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New access to trifluoromethyl acrylates and acrylic acids and their subsequent use in organometallic chemistry

Pan Xiao

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Normandie Université

THESE

Pour obtenir le diplôme de doctorat

Spécialité Chimie Organique

Préparée au sein de l'Institut National des Sciences Appliquées de Rouen

New Access to Trifluoromethyl Acrylates and Acrylic Acids and Their Subsequent Use in Organometallic Chemistry

Présentée et soutenue par
Pan XIAO

Thèse soutenue publiquement le 12 Avril 2021
devant le jury composé de

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肖盼 (XIAO Pan)

In Mont Saint Aignan

Abstract

Owing to the unique properties of the trifluoromethyl (CF₃) group, CF₃-substituted alkenes play important roles in pharmaceuticals, agrochemicals, and materials science. Among various trifluoromethyl alkene derivatives, CF₃-containing acrylates and acrylic acids have great application potential. Despite obvious interest in such kinds of scaffolds, the methods for their synthesis as well as their substrate scope remain relatively limited. In this Ph.D. thesis, we mainly focused on the synthesis of 3-aryl-2-(trifluoromethyl)acrylates and acrylic acids. Subsequent transformations of these compounds were further investigated.

In the first part of this thesis, we reported the synthesis of diverse methyl and *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates from aryl iodides and the corresponding 2-(trifluoromethyl)acrylates by Mizoroki-Heck reaction in the presence of palladium catalyst and silver(I) additive. The one-pot synthesis of 3-trifluoromethyl coumarin derivatives was further achieved starting from *ortho*-iodophenols and methyl 2-(trifluoromethyl)acrylate by tandem Mizoroki-Heck reaction and intramolecular cyclization.

In the second part of this thesis, we demonstrated that the palladium-catalysed silver(I) additive-mediated Mizoroki-Heck reaction could be extended to the synthesis of 3-aryl-2-(trifluoromethyl)acrylic acids. Similarly, the reaction between *ortho*-iodophenols and 2-(trifluoromethyl)acrylic acid could also give access to 3-trifluoromethyl coumarin derivatives. Furthermore, we achieved the construction of more complex alkyl 3-aryl-2-(trifluoromethyl)acrylates by three-component reactions between aryl iodides, 2-(trifluoromethyl)acrylic acid, and alkyl iodides.

In the last part of this thesis, we developed a method for palladium-catalysed copper(I)-mediated oxidative decarboxylative cross-coupling of heteroarenes with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids. Diverse trisubstituted CF₃-alkenes were generated in relatively low yields but with high *E/Z* selectivity.

Résumé

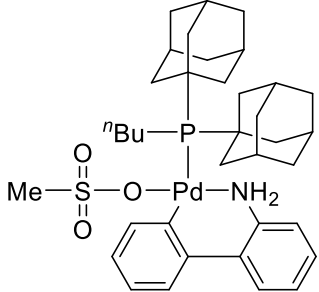
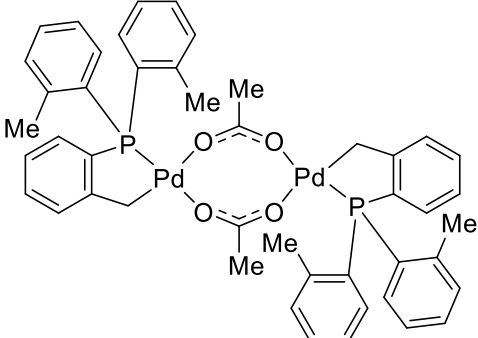
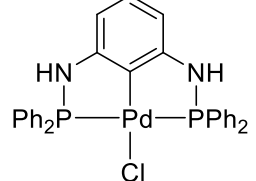
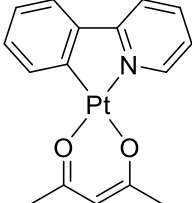
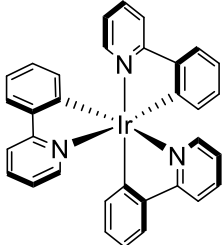
En raison des propriétés uniques du groupement trifluorométhyle (CF_3), les alcènes substitués par un CF_3 jouent un rôle important en chimie pharmaceutique, agrochimie et science des matériaux. Parmi les divers dérivés trifluorométhylés, les acrylates et les acides acryliques contenant un groupement CF_3 présentent un grand potentiel d'applications. Malgré l'intérêt évident de tels « briques de construction », leur méthode de synthèse ainsi que leur étendue d'applications restent relativement limitées. Au cours de cette thèse, nous nous sommes concentrés sur la synthèse des 3-aryl-2-trifluorométhylacrylates ainsi que des acides acryliques correspondants. Des transformations ultérieures de ces composés ont également été étudiées.

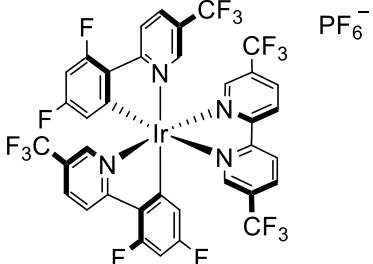
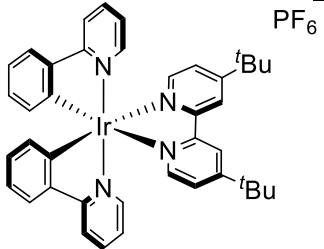
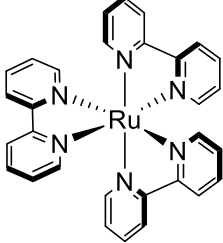
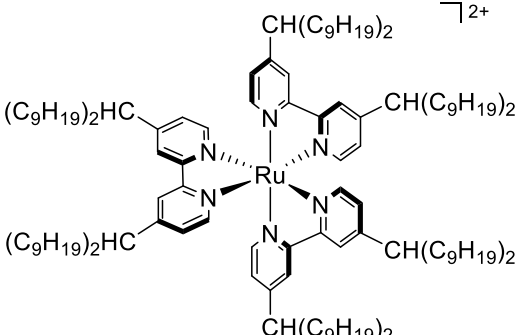
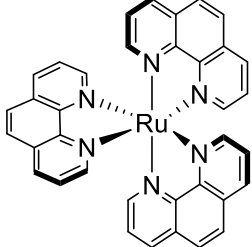
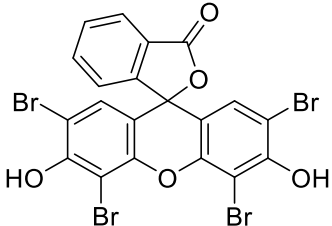
Dans la première partie de la thèse, nous présentons les résultats obtenus pour la synthèse de divers 3-aryl-2-trifluorométhylacrylates de méthyle ou de *tert*-butyle. Ces produits trifluorométhylés ont été obtenus à partir de composés aromatiques iodés et des 2-trifluorométhylacrylates correspondants par une réaction de Mizoroki-Heck en présence d'un catalyseur au palladium et d'un additif à base d'argent (I). La synthèse « en un seul pot » de 3-trifluorométhyl coumarines a également été effectuée à partir des *ortho*-iodophénols et du 2-trifluorométhylacrylate de méthyle par une réaction tandem de Mizoroki-Heck et de cyclisation intramoléculaire.

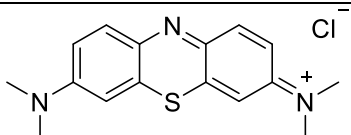
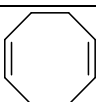
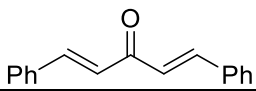
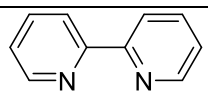
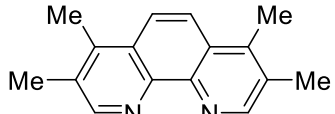
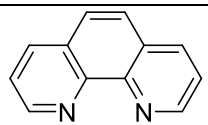
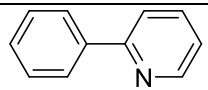
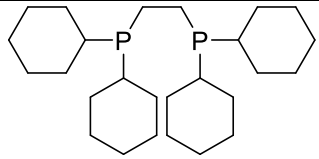
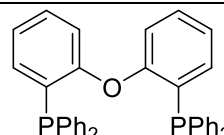
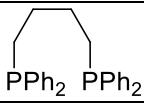
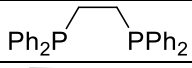
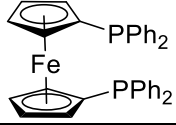
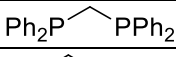
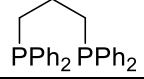
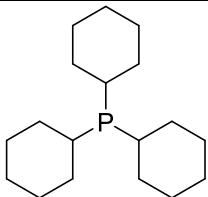
Dans la seconde partie de la thèse, nous avons démontré que la réaction de Mizoroki-Heck catalysée au palladium en présence d'additif à base d'argent pouvait être étendue à la synthèse des acides acryliques 3-aryl-2-trifluorométhylés. De façon similaire, la réaction entre des *ortho*-iodophénols et de l'acide acrylique 2-trifluorométhylé donne accès aux coumarines 3-trifluorométhylés. De plus, nous avons effectué la construction d'acrylates 3-aryl-2-trifluorométhylés d'alkyle plus complexes par des réactions multi-composants entre des iodures aromatiques, de l'acide 2-trifluorométhyl acrylique et des iodoalcanes.

Dans la dernière partie de la thèse, nous avons développé une méthode de couplage croisé décarboxylatif oxydatif catalysé par le palladium en présence de sel de cuivre (I) entre des hétéroarènes et des acides acryliques 3-aryl-2-trifluorométhylés. Divers alcènes trisubstitués ont été obtenus en rendements relativement faibles mais avec une sélectivité E/Z élevée.

Structures of catalysts and ligands

| Palladium-catalyst | |
|----------------------------------|--|
| cataCXium-A-Pd-G3 |  |
| Herrmann-Beller palladacycle |  |
| PCP Pincer-Pd complex |  |
| Platinum-catalyst | |
| Pt(ppy)(acac) |  |
| Iridium-catalyst | |
| <i>fac</i> -Ir(ppy) ₃ |  |

| | |
|--|---|
| $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(5,5'\text{-d}(\text{CF}_3)\text{bpy})]\text{PF}_6$ |  |
| $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})](\text{PF}_6)$ |  |
| Ruthenium-catalyst | |
| $\text{Ru}(\text{bpy})_3\text{X}_2$ ($\text{X} = \text{Cl}, \text{PF}_6$) |  <p style="text-align: center;">($\text{X} = \text{Cl}, \text{PF}_6$)</p> |
| $\text{Ru}[(\text{DNM})_2\text{bpy}]_3^{2+}$ |  |
| $\text{Ru}(\text{Phen})_3\text{Cl}_2$ |  |
| Organocatalyst | |
| Eosin-Y |  |

| | |
|--------------------------|--|
| Methylene Blue |  |
| Alkene ligands | |
| COD |  |
| dba |  |
| Nitrogen ligands | |
| bpy |  |
| Me ₄ Phen |  |
| Phen |  |
| ppy |  |
| Phosphine ligands | |
| dcpe |  |
| DPEPhos |  |
| dppb |  |
| dppe |  |
| dppf |  |
| dppm |  |
| dppp |  |
| PCy ₃ |  |

Abbreviations and Acronyms

| | |
|---------|---|
| Ac | acetyl |
| acac | acetylacetyl |
| AM1 | Austin Model 1 |
| BHT | 2,6- <i>di-tert</i> -butyl-4-methylphenol |
| Bn | benzyl |
| Boc | <i>tert</i> -butoxycarbonyl |
| BPO | benzoyl peroxide |
| bpy | bipyridine |
| BTP | 2-bromo-3,3,3-trifluoropropene |
| Bz | benzoyl |
| Cbz | benzyloxycarbonyl |
| COD | 1,5-cyclooctadiene |
| Cy | cyclohexyl |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | 1,2-dichloroethane |
| DCM | dichloromethane |
| dcpe | 1,2- <i>bis</i> (dicyclohexylphosphino)ethane |
| DDQ | 2,3-dichloro-5,6-dicyano- <i>p</i> -benzoquinone |
| DMA | <i>N,N</i> -dimethylacetamide |
| DME | 1,2-dimethoxyethane |
| DMF | <i>N,N</i> -dimethylformamide |
| DMI | 1,3-dimethylimidazolidin-2-one |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidone |
| DMSO | dimethylsulfoxide |
| DPEPhos | (oxydi-2,1-phenylene) <i>bis</i> (diphenylphosphine) |
| dppb | 1,4- <i>bis</i> (diphenylphosphino)butane |
| dppe | 1,2- <i>bis</i> (diphenylphosphino)ethane |
| dppf | 1,1'- <i>bis</i> (diphenylphosphino)ferrocene |
| dppm | <i>bis</i> (diphenylphosphino)methane |
| dppp | 1,3- <i>bis</i> (diphenylphosphino)propane |
| DCC | dicyclohexylcarbodiimide |
| DMAP | <i>N,N</i> -4-dimethylaminopyridine |
| DSSC | dye-sensitized solar cells |
| equiv | equivalent |

| | |
|--------------------------------|--|
| <i>fac</i> | facial |
| FG | functional group |
| GABA-AT | γ -aminobutyric acid aminotransferase |
| GC-MS | gas chromatography-mass spectrometry |
| HOESY | heteronuclear overhauser effect spectroscopy |
| HOMO | highest occupied molecule orbital |
| HRMS | high resolution mass spectrometry |
| ICP-AES | inductively coupled plasma atomic emission spectroscopy |
| IPCE | incident photon-to-current efficiency |
| ^{<i>i</i>} Pr | isopropyl |
| LCD | liquid crystal display |
| LC-MS | liquid chromatography-mass spectrometry |
| LED | light-emitting diode |
| LUMO | lowest unoccupied molecular orbital |
| Me ₄ Phen | 3,4,7,8-tetramethyl-1,10-phenanthroline |
| MNDO | Modified Neglect of Diatomic Overlap |
| MOM | methoxymethyl |
| MRI | magnetic resonance imaging |
| MS | mass spectrometry |
| MS | molecular sieves |
| ^{<i>n</i>} Bu | <i>n</i> -butyl |
| NMC | <i>N</i> -methylcaprolactam |
| NMP | <i>N</i> -methyl-2-pyrrolidone |
| NMR | nuclear magnetic resonance |
| Nf | nonafluorobutanesulfonyl |
| PCy ₃ | tricyclohexylphosphine |
| PET | positron emission tomography |
| Phen | 1,10-phenanthroline |
| Pin | pinacol |
| Piv | pivaloyl |
| P(mesityl) ₃ | trimesitylphosphine |
| P(<i>m</i> -Tol) ₃ | tri(<i>m</i> -tolyl)phosphine |
| P(<i>o</i> -Tol) ₃ | tri(<i>o</i> -tolyl)phosphine |
| ppy | 2-phenylpyridyl |
| rac-BINAP | (\pm)-2,2'- <i>bis</i> (diphenylphosphino)-1,1'-binaphthyl |
| R _f | perfluoroalkyl |
| rt | room temperature |
| SuFEx | sulfur(VI) fluoride exchange |

| | |
|----------------------|---|
| T | temperature |
| t | time |
| TBAF | tetra- <i>n</i> -butylammonium fluoride |
| TBAI | tetra- <i>n</i> -butylammonium iodide |
| ^t Bu | <i>tert</i> -butyl |
| ^t BuXPhos | 2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetate |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TM | transition metal |
| TMEDA | <i>N,N,N',N'</i> -tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Ts | <i>p</i> -toluenesulfonyl |
| T3P | propylphosphonic anhydride |
| UV-B | 280-315 nm ultraviolet light |
| Xantphos | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene |
| XPhos | 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl |

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Chapter 1

General introduction

1 General introduction

1.1 A brief introduction of organofluorine chemistry

Fluorine (atomic number 9) ranks 24th in universal abundance and 13th in terrestrial abundance, and it is the most abundant halogen in the Earth's crust.¹ In nature, fluorine exists mainly in the form of inorganic minerals such as fluorspar (CaF₂); by contrast, natural fluorinated organic compounds are rare (less than 20).² Most of the fluorinated compounds are synthesized by organic chemists. Due to the high electronegativity, small size, and low polarizability of fluorine atom, fluorinated compounds exhibit unique physical, chemical, and physiological properties, such as miscibility, hydrogen bonding, stability of C–F bond, lipophilicity, and metabolic stability. These properties contribute to their wide applications in agrochemicals, pharmaceuticals, and materials science.³ Indeed, fluorinated compounds play an important role in modern agrochemicals.⁴ It has also been reported that about 20% of marketed drugs contained at least one fluorine atom.⁵ In nuclear medicine, ¹⁸F-labeled molecules are the most frequently used radiotracers in positron emission tomography (PET), which is a valuable research tool to track diseases at an early stage and support drug discovery.⁶ Based on the high sensitivity of ¹⁹F nuclei in nuclear magnetic resonance (NMR) experiments, polyfluorinated (fluorous) molecules are successfully used in ¹⁹F magnetic resonance imaging (MRI).⁷ Besides, the introduction of fluorine promotes the development of new materials as represented by photovoltaic solar cells.⁸

In this context, the development of novel, mild, and efficient synthetic methodologies for the construction of fluorine-containing organic molecules is of great significance. There are two major strategies for the synthesis of fluorinated

¹ (a) A. G. W. Cameron, *Space Sci. Rev.* **1973**, *15*, 121–146; (b) E. A. Paul, P. M. Huang, in *The Handbook of Environmental Chemistry*, ed. O. Hutzinger, Springer Verlag, Berlin, **1980**, Vol 1, Part A, pp. 69–71.

² D. B. Harper, D. O'Hagan, *Nat. Prod. Rep.* **1994**, 123–133.

³ (a) T. Hiyama in *Organofluorine Compounds: Chemistry and Applications* (Ed.: H. Yamamoto), Springer-Verlag, Berlin, **2000**; (b) K. Uneyama in *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; (c) J.-P. Bégué, D. Bonnet-Delpon in *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Inc., Hoboken, NJ, **2008**; (d) I. Ojima in *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**; (e) P. Kirsch in *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed.*, Wiley-VCH, Weinheim, **2013**; (f) D. W. Smith, S. T. Iacono, S. S. Iyer in *Handbook of Fluoropolymer Science and Technology*, John Wiley & Sons, Inc., Hoboken, NJ, **2014**.

⁴ (a) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589; (b) P. Jeschke, *Pest Manag. Sci.* **2010**, *66*, 10–27.

⁵ (a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640; (b) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.

⁶ S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719–766.

⁷ I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo, G. Resnati, *Chem. Rev.* **2015**, *115*, 1106–1129.

⁸ A. C. Stuart, J. R. Tumbleston, H. Zhou, W. Li, S. Liu, H. Ade, W. You, *J. Am. Chem. Soc.* **2013**, *135*, 1806–1815.

compounds: direct fluorination and introduction of fluorine-containing moiety (**Figure 1**).⁹ The former is the direct introduction of one or more fluorine atom(s) into a specific position of organic molecules by using nucleophilic, electrophilic, and radical fluorinating reagents.¹⁰ The second, which generally does not involve the formation and cleavage of the C–F bond, mainly uses reagents or intermediates bearing fluorine-containing moiety (e.g. CF₃, OCF₃, SCF₃, CF₂H, CF₂R, or CFH₂ groups) to construct the target fluorinated molecules.¹¹ In spite of these advances, it is still interesting to explore mild and efficient methods to give access to fluorinated compounds.

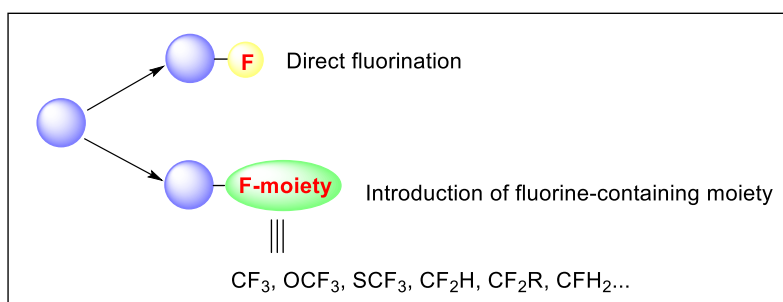


Figure 1 Strategies for the synthesis of fluorinated compounds

1.2 Introduction of trifluoromethyl (CF₃) group and trifluoromethylalkenes

1.2.1 Effect of CF₃ group on the properties of organic compounds

Among various fluorine-containing substituents, the trifluoromethyl (CF₃) group is one of the most interesting substituents. Indeed, of the 17 fluoro-pharmaceuticals registered in 2019, 8 drugs contain the CF₃ group (excluding the OCF₃ group).^{5a} The popularity of CF₃-containing compounds is attributed to the effect of the CF₃ group on the physical and chemical properties of these compounds, such as lipophilicity, acidity, steric hindrance, etc.^{3a-e, 12} These important properties are discussed hereafter.

1.2.1.1 Lipophilicity

Lipophilicity of a drug molecule plays an important role in the absorption and distribution of the orally administered drug.¹³ The Hansch-Leo hydrophobic parameter π , which derives from the logarithm of partition coefficient between

⁹ (a) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; (b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

¹⁰ P. A. Champagne, J. Desroches, J. D. Hamel, M. Vandamme, J. F. Paquin, *Chem. Rev.* **2015**, *115*, 9073–9174.

¹¹ (a) D. Cahard, J.-A. Ma, *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*, Vol. 1 & 2 Wiley-VCH, Weinheim, **2020**; (b) For a recent issue on fluorine chemistry, see: *Chem. Rev.* **2015**, *115*, 563–1306.

¹² B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11.

¹³ S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330.

octanol and water ($\log P$), is a common quantitative measurement of aromatic substituent effects on lipophilicity.¹² π is defined as: $\pi = \log P_{C_6H_5X} - \log P_{C_6H_6}$ ($P_{C_6H_5X}$ is the partition coefficient of substituted benzene; $P_{C_6H_6}$ is the partition coefficient of the parent compound benzene).^{3c,14} A larger π or $\log P_{C_6H_5X}$ value indicates that the substituent or the substituted compound is more lipophilic.¹² According to the π value in **Table 1**, the introduction of a fluorine atom or fluorine-containing moiety (including CF_3 group) can effectively increase the lipophilicity of aromatic compounds.^{3c,12,15} Better lipophilicity is also observed for some CF_3 -substituted alkyl alcohols, but this does not mean that the lipophilicity of CF_3 -containing compounds always increases. Indeed, the incorporation of the CF_3 group into saturated alkyl molecules causes a decrease in lipophilicity.^{3c,12}

Table 1 Hansch-Leo hydrophobic parameter π ($\log P_{C_6H_5X} - \log P_{C_6H_6}$)

| Substituent | π | Substituent | π |
|-------------|-------|--------------------------|-------------|
| H | 0 | F | 0.14 |
| CH_3 | 0.56 | CF_3 | 0.88 |
| OCH_3 | -0.02 | OCF_3 | 1.04 |
| SCH_3 | 0.16 | SCF_3 | 1.44 |

1.2.1.2 Electronic effect

Due to the high electronegativity of the fluorine atom, the CF_3 group has a strongly negative inductive effect on both sp^3 - and sp^2 -carbons ($-I_\sigma$ and $-I_\pi$ effects) (**Figure 2**, a-b). Its electron-withdrawing property for the π -electron system also comes from negative hyperconjugation (**Figure 2**, c), and no positive resonance effect (+R) is observed.^{3a-c}

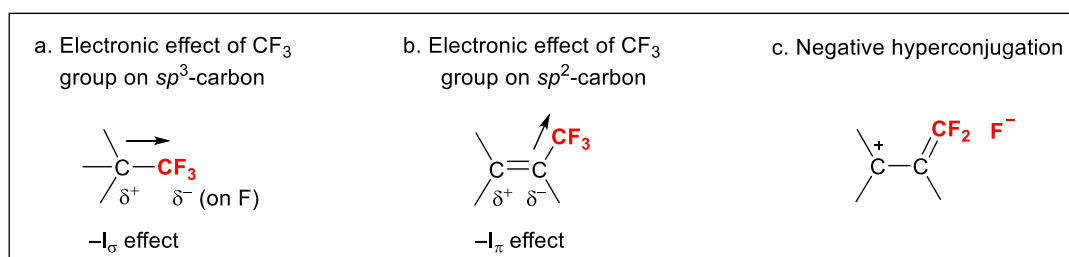


Figure 2 Electronic effects of CF_3 group

1.2.1.3 Acidity and basicity

Because of its strong electron-withdrawing property, CF_3 substituent tends to remarkably enhance the acidity of aliphatic carboxylic acids and alcohols. For example, the acidities of CF_3CO_2H and CF_3CH_2OH are three to four orders of

¹⁴ T. Fujita, J. Iwasa, C. Hansch, *J. Am. Chem. Soc.* **1964**, *86*, 5175–5180.

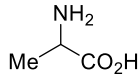
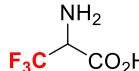
¹⁵ C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207–1216.

magnitude higher than those of non-fluorinated counterparts. Besides, the basicity of alkyl amines is obviously decreased. Indeed, the basicity of $\text{CF}_3\text{CH}_2\text{NH}_2$ is much weaker than $\text{CH}_3\text{CH}_2\text{NH}_2$ (**Table 2**).^{3a-c,12} Thus, the introduction of the CF_3 group into suitable positions of amino acids can adjust their acidity and basicity (**Table 3**), thereby modifying their biological activities.^{3b} The influence of the CF_3 group on the acidity of benzoic acids, phenols, and carbon acids is relatively complicated.^{3b,12}

Table 2 Acidity of alkyl acids and alcohols and basicity of alkyl amines

| Acidity | | Acidity | | Basicity | |
|----------------------------------|------------------------------------|-----------------------------------|--------------------------|-------------------------------------|------------------------------|
| Acids | $\text{pK}_a(\text{CO}_2\text{H})$ | Alcohols | $\text{pK}_a(\text{OH})$ | Amines | $\text{pK}_a(\text{NH}_3^+)$ |
| $\text{CH}_3\text{CO}_2\text{H}$ | 4.76 | $\text{CH}_3\text{CH}_2\text{OH}$ | 15.9 | $\text{CH}_3\text{CH}_2\text{NH}_2$ | 10.7 |
| $\text{CF}_3\text{CO}_2\text{H}$ | 0.52 | $\text{CF}_3\text{CH}_2\text{OH}$ | 12.4 | $\text{CF}_3\text{CH}_2\text{NH}_2$ | 5.9 |

Table 3 Acidity and basicity of amino acids

| Amino acids | $\text{pK}_a(\text{CO}_2\text{H})$ | $\text{pK}_a(\text{NH}_3^+)$ |
|--|------------------------------------|------------------------------|
|  | 2.3 | 9.9 |
|  | 1.2 | 5.4 |

1.2.1.4 Steric effect

Studies have shown that the steric size of the trifluoromethyl group is much larger than a methyl group but smaller than a *tert*-butyl group.^{3b} It is generally considered that the steric size of the trifluoromethyl group is at least as large as an isopropyl group,^{3c-d,12} but it was also reported that the van der Waals volume of the trifluoromethyl group is close to that of an ethyl group even though they have significantly different shapes.¹⁶

The steric variations combined with stereoelectronic effects can cause changes of conformational preference upon fluorine substitution.^{13,16,17} For example, the methoxy group in $\text{Ar}-\text{OCH}_3$ prefers to lie in the plane of the aromatic ring due to the conjugation of the aromatic π system with the p orbital of the sp^2 -hybridized oxygen atom. However, the trifluoromethoxy group in $\text{Ar}-\text{OCF}_3$ tends to come out of the plane (dihedral angle for $\text{C}_{\text{Ar}}-\text{C}_{\text{Ar}}-\text{O}-\text{C}(\text{F}_3)$ up to 90°) because of steric effect and stereoelectronic effect. The latter is understood as the conjugation between the aromatic π system and O is reduced as a result of negative hyperconjugation between the lone pairs of now sp^3 -hybridized oxygen and the low-lying C-F antibonding orbital ($n_{\text{O}}-\sigma_{\text{C-F}}^*$ interaction).¹⁶ The steric dissimilarity between methyl

¹⁶ K. Müller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881–1886.

¹⁷ (a) Q. A. Huchet, W. B. Schweizer, B. Kuhn, E. M. Carreira, K. Müller, *Chem. Eur. J.* **2016**, 22, 16920–16928; (b) M. Bilka-Markowska, T. Siodla, E. Patyk-Kaźmierczak, A. Katrusiak, H. Koroniak, *New J. Chem.* **2017**, 41, 12631–12644.

and trifluoromethyl groups can also lead to differences in reactivity and product selectivity in many reactions.^{3b}

1.2.2 Applications of trifluoromethylalkenes

Thanks to the unique properties of the CF₃ group, trifluoromethylalkenes exhibit great potential in pharmaceuticals, agrochemicals, as well as materials science. Illustrative examples are shown in **Figure 3**. For instance, Panomifene is a trifluoromethyl-bearing analogue of Tamoxifen, an antiestrogen used for prevention and treatment of breast cancer, and their metabolism has some similar routes.¹⁸ As one of the second-generation epothilones, the trifluoromethyl-containing Fludelone exhibits remarkable antitumor activity.¹⁹ Cyhalothrin, with a vinyl-CF₃ structure, is used as an agricultural insecticide as well as an acaricide.²⁰ Additionally, the introduction of a CF₃ group into the terminal alkenyl chain makes the aromatic liquid crystals suitable for LCD (liquid crystal display) applications.²¹

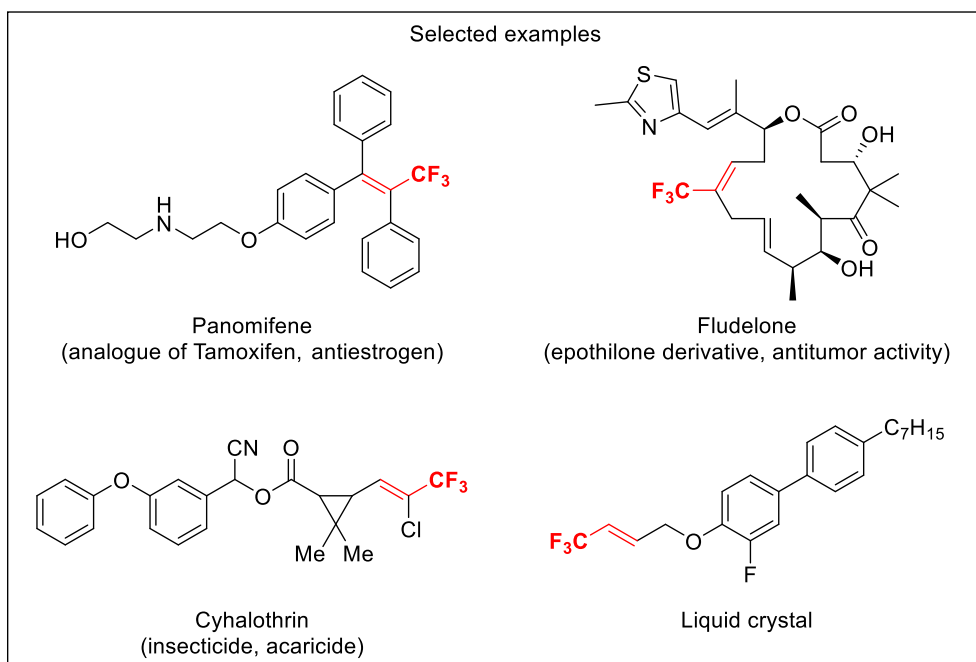


Figure 3 Trifluoromethylalkenes in pharmaceuticals, agrochemicals, and materials science

Many of the peptide-based drug candidates have encountered clinical difficulties because of their poor *in vivo* stability and physicochemical properties.²² In this

¹⁸ K. Monostory, K. Jemnitz, L. Vereczkey, G. Czira, *Drug Meta. Dispos.* **1997**, *25*, 1370–1378.

¹⁹ A. Rivkin, T.-C. Chou, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2005**, *44*, 2838–2850.

²⁰ Cyhalothrin: <http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/194.htm> (Pesticide Properties Database, University of Hertfordshire)

²¹ (a) G. W. Skelton, J. C. Jones, S. M. Kelly, V. Minter, R. P. Tuffin, *Liq. Cryst.* **2001**, *28*, 749–759; (b) S. M. Kelly, G. Skelton, C. Jones, V. Minter, R. Tuffin, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A Mol. Cryst. Liq. Cryst.* **2001**, *364*, 873–880.

²² (a) E. M. Cornford, L. D. Braun, P. D. Crane, W. H. Oldendorf, *Endocrinology* **1978**, *103*, 1297–1303; (b) B. P. Roques, F. Noble, in *Discovery of Novel Opioid Medications* (Eds.: R. S. Rapaka, H. Sorer), U.S. Department of Health & Human Services, Rockville MD, **1995**, pp. 104–145.

context, it is highly interesting to develop peptidomimetics that exhibit better metabolic stability while maintaining high biological activity.²³ Studies have shown that the trifluoromethylalkene group is one of the superior mimics of peptide bond because of the relatively close electrostatic potential surface and dipole moment (μ) between the CF_3 -alkene group and the parent amide bond (Figure 4).^{3d,24} A representative peptidomimetic developed by Wipf is the trifluoromethylalkene analogue of Gramicidin S, a cyclodecapeptide antibiotic that is effective against a broad range of Gram-negative and Gram-positive bacteria as well as some fungi (Figure 5).^{24b} Similar solution-state and solid-state conformations were observed between the trifluoromethylalkene analogue and the parent cyclopeptide.

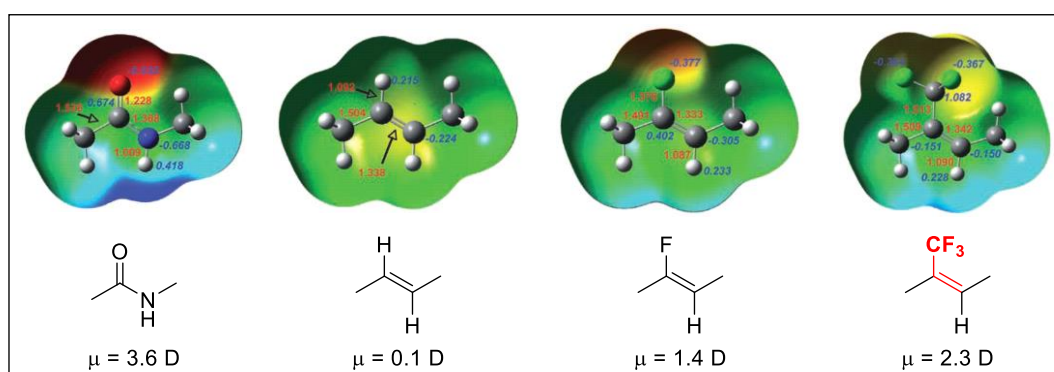


Figure 4 Electrostatic potentials (color alteration from red to blue describes the shift of the electronically rich to deficient circumstance) and dipole moments of amide bond and alkene isosteres

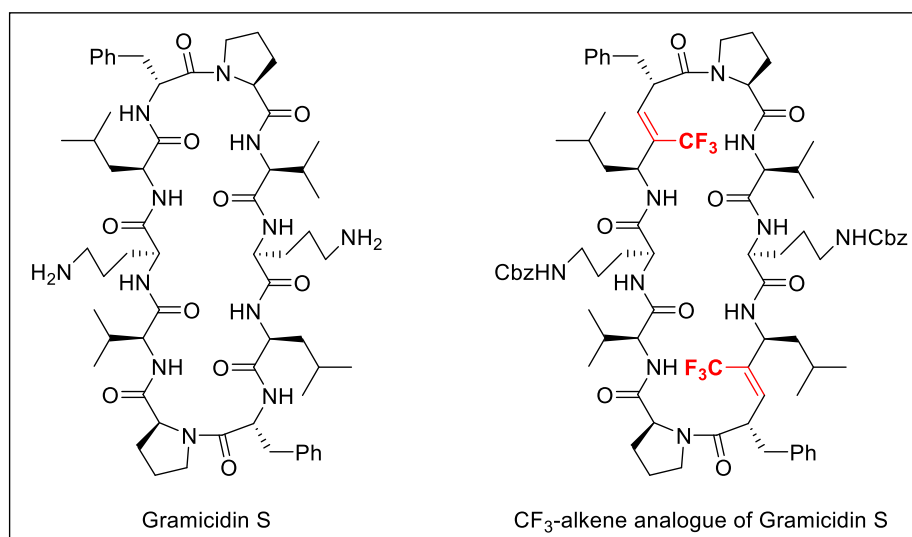


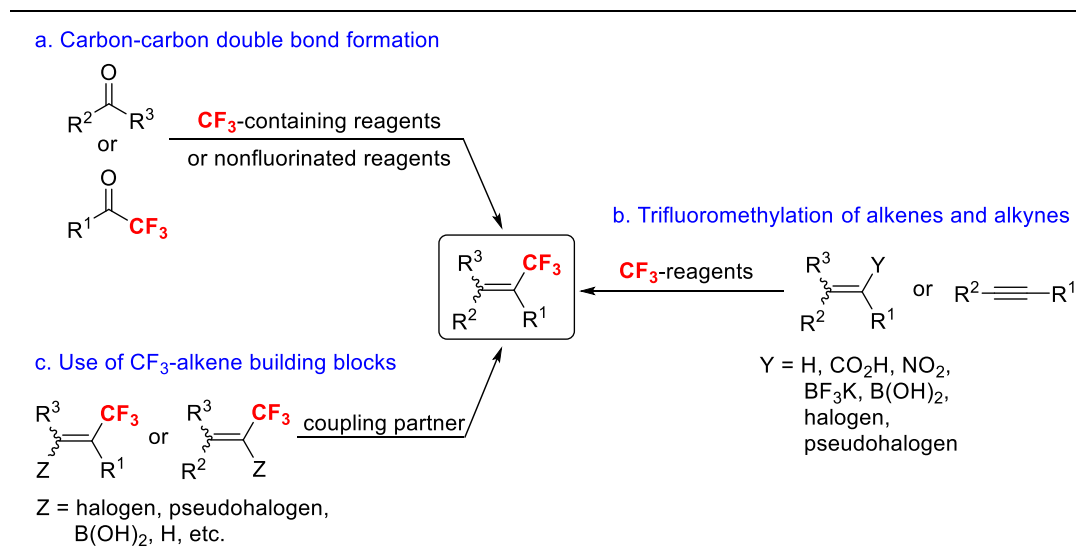
Figure 5 Trifluoromethylalkene analogue of Gramicidin S

²³ D. F. Veber, R. M. Freidinger, *Trends Neurosci.* **1985**, *8*, 392–396.

²⁴ (a) P. Wipf, T. C. Henninger, S. J. Geib, *J. Org. Chem.* **1998**, *63*, 6088–6089; (b) J. Xiao, B. Weisblum, P. Wipf, *J. Am. Chem. Soc.* **2005**, *127*, 5742–5743; (c) K. Kobayashi, T. Narumi, S. Oishi, H. Ohno, N. Fujii, *J. Org. Chem.* **2008**, *73*, 3942–3945; (d) V. Eeda, M. Selvaraju, R. A. Altman, *J. Fluorine Chem.* **2019**, *218*, 90–98.

1.3 Access to trifluoromethylalkenes

Given the importance of trifluoromethylalkenes, various methodologies have been developed to construct this scaffold, and the main strategies are as follows: a. carbon-carbon double bond formation from aldehydes and ketones, b. trifluoromethylation of alkenes and alkynes, c. use of CF₃-alkene building blocks (**Scheme 1**). The progress of the past two decades to synthesize CF₃-alkenes is summarized below.



Scheme 1 Strategies for the construction of trifluoromethylalkenes

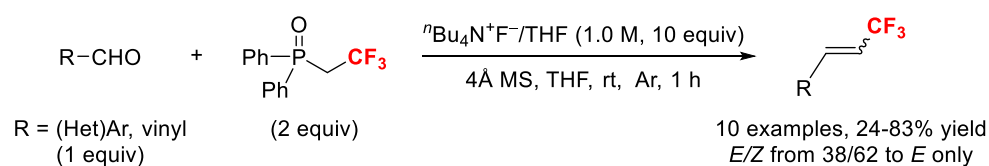
1.3.1 Carbon-carbon double bond formation from aldehydes and ketones

The carbon-carbon double bond formation strategy is a basic tool for the construction of alkenes, and several named reactions have been applied to the synthesis of trifluoromethylalkenes in the past two decades. In 2002, Ishibashi and co-workers reported a ⁿBu₄N⁺F⁻ (TBAF)-mediated Horner reaction to synthesize trifluoromethylalkenes using aldehydes and 2,2,2-trifluoroethyldiphenylphosphine oxide (**Scheme 2**, Eq. a).²⁵ Both of the (hetero)aryl and vinyl aldehydes were amenable to this reaction system, and the corresponding trifluoromethylalkenes were obtained in up to 83% yield with moderate to excellent *E/Z* selectivity. Later, Hanamoto and co-workers utilized the Wittig reaction between aldehydes and (2,2,2-trifluoroethyl)triphenylphosphonium trifluoromethanesulfonate to prepare trifluoromethylalkenes (**Scheme 2**, Eq. b).²⁶ Only electron-deficient (hetero)aromatic aldehydes proceeded well in the reaction conditions and low to moderate *E/Z* selectivity was observed.

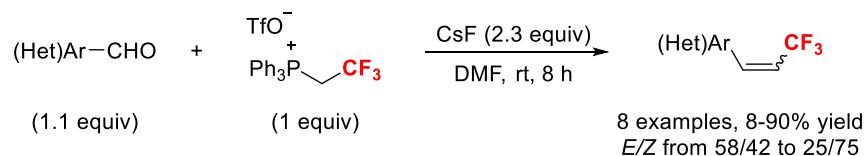
²⁵ T. Kobayashi, T. Eda, O. Tamura, H. Ishibashi, *J. Org. Chem.* **2002**, *67*, 3156–3159.

²⁶ T. Hanamoto, N. Morita, K. Shindo, *Eur. J. Org. Chem.* **2003**, 4279–4285.

Eq. a) In 2002, Ishibashi *et al.* (Horner reaction)



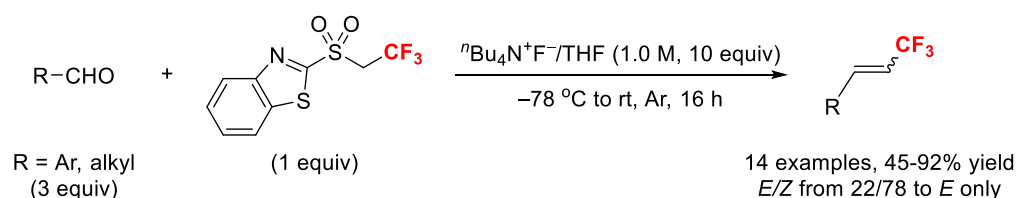
Eq. b) In 2003, Hanamoto *et al.* (Wittig reaction)



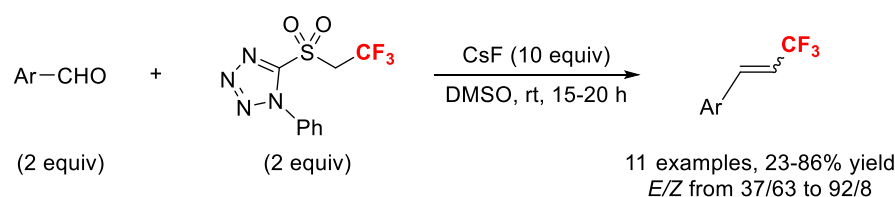
Scheme 2 Synthesis of trifluoromethylalkenes by Horner and Wittig reactions

In 2013, Bräse and co-workers developed a modified Julia-Kocienski reaction to construct trifluoromethylalkenes from aryl or alkyl aldehydes and 2-[(2,2,2-trifluoroethyl)sulfonyl]benzo[*d*]thiazole (**Scheme 3**, Eq. a).²⁷ Moderate to excellent yields of the products were obtained, but *E/Z* selectivity was strongly substrate-dependent, ranging from 22/78 to *E* only. Similarly, Zajc and co-workers reported a Julia-Kocienski reaction by using aryl aldehydes and 1-phenyl-1*H*-tetrazol-5-yl 2,2,2-trifluoroethyl sulfone, affording the β -trifluoromethylstyrenes in low to good yields with *E/Z* selectivity up to 92/8 (**Scheme 3**, Eq. b).²⁸

Eq. a) In 2013, Bräse *et al.* (Julia–Kocienski olefination)



Eq. b) In 2013, Zajc *et al.* (Julia–Kocienski olefination)



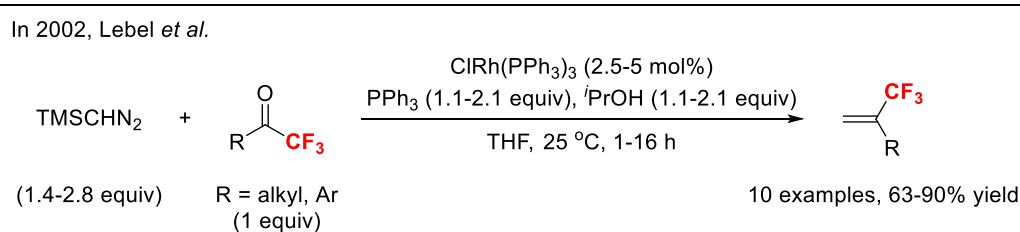
Scheme 3 Synthesis of trifluoromethylalkenes by Julia-Kocienski reaction

In addition to the named reactions, Lebel and Paquet developed a rhodium-catalyzed protocol for the methylenation of trifluoromethylated ketones with

²⁷ A. Hafner, T. S. Fischer, S. Bräse, *Eur. J. Org. Chem.* **2013**, 7996–8003.

²⁸ D. O. Aveni, S. K. Mandal, B. Zajc, *Tetrahedron Lett.* **2013**, 54, 6008–6011.

trimethylsilyldiazomethane. Diverse trifluoromethylated terminal alkenes were constructed in moderate to good yields (**Scheme 4**).²⁹



Scheme 4 Synthesis of trifluoromethylalkenes by methylenation of trifluoromethylated ketones

1.3.2 Trifluoromethylation of alkenes and alkynes

With the development of trifluoromethylating reagents, many research interests have focused on the trifluoromethylation of alkenes and alkynes. As shown in **Figure 6**, a variety of trifluoromethylating reagents have been used for the synthesis of trifluoromethylalkenes. These reagents are Togni's reagents I & II, CF_3I , $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois reagent), $\text{CF}_3\text{SO}_2\text{Cl}$, Umemoto's reagent, Yagupolskii-type reagent, Yagupolskii/Umemoto-like reagent, TMSCF_3 (Ruppert-Prakash reagent), TESCF_3 , CF_3H , CuCF_3 , and $(\text{Phen})\text{Cu}(\text{CF}_3)_3$. Among them, Togni's reagent II is one of the most widely used reagents in trifluoromethylation of alkenes and alkynes.

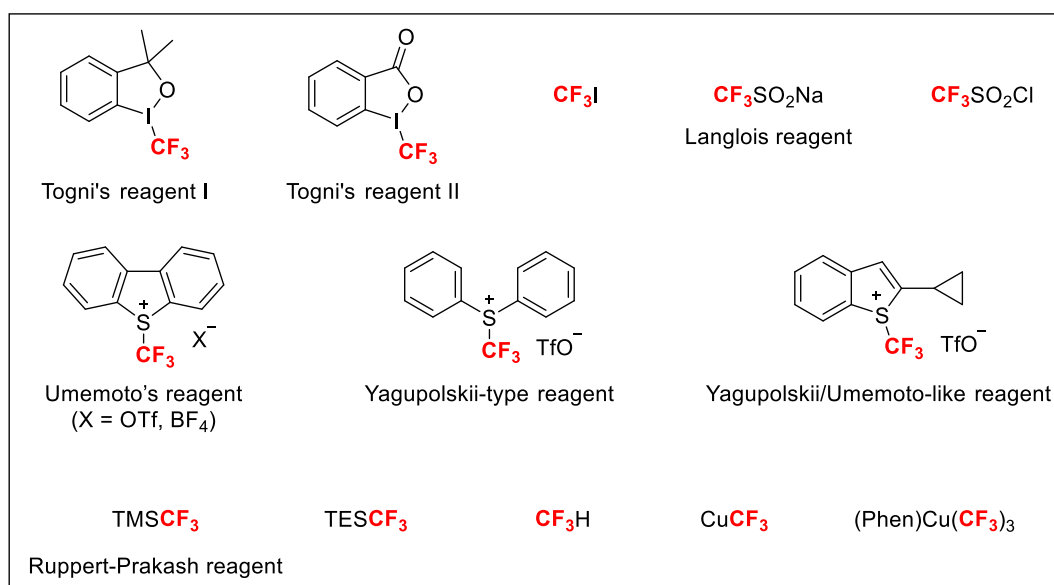


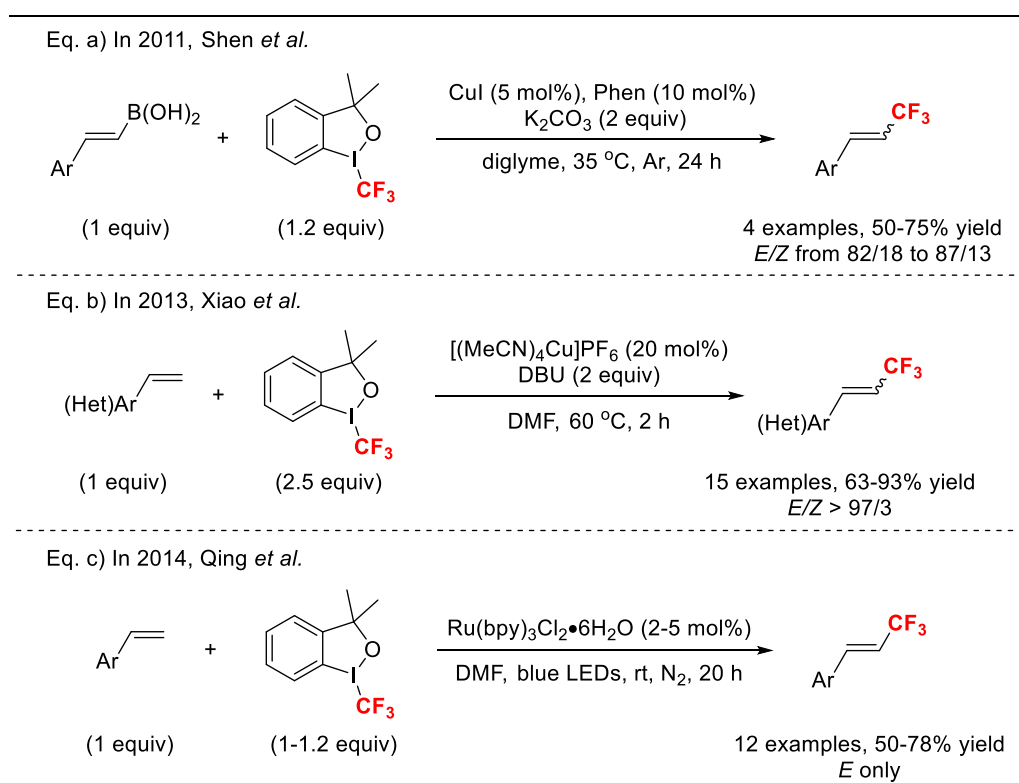
Figure 6 Trifluoromethylating reagents used in the synthesis of trifluoromethylalkenes

1.3.2.1 Trifluoromethylation with Togni's reagent I

Since their first report in 2006, Togni's reagents I & II have shown great potential in trifluoromethylation reactions.³⁰ Three methods have been developed to give access

²⁹ H. Lebel, V. Paquet, *Org. Lett.* **2002**, *4*, 1671–1674.

to trifluoromethylalkenes by Togni's reagent I. In 2011, Shen and a co-worker reported a copper-catalysed method for the trifluoromethylation of vinyl boronic acids with Togni's reagent I (**Scheme 5**, Eq. a).³¹ Four examples of β -trifluoromethylstyrenes were shown, and relatively good *E/Z* selectivity was obtained with *E* isomer as the major product. Two years later, Xiao and co-workers achieved the trifluoromethylation of terminal alkenes using Togni's reagent I in the presence of copper-catalyst (**Scheme 5**, Eq. b).³² Various (hetero)aryl-substituted alkenes were transformed to the trifluoromethylated products in moderate to excellent yields with high *E/Z* selectivity (*E/Z* > 97/3). Then, Qing and co-workers developed a visible-light-induced method for olefinic C-H trifluoromethylation of styrenes with Togni's reagent I in the presence of ruthenium-photocatalyst (**Scheme 5**, Eq. c).³³ The thermodynamically stable (*E*)- β -trifluoromethylstyrenes were prepared in moderate to good yields.



Scheme 5 Trifluoromethylation of vinyl-B(OH)₂ and vinyl C-H bond with Togni's reagent I

1.3.2.2 Trifluoromethylation with Togni's reagent II

Compared with Togni's reagent I, Togni's reagent II was much more explored for trifluoromethylation of alkenes as well as alkynes. Many alkenes including terminal

³⁰ (a) P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579–2586; (b) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650–682.

³¹ T. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342–2345.

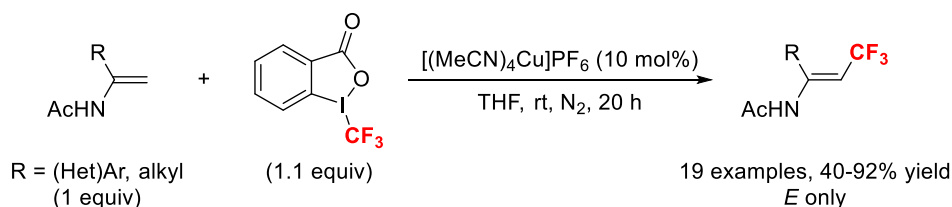
³² X.-P. Wang, J.-H. Lin, C.-P. Zhang, J.-C. Xiao, X. Zheng, *Beilstein J. Org. Chem.* **2013**, *9*, 2635–2640.

³³ Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *J. Org. Chem.* **2014**, *79*, 10434–10446.

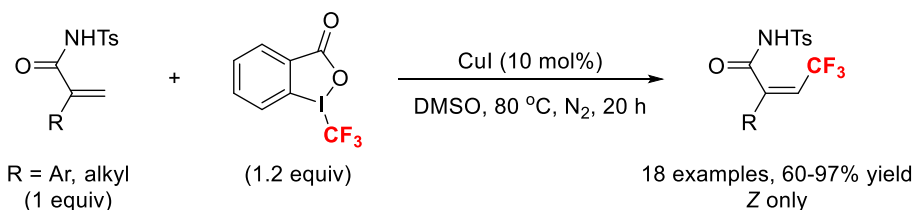
alkenes, cyclic alkenes, vinyl-CO₂H, vinyl-BF₃K, and vinyl-NO₂ could react with Togni's reagent II to provide vinyl-CF₃ compounds. Additionally, the reaction of terminal or internal alkynes with Togni's reagent II could also allow the formation of trifluoromethylated olefins.

Trifluoromethylation of vinyl C-H bond with Togni's reagent II. In 2012, Loh and a co-worker developed a copper-catalysed method for the olefinic C-H trifluoromethylation of enamides using Togni's reagent II (**Scheme 6**, Eq. a).³⁴ Various stereospecific (*E*)-β-trifluoromethyl substituted enamides were produced in moderate to excellent yields. Shortly after, the same group reported another copper-catalysed protocol for the olefinic C-H trifluoromethylation of electron-deficient alkenes with Togni's reagent II (**Scheme 6**, Eq. b).³⁵ The directing group (-CONHTs)

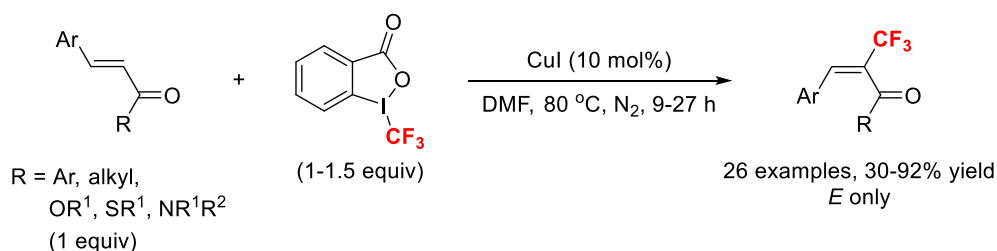
Eq. a) In 2012, Loh *et al.*



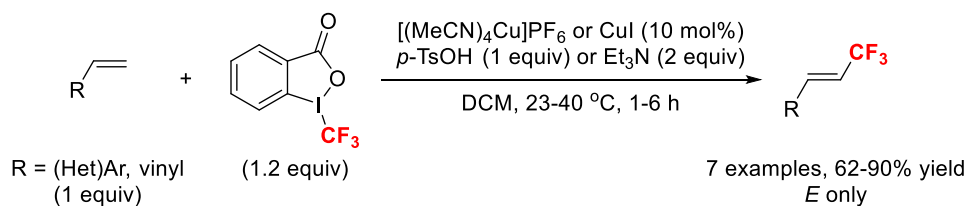
Eq. b) In 2013, Loh *et al.*



Eq. c) In 2014, Bi *et al.*



Eq. d) In 2014, Sodeoka *et al.*



Scheme 6 Copper-catalysed trifluoromethylation of vinyl C-H bond with Togni's reagent II

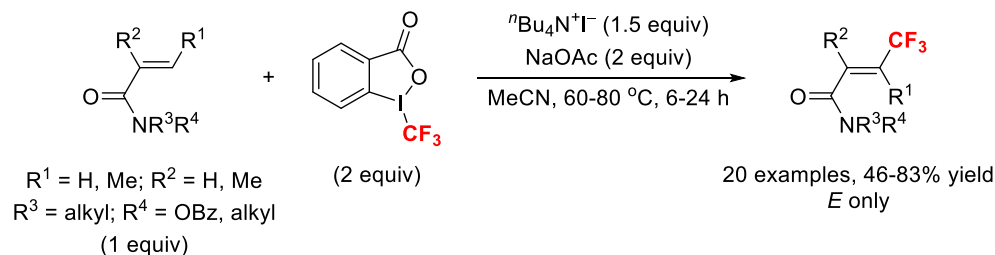
³⁴ C. Feng, T.-P. Loh, *Chem. Sci.* **2012**, *3*, 3458–3462.

³⁵ C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2013**, *52*, 12414–12417.

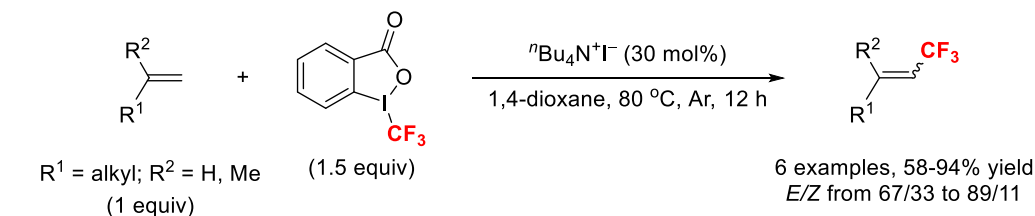
was crucial for the success of the C-CF₃ bond formation and stereospecific (*Z*)-products were obtained in good to excellent yields. Similarly, the copper-catalysed vinyl C-H trifluoromethylation of α,β -unsaturated carbonyl compounds and terminal alkenes by using Togni's reagent II was also realized by Bi and Sodeoka, respectively (**Scheme 6**, Eqs. c-d).³⁶⁻³⁷ Both of the cases provided the stereospecific (*E*)-products.

Besides the copper-catalysed reactions, Liu, Tan, and co-workers reported a ⁿBu₄N⁺I⁻ (TBAI)-mediated method for the vinyl C-H trifluoromethylation of acrylamides with Togni's reagent II (**Scheme 7**, Eq. a).³⁸ A broad substrate scope with excellent regio- and stereo-selectivity was achieved. Afterwards, Sodeoka and co-workers realized the TBAI-catalysed protocol for the vinylic trifluoromethylation of alkyl-substituted alkenes using Togni's reagent II (**Scheme 7**, Eq. b).³⁹ The related trifluoromethylalkenes were produced in moderate to excellent yields with moderate to good *E/Z* selectivity.

Eq. a) In 2014, Liu, Tan *et al.*



Eq. b) In 2015, Sodeoka *et al.*



Scheme 7 TBAI-mediated (or -catalysed) trifluoromethylation of vinyl C-H bond with Togni's reagent II

Trifluoromethylation of quinones with Togni's reagent II. In 2013, Szabó and co-workers demonstrated that quinones could react with Togni's reagent II to generate trifluoromethylated quinones in the presence of copper-salt and bis(pinacolato)diboron (B₂Pin₂) (**Scheme 8**).⁴⁰ This strategy provided a simplified synthetic route for the construction of trifluoromethylated quinones, which were conventionally difficult to synthesize in one step.

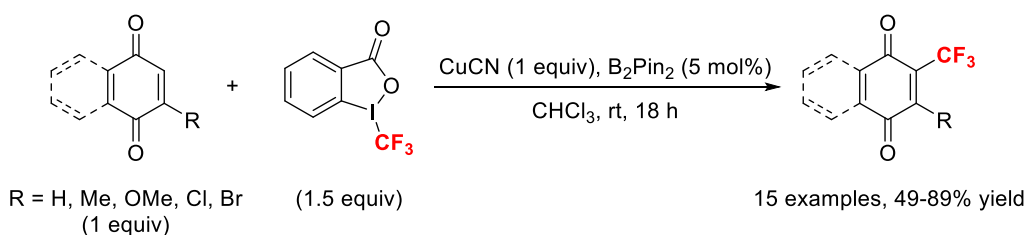
³⁶ Z. Fang, Y. Ning, P. Mi, P. Liao, X. Bi, *Org. Lett.* **2014**, *16*, 1522–1525.

³⁷ H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *J. Fluorine Chem.* **2014**, *167*, 172–178.

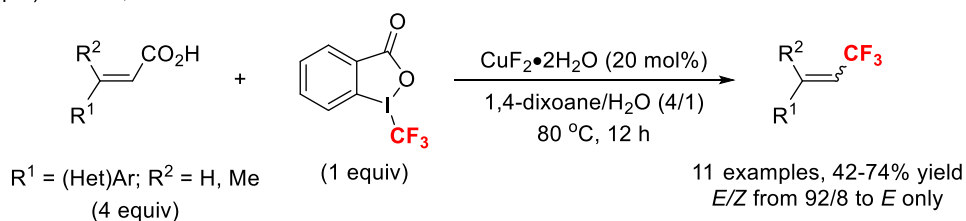
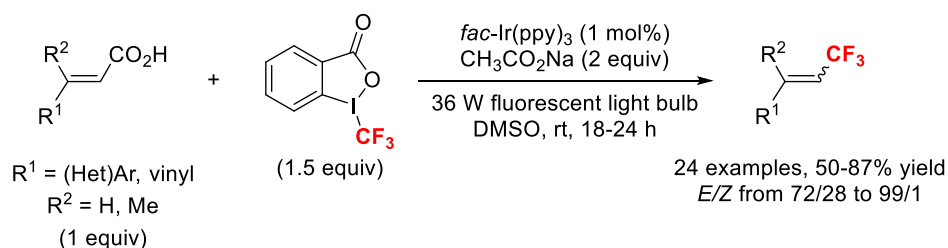
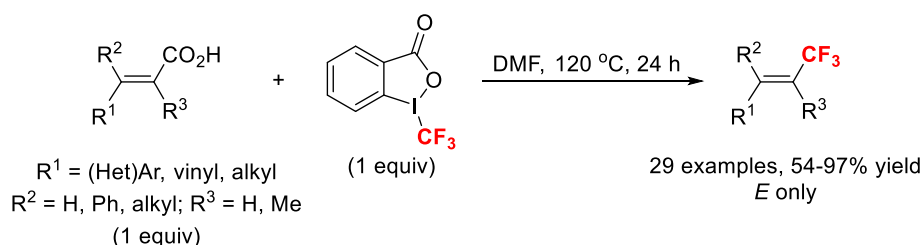
³⁸ L. Li, J.-Y. Guo, X.-G. Liu, S. Chen, Y. Wang, B. Tan, X.-Y. Liu, *Org. Lett.* **2014**, *16*, 6032–6035.

³⁹ H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka, *Chem. Asian J.* **2015**, *10*, 2190–2199.

⁴⁰ N. O. Ilchenko, P. G. Janson, K. J. Szabó, *Chem. Commun.* **2013**, *49*, 6614–6616.

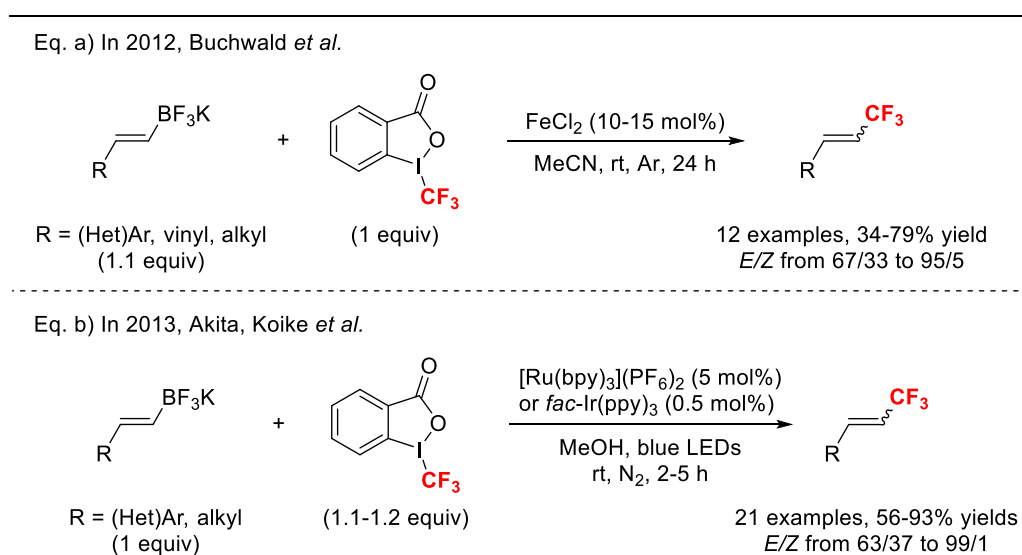
In 2013, Szabó *et al.***Scheme 8** Trifluoromethylation of quinones with Togni's reagent II

Trifluoromethylation of vinyl-CO₂H with Togni's reagent II. In 2012, Hu and co-workers achieved the copper-catalysed decarboxylative trifluoromethylation of β -substituted acrylic acids with Togni's reagent II (**Scheme 9**, Eq. a).⁴¹ The corresponding CF₃-substituted alkenes were obtained in moderate to good yields with high *E/Z* selectivity. Then, Zhu and co-workers realized the decarboxylative trifluoromethylation of β -substituted acrylic acids using Togni's reagent II via visible-light-induced photoredox catalysis (**Scheme 9**, Eq. b).⁴² A wide range of α,β -unsaturated carboxylic acids were transformed to the trifluoromethylalkenes, and up

Eq. a) In 2012, Hu *et al.*Eq. b) In 2014, Zhu *et al.*Eq. c) In 2015, Yi *et al.***Scheme 9** Trifluoromethylation of vinyl-CO₂H with Togni's reagent II⁴¹ Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 3944–3947.⁴² P. Xu, A. Abdukader, K. Hu, Y. Cheng, C. Zhu, *Chem. Commun.* **2014**, *50*, 2308–2310.

to 99/1 of the *E/Z* ratio was obtained. In addition, Yi and co-workers found that decarboxylative trifluoromethylation reaction between α,β -unsaturated carboxylic acids and Togni's reagent II could also proceed well under metal-free conditions (**Scheme 9**, Eq. c).⁴³ Various (*E*)-trifluoromethylalkenes were generated in moderate to high yields.

Trifluoromethylation of vinyl-BF₃K with Togni's reagent II. The reaction of potassium vinyltrifluoroborates with Togni's reagent II provided another route for the synthesis of trifluoromethylalkenes. Buchwald and co-workers demonstrated that the trifluoromethylation of vinyl-BF₃K could be performed under iron-catalysis (**Scheme 10**, Eq. a).⁴⁴ By contrast, Akita, Koike, and co-workers conducted the reactions under visible light-promoted photoredox catalysis (**Scheme 10**, Eq. b).⁴⁵ The latter conditions gave relatively better yields. Both of the methods provided moderate to excellent *E/Z* selectivity.



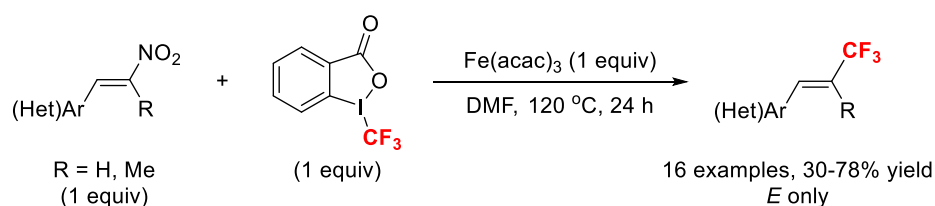
Scheme 10 Trifluoromethylation of vinyl-BF₃K with Togni's reagent II

Trifluoromethylation of vinyl-NO₂ with Togni's reagent II. Following the decarboxylative trifluoromethylation of α,β -unsaturated carboxylic acids (**Scheme 9**, Eq. c), Yi and co-workers further investigated the denitrative trifluoromethylation of β -nitrostyrenes with Togni's reagent II, and good results were obtained when Fe(acac)₃ was used (**Scheme 11**).⁴³ The highly stereoselective (*E*)-trifluoromethylated alkenes were formed in fair to good yields.

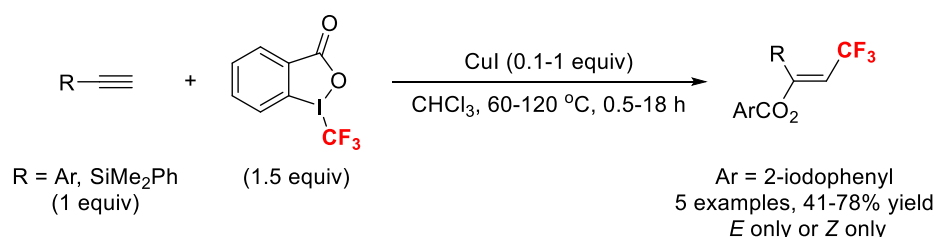
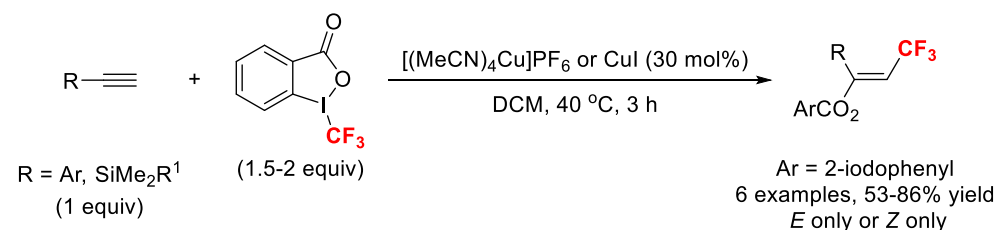
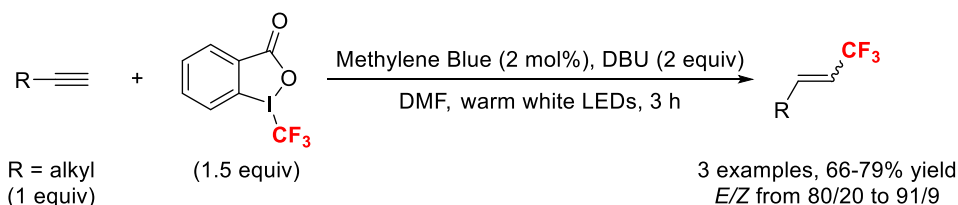
⁴³ J.-J. Ma, W.-B. Yi, G.-P. Lu, C. Cai, *Adv. Synth. Catal.* **2015**, 357, 3447–3452.

⁴⁴ A. T. Parsons, T. D. Senecal, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, 51, 2947–2950.

⁴⁵ Y. Yasu, T. Koike, M. Akita, *Chem. Commun.* **2013**, 49, 2037–2039.

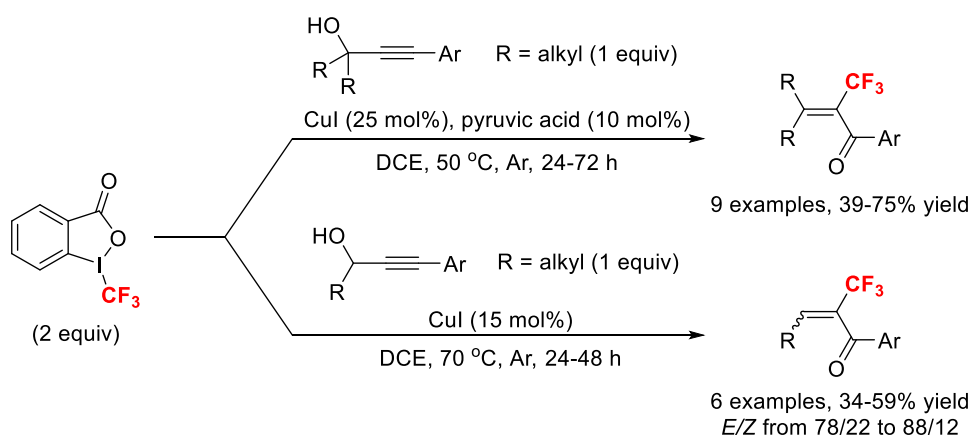
In 2015, Yi *et al.***Scheme 11** Trifluoromethylation of vinyl-NO₂ with Togni's reagent II

Trifluoromethylation of terminal alkynes with Togni's reagent II. The addition of the trifluoromethyl group to terminal alkynes also enabled the generation of trifluoromethylalkenes. In 2012, Szabó and Sodeoka independently studied the trifluoromethyl-benzoyloxylation of terminal alkynes using Togni's reagent II in the presence of copper-salt (**Scheme 12**, Eqs. a-b).⁴⁶⁻⁴⁷ In both of the cases, regio- and stereospecific trifluoromethylated olefins were produced in moderate to good yields. Two years later, Scaiano and co-workers showed that methylene blue could be used as a photosensitizer to promote the hydrotrifluoromethylation of terminal alkynes under visible light irradiation (**Scheme 12**, Eq. c).⁴⁸ Three examples of trifluoromethylalkenes were shown and good *E/Z* selectivity was obtained.

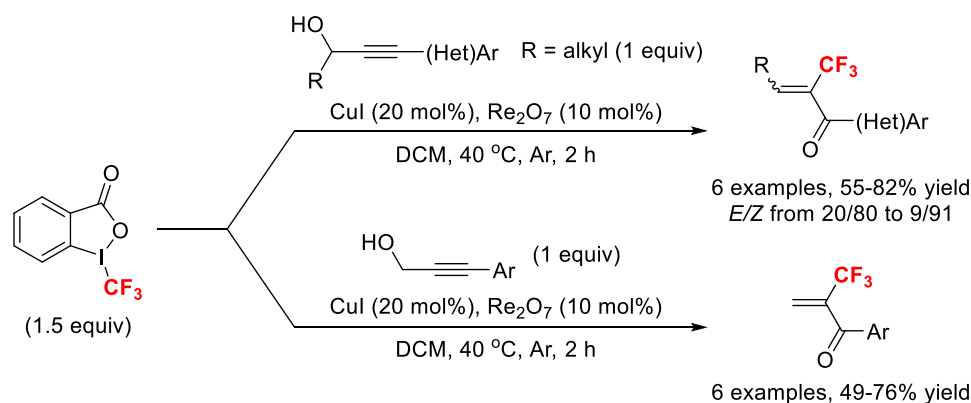
Eq. a) In 2012, Szabó *et al.*Eq. b) In 2012, Sodeoka *et al.*Eq. c) In 2014, Scaiano *et al.***Scheme 12** Trifluoromethylation of terminal alkynes with Togni's reagent II⁴⁶ P. G. Janson, I. Ghoneim, N. O. Ilchenko, K. J. Szabó, *Org. Lett.* **2012**, *14*, 2882–2885.⁴⁷ H. Egami, R. Shimizu, M. Sodeoka, *Tetrahedron Lett.* **2012**, *53*, 5503–5506.⁴⁸ S. P. Pitre, C. D. McTiernan, H. Ismaili, J. C. Scaiano, *ACS Catal.* **2014**, *4*, 2530–2535.

Trifluoromethylation of (homo)propargylic alcohols or propargyl acetates with Togni's reagent II. In 2014, Liu, Tan, and co-workers achieved the synthesis of α -trifluoromethyl enones using propargylic alcohols and Togni's reagent II through copper-catalysed tandem Meyer-Schuster-type rearrangement and trifluoromethylation (**Scheme 13**, Eq. a).⁴⁹ Tertiary and secondary propargylic alcohols were amenable to the reaction conditions and the *E* isomer was the major product when secondary propargylic alcohol was involved. Around the same time, Sodeoka, Hamashima, and co-workers reported a similar transformation by using copper/rhenium-cocatalysts (**Scheme 13**, Eq. b).⁵⁰ They investigated the substrate scope of secondary and primary propargylic alcohols, and in this case, the *Z* isomer was the major product when secondary propargylic alcohol was used. Besides, Xiao, Lin, and co-workers developed a copper/gold-cocatalysed protocol to convert propargyl acetates to α -trifluoromethyl enones, which exhibited excellent *E/Z* selectivity (*E/Z* > 97/3) (**Scheme 14**).⁵¹

Eq. a) In 2014, Liu, Tan *et al.*



Eq. b) In 2014, Sodeoka, Hamashima *et al.*

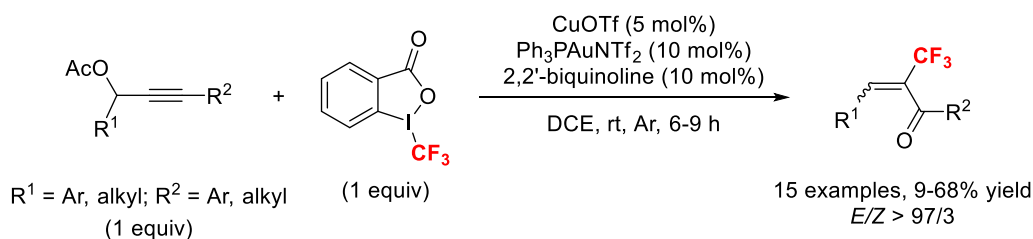


Scheme 13 Trifluoromethylation of propargylic alcohols with Togni's reagent II

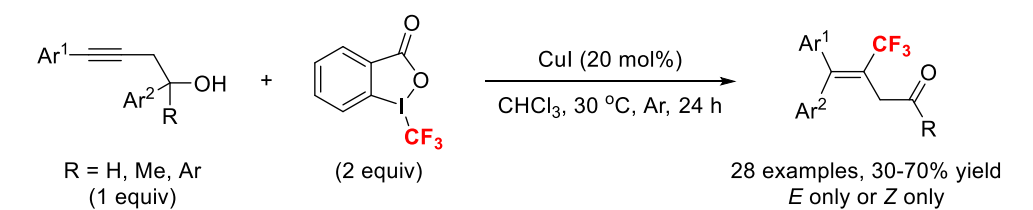
⁴⁹ Y.-P. Xiong, M.-Y. Wu, X.-Y. Zhang, C.-L. Ma, L. Huang, L.-J. Zhao, B. Tan, X.-Y. Liu, *Org. Lett.* **2014**, *16*, 1000–1003.

⁵⁰ H. Egami, T. Ide, M. Fujita, T. Tojo, Y. Hamashima, M. Sodeoka, *Chem. Eur. J.* **2014**, *20*, 12061–12065.

⁵¹ Y.-L. Ji, J.-H. Lin, J.-C. Xiao, Y.-C. Gu, *Eur. J. Org. Chem.* **2014**, 7948–7954.

In 2014, Xiao, Lin *et al.***Scheme 14** Trifluoromethylation of propargyl acetates with Togni's reagent II

In addition to propargylic alcohols and propargyl acetates, the trifluoromethylation of homopropargylic alcohols was explored as well. Liang, Liu, and co-workers reported a copper-catalysed method for the construction of trifluoromethyl-substituted 3-butenals or 3-buten-1-one derivatives using homopropargylic alcohols and Togni's reagent II (**Scheme 15**).⁵² The reaction process goes through trifluoromethylation, 1,4-aryl migration, and carbonyl moiety formation. High regioselectivity was achieved in this chemistry.

In 2014, Liang, Liu *et al.***Scheme 15** Trifluoromethylation of homopropargylic alcohols with Togni's reagent II

1.3.2.3 Trifluoromethylation with CF_3I

Trifluoromethylation of vinyl C-H bond with CF_3I . In 2012, Cho and co-workers developed a method for trifluoromethylation of terminal alkenes with CF_3I in the presence of ruthenium-photocatalyst under visible light irradiation (**Scheme 16**, Eq. a).⁵³ Various alkyl-substituted terminal olefins were converted to the corresponding trifluoromethylated alkenes in good to excellent yields with only E -configuration. Later, the same group performed a similar transformation by visible-light-induced photoredox catalysis in the presence of platinum-catalyst, and the related trifluoromethylalkenes were generated in good to excellent yields with high E/Z selectivity (**Scheme 16**, Eq. b).⁵⁴ Besides, the photocatalytic trifluoromethylation of styrenes was achieved by using iridium-photocatalyst (**Scheme 16**, Eq. c).⁵⁵ This chemistry could be conducted in batch or continuous-flow conditions, and the latter conditions provided better E/Z selectivity than the former conditions. In 2015, Zhang

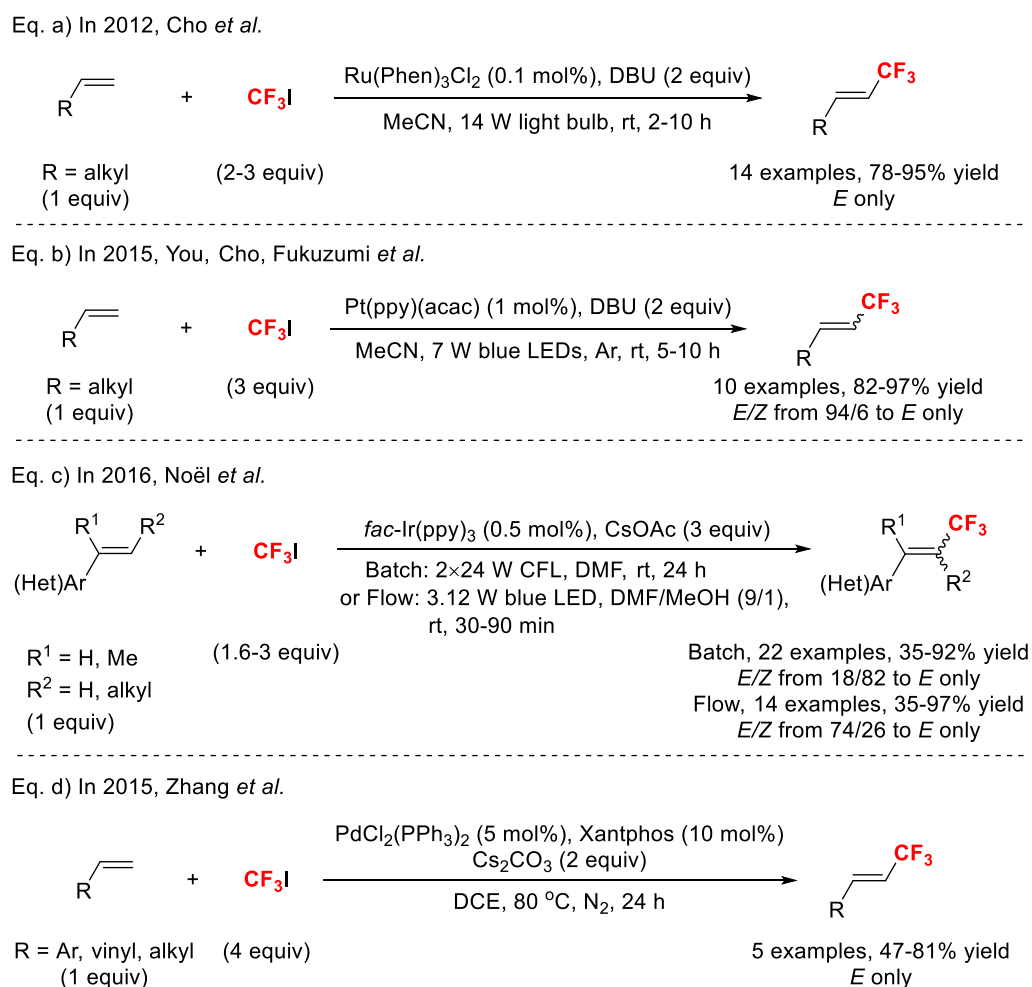
⁵² P. Gao, Y.-W. Shen, R. Fang, X.-H. Hao, Z.-H. Qiu, F. Yang, X.-B. Yan, Q. Wang, X.-J. Gong, X.-Y. Liu, Y.-M. Liang, *Angew. Chem. Int. Ed.* **2014**, *53*, 7629–7633.

⁵³ N. Iqbal, S. Choi, E. Kim, E. J. Cho, *J. Org. Chem.* **2012**, *77*, 11383–11387.

⁵⁴ W. J. Choi, S. Choi, K. Ohkubo, S. Fukuzumi, E. J. Cho, Y. You, *Chem. Sci.* **2015**, *6*, 1454–1464.

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

and co-workers developed a palladium-catalysed trifluoromethylation of terminal alkenes using CF_3I (**Scheme 16**, Eq. d).⁵⁶ Five trifluoromethylalkenes were prepared in moderate to good yields with only *E*-configuration.



Scheme 16 Trifluoromethylation of vinyl C-H bond with CF_3I

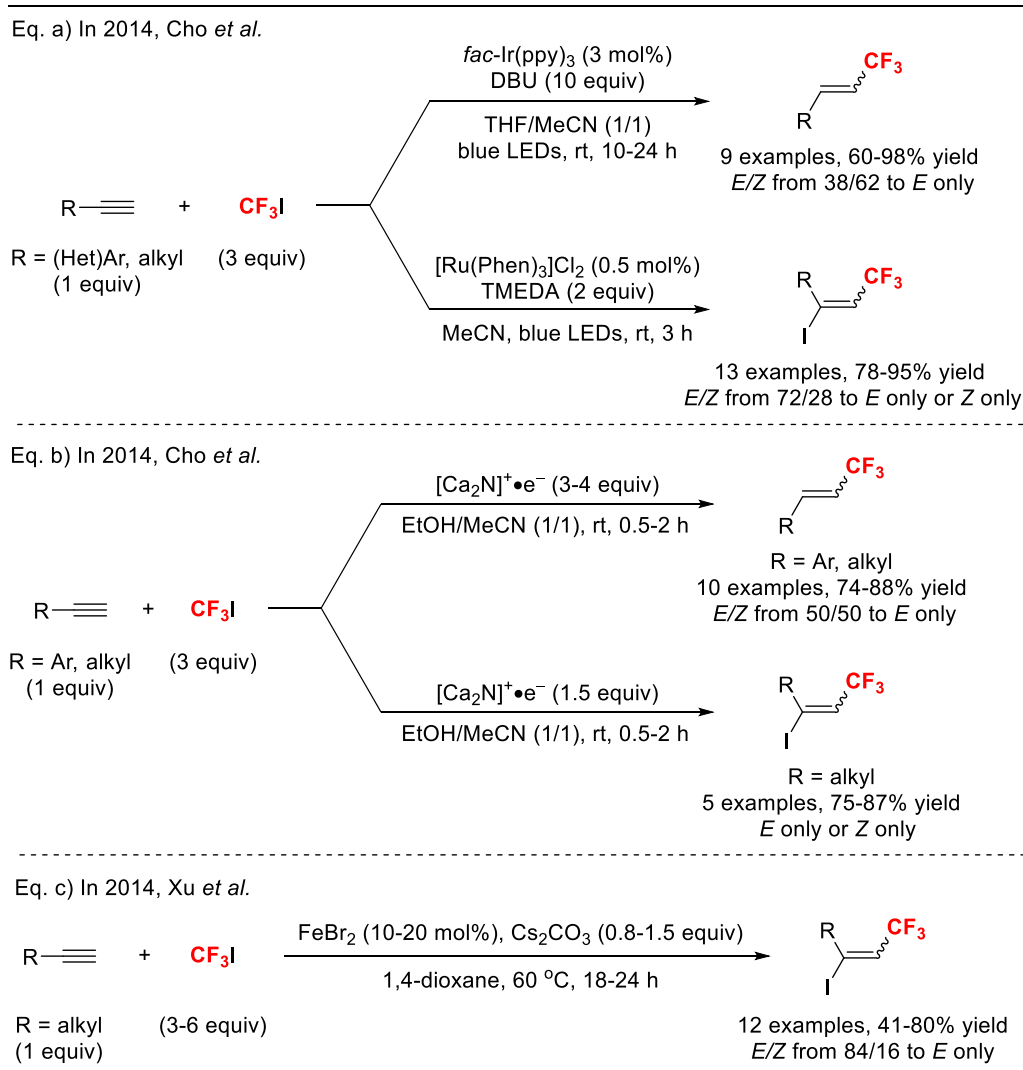
Trifluoromethylation of terminal alkynes with CF_3I . In 2014, Cho and co-workers achieved the visible light photoredox-catalysed hydrotrifluoromethylation and iodotrifluoromethylation of terminal alkynes with CF_3I by adjusting the photocatalyst and base (**Scheme 17**, Eq. a).⁵⁷ When *fac*- $\text{Ir}(\text{ppy})_3$ and DBU were used, the related trifluoromethylalkenes were generated in moderate to excellent yields with low to excellent *E/Z* selectivity. By contrast, the use of $[\text{Ru}(\text{Phen})_3]\text{Cl}_2$ and TMEDA allowed the formation of trifluoromethylated alkenyl iodides, which have better yields and higher *E/Z* selectivity. Shortly after, the same group demonstrated that the controlled trifluoromethylation of terminal alkynes could also be realized by the use of inorganic electride $[\text{Ca}_2\text{N}]^+\bullet\text{e}^-$ (**Scheme 17**, Eq. b).⁵⁸ The hydrotrifluoromethylation

⁵⁶ Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu, X. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 1270–1274.

⁵⁷ N. Iqbal, J. Jung, S. Park, E. J. Cho, *Angew. Chem. Int. Ed.* **2014**, *53*, 539–542.

⁵⁸ S. Choi, Y. J. Kim, S. M. Kim, J. W. Yang, S. W. Kim, E. J. Cho, *Nat. Commun.* **2014**, *5*, 4881.

and iodotrifluoromethylation processes were only determined by the amount of $[\text{Ca}_2\text{N}]^+\bullet\text{e}^-$ electrone. Similarly, better stereoselectivity was observed in the case of iodotrifluoromethylation. Meanwhile, Xu and co-workers reported a method for iron-catalysed iodotrifluoromethylation of terminal alkynes using CF_3I (Scheme 17, Eq. c).⁵⁹ The corresponding trifluoromethylated alkenyl iodides were constructed in moderate to good yields with good to excellent *E/Z* selectivity.



Scheme 17 Trifluoromethylation of terminal alkynes with CF_3I

1.3.2.4 Trifluoromethylation with $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois reagent)

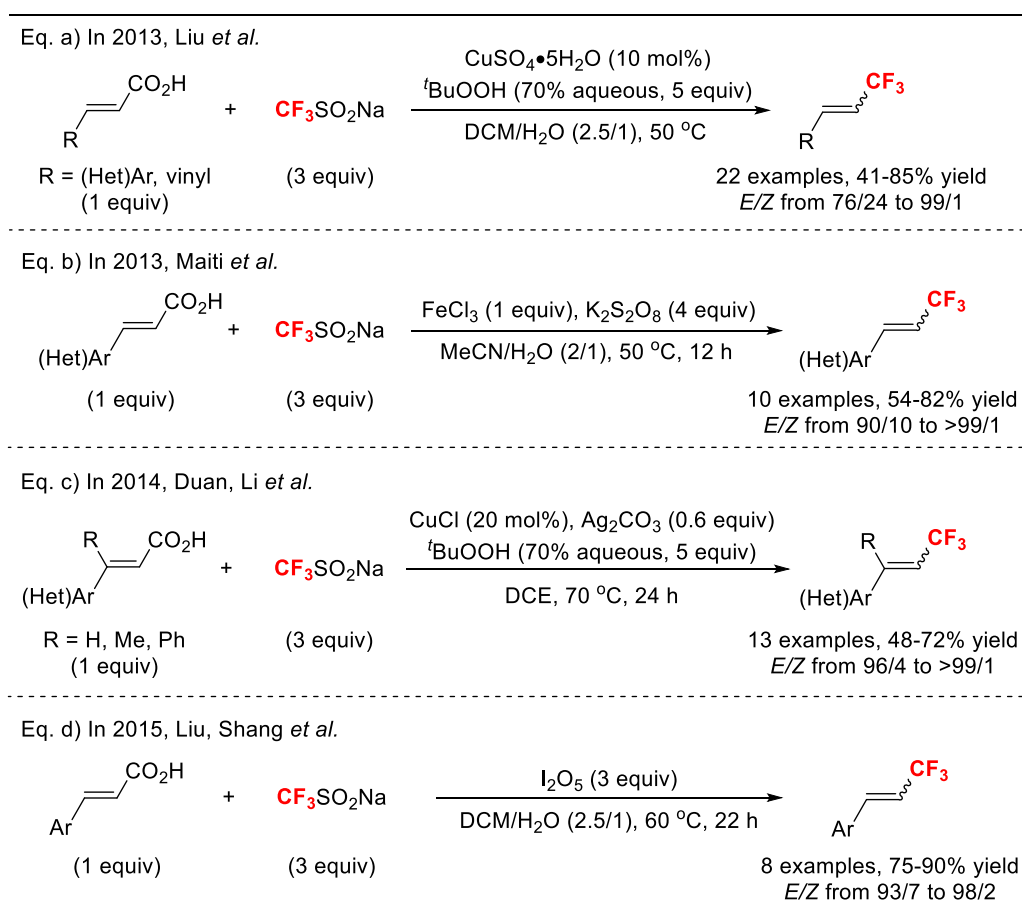
After the first report of $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois reagent) in trifluoromethylation reactions in 1991,⁶⁰ $\text{CF}_3\text{SO}_2\text{Na}$ has proved to be a useful trifluoromethylating reagents and has found many applications in the construction of trifluoromethylalkenes.⁶¹

⁵⁹ T. Xu, C. W. Cheung, X. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 4910–4914.

⁶⁰ B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*, 7525–7528.

⁶¹ (a) C. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 2895–2906; (b) H. Guyon, H. Chachignon, D. Cahard, *Beilstein J. Org. Chem.* **2017**, *13*, 2764–2799.

Trifluoromethylation of vinyl-CO₂H with Langlois reagent. The methods for the synthesis of trifluoromethylalkenes by decarboxylative trifluoromethylation of α,β -unsaturated carboxylic acids with CF₃SO₂Na were reported from 2013 to 2015 (**Scheme 18**).⁶²⁻⁶⁵ The trifluoromethylation process usually occurred in the presence of metal (copper, iron, or silver)-salt and oxidant (^tBuOOH or K₂S₂O₈), and the related trifluoromethylated olefins were generated in moderate to good yields with up to 99/1 of *E/Z* ratio (**Scheme 18**, Eqs. a-c).⁶²⁻⁶⁴ A metal-free protocol was also developed by using I₂O₅ as an oxidant, resulting in the formation of β -trifluoromethylstyrenes in good yields with high *E/Z* selectivity (**Scheme 18**, Eq. d).⁶⁵



Scheme 18 Trifluoromethylation of vinyl-CO₂H with CF₃SO₂Na

Trifluoromethylation of vinyl-B(OH)₂, vinyl-NO₂, vinyl C-H, and vinyl-F with Langlois reagent. In 2013, Beller and co-workers developed a copper-catalysed method for the synthesis of trifluoromethylalkenes from vinyl boronic acids and CF₃SO₂Na with ^tBuOOH as an oxidant (**Scheme 19**, Eq. a).⁶⁶ Several (*E*)- β -trifluoromethylstyrenes were produced in moderate to good yields. Later, Duan and co-workers reported a

⁶² Z. Li, Z. Cui, Z.-Q. Liu, *Org. Lett.* **2013**, *15*, 406–409.

