil.

Yield = 51%, E/Z = 4 : 96

^1H NMR of the Z-isomer (400 MHz, CDCl_3) δ (ppm): 8.05 (dd, $J_1 = 7.9$, $J_2 = 1.4$ Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.58 (td, $J_1 = 7.6$ Hz, $J_2 = 1.4$ Hz, 1H), 7.45 (td, $J_1 = 7.7$

Hz, $J_2 = 1.3$ Hz, 1H), 7.36 (d, $J = 35.0$ Hz, 1H), 3.92 (s, 3H).

^{13}C NMR of the Z-isomer (100 MHz, CDCl_3) δ (ppm): 166.8, 145.1 (dq, $J_1 = 265$ Hz, $J_2 = 38$ Hz), 132.4, 131.0, 130.9 (d, $J = 9$ Hz), 130.3 (d, $J = 3$ Hz), 129.2, 129.0, 118.8 (qd, $J_1 = 270$ Hz, $J_2 = 42$ Hz), 110.6 (qd, $J_1 = 4$ Hz, $J_2 = 1$ Hz), 52.3.

^{19}F NMR of the Z-isomer (376 MHz, CDCl_3) δ (ppm): -72.2 (d, $J = 11.0$ Hz), -134.3 (dq, $J_1 = 34.1$ Hz, $J_2 = 10.9$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_9\text{F}_4\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 249.0539, found: 249.0539.

(Z)-4-(2,3,3,3-Tetrafluoroprop-1-en-1-yl)benzonitrile (**10c**)

Light yellow oil.

Yield = 53%, $E/Z = 5 : 95$

^1H NMR of the Z-isomer (400 MHz, CDCl_3) δ (ppm): 7.76 – 7.63 (m, 4H), 6.41 (d, $J = 34.4$ Hz, 1H).

^{13}C NMR of the Z-isomer (100 MHz, CDCl_3) δ (ppm): 146.9 (dq, $J_1 = 270$ Hz, $J_2 = 39$ Hz), 133.9 (d, $J = 4$ Hz), 132.6, 130.1 (d, $J = 7$ Hz), 118.3 (qd, $J_1 = 270$ Hz, $J_2 = 40$ Hz), 118.1, 113.2 (d, $J = 3$ Hz), 110.0 (dq, $J_1 = 7$ Hz, $J_2 = 2$ Hz).

^{19}F NMR of the Z-isomer (376 MHz, CDCl_3) δ (ppm): -72.3 (d, $J = 10.5$ Hz), -127.0 (dq, $J_1 = 34.2$ Hz, $J_2 = 10.5$ Hz).

HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_6\text{F}_4\text{N}^+$ $[\text{M}+\text{H}]^+$ 216.0436, found: 216.0439.

(Z)-3-(2,3,3,3-Tetrafluoroprop-1-en-1-yl)benzonitrile (**10d**)

Colorless oil.

Yield = 47%, $E/Z = 1 : 99$

^1H NMR of the Z-isomer (400 MHz, CDCl_3) δ (ppm): 7.87 (t, $J = 1.8$ Hz, 1H), 7.79 (dt, $J_1 = 7.9$ Hz, $J_2 = 1.5$ Hz, 1H), 7.68 (dt, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 6.38 (d, $J = 34.3$ Hz, 1H).

^{13}C NMR of the Z-isomer (100 MHz, CDCl_3) δ (ppm): 146.6 (dq, $J_1 = 269$ Hz, $J_2 = 39$ Hz), 133.6 (d, $J = 7$ Hz), 132.9 (d, $J = 7$ Hz), 132.8 (d, $J = 3$ Hz), 132.8 (d, $J = 3$ Hz), 129.8, 118.4 (qd, $J_1 = 270$ Hz, $J_2 = 40$ Hz), 118.0, 113.5, 109.5 (dq, $J_1 = 7$ Hz, $J_2 = 3$ Hz).

^{19}F NMR of the Z-isomer (376 MHz, CDCl_3) δ (ppm): -72.3 (d, $J = 10.5$ Hz), -128.3 (dq, $J_1 = 34.5$ Hz, $J_2 = 10.8$ Hz).

HRMS (ESI, m/z): calcd for C₁₀H₆F₄N⁺ [M+H]⁺ 216.0436, found: 216.0434.

Diethyl (Z)-(4-(2,3,3,3-tetrafluoroprop-1-en-1-yl)phenyl)phosphonate (**10e**)

Colorless oil.

Yield = 51%, *E/Z* = 4 : 96

¹H NMR of the Z-isomer (400 MHz, CDCl₃) δ (ppm): 7.92 – 7.81 (m, 2H), 7.72 – 7.60 (m, 2H), 6.40 (d, *J* = 35.0 Hz, 1H), 4.24 – 4.03 (m, 4H), 1.33 (td, *J*₁ = 7.1, *J*₂ = 0.5 Hz, 6H).

¹³C NMR of the Z-isomer (100 MHz, CDCl₃) δ (ppm): 146.5 (dq, *J*₁ = 231 Hz, *J*₂ = 39 Hz), 133.4 (t, *J* = 4 Hz), 132.2 (d, *J* = 10 Hz), 129.6 (d, *J* = 8 Hz), 129.4 (d, *J* = 8 Hz), 118.5 (qd, *J*₁ = 270 Hz, *J*₂ = 41 Hz), 110.6 (m), 62.3 (d, *J* = 5 Hz), 16.3 (d, *J* = 6 Hz).

¹⁹F NMR of the Z-isomer (376 MHz, CDCl₃) δ (ppm): -72.2 (d, *J* = 10.9 Hz), -128.6 (dq, *J*₁ = 34.9 Hz, *J*₂ = 10.9 Hz).

HRMS (ESI, m/z): calcd for C₁₃H₁₆F₄O₃P⁺ [M+H]⁺ 327.0773, found: 327.0782.

(Z)-N,N-Diethyl-4-(2,3,3,3-tetrafluoroprop-1-en-1-yl)benzamide (**10f**)

Light yellow solid.

Yield = 47%, *E/Z* = 9 : 91

¹H NMR of the Z-isomer (400 MHz, CDCl₃) δ (ppm): 7.60 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.38 (m, 2H), 6.37 (d, *J* = 35.4 Hz, 1H), 3.55 (s, 2H), 3.25 (s, 2H), 1.25 (s, 3H), 1.12 (s, 3H).

¹³C NMR of the Z-isomer (100 MHz, CDCl₃) δ (ppm): 170.3, 145.5 (dq, *J*₁ = 269 Hz, *J*₂ = 38 Hz), 138.3 (d, *J* = 3 Hz), 130.4 (d, *J* = 3 Hz), 129.7 (d, *J* = 8 Hz), 126.9, 118.7 (qd, *J*₁ = 270 Hz, *J*₂ = 40 Hz), 110.8 (m), 43.3, 39.4, 14.2, 12.9.

¹⁹F NMR of the Z-isomer (376 MHz, CDCl₃) δ (ppm): -72.1 (d, *J* = 11.0 Hz), -130.6 (dq, *J*₁ = 35.5 Hz, *J*₂ = 11.1 Hz).

HRMS (ESI, m/z): calcd for C₁₄H₁₆F₄NO⁺ [M+H]⁺ 290.1168, found: 290.1170.

1. References

1. S. Kim, J. Rojas-Martin, F. D. Toste, *Chem. Sci.* **2016**, 7, 85–88.
2. A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan, J. D. Weaver, *J. Organomet. Chem.* **2015**, 776, 51–59.
3. G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu, R. R. Knowles, *Nature* **2016**, 539, 268–271.
4. S. B. Lang, R. J. Wiles, C. B. Kelly, G. A. Molander, *Angew. Chem. Int. Ed.* **2017**, 56, 15073–15077.
5. P. Tian, C. Feng, T.-P. Loh, *Nat. Commun.* **2015**, 6, 7472.

Chapter 4

BIOCOMPATIBLE DISULFIDE BRIDGING AND APPLICATION TO SITE-SELECTIVE BIOCONJUGATION

4.1 Introduction

4.1.1 Antibody-drug conjugates

In the past century, various therapies have been developed for cancer treatment. Among them, biological therapy has drawn increasing attention, owing to its exquisite selectivity and low toxicity to normal cells. Currently, 13 therapeutic antibodies have been approved by FDA for cancer treatment.⁷⁴ However, despite the excellent selectivity of naked antibodies in tumor-cell killing, the lack of clinical efficiency still remains a drawback. On the other hand, chemotherapeutics involving small molecule

Figure 4-1. ADCs in the market.

drugs, lead to efficient cytotoxicity with low target specificity. Thus, Antibody-drug conjugates (ADCs) (Scheme 4-1), which combine tumor targeting specificity of

⁷⁴ Reichert, J. M. *mAbs* **2012**, 4, 413–415.

antibodies with potent cytotoxic drugs, have become one of the most promising and fastest growing therapies in cancer treatment. Until 2018, 4 ADCs (Adcetris[®], Kadcyla[®], Besponsa[®] and Mylotarg[®]) have been approved by FDA. Meanwhile, more than 60 ADCs are currently in different phases of clinical trials.

The development of target-specific monoclonal antibodies (mAbs) and cytotoxic drugs has promoted the evolution of new ADCs. Meanwhile, linker, a fragment in conjugate drug and mAb, plays another important role in ADC, as it impacts the efficacy and stability of ADC in blood.⁷⁵ Therefore, designing suitable linkers has become one of the most important key factors in the development of ADCs.

4.1.2 Biocompatible thiol-selective modification

Rare amino acids are often chosen as sites for bioconjugation in the design of new antibody drug conjugates as to reduce the amount of expensive payload necessary for bioconjugation. Among them, amino side chains such lysine and cysteine residues are two major reaction sites targeted for bioconjugation of mAbs. However, large abundant of lysine existing in the mAbs may lead to poor control of drug to antibody ratio (DAR) and randomly afford heterogeneous products with unpredictable toxicities in the bioconjugation of ADCs.⁷⁶ In contrast, cysteine, perhaps the lowest abundance amino acids in the peptides and proteins, is one of the most important and convenient amino acids for bioconjugation, owing to the free thiol group which could readily serve as nucleophilic groups for further modification. Thus, a variety of reagents have been

⁷⁵ Beck, A.; Goetsch, L.; Dumontet, C.; Corvaia, N. *Nat Rev Drug Discov.* **2017**, *16*, 315–37.