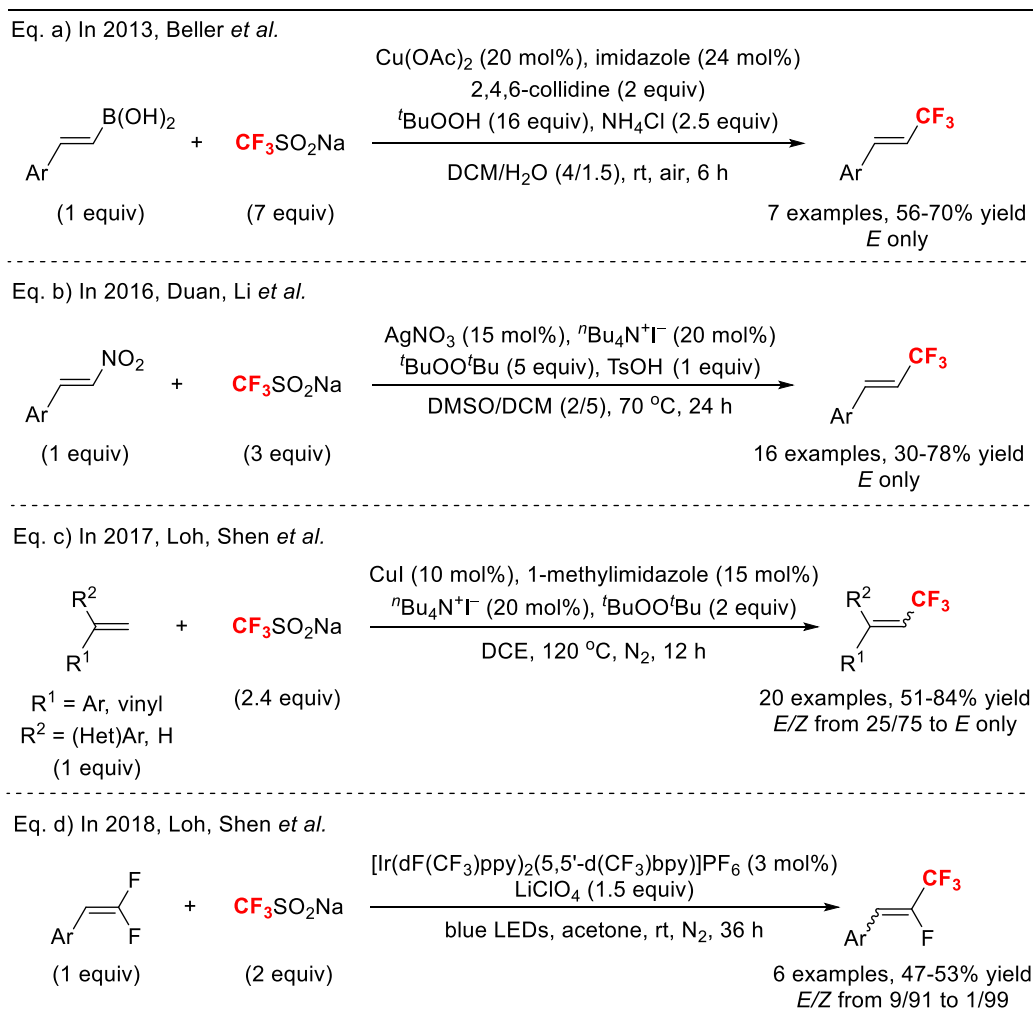
⁶³ T. Patra, A. Deb, S. Manna, U. Sharma, D. Maiti, *Eur. J. Org. Chem.* **2013**, 5247–5250.

⁶⁴ J. Yin, Y. Li, R. Zhang, K. Jin, C. Duan, *Synthesis* **2014**, *46*, 607–612.

⁶⁵ X.-J. Shang, Z. Li, Z.-Q. Liu, *Tetrahedron Lett.* **2015**, *56*, 233–235.

⁶⁶ Y. Li, L. Wu, H. Neumann, M. Beller, *Chem. Commun.* **2013**, *49*, 2628–2630.

silver-catalysed denitrative trifluoromethylation of β -nitrostyrenes using $\text{CF}_3\text{SO}_2\text{Na}$ in the presence of $^t\text{BuOO}^t\text{Bu}$ (**Scheme 19**, Eq. b).⁶⁷ Diverse (*E*)- β -trifluoromethylstyrenes were prepared in fair to good yields. Then, Loh, Shen, and co-workers demonstrated that the combination of copper-catalyst and $^t\text{BuOO}^t\text{Bu}$ could promote the trifluoromethylation of vinyl C-H bond of terminal alkenes with $\text{CF}_3\text{SO}_2\text{Na}$ (**Scheme 19**, Eq. c).⁶⁸ The *E/Z* selectivity of vinyl- CF_3 products was highly substrate-dependent and it was ranging from 25/75 to *E* only. Additionally, Loh, Shen, and co-workers further explored the defluorinative trifluoromethylation of *gem*-difluoroalkenes with $\text{CF}_3\text{SO}_2\text{Na}$ under visible-light photoredox catalysis (**Scheme 19**, Eq. d).⁶⁹ The corresponding fluorine- and trifluoromethyl-substituted alkenes were generated in moderate yields with *Z* isomer as the major product.



Scheme 19 Trifluoromethylation of vinyl- $\text{B}(\text{OH})_2$, vinyl- NO_2 , vinyl C-H, and vinyl-F with $\text{CF}_3\text{SO}_2\text{Na}$

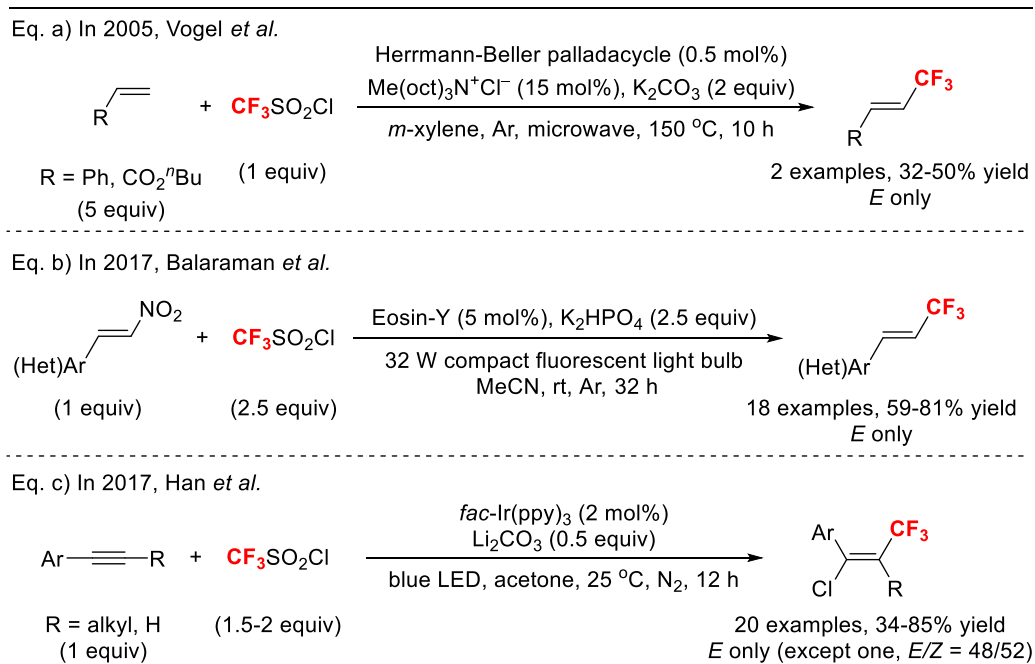
Trifluoromethylation of terminal alkynes with Langlois reagent. In 2014, Liu, and co-workers achieved the iodotrifluoromethylation of terminal alkynes using

⁶⁷ P. Huang, Y. Li, X. Fu, R. Zhang, K. Jin, W. Wang, C. Duan, *Tetrahedron Lett.* **2016**, *57*, 4705–4708.

⁶⁸ L.-H. Wu, K. Zhao, Z.-L. Shen, T.-P. Loh, *Org. Chem. Front.* **2017**, *4*, 1872–1875.

⁶⁹ L.-H. Wu, J.-K. Cheng, L. Shen, Z.-L. Shen, T.-P. Loh, *Adv. Synth. Catal.* **2018**, *360*, 3894–3899.

Umemoto's reagent⁷⁸ was one of the most widely used trifluoromethylating reagents.⁷⁹



Scheme 21 Trifluoromethylation of terminal alkenes, vinyl-NO₂, and alkynes with CF₃SO₂Cl

Trifluoromethylation of vinyl-B(OH)₂ with Umemoto's reagent and Yagupolskii/Umemoto-like reagent. In 2011, Liu and co-workers reported a copper-catalysed method for trifluoromethylation of boronic acids with Umemoto's reagent, and one vinyl boronic acid was successfully converted to the trifluoromethylated alkene in 46% yield with 94/6 of E/Z ratio (**Scheme 22**, Eq. a).⁸⁰ Under similar reaction conditions, Shibata and co-worker utilized 2-cyclopropyl-1-(trifluoromethyl)benzo[*b*]thiophenium triflate, a Yagupolskii/Umemoto-like reagent, to transform vinyl boronic acids to the corresponding trifluoromethylalkenes (**Scheme 22**, Eq. b).⁸¹ Two β-trifluoromethylstyrenes were constructed in good yields with high E/Z selectivity.

Trifluoromethylation of vinyl C-H bond with Umemoto's reagent. In 2014, Besset, Cahard, and co-worker reported a copper-mediated method for trifluoromethylation of acrylamides using Umemoto's reagent (**Scheme 23**, Eq. a).⁸² High regio- and stereoselectivity were achieved thanks to the amide-directing group. Afterwards, two photocatalytic protocols were developed to give access to trifluoromethyl substituted alkenes by olefinic C-H trifluoromethylation with Umemoto's reagent.

⁷⁸ (a) T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, *31*, 3579–3582; (b) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164.

⁷⁹ C. Zhang, *Org. Biomol. Chem.* **2014**, *12*, 6580–6589.

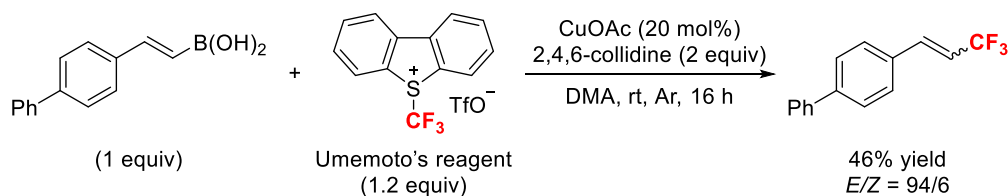
⁸⁰ J. Xu, D.-F. Luo, B. Xiao, Z.-J. Liu, T.-J. Gong, Y. Fu, L. Liu, *Chem. Commun.* **2011**, *47*, 4300–4302.

⁸¹ S. Arimori, N. Shibata, *Org. Lett.* **2015**, *17*, 1632–1635.

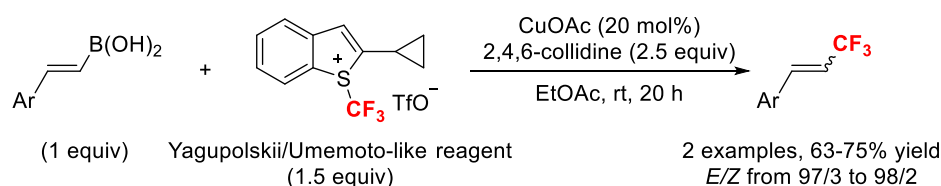
⁸² T. Besset, D. Cahard, X. Pannecoucke, *J. Org. Chem.* **2014**, *79*, 413–418.

When multisubstituted alkenes were used as substrates and $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$ as the photocatalyst, the corresponding CF_3 -alkenes were prepared in fair to good yields with *E/Z* ratio ranging from 17/83 to 91/9 (**Scheme 23**, Eq. b).⁸³ By contrast, in the presence of *fac*- $\text{Ir}(\text{ppy})_3$, styrenes were converted to the β -trifluoromethylstyrenes with *Z* isomer as the major product (**Scheme 23**, Eq. c).³³

Eq. a) In 2011, Liu *et al.*

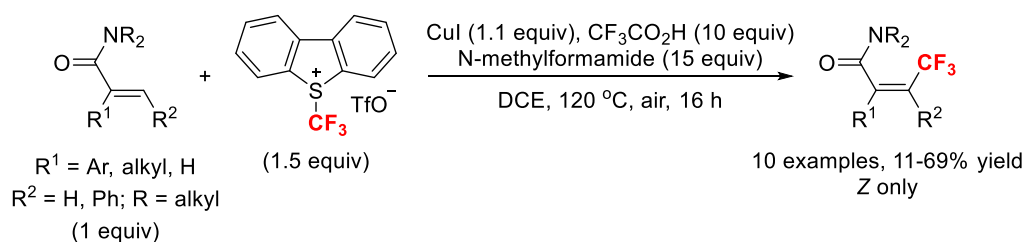


Eq. b) In 2015, Shibata *et al.*

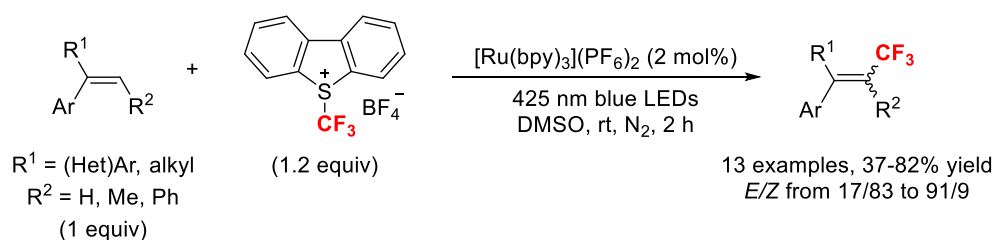


Scheme 22 Trifluoromethylation of vinyl- $\text{B}(\text{OH})_2$ with Umemoto's reagent and Yagupolskii/Umemoto-like reagent

Eq. a) In 2014, Besset, Cahard *et al.*



Eq. b) In 2014, Akita, Koike *et al.*



Eq. c) In 2014, Qing *et al.*

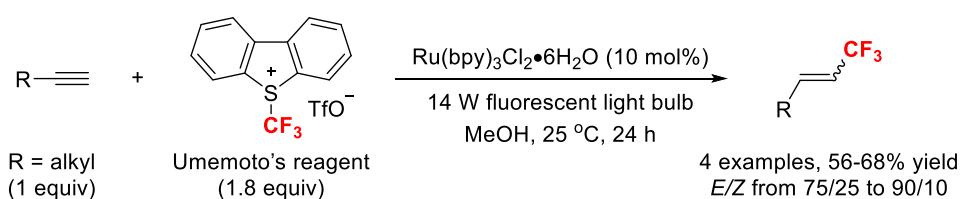


Scheme 23 Trifluoromethylation of vinyl C-H bond with Umemoto's reagent

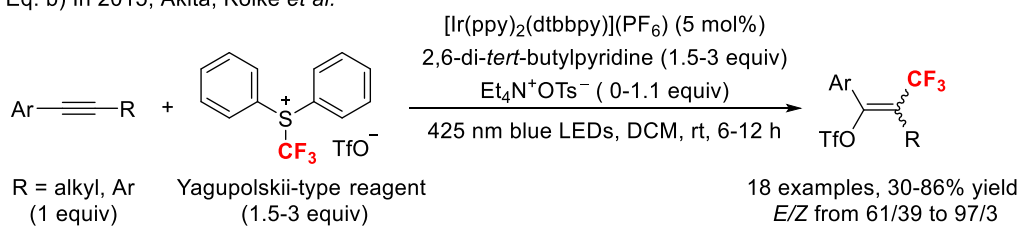
⁸³ R. Tomita, Y. Yasu, T. Koike, M. Akita, *Beilstein J. Org. Chem.* **2014**, *10*, 1099–1106.

Trifluoromethylation of alkynes with Umemoto's reagent and Yagupolskii-type reagent. In 2013, Gouverneur and co-workers achieved the hydrotrifluoromethylation of terminal alkynes using Umemoto's reagent under visible light-mediated photoredox catalysis (**Scheme 24**, Eq. a).⁸⁴ Four trifluoromethylated olefins were synthesized in moderate yields with moderate to good *E/Z* selectivity. Later, Akita, Koike, and co-worker realized the photocatalytic sulfonyloxytrifluoromethylation of internal alkynes with Yagupolskii-type reagent, which provided both of the CF₃ and OTf groups to the alkene products (**Scheme 24**, Eq. b).⁸⁵ Many tetrasubstituted trifluoromethylated alkenes were obtained in synthetically acceptable to good yields with *Z* isomer as the major product.

Eq. a) In 2013, Gouverneur *et al.*



Eq. b) In 2015, Akita, Koike *et al.*



Scheme 24 Trifluoromethylation of alkynes with Umemoto's reagent and Yagupolskii-type reagent

1.3.2.7 Trifluoromethylation with TMSCF₃ (Ruppert-Prakash reagent) and TESCF₃

TMSCF₃ (trifluoromethyltrimethylsilane, Ruppert-Prakash reagent) was first synthesized and used in trifluoromethylation reactions in the 1980s,⁸⁶ and it has gradually been developed into a practical trifluoromethylating reagent.⁸⁷ Several methods for the synthesis of trifluoromethylalkenes by using TMSCF₃ were reported.

Trifluoromethylation of vinyl-B(OH)₂ with TMSCF₃. In 2010, Qing and a co-worker developed a copper-mediated method for trifluoromethylation of boronic acids, and two (*E*)-alkenylboronic acids were subjected to the reaction conditions, leading to

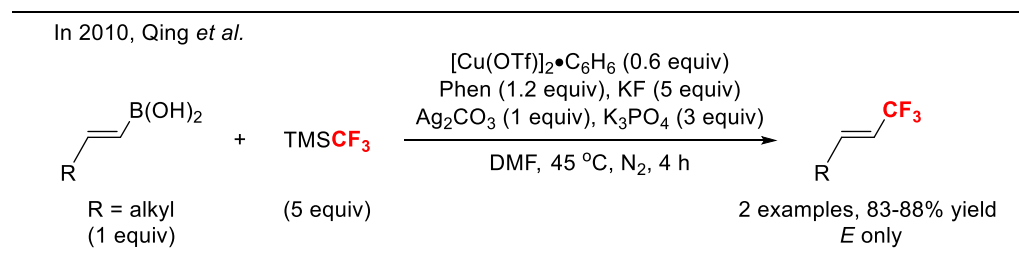
⁸⁴ S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Médebielle, V. Gouverneur, *J. Am. Chem. Soc.* **2013**, *135*, 2505–2508.

⁸⁵ R. Tomita, T. Koike, M. Akita, *Angew. Chem. Int. Ed.* **2015**, *54*, 12923–12927.

⁸⁶ (a) I. Ruppert, K. Schlich, W. Volbach, *Tetrahedron Lett.* **1984**, *25*, 2195–2198; (b) G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

⁸⁷ X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730.

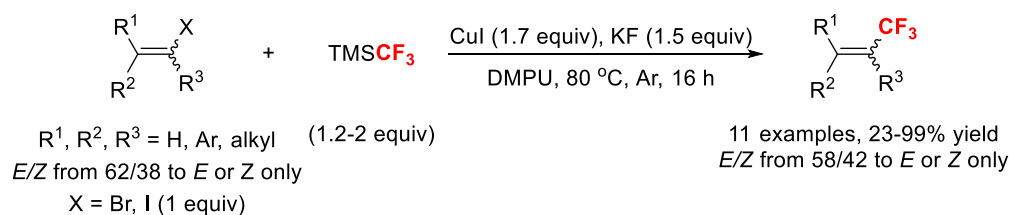
the formation of the corresponding trifluoromethylated olefins in good yields with retention of *E*-configuration (**Scheme 25**).⁸⁸



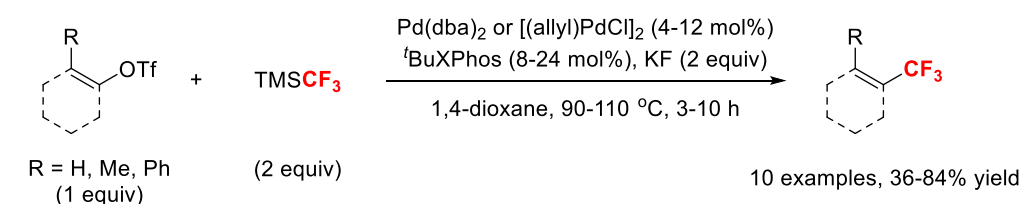
Scheme 25 Trifluoromethylation of vinyl-B(OH)₂ with TMSCF₃

Trifluoromethylation of vinyl halides and pseudohalides with TMSCF₃ or TESCF₃. In 2011, Bräse and a co-worker reported a protocol for copper-mediated trifluoromethylation of vinyl bromides/iodides using TMSCF₃ (**Scheme 26**, Eq. a).⁸⁹ Diverse trifluoromethyl alkenes were constructed in low to excellent yields, and the *E/Z* ratio of products largely depended on the *E/Z* ratio of substrates. In the same year, Buchwald and a co-worker realized the trifluoromethylation of vinyl sulfonates with TMSCF₃ or TESCF₃ under palladium-catalysis (**Scheme 26**, Eqs. b-c).⁹⁰ A variety of cyclohexenyl triflates and nonaflates were amenable to the reaction conditions, and the related cyclic trifluoromethylalkenes were generated in fair to good yields.

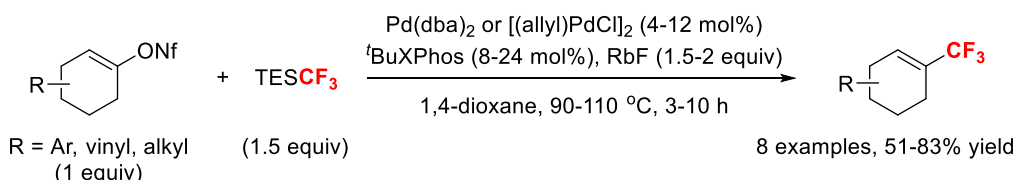
Eq. a) In 2011, Bräse *et al.*



Eq. b) In 2011, Buchwald *et al.*



Eq. c) In 2011, Buchwald *et al.*



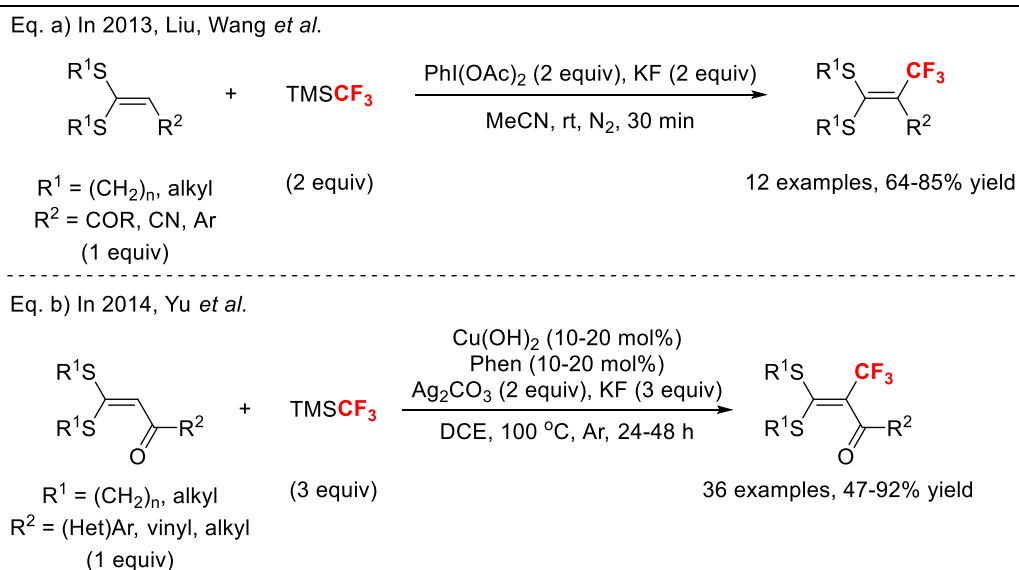
Scheme 26 Trifluoromethylation of vinyl halides and pseudohalides with TMSCF₃ or TESCF₃

⁸⁸ L. Chu, F.-L. Qing, *Org. Lett.* **2010**, *12*, 5060–5063.

⁸⁹ A. Hafner, S. Bräse, *Adv. Synth. Catal.* **2011**, *353*, 3044–3048.

⁹⁰ E. J. Cho, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 6552–6555.

Trifluoromethylation of vinyl C-H bond with TMSCF₃. In 2013, Liu, Wang, and co-workers achieved the olefinic C-H trifluoromethylation of ketene dithioacetals with TMSCF₃ in the presence of PhI(OAc)₂, allowing the formation of trifluoromethyl-containing tetrasubstituted alkenes in good yields (**Scheme 27**, Eq. a).⁹¹ Then, Yu and co-workers reported a copper-catalysed, silver-mediated protocol for olefinic C-H trifluoromethylation of dithioalkyl α -oxoketene acetals with TMSCF₃ (**Scheme 27**, Eq. b).⁹² A broad range of substrates was converted to the corresponding trifluoromethyl-containing tetrasubstituted alkenes in moderate to excellent yields.



Scheme 27 Trifluoromethylation of vinyl C-H bond with TMSCF₃

1.3.2.8 Trifluoromethylation with CuCF₃ and (Phen)Cu(CF₃)₃

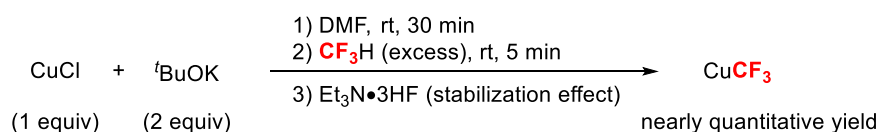
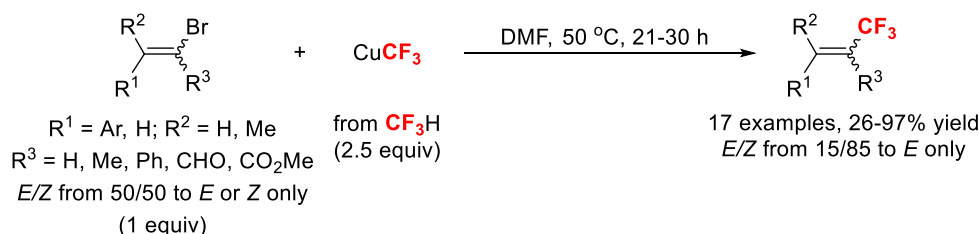
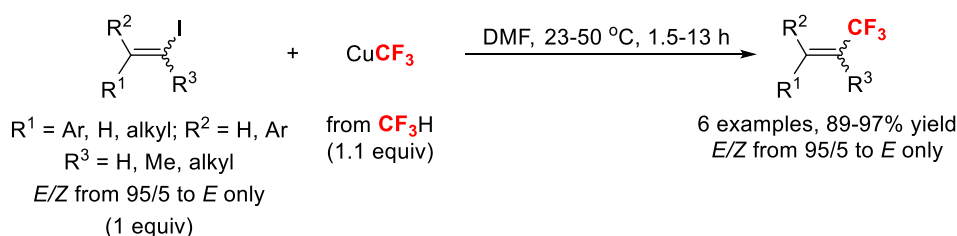
Trifluoromethylation of vinyl halides with CuCF₃. In 2011, Grushin and co-workers achieved the direct cupration of CF₃H under treatment with CuCl/^tBuOK (1/2). The CuCF₃ species was formed in nearly quantitative yield, and it could be stabilized by Et₃N•3HF (**Scheme 28**, Eq. a).⁹³ Later, they realized the trifluoromethylation of vinyl halides with the CuCF₃ species derived from CF₃H. A variety of vinyl bromides and iodides were transformed to the corresponding trifluoromethylalkenes in low to excellent yields (**Scheme 28**, Eqs. b-c).⁹⁴ The *E/Z* ratio of products was related to that of vinyl halides, and most of the time the reaction occurred with the retention of configuration.

⁹¹ C. Xu, J. Liu, W. Ming, Y. Liu, J. Liu, M. Wang, Q. Liu, *Chem. Eur. J.* **2013**, *19*, 9104–9109.

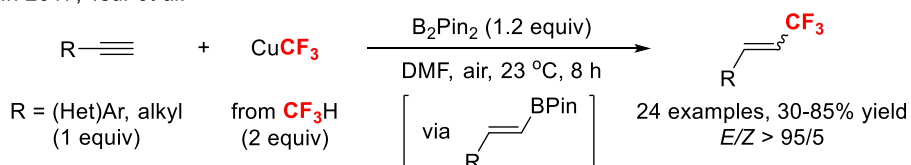
⁹² Z. Mao, F. Huang, H. Yu, J. Chen, Z. Yu, Z. Xu, *Chem. Eur. J.* **2014**, *20*, 3439–3445.

⁹³ A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913.

⁹⁴ A. Lishchynskiy, Z. Mazloomi, V. V. Grushin, *Synlett* **2015**, *26*, 45–50.

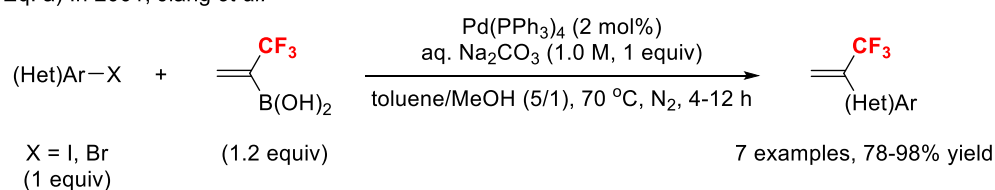
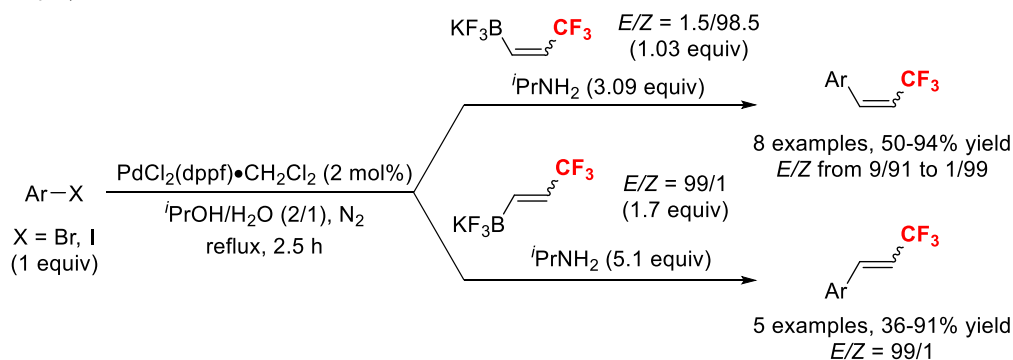
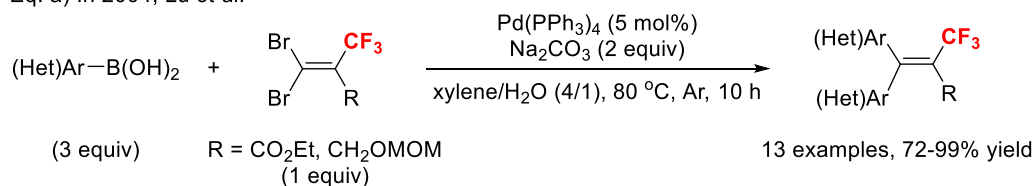
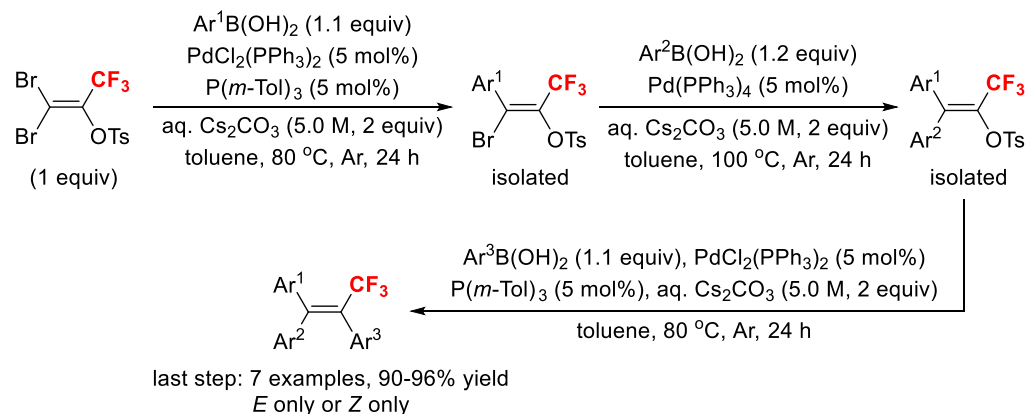
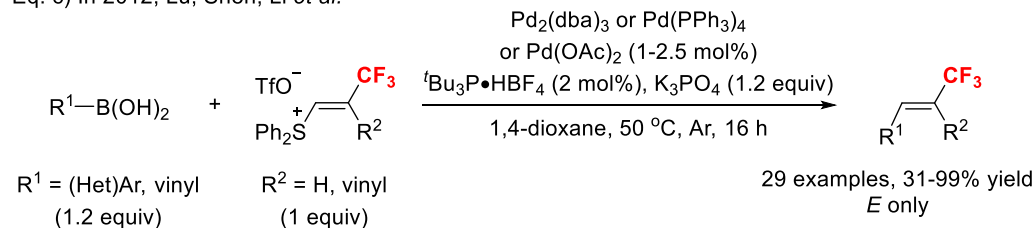
Eq. a) In 2011, Grushin *et al.*Eq. b) In 2015, Grushin *et al.*Eq. c) In 2015, Grushin *et al.***Scheme 28** Trifluoromethylation of vinyl halides with CuCF₃

Trifluoromethylation of terminal alkynes with CuCF₃. Following the work of Grushin, Tsui and co-workers developed a method for the synthesis of trifluoromethylalkenes using terminal alkynes and CF₃H-derived CuCF₃ in the presence of B₂Pin₂ (**Scheme 29**).⁹⁵ The reaction went through a domino hydroboration/trifluoromethylation process, leading to the formation of hydrotrifluoromethylated alkenyl products in acceptable to good yields with high E/Z selectivity (E/Z > 95/5).

In 2017, Tsui *et al.***Scheme 29** Trifluoromethylation of terminal alkynes with CuCF₃

Trifluoromethylation of vinyl C-H bond with (Phen)Cu(CF₃)₃. In 2019, Zhang and co-workers reported a protocol for DBU-mediated trifluoromethylation of olefinic C-H bond of 1,1-diarylalkenes with (Phen)Cu(CF₃)₃ (**Scheme 30**).⁹⁶ The related trifluoromethyl olefins were produced in low to good yields with the E/Z ratio ranging from 29/71 to 84/16.

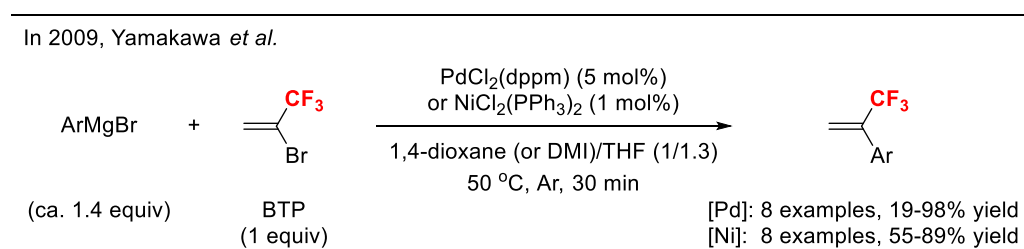
⁹⁵ L. He, X. Yang, G. C. Tsui, *J. Org. Chem.* **2017**, *82*, 6192–6201.⁹⁶ H.-R. Zhang, C. Xiao, S.-L. Zhang, X. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 5305–5310.

Eq. a) In 2001, Jiang *et al.*Eq. b) In 2015, Ramachandran *et al.***Scheme 31** Suzuki-Miyaura coupling of aromatic halides with CF₃-substituted vinyl-B(OH)₂/-BF₃KEq. a) In 2004, Lu *et al.*Eq. b) In 2007, Shimizu *et al.*Eq. c) In 2012, Lu, Shen, Li *et al.***Scheme 32** Suzuki-Miyaura coupling of boronic acids with CF₃-substituted vinyl halides and pseudohalides

palladium-catalysed stereocontrolled threefold Suzuki-Miyaura coupling of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene with aromatic boronic acids (**Scheme 32**, Eq. b).¹⁰⁰ The starting material 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene was prepared by the reaction of 3,3-dibromo-1,1,1-trifluoroacetone with *p*-toluenesulfonyl chloride in the presence of Et₃N. In 2012, Lu, Shen, Li, and co-workers prepared some (*E*)-(β-trifluoromethyl)vinyldiphenylsulfonium salts from 3,3,3-trifluoropropene or 1,1,1-trifluoroacetone via five to six steps. Then, they realized the palladium-catalysed Suzuki-Miyaura coupling of boronic acids with these (*E*)-(β-trifluoromethyl)vinyldiphenylsulfonium salts, and various trifluoromethyl-bearing (*E*)-alkenes and (*E,E*)-dienes were obtained in fair to excellent yields (**Scheme 32**, Eq. c).¹⁰¹

1.3.3.2 Kumada coupling reaction

In 2009, Yamakawa and co-workers utilized Kumada coupling reaction to synthesize α-trifluoromethylstyrenes from aryl Grignard reagents and commercially available 2-bromo-3,3,3-trifluoropropene (BTP) (**Scheme 33**).¹⁰² Low to excellent yields of the products were obtained in palladium-catalysed conditions, and moderate to good yields were observed in the case of nickel-catalysis.



Scheme 33 Kumada coupling reaction between aryl Grignard reagents and 2-bromo-3,3,3-trifluoropropene

1.3.3.3 Hiyama coupling reaction

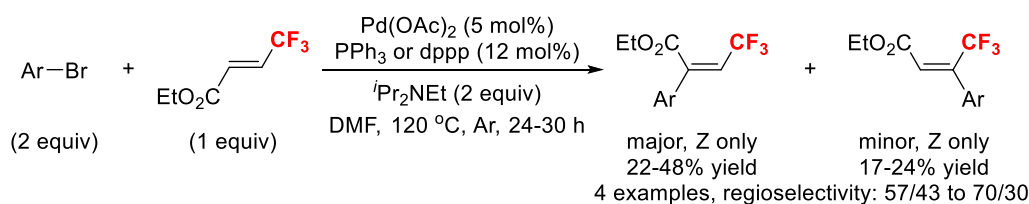
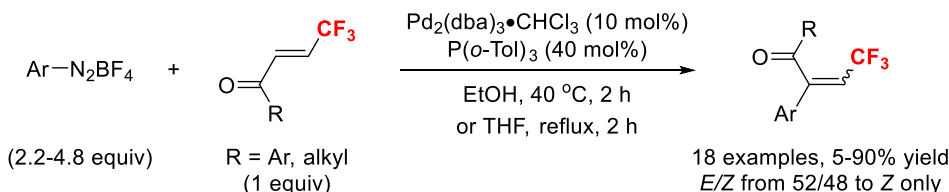
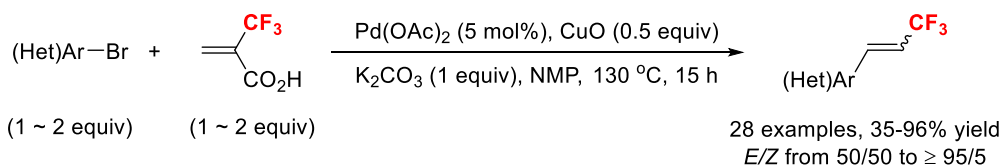
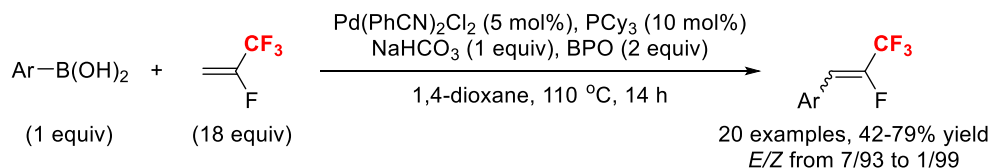
In 2012, Ando and co-workers prepared the (*E*)-trimethyl-(3,3,3-trifluoroprop-1-enyl)silane starting from the *in situ* generated CF₃CHO gas and TMSCH₂MgCl by two steps. Afterwards, they were able to construct β-trifluoromethylstyrenes by palladium-catalysed Hiyama coupling of aryl iodides with the pre-synthesized (*E*)-trimethyl-(3,3,3-trifluoroprop-1-enyl)silane (**Scheme 34**).¹⁰³ The desired products were generated in fair to good yields with retention of *E*-configuration.

¹⁰⁰ Y. Takeda, M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2007**, *46*, 8659–8661.

¹⁰¹ H. Lin, X. Dong, Y. Li, Q. Shen, L. Lu, *Eur. J. Org. Chem.* **2012**, 4675–4679.

¹⁰² (a) O. Kobayashi, D. Uraguchi, T. Yamakawa, *J. Mol. Catal. A Chem.* **2009**, *302*, 7–10; (b) O. Kobayashi, D. Uraguchi, T. Yamakawa, *J. Fluorine Chem.* **2009**, *130*, 591–594.

¹⁰³ M. Omote, M. Tanaka, A. Ikeda, S. Nomura, A. Tarui, K. Sato, A. Ando, *Org. Lett.* **2012**, *14*, 2286–2289.

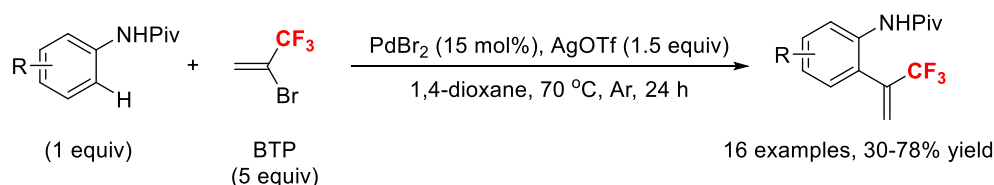
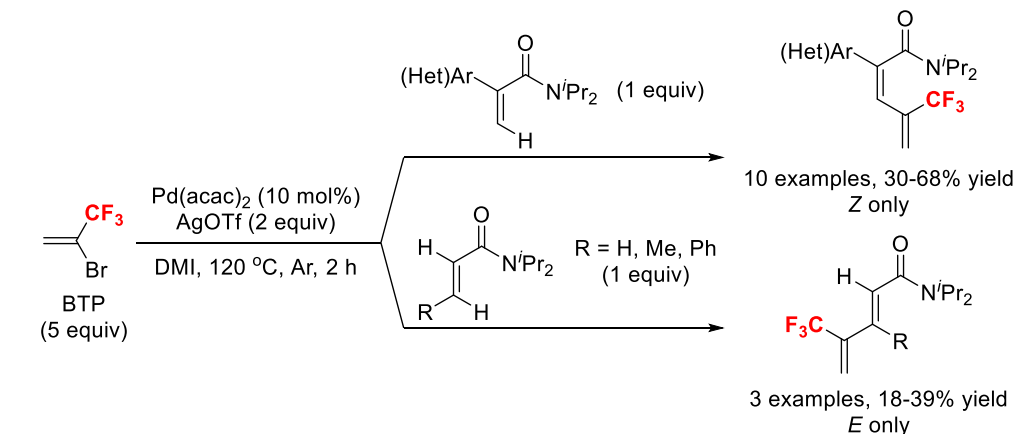
Eq. a) In 2000, Gong *et al.*Eq. b) In 2006 & 2009, Konno *et al.*Eq. c) In 2015, Nicholls *et al.*Eq. d) In 2015, Lu, Liu *et al.***Scheme 35** Mizoroki-Heck reaction to give access to trifluoromethylalkenes

1.3.3.5 C-H bond functionalization

In 2016, Bouillon and co-workers developed a method for the synthesis of α -trifluoromethylstyrenes from BTP by palladium-catalysed directed aryl C-H bond functionalization (**Scheme 36**, Eq. a).¹⁰⁸ Pivalamide served as an effective directing group, and the desired products were obtained in acceptable to good yields. The same research group further investigated the directed vinyl C-H bond functionalization with BTP under palladium-catalysis (**Scheme 36**, Eq. b).¹⁰⁹ A tertiary amide (-CONⁱPr₂) was used as a directing group, leading to the formation of 3-trifluoromethyl-substituted 1,3-butadienes. When α -(hetero)aryl-substituted acrylamides were used as substrates, the stereospecific (Z)-products were generated in acceptable to good yields. In contrast, non-substituted or β -substituted acrylamides allowed the formation of stereospecific (E)-products, albeit in low yields.

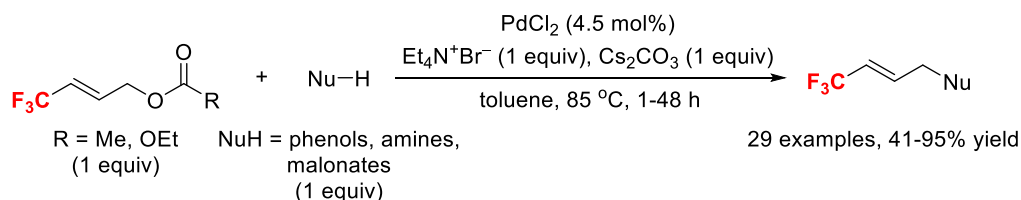
¹⁰⁸ Q. Zhao, T. Besset, T. Poisson, J.-P. Bouillon, X. Pannecoucke, *Eur. J. Org. Chem.* **2016**, 76–82.

¹⁰⁹ Q. Zhao, V. Tognetti, L. Joubert, T. Besset, X. Pannecoucke, J.-P. Bouillon, T. Poisson, *Org. Lett.* **2017**, *19*, 2106–2109.

Eq. a) In 2016, Bouillon *et al.*Eq. b) In 2017, Poisson, Bouillon *et al.***Scheme 36** Aryl and vinyl sp^2 C-H bond functionalization with BTP

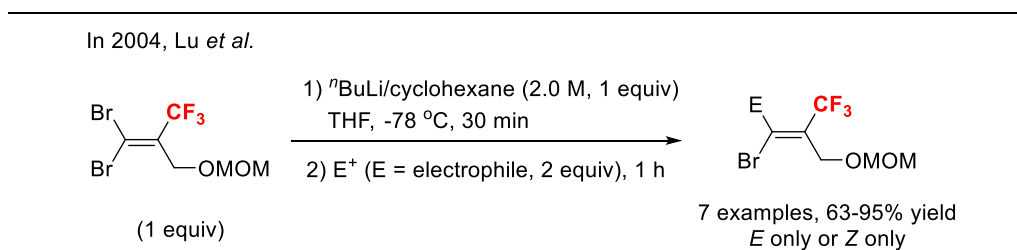
1.3.3.6 Tsuji-Trost reaction

In 2015, Paquin and co-workers reported the preparation of ethyl (4,4,4-trifluorobut-2-en-1-yl)carbonate and 4,4,4-trifluorobut-2-en-1-yl acetate starting from ethyl (*E*)-4,4,4-trifluorocrotonate via two steps. Then, they realized Tsuji-Trost reaction using the pre-synthesized ethyl (4,4,4-trifluorobut-2-en-1-yl)carbonate or 4,4,4-trifluorobut-2-en-1-yl acetate with nucleophiles in the presence of palladium nanoparticles which were derived from PdCl_2 (**Scheme 37**).¹¹⁰ A variety of nucleophiles including phenols, amines, and malonates were amenable to this reaction system, affording the corresponding products in moderate to excellent yields. High regioselectivity was usually obtained except that isomerization of double bond was observed in the case of phenols.

In 2015, Paquin *et al.***Scheme 37** Tsuji-Trost reaction of 4,4,4-trifluorobut-2-en-1-yl carbonate or ester with nucleophiles¹¹⁰ R. Hemelaere, J. Desroches, J.-F. Paquin, *Org. Lett.* **2015**, *17*, 1770–1773.

1.3.3.7 Modification of vinyl C-Br bond via lithium-bromine exchange

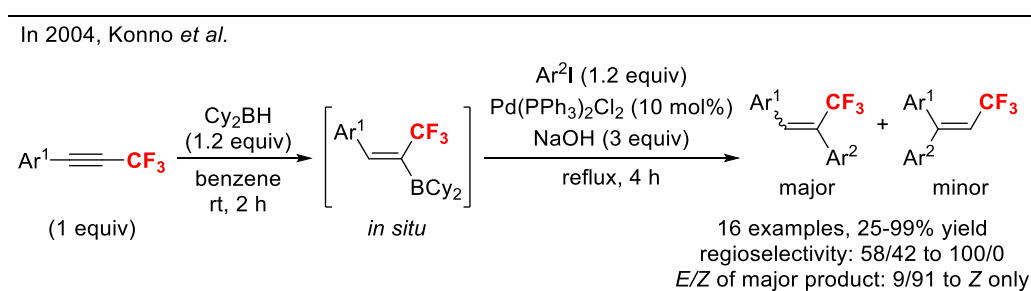
In 2004, Lu and co-workers achieved the construction of *O*-protected 2-trifluoromethyl-3-bromoallylic alcohols from the pre-synthesized 2-trifluoromethyl-3,3-dibromoallylic alcohol derivative by the process of lithium-bromine exchange and treatment with electrophiles (**Scheme 38**).¹¹¹ The *in situ* generated lithium carbenoid species could be trapped by many electrophiles including iodine, TMSCl, ⁿBu₃SnCl, aldehydes, ketone, and MeI, furnishing the related products in moderate to excellent yields with a stereospecific configuration.



Scheme 38 Modification of vinyl C-Br bond via lithium-bromine exchange

1.3.4 Miscellaneous reactions

Besides the above-mentioned three major strategies, some other methods were also reported to give access to trifluoromethylalkenes. In 2004, Konno and co-workers developed a method for the synthesis of trisubstituted CF₃-alkenes from trifluoromethylated internal alkynes (**Scheme 39**).¹¹² The reaction process underwent a sequential *cis*-hydroboration and palladium-catalysed Suzuki-Miyaura coupling. In most of the cases, excellent regioselectivity was observed, and the major regioisomer exhibited a high *E/Z* selectivity.



Scheme 39 Synthesis of trifluoromethylalkenes from trifluoromethylated alkynes

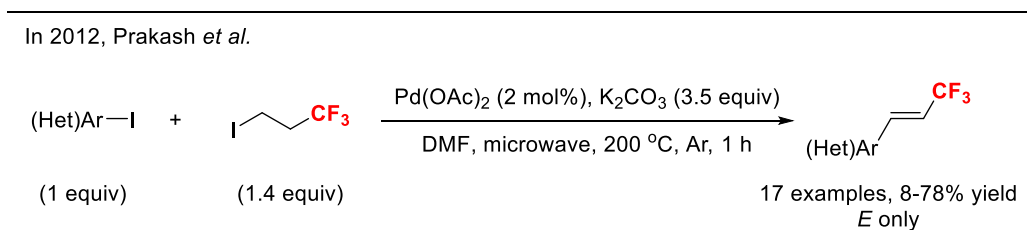
In 2012, Prakash and co-workers developed a palladium-catalysed protocol for the preparation of β -trifluoromethylstyrenes using (hetero)aryl iodides and 1-iodo-3,3,3-trifluoropropane under microwave conditions (**Scheme 40**).¹¹³ A domino elimination/Mizoroki-Heck coupling sequence was considered to be involved in the

¹¹¹ Y. Li, L. Lu, X. Zhao, *Org. Lett.* **2004**, *6*, 4467–4470.

¹¹² T. Konno, J. Chae, T. Tanaka, T. Ishihara, H. Yamanaka, *Chem. Commun.* **2004**, *4*, 690–691.

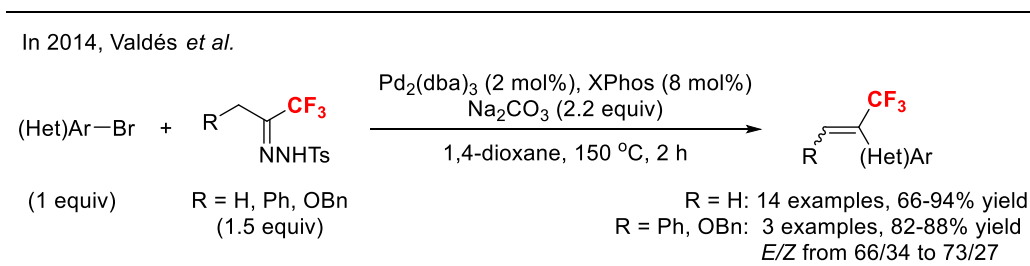
¹¹³ G. K. S. Prakash, H. S. Krishnan, P. V. Jog, A. P. Iyer, G. A. Olah, *Org. Lett.* **2012**, *14*, 1146–1149.

reaction process. Various (*E*)- β -trifluoromethylstyrenes were produced in low to good yields.



Scheme 40 Synthesis of trifluoromethylalkenes from 1-iodo-3,3,3-trifluoropropane

Later, Valdés and co-workers performed a palladium-catalysed cross-coupling reaction of (hetero)aromatic bromides with CF_3 -substituted tosylhydrazones (**Scheme 41**).¹¹⁴ When 1,1,1-trifluoroacetone tosylhydrazone ($\text{R} = \text{H}$) was used, various α -trifluoromethylstyrenes were obtained in good to excellent yields. When other CF_3 -substituted tosylhydrazones ($\text{R} = \text{Ph}$, OBn) were used, the related trisubstituted CF_3 -alkenes were generated in good yields with moderate *E/Z* selectivity.



Scheme 41 Synthesis of trifluoromethylalkenes from CF_3 -substituted tosylhydrazones

As we mentioned previously, the Mizoroki-Heck reaction can be used to produce trifluoromethylalkenes. And the Mizoroki-Heck reaction has been extensively used during my Ph.D. research; therefore, the next part will be devoted to the overview of the Mizoroki-Heck reaction in organofluorine chemistry.

1.4 Palladium-catalysed Mizoroki-Heck-type reaction with fluorine-containing alkenes as coupling partners

Mizoroki-Heck reaction, first reported by Mizoroki¹¹⁵ and Heck¹¹⁶ independently in the early 1970s, is a carbon-carbon cross-coupling reaction between unsaturated halides and alkenes in the presence of palladium catalyst and base, contributing to the formation of substituted alkenes. Owing to its simplicity and high efficiency in

¹¹⁴ A. Jiménez-Aquino, J. A. Vega, A. A. Trabanco, C. Valdés, *Adv. Synth. Catal.* **2014**, 356, 1079–1084.

¹¹⁵ T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, 44, 581–581.

¹¹⁶ K. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, 37, 2320–2322.

carbon-carbon bond formation, the Mizoroki-Heck reaction has aroused widespread research interest, and Heck was awarded the 2010 Nobel Prize in Chemistry.¹¹⁷

The palladium-catalysed Mizoroki-Heck-type reaction by using fluorine-containing alkenes as coupling partners is highly attractive,¹¹⁸ because it is able to give access to fluorine-bearing functional molecules such as fluorinated distyrylbenzene chromophores,¹¹⁹ fluorous-soluble phosphines,¹²⁰ and fluoro-tagged oligo(phenylene vinylene)s.¹²¹ Besides, the Mizoroki-Heck coupling of aryl iodides with trifluoroethyl 2-acetoxyacrylate laid the foundation for the synthesis of the natural product Pulvinone.¹²² More importantly, the Mizoroki-Heck reaction was applied to the construction of chromophores based on a hexafluorocyclopentene “core”, which showed potential applications in organic photovoltaic cells.¹²³

1.4.1 Challenge

Despite the benefits mentioned above, fluorine-containing alkenes were much less investigated in the Mizoroki-Heck reaction when compared with non-fluorinated alkenes. The main challenge might be that the reaction intermediate is prone to β -fluoride elimination instead of the usual β -hydride elimination. In 1991, Heitz and a co-worker tried to prepare β,β -difluorostyrenes from aryl iodides and 1,1-difluoroethene by palladium-catalysed Mizoroki-Heck reaction. Unexpectedly, α -fluorostyrenes were generated as the major products with only traces of β,β -difluorostyrenes (**Scheme 42**, Eq. a).¹²⁴ They further tested the reactivity of fluoroethene and 1,1,2-trifluoroethene, and both of the cases provided defluorinative arylated products (**Scheme 42**, Eq. b).¹²⁴ Based on experimental and MNDO-computational results, a charge-controlled reaction mechanism was proposed (**Scheme 42**, Eq. c).¹²⁴ Oxidative addition of aryl halide to Pd(0) species generates $\text{ArPd}^{\text{II}}\text{X}$, which then coordinates to 1,1-difluoroethene. The lack of steric hindrance causes the charge-controlled insertion, and the formation of intermediate **B** is favoured. Subsequent β -fluoride elimination yields the α -fluorostyrene.

¹¹⁷ S. Jagtap, *Catalysts* **2017**, *7*, 267.

¹¹⁸ J. Yang, H.-W. Zhao, J. He, C.-P. Zhang, *Catalysts* **2018**, *8*, 23.

¹¹⁹ M. L. Renak, G. P. Bartholomew, S. Wang, P. J. Ricatto, R. J. Lachicotte, G. C. Bazan, *J. Am. Chem. Soc.* **1999**, *121*, 7787–7799.

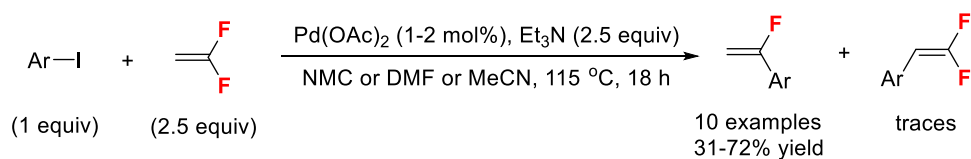
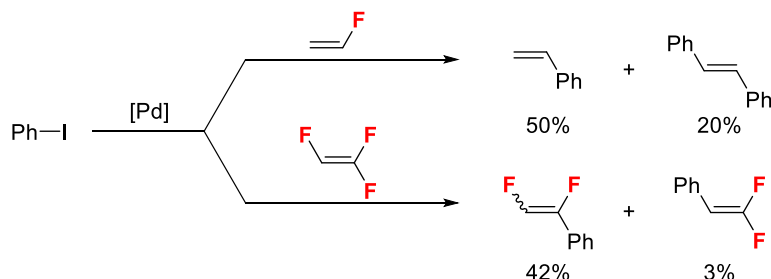
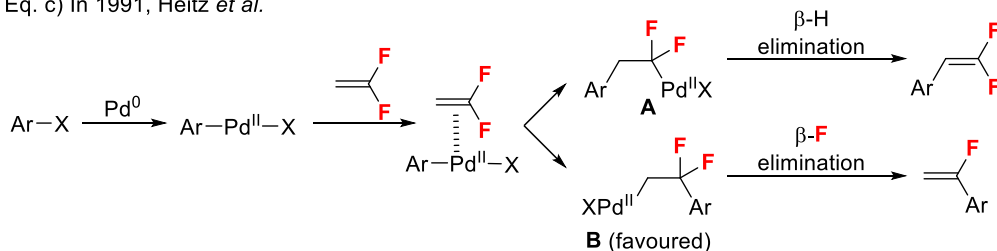
¹²⁰ W. Chen, L. Xu, J. Xiao, *Org. Lett.* **2000**, *2*, 2675–2677.

¹²¹ H. Jian, J. M. Tour, *J. Org. Chem.* **2005**, *70*, 3396–3424.

¹²² D. Bernier, R. Brückner, *Synthesis* **2007**, 2249–2272.

¹²³ C. Fan, P. Yang, X. Wang, G. Liu, X. Jiang, H. Chen, X. Tao, M. Wang, M. Jiang, *Sol. Energy Mater. Sol. Cells* **2011**, *95*, 992–1000.

¹²⁴ W. Heitz, A. Knebelkamp, *Makromol. Chem., Rapid Commun.* **1991**, *12*, 69–75.

Eq. a) In 1991, Heitz *et al.*Eq. b) In 1991, Heitz *et al.*Eq. c) In 1991, Heitz *et al.***Scheme 42** Palladium-catalysed defluorinative arylation of fluorinated alkenes

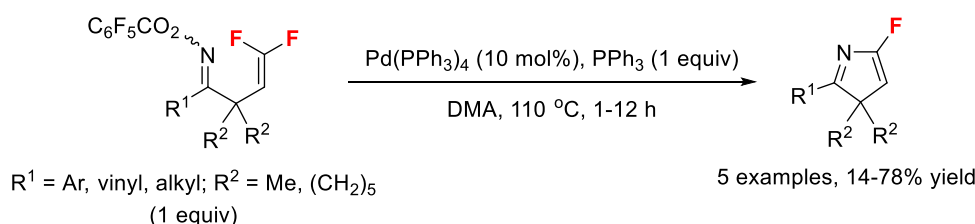
The β -fluoride elimination was also observed in palladium-catalysed unusual 5-*endo-trig* Mizoroki-Heck-type cyclization of 3,3-difluoroallyl ketone oximes and 2-(trifluoromethyl)allyl ketone oximes, providing 5-fluoro-3*H*-pyrroles and 4-difluoromethylene-substituted 1-pyrrolines in low to good yields (**Scheme 43**, Eqs. a-b).¹²⁵⁻¹²⁶

One of the solutions to this problem might be introducing another substituent to the fluorine-bearing carbon center, disturbing the electronic distribution in the alkene, and thus the steric controlled insertion would be predominant, avoiding the unwanted β -fluoride elimination.

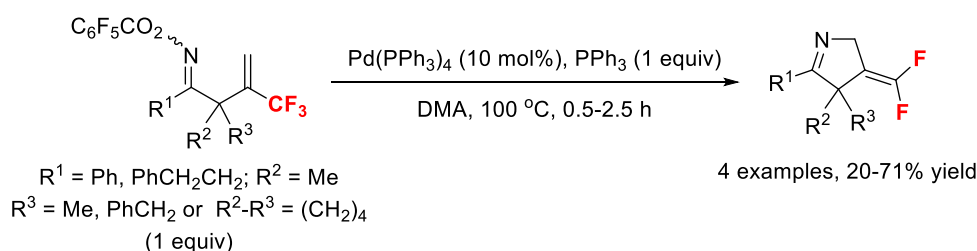
¹²⁵ (a) K. Sakoda, J. Mihara, J. Ichikawa, *Chem. Commun.* **2005**, 4684–4686; (b) J. Ichikawa, K. Sakoda, J. Mihara, N. Ito, *J. Fluorine Chem.* **2006**, *127*, 489–504.

¹²⁶ J. Ichikawa, R. Nadano, N. Ito, *Chem. Commun.* **2006**, 4425–4427.

Eq. a) In 2005 & 2006, Ichikawa *et al.*



Eq. b) In 2006, Ichikawa *et al.*



Scheme 43 Palladium-catalysed 5-*endo-trig* Mizoroki-Heck-type cyclization followed by defluorination

1.4.2 Palladium-catalysed Mizoroki-Heck-type reaction involving fluorine-containing alkenes

So far, several kinds of fluorine-containing alkenes including vinyl-F, vinyl-SO₂F, vinyl-CF₂CF₂Br, vinyl-R_f (R_f = perfluoroalkyl), vinyl-SOR_f, and vinyl-C₆F₅ have been used in Mizoroki-Heck-type reactions; therefore, many valuable fluorine-bearing olefins were constructed.

1.4.2.1 Monofluoroalkenes as coupling partners

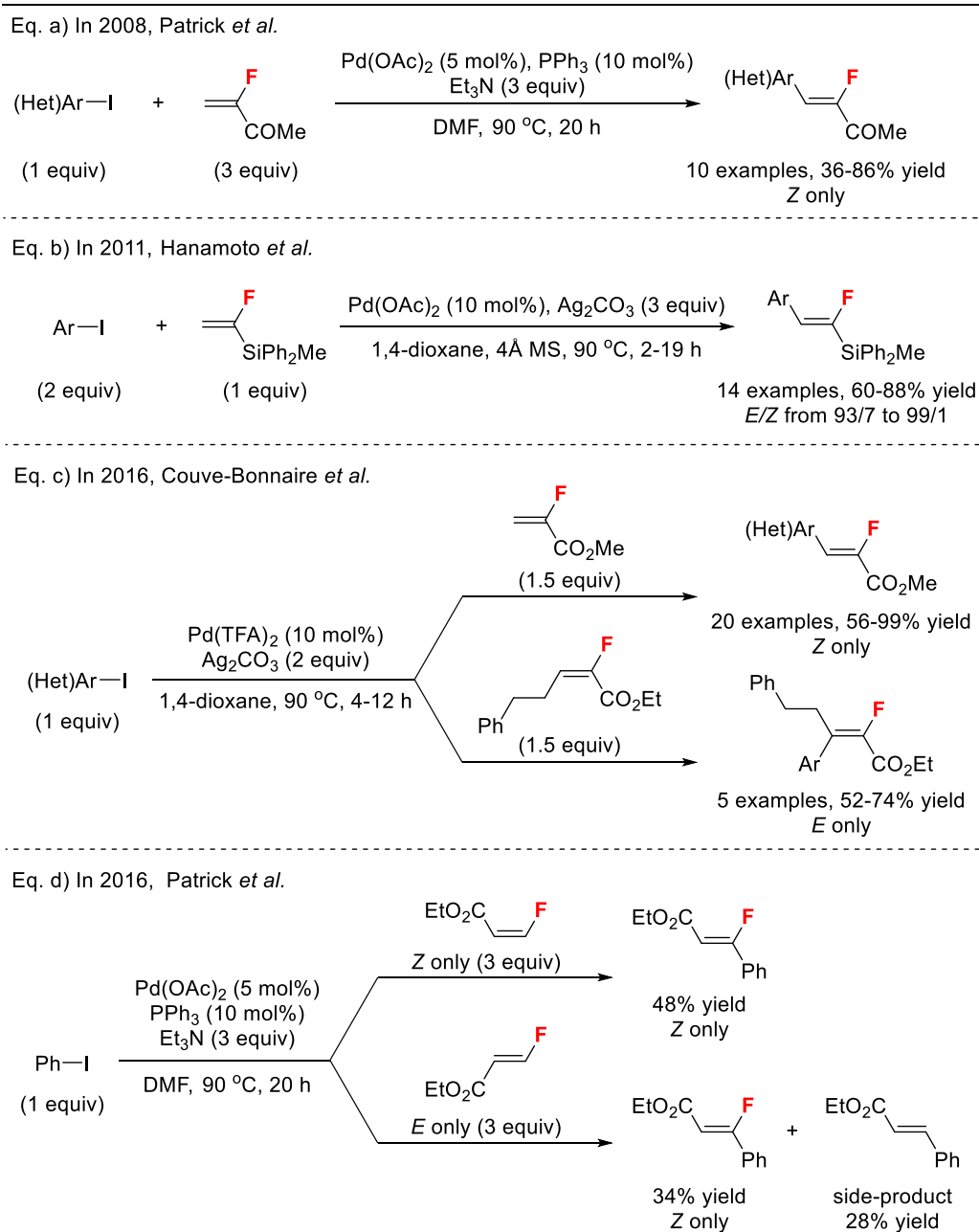
In 2008, Patrick and co-workers reported a Mizoroki-Heck coupling of (hetero)aryl iodides with 3-fluorobut-3-en-2-one in the presence of Pd(OAc)₂, PPh₃, and Et₃N (**Scheme 44**, Eq. a).¹²⁷ Highly stereoselective (*Z*)-3-fluoro-4-arylbut-3-en-2-one were produced in fair to good yields. Neither fluoride elimination nor conjugate addition was observed in this reaction system. Then, Hanamoto and a co-worker achieved the Mizoroki-Heck coupling of iodoarenes with (1-fluorovinyl)methyldiphenylsilane in the presence of Pd(OAc)₂ and Ag₂CO₃ (**Scheme 44**, Eq. b).¹²⁸ The corresponding β-aryl-(α-fluorovinyl)methyldiphenylsilanes were generated in good yields with high *E/Z* selectivity, ranging from 93/7 to 99/1. Later, Couve-Bonnaire and co-workers succeeded in the construction of tri- and tetrasubstituted α-fluoroacrylates by ligand-free Mizoroki-Heck reaction with Pd(TFA)₂ and Ag₂CO₃ (**Scheme 44**, Eq. c).¹²⁹ When methyl α-fluoroacrylate was used as coupling partner, the related trisubstituted α-fluoroacrylates were stereospecifically formed in *Z*-configuration with moderate to excellent yields. By contrast, stereospecific (*E*)-tetrasubstituted α-

¹²⁷ T. B. Patrick, T. Y. Agboka, K. Gorrell, *J. Fluorine Chem.* **2008**, *129*, 983–985.

¹²⁸ K. Hirota, T. Hanamoto, *J. Org. Chem.* **2011**, *76*, 8564–8568.

¹²⁹ K. Rousée, J.-P. Bouillon, S. Couve-Bonnaire, X. Pannecoucke, *Org. Lett.* **2016**, *18*, 540–543.

fluoroacrylates were obtained when more hindered ethyl (*E*)-2-fluoro-5-phenylpent-2-enoate was involved. Shortly after, Patrick and a co-worker investigated the Mizoroki-Heck reaction of ethyl (*Z*)- and (*E*)-3-fluoropropenoate with iodobenzene in the presence of Pd(OAc)₂, PPh₃, and Et₃N (**Scheme 44**, Eq. d).¹³⁰ Both of the conditions provided the regio- and stereo-selective (*Z*)-product in fair yields, but defluorinative side-product was also observed in the case of ethyl (*E*)-3-fluoropropenoate.



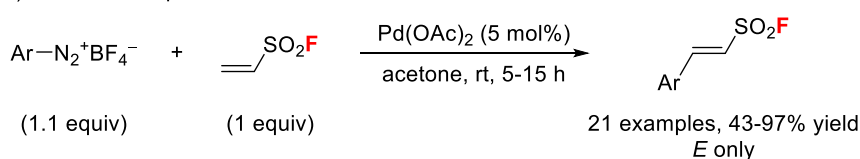
Scheme 44 Mizoroki-Heck reaction with monofluoroalkenes

¹³⁰ T. B. Patrick, A. A. Blay, *J. Fluorine Chem.* **2016**, *189*, 68–69.

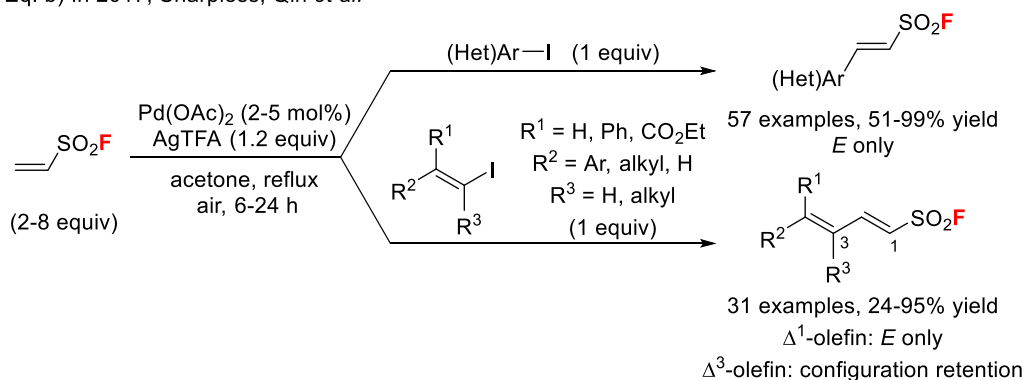
1.4.2.2 Ethenesulfonyl fluoride as the coupling partner

In 2016, Sharpless, Wu, and co-workers achieved the Heck-Matsuda coupling of arenediazonium tetrafluoroborates with ethenesulfonyl fluoride under the catalysis of Pd(OAc)₂, giving access to (*E*)-β-arylethenesulfonyl fluorides, which were effectively used in sulfur(VI) fluoride exchange (SuFEx) click chemistry (**Scheme 45**, Eq. a).¹³¹ Shortly after, the same group synthesized a broad range of (*E*)-β-(hetero)arylethenesulfonyl fluorides and dienylsulfonyl fluorides from ethenesulfonyl fluoride with (hetero)aryl and alkenyl iodides by palladium-catalysed Mizoroki-Heck reaction (**Scheme 45**, Eq. b).¹³² Around the same time, Arvidsson and Qin independently reported the oxidative Mizoroki-Heck coupling of (hetero)aryl

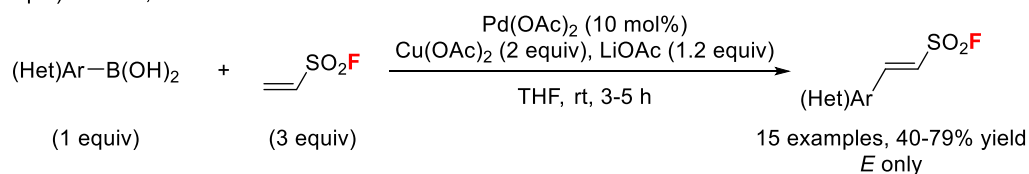
Eq. a) In 2016, Sharpless, Wu *et al.*



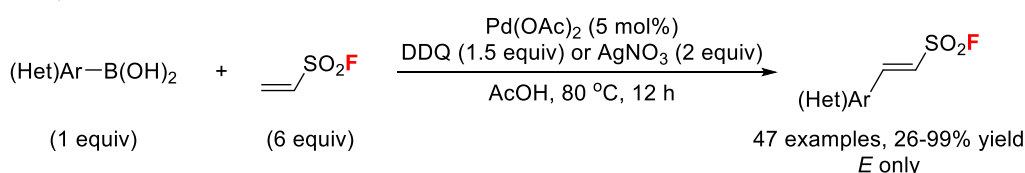
Eq. b) In 2017, Sharpless, Qin *et al.*



Eq. c) In 2017, Arvidsson *et al.*



Eq. d) In 2017, Qin *et al.*



Scheme 45 Mizoroki-Heck-type reaction with ethenesulfonyl fluoride

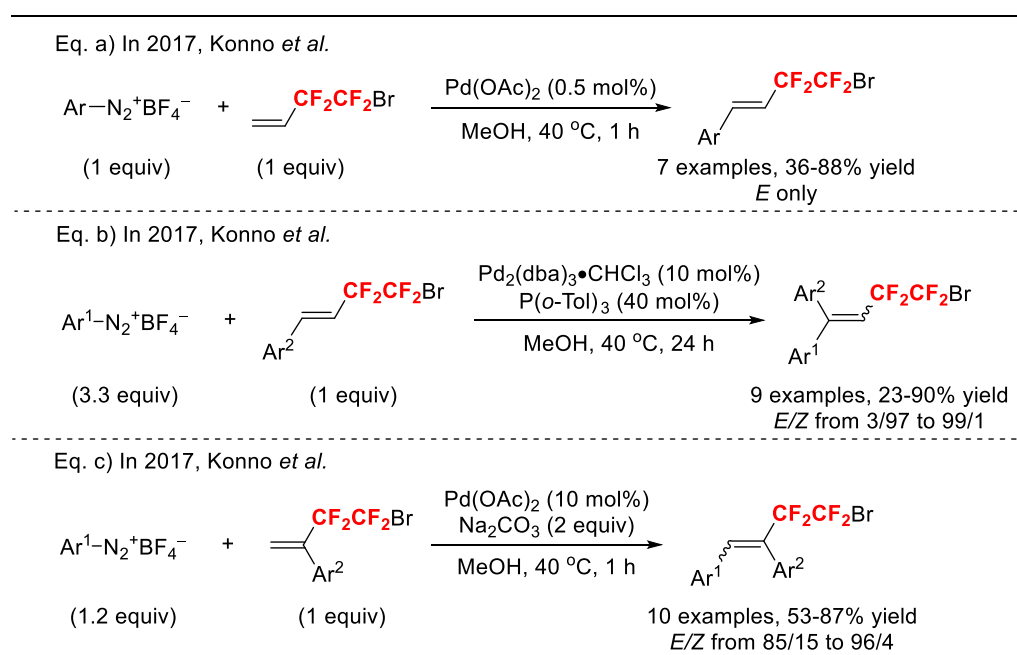
¹³¹ H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2016**, *55*, 14155–14158.

¹³² G.-F. Zha, Q. Zheng, J. Leng, P. Wu, H.-L. Qin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2017**, *56*, 4849–4852.

boronic acids with ethenesulfonyl fluoride in the presence of Pd(OAc)₂ and oxidant, allowing the formation of (*E*)-β-(hetero)arylethanesulfonyl fluorides (**Scheme 45**, Eqs. c-d).¹³³⁻¹³⁴

1.4.2.3 Vinyl-CF₂CF₂Br as coupling partners

In 2017, Konno and co-workers realized the palladium-catalysed Heck-Matsuda coupling of arenediazonium tetrafluoroborates with vinyl-CF₂CF₂Br (**Scheme 46**, Eqs. a-c).¹³⁵ A variety of polysubstituted BrCF₂CF₂-containing alkenes were generated in low to excellent yields with high regio- and stereo-selectivity.



Scheme 46 Heck-Matsuda reaction with vinyl-CF₂CF₂Br

1.4.2.4 Perfluoroalkylalkenes as coupling partners

Trifluoromethylalkenes as coupling partners. In the early 1980s, Ojima and co-workers achieved the palladium-catalysed Mizoroki-Heck coupling of (hetero)aryl and vinyl halides with 3,3,3-trifluoropropene, leading to the formation of the corresponding trifluoromethyl olefins in low to excellent yields with only *E*-configuration (**Scheme 47**, Eq. a).¹³⁶ Fifteen years later, Shi and co-workers used (*Z*)-3,3,3-trifluoro-1-methoxyprop-1-ene as a coupling partner to conduct the Mizoroki-Heck reaction with (hetero)aryl and vinyl halides or triflates under palladium-catalysis (**Scheme 47**, Eq. b).¹³⁷ The related trisubstituted alkenes were obtained in

¹³³ P. K. Chinthakindi, K. B. Govender, A. S. Kumar, H. G. Kruger, T. Govender, T. Naicker, P. I. Arvidsson, *Org. Lett.* **2017**, *19*, 480–483.

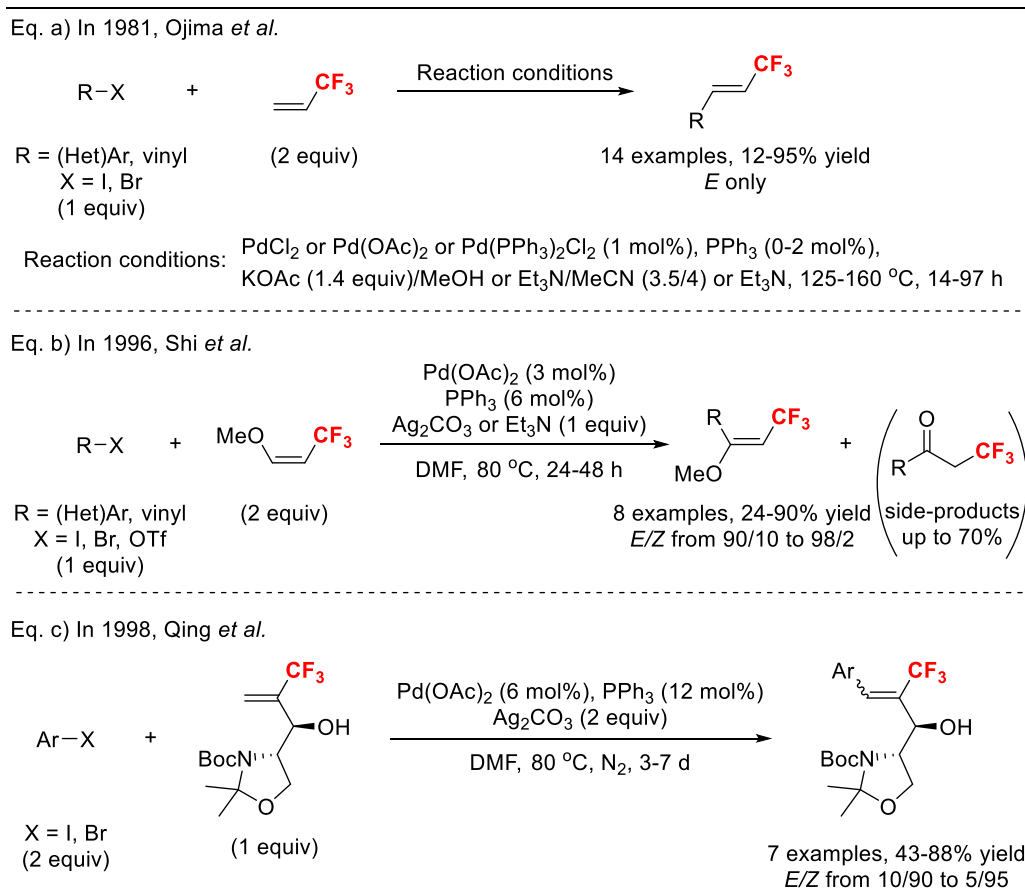
¹³⁴ G.-F. Zha, G. A. L. Bare, J. Leng, Z.-P. Shang, Z. Luo, H.-L. Qin, *Adv. Synth. Catal.* **2017**, *359*, 3237–3242.

¹³⁵ Y. Sakaguchi, S. Yamada, T. Konno, T. Agou, T. Kubota, *J. Org. Chem.* **2017**, *82*, 1618–1631.

¹³⁶ T. Fuchikami, M. Yatabe, I. Ojima, *Synthesis* **1981**, 365–366.

¹³⁷ G.-Q. Shi, X.-H. Huang, F. Hong, *J. Chem. Soc., Perkin Trans. 1* **1996**, 763–765.

low to excellent yields with high *E/Z* ratio (90/10 to 98/2). In some cases, a trifluoromethyl-containing ketone was observed as the side-product. In 1998, Qing and co-workers reported a Mizoroki-Heck coupling of aryl halides with (4*S*)-4-[(1*R*)-1-hydroxy-2-trifluoromethylpropenyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester in the presence of Pd(OAc)₂, PPh₃, and Ag₂CO₃. The corresponding arylated products were constructed in moderate to good yields with *Z* isomer as the major product (**Scheme 47**, Eq. c).¹³⁸ Four other Mizoroki-Heck-type reactions involving trifluoromethylalkenes which were developed after 2000 have been summarized in **Scheme 35** (see page 35).¹⁰⁴⁻¹⁰⁷



Scheme 47 Mizoroki-Heck reaction with trifluoromethylalkenes

Perfluoroalkylalkenes (excluding trifluoromethylalkenes) as coupling partners. The Mizoroki-Heck coupling of aryl halides with perfluoroalkylalkenes was reported by Xiao, Cai, Gladysz and Bazzi groups (**Scheme 48**, Eqs. a-c).¹³⁹⁻¹⁴¹ Several palladium-catalysts including Herrmann-Beller palladacycle, Pd(OAc)₂, and PCP Pincer-Pd complex effectively promoted the cross-coupling reactions, allowing the construction of diverse fluorous ponytail-substituted aromatics. In the conditions

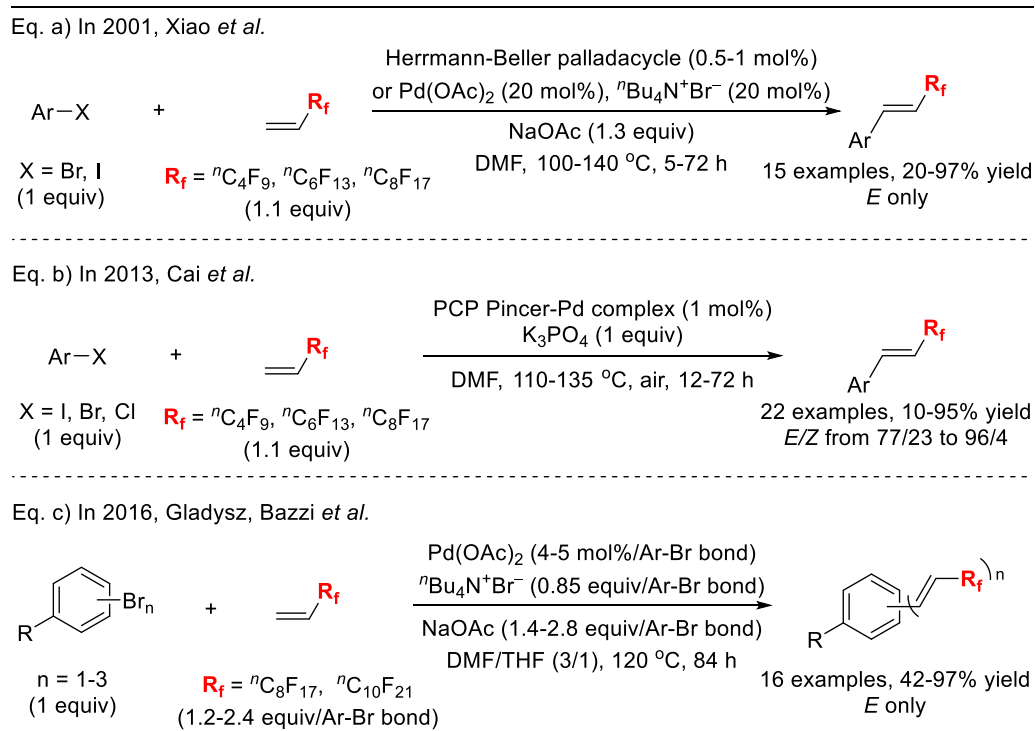
¹³⁸ S. Peng, F.-L. Qing, Y. Guo, *Synlett* **1998**, 859–860.

¹³⁹ W. Chen, L. Xu, J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 4275–4278.

¹⁴⁰ J. Feng, C. Cai, *J. Fluorine Chem.* **2013**, *146*, 6–10.

¹⁴¹ H.-L. Su, J. Balogh, M. Al-Hashimi, D. G. Seapy, H. S. Bazzi, J. A. Gladysz, *Org. Biomol. Chem.* **2016**, *14*, 10058–10069.

with Herrmann-Beller palladacycle or $\text{Pd}(\text{OAc})_2$ as a catalyst, only *E* isomers of the products were obtained (**Scheme 48**, Eqs. a, c). By contrast, when the PCP Pincer-Pd complex was used as catalyst, the *E/Z* ratio of products changed from 77/23 to 96/4 (**Scheme 48**, Eq. b).



Scheme 48 Mizoroki-Heck reaction with perfluoroalkylalkenes

Genêt and Matsugi demonstrated that the installation of perfluoroalkyl tails on aromatic rings could also be achieved by palladium-catalysed Heck-Matsuda reaction with arenediazonium salts and perfluoroalkylalkenes (**Scheme 49**, Eqs. a-b).¹⁴²⁻¹⁴³ The related products were stereospecifically generated in good to excellent yields towards *E*-isomers.

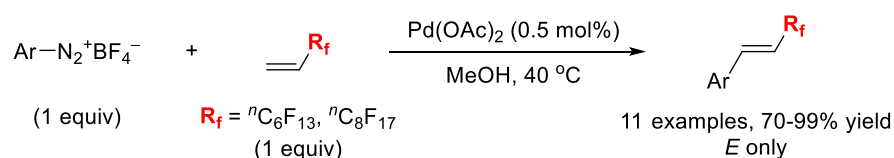
In 2019, Cho and a co-worker reported an oxidative Mizoroki-Heck reaction between aryl boronic acids and perfluoroalkyl alkenes with $\text{Pd}(\text{OAc})_2$ as catalyst and O_2 as oxidant (**Scheme 50**).¹⁴⁴ The corresponding fluorinated ponytail-substituted aromatics were produced in moderate to good yields with only *E*-configuration.

¹⁴² S. Darses, M. Pucheault, J.-P. Genêt, *Eur. J. Org. Chem.* **2001**, 1121–1128.

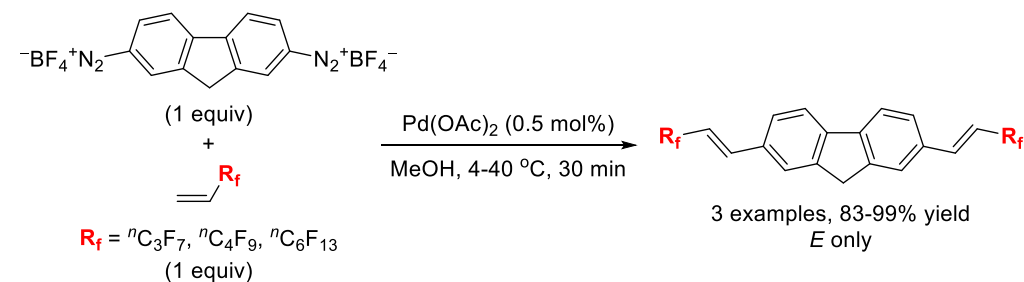
¹⁴³ Y. Sugiyama, N. Endo, K. Ishihara, Y. Kobayashi, H. Hamamoto, T. Shioiri, M. Matsugi, *Tetrahedron* **2015**, *71*, 4958–4966.

¹⁴⁴ D. S. Lee, E. J. Cho, *Org. Biomol. Chem.* **2019**, *17*, 4317–4325.

Eq. a) In 2001, Genêt *et al.*

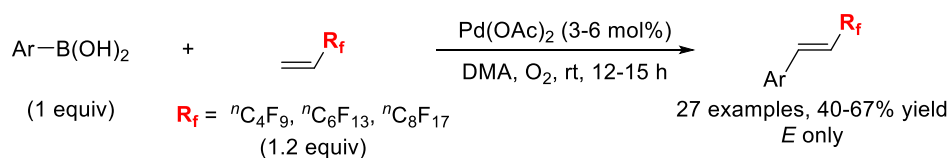


Eq. b) In 2015, Matsugi *et al.*



Scheme 49 Heck-Matsuda reaction with perfluoroalkylalkenes

In 2019, Cho *et al.*

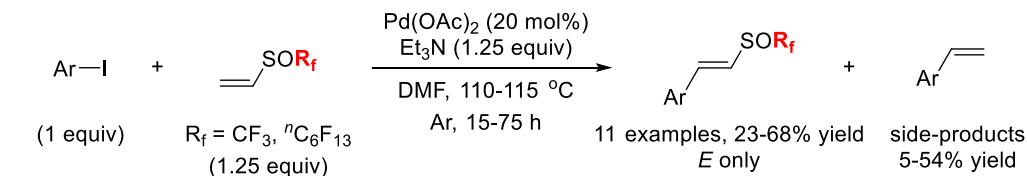


Scheme 50 Oxidative Mizoroki-Heck reaction with perfluoroalkylalkenes

1.4.2.5 Perfluoroalkyl vinyl sulfoxides as coupling partners

In 2015, Sokolenko and co-workers realized the synthesis of (*E*)-1-aryl-2-perfluoroalkylsulfinylethylenes from iodoarenes and perfluoroalkyl vinyl sulfoxides by Mizoroki-Heck reaction in the presence of Pd(OAc)₂ and Et₃N (**Scheme 51**).¹⁴⁵ The desired products were generated in low to moderate yields, and side-products without the perfluoroalkylsulfinyl moiety were also formed.

In 2015, Sokolenko *et al.*

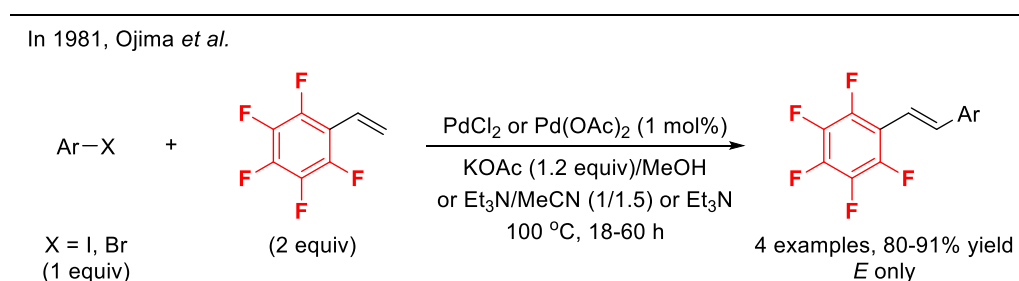


Scheme 51 Mizoroki-Heck reaction with perfluoroalkyl vinyl sulfoxides

¹⁴⁵ L. V. Sokolenko, Y. L. Yagupolskii, Y. G. Vlasenko, L. N. Babichenko, V. O. Lipetskij, E. Anselmi, E. Magnier, *Tetrahedron Lett.* **2015**, *56*, 1259–1262.

1.4.2.6 2,3,4,5,6-Pentafluorostyrene as coupling partner

In 1981, Ojima and co-workers achieved the Mizoroki-Heck coupling of aryl halides with 2,3,4,5,6-pentafluorostyrene under palladium-catalysis (**Scheme 52**).¹³⁶ Four (*E*)-2,3,4,5,6-pentafluorostilbenes were constructed in good to excellent yields.



Scheme 52 Mizoroki-Heck reaction with 2,3,4,5,6-pentafluorostyrene

In addition to the Mizoroki-Heck reaction, we have also been interested in the decarboxylative cross-coupling reactions, and thus next we will introduce the applications of palladium-catalysed decarboxylative cross-coupling reactions in organofluorine chemistry.

1.5 Palladium-catalysed decarboxylative cross-coupling reactions with fluorine-containing carboxylic acids

1.5.1 A brief history of transition metal-catalysed (or -mediated) decarboxylative cross-coupling reactions

Transition metal-catalysed (or -mediated) decarboxylative cross-coupling reactions were developed relatively slowly since the discovery of the first copper-mediated protodecarboxylation in the early 1930s.¹⁴⁶ Around 40 years later, more detailed researches on this process were carried out by Sheppard,^{147a} Cohen,^{147b} as well as Nilsson,^{147c} and organocopper species turned out to be the key intermediate generated after decarboxylation (**Scheme 53**, Eq. a). More importantly, in the 1960s, Nilsson pioneered the redox-neutral decarboxylative cross-coupling reactions between benzoic acids and aryl halides mediated by a nearly stoichiometric amount of copper(I) species.¹⁴⁸ Another 40 years later, inspired by Nilsson's work, Goossen *et al.* greatly improved the redox-neutral decarboxylative cross-coupling reactions through a catalytic way (**Scheme 53**, Eq. b).¹⁴⁹ Besides, Meyers and co-workers

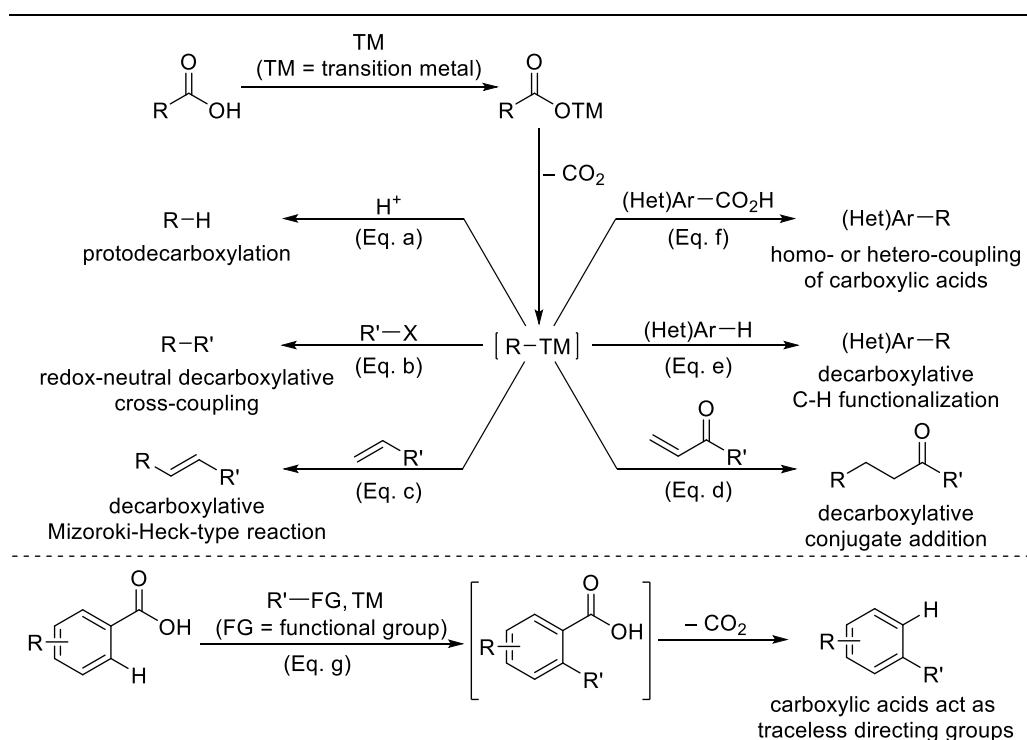
¹⁴⁶ A. F. Shepard, N. R. Winslow, J. R. Johnson, *J. Am. Chem. Soc.* **1930**, *52*, 2083–2090.