⁷⁶ Wang, L.; Amphlett, G.; Blattler, W. A.; Lambert, J. M.; Zhang, W. *Protein Sci.* **2005**, *14*, 2436–2446.

designed to modify thiol side chains of cysteines in the peptides and proteins.

Scheme 4-1. Thiol-selective modification with maleimide

As thiol groups usually serves as nucleophiles, treating cysteine with Michael acceptors is one of the feasible strategies to achieve cysteine residue modification in the peptides or proteins. In 2005, Haddleton's group reported polymeric bioconjugation with glutathione and bovine serum albumin (BSA) in the buffer solution (Scheme 4-1).⁷⁷ Maleimide was assembled with polyethylene glycol (PEG) in N-terminal site and selectively underwent Michael addition with cysteine residues in the peptides to afford a series of bioconjugates.

Scheme 4-2. Thiol-selective modification with bromomaleimide

In addition to conventional maleimides, a novel class of bromomaleimides was

⁷⁷ Mantovani, G.; Lecolley, F.; Tao, L.; Haddleton, D. M.; Clerx, J.; Cornelissen, J. J. L. M.; Velonia, K. *J. Am. Chem. Soc.* **2005**, *127*, 2966–2973.

developed by Caddick, Baker and et al in 2010 (Scheme 4-2).⁷⁸ Instead of Michael addition, a substitution reaction was involved and cysteine residues was selectively modified by bromomaleimides in this reaction. Meanwhile, the modification is reversible, recovering the unmodified peptides or proteins in the presence of excess TCEP.

Scheme 4-3. Thiol-selective modification with Julia-Kociński-like reagents

Maleimide has been widely applied in the bioconjugation of peptide and proteins. However, the stability of its corresponding product still remains a problem, which would undergo retro-Michael reaction in the presence of other thiol groups, to yield undesired heterogeneous mixtures.⁷⁹ In 2013, Barbas's group described a site-selective modification of thiols by using Julia-Kociński-like reagents (Scheme 4-3).⁸⁰ It is compatible to protein conjugation with exquisite site-selectivity and has showed relatively good stability compared to maleimide products.

⁷⁸ Smith, M. E. B.; Schumacher, F. F.; Ryan, C. P.; Tedaldi, L. M.; Papaioannou, D.; Waksman, G.; Caddick, S.; Baker, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 1960–1965.

⁷⁹ Baldwin, A. D.; Kiick, K. L. *Bioconjugate Chem.* **2011**, *22*, 1946–1953.

⁸⁰ Toda, N.; Asano, S.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 12592–12596.

Scheme 4-4. π -Clamp-mediated modification of cysteines

Recently, Pentelute's group developed a novel strategy to achieve sequence- and site-selective modification of cysteines with perfluoroaromatic reagents in the specific amino acid sequence (Scheme 4-4).⁸¹ The authors proposed it's π -clamp that affects the selectivity in specific sequence and is successfully applied in the protein bioconjugation.

Scheme 4-5. Thiol-selective modification with allenamides

In 2014, our group along reported a new approach to site-selectively to modify thiol side chains in peptides and proteins using allenamides (Scheme 4-5).⁸² The reagent demonstrated good reactivity and selectivity.

4.1.3 Biocompatible disulfide bridging modification

Modification of cysteine has been widely applied in biochemical conjugation, owing to cysteine's relatively low abundance in the proteins and the good selectivity of thiol side chain in the cysteine.⁸³ However, relatively rare unpaired thiol side chain

⁸¹ Zhang, C.; Welborn, M.; Zhu, T.; Yang, N. J.; Santos, M. S.; Voorhis, T. V.; Pentelute, B. L. *Nature Chem.* **2016**, 8, 120–128.

⁸² Abbas, A.; Xing, B.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2014**, 53, 7491–7494.

⁸³ Cal, P. M. S. D.; Bernardes, G. J. L.; Gois, P. M. P. *Angew. Chem. Int. Ed.* **2014**, 53, 10585–10587.

exists in the native proteins. Normally, reduction of disulfide is chosen to release free thiol cysteine residues in the thiol-selective modification. Disulfide bonds are essential for maintaining the tertiary structure of proteins and direct reducing disulfide possibly has negative effect on the stability and bioactivity of proteins. Meanwhile, for the thiol-modified ADCs, high DAR (>4) is undesirable which leads to low tolerability and efficacy *in vivo*.⁸⁴ Thus, developing new strategies to maintain the structure of proteins and decreasing the reaction site during cysteine-based bioconjugation is urgently needed. In recent years, disulfide bridging modification has merged as promising approaches to access protein bioconjugation with minimum impact on stability and bioactivity of proteins.

Scheme 4-6. Disulfide rebridging with dibromomaleimides and dithiophenolmaleimide

In 2010, Baker's group has pioneered the use of substituted maleimides to achieve single thiol-selective modification and disulfide bridging.⁵⁰ In 2012, Haddleton's group developed a polymeric dibromomaleimide reagent to successfully achieve disulfide rebridging of salmon calcitonin in the buffer solution.⁸⁵ Meanwhile, Baker's group also described dithiophenolmaleimide as a new maleimide reagent, to achieve the site-

⁸⁴ Hamblett, K. J.; Senter, P. D.; Chace, D. F.; Sun, M. M. C.; Lenox, J.; Cervený, C. G.; Kissler, K. M.; Bernhardt, S. X.; Kopcha, A. K.; Zabinski, R. F.; Meyer, D. L.; Francisco, J. a. *Clin. Cancer Res.* **2004**, *10*, 7063–7070.

⁸⁵ Jones, M. W.; Strickland, R. A.; Schumacher, F. F.; Caddick, S.; Baker, J. R.; Gibson, M. I.; Haddleton, D. J. *Am. Chem. Soc.* **2012**, *134*, 1847–1852.

specific disulfide rebridging bioconjugation (Scheme 4-6).⁸⁶

Scheme 4-7. Disulfide rebridging with dibromopyridazinediones

Later in 2015, Chudasama and Caddick et al developed dibromopyridazinedione as new reagent to make a novel ADC candidate through disulfide rebridging (Scheme 4-7).⁸⁷ As more than one modification site were obtained in the compound, two different payloads could be assembled in the fragment.

Scheme 4-8. Disulfide rebridging with bis-alkylating reagent

In addition to substitution reactions, Michael addition has also been applied to the disulfide bridging conjugations. In 2014, Godwin's group used bis-alkylating reagent to achieve the conjugation of cytotoxic drug to monoclonal antibody through disulfide rebridging, which developed a new approach to produce ADCs (Scheme 4-8).⁸⁸ Two

⁸⁶ Schumacher, F. F.; Sanchania, V. A.; Tolner, B.; Wright, Z. V. F.; Ryan, C. P.; Smith, M. E. B.; Ward, J. M.; Caddick, S.; Kay, C. W. M.; Aeppli, G.; Chester, K. A.; Baker, J. R. *Sci. Rep.* 2013, 3, 1–8.

⁸⁷ Maruani, A.; Smith, M. E. B.; Miranda, E.; Chester, K. A.; Chudasama, V.; Caddick, S. *Nat. Commun.* **2015**, 6, 6645.

⁸⁸ Badescu, G.; Bryant, P.; Bird, M.; Henseleit, K.; Swierkosz, J.; Parekh, V.; Tommasi, R.; Pawlisz, E.; Jurlewicz,

Michael additions along with elimination was involved in the conjugation process. This transformation is not suitable under high pH reaction conditions, as byproducts would be obtained.

Scheme 4-9. Disulfide rebridging with organic arsenicals

Recently, trivalent organic arsenicals have been developed as a novel type of disulfide rebridging reagents by Davis and co-workers (Scheme 4-9).⁸⁹ The arsenic reagents were proved to be efficient to undergo conjugation with peptide sCT through bridging disulfide. This reaction is reversible and would release peptide from conjugate in the presence of excess other thiol reagents.

Scheme 4-10. Disulfide rebridging with 1,3-dichloroacetone

In 2015, Micoli's group reported that 1,3-dichloroacetone could selectively react

K.; Farys, M.; Camper, N.; Sheng, X.-B.; Fisher, M.; Grygorash, R.; Kyle, A.; Abhilash, A.; Frigerio, M.; Edwards, J.; Godwin, A. *Bioconjugate Chem.* **2014**, 25, 1124–1136.

⁸⁹ Wilson, P.; Anastasaki, A.; Owen, M. R.; Kempe, K.; Haddleton, D. M.; Mann, S. K.; Johnston, A. P. R.; Quinn, J. F.; Whittaker, M. R.; Hogg, P. J.; Davis, T. P. *J. Am. Chem. Soc.* **2015**, 137, 4215–4222.

with dithiol groups to achieve disulfide rebridging efficiently (Scheme 4-10).⁹⁰ The following formation of imine with amino-contained linkers was convenient to give desired bioconjugate.

A variety of strategies and reagents have been developed to access disulfide bridging efficiently. During the disulfide bridging, the minimal change of the protein is preferred. Trapping two cysteine residues with one reaction site would minimize the influence on the structure of proteins. Thus, our goal aims to develop a new class of reagents to efficiently effect disulfide bridging, which have low toxicity and have minimal impact on the structures and bioactivities of the proteins.

⁹⁰ Stefanetti, G.; Hu, Q.-Y.; Usera, A.; Robinson, Z.; Allan, M.; Singh, A.; Imase, H.; Cobb, J.; Zhai, H.; Quinn, D.; Lei, M.; Saul, A.; Adamo, R.; MacLennan, C. A.; Micoli, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 13198–131203.

4.2 Results and Discussion

Table 4-1. Optimization of disulfide bridging reagents

^aReaction condition: 11 (0.1 mmol), 12 (0.21 mmol), PBS buffer (0.2 M) (0.8 mL), DMSO (0.2 mL), rt, 2 h

To explore the disulfide bridging reactions, commercially available compound ethyl 2-mercaptoacetate (**12a**) was chosen as a model compound to mimic thiol side chain in peptides and proteins, (Table 4-1). Initially, 2,2-dichloro-1-phenylethane-1-one (**11a**) was employed to react with **12a** in the buffer solution (pH = 7.6). The desired dithiolacetal was readily obtained without other byproducts in moderate yield.

Subsequently, we proceeded on with the study of substrates with different leaving groups. Changing chloride to bromide (**11ab** and **11ac**) resulted in lower yield of the desired along with byproducts while substrate with acetoxy group (**11ad**) gave no desired product.