¹⁴⁷ (a) A. Cairncross, J. R. Roland, R. M. Henderson, W. A. Sheppard, *J. Am. Chem. Soc.* **1970**, *92*, 3187–3189; (b) T. Cohen, R. A. Schambach, *J. Am. Chem. Soc.* **1970**, *92*, 3189–3190; (c) J. Chodowska-Palicka, M. Nilsson, *Acta Chem. Scand.* **1970**, *24*, 3353–3361.

¹⁴⁸ (a) M. Nilsson, *Acta Chem. Scand.* **1966**, *20*, 423–426; (b) M. Nilsson, C. Ullenius, *Acta Chem. Scand.* **1968**, *22*, 1998–2002; (c) C. Björklund, M. Nilsson, *Acta Chem. Scand.* **1968**, *22*, 2585–2588.

¹⁴⁹ L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664.

opened the door to transition metal-catalysed decarboxylative Mizoroki-Heck-type reaction in 2002 (**Scheme 53**, Eq. c).¹⁵⁰ With these good beginnings, a series of catalytic decarboxylative cross-coupling strategies have been further developed, such as decarboxylative conjugate addition (**Scheme 53**, Eq. d),¹⁵¹ oxidative decarboxylative cross-coupling (**Scheme 53**, Eqs. e-f),¹⁵² and C-H bond functionalization using carboxylic acids as traceless directing groups (**Scheme 53**, Eq. g).¹⁵³ These impressive advances of transition metal-catalysed decarboxylative cross-coupling reactions are even like a reform of the “traditional” transition metal-catalysed cross-coupling reactions.¹⁵⁴



Scheme 53 Transition metal-catalysed (or -mediated) decarboxylative cross-coupling reactions

As versatile building blocks, carboxylic acids exhibit many advantages such as low cost, wide availability, good stability, convenience of handling, and extrusion of CO₂

¹⁵⁰ (a) A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251; (b) D. Tanaka, A. G. Myers, *Org. Lett.* **2004**, *6*, 433–436; (c) D. Tanaka, S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333.

¹⁵¹ Z.-M. Sun, P. Zhao, *Angew. Chem. Int. Ed.* **2009**, *48*, 6726–6730.

¹⁵² G. J. P. Perry, I. Larrosa, *Eur. J. Org. Chem.* **2017**, 3517–3527.

¹⁵³ (a) M. Font, J. M. Quibell, G. J. P. Perry, I. Larrosa, *Chem. Commun.* **2017**, *53*, 5584–5597; (b) Y. Wei, P. Hu, M. Zhang, W. Su, *Chem. Rev.* **2017**, *117*, 8864–8907.

¹⁵⁴ For selected reviews on “traditional” transition metal-catalysed cross-coupling reactions: (a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359–1469; (b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710; (c) C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

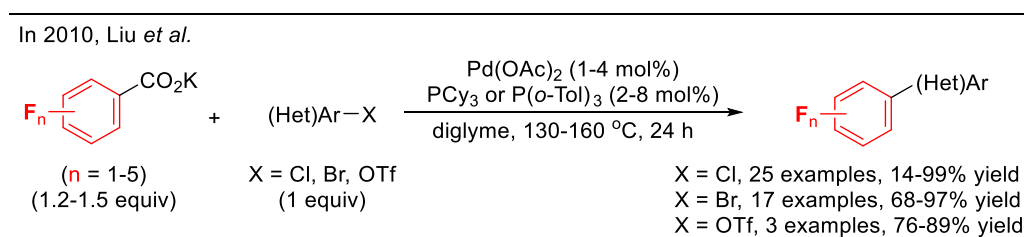
as a readily removed by-product; therefore, it is highly interesting to explore the transition metal-catalysed decarboxylative cross-coupling reactions.^{152-153,155}

1.5.2 Palladium-catalysed decarboxylative cross-coupling reactions using fluorine-containing carboxylic acids

Palladium-catalysed decarboxylative cross-coupling reactions have become a novel tool for the construction of fluorine-containing organic molecules. Polyfluorobenzoic acids proved to be versatile coupling partners in decarboxylative cross-coupling reactions. Trifluoromethyl-substituted aryl carboxylic acids were also investigated in decarboxylation. Besides, two decarboxylative protocols that involved fluorine-bearing acrylic acids were developed as well.

1.5.2.1 Fluorine-containing aryl carboxylic acids as coupling partners

Redox-neutral decarboxylative cross-coupling reaction. In 2010, Liu and co-workers developed a palladium-catalysed method for decarboxylative cross-coupling of potassium polyfluorobenzoates with (hetero)aryl halides or triflates (**Scheme 54**).¹⁵⁶ A broad range of mono-, di-, tri-, tetra-, and penta-fluorinated biaryl products were synthesized in up to 99% yield.



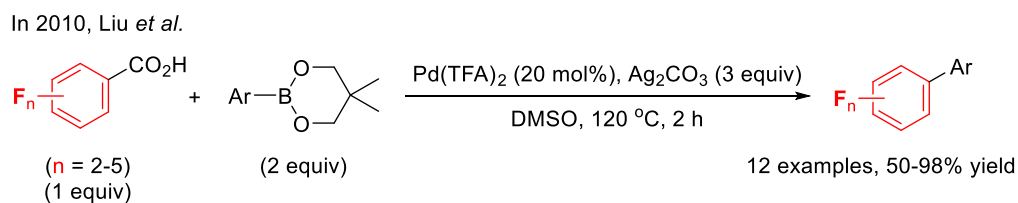
Scheme 54 Redox-neutral decarboxylative cross-coupling reaction with potassium polyfluorobenzoates

Decarboxylative Suzuki-type reaction. Liu and co-workers further developed a palladium-catalysed, silver-mediated protocol for decarboxylative Suzuki-type reactions (**Scheme 55**).¹⁵⁷ With polyfluorobenzoic acids and aryl boronate esters as starting materials, the corresponding di-, tri-, tetra-, and penta-fluorinated biaryl compounds were constructed in moderate to excellent yields.

¹⁵⁵ For recent reviews on transition metal-catalysed decarboxylative cross-coupling reactions with carboxylic acids: (a) L. J. Goossen, N. Rodríguez, K. Goossen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; (b) L. J. Goossen, F. Collet, K. Goossen, *Isr. J. Chem.* **2010**, *50*, 617–629; (c) R. Shang, L. Liu, *Sci. China Chem.* **2011**, *54*, 1670–1687; (d) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; (e) J. Cornella, I. Larrosa, *Synthesis* **2012**, *44*, 653–676; (f) W. I. Dzik, P. P. Lange, L. J. Goossen, *Chem. Sci.* **2012**, *3*, 2671–2678; (g) K. Park, S. Lee, *RSC Adv.* **2013**, *3*, 14165–14182; (h) J. Miao, H. Ge, *Synlett* **2014**, *25*, 911–919; (i) S. Sarhandi, Z. Rahmani, R. Moghadami, M. Vali, E. Vessally, *Chem. Rev. Lett.* **2018**, *1*, 9–15; (j) M. A. Idris, S. Lee, *Synthesis* **2020**, *52*, 2277–2298.

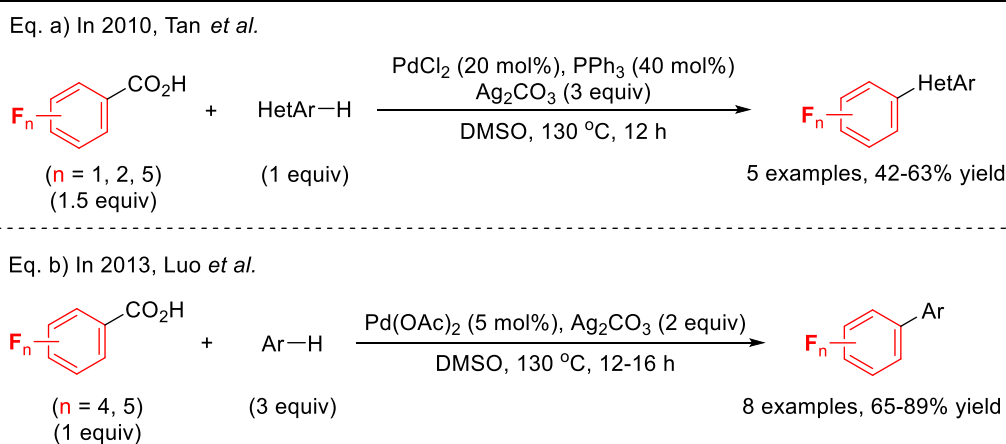
¹⁵⁶ R. Shang, Q. Xu, Y.-Y. Jiang, Y. Wang, L. Liu, *Org. Lett.* **2010**, *12*, 1000–1003.

¹⁵⁷ J.-J. Dai, J.-H. Liu, D.-F. Luo, L. Liu, *Chem. Commun.* **2011**, *47*, 677–679.



Scheme 55 Decarboxylative Suzuki-type reaction with polyfluorobenzoic acids

Decarboxylative C-H bond functionalization. In 2010, Tan and co-workers developed a method for palladium-catalysed, silver-mediated decarboxylative cross-coupling of polyfluorobenzoic acids with heteroarenes, leading to the formation of heteroarylated polyfluoroarenes in moderate yields (**Scheme 56**, Eq. a).¹⁵⁸ Then, Luo and co-workers expanded the substrate scope from heteroarenes to simple arenes, and the corresponding polyfluorobiaryls were obtained in moderate to good yields (**Scheme 56**, Eq. b).¹⁵⁹



Scheme 56 Decarboxylative C-H bond functionalization with polyfluorobenzoic acids

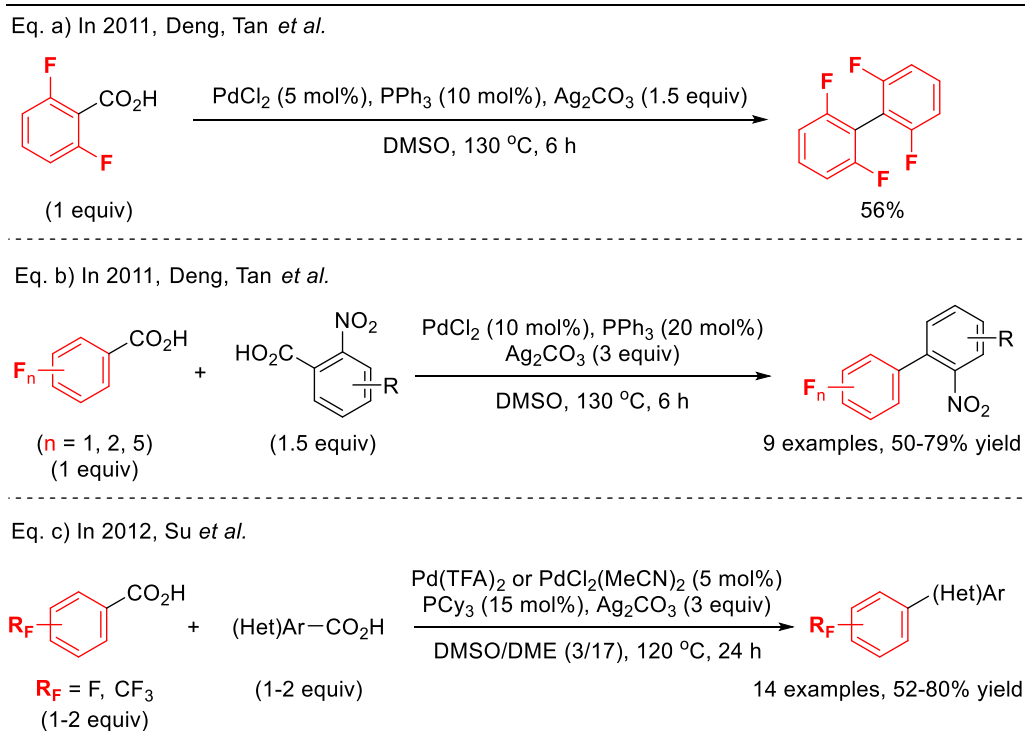
Decarboxylative homo- or hetero-coupling of aryl carboxylic acids. The construction of symmetrical or unsymmetrical biaryl compounds could be achieved by palladium-catalysed decarboxylative homo- or hetero-coupling of aromatic carboxylic acids. In 2011, Deng, Tan, and co-workers reported a protocol for palladium-catalysed, silver-mediated decarboxylative homocoupling of aryl carboxylic acids, and one example for the synthesis of the symmetric *ortho*-fluorinated biaryl compound was shown (**Scheme 57**, Eq. a).¹⁶⁰ The same research group also realized the synthesis of unsymmetric polyfluorobiaryls through decarboxylative heterocoupling of polyfluorobenzoic acids with *ortho*-nitrobenzoic acids in the presence of palladium catalyst and silver base (**Scheme 57**, Eq. b).¹⁶⁰ Mono-, di-, and penta-fluorobiaryl compounds were obtained in moderate to good yields, but homocoupling side-products of both starting materials were observed as well. Shortly after, Su and co-

¹⁵⁸ K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564–1567.

¹⁵⁹ H.-Q. Luo, W. Dong, T.-P. Loh, *Tetrahedron Lett.* **2013**, *54*, 2833–2836.

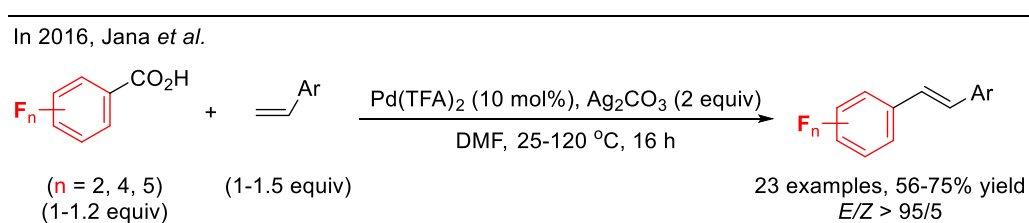
¹⁶⁰ K. Xie, S. Wang, Z. Yang, J. Liu, A. Wang, X. Li, Z. Tan, C.-C. Guo, W. Deng, *Eur. J. Org. Chem.* **2011**, 5787–5790.

workers developed another palladium-catalysed, silver-mediated method for decarboxylative heterocoupling of different carboxylic acids. Many of the fluorine- or trifluoromethyl-containing biaryl compounds were generated in moderate to good yields (**Scheme 57**, Eq. c).¹⁶¹



Scheme 57 Decarboxylative homo- or hetero-coupling of aryl carboxylic acids

Decarboxylative Mizoroki-Heck-type reaction. In 2016, Jana reported a protocol for palladium-catalysed, silver-mediated decarboxylative Mizoroki-Heck-type coupling of polyfluorobenzoic acids with styrenes (**Scheme 58**).¹⁶² Pentafluorobenzoic acid could be converted to the corresponding products at room temperature. However, a high temperature of 120 °C was required to enable the reactions to occur for tetra- and di-fluorobenzoic acids. Moderate to good yields of final products were obtained with excellent *E/Z* selectivity (> 95/5).



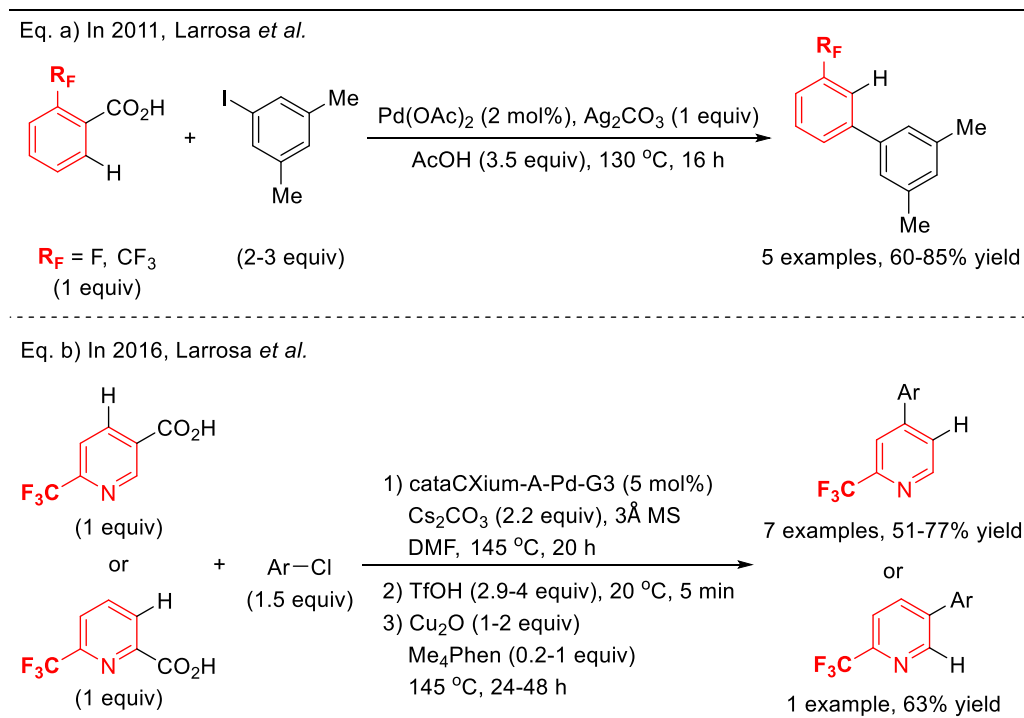
Scheme 58 Decarboxylative Mizoroki-Heck-type reaction with polyfluorobenzoic acids

Carboxylic acids act as traceless directing groups. In 2011, Larrosa and co-workers developed a method for formal *meta* C-H bond arylation using *ortho*-substituted

¹⁶¹ P. Hu, Y. Shang, W. Su, *Angew. Chem. Int. Ed.* **2012**, *51*, 5945–5949.

¹⁶² A. Hossian, S. K. Bhunia, R. Jana, *J. Org. Chem.* **2016**, *81*, 2521–2533.

benzoic acids and aryl iodide in the presence of palladium-catalyst and silver-base. The one-pot tandem *ortho*-arylation and protodecarboxylation resulted in the *meta* C-H bond arylation of fluorine- or trifluoromethyl-substituent (**Scheme 59**, Eq. a).¹⁶³ Besides, the formal C-H bond arylation of pyridine derivatives was also developed with carboxylic acids as traceless directing groups. The palladium-catalysed C-H arylation and copper-mediated protodecarboxylation processes were amenable to diverse CF₃-pyridyl carboxylic acids, affording the corresponding products in moderate to good yields (**Scheme 59**, Eq. b).¹⁶⁴



Scheme 59 Carboxylic acids act as traceless directing groups

1.5.2.2 Fluorine-containing acrylic acids as coupling partners

Compared with fluorine-bearing aryl carboxylic acids, fluorine-containing acrylic acids were much less investigated in transition metal-catalysed decarboxylative cross-coupling reactions, and only two methods were reported.

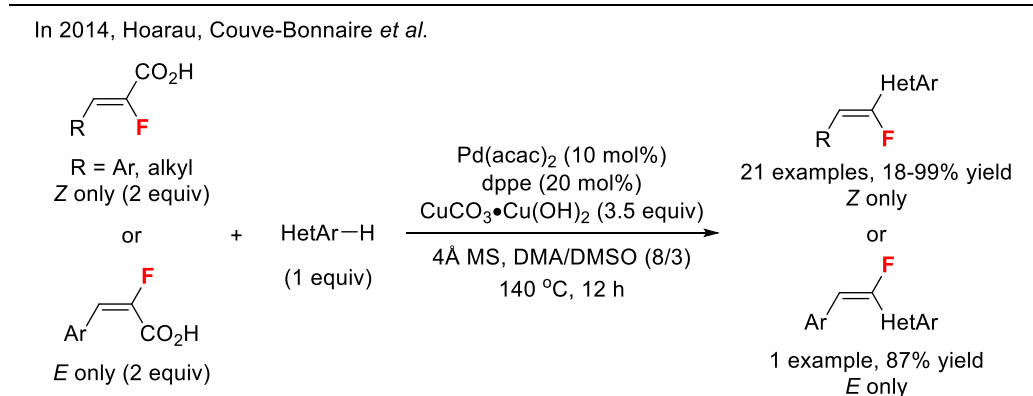
Decarboxylative C-H bond functionalization. In 2014, Hoarau, Couve-Bonnaire, and co-workers reported that the C-H bond functionalization of various heteroarenes could be realized by using β -substituted α -fluoroacrylic acids in the presence of palladium-catalyst and copper-base (**Scheme 60**).¹⁶⁵ When *Z* or *E* isomers of β -substituted α -fluoroacrylic acids were subjected to the reaction conditions, the

¹⁶³ J. Cornella, M. Righi, I. Larrosa, *Angew. Chem. Int. Ed.* **2011**, *50*, 9429–9432.

¹⁶⁴ A. J. S. Johnston, K. B. Ling, D. Sale, N. Lebrasseur, I. Larrosa, *Org. Lett.* **2016**, *18*, 6094–6097.

¹⁶⁵ K. Rousée, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher, C. Hoarau, *Chem. Eur. J.* **2014**, *20*, 1500–1504.

corresponding stereospecific (*Z*)- or (*E*)- α -heteroaryl monofluoroalkenes were constructed in up to 99% yield.



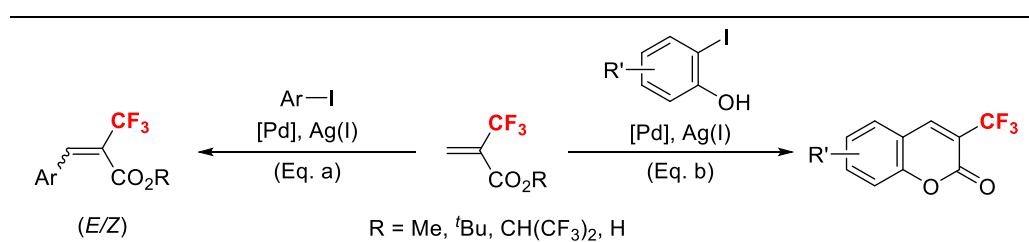
Scheme 60 Decarboxylative C-H bond functionalization with β -substituted α -fluoroacrylic acids

Decarboxylation combined with Mizoroki-Heck reaction. Another method was a combination of decarboxylation with Mizoroki-Heck reaction involving 2-(trifluoromethyl)acrylic acid, and it has been summarized in **Scheme 35**, Eq. c (see page 35).¹⁰⁶

1.6 Objectives

Given that the construction of trifluoromethylalkenes is of high interest (see § 1.2.2), in this Ph.D. thesis, our research aims at the development of new methodologies for the synthesis of trifluoromethyl-substituted alkenes.

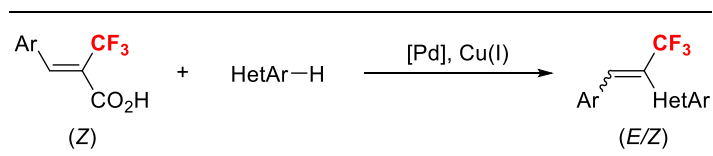
The first objective focuses on the synthesis of 3-aryl-2-(trifluoromethyl)acrylates and acrylic acids by palladium-catalyzed Mizoroki-Heck reaction (**Scheme 61**, Eq. a). At the same time, we would like to achieve the one-pot synthesis of trifluoromethylated coumarin derivatives through the tandem Mizoroki-Heck coupling and intramolecular cyclization (**Scheme 61**, Eq. b).



Scheme 61

The second objective is to perform the palladium-catalysed oxidative decarboxylative cross-coupling of heteroarenes with 3-aryl-2-(trifluoromethyl)acrylic acids, which were rarely investigated in decarboxylative cross-coupling reactions (**Scheme 62**). To our knowledge, only Nicholls used a decarboxylative protocol to get trifluoromethylalkenes from 2-(trifluoromethyl)acrylic acid through a combination of

decarboxylation and Mizoroki-Heck reaction (see page 35, **Scheme 35**, Eq. c).¹⁰⁶ In our case, we would like to develop for the first time an oxidative decarboxylative cross-coupling reaction with 3-aryl-2-(trifluoromethyl)acrylic acids.

**Scheme 62**

Chapter 2

Access to 3-aryl-2-(trifluoromethyl) acrylates by palladium-catalysed Mizoroki-Heck reaction

2 Access to 3-aryl-2-(trifluoromethyl)acrylates by palladium-catalysed Mizoroki-Heck reaction

2.1 State of the art

Among various trifluoromethylalkenes, alkyl 2-(trifluoromethyl)acrylates are valuable comonomers that have been widely used in the synthesis of fluorinated copolymers.¹⁶⁶⁻¹⁶⁷ Materials constructed from these fluorinated comonomers are applicable in the fields of optics, lithography, adsorbents, molecularly imprinted polymers, nanocomposites, multicompartamental micelles, lithium-ion batteries, polymer electrolyte membranes for fuel cell, and protective stone coatings.^{166a} Three examples concerning the applications of alkyl 2-(trifluoromethyl)acrylate copolymers in 157 nm lithography are shown in **Figure 7**.^{166a}

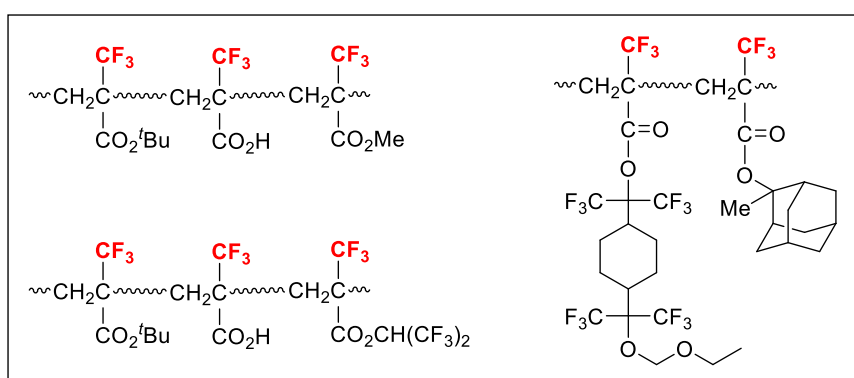


Figure 7 Alkyl 2-(trifluoromethyl)acrylate copolymers for 157 nm lithography

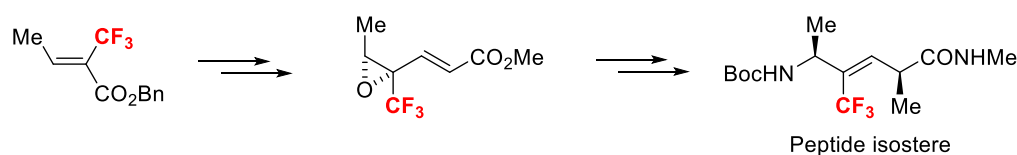
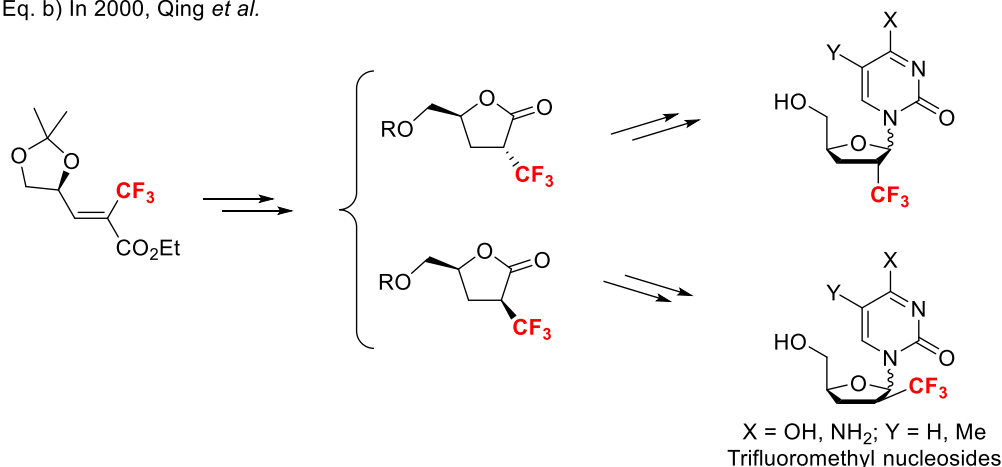
Besides, 3-substituted-2-(trifluoromethyl)acrylates are useful synthetic intermediates for the construction of peptide isosteres and trifluoromethyl nucleosides (**Scheme 63**, Eqs. a-b).^{24a,168}

Although many methodologies have been developed to give access to diverse trifluoromethylalkenes (see page 9, § 1.3), only a few reports, hereafter described, concentrated on the preparation of 3-substituted-2-(trifluoromethyl)acrylates.

¹⁶⁶ For selected reviews: (a) Y. Patil, B. Améduri, *Prog. Polym. Sci.* **2013**, *38*, 703–739; (b) B. Améduri, *Chem. Eur. J.* **2018**, *24*, 18830–18841.

¹⁶⁷ For selected examples: (a) S. Banerjee, V. Ladmiraal, C. Totée, B. Améduri, *Eur. Polym. J.* **2018**, *104*, 164–169; (b) S. Banerjee, M. Guerre, B. Améduri, V. Ladmiraal, *Polym. Chem.* **2018**, *9*, 3511–3521.

¹⁶⁸ X. Zhang, F.-L. Qing, Y. Yu, *J. Org. Chem.* **2000**, *65*, 7075–7082.

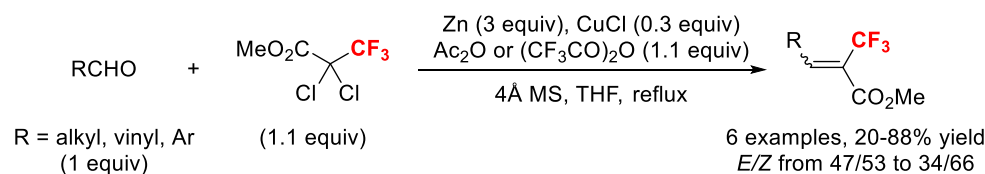
Eq. a) In 1998, Wipf *et al.*Eq. b) In 2000, Qing *et al.***Scheme 63** 3-Substituted-2-(trifluoromethyl)acrylates as useful synthetic intermediates

2.1.1 Carbon-carbon double bond formation reactions

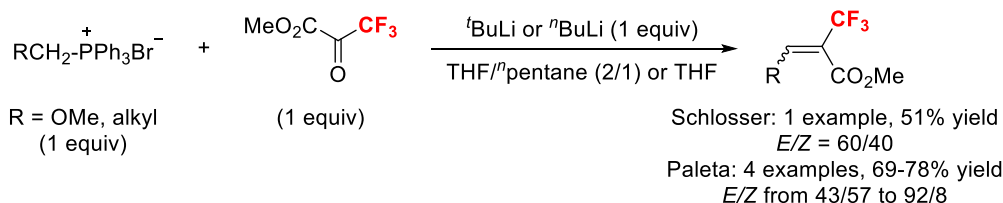
In 1991, Allmendinger and co-worker reported the first general method (based on Reformatsky reaction) for the synthesis of 3-substituted-2-(trifluoromethyl)acrylates from aldehydes and methyl 2,2-dichloro-3,3,3-trifluoropropanoate in the presence of Zn, CuCl, and anhydride, affording the corresponding products in low to good yields with poor *E/Z* selectivity (**Scheme 64**, Eq a).¹⁶⁹ Then, in 2000, Schlosser and co-worker utilized Wittig reaction to give only one specific 3-substituted-2-(trifluoromethyl)acrylate with methyl 3,3,3-trifluoropyruvate as the fluorinated reagent, and moderate yield with low *E/Z* selectivity was obtained (**Scheme 64**, Eq b).¹⁷⁰ Two years later, Paleta and co-workers used a similar protocol to get four other 3-alkyl-2-(trifluoromethyl)acrylates, which exhibited good yields with the *E/Z* ratio changing from 43/57 to 92/8 (**Scheme 64**, Eq b).¹⁷¹ In 2006, Zhu and co-workers developed a copper-catalysed method for the construction of 3-substituted-2-(trifluoromethyl) acrylates using aldehydes and trifluoromethylated diazo compound, providing the desired products in acceptable to good yields with moderate to good *E/Z* selectivity (**Scheme 64**, Eq c).¹⁷²

¹⁶⁹ T. Allmendinger, R. W. Lang, *Tetrahedron Lett.* **1991**, 32, 339–340.¹⁷⁰ J.-N. Volle, M. Schlosser, *Eur. J. Org. Chem.* **2000**, 823–828.¹⁷¹ J. Paleček, J. Kvičala, O. Paleta, *J. Fluorine Chem.* **2002**, 113, 177–183.¹⁷² W. Pang, S. Zhu, H. Jiang, S. Zhu, *Tetrahedron* **2006**, 62, 11760–11765.

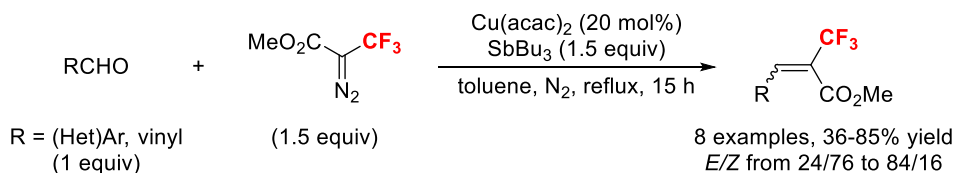
Eq. a) In 1991, Allmendinger *et al.*



Eq. b) In 2000, Schlosser *et al.*; in 2002, Paleta *et al.*



Eq. c) In 2006, Zhu *et al.*



Scheme 64 Carbon-carbon double bond formation reactions to synthesize 3-substituted 2-trifluoromethylacrylates

2.1.2 Trifluoromethylation of acrylates

2.1.2.1 Trifluoromethylation using Chen's reagent (FSO₂CF₂CO₂Me)

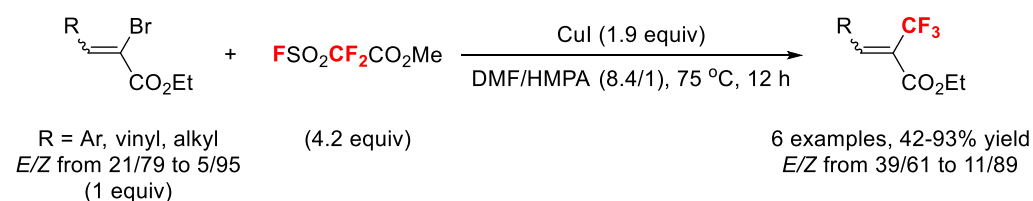
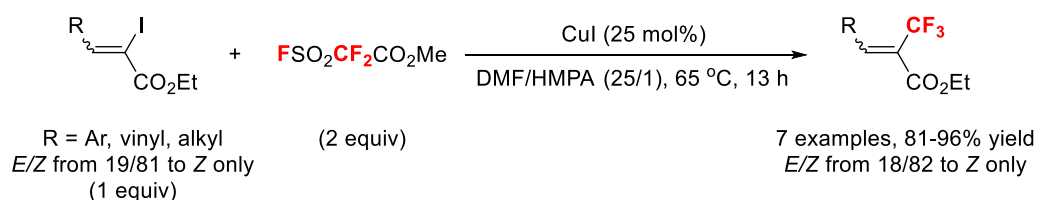
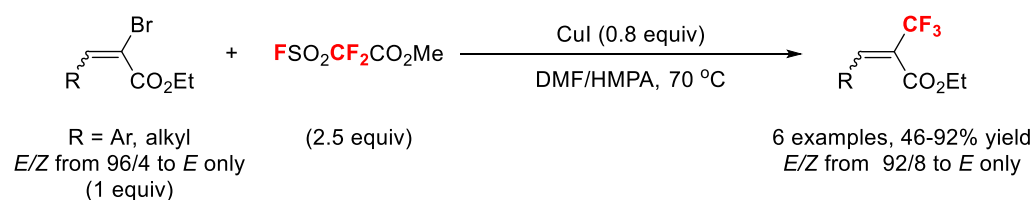
In the early 2000s, Qing and co-workers reported a method for the synthesis of 3-substituted-2-(trifluoromethyl)acrylates through the coupling reaction of 2-bromo (or 2-iodo)-acrylates with CuCF₃ which was generated *in situ* from Chen's reagent (FSO₂CF₂CO₂Me)¹⁷³ and CuI (**Scheme 65**).¹⁷⁴⁻¹⁷⁶ With 2-bromo-acrylates (*Z* major) as substrates, fair to good yields (42-93%) and stereoselectivity (*E/Z* from 39/61 to 11/89) were obtained; by contrast, the yields (81-96%) and stereoselectivity (*E/Z* from 18/82 to *Z* only) were improved when 2-iodo-acrylates (*Z* major) were used as substrates (**Scheme 65**, Eqs. a-b).¹⁷⁴⁻¹⁷⁵ In these reactions, the *E/Z* ratio of vinyl halides largely determined the *E/Z* selectivity of products, and therefore the opposite stereoselectivity (*E/Z* from 92/8 to *E* only) was observed when *E* major isomers of 2-bromo-acrylates were involved instead of the *Z* major ones (**Scheme 65**, Eq. c).¹⁷⁶

¹⁷³ For the first example on Chen's reagent: (a) Q.-Y. Chen, S.-W. Wu, *J. Chem. Soc., Chem. Commun.* **1989**, 705-706. For reviews on Chen's reagent: (b) S. Roy, B. T. Gregg, G. W. Gribble, V.-D. Le, S. Roy, *Tetrahedron* **2011**, *67*, 2161-2195; (c) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Coord. Chem. Rev.* **2014**, *261*, 28-72; (d) S. L. Clarke, G. P. McGlacken, *Chem. Eur. J.* **2017**, *23*, 1219-1230; (e) Q. Xie, J. Hu, *Chin. J. Chem.* **2020**, *38*, 202-212.

¹⁷⁴ X. Zhang, F.-L. Qing, Y. Yang, J. Yu, X.-K. Fu, *Tetrahedron Lett.* **2000**, *41*, 2953-2955.

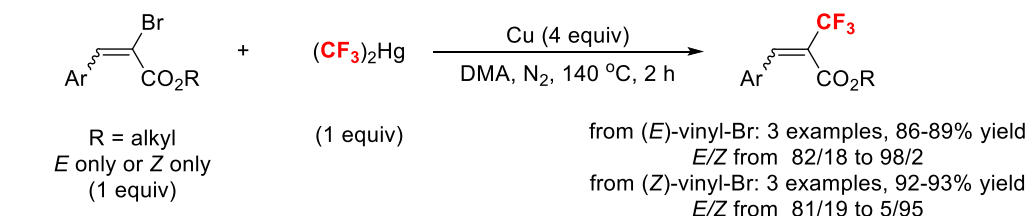
¹⁷⁵ X. Zhang, F.-L. Qing, Y. Peng, *J. Fluorine Chem.* **2001**, *108*, 79-82.

¹⁷⁶ F.-L. Qing, X. Zhang, *Tetrahedron Lett.* **2001**, *42*, 5929-5931.

Eq. a) In 2000, Qing *et al.*Eq. b) In 2001, Qing *et al.*Eq. c) In 2001, Qing *et al.***Scheme 65** Trifluoromethylation of 2-bromo (or 2-iodo)-acrylates using Chen's reagent

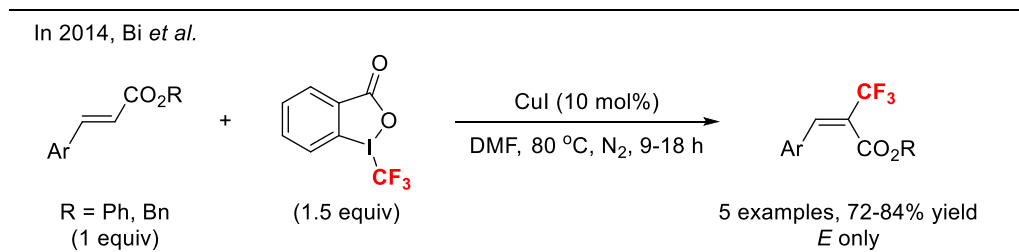
2.1.2.2 Trifluoromethylation using $(\text{CF}_3)_2\text{Hg}$

In 2007, Robins and a co-worker demonstrated that the CuCF_3 species could also be generated *in situ* from $(\text{CF}_3)_2\text{Hg}$ and copper powder, and the resulting CuCF_3 reacted with 2-bromo-acrylates to provide 3-aryl-2-(trifluoromethyl)acrylates (**Scheme 66**).¹⁷⁷ When *E* isomers of 2-bromo-acrylates were used as substrates, the related products were obtained with *E* isomers as the major products; however, when starting from *Z* isomers of 2-bromo-acrylates, the *E/Z* ratio of products varied from 81/19 to 5/95. The *E/Z* selectivity seemed to be influenced by the nature of the ester group and the aromatic ring.

In 2007, Robins *et al.***Scheme 66** Trifluoromethylation of 2-bromo-acrylates using $(\text{CF}_3)_2\text{Hg}$ ¹⁷⁷ I. Nowak, M. J. Robins, *J. Org. Chem.* **2007**, *72*, 2678–2681.

2.1.2.3 Trifluoromethylation using Togni's reagent II

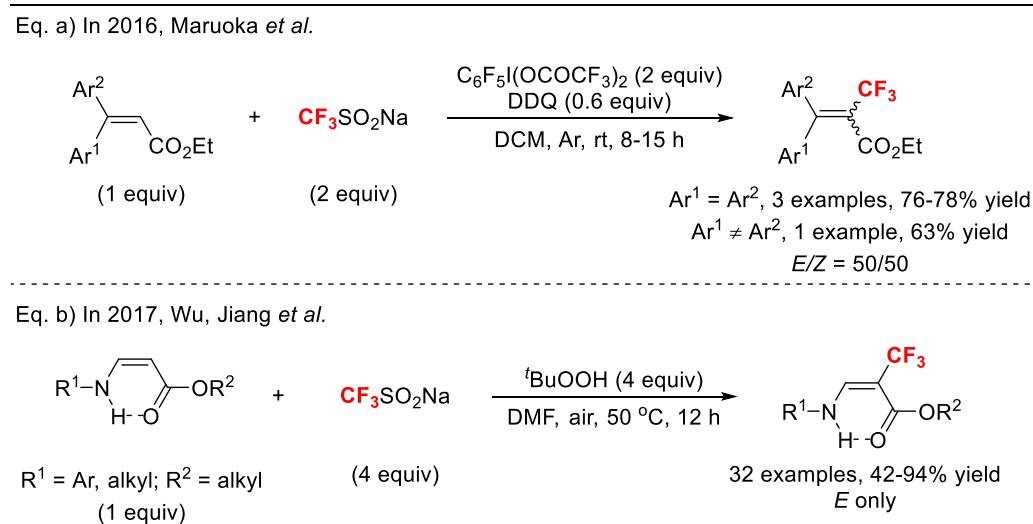
In 2014, Bi and co-workers achieved the olefinic C-H trifluoromethylation of 3-aryl-acrylates using Togni's reagent II under copper-catalysis. Five 3-aryl-2-(trifluoromethyl)acrylates were constructed in good yields with only *E*-configuration (**Scheme 67**).³⁶



Scheme 67 Olefinic C-H trifluoromethylation of acrylates using Togni's reagent II

2.1.2.4 Trifluoromethylation using Langlois reagent (CF₃SO₂Na)

In 2016, Maruoka and co-workers developed a method for olefinic C-H trifluoromethylation of acrylates using Langlois reagent (CF₃SO₂Na) with hypervalent iodine (III) reagent and DDQ as oxidants (**Scheme 68**, Eq. a).¹⁷⁸ The corresponding 3,3-diaryl-2-(trifluoromethyl)acrylates were produced in good yields, and the *E/Z* mixture of one product was obtained when two aryl groups were different. Then, Wu, Jiang, and co-workers achieved the synthesis of various 3-amino-2-(trifluoromethyl)acrylates from 3-amino-acrylates and CF₃SO₂Na with ^tBuOOH as oxidant (**Scheme 68**, Eq. b).¹⁷⁹ The stereospecific *E*-products were constructed thanks to the intramolecular hydrogen bonding between N-H and C=O moieties.



Scheme 68 Olefinic C-H trifluoromethylation of acrylates using Langlois reagent

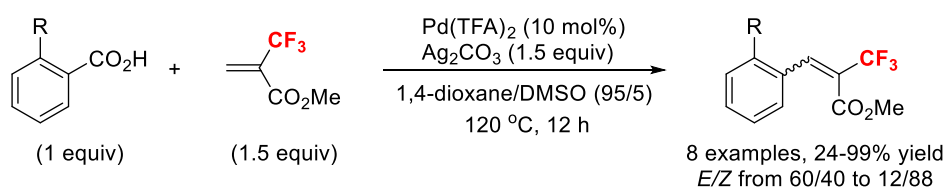
¹⁷⁸ R. Sakamoto, H. Kashiwagi, S. Selvakumar, S. A. Moteki, K. Maruoka, *Org. Biomol. Chem.* **2016**, *14*, 6417–6421.

¹⁷⁹ H. Jiang, W. Huang, Y. Yu, S. Yi, J. Li, W. Wu, *Chem. Commun.* **2017**, *53*, 7473–7476.

2.1.3 Decarboxylative Mizoroki-Heck reaction

In 2018, our group reported a decarboxylative Mizoroki-Heck reaction between aryl carboxylic acids and methyl 2-(trifluoromethyl)acrylate in the presence of palladium catalyst and silver base (**Scheme 69**).¹⁸⁰ 3-Aryl-2-(trifluoromethyl)acrylates were synthesized in low to excellent yields with *E/Z* ratio ranging from 60/40 to 12/88. Unfortunately, the substrate scope was only limited to *ortho*-substituted benzoic acids and low yields were obtained when electron-deficient groups were involved in the aryl substrates.

In 2018, Couve-Bonnaire, Bouillon *et al.*

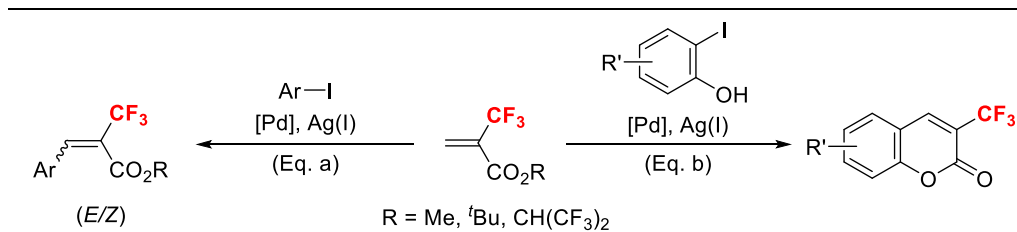


Scheme 69 Decarboxylative Mizoroki-Heck reaction using methyl 2-(trifluoromethyl)acrylate

2.2 Objectives

For the above-mentioned methods to give access to 3-substituted-2-(trifluoromethyl)acrylates, most of them showed limited substrate scope. Some methods used relatively unstable or highly toxic starting materials or required multistep synthesis of substrates and/or reagents. Besides, compared with the strategies of carbon-carbon double bond formation and trifluoromethylation of acrylates, the methodologies involving the direct use of commercially available 2-(trifluoromethyl)acrylates were much less explored.

In this context, at the beginning of my thesis, we aimed at the synthesis of 3-aryl-2-(trifluoromethyl)acrylates from aryl iodides and 2-(trifluoromethyl)acrylates by palladium-catalysed Mizoroki-Heck reaction (**Scheme 70**, Eq.a). We also wanted to explore the one-pot synthesis of trifluoromethylated coumarin derivatives by tandem Mizoroki-Heck reaction and intramolecular cyclization (**Scheme 70**, Eq. b).



Scheme 70

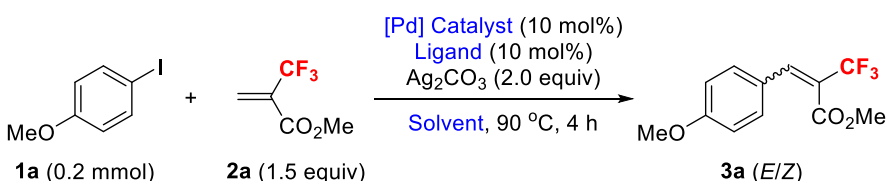
¹⁸⁰ O. Bouazzaoui, K. Rousée, J. K. Mulengi, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *Eur. J. Org. Chem.* **2018**, 3705–3715.

2.3 Access to methyl 3-aryl-2-(trifluoromethyl)acrylates by Mizoroki-Heck reaction with Pd(TFA)₂ and AgOTf

2.3.1 Optimization of reaction conditions

At the beginning of our investigation, 4-iodoanisole (**1a**) and methyl 2-(trifluoromethyl)acrylate (**2a**) were used as the model substrate and fluorine-containing reagent, respectively. The first attempt of the Mizoroki-Heck coupling was conducted in the presence of Pd(TFA)₂ and Ag₂CO₃ with 1,4-dioxane as a solvent, which proved to be effective conditions for the synthesis of tri- or tetrasubstituted 2-fluoroacrylates.¹²⁹ An encouraging result was obtained with the desired product (**3a**) formed in 86% ¹⁹F NMR yield with an *E/Z* ratio of 76/24 (Table 4, entry 1). Then, a series of polar and non-polar solvents were tested instead of 1,4-dioxane (Table 4, entries 2-7). The less polar solvent toluene gave a higher yield, but with a lower *E/Z* selectivity (Table 4, entry 4); the other tested solvents did not give better results in both of the yield and *E/Z* selectivity when compared with 1,4-dioxane (Table 4, entries 1-3, 5-7). A screening of palladium-catalyst showed that the more

Table 4 Screening of solvent, palladium-catalyst, and ligand with Ag₂CO₃ as base^a



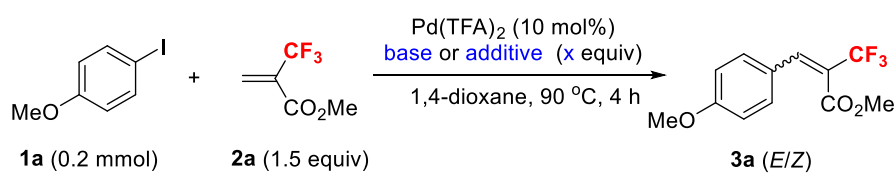
| Entry | Solvent | [Pd] Catalyst | Ligand | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-----------------|-------------------------|------------------------------------|--|--|-------------------------------|
| 1 | 1,4-dioxane | Pd(TFA) ₂ | — | 86% | 76/24 |
| 2 | DMF | Pd(TFA) ₂ | — | 16% | 60/40 |
| 3 | 1,4-dioxane/DMSO (95/5) | Pd(TFA) ₂ | — | 24% | 72/28 |
| 4 | toluene | Pd(TFA) ₂ | — | 93% | 66/34 |
| 5 | heptane | Pd(TFA) ₂ | — | 29% | 68/32 |
| 6 | chlorobenzene | Pd(TFA) ₂ | — | 79% | 65/35 |
| 7 | 1,2-dichloroethane | Pd(TFA) ₂ | — | 57% | 64/36 |
| ----- | | | | | |
| 8 | 1,4-dioxane | Pd(OAc) ₂ | — | 22% | 74/26 |
| 9 | 1,4-dioxane | PdBr ₂ | — | 4% | — |
| 10 | 1,4-dioxane | Pd(PPh ₃) ₄ | — | 3% | — |
| ----- | | | | | |
| 11 ^d | 1,4-dioxane | Pd(TFA) ₂ | — | 77% | 78/22 |
| 12 ^d | 1,4-dioxane | Pd(TFA) ₂ | PPh ₃ | 83% | 64/36 |
| 13 ^d | 1,4-dioxane | Pd(TFA) ₂ | dppe | 81% | 69/31 |
| 14 ^d | 1,4-dioxane | Pd(TFA) ₂ | PCy ₃ •HBF ₄ | 90% | 75/25 |
| 15 ^d | 1,4-dioxane | Pd(TFA) ₂ | P ^t Bu ₃ •HBF ₄ | 5% | — |
| 16 ^d | 1,4-dioxane | Pd(TFA) ₂ | Xantphos | 73% | 57/43 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), [Pd] catalyst (10 mol%), Ag₂CO₃ (2.0 equiv), solvent (1.0 mL), 90 °C, 4 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dAg₂CO₃ (1.0 equiv).

electrophilic Pd(TFA)₂ gave much higher yield than Pd(OAc)₂, PdBr₂, and Pd(PPh₃)₄ (**Table 4**, entries 1, 8-10). Subsequently, the effect of the ligand on *E/Z* selectivity was investigated. Some monodentate and bidentate phosphine ligands were added to the reaction systems; however, no better selectivity was observed in the presence of ligand than without ligand (**Table 4**, entries 11-16).

In addition to Ag₂CO₃ (**Table 5**, entry 6), other bases including Et₃N, K₂CO₃, and copper-bases were tested as well, but very low yields were obtained for all of these conditions (**Table 5**, entries 1-5). Silver cation seems to be essential for the success of the reaction; thus, more silver(I) additives were investigated (**Table 5**, entries 7-11). Most of the silver(I) additives could afford **3a** in good yields, and among them, AgOTf provided the highest yield of **3a** with no decrease of *E/Z* selectivity (**Table 5**, entry 11). The combination of AgOTf with organic or inorganic base inhibited the reaction to some extent (**Table 5**, entries 12-13). Besides, in the absence of base or additive, the yield of **3a** decreased dramatically even if the reaction time was extended to 24 h (**Table 5**, entry 14).

Table 5 Screening of base or additive^a



| Entry | base or additive (x equiv) | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-----------------|--|--|-------------------------------|
| 1 | Et ₃ N (2.0) | 15% | 67/33 |
| 2 | K ₂ CO ₃ (2.0) | 17% | 67/33 |
| 3 | CuCO ₃ •Cu(OH) ₂ (2.0) | 18% | 82/18 |
| 4 | Cu(OAc) ₂ (2.0) | 10% | 67/33 |
| 5 | CuOAc (2.0) | 5% | — |
| ----- | | | |
| 6 | Ag ₂ CO ₃ (2.0) | 86% | 76/24 |
| 7 | AgOAc (2.0) | 74% | 74/26 |
| 8 | AgNO ₃ (2.0) | 34% | 76/24 |
| 9 | AgTFA (2.0) | 86% | 77/23 |
| 10 | Ag ₃ PO ₄ (2.0) | 63% | 70/30 |
| 11 | AgOTf (2.0) | 93% | 77/23 |
| ----- | | | |
| 12 | AgOTf/Et ₃ N (1.5/2.0) | 40% | 58/42 |
| 13 | AgOTf/K ₂ CO ₃ (0.5/1.0) | 68% | 72/28 |
| 14 ^d | — | 19% | 78/22 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), 1,4-dioxane (1.0 mL), 90 °C. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^d24 h.

It is worth noting that 4-iodoanisole could react very fast with **2a** in the presence of AgOTf and enabled the reaction to be completed in 5 minutes (**Table 6**, entries 1-3). However, some other substrates (e.g. 3-OMe-C₆H₄I or 4-CN-C₆H₄I) reacted slower

than 4-iodoanisole, and therefore 2 hours was chosen as a suitable reaction time (**Table 6**, entries 4-7).

Table 6 Screening of reaction time^a

| Entry | Ar | t | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|----------------|-------------------------------------|-------|--|------------------------|
| 1 ^d | 4-OMe-C ₆ H ₄ | 4 h | 93% | 77/23 |
| 2 | 4-OMe-C ₆ H ₄ | 2 h | 93% | 76/24 |
| 3 | 4-OMe-C ₆ H ₄ | 5 min | 93% | 75/25 |
| 4 | 3-OMe-C ₆ H ₄ | 5 min | 34% | 71/29 |
| 5 | 3-OMe-C ₆ H ₄ | 2 h | 90% | 72/28 |
| 6 ^e | 4-CN-C ₆ H ₄ | 5 min | 39% | 64/36 |
| 7 ^e | 4-CN-C ₆ H ₄ | 2 h | 89% | 64/36 |

^aReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL). ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dAgOTf (0.4 mmol, 2.0 equiv). ^eAgOTf (0.2 mmol, 1.0 equiv).

Then, the effect of reaction temperature on this Mizoroki-Heck reaction was explored. It is clear that an increase of temperature to 110 °C or a decrease of temperature to 60 °C gave the yield and E/Z ratio comparable to that of 90 °C (**Table 7**, entries 1-4). However, the reaction efficiency was greatly reduced when the reaction was carried out at room temperature (**Table 7**, entry 5). Considering that **1a** was one of the most reactive substrates, 90 °C was selected as an appropriate reaction temperature to ensure the reactivity of other substrates.

Table 7 Screening of reaction temperature^a

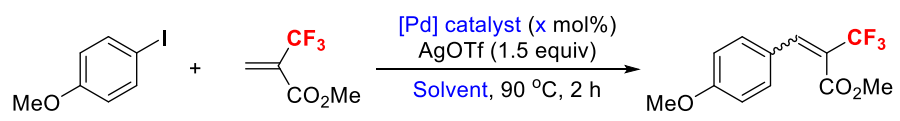
| Entry | T (°C) | t | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|-------|--------|-----|--|------------------------|
| 1 | 110 | 2 h | 90% | 77/23 |
| 2 | 90 | 2 h | 93% | 76/24 |
| 3 | 70 | 2 h | 93% | 75/25 |
| 4 | 60 | 4 h | 90% | 74/26 |
| 5 | rt | 4 h | 36% | 70/30 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL). ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

2.3.2 Comparison of different effects of Ag₂CO₃ and AgOTf on the reaction system

Given that AgOTf cannot be taken as a base but more as a halogen scavenger,¹⁸¹ enabling the generation of cationic palladium intermediate, we speculated that a highly polar solvent should be advantageous for the reaction because it could stabilize the above-mentioned intermediate. As expected, with AgOTf, DMF provided a higher yield (98%) than 1,4-dioxane (93%), albeit with a lower *E/Z* selectivity (**Table 8**, entries 1-2). On the contrary, the less polar solvent toluene gave a poor yield (29%) with no decrease of *E/Z* selectivity (**Table 8**, entry 3). The results of solvents exhibit an opposite reaction trend between Ag₂CO₃ and AgOTf (**Table 4**, entries 1, 2-4; **Table 8**, entries 1-3), probably suggesting a different reaction mechanism between these two silver(I) additives. Further exploration of palladium catalysts in

Table 8 Exploring the effect of AgOTf on the reaction system^a



| Entry | Solvent | [Pd] catalyst (x mol%) | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-----------------|-------------|---|--|-------------------------------|
| 1 | 1,4-dioxane | Pd(TFA) ₂ (10) | 93% (86%) ^d | 76/24 |
| 2 | DMF | Pd(TFA) ₂ (10) | 98% | 64/36 |
| 3 | toluene | Pd(TFA) ₂ (10) | 29% | 77/23 |
| 4 | 1,4-dioxane | Pd(OAc) ₂ (10) | 91% (84%) ^d | 76/24 |
| 5 | 1,4-dioxane | PdBr ₂ (10) | 87% | 74/26 |
| 6 | 1,4-dioxane | Pd(acac) ₂ (10) | 78% | 76/24 |
| 7 | 1,4-dioxane | Pd(PPh ₃) ₄ (10) | 59% | 75/25 |
| 8 | 1,4-dioxane | Pd(dba) ₂ (10) | traces | — |
| 9 | 1,4-dioxane | Pd ₂ (dba) ₃ (5) | traces | — |
| 10 ^e | 1,4-dioxane | Pd(TFA) ₂ (10) | 72% | 76/24 |
| 11 ^f | 1,4-dioxane | Pd(TFA) ₂ (10) | 93% | 76/24 |
| 12 ^g | 1,4-dioxane | Pd(TFA) ₂ (10) | 62% | 78/22 |
| 13 | 1,4-dioxane | Pd(TFA) ₂ (1.5) | 92% (86%) ^d | 76/24 |
| 14 | 1,4-dioxane | Pd(TFA) ₂ (0.5) | 90% (84%) ^d | 76/24 |
| 15 | 1,4-dioxane | Pd(TFA) ₂ (0.1) | 81% | 74/26 |
| 16 ^h | 1,4-dioxane | Pd(TFA) ₂ (1.5) | 15% | 78/22 |
| 17 | 1,4-dioxane | — | 0 | — |

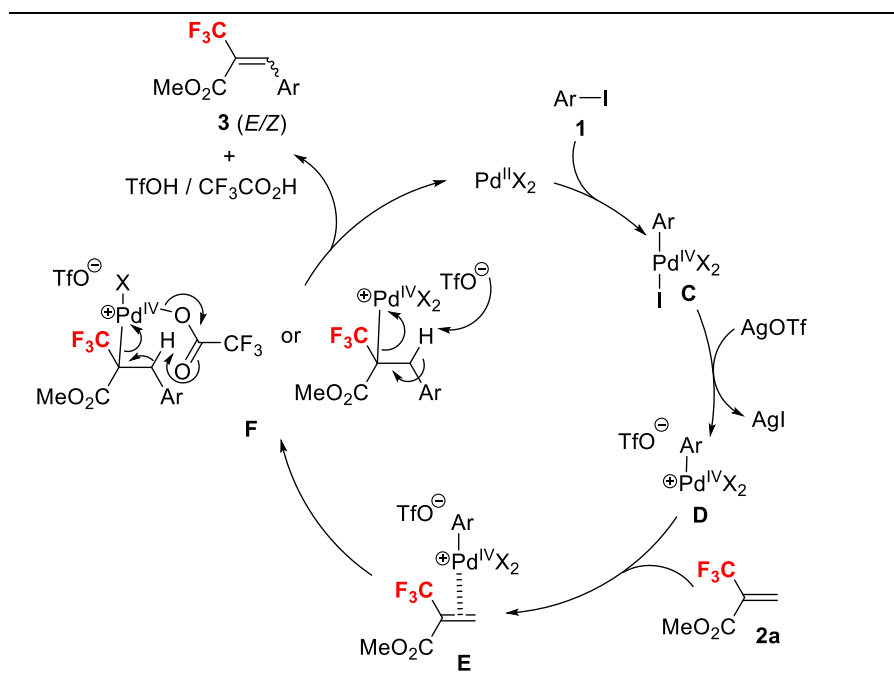
^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), [Pd] catalyst, AgOTf (0.3 mmol, 1.5 equiv), solvent (1.0 mL), 90 °C, 2 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dIsolated yield. ^ePPh₃ (30 mol%). ^fP^tBu₃•HBF₄ (30 mol%). ^gdppe (15 mol%). ^hAg₂CO₃ (0.4 mmol, 2.0 equiv), 4 h.

¹⁸¹ (a) K. Karabelas, A. Hallberg, *J. Org. Chem.* **1988**, *53*, 4909–4914; (b) J.-M. Weibel, A. Blanc, P. Pale, *Chem. Rev.* **2008**, *108*, 3149–3173; (c) J.-M. Weibel, A. Blanc, P. Pale, in *Silver in Organic Chemistry* (Ed.: M. Harmata), John Wiley & Sons, Inc.: Hoboken, NJ, **2010**, pp. 297–310.

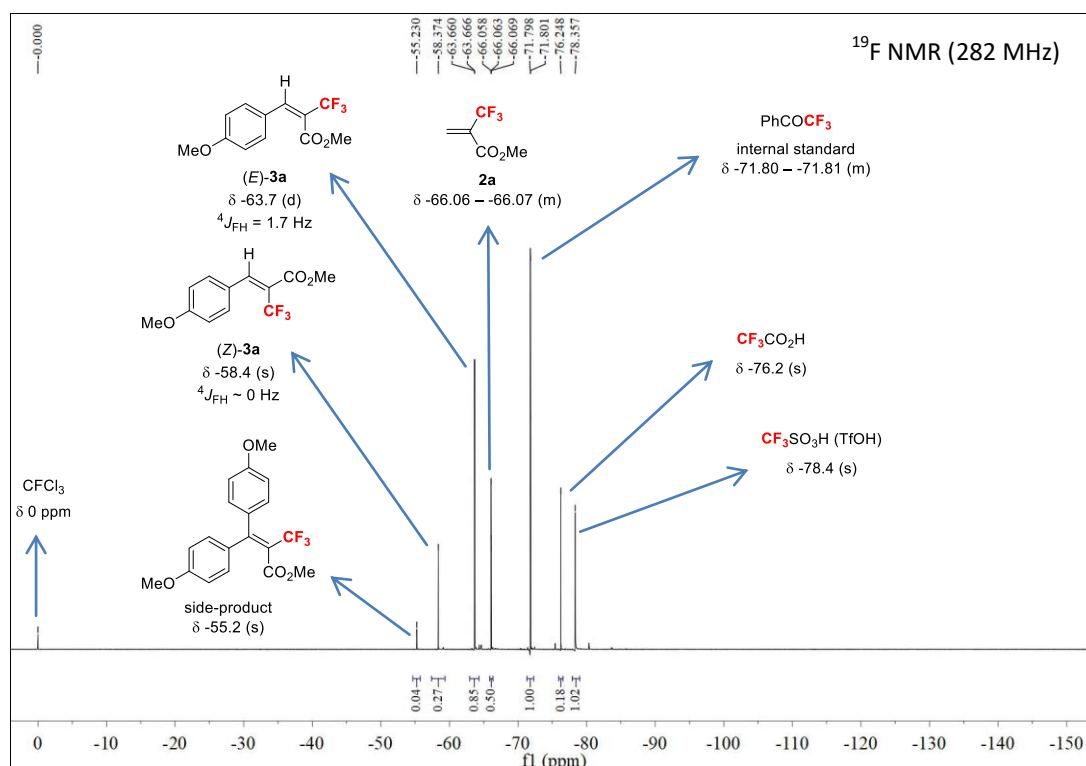
the presence of AgOTf provided more evidence for this hypothesis (**Table 4**, entries 1, 8-10; **Table 8**, entries 1, 4-7). With AgOTf, a good yield of **3a** was also obtained when Pd(OAc)₂, PdBr₂, or Pd(acac)₂ was used as catalyst instead of the more electrophilic Pd(TFA)₂ (**Table 8**, entries 1, 4-6). The yield decreased a lot when Pd(PPh₃)₄, a Pd(0) catalyst, was utilized (**Table 8**, entry 7). What's more, only traces of product was formed in the cases of Pd(0) catalysts without stabilization of phosphine ligand (**Table 8**, entries 8-9). Attempts to improve the *E/Z* selectivity by addition of phosphine ligands (PPh₃, P^tBu₃•HBF₄, or dppe) proved to be almost ineffective (**Table 8**, entries 10-12). The yield and *E/Z* selectivity of **3a** could be kept almost the same when the catalyst loading of Pd(TFA)₂ was decreased to 1.5 mol% or even 0.5 mol% with AgOTf as the additive (**Table 8**, entries 13-15). However, in the presence of Ag₂CO₃, a very low yield was obtained with 1.5 mol% of Pd(TFA)₂ (**Table 8**, entry 16). No desired product was detected in the absence of palladium catalyst (**Table 8**, entry 17).

2.3.3 Proposed reaction mechanism with AgOTf

On the basis of the aforementioned experimental results, a plausible reaction mechanism for the Mizoroki-Heck reaction with AgOTf is proposed (**Scheme 71**). After oxidative addition of ArI (**1**), Pd^{II}X₂ is converted to Pd^{IV} complex **C**, which then releases cationic palladium species **D** under treatment with AgOTf, a halogen abstracter. As indicated above, the intermediate **D** is stabilized by polar solvent and electron-rich aryl moiety. Then, coordination of carbon-carbon double bond to the palladium species **D** gives rise to the intermediate **E**. This coordination is favored according to the frontier molecular orbital theory. More specifically, the energy gap between the HOMO of CF₃-substituted electron-deficient acrylate **2a** and the LUMO of the cationic palladium intermediate **D** is narrowed thanks to the electrophilic nature of complex **D**. The intermediate **E** is then transformed to complex **F** after the insertion of aryl moiety into a double bond. Intramolecular concerted deprotonation by TFA ligand or intermolecular deprotonation by the close triflate counteranion produces the desired product **3** (*E/Z*) and regenerates Pd^{II}X₂. As a matter of fact, the resulting reaction mixture was strongly acidic (pH around 1), and both of the CF₃CO₂H (δ -76.2 ppm) and TfOH (δ -78.4 ppm) were observed in the ¹⁹F NMR spectrum of the ended reaction mixture (**Figure 8**). The *E/Z* selectivity will be explained later in § 2.4.4 (see page 81).



Scheme 71 Proposed reaction mechanism with AgOTf

Figure 8 ^{19}F NMR spectrum of the ended reaction mixture with AgOTf as additive (for detailed reaction conditions; see Table 8, entry 1)

2.3.4 Substrate scope of the reaction

As shown in § 2.3.1 and § 2.3.2, with 4-iodoanisole (**1a**) as substrate, several kinds of conditions could provide similar good results, but for some other substrates, longer reaction time and more catalyst loading were required to ensure the completion of

the reaction. In order to set up a general method, the following conditions were finally chosen as the optimized reaction conditions: aryl iodide **1** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), AgOTf (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 or 1.5 mol%), 1,4-dioxane (1.0 mL), 90 °C, 2 h (**Table 8**, entries 1, 13).

The investigation of substrate scope showed that a variety of aryl iodides (**1**) could be transformed to the corresponding 3-aryl-2-(trifluoromethyl)acrylates (**3**) in moderate to excellent yields (**Table 9**). Many functional groups, such as unprotected hydroxy, cyano, nitro, and acid groups, were compatible in the reaction system. In the presence of the iodine group, other halogens (chlorine or bromine) were kept intact, furnishing the post-functionalizable products **3e-f** in good yields. In addition to *para*-substituted electron-rich iodoarenes (**1a-b**), substrates bearing valuable electron-withdrawing groups including cyano (**1g**), nitro (**1h**), amide (**1i**), ester (**1j**), and ketone (**1k**) moieties also worked well in this reaction system, affording the corresponding products in 53-92% yield. Interestingly, substrates with carboxylic acid (**1l**) and boronic acid pinacol ester (**1m**), which are relatively reactive functional groups in the presence of palladium-catalyst, still displayed good chemoselectivity furnishing **3l** in good yield (88%) and **3m** in moderate yield (59%; of note, some of the product **3m** was lost during purification because of its instability even though very fast column chromatography was done). Besides, the reactions proceeded smoothly when substituents were on the *meta*- or *ortho*-position of aryl iodides (**3n-u**), and good yields were always obtained except for the case of methoxy group on *ortho*-position (**3r**, 54% yield). Additionally, diverse *poly*-substituted aryl iodides could be transformed into the corresponding products (**3v-3aa**) in fair to good yields. It is worth noting that **3z** and **3aa** were trifluoromethyl-containing analogues of methyl 3,4,5-trimethoxycinnamate (an anti-inflammatory reagent)¹⁸² and methyl caffeate (an antimicrobial and antitumoral reagent),¹⁸³ respectively. The reaction could easily be scaled up under optimized reaction conditions; for example, when 3.5 mmol of **1c** was used, 92% of the isolated yield of **3c** was obtained. Some substrates were selected to test with 1.5 mol% Pd(TFA)₂, and in most of the cases, similar yields and *E/Z* selectivity were obtained when compared with the results involving 10 mol% palladium catalyst. Notably, in a few cases, the aryl substrates could go through a double Mizoroki-Heck coupling with **2a** and led to the formation of 3,3-diaryl-2-(trifluoromethyl)acrylates as side-products, which showed signals at around δ -55 ppm in the ¹⁹F NMR spectra of the ended reaction mixture (see page 70, **Figure 8** for the chemical shift of the side-product of **3a**). Nevertheless, this kind of side-product, when detected, was always in a very low proportion (< 4%).

¹⁸² S. Kumar, P. Arya, C. Mukherjee, B. K. Singh, N. Singh, V. S. Parmar, A. K. Prasad, B. Ghosh, *Biochemistry* **2005**, *44*, 15944–15952.

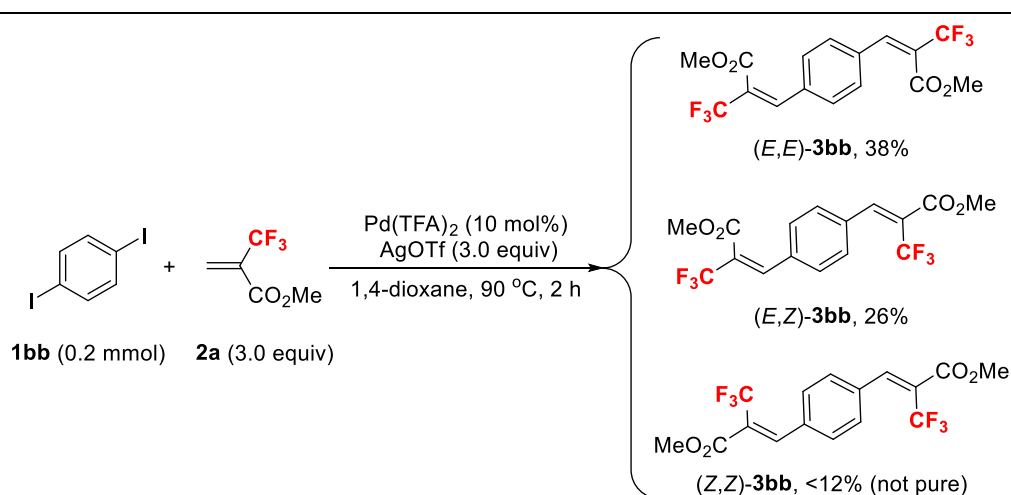
¹⁸³ N.-H. Nam, Y.-J. You, Y. Kim, D.-H. Hong, H.-M. Kim, B. Z. Ahn, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1173–1176.

Table 9 Substrate scope of the reaction^a

| 1 | 2a | 3 (E/Z) ^b |
|---|---|----------------------|
| <i>para</i> -substituted | | |
| | | |
| 3a : R = OMe, | 86% ^c (E/Z = 75/25) 89% ^d (E/Z = 75/25) | |
| 3b : R = OH, | 76% (E/Z = 78/22) 77% ^d (E/Z = 76/24) | |
| 3c : R = H, | 85% (E/Z = 72/28) 85% ^d (E/Z = 72/28) 92% ^e (E/Z = 72/28) | |
| 3d : R = Ph, | 81% (E/Z = 79/21) | |
| 3e : R = Cl, | 85% (E/Z = 74/26) | |
| 3f : R = Br, | 89% (E/Z = 73/27) | |
| 3g : R = CN, | 84% ^f (E/Z = 63/37) 88% ^d (E/Z = 62/38) | |
| 3h : R = NO ₂ , | 86% (E/Z = 55/45) | |
| 3i : R = NHAc, | 53% ^g (E/Z = 75/25) | |
| 3j : R = CO ₂ Me, | 92% (E/Z = 74/26) | |
| 3k : R = COCH ₃ , | 71% (E/Z = 72/28) | |
| 3l : R = CO ₂ H, | 88% (E/Z = 76/24) | |
| 3m : R = | 59% (E/Z = 68/32) | |
| <i>meta</i> -substituted | | |
| | | |
| 3n : R = OMe, | 82% (E/Z = 73/27) 74% ^d (E/Z = 75/25) | |
| 3o : R = Me, | 91% (E/Z = 72/28) | |
| 3p : R = NO ₂ , | 84% ^d (E/Z = 62/38) | |
| 3q : R = CN, | 85% ^d (E/Z = 70/30) | |
| <i>ortho</i> -substituted | | |
| | | |
| 3r : R = OMe, | 54% (E/Z = 73/27) 54% ^d (E/Z = 71/29) | |
| 3s : R = Me, | 79% (E/Z = 65/35) | |
| 3t : R = NO ₂ , | 84% (E/Z = 64/36) 82% ^d (E/Z = 63/37) | |
| 3u : R = CO ₂ Me, | 80% (E/Z = 78/22) | |
| <i>poly</i> -substituted | | |
| | | |
| 3v : 90% (E/Z = 74/26) 74% ^d (E/Z = 74/26) | | |
| | | |
| 3w : 80% (E/Z = 74/26) | | |
| | | |
| 3x : 83% ^h (E/Z = 75/25) | | |
| | | |
| 3y : 81% (E/Z = 63/37) | | |
| | | |
| 3z , 89% ^d (E/Z = 75/25) | | |
| | | |
| 3aa , 45% ⁱ (E/Z = 71/29) | | |

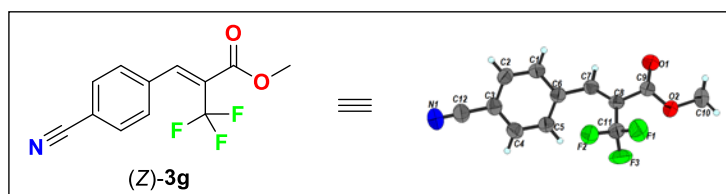
^aReaction conditions: ArI **1** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h. ^bYields based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^cReaction proceeded in 5 min. ^dPd(TFA)₂ (1.5 mol%). ^eScaled up: **1c** (3.5 mmol, 1.0 equiv). ^f**2a** (0.24 mmol, 1.2 equiv). ^g24 h. ^hScaled up: **1x** (1.0 mmol, 1.0 equiv). ⁱPd(TFA)₂ (0.5 mol%), 30 min.

Furthermore, the bis-Mizoroki-Heck reaction between 1,4-diiodobenzene (**1bb**) and **2a** could proceed smoothly with increased amounts of **2a** and AgOTf. The corresponding three isomers (*E,E*-**3bb**, (*E,Z*)-**3bb**, and (*Z,Z*)-**3bb**) were separated in 38%, 26%, and <12% yields, respectively (**Scheme 72**).



Scheme 72 Bis-Mizoroki-Heck reaction with 1,4-diiodobenzene

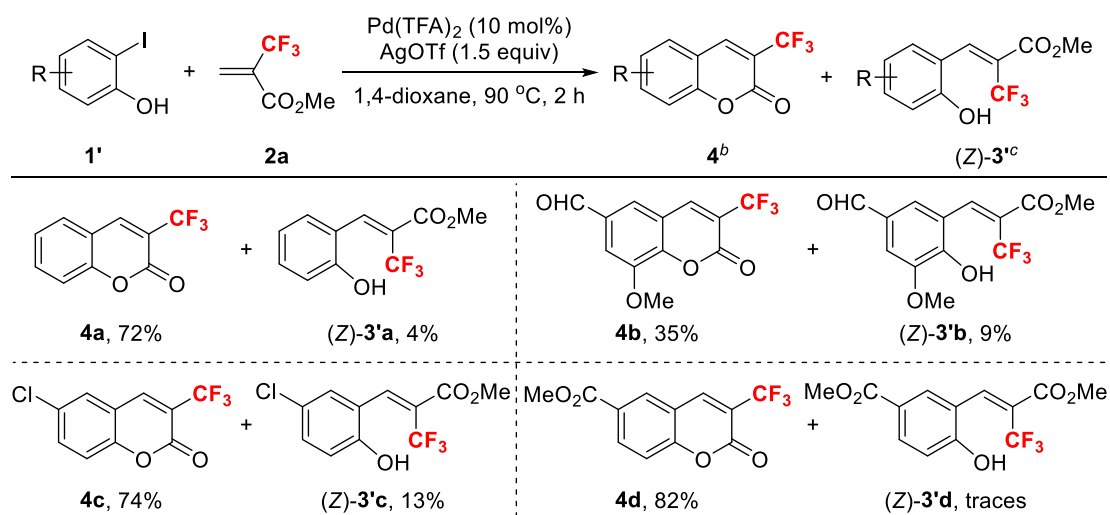
The *E* and *Z* isomers of the Mizoroki-Heck reaction were assigned by ¹⁹F NMR spectra [see page 70, **Figure 8** for chemical shifts and coupling constants of (*E*)-**3a** and (*Z*)-**3a**]. In addition, the X-ray crystallographic analysis of the minor isomer of **3g** led us to unambiguously determine the relative configuration of (*Z*)-isomer (**Figure 9**). As shown in **Table 9**, the major isomer was always (*E*)-product with most of the *E/Z* ratio ranging from 71/29 to 79/21. However, in the presence of strong electron-withdrawing cyano and nitro groups (**3g**, **3h**, **3p**, **3q**, **3t**), the *E/Z* selectivity was lower. Some of them probably due to the isomerization of (*E*)-isomer to (*Z*)-isomer under acidic conditions. Indeed, the *E/Z* ratio of isolated product of **3h** or **3p** was worse than that observed in ¹⁹F NMR spectrum of ended reaction mixture (**3h**, reaction mixture: *E/Z* = 73/27, isolation: *E/Z* = 55/45; **3p**, reaction mixture: *E/Z* = 74/26, isolation: *E/Z* = 62/38). The same situation also occurred in other two substrates (**3m**, reaction mixture: *E/Z* = 73/27, isolation: *E/Z* = 68/32; **3y**, reaction mixture: *E/Z* = 74/26, isolation: *E/Z* = 63/37). Besides, the *E/Z* selectivity was worse when it was methyl group (**3s**) on the *ortho*-position.

Figure 9 X-ray crystallographic analysis of (*Z*)-**3g**

2.3.5 One-pot synthesis of 3-trifluoromethyl coumarins

Given that (*E*)-isomer was the major isomer of the resulting 3-aryl-2-(trifluoromethyl)acrylate (**3**) and a strongly acidic media was obtained at the end of the reaction, we wondered with *ortho*-iodophenols (**1'**) as substrates, if the intramolecular cyclization between ester and hydroxyl group would proceed after the Mizoroki-Heck reaction. Delightfully, with 2-iodophenol as substrate, the corresponding trifluoromethyl-substituted coumarin **4a** was formed in one pot with a good yield (72%) (Table 10). Inspired by this result, three other relevant substrates were further tested and all of them could be converted to 3-trifluoromethyl coumarin derivatives with acceptable to good yields (**4b-d**). Notably, only a very low amount of (*Z*)-3-aryl-2-(trifluoromethyl)acrylates [(*Z*)-**3'**] and almost no (*E*)-3-aryl-2-(trifluoromethyl)acrylates [(*E*)-**3'**] were observed in ¹⁹F NMR spectrum of the ended reaction mixture.

Table 10 One-pot synthesis of 3-trifluoromethyl coumarin derivatives^a



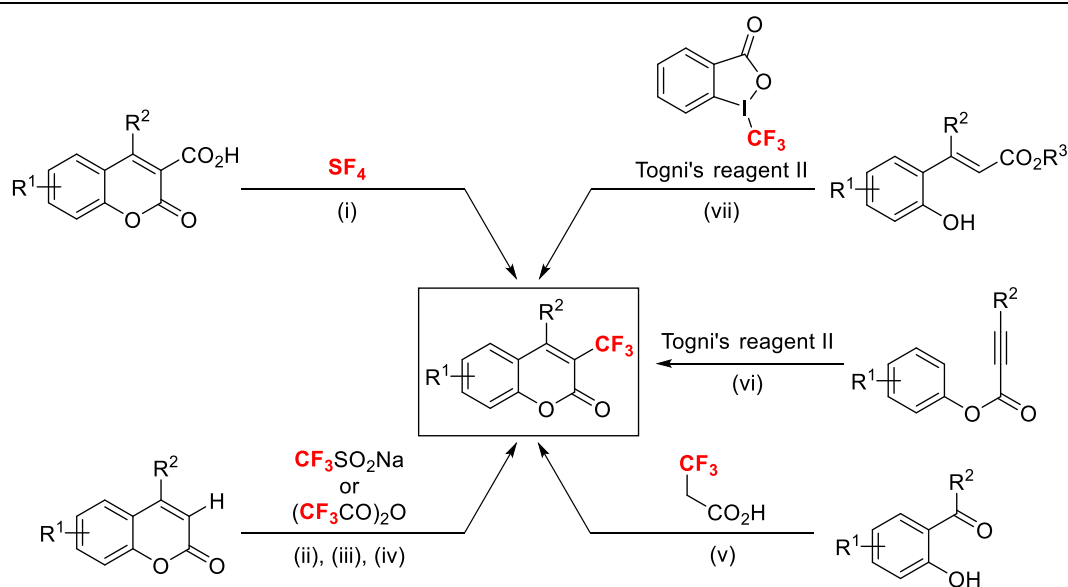
^aReaction conditions: *ortho*-iodophenol **1'** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h.

^bYields based on isolated product after silica gel column chromatography. ^c¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard.

The known methods for the synthesis of 3-trifluoromethyl coumarins usually involved the installation of trifluoromethyl moiety on coumarin scaffolds or required specially designed substrates (Scheme 73).¹⁸⁴ Our strategy provides a nice synthetic alternative for the construction of the valuable coumarin scaffold which shows

¹⁸⁴ (a) W. Dmowski, K. Piasecka-Maciejewska, *Org. Prep. Proced. Int.* **2002**, *34*, 514–517; (b) J. K. Augustine, A. Bombrun, B. Ramappa, C. Boodappa, *Tetrahedron Lett.* **2012**, *53*, 4422–4425; (c) X.-H. Cao, X. Pan, P.-J. Zhou, J.-P. Zou, O. T. Asekun, *Chem. Commun.* **2014**, *50*, 3359–3362; (d) Y. Li, Y. Lu, G. Qiu, Q. Ding, *Org. Lett.* **2014**, *16*, 4240–4243; (e) X. Zhang, P. Huang, Y. Li, C. Duan, *Org. Biomol. Chem.* **2015**, *13*, 10917–10922; (f) S. Chaabouni, F. Simonet, A. François, S. Abid, C. Galaup, S. Chassaing, *Eur. J. Org. Chem.* **2017**, 271–277; (g) X. Zhang, Y. Li, X. Hao, K. Jin, R. Zhang, C. Duan, *Tetrahedron* **2018**, *74*, 1742–1748.

various applications in medicine and fluorescence.¹⁸⁵ Based on the same idea, we tried to produce the related 3-trifluoromethyl quinolinone derivatives from *ortho*-iodoanilines but unfortunately without success.



(i) SF_4 (9 equiv), 90–120 °C, 3–6 h; 2 examples, 32–36% yield. (ii) $\text{CF}_3\text{SO}_2\text{Na}$ (3 equiv), $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (4 equiv), AcOH, 25 °C, 24 h; 17 examples, 44–70% yield. (iii) $\text{CF}_3\text{SO}_2\text{Na}$ (2 equiv), CuCl (20 mol%), $t\text{BuOOH}$ (4 equiv, 70% in water), DMSO, in continuous-flow reactor; 11 examples, 39–71% yield. (iv) $(\text{CF}_3\text{CO})_2\text{O}$ (2 equiv), $\text{Ru}[(\text{DNM})_2\text{bpy}]_3^{2+}$ (1 mol%), pyridine *N*-oxide (2 equiv), MeCN/DCM (1/1), 15 W blue LED, rt, 24 h; 12 examples, 23–85% yield. (v) $\text{CF}_3\text{CH}_2\text{CO}_2\text{H}$ (1 equiv), T3P (2 equiv, 50% solution in EtOAc), Et_3N (2 equiv), $n\text{BuOAc}$, 120 °C; 1 example, 91% yield. (vi) Togni's reagent II (1.5 equiv), $\text{Cu}(\text{OAc})_2$ (10 mol%), K_2CO_3 (2 equiv), MeCN, 60 °C, N_2 , 12 h; 17 examples, 26–70% yield. (vii) Togni's reagent II (1.5 equiv), CuI (10 mol%), DMF, 80 °C, dark, 7 h; 11 examples, 40–83% yield.

Scheme 73 The known methods for the synthesis of 3-trifluoromethyl coumarins

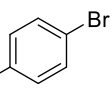
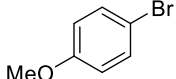
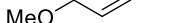
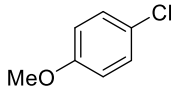
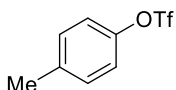
2.3.6 Limitations of the reaction

Although aryl iodides reacted well with methyl 2-(trifluoromethyl)acrylate (**2a**) by Mizoroki-Heck reaction in the presence of $\text{Pd}(\text{TFA})_2$ and AgOTf, other aryl halides and pseudohalides were poor substrates. With the optimized conditions of 4-iodoanisole, 4-bromoanisole could provide **3a** in 34% yield with 76/24 of *E/Z* ratio (**Table 11**, entry 1). However, 4-chloroanisole and *p*-tolyl triflate failed to give the desired product (**Table 11**, entries 7–8). In order to improve the yield of **3a** with 4-bromoanisole as substrate, we tried to adjust the silver(I) additive, reaction time, palladium catalyst, and temperature, yet almost no better results were obtained (**Table 11**, entries 2–6).

¹⁸⁵ (a) S. Nad, H. Pal, *J. Phys. Chem. A* **2000**, *104*, 673–680; (b) J. E. T. Corrie, V. R. N. Munasinghe, W. Rettig, *J. Heterocyclic Chem.* **2000**, *37*, 1447–1455; (c) X.-M. Peng, G. L.V. Damu, C.-H. Zhou, *Curr. Pharm. Des.* **2013**, *19*, 3884–3930; (d) H. Schill, S. Nizamov, F. Bottanelli, J. Bierwagen, V. N. Belov, S. W. Hell, *Chem. Eur. J.* **2013**, *19*, 16556–16565; (e) S. Sandhu, Y. Bansal, O. Silakari, G. Bansal, *Bioorg. Med. Chem.* **2014**, *22*, 3806–3814; (f) J. Grover, S. M. Jachak, *RSC Adv.* **2015**, *5*, 38892–38905; (g) K. P. Barot, S. V. Jain, L. Kremer, S. Singh, M. D. Ghate, *Med. Chem. Res.* **2015**, *24*, 2771–2798.

Table 11 Mizoroki-Heck reaction with aryl bromide, aryl chloride, and aryl triflate^a

$$\text{Ar-X} + \text{CH}_2=\text{C}(\text{CF}_3)\text{CO}_2\text{Me} \xrightarrow[\text{1,4-dioxane, T, t}]{\text{Pd(TFA)}_2 (10 \text{ mol}\%), \text{AgOTf} (1.5 \text{ equiv})} \text{Ar-CH}=\text{C}(\text{CF}_3)\text{CO}_2\text{Me}$$

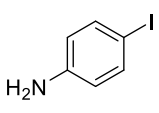
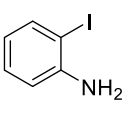
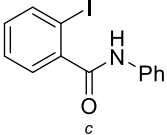
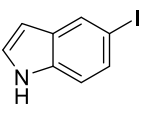
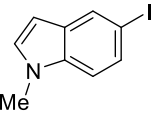
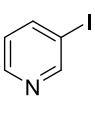
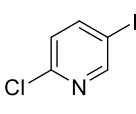
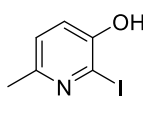
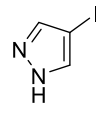
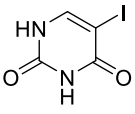

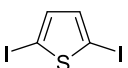
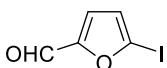
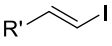
| Entry | Ar-X | T (°C) | t | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|----------------|---|--------|------|--|------------------------|
| 1 | | 90 | 2 h | 34% | 76/24 |
| 2 ^d |  | 90 | 2 h | traces | — |
| 3 |  | 90 | 18 h | 36% | 77/23 |
| 4 ^e |  | 90 | 24 h | traces | — |
| 5 | | 120 | 2 h | 15% | 72/28 |
| 6 | | 60 | 18 h | traces | — |
| ----- | | | | | |
| 7 |  | 90 | 18 h | 0 | — |
| ----- | | | | | |
| 8 |  | 90 | 2 h | traces | — |

^aReaction conditions: ArX (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), 1,4-dioxane (1.0 mL). ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dAg₂CO₃ (2.0 equiv). ^ePd(PPh₃)₄ (10 mol%).

In terms of the substrate scope of aryl iodides, some limitations cannot be ignored (**Table 12**). Specifically, aryl iodides bearing amino group and nitrogen-, sulfur-,

Table 12 Limitations of substrate scope^a

$$\text{R-I} + \text{CH}_2=\text{C}(\text{CF}_3)\text{CO}_2\text{Me} \xrightarrow[\text{1,4-dioxane, 90 °C, 2 h}]{\text{Pd(TFA)}_2 (10 \text{ mol}\%), \text{AgOTf} (1.5 \text{ equiv})} \text{R-CH}=\text{C}(\text{CF}_3)\text{CO}_2\text{Me}$$

| | | | | |
|---|---|---|---|--|
|  |  |  |  |  |
| traces | - ^c | - ^c | - ^c ; 6% ^d | - ^c |
|  |  |  |  |  |
| - ^c | 5% | - ^c | - ^c | traces |
|  |  |  |  | alkyl-I |
| traces | traces | <34%; 9% ^d | R' = C ₄ H ₉ , - ^c R' = C ₆ H ₁₃ , - ^c | alkyl = C ₇ H ₁₅ , - ^c alkyl = C ₈ F ₁₇ , - ^c |

^aReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cNo desired product. ^dAg₂CO₃ (2.0 equiv).

oxygen-containing heteroaryl iodides were not amenable to the optimized reaction conditions, probably because of the reduced catalytic activity of palladium-catalyst under heteroatom coordination. Further testing of vinyl iodides and alkyl iodides showed no reaction.

Besides the limitations of substrate scope, another drawback of this reaction is the poor *E/Z* selectivity.

2.4 Access to *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates by Mizoroki-Heck reaction with Pd(TFA)₂ and Ag₂CO₃

In order to study the stereoselectivity of the reaction, we decided to change the methyl ester group to the bulkier *tert*-butyl ester group, and this part presents the results obtained with *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**). Notably, this part was done in collaboration with my Ph.D. colleague Claire Schlinquer.

2.4.1 Optimization of reaction conditions

Following the optimized reaction conditions of methyl 2-(trifluoromethyl)acrylate (**2a**), *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**) was then tested in the Mizoroki-Heck reaction. To our surprise, no desired product **5a** was observed in the ¹⁹F NMR spectrum with AgOTf as an additive (**Table 13**, entry 1). When AgOAc or Ag₂CO₃ was used instead of AgOTf, good yield (76% or 88%) and good *E/Z* selectivity (83/17 or 84/16) were obtained (**Table 13**, entries 2-3). These results reveal the importance of base in the reaction system of **2b**. Of course, silver cation also plays a crucial role in the reaction efficiency because the addition of K₂CO₃ provided only 20% of the yield of **5a** with lower *E/Z* selectivity (**Table 13**, entry 4). When less electrophilic palladium-catalyst Pd(OAc)₂ or PdBr₂ was involved, the result was very unsatisfactory (**Table 13**, entries 5-6), which was consistent with the case of **2a** in the presence of Ag₂CO₃ (see page 65, **Table 4**, entries 8-9). Decrease of Pd(TFA)₂-catalyst loading to 5 mol% obviously reduced the yield of the desired product with no influence of *E/Z* ratio (**Table 13**, entry 7). Shortening the reaction time to two hours did not cut down the yield and *E/Z* ratio of **5a** (**Table 13**, entry 8). Unfortunately, the addition of monodentate or bidentate phosphine ligands did not improve the *E/Z* selectivity (**Table 13**, entries 9-12).

Table 13 Optimization of reaction conditions^a

| Entry | Base or Additive (z equiv) | [Pd] Catalyst (x mol%) | Ligand (y mol%) | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-----------------|---------------------------------------|---------------------------|---|--|-------------------------------|
| 1 | AgOTf (1.5) | Pd(TFA) ₂ (10) | — | 0 | — |
| 2 | AgOAc (2.0) | Pd(TFA) ₂ (10) | — | 76% | 83/17 |
| 3 | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | — | 88% | 84/16 |
| 4 | K ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | — | 20% | 71/29 |
| 5 | Ag ₂ CO ₃ (2.0) | Pd(OAc) ₂ (10) | — | 14% | 76/24 |
| 6 | Ag ₂ CO ₃ (2.0) | PdBr ₂ (10) | — | traces | — |
| 7 | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (5) | — | 56% | 84/16 |
| 8 ^d | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | — | 90% (84%) ^e | 85/15 |
| 9 ^d | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | PPh ₃ (20) | 87% | 58/42 |
| 10 ^d | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | dppe (10) | 82% | 76/24 |
| 11 ^d | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | Xantphos (10) | 80% | 71/29 |
| 12 ^d | Ag ₂ CO ₃ (2.0) | Pd(TFA) ₂ (10) | P ^t Bu ₃ •HBF ₄ (20) | 45% | 80/20 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2b** (0.3 mmol, 1.5 equiv), [Pd] catalyst (x mol%), ligand (y mol%), base or additive (z equiv), 1,4-dioxane (1.0 mL), 90 °C, 4 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^d2 h. ^eIsolated yield.