Table 4-2. Optimization of disulfide bridging reagents

^aReaction condition: 11 (0.1 mmol), 12 (0.21 mmol), PBS buffer (0.2 M) (0.8 mL), DMSO (0.2 mL), rt, 2 h

The efficiency of different substituents was then investigated under standard

reaction conditions. In addition to phenyl group, aliphatic and methoxyl groups (**11b** and **11c**) were also tested and furnished the corresponding dithiolacetal products in 36-39% yields. It is likely that electron-deficient substrates was preferred in this reaction. However, in the presence of substrate with sulfonyl group (**11d**), no desired product was obtained.

Table 4-3. Optimization of disulfide bridging reagents

^aReaction condition: **11** (0.1 mmol), **12** (0.21 mmol), PBS buffer (0.2 M) (0.8 mL), DMSO (0.2 mL), rt, 2 h

Based on the results, substrates with aromatic group is more suitable for this

reaction. We continued to investigate phenyl groups with both electron-withdrawing and -donating groups. Importantly, the substrate bearing ester group gave dithiolacetal product **13fa** in 72% yield while methoxy group only furnished **13ea** in 55% yield. Therefore, we chose **11f** as the standard substrate for further investigation.

Table 4-4. Disulfide bridging with small molecules

<p>11f</p>	<p>12</p>
<p>pH = 7.6 DMSO, rt, 2 h</p>	
<p>13</p>	
<p>12a</p>	<p>13fa, 72%</p>
<p>12b</p>	<p>13fb, 52%</p>
<p>12c</p>	<p>13fc, 83%</p>
<p>12d</p>	<p>13fd, 74%</p>
<p>12e</p>	<p>13fe, 52%</p>

With the optimum results in hand, different thiol substrates were investigated under the standard reaction conditions (Table 4-4). All substrates with single thiol group underwent dithiolacetal formation reaction smoothly. While substrates bearing longer aliphatic chain (**12b**) would proceed with slight decrease in yield (from 72% of **13fa** to 52% of **13fb**). Notably, **11f** was found to be effective to trap N-Ac-Cysteine ester **12c** in this transformation to give the corresponding **13fc** as single product in 83% high yield. Meanwhile, when ethane-1,2-dithiol (**12d**) and propane-1,3-dithiol (**12e**) were employed in the reactions, cyclization products **13fd** and **13fe** could also proceed smoothly in 74% and 52% yields respectively. These results indicate that various thiol substrates are compatible to this reaction.

Table 4-5. Disulfide bridging in different pH values

11f	12c	13fc
pH = 6.0	pH = 7.0	pH = 7.6
13fc , 14%	13fc , 52%	13fc , 83%

^aReaction condition: **11** (0.1 mmol), **12** (0.21 mmol), PBS buffer (0.2 M) (0.8 mL), DMSO (0.2 mL), rt, 2 h

To further investigate the reaction conditions, the disulfide bridging was carried out in different pH buffers (Table 4-5). The yield of **13fc** was sharply depressed with only 14%, when **11f** and **12c** were reacted under acidic conditions. Neutral conditions could sustain the reaction to give moderate yield while weakly alkaline conditions (pH

7.6), which is biocompatible, were found to be the optimum reaction conditions.

Scheme 4-11. Site-selectivity investigation

Scheme 4-12. Selectivity between cysteine and aliphatic thiol substrate

Subsequently, the site-selectivity of **11f** towards thiol group, was further investigated. Glycine methyl ester (**12f**) and methyl 2-hydroxyacetate (**12g**) were

chosen to mimic the amino group and hydroxyl group widely found in peptides and proteins. To our delight, the substrate **11f** has excellent site-selectivity, only desired dithiolacetal product was assembled in good yields and no **13ff** or **13fg** was investigated. Interestingly, when treating **11f** with mixture of cysteine **12c** and 1-hexanethiol **12f** under standard reaction conditions, only cysteine-containing product **13fc** was obtained in excellent yield. This result is possibly attributed to the ester group in the cysteine (**12c**), which acts as the electron-withdrawing group to make thiolate anion, a nucleophile, more stable in buffer solution. The result demonstrated that **11f** is inclined to react with functionalized thiol substrates such as cysteine, regardless of other nucleophiles existing in the reaction. This reaction is highly chemoselective.

Scheme 4-12. Modification of glutathione

Later, we applied **11f** for the reaction with peptides containing different functionalities. Commercially available tripeptide glutathione was chosen to react with **11f** in buffer solution and the disulfide bridging compound **13fh** was obtained as confirmed by LC-MS.

Scheme 4-12. Disulfide rebridging of N-Ac-oxytocin

Oxytocin is a nonapeptide which could be produced by hypothalamus. It is widely used during and after childbirth and served as an important hormone in social bonding and sexual reproduction. In this case, N-Ac-Oxytocin **12i** was chosen to further evaluate the ability of **11f** to bridge disulfide bond. Initially, **12i** was treated with TCEP for 0.5 hour to obtain the free thiol groups from the two cysteine residues in the peptide. Then, the solution was treated with dichloroacetyl substrate **11f** and kept at room temperature for 2 hours. The desired disulfide bridged product **13fi** was obtained with 90% yield, which was confirmed by RP-HPLC and LC-MS (Figure 4).

Figure 4. RP-HPLC analysis of reduced N-Ac-oxytocin disulfide bridging with **11f** and LC-MS analysis of **13fi**

4.3 Conclusion

In conclusion, a new class of linker for sulfur bioconjugation has been developed. The α,α -dichloroacetophenone derivatives (**11**) have been found to undergo conjugation with thiol substrates efficiently under biocompatible buffer solutions, yielding the corresponding disulfide products in good yields. This linker is highly selective towards sulfur and did not react with amine and hydroxy groups commonly found in proteins and peptides. It has also been found to work with complex peptides such as N-Ac-oxytocin and glutathione. The application of this reagent for the development of new antibody drug conjugates (ADCs) is currently in progress. The application of this linker in organic synthesis is another project under investigation in our group.

4.4 Experiment section

General Information

The methyl 2,2-dichloroacetate (**11c**), ethyl 2-mercaptoacetate (**12a**), ethyl 3-mercaptopropanoate (**12b**) ethane-1,2-dithiol (**12d**), propane-1,3-dithiol (**12e**) and glutathione (**12h**) were purchased from Alfa-Aesar, N-Ac-oxytocin (**12i**) was purchased from GL Biochem. ¹H NMR and ¹³C NMR spectra were carried out on a Bruker Advance 400 NMR spectrometer. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard. Coupling constants, *J*, are reported in Hertz. *E/Z* isomer ratio was confirmed via NMR spectra analysis of the crude product. HRMS was carried out on Waters Q-ToF Mass spectrometer. LC-MS spectra were recorded on ThermoFinnigan LCQ Fleet MS.

RP-HPLC

RP-HPLC spectra were performed by using Discovery® BIO Wide Pore C18 HPLC Column (5 μ m) 250 x 4.6 mm. The HPLC system comprised of SHIMADZU LC-20AD pump; SHIMADZU SIL-20A was used to inject sample automatically. SHIMADZU SPD-M20A was used as sample detector. Mobile phase A: 100 % v/v water, and 0.05 % v/v TFA; mobile phase B: 100 % v/v MeCN and 0.05 % v/v TFA.

General procedure to synthesize products 13aa-13fe

To a 4 mL glass vial, charged with **11** (0.1 mmol, 1 equiv) in DMSO (0.2 mL) was sequentially added **12** (0.22 mmol, 1.1 equiv) and PBS (0.2M, pH = 7.6) buffer solution

(0.8 mL) at ambient temperature. The mixture was kept stirring at ambient temperature for 2 hours. The reaction mixture was diluted with EtOAc (10 mL), washed with water (2×20 mL), brine (20 mL), and concentrated under vacuum. Purification by column chromatograph with EtOAc and hexane as eluent affords the target product **13**.

Modification of glutathione (GSH) **12h**

To a 4 mL glass vial, charged with **11f** (0.02 mmol, 1 equiv) in CH₃CN (0.2 mL) was sequentially added glutathione **12h** (0.04 mmol, 1 equiv) in NH₄HCO₃ (0.1 M) buffer solution (0.8 mL) at ambient temperature. The vial was kept stirring at ambient temperature for 2 hours. LC-MS was done to ensure the target product was obtained.

Modification of N-Ac-oxytocin **12i**

To a 8 mL sample vial, N-Ac-oxytocin **12i** (3.0 mg, 2.86 μmol) was dissolved in 0.6

mL of H₂O, along with TCEP (0.9 mg, 3.15 μ mol) and kept stirring for 30 minutes. Upon complete reduction of the disulfide bridge (as observed by RP-HPLC), 1.2 mL of NH₄HCO₃ (0.1 M) buffer solution was added to the solution, followed by a solution of the **11f** (0.8 mg, 3.15 μ mol) in 0.2 mL of CH₃CN. The vial was sealed and stirred at ambient temperature for 2 h, a sample was taken for RP-HPLC. the formation of a new peak was observed, which was confirmed by and LCMS analysis as the rebridged product **13fi**.

HPLC conditions

Flow rate: 0.8 mL/min

Gradient: 10–90% CH₃CN (0.05% TFA) / H₂O (0.05% TFA), 25 min

Before adding **11f**

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.668	2513977	271218	100.000	100.000
Total		2513977	271218	100.000	100.000

Adding **11f** and stirring 2 hours

PeakTable

PDA Ch2 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.804	244016	30527	5.417	6.403
2	16.371	4260848	446272	94.583	93.597
Total		4504865	476799	100.000	100.000

Characterization data for the products

2,2-Dichloro-1-phenylethan-1-one (**11a**)

Colorless oil.

¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.13 – 8.04 (m, 2H), 7.71 – 7.61 (m, 1H), 7.58 – 7.47 (m, 2H), 6.68 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm): 185.9, 134.5, 131.3, 129.7, 128.9, 67.8.

HRMS (ESI, m/z): calcd for C₈H₇Cl₂O⁺ [M+H]⁺ 220.9772, found: 220.9767.

2-Bromo-2-chloro-1-phenylethan-1-one (**11ab**)

Pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.11 – 8.06 (m, 2H), 7.67 – 7.62 (m, 1H), 7.56 – 7.49 (m, 2H), 6.75 (s, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 186.0, 134.5, 131.2, 129.7, 129.6, 128.9, 54.1.