2.4.2 Substrate scope of the reaction

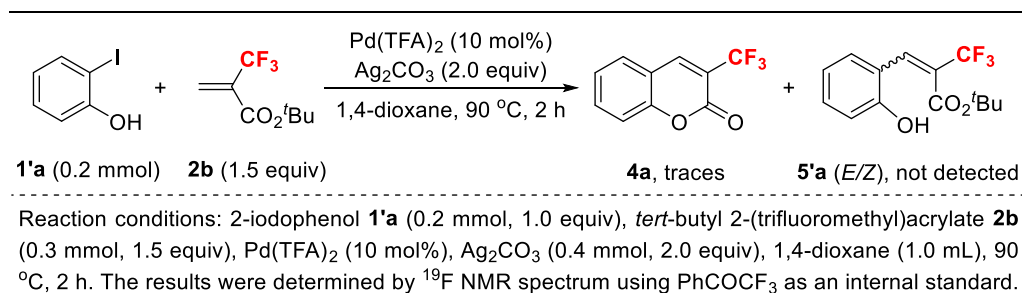
With the optimized reaction conditions in hand (**Table 13**, entry 8), the Mizoroki-Heck reaction of *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**) with various aryl iodides was further investigated (**Table 14**). Aryl iodide bearing methoxy or bromo group on the *para*-position was converted to the corresponding product (**5a** or **5b**) in good yield with good *E/Z* ratio. In comparison, worse results of both yield and *E/Z* selectivity were obtained with *para*-substituted cyano or nitro group (**5c** or **5d**). *Meta*- and *poly*-substituted aryl iodides were then subjected to the reaction conditions and the related products (**5e-f**, **5j-k**) were generated in good yields with good *E/Z* ratio, regardless of the electronic properties of the substituents. Probably due to steric effects, lower *E/Z* selectivity (**5g-i**) was observed in the case of *ortho*-substituted aryl iodides. The reaction could readily be scaled up to 4.0 mmol with **1a**, affording **5a** in the same yield and *E/Z* ratio as the case of 0.2 mmol scale.

Table 14 Substrate scope of the reaction^a

| $\text{Ar-I} + \text{CF}_3\text{C}(\text{CO}_2^t\text{Bu})=\text{CH}_2 \xrightarrow[\text{1,4-dioxane, 90 }^\circ\text{C, 2 h}]{\text{Pd(TFA)}_2 (10 \text{ mol}\%), \text{Ag}_2\text{CO}_3 (2.0 \text{ equiv})} \text{Ar-CH}=\text{C}(\text{CF}_3)\text{CO}_2^t\text{Bu}$ | | |
|--|--------------------------------|---|
| 1 | 2b | 5 (E/Z) ^b |
| <i>para</i> -substituted | | <i>meta</i> -substituted |
| | | |
| 5a: R = OMe, 84% (E/Z = 85/15) | 84% ^c (E/Z = 85/15) | 5e: R = OMe, 87% (E/Z = 87/13) |
| 5b: R = Br, 90% (E/Z = 85/15) | | 5f: R = NO ₂ , 89% (E/Z = 83/17) |
| 5c: R = CN, 79% (E/Z = 75/25) | | |
| 5d: R = NO ₂ , 54% (E/Z = 52/48) | | |
| <i>ortho</i> -substituted | | <i>poly</i> -substituted |
| | | |
| 5g: R = OMe, 53% (E/Z = 69/31) | | 5j: <78% ^d (E/Z = 86/14) |
| 5h: R = Me, 77% (E/Z = 77/23) | | |
| 5i: R = CO ₂ Me, 99% (E/Z = 67/33) | | 5k: 81% (E/Z = 87/13) |

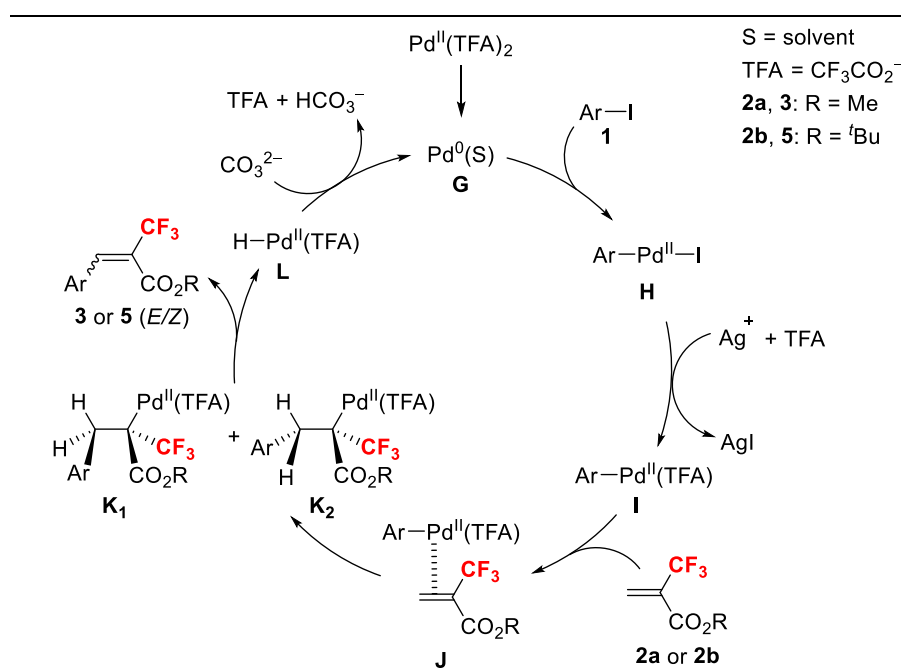
^aReaction conditions: ArI **1** (0.2 mmol, 1.0 equiv), *tert*-butyl 2-(trifluoromethyl)acrylate **2b** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (0.4 mmol, 2.0 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h. ^bYields based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^cScaled up: **1a** (4.0 mmol, 1.0 equiv), 15 h. ^dNot pure (contaminated by a fluorinated derivative).

We then investigated the synthesis of 3-trifluoromethyl coumarin **4a** in Ag₂CO₃-mediated reaction conditions with **2b**. However, only traces of 3-trifluoromethyl coumarin **4a** was observed and no Heck-type product **5'a** was detected in the ¹⁹F NMR spectrum (**Scheme 74**). These results reveal that 2-iodophenol is a poor substrate in this Mizoroki-Heck reaction. Besides, assuming we can successfully obtain the Heck-type product **5'a**, we still doubt whether **4a** can be generated by intramolecular cyclization due to the neutral media of the ended reaction mixture (pH around 6) as well as the large steric hindrance of the *tert*-butyl ester group.

**Scheme 74** Investigation of the one-pot synthesis of 3-trifluoromethyl coumarin **4a**

2.4.3 Proposed reaction mechanism with Ag_2CO_3

Combining the reaction results in **Table 4** and **Table 13**, a neutral Pd^0 - Pd^{II} catalytic cycle was proposed for Ag_2CO_3 -mediated reaction systems with 2-(trifluoromethyl)acrylates (**2a** and **2b**) (**Scheme 75**). First, $\text{Pd}^{\text{II}}(\text{TFA})_2$ is converted to Pd^0 species **G** in which palladium (0) may be stabilized by solvent. Oxidative addition of Ar-I to Pd^0 generates $\text{ArPd}^{\text{II}}\text{I}$ (**H**). Silver cation serves as a halide scavenger,¹⁸¹ leading to the formation of intermediate **I** [$\text{ArPd}^{\text{II}}(\text{TFA})$]. The generation of $\text{ArPd}^{\text{II}}(\text{TFA})$ as active species is consistent with Amatore and Jutand's work, in which $\text{PhPd}^{\text{II}}(\text{OAc})(\text{PPh}_3)_2$ (not $\text{PhPd}^{\text{II}}\text{I}(\text{PPh}_3)_2$) is the reactive intermediate although, in their study, the presence of phosphine ligand was crucial.¹⁸⁶ Then, coordination of **2a** (or **2b**) to $\text{ArPd}^{\text{II}}(\text{TFA})$ gives rise to intermediate **J**, which is favored by narrowed HOMO-LUMO gap between **2a** (or **2b**) and $\text{ArPd}^{\text{II}}(\text{TFA})$ thanks to the presence of electrophilic TFA. Intermediate **J** undergoes *syn*-insertion and rotation, providing conformers **K**₁ and **K**₂. Subsequent *syn*- β -hydride elimination and dissociation furnish product **3** (or **5**) (*E/Z*) with the liberation of $\text{HPd}^{\text{II}}(\text{TFA})$ (**L**). Under the treatment with base, Pd^0 species **G** is regenerated for the next catalytic cycle. We can notice that at the end of the reaction, the pH value of the reaction media was around 6, which is consistent with a "neutral process".



Scheme 75 Proposed reaction mechanism with Ag_2CO_3

¹⁸⁶ (a) C. Amatore, E. Carré, A. Jutand, M. A. M'Barki, G. Meyer, *Organometallics* **1995**, *14*, 5605–5614; (b) C. Amatore, A. Jutand, *J. Organomet. Chem.* **1999**, *576*, 254–278; (c) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321.

2.4.4 Comparison of reactivity and *E/Z* selectivity between different 2-(trifluoromethyl)acrylates (**2**)

In **Table 15**, we compared the reactivity and *E/Z* selectivity between different 2-(trifluoromethyl)acrylates (**2**) with electron-rich or electron-poor aryl iodide in the presence of Ag₂CO₃ or AgOTf.

In terms of reactivity, **2a** exhibited good reactivity regardless of the electronic properties of aryl iodides as well as the nature of silver(I) additives (**Table 15**, entries 1-4). However, an extremely large disparity was observed for the reactivity of **2b** when different silver(I) additives were involved. With Ag₂CO₃, good yields of **5a** and **5c** were obtained (**Table 15**, entries 5, 7); with AgOTf, almost no desired product was detected (**Table 15**, entries 6, 8). We further examined the reactivity of **2c** in the presence of different silver(I) additives, a diametrically opposite reactivity was observed when compared with **2b** (**Table 15**, comparing entries 5, 9 and entries 6, 10). These results indicate that both of the cationic and neutral palladium-catalysed reaction mechanisms are suitable for **2a** (see page 70, **Scheme 71** and page 80, **Scheme 75**); by contrast, **2b** is only reactive under neutral palladium-catalysed conditions, and **2c** is only reactive in cationic palladium-catalysed conditions. So far, we cannot explain why there is such a huge difference in reactivity between **2a**, **2b**, and **2c** when different silver(I) additives are involved. It may be related to the electronic properties of the ester group in **2**.

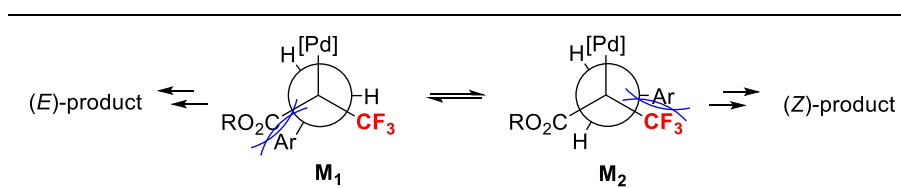
Regarding *E/Z* selectivity, it does not seem to be directly related to the reaction mechanism, because the same *E/Z* ratio of product **3a** or **3g** was observed for both of the Ag₂CO₃- and AgOTf-mediated reaction systems when the same aryl iodide was used (**Table 15**, comparing entries 1, 2 or entries 3, 4). But the electronic properties of aryl iodides have an effect on the *E/Z* selectivity. Electron-rich 4-iodoanisole provided the product in a better *E/Z* ratio than the case of electron-poor 4-iodobenzonitrile (**Table 15**, comparing entries 1, 3 or entries 2, 4 or entries 5, 7). Besides, the ester group in 2-(trifluoromethyl)acrylates (**2**) also affects the *E/Z* selectivity. In Ag₂CO₃-mediated conditions, the product of **2a** showed lower *E/Z* selectivity than the product of **2b** (**Table 15**, comparing entries 1, 5 or entries 3, 7). In AgOTf-mediated conditions, a higher *E/Z* ratio of the product of **2a** was obtained than that of **2c** (**Table 15**, comparing entries 2, 10).

Table 15 Comparison of reactivity and *E/Z* selectivity between **2a**, **2b**, and **2c**^a

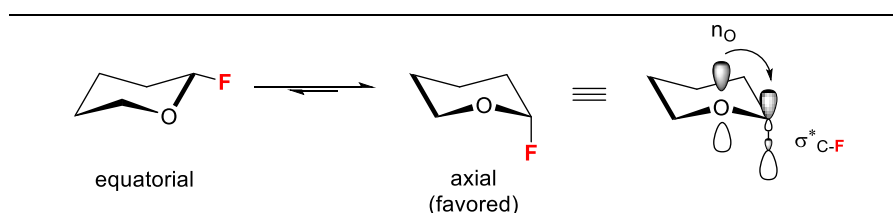
| Entry | R' | 2, R | Silver(I) additive (y equiv) | product, yield ^b | <i>E/Z</i> ratio ^c |
|----------------|-----|---|---------------------------------------|------------------------------|-------------------------------|
| 1 ^d | OMe | 2a , Me | Ag ₂ CO ₃ (2.0) | 3a , 75% | 76/24 |
| 2 | OMe | 2a , Me | AgOTf (1.5) | 3a , 86% | 76/24 |
| 3 ^d | CN | 2a , Me | Ag ₂ CO ₃ (2.0) | 3g , 68% | 64/36 |
| 4 ^e | CN | 2a , Me | AgOTf (1.5) | 3g , 84% | 63/37 |
| ----- | | | | | |
| 5 | OMe | 2b , ^t Bu | Ag ₂ CO ₃ (2.0) | 5a , 84% | 85/15 |
| 6 ^d | OMe | 2b , ^t Bu | AgOTf (1.5) | 5a , 0 | — |
| 7 | CN | 2b , ^t Bu | Ag ₂ CO ₃ (2.0) | 5c , 79% | 75/25 |
| 8 ^d | CN | 2b , ^t Bu | AgOTf (1.5) | 5c , traces | — |
| ----- | | | | | |
| 9 | OMe | 2c , CH(CF ₃) ₂ | Ag ₂ CO ₃ (2.0) | 6a , traces | — |
| 10 | OMe | 2c , CH(CF ₃) ₂ | AgOTf (1.5) | 6a , 70% ^f | 63/37 |

^aReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), silver(I) additive (y equiv), 1,4-dioxane (1.0 mL), 90 °C, 4 h. ^bYields based on isolated product after silica gel column chromatography. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^d4 h. ^e**2a** (0.24 mmol, 1.2 equiv). ^fNot pure (contaminated with non-fluorinated compound).

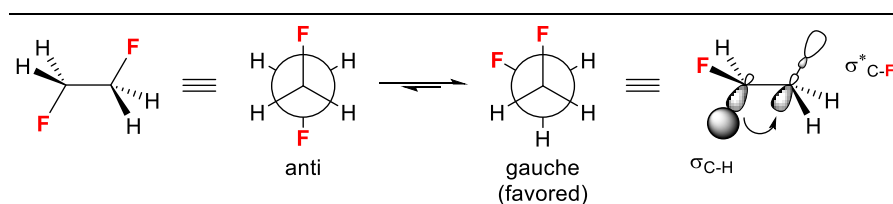
To explain the *E/Z* selectivity, we first analysed the steric effects. In **Scheme 76**, we showed the Newman projection of conformers **M**₁ and **M**₂, which are intermediates in the cationic and neutral palladium-catalytic cycle (see page 70, **Scheme 71**, intermediate **F**; page 80, **Scheme 75**, intermediates **K**₁, **K**₂). *syn*-β-Hydride elimination of **M**₁ and **M**₂ leads to the generation of (*E*)-product and (*Z*)-product, respectively. From CO₂Me (**2a**) to CO₂^tBu (**2b**), the steric repulsion between the ester group and the aryl group in conformer **M**₁ is increased, and the stability of conformer **M**₁ is reduced; therefore, it is not conducive to the formation of (*E*)-product. According to this analysis, a lower *E/Z* ratio should be obtained for the product of **2b** when compared with **2a**. Yet, this speculation is exactly the opposite of the experimental results (**Table 15**, comparing entries 1, 5 or entries 3, 7). Obviously, the current *E/Z* selectivity between **2a** and **2b** cannot be explained from the perspective of steric hindrance. On the other hand, steric effects seem to be reasonable to explain the *E/Z* selectivity between **2a** (CO₂Me) and **2c** [CO₂CH(CF₃)₂] (**Table 15**, comparing entries 2, 10), but the influence of electronic properties cannot be ruled out because of the existence of two strongly electron-withdrawing CF₃ groups in the ester moiety of **2c**.

**Scheme 76** Steric effects on *E/Z* selectivity

In view of the limitations of steric effects in explaining *E/Z* selectivity, we turned our attention to stereoelectronic effects which analyze structure and reactivity through orbital interactions.¹⁸⁷ Indeed, some conformations of fluorine-containing compounds showed electronic preference rather than steric preference, such as anomeric effect and gauche effect.¹⁸⁸ For example, 2-fluoropyran prefers axial orientation to equatorial orientation (**Scheme 77**). This phenomenon is difficult to explain from steric considerations because an equatorial conformation is usually advantageous in avoiding 1,3-diaxial interactions. A widely accepted explanation is the negative hyperconjugative interaction between the oxygen lone pair and the low-lying $\sigma^*_{\text{C-F}}$ antibonding orbital. In other words, the stability of axial conformation comes from the lone pair (HOMO) donation from adjacent oxygen into the $\sigma^*_{\text{C-F}}$ antibonding orbital (LUMO) (anomeric effect) (**Scheme 77**).¹⁸⁷⁻¹⁸⁸ Another example is the gauche effect of 1,2-difluoroethane, in which the gauche conformation is more stable than the *anti* conformation (**Scheme 78**). The principal cause of the gauche effect is considered to be hyperconjugation, and the gauche conformation is stabilized by donation of electron density from $\sigma_{\text{C-H}}$ orbital to low-lying $\sigma^*_{\text{C-F}}$ antibonding orbital. Owing to the high electronegativity of the fluorine atom, the $\sigma_{\text{C-F}}$ orbital is a worse electron donor than $\sigma_{\text{C-H}}$ orbital; therefore, *anti* conformation is less favored.¹⁸⁷⁻¹⁸⁸



Scheme 77 Anomeric effect involving $n_{\text{O}} \rightarrow \sigma^*_{\text{C-F}}$ interaction



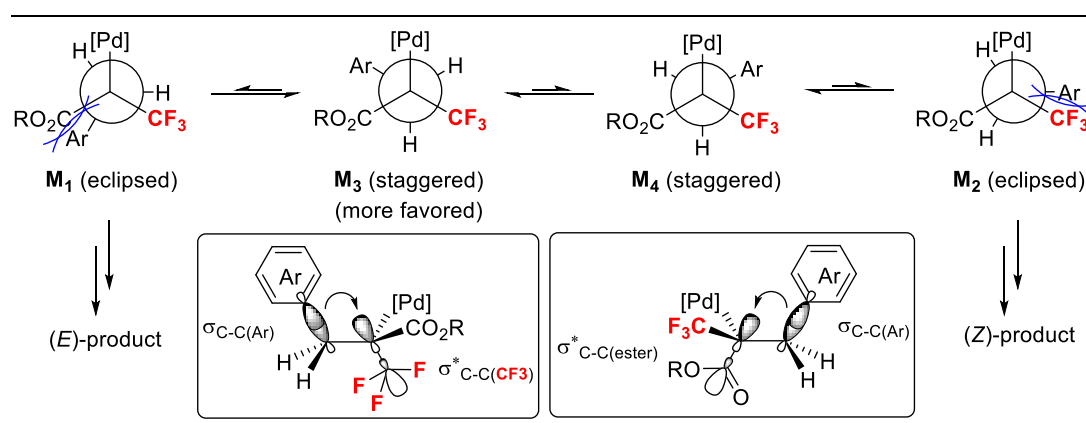
Scheme 78 Gauche effect involving $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-F}}$ interaction

Inspired by the anomeric effect and gauche effect in fluorine-containing molecules, we speculate that stereoelectronic effects may help us to explain the *E/Z* selectivity in our reaction system. In **Scheme 79**, we showed another two staggered conformers (**M₃** and **M₄**) of **M₁** and **M₂**. Due to the strong electron-withdrawing properties of the trifluoromethyl group, the C-C(CF₃) σ^* antibonding orbital is likely to exhibit low

¹⁸⁷ For selected reviews: (a) I. V. Alabugin, *Stereoelectronic Effects: A Bridge between Structure and Reactivity*, John Wiley & Sons, Ltd., Chichester, **2016**; (b) V. K. Yadav, *Steric and Stereoelectronic Effects in Organic Chemistry*, Springer, Singapore, **2016**.

¹⁸⁸ D. O'hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319.

energy, and $\sigma^*_{\text{C-C}(\text{CF}_3)}$ orbital would be a good electron acceptor. On the other hand, C-C(Ar) σ orbital might be a better electron donor than C-H σ orbital because of the presence of the aryl group. When aryl moiety is placed in the *anti* position of CF₃ group as shown in staggered conformation **M**₃, hyperconjugative interaction between $\sigma_{\text{C-C}(\text{Ar})}$ orbital and $\sigma^*_{\text{C-C}(\text{CF}_3)}$ antibonding orbital enhances the stability of conformer **M**₃. Although conformer **M**₄ could also be stabilized to some extent by hyperconjugative interaction between $\sigma_{\text{C-C}(\text{Ar})}$ orbital and $\sigma^*_{\text{C-C}(\text{ester})}$ antibonding orbital, conformer **M**₃ is more favored than conformer **M**₄ because $\sigma^*_{\text{C-C}(\text{CF}_3)}$ orbital is a better electron acceptor than $\sigma^*_{\text{C-C}(\text{ester})}$ orbital.



Scheme 79 Stereoelectronic effects on *E/Z* selectivity

Based on this analysis, it is easier to understand the *E/Z* selectivity in our reaction systems. Since **M**₃ is the preferred conformation, the chance of forming **M**₁ is greater than that of **M**₂, and thus (*E*)-products are the major isomers after *syn*- β -hydride elimination. Indeed, in our reaction conditions, (*E*)-isomers were always the major products no matter what kind of aryl iodides, 2-(trifluoromethyl)acrylates (**2**), or silver(I) additives were involved. The effects of the electronic properties of aryl iodides on *E/Z* selectivity can also be explained by this hyperconjugative interaction in **M**₃. When an electron-donating group is introduced to the aryl ring, the C-C(Ar) σ orbital would show stronger electron-donating ability, which facilitates hyperconjugative interaction and further stabilizes conformer **M**₃. On the contrary, with aryl moiety bearing a strong electron-withdrawing group, the C-C(Ar) σ orbital would show weaker electron-donating ability, and cause the reduction of stability of conformer **M**₃. According to this analysis, electron-rich aryl iodides should give higher *E/Z* ratio of products than electron-poor aryl iodides, which is consistent with the experimental results (see page 82, **Table 15**, comparing entries 1, 3 or entries 2, 4 or entries 5, 7). Additionally, the hyperconjugation model can be successfully used to interpret the effects of ester groups on *E/Z* selectivity. From CO₂Me (**2a**) to CO₂^tBu (**2b**), the electron-withdrawing property of ester group is decreased, so C-C(CO₂^tBu) σ^* antibonding orbital is a worse electron acceptor than C-C(CO₂Me) σ^* antibonding orbital, resulting in a weaker hyperconjugative interaction between C-C(Ar) σ orbital

and C-C(CO₂^tBu) σ^* antibonding orbital in conformer **M**₄. The reduced stability of conformer **M**₄ with CO₂^tBu leads to the decrease of (*Z*)-products. Indeed, CO₂^tBu (**2b**) provided higher *E/Z* ratio of products than CO₂Me (**2a**) (see page 82, **Table 15**, comparing entries 1, 5 or entries 3, 7). When an ester group with a stronger electron-withdrawing ability than CO₂Me is involved, the opposite result should be obtained. This inference is confirmed by the result of **2c** [CO₂CH(CF₃)₂], which afforded a worse *E/Z* ratio of products than CO₂Me (**2a**) (see page 82, **Table 15**, comparing entries 2, 10).

Further computational studies are needed to confirm the speculation of the stereoelectronic effects on *E/Z* selectivity. Of course, in some cases, both steric effects and stereoelectronic effects need to be considered comprehensively.

2.5 Access to methyl 3-aryl-2-(trifluoromethyl)acrylates by Mizoroki-Heck reaction with Pd/C and AgOTf

Compared with common palladium(II) catalysts in cross-coupling reactions, we wondered if solid-supported palladium catalysts, such as Pd/C (a cheaper palladium catalyst), could catalyse the Mizoroki-Heck reaction between aryl iodides and 2-(trifluoromethyl)acrylates (**2**). This part was done in collaboration with my Ph.D. colleague Claire Schlinquer.

2.5.1 Optimization of reaction conditions

To our delight, the reaction of 4-iodoanisole (**1a**) with methyl 2-(trifluoromethyl)acrylate (**2a**) proceeded well in the presence of Pd/C and AgOTf, furnishing the desired product **3a** in 87% ¹⁹F NMR yield (80% isolated yield) with 76/24 of *E/Z* ratio (**Table 16**, entry 1). Pd(OH)₂/C was also effective in catalysing this reaction, although the yield of **3a** was slightly reduced (**Table 16**, entry 2). The decrease of catalyst loading of Pd/C or reaction time did not significantly reduce the yield of the desired product (**Table 16**, entries 3-5). The addition of ligands was not helpful to improve the yield and selectivity (**Table 16**, entries 6-7). Changing solvents and additives had a huge impact on the reaction since no reaction occurred under most of the tested conditions (**Table 16**, entries 8-12). Of note, in the presence of Pd/C, no desired product **3a** was detected when Ag₂CO₃ was used as an additive instead of AgOTf (**Table 16**, entry 9), which is not the case of the reaction system with Pd(TFA)₂ and Ag₂CO₃ (see page 65, **Table 4**, entry 1). Different from **2a**, **2b** was unreactive in the presence of Pd/C or Pd(OH)₂/C (**Table 16**, entries 13-15). This is not surprising because **2b** was unreactive in the presence of AgOTf and Pd/C was ineffective with Ag₂CO₃.

Table 16 Optimization of reaction conditions^a

| Entry | 2 | [Pd]/C (x mol% [Pd]) | additive (y equiv) | solvent | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|----------------|-----------|--|---------------------------------------|-------------|--|------------------------|
| 1 | 2a | Pd/C ^d (10) | AgOTf (1.5) | 1,4-dioxane | 3a , 87% (80%) ^e | 76/24 |
| 2 | 2a | Pd(OH) ₂ /C ^f (10) | AgOTf (1.5) | 1,4-dioxane | 3a , 76% | 76/24 |
| 3 | 2a | Pd/C ^d (5) | AgOTf (1.5) | 1,4-dioxane | 3a , 83% (76%) ^e | 73/27 |
| 4 | 2a | Pd/C ^d (1) | AgOTf (1.5) | 1,4-dioxane | 3a , 80% | 76/24 |
| 5 ^g | 2a | Pd/C ^d (10) | AgOTf (1.5) | 1,4-dioxane | 3a , 78% | 76/24 |
| 6 ^h | 2a | Pd/C ^d (10) | AgOTf (1.5) | 1,4-dioxane | 3a , 84% | 76/24 |
| 7 ⁱ | 2a | Pd/C ^d (10) | AgOTf (1.5) | 1,4-dioxane | 3a , 84% | 75/25 |
| 8 | 2a | Pd/C ^d (10) | AgOTf (1.5) | DMF | 3a , 18% | 68/32 |
| 9 | 2a | Pd/C ^d (10) | Ag ₂ CO ₃ (2.0) | 1,4-dioxane | 3a , — | — |
| 10 | 2a | Pd/C ^d (10) | Cu(OTf) ₂ (1.5) | 1,4-dioxane | 3a , traces | — |
| 11 | 2a | Pd/C ^d (10) | NaOAc (1.5) | DMA | 3a , — | — |
| 12 | 2a | Pd/C ^d (10) | — | 1,4-dioxane | 3a , — | — |
| 13 | 2b | Pd/C ^d (10) | AgOTf (1.5) | 1,4-dioxane | 5a , traces | — |
| 14 | 2b | Pd/C ^d (10) | Ag ₂ CO ₃ (2.0) | 1,4-dioxane | 5a , traces | — |
| 15 | 2b | Pd(OH) ₂ /C ^f (10) | Ag ₂ CO ₃ (2.0) | 1,4-dioxane | 5a , — | — |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), [Pd]/C (x mol% [Pd]), additive (y equiv), solvent, 90 °C, 4 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dPd/C (Palladium, 10% on carbon, type 487, dry). ^eIsolated yield. ^fPd(OH)₂/C (Palladium hydroxide on carbon, wet, Degussa type, E101 NE/W, Pd content 20%). ^g2 h. ^hPPh₃ (20 mol%). ⁱXantphos (10 mol%).

2.5.2 Substrate scope of the reaction

To study the generality of the current Pd/C-catalysed Mizoroki-Heck reaction, a variety of aryl iodides were subjected to the reaction conditions and the corresponding 3-aryl-2-(trifluoromethyl)acrylates (**3**) were successfully constructed (**Table 17**). During the investigation of substrate scope, we found that the increase of reaction temperature to 110 °C was required to ensure the reaction efficiency of most of the substrates and we could see the influence of temperature in **Table 17**. Diverse functional groups, such as methoxy, hydroxy, chloro, bromo, cyano, ester, ketone, and nitro groups, were compatible in the reaction system. Many of the *para*-, *meta*-, *ortho*-, and *poly*-substituted aryl iodides reacted well with **2a**, leading to the formation of methyl 3-aryl-2-(trifluoromethyl)acrylates in moderate to good yields. Unfortunately, some products (**3s**, **3cc**, **3dd**) were contaminated by a small amount of fluorine-containing side-products (probably some polymers) and failed to provide the pure compounds. Like with Pd(TFA)₂, 5-iodo-2-furaldehyde was also a poor substrate in this Pd/C-catalysed reaction system, and a low yield of **3ee** was

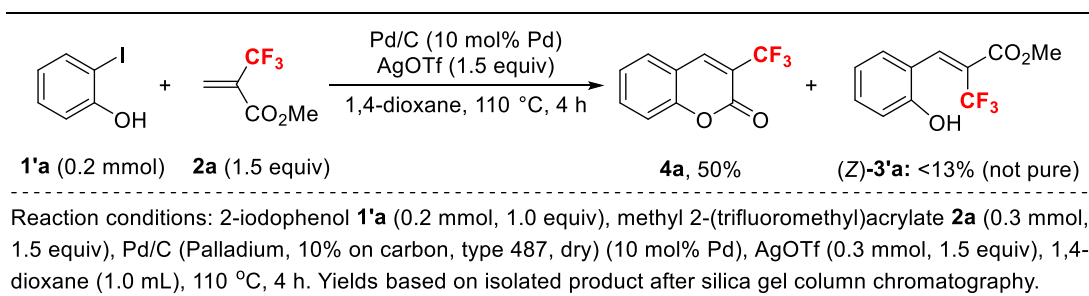
observed in the ^{19}F NMR spectrum. Concerning the *E/Z* ratio, a similar trend of *E/Z* selectivity was observed for both Pd/C catalysis and Pd(TFA)₂ catalysis when comparing the *E/Z* ratio of products in **Table 17** and **Table 9** (see page 72).

Table 17 Substrate scope of the reaction^a

| Ar-I | | + | | $\xrightarrow[\text{AgOTf (1.5 equiv)}]{\text{Pd/C (10 mol\% Pd)}}$ | |
|---------------------------|-------------------------|----------------------|---------------|---|----------------------------|
| 1 | | | 2a | | 3 (E/Z)^b |
| <i>para</i> -substituted | | | | | |
| | | | | | |
| 3a: | R = OMe, | 80% ^c | (E/Z = 76/24) | | |
| 3b: | R = OH, | 67% ^c | (E/Z = 73/27) | | |
| 3cc: | R = Me, | 54% ^{c,d} | (E/Z = 71/29) | | |
| | | 88% ^{c,d,e} | (E/Z = 74/26) | | |
| 3c: | R = H, | 63% ^c | (E/Z = 72/28) | | |
| 3f: | R = Br, | 78% | (E/Z = 73/27) | | |
| 3g: | R = CN, | 85% | (E/Z = 67/33) | | |
| 3h: | R = NO ₂ , | 58% ^{c,d} | (E/Z = 73/27) | | |
| | | 37% ^{c,d,e} | (E/Z = 73/27) | | |
| | | 88% | (E/Z = 55/45) | | |
| 3j: | R = CO ₂ Me, | 75% | (E/Z = 74/26) | | |
| 3k: | R = COMe, | 54% ^{c,d} | (E/Z = 71/29) | | |
| | | 56% ^{c,d,e} | (E/Z = 69/31) | | |
| | | 62% | (E/Z = 72/28) | | |
| <i>meta</i> -substituted | | | | | |
| | | | | | |
| 3o: | R = Me, | 42% | (E/Z = 72/28) | | |
| 3p: | R = NO ₂ , | 24% ^{c,d} | (E/Z = 70/30) | | |
| | | 71% | (E/Z = 70/30) | | |
| 3q: | R = CN, | 52% | (E/Z = 70/30) | | |
| <i>ortho</i> -substituted | | | | | |
| | | | | | |
| 3s: | R = Me, | 83% ^d | (E/Z = 66/34) | | |
| 3dd: | R = CN, | 98% ^d | (E/Z = 60/40) | | |
| 3t: | R = NO ₂ , | 88% | (E/Z = 64/36) | | |
| <i>poly</i> -substituted | | | | | |
| | | | | | |
| 3v: | | 68% | (E/Z = 74/26) | | |
| <i>heterocycles</i> | | | | | |
| | | | | | |
| 3ee: | | 29% ^d | (E/Z = 83/17) | | |

^aReaction conditions: Ar-I (**1**) (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (10 mol% Pd), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 110 °C, 4 h. ^bYields based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ^{19}F NMR spectrum of isolated product. ^c90 °C. ^d ^{19}F NMR yields were obtained by using PhCOCF₃ as an internal standard; *E/Z* ratio was determined by ^{19}F NMR spectrum of ended reaction mixture. ^e24 h.

We then explored the possibility of the one-pot synthesis of 3-trifluoromethyl coumarin derivatives under Pd/C catalysis. When 2-iodophenol was involved in the reaction conditions, the CF₃-coumarin **4a** was successfully produced in 50% yield along with around 13% yield of (*Z*)-**3'a** (**Scheme 80**). The intramolecular cyclization still benefits from the strongly acidic reaction media at the end of the reaction (pH around 1).



Scheme 80 Investigation of the one-pot synthesis of 3-trifluoromethyl coumarin

2.5.3 Catalytic pathway with Pd/C catalyst

Concerning the catalytic process with Pd/C catalyst, there are two main catalytic modes: a. nanoparticle catalysis, b. leaching-driven catalysis (**Figure 10**). The former is heterogeneous catalysis that occurs on the surface of Pd nanoparticles, while the latter is homogeneous catalysis that occurs on the dissolved Pd species, leaching from Pd nanoparticles.¹⁸⁹

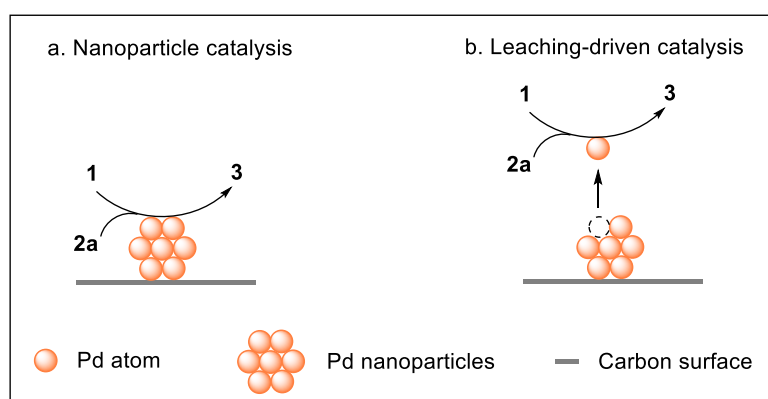


Figure 10 Two catalytic modes with Pd/C catalyst

In order to figure out which process exists in our reaction system, we first did some poisoning experiments. Hg(0) has long been used as a poisoning reagent for heterogeneous metal-particle catalysts because of its ability to adsorb on the metal surface or amalgamate metal.¹⁹⁰⁻¹⁹¹ Besides, some small molecules, such as CS₂, can poison catalysts through strongly binding to the metal center, thereby preventing the substrate from approaching the active site. For heterogeneous catalysts, less than 1.0 equivalent of CS₂ per metal atom is sufficient to completely inhibit the reaction because only a part of metal atoms are distributed on the surface of the metal particle. By contrast, more than 1.0 equivalent of CS₂ per metal atom is

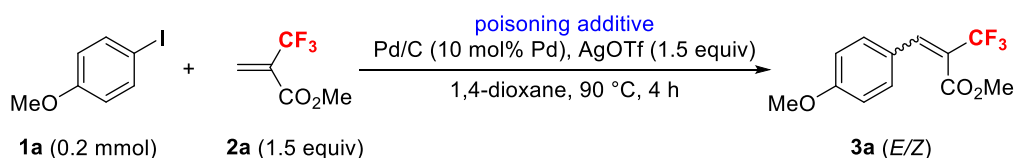
¹⁸⁹ (a) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609–679; (b) D. B. Eremin, V. P. Ananikov, *Coord. Chem. Rev.* **2017**, *346*, 2–19.

¹⁹⁰ J. A. Widegren, R. G. Finke, *J. Mol. Catal. A Chem.* **2003**, *198*, 317–341.

¹⁹¹ (a) J. Aydin, J. M. Larsson, N. Selander, K. J. Szabó, *Org. Lett.* **2009**, *11*, 2852–2854; (b) O. N. Gorunova, I. M. Novitskiy, Y. K. Grishin, I. P. Gloriovov, V. A. Roznyatovsky, V. N. Khrustalev, K. A. Kochetkov, V. V. Dunina, *Organometallics* **2018**, *37*, 2842–2858.

required to completely inhibit the homogeneous catalysis.^{190,192} In the reaction system of **1a** and **2a** with Pd/C and AgOTf, the addition of excess Hg(0) or substoichiometric amount of CS₂ per metal atom could completely inhibit the reaction (**Table 18**, entries 2-3). These results indicate that palladium nanoparticle is likely to be the key active species in Pd/C catalysis.

Table 18 Poisoning experiments with Pd/C and AgOTf^a



| Entry | poisoning additive | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|-------|---|--|------------------------|
| 1 | — | 87% | 76/24 |
| 2 | Hg (one drop) | — | — |
| 3 | CS ₂ (0.5 equiv per Pd atom) | traces | — |
| 4 | CS ₂ (2.0 equiv per Pd atom) | — | — |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (10 mol% Pd), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, 4 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

However, the reactions catalyzed by Pd(TFA)₂, which are generally regarded as a homogeneous catalyst, were also affected by Hg(0) and CS₂. About half of the reaction was suppressed when the poisoning experiment was carried out in the reaction system of **1a** and **2a** with Pd(TFA)₂ and AgOTf (**Table 19**, entries 2-3). In comparison, almost complete inhibition was observed when excess Hg(0) or substoichiometric amount of CS₂ per metal atom was added to the reaction system of **1a** and **2b** with Pd(TFA)₂ and Ag₂CO₃ (**Table 20**, entries 2-3). These results may imply the *in-situ* formation of active palladium nanoparticles from Pd(TFA)₂ in the absence of ligand stabilization,^{189b} but this may also indicate that it is problematic to judge heterogeneous or homogeneous catalysis through poisoning experiments. Indeed, in the review of Jones,^{189a} they suggested that the inhibitory effect of Hg(0) on the reaction cannot be used as evidence of heterogeneous catalysis, but can prove the presence of Pd(0) (soluble or particles) in the reaction system. Besides, Hg(0) itself may affect the reaction instead of poisoning the catalyst. Jones and co-workers also pointed out the limitations of CS₂ poisoning. Since the exact number of active catalytic species is uncertain, it is difficult to establish an appropriate equivalent of CS₂. Therefore, the CS₂ test is not convincing evidence to distinguish between homogeneous and heterogeneous catalysis. Based on these analyses, it is still uncertain whether nanoparticle catalysis or leaching-driven catalysis is present in the system of Pd/C catalysis despite the inhibitory effects of Hg(0) and CS₂.

¹⁹² B. J. Hornstein, J. D. Aiken III, R. G. Finke, *Inorg. Chem.* **2002**, *41*, 1625–1638.

Table 19 Poisoning experiments with Pd(TFA)₂ and AgOTf^a

| Entry | poisoning additive | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-------|---|--|-------------------------------|
| 1 | — | 93% | 76/24 |
| 2 | Hg (one drop) | 42% | 74/26 |
| 3 | CS ₂ (0.5 equiv per Pd atom) | 38% | 78/22 |
| 4 | CS ₂ (2.0 equiv per Pd atom) | — | — |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

Table 20 Poisoning experiments with Pd(TFA)₂ and Ag₂CO₃^a

| Entry | poisoning additive | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-------|---|--|-------------------------------|
| 1 | — | 90% | 85/15 |
| 2 | Hg (one drop) | — | — |
| 3 | CS ₂ (0.5 equiv per Pd atom) | 5% | — |
| 4 | CS ₂ (2.0 equiv per Pd atom) | — | — |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), *tert*-butyl 2-(trifluoromethyl)acrylate **2b** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (0.4 mmol, 2 equiv), 1,4-dioxane (1.0 mL), 90 °C, 2 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

We then turned our attention to the leaching process, forming soluble Pd species from Pd/C. A good way to identify the occurrence of leaching is to measure the Pd content in the solution.¹⁹³ After removing insoluble solids from the reaction mixture at the beginning or at the end of the reaction (5 min or 4 h), we measured the content of Pd in the crude of the filtrate by ICP-AES (Inductively Coupled Plasma Atomic Emission Spectroscopy). The mass concentrations of Pd in the crude of filtrates are 58 ppm for 5 min reaction and 11 ppm for 4 h reaction, respectively (**Table 21**). These results indicate a low concentration of Pd in the solution, but the homogeneous catalytic process cannot be ruled out because the dissolved Pd species tends to redeposit into the nanoparticles at a certain point, usually at the end of the transformation.^{189b}

¹⁹³ K. Köhler, R. G. Heidenreich, J. G. E. Krauter, J. Pietsch, *Chem. Eur. J.* **2002**, *8*, 622–631.

Table 21 Measurement of Pd content in the crude of filtrate^a

| Entry | t | Weight of crude of filtrate (mg) | Content of Pd in the crude of filtrate (mg) ^b | Mass concentration of Pd in the crude of filtrate (ppm) |
|-------|-------|----------------------------------|--|---|
| 1 | 5 min | 69.2 | 0.003995 | 58 |
| 2 | 4 h | 70.9 | 0.000785 | 11 |

^aReaction conditions: **1c** (0.2 mmol, 1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (10 mol% Pd), AgOTf (0.3 mmol, 1.5 equiv), 1,4-dioxane (1.0 mL), 90 °C, t; then, hot filtration to remove insoluble solids, and the filtrate was evaporated under reduced pressure, dried in vacuo to provide the crude of filtrate. ^bContent of Pd in the crude of filtrate was determined by ICP-AES.

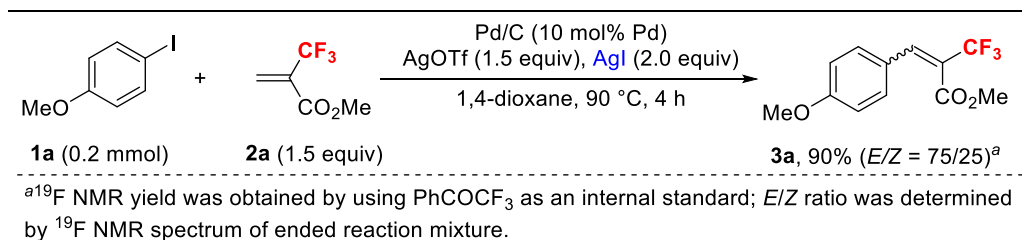
Köhler and co-workers proposed that the poor recycling capacity of the Pd/C catalyst could provide indirect evidence for leaching-driven catalysis because the leaching-redeposition process leads to the change of Pd dispersion and incorporation of impurities. Consequently, the catalytic activity is reduced, which is not conducive to the recycling of the catalyst.¹⁹³ Consistent with the research results of Köhler, the catalyst recycling ability of Pd/C was unsatisfactory in our reaction system (**Table 22**). In 0.2 mmol scale reactions, only the first reuse of Pd/C catalyst can give results comparable to the initial catalysis, and a sharp drop in the yield of **3a** was observed for the second reuse of Pd/C catalyst regardless of room temperature filtration or hot filtration (**Table 22**, entries 1-3 and entries 4-6). In order to avoid the influence of weight loss of Pd/C during filtration in small-scale reactions, we tried to scale up the reaction to 1.0 mmol. Surprisingly, under the same conditions as the 0.2 mmol scale reaction, only traces of **3a** could be observed in the ¹⁹F NMR spectrum for the 1.0 mmol scale reaction in the presence of the fresh catalyst. Increasing the reaction temperature to 110 °C and extending the reaction time to 15 h allowed us to obtain **3a** in 69% yield with 80/20 of *E/Z* ratio (**Table 22**, entry 7). We then studied the recycling of catalyst under the modified 1.0 mmol scale reaction, but even the first reuse of Pd/C catalyst proved to be inefficient (**Table 22**, entry 8). It is still not clear why there is such a difference between 0.2 mmol and 1.0 mmol scale reactions.

It is worth noting that the generated AgI in our reaction system could not be removed from the Pd/C catalyst and was added to the next reaction conditions with the reuse of the Pd/C catalyst. We wondered if the presence of AgI would affect the ability of catalyst recycling. Comparing the results of **Scheme 81** and entry 1 of **Table 16** (see page 86), it turns out that the presence of AgI has no effect on the efficiency and selectivity of the reaction. Therefore, the presence of AgI is unlikely to be the cause of the failure of catalyst recycling.

Table 22 Recycling study of Pd/C catalyst^a

| Entry | Pd/C | 1a (x mmol) | filtration temperature | yield ^b | <i>E/Z</i> ratio ^c |
|----------------|-----------------------------|--------------------|------------------------|---------------------|-------------------------------|
| 1 | fresh catalyst ^d | 0.2 | rt | 80% | 76/24 |
| 2 | 1st reuse | 0.2 | rt | 75% | 76/24 |
| 3 | 2nd reuse | 0.2 | rt | 21% ^e | 69/31 ^f |
| ----- | | | | | |
| 4 | fresh catalyst ^d | 0.2 | hot (~ 90 °C) | 79% ^e | 76/24 ^f |
| 5 | 1st reuse | 0.2 | hot (~ 90 °C) | 69% | 76/24 |
| 6 | 2nd reuse | 0.2 | hot (~ 90 °C) | 25% ^e | 84/16 ^f |
| ----- | | | | | |
| 7 ^g | fresh catalyst ^d | 1.0 | rt | 69% | 80/20 |
| 8 ^g | 1st reuse | 1.0 | rt | traces ^e | — |

^aReaction conditions: **1a** (1.0 equiv), methyl 2-(trifluoromethyl)acrylate **2a** (1.5 equiv), Pd/C, AgOTf (1.5 equiv), 1,4-dioxane, 90 °C, 4 h. ^bYields based on isolated product after silica gel column chromatography. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^dPd/C (Palladium, 10% on carbon, type 487, dry) (10 mol% Pd). ^e¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^f*E/Z* ratio was determined by ¹⁹F NMR spectrum of filtrate. ^g110 °C, 15 h.

**Scheme 81** Effect of AgI on the reaction efficiency

Considering all the experimental results from **Table 18** to **Table 22** as well as **Scheme 81**, no definite conclusion can be provided whether it is heterogeneous nanoparticle catalysis or leaching-driven homogeneous catalysis.

2.6 Conclusion

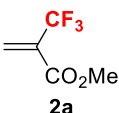
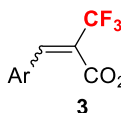
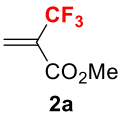
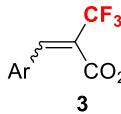
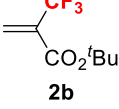
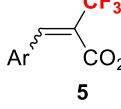
In conclusion, we have achieved the synthesis of diverse methyl or *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates from aryl iodides (**1**) and 2-(trifluoromethyl)acrylates (**2**) by Mizoroki-Heck reaction in the presence of palladium catalyst and silver(I) additive.¹⁹⁴

Different 2-(trifluoromethyl)acrylates (**2**) exhibited significantly different reactivity (**Table 23**). Methyl 2-(trifluoromethyl)acrylate (**2a**) was quite reactive in several

¹⁹⁴ (a) P. Xiao, C. Schlinquer, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *J. Org. Chem.* **2019**, *84*, 2072–2082; (b) P. Xiao, C. Schlinquer, X. Pannecoucke, S. Couve-Bonnaire, J.-P. Bouillon, *J. Fluorine Chem.* **2020**, *233*, 109483.

different palladium-catalysed, silver (I) additive-mediated reaction conditions such as the conditions of Pd(TFA)₂-AgOTf and Pd/C-AgOTf (**Table 23**, entries 1-2), offering a good alternative and a general method to access these valuable products. In comparison, *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**) only worked well in the presence of Pd(TFA)₂ and Ag₂CO₃ (**Table 23**, entry 3). Different reaction mechanisms were proposed for different palladium-catalysed, silver (I) additive-mediated reaction systems.

Table 23 Reactivity of different 2-(trifluoromethyl)acrylates in Mizoroki-Heck reaction

| $\text{Ar-I} + \text{CH}_2=\text{C}(\text{CF}_3)\text{CO}_2\text{R} \xrightarrow{\text{Reaction conditions}} \text{Ar-CH}=\text{C}(\text{CF}_3)\text{CO}_2\text{R}$ | | | |
|---|---|--|---|
| 1 (1.0 equiv) | 2 (1.5 equiv) | 3 or 5 (<i>E</i> major) | |
| Entry | 2 | Reaction conditions | Results |
| 1 |  | Pd(TFA) ₂ (10 or 1.5 mol%) AgOTf (1.5 equiv) 1,4-dioxane, 90 °C, 2 h |  27 examples 45-92% yield <i>E/Z</i> from 55/45 to 79/21 |
| 2 |  | Pd/C (10 mol%) AgOTf (1.5 equiv) 1,4-dioxane, 90 or 110 °C, 4 h |  18 examples 29-98% yield <i>E/Z</i> from 55/45 to 76/24 |
| 3 |  | Pd(TFA) ₂ (10 mol%) Ag ₂ CO ₃ (2.0 equiv) 1,4-dioxane, 90 °C, 2 h |  11 examples 53-99% yield <i>E/Z</i> from 52/48 to 87/13 |

Regarding the *E/Z* selectivity, *E* isomers were always the major products. Moderate *E/Z* selectivity for products **3** was obtained and products **5** exhibited a better *E/Z* ratio. Both electronic properties of aryl iodides and 2-(trifluoromethyl)acrylates affect the *E/Z* selectivity. Stereoelectronic effects provide an important perspective for explaining the current *E/Z* selectivity.

Importantly, the efficient one-pot synthesis of 3-trifluoromethyl coumarin derivatives was achieved starting from *ortho*-iodophenols and methyl 2-(trifluoromethyl)acrylate by tandem Mizoroki-Heck reaction and intramolecular cyclization. This method constitutes a straightforward alternative to the synthesis of 3-trifluoromethyl coumarin derivatives.

Chapter 3

Access to 3-aryl-2-(trifluoromethyl) acrylic acids by palladium-catalysed Mizoroki-Heck reaction

3 Access to 3-aryl-2-(trifluoromethyl)acrylic acids by palladium-catalysed Mizoroki-Heck reaction

3.1 State of the art

Organic molecules containing 2-(trifluoromethyl)acrylic acid scaffolds have been used in the fields of medicinal chemistry and materials science. For instance, both (*E*)- and (*Z*)-4-amino-2-(trifluoromethyl)but-2-enoic acids have inactivation effects on γ -aminobutyric acid aminotransferase (GABA-AT) which is related to several kinds of diseases including Parkinson's disease, Alzheimer's disease, and Huntington's chorea (**Figure 11**, left).¹⁹⁵ Besides, the photosensitized dye **MCL27** (*E/Z* = 51/49) can be used in the dye-sensitized solar cells (DSSCs) and the latter shows high IPCE (incident photon-to-current efficiency) performances. This kind of 3-aryl-2-(trifluoromethyl)acrylic acids have broad application prospects in new DSSC dyes (**Figure 11**, right).¹⁹⁶

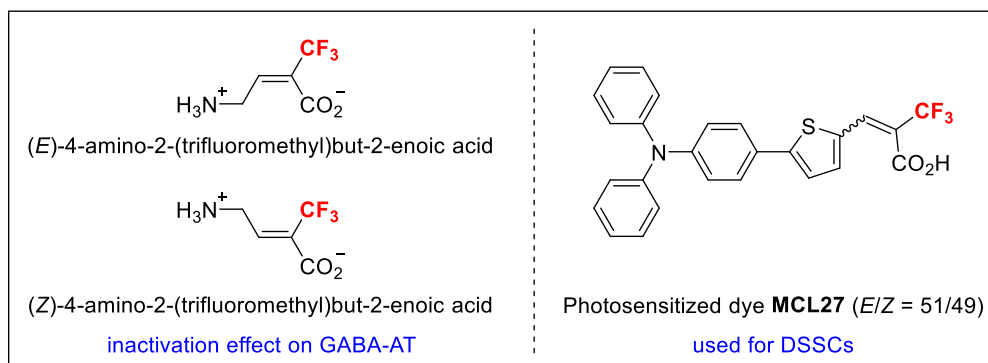


Figure 11 Applications of 3-substituted 2-(trifluoromethyl)acrylic acids in medicinal chemistry and materials science

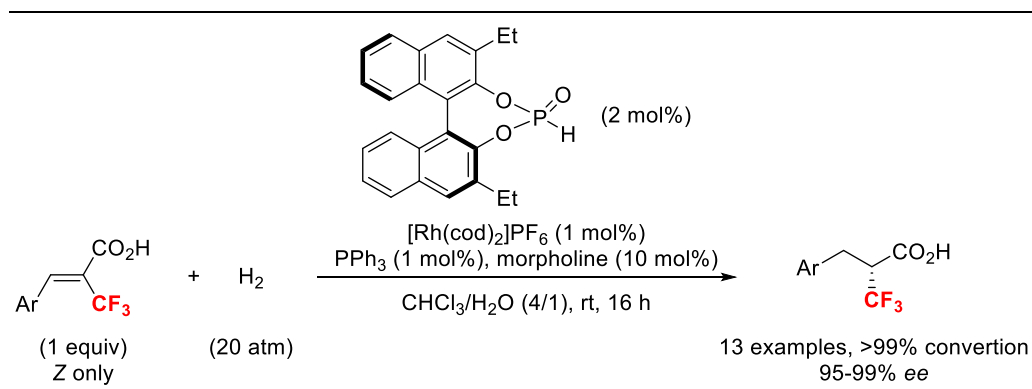
3-Aryl-2-(trifluoromethyl)acrylic acids were also valuable synthetic intermediates for the preparation of optically active CF_3 -containing propanoic acid derivatives which are biologically important (**Scheme 82**).¹⁹⁷ Furthermore, Fang and co-workers proposed that 3-aryl-2-(trifluoromethyl)acrylic acids would be valuable building blocks for the synthesis of CF_3 -substituted amino acids and alcohols with good biological importance, as well as the synthesis of 2-(trifluoromethyl)acrylic acid-

¹⁹⁵ T. R. Johnson, R. B. Silverman, *Bioorg. Med. Chem.* **1999**, *7*, 1625–1636.

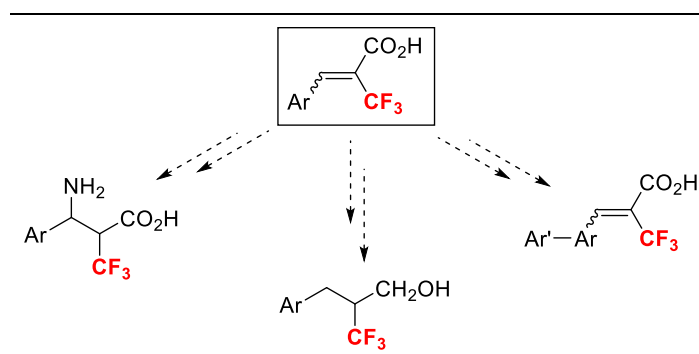
¹⁹⁶ S. Iwata, S. Oshio, S. Kobayashi, M. Aoyama, K. Tanaka, *Chem. Lett.* **2015**, *44*, 1398–1400.

¹⁹⁷ K. Dong, Y. Li, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 14191–14195.

containing π -conjugated molecules which exhibited application value in the field of optoelectronics (**Scheme 83**).¹⁹⁸



Scheme 82 Construction of chiral CF₃-containing propanoic acid derivatives from 3-aryl-2-(trifluoromethyl)acrylic acids



Scheme 83 Possible transformations with 3-aryl-2-(trifluoromethyl)acrylic acids as building blocks

In spite of the obvious interest of 3-aryl-2-(trifluoromethyl)acrylic acids, only three methodologies have been developed for their synthesis. In 1973, an indirect example for the synthesis of 3-(4-(dimethylamino)phenyl)-2-(trifluoromethyl)acrylic acid was reported by hydrolysis of the corresponding acryloyl fluoride, which was obtained from the reaction of 3,3-difluoro-2-(trifluoromethyl)acryloyl fluoride and 4-(dimethylamino)benzaldehyde (**Scheme 84**, Eq. a).¹⁹⁹ Four years later, the preparation of 2-(trifluoromethyl)acrylic acid derivatives was realized through the reaction of 3,3,3-trifluoro-2-(trifluoromethyl)propanoic acid with Grignard reagents. Two kinds of tetrasubstituted 2-(trifluoromethyl)acrylic acids were both generated in low yields (**Scheme 84**, Eq. b).²⁰⁰ Over the next three decades, no other related synthetic methods were developed. Then in 2011, Fang and co-workers achieved the synthesis of 3-aryl-2-(trifluoromethyl)acrylic acids from 3,3,3-trifluoropropanoic acid and aryl aldehydes by Knoevenagel reaction in the presence of TiCl₄ and Et₃N (**Scheme 84**, Eq. c).¹⁹⁸ All of these methods show a fairly narrow substrate scope.

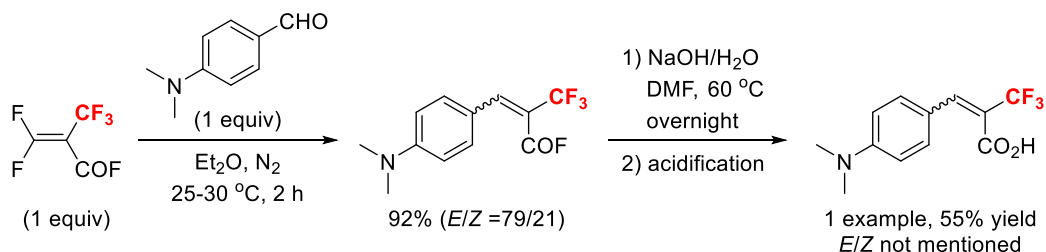
¹⁹⁸ Y. Liu, H. Lai, B. Rong, T. Zhou, J. Hong, C. Yuan, S. Zhao, X. Zhao, B. Jiang, Q. Fang, *Adv. Synth. Catal.* **2011**, *353*, 3161–3165.

¹⁹⁹ D. C. England, L. Solomon, C. G. Krespan, *J. Fluorine Chem.* **1973**, *3*, 63–89.

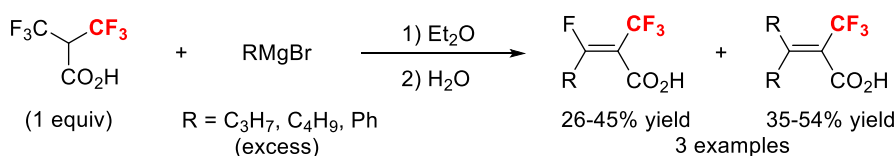
²⁰⁰ V. L. Isaev, T. D. Truskanova, N. V. Sotnikov, R. N. Sterlin, I. L. Knunyants, *Zh. Vses. Khim. O-va. im. D. I. Mendeleeva* **1977**, *22*, 711–713.

Besides, the first method released highly toxic carbonyl fluoride (COF₂) as a side product; the second strategy got two kinds of products without a major one. To date, the last method is the best one, giving high yield and selectivity (Z major). Nevertheless, this method used strongly corrosive TiCl₄ and required a long reaction time (40 h).

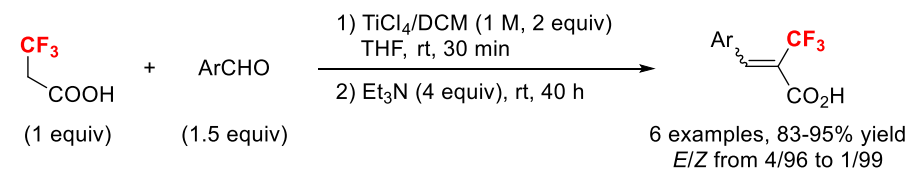
Eq. a) In 1973, England *et al.*



Eq. b) In 1977, Isaev *et al.*



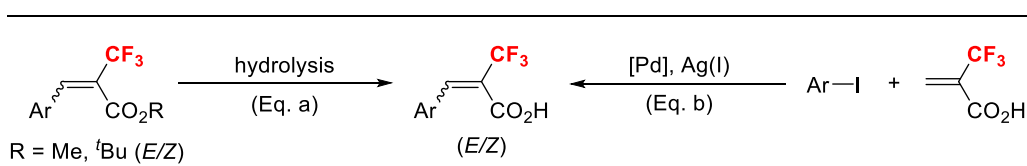
Eq. c) In 2011, Fang *et al.*



Scheme 84 Methods for the synthesis of 3-aryl-2-(trifluoromethyl)acrylic acids

3.2 Objectives

Although 3-aryl-2-(trifluoromethyl)acrylic acids are interesting compounds as mentioned above, the methodologies for their preparation are underdeveloped. Therefore, the second objective of this thesis focuses on the construction of 3-aryl-2-(trifluoromethyl)acrylic acids either by hydrolysis of the corresponding 3-aryl-2-(trifluoromethyl)acrylates or by palladium-catalysed Mizoroki-Heck coupling of aryl iodides with 2-(trifluoromethyl)acrylic acid (**Scheme 85**). The 3-aryl-2-(trifluoromethyl)acrylic acids are intended to be used in decarboxylative cross-coupling reactions as well as radical chemistry later.



Scheme 85

3.3 Hydrolysis of 3-aryl-2-(trifluoromethyl)acrylates

Since a variety of methyl 3-aryl-2-(trifluoromethyl)acrylates were obtained before, we initially wanted to convert them directly into 3-aryl-2-(trifluoromethyl)acrylic acids by hydrolysis. The *E/Z* mixture of methyl 3-phenyl-2-(trifluoromethyl)acrylate was selected as a model substrate to test the hydrolysis conditions. Firstly, potassium hydroxide¹²⁹ was used to promote hydrolysis, but no desired product was obtained and the starting material seemed to be defluorinated (**Table 24**, entry 1). Then, sodium hydroxide²⁰¹ and lithium hydroxide²⁰² were tested, respectively, just affording the desired product in low yield with impurities (**Table 24**, entries 2-3). The combination of lithium hydroxide and hydrogen peroxide²⁰³ proved to be unsuccessful because only the side-product benzoic acid was formed (**Table 24**, entry 4).

Table 24 Hydrolysis of methyl 3-phenyl-2-(trifluoromethyl)acrylate in alkaline conditions

COC(=C(C(F)(F)F)C1=CC=CC=C1) >> OC(=C(C(F)(F)F)C1=CC=CC=C1)

| Entry | Alkaline conditions | Results |
|-------|---|--|
| 1 | KOH (10 equiv), EtOH/H ₂ O (5/1) reflux, 28 h | Starting material decomposed No desired product |
| 2 | NaOH (10 equiv), 1,4-dioxane/H ₂ O (5/1) rt, 7 h; 90 °C, 24 h | Starting material decomposed Desired product: 27% (impure, <i>E</i> only) |
| 3 | LiOH (10 equiv), THF/H ₂ O (5/1) reflux, 18 h | Starting material decomposed Desired product: 28% (impure, <i>E/Z</i> = 71/29) |
| 4 | LiOH (20 equiv), aqueous H ₂ O ₂ (30%) (10 equiv), THF/H ₂ O/MeOH (4/1/1) rt, 16 h; reflux, 24 h | Side product: PhCO ₂ H, 93% |

Because alkaline conditions could not provide satisfactory results, we then tried the hydrolysis under acidic conditions. Unfortunately, the tested Brønsted acids (*p*-toluenesulfonic acid monohydrate,²⁰⁴ trifluoroacetic acid,²⁰⁵ and dilute sulfuric acid) did not work at all for the hydrolysis of methyl 3-phenyl-2-(trifluoromethyl)acrylate, and only the substrate was recovered (**Table 25**, entries 1-3). Later, we tried Lewis acid boron tribromide,²⁰⁶ which is often used for the demethylation of ether compounds. Some desired product was generated with boron tribromide; however, it was difficult to do purification and to confirm the isolated yield (**Table 25**, entry 4).

²⁰¹ D. M. Goldstein, K. A. Brameld, WO Patent 2012158795, **2012**.

²⁰² C. W. Wullschleger, J. Li, A. Edenharter, K.-H. Altmann, *Synlett* **2016**, 27, 2726–2730.

²⁰³ H. Liu, S. Song, C.-Q. Wang, C. Feng, T.-P. Loh, *ChemSusChem* **2017**, 10, 58–61.

²⁰⁴ Y. Cheburkov, G. G. I. Moore, *J. Fluorine Chem.* **2003**, 123, 227–231.

²⁰⁵ A. D. Ievins, A. O. Moughton, R. K. O'Reilly, *Macromolecules* **2008**, 41, 3571–3578.

²⁰⁶ M. Castella, F. López-Calahorra, D. Velasco, H. Finkelmann, *Liq. Cryst.* **2002**, 29, 559–565.

Table 25 Hydrolysis of methyl 3-phenyl-2-(trifluoromethyl)acrylate in acidic conditions

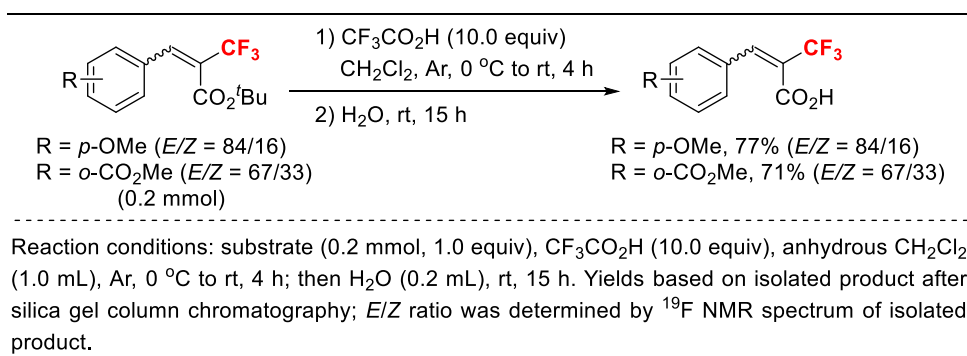
(*E/Z* = 73/27)
(0.2 mmol)

Acidic conditions

(*E/Z*)

| Entry | Acidic conditions | Results |
|-------|--|---|
| 1 | <i>p</i> -TsOH•H ₂ O 150 °C, 30 min | Starting material recovered No desired product |
| 2 | CF ₃ CO ₂ H (10.0 equiv) CH ₂ Cl ₂ , Ar, 0 °C to rt, 4 h then H ₂ O, rt, 15 h | Starting material recovered No desired product |
| 3 | aq. H ₂ SO ₄ (20 wt%) (10.0 equiv) DMF/MeCN (1/1), 80 °C, 6 h | Starting material recovered No desired product |
| 4 | BBr ₃ /CH ₂ Cl ₂ (1.0 M) (5.0 equiv) CH ₂ Cl ₂ 0.8 mL, -78 °C; then 0 °C, 5.5 h | Complex mixture |

Considering that *tert*-butyl esters were more prone to acidic hydrolysis than methyl esters, we then turned our attention to the hydrolysis of *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates under acidic conditions. To our delight, *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates could be smoothly converted into the corresponding acrylic acids in the presence of trifluoroacetic acid.²⁰⁵ As shown in **Scheme 86**, two examples were done by He Wang, a master student in INSA Rouen Normandie. Good yields of products were obtained and the retention of the *E/Z* ratio was observed.

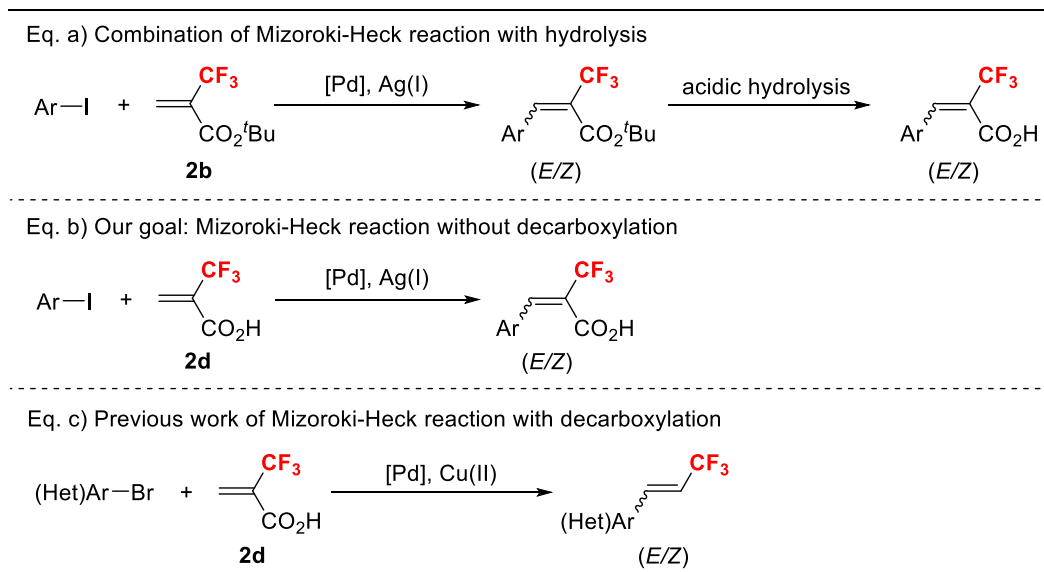
**Scheme 86** Hydrolysis of *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates in acidic conditions

Comparing the hydrolysis ability of methyl and *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates, the former were poor substrates in both alkaline and acidic conditions, while the latter were good substrates in acidic conditions.

3.4 Access to 3-aryl-2-(trifluoromethyl)acrylic acids by Mizoroki-Heck reaction with Pd(TFA)₂ and Ag₂CO₃

Although the construction of 3-aryl-2-(trifluoromethyl)acrylic acids could be achieved by arylation of *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**) with subsequent hydrolysis

(**Scheme 87**, Eq. a), the two-step process was complicated. Moreover, the price of 2-(trifluoromethyl)acrylic acid (**2d**) (0.70 \$/mmol) was five to six times cheaper than that of **2b**. In this context, it was worth trying to synthesize 3-aryl-2-(trifluoromethyl)acrylic acids directly from aryl iodides and **2d** by Mizoroki-Heck reaction avoiding decarboxylation process (**Scheme 87**, Eq. b). Indeed, the cross-coupling of (hetero)aryl bromides with **2d** has already been investigated, but the decarboxylated products were generated instead of 3-aryl-2-(trifluoromethyl)acrylic acids (**Scheme 87**, Eq. c).¹⁰⁶



Scheme 87

3.4.1 Optimization of reaction conditions

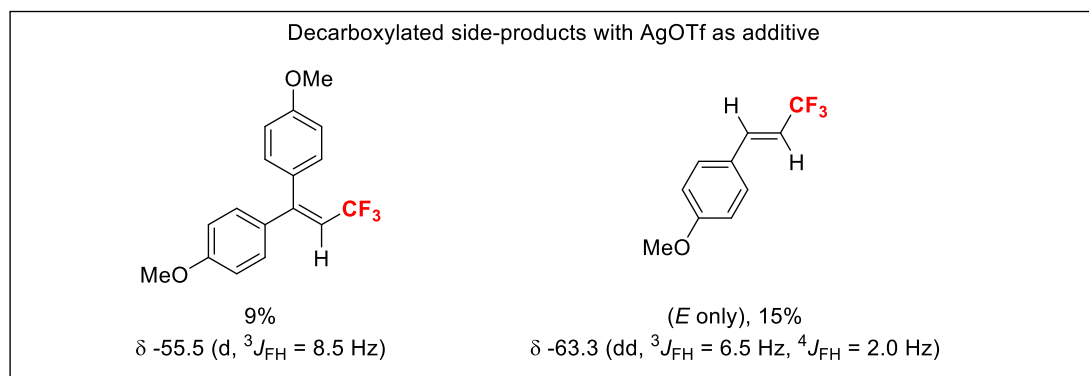
Following the optimized reaction conditions of Mizoroki-Heck reaction between 4-iodoanisole (**1a**) and *tert*-butyl 2-(trifluoromethyl)acrylate (**2b**) (see page 78, **Table 13**, entry 3), we started to test the possibility of Mizoroki-Heck reaction between **1a** and 2-(trifluoromethyl)acrylic acid (**2d**). In the presence of 1,4-dioxane, Pd(TFA)₂, and Ag₂CO₃, the desired product **7a** was formed in 91% of ¹⁹F NMR yield with 62/38 of *E/Z* ratio (**Table 26**, entry 1). Using DMF as a solvent, worse results were obtained for both the yield and *E/Z* selectivity (**Table 26**, entry 2). Although a better yield of **7a** was observed in the ¹⁹F NMR spectrum with toluene as solvent, we failed to get the pure isolated product (**Table 26**, entry 3). Hence, 1,4-dioxane was chosen as the optimal solvent. Decreasing the catalyst loading of Pd(TFA)₂ to 5 mol% did not reduce the yield of the desired product (**Table 26**, entry 4), but a worse result was obtained when 1.5 mol% Pd(TFA)₂ was involved (**Table 26**, entry 5). Pd(OAc)₂ and PdBr₂ were also effective in catalysing the cross-coupling of **1a** with **2d**, although the yield of **7a** was slightly lower than that of Pd(TFA)₂ (**Table 26**, entries 4, 6-7). In contrast, only traces of **7a** was detected when Pd/C was involved (**Table 26**, entry 8). No desired product was observed with K₂CO₃ as an additive (**Table 26**, entry 9),

probably because **2d** was deprotonated by K_2CO_3 to give the potassium salt of **2d**, which would be difficult to dissolve in 1,4-dioxane. Besides, the use of AgOTf gave only 35% yield of **7a**, and two decarboxylated side-products were formed as well (Table 26, entry 10; see the structures of side-products at the bottom of Table 26). In contrast, with Ag_2CO_3 as the additive, no decarboxylation process occurred. Unfortunately, adding phosphine ligands to the reaction conditions did not give better *E/Z* selectivity (Table 26, entries 11-13).

Table 26 Screening of solvents, [Pd] catalysts, additives, and ligands^a

| Entry | Solvent | [Pd] Catalyst (x mol%) | Additive | ¹⁹ F NMR yield ^b | <i>E/Z</i> ratio ^c |
|-----------------|-------------|----------------------------|---------------------------------|--|-------------------------------|
| 1 | 1,4-dioxane | Pd(TFA) ₂ (10) | Ag ₂ CO ₃ | 91% | 62/38 |
| 2 | DMF | Pd(TFA) ₂ (10) | Ag ₂ CO ₃ | 74% | 48/52 |
| 3 | Toluene | Pd(TFA) ₂ (10) | Ag ₂ CO ₃ | >99% ^d | 62/38 |
| 4 | 1,4-dioxane | Pd(TFA) ₂ (5) | Ag ₂ CO ₃ | 91% | 66/34 |
| 5 | 1,4-dioxane | Pd(TFA) ₂ (1.5) | Ag ₂ CO ₃ | 80% | 68/32 |
| 6 | 1,4-dioxane | Pd(OAc) ₂ (5) | Ag ₂ CO ₃ | 86% | 65/35 |
| 7 | 1,4-dioxane | PdBr ₂ (5) | Ag ₂ CO ₃ | 74% | 66/34 |
| 8 | 1,4-dioxane | Pd/C ^e (10) | Ag ₂ CO ₃ | traces | — |
| 9 | 1,4-dioxane | Pd(TFA) ₂ (5) | K ₂ CO ₃ | — | — |
| 10 | 1,4-dioxane | Pd(TFA) ₂ (5) | AgOTf | 35% ^f | 66/34 |
| 11 ^g | 1,4-dioxane | Pd(TFA) ₂ (5) | Ag ₂ CO ₃ | 99% | 60/40 |
| 12 ^h | 1,4-dioxane | Pd(TFA) ₂ (5) | Ag ₂ CO ₃ | 96% | 66/34 |
| 13 ⁱ | 1,4-dioxane | Pd(TFA) ₂ (5) | Ag ₂ CO ₃ | 39% | 63/37 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), [Pd] catalyst (x mol%), additive (2.0 equiv), solvent (1.0 mL), 0.2 M, 90 °C, 4 h. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dFailed to get pure isolated product. ^ePd/C (palladium, 10% on carbon, type 487, dry). ^fAlongside with decarboxylated side-products (see bottom for structures). ^gPPh₃ (10 mol%), 1 h. ^hP^tBu₃•HBF₄ (10 mol%), 1 h. ⁱdppe (5 mol%), 1 h.



Then, we screened the equivalents of Ag_2CO_3 , temperature, concentration, and reaction time (Table 27). Good yield of **7a** was obtained in most of the tested conditions, and the optimized reaction conditions were determined as follows: **1a** (0.2

mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (1.1 equiv), 1,4-dioxane (0.5 mL), concentration (0.4 M), 90 °C, 1 h (**Table 27**, entry 12).

Table 27 Screening of Ag₂CO₃ equivalent, temperature, concentration, and reaction time^a

| Entry | Ag ₂ CO ₃ (x equiv) | T (°C) | concentration (y M) | t | ¹⁹ F NMR yield ^b | E/Z ratio ^c |
|-------|---|--------|---------------------|--------|--|------------------------|
| 1 | Ag ₂ CO ₃ (2.0) | 90 | 0.2 | 4 h | 91% | 66/34 |
| 2 | Ag ₂ CO ₃ (1.5) | 90 | 0.2 | 4 h | 88% | 66/34 |
| 3 | Ag ₂ CO ₃ (1.1) | 90 | 0.2 | 4 h | 85% | 64/36 |
| 4 | Ag ₂ CO ₃ (0.5) | 90 | 0.2 | 4 h | 61% | 64/36 |
| 5 | Ag ₂ CO ₃ (1.1) | 110 | 0.2 | 4 h | 84% | 66/34 |
| 6 | Ag ₂ CO ₃ (1.1) | 70 | 0.2 | 4 h | 85% | 61/39 |
| 7 | Ag ₂ CO ₃ (1.1) | 50 | 0.2 | 4 h | 10% | 56/44 |
| 8 | Ag ₂ CO ₃ (1.1) | 90 | 0.1 | 4 h | 74% | 67/33 |
| 9 | Ag ₂ CO ₃ (1.1) | 90 | 0.4 | 4 h | 95% | 64/36 |
| 10 | Ag ₂ CO ₃ (1.1) | 70 | 0.4 | 4 h | 89% | 61/39 |
| 11 | Ag ₂ CO ₃ (1.1) | 90 | 0.4 | 2 h | 95% | 63/37 |
| 12 | Ag ₂ CO ₃ (1.1) | 90 | 0.4 | 1 h | 93% | 64/36 |
| 13 | Ag ₂ CO ₃ (1.1) | 90 | 0.4 | 30 min | 91% | 63/37 |

^aReaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (x equiv), 1,4-dioxane, T, t. ^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

3.4.2 Substrate scope of the reaction

The substrate scope was then investigated with the optimized reaction conditions in hand. A temperature increase to 110 °C was required for some substrates to get better yields. Plenty of aryl iodides (**1**) successfully reacted with 2-(trifluoromethyl)acrylic acid (**2d**), furnishing the corresponding 3-aryl-2-(trifluoromethyl)acrylic acids (**7**) in moderate to excellent yields (**Table 28**). Diverse electron-donating groups (OMe, Me), electron-withdrawing groups (COMe, CO₂Me, CN, NO₂), and halogen groups were compatible in this reaction system. For the *para*-substituted substrates, high yields (88-98%) of products were usually obtained with similar E/Z ratios (around 64/36) (**7a-g**), except for 4-iodobenzonitrile which furnished a worse isolated yield and even opposite E/Z ratio (**7h**, 77%, E/Z = 46/54). Similar trends occurred on the *meta*-substituted substrates with **7i-k** formed in 85-98% yield (E/Z around 64/36), and lower yields with worse E/Z selectivity were also observed for **7l-m** when strongly electron-withdrawing groups (nitro, cyano) were involved. For aryl iodides bearing *ortho*-substituents, the results were inferior in both yield and E/Z selectivity (**7n-q**). Among them, a total reversion of the E/Z ratio was observed for chlorine or ester substituted aryl iodide (**7p-q**). *Poly*-substituted aryl

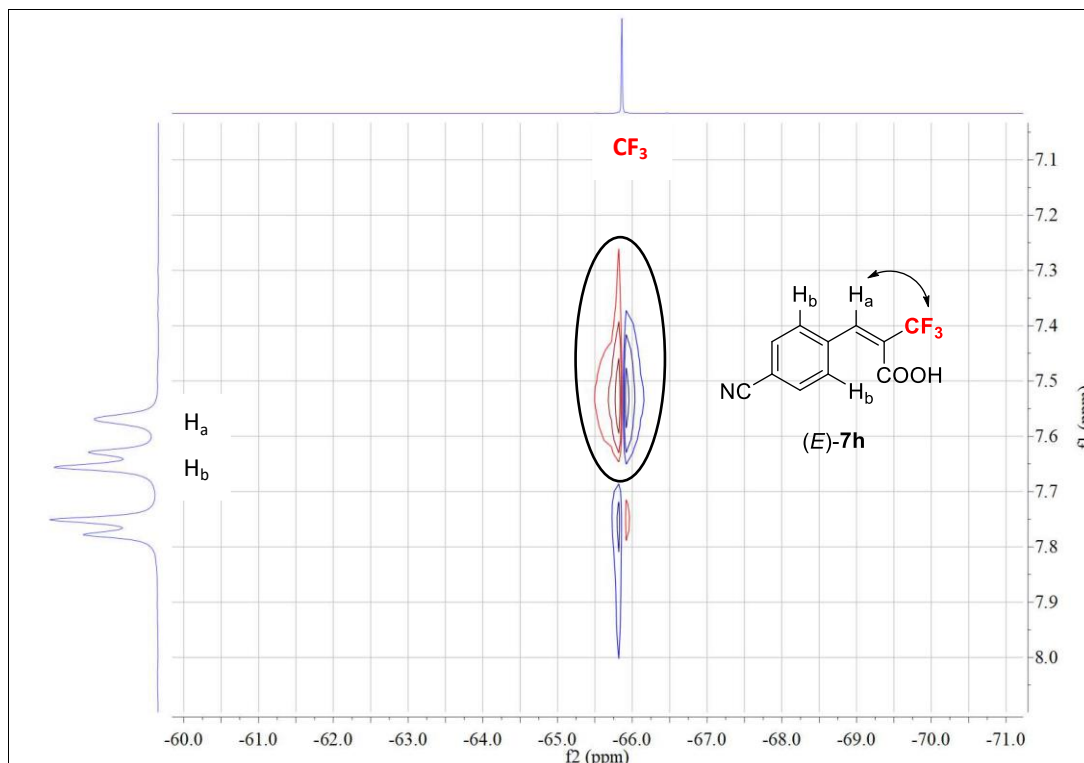
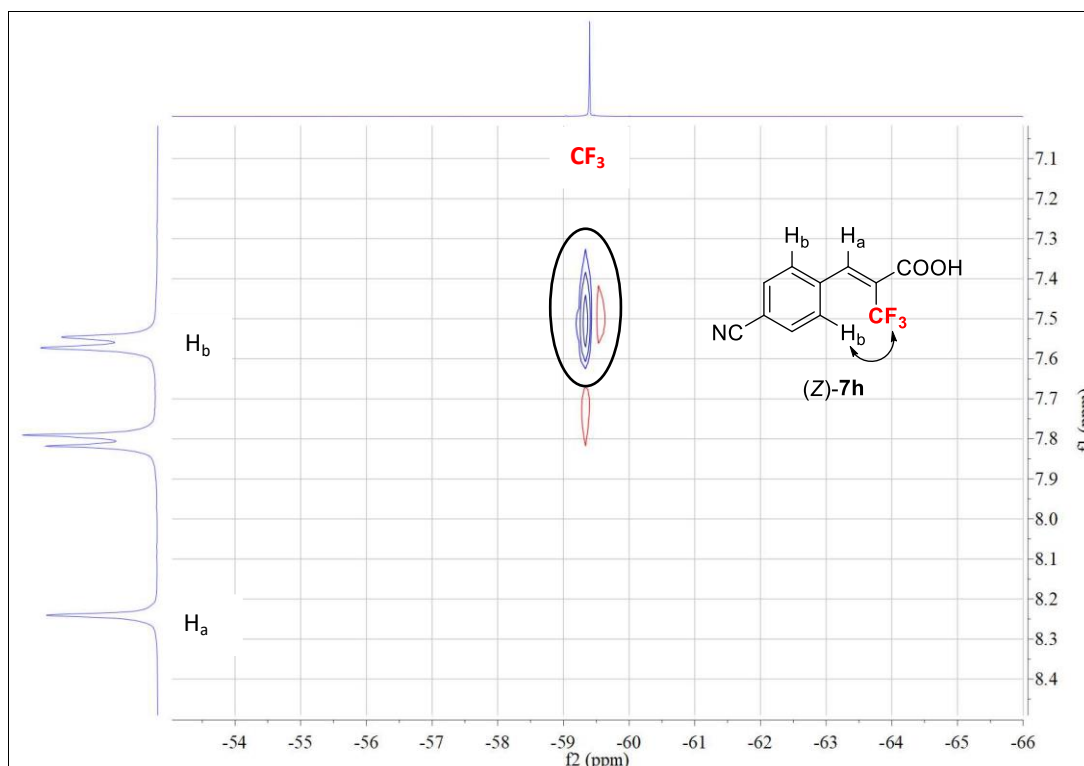
iodides also worked well in this reaction system, giving the corresponding products in good yields (**7r-t**). Larger scale reactions (2.0 mmol) were done, and similar yields of **7a**, **7c**, **7h** were obtained compared to those of small-scale reactions (0.2 mmol).

Table 28 Substrate scope of the reaction^a

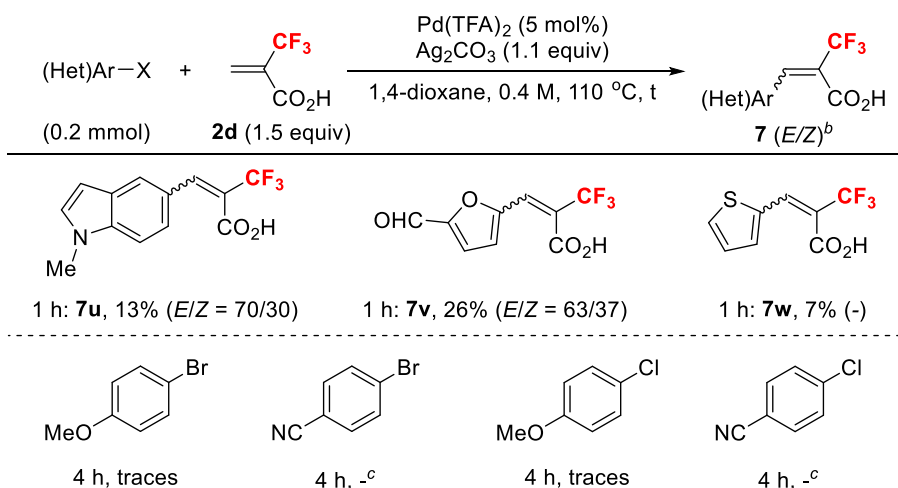
| $\text{Ar-I} + \text{CH}_2=\text{C}(\text{CF}_3)\text{CO}_2\text{H} \xrightarrow[\text{1,4-dioxane, 1 h, 0.4 M}]{\text{Pd(TFA)}_2 (5 \text{ mol}\%), \text{Ag}_2\text{CO}_3 (1.1 \text{ equiv})}$ $\text{Ar}-\text{CH}=\text{C}(\text{CF}_3)\text{CO}_2\text{H} \quad \mathbf{7 (E/Z)}^b$ | | |
|---|--|--|
| 1 | 2d | 7 (E/Z)^b |
| <i>para</i> -substituted | | |
| | | |
| 7a : R = OMe, | 89% ^c (E/Z = 64/36) 89% ^{c,d} (E/Z = 64/36) | (Z)-7h |
| 7b : R = Me, | 88% ^c (E/Z = 65/35) | |
| 7c : R = H, | 96% ^c (E/Z = 64/36) 90% ^{c,d} (E/Z = 64/36) | |
| 7d : R = Cl, | 98% ^e (E/Z = 63/37) | |
| 7e : R = Br, | 90% ^e (E/Z = 64/36) | |
| 7f : R = COMe, | 90% ^e (E/Z = 61/39) | |
| 7g : R = CO ₂ Me, | 88% ^c (E/Z = 64/36) | |
| 7h : R = CN, | 77% ^e (E/Z = 46/54) 79% ^{d,e} (E/Z = 53/47) | |
| <i>meta</i> -substituted | | |
| | | |
| 7i : R = OMe, | 85% ^e (E/Z = 67/33) | |
| 7j : R = Me, | 98% ^c (E/Z = 64/36) | |
| 7k : R = Cl, | 89% ^e (E/Z = 63/37) | |
| 7l : R = NO ₂ , | 82% ^e (E/Z = 52/48) | |
| 7m : R = CN, | 66% ^e (E/Z = 55/45) | |
| 7n : R = OMe, | 78% ^e (E/Z = 54/46) | |
| 7o : R = Me, | 86% ^e (E/Z = 57/43) | |
| 7p : R = Cl, | 63% ^e (E/Z = 37/63) | |
| 7q : R = CO ₂ Me, | 73% ^e (E/Z = 30/70) | |
| <i>poly</i> -substituted | | |
| | | |
| 7r : 76% ^e (E/Z = 66/34) | 7s : 79% ^c (E/Z = 71/29) | 7t : 91% ^c (E/Z = 65/35) |

^aReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (0.22 mmol, 1.1 equiv), 1,4-dioxane (0.5 mL), 0.4 M, 1 h. ^bYields based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c90 °C. ^d2.0 mmol scale reaction. ^e110 °C.

E and Z isomers of this reaction were assigned by ¹⁹F NMR spectra with the help of ¹⁹F-¹H HOESY experiments. The ¹⁹F-¹H spatial correlation of (E)-**7h** and (Z)-**7h** are shown in **Figure 12** and **Figure 13**, respectively. In addition, the configuration of (Z)-**7h** was unambiguously determined by X-ray crystallographic analysis (see **Table 28**).

Figure 12 ^{19}F - ^1H HOESY spectrum of (*E*)-7hFigure 13 ^{19}F - ^1H HOESY spectrum of (*Z*)-7h

Some limitations of the substrate scope were found as shown in **Table 29**. When heteroaryl iodides were subjected to the reaction conditions, very low yields were detected in the ^{19}F NMR spectrum (**7u-w**). Besides, aryl bromides and chlorides proved to be unreactive in the Mizoroki-Heck reaction with **2d**.

Table 29 Limitations of substrate scope^a

^aReaction conditions: (Het)Ar-X (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (1.1 equiv), 1,4-dioxane (0.5 mL), 0.4 M, 110 °C, 1 or 4 h.

^b¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard; *E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^cNo desired product.

3.4.3 Investigation of reaction intermediates

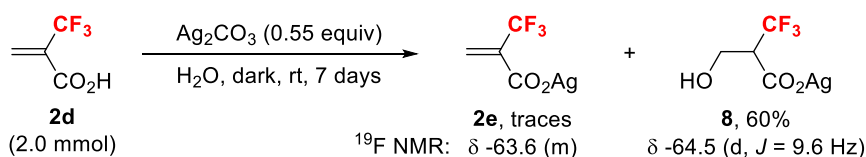
Since both acid (**2d**) and base (Ag₂CO₃) existed in our reaction system, we speculated that one of the reaction intermediates is the silver salt of **2d**, which is believed to be generated by the acid-base reaction. To confirm this inference, we first tried to synthesize the silver carboxylate salt (**2e**) from **2d** and Ag₂CO₃ in water.²⁰⁷ Frustratingly, only traces of **2e** was detected and an unexpected side-product **8** was formed in 60% isolated yield (**Scheme 88**, Eq. a). The side-product **8** is likely to come from the Michael reaction between water and **2d** or **2e**. Considering that water was finally removed by rotary evaporator at 60 °C and that heating conditions may promote the side reaction, we then modified the way of removing water. When the freeze dryer was used to remove water, the target compound **2e** was obtained as the major product along with 12% of side-product **8** (**Scheme 88**, Eq. b). However, we failed to separate **2e** from **8** by recrystallization. Afterwards, we tried to synthesize **2e** from **2d** and AgF in organic solvents.²⁰⁸ Gratifyingly, the pure product of **2e** was obtained in 74% isolated yield in this case (**Scheme 88**, Eq. c).

With **2e** in hand, we carried out the cross-coupling reaction between aryl iodides (**1**) and **2e** (instead of **2d**/Ag₂CO₃) in the presence of Pd(TFA)₂. Comparable results were obtained for **7a**, **7h**, and **7v** between the reaction system of **2e** and that of **2d**/Ag₂CO₃ (**Table 30**). These results indicate that **2e** is indeed an intermediate in the reaction system of **2d**/Ag₂CO₃.

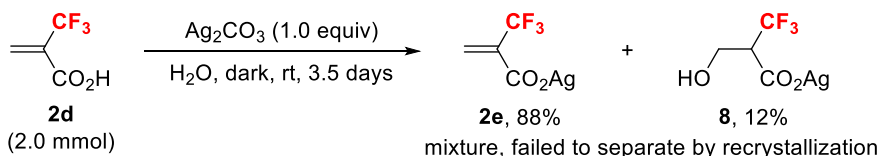
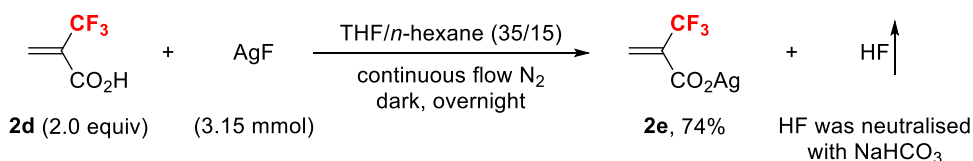
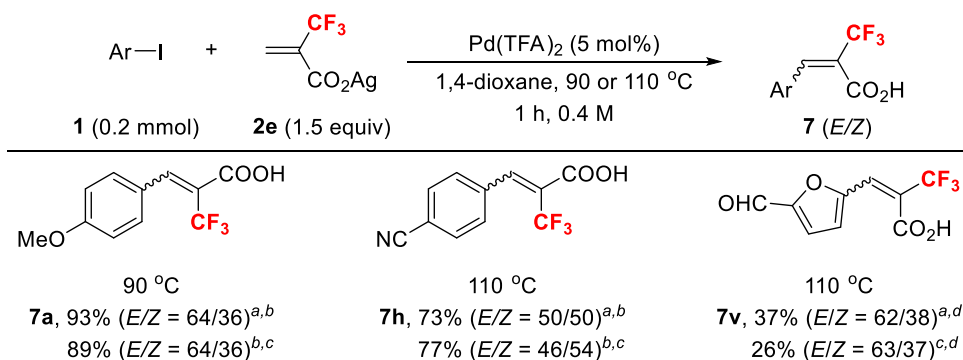
²⁰⁷ E. Sztyk, I. Łakomska, A. Grodzicki, *Thermochim. Acta* **1993**, *223*, 207–212.

²⁰⁸ J. Torroba, J. Aynsley, P. A. Tuzimoto, D. W. Bruce, *RSC Adv.* **2012**, *2*, 12866–12869.

Eq. a) Remove of water: evaporation at 60 °C with rotary evaporator

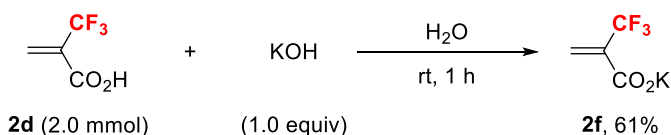
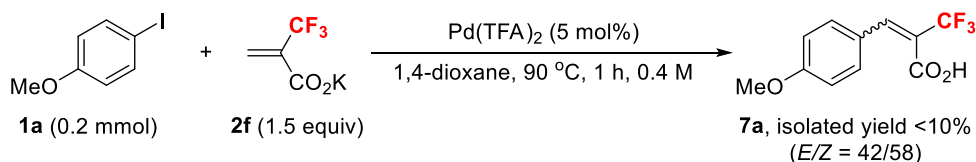


Eq. b) Remove of water: drying with freeze dryer for 20 h

Eq. c) Synthesis of **2e** from **2d** and AgFScheme 88 Synthesis of silver carboxylate salt **2e**Table 30 Mizoroki-Heck reaction between aryl iodides (**1**) and **2e**

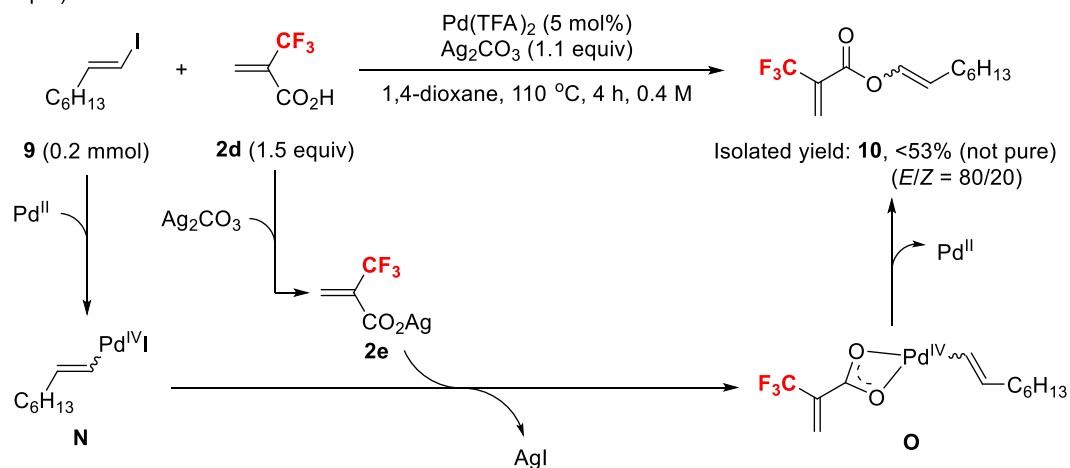
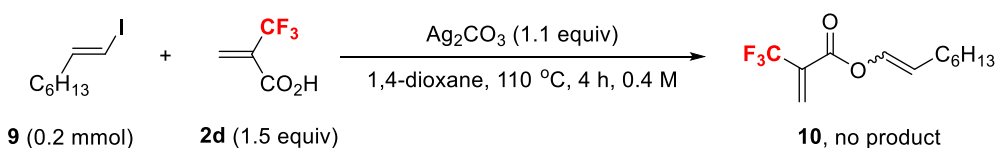
^aReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2e** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), 1,4-dioxane (0.5 mL), 0.4 M, 90 or 110 °C, 1 h. ^bYields based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^cReaction conditions: **1** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (0.22 mmol, 1.1 equiv), 1,4-dioxane (0.5 mL), 0.4 M, 90 or 110 °C, 1 h. ^d¹⁹F NMR yields were obtained by using PhCOCF₃ as an internal standard; *E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture.

The potassium carboxylate salt **2f** was also produced by neutralization of **2d** with aqueous KOH (Scheme 89, Eq. a). Similarly, the cross-coupling reaction between **1a** and **2f** (instead of **2d**/Ag₂CO₃) was conducted in the presence of Pd(TFA)₂, but less than 10% yield of **7a** (not pure) was obtained with worse *E/Z* selectivity. The remarkable decrease of reaction efficiency of **2f** compared to **2e** suggests that silver cation plays an important role in the reaction.

Eq. a) Synthesis of **2f** from **2d** and KOHEq. b) Cross-coupling of **1a** with **2f****Scheme 89** Synthesis of **2f** and the cross-coupling reaction between **1a** and **2f**

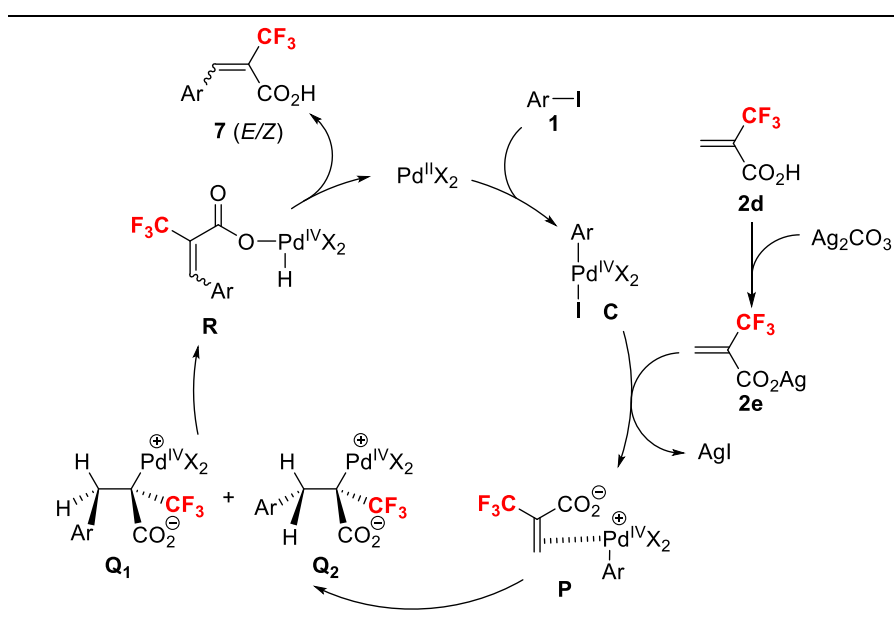
When we investigated the Mizoroki-Heck reaction between vinyl iodide **9** and **2d**, no Heck-type product was observed, but the esterified product **10** was separated in around 53% yield with 80/20 of *E/Z* ratio (**Scheme 90**, Eq. a). In the absence of Pd(TFA)₂, no product of **10** was observed (**Scheme 90**, Eq. b), which suggests that palladium catalyst is essential for the generation of **10**. Regarding the formation of **10**, we proposed a reaction process (**Scheme 90**, Eq. a). Oxidative addition of vinyl iodide **9** to Pd^{II} species gives intermediate **N**, which undergoes transmetalation with the *in situ* generated silver carboxylate **2e** to provide intermediate **O**. Subsequent reductive elimination leads to the formation of ester **10**. The release of insoluble AgI may be an important driving force for this process. In the Mizoroki-Heck reaction of **1** and **2d**, an intermediate similar to complex **O** may also exist.

Eq. a)

Eq. b) Without Pd(TFA)₂**Scheme 90** Esterification reaction between **9** and **2d**

3.4.4 Proposed reaction mechanism

In light of our observations, a reaction mechanism was proposed in **Scheme 91**. After oxidative addition of ArI (**1**), Pd^{II}X₂ is converted to Pd^{IV} complex **C**. At the same time, silver carboxylate salt **2e** is generated from **2d** and Ag₂CO₃. Transmetalation between complex **C** and **2e** leads to the formation of neutral complex **P**. During this step, silver cation plays an important role as a halide abstracter.¹⁸¹ Then, complex **P** undergoes *syn*-insertion and rotation, providing two conformers **Q**₁ and **Q**₂. Subsequent *syn*-β-hydride elimination leads to the formation of intermediate **R**, which goes through reductive elimination to complete the catalytic cycle and release the final product **7** (*E/Z*). As analysed in § 2.4.4, the *E/Z* selectivity of this reaction can be explained by considering both steric effects and stereoelectronic effects.



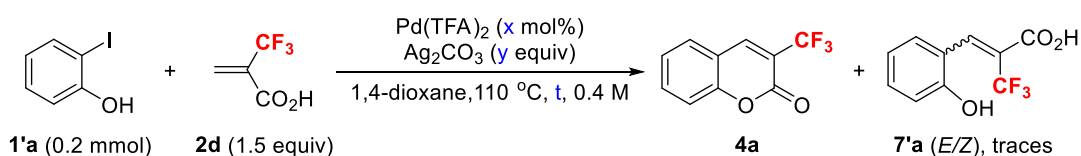
Scheme 91 Proposed reaction mechanism

3.5 One-pot synthesis of 3-trifluoromethyl coumarins

We further tested the possibility of one-pot synthesis of 3-trifluoromethyl coumarin **4a** from 2-iodophenol (**1'a**) and **2d**. Under the optimized conditions of Mizoroki-Heck reaction between aryl iodides with **2d**, **1'a** reacted with **2d** to provide the desired product **4a** in 70% ¹⁹F NMR yield (45% isolated yield) (**Table 31**, entry 1). To get a better yield of **4a**, we did a brief optimization of the reaction conditions. Adding more Pd(TFA)₂ to the reaction system led to a reduction in the yield of **4a** (**Table 31**, entries 2-3). In contrast, decreasing the catalyst loading to 1.5 mol% did not decrease the yield of **4a** (**Table 31**, entry 4). Extending the reaction time to 15 h did not increase the yield of **4a** (**Table 31**, entry 5). We then adjusted the amount of Ag₂CO₃, and a slightly better yield was obtained when 0.5 equiv of Ag₂CO₃ was involved (**Table 31**, entry 7). By contrast, a significant reduction in the yield of **4a** was

observed when 2.0 or 0.2 equiv of Ag_2CO_3 was added (**Table 31**, entry 6 or 9). In most of the conditions, the silver mirror was formed in the reaction system, which is not the case of previous Mizoroki-Heck reactions as well as the cases of synthesis of 3-trifluoromethyl coumarins from **1'** and methyl 2-(trifluoromethyl)acrylate (**2a**). It means that in addition to acting as a halogen scavenger, the silver(I) additive also served as an oxidant in this reaction, probably resulting in some side-reactions. It can be used to explain why increasing the amount of Ag_2CO_3 to 2.0 equiv caused a significant decrease in yield (**Table 31**, entry 6). Of note, in all the tested conditions, just traces of **7'a** (*E/Z*) were detected in the ^{19}F NMR spectrum.

Table 31 Optimization of parameters for the synthesis of 3-trifluoromethyl coumarins^a

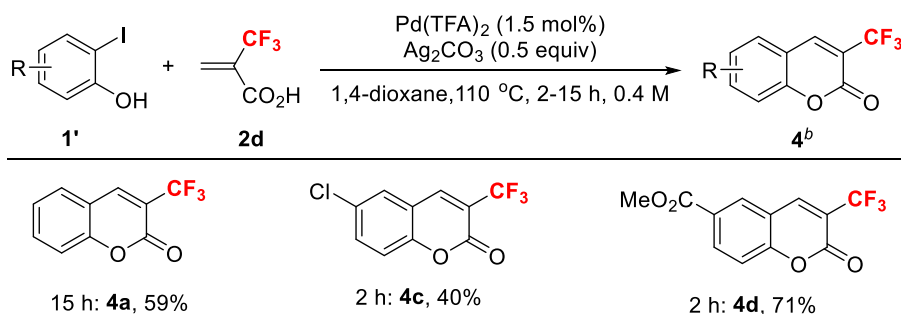


| Entry | $\text{Pd}(\text{TFA})_2$ (x mol%) | Ag_2CO_3 (y equiv) | t | 4a , ^{19}F NMR yield ^b |
|-------|---------------------------------------|---------------------------------------|------|--|
| 1 | 5 mol% | 1.1 equiv | 1 h | 70% (45%) ^c |
| 2 | 10 mol% | 1.1 equiv | 1 h | 58% |
| 3 | 20 mol% | 1.1 equiv | 1 h | 39% |
| 4 | 1.5 mol% | 1.1 equiv | 1 h | 70% |
| ----- | | | | |
| 5 | 1.5 mol% | 1.1 equiv | 15 h | 71% |
| 6 | 1.5 mol% | 2.0 equiv | 15 h | 13% |
| 7 | 1.5 mol% | 0.5 equiv | 15 h | 82% (59%) ^c |
| 8 | 1.5 mol% | 0.5 equiv | 1 h | 78% |
| 9 | 1.5 mol% | 0.2 equiv | 1 h | 20% |

^aReaction conditions: **1'a** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), $\text{Pd}(\text{TFA})_2$ (x mol%), Ag_2CO_3 (y equiv), 1,4-dioxane (0.5 mL), 110 °C, 0.4 M. ^b ^{19}F NMR yields were obtained by using PhCOCF_3 as an internal standard. ^cIsolated yield.

With less palladium catalyst and Ag_2CO_3 , several 3-trifluoromethyl coumarin derivatives (**4a**, **4c-d**) were produced in 40-71% yield (**Table 32**). Compared with the

Table 32 One-pot synthesis of 3-trifluoromethyl coumarin derivatives^a



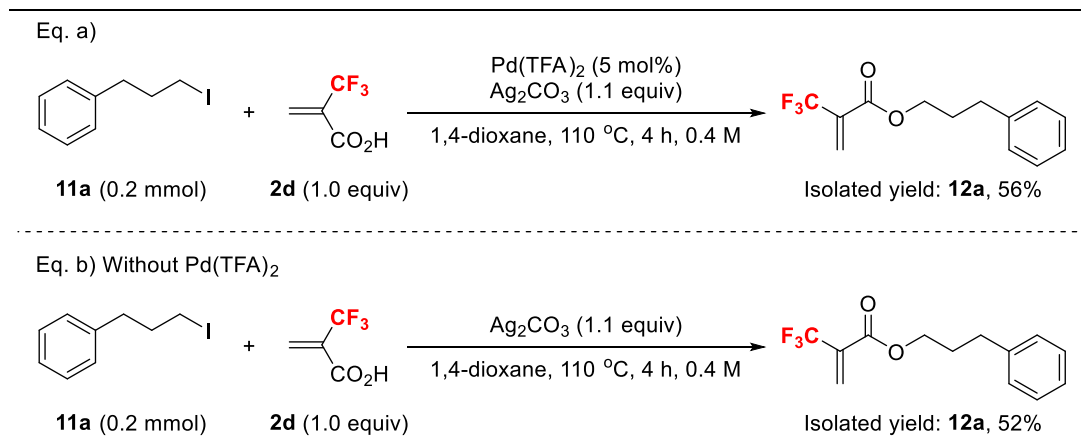
^aReaction conditions: **1'** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), $\text{Pd}(\text{TFA})_2$ (1.5 mol%), Ag_2CO_3 (0.5 equiv), 1,4-dioxane (0.5 mL), 110 °C, 0.4 M. ^bYields based on isolated product after silica gel column chromatography.

reaction system of **1'** and **2a** in the presence of Pd(TFA)₂/AgOTf (see page 74, **Table 10**), the reaction system of **1'** and **2d** with Pd(TFA)₂/Ag₂CO₃ provided inferior results. One of the reasons may be that the reaction media of the latter is weakly acidic at the end of the reaction (pH around 5).

3.6 Access to 3-aryl-2-(trifluoromethyl)acrylates by one-pot three-component reaction

3.6.1 Esterification reaction between **11a** and **2d**

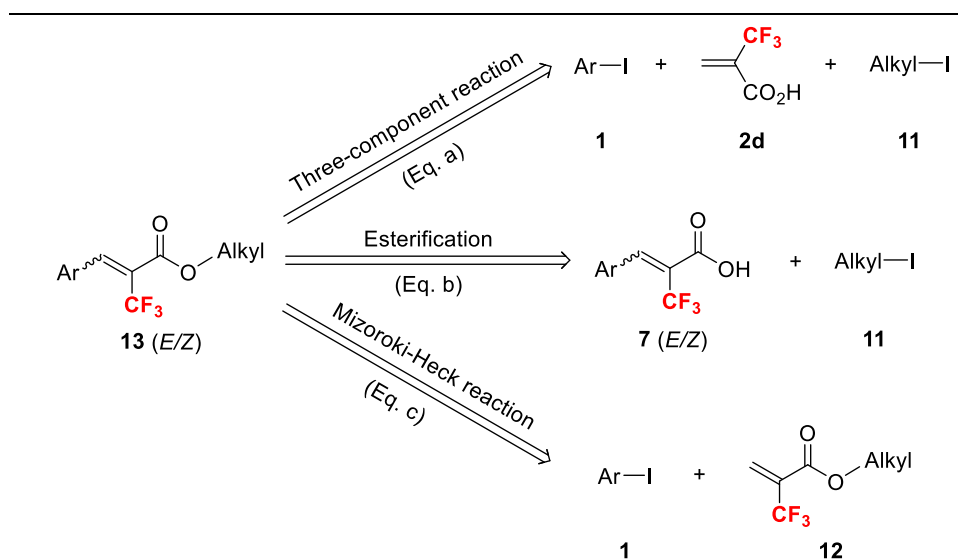
When we investigated the Mizoroki-Heck reaction between alkyl iodide **11a** and **2d**, no Heck-type product was observed, but the esterified product **12a** was separated in 56% yield (**Scheme 92**, Eq. a). In the absence of palladium catalyst, **11a** could also react with **2d** to afford **12a** in 52% isolated yield (**Scheme 92**, Eq. b). Obviously, a nucleophilic substitution reaction occurs between **11a** and **2d**.



Scheme 92 Esterification reaction between **11a** and **2d**

3.6.2 Predictions of the three-component reaction

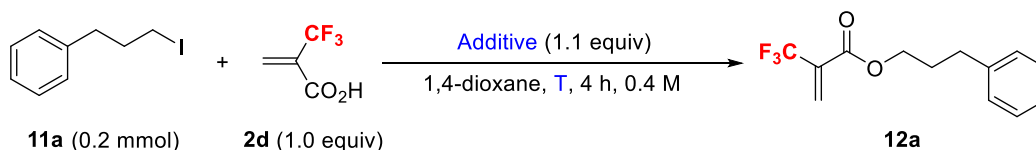
Inspired by the nucleophilic substitution reaction between **11a** and **2d**, we envisioned that the synthesis of more complex 3-aryl-2-(trifluoromethyl)acrylates (**13**) could be achieved by one-pot three-component reactions starting from aryl iodides (**1**), 2-(trifluoromethyl)acrylic acid (**2d**), and alkyl iodides (**11**) (**Scheme 93**, Eq. a). This one-pot process would avoid the purification of highly polar acid intermediates **7** used in esterification reactions (**Scheme 93**, Eq. b). Although it is possible to synthesize **13** by Mizoroki-Heck reaction with aryl iodides (**1**) and alkyl 2-(trifluoromethyl)acrylates (**12**) (**Scheme 93**, Eq. c), the reagents **12** are hardly ever commercially available [except for methyl and *tert*-butyl 2-(trifluoromethyl)acrylates (**2a-b**)]. The limited source of reagents **12** will limit the diversity of **13**. That is why the three-component reaction would allow easy expansion of the accessibility of acrylates **13**.



3.6.3 Optimization of reaction conditions

Before exploring the three-component reaction, we did a brief optimization of reaction conditions for the reaction of **11a** with **2d** in the absence of palladium catalyst (**Table 33**). When K_2CO_3 or AgOTf was added to the reaction mixture instead of Ag_2CO_3 , only traces of **12a** was observed (**Table 33**, entries 2-3). These results indicate that both base and silver cation play an important role in this reaction. A screening of reaction temperature showed that 50 °C was a suitable temperature for the synthesis of **12a** (**Table 33**, entries 1, 4-6). Notably, the corresponding alkyl bromide and alkyl chloride of **11a** failed to give access to **12a** (**Table 33**, entries 7-8).

Table 33 Optimization of reaction conditions for the reaction of **11a** with **2d**^a

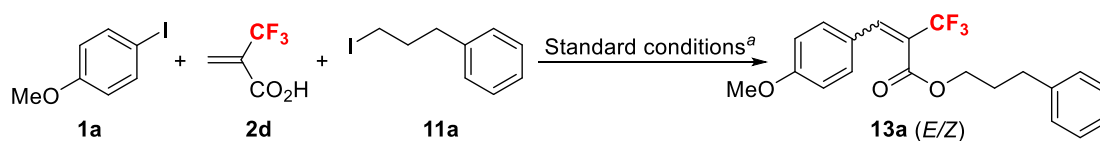


| Entry | Additive | T (°C) | 12a , yield ^b |
|----------------|------------|--------|---------------------------------|
| 1 | Ag_2CO_3 | 110 | 52% |
| 2 | K_2CO_3 | 110 | traces |
| 3 | AgOTf | 110 | traces |
| 4 | Ag_2CO_3 | 90 | 70% |
| 5 | Ag_2CO_3 | 70 | 67% |
| 6 | Ag_2CO_3 | 50 | 76% |
| 7 ^c | Ag_2CO_3 | 50 | traces |
| 8 ^d | Ag_2CO_3 | 50 | — |

^aReaction conditions: **11a** (0.2 mmol, 1.0 equiv), **2d** (0.2 mmol, 1.0 equiv), additive (1.1 equiv), 1,4-dioxane (0.5 mL), 0.4 M, 4 h. ^bYields based on isolated product after silica gel column chromatography. ^c(3-Bromopropyl)benzene (0.2 mmol) instead of **11a**. ^d(3-Chloropropyl)benzene (0.2 mmol) instead of **11a**.

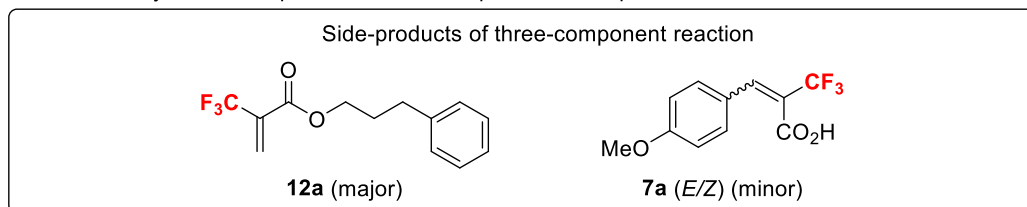
Then, we started to investigate the three-component reaction with **1a**, **2d**, and **11a** (**Table 34**). To our delight, the desired product **13a** could be synthesized in 77% isolated yield by a one-pot one-step protocol: **1a** (0.2 mmol, 1.0 equiv), **2d** (0.4 mmol, 2.0 equiv), **11a** (0.8 mmol, 4.0 equiv), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (0.8 mmol, 4.0 equiv), 1,4-dioxane (1.0 mL), 0.2 M, 50 °C, 4 h; then 90 °C, 2 h (**Table 34**, entry 1). No better results were obtained for other tested conditions (**Table 34**, entries 2-4). Side-products **12a** and **7a** were formed in the reaction conditions with **12a** as the major side-product (**Table 34**, bottom).

Table 34 Optimization of three-component reaction (one-pot, 1 step)

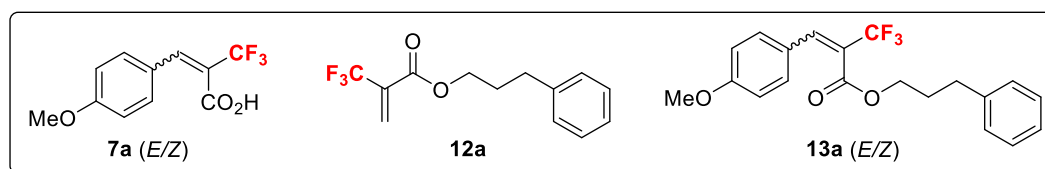


| Entry | Change from standard conditions | 13a , yield ^b | <i>E/Z</i> ratio ^c |
|-------|--|---------------------------------|-------------------------------|
| 1 | None | 77% | 60/40 |
| 2 | 90 °C, 6 h | <77% ^d | 63/37 |
| 3 | 11a (3.0 equiv) instead of (4.0 equiv) | 73% | 60/40 |
| 4 | 1a/2d/11a/Ag₂CO₃/Pd(TFA)₂ = 1.0/1.5/1.5/2.5/10 mol%, 1,4-dioxane (0.5 mL), 0.4 M, 110 °C, 4 h | <56% ^d | 65/35 |

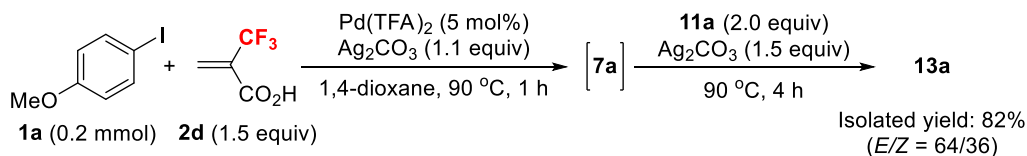
^aStandard conditions: **1a** (0.2 mmol, 1.0 equiv), **2d** (0.4 mmol, 2.0 equiv), **11a** (0.8 mmol, 4.0 equiv), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (0.8 mmol, 4.0 equiv), 1,4-dioxane (1.0 mL), 0.2 M, 50 °C, 4 h; then 90 °C, 2 h. ^bYields based on isolated product after silica gel column chromatography. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^dNot pure.



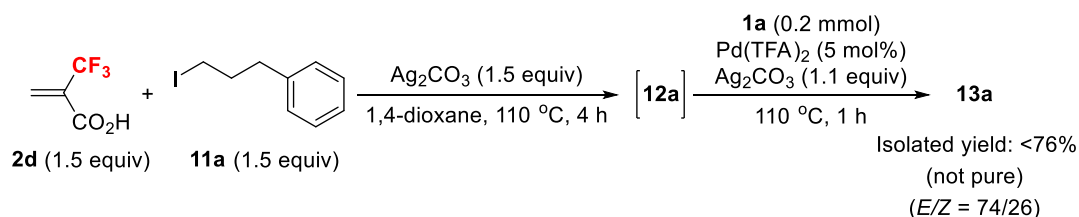
In addition, the three-component reaction could also be realized by one-pot two-step processes (**Scheme 94**). Firstly, the Mizoroki-Heck reaction between **1a** and **2d** was conducted, and then alkyl iodide **11a** was added to react with the *in situ* generated intermediate **7a**, leading to the formation of **13a** in 82% isolated yield with 64/36 of *E/Z* ratio (**Scheme 94**, Eq. a). Afterwards, a reverse process was studied. The esterification reaction between **2d** and **11a** was first carried out to generate intermediate **12a**, which then reacted with **1a** by Mizoroki-Heck reaction allowing the formation of **13a** in around 76% isolated yield (but contained some impurities) with 74/26 of *E/Z* ratio (**Scheme 94**, Eq. b). Although the one-pot two-step reactions are more complicated in terms of adding reactants, the amounts of reagents and catalyst are less than the case of the one-pot one-step reaction, and the results obtained are also good. That is why both one-step and two-step protocols will be applied to the study of substrate scope of the three-component reaction.



Eq. a) Step 1, Mizoroki-Heck reaction to generate **7a**; step 2, esterification to obtain **13a**



Eq. b) Step 1, esterification to generate **12a**; step 2, Mizoroki-Heck reaction to obtain **13a**

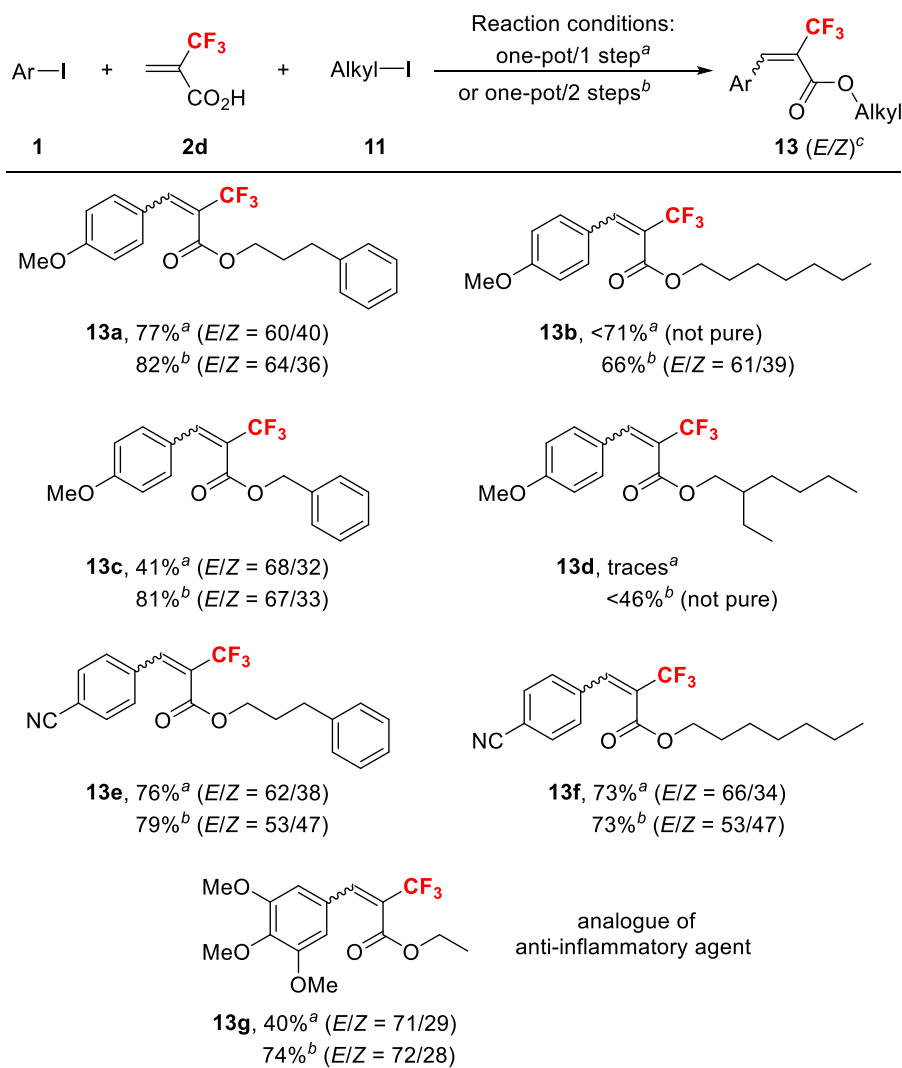


Scheme 94 Three-component reaction (one-pot, 2 steps)

3.6.4 Substrate scope of the three-component reaction

We investigated the substrate scope of the three-component reaction by one-pot one-step and one-pot two-step reaction conditions, respectively (**Table 35**). Diverse alkyl iodides (**11**) were amenable to the reaction conditions and the relatively complex 3-aryl-2-(trifluoromethyl)acrylates (**13**) were synthesized in moderate to good yields, except that unsatisfactory results were obtained for **13d** which is a fluorinated analogue of UV-B screen.²⁰⁹ With electron-rich aryl iodides as substrates, the one-pot two-step protocol provided better results than those of one-pot one-step reactions (**13a-d**, **13g**). By contrast, similar results were obtained for both of the conditions when electron-poor 4-iodobenzonitrile was involved (**13e-f**). It is worth noting that compound **13g** is a fluoroanalogue of anti-inflammatory agent.¹⁸² The main drawback of this chemistry is the poor *E/Z* selectivity for all examples.

²⁰⁹ A. Alexander, R. K. Choudhary, US Patent No. 5527947, 1996.

Table 35 Substrate scope of the three-component reaction

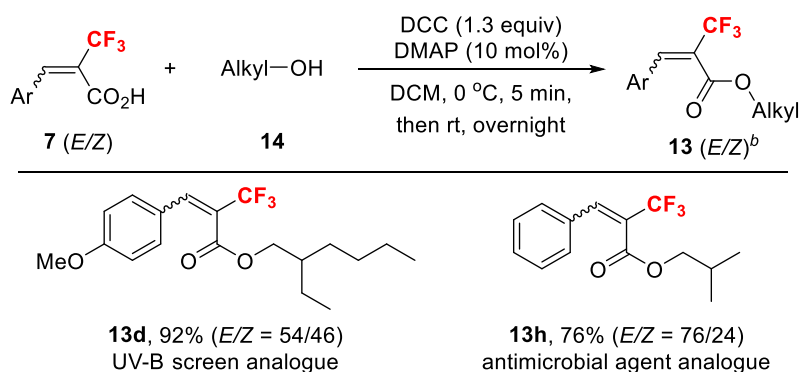
^aReaction conditions (one-pot/1 step): **1** (0.2 mmol, 1.0 equiv), **2d** (0.4 mmol, 2.0 equiv), **11** (0.8 mmol, 4.0 equiv), Pd(TFA)₂ (10 mol%), Ag₂CO₃ (0.8 mmol, 4.0 equiv), 1,4-dioxane (1.0 mL), 0.2 M, 50 °C, 4 h; then 90 °C, 2 h. ^bReaction conditions (one-pot/2 steps): **1** (0.2 mmol, 1.0 equiv), **2d** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (5 mol%), Ag₂CO₃ (0.22 mmol, 1.1 equiv), 1,4-dioxane (0.5 mL), 0.4 M, 90 or 110 °C, 1 h; then **11** (0.4 mmol, 2.0 equiv), Ag₂CO₃ (0.3 mmol, 1.5 equiv), 90 °C, 4 h. ^cYields based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product.

3.7 Esterification between acids (**7**) and alcohols (**14**)

Since branched alkyl iodides were poor substrates in three-component reaction for the synthesis of 3-aryl-2-(trifluoromethyl)acrylates, we turned our attention to the esterification reaction between pre-synthesized acids (**7**) and alcohols (**14**) (**Table 36**). In the presence of DCC (dicyclohexylcarbodiimide) and DMAP (*N,N*-4-dimethylaminopyridine), the esterified products **13d** and **13h** were successfully

synthesized. The former is a fluorinated analogue of UV-B screen²⁰⁹ and the latter is an analogue of an antimicrobial agent.²¹⁰

Table 36 Esterification between acids (**7**) and alcohols (**14**)^a



^aReaction conditions: **14** (0.2 mmol, 1.0 equiv), **7** (0.24 mmol, 1.2 equiv), DCC (1.3 equiv), DMAP (10 mol%), DCM, 0 °C, 5 min; then rt, overnight.

^bYields based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product.

3.8 Conclusion

To conclude, we have applied the Mizoroki-Heck reaction to the synthesis of 3-aryl-2-(trifluoromethyl)acrylic acids (**7**), scarcely studied in the literature despite their great potential. Various functional groups were compatible in the reaction system and good to excellent yields of **7** were obtained (Scheme 95, Eq. a).²¹¹ Nevertheless, the *E/Z* selectivity of the reaction was quite low. The *in situ* generated silver carboxylate salt **2e** proved to be one of the intermediates in the reaction mechanism.

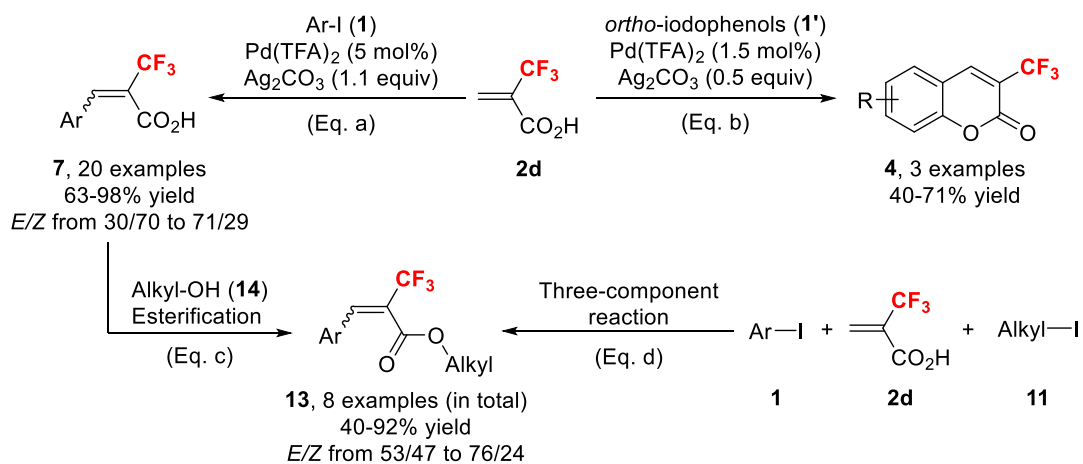
The one-pot synthesis of 3-trifluoromethyl coumarin derivatives was also achieved starting from *ortho*-iodophenols (**1'**) and 2-(trifluoromethyl)acrylic acid (**2d**) by tandem Mizoroki-Heck reaction and intramolecular cyclization (Scheme 95, Eq. b).

Additionally, the access to more complex 3-aryl-2-(trifluoromethyl)acrylates (**13**) was developed either by the classical esterification reaction between **7** and alcohol (**14**) or by the three-component reaction between aryl iodides (**1**), **2d**, and alkyl iodides (**11**) (Scheme 95, Eqs. c-d).

Some of the synthesized 3-aryl-2-(trifluoromethyl)acrylates are fluorinated analogues of therapeutic and cosmetic agents.

²¹⁰ B. Narasimhan, D. Belsare, D. Pharande, V. Mourya, *Eur. J. Med. Chem.* **2004**, *39*, 827–834.

²¹¹ P. Xiao, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *Adv. Synth. Catal.* **2020**, *362*, 949–954.



Scheme 95

Chapter 4

Palladium-catalysed oxidative decarboxylative cross-coupling of heteroarenes with CF₃-acrylic acids

4 Palladium-catalysed oxidative decarboxylative cross-coupling of heteroarenes with CF₃-acrylic acids

4.1 State of the art

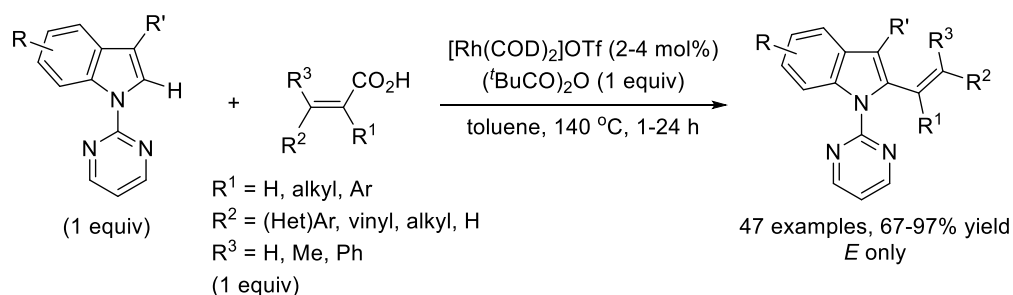
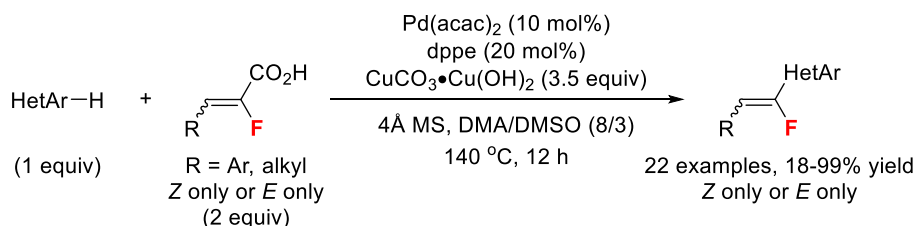
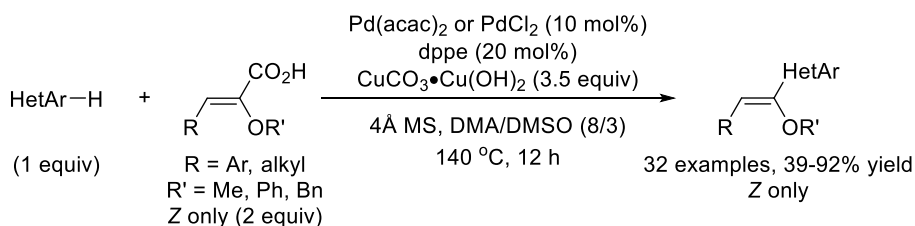
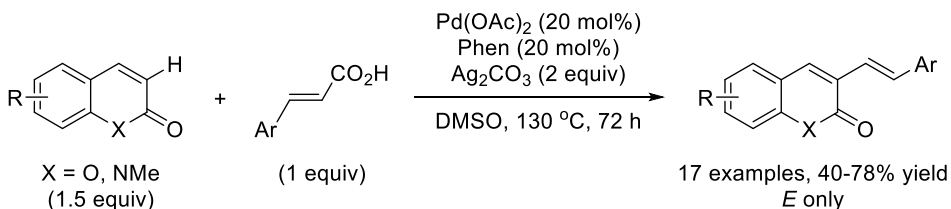
In § 1.5.1 (see page 48), we demonstrated that transition metal-catalysed (or -mediated) decarboxylative cross-coupling reactions have aroused widespread research interest in the past two decades.^{152-153,155} Among them, the oxidative decarboxylative cross-coupling reaction between (hetero)arenes and carboxylic acids proved to be atom-economic. Although benzoic acids have been widely investigated in this kind of oxidative decarboxylative cross-coupling reaction,¹⁵² acrylic acids were far less explored. As far as we know, only four general methods have been developed for the olefination of heteroarenes by C-H/C-CO₂H coupling (**Scheme 96**).

In 2014, Li, Xu, and co-workers developed a method for the directed C2-olefination of *N*-protected indoles with acrylic acids in the presence of [Rh(COD)₂]OTf and (t-BuCO)₂O (**Scheme 96**, Eq. a).²¹² A broad range of C2-alkenylated indole derivatives was produced in good to excellent yields, and in almost all cases only (*E*)-products were obtained. Shortly after, Hoarau, Couve-Bonnaire, and co-workers reported that the C-H fluoroalkenylation of various heteroarenes, such as 1,3,4-oxadiazoles, benzothiazoles, benzoxazoles, and oxazoles, could be realized using β-substituted α-fluoroacrylic acids in the presence of palladium catalyst and copper base (**Scheme 96**, Eq. b).¹⁶⁵ When *Z* or *E* isomers of β-substituted α-fluoroacrylic acids were subjected to the reaction conditions, the corresponding stereospecific (*Z*)- or (*E*)-α-heteroaryl monofluoroalkenes were constructed in up to 99% yield. The same research group also achieved the stereospecific C-H alkoxyalkenylation of various heteroarenes under similar reaction conditions (**Scheme 96**, Eq. c).²¹³ During this period, Chen, Pan, and co-workers developed a palladium-catalysed, silver-mediated protocol for regioselective olefination of coumarins (**Scheme 96**, Eq. d).²¹⁴ Various 3-styrylcoumarins were synthesized in moderate to good yields with only *E*-configuration.

²¹² L. Zhang, R. Qiu, X. Xue, Y. Pan, C. Xu, D. Wang, X. Wang, L. Xu, H. Li, *Chem. Commun.* **2014**, 50, 12385–12388.

²¹³ J.-B. E. Y. Rouchet, M. Hachem, C. Schneider, C. Hoarau, *ACS Catal.* **2017**, 7, 5363–5369.

²¹⁴ X. Wang, S.-Y. Li, Y.-M. Pan, H.-S. Wang, Z.-F. Chen, K.-B. Huang, *J. Org. Chem.* **2015**, 80, 2407–2412.

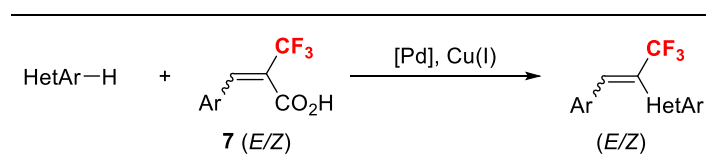
Eq. a) In 2014, Li, Xu *et al.*Eq. b) In 2014, Hoarau, Couve-Bonnaire *et al.*Eq. c) In 2017, Hoarau *et al.*Eq. d) In 2015, Chen, Pan *et al.*

Scheme 96 Oxidative decarboxylative cross-coupling of heteroarenes with acrylic acids

4.2 Objectives

In **Chapter 3**, we provided a general method to access 3-aryl-2-(trifluoromethyl)acrylic acids (**7**), which have never been used in decarboxylative cross-coupling reactions. The last objective of this thesis is to achieve the decarboxylative C-H trifluoromethylalkenylation of heteroarenes with **7** (**Scheme 97**). This would allow the formation of CF₃-alkenes with great potential (see page 7, § 1.2.2). As a reminder, only Nicholls used a decarboxylative protocol to get trifluoromethylalkenes from 2-(trifluoromethyl)acrylic acid (**2d**) via the combination of Mizoroki-Heck reaction and decarboxylation (see page 35, **Scheme 35**, Eq. c),¹⁰⁶ but to our knowledge, no decarboxylative C-H trifluoromethylalkenylation reaction has been developed so far. Taking into account the large steric hindrance of CF₃

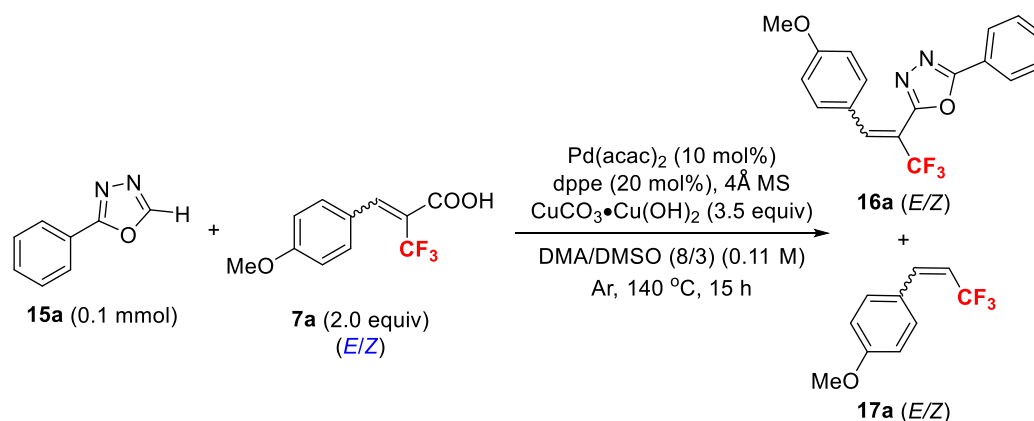
moiety as well as its strong electron-withdrawing effect, the corresponding organometallic intermediates would probably be highly unstable, highlighting the difficulty of this study.



Scheme 97

4.3 Preliminary attempts

Based on the reaction conditions developed previously in the laboratory for the decarboxylative C-H fluoroalkenylation and alkoxyalkenylation of heteroarenes (Scheme 96, Eqs. b-c),^{165,213} we explored the possibility of oxidative decarboxylative cross-coupling of 2-phenyl-1,3,4-oxadiazole (**15a**) with **7a** in the presence of Pd(acac)₂, dppe, CuCO₃•Cu(OH)₂, 4Å molecular sieves, and DMA/DMSO (Table 37). In Scheme 86 (see page 101) and Table 28 (see page 105), we showed that **7a** was synthesized with different *E/Z* ratios (84/16 and 64/36). We then tested the reactivity of **7a** with these two *E/Z* ratios, and the desired product **16a** was obtained in low isolated yield but with high *E/Z* selectivity (Table 37, entries 1-2). From the ¹⁹F NMR spectrum of the final reaction mixture, **7a** was all consumed and a lot of side-

Table 37 Preliminary attempts^a

| Entry | <i>E/Z</i> of 7a | yield of 16a (<i>E/Z</i>) ^b | 16a/17a ratio ^c |
|-------|-------------------------|---|--|
| 1 | 84/16 | <15% (<i>E/Z</i> = 98/2) | 10/90 (16a , <i>E/Z</i> = 92/8; 17a , <i>E/Z</i> = 88/12) |
| 2 | 64/36 | <13% (<i>E/Z</i> = 98/2) | 13/87 (16a , <i>E/Z</i> = 95/5; 17a , <i>E/Z</i> = 74/26) |
| 3 | 2/98 | <32% (<i>E/Z</i> = 97/3) | 23/77 (16a , <i>E/Z</i> = 92/8; 17a , <i>E/Z</i> = 22/78) |

^aReaction conditions: **15a** (0.1 mmol, 1.0 equiv), **7a** (2.0 equiv), Pd(acac)₂ (10 mol%), dppe (20 mol%), CuCO₃•Cu(OH)₂ (3.5 equiv), 4Å MS 40-50 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 10 mL sealed reaction tube. ^bYields (not pure) based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16a/17a** ratio and their *E/Z* ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

product **17a** was formed through protodecarboxylation. Using the protocol of Fang (see page 99, **Scheme 84**, Eq. c),¹⁹⁸ we synthesized the *Z* isomer of **7a** and checked its reactivity in the reaction conditions. In this case, a better isolated yield of **16a** was obtained with high *E/Z* selectivity (**Table 37**, entry 3). Of note, the *E* isomer was the dominant product for **16a**, no matter what the *E/Z* ratio of **7a** was. Besides, in all cases, the product **16a** was contaminated by a non-fluorinated side-product, which will be revealed later.

4.4 Optimization of reaction conditions

Further optimization of reaction conditions was needed to get better results. Since the melting point of **15a** (Mp < 30 °C)²¹⁵ is close to room temperature, it is not convenient to weigh it. We then chose 2-(*p*-tolyl)-1,3,4-oxadiazole (**15b**) (Mp 84-86 °C)²¹⁵ as the model substrate to do optimization. Besides, (*Z*)-**7a** was selected as the suitable coupling partner.

4.4.1 Screening of [Pd] catalysts

Using **15b** and (*Z*)-**7a** as substrate and coupling partner, respectively, the corresponding product **16b** was separated in 19% yield with 99/1 of *E/Z* ratio when Pd(acac)₂ was used as a catalyst (**Table 38**, entry 1). We then tested some other palladium catalysts including Pd(OAc)₂, Pd(TFA)₂, PdBr₂, and PdCl₂; the yield of **16b** was slightly increased, with PdBr₂ and PdCl₂ giving the best results (**Table 38**, entries 2-5). PdCl₂ was selected as a suitable catalyst for subsequent optimization.

No (*Z*)-**7a** was recovered in the reaction mixture and side-product **17a** was formed. The ratio of **16b/17a** and their *E/Z* ratio were determined by the ¹⁹F NMR spectrum of the ended reaction mixture (**Figure 14**). The *E/Z* ratio of the isolated product was usually higher than that of the final reaction mixture, probably because the *E* and *Z* isomers of **16b** could be partially separated by silica gel column chromatography.

Unfortunately, in all cases, the desired product **16b** was contaminated by a little bit of non-fluorinated side-product **18b** which was confirmed by ¹H NMR spectrum and LC-MS (*m/z*: 237.2 [M+H]⁺). The phenyl group in **18b** should come from the phosphine ligand dppe.²¹⁶

²¹⁵ T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900–6901.

²¹⁶ (a) M.-T. Ma, J.-M. Lu, *Tetrahedron* **2013**, *69*, 2102–2106; (b) D. Lu, Y. Xu, W. Liu, L. Guo, X. Sun, *Helv. Chim. Acta* **2015**, *98*, 116–122; (c) H. Zhou, J. Li, H. Yang, C. Xia, G. Jiang, *Org. Lett.* **2015**, *17*, 4628–4631.

Table 38 Screening of [Pd] catalysts^a

| Entry | [Pd] catalyst | yield of 16b (E/Z) + 18b ^b | 16b/17a ratio ^c |
|-------|-----------------------|---|--|
| 1 | Pd(acac) ₂ | 19% (E/Z = 99/1) + 2% | 16/84 (16b , E/Z = 93/7; 17a , E/Z = 28/72) |
| 2 | Pd(OAc) ₂ | 28% (E/Z = 98/2) + 3% | 23/77 (16b , E/Z = 93/7; 17a , E/Z = 28/72) |
| 3 | Pd(TFA) ₂ | 24% (E/Z > 99/1) + 1% | 19/81 (16b , E/Z = 91/9; 17a , E/Z = 29/71) |
| 4 | PdBr ₂ | 33% (E/Z > 91/9) + 2% | 27/73 (16b , E/Z = 92/8; 17a , E/Z = 38/62) |
| 5 | PdCl ₂ | 32% (E/Z > 98/2) + 1% | 28/72 (16b , E/Z = 93/7; 17a , E/Z = 33/67) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (Z)-**7a** (2.0 equiv), [Pd] catalyst (10 mol%), dppe (20 mol%), CuCO₃•Cu(OH)₂ (3.5 equiv), 4Å MS 40-50 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 10 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

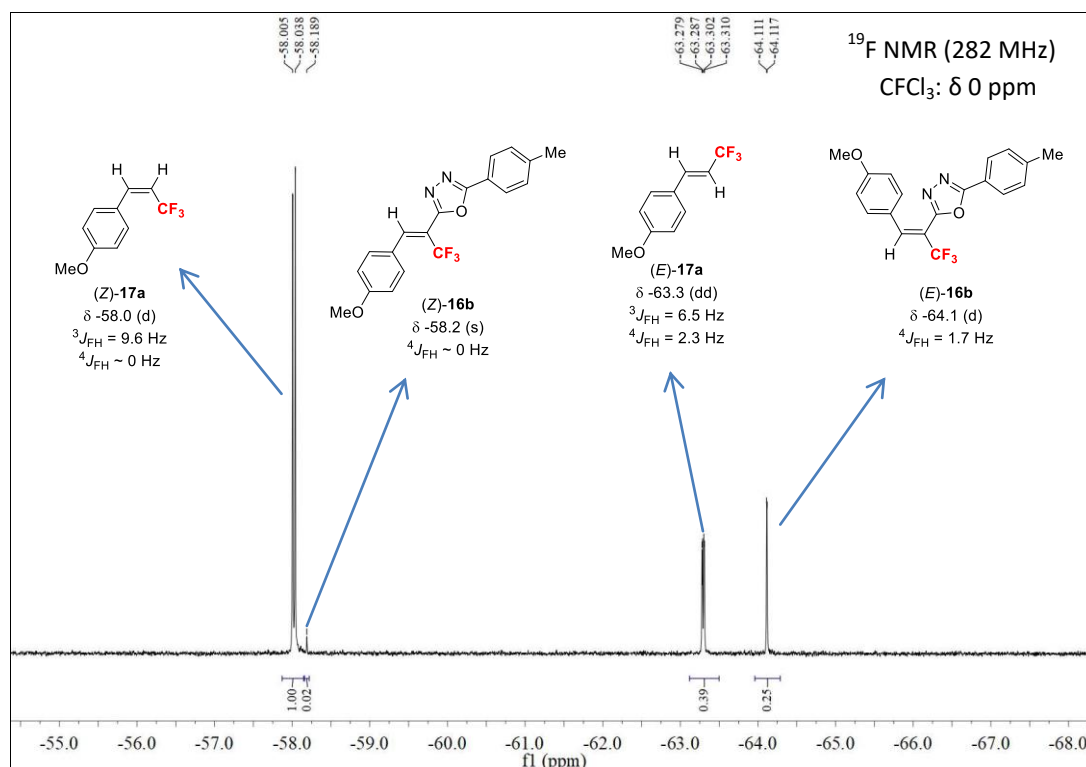


Figure 14 ¹⁹F NMR spectrum of the ended reaction mixture (for detailed reaction conditions; see **Table 38**, entry 1)

4.4.2 Screening of the amount of activated 4Å molecular sieves

Since a lot of side-product **17a** was formed in our reaction system, we tried to add more activated 4Å molecular sieves in order to reduce the water content, thereby suppressing the protodecarboxylation process. Indeed, increasing the amount of activated 4Å molecular sieves could improve the yield of **16b**, but by a small margin (**Table 39**). Taking into account that too many molecular sieves were not conducive to the stability of stirring, it was considered that 100 mg was the appropriate amount of molecular sieves (**Table 39**, entry 2).

Table 39 Screening of the amount of activated 4Å molecular sieves^a

| Entry | 4Å MS | yield of 16b (E/Z) + 18b ^b | 16b/17a ratio ^c |
|-------|----------|---|--|
| 1 | 40-50 mg | 32% (E/Z > 98/2) + 1% | 28/72 (16b , E/Z = 93/7; 17a , E/Z = 33/67) |
| 2 | 100 mg | 37% (E/Z = 99/1) + 2% | 29/71 (16b , E/Z = 92/8; 17a , E/Z = 40/60) |
| 3 | 150 mg | 39% (E/Z = 99/1) + 2% | 32/68 (16b , E/Z = 94/6; 17a , E/Z = 46/54) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (Z)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), CuCO₃•Cu(OH)₂ (3.5 equiv), 4Å MS, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 10 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

4.4.3 Screening of phosphine ligands

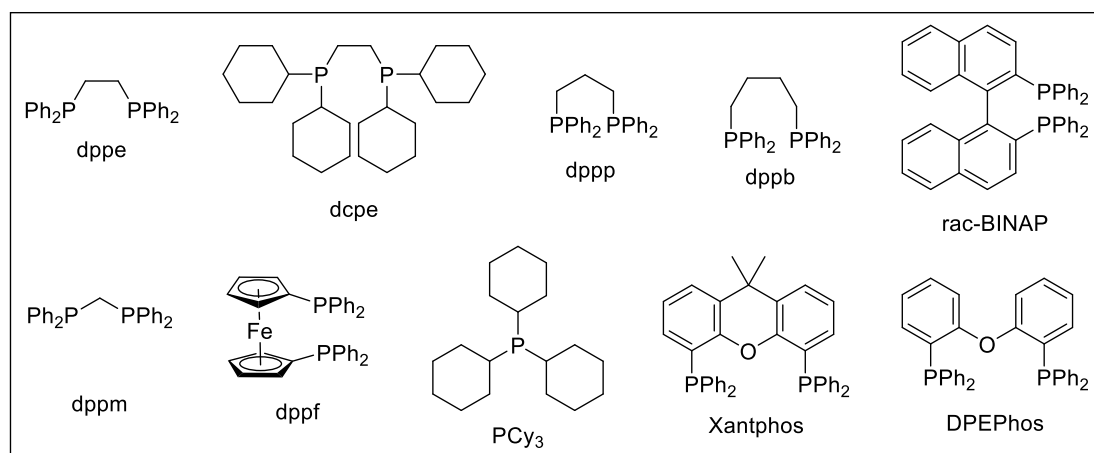
In addition to dppe, a series of other phosphine ligands were subjected to the reaction conditions; however, much worse results were observed (**Table 40**; for structures of ligands, see **Figure 15**). A low yield of **16b** was obtained when dcpe, dppp, dppb, or rac-BINAP was involved in the reaction conditions (**Table 40**, entries 2-5). Only traces of **16b** were observed in the presence of dppm, dppf, PCy₃, PPh₃, Xantphos, or DPEPhos (**Table 40**, bottom). In the end, dppe was still the optimal ligand (**Table 40**, entry 1).

Table 40 Screening of phosphine ligands^a

| Entry | Ligand | yield of 16b (<i>E/Z</i>) + 18b ^b | 16b/17a ratio ^c |
|-------|-----------|--|---|
| 1 | dppe | 37% (<i>E/Z</i> = 99/1) + 2% | 29/71 (16b , <i>E/Z</i> = 92/8; 17a , <i>E/Z</i> = 40/60) |
| 2 | dcpe | 7% (<i>E/Z</i> = 99/1) + 0% | 5/95 (16b , <i>E/Z</i> = 92/8; 17a , <i>E/Z</i> = 60/40) |
| 3 | dppp | 15% (<i>E/Z</i> = 95/5) + 1% | 11/89 (16b , <i>E/Z</i> = 90/10; 17a , <i>E/Z</i> = 42/58) |
| 4 | dppb | 8% (<i>E/Z</i> = 92/8) + 1% | 9/91 (16b , <i>E/Z</i> = 87/13; 17a , <i>E/Z</i> = 27/73) |
| 5 | rac-BINAP | 11% (<i>E/Z</i> = 93/7) + 1% | 15/85 (16b , <i>E/Z</i> = 86/14; 17a , <i>E/Z</i> = 20/80) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (*Z*)-**7a** (2.0 equiv), PdCl₂ (10 mol%), Ligand (20 mol%), CuCO₃•Cu(OH)₂ (3.5 equiv), 4Å MS 100 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 10 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their *E/Z* ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

Traces of **16b** were observed with the following ligands: dppm, dppf, PCy₃, PPh₃, Xantphos, DPEPhos

**Figure 15** Structures of phosphine ligands

4.4.4 Screening of reaction concentration

It has been reported that reaction concentration played an important role in the reaction efficiency of oxidative decarboxylative cross-coupling reactions,^{165,213} we then studied the effect of concentration on our reaction (**Table 41**). Reducing the reaction concentration to 0.056 M led to a similar result to that of 0.11 M (**Table 41**, entries 1-2). In comparison, as the reaction concentration increased, the yield of **16b**

decreased (**Table 41**, entries 2-4). Finally, the reaction concentration was maintained at 0.11 M for subsequent optimization (**Table 41**, entry 2).

Table 41 Screening of reaction concentration^a

| Entry | concentration (x M) | yield of 16b (E/Z) + 18b ^b | 16b/17a ratio ^c |
|-------|---------------------|---|---|
| 1 | 0.056 | 36% (E/Z = 99/1) + 1% | 27/73 (16b , E/Z = 90/10; 17a , E/Z = 40/60) |
| 2 | 0.11 | 37% (E/Z = 99/1) + 2% | 29/71 (16b , E/Z = 92/8; 17a , E/Z = 40/60) |
| 3 | 0.22 | 31% (E/Z = 99/1) + 2% | 24/76 (16b , E/Z = 91/9; 17a , E/Z = 44/56) |
| 4 | 0.40 | 26% (E/Z = 97/3) + 2% | 21/79 (16b , E/Z = 88/12; 17a , E/Z = 50/50) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (**Z**)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), CuCO₃•Cu(OH)₂ (3.5 equiv), 4Å MS 100 mg, DMA/DMSO (8/3) (x M), Ar, 140 °C, 15 h, in 10 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

4.4.5 Screening of additives

Before the investigation of additives, we first expanded the volume of the reaction tube from 10 mL to 20 mL (**Figure 16**). To our delight, the isolated yield of **16b** increased from 37% to 46% (**Table 42**, entries 1-2). The increase in yield may be due to the larger reaction tube and stir bar having a better stirring effect, or it may be due to the increased volume that facilitates the release of CO₂.

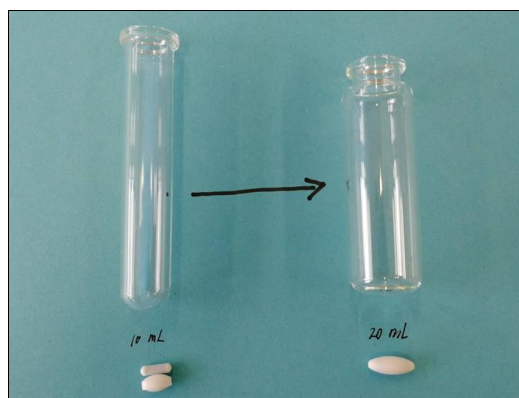


Figure 16 Changing of the reaction tube

Using the 20 mL reaction tube, we started to explore different additives. The addition of Cu₂O improved the yield of **16b** to 54%, and both the sealed reaction system and argon balloon-protected reaction system provided similar results (**Table 42**, entries 3-4). No better results were obtained with other tested Cu(I) or Cu(II) additives (**Table 42**, entries 5-8). Compared to copper additives, silver additives including Ag₂CO₃ and Ag₂O proved to be ineffective in promoting the reaction (**Table 42**, entries 9-10). Some other single and combined additives are listed at the bottom of **Table 42** because they could hardly give the desired product **16b**. Based on these results, Cu₂O was the best additive.

Table 42 Screening of additives^a

| Entry | Additive | yield of 16b (E/Z) + 18b ^b | 16b/17a ratio ^c |
|----------------|--|---|---|
| 1 ^d | CuCO ₃ •Cu(OH) ₂ | 37% (E/Z = 99/1) + 2% | 29/71 (16b , E/Z = 92/8; 17a , E/Z = 40/60) |
| 2 | CuCO ₃ •Cu(OH) ₂ | 46% (E/Z = 98/2) + 3% | 32/68 (16b , E/Z = 93/7; 17a , E/Z = 42/58) |
| 3 | Cu ₂ O | 54% (E/Z = 98/2) + 3% | 40/60 (16b , E/Z = 91/9; 17a , E/Z = 25/75) |
| 4 ^e | Cu ₂ O | 54% (E/Z = 97/3) + 1% | 38/62 (16b , E/Z = 91/9; 17a , E/Z = 20/80) |
| 5 | CuO | 16% (E/Z = 97/3) + 1% | 10/90 (16b , E/Z = 91/9; 17a , E/Z = 73/27) |
| 6 | Cu(OH) ₂ | 31% (E/Z > 98/2) + 1% | 26/74 (16b , E/Z = 93/7; 17a , E/Z = 34/66) |
| 7 | CuOAc | 23% (E/Z > 99/1) + 2% | 18/82 (16b , E/Z = 88/12; 17a , E/Z = 17/83) |
| 8 | Cu(OAc) ₂ | 25% (E/Z = 97/3) + 5% | 16/84 (16b , E/Z = 91/9; 17a , E/Z = 15/85) |
| 9 | Ag ₂ CO ₃ | 8% (E/Z > 97/3) + 1% | 9/91 (16b , E/Z = 82/18; 17a , E/Z = 12/88) |
| 10 | Ag ₂ O | 14% (E/Z > 97/3) + 1% | 8/92 (16b , E/Z = 90/10; 17a , E/Z = 11/89) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (Z)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Additive (3.5 equiv), 4Å MS 100 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dIn 10 mL sealed reaction tube. ^eNot sealed tube, but with an argon balloon.

Traces or no product of **16b** was observed with the following additives: Cu(OTf)₂ (3.5 equiv), AgOAc (3.5 equiv), Ag₃PO₄ (3.5 equiv), Cs₂CO₃ (3.5 equiv), Cu₂O/Ag₂CO₃ (2.0/1.5 equiv), Cu₂O/K₂CO₃ (1.5/2.0 equiv), LiOAc/LiCl (2.0/1.5 equiv).

4.4.6 Screening of solvents

With Cu₂O as the additive, we then studied the effect of solvents on the reaction (**Table 43**). Changing the ratio of DMA/DMSO from 8/3 to 9/1 did not change the yield of **16b** (**Table 43**, entries 1-2), and other combinations of solvents did not give better results (**Table 43**, entries 3-4). Single solvents were also tested, and comparable yields of **16b** were obtained with DMA, DMSO, and DMF (**Table 43**, entries 5-7). By contrast, NMP, DMI, and DMPU provided inferior results (**Table 43**, entries 8-10), and only traces of **16b** were observed in the presence of 1,4-dioxane, toluene, or PhCF₃ (**Table 43**, entries 11-13). Although the result of DMA was similar to that of DMA/DMSO (8/3) (**Table 43**, entries 1, 5), the latter was more advantageous when other 1,3,4-oxadiazoles were used as substrates. Thus, DMA/DMSO (8/3) was considered to be the optimal solvents.

Table 43 Screening of solvents^a

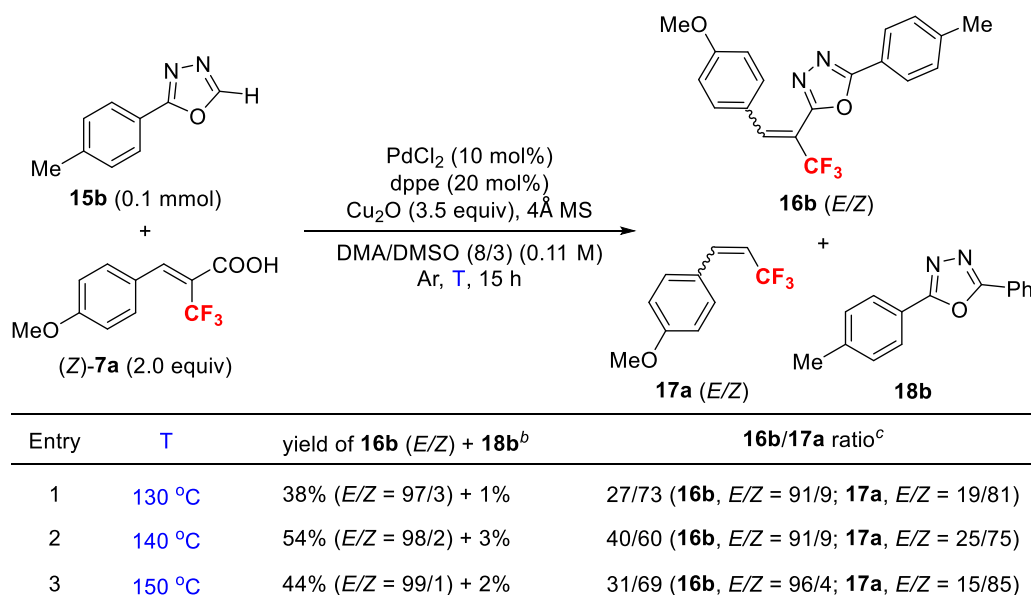
| Entry | Solvent | yield of 16b (E/Z) + 18b ^b | 16b/17a ratio ^c |
|-------|---------------------|---|---|
| 1 | DMA/DMSO (8/3) | 54% (E/Z = 98/2) + 3% | 40/60 (16b , E/Z = 91/9; 17a , E/Z = 25/75) |
| 2 | DMA/DMSO (9/1) | 54% (E/Z = 99/1) + 2% | 39/61 (16b , E/Z = 92/8; 17a , E/Z = 24/76) |
| 3 | DMF/DMSO (8/3) | 48% (E/Z = 98/2) + 2% | 34/66 (16b , E/Z = 92/8; 17a , E/Z = 33/67) |
| 4 | NMP/quinoline (3/1) | 12% (E/Z = 96/4) + 1% | 12/88 (16b , E/Z = 88/12; 17a , E/Z = 45/55) |
| 5 | DMA | 55% (E/Z = 99/1) + 3% | 36/64 (16b , E/Z = 93/7; 17a , E/Z = 31/69) |
| 6 | DMSO | 48% (E/Z = 96/4) + 1% | 31/69 (16b , E/Z = 94/6; 17a , E/Z = 10/90) |
| 7 | DMF | 50% (E/Z = 98/2) + 2% | 34/66 (16b , E/Z = 92/8; 17a , E/Z = 43/57) |
| 8 | NMP | 34% (E/Z = 97/3) + 1% | 23/77 (16b , E/Z = 91/9; 17a , E/Z = 46/54) |
| 9 | DMI | 24% (E/Z = 99/1) + 1% | 16/84 (16b , E/Z = 91/9; 17a , E/Z = 54/46) |
| 10 | DMPU | 39% (E/Z = 99/1) + 2% | 29/71 (16b , E/Z = 93/7; 17a , E/Z = 30/70) |
| 11 | 1,4-dioxane | traces of 16b | — |
| 12 | toluene | traces of 16b | — |
| 13 | PhCF ₃ | traces of 16b | — |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (Z)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4 Å MS 100 mg, Solvent (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

4.4.7 Screening of reaction temperature

Then, we turned our attention to the reaction temperature. Unfortunately, no matter the temperature decreased or increased from 140 °C, the yield of **16b** was reduced (**Table 44**). Therefore, 140 °C was the best reaction temperature.

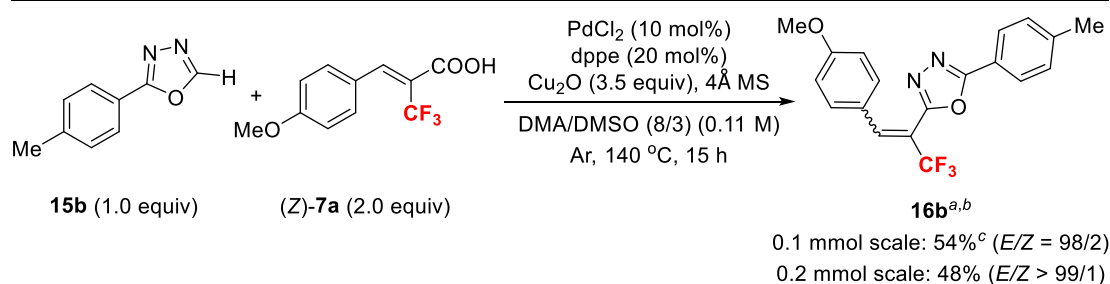
Table 44 Screening of reaction temperature^a



^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), (**Z**)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4 Å MS 100 mg, DMA/DMSO (8/3) (0.11 M), Ar, T, 15 h, in 20 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; E/Z ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their E/Z ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture.

4.4.8 The optimized reaction conditions

Further adjustments of the reaction time, the equivalents of (**Z**)-**7a**, PdCl₂, Cu₂O, dppe, and the inversion of the **15b**/**(Z)**-**7a** ratio did not give better results. So far, the optimized reaction conditions are as follows: **15b** (1.0 equiv), (**Z**)-**7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4 Å MS 100 mg/0.1 mmol of **15b**, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube (**Scheme 98**). In 0.1 mmol scale reaction, 54% of **16b** was obtained, but it was contaminated by 3% of **18b** (2-phenyl-5-(*p*-tolyl)-1,3,4-oxadiazole). When a 0.2 mmol scale reaction was conducted, the yield of **16b** was decreased to 48%, but luckily the pure product was isolated after careful silica gel column chromatography.



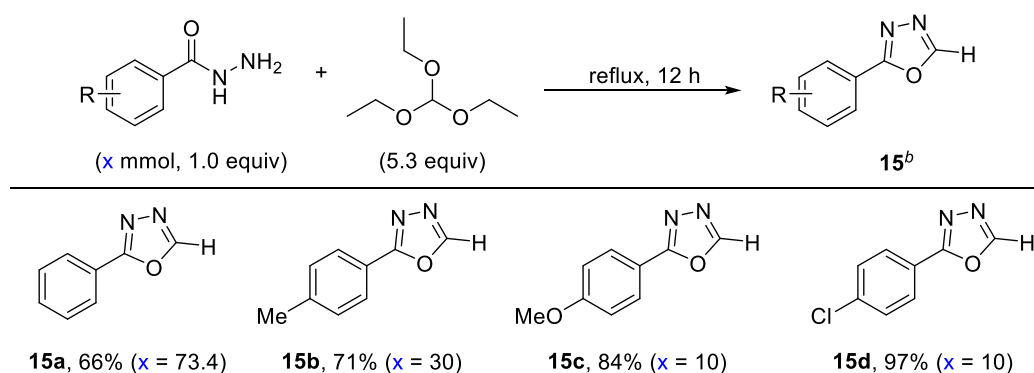
^aReaction conditions: **15b** (1.0 equiv), **(Z)-7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4Å MS 100 mg/0.1 mmol of **15b**, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube. ^bYield of **16b** was based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^cNot pure, **16b** was contaminated by 3% of **18b**.

Scheme 98 The optimized reaction conditions

4.5 Preparation of starting materials

4.5.1 Preparation of 1,3,4-oxadiazoles and sources of some other heteroarenes

Before the investigation of substrate scope, we first prepared some starting materials. 1,3,4-Oxadiazole derivatives could be easily prepared from hydrazides and triethyl orthoformate under reflux conditions for 12 h (**Table 45**).²¹⁷ Four compounds **15a-d** were synthesized in good to excellent yields. Besides, we borrowed some other 1,3,4-oxadiazole, oxazole, and thiazole derivatives (**15e-i**) from Hoarau's laboratory (**Figure 17**, left). Benzoxazole (**15j**) and benzimidazole (**15k**) were commercially available and were used as received without further purification (**Figure 17**, right).

Table 45 Synthesis of 1,3,4-oxadiazole derivatives^a

^aReaction conditions: hydrazide (1.0 equiv), triethyl orthoformate (5.3 equiv), reflux, 12 h. ^bYields based on isolated product after silica gel column chromatography.

²¹⁷ J. Hédouin, C. Schneider, I. Gillaizeau, C. Hoarau, *Org. Lett.* **2018**, *20*, 6027–6032.

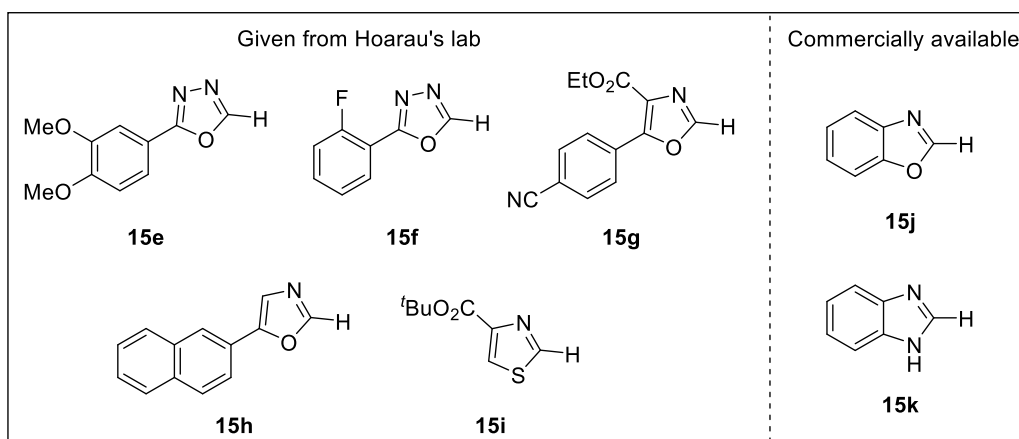
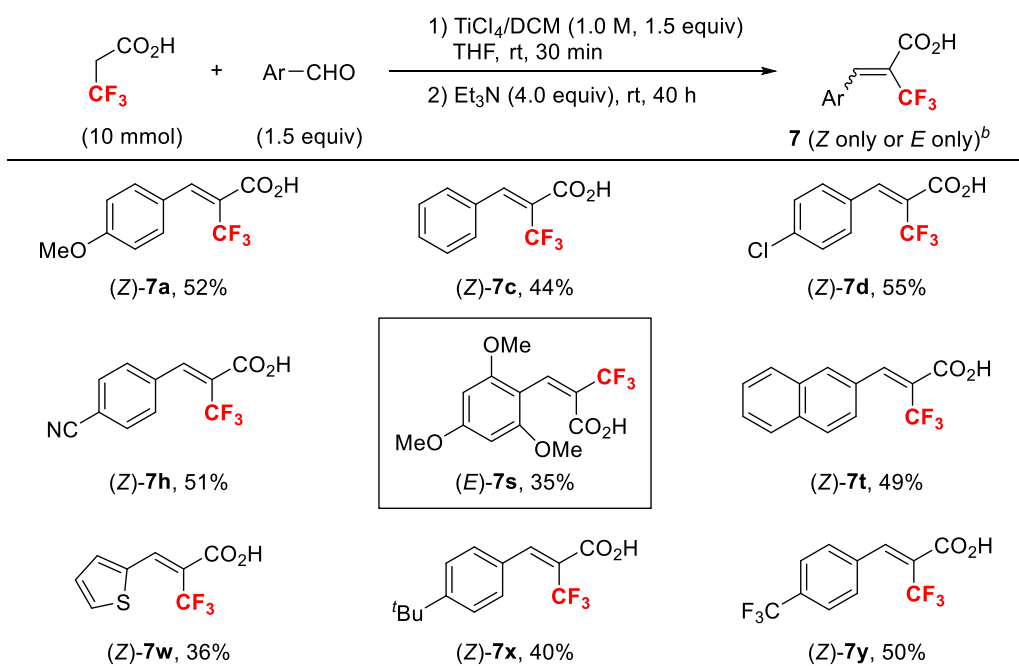


Figure 17 Sources of heteroarenes 15e-k

4.5.2 Preparation of (*Z*)- or (*E*)-3-aryl-2-(trifluoromethyl)acrylic acids (**7**)

Using Fang's protocol,¹⁹⁸ we aimed to prepare some (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids (**7**) from 3,3,3-trifluoropropionic acid and aryl aldehydes in the presence of TiCl₄/DCM and then Et₃N (**Table 46**). Unfortunately, the pure (*Z*)-products were difficult to separate from their *E* isomers by silica gel column chromatography, and thus subsequent recrystallization was required. *Z* isomers of **7a**, **7c**, **7d**, **7h**, **7t**, **7w**, **7x**, and **7y** were obtained in 36-55% yield. In contrast, due to steric hindrance, the product **7s** was obtained with *E*-configuration.

Table 46 Synthesis of (*Z*)- or (*E*)-3-aryl-2-(trifluoromethyl)acrylic acids^a

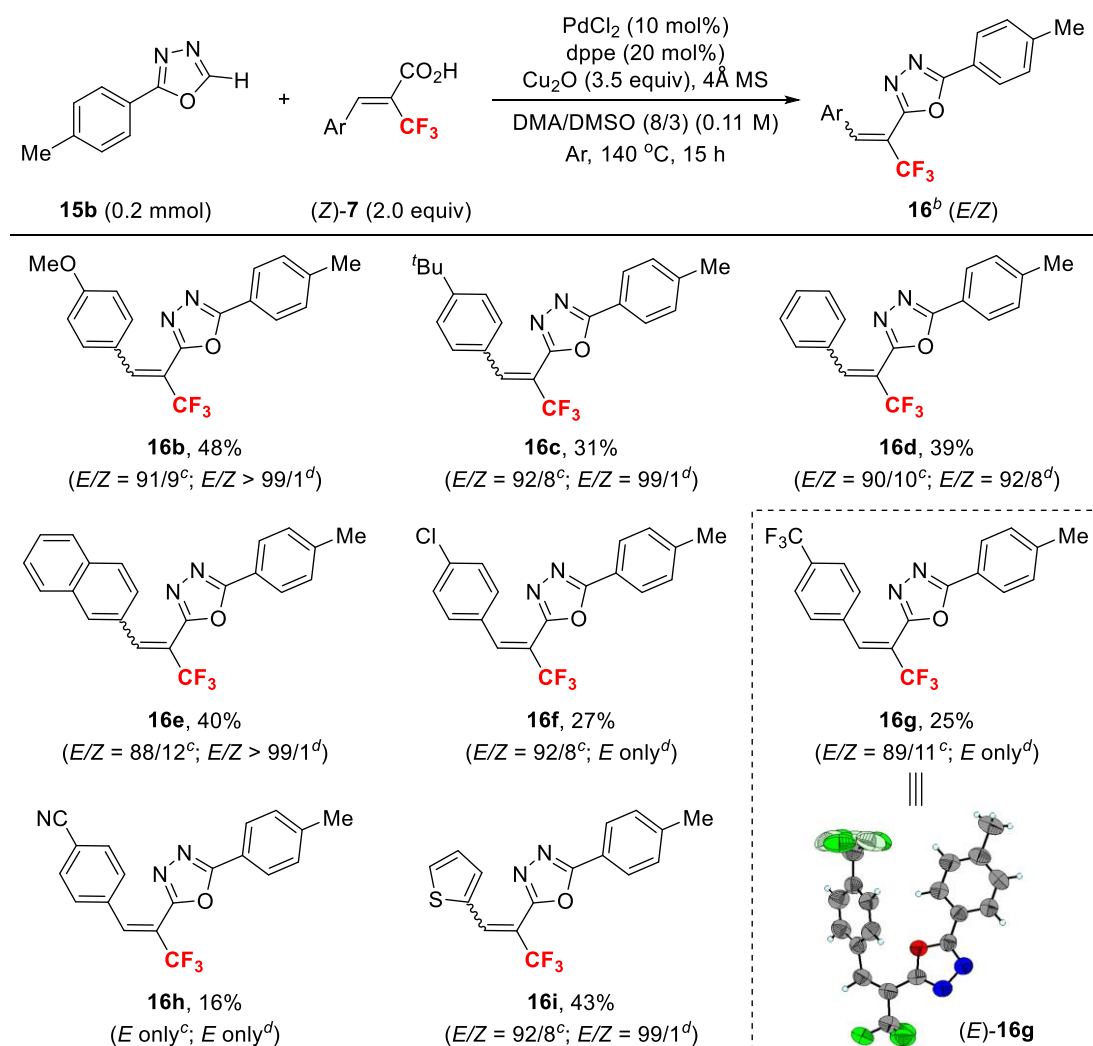
^aReaction conditions: 3,3,3-trifluoropropionic acid (10 mmol, 1.0 equiv), aryl aldehyde (1.5 equiv), TiCl₄/DCM (1.0 M, 1.5 equiv), THF (50 mL), rt, 30 min; then Et₃N (4.0 equiv), rt, 40 h. ^bYields based on isolated product after silica gel column chromatography and subsequent recrystallization; *Z* or *E* isomers were determined by ¹⁹F NMR spectrum of recrystallized products.

4.6 Substrate scope of the reaction

With the starting materials in hand, we investigated the generality of the oxidative decarboxylative cross-coupling of heteroarenes (**15**) with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids ((*Z*)-**7**).

Firstly, with **15b** as substrate, a series of (*Z*)-**7** were subjected to the reaction conditions, and the corresponding products **16** were obtained in 16-48% yield (**Table 47**). With *para*-substituted electron-donating groups (OMe, ^tBu), **16b** and **16c** were generated in 48% and 31% yields, respectively. In the presence of electronically neutral phenyl and naphthyl groups, **16d** and **16e** were produced in 39-40% yield. By contrast, less than 30% yields of products (**16f-h**) were obtained when halogen group

Table 47 Substrate scope of (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids ((*Z*)-**7**)^a



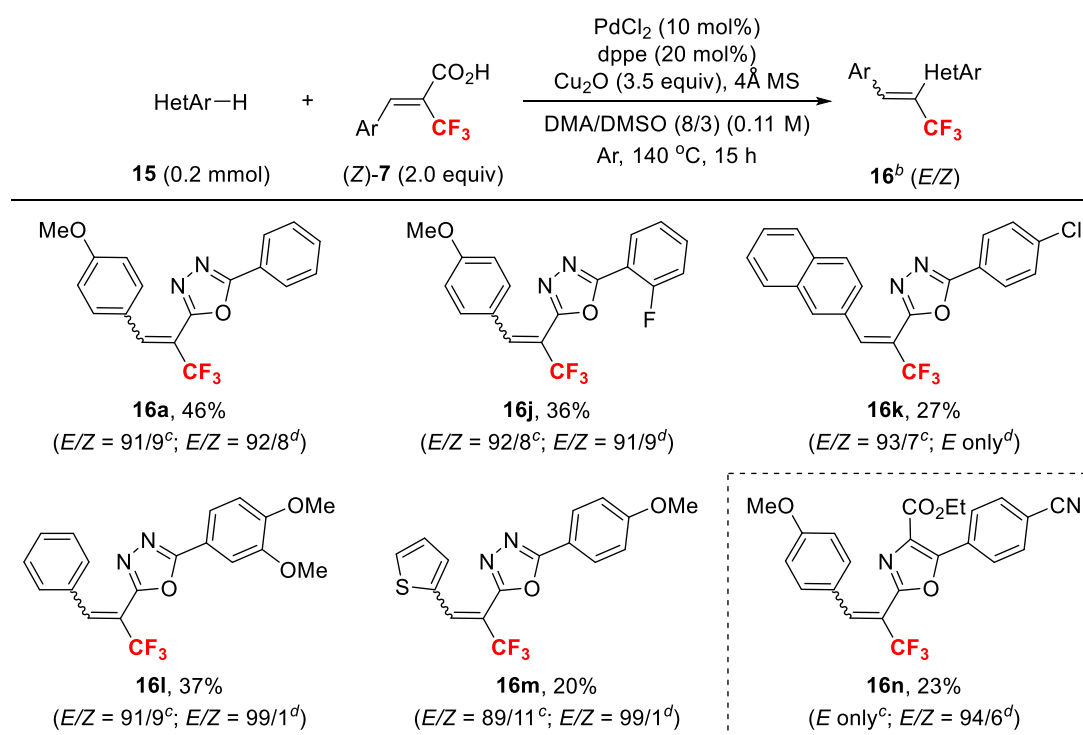
^aReaction conditions: **15b** (0.2 mmol, 1.0 equiv), (*Z*)-**7** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4Å MS 200 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube.

^bYields were based on isolated product after silica gel column chromatography. ^c*E/Z* ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^d*E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product.

(Cl) or electron-withdrawing groups (CF₃, CN) were introduced in the *para* position. Gratifying, the thienyl group was compatible in the reaction system and the product **16i** could be generated in 43% yield.

We then tested the reactivity of some other heteroarenes (**15**), and the corresponding products **16** were produced in 20-46% yield (**Table 48**). The reaction between 2-phenyl-1,3,4-oxadiazole (**15a**) and **7a** proceeded smoothly and allowed the formation of **16a** in 46% yield. Other 1,3,4-oxadiazoles bearing halogen or methoxy groups were also subjected to the reaction conditions, but lower yields of **16j-m** were obtained. One example involving oxazole derivative was shown, but the low yield was still observed for **16n**.

Table 48 Substrate scope of heteroarenes (**15**)^a



^aReaction conditions: **15** (0.2 mmol, 1.0 equiv), (Z)-**7** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4Å MS 200 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube.

^bYields were based on isolated product after silica gel column chromatography. ^cE/Z ratio was determined by ¹⁹F NMR spectrum of ended reaction mixture. ^dE/Z ratio was determined by ¹⁹F NMR spectrum of isolated product.

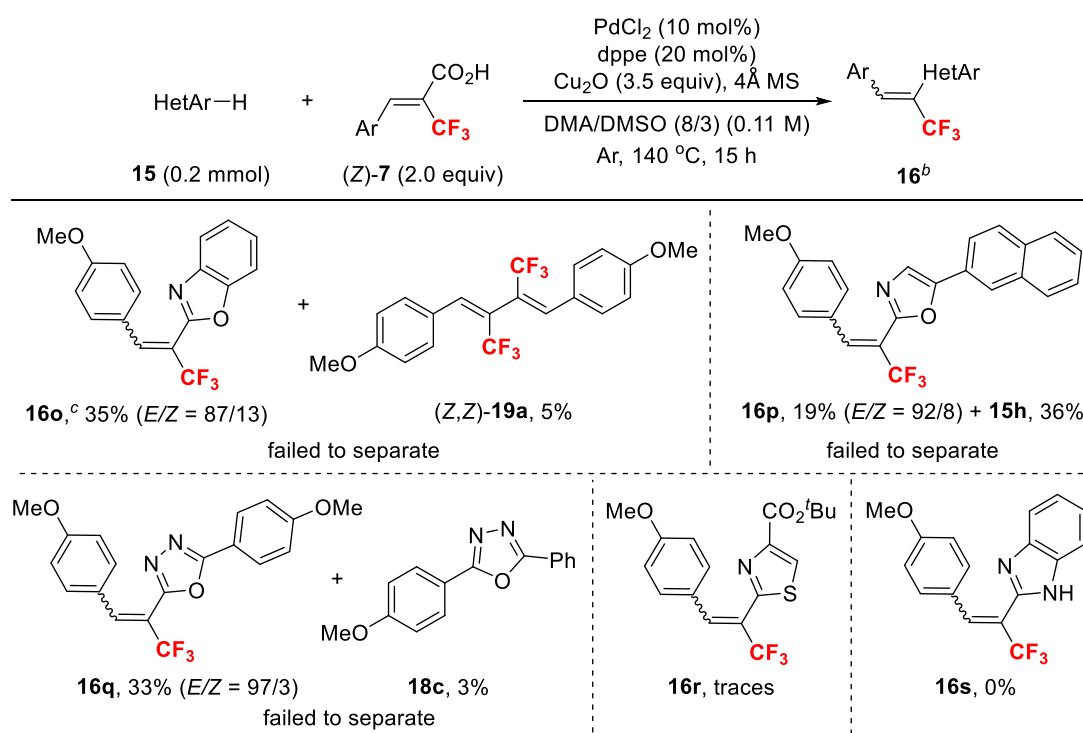
The *E* and *Z* isomers of this reaction were assigned by ¹⁹F NMR spectra [see page 125, **Figure 14** for chemical shifts and coupling constants of (*E*)-**16b** and (*Z*)-**16b**]. In addition, the configuration of (*E*)-**16g** was unambiguously determined by X-ray crystallographic analysis (**Table 47**). It is clear that high *E/Z* selectivity was obtained in all cases (**Table 47**, **Table 48**), and the *E/Z* ratio of isolated product was usually higher than that of the final reaction mixture, probably because the *E* and *Z* isomers of **16** could be partially separated by silica gel column chromatography. It is

noteworthy that *E* isomers were always the major products of **16** despite (*Z*)-**7** being used, which is not the case of previous reports.^{165,213}

4.7 Limitations of the reaction

In addition to the problem of low yields of **16**, other limitations also exist. As shown in **Table 49**, some products (**16o-q**) encountered the problem of purification. **16o** was contaminated by the side product (*Z,Z*)-**19a** which came from the decarboxylative homocoupling of (*Z*)-**7a**. **16p** and **16q** could not be separated from the substrate **15h** and the side-product **18c**, respectively. Furthermore, with *tert*-butyl thiazole-4-carboxylate or benzimidazole as substrate, almost no product (**16r** or **16s**) was formed in the reaction system.

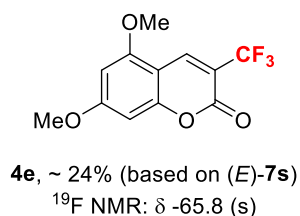
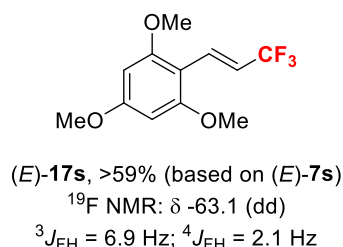
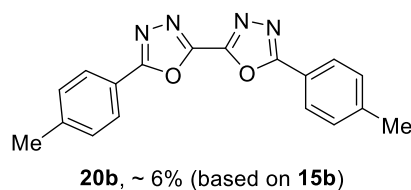
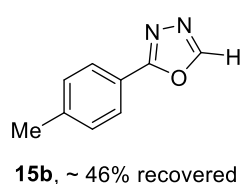
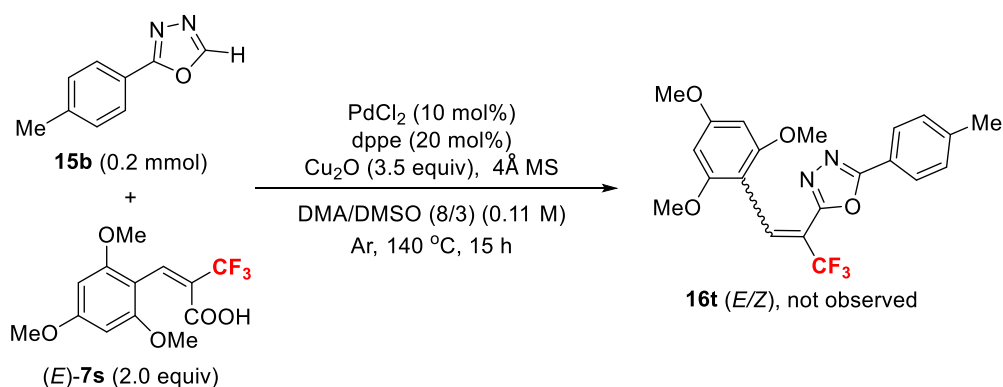
Table 49 Limitations of substrate scope of heteroarenes (**15**)^a



^aReaction conditions: **15** (0.2 mmol, 1.0 equiv), (*Z*)-**7** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4Å MS 200 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube.

^bYields (not pure) were based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c0.1 mmol scale with 100 mg 4Å MS.

In addition to (*Z*)-**7**, we also tested the reactivity of (*E*)-**7s** in the reaction conditions (**Table 50**), but no desired product **16t** was observed probably because of steric hindrance. Some substrate **15b** was recovered with the formation of homocoupling side-product **20b**. No (*E*)-**7s** was recovered and side-products (*E*)-**17s** (major product favored by steric “decongestion”) and **4e** were generated.

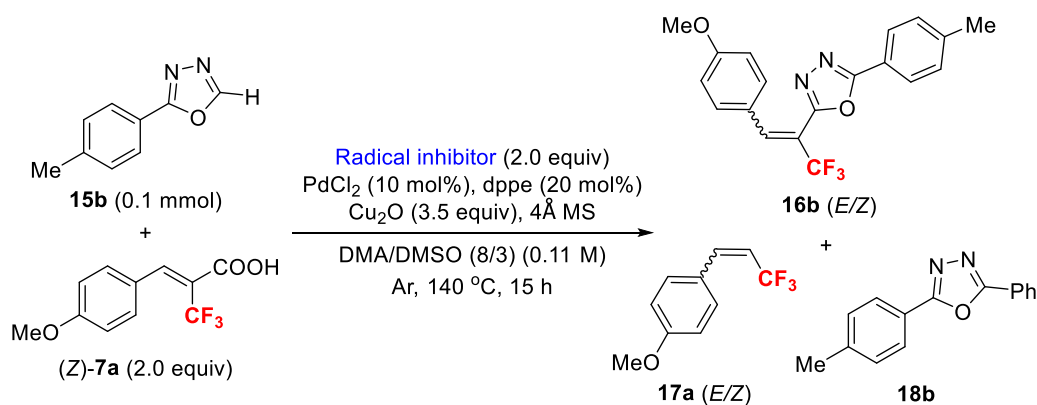
Table 50 Exploring the reactivity of (*E*)-**7s**^a

^aReaction conditions: **15b** (0.2 mmol, 1.0 equiv), (*E*)-**7s** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), 4Å MS 200 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube.

4.8 Investigation of the reaction mechanism

4.8.1 Addition of radical inhibitors

In order to figure out if the reaction undergoes a radical process, we added radical inhibitors to our reaction system. In the presence of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl), the reaction still proceeded well and **16b** was generated in 49% yield (Table 51, entry 2). BHT (2,6-di-*tert*-butyl-4-methylphenol) inhibited the reaction to a certain extent, but 31% yield of **16b** was still obtained (Table 51, entry 3). Based on these results, the reaction is unlikely to undergo a radical process.

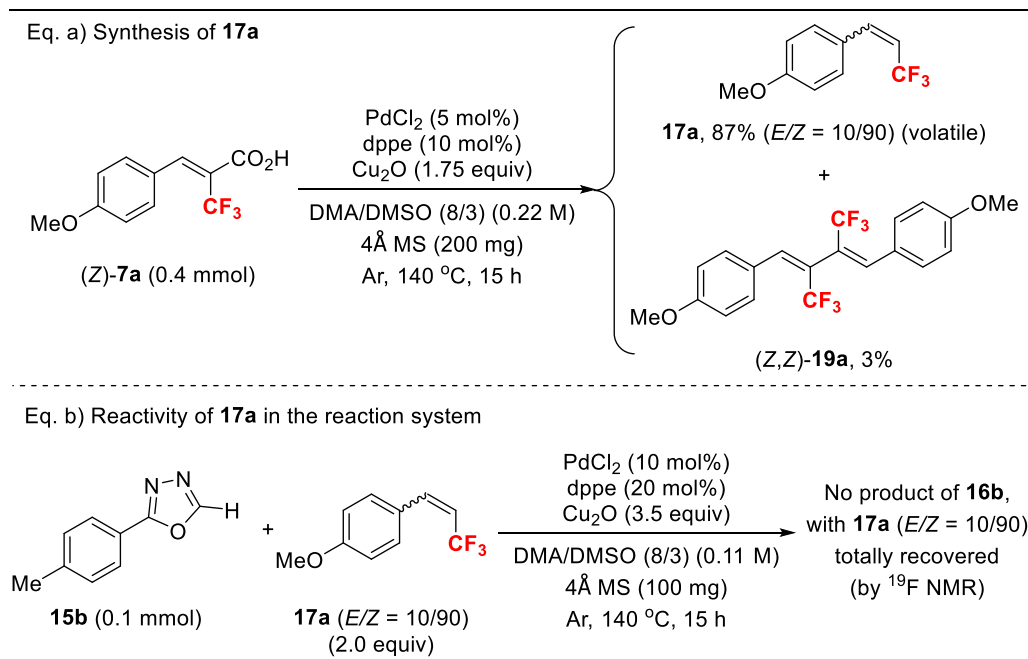
Table 51 Addition of radical inhibitors^a

| Entry | Radical inhibitor | yield of 16b (<i>E/Z</i>) + 18b ^b | 16b/17a ratio ^c |
|-------|-------------------|--|--|
| 1 | — | 54% (<i>E/Z</i> = 98/2) + 3% | 40/60 (16b , <i>E/Z</i> = 91/9; 17a , <i>E/Z</i> = 25/75) |
| 2 | TEMPO | 49% (<i>E/Z</i> > 99/1) + 2% | 34/66 (16b , <i>E/Z</i> = 92/8; 17a , <i>E/Z</i> = 14/86) |
| 3 | BHT | 31% (<i>E/Z</i> = 98/2) + 2% | 21/79 (16b , <i>E/Z</i> = 93/7; 17a , <i>E/Z</i> = 40/60) |

^aReaction conditions: **15b** (0.1 mmol, 1.0 equiv), **(Z)-7a** (2.0 equiv), PdCl₂ (10 mol%), dppe (20 mol%), Cu₂O (3.5 equiv), radical inhibitor (2.0 equiv), 4Å MS 100 mg, DMA/DMSO (8/3) (0.11 M), Ar, 140 °C, 15 h, in 20 mL sealed reaction tube. ^bYield of **16b** (contaminated by **18b**) was based on isolated product after silica gel column chromatography; *E/Z* ratio was determined by ¹⁹F NMR spectrum of isolated product. ^c**16b/17a** ratio and their *E/Z* ratio were determined by ¹⁹F NMR spectrum of ended reaction mixture. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

4.8.2 Investigation of the possible reaction intermediate

Since a large amount of **17a** was formed during the reaction, we wondered whether **17a** was one of the reaction intermediates. Then, we synthesized some **17a** under our reaction conditions but in the absence of substrate **15b** (Scheme 99, Eq. a). **17a** was isolated in 87% yield with *E/Z* = 10/90. Besides, we also separated 3% of (*Z,Z*)-**19a**, which was not observed in the optimized reaction conditions. Afterwards, we tested the possibility of the cross-coupling reaction between **15b** and **17a** in the standard conditions (Scheme 99, Eq. b). However, no desired product **16b** was formed and only **17a** (*E/Z* = 10/90) was recovered according to the ¹⁹F NMR spectrum of the ended reaction mixture. Therefore, **17a** was not considered to be a reaction intermediate.



Scheme 99 Investigation of the possible reaction intermediate

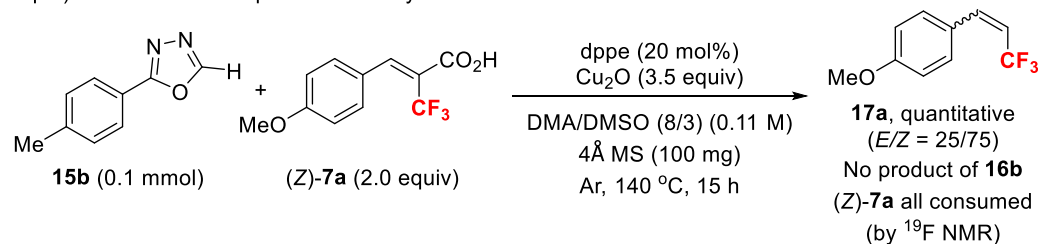
4.8.3 Investigation of the roles of palladium catalyst and copper additive

The control experiment was conducted in the absence of palladium catalyst or copper additive, and no desired product **16b** was formed in both cases (Scheme 100). It means that both palladium catalyst and copper additive are essential for the success of the reaction. In the absence of PdCl₂, (*Z*)-**7a** was all converted to the side-product **17a** with $E/Z = 25/75$ (Scheme 100, Eq. a). By comparison, in the absence of Cu₂O, (*Z*)-**7a** mainly went through isomerization and 82/18 of E/Z ratio was finally reached for **7a**. Only a small amount of decarboxylated side-product (*E*)-**17a** was formed (Scheme 100, Eq. b). Although decarboxylation and double bond isomerization occurred in both cases, the copper additive was more conducive to decarboxylation,²¹⁸ while the palladium catalyst seemed to be more favorable to double bond isomerization.²¹⁹

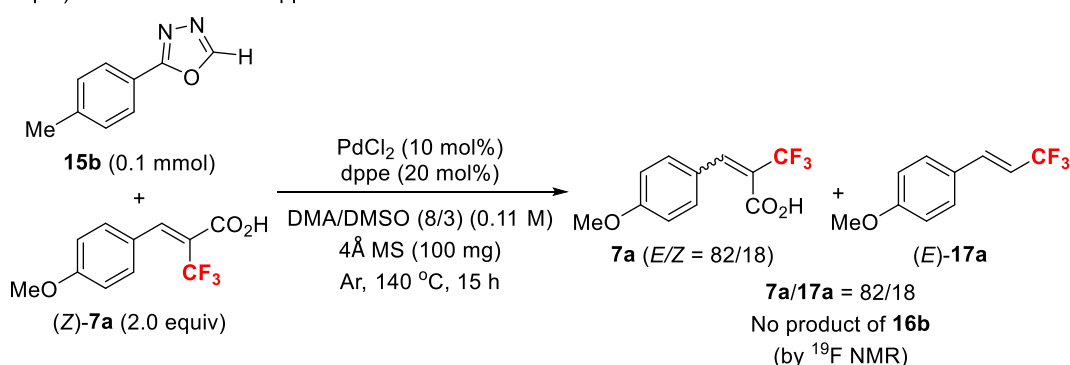
²¹⁸ L. J. Gooßen, N. Rodríguez, C. Linder, P. P. Lange, A. Fromm, *ChemCatChem* **2010**, *2*, 430–442.

²¹⁹ (a) P. M. Henry, *J. Am. Chem. Soc.* **1971**, *93*, 3547–3549; (b) A. Sen, T.-W. Lai, *Inorg. Chem.* **1981**, *20*, 4036–4038; (c) A. Sen, T.-W. Lai, *Inorg. Chem.* **1984**, *23*, 3257–3258; (d) J. Yu, M. J. Gaunt, J. B. Spencer, *J. Org. Chem.* **2002**, *67*, 4627–4629; (e) L. Canovese, C. Santo, F. Visentin, *Organometallics* **2008**, *27*, 3577–3581; (f) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.

Eq. a) In the absence of palladium catalyst

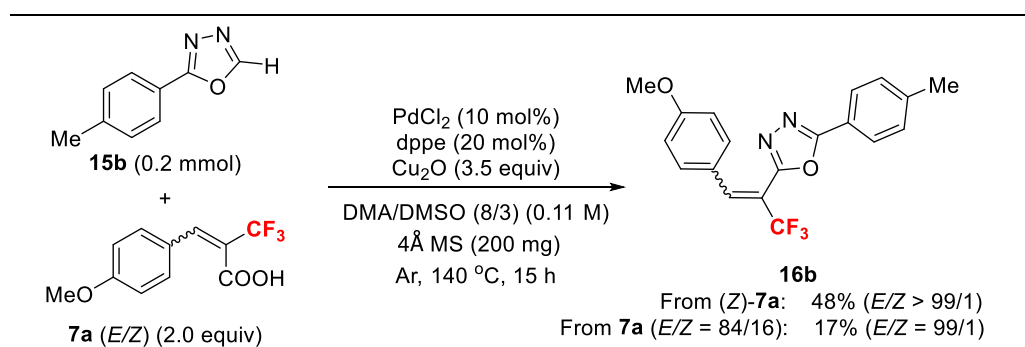


Eq. b) In the absence of copper additive



Scheme 100 Investigation of the roles of palladium catalyst and copper additive

Although it was possible for $(Z)\text{-7a}$ to be transformed to $(E)\text{-7a}$ in the reaction conditions, $(E)\text{-7a}$ did not seem to be the right starting material because using 7a ($E/Z = 84/16$) instead of $(Z)\text{-7a}$ as coupling partner led to much worse results (Scheme 101). This suggests that the double bond isomerization mainly occurs during the process or after the process of the reaction rather than at the beginning of the reaction.

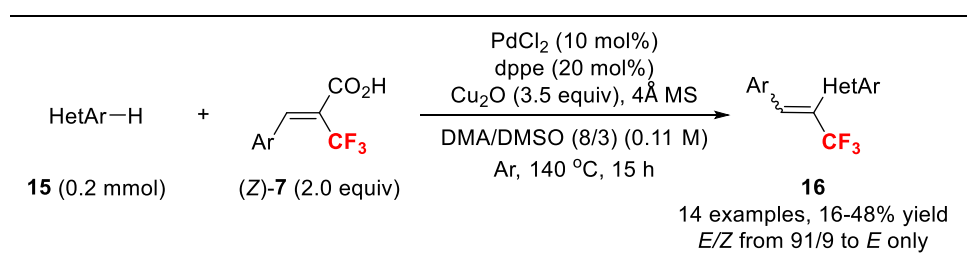
Scheme 101 Comparison of the reactivity of $(Z)\text{-7a}$ and 7a ($E/Z = 84/16$)

4.9 Proposed reaction mechanism

Based on the above-mentioned control experiments as well as previous reports,^{165,213} a plausible reaction mechanism was proposed in Scheme 102. The palladium-catalytic cycle starts with the palladation of heteroarene (**15**) with the assistance of Cu_2O , and Pd^{II} -complex **S** is generated. At the same time, $(Z)\text{-7}$ reacts with $[\text{Cu}]$ species to give copper(I) acrylate **T**, which undergoes decarboxylation to form vinyl copper(I) intermediate **U**. On one hand, protodecarboxylation of **U** occurs,

4.10 Conclusion

In conclusion, we have achieved the oxidative decarboxylative cross-coupling of heteroarenes with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids (**Scheme 104**). Many functional groups were compatible in the reaction system, but relatively low yields of products were obtained (16-48% yield). Double bond isomerization occurred in the reaction with the *E/Z* ratio of products ranging from 91/9 to 100/0. A palladium catalytic cycle was proposed in the reaction mechanism and copper additive was considered to be in charge of the decarboxylation of CF₃-acrylic acids. Further research is needed to figure out how the double bond isomerization occurred.



Scheme 104

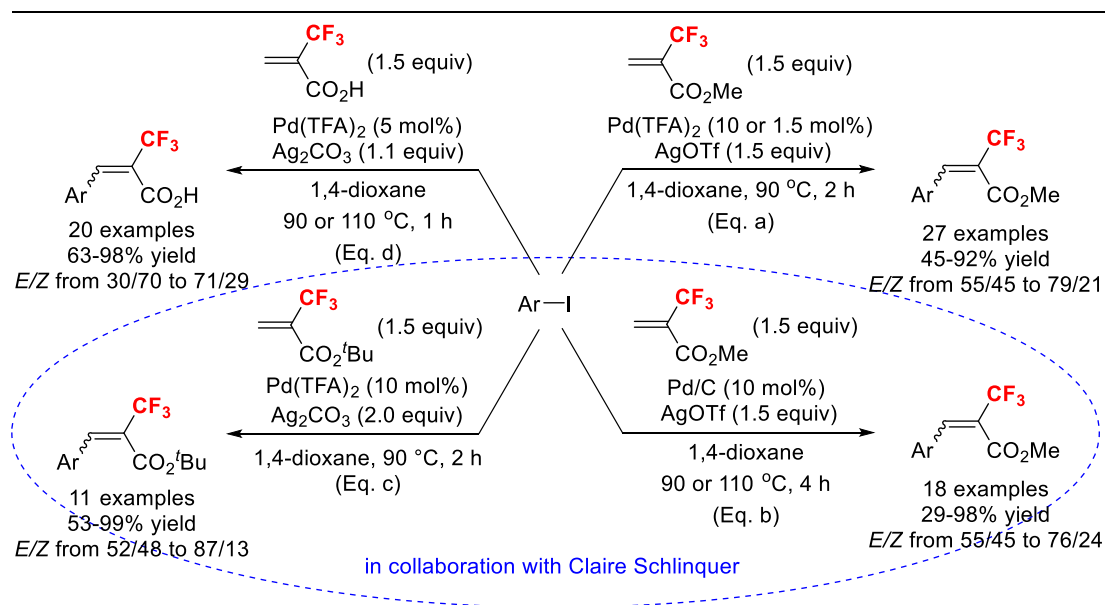
5 Conclusion and perspectives

5 Conclusion and perspectives

5.1 Conclusion

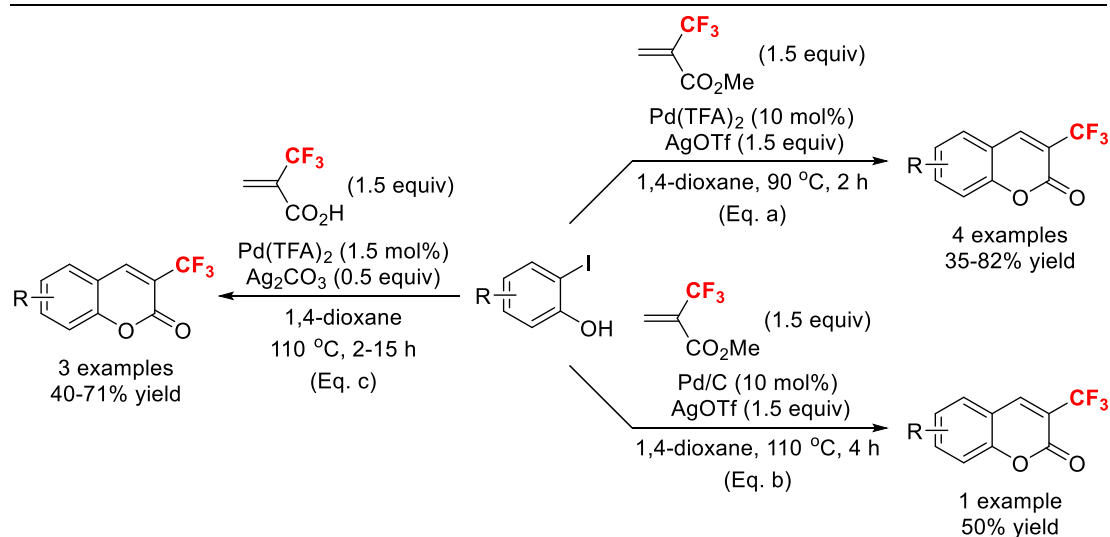
Thanks to the unique properties of the CF₃ group, trifluoromethylalkenes exhibit great potential in pharmaceuticals, agrochemicals, as well as materials science. Among various trifluoromethyl alkene derivatives, CF₃-containing acrylates and acrylic acids have great application potential. Despite obvious interest in such kinds of scaffolds, the methods for their synthesis as well as their substrate scope remain relatively limited. In this Ph.D. thesis, we mainly focused on the synthesis and subsequent transformations of 3-aryl-2-(trifluoromethyl)acrylates and acrylic acids.^{194,211}

First of all, a broad range of methyl 3-aryl-2-(trifluoromethyl)acrylates were constructed from aryl iodides and methyl 2-(trifluoromethyl)acrylate by Mizoroki-Heck reaction with Pd(TFA)₂ (or Pd/C) as catalyst and AgOTf as additive (**Scheme 105**, Eqs. a-b). The synthesis of *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates and 3-aryl-2-(trifluoromethyl)acrylic acids were further achieved by modified Mizoroki-Heck reaction, in which Ag₂CO₃ was an effective additive instead of AgOTf (**Scheme 105**, Eqs. c-d). For these reactions, good yields could usually be obtained, but in most cases, the *E/Z* selectivity was not satisfactory. Notably, the work in the dotted frame was done in collaboration with my Ph.D. colleague Claire Schlinquer.



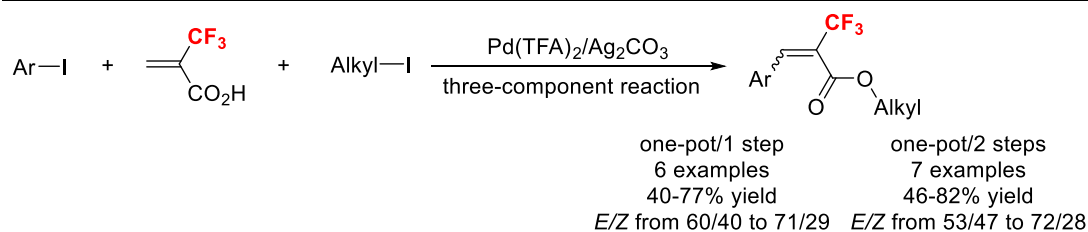
Scheme 105 Synthesis of 3-aryl-2-(trifluoromethyl)acrylates and acrylic acids by Mizoroki-Heck reaction

Next, starting from *ortho*-iodophenols and methyl 2-(trifluoromethyl)acrylate (or 2-(trifluoromethyl)acrylic acid), the related 3-trifluoromethyl coumarin derivatives could be generated in synthetically acceptable to good yields (**Scheme 106**). This strategy provides a good alternative for the construction of the valuable coumarin scaffold which shows various applications in medicine and fluorescence.



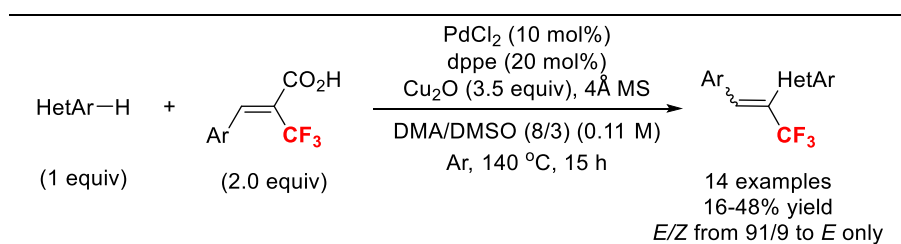
Scheme 106 Access to 3-trifluoromethyl coumarin derivatives

Then, we developed a three-component reaction to give access to more complex alkyl 3-aryl-2-(trifluoromethyl)acrylates in the presence of Pd(TFA)₂ and Ag₂CO₃ (**Scheme 107**). The three-component reaction of aryl iodides, 2-(trifluoromethyl)acrylic acid, and alkyl iodides could be performed through a one-pot/one-step process or a one-pot/two-step process. Moderate to good yields of products were obtained, but poor *E/Z* selectivity was observed.



Scheme 107 Access to more complex 3-aryl-2-(trifluoromethyl)acrylates by three-component reaction

Finally, we achieved the oxidative decarboxylative cross-coupling of heteroarenes with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids (**Scheme 108**). Many functional groups were compatible in the reaction system, but relatively low yields of products were obtained. Double bond isomerization occurred in the reaction with the *E/Z* ratio of products ranging from 91/9 to 100/0.



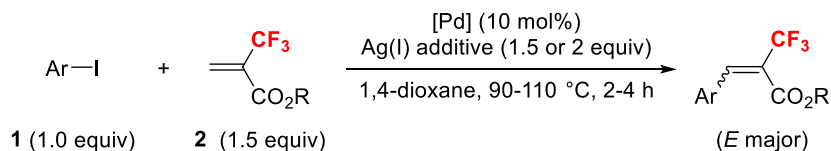
Scheme 108 Oxidative decarboxylative cross-coupling of heteroarenes with (Z)-3-aryl-2-(trifluoromethyl)acrylic acids

5.2 Perspectives

5.2.1 Reactivity and *E/Z* selectivity of 2-CF₃-acrylates or acrylic acid in Mizoroki-Heck reaction

In the Mizoroki-Heck reaction of aryl iodides with 2-CF₃-acrylates or acrylic acid (**2a-d**), significant differences in reactivity were observed between different 2-CF₃-acrylates and acrylic acids (**Table 52**). Methyl 2-(trifluoromethyl)acrylate (**2a**) was quite reactive in several different palladium-catalysed, silver(I) additive-mediated reaction conditions including the conditions of Pd(TFA)₂-AgOTf, Pd(TFA)₂-Ag₂CO₃, and Pd/C-AgOTf. In comparison, **2b**, **2c**, or **2d** could just work well in a certain combination of palladium catalyst and silver (I) additive. Further experimental and

Table 52 Reactivity of different CF₃-acrylates or acrylic acids in Mizoroki-Heck reaction



| | Pd(TFA) ₂ | | Pd/C | |
|--|----------------------|---------------------------------|------------|---------------------------------|
| | AgOTf | Ag ₂ CO ₃ | AgOTf | Ag ₂ CO ₃ |
| $\text{C}(\text{CF}_3)=\text{CH}-\text{CO}_2\text{Me}$ 2a | ✓ | ✓ | ✓ | ✗ |
| $\text{C}(\text{CF}_3)=\text{CH}-\text{CO}_2^t\text{Bu}$ 2b | ✗ | ✓ | ✗ | ✗ |
| $\text{C}(\text{CF}_3)=\text{CH}-\text{CO}_2\text{CH}(\text{CF}_3)_2$ 2c | ✓ | ✗ | not tested | not tested |
| $\text{C}(\text{CF}_3)=\text{CH}-\text{CO}_2\text{H}$ 2d | poor result | ✓ | not tested | ✗ |

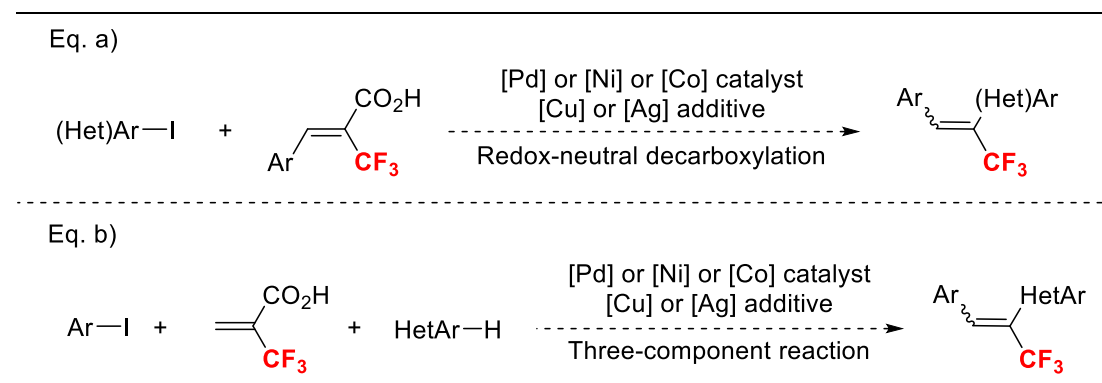
computational studies are needed to find out the reason for the huge difference in reactivity. Besides, it is interesting to test the reactivity of some other 2-CF₃-acrylates (with diverse electronic properties and steric variations) in the Mizoroki-Heck reaction and find out the law of the reactivity.

Also, in the Mizoroki-Heck reaction, it is difficult to explain the *E/Z* selectivity by steric effects. We think stereoelectronic effects can provide a point of view to interpret the current *E/Z* selectivity (see page 84, **Scheme 79**), but the further computational study is needed to better understand this *E/Z* selectivity.

5.2.2 Decarboxylative cross-coupling reactions with 2-CF₃-acrylic acids

In our oxidative decarboxylative cross-coupling reaction between heteroarenes with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids, the details of double bond isomerization are not clear and thus further investigation is required to explain the reason.

In addition, it would be possible to achieve the synthesis of valuable CF₃-alkenes by redox-neutral decarboxylative cross-coupling of (hetero)aryl iodides with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids in the presence of transition metal catalyst and additive (**Scheme 109**, Eq. a). It would also be interesting to explore the three-component cross-coupling reaction between aryl iodides, 2-(trifluoromethyl)acrylic acid, and heteroarenes by the combination of Mizoroki-Heck reaction and oxidative decarboxylative cross-coupling reaction (**Scheme 109**, Eq. b).

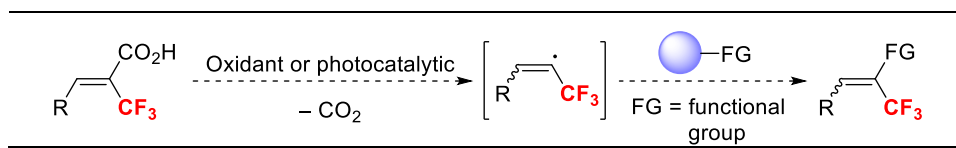


Scheme 109

5.2.3 Decarboxylative radical reactions with 2-CF₃-acrylic acids

We also wonder if it would be possible to generate α -trifluoromethyl-vinyl radical species by decarboxylation of 3-substituted-2-(trifluoromethyl)acrylic acids under oxidative conditions or photoredox-catalysed conditions (Scheme 110). This kind of α -CF₃-vinyl radical species is likely to be unstable, and thus it would be quite

challenging to achieve the radical decarboxylative functionalization of 3-substituted-2-(trifluoromethyl)acrylic acids.



Scheme 110

Experimental Section

Experimental Section

General information

All reactions were carried out using glasswares and magnetic stirring under an atmosphere of air or argon unless otherwise stated. Reaction temperatures were reported as the temperature of the bath surrounding the vessel.

Thin layer chromatography (TLC) analyses were done using aluminium sheets coated with silica gel (60 F₂₅₄ from Merck). Flash column chromatography was carried out using Silicaflash P60 silica gel (40-60 μm).

NMR spectra were recorded using a Bruker Avance-300 spectrometer operating at 300 MHz (¹H), 282 MHz (¹⁹F), and 75 MHz (¹³C). ¹H and ¹³C NMR chemical shifts (δ) were calibrated on residual proton and carbon resonances of CDCl₃ (¹H, δ = 7.26 ppm and ¹³C, δ = 77.16 ppm) or CD₃OD (¹H, δ = 3.31 ppm and ¹³C, δ = 49.00 ppm) or (CD₃)₂SO (¹H, δ = 2.50 ppm and ¹³C, δ = 39.52 ppm); ¹⁹F NMR chemical shifts (δ) were determined relative to CCl₃F as an internal standard (¹⁹F, δ = 0.0 ppm). The multiplicity signals were indicated with the common abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and the combinations thereof.

Melting points (Mp) were determined on a Fisher Scientific hot stage melting point apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100 FT IR spectrometer. HRMS were recorded with a Waters LCP Premier XR spectrometer with a TOF analyzer. Crystallographic data were collected using a Bruker SMART APEX diffractometer with a CCD area detector.

Materials

Methyl 2-(trifluoromethyl)acrylate, 2-(trifluoromethyl)acrylic acid, and 3,3,3-trifluoropropionic acid were purchased from Fluorochem. Pd/C (Palladium, 10% on carbon, type 487, dry) was purchased from Alfa Aesar. CuCO₃•Cu(OH)₂ (copper(II) carbonate basic, extra pure, SLR) and Cu₂O (copper(I) oxide, extra pure, SLR) were purchased from Fisher Chemical. Dry 1,4-dioxane (in sealed bottle without molecular sieves), DMA (*N,N*-dimethylacetamide, dry, in sealed bottle with molecular sieves), DMF (*N,N*-dimethylformamide, in sealed bottle with molecular sieves), and DMSO (dimethylsulfoxide, in sealed bottle with molecular sieves) were purchased from Acros Organics. Dry DMI (1,3-dimethyl-2-imidazolidinone, in sealed bottle with molecular sieves) was purchased from Sigma-Aldrich Ltd. Dry tetrahydrofuran and toluene were distilled from sodium with benzophenone. Dry dichloromethane, DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone), and NMP (*N*-methyl-2-

pyrrolidinone) were distilled from calcium hydride. 4Å molecular sieves were activated at 400 °C in an oven and were stored in a glove box. Other solvents and commercially available reagents were purchased from standard chemical suppliers (Fisher Scientific, Sigma-Aldrich, and Fluorochem) and used as received without further purification.

Aryl and alkyl iodides **1x**,²²⁰ **1aa**,²²⁰ **11a**,²²¹ **11c**,²²² and **11d**²²³ were prepared according to the reported methods and the analytical data were in agreement with those reported in the literature (**Figure 18**).

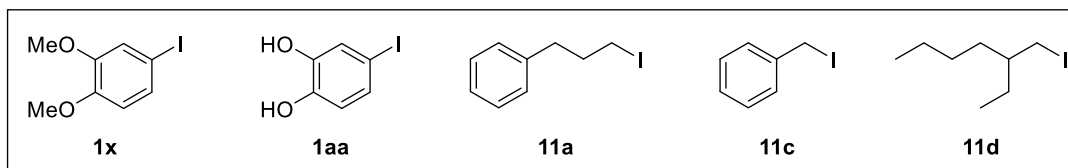


Figure 18 Pre-synthesized known aryl and alkyl iodides

1. Access to 3-aryl-2-(trifluoromethyl)acrylates by palladium-catalysed Mizoroki-Heck reaction

1.1 Relationship between actual yield and tested ¹⁹F NMR yield of **3a**

In the process of optimization of reaction conditions, the tested ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard sometimes gave more than 100% yield, so it was important to figure out the relationship between actual yield and tested ¹⁹F NMR yield. With the desired product **3a** in hand, PhCOCF₃ was used as an internal standard and 1,4-dioxane was used as a solvent, and then five groups of control experiments were carried out (**Table 53**). It is obvious that the tested ¹⁹F NMR yield was always higher than the corresponding actual yield and an average ratio between actual yield and the tested ¹⁹F NMR yield was obtained (**Formula 1**). Therefore, all of the ¹⁹F NMR yields in **Chapter 2** were corrected according to **Formula 2**.

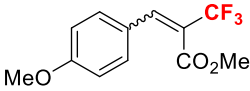
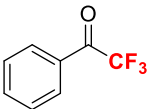
²²⁰ M. Castella, F. López-Calahorra, D. Velasco, H. Finkelmann, *Liq. Cryst.* **2002**, *29*, 559–565.

²²¹ (a) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574–11577; (b) X. Wang, X. Ji, C. Shao, Y. Zhang, Y. Zhang, *Org. Biomol. Chem.* **2017**, *15*, 5616–5624.

²²² T. H. Cam, F. Bouilhère, S. Johannesen, A. Zulauf, C. Panel, A. Pouilhès, D. Gori, V. Alezra, C. Kouklovsky, *J. Org. Chem.* **2009**, *74*, 4177–4187.

²²³ L. R. Jones, J. S. Schumm, J. M. Tour, *J. Org. Chem.* **1997**, *62*, 1388–1410.

Table 53 Relationship between actual yield and tested ^{19}F NMR yield of **3a**

| Test object | | Internal Standard | Solvent | | |
|--|-----------|---|---------------------------|---|--|
|  3a | |  | 1,4-dioxane | | |
| entry | 3a | Internal Standard | Actual yield ^a | Tested ^{19}F NMR yield ^b | Actual yield Tested ^{19}F NMR yield |
| 1 | 0.02 mmol | 0.10 mmol | 19% | 24% | 79% |
| 2 | 0.04 mmol | 0.10 mmol | 40% | 47% | 85% |
| 3 | 0.06 mmol | 0.10 mmol | 60% | 75% | 80% |
| 4 | 0.08 mmol | 0.10 mmol | 80% | 94% | 85% |
| 5 | 0.10 mmol | 0.10 mmol | 100% | 123% | 81% |

^aActual yield was the actual ratio between **3a** and internal standard PhCOCF₃. ^bTested ^{19}F NMR yield was the ratio of **3a** to internal standard PhCOCF₃ according to the ^{19}F NMR spectrum.

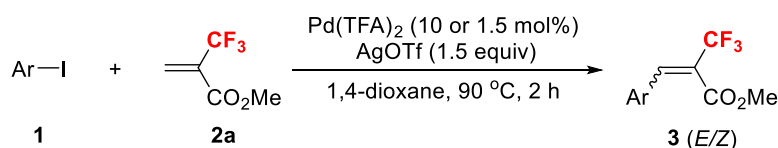
Formula 1

$$\frac{\text{Actual yield}}{\text{Tested } ^{19}\text{F NMR yield}} \text{ (average value)} = \frac{79\% + 85\% + 80\% + 85\% + 81\%}{5} = 82\%$$

Formula 2

$$^{19}\text{F NMR yield} = 82\% \times \text{Tested } ^{19}\text{F NMR yield}$$

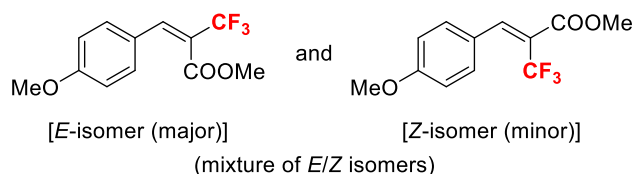
1.2 Synthesis of methyl 3-aryl-2-(trifluoromethyl)acrylates (**3**) by Mizoroki-Heck reaction with Pd(TFA)₂ and AgOTf



General procedure I (with 10 mol% Pd(TFA)₂): To a vial (2 mL) were added iodoarene **1** (0.2 mmol, 1.0 equiv), AgOTf (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (0.02 mmol, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or CHCl₃/MeOH).

General procedure II (with 1.5 mol% Pd(TFA)₂): To a vial (2 mL) were added iodoarene **1** (0.2 mmol, 1.0 equiv), AgOTf (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (0.003 mmol, 1.5 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), and

1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc or CH₃Cl/MeOH).

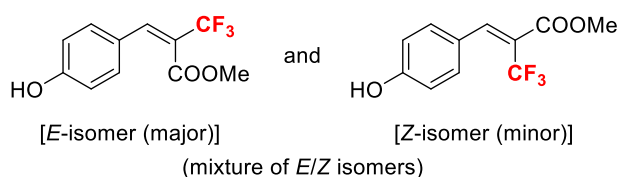


Methyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**E-3a**) and Methyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**Z-3a**)

According to general procedure I: 4-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 5 minutes. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), affording compound **3a** in 86% yield [mixture of *E/Z* isomers (75/25), 44.5 mg] as a yellow oil.

According to general procedure II: 4-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), affording compound **3a** in 89% yield [mixture of *E/Z* isomers (75/25), 46.1 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.01 (s, 1H, *Z*), 7.51 – 7.29 (m, 2H, *Z* + 3H, *E*), 6.99 – 6.84 (m, 2H, *Z* + 2H, *E*), 3.88 (s, 3H, *Z*), 3.86 – 3.83 (m, 3H, *Z* + 3H, *E*), 3.82 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -63.8 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.5 – 164.3 (m), 161.70, 161.66, 148.3 (q, *J* = 3.0 Hz), 140.4 (q, *J* = 5.7 Hz), 132.4 (q, *J* = 2.7 Hz), 131.7, 124.7, 124.5, 122.6 (q, *J* = 271.0 Hz), 122.3 (q, *J* = 272.0 Hz), 120.4 (q, *J* = 31.0 Hz), 119.6 (q, *J* = 32.0 Hz), 114.2, 114.0, 55.4, 52.7, 52.6. IR: 2960, 2847, 1726, 1604, 1513, 1439, 1322, 1281, 1260, 1155, 1116, 1028, 832, 523 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₂H₁₁F₃O₃ (*m/z*): 260.0660 [*M*]⁺, found: 260.0659.

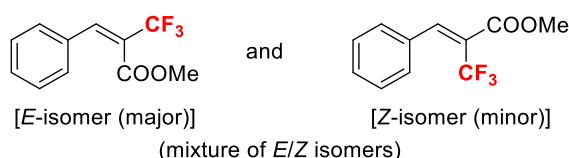


Methyl (*E*)-3-(4-hydroxyphenyl)-2-(trifluoromethyl)acrylate (*E*-3b) and Methyl (*Z*)-3-(4-hydroxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-3b)

According to general procedure I: 4-Iodophenol (0.2 mmol, 44.0 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **3b** in 76% yield [mixture of *E/Z* isomers (78/22), 37.3 mg] as a pale yellow solid.

According to general procedure II: 4-Iodophenol (0.2 mmol, 44.0 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **3b** in 77% yield [mixture of *E/Z* isomers (76/24), 37.8 mg] as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 8.00 (s, 1H, *Z*), 7.42 – 7.27 (m, 2H, *Z* + 3H, *E*), 6.91 – 6.73 (m, 2H, *Z* + 2H, *E*), 6.06 (s, 1H, *E*), 5.95 (s, 1H, *Z*), 3.89 (s, 3H, *Z*), 3.85 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -63.8 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.1 – 165.0 (m), 165.0 (q, *J* = 2.0 Hz), 158.22, 158.19, 148.7 (q, *J* = 2.7 Hz), 141.0 (q, *J* = 5.7 Hz), 132.7 (q, *J* = 2.7 Hz), 131.8, 124.7, 124.5, 122.5 (q, *J* = 271.1 Hz), 122.3 (q, *J* = 272.2 Hz), 120.2 (q, *J* = 31.1 Hz), 119.5 (q, *J* = 32.3 Hz), 115.9, 115.6, 53.0, 52.9. IR: 3292, 1699, 1608, 1515, 1438, 1383, 1279, 1250, 1210, 1157, 1126, 1109, 1019, 843, 493 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₁H₉F₃O₃ (*m/z*): 246.0504 [*M*]⁺, found: 246.0496.

**Methyl (*E*)-3-phenyl-2-(trifluoromethyl)acrylate (*E*-3c) and Methyl (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (*Z*-3c)**

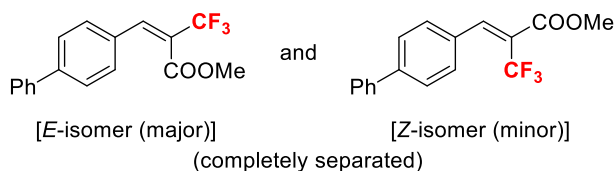
According to general procedure I: Iodobenzene (0.2 mmol, 40.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 30/1, v/v), affording compound **3c** in 85% yield [mixture of *E/Z* isomers (72/28), 39.3 mg] as a yellow oil.

According to general procedure II: Iodobenzene (0.2 mmol, 40.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted

for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 40/1, v/v), affording compound **3c** in 85% yield [mixture of *E/Z* isomers (72/28), 39.0 mg] as a yellow oil.

Larger scale reaction: To a 100 mL reaction tube were added iodobenzene (3.5 mmol, 714.0 mg, 1.0 equiv), AgOTf (5.25 mmol, 1348.9 mg, 1.5 equiv), Pd(TFA)₂ (0.35 mmol, 112.9 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate (5.25 mmol, 809.0 mg, 1.5 equiv), and 1,4-dioxane (17.5 mL). The reaction tube was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 100 mL flask (with the tube washed with 50 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, 40/1, v/v), affording compound **3c** in 92% yield [mixture of *E/Z* isomers (72/28), 739.8 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.12 (s, 1H, *Z*), 7.53 – 7.34 (m, 5H, *Z* + 6H, *E*), 3.90 (s, 3H, *Z*), 3.79 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.4 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.9, 148.6 (q, *J* = 2.9 Hz), 140.6 (q, *J* = 5.7 Hz), 132.6, 132.3, 130.5, 130.3, 129.4 (q, *J* = 2.3 Hz), 129.2, 128.8, 128.4, 123.3 (q, *J* = 31.3 Hz), 122.5 (q, *J* = 31.9 Hz), 122.2 (q, *J* = 271.4 Hz), 122.0 (q, *J* = 272.6 Hz), 52.9, 52.7. IR: 2961, 1730, 1645, 1438, 1386, 1278, 1231, 1158, 1125, 1033, 1020, 755, 693 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₁H₉F₃O₂ (m/z): 230.0555 [M]⁺, found: 230.0544.



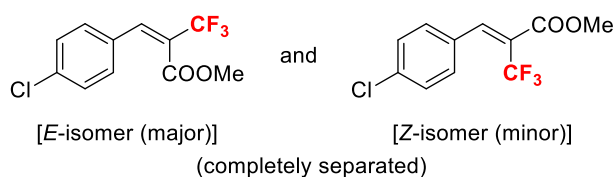
Methyl (*E*)-3-([1,1'-biphenyl]-4-yl)-2-(trifluoromethyl)acrylate (**E-3d**) and Methyl (*Z*)-3-([1,1'-biphenyl]-4-yl)-2-(trifluoromethyl)acrylate (**Z-3d**)

According to general procedure I: 4-Iodobiphenyl (0.2 mmol, 56.0 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 30/1, v/v), affording compound **3d** in 81% yield [mixture of *E/Z* isomers (79/21), 49.4 mg. *E/Z* isomers were completely separated by column: compound **E-3d** 39.1 mg, yellow oil; impure *Z*-isomer was subsequently washed with petroleum ether (0.5 mL × 3) to obtain pure compound **Z-3d** 10.3 mg, white solid].

[**E-3d** (major)] ¹H NMR (300 MHz, CDCl₃): δ 7.68 – 7.60 (m, 4H), 7.54 – 7.44 (m, 5H), 7.44 – 7.36 (m, 1H), 3.84 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.2 (d, *J* = 1.7 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.0, 143.4, 140.2 (q, *J* = 5.7 Hz), 140.0, 131.1, 130.0, 129.1, 128.2, 127.3, 127.2, 122.9 (q, *J* = 31.2 Hz), 122.3 (q, *J* = 271.4 Hz), 52.8.

IR: 3034, 2954, 1730, 1645, 1492, 1439, 1384, 1322, 1293, 1280, 1230, 1158, 1124, 1018, 763, 696 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_2$ (m/z): 306.0868 $[\text{M}]^+$, found: 306.0868.

[**Z-3d** (minor)] Mp 84-85 $^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 8.13 (s, 1H), 7.68 – 7.59 (m, 4H), 7.54 – 7.43 (m, 4H), 7.43 – 7.34 (m, 1H), 3.92 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.1 (q, $J = 2.0$ Hz), 148.2 (q, $J = 2.9$ Hz), 143.2, 140.1, 131.4, 130.4 (q, $J = 2.6$ Hz), 129.1, 128.2, 127.3, 127.1, 122.2 (q, $J = 32.0$ Hz), 122.1 (q, $J = 272.5$ Hz), 53.0. IR: 3040, 2961, 2921, 2855, 1731, 1714, 1631, 1438, 1379, 1278, 1206, 1126, 1038, 845, 753, 701 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_2$ (m/z): 306.0868 $[\text{M}]^+$, found: 306.0855.

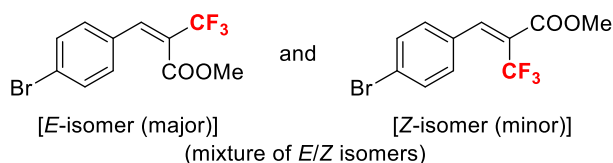


Methyl (*E*)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylate (**E-3e**) and Methyl (*Z*)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylate (**Z-3e**)

According to general procedure I: 1-Chloro-4-iodobenzene (0.2 mmol, 47.7 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **3e** in 85% yield [mixture of *E/Z* isomers (74/26), 45.2 mg. *E/Z* isomers were completely separated by column: **E-3e** 33.5 mg, yellow oil; **Z-3e** 11.7 mg, yellow oil].

[**E-3e** (major)] ^1H NMR (300 MHz, CDCl_3): δ 7.43 – 7.28 (m, 5H), 3.80 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -64.4 (d, $J = 1.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.6 – 163.5 (m), 139.6 (q, $J = 5.8$ Hz), 136.7, 130.7, 130.6, 129.1, 123.8 (q, $J = 31.4$ Hz), 122.1 (q, $J = 271.5$ Hz), 52.9. IR: 2961, 1732, 1650, 1492, 1312, 1290, 1273, 1232, 1160, 1128, 1095, 1015, 842, 816, 502, 434 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{11}\text{H}_8^{35}\text{ClF}_3\text{O}_2$ (m/z): 264.0165 $[\text{M}]^+$, found: 264.0156.

[**Z-3e** (minor)] ^1H NMR (300 MHz, CDCl_3): δ 8.03 (s, 1H), 7.43 – 7.30 (m, 4H), 3.90 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.6 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.7 (q, $J = 2.0$ Hz), 147.2 (q, $J = 2.9$ Hz), 136.6, 131.0, 130.8 (q, $J = 2.5$ Hz), 128.8, 123.0 (q, $J = 32.0$ Hz), 121.8 (q, $J = 272.7$ Hz), 53.1. IR: 2961, 2921, 2855, 1731, 1640, 1491, 1438, 1392, 1279, 1257, 1131, 1091, 1041, 828, 788, 755 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{11}\text{H}_8^{35}\text{ClF}_3\text{O}_2$ (m/z): 264.0165 $[\text{M}]^+$, found: 264.0152.



Methyl (*E*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylate (*E*-3f) and Methyl (*Z*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylate (*Z*-3f)

According to general procedure I: 1-Bromo-4-iodobenzene (0.2 mmol, 56.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **3f** in 89% yield [mixture of *E/Z* isomers (73/27), 55.0 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.92 (s, 1H, *Z*), 7.50 – 7.40 (m, 2H, *Z* + 2H, *E*), 7.27 (s, 1H, *E*), 7.17 (d, *J* = 8.4 Hz, 2H, *Z* + 2H, *E*), 3.81 (s, 3H, *Z*), 3.71 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.5 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.7 (q, *J* = 1.9 Hz), 163.6 – 163.5 (m), 147.2 (q, *J* = 2.9 Hz), 139.6 (q, *J* = 5.8 Hz), 132.0, 131.7, 131.4, 131.2, 130.9 (q, *J* = 2.4 Hz), 130.8, 125.0, 124.9, 123.9 (q, *J* = 31.4 Hz), 123.1 (q, *J* = 32.0 Hz), 122.1 (q, *J* = 271.6 Hz), 121.8 (q, *J* = 272.7 Hz), 53.0, 52.8. IR: 2961, 1731, 1645, 1589, 1489, 1439, 1385, 1312, 1288, 1274, 1230, 1161, 1128, 1073, 1021, 1011, 839, 814, 498 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈⁷⁹BrF₃O₂Na (m/z): 330.9557 [M+Na]⁺, found: 330.9554.



Methyl (*E*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (*E*-3g) and Methyl (*Z*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (*Z*-3g)

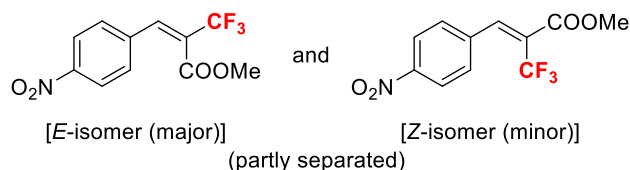
According to general procedure I: 4-Iodobenzonitrile (0.2 mmol, 45.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.24 mmol, 37.0 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 5/1, v/v), affording compound **3g** in 84% yield [mixture of *E/Z* isomers (63/37), 42.7 mg. *E/Z* isomers were completely separated by column: compound **E-3g** 27.1 mg, white solid; impure *Z*-isomer was subsequently washed with petroleum ether (0.5 mL × 5) to obtain pure compound **Z-3g** 15.6 mg, white solid].

According to general procedure II: 4-Iodobenzonitrile (0.2 mmol, 45.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-

(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 5/1, v/v), affording compound **3g** in 88% yield [mixture of *E/Z* isomers (62/38), 45.1 mg].

[**E-3g** (major)] Mp <44 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.52 – 7.42 (m, 3H), 3.78 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.7 (d, *J* = 1.4 Hz). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 162.9 – 162.7 (m), 139.2 (q, *J* = 5.8 Hz), 136.9, 132.4, 129.5, 126.2 (q, *J* = 31.7 Hz), 121.7 (q, *J* = 271.9 Hz), 118.2, 113.8, 53.0. IR: 2959, 2231, 1732, 1653, 1440, 1381, 1292, 1275, 1235, 1160, 1129, 1020, 554 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₂H₈F₃NO₂ (*m/z*): 255.0507 [M]⁺, found: 255.0512.

[**Z-3g** (minor)] Mp 120-121 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.09 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 3.92 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.1 (q, *J* = 1.8 Hz), 146.0 (q, *J* = 3.0 Hz), 137.3, 132.1, 129.4 (q, *J* = 2.3 Hz), 125.2 (q, *J* = 32.0 Hz), 121.5 (q, *J* = 273.0 Hz), 118.2, 113.6, 53.2. IR: 2230, 1716, 1639, 1440, 1386, 1289, 1225, 1149, 1127, 1041, 837, 657, 555 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₂H₈F₃NO₂ (*m/z*): 255.0507 [M]⁺, found: 255.0511.

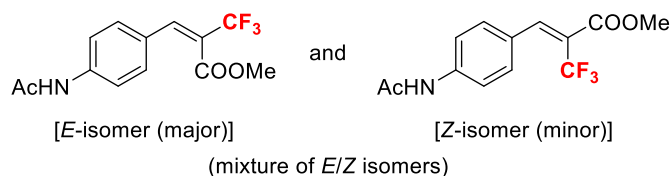


Methyl (*E*)-3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (**E-3h**) and Methyl (*Z*)-3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (**Z-3h**)

According to general procedure I: 1-Iodo-4-nitrobenzene (0.2 mmol, 49.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 7/1, v/v), affording compound **3h** in 86% yield [mixture of *E/Z* isomers (55/45), 47.6 mg; among which, partly pure compound **Z-3h** was obtained] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.25 (m, 2H, *Z* + 2H, *E*), 8.12 (s, 1H, *Z*), 7.63 – 7.43 (m, 2H, *Z* + 3H, *E*), 3.92 (s, 3H, *Z*), 3.78 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.8 (d, *J* = 1.1 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.0 (q, *J* = 1.8 Hz), 162.8 – 162.6 (m), 148.6, 148.4, 145.6 (q, *J* = 3.0 Hz), 139.2, 139.0 (q, *J* = 5.9 Hz), 138.9, 129.8, 129.6 (q, *J* = 2.3 Hz), 126.7 (q, *J* = 31.7 Hz), 125.7 (q, *J* = 32.0 Hz), 123.8, 123.6, 121.6 (q, *J* = 272.1 Hz), 121.4 (q, *J* = 272.9 Hz), 53.3, 53.0. IR: 2963, 1732, 1600, 1522, 1439, 1347, 1277, 1132, 1042, 855, 691 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈F₃NO₄Na (*m/z*): 298.0303 [M+Na]⁺, found: 298.0312.

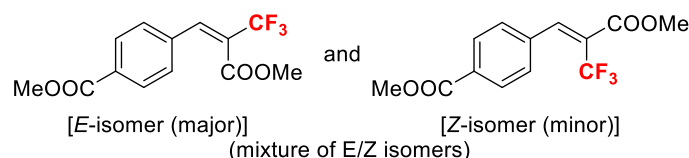
[Z-3h] White solid. Mp 78-79 °C. ^1H NMR (300 MHz, CDCl_3): δ 8.27 (d, $J = 8.7$ Hz, 2H), 8.13 (s, 1H), 7.52 (d, $J = 8.4$ Hz, 2H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.0 (q, $J = 1.8$ Hz), 148.4, 145.7 (q, $J = 3.0$ Hz), 139.2, 129.7 (q, $J = 2.3$ Hz), 125.8 (q, $J = 32.0$ Hz), 121.4 (q, $J = 273.0$ Hz), 53.3. IR: 3107, 2968, 1722, 1638, 1598, 1518, 1429, 1348, 1276, 1206, 1143, 1126, 1041, 856, 693 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{NO}_4$ (m/z): 275.0405 $[\text{M}]^+$, found: 275.0396.



Methyl (*E*)-3-(4-acetamidophenyl)-2-(trifluoromethyl)acrylate (*E*-3i) and Methyl (*Z*)-3-(4-acetamidophenyl)-2-(trifluoromethyl)acrylate (*Z*-3i)

According to general procedure I: *N*-(4-iodophenyl)acetamide (0.2 mmol, 52.2 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 24 hours. The reaction mixture was filtered with celite, and then 4 mL water and 2 mL saturated aqueous sodium carbonate were added, followed by the extraction with EtOAc (3 \times 10 mL). The combined organic phase was dried over anhydrous MgSO_4 and the solvent was evaporated. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 3/1 to 1/1, v/v), affording compound **3i** in 53% yield [mixture of *E/Z* isomers (75/25), 30.6 mg] as a pale yellow solid.

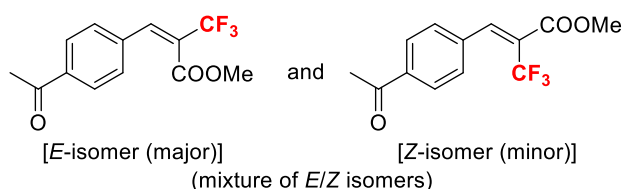
^1H NMR (300 MHz, CDCl_3): δ 8.10 – 7.85 (m, 2H, *Z* + 1H, *E*), 7.64 – 7.48 (m, 2H, *Z* + 2H, *E*), 7.44 – 7.28 (m, 2H, *Z* + 3H, *E*), 3.88 (s, 3H, *Z*), 3.80 (s, 3H, *E*), 2.17 (s, 3H, *Z* + 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s, *Z*), -64.0 (s, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 169.11, 169.06, 164.3, 164.2 (q, $J = 2.0$ Hz), 148.0 (q, $J = 2.6$ Hz), 140.5 – 139.8 (m), 131.2 (q, $J = 2.6$ Hz), 130.6, 127.9, 127.6, 122.3 (q, $J = 271.3$ Hz), 122.1 (q, $J = 272.6$ Hz), 121.7 (q, $J = 31.4$ Hz), 121.0 (q, $J = 31.8$ Hz), 119.4, 119.2, 52.9, 52.8, 24.7. IR: 3303, 2958, 1724, 1665, 1598, 1541, 1412, 1315, 1289, 1236, 1153, 1132, 1027, 823 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{NO}_3$ (m/z): 288.0848 $[\text{M}+\text{H}]^+$, found: 288.0852.



Methyl (*E*)-4-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (*E*-3j) and Methyl (*Z*)-4-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (*Z*-3j)

According to general procedure I: Methyl 4-iodobenzoate (0.2 mmol, 52.4 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **3j** in 92% yield [mixture of *E/Z* isomers (74/26), 52.9 mg] as a yellow oil.

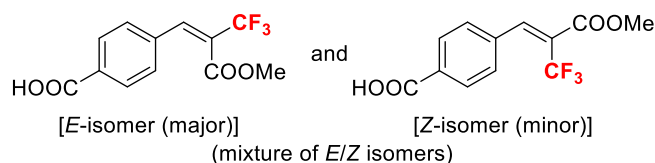
¹H NMR (300 MHz, CDCl₃): δ 8.11 (s, 1H, *Z*), 8.09 – 7.99 (m, 2H, *Z* + 2H, *E*), 7.46 (s, 1H, *E*), 7.41 (d, *J* = 8.1 Hz, 2H, *Z* + 2H, *E*), 3.92 (s, 3H, *Z* + 3H, *E*), 3.90 (s, 3H, *Z*), 3.75 (s, 3H, *Z*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.6 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 166.34, 166.29, 163.4 (q, *J* = 1.9 Hz), 163.3 – 163.2 (m), 142.2 (q, *J* = 3.0 Hz), 139.7 (q, *J* = 5.7 Hz), 137.1, 136.7, 131.5, 131.3, 129.8, 129.5, 128.9, 125.1 (q, *J* = 30.2 Hz), 124.2 (q, *J* = 32.0 Hz), 121.9 (q, *J* = 271.7 Hz), 121.6 (q, *J* = 272.9 Hz), 53.0, 52.8, 52.4. IR: 2961, 1721, 1650, 1437, 1384, 1272, 1234, 1131, 1108, 1020, 766, 698 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₃H₁₁F₃O₄ (*m/z*): 288.0609 [M]⁺, found: 288.0599.



Methyl (*E*)-3-(4-acetylphenyl)-2-(trifluoromethyl)acrylate (**E-3k**) and Methyl (*Z*)-3-(4-acetylphenyl)-2-(trifluoromethyl)acrylate (**Z-3k**)

According to general procedure I: 1-(4-iodophenyl)ethan-1-one (0.2 mmol, 49.2 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 8/1, v/v), affording compound **3k** in 71% yield [mixture of *E/Z* isomers (78/22), 38.9 mg] as a yellow oil.

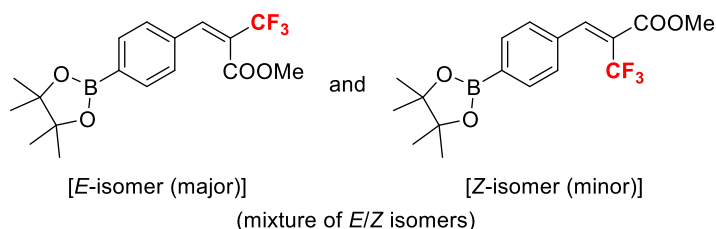
¹H NMR (300 MHz, CDCl₃): δ 8.10 (s, 1H, *Z*), 8.01 – 7.91 (m, 2H, *Z* + 2H, *E*), 7.57 – 7.38 (m, 2H, *Z* + 3H, *E*), 3.89 (s, 3H, *Z*), 3.76 (s, 3H, *E*), 2.60 (s, 3H, *Z* + 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.6 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 197.4, 197.3, 163.4 (q, *J* = 1.8 Hz), 163.3 – 163.2 (m), 147.1 (q, *J* = 2.8 Hz), 139.7 (q, *J* = 5.7 Hz), 138.0, 137.8, 137.2, 136.8, 129.5 – 128.9 (m), 128.5, 128.2, 125.2 (q, *J* = 31.5 Hz), 124.3 (q, *J* = 31.9 Hz), 121.9 (q, *J* = 271.7 Hz), 121.6 (q, *J* = 272.9 Hz), 53.1, 52.9, 26.8. IR: 2961, 1731, 1685, 1649, 1606, 1439, 1361, 1262, 1234, 1161, 1128, 1021, 835, 693, 598 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₃H₁₁F₃O₃Na (*m/z*): 295.0558 [M+Na]⁺, found: 295.0562.



(*E*)-4-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoic acid (*E*-3I) and (*Z*)-4-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoic acid (*Z*-3I)

According to general procedure I: 4-Iodobenzoic acid (0.2 mmol, 49.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc (AcOH), 5/1 (1%) CH₃COOH, v/v (v)), affording compound **3I** in 88% yield [mixture of *E/Z* isomers (76/24), 48.1 mg] as a white solid.

¹H NMR (300 MHz, CD₃OD): δ 8.20 (s, 1H, *Z*), 8.04 (d, *J* = 7.8 Hz, 2H, *Z* + 2H, *E*), 7.64 (s, 1H, *E*), 7.48 (d, *J* = 7.8 Hz, 2H, *Z* + 2H, *E*), 3.88 (s, 3H, *Z*), 3.75 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.2 (s, *Z*), -65.5 (d, *J* = 0.8 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 169.0, 168.9, 164.8 – 164.7 (m), 164.5 (q, *J* = 1.9 Hz), 148.7 (q, *J* = 3.0 Hz), 141.0 (q, *J* = 5.8 Hz), 138.5, 138.1, 133.3, 133.0, 130.9, 130.5, 130.0, 129.9 (q, *J* = 2.3 Hz), 125.9 (q, *J* = 31.4 Hz), 124.9 (q, *J* = 31.5 Hz), 123.3 (q, *J* = 270.8 Hz), 123.1 (q, *J* = 272.1 Hz), 53.4, 53.3. IR: 2961, 2815, 2670, 2550, 1734, 1683, 1610, 1571, 1425, 1277, 1239, 1211, 1135, 1020, 929, 768, 696, 548 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₂H₉F₃O₄Na (m/z): 297.0351 [M+Na]⁺, found: 297.0345.

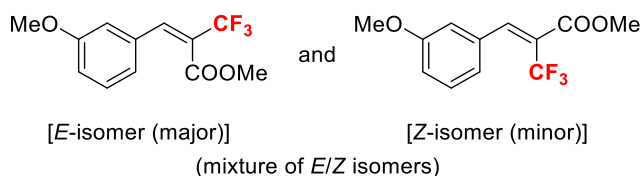


Methyl (*E*)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-(trifluoromethyl)acrylate (*E*-3m) and Methyl (*Z*)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-(trifluoromethyl)acrylate (*Z*-3m)

According to general procedure I: 4-Iodobenzeneboronic acid pinacol ester (0.2 mmol, 66.0 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. Because of the instability of product, the reaction mixture was directly purified by flash silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 20/1, v/v), affording compound **3m** in 59% yield [mixture of *E/Z* isomers (68/32), 41.9 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.11 (s, 1H, *Z*), 7.90 – 7.77 (m, 2H, *Z* + 2H, *E*), 7.44 (s, 1H, *E*), 7.42 – 7.28 (m, 2H, *Z* + 2H, *E*), 3.89 (s, 3H, *Z*), 3.76 (s, 3H, *E*), 1.35 (s, 12H, *Z* + 12H,

E). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s, *Z*), -64.5 (d, $J = 1.1$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.9 – 163.7 (m), 148.5 (q, $J = 2.9$ Hz), 140.4 (q, $J = 5.7$ Hz), 135.2, 135.0, 134.9, 134.7, 128.4 (q, $J = 2.3$ Hz), 128.2, 124.0 (q, $J = 31.2$ Hz), 123.0 (q, $J = 32.3$ Hz), 122.1 (q, $J = 271.4$ Hz), 121.9 (q, $J = 272.7$ Hz), 84.24, 84.23, 52.9, 52.7, 25.0. IR: 2980, 1733, 1610, 1439, 1398, 1359, 1276, 1227, 1163, 1134, 1089, 1021, 858, 656 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{17}\text{H}_{20}^{11}\text{BF}_3\text{O}_4$ (m/z): 356.1407 [M] $^-$, found: 356.1401.

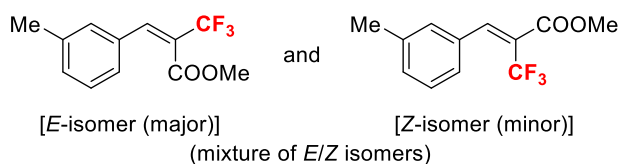


Methyl (*E*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylate (**E-3n**) and Methyl (*Z*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylate (**Z-3n**)

According to general procedure I: 3-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), affording compound **3n** in 82% yield [mixture of *E/Z* isomers (73/27), 42.7 mg] as a yellow oil.

According to general procedure II: 3-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), affording compound **3n** in 74% yield [mixture of *E/Z* isomers (75/25), 38.4 mg] as a yellow oil.

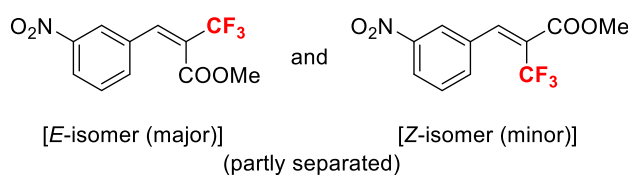
^1H NMR (300 MHz, CDCl_3): δ 7.99 (s, 1H, *Z*), 7.30 (d, $J = 0.9$ Hz, 1H, *E*), 7.26 – 7.17 (m, 1H, *Z* + 1H, *E*), 6.94 – 6.79 (m, 3H, *Z* + 3H, *E*), 3.81 (s, 3H, *Z*), 3.78 – 3.67 (m, 3H, *Z* + 6H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -64.4 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.0 – 163.8 (m), 159.8, 159.4, 148.5 (q, $J = 3.0$ Hz), 140.1 (q, $J = 5.7$ Hz), 133.9, 133.6, 129.8, 129.5, 123.6 (q, $J = 31.4$ Hz), 122.8 (q, $J = 31.8$ Hz), 122.2 (q, $J = 271.4$ Hz), 121.9 (q, $J = 272.7$ Hz), 121.8 (q, $J = 2.4$ Hz), 121.6, 116.4, 116.0, 114.5 (q, $J = 2.4$ Hz), 114.3, 55.4, 52.9, 52.8. IR: 2958, 2845, 1731, 1581, 1436, 1302, 1254, 1227, 1125, 1203, 784, 690 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_3$ (m/z): 260.0660 [M] $^+$, found: 260.0650.



Methyl (*E*)-3-(*m*-tolyl)-2-(trifluoromethyl)acrylate (*E*-3o) and Methyl (*Z*)-3-(*m*-tolyl)-2-(trifluoromethyl)acrylate (*Z*-3o)

According to general procedure I: 3-Iodotoluene (0.2 mmol, 43.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 50/1 to 40/1, v/v), affording compound **3o** in 91% yield [mixture of *E/Z* isomers (72/28), 44.3 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.00 (s, 1H, *Z*), 7.30 (s, 1H, *E*), 7.25 – 7.05 (m, 4H, *Z* + 4H, *E*), 3.81 (s, 3H, *Z*), 3.70 (s, 3H, *E*), 2.39 – 2.21 (s, 3H, *Z* + 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.3 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.2 – 163.9 (m), 148.9 (q, *J* = 2.9 Hz), 140.6 (q, *J* = 5.7 Hz), 138.5, 138.1, 132.6, 132.3, 131.3, 131.1, 130.2 – 129.9 (m), 128.7, 128.3, 126.6 (q, *J* = 2.6 Hz), 126.2, 123.1 (q, *J* = 31.2 Hz), 122.29 (q, *J* = 31.7 Hz), 122.26 (q, *J* = 271.3 Hz), 122.0 (q, *J* = 272.7 Hz), 52.9, 52.7, 21.4. IR: 2958, 1731, 1647, 1438, 1383, 1284, 1224, 1152, 1126, 1032, 784, 694 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₂H₁₁F₃O₂ (m/z): 244.0711 [M]⁺, found: 244.0704.



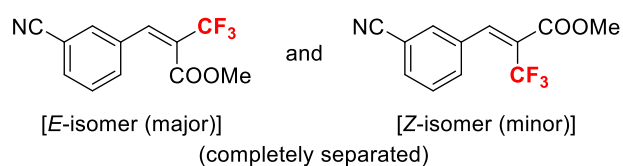
Methyl (*E*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylate (*E*-3p) and Methyl (*Z*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylate (*Z*-3p)

According to general procedure II: 1-Iodo-3-nitrobenzene (0.2 mmol, 49.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 8/1, v/v), affording compound **3p** in 84% yield [mixture of *E/Z* isomers (62/38), 42.0 mg; among which, partly pure compound **E-3p** was obtained] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.39 – 8.20 (m, 2H, *Z* + 2H, *E*), 8.11 (s, 1H, *Z*), 7.69 (t, *J* = 6.6 Hz, 1H, *Z* + 1H, *E*), 7.65 – 7.55 (m, 1H, *Z* + 1H, *E*), 7.50 (s, 1H, *E*), 3.92 (2s, 3H, *Z*), 3.81 (2s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.7 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.0 (q, *J* = 1.8 Hz), 162.8, 148.3, 148.2, 145.4 (q, *J* = 3.0 Hz), 138.7 (q, *J* = 5.8 Hz), 134.9, 134.6 (q, *J* = 2.5 Hz), 134.3, 134.0, 129.8, 129.6, 126.1 (q, *J* = 31.7 Hz), 125.3 (q, *J* = 32.0 Hz), 124.8, 124.7, 123.9, 123.8 (q, *J* = 2.3 Hz), 121.7 (q, *J* = 272.0 Hz), 121.5 (q, *J* = 273.0 Hz), 53.2, 53.0. IR: 2958, 1731, 1531, 1439,

1352, 1274, 1236, 1163, 1130, 1025, 731, 678 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{NO}_4$ (m/z): 275.0405 $[\text{M}]^-$, found: 275.0411.

[**E-3p**] Yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 8.39 – 8.20 (m, 2H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.65 – 7.57 (m, 1H), 7.50 (s, 1H), 3.81 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ -64.7 (d, $J = 1.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 162.8, 148.4, 135.0 (q, $J = 5.8$ Hz), 134.9, 134.0, 129.8, 126.1 (q, $J = 31.7$ Hz), 124.9, 123.9, 121.7 (q, $J = 272.0$ Hz), 53.0. IR: 3093, 2960, 1731, 1531, 1439, 1353, 1302, 1274, 1236, 1163, 1130, 1023, 822, 736, 676 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{NO}_4$ (m/z): 275.0405 $[\text{M}]^-$, found: 275.0411.

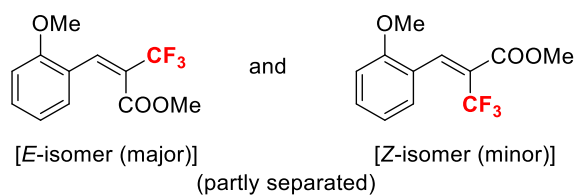


Methyl (**E**)-3-(3-cyanophenyl)-2-(trifluoromethyl)acrylate (**E-3q**) and Methyl (**Z**)-3-(3-cyanophenyl)-2-(trifluoromethyl)acrylate (**Z-3q**)

According to general procedure II: 3-Iodobenzonitrile (0.2 mmol, 45.8 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 7/1, v/v), affording compound **3q** in 85% yield [mixture of *E/Z* isomers (70/30), 43.6 mg. *E/Z* isomers were completely separated by column: compound **E-3q** 30.4 mg, colorless oil; impure *Z*-isomer was subsequently washed with petroleum ether (0.3 mL \times 3) to obtain pure compound **Z-3q** 13.2 mg, white solid].

[**E-3q** (major)] ^1H NMR (300 MHz, CDCl_3): δ 7.69 (d, $J = 8.1$ Hz, 2H), 7.64 – 7.48 (m, 2H), 7.44 (s, 1H), 3.79 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -64.7 (d, $J = 1.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.8, 139.0 (q, $J = 5.8$ Hz), 133.8, 133.5, 133.1, 132.4, 129.6, 125.8 (q, $J = 31.7$ Hz), 121.7 (q, $J = 271.9$ Hz), 118.0, 113.2, 53.0. IR: 2958, 2234, 1731, 1654, 1440, 1379, 1296, 1282, 1229, 1129, 1024, 799, 686 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_2\text{Na}$ (m/z): 278.0405 $[\text{M}+\text{Na}]^+$, found: 278.0414.

[**Z-3q** (minor)] Mp 55-56 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 8.05 (s, 1H), 7.70 (d, $J = 7.5$ Hz, 1H), 7.64 (s, 1H), 7.62 – 7.48 (m, 2H), 3.92 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.1 (q, $J = 1.9$ Hz), 145.5 (q, $J = 3.0$ Hz), 134.0, 133.3, 133.0 (q, $J = 2.3$ Hz), 132.2 (q, $J = 2.3$ Hz), 129.4, 125.1 (q, $J = 32.0$ Hz), 121.5 (q, $J = 272.9$ Hz), 118.0, 113.1, 53.3. IR: 2958, 2237, 1731, 1648, 1439, 1391, 1282, 1125, 1131, 1042, 804, 688 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}_2\text{Na}$ (m/z): 278.0405 $[\text{M}+\text{Na}]^+$, found: 278.0402.



Methyl (*E*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-3r**) and Methyl (*Z*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-**3r**)**

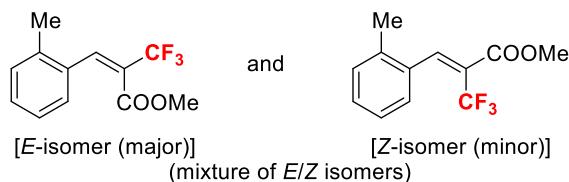
According to general procedure I: 2-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 20/1, v/v), affording compound **3r** in 54% yield [mixture of *E/Z* isomers (73/27), 28.2 mg; *E/Z* isomers were partly separated by column] as a yellow oil.

According to general procedure II: 2-Iodoanisole (0.2 mmol, 46.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 20/1, v/v), affording compound **3r** in 54% yield [mixture of *E/Z* isomers (71/29), 28.0 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.17 (s, 1H, *Z*), 7.57 (s, 1H, *E*), 7.37 – 7.26 (m, 1H, *Z* + 1H, *E*), 7.24 – 7.15 (m, 1H, *Z* + 1H, *E*), 6.93 – 6.79 (m, 2H, *Z* + 2H, *E*), 3.81 (s, 3H, *Z*), 3.80 – 3.73 (m, 3H, *Z* + 3H, *E*), 3.65 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -59.3 (d, *J* = 0.6 Hz, *Z*), -64.2 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.1 – 164.0 (m), 163.9 (q, *J* = 2.1 Hz), 157.61, 157.57, 145.2 (q, *J* = 3.0 Hz), 137.5 (q, *J* = 5.9 Hz), 132.1, 132.0, 130.5 (q, *J* = 3.6 Hz), 130.0, 123.0 (q, *J* = 30.9 Hz), 122.4 (q, *J* = 271.2 Hz), 122.2 (q, *J* = 272.4 Hz), 122.1 (q, *J* = 31.5 Hz), 121.9, 121.7, 110.9, 110.5, 55.64, 55.58, 52.8, 52.4. IR: 2961, 2842, 1729, 1646, 1600, 1490, 1466, 1437, 1276, 1252, 1224, 1158, 1123, 1114, 1021, 752 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₂H₁₁F₃O₃ (m/z): 260.0660 [M]⁺, found: 260.0661.

[*E*-**3r** (major)] ¹H NMR (300 MHz, CDCl₃): δ 7.65 (s, 1H), 7.43 – 7.35 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.98 – 6.88 (m, 2H), 3.85 (s, 3H), 3.74 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.2 (d, *J* = 1.7 Hz).

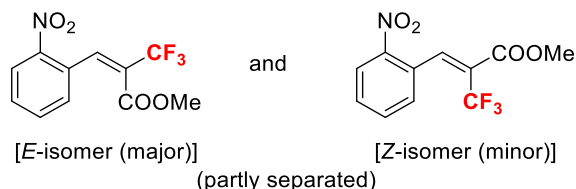
[*Z*-**3r** (minor)] ¹H NMR (300 MHz, CDCl₃): δ 8.24 (s, 1H), 7.44 – 7.36 (m, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -59.3 (d, *J* = 1.1 Hz).



Methyl (*E*)-3-(*o*-tolyl)-2-(trifluoromethyl)acrylate (*E*-3s) and Methyl (*Z*)-3-(*o*-tolyl)-2-(trifluoromethyl)acrylate (*Z*-3s)

According to general procedure I: 2-Iodotoluene (0.2 mmol, 43.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 50/1 to 30/1, v/v), affording compound **3s** in 79% yield [mixture of *E/Z* isomers (65/35), 38.6 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.13 (s, 1H, *Z*), 7.56 (s, 1H, *E*), 7.26 – 7.05 (m, 4H, *Z* + 4H, *E*), 3.82 (s, 3H, *Z*), 3.59 (s, 3H, *E*), 2.24 (s, 3H, *E*), 2.22 (s, 3H, *Z*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.9 (s, *Z*), -64.5 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.6 (q, *J* = 1.7 Hz), 163.6 – 163.4 (m), 148.5 (q, *J* = 3.0 Hz), 141.3 (q, *J* = 5.7 Hz), 136.7, 136.0, 132.6, 132.3, 130.3, 130.01, 129.95, 129.8, 128.3 (q, *J* = 3.1 Hz), 128.0, 125.9, 125.7, 124.6 (q, *J* = 30.9 Hz), 123.6 (q, *J* = 31.2 Hz), 122.1 (q, *J* = 271.4 Hz), 122.0 (q, *J* = 272.9 Hz), 52.9, 52.5, 20.0, 19.8. IR: 2961, 1732, 1647, 1438, 1379, 1294, 1276, 1238, 1216, 1160, 1129, 1032, 1021, 751 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₂H₁₁F₃O₂Na (m/z): 267.0609 [M+Na]⁺, found: 267.0613.



Methyl (*E*)-3-(2-nitrophenyl)-2-(trifluoromethyl)acrylate (*E*-3t) and Methyl (*Z*)-3-(2-nitrophenyl)-2-(trifluoromethyl)acrylate (*Z*-3t)

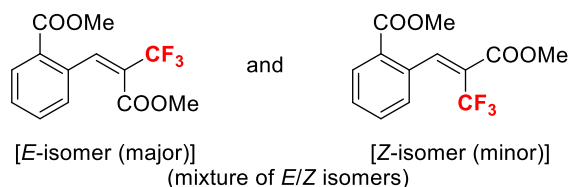
According to general procedure I: 1-Iodo-2-nitrobenzene (0.2 mmol, 49.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 8/1, v/v), affording compound **3t** in 86% yield [mixture of *E/Z* isomers (64/36), 47.3 mg; among them, partly pure compound **Z-3t** was obtained] as a yellow oil.

According to general procedure II: 1-Iodo-2-nitrobenzene (0.2 mmol, 49.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted

for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 8/1, v/v), affording compound **3t** in 82% yield [mixture of *E/Z* isomers (63/37), 45.4 mg; among them, partly pure compound **Z-3t** was obtained] as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 8.46 (s, 1H, *Z*), 8.32 – 8.22 (m, 1H, *Z* + 1H, *E*), 8.04 (s, 1H, *E*), 7.75 – 7.55 (m, 2H, *Z* + 2H, *E*), 7.33 (t, $J = 7.8$ Hz, 1H, *Z* + 1H, *E*), 3.92 (s, 3H, *Z*), 3.61 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.6 (s, *Z*), -64.8 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.7 (q, $J = 1.5$ Hz), 162.1, 146.5, 146.2 (q, $J = 3.2$ Hz), 145.9, 142.9 (q, $J = 6.3$ Hz), 134.1, 133.9, 130.4, 130.3, 130.2, 130.1 (q, $J = 2.7$ Hz), 129.9 – 129.8 (m), 124.98, 124.95, 124.0 (q, $J = 31.4$ Hz), 123.0 (q, $J = 31.0$ Hz), 121.73 (q, $J = 271.5$ Hz), 121.70 (q, $J = 272.9$ Hz), 53.1, 52.5. IR: 2961, 1731, 1524, 1439, 1343, 1277, 1236, 1131, 1045, 1024, 865, 789, 793 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{NO}_4$ (m/z): 276.0484 [$\text{M}+\text{H}$] $^+$, found: 276.0480.

[Z-3t] Pale yellow solid. Mp 77-78 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 8.46 (s, 1H), 8.28 (dd, $J = 8.3, 1.4$ Hz, 1H), 7.71 (td, $J = 7.5, 1.5$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.6 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.7 (q, $J = 1.5$ Hz), 146.2 (q, $J = 3.2$ Hz), 146.0, 134.0, 130.4, 130.1 (q, $J = 2.7$ Hz), 130.0, 125.0, 123.1 (q, $J = 31.0$ Hz), 121.7 (q, $J = 272.9$ Hz), 53.1. IR: 2974, 2921, 2855, 1731, 1611, 1525, 1440, 1386, 1338, 1284, 1265, 1154, 1126, 1052, 728 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{11}\text{H}_9\text{F}_3\text{NO}_4$ (m/z): 276.0484 [$\text{M}+\text{H}$] $^+$, found: 276.0481.

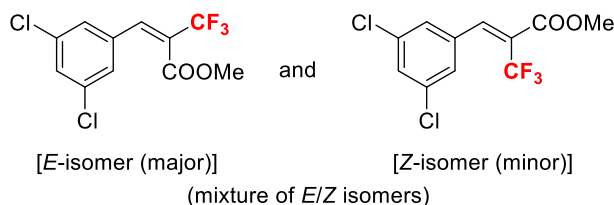


Methyl (*E*)-2-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (E-3u**) and Methyl (*Z*)-2-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (**Z-3u**)**

According to general procedure I: Methyl 2-iodobenzoate (0.2 mmol, 52.4 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA) $_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **3u** in 80% yield [mixture of *E/Z* isomers (78/22), 46.0 mg] as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 8.51 (s, 1H, *Z*), δ 8.07 (s, 1H, *E*), δ 8.02 (d, $J = 7.8$ Hz, 1H, *Z* + 1H, *E*), 7.53 – 7.35 (m, 2H, *Z* + 2H, *E*), 7.16 (d, $J = 7.5$ Hz, 1H, *Z* + 1H, *E*), 3.83 (s, 6H, *Z* + 3H, *E*), 3.51 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.2 (s, *Z*), -64.5 (d, $J = 1.4$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 166.5, 166.4, 163.4 (q, $J = 1.7$ Hz), 163.0, 150.2 (q,

$J = 3.2$ Hz), 145.5 (q, $J = 6.0$ Hz), 135.9, 135.7, 132.5, 132.4, 130.8, 130.6, 129.34, 129.29, 129.1 – 128.9 (m), 128.2, 127.7, 122.7 (q, $J = 31.0$ Hz), 122.2 (q, $J = 271.3$ Hz), 122.1 (q, $J = 272.8$ Hz), 121.4 (q, $J = 30.6$ Hz), 52.9, 52.5, 52.4, 52.3. IR: 2961, 1717, 1649, 1437, 1376, 1264, 1127, 1082, 1023, 755, 700 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{13}\text{H}_{11}\text{F}_3\text{O}_4$ (m/z): 288.0609 $[\text{M}]^+$, found: 288.0614.

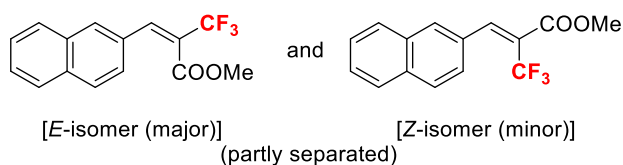


Methyl (*E*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylate (**E-3v**) and Methyl (*Z*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylate (**Z-3v**)

According to general procedure I: 3,5-Dichloriodobenzene (0.2 mmol, 54.6 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **3v** in 90% yield [mixture of *E/Z* isomers (74/26), 54.1 mg] as a yellow oil.

According to general procedure II: 3,5-Dichloriodobenzene (0.2 mmol, 54.6 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **3v** in 74% yield [mixture of *E/Z* isomers (74/26), 44.0 mg] as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 7.88 (s, 1H, *Z*), 7.35 – 7.29 (m, 1H, *Z* + 1H, *E*), 7.25 (s, 1H, *E*), 7.21 – 7.12 (m, 2H, *Z* + 2H, *E*), 3.83 (s, 3H, *Z*), 3.73 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.6 (s, *Z*), -64.7 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.1 (q, $J = 1.7$ Hz), 162.9 – 162.8 (m), 145.2 (q, $J = 3.0$ Hz), 138.1 (q, $J = 5.8$ Hz), 135.5, 135.4, 135.2, 130.1, 129.9, 127.3, 127.1 (q, $J = 2.4$ Hz), 126.0 (q, $J = 31.7$ Hz), 125.1 (q, $J = 32.1$ Hz), 121.7 (q, $J = 271.9$ Hz), 121.4 (q, $J = 273.0$ Hz), 53.2, 53.0. IR: 3087, 2954, 1734, 1653, 1587, 1562, 1439, 1377, 1285, 1216, 1167, 1134, 1025, 861, 802, 678 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_7^{35}\text{Cl}_2\text{F}_3\text{O}_2\text{Na}$ (m/z): 320.9673 $[\text{M}+\text{Na}]^+$, found: 320.9666.

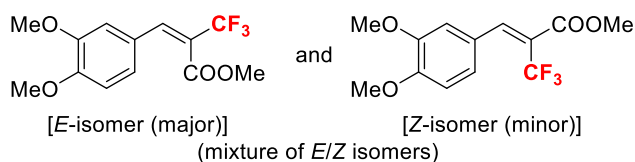


Methyl (*E*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylate (*E*-3w) and methyl (*Z*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylate (*Z*-3w)

According to general procedure I: 2-Iodonaphthalene (0.2 mmol, 50.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours according to the general procedure. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **3w** in 80% yield [mixture of *E/Z* isomers (74/26), 44.7 mg; among them, partly pure compound *E*-**3w** was obtained] as a yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 8.27 (s, 1H, *Z*), 7.93 – 7.79 (m, 4H, *Z* + 4H, *E*), 7.62 – 7.41 (m, 3H, *Z* + 4H, *E*), 3.94 (s, 3H, *Z*), 3.81 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.3 (s, *Z*), -64.2 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.1 – 164.0 (m), 148.7 (q, *J* = 2.9 Hz), 140.7 (q, *J* = 5.7 Hz), 134.1, 133.9, 133.0, 132.7, 130.4, 130.3 (q, *J* = 2.1 Hz), 130.0, 129.8, 128.8, 128.7, 128.4, 128.1, 127.85, 127.83, 127.8, 126.94, 127.89, 126.1 (q, *J* = 2.7 Hz), 125.4, 123.2 (q, *J* = 31.2 Hz), 122.39 (q, *J* = 31.8 Hz), 122.35 (q, *J* = 271.5 Hz), 122.1 (q, *J* = 272.6 Hz), 52.9, 52.7. IR: 2956, 2924, 1728, 1643, 1438, 1352, 1282, 1269, 1233, 1122, 1019, 815, 744, 475 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₅H₁₁F₃O₂ (m/z): 280.0711 [M]⁺, found: 280.0707.

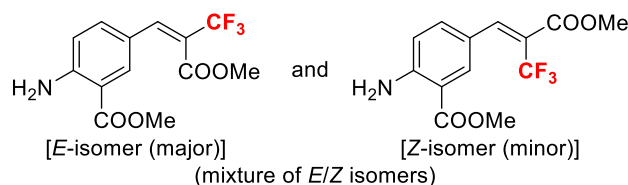
[*E*-**3w**] Mp <46 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.91 – 7.81 (m, 4H), 7.61 – 7.50 (m, 3H), 7.44 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.81 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.2 (d, *J* = 1.4 Hz).



Methyl (*E*)-3-(3,4-dimethoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-3x) and Methyl (*Z*)-3-(3,4-dimethoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-3x)

Larger scale reaction: To a 10 mL reaction tube were added 4-iodo-1,2-dimethoxybenzene (1.0 mmol, 264.1 mg, 1.0 equiv), AgOTf (1.5 mmol, 385.4 mg, 1.5 equiv), Pd(TFA)₂ (0.015 mmol, 4.8 mg, 1.5 mol%), methyl 2-(trifluoromethyl)acrylate (1.5 mmol, 231.1 mg, 1.5 equiv), and 1,4-dioxane (5 mL). The reaction tube was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the tube washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **3x** in 83% yield [mixture of *E/Z* isomers (75/25), 242.2 mg] as a yellow oil.

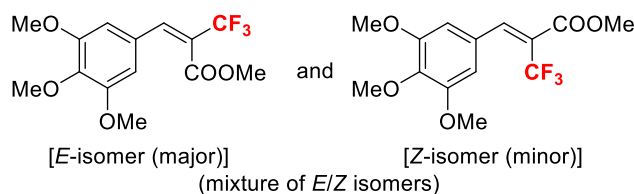
^1H NMR (300 MHz, CDCl_3): δ 7.98 (s, 1H, *Z*), 7.30 (s, 1H, *E*), 7.10 – 6.96 (m, 2H, *Z* + 2H, *E*), 6.93 – 6.80 (m, 1H, *Z* + 1H, *E*), 3.93 – 3.89 (m, 3H, *Z* + 3H, *E*), 3.89 – 3.83 (m, 6H, *Z* + 3H, *E*), 3.81 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.3 (s, *Z*), -63.8 (d, J = 1.7 Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.5 – 164.2 (m), 151.32, 151.29, 148.9, 148.6, 148.4 (q, J = 2.9 Hz), 140.4 (q, J = 5.7 Hz), 124.8, 124.8 – 124.6 (m), 124.1, 122.5 (q, J = 271.2 Hz), 122.3 (q, J = 272.2 Hz), 120.6 (q, J = 31.1 Hz), 119.8 (q, J = 32.0 Hz), 112.9 (q, J = 3.0 Hz), 112.1, 110.9, 110.7, 56.0, 56.9, 52.75, 52.66. IR: 2958, 2842, 1726, 1599, 1515, 1440, 1258, 1225, 1140, 1117, 1020, 808, 574 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{O}_4$ (m/z): 291.0844 [$\text{M}+\text{H}$] $^+$, found: 291.0851.



Methyl (*E*)-2-amino-5-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (*E*-3y) and Methyl (*Z*)-2-amino-5-(3,3,3-trifluoro-2-(methoxycarbonyl)prop-1-en-1-yl)benzoate (*Z*-3y)

According to general procedure I: Methyl 2-amino-5-iodobenzoate (0.2 mmol, 55.4 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA) $_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **3y** in 81% yield [mixture of *E/Z* isomers (63/37), 49.3 mg] as a yellow solid.

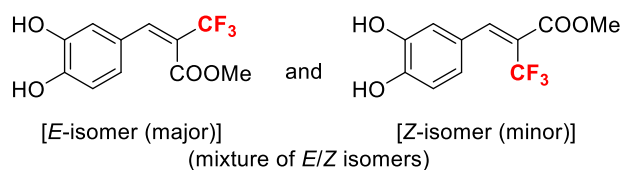
^1H NMR (300 MHz, CDCl_3): δ 8.19 – 7.95 (m, 1H, *Z* + 1H, *E*), 7.89 (s, 1H, *Z*), 7.41 (t, J = 8.0 Hz, 1H, *Z* + 1H, *E*), 7.23 (s, 1H, *E*), 6.76 – 6.55 (m, 1H, *Z* + 1H, *E*), 6.18 (br, 2H, *Z* + 2H, *E*), 3.92 – 3.78 (m, 6H, *Z* + 6H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -63.4 (d, J = 1.7 Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.0, 167.9, 164.6 (q, J = 2.3 Hz), 164.5, 152.4, 152.3, 148.1 (q, J = 2.7 Hz), 140.7 (q, J = 5.8 Hz), 136.3 (q, J = 2.2 Hz), 136.0 (q, J = 3.8 Hz), 135.3, 135.2, 122.8 (q, J = 270.8 Hz), 122.6 (q, J = 271.8 Hz), 119.8, 119.7, 118.3 (q, J = 30.9 Hz), 117.5 (q, J = 32.3 Hz), 116.7, 116.6, 110.2, 110.1, 52.6, 52.5, 51.92, 51.88. IR: 3477, 3364, 2961, 1722, 1694, 1610, 1499, 1440, 1278, 1256, 1202, 1152, 1116, 1024, 825, 546, 492 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}_4\text{Na}$ (m/z): 326.0616 [$\text{M}+\text{Na}$] $^+$, found: 326.0622.



Methyl (*E*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylate (*E*-3z) and Methyl (*Z*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylate (*Z*-3z)

According to general procedure II: 5-Iodo-1,2,3-trimethoxybenzene (0.2 mmol, 58.8 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.003 mmol, 1.0 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **3z** in 89% yield [mixture of *E/Z* isomers (75/25), 57.0 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.97 (s, 1H, *Z*), 7.28 (s, 1H, *E*), 6.80 – 6.54 (m, 2H, *Z* + 2H, *E*), 3.99 – 3.67 (m, 12H, *Z* + 12H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, *Z*), -64.1 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.3 – 164.1 (m), 164.0 (q, *J* = 2.2 Hz), 153.2, 153.0, 148.4 (q, *J* = 2.9 Hz), 140.2, 140.1, 139.9 (q, *J* = 5.7 Hz), 127.5, 127.4, 122.4 (q, *J* = 31.3 Hz), 122.2 (q, *J* = 271.4 Hz), 122.0 (q, *J* = 271.5 Hz), 121.5 (q, *J* = 32.1 Hz), 107.3 (q, *J* = 2.6 Hz), 106.8, 61.0, 60.98, 56.20, 56.18, 52.80, 52.77. IR: 2954, 2842, 1729, 1582, 1507, 1456, 1422, 1271, 1227, 1118, 1026, 1002 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₄H₁₅F₃O₅Na (m/z): 343.0769 [M+Na]⁺, found: 343.0766.

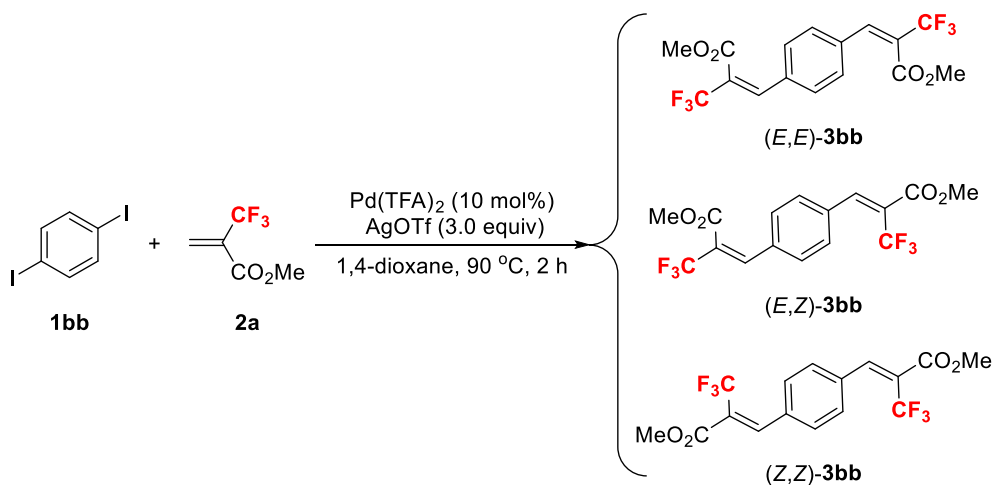


Methyl (*E*)-3-(3,4-dihydroxyphenyl)-2-(trifluoromethyl)acrylate (*E*-3aa) and Methyl (*Z*)-3-(3,4-dihydroxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-3aa)

0.2 mmol scale, with 0.5 mol% Pd(TFA)₂: Firstly, 1.0 mg Pd(TFA)₂ was dissolved in 3.0 mL 1,4-dioxane by ultrasound. To a vial (2 mL) were added 4-iodobenzene-1,2-diol (0.2 mmol, 47.2 mg), AgOTf (0.3 mmol, 77.1 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg), and 1.0 mL of the above prepared Pd(TFA)₂/1,4-dioxane solution [0.5 mol% Pd(TFA)₂]. The vial was then sealed. The reaction mixture was stirred at 90 °C for 30 min and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (CHCl₃/MeOH, from 100/1 to 60/1, v/v), affording compound **3aa** in 45% yield [mixture of *E/Z* isomers (*E/Z* = 71/29), 23.7 mg] as a pale yellow solid.

¹H NMR (300 MHz, CD₃OD): δ 7.94 (s, 1H, *Z*), 7.28 (d, *J* = 1.2 Hz, 1H, *E*), 7.00 (s, 1H, *Z*), 6.98 – 6.71 (m, 2H, *Z* + 3H, *E*), 3.84 (s, 3H, *Z*), 3.82 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.2 (s, *Z*), -64.7 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 166.2 – 166.0 (m), 165.7 (q, *J* = 2.3 Hz), 150.2 (q, *J* = 2.9 Hz), 150.0, 149.8, 146.5, 146.3, 141.2 (q, *J* = 5.8 Hz), 125.4 (q, *J* = 2.4 Hz), 125.0, 124.5, 124.1 (q, *J* = 269.9 Hz), 123.8 (q, *J* = 270.5 Hz), 120.2 (q, *J* = 31.1 Hz), 119.1 (q, *J* = 32.1 Hz), 118.3 (q, *J* = 3.2 Hz),

117.0, 116.3, 116.1, 53.1, 53.0. IR: 3508, 3338, 1694, 1602, 1524, 1443, 1255, 1112, 1023, 933 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{O}_4$ (m/z): 261.0375 $[\text{M}-\text{H}]^-$, found: 261.0365.



Dimethyl 3,3'-(1,4-phenylene)(2E,2'E)-bis(2-(trifluoromethyl)acrylate) ((E,E)-3bb) and **Dimethyl 3,3'-(1,4-phenylene)(2E,2'Z)-bis(2-(trifluoromethyl)acrylate) ((E,Z)-3bb)** and **Dimethyl 3,3'-(1,4-phenylene)(2Z,2'Z)-bis(2-(trifluoromethyl)acrylate) ((Z,Z)-3bb)**

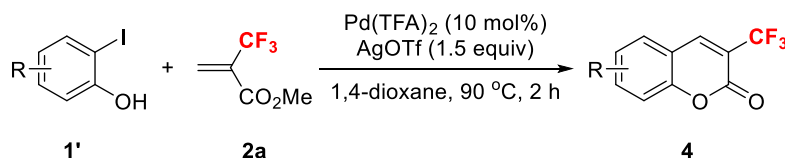
To a vial (2 mL) were added 1,4-diiodobenzene **1bb** (0.2 mmol, 66.0 mg, 1.0 equiv), AgOTf (0.6 mmol, 154.2 mg, 3.0 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.6 mmol, 92.5 mg, 3.0 equiv), and 1,4-dioxane (1.0 mL). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 10/1, v/v), affording compound **3bb** in three isomers [compound (**E,E**)-**3bb**, 38%, 29.5 mg, white solid; compound (**E,Z**)-**3bb**, 26%, 19.8 mg, colorless oil; compound (**Z,Z**)-**3bb**, <12%, not pure].

[(E,E)-3bb] Mp 84-85 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.53 – 7.32 (m, 6H), 3.79 (s, 6H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.5 (d, $J = 1.4$ Hz, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.5 (q, $J = 0.5$ Hz), 139.6 (q, $J = 5.7$ Hz), 134.2, 129.4, 124.7 (q, $J = 31.5$ Hz), 122.0 (q, $J = 271.7$ Hz), 52.9. IR: 2968, 2921, 2855, 1715, 1638, 1446, 1392, 1308, 1277, 1153, 1118, 1034, 943, 703 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{16}\text{H}_{12}\text{F}_6\text{O}_4$ (m/z): 382.0640 $[\text{M}]^-$, found: 382.0642.

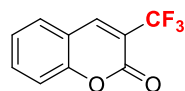
[(E,Z)-3bb] ¹H NMR (300 MHz, CDCl₃): δ 8.08 (s, 1H), 7.47 – 7.36 (m, 5H), 3.91 (s, 3H), 3.78 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, Z), -64.5 (d, $J = 1.4$ Hz, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.6 (q, $J = 1.9$ Hz), 163.5 (q, $J = 0.7$ Hz), 147.2 (q, $J = 3.0$ Hz), 139.7 (q, $J = 5.7$ Hz), 134.5, 134.0, 129.5 (q, $J = 2.4$ Hz), 129.1, 124.7 (q, $J = 31.4$ Hz).

Hz), 123.8 (q, $J = 32.0$ Hz), 122.0 (q, $J = 271.7$ Hz), 121.8 (q, $J = 272.7$ Hz), 53.1, 52.8. IR: 2960, 1728, 1645, 1439, 1385, 1278, 1218, 1160, 1124, 1040, 705 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{16}\text{H}_{12}\text{F}_6\text{O}_4$ (m/z): 382.0640 $[\text{M}]^-$, found: 382.0632.

1.3 Synthesis of 3-trifluoromethyl coumarin derivatives (**4**) from *o*-iodophenols (**1'**) and methyl 2-(trifluoromethyl)acrylate (**2a**) with $\text{Pd}(\text{TFA})_2$ and AgOTf



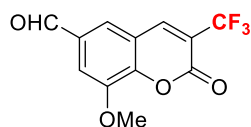
General procedure III: To a vial (2 mL) were added *o*-iodophenol **1'** (0.2 mmol, 1.0 equiv), AgOTf (0.3 mmol, 1.5 equiv), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



3-(Trifluoromethyl)-2H-chromen-2-one (**4a**)^{184a,c,e-g}

According to general procedure III: 2-Iodophenol (0.2 mmol, 44.0 mg), AgOTf (0.3 mmol, 77.1 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **4a** in 72% yield (30.8 mg) as a pale yellow solid.

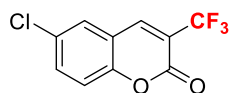
Mp 121-122 °C. ^1H NMR (300 MHz, CDCl_3): δ 8.16 (s, 1H), 7.75 – 7.57 (m, 2H), 7.49 – 7.31 (m, 2H). ^{19}F NMR (282 MHz, CDCl_3): δ -66.7 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 156.1 – 155.9 (m), 154.7, 143.5 (q, $J = 4.8$ Hz), 134.6, 129.6, 125.4, 121.5 (q, $J = 270.3$ Hz), 118.0 (q, $J = 33.1$ Hz), 117.1, 116.9. IR: 3074, 2921, 1727, 1636, 1610, 1573, 1460, 1383, 1242, 1175, 1119, 975, 759, 733, 588, 464 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{10}\text{H}_5\text{F}_3\text{O}_2\text{Na}$ (m/z): 237.0139 $[\text{M}+\text{Na}]^+$, found: 237.0132.



8-Methoxy-2-oxo-3-(trifluoromethyl)-2H-chromene-6-carbaldehyde (4b)

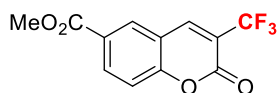
According to general procedure III: 5-Iodovanillin (0.2 mmol, 55.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 5/1 to 3/1, v/v), and was subsequently washed with MeOH (0.5 mL × 2), affording compound **4b** in 35% yield (18.8 mg) as a white solid.

Mp 162-163 °C. ¹H NMR [300 MHz, (CD₃)₂SO]: δ 10.01 (s, 1H), 8.87 (s, 1H), 8.05 (s, 1H), 7.83 (s, 1H), 4.02 (s, 3H). ¹⁹F NMR [282 MHz, (CD₃)₂SO]: δ -64.9 (s). ¹³C{¹H} NMR [75 MHz, (CD₃)₂SO]: δ 191.3, 155.0 – 154.7 (m), 147.4, 147.1, 145.1 (q, *J* = 4.8 Hz), 132.8, 124.3, 121.5 (q, *J* = 269.9 Hz), 117.8, 116.8 (q, *J* = 32.4 Hz), 114.4, 56.3. IR: 3067, 2868, 1738, 1698, 1636, 1593, 1464, 1384, 1278, 1134, 1112, 952, 684 cm⁻¹. HRMS (AP-TOF): Calcd for C₁₂H₇F₃O₄ (m/z): 272.0296 [M]⁻, found: 272.0301.

**6-Chloro-3-(trifluoromethyl)-2H-chromen-2-one (4c)**^{184g}

According to general procedure III: 4-Chloro-2-iodophenol (0.2 mmol, 50.9 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **4c** in 74% yield (36.8 mg) as a white solid.

Mp 167-168 °C. ¹H NMR (300 MHz, CD₃OD): δ 8.49 (s, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.72 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 1H). ¹⁹F NMR (282 MHz, CD₃OD): δ -67.7 (s). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 157.0 – 156.9 (m), 154.5, 144.7 (q, *J* = 5.0 Hz), 135.3, 131.4, 130.3, 122.9 (q, *J* = 269.4 Hz), 119.7, 119.5, 119.2 (q, *J* = 33.0 Hz). IR: 3064, 1721, 1635, 1602, 1570, 1378, 1301, 1243, 1213, 1175, 1144, 1086, 980, 824, 679 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₀H₄³⁵ClF₃O₂ (m/z): 247.9852 [M]⁺, found: 247.9853.

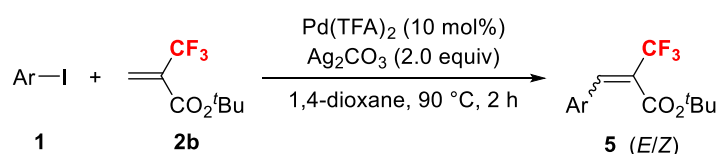
**Methyl 2-oxo-3-(trifluoromethyl)-2H-chromene-6-carboxylate (4d)**

According to general procedure III: Methyl 4-hydroxy-3-iodobenzoate (0.2 mmol, 55.6 mg), AgOTf (0.3 mmol, 77.1 mg), and Pd(TFA)₂ (0.02 mmol, 6.5 mg), methyl 2-(trifluoromethyl)acrylate (0.3 mmol, 46.2 mg) in 1,4-dioxane (1.0 mL) were reacted for 2 hours. The crude was purified by silica gel column chromatography (petroleum

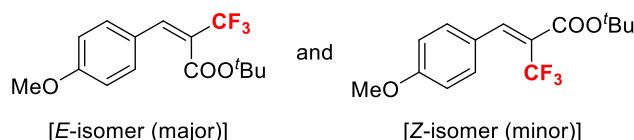
ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **4d** in 82% yield (44.7 mg) as a white solid.

Mp 177-178 °C. ^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 8.89 (s, 1H), 8.55 (d, $J = 1.8$ Hz, 1H), 8.24 (dd, $J = 8.7, 2.1$ Hz, 1H), 7.59 (d, $J = 8.7$ Hz, 1H), 3.90 (s, 3H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -64.9 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 164.8, 157.0, 155.4 – 155.2 (m), 144.9 (q, $J = 4.9$ Hz), 134.7, 132.0, 126.3, 121.6 (q, $J = 270.0$ Hz), 117.2, 117.1, 116.6 (q, $J = 32.3$ Hz), 52.6. IR: 3073, 2965, 2924, 2852, 1750, 1710, 1639, 1615, 1443, 1378, 1306, 1243, 1216, 1172, 1140, 965, 768 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{12}\text{H}_7\text{F}_3\text{O}_4$ (m/z): 272.0296 [M] $^+$, found: 272.0294.

1.4 Synthesis of *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates (**5**) by Mizoroki-Heck reaction with $\text{Pd}(\text{TFA})_2$ and Ag_2CO_3



General procedure IV: To a vial (2 mL) were added iodoarene **1** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.4 mmol, 2.0 equiv), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 10 mol%), *tert*-butyl 2-(trifluoromethyl)acrylate **2b** (0.3 mmol, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL CH_2Cl_2) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



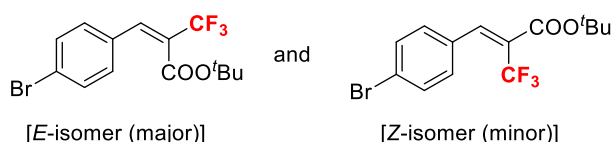
Tert-butyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**E-5a**) and *Tert*-butyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**Z-5a**)

According to general procedure IV: 4-Iodoanisole (0.2 mmol, 46.8 mg), Ag_2CO_3 (0.4 mmol, 110.3 mg), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **5a** in 84% yield [mixture of *E/Z* isomers (85/15), 50.6 mg] as a yellow oil.

Bigger scale reaction: To a 100 mL reaction tube were added 4-iodoanisole (4.0 mmol, 936.1 mg), Ag_2CO_3 (8.0 mmol, 2.21 g), $\text{Pd}(\text{TFA})_2$ (0.4 mmol, 129.0 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (6.0 mmol, 1.18 g), and 1,4-dioxane (20 mL).

The reaction tube was then sealed. The reaction mixture was stirred at 90 °C for 15 hours and was then cooled to room temperature. The reaction mixture was transferred to a 100 mL flask (with the reaction tube washed with 20 mL CH₂Cl₂) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **5a** in 84% yield [mixture of *E/Z* isomers (85/15), 1.04 g] as a yellow oil.

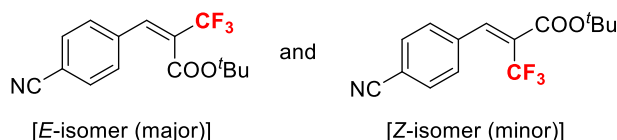
¹H NMR (300 MHz, CDCl₃): δ 7.87 (s, 1H, *Z*), 7.50 – 7.37 (m, 2H, *Z* + 2H, *E*), 7.20 (s, 1H, *E*), 6.98 – 6.85 (m, 2H, *Z* + 2H, *E*), 3.83 (s, 3H, *Z* + 3H, *E*), 1.56 (s, 9H, *Z*), 1.50 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.0 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.1 (q, *J* = 2.1 Hz), 163.0 – 162.9 (m), 161.4 – 161.3 (m), 146.8 (q, *J* = 2.9 Hz), 138.3 (q, *J* = 5.8 Hz), 132.1 (q, *J* = 2.7 Hz), 131.5, 125.0, 124.9, 122.8 (q, *J* = 271.1 Hz), 122.6 (q, *J* = 30.5 Hz), 122.5 (q, *J* = 272.0 Hz), 121.7 (q, *J* = 31.5 Hz), 114.0, 113.9, 83.4, 82.8, 55.4, 28.1, 27.9. IR (Neat): 2981, 2938, 2843, 1721, 1606, 1514, 1370, 1280, 1260, 1242, 1150, 1122, 1030, 1007, 828 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₅H₁₈F₃O₃ (*m/z*): 303.1208 [M+H]⁺, found: 303.1213.



***Tert*-butyl (*E*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylate (*E*-5b) and *Tert*-butyl (*Z*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylate (*Z*-5b)**

According to general procedure IV: 1-Bromo-4-iodobenzene (0.2 mmol, 56.4 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoro-methyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **5b** in 90% yield [mixture of *E/Z* isomers (85/15), 63.3 mg] as a yellow oil.

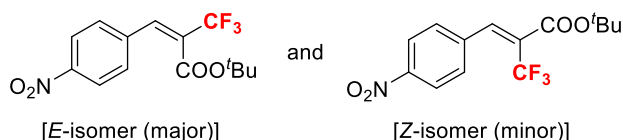
¹H NMR (300 MHz, CDCl₃): δ 7.79 (s, 1H, *Z*), 7.43 (d, *J* = 8.4 Hz, 2H, *Z* + 2H, *E*), 7.20 (d, *J* = 8.4 Hz, 2H, *Z* + 2H, *E*), 7.15 (s, 1H, *E*), 1.48 (s, 9H, *Z*), 1.37 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -64.6 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 162.3, 162.1, 145.7 – 145.5 (m), 137.5 (q, *J* = 5.7 Hz), 131.8, 131.6, 130.9 – 130.6 (m), 126.1 (q, *J* = 30.9 Hz), 125.1 (q, *J* = 30.9 Hz), 124.53, 124.46, 122.2 (q, *J* = 271.7 Hz), 122.0 (q, *J* = 272.3 Hz), 83.9, 83.4, 28.1, 27.8. IR (Neat): 2982, 2933, 1723, 1650, 1489, 1370, 1289, 1274, 1244, 1152, 1130, 1073, 1010, 915, 868, 839, 815 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₄H₁₅BrF₃O₂ (*m/z*): 351.0208 [M+H]⁺, found: 351.0192.



***Tert*-butyl (*E*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (*E*-5c) and *Tert*-butyl (*Z*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (*Z*-5c)**

According to general procedure IV: 4-Iodobenzonitrile (0.2 mmol, 45.8 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 15/1, v/v), affording compound **5c** in 79% yield [mixture of *E/Z* isomers (75/25), 46.7 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.94 (s, 1H, *Z*), 7.68 (d, *J* = 8.4 Hz, 2H, *Z* + 2H, *E*), 7.49 (d, *J* = 8.1 Hz, 2H, *E*), 7.43 (d, *J* = 8.1 Hz, 2H, *Z*), 7.34 (s, 1H, *E*), 1.55 (s, 9H, *Z*), 1.40 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.4 (s, *Z*), -64.9 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 161.6 (q, *J* = 1.7 Hz), 161.4 – 161.2 (m), 144.5 (q, *J* = 3.1 Hz), 137.6, 137.4, 137.1 (q, *J* = 5.8 Hz), 132.2, 132.0, 129.5, 129.3 (q, *J* = 2.3 Hz), 128.2 (q, *J* = 31.0 Hz), 127.0 (q, *J* = 31.4 Hz), 121.8 (q, *J* = 272.0 Hz), 121.6 (q, *J* = 272.8 Hz), 118.3, 118.2, 113.4, 113.2, 84.3, 83.8, 28.0, 27.7. IR (Neat): 2983, 2928, 2231, 1724, 1371, 1318, 1292, 1276, 1247, 1133, 1010, 915, 838 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₅H₁₅F₃NO₂ (*m/z*): 298.1055 [M+H]⁺, found: 298.1054.

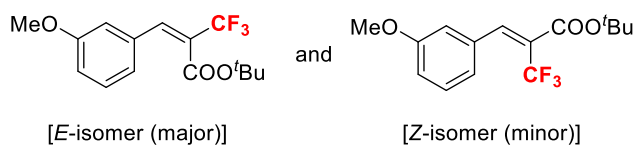


***Tert*-butyl (*E*)-3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (*E*-5d) and *Tert*-butyl (*Z*)-3-(4-nitrophenyl)-2-(trifluoromethyl)acrylate (*Z*-5d)**

According to general procedure IV: 1-Iodo-4-nitrobenzene (0.2 mmol, 49.8 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 15/1, v/v), affording compound **5d** in 54% yield [mixture of *E/Z* isomers (52/48), 34.0 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.25 (d, *J* = 8.7 Hz, 2H, *Z* + 2H, *E*), 7.98 (s, 1H, *Z*), 7.56 (d, *J* = 8.7 Hz, 2H, *E*), 7.50 (d, *J* = 8.7 Hz, 2H, *Z*), 7.39 (s, 1H, *E*), 1.57 (s, 9H, *Z*), 1.42 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.4 (s, *Z*), -65.0 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 161.5 (q, *J* = 1.7 Hz), 161.3, 148.4, 148.3, 144.1 (q, *J* = 2.9 Hz), 139.6, 139.3, 136.7 (q, *J* = 5.8 Hz), 129.8, 129.6 (q, *J* = 2.2 Hz), 128.7 (q, *J* = 31.1 Hz), 127.5 (q, *J* = 31.3 Hz), 123.7, 123.6, 121.8 (q, *J* = 272.1 Hz), 121.6 (q, *J* = 272.9 Hz), 84.5,

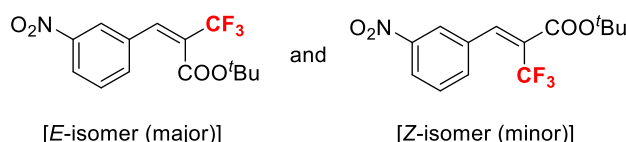
84.0, 28.1, 27.8. IR (Neat): 2983, 2934, 1724, 1602, 1523, 1371, 1347, 1278, 1248, 1134, 1013, 850, 692 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{14}\text{H}_{15}\text{F}_3\text{NO}_4$ (m/z): 318.0953 $[\text{M}+\text{H}]^+$, found: 318.0940.



***Tert*-butyl (*E*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-5e) and *Tert*-butyl (*Z*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-5e)**

According to general procedure IV: 3-Iodoanisoole (0.2 mmol, 46.8 mg), Ag_2CO_3 (0.4 mmol, 110.3 mg), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 120/1 to 90/1, v/v), affording compound **5e** in 87% yield [mixture of *E/Z* isomers (87/13), 52.6 mg] as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 7.85 (s, 1H, *Z*), 7.25 – 7.16 (m, 2H, *Z* + 2H, *E*), 6.93 – 6.80 (m, 2H, *Z* + 3H, *E*), 3.76 – 3.68 (m, 3H, *Z* + 3H, *E*), 1.48 (s, 9H, *Z*), 1.36 (s, 9H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -64.5 (d, $J = 1.4$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.6 – 162.5 (m), 162.5 – 162.3 (m), 159.6, 159.3, 146.9 (q, $J = 3.0$ Hz), 138.4 (q, $J = 5.8$ Hz), 134.2, 134.0, 129.6, 129.4, 125.7 (q, $J = 30.7$ Hz), 124.7 (q, $J = 31.4$ Hz), 122.4 (q, $J = 271.5$ Hz), 122.0 (q, $J = 272.5$ Hz), 121.8 – 121.4 (m), 115.8, 115.7, 114.3, 83.6, 83.2, 55.40, 55.37, 28.1, 27.8. IR (Neat): 2982, 1724, 1600, 1581, 1489, 1458, 1370, 1300, 1241, 1149, 1127, 1043, 1011, 843, 689 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{O}_3$ (m/z): 303.1208 $[\text{M}+\text{H}]^+$, found: 303.1206.

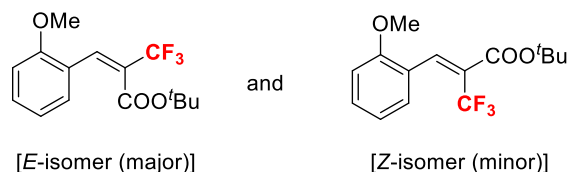


***Tert*-butyl (*E*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylate (*E*-5f) and *Tert*-butyl (*Z*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylate (*Z*-5f)**

According to general procedure IV: 1-Iodo-3-nitrobenzene (0.2 mmol, 49.8 mg), Ag_2CO_3 (0.4 mmol, 110.3 mg), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 50/1, v/v), affording compound **5f** in 89% yield [mixture of *E/Z* isomers (83/17), 56.4 mg] as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 8.32 – 8.19 (m, 2H, *Z* + 2H, *E*), 7.97 (s, 1H, *Z*), 7.74 – 7.64 (m, 1H, *Z* + 1H, *E*), 7.59 (t, $J = 8.0$ Hz, 1H, *Z* + 1H, *E*), 7.36 (s, 1H, *E*), 1.56 (s, 9H, *Z*), 1.45 (s, 9H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -64.9 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$

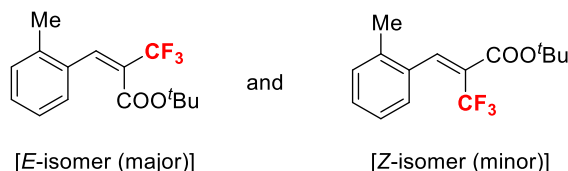
NMR (75 MHz, CDCl₃): δ 161.6 (q, $J = 1.8$ Hz), 161.5 – 161.4 (m), 148.3, 148.1, 143.9 (q, $J = 3.0$ Hz), 136.4 (q, $J = 5.9$ Hz), 135.0, 134.7 – 134.5 (m), 134.4, 129.7, 129.5, 128.1 (q, $J = 31.1$ Hz), 127.2 (q, $J = 31.4$ Hz), 124.5, 124.3, 123.7, 121.9 (q, $J = 272.0$ Hz), 121.7 (q, $J = 272.8$ Hz), 84.6, 83.9, 28.0, 27.8. IR (neat): 2983, 2934, 1723, 1532, 1352, 1300, 1274, 1247, 1133, 1014, 922, 840, 735, 675 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₄H₁₅F₃NO₄ (m/z): 318.0953 [M+H]⁺, found: 318.0940.



***Tert*-butyl (*E*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-5g) and *Tert*-butyl (*Z*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-5g)**

According to general procedure IV: 2-Iodoanisole (0.2 mmol, 46.8 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 60/1, v/v), affording compound **5g** in 53% yield [mixture of *E/Z* isomers (69/31), 31.8 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.12 (s, 1H, *Z*), 7.59 (s, 1H, *E*), 7.43 – 7.27 (m, 2H, *Z* + 2H, *E*), 6.99 – 6.86 (m, 2H, *Z* + 2H, *E*), 3.86 (s, 3H, *Z*), 3.85 (s, 3H, *E*), 1.57 (s, 9H, *Z*), 1.40 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -59.2 (s, *Z*), -64.4 (d, $J = 1.4$ Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 162.7 (q, $J = 1.8$ Hz), 162.6 – 162.5 (m), 157.5, 143.7 (q, $J = 3.0$ Hz), 136.0 (q, $J = 6.0$ Hz), 131.7, 131.6, 130.5 (q, $J = 3.5$ Hz), 130.0, 125.0 (q, $J = 30.3$ Hz), 124.0 (q, $J = 31.0$ Hz), 122.6 (q, $J = 271.4$ Hz), 122.4 (q, $J = 272.4$ Hz), 122.2, 120.2, 110.7, 110.4, 83.0, 82.8, 55.6, 28.2, 27.8. IR (Neat): 2981, 1722, 1646, 1601, 1490, 1466, 1439, 1370, 1284, 1239, 1154, 1127, 1114, 1009, 843, 751 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₅H₁₈F₃O₃ (m/z): 303.1208 [M+H]⁺, found: 303.1206.

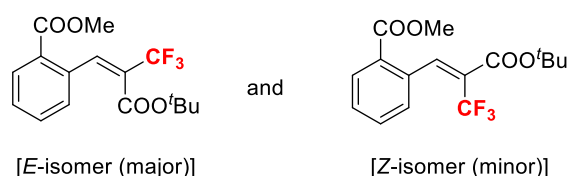


***Tert*-butyl (*E*)-3-(2-methylphenyl)-2-(trifluoromethyl)acrylate (*E*-5h) and *Tert*-butyl (*Z*)-3-(2-methylphenyl)-2-(trifluoromethyl)acrylate (*Z*-5h)**

According to general procedure IV: 2-Iodotoluene (0.2 mmol, 43.6 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 60/1, v/v),

affording compound **5h** in 77% yield [mixture of *E/Z* isomers (77/23), 44.3 mg] as a yellow oil.

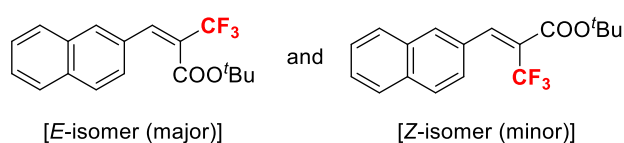
^1H NMR (300 MHz, CDCl_3): δ 8.01 (s, 1H, *Z*), 7.46 (s, 1H, *E*), 7.23 – 7.16 (m, 1H, *Z* + 1H, *E*), 7.16 – 7.04 (m, 3H, *Z* + 3H, *E*), 2.22 (s, 3H, *Z* + 3H, *E*), 1.49 (s, 9H, *Z*), 1.21 (s, 9H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.8 (s, *Z*), -64.8 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.3 (q, $J = 1.6$ Hz), 162.0 – 161.9 (m), 147.0 (q, $J = 3.1$ Hz), 139.9 (q, $J = 5.7$ Hz), 136.2, 136.0, 133.1, 132.9, 130.1, 129.9, 129.53, 129.50, 128.3 (q, $J = 3.2$ Hz), 128.2 – 128.1 (m), 126.8 (q, $J = 30.3$ Hz), 125.8, 125.7, 125.3 (q, $J = 30.7$ Hz), 122.2 (q, $J = 271.5$ Hz), 122.1 (q, $J = 272.8$ Hz), 83.14, 83.11, 28.1, 27.6, 20.1, 19.8. IR (Neat): 2981, 1725, 1649, 1370, 1296, 1278, 1247, 1155, 1132, 1011, 843, 749 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{15}\text{H}_{18}\text{F}_3\text{O}_2$ (m/z): 287.1259 [$\text{M}+\text{H}$] $^+$, found: 287.1257.



(*E*)-methyl 2-(2-(*tert*-butoxycarbonyl)-3,3,3-trifluoroprop-1-en-1-yl)benzoate (*E*-5i)
and (*Z*)-methyl 2-(2-(*tert*-butoxycarbonyl)-3,3,3-trifluoroprop-1-en-1-yl)benzoate (*Z*-5i)

According to general procedure IV: Methyl 2-iodobenzoate (0.2 mmol, 52.4 mg), Ag_2CO_3 (0.4 mmol, 110.3 mg), $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 90/1 to 50/1, v/v), affording compound **5i** in 99% yield [mixture of *E/Z* isomers (67/33), 65.5 mg] as a yellow oil.

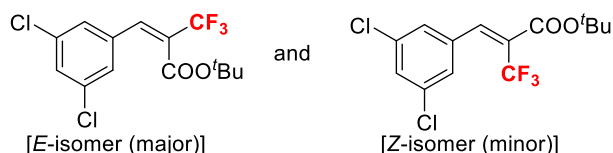
^1H NMR (300 MHz, CDCl_3): δ 8.36 (s, 1H, *Z*), 8.05 – 7.97 (m, 1H, *Z* + 1H, *E*), 7.96 (s, 1H, *E*), 7.51 – 7.42 (m, 1H, *Z* + 1H, *E*), 7.42 – 7.34 (m, 1H, *Z* + 1H, *E*), 7.21 – 7.13 (m, 1H, *Z* + 1H, *E*), 3.82 (s, 3H, *Z* + 3H, *E*), 1.50 (s, 9H, *Z*), 1.13 (s, 9H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.0 (s, *Z*), -64.7 (d, $J = 1.4$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 166.5, 166.4, 162.1 (q, $J = 1.6$ Hz), 161.5, 148.7 (q, $J = 3.2$ Hz), 143.3 (q, $J = 6.1$ Hz), 136.4, 135.9, 132.3, 130.7, 130.6, 129.4 – 129.1 (m), 129.1, 129.0, 128.2, 127.8, 124.7 (q, $J = 30.0$ Hz), 123.2 (q, $J = 30.3$ Hz), 122.3 (q, $J = 271.4$ Hz), 122.2 (q, $J = 272.6$ Hz), 82.9, 82.8, 52.4, 52.3, 28.1, 27.5. IR (Neat): 2982, 1718, 1650, 1370, 1292, 1281, 1264, 1156, 1130, 1082, 1013, 843, 753 cm^{-1} . HRMS (AP-TOF): Calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{O}_4$ (m/z): 330.1079 [M] $^-$, found: 330.1077.



***Tert*-butyl (*E*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylate (*E*-5j) and *Tert*-butyl (*Z*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylate (*Z*-5j)**

According to general procedure IV: 2-Iodonaphthalene (0.2 mmol, 50.8 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 60/1, v/v), affording compound **5j** in less than 78% yield [mixture of *E/Z* isomers (86/14), 50.6 mg, not pure] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.14 (s, 1H, *Z*), 7.94 – 7.78 (m, 4H, *Z* + 4H, *E*), 7.58 – 7.45 (m, 3H, *Z* + 4H, *E*), 1.62 (s, 9H, *Z*), 1.47 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.3 (s, *Z*), -64.4 (d, *J* = 1.1 Hz, *E*). ¹³C NMR was not tested because of the impurity. IR (Neat): 3059, 2983, 2937, 1722, 1651, 1370, 1281, 1270, 1247, 1152, 1121, 1009, 842, 825, 750 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₈H₁₈F₃O₂ (*m/z*): 323.1259 [M+H]⁺, found: 323.1269.

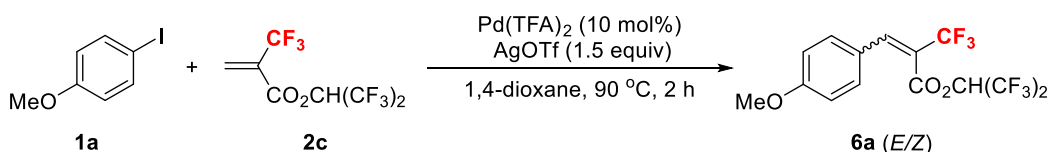


***Tert*-butyl (*E*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylate (*E*-5k) and *Tert*-butyl (*Z*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylate (*Z*-5k)**

According to general procedure IV: 3,5-Dichloro-1-iodobenzene (0.2 mmol, 54.6 mg), Ag₂CO₃ (0.4 mmol, 110.3 mg), Pd(TFA)₂ (0.02 mmol, 6.4 mg), and *tert*-butyl 2-(trifluoromethyl)acrylate (0.3 mmol, 58.9 mg) in 1,4-dioxane (1.0 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 60/1, v/v), affording compound **5k** in 81% yield [mixture of *E/Z* isomers (87/13), 55.5 mg] as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.74 (s, 1H, *Z*), 7.33 – 7.28 (m, 1H, *Z* + 1H, *E*), 7.24 – 7.17 (m, 1H, *Z* + 2H, *E*), 7.15 – 7.09 (m, 1H, *Z* + 1H, *E*), 1.48 (s, 9H, *Z*), 1.38 (s, 9H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.5 (s, *Z*), -65.0 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 161.6 (q, *J* = 1.7 Hz), 161.6 – 161.4 (m), 143.7 (q, *J* = 3.1 Hz), 135.9, 135.6, 135.5 (q, *J* = 5.7 Hz), 135.3, 135.1, 129.7, 129.6, 128.1 (q, *J* = 31.1 Hz), 127.2, 126.9 (q, *J* = 2.3 Hz), 121.8 (q, *J* = 271.9 Hz), 121.6 (q, *J* = 272.4 Hz), 84.5, 83.8, 28.1, 27.8. IR (Neat): 2983, 1726, 1563, 1370, 1285, 1240, 1218, 1135, 1014, 841, 803 cm⁻¹. HRMS (CI-TOF): Calcd for C₁₄H₁₄Cl₂F₃O₂ (*m/z*): 341.0323 [M+H]⁺, found: 341.0313.

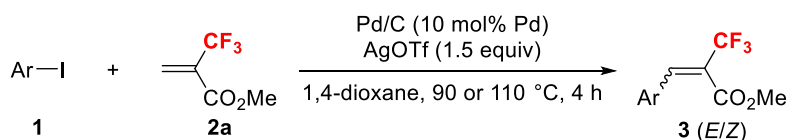
1.5 Synthesis of 1,1,1,3,3,3-hexafluoropropan-2-yl 3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (6a) by Mizoroki-Heck reaction with Pd(TFA)₂ and AgOTf



1,1,1,3,3,3-Hexafluoropropan-2-yl 2-(trifluoromethyl)acrylate (**2c**) was pre-synthesized according to the reported method and the analytical data were in agreement with those reported in the literature.²²⁴

To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), **2c** (0.3 mmol, 87.0 mg, 1.5 equiv), and 1,4-dioxane (1.0 mL). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL CH₂Cl₂) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 30/1, v/v), affording compound **6a** in less than 70% yield [mixture of *E/Z* isomers (63/37), 55.1 mg, not pure according to ¹³C NMR spectrum]. ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s, 3F, *Z*), -63.5 (s, 3F, *E*), -73.4 (d, *J* = 5.9 Hz, 6F, *E*), -73.7 (d, *J* = 5.9 Hz, 6F, *Z*).

1.6 Synthesis of methyl 3-aryl-2-(trifluoromethyl)acrylates (**3**) by Mizoroki-Heck reaction with Pd/C and AgOTf

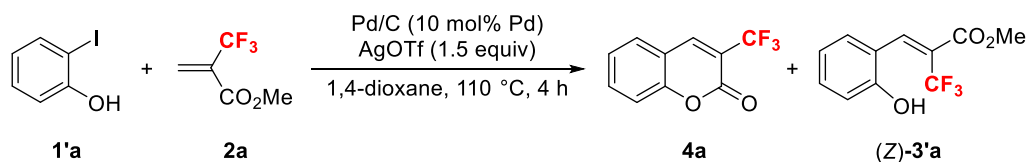


General procedure V: To a vial (2 mL) were added iodoarene **1** (0.2 mmol, 1.0 equiv), AgOTf (0.3 mmol, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 or 110 °C for 4 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL CH₂Cl₂) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).

The analytical data of **3a**, **3b**, **3c**, **3f**, **3g**, **3h**, **3j**, **3k**, **3o**, **3p**, **3q**, **3t**, **3v**, and **3w** were in agreement with those reported in § 1.2 of the experimental section. **3s**, **3cc**, **3dd**, and **3ee** did not get pure products with only ¹⁹F NMR yield in **Table 17** (see page 87).

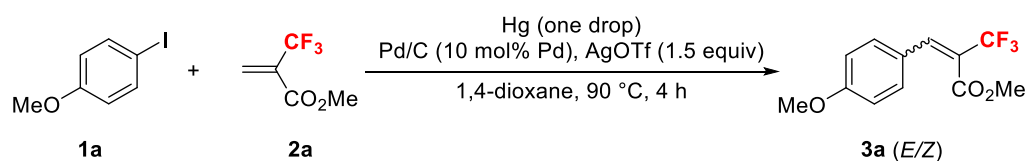
²²⁴ Y. Umino, T. Narita, H. Hamana, *J. Polym. Sci. Part A Polym. Chem.* **2008**, *46*, 7011–7021.

1.7 Synthesis of 3-(trifluoromethyl)-2*H*-chromen-2-one (**4a**) from 2-iodophenol (**1'a**) and methyl 2-(trifluoromethyl)acrylate (**2a**) with Pd/C and AgOTf

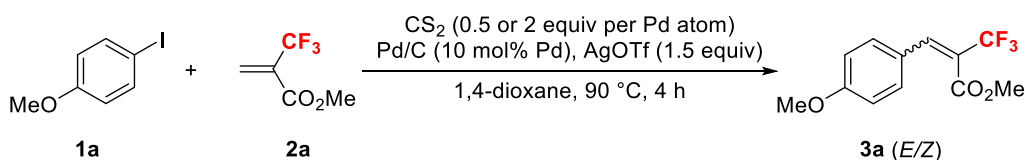


To a vial (2 mL) were added 2-iodophenol **1'a** (0.2 mmol, 44.0 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 21.3 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv), and 1,4-dioxane (1.0 mL). The vial was then sealed. The reaction mixture was stirred at 110 °C for 4 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL CH₂Cl₂) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording 3-(trifluoromethyl)-2*H*-chromen-2-one (**4a**) in 50% yield (21.3 mg) as a white solid. The analytical data of **4a** were in agreement with those reported in § 1.3 of experimental section. Methyl (*Z*)-3-(2-hydroxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-**3'a**) was obtained in less than 13% yield (5.5 mg) because we failed to obtain the pure isolated product. [Characterization of (*Z*-**3'a**): ¹H NMR (300 MHz, CDCl₃): δ 8.27 (s, 1H), 7.36 – 7.20 (m, 2H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.41 (s, 1H), 3.91 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -59.3 (s).

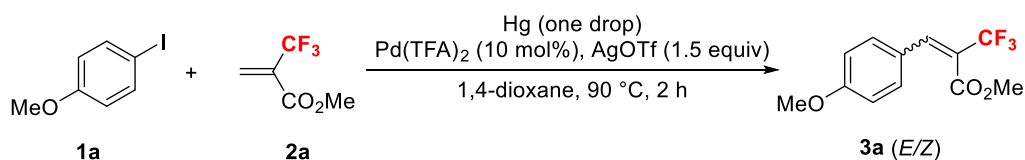
1.8 Palladium catalyst poisoning experiments



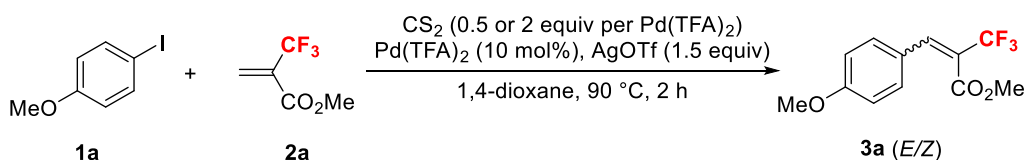
To a vial (2 mL) were added Hg (one drop, 227 equiv of Pd/C), 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 21.3 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 hours and was then cooled to room temperature. Internal standard PhCOCF₃ (1.0 equiv) was added to the ended reaction mixture and the result was tested by ¹⁹F NMR spectrum.



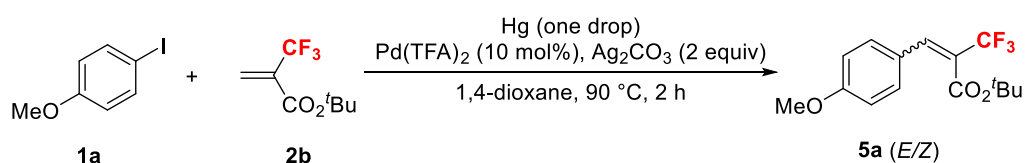
To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 21.3 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv), 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene), and CS_2 (0.5 or 2 equiv per Pd atom). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 hours and was then cooled to room temperature. Internal standard PhCOCF_3 (1.0 equiv) was added to the ended reaction mixture and the result was tested by ^{19}F NMR spectrum.



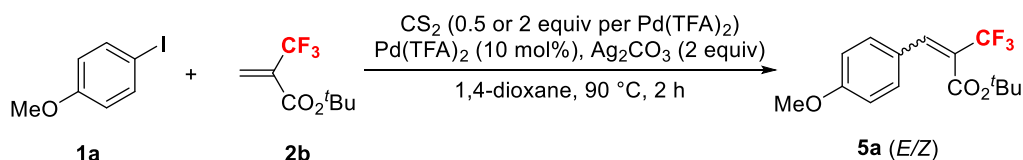
To a vial (2 mL) were added Hg (one drop, 376 equiv of Pd(TFA)₂), 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. Internal standard PhCOCF_3 (1.0 equiv) was added to the ended reaction mixture and the result was tested by ^{19}F NMR spectrum.



To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv), 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene), and CS_2 (0.5 or 2 equiv per Pd(TFA)₂). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. Internal standard PhCOCF_3 (1.0 equiv) was added to the ended reaction mixture and the result was tested by ^{19}F NMR spectrum.

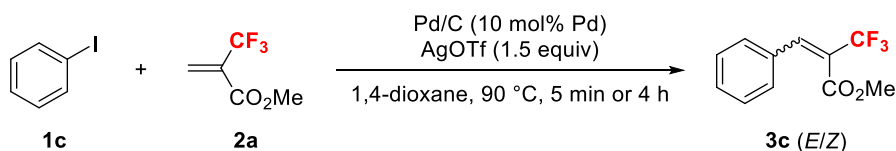


To a vial (2 mL) were added Hg (one drop, 199 equiv of Pd(TFA)₂), 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), Ag₂CO₃ (0.4 mmol, 110.3 mg, 2.0 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), *tert*-butyl 2-(trifluoromethyl)acrylate **2b** (0.3 mmol, 58.9 mg, 1.5 equiv), and 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. Internal standard PhCOCF₃ (1.0 equiv) was added to the ended reaction mixture and the result was tested by ¹⁹F NMR spectrum.



To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), Ag₂CO₃ (0.4 mmol, 110.3 mg, 2.0 equiv), Pd(TFA)₂ (0.02 mmol, 6.5 mg, 10 mol%), *tert*-butyl 2-(trifluoromethyl)acrylate **2b** (0.3 mmol, 58.9 mg, 1.5 equiv), 1,4-dioxane (1.0 mL, 5 mL/mmol of iodoarene), and CS₂ (0.5 or 2 equiv per Pd(TFA)₂). The vial was then sealed. The reaction mixture was stirred at 90 °C for 2 hours and was then cooled to room temperature. Internal standard PhCOCF₃ (1.0 equiv) was added to the ended reaction mixture and the result was tested by ¹⁹F NMR spectrum.

1.9 Measurement of Pd content in the crude of the filtrate by ICP-AES

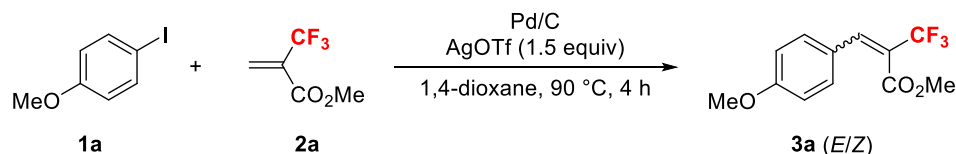


To a vial (2 mL) were added Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 21.3 mg, 10 mol%), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), iodobenzene **1c** (0.2 mmol, 40.8 mg, 1.0 equiv), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 5 min or 4 hours and was filtered immediately at hot state (with a hot sand-core funnel). The resulting filtrate was evaporated to remove the solvent, drying with a vacuum pump, and the crude was obtained to test Pd content by ICP-AES. The results are shown in **Table 54**.

Table 54 Pd content in the crude of the filtrate

| Reaction time | Weight of crude of filtrate (mg) | Content of Pd in the crude of filtrate (mg) | Mass concentration of Pd in the crude of filtrate (mg/kg) |
|---------------|----------------------------------|---|---|
| 5 min | 69.2 | 0.003995 | 58 |
| 4 hours | 70.9 | 0.000785 | 11 |

1.10 Recycling study of Pd/C catalyst



(a) 0.2 mmol scale, room temperature filtration

Original reaction with fresh catalyst: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 23.1 mg, 10 mol%), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was then cooled to room temperature. The reaction mixture was filtered with filter paper and the dark solid was washed with Et₂O (20 mL). After dried under reduced pressure of water-bump, 68.5 mg dark solid was obtained. The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. The desired product was formed in 87% ¹⁹F NMR yield [mixture of *E/Z* isomers (76/24)]. After purification by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), the isolated product **3a** was obtained in 80% yield [mixture of *E/Z* isomers (76/24), 41.6 mg].

First reuse of Pd/C: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), the resulting dark solid of the original reaction (68.5 mg), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was then cooled to room temperature. The reaction mixture was filtered with filter paper and the dark solid was washed with Et₂O (20 mL). After dried under reduced pressure of water-bump, 79.3 mg dark solid was obtained. The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. The desired product was formed in 78% ¹⁹F NMR yield [mixture of *E/Z* isomers (76/24)]. After purification by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), the isolated product **3a** was obtained in 75% yield [mixture of *E/Z* isomers (76/24), 39.1 mg].

Second reuse of Pd/C: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), the resulting dark solid of first reuse (79.3 mg), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was then cooled to room temperature. The reaction mixture was filtered with filter paper and the dark solid was washed with Et₂O (20 mL). The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with

PhCOCF₃ as an internal standard. The desired product was formed in 21% ¹⁹F NMR yield [mixture of *E/Z* isomers (69/31)].

(b) 0.2 mmol scale, hot filtration

Original reaction with fresh catalyst: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 23.1 mg, 10 mol%), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was filtered immediately at hot state with filter paper and the dark solid was washed with Et₂O (20 mL). After dried under reduced pressure of water-bump, 66.0 mg dark solid was obtained. The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. The desired product was formed in 79% ¹⁹F NMR yield [mixture of *E/Z* isomers (76/24)].

First reuse of Pd/C: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), the resulting dark solid of the original reaction (66.0 mg), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was filtered immediately at hot state with filter paper and the dark solid was washed with Et₂O (20 mL). After dried under reduced pressure of water-bump, 106.4 mg dark solid was obtained. The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. The desired product was formed in 80% ¹⁹F NMR yield [mixture of *E/Z* isomers (76/24)]. After purification by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), the isolated product **3a** was obtained in 69% yield [mixture of *E/Z* isomers (76/24), 36.1 mg].

Second reuse of Pd/C: To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), the resulting dark solid of first reuse (106.4 mg), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was filtered immediately at hot state with filter paper and the dark solid was washed with Et₂O (20 mL). The filtrate was removed solvent and tested ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. The desired was formed in 25% ¹⁹F NMR yield [mixture of *E/Z* isomers (84/16)].

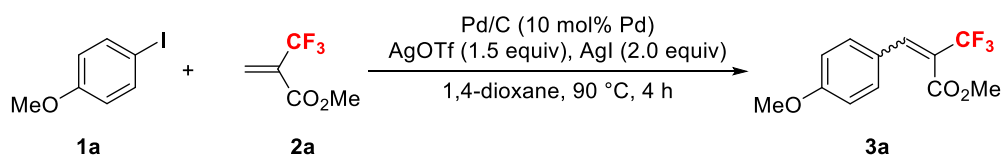
(c) 1.0 mmol scale, room temperature filtration

Original reaction with fresh catalyst: To a reaction tube (20 mL) were added 4-iodoanisole **1a** (1.0 mmol, 234.0 mg, 1.0 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.1 mmol, 106.4 mg, 10 mol%), AgOTf (1.5 mmol, 385.4 mg, 1.5 equiv), 1,4-dioxane (5.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (1.5 mmol,

231.1 mg, 1.5 equiv). The reaction tube was then sealed. The reaction mixture was stirred at 110 °C for 15 h and was then cooled to room temperature. The reaction mixture was filtered with a sand-core funnel and the dark solid was washed with Et₂O (50 mL). After dried under reduced pressure of water-bump, 374.4 mg dark solid was obtained. The filtrate was removed solvent and purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 15/1, v/v), the isolated product **3a** was obtained in 69% yield [mixture of *E/Z* isomers (80/20), 178.4 mg].

First reuse of Pd/C: To a reaction tube (20 mL) were added 4-iodoanisole **1a** (1.0 mmol, 234.0 mg, 1.0 equiv), the resulting dark solid of the original reaction (374.4 mg), AgOTf (1.5 mmol, 385.4 mg, 1.5 equiv), 1,4-dioxane (5.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (1.5 mmol, 231.1 mg, 1.5 equiv). The reaction tube was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was then cooled to room temperature. The reaction mixture was filtered with a sand-core funnel and the dark solid was washed with Et₂O (50 mL). The filtrate was removed solvent and tested by ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard. Only traces of **3a** was observed in the ¹⁹F NMR spectrum.

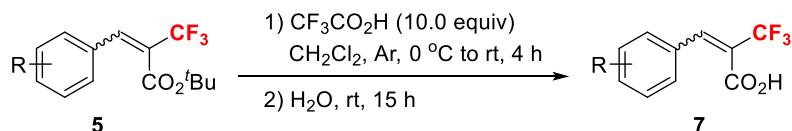
1.11 Effect of AgI on the reaction efficiency



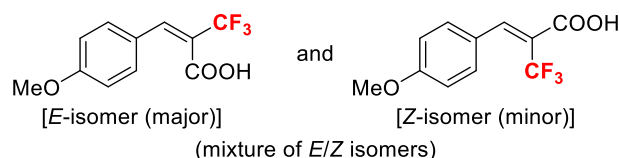
To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), Pd/C (Palladium, 10% on carbon, type 487, dry) (0.02 mmol, 23.1 mg, 10 mol%), AgOTf (0.3 mmol, 77.1 mg, 1.5 equiv), AgI (0.4 mmol, 93.9 mg, 2.0 equiv), 1,4-dioxane (1.0 mL), and methyl 2-(trifluoromethyl)acrylate **2a** (0.3 mmol, 46.2 mg, 1.5 equiv). The vial was then sealed. The reaction mixture was stirred at 90 °C for 4 h and was then cooled to room temperature. Internal standard PhCOCF₃ (1.0 equiv) was added to the ended reaction mixture and the result was tested by ¹⁹F NMR spectrum. The desired product was formed in 90% ¹⁹F NMR yield [mixture of *E/Z* isomers (75/25)].

2. Access to 3-aryl-2-(trifluoromethyl)acrylic acids by palladium-catalysed Mizoroki-Heck reaction

2.1 Hydrolysis of *tert*-butyl 3-aryl-2-(trifluoromethyl)acrylates in acidic conditions



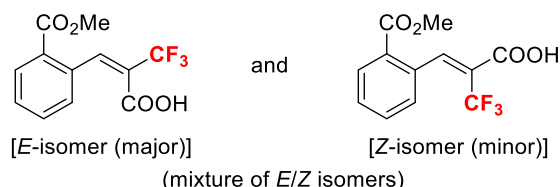
To an oven-dried 10 mL reaction tube was added *tert*-butyl α -trifluoromethylacrylate **5** (0.2 mmol, 1.0 equiv), and the tube was then evacuated and filled with argon three times. Anhydrous CH₂Cl₂ (1.0 mL) was added, and the mixture was cooled to 0 °C. CF₃CO₂H (10.0 equiv) was added dropwise at 0 °C and the reaction mixture was then allowed to stir at room temperature for 4 hours. Water (0.2 mL) was added and the two-phase reaction mixture was further stirred at room temperature for 15 hours. Water (5 mL) was added and the product was extracted with CH₂Cl₂ (3 \times 10 mL), and the combined organic phase was dried over anhydrous Na₂SO₄. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: CH₂Cl₂/MeOH (AcOH %)).



(*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*E*-7a) and **(*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7a)**

The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7a** in 77% yield (mixture of *E/Z* isomers (84/16), 37.8 mg) as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 11.30 (s, 1H, *Z* + 1H, *E*), 8.17 (s, 1H, *Z*), 7.58 – 7.43 (m, 2H, *Z* + 3H, *E*), 7.00 – 6.83 (m, 2H, *Z* + 2H, *E*), 3.87 (s, 3H, *Z*), 3.85 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.6 (s, *Z*), -63.7 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.4, 169.0, 162.2, 162.0, 150.8 (q, *J* = 2.4 Hz), 144.0 (q, *J* = 5.6 Hz), 133.1 (q, *J* = 2.7 Hz), 132.5, 124.4, 124.2, 122.6 (q, *J* = 271.3 Hz), 122.2 (q, *J* = 272.3 Hz), 119.0 (q, *J* = 31.1 Hz), 118.2 (q, *J* = 32.2 Hz), 114.2, 114.1, 55.6, 55.5. IR: 2850, 1698, 1599, 1514, 1424, 1268, 1154, 1134, 1019, 838, 527 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈F₃O₃ (*m/z*): 245.0426 [M-H]⁻, found: 245.0429.



(*E*)-3-(2-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (*E*-7q) and **(*Z*)-3-(2-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7q)**

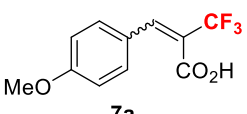
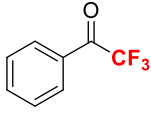
The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), 60/1 (0.5%), v/v), affording compound **7q** in 71% yield (mixture of *E/Z* isomers (67/33), 39.0 mg) as a white solid.

¹H NMR (300 MHz, CD₃OD): δ 8.56 (s, 1H, *Z*), 8.18 – 7.99 (m, 1H, *Z* + 2H, *E*), 7.68 – 7.42 (m, 2H, *Z* + 2H, *E*), 7.32 (d, *J* = 7.5 Hz, 1H, *E*), 7.28 (d, *J* = 7.8 Hz, 1H, *Z*), 3.89 (s, 3H, *Z*), 3.88 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.3 (s, *Z*), -65.7 (d, *J* = 2.0 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 167.9, 167.7, 165.5 – 165.3 (m), 165.2, 151.3 (q, *J* = 3.2 Hz), 145.6 (q, *J* = 6.2 Hz), 137.3, 137.1, 133.53, 133.51, 131.5, 131.4, 130.4 – 130.0 (m), 129.9 (q, *J* = 2.8 Hz), 129.5, 128.9, 124.4 (q, *J* = 30.2 Hz), 123.8 (q, *J* = 270.3 Hz), 123.7 (q, *J* = 271.9 Hz), 122.9 (q, *J* = 29.8 Hz), 52.8, 52.7. IR: 2954, 1699, 1635, 1438, 1270, 1135, 1088, 755, 695 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₂H₈F₃O₄ (*m/z*): 273.0375 [M-H]⁻, found: 273.0376.

2.2 Relationship between actual yield and tested ¹⁹F NMR yield of **7a**

In the process of optimization of reaction conditions, the tested ¹⁹F NMR spectrum with PhCOCF₃ as an internal standard often gave more than 100% yield, so it was important to figure out the relationship between actual yield and tested ¹⁹F NMR yield. With some desired product **7a** in hand, PhCOCF₃ was used as an internal standard and 1,4-dioxane was used as a solvent, and then five groups of control experiments were carried out (**Table 55**). It is obvious that the tested ¹⁹F NMR yield was always higher than the corresponding actual yield and an average ratio between actual yield and the tested ¹⁹F NMR yield was obtained (**Formula 3**). Therefore, in **Table 26-Table 30**, all of the ¹⁹F NMR yields were corrected according to **Formula 4**.

Table 55 Relationship between actual yield and tested ¹⁹F NMR yield of **7a**

| | | Test object | Internal Standard | Solvent | |
|-------|-----------|---|---|---|---|
| | |  |  | 1,4-dioxane | |
| Entry | 7a | Internal Standard | Actual yield ^a | Tested ¹⁹ F NMR yield ^b | Actual yield / Tested ¹⁹ F NMR yield |
| 1 | 0.02 mmol | 0.10 mmol | 20% | 33% | 61% |
| 2 | 0.04 mmol | 0.10 mmol | 40% | 63% | 63% |
| 3 | 0.06 mmol | 0.10 mmol | 60% | 92% | 65% |
| 4 | 0.08 mmol | 0.10 mmol | 80% | 128% | 63% |
| 5 | 0.10 mmol | 0.10 mmol | 100% | 155% | 65% |

^aActual yield was the actual ratio between **7a** and internal standard PhCOCF₃. ^bTested ¹⁹F NMR yield was the ratio of **7a** to internal standard PhCOCF₃ according to the ¹⁹F NMR spectrum.

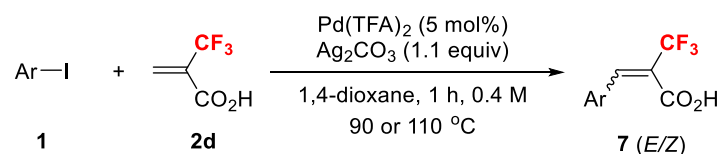
Formula 3

$$\frac{\text{Actual yield}}{\text{Tested } ^{19}\text{F NMR yield}} \text{ (average value)} = \frac{61\% + 63\% + 65\% + 63\% + 65\%}{5} = 63\%$$

Formula 4

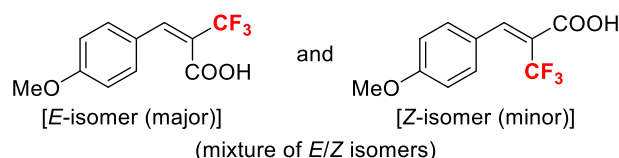
$$^{19}\text{F NMR yield} = 63\% \times \text{Tested } ^{19}\text{F NMR yield}$$

2.3 Synthesis of 3-aryl-2-(trifluoromethyl)acrylic acids (**7**) by Mizoroki-Heck reaction with Pd(TFA)₂ and Ag₂CO₃



General procedure VI: To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.3 mmol, 1.5 equiv), iodoarene **1** (0.2 mmol, 1.0 equiv), Ag₂CO₃ (0.22 mmol, 1.1 equiv), Pd(TFA)₂ (0.01 mmol, 5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 or 110 °C for 1 hour and was then cooled to room temperature. The resulting reaction mixture was purified directly by silica gel column chromatography (TLC: CH₂Cl₂/MeOH (AcOH), 20/1 (1%)).

Procedure for larger-scale reaction: To a reaction tube (10 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (3.0 mmol, 1.5 equiv), iodoarene **1** (2.0 mmol, 1.0 equiv), Ag₂CO₃ (2.2 mmol, 1.1 equiv), Pd(TFA)₂ (0.1 mmol, 5 mol%), and 1,4-dioxane (5 mL, 0.4 M of iodoarene). The tube was then sealed. The reaction mixture was stirred at 90 or 110 °C for 1 hour and was then cooled to room temperature. The reaction mixture was transferred to a 100 mL flask (with the tube washed with 30 mL CH₂Cl₂) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (TLC: CH₂Cl₂/MeOH (AcOH), 20/1 (1%)).



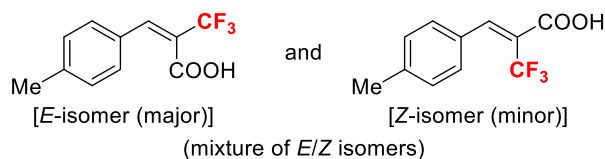
(*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*E*-7a) and **(*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7a)**

According to general procedure VI: 4-Iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h.

The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7a** in 89% yield (mixture of *E/Z* isomers (64/36), 43.6 mg) as a pale yellow solid.

Larger scale reaction: 4-Iodoanisole (2.0 mmol, 468.0 mg), 2-(trifluoromethyl)acrylic acid (3.0 mmol, 420.2 mg), Ag₂CO₃ (2.2 mmol, 606.7 mg), and Pd(TFA)₂ (0.1 mmol, 32.2 mg) in 1,4-dioxane (5 mL) were reacted at 90 °C for 1 h. The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7a** in 89% yield (mixture of *E/Z* isomers (64/36), 439.3 mg) as a pale yellow solid.

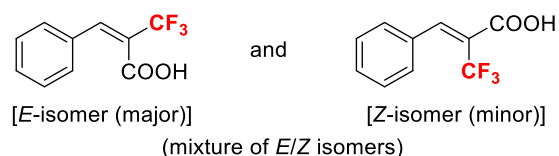
¹H NMR (300 MHz, CDCl₃): δ 10.85 (s, 1H, *Z* + 1H, *E*), 8.17 (s, 1H, *Z*), 7.76 – 7.38 (m, 2H, *Z* + 3H, *E*), 7.14 – 6.80 (m, 2H, *Z* + 2H, *E*), 3.87 (s, 3H, *Z*), 3.85 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.6 (s, *Z*), -63.7 (d, *J* = 1.1 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.4, 169.0, 162.2, 162.0, 150.8 (q, *J* = 2.4 Hz), 144.0 (q, *J* = 5.6 Hz), 133.1 (q, *J* = 2.7 Hz), 132.5, 124.4, 124.2, 122.6 (q, *J* = 271.3 Hz), 122.2 (q, *J* = 272.3 Hz), 119.0 (q, *J* = 31.1 Hz), 118.2 (q, *J* = 32.2 Hz), 114.2, 114.1, 55.6, 55.5. IR: 2850, 1698, 1599, 1514, 1424, 1268, 1154, 1134, 1019, 838, 527 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈F₃O₃ (*m/z*): 245.0426 [M-H]⁻, found: 245.0429.



(*E*)-3-(*p*-tolyl)-2-(trifluoromethyl)acrylic acid (*E*-7b) and (*Z*)-3-(*p*-tolyl)-2-(trifluoromethyl)acrylic acid (*Z*-7b)

According to general procedure VI: 4-Iodotoluene (0.2 mmol, 43.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7b** in 88% yield (mixture of *E/Z* isomers (65/35), 40.3 mg) as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 11.19 (s, 1H, *Z* + 1H, *E*), 8.12 (s, 1H, *Z*), 7.47 (s, 1H, *E*), 7.28 (t, *J* = 8.3 Hz, 2H, *Z* + 2H, *E*), 7.13 (t, *J* = 7.2 Hz, 2H, *Z* + 2H, *E*), 2.31 (s, 3H, *Z*), 2.29 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.6 (s, *Z*), -64.1 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.3 – 169.1 (m), 168.9, 151.3 (q, *J* = 2.5 Hz), 144.2 (q, *J* = 5.6 Hz), 141.8, 141.7, 130.3 (q, *J* = 2.5 Hz), 129.9, 129.5, 129.31, 129.27, 129.1, 122.3 (q, *J* = 271.5 Hz), 121.9 (q, *J* = 272.5 Hz), 120.9 (q, *J* = 30.8 Hz), 120.1 (q, *J* = 32.1 Hz), 21.7, 21.6. IR: 2854, 1698, 1607, 1435, 1278, 1141, 1017, 1003, 933, 828, 719, 502 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈F₃O₂ (*m/z*): 229.0476 [M-H]⁻, found: 229.0481.

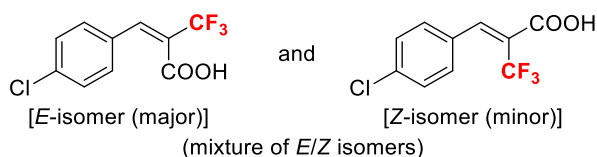


(*E*)-3-phenyl-2-(trifluoromethyl)acrylic acid (*E*-7c) and (*Z*)-3-phenyl-2-(trifluoromethyl)acrylic acid (*Z*-7c)

According to general procedure VI: Iodobenzene (0.2 mmol, 40.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7c** in 96% yield (mixture of *E/Z* isomers (64/36), 41.4 mg) as a pale yellow solid.

Larger scale reaction: Iodobenzene (2.0 mmol, 408.0 mg), 2-(trifluoromethyl)acrylic acid (3.0 mmol, 420.2 mg), Ag₂CO₃ (2.2 mmol, 606.7 mg), and Pd(TFA)₂ (0.1 mmol, 32.2 mg) in 1,4-dioxane (5 mL) were reacted at 90 °C for 1 h. The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7c** in 90% yield (mixture of *E/Z* isomers (64/36), 390.6 mg) as a pale yellow solid.

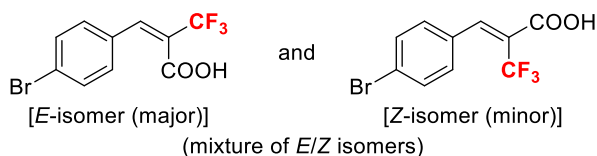
¹H NMR (300 MHz, CDCl₃): δ 10.50 (s, 1H, *Z* + 1H, *E*), 8.27 (s, 1H, *Z*), 7.61 (s, 1H, *E*), 7.56 – 7.31 (m, 5H, *Z* + 5H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.6 (s, *Z*), -64.3 (s, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.9, 168.6, 151.1 (q, *J* = 2.6 Hz), 144.0 (q, *J* = 5.7 Hz), 132.2, 132.0, 130.8, 129.8 (q, *J* = 2.4 Hz), 129.6, 128.8, 128.5, 122.2 (q, *J* = 271.7 Hz), 122.1 (q, *J* = 31.1 Hz), 121.7 (q, *J* = 272.6 Hz), 121.4 (q, *J* = 32.1 Hz). IR: 2850, 1699, 1635, 1435, 1277, 1164, 1127, 1018, 911, 694 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₀H₆F₃O₂ (*m/z*): 215.0320 [M-H]⁻, found: 215.0322.



(*E*)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7d) and (*Z*)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7d)

According to general procedure VI: 1-Chloro-4-iodobenzene (0.2 mmol, 47.7 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7d** in 98% yield (mixture of *E/Z* isomers (63/37), 49.3 mg) as a yellow solid.

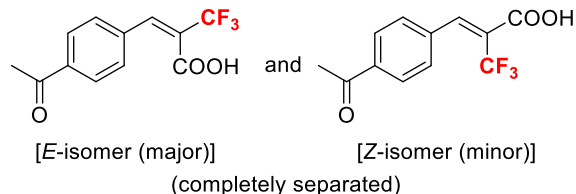
^1H NMR (300 MHz, CDCl_3): δ 10.90 (s, 1H, Z + 1H, E), 8.19 (s, 1H, Z), 7.57 (s, 1H, E), 7.54 – 7.29 (m, 4H, Z + 4H, E). ^{19}F NMR (282 MHz, CDCl_3): δ -58.7 (s, Z), -64.4 (d, $J = 1.1$ Hz, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.8 – 168.5 (m), 168.1, 149.6 (q, $J = 2.6$ Hz), 143.1 (q, $J = 5.7$ Hz), 137.2, 137.1, 131.1 (q, $J = 2.4$ Hz), 130.9, 130.5, 130.4, 129.1, 128.9, 122.6 (q, $J = 31.1$ Hz), 122.0 (q, $J = 271.8$ Hz), 121.9 (q, $J = 32.2$ Hz), 121.6 (q, $J = 272.8$ Hz). IR: 2922, 1694, 1621, 1490, 1429, 1289, 1162, 1130, 1091, 1015, 924, 829 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{10}\text{H}_5\text{ClF}_3\text{O}_2$ (m/z): 248.9930 $[\text{M}-\text{H}]^-$, found: 248.9928.



(*E*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7e) and (*Z*)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7e)

According to general procedure VI: 1-Bromo-4-iodobenzene (0.2 mmol, 56.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 $^\circ\text{C}$ for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7e** in 90% yield (mixture of *E/Z* isomers (64/36), 53.4 mg) as a white solid.

^1H NMR (300 MHz, CDCl_3): δ 10.32 (s, 1H, Z + 1H, E), 8.07 (s, 1H, Z), 7.58 – 7.39 (m, 2H, Z + 3H, E), 7.34 – 7.14 (m, 2H, Z + 2H, E). ^{19}F NMR (282 MHz, CDCl_3): δ -58.7 (s, Z), -64.4 (s, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.7 – 168.5 (m), 168.1, 149.7 (q, $J = 2.6$ Hz), 143.2 (q, $J = 5.7$ Hz), 132.0, 131.9, 131.2 (q, $J = 2.5$ Hz), 131.1, 131.0, 130.9, 125.6, 125.5, 122.6 (q, $J = 31.1$ Hz), 122.0 (q, $J = 271.9$ Hz), 121.9 (q, $J = 32.6$ Hz), 121.6 (q, $J = 272.8$ Hz). IR: 2841, 1704, 1632, 1488, 1438, 1287, 1256, 1145, 1073, 1013, 925, 827, 728, 497 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{10}\text{H}_5\text{BrF}_3\text{O}_2$ (m/z): 292.9425 $[\text{M}-\text{H}]^-$, found: 292.9427.



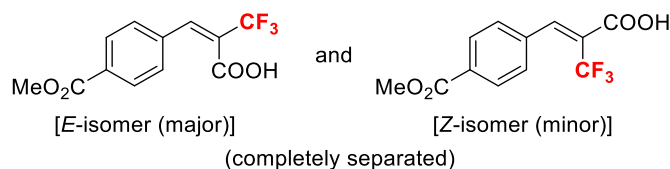
(*E*)-3-(4-acetylphenyl)-2-(trifluoromethyl)acrylic acid (*E*-7f) and (*Z*)-3-(4-acetylphenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7f)

According to general procedure VI: 1-(4-iodophenyl)ethan-1-one (0.2 mmol, 49.2 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 $^\circ\text{C}$ for 1 h. The reaction mixture was purified by silica gel column chromatography

(CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 40/1 (0.5%), v/v) affording compound **7f** in 90% yield [mixture of *E/Z* isomers (61/39), 46.4 mg]. *E/Z* isomers were completely separated by column: impure *E*-isomer was subsequently washed with *n*-pentane (0.3 mL × 3) by ultrasound to obtain pure compound **E-7f**, 28.3 mg, yellow solid; impure *Z*-isomer was subsequently washed with CHCl₃ (0.1 mL) to obtain pure compound **Z-7f**, 18.1 mg, yellow solid.

[E-7f (major)]: Mp 101-102 °C. ¹H NMR (300 MHz, CDCl₃): δ 10.88 (s, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.61 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 2H), 2.62 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.6 (s). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 198.6, 166.5, 142.0 (q, *J* = 5.4 Hz), 137.9, 136.9, 129.4, 128.7, 124.6 (q, *J* = 31.6 Hz), 121.8 (q, *J* = 272.0 Hz), 26.8. IR: 2927, 1730, 1646, 1605, 1404, 1365, 1301, 1276, 1208, 1155, 1133, 1015, 911, 839, 596 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₂H₈F₃O₃ (*m/z*): 257.0426 [M-H]⁻, found: 257.0420.

[Z-7f (minor)]: Mp 159-160 °C. ¹H NMR [300 MHz, (CD₃)₂SO]: δ 8.21 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 2.58 (s, 3H). ¹⁹F NMR [282 MHz, (CD₃)₂SO]: δ -57.0 (s). ¹³C{¹H} NMR [75 MHz, (CD₃)₂SO]: δ 197.8, 163.7 (q, *J* = 1.7 Hz), 147.1 (q, *J* = 3.1 Hz), 137.4, 129.1 (q, *J* = 2.4 Hz), 128.2, 123.9 (q, *J* = 30.0 Hz), 122.1 (q, *J* = 272.6 Hz), 26.9. IR: 2923, 1723, 1652, 1602, 1410, 1381, 1248, 1200, 1126, 831, 690 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₂H₈F₃O₃ (*m/z*): 257.0426 [M-H]⁻, found: 257.0420.



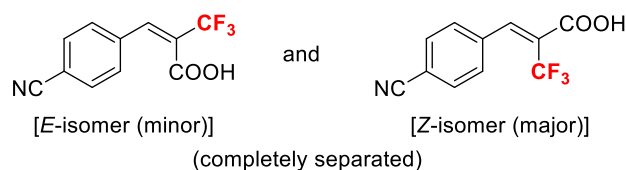
(E)-3-(4-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (E-7g) and (Z)-3-(4-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (Z-7g)

According to general procedure VI: Methyl 4-iodobenzoate (0.2 mmol, 52.4 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 40/1 (0.5%), v/v), affording compound **7g** in 88% yield [mixture of *E/Z* isomers (64/36), 48.5 mg]. *E/Z* isomers were completely separated by column: **E-7g**, 31.1 mg, brown solid; **Z-7g**, 17.4 mg, brown solid.

[E-7g (major)]: Mp 129-130 °C. ¹H NMR (300 MHz, CDCl₃): δ 10.51 (s, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 3.93 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.6 (s). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 166.7, 166.6, 142.4 (q, *J* = 5.5 Hz), 136.6, 131.6, 129.9, 129.2, 124.3 (q, *J* = 31.2 Hz), 121.8 (q, *J* = 272.1 Hz), 52.7. IR: 2971, 1724, 1693, 1652, 1146, 1405, 1322, 1297, 1279, 1198, 1162, 1126, 1014, 946,

762, 695, 667 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{O}_4$ (m/z): 273.0375 $[\text{M-H}]^-$, found: 273.0370.

[Z-7g (minor)]: Mp 148-149 $^{\circ}\text{C}$. ^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: 13.92 (s, 1H), 8.24 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.1$ Hz, 2H), 3.86 (s, 3H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -57.0 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 165.7, 163.8 – 163.2 (m), 146.9 (q, $J = 3.0$ Hz), 137.5, 130.4, 129.7 – 128.2 (m), 123.9 (q, $J = 30.0$ Hz), 121.9 (q, $J = 272.7$ Hz), 52.4. IR: 2964, 1724, 1698, 1627, 1570, 1420, 1381, 1287, 1265, 1224, 1162, 1135, 1109, 1019, 872, 758, 696 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{O}_4$ (m/z): 273.0375 $[\text{M-H}]^-$, found: 273.0370.



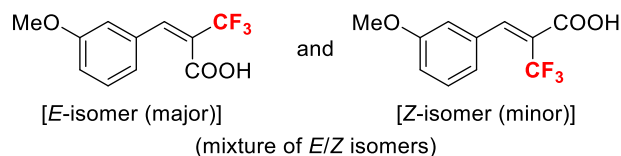
(E)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylic acid (E-7h) and (Z)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylic acid (Z-7h)

According to general procedure VI: 4-Iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 $^{\circ}\text{C}$ for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 30/1 (0.5%), v/v) affording compound **7h** in 77% yield [mixture of *E/Z* isomers (46/54), 37.2 mg]. *E/Z* isomers were completely separated by column: **E-7h**, 17.0 mg, yellow solid; **Z-7h**, 20.2 mg, white solid.

Larger scale reaction: 4-Iodobenzonitrile (2.0 mmol, 458.0 mg), 2-(trifluoromethyl)acrylic acid (3.0 mmol, 420.2 mg), Ag_2CO_3 (2.2 mmol, 606.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.1 mmol, 32.2 mg) in 1,4-dioxane (5 mL) were reacted at 110 $^{\circ}\text{C}$ for 1 h. The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 30/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.5 mL \times 3), affording compound **7h** in 79% yield [mixture of *E/Z* isomers (53/47), 379.2 mg]. *E/Z* isomers were partly separated by column.

[E-7h (minor)]: Mp 114-115 $^{\circ}\text{C}$. ^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 14.14 (s, 1H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.82 – 7.57 (m, 3H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -62.8 (d, $J = 0.8$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 163.7, 137.4 (q, $J = 5.9$ Hz), 137.1, 132.4, 129.8, 126.0 (q, $J = 30.1$ Hz), 122.2 (q, $J = 271.7$ Hz), 118.4, 112.3. IR: 3051, 2247, 1708, 1646, 1407, 1291, 1272, 1161, 1131, 1010, 925, 839, 554 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_5\text{F}_3\text{NO}_2$ (m/z): 240.0272 $[\text{M-H}]^-$, found: 240.0269.

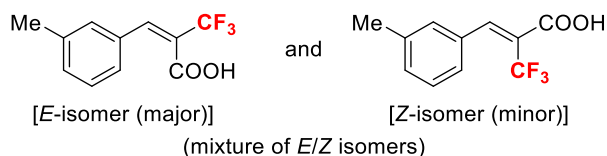
[Z-7h (major)]: Mp 162-163 °C. ^1H NMR (300 MHz, CD_3OD): 8.23 (s, 1H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.55 (d, $J = 8.1$ Hz, 2H). ^{19}F NMR (282 MHz, CD_3OD): δ -59.4 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CD_3OD): δ 164.9 (q, $J = 1.7$ Hz), 147.1 (q, $J = 3.0$ Hz), 139.3, 133.1, 130.4 (q, $J = 2.3$ Hz), 126.5 (q, $J = 30.9$ Hz), 123.2 (q, $J = 272.1$ Hz), 119.2, 114.2. IR: 2987, 2227, 1705, 1434, 1391, 1282, 1232, 1168, 1129, 1034, 917, 836, 708, 634, 557 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_5\text{F}_3\text{NO}_2$ (m/z): 240.0272 [M-H] $^-$, found: 240.0269.



(*E*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*E*-7i) and (*Z*)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7i)

According to general procedure VI: 1-Iodo-3-methoxybenzene (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), and the resulting impure product was subsequently purified by extraction. NaOH (0.6 mmol, 24 mg) was dissolved in 15.0 mL H_2O and was then added to 15.0 mL CH_2Cl_2 solution of the impure compound **7i**. The mixture was stirred for 30 min and the aqueous phase was extracted with CH_2Cl_2 (15 mL \times 3). The remained aqueous phase was then acidified with 1.0 M HCl aqueous solution, and was then extracted with CH_2Cl_2 (15 mL \times 3). The second combined organic phase was dried with anhydrous MgSO_4 , and was then filtered. After removing solvents under reduced pressure, the pure product **7i** was obtained in 85% yield (mixture of *E/Z* isomers (67/33), 41.7 mg) as a brown oil.

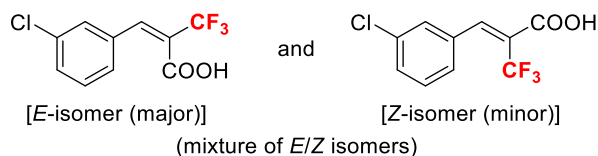
^1H NMR (300 MHz, CDCl_3): δ 10.27 (s, 1H, *Z* + 1H, *E*), 8.22 (s, 1H, *Z*), 7.56 (s, 1H, *E*), 7.39 – 7.28 (m, 1H, *Z* + 1H, *E*), 7.10 – 6.91 (m, 3H, *Z* + 3H, *E*), 3.84 (s, 3H, *Z*), 3.80 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.6 (s, *Z*), -64.3 (d, $J = 0.8$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.7 (q, $J = 1.8$ Hz), 168.4, 159.6, 159.4, 150.9 (q, $J = 2.6$ Hz), 143.4 (q, $J = 5.6$ Hz), 133.4, 133.2, 129.9, 129.6, 122.5 (q, $J = 31.1$ Hz), 122.14 (q, $J = 2.4$ Hz), 122.10 (q, $J = 271.7$ Hz), 122.0, 121.67 (q, $J = 272.8$ Hz), 121.65 (q, $J = 32.2$ Hz), 116.7, 116.6, 114.7 (q, $J = 2.5$ Hz), 114.5, 55.5, 55.4. IR: 2844, 1705, 1600, 1581, 1425, 1298, 1253, 1237, 1126, 1040, 1013, 782, 687 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{O}_3$ (m/z): 245.0426 [M-H] $^-$, found: 245.0434.



(E)-3-(*m*-tolyl)-2-(trifluoromethyl)acrylic acid (E-7j) and **(Z)-3-(*m*-tolyl)-2-(trifluoromethyl)acrylic acid (Z-7j)**

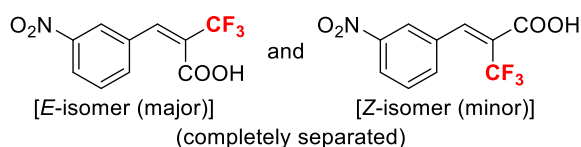
According to general procedure VI: 1-Iodo-3-methylbenzene (0.2 mmol, 43.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7j** in 98% yield (mixture of *E/Z* isomers (64/36), 45.2 mg) as an off-white solid.

¹H NMR (300 MHz, CDCl₃): δ 11.81 (s, 1H, Z + 1H, E), 8.15 (s, 1H, Z), 7.50 (s, 1H, E), 7.29 – 7.10 (m, 4H, Z + 4H, E), 2.30 (s, 3H, Z), 2.28 (s, 3H, E). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.6 (s, Z), -64.3 (s, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 169.1 (q, *J* = 2.0 Hz), 168.8, 151.4 (q, *J* = 2.5 Hz), 144.1 (q, *J* = 5.6 Hz), 138.5, 138.3, 132.2, 132.0, 131.7, 130.4 (q, *J* = 2.0 Hz), 130.2, 128.7, 128.4, 126.9 (q, *J* = 2.5 Hz), 126.5, 122.2 (q, *J* = 271.6 Hz), 121.9 (q, *J* = 31.0 Hz), 121.8 (q, *J* = 272.6 Hz), 121.1 (q, *J* = 32.2 Hz), 21.40, 21.37. IR: 2861, 1704, 1621, 1435, 1279, 1241, 1140, 915, 694 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₈F₃O₂ (*m/z*): 229.0476 [M-H]⁻, found: 229.0476.

**(E)-3-(3-chlorophenyl)-2-(trifluoromethyl)acrylic acid (E-7k)** and **(Z)-3-(3-chlorophenyl)-2-(trifluoromethyl)acrylic acid (Z-7k)**

According to general procedure VI: 1-Chloro-3-iodobenzene (0.2 mmol, 47.7 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7k** in 89% yield (mixture of *E/Z* isomers (63/37), 44.7 mg) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 10.59 (s, 1H, Z + 1H, E), 8.18 (s, 1H, Z), 7.63 – 7.52 (m, 1H, E), 7.51 – 7.27 (m, 4H, Z + 4H, E). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s, Z), -64.5 (d, *J* = 1.4 Hz, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 168.6 – 168.3 (m), 167.9, 149.3 (q, *J* = 2.5 Hz), 142.7 (q, *J* = 5.7 Hz), 134.7, 134.6, 133.9, 133.8, 130.7, 130.0, 129.8, 129.4 – 129.1 (m), 127.5 (q, *J* = 2.4 Hz), 127.3, 123.6 (q, *J* = 31.3 Hz), 122.8 (q, *J* = 32.3 Hz), 121.8 (q, *J* = 272.0 Hz), 121.4 (q, *J* = 272.9 Hz). IR: 3044, 1706, 1642, 1568, 1425, 1292, 1162, 1131, 1013, 928, 893, 779, 683 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₀H₅ClF₃O₂ (*m/z*): 248.9930 [M-H]⁻, found: 248.9932.



(*E*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7I) and (*Z*)-3-(3-nitrophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7I)

According to general procedure VI: 1-Iodo-3-nitrobenzene (0.2 mmol, 49.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7I** in 82% yield [mixture of *E/Z* isomers (52/48), 42.8 mg]. *E/Z* isomers were completely separated by column: impure *E*-isomer was subsequently washed with CHCl₃ (0.05 mL × 3) to obtain pure compound ***E*-7I**, 22.4 mg, white solid; pure compound ***Z*-7I**, 20.4 mg, white solid.

[***E*-7I** (major)]: Mp 134-135 °C. ¹H NMR (300 MHz, CD₃OD): δ 8.41 (s, 1H), 8.28 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.57 (m, 2H). ¹⁹F NMR (282 MHz, CD₃OD): δ -65.8 (d, *J* = 1.7 Hz). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 165.3, 149.6, 138.7 (q, *J* = 6.0 Hz), 136.3, 135.7, 130.9, 127.8 (q, *J* = 30.9 Hz), 125.5, 124.8, 123.5 (q, *J* = 270.9 Hz). IR: 1699, 1637, 1533, 1426, 1353, 1300, 1252, 1128, 1015, 921, 817, 739, 678 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₀H₅F₃NO₄ (*m/z*): 260.0171 [M-H]⁻, found: 260.0172.

[***Z*-7I** (minor)]: Mp 134-135 °C. ¹H NMR (300 MHz, CD₃OD): δ 8.39 – 8.17 (m, 3H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.4 (s). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 165.0 (q, *J* = 1.6 Hz), 149.4, 146.6 (q, *J* = 3.0 Hz), 136.1, 135.7 (q, *J* = 2.3 Hz), 130.8, 126.6 (q, *J* = 30.8 Hz), 125.2, 124.4 (q, *J* = 2.5 Hz), 123.3 (q, *J* = 272.0 Hz). IR: 1708, 1644, 1530, 1428, 1352, 1294, 1177, 1138, 1018, 906, 677, 650 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₀H₅F₃NO₄ (*m/z*): 260.0171 [M-H]⁻, found: 260.0172.



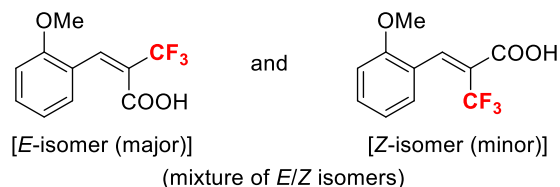
(*E*)-3-(3-cyanophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7m) and (*Z*)-3-(3-cyanophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7m)

According to general procedure VI: 3-Iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography

(CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 30/1 (0.5%), v/v), affording compound **7m** in 66% yield [mixture of *E/Z* isomers (55/45), 31.6 mg]. *E/Z* isomers were completely separated by column: impure *Z*-isomer was subsequently washed with *n*-pentane (0.3 mL × 3) to obtain pure compound **Z-7m**, 14.3 mg, white solid; pure compound **E-7m**, 17.3 mg, yellow solid.

[E-7m (major)]: Mp 120-121 °C. ¹H NMR [300 MHz, (CD₃)₂SO]: 14.01 (s, 1H), 7.97 (s, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.75 – 7.52 (m, 2H). ¹⁹F NMR [282 MHz, (CD₃)₂SO]: δ -62.8 (s). ¹³C{¹H} NMR (75 MHz, (CD₃)₂SO): δ 163.7, 137.2 (q, *J* = 5.8 Hz), 133.7, 133.6, 133.4, 132.7, 129.8, 125.6 (q, *J* = 32.9 Hz), 122.3 (q, *J* = 271.5 Hz), 118.3, 111.7. IR: 3073, 2924, 2233, 1729, 1696, 1650, 1405, 1280, 1176, 1141, 1011, 947, 813, 687 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₅F₃NO₂ (*m/z*): 240.0272 [M-H]⁻, found: 240.0277.

[Z-7m (minor)]: Mp 119-120 °C. ¹H NMR (300 MHz, CDCl₃): δ 11.88 (s, 1H), 8.22 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.67 – 7.53 (m, 2H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 167.6, 147.7 (q, *J* = 2.8 Hz), 133.7, 133.6, 133.2 (q, *J* = 2.4 Hz), 132.4 (q, *J* = 2.3 Hz), 129.5, 124.1 (q, *J* = 31.7 Hz), 121.3 (q, *J* = 273.1 Hz), 117.9, 113.1. IR: 3064, 2988, 2259, 1733, 1702, 1642, 1419, 1364, 1197, 1135, 1119, 1023, 802, 685 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₁H₅F₃NO₂ (*m/z*): 240.0272 [M-H]⁻, found: 240.0277.

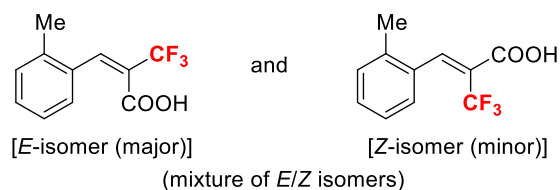


(*E*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*E*-7n) and (*Z*)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7n)

According to general procedure VI: 1-Iodo-2-methoxybenzene (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7n** in 78% yield (mixture of *E/Z* isomers (54/46), 38.6 mg) as a yellow solid.

¹H NMR (300 MHz, CD₃OD): 8.23 (s, 1H, *Z*), 7.63 – 7.52 (m, 1H, *E*), 7.49 – 7.31 (m, 1H, *Z* + 2H, *E*), 7.25 (d, *J* = 7.5 Hz, 1H, *Z*), 7.08 – 6.84 (m, 2H, *Z* + 2H, *E*), 3.86 (s, 3H, *Z*), 3.85 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CD₃OD): δ -60.2 (s, *Z*), -65.3 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 166.5, 166.0 – 165.8 (m), 159.0, 158.9 – 158.8 (m), 146.0 (q, *J* = 3.0 Hz), 136.9 (q, *J* = 6.1 Hz), 133.01, 133.00, 131.1 (q, *J* = 3.6 Hz), 131.0 – 130.9 (m), 125.0 (q, *J* = 31.1 Hz), 124.0 (q, *J* = 270.3 Hz), 123.8 (q, *J* = 271.6 Hz), 123.6

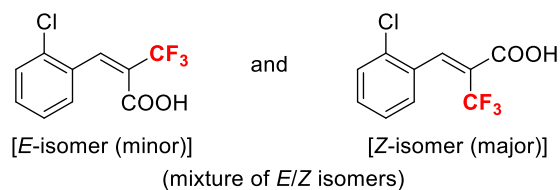
(q, $J = 30.4$ Hz), 123.1, 122.8, 121.3, 121.1, 112.0, 111.7, 56.1, 55.9. IR: 2844, 1698, 1624, 1600, 1489, 1433, 1282, 1247, 1157, 1129, 1115, 1022, 1010, 920, 749 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{O}_3$ (m/z): 245.0426 $[\text{M}-\text{H}]^-$, found: 245.0434.



(*E*)-3-(*o*-tolyl)-2-(trifluoromethyl)acrylic acid (*E*-7o) and (*Z*)-3-(*o*-tolyl)-2-(trifluoromethyl)acrylic acid (*Z*-7o)

According to general procedure VI: 2-Iodotoluene (0.2 mmol, 43.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v) affording compound **7o** in 86% yield (mixture of *E/Z* isomers (57/43), 39.7 mg) as a pale yellow solid.

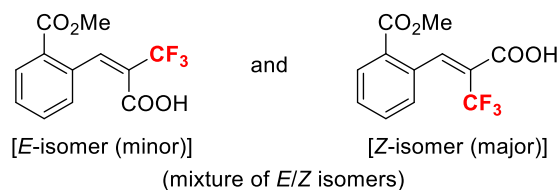
^1H NMR (300 MHz, CDCl_3): δ 10.51 (s, 1H, *Z* + 1H, *E*), 8.27 (s, 1H, *Z*), 7.72 (s, 1H, *E*), 7.27 – 7.19 (m, 1H, *Z* + 1H, *E*), 7.18 – 7.05 (m, 3H, *Z* + 3H, *E*), 2.23 (s, 3H, *Z* + 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -59.0 (s, *Z*), -64.5 (d, $J = 1.7$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.7, 168.2, 150.9, 150.0 (q, $J = 5.0$ Hz), 136.6, 136.3, 132.14, 132.06, 130.3 (m), 130.1, 128.5, 128.3, 126.0, 125.8, 123.4 (q, $J = 31.9$ Hz), 122.5 (q, $J = 32.2$ Hz), 122.0 (q, $J = 272.4$ Hz), 121.7 (q, $J = 273.4$ Hz), 20.1, 19.9. IR: 2854, 1697, 1626, 1429, 1296, 1234, 1159, 1120, 1022, 1009, 927, 748, 652 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{O}_2$ (m/z): 299.0476 $[\text{M}-\text{H}]^-$, found: 299.0478.



(*E*)-3-(2-chlorophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7p) and (*Z*)-3-(2-chlorophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7p)

According to general procedure VI: 1-Chloro-2-iodobenzene (0.2 mmol, 47.7 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.3 mL \times 3), affording compound **7p** in 63% yield (mixture of *E/Z* isomers (37/63), 31.6 mg) as a pale yellow solid.

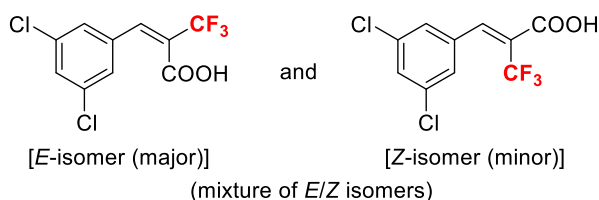
^1H NMR (300 MHz, CDCl_3): δ 11.62 (s, 1H, Z + 1H, E), 8.27 (s, 1H, Z), 7.76 (s, 1H, E), 7.44 – 7.14 (m, 4H, Z + 4H, E). ^{19}F NMR (282 MHz, CDCl_3): δ -59.1 (s, Z), -64.7 (s, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.3 – 168.0 (m), 167.6, 148.0 (q, J = 2.6 Hz), 142.8 (q, J = 5.8 Hz), 133.7, 133.5, 131.6, 131.50, 131.48, 131.4, 130.3 (q, J = 3.4 Hz), 130.8, 129.7, 129.5, 126.9, 126.7, 124.3 (q, J = 31.2 Hz), 123.4 (q, J = 31.8 Hz), 121.8 (q, J = 271.9 Hz), 121.5 (q, J = 273.1 Hz). IR: 1670, 1631, 1423, 1290, 1262, 1218, 1155, 1131, 1056, 1038, 1020, 918, 754, 738, 647 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{10}\text{H}_5\text{ClF}_3\text{O}_2$ (m/z): 248.9930 $[\text{M}-\text{H}]^-$, found: 248.9932.



(*E*)-3-(2-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (*E*-7q) and (*Z*)-3-(2-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7q)

According to general procedure VI: Methyl 2-iodobenzoate (0.2 mmol, 52.4 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 $^\circ\text{C}$ for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), 60/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.3 mL \times 4), affording compound **7q** in 73% yield (mixture of *E/Z* isomers (30/70), 40.2 mg) as a white solid.

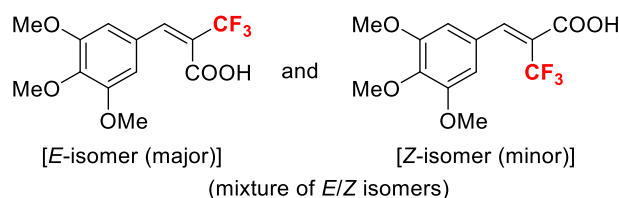
^1H NMR (300 MHz, CD_3OD): δ 8.57 (s, 1H, Z), 8.26 – 7.99 (m, 1H, Z + 2H, E), 7.70 – 7.43 (m, 2H, Z + 2H, E), 7.32 (d, J = 7.5 Hz, 1H, E), 7.27 (d, J = 7.5 Hz, 1H, Z), 3.89 (s, 3H, Z), 3.88 (s, 3H, E). ^{19}F NMR (282 MHz, CD_3OD): δ -59.2 (s, Z), -65.7 (d, J = 1.7 Hz, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CD_3OD): δ 167.9, 167.7, 165.5 – 165.3 (m), 165.2, 151.3 (q, J = 3.2 Hz), 145.6 (q, J = 6.2 Hz), 137.3, 137.1, 133.53, 133.51, 131.5, 131.4, 130.4 – 130.0 (m), 129.9 (q, J = 2.8 Hz), 129.5, 128.9, 124.4 (q, J = 30.2 Hz), 123.8 (q, J = 270.3 Hz), 123.7 (q, J = 271.9 Hz), 122.9 (q, J = 29.8 Hz), 52.8, 52.7. IR: 2954, 1699, 1635, 1438, 1270, 1135, 1088, 755, 695 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{O}_4$ (m/z): 273.0375 $[\text{M}-\text{H}]^-$, found: 273.0376.



(*E*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylic acid (*E*-7r) and (*Z*)-3-(3,5-dichlorophenyl)-2-(trifluoromethyl)acrylic acid (*Z*-7r)

According to general procedure VI: 1,3-Dichloro-5-iodobenzene (0.2 mmol, 54.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.3 mL \times 2), affording compound **7r** in 76% yield (mixture of *E/Z* isomers (66/34), 43.2 mg) as a white solid.

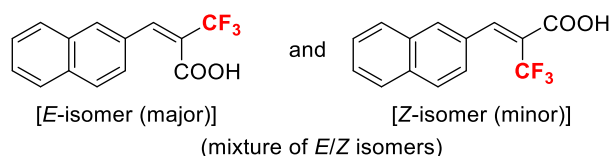
^1H NMR (300 MHz, CDCl_3): δ 11.58 (s, 1H, *Z* + 1H, *E*), 8.03 (s, 1H, *Z*), 7.46 (s, 1H, *E*), 7.41 – 7.29 (m, 1H, *Z* + 1H, *E*), 7.29 – 7.20 (m, 2H, *Z* + 1H, *E*), 7.18 (s, 1H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.7 (s, *Z*), -64.3 (s, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.1 – 167.9 (m), 167.2, 147.9 (q, $J = 2.7$ Hz), 141.8 (q, $J = 5.7$ Hz), 135.5, 135.4, 134.94, 134.91, 130.4, 127.3, 127.23, 127.20, 124.8 (q, $J = 31.6$ Hz), 124.0 (q, $J = 32.8$ Hz), 121.6 (q, $J = 272.1$ Hz), 121.2 (q, $J = 273.2$ Hz). IR: 3075, 1730, 1698, 1606, 1562, 1406, 1386, 1292, 1169, 1143, 1017, 941, 862, 792, 675 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{10}\text{H}_4\text{Cl}_2\text{F}_3\text{O}_2$ (m/z): 282.9540 $[\text{M}-\text{H}]^-$, found: 282.9544.



(*E*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (*E*-7s) and (*Z*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (*Z*-7s)

According to general procedure VI: 5-Iodo-1,2,3-trimethoxybenzene (0.2 mmol, 58.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.3 mL \times 4), affording compound **7s** in 79% yield (mixture of *E/Z* isomers (71/29), 48.5 mg) as a brown solid.

^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$): δ 8.09 (s, 1H, *Z*), 7.41 (s, 1H, *E*), 6.96 (s, 2H, *E*), 6.80 (s, 2H, *Z*), 3.77 (s, 9H, *E*), 3.71 (s, 9H, *Z*). ^{19}F NMR (282 MHz, $(\text{CD}_3)_2\text{SO}$): δ -56.8 (s, *Z*), -62.2 (s, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$): δ 164.9, 164.1, 152.8, 152.6, 147.9 (d, $J = 3.1$ Hz), 139.5, 139.3, 137.5 (q, $J = 5.8$ Hz), 127.6, 127.3, 122.7 (q, $J = 271.1$ Hz), 122.6 (q, $J = 30.4$ Hz), 122.3 (q, $J = 272.4$ Hz), 121.4 (q, $J = 31.8$ Hz), 107.3, 60.2, 56.0, 55.9. IR: 2924, 2853, 1696, 1583, 1506, 1463, 1417, 1273, 1237, 1121, 1023, 1000, 839 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_5\text{F}_3$ (m/z): 307.0793 $[\text{M}+\text{H}]^+$, found: 307.0787.

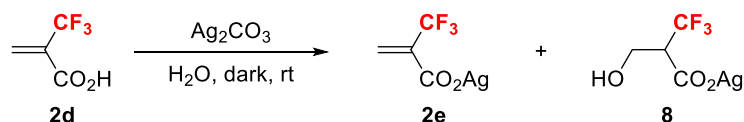


(*E*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylic acid (*E*-7t) and (*Z*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylic acid (*Z*-7t)

According to general procedure VI: 2-Iodonaphthalene (0.2 mmol, 50.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), 60/1 (0.5%), v/v), and the resulting impure product was subsequently washed with *n*-pentane (0.3 mL × 3), affording compound **7t** in 91% yield (mixture of *E/Z* isomers (65/35), 48.2 mg) as a pale yellow solid.

¹H NMR (300 MHz, CD₃OD): δ 8.31 (s, 1H, *Z*), 7.98 (s, 1H, *E*), 7.95 – 7.74 (m, 4H, *Z* + 3H, *E*), 7.62 – 7.41 (m, 3H, *Z* + 4H, *E*). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.1 (s, *Z*), -65.2 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CD₃OD): δ 166.6, 165.9 (q, *J* = 2.0 Hz), 149.4 (q, *J* = 3.0 Hz), 140.0 (q, *J* = 5.9 Hz), 135.3, 135.1, 134.3, 134.0, 131.49, 131.46, 131.1, 130.9 (q, *J* = 2.2 Hz), 129.6, 129.2, 128.9, 128.7, 128.6, 127.8, 127.7, 126.9 (q, *J* = 2.8 Hz), 126.5, 125.2 (q, *J* = 30.6 Hz), 123.94 (q, *J* = 270.5 Hz), 123.87 (q, *J* = 31.2 Hz), 123.6 (q, *J* = 271.8 Hz). IR: 2861, 1698, 1614, 1435, 1293, 1268, 1129, 1018, 928, 865, 824, 753, 711, 477 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₄H₈F₃O₂ (*m/z*): 265.0476 [M-H]⁻, found: 265.0482.

2.4 Synthesis of silver 2-(trifluoromethyl)acrylate (2e**)**



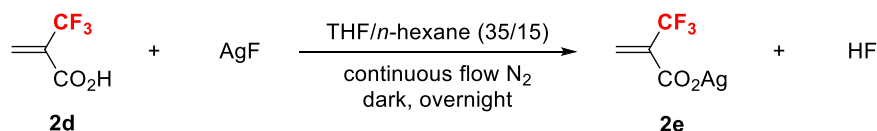
(a) Removal of water: evaporation at 60 °C with rotary evaporator

To a 50 mL round-bottom flask were added 2-(trifluoromethyl)acrylic acid **2d** (2.0 mmol, 280.1 mg, 1.0 equiv), Ag₂CO₃ (1.1 mmol, 303.3 mg, 0.55 equiv), and water (4 mL). The reaction mixture was stirred at room temperature in dark for one week. The excess Ag₂CO₃ was removed by filtration and washed with 10 mL water. The aqueous filtrate was washed with CH₂Cl₂ (3 × 10 mL) to remove the possible remaining **2d**. Then, the resulting aqueous phase was evaporated at 60 °C with rotary evaporator, affording 319.1 mg white solid. However, the white solid proved to be the side product ((3,3,3-trifluoro-2-(hydroxymethyl)propanoyl)oxy)silver **8** (60% yield) with only traces of silver 2-(trifluoromethyl)acrylate **2e**.

[Characterization of **8**]: ^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 5.00 (s, 1H), 3.84 – 3.68 (m, 2H), 3.23 – 3.04 (m, 1H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -64.5 (d, $J = 9.6$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 169.0 (q, $J = 2.6$ Hz), 125.9 (q, $J = 278.2$ Hz), 58.7 (q, $J = 3.1$ Hz), 54.1 (q, $J = 22.8$ Hz). IR: 3196, 1613, 1566, 1391, 1321, 1231, 1175, 1124, 1023, 903, 696 cm^{-1} .

(b) Removal of water: drying with freeze dryer for 20 h

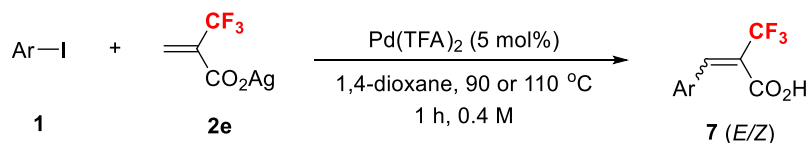
To a 50 mL round-bottom flask were added 2-(trifluoromethyl)acrylic acid **2d** (2.0 mmol, 280.1 mg, 1.0 equiv), Ag_2CO_3 (2.0 mmol, 551.5 mg, 1.0 equiv), and water (8 mL). The reaction mixture was stirred at room temperature in dark for 3.5 days. The excess Ag_2CO_3 was removed by filtration and washed with 20 mL water. The aqueous filtrate was washed with CH_2Cl_2 (3×15 mL) to remove the possible remaining **2d**. Then, the resulting aqueous phase was under freeze drying for 20 hours, affording 505.7 mg white solid. However, the white solid proved to be the mixture of desired product **2e** (88%) and side-product **8** (12%). We failed to get pure **2e** by recrystallization using EtOH/*n*-pentane.



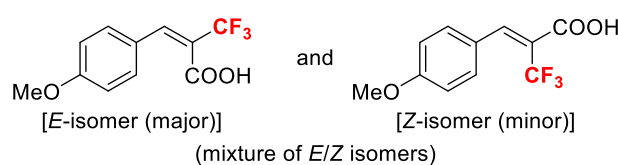
The synthetic method was according to a published paper.²⁰⁸ To a 100 mL oven-dried three-necked round bottom flask was added AgF (3.15 mmol, 0.40 g, 1.0 equiv) in dark, and the flask was evacuated and filled with N_2 three times. Anhydrous THF (35 mL) and *n*-hexane (15 mL) were then added. A bubbling trap containing saturated NaHCO_3 aqueous (150 mL) was connected to one of the necks while a small, continuous flow of N_2 passed through the reaction system. 2-(Trifluoromethyl)acrylic acid **2d** (6.3 mmol, 0.88 g, 2.0 equiv) was added to the reaction mixture. The N_2 current remained throughout the entire reaction in order to remove the generated HF from the reaction system to be neutralized with NaHCO_3 in the trap. The reaction mixture was stirred at room temperature overnight in dark and the brownish AgF was completely consumed. The mixture was then reduced to ca. 25% of their initial volume by evaporation after which cold *n*-hexane (0 °C, 10 mL) was added to precipitate the product as a white solid, which was separated by filtration, washed with cold *n*-hexane (0 °C, 3×10 mL) and dried *in vacuo*. Silver 2-(trifluoromethyl)acrylate (**2e**) was obtained in 74% yield (575 mg) as a white solid.

[Characterization of **2e**]: ^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 6.45 – 6.35 (m, 1H), 6.18 – 6.08 (m, 1H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -63.6 (m). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 164.5, 136.1 (q, $J = 27.8$ Hz), 128.4 (q, $J = 5.4$ Hz), 123.0 (q, $J = 270.5$ Hz). IR: 1655, 1538, 1520, 1419, 1393, 1171, 1131, 1106, 995, 821, 696 cm^{-1} .

2.5 Mizoroki-Heck reaction between aryl iodides (**1**) and silver 2-(trifluoromethyl)acrylate (**2e**)

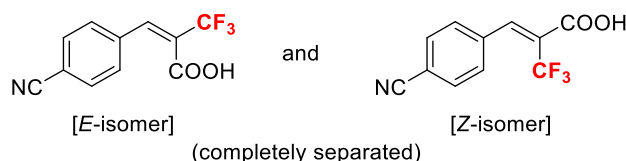


To a vial (2 mL) were added iodoarene **1** (0.2 mmol, 1.0 equiv), silver 2-(trifluoromethyl)acrylate **2e** (0.3 mmol, 1.5 equiv), Pd(TFA)₂ (0.01 mmol, 5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 or 110 °C for 1 hour and was then cooled to room temperature. The resulting reaction mixture was purified directly by silica gel column chromatography (TLC: CH₂Cl₂/MeOH (AcOH), 20/1 (1%)).



(*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (**E-7a**) and (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (**Z-7a**)

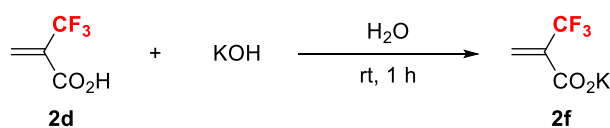
4-Iodoanisole (0.2 mmol, 46.8 mg), silver 2-(trifluoromethyl)acrylate **2e** (0.3 mmol, 74.1 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7a** in 93% yield (mixture of *E/Z* isomers (64/36), 46.0 mg) as a pale yellow solid. The analytical data of **7a** were in agreement with those reported in § 2.3 of experimental section.



(*E*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylic acid (**E-7h**) and (*Z*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylic acid (**Z-7h**)

4-Iodobenzonitrile (0.2 mmol, 45.8 mg), silver 2-(trifluoromethyl)acrylate **2e** (0.3 mmol, 74.1 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. The reaction mixture was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.5%) to 20/1 (0.5%), v/v) affording compound **7h** in 73% yield [mixture of *E/Z* isomers (50/50), 35.2 mg]. The analytical data of **7h** were in agreement with those reported in § 2.3 of experimental section.

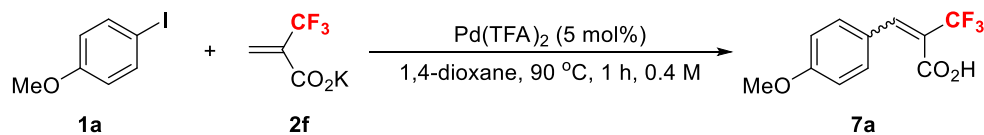
2.6 Synthesis of potassium 2-(trifluoromethyl)acrylate (**2f**)



To a 25 mL round bottom flask was added 2-(trifluoromethyl)acrylic acid **2d** (2.0 mmol, 280 mg, 1.0 equiv). KOH (2.0 mmol, 112 mg, 1.0 equiv) was dissolved in water (8 mL) and was added to the flask at once. The reaction mixture was then stirred at room temperature for 1 h. The resulting reaction mixture was extracted with CH_2Cl_2 (3 \times 10 mL) to remove the possible remaining **2d**. Then, the water was removed with freeze drier for 20 h. Potassium 2-(trifluoromethyl)acrylate (**2f**) was obtained in 61% yield (218 mg) as a white solid.

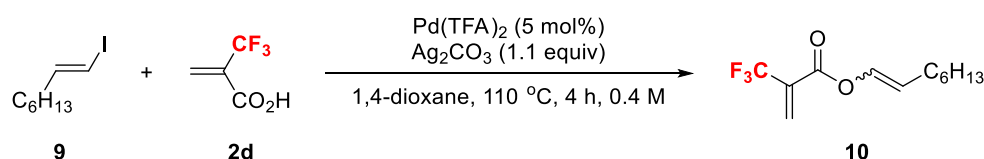
^1H NMR [300 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 6.16 – 6.07 (m, 1H), 5.86 – 5.78 (m, 1H). ^{19}F NMR [282 MHz, $(\text{CD}_3)_2\text{SO}$]: δ -63.0 (m). $^{13}\text{C}\{^1\text{H}\}$ NMR [75 MHz, $(\text{CD}_3)_2\text{SO}$]: δ 163.3, 139.0 (q, J = 25.7 Hz), 124.7 (q, J = 5.7 Hz), 123.7 (q, J = 270.8 Hz). IR: 1664, 1582, 1373, 1320, 1152, 1102, 985, 833, 798, 689 cm^{-1} .

2.7 Mizoroki-Heck reaction between 4-iodoanisole (**1a**) and potassium 2-(trifluoromethyl)acrylate (**2f**)



To a vial (2 mL) were added 4-iodoanisole **1a** (0.2 mmol, 46.8 mg, 1.0 equiv), potassium 2-(trifluoromethyl)acrylate **2f** (0.3 mmol, 53.4 mg, 1.5 equiv), Pd(TFA)_2 (0.01 mmol, 3.2 mg, 5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 $^\circ\text{C}$ for 1 hour and was then cooled to room temperature. The resulting reaction mixture was purified directly by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.5%) to 60/1 (0.5%), v/v), affording compound **7a** in less than 10% yield (mixture of *E/Z* isomers (42/58), 5.1 mg, not pure) as a white solid. The analytical data of **7a** were in agreement with those reported in § 2.3 of experimental section.

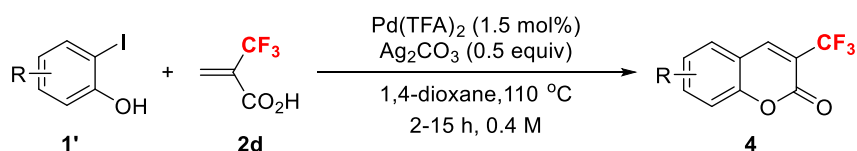
2.8 Esterification reaction between (*E*)-1-iodooct-1-ene (**9**) and 2-(trifluoromethyl)acrylic acid (**2d**)



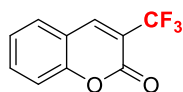
To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.3 mmol, 42.0 mg, 1.5 equiv), Ag_2CO_3 (0.22 mmol, 60.7 mg, 1.1 equiv), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg, 5 mol%), 1,4-dioxane (0.5 mL), and (*E*)-1-iodooct-1-ene **9** (0.2 mmol, 47.6 mg, 1.0 equiv). The vial was then sealed. The reaction mixture was stirred at 110 °C for 4 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 200/1 to 70/1, v/v), affording compound **10** in less than 53% yield (26.4 mg, impure) as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 7.23 – 7.06 (m, 1H, Z + 1H, *E*), 6.90 – 6.74 (m, 1H, Z + 1H, *E*), 6.63 – 6.46 (m, 1H, Z + 1H, *E*), 5.58 (dt, $J = 12.3, 7.5$ Hz, 1H, *E*), 5.10 – 4.99 (m, 1H, Z), 2.18 (q, $J = 7.2$ Hz, 2H, Z), 2.04 (q, $J = 7.2$ Hz, 2H, *E*), 1.45 – 1.19 (m, 8H, Z + 8H, *E*), 0.96 – 0.81 (m, 3H, Z + 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -66.02 to -66.08 (m, Z), -66.18 to -66.21 (m, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 158.7 – 158.6 (m), 158.6 – 158.5 (m), 134.8, 134.0 (q, $J = 5.1$ Hz), 133.7 (q, $J = 5.0$ Hz), 133.5, 131.1 (q, $J = 31.8$ Hz), 131.0 (q, $J = 32.2$ Hz), 121.30 (q, $J = 270.3$ Hz), 121.25 (q, $J = 270.9$ Hz), 117.4, 116.6, 31.8, 31.7, 29.5, 29.1, 28.92, 28.86, 27.4, 24.6, 22.7, 14.21, 14.19. IR: 2959, 2929, 2858, 1746, 1459, 1406, 1367, 1349, 1238, 1150, 1110, 931, 805, 695 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{12}\text{H}_{18}\text{F}_3\text{O}_2$ (m/z): 251.1259 [$\text{M}+\text{H}$] $^+$, found: 251.1250.

2.9 Synthesis of 3-trifluoromethyl coumarin derivatives (**4**) from *o*-iodophenols (**1'**) and 2-(trifluoromethyl)acrylic acid (**2d**) with $\text{Pd}(\text{TFA})_2$ and Ag_2CO_3

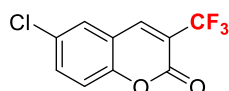


General procedure VII: To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.3 mmol, 1.5 equiv), *o*-iodophenol **1'** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.1 mmol, 0.5 equiv), $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of *o*-iodophenol). The vial was then sealed. The reaction mixture was stirred at 110 °C for 2 or 15 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



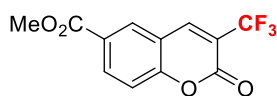
3-(Trifluoromethyl)-2H-chromen-2-one (**4a**)

According to general procedure VII: 2-Iodophenol (0.2 mmol, 44.0 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.1 mmol, 27.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 15 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **4a** in 59% yield (25.4 mg) as a white solid. The analytical data of **4a** were in agreement with those reported in § 1.3 of experimental section.



6-Chloro-3-(trifluoromethyl)-2H-chromen-2-one (**4c**)

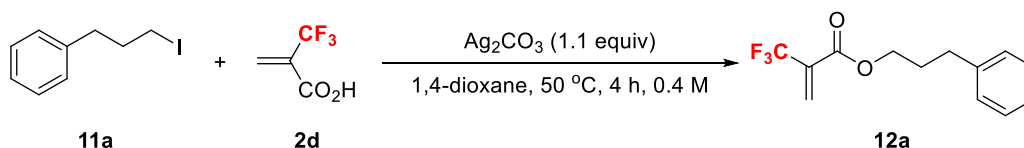
According to general procedure VII: 4-Chloro-2-iodophenol (0.2 mmol, 50.9 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.1 mmol, 27.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **4c** in 40% yield (20.0 mg) as a white solid. The analytical data of **4c** were in agreement with those reported in § 1.3 of experimental section.



Methyl 2-oxo-3-(trifluoromethyl)-2H-chromene-6-carboxylate (**4d**)

According to general procedure VII: Methyl 4-hydroxy-3-iodobenzoate (0.2 mmol, 55.6 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.1 mmol, 27.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.003 mmol, 1.0 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 5/1, v/v), affording compound **4d** in 71% yield (38.6 mg) as a white solid. The analytical data of **4d** were in agreement with those reported in § 1.3 of experimental section.

2.10 Esterification reaction between (3-iodopropyl)benzene (**11a**) and 2-(trifluoromethyl)acrylic acid (**2d**)

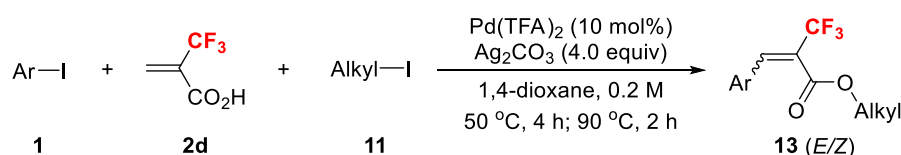


To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.2 mmol, 28.0 mg, 1.0 equiv), Ag_2CO_3 (0.22 mmol, 60.7 mg, 1.1 equiv), (3-iodopropyl)benzene **11a** (0.2 mmol, 49.2 mg, 1.0 equiv), and 1,4-dioxane (0.5 mL). The vial was then sealed. The reaction mixture was stirred at 50 °C for 4 hours and was then cooled to room

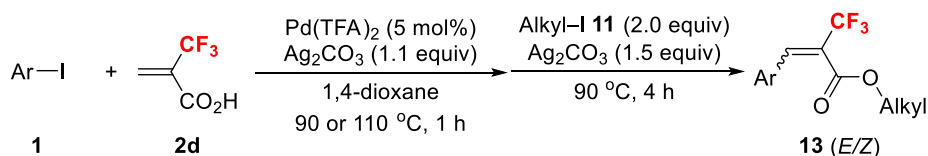
temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 60/1, v/v), affording compound **12a** in 76% yield (39.1 mg) as a colorless oil.

^1H NMR (300 MHz, CDCl_3): δ 7.27 – 7.17 (m, 2H), 7.17 – 7.05 (m, 3H), 6.61 (q, $J = 1.8$ Hz, 1H), 6.42 – 6.28 (m, 1H), 4.19 (t, $J = 6.3$ Hz, 2H), 2.65 (t, $J = 7.5$ Hz, 2H), 2.06 – 1.85 (m, 2H). ^{19}F NMR (282 MHz, CDCl_3): δ -65.5 (m). ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 161.4, 141.0, 133.0 (q, $J = 5.1$ Hz), 131.6 (q, $J = 31.9$ Hz), 128.6, 128.5, 126.2, 121.5 (q, $J = 270.8$ Hz), 65.2, 32.1, 30.1. IR: 3029, 2960, 1734, 1497, 1455, 1405, 1396, 1344, 1248, 1141, 1114, 1096, 991, 810, 745, 698 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{O}_2$ (m/z): 259.0946 $[\text{M}+\text{H}]^+$, found: 259.0940.

2.11 Synthesis of alkyl 3-aryl-2-(trifluoromethyl)acrylates (**13**) by three-component reaction

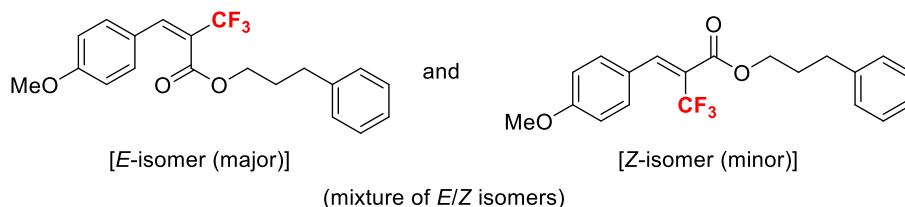


General procedure VIII (one pot, 1 step): To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.4 mmol, 2.0 equiv), iodoarene **1** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.8 mmol, 4.0 equiv), Pd(TFA)_2 (0.02 mmol, 10 mol%), alkyl iodide **11** (0.8 mmol, 4.0 equiv), and 1,4-dioxane (1.0 mL, 0.2 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 50 $^\circ\text{C}$ for 4 hours and was then heated to 90 $^\circ\text{C}$, and further stirred at 90 $^\circ\text{C}$ for 2 hours. After allowed to cool to room temperature, the reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



General procedure IX (one pot, 2 steps): To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **2d** (0.3 mmol, 1.5 equiv), iodoarene **1** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.22 mmol, 1.1 equiv), Pd(TFA)_2 (0.01 mmol, 5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 or 110 $^\circ\text{C}$ for 1 hour and was then cooled to room temperature.

Alkyl iodide **11** (0.4 mmol, 2.0 equiv), and Ag_2CO_3 (0.3 mmol, 1.5 equiv) were added at room temperature and the vial was sealed again. The reaction mixture was stirred at 90 °C for 4 hours and was then cooled to room temperature. The reaction mixture was transferred to a 50 mL flask (with the vial washed with 20 mL EtOAc) and was mixed with celite. After removing solvents under reduced pressure, the crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



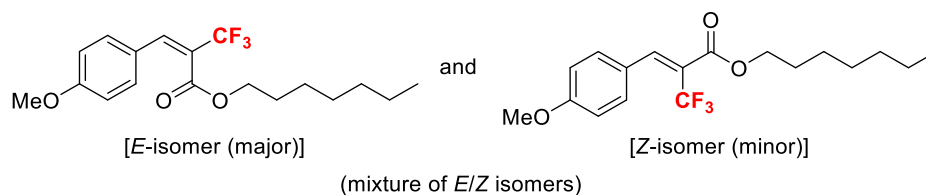
3-Phenylpropyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**E-13a**) and 3-Phenylpropyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**Z-13a**)

According to general procedure VIII: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), (3-iodopropyl)benzene (0.8 mmol, 196.9 mg), Ag_2CO_3 (0.8 mmol, 220.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 °C for 4 h and then at 90 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 15/1, v/v), affording compound **13a** in 77% yield (mixture of *E/Z* isomers (60/40), 56.4 mg) as a yellow oil.

According to general procedure IX: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. Then (3-iodopropyl)benzene (0.4 mmol, 98.4 mg), Ag_2CO_3 (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 °C for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 15/1, v/v), affording compound **13a** in 82% yield (mixture of *E/Z* isomers (64/36), 59.5 mg) as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 7.88 (s, 1H, *Z*), 7.39 – 7.28 (m, 2H, *Z* + 2H, *E*), 7.27 – 7.23 (m, 1H, *E*), 7.23 – 7.06 (m, 4H, *Z* + 4H, *E*), 7.05 – 6.99 (m, 1H, *Z* + 1H, *E*), 6.88 – 6.75 (m, 2H, *Z* + 2H, *E*), 4.28 – 4.10 (m, 2H, *Z* + 2H, *E*), 3.74 (s, 3H, *Z*), 3.71 (s, 3H, *E*), 2.66 (t, $J = 7.5$ Hz, 2H, *Z*), 2.51 (t, $J = 7.7$ Hz, 2H, *E*), 2.03 – 1.92 (m, 2H, *Z*), 1.91 – 1.78 (m, 2H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.3 (s, *Z*), -63.7 (d, $J = 1.4$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.0 (q, $J = 2.0$ Hz), 163.9, 161.63, 161.59, 148.2 (q, $J = 2.8$ Hz), 141.1, 141.0, 140.3 (q, $J = 5.8$ Hz), 132.4 (q, $J = 2.8$ Hz), 131.7, 128.59, 128.56, 128.5, 126.18, 126.16, 124.74, 124.65, 122.7 (q, $J = 271.2$ Hz), 122.4 (q, $J = 272.2$ Hz), 120.8 (q, $J = 30.8$ Hz), 119.9 (q, $J = 32.1$ Hz), 114.2, 113.9, 65.11, 65.06, 55.46, 55.44, 32.2, 32.0, 30.2, 30.0. IR: 3028, 2959, 2842, 1724, 1604, 1513, 1400, 1308, 1280, 1260,

1201, 1173, 1157, 1122, 1028, 830, 699 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{20}\text{H}_{20}\text{F}_3\text{O}_3$ (m/z): 365.1365 $[\text{M}+\text{H}]^+$, found: 365.1357.

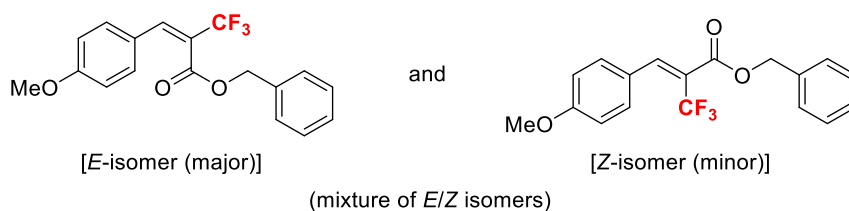


***n*-Heptyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-13b) and *n*-Heptyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-13b)**

According to general procedure VIII: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), 1-iodoheptane (0.8 mmol, 180.9 mg), Ag_2CO_3 (0.8 mmol, 220.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 $^\circ\text{C}$ for 4 h and then at 90 $^\circ\text{C}$ for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 100/1 to 80/1, v/v), affording compound **13b** in less than 71% yield (49.1 mg, not pure) as a yellow oil.

According to general procedure IX: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 $^\circ\text{C}$ for 1 h. Then 1-iodoheptane (0.4 mmol, 90.4 mg), Ag_2CO_3 (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 $^\circ\text{C}$ for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 120/1 to 80/1, v/v), affording compound **13b** in 66% yield (mixture of *E/Z* isomers (61/39), 45.6 mg) as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 7.99 (s, 1H, *Z*), 7.47 – 7.36 (m, 2H, *Z* + 2H, *E*), 7.35 – 7.28 (m, 1H, *E*), 6.96 – 6.85 (m, 2H, *Z* + 2H, *E*), 4.32 – 4.18 (m, 2H, *Z* + 2H, *E*), 3.84 (s, 3H, *Z*), 3.83 (s, 3H, *E*), 1.79 – 1.67 (m, 2H, *Z*), 1.67 – 1.55 (m, 2H, *E*), 1.48 – 1.14 (m, 8H, *Z* + 8H, *E*), 0.96 – 0.81 (m, 3H, *Z* + 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.5 (s, *Z*), -63.9 (d, $J = 1.4$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.1 – 164.0 (m), 164.0 – 163.9 (m), 161.6, 161.5, 148.0 (q, $J = 2.0$ Hz), 139.9 (q, $J = 5.8$ Hz), 132.4 (q, $J = 2.7$ Hz), 131.6, 124.8, 124.7, 122.6 (q, $J = 271.2$ Hz), 122.4 (q, $J = 272.2$ Hz), 121.0 (q, $J = 30.9$ Hz), 120.1 (q, $J = 32.1$ Hz), 114.1, 113.9, 66.10, 66.08, 55.46, 55.44, 31.82, 31.78, 29.0, 28.9, 28.6, 28.4, 25.9, 25.8, 22.70, 22.66, 14.17, 14.15. IR: 2958, 2931, 2859, 1725, 1605, 1513, 1279, 1260, 1227, 1202, 1174, 1158, 1126, 1030, 831 cm^{-1} . HRMS (CI-TOF): Calcd for $\text{C}_{18}\text{H}_{24}\text{F}_3\text{O}_3$ (m/z): 345.1678 $[\text{M}+\text{H}]^+$, found: 345.1683.

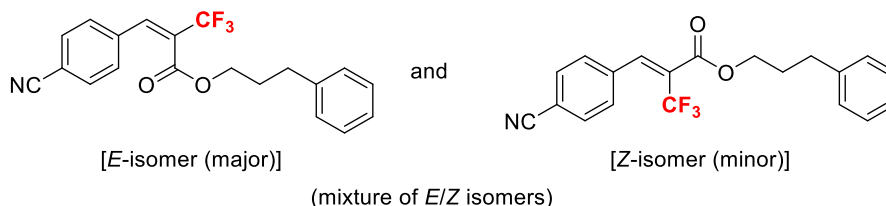


Benzyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**E-13c**) and Benzyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (**Z-13c**)

According to general procedure VIII: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), (iodomethyl)benzene (0.8 mmol, 174.4 mg), Ag₂CO₃ (0.8 mmol, 220.6 mg), and Pd(TFA)₂ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 °C for 4 h and then at 90 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 80/1 to 20/1, v/v), affording compound **13c** in 41% yield (mixture of *E/Z* isomers (68/32), 27.5 mg) as a yellow oil.

According to general procedure IX: 4-iodoanisole (0.2 mmol, 46.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. Then (iodomethyl)benzene (0.4 mmol, 90.4 mg), Ag₂CO₃ (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 °C for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 80/1 to 20/1, v/v), affording compound **13c** in 81% yield (mixture of *E/Z* isomers (67/33), 54.4 mg) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.05 (s, 1H, *Z*), 7.48 – 7.40 (m, 2H, *Z* + 2H, *E*), 7.40 – 7.27 (m, 5H, *Z* + 6H, *E*), 6.96 – 6.90 (m, 2H, *Z*), 6.81 – 6.75 (m, 2H, *E*), 5.34 (s, 2H, *Z*), 5.29 (s, 2H, *E*), 3.85 (s, 3H, *Z*), 3.82 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.3 (s, *Z*), -63.7 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.8 – 163.7 (m), 161.7, 161.5, 148.5 (q, *J* = 2.8 Hz), 140.4 (q, *J* = 5.8 Hz), 135.5, 134.8, 132.5 (q, *J* = 2.7 Hz), 131.7, 128.8, 128.7, 128.6, 128.5, 128.2, 124.7, 124.5, 122.6 (q, *J* = 271.2 Hz), 122.4 (q, *J* = 272.3 Hz), 120.6 (q, *J* = 31.0 Hz), 119.7 (q, *J* = 32.1 Hz), 114.1, 114.0, 67.6, 67.5, 55.45, 55.41. IR: 2918, 2846, 1724, 1604, 1513, 1280, 1260, 1199, 1157, 1118, 1026, 830, 696 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₈H₁₅O₃F₃Na (*m/z*): 359.0871 [M+Na]⁺, found: 359.0874.

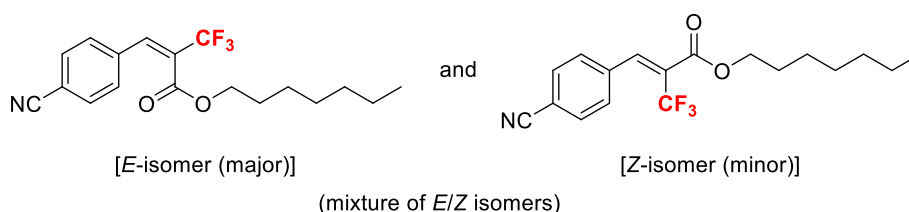


3-Phenylpropyl (E)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (E-13e) and 3-Phenylpropyl (Z)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (Z-13e)

According to general procedure VIII: 4-iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), (3-iodopropyl)benzene (0.8 mmol, 196.9 mg), Ag₂CO₃ (0.8 mmol, 220.6 mg), and Pd(TFA)₂ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 °C for 4 h and then at 90 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 10/1, v/v), and was subsequently washed with *n*-pentane (0.2 mL × 2), affording compound **13e** in 76% yield (mixture of *E/Z* isomers (62/38), 54.6 mg) as a yellow oil.

According to general procedure IX: 4-iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. Then (3-iodopropyl)benzene (0.4 mmol, 98.4 mg), Ag₂CO₃ (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 °C for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 10/1, v/v), affording compound **13e** in 79% yield (mixture of *E/Z* isomers (53/47), 56.7 mg) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.92 (s, 1H, Z), 7.67 – 7.53 (m, 2H, Z + 2H, E), 7.50 – 7.30 (m, 2H, Z + 3H, E), 7.27 – 7.15 (m, 2H, Z + 2H, E), 7.15 – 7.06 (m, 2H, Z + 2H, E), 7.01 (d, *J* = 6.9 Hz, 1H, Z + 1H, E), 4.25 (t, *J* = 6.5 Hz, 2H, Z), 4.11 (t, *J* = 6.5 Hz, 2H, E), 2.68 (t, *J* = 7.7 Hz, 2H, Z), 2.48 (t, *J* = 7.7 Hz, 2H, E), 2.08 – 1.92 (m, 2H, Z), 1.89 – 1.73 (m, 2H, E). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.3 (s, Z), -64.6 (d, *J* = 1.7 Hz, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 162.6 (q, *J* = 1.7 Hz), 162.4 – 162.2 (m), 145.8 (q, *J* = 3.0 Hz), 140.9, 140.6, 139.1 (q, *J* = 5.8 Hz), 137.3, 137.0, 132.3, 132.1, 129.5, 129.4 (q, *J* = 2.3 Hz), 128.61, 128.60, 128.5, 128.4, 126.5 (q, *J* = 31.5 Hz), 126.3, 126.2, 125.4 (q, *J* = 31.9 Hz), 121.7 (q, *J* = 272.0 Hz), 121.5 (q, *J* = 273.0 Hz), 118.2, 118.1, 113.7, 113.5, 65.8, 65.5, 32.2, 31.8, 30.0, 29.8. IR: 3028, 2959, 2924, 2860, 2232, 1728, 1650, 1498, 1455, 1397, 1274, 1224, 1206, 1162, 1133, 1018, 836, 746, 699, 554 cm⁻¹. HRMS (ES-TOF): Calcd for C₂₀H₁₇NO₂F₃ (*m/z*): 360.1211 [M+H]⁺, found: 360.1210.



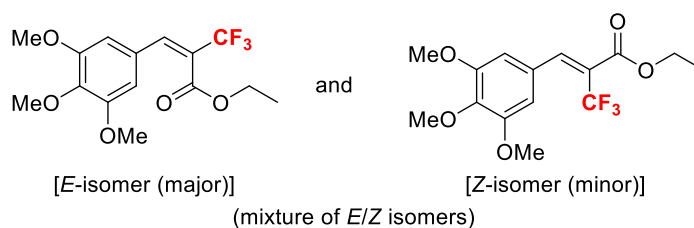
***n*-Heptyl (E)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (E-13f) and *n*-Heptyl (Z)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylate (Z-13f)**

According to general procedure VIII: 4-iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), 1-iodoheptane (0.8 mmol, 180.9

mg), Ag_2CO_3 (0.8 mmol, 220.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 °C for 4 h and then at 90 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 15/1, v/v), affording compound **13f** in 73% yield (mixture of *E/Z* isomers (66/34), 49.5 mg) as a yellow oil.

According to general procedure IX: 4-iodobenzonitrile (0.2 mmol, 45.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag_2CO_3 (0.22 mmol, 60.7 mg), and $\text{Pd}(\text{TFA})_2$ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 110 °C for 1 h. Then 1-iodoheptane (0.4 mmol, 90.4 mg), Ag_2CO_3 (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 °C for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 80/1 to 15/1, v/v), affording compound **13f** in 73% yield (mixture of *E/Z* isomers (53/47), 49.7 mg) as a yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 8.06 (s, 1H, *Z*), 7.73 – 7.62 (m, 2H, *Z* + 2H, *E*), 7.51 – 7.40 (m, 2H, *Z* + 3H, *E*), 4.30 (t, $J = 6.8$ Hz, 2H, *Z*), 4.17 (t, $J = 6.6$ Hz, 2H, *E*), 1.80 – 1.67 (m, 2H, *Z*), 1.60 – 1.47 (m, 2H, *E*), 1.46 – 1.08 (m, 8H, *Z* + 8H, *E*), 0.95 – 0.77 (m, 3H, *Z* + 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -64.8 (d, $J = 2.0$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.7 (q, $J = 1.7$ Hz), 162.5 – 162.4 (m), 145.6 (q, $J = 3.0$ Hz), 138.7 (q, $J = 5.8$ Hz), 137.4, 137.2, 132.3, 132.1, 129.5, 129.4 (q, $J = 2.4$ Hz), 126.7 (q, $J = 31.5$ Hz), 125.6 (q, $J = 31.9$ Hz), 121.7 (q, $J = 272.1$ Hz), 121.5 (q, $J = 273.0$ Hz), 118.2, 118.1, 113.7, 113.5, 66.7, 66.6, 31.75, 31.71, 28.9, 28.8, 28.5, 28.2, 25.8, 25.7, 22.64, 22.61, 14.12, 14.11. IR: 2958, 2927, 2858, 2232, 1729, 1650, 1466, 1379, 1275, 1223, 1207, 1163, 1136, 1017, 836, 555 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_2\text{F}_3$ (m/z): 340.1524 [$\text{M}+\text{H}$] $^+$, found: 340.1527.



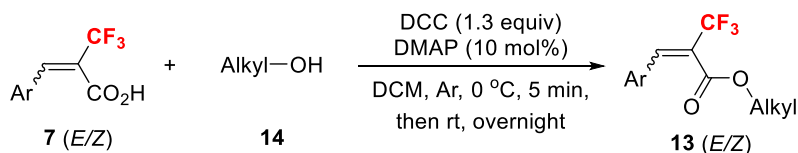
Ethyl (*E*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylate (**E-13g**) and Ethyl (*Z*)-2-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)acrylate (**Z-13g**)

According to general procedure VIII: 5-iodo-1,2,3-trimethoxybenzene (0.2 mmol, 58.8 mg), 2-(trifluoromethyl)acrylic acid (0.4 mmol, 56.0 mg), iodoethane (0.8 mmol, 124.8 mg), Ag_2CO_3 (0.8 mmol, 220.6 mg), and $\text{Pd}(\text{TFA})_2$ (0.02 mmol, 6.4 mg) in 1,4-dioxane (1.0 mL) were reacted at 50 °C for 4 h and then at 90 °C for 2 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 25/1 to 5/1, v/v), affording compound **13g** in 40% yield (mixture of *E/Z* isomers (71/29), 26.8 mg) as a yellow oil.

According to general procedure IX: 5-iodo-1,2,3-trimethoxybenzene (0.2 mmol, 58.8 mg), 2-(trifluoromethyl)acrylic acid (0.3 mmol, 42.0 mg), Ag₂CO₃ (0.22 mmol, 60.7 mg), and Pd(TFA)₂ (0.01 mmol, 3.2 mg) in 1,4-dioxane (0.5 mL) were reacted at 90 °C for 1 h. Then iodoethane (0.4 mmol, 62.4 mg), Ag₂CO₃ (0.3 mmol, 82.7 mg) were added at room temperature and stirred at 90 °C for 4 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 25/1 to 5/1, v/v), affording compound **13g** in 74% yield (mixture of *E/Z* isomers (72/28), 49.6 mg) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 7.96 (s, 1H, *Z*), 7.27 (q, *J* = 1.8 Hz, 1H, *E*), 6.67 (s, 2H, *E*), 6.65 (s, 2H, *Z*), 4.39 – 4.21 (m, 2H, *Z* + 2H, *E*), 3.90 – 3.80 (m, 9H, *Z* + 9H, *E*), 1.36 (t, *J* = 7.1 Hz, 3H, *Z*), 1.23 (t, *J* = 7.2 Hz, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, *Z*), -64.1 (d, *J* = 1.7 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 163.8 – 163.7 (m), 163.6 (q, *J* = 2.0 Hz), 153.2, 153.0, 148.0 (q, *J* = 3.0 Hz), 140.1, 140.0, 139.6 (q, *J* = 5.8 Hz), 127.7, 127.6, 123.1 (q, *J* = 31.2 Hz), 122.3 (q, *J* = 271.5 Hz), 122.04 (q, *J* = 272.5 Hz), 122.00 (q, *J* = 32.0 Hz), 107.3 (q, *J* = 2.7 Hz), 106.8, 62.13, 62.07, 61.0, 56.24, 56.21, 14.2, 13.9. IR: 2943, 2841, 1726, 1582, 1507, 1456, 1398, 1383, 1271, 1222, 1119, 1028, 1003, 930, 830 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₅H₁₈O₅F₃ (*m/z*): 335.1106 [M+H]⁺, found: 335.1101.

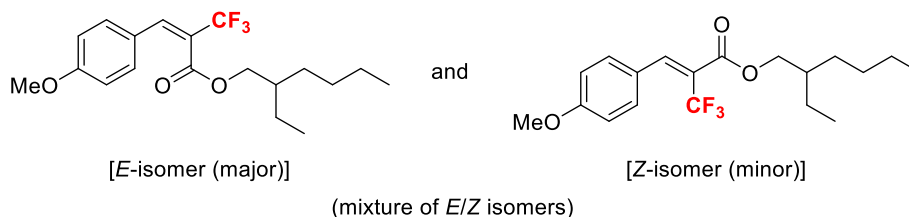
2.12 Synthesis of alkyl 3-aryl-2-(trifluoromethyl)acrylates (**13**) by esterification of 3-aryl-2-(trifluoromethyl)acrylic acids (**7**) with alkyl alcohols (**14**)



General procedure X: The synthetic method was according to a published paper.²²⁵ To a 10 mL oven-dried reaction tube were added 3-aryl-2-(trifluoromethyl)acrylic acid **7** (0.24 mmol, 1.2 equiv, mixture of *E/Z* isomers) and DMAP (0.02 mmol, 10 mol%). The tube was evacuated and filled with argon three times. Alkyl alcohol **14** (0.2 mmol, 1.0 equiv) and anhydrous CH₂Cl₂ (1 mL) were added. The reaction tube was cooled to 0 °C with an ice-water bath, and DCC (0.26 mmol, 1.3 equiv) was added quickly at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and then stirred at room temperature overnight. The reaction mixture was filtered with celite to remove the generated urea solid. The resulting CH₂Cl₂ solution (20 mL) was washed with 1.0 N aqueous HCl (10 mL) and saturated aqueous NaHCO₃ (10 mL), respectively. The organic phase was dried over anhydrous MgSO₄, evaporated under

²²⁵ B. Neises, W. Steglich, *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.

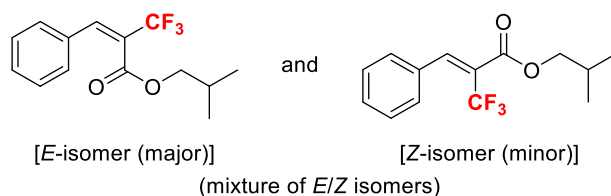
reduced pressure. The crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



2-Ethylhexyl (*E*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (*E*-13d) and 2-Ethylhexyl (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylate (*Z*-13d)

According to general procedure X: 2-Ethylhexan-1-ol (0.2 mmol, 26.0 mg), 3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (0.24 mmol, 59.1 mg, mixture of *E/Z* isomers (64/36)), DMAP (10 mol%, 2.4 mg), and DCC (0.26 mmol, 53.6 mg) in CH₂Cl₂ (1 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 60/1 to 20/1, v/v), affording compound **13d** in 92% yield (mixture of *E/Z* isomers (54/46), 65.6 mg) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 8.00 (s, 1H, *Z*), 7.47 – 7.37 (m, 2H, *Z* + 2H, *E*), 7.33 – 7.28 (m, 1H, *E*), 6.95 – 6.85 (m, 2H, *Z* + 2H, *E*), 4.21 (d, *J* = 5.7 Hz, 2H, *Z*), 4.15 (d, *J* = 5.7 Hz, 2H, *E*), 3.84 (s, 3H, *Z*), 3.83 (s, 3H, *E*), 1.74 – 1.61 (m, 1H, *Z*), 1.61 – 1.50 (m, 1H, *E*), 1.50 – 1.15 (m, 8H, *Z* + 8H, *E*), 0.99 – 0.76 (m, 6H, *Z* + 6H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.4 (s, *Z*), -63.8 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 164.2 (q, *J* = 2.0 Hz), 164.1 – 164.0 (m), 161.6, 161.5, 148.1 (q, *J* = 2.9 Hz), 140.0 (q, *J* = 5.8 Hz), 132.4 (q, *J* = 2.8 Hz), 131.6, 124.8, 124.7, 122.7 (q, *J* = 271.1 Hz), 122.4 (q, *J* = 272.2 Hz), 121.0 (q, *J* = 30.9 Hz), 120.1 (q, *J* = 32.1 Hz), 114.1, 113.9, 68.2, 68.1, 55.45, 55.42, 38.9, 38.7, 30.5, 30.3, 29.0, 28.9, 23.9, 23.6, 23.1, 23.0, 14.13, 14.09, 11.1, 11.0. IR: 2961, 2933, 2862, 1724, 1605, 1513, 1463, 1279, 1260, 1201, 1174, 1159, 1126, 1031, 831 cm⁻¹. HRMS (ES-TOF): Calcd for C₁₉H₂₅O₃F₃Na (*m/z*): 381.1653 [M+Na]⁺, found: 381.1649.



iso-butyl (*E*)-3-phenyl-2-(trifluoromethyl)acrylate (*E*-13h) and iso-butyl (*Z*)-3-phenyl-2-(trifluoromethyl)acrylate (*Z*-13h)

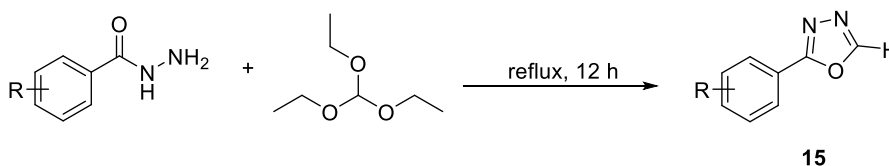
According to general procedure X: 2-Methylpropan-1-ol (0.2 mmol, 14.8 mg), 3-phenyl-2-(trifluoromethyl)acrylic acid (0.24 mmol, 51.8 mg, mixture of *E/Z* isomers (64/36)), DMAP (10 mol%, 2.4 mg), and DCC (0.26 mmol, 53.6 mg) in CH₂Cl₂ (1 mL). The crude was purified by silica gel column chromatography (petroleum

ether/EtOAc, from 80/1 to 50/1, v/v), affording compound **13h** in 76% yield (mixture of *E/Z* isomers (76/24), 41.5 mg) as a colorless oil.

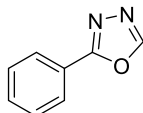
^1H NMR (300 MHz, CDCl_3): δ 8.11 (s, 1H, *Z*), 7.45 – 7.36 (m, 5H, *Z* + 6H, *E*), 4.10 (d, J = 6.6 Hz, 2H, *Z*), 3.98 (d, J = 6.6 Hz, 2H, *E*), 2.14 – 1.98 (m, 1H, *Z*), 1.97 – 1.78 (m, 1H, *E*), 1.01 (d, J = 6.6 Hz, 6H, *Z*), 0.83 (d, J = 6.9 Hz, 6H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.4 (s, *Z*), -64.4 (d, J = 1.4 Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 163.6 (q, J = 2.0 Hz), 163.6 – 163.5 (m), 148.4 (q, J = 3.0 Hz), 140.3 (q, J = 5.8 Hz), 132.8, 132.6, 130.3, 130.2, 129.4 (q, J = 2.4 Hz), 129.2, 128.7, 128.4, 123.9 (q, J = 31.1 Hz), 122.9 (q, J = 31.9 Hz), 122.3 (q, J = 271.4 Hz), 122.1 (q, J = 272.5 Hz), 72.14, 72.12, 27.9, 27.6, 19.1, 18.9. IR: 2965, 2876, 1728, 1645, 1386, 1278, 1225, 1202, 1160, 1128, 1018, 754, 693 cm^{-1} . HRMS (ES-TOF): Calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{F}_3\text{Na}$ (m/z): 295.0922 [$\text{M} + \text{Na}$] $^+$, found: 295.0921.

3. Palladium-catalysed oxidative decarboxylative cross-coupling of heteroarenes with CF_3 -acrylic acids

3.1 Preparation of 1,3,4-oxadiazole derivatives (15)



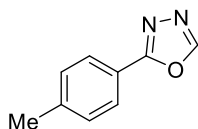
General procedure XI: The synthetic method was according to a published paper.²¹⁷ To a two-neck round-bottom flask were added hydrazide (1.0 equiv) and triethyl orthoformate (5.3 equiv). The reaction mixture was refluxing for 12 hours and then the formed ethanol and residual triethyl orthoformate were removed under reduced pressure. The crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



2-Phenyl-1,3,4-oxadiazole (15a)

According to general procedure XI: Benzohydrazide (73.4 mmol, 10 g) and triethyl orthoformate (389 mmol, 65 mL) were refluxing for 12 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 9/1 to 4/1, v/v), affording compound **15a** in 66% yield (7.09 g) as colorless solid-liquid mixture.

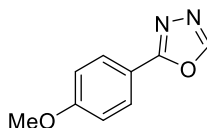
^1H NMR (300 MHz, CDCl_3): δ 8.47 (s, 1H), 8.18 – 7.95 (m, 2H), 7.64 – 7.40 (m, 3H). The analytical data of **15a** were in agreement with those reported in the literature.²¹⁷



2-(*p*-Tolyl)-1,3,4-oxadiazole (**15b**)

According to general procedure XI: 4-Methylbenzohydrazide (30 mmol, 4.51 g) and triethyl orthoformate (159 mmol, 26.4 mL) were refluxing for 12 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 9/1 to 4/1, v/v), affording compound **15b** in 71% yield (3.43 g) as white solid.

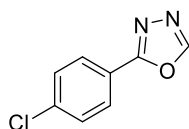
^1H NMR (300 MHz, CDCl_3): δ 8.44 (s, 1H), 7.96 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 2.42 (s, 3H). The analytical data of **15b** were in agreement with those reported in the literature.²¹⁷



2-(4-Methoxyphenyl)-1,3,4-oxadiazole (**15c**)

According to general procedure XI: 4-Methoxybenzohydrazide (10 mmol, 1.66 g) and triethyl orthoformate (53 mmol, 8.8 mL) were refluxing for 12 h. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 5/1 to 2/1, v/v), affording compound **15c** in 84% yield (1.48 g) as white solid.

^1H NMR (300 MHz, CDCl_3): δ 8.41 (s, 1H), 8.00 (d, $J = 9.0$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 3.87 (s, 3H). The analytical data of **15c** were in agreement with those reported in the literature.²¹⁷



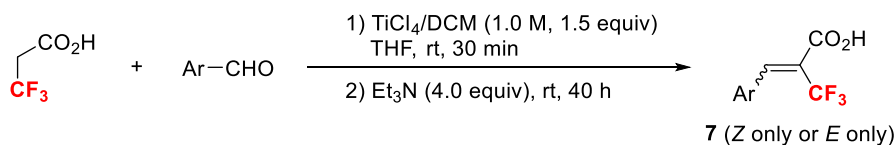
2-(4-Chlorophenyl)-1,3,4-oxadiazole (**15d**)

According to general procedure XI: 4-Chlorobenzohydrazide (10 mmol, 1.71 g) and triethyl orthoformate (53 mmol, 8.8 mL). The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 5/1 to 3/1, v/v), affording compound **15d** in 97% yield (1.75 g) as white solid.

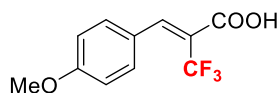
^1H NMR (300 MHz, CDCl_3): δ 8.48 (s, 1H), 8.01 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.7$ Hz, 2H). The analytical data of **15d** were in agreement with those reported in the literature.²²⁶

²²⁶ T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900–6901.

3.2 Preparation of (Z)- or (E)-3-aryl-2-(trifluoromethyl)acrylic acids (7)



General procedure XII: The synthetic method was according to a published paper.¹⁹⁸ To a stirred solution of 3,3,3-trifluoropropionic acid (10 mmol, 1.0 equiv), aryl aldehyde (15 mmol, 1.5 equiv) in anhydrous THF (50 mL) was added TiCl₄/CH₂Cl₂ (1.0 M, 15 mmol, 15 mL, 1.5 equiv) at room temperature. The mixture was vigorously stirred for 0.5 h, followed by adding dropwise Et₃N (40 mmol, 5.6 mL, 4.0 equiv). After being further stirred for 40 h at room temperature, the reaction was quenched by adding water (40 mL), and the obtained mixture was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phase was dried over anhydrous MgSO₄, followed by concentration under reduced pressure. The crude was firstly purified by silica gel column chromatography (TLC: CH₂Cl₂/MeOH (AcOH), 20/1 (1%), v/v (v)) to give the initially purified product as a solid. The solid was further purified by recrystallization from CH₂Cl₂/*n*-pentane or EtOAc/*n*-pentane to give the pure (Z)- or (E)-product.



(Z)-3-(4-Methoxyphenyl)-2-(trifluoromethyl)acrylic acid (Z-7a)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 4-methoxybenzaldehyde (15 mmol, 2.04 g), TiCl₄/CH₂Cl₂ (1.0 M, 15 mmol, 15 mL), Et₃N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH, from 50/1 to 15/1, v/v) to give the initially purified product (2.59 g) as an orange solid. The solid was further purified by recrystallization with CH₂Cl₂/*n*-pentane, and the white crystal of **Z-7a** was obtained in 52% yield (1.27 g, Z only, determined by ¹⁹F NMR spectrum).

¹H NMR (300 MHz, CDCl₃): δ 11.77 (s, 1H), 8.17 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s). The analytical data of **Z-7a** were in agreement with those reported in the literature.¹⁹⁸

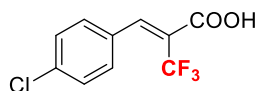


(Z)-3-Phenyl-2-(trifluoromethyl)acrylic acid (Z-7c)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), benzaldehyde (15 mmol, 1.59 g), TiCl₄/CH₂Cl₂ (1.0 M, 15 mmol, 15 mL), Et₃N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.1%) to 50/1 (0.1%),

v/v (v)) to give the initially purified product (2.09 g) as an orange solid. The solid was further purified by recrystallization with CH₂Cl₂/*n*-pentane, and the white crystal of **Z-7c** was obtained in 44% yield (958 mg, *Z* only, determined by ¹⁹F NMR spectrum).

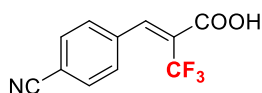
¹H NMR (300 MHz, CDCl₃): δ 11.72 (s, 1H), 8.28 (s, 1H), 7.44 (s, 5H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s). The analytical data of **Z-7c** were in agreement with those reported in the literature.¹⁹⁷⁻¹⁹⁸



(Z)-3-(4-Chlorophenyl)-2-(trifluoromethyl)acrylic acid (Z-7d)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 4-chlorobenzaldehyde (15 mmol, 2.11 g), TiCl₄/CH₂Cl₂ (1.0 M, 15 mmol, 15 mL), Et₃N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.1%) to 30/1 (0.1%), v/v (v)) to give the initially purified product (2.52 g) as a yellow solid. The solid was further purified by recrystallization with CH₂Cl₂/*n*-pentane, and the white crystal of **Z-7d** was obtained in 55% yield (1.39 g, *Z* only, determined by ¹⁹F NMR spectrum).

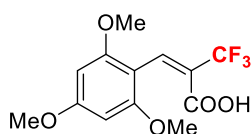
¹H NMR (300 MHz, CDCl₃): δ 11.18 (s, 1H), 8.19 (s, 1H), 7.45 – 7.35 (m, 4H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.7 (s). The analytical data of **Z-7d** were in agreement with those reported in the literature.¹⁹⁷



(Z)-3-(4-Cyanophenyl)-2-(trifluoromethyl)acrylic acid (Z-7h)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 4-cyanobenzaldehyde (15 mmol, 1.97 g), TiCl₄/CH₂Cl₂ (1.0 M, 15 mmol, 15 mL), Et₃N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography (CH₂Cl₂/MeOH (AcOH), from 100/1 (0.2%) to 30/1 (0.5%), v/v (v)) to give the initially purified product (2.29 g) as a gray solid. The solid was further purified by recrystallization with CH₂Cl₂/*n*-pentane, and the colorless crystal of **Z-7h** was obtained in 51% yield (1.22 g, *Z* only, determined by ¹⁹F NMR spectrum).

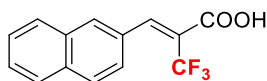
¹H NMR (300 MHz, CD₃OD): 8.23 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H). ¹⁹F NMR (282 MHz, CD₃OD): δ -59.4 (s). The analytical data of **Z-7h** were in agreement with those reported in the literature.²¹¹



(E)-2-(Trifluoromethyl)-3-(2,4,6-trimethoxyphenyl)acrylic acid (E-7s)

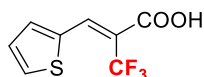
According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 2,4,6-trimethoxybenzaldehyde (15 mmol, 2.94 g), $\text{TiCl}_4/\text{CH}_2\text{Cl}_2$ (1.0 M, 15 mmol, 15 mL), Et_3N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.1%) to 20/1 (0.1%), v/v (v)) to give the initially purified product (2.95 g) as a black solid. Acidic-basic extraction was done to remove the black stuff. K_2CO_3 (15 mmol, 2.07 g) was dissolved in water (20 mL) and was added dropwise to the CH_2Cl_2 (20 mL) solution of the black solid. The two phase mixture was stirred at room temperature for 36 h. After separation of the two phase, the basic aqueous phase was extracted with CH_2Cl_2 (2×20 mL) and was then acidified to pH 1 with 1 N HCl. The acidic aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over anhydrous MgSO_4 , and then solvent was removed under reduced pressure. Yellow solid (2.08 g) was obtained, but 5% fluorinated impurity was involved. The solid was further purified by recrystallization with EtOAc/n -pentane, and the yellow crystal of **E-7s** was obtained in 35% yield (1.07 g, *E* only, determined by ^{19}F NMR spectrum).

Mp 196 °C (or decomposition). ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$): δ 12.93 (s, 1H), 7.27 (q, $J = 1.9$ Hz, 1H), 6.26 (s, 2H), 3.82 (s, 3H), 3.76 (s, 6H). ^{19}F NMR (282 MHz, $(\text{CD}_3)_2\text{SO}$): δ -62.0 (d, $J = 1.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$): δ 164.4, 163.2, 159.1, 131.5 (q, $J = 6.4$ Hz), 123.3 (q, $J = 270.6$ Hz), 121.8 (q, $J = 28.5$ Hz), 103.3, 90.8, 55.6, 55.5. IR: 3012, 2947, 2847, 1699, 1627, 1607, 1582, 1459, 1433, 1287, 1258, 1229, 1209, 1149, 1124, 1019, 1010, 812 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{O}_5$ (m/z): 306.0715 [M] $^+$, found: 306.0703.

**(Z)-3-(Naphthalen-2-yl)-2-(trifluoromethyl)acrylic acid (Z-7t)**

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 2-naphthaldehyde (15 mmol, 2.34 g), $\text{TiCl}_4/\text{CH}_2\text{Cl}_2$ (1.0 M, 15 mmol, 15 mL), Et_3N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.1%) to 20/1 (0.1%), v/v (v)) to give the initially purified product (2.71 g) as a yellow solid. The solid was further purified by recrystallization with EtOAc/n -pentane, and the yellow crystal of **Z-7t** was obtained in 49% yield (1.30 g, *Z* only, determined by ^{19}F NMR spectrum).

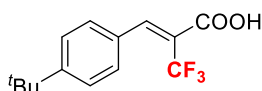
^1H NMR (300 MHz, CD_3OD): δ 8.34 (s, 1H), 7.97 – 7.84 (m, 4H), 7.61 – 7.46 (m, 3H). ^{19}F NMR (282 MHz, CD_3OD): δ -59.2 (s). The analytical data of **Z-7t** were in agreement with those reported in the literature.¹⁹⁷



(Z)-3-(Thiophen-2-yl)-2-(trifluoromethyl)acrylic acid (**Z-7w**)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 2-thiophenecarboxaldehyde (15 mmol, 1.68 g), $\text{TiCl}_4/\text{CH}_2\text{Cl}_2$ (1.0 M, 15 mmol, 15 mL), Et_3N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.1%) to 20/1 (0.1%), v/v (v)) to give the initially purified product (2.22 g) as a brown solid. The solid was further purified by recrystallization with EtOAc/n -pentane, and the yellow crystal of **Z-7w** was obtained in 36% yield (808 mg, *Z* only, determined by ^{19}F NMR spectrum).

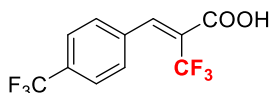
^1H NMR (300 MHz, CDCl_3): δ 8.26 (s, 1H), 7.76 (d, $J = 5.1$ Hz, 1H), 7.59 (d, $J = 3.9$ Hz, 1H), 7.21 – 7.13 (m, 1H). ^{19}F NMR (282 MHz, CDCl_3): δ -59.1 (s). The analytical data of **Z-7w** were in agreement with those reported in the literature.¹⁹⁷



(Z)-3-(4-(*tert*-Butyl)phenyl)-2-(trifluoromethyl)acrylic acid (**Z-7x**)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 4-(*tert*-butyl)benzaldehyde (15 mmol, 2.43 g), $\text{TiCl}_4/\text{CH}_2\text{Cl}_2$ (1.0 M, 15 mmol, 15 mL), Et_3N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.1%) to 20/1 (0.1%), v/v (v)) to give the initially purified product (3.04 g) as an orange solid. The solid was further purified by recrystallization with $\text{CH}_2\text{Cl}_2/n$ -pentane, and the pale-yellow crystal of **Z-7x** was obtained in 40% yield (1.08 g, *Z* only, determined by ^{19}F NMR spectrum).

^1H NMR (300 MHz, CDCl_3): δ 11.94 (s, 1H), 8.24 (s, 1H), 7.53 – 7.36 (m, 4H), 1.35 (s, 9H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.7 (s). The analytical data of **Z-7x** were in agreement with those reported in the literature.¹⁹⁸



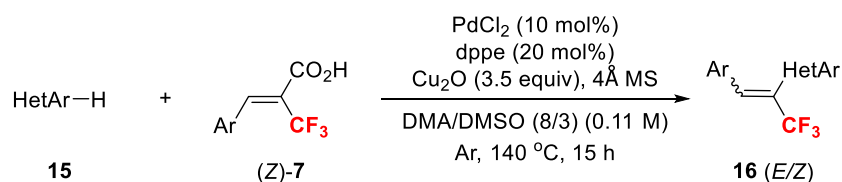
(Z)-2-(Trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)acrylic acid (**Z-7y**)

According to general procedure XII: 3,3,3-Trifluoropropionic acid (10 mmol, 1.28 g), 4-(trifluoromethyl)benzaldehyde (15 mmol, 2.61 g), $\text{TiCl}_4/\text{CH}_2\text{Cl}_2$ (1.0 M, 15 mmol, 15 mL), Et_3N (40 mmol, 5.6 mL), and anhydrous THF (50 mL). The crude was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ (AcOH), from 100/1 (0.1%) to 30/1 (0.2%), v/v (v)) to give the initially purified product (2.81 g) as a yellow solid. The

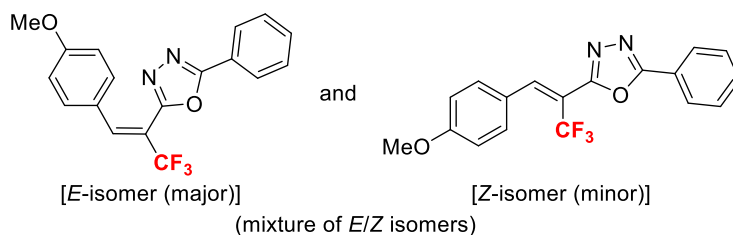
solid was further purified by recrystallization with $\text{CH}_2\text{Cl}_2/n$ -pentane, and the white crystal of **Z-7y** was obtained in 50% yield (1.41 g, *Z* only, determined by ^{19}F NMR spectrum).

Mp 114 °C. ^1H NMR (300 MHz, CDCl_3): δ 12.22 (s, 1H), 8.29 (s, 1H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.52 (d, $J = 8.1$ Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.7 (s), -63.6 (s). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 168.5 (q, $J = 1.9$ Hz), 149.1 (q, $J = 2.8$ Hz), 135.9 (q, $J = 1.5$ Hz), 132.3 (q, $J = 32.7$ Hz), 129.5 (q, $J = 2.3$ Hz), 125.5 (q, $J = 3.8$ Hz), 123.81 (q, $J = 270.7$ Hz), 123.77 (q, $J = 32.2$ Hz), 121.5 (q, $J = 273.0$ Hz). IR: 2847, 2647, 2541, 1712, 1646, 1435, 1387, 1320, 1302, 1224, 1168, 1131, 1113, 1067, 1028, 1019, 926, 862 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{11}\text{H}_6\text{F}_6\text{O}_2$ (m/z): 284.0272 [M] $^+$, found: 284.0261.

3.3 Palladium-catalysed oxidative decarboxylative cross-coupling of heteroarenes (**15**) with (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acids (**7**)



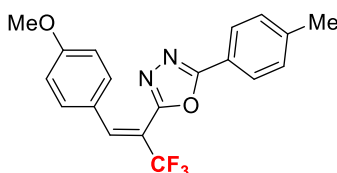
General procedure XIII: A heating gun-dried reaction tube (20 mL) was evacuated and filled with argon three times. The tube was put into the glove box and was added activated 4Å molecular sieves (100 mg/0.1 mmol of **15**). After being removed from the glove box, the reaction tube was charged with heteroarene **15** (0.2 mmol, 1.0 equiv), (*Z*)-3-aryl-2-(trifluoromethyl)acrylic acid **7** (0.4 mmol, 2.0 equiv), PdCl_2 (0.02 mmol, 10 mol%), dppe (1,2-bis(diphenylphosphino)ethane, 0.04 mmol, 20 mol%), and Cu_2O (0.7 mmol, 3.5 equiv). The tube was carefully evacuated and filled with argon three times. Anhydrous DMA (1.3 mL) and DMSO (0.5 mL) were added and the reaction tube was sealed. The reaction mixture was stirred at 140 °C for 15 h and then cooled to room temperature. The reaction mixture was filtered through celite with EtOAc (30 mL), and the resulting organic phase was washed with brine (2 × 10 mL). The organic phase was dried over anhydrous MgSO_4 , and the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc).



(E)-2-Phenyl-5-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (E-16a) and **(Z)-2-Phenyl-5-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (Z-16a)**

According to general procedure XIII: 2-Phenyl-1,3,4-oxadiazole (0.2 mmol, 29.2 mg), (Z)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 98.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 91/9. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v), affording compound **16a** in 46% yield (*E/Z* = 92/8, 32.1 mg) as pale-yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 8.10 (dd, *J* = 7.8, 1.5 Hz, 2H, *Z*), 8.05 (s, 1H, *Z*), 8.01 (dd, *J* = 8.1, 1.2 Hz, 2H, *E*), 7.63 (s, 1H, *E*), 7.59 – 7.44 (m, 5H, *Z* + 3H, *E*), 7.37 (d, *J* = 8.7 Hz, 2H, *E*), 6.96 (d, *J* = 8.7 Hz, 2H, *Z*), 6.86 (d, *J* = 8.7 Hz, 2H, *E*), 3.87 (s, 3H, *Z*), 3.81 (s, 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, *Z*), -64.1 (s, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.4, 162.1, 158.6, 142.5 (q, *J* = 5.3 Hz), 132.3, 132.2, 129.2, 127.2, 124.2, 123.4, 122.6 (q, *J* = 271.5 Hz), 114.4, 111.6 (q, *J* = 32.7 Hz), 55.5 (only showed the data for *E* isomer, because *Z* isomer was very little and many peaks were not observed). IR: 2935, 2841, 1603, 1549, 1513, 1280, 1263, 1164, 1129, 1104, 1019, 923, 909, 831 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₈H₁₂F₃N₂O₂ (*m/z*): 345.0851 [M-H]⁺, found: 345.0854.

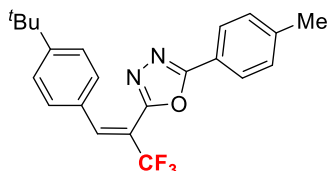


(E)-2-(p-Tolyl)-5-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (E-16b)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (Z)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 98.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 91/9. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v), affording compound **16b** in 48% yield (*E/Z* > 99/1, 34.6 mg) as off-white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.61 (q, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 2.42 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, *Z*), -64.1 (d, *J* = 1.4 Hz, *E*). ¹³C{¹H} NMR (75

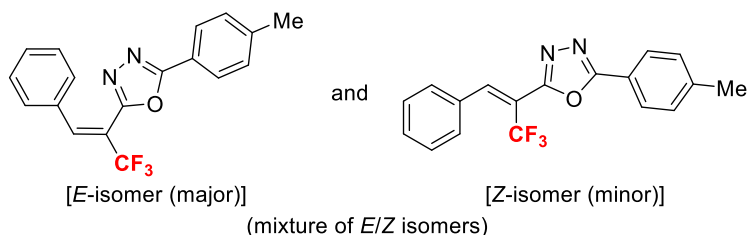
MHz, CDCl₃): δ 165.6, 162.0, 158.3, 142.9, 142.3 (q, $J = 5.3$ Hz), 132.2, 129.9, 127.2, 124.2, 122.6 (q, $J = 271.5$ Hz), 120.6, 114.3, 111.7 (q, $J = 32.7$ Hz), 55.5, 21.7. IR: 3012, 2918, 2847, 1637, 1606, 1553, 1515, 1498, 1320, 1282, 1266, 1163, 1104, 1026, 1015, 954, 937, 924, 829 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₉H₁₄F₃N₂O₂ (m/z): 359.1007 [M-H]⁺, found: 359.1000.



(E)-2-(1-(4-(tert-Butyl)phenyl)-3,3,3-trifluoroprop-1-en-2-yl)-5-(p-tolyl)-1,3,4-oxadiazole (E-16c)

According to general procedure XIII: 2-(p-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (Z)-3-(4-(tert-butyl)phenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 108.9 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the E/Z ratio of the product was 92/8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 40/1 to 20/1, v/v), affording compound **16c** in 31% yield (E/Z = 99/1, 24.2 mg) as white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.74 (d, $J = 8.1$ Hz, 2H), 7.62 (s, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.26 – 7.13 (m, 4H), 2.33 (s, 3H), 1.23 (s, 9H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, Z), -64.5 (d, $J = 0.8$ Hz, E). ¹³C{¹H} NMR (75 MHz, CDCl₃): 165.5, 158.1, 154.7, 142.9, 142.7 (q, $J = 5.2$ Hz), 129.9, 129.7, 129.2, 127.2, 125.9, 122.4 (q, $J = 271.8$ Hz), 120.6, 114.0 (q, $J = 32.8$ Hz), 35.1, 31.2, 21.8. IR: 2965, 2871, 1639, 1614, 1496, 1320, 1297, 1281, 1158, 1137, 1107, 1017, 943, 906, 839, 829, 726 cm⁻¹. HRMS (EI-TOF): Calcd for C₂₂H₂₀F₃N₂O (m/z): 385.1528 [M-H]⁺, found: 385.1515.

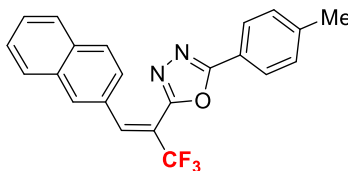


(E)-2-(p-Tolyl)-5-(3,3,3-trifluoro-1-phenylprop-1-en-2-yl)-1,3,4-oxadiazole (E-16d)
and **(Z)-2-(p-Tolyl)-5-(3,3,3-trifluoro-1-phenylprop-1-en-2-yl)-1,3,4-oxadiazole (Z-16d)**

According to general procedure XIII: 2-(p-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (Z)-3-phenyl-2-(trifluoromethyl)acrylic acid (0.4 mmol, 86.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å

molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 90/10. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v), affording compound **16d** in 39% yield (*E/Z* = 92/8, 25.8 mg) as off-white solid.

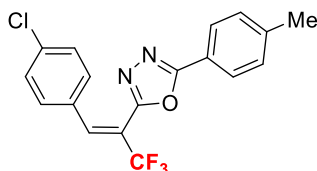
^1H NMR (300 MHz, CDCl_3): δ 8.07 (s, 1H, *Z*), 7.92 (d, $J = 7.8$ Hz, 2H, *Z*), 7.72 (d, $J = 8.1$ Hz, 2H, *E*), 7.65 (s, 1H, *E*), 7.45 – 7.23 (m, 7H, *Z* + 5H, *E*), 7.19 (d, $J = 7.8$ Hz, 2H, *E*), 2.36 (s, 3H, *Z*), 2.33 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.2 (s, *Z*), -64.7 (s, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 165.6, 157.9, 143.0, 142.8 (q, $J = 5.3$ Hz), 132.1, 130.9, 129.9, 129.6, 128.9, 127.2, 122.3 (q, $J = 271.9$ Hz), 120.5, 115.1 (q, $J = 32.8$ Hz), 21.8 (only showed the data for *E* isomer, because *Z* isomer was very little and many peaks were not observed). IR: 3024, 2924, 1642, 1615, 1496, 1295, 1278, 1222, 1163, 1130, 1016, 987, 951, 922, 823, 750 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{18}\text{H}_{12}\text{F}_3\text{N}_2\text{O}$ (m/z): 329.0902 [M-H] $^+$, found: 329.0902.



(*E*)-2-(*p*-Tolyl)-5-(3,3,3-trifluoro-1-(naphthalen-2-yl)prop-1-en-2-yl)-1,3,4-oxadiazole (*E*-16e)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (*Z*)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 106.5 mg), PdCl_2 (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu_2O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 88/12. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v), affording compound **16e** in 40% yield (*E/Z* > 99/1, 30.4 mg) as pale-yellow solid.

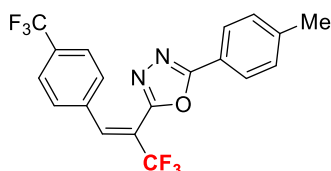
^1H NMR (300 MHz, CDCl_3): δ 7.98 (s, 1H), 7.88 (s, 1H), 7.85 – 7.72 (m, 5H), 7.60 – 7.47 (m, 2H), 7.31 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.23 (d, $J = 7.8$ Hz, 2H), 2.39 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -64.5 (d, $J = 1.1$ Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 165.7, 158.1, 143.0, 142.7 (q, $J = 5.3$ Hz), 134.2, 132.9, 131.5, 129.9, 129.4, 128.8, 128.6, 128.0, 127.9, 127.2, 127.0, 125.3, 122.4 (q, $J = 271.6$ Hz), 120.5, 114.8 (q, $J = 32.8$ Hz), 21.8. IR: 3065, 2924, 2853, 1657, 1614, 1494, 1288, 1223, 1188, 1165, 1121, 1086, 1013, 943, 825, 812, 749 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{22}\text{H}_{14}\text{F}_3\text{N}_2\text{O}$ (m/z): 379.1058 [M-H] $^+$, found: 379.1044.



(E)-2-(1-(4-Chlorophenyl)-3,3,3-trifluoroprop-1-en-2-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole (E-16f)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (*Z*)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 100.2 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 92/8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 20/1, v/v), affording compound **16f** in 27% yield (*E* only, 19.5 mg) as white solid.

Mp 115 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.67 (q, *J* = 1.7 Hz, 1H), 7.35 (s, 4H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -64.7 (d, *J* = 1.1 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.7, 157.7, 143.2, 141.3 (q, *J* = 5.4 Hz), 137.2, 131.0, 130.4, 130.0, 129.2, 127.2, 122.2 (q, *J* = 272.1 Hz), 120.3, 115.6 (q, *J* = 32.9 Hz), 21.8. IR: 3024, 2924, 2859, 1643, 1497, 1488, 1400, 1313, 1292, 1273, 1220, 1163, 1133, 1086, 1018, 940, 823, 750 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₈H₁₁³⁵ClF₃N₂O (*m/z*): 363.0512 [M-H]⁺, found: 363.0508.

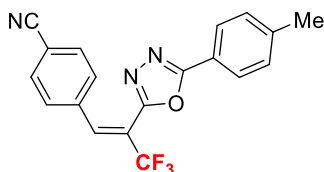


(E)-2-(*p*-Tolyl)-5-(3,3,3-trifluoro-1-(4-(trifluoromethyl)phenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (E-16g)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (*Z*)-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)acrylic acid (0.4 mmol, 113.7 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 89/11. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 20/1, v/v), and the resulting impure product was washed with *n*-pentane (2 × 0.2 mL), affording compound **16g** in 25% yield (*E* only, 20.1 mg) as white solid.

Mp 152 °C. ¹H NMR (300 MHz, CDCl₃): 7.71 (s, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 2.34 (s, 3H). ¹⁹F NMR (282

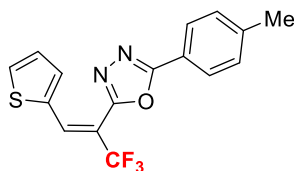
MHz, CDCl₃): δ -63.5 (s, phenyl-CF₃), -64.9 (d, J = 0.8 Hz, vinyl-CF₃, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.7, 157.4, 143.3, 140.8 (q, J = 5.3 Hz), 135.9 (q, J = 1.4 Hz), 132.3 (q, J = 32.7 Hz), 130.0, 129.7, 127.2, 125.8 (q, J = 3.7 Hz), 123.7 (q, J = 270.8 Hz), 121.9 (q, J = 272.4 Hz), 120.2, 117.8 (q, J = 33.0 Hz), 21.8. IR: 2929, 1653, 1614, 1553, 1495, 1410, 1322, 1281, 1167, 1125, 1065, 1019, 946, 893, 826, 719 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₉H₁₁F₆N₂O (m/z): 397.0776 [M-H]⁺, found: 397.0772.



(*E*)-4-(3,3,3-Trifluoro-2-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)prop-1-en-1-yl)benzonitrile (*E*-16h)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (*Z*)-3-(4-cyanophenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 96.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that only *E* isomer was obtained. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 10/1, v/v), affording compound **16h** in 16% yield (*E/Z* = 99/1, 11.1 mg) as white solid.

¹H NMR (300 MHz, CDCl₃): δ 7.79 (d, J = 8.4 Hz, 2H), 7.74 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.2 (s, *Z*), -65.0 (d, J = 1.1 Hz, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 165.8, 157.2, 143.5, 140.2 (q, J = 5.4 Hz), 136.6, 132.5, 130.1, 127.2, 121.8 (q, J = 272.7 Hz), 120.1, 118.3 (q, J = 33.1 Hz), 118.1, 114.2, 21.8. IR: 3106, 3029, 2924, 2853, 2230, 1614, 1559, 1496, 1402, 1316, 1294, 1276, 1222, 1163, 1135, 1088, 1018, 947, 850, 835, 821, 750 cm⁻¹. HRMS (EI-TOF): Calcd for C₁₉H₁₁F₃N₃O (m/z): 354.0854 [M-H]⁺, found: 354.0843.

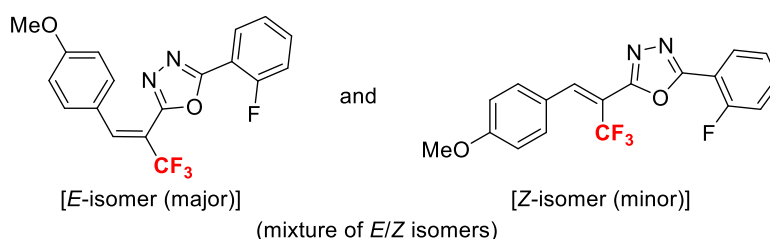


(*E*)-2-(*p*-Tolyl)-5-(3,3,3-trifluoro-1-(thiophen-2-yl)prop-1-en-2-yl)-1,3,4-oxadiazole (*E*-16i)

According to general procedure XIII: 2-(*p*-Tolyl)-1,3,4-oxadiazole (0.2 mmol, 32.0 mg), (*Z*)-3-(thiophen-2-yl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 88.9 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 92/8. The

crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 20/1 to 15/1, v/v), affording compound **16i** in 43% yield (*E/Z* = 99/1, 28.7 mg) as yellow solid.

^1H NMR (300 MHz, CDCl_3): δ 8.01 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 2.44 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -59.1 (s, *Z*), -63.7 (d, J = 0.8 Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 165.9, 157.7, 143.0, 136.9, 134.9, 134.6 (q, J = 5.6 Hz), 133.2, 130.0, 127.7, 127.3, 122.7 (q, J = 271.2 Hz), 120.6, 109.5 (q, J = 33.1 Hz), 21.8. IR: 3100, 2924, 1620, 1551, 1496, 1415, 1285, 1264, 1213, 1145, 1116, 1064, 1035, 931, 912, 820, 739 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{N}_2\text{OS}$ (m/z): 335.0466 $[\text{M}-\text{H}]^+$, found: 335.0480.

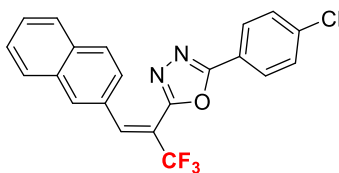


(*E*)-2-(2-Fluorophenyl)-5-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (*E*-16j) and (*Z*)-2-(2-Fluorophenyl)-5-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)-1,3,4-oxadiazole (*Z*-16j)

According to general procedure XIII: 2-(2-Fluorophenyl)-1,3,4-oxadiazole (0.2 mmol, 32.8 mg), (*Z*)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 98.5 mg), PdCl_2 (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu_2O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 91/9. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 10/1 to 7/1, v/v), affording compound **16j** in 36% yield (*E/Z* = 91/9, 26.0 mg) as pale-yellow solid.

^1H NMR (300 MHz, CDCl_3): δ 8.07 – 8.00 (m, 1H, *Z*), 7.98 (s, 1H, *Z*), 7.97 – 7.85 (m, 1H, *E*), 7.56 (s, 1H, *E*), 7.53 – 7.41 (m, 3H, *Z* + 1H, *E*), 7.31 (d, J = 8.7 Hz, 2H, *E*), 7.26 – 7.09 (m, 2H, *Z* + 2H, *E*), 6.88 (d, J = 9.0 Hz, 2H, *Z*), 6.78 (d, J = 8.7 Hz, 2H, *E*), 3.79 (s, 3H, *Z*), 3.74 (s, 3H, *E*). ^{19}F NMR (282 MHz, CDCl_3): δ -58.2 (s, CF_3 , *Z*), -64.1 (d, J = 0.8 Hz, CF_3 , *E*), -109.6 to -109.7 (m, F, *E*), -110.2 to -110.3 (m, F, *Z*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 162.3 (d, J = 5.1 Hz), 162.1, 160.3 (d, J = 257.9 Hz), 158.9, 142.8 (q, J = 5.2 Hz), 134.1 (d, J = 8.5 Hz), 132.3, 130.0 (d, J = 1.1 Hz), 124.8 (d, J = 3.8 Hz), 124.1, 122.6 (q, J = 271.6 Hz), 117.2 (d, J = 20.6 Hz), 114.4, 112.0 (d, J = 11.6 Hz), 111.4 (q, J = 32.7 Hz), 55.5 (only showed the data for *E* isomer, because *Z* isomer was very little and many peaks were not observed). IR: 2924, 2853, 1602, 1574, 1512, 1466, 1427, 1320,

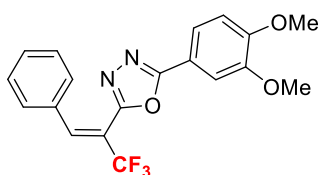
1283, 1266, 1225, 1169, 1156, 1101, 1028, 1016, 943, 831, 768, 758 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{18}\text{H}_{11}\text{F}_4\text{N}_2\text{O}_2$ (m/z): 363.0757 $[\text{M}-\text{H}]^+$, found: 363.0771.



(E)-2-(4-Chlorophenyl)-5-(3,3,3-trifluoro-1-(naphthalen-2-yl)prop-1-en-2-yl)-1,3,4-oxadiazole (E-16k)

According to general procedure XIII: 2-(4-Chlorophenyl)-1,3,4-oxadiazole (0.2 mmol, 36.1 mg), (Z)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 106.5 mg), PdCl_2 (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu_2O (0.7 mmol, 100.2 mg), 4 Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 93/7. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 30/1 to 20/1, v/v), affording compound **16k** in 27% yield (*E* only, 21.8 mg) as white solid.

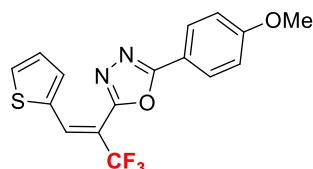
Mp 110 °C. ^1H NMR (300 MHz, CDCl_3): δ 7.98 (s, 1H), 7.91 (s, 1H), 7.88 – 7.72 (m, 5H), 7.61 – 7.48 (m, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.7, 1.8 Hz, 1H). ^{19}F NMR (282 MHz, CDCl_3): δ -64.4 (d, J = 0.8 Hz, *E*). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 164.7, 158.5, 143.2 (q, J = 5.3 Hz), 138.7, 134.3, 132.9, 131.4, 129.6, 129.4, 128.8, 128.6, 128.5, 128.2, 127.9, 127.2, 125.3, 122.3 (q, J = 272.0 Hz), 121.7, 114.7 (q, J = 32.9 Hz). IR: 3065, 2924, 2853, 1643, 1605, 1480, 1282, 1269, 1164, 1116, 1092, 1010, 943, 842, 826, 745 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{21}\text{H}_{11}^{35}\text{ClF}_3\text{N}_2\text{O}$ (m/z): 399.0512 $[\text{M}-\text{H}]^+$, found: 399.0507.



(E)-2-(3,4-Dimethoxyphenyl)-5-(3,3,3-trifluoro-1-phenylprop-1-en-2-yl)-1,3,4-oxadiazole (E-16l)

According to general procedure XIII: 2-(3,4-Dimethoxyphenyl)-1,3,4-oxadiazole (0.2 mmol, 41.2 mg), (Z)-3-phenyl-2-(trifluoromethyl)acrylic acid (0.4 mmol, 86.5 mg), PdCl_2 (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu_2O (0.7 mmol, 100.2 mg), 4 Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the *E/Z* ratio of the product was 92/8. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 7/1 to 4/1, v/v), affording compound **16l** in 37% yield (*E/Z* = 99/1, 28.0 mg) as pale-yellow oil.

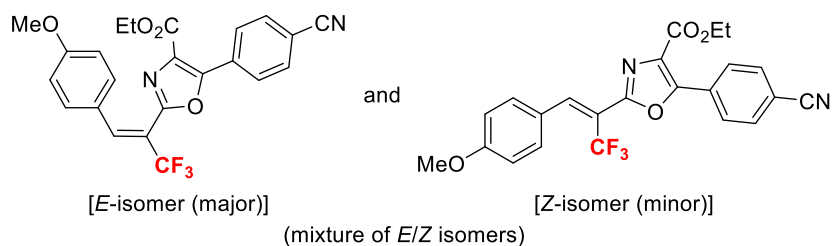
^1H NMR (300 MHz, CDCl_3): δ 7.73 (q, J = 1.7 Hz, 1H), 7.45 (dd, J = 8.4, 1.8 Hz, 1H), 7.42 – 7.30 (m, 6H), 6.90 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -58.1 (s, Z), -64.7 (d, J = 1.1 Hz, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 165.4, 157.8, 152.5, 149.5, 142.6 (q, J = 5.3 Hz), 132.2, 130.8, 129.6, 128.8, 122.2 (q, J = 271.9 Hz), 120.9, 115.7, 115.3 (q, J = 32.8 Hz), 111.2, 109.6, 56.21, 56.16. IR: 3006, 2941, 2841, 1641, 1607, 1507, 1497, 1464, 1441, 1297, 1276, 1262, 1223, 1163, 1128, 1021, 994, 950, 862, 762 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_3$ (m/z): 375.0957 $[\text{M}-\text{H}]^+$, found: 375.0961.



(E)-2-(4-Methoxyphenyl)-5-(3,3,3-trifluoro-1-(thiophen-2-yl)prop-1-en-2-yl)-1,3,4-oxadiazole (E-16m)

According to general procedure XIII: 2-(4-Methoxyphenyl)-1,3,4-oxadiazole (0.2 mmol, 35.2 mg), (Z)-3-(thiophen-2-yl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 88.9 mg), PdCl_2 (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu_2O (0.7 mmol, 100.2 mg), 4 Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ^{19}F NMR spectrum of the final reaction mixture showed that the E/Z ratio of the product was 89/11. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v), affording compound **16m** in 20% yield (E/Z = 99/1, 14.1 mg) as yellow solid.

^1H NMR (300 MHz, CDCl_3): δ 8.06 (d, J = 9.0 Hz, 2H), 7.75 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3): δ -59.1 (s, Z), -63.7 (d, J = 1.4 Hz, E). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ 165.7, 162.9, 157.5, 136.9, 135.0, 134.5 (q, J = 5.7 Hz), 133.1, 129.2, 127.7, 122.8 (q, J = 271.2 Hz), 115.9, 114.8, 109.6 (q, J = 33.0 Hz), 55.6. IR: 3082, 3018, 1618, 1549, 1494, 1417, 1306, 1290, 1257, 1220, 1163, 1113, 1074, 1021, 931, 832, 751 cm^{-1} . HRMS (EI-TOF): Calcd for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2\text{S}$ (m/z): 351.0415 $[\text{M}-\text{H}]^+$, found: 351.0412.

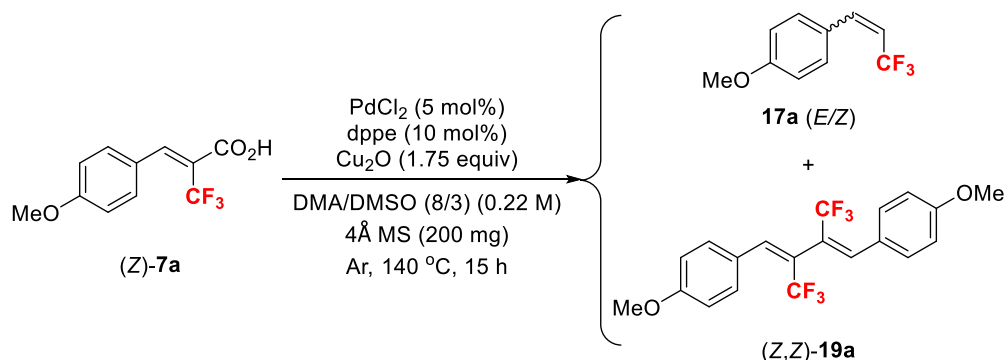


Ethyl (E)-5-(4-cyanophenyl)-2-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)oxazole-4-carboxylate (E-16n) and Ethyl (Z)-5-(4-cyanophenyl)-2-(3,3,3-trifluoro-1-(4-methoxyphenyl)prop-1-en-2-yl)oxazole-4-carboxylate (Z-16n)

According to general procedure XIII: Ethyl 5-(4-cyanophenyl)oxazole-4-carboxylate (0.2 mmol, 48.4 mg), (Z)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (0.4 mmol, 98.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2 mg), 4Å molecular sieves (200 mg), DMA (1.3 mL), and DMSO (0.5 mL). ¹⁹F NMR spectrum of the final reaction mixture showed that only *E* isomer was obtained. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, from 15/1 to 10/1, v/v), affording compound **16n** in 23% yield (*E/Z* = 94/6, 20.6 mg) as pale-yellow solid.

¹H NMR (300 MHz, CDCl₃): δ 8.19 (d, *J* = 8.4 Hz, 2H, *Z*), 8.03 (m, 1H, *Z* + 2H, *E*), 7.70 (d, *J* = 8.4 Hz, 2H, *Z*), 7.63 (d, *J* = 8.4 Hz, 2H, *E*), 7.52 (s, 1H, *E*), 7.44 (d, *J* = 8.7 Hz, 2H, *Z*), 7.21 (d, *J* = 8.7 Hz, 2H, *E*), 6.88 (d, *J* = 9.0 Hz, 2H, *Z*), 6.78 (d, *J* = 8.7 Hz, 2H, *E*), 4.38 (q, *J* = 7.0 Hz, 2H, *Z* + 2H, *E*), 3.79 (s, 3H, *Z*), 3.75 (s, 3H, *E*), 1.36 (t, *J* = 7.2 Hz, 3H, *Z* + 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.0 (s, *Z*), -64.0 (s, *E*). ¹³C{¹H} NMR (75 MHz, CDCl₃): δ 161.9, 161.7, 154.2, 153.3, 142.0 (q, *J* = 5.2 Hz), 132.3, 132.0, 130.5, 130.1, 129.0, 124.5, 122.6 (q, *J* = 271.5 Hz), 118.3, 114.4, 114.2 (q, *J* = 32.3 Hz), 113.9, 62.2, 55.6, 14.3 (only showed the data for *E* isomer, because *Z* isomer was very little and many peaks were not observed). IR: 3112, 2982, 2841, 2230, 1717, 1643, 1601, 1510, 1502, 1320, 1287, 1263, 1198, 1166, 1112, 1092, 1030, 1017, 848, 829 cm⁻¹. HRMS (EI-TOF): Calcd for C₂₃H₁₆F₃N₂O₄ (*m/z*): 441.1062 [M-H]⁺, found: 441.1074.

3.4 Synthesis of 1-methoxy-4-(3,3,3-trifluoroprop-1-en-1-yl)benzene (17a) and its subsequent attempt in cross-coupling reaction with 2-(*p*-tolyl)-1,3,4-oxadiazole (15b)

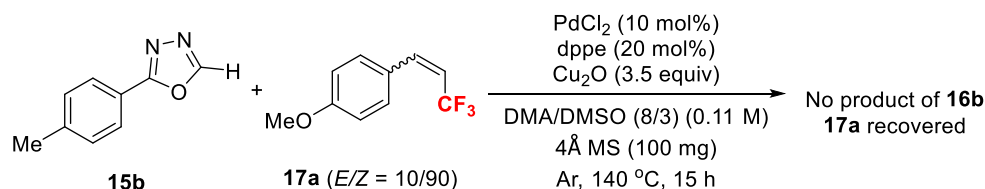


A heating gun-dried reaction tube (20 mL) was evacuated