HRMS (ESI, m/z): calcd for C₈H₈BrClO⁺ [M+H]⁺ 232.9369, found: 232.9374.

2,2-Dibromo-1-phenylethan-1-one (**11ac**)

Yellow solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.03 – 7.95 (m, 2H), 7.65 – 7.59 (m, 1H), 7.55 – 7.46 (m, 2H), 4.46 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 185.9, 134.4, 130.8, 129.7, 128.9, 39.6.

HRMS (ESI, m/z): calcd for C₈H₇Br₂O⁺ [M+H]⁺ 276.8864, found: 276.8871.

1,1-Dichloro-4-phenylbutan-2-one (**11b**)

Colorless oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.33 – 7.28 (m, 2H), 7.22 (m, 3H), 5.79 (s, 1H), 3.18 – 3.13 (m, 2H), 2.98 (t, *J* = 7.5 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 196.22, 139.9, 128.6, 128.3, 126.4, 69.8, 36.7, 29.8.

HRMS (ESI, m/z): calcd for C₁₀H₁₁Cl₂O⁺ [M+H]⁺ 217.0187, found: 217.0190.

1-((Dichloromethyl)sulfonyl)-4-methylbenzene (**11d**)

White solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.00 – 7.86 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.23 (s, 1H), 2.50 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 147.0, 131.2, 129.9, 128.9, 79.9, 21.9.

HRMS (ESI, m/z): calcd for C₈H₉Cl₂O₂S⁺ [M+H]⁺ 238.9700, found: 238.9693.

2,2-Dichloro-1-(4-methoxyphenyl)ethan-1-one (**11e**)

White solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.11 – 8.05 (m, 2H), 7.01 – 6.96 (m, 2H), 6.63 (s, 1H), 3.90 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 184.6, 164.6, 132.2, 123.9, 114.2, 67.8, 55.6.

HRMS (ESI, m/z): calcd for C₉H₉Cl₂O₂⁺ [M+H]⁺ 218.9980, found: 218.9989.

Methyl 4-(2,2-dichloroacetyl)benzoate (**11f**)

White solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.22 – 8.12 (m, 4H), 6.64 (s, 1H), 3.97 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 185.5, 165.8, 135.1, 134.6, 129.9, 129.7, 67.8, 52.6.

HRMS (ESI, m/z): calcd for C₁₀H₉Cl₂O₃⁺ [M+H]⁺ 246.9929, found: 246.9927.

Methyl acetylcysteinate (**12c**)

White solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.35 (br, 1H), 4.90 (dt, *J* = 7.8, 4.0 Hz, 1H), 3.80 (s, 3H), 3.08 – 2.96 (m, 2H), 2.07 (s, 3H), 1.33 (t, *J* = 9.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 170.6, 169.8, 53.5, 52.8, 26.8, 23.1.

HRMS (ESI, *m/z*): calcd for C₆H₁₂NO₃S⁺ [M+H]⁺ 178.0538, found: 178.0543.

Diethyl 2,2'-(2-oxo-2-phenylethane-1,1-diyl)bis(sulfanediyl)diacetate (**13aa**)

Yellow oil.

Yield = 64%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.04 – 7.94 (m, 2H), 7.64 – 7.54 (m, 1H), 7.52 – 7.42 (m, 2H), 5.97 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 4H), 3.59 (d, *J* = 15.7 Hz, 2H), 3.33 (d, *J* = 15.7 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 169.8, 134.2, 133.8, 128.9, 128.7, 61.6, 54.1, 31.5, 14.0.

HRMS (ESI, *m/z*): calcd for C₁₆H₂₁O₅S₂⁺ [M+H]⁺ 357.0830, found: 357.0843.

Diethyl 2,2'-(2-oxo-4-phenylbutane-1,1-diyl)bis(sulfanediyl)diacetate (**13ba**)

Colorless oil.

Yield = 36%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 – 7.10 (m, 5H), 4.92 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 4H), 3.40 (d, *J* = 15.8 Hz, 2H), 3.19 (d, *J* = 15.7 Hz, 2H), 3.08 (ddd, *J*₁ = 8.0 Hz, *J*₂ = 7.0 Hz, *J*₃ = 0.9 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 201.0, 169.7, 128.4, 128.4, 126.4, 61.6, 58.1, 41.2, 31.5, 29.8, 14.1.

HRMS (ESI, *m/z*): calcd for C₁₈H₂₅O₅S₂⁺ [M+H]⁺ 385.1143, found: 385.1134.

Diethyl 2,2'-(2-methoxy-2-oxoethane-1,1-diyl)bis(sulfanediyl)diacetate (**13ca**)

Colorless oil.

Yield = 39%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.83 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.78 (s,

3H), 3.54 (d, $J = 15.8$ Hz, 2H), 3.41 (d, $J = 15.8$ Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 169.6, 168.8, 61.7, 53.1, 51.0, 32.4, 14.1.

HRMS (ESI, m/z): calcd for $\text{C}_{11}\text{H}_{19}\text{O}_6\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 311.0623, found: 311.0623.

Diethyl 2,2'-(2-(4-methoxyphenyl)-2-oxoethane-1,1-diyl)bis(sulfanediyl)diacetate (**13ea**)

Yellow oil.

Yield = 55%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.03 – 7.94 (m, 2H), 7.00 – 6.88 (m, 2H), 5.92 (s, 1H), 4.15 (q, $J = 7.1$ Hz, 4H), 3.87 (s, 3H), 3.60 (d, $J = 15.7$ Hz, 2H), 3.32 (d, $J = 15.7$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 190.3, 170.0, 164.1, 131.3, 126.9, 114.0, 61.6, 55.5, 54.0, 31.5, 14.1.

HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{23}\text{O}_6\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 387.0936, found: 387.0928.

Diethyl 2,2'-(2-(4-(methoxycarbonyl)phenyl)-2-oxoethane-1,1-diyl)bis(sulfanediyl)diacetate (**13fa**)

Yellow solid.

Yield = 72%

^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.16 – 8.09 (m, 2H), 8.07 – 8.01 (m, 2H), 5.96 (s, 1H), 4.15 (q, $J = 7.1$ Hz, 4H), 3.94 (s, 3H), 3.57 (d, $J = 15.8$ Hz, 2H), 3.33 (d, $J = 15.7$ Hz, 2H), 1.24 (t, $J = 7.2$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 191.0, 169.7, 137.6, 134.4, 129.9, 128.8, 61.7, 54.3, 52.5, 31.4, 14.0.

HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{23}\text{O}_7\text{S}_2^+$ $[\text{M}+\text{H}]^+$ 415.0885, found: 415.0874.

Diethyl 3,3'-(2-(4-(methoxycarbonyl)phenyl)-2-oxoethane-1,1-diyl)bis(sulfanediyl)dipropionate (**13fb**)

Yellow oil.

Yield = 52%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.16 – 8.08 (m, 2H), 8.07 – 7.99 (m, 2H), 5.50 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 4H), 3.95 (s, 3H), 2.99 (m, 2H), 2.93 – 2.84 (m, 2H), 2.63 (td, *J*₁ = 7.1 Hz, *J*₂ = 1.7 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 191.1, 171.6, 137.7, 134.2, 129.9, 128.8, 60.8, 55.2, 52.5, 34.4, 25.1, 14.2.

HRMS (ESI, *m/z*): calcd for C₂₀H₂₇O₇S₂⁺ [*M*+*H*]⁺ 443.1198, found: 443.1179.

Dimethyl 3,3'-((2-(4-(methoxycarbonyl)phenyl)-2-oxoethane-1,1-diyl)bis(sulfanediy-1))bis(2-acetamidopropanoate) (**13fc**)

White solid.

Yield = 83%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.16 – 8.08 (m, 2H), 8.02 (m, 2H), 6.52 (m, 2H), 5.59 (s, 1H), 4.83 (ddt, *J*₁ = 19.7 Hz, *J*₂ = 7.5 Hz, *J*₃ = 5.1 Hz, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.28 – 3.13 (m, 2H), 2.99 (m, 2H), 2.00 (s, 6H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 190.9, 171.0, 170.2, 170.0, 165.8, 137.2, 134.4, 129.8, 128.8, 54.5, 52.7, 52.7, 52.5, 51.7, 51.2, 32.4, 32.1, 22.9, 22.9.

HRMS (ESI, *m/z*): calcd for C₂₂H₂₉N₂O₉S₂⁺ [*M*+*H*]⁺ 529.1314, found: 529.1318.

Methyl 4-(1,3-dithiolane-2-carbonyl)benzoate (**13fd**)

White solid.

Yield = 74%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.17 – 8.08 (m, 2H), 8.06 – 7.95 (m, 2H), 5.77 (s, 1H), 3.95 (s, 3H), 3.37 (m, 4H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 191.4, 166.0, 138.3, 134.1, 129.8, 128.6, 53.9, 52.5, 38.8.

HRMS (ESI, *m/z*): calcd for C₁₂H₁₃O₃S₂⁺ [*M*+*H*]⁺ 269.0306, found: 269.0298.

Methyl 4-(1,3-dithiane-2-carbonyl)benzoate (**13fe**)

White solid.

Yield = 52%

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.17 – 8.07 (m, 2H), 8.04 – 7.95 (m, 2H), 5.11 (s, 1H), 3.95 (s, 3H), 3.36 (ddd, $J_1 = 14.1$ Hz, $J_2 = 11.2$ Hz, $J_3 = 2.9$ Hz, 2H), 2.68 (ddd, $J_1 = 14.0$ Hz, $J_2 = 5.7$ Hz, $J_3 = 3.1$ Hz, 2H), 2.22 – 1.99 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 191.8, 166.0, 138.2, 134.0, 129.9, 128.6, 52.5, 42.5, 26.3, 25.0.

HRMS (ESI, m/z): calcd for C₁₃H₁₅O₃S₂⁺ [M+H]⁺ 283.0463, found: 283.0462.

List of publications

1. Wu, L.-H.; Zhao, K.; Shen, Z.-L.; Loh, T.-P. *Org. Chem. Front.* **2017**, 4, 1872-1875.
2. Wu, L.-H.; Cheng, J.-K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Visible Light-Mediated Trifluoromethylation of Fluorinated Alkenes via C–F Bond Cleavage*, *Adv. Synth. Catal.* Accepted.
3. Cheng, J.-K.; Shen, L.; Wu, L.-H.; Hu, X.-H.; Loh, T.-P. *Chem. Commun.* **2017**, 53, 12830-12833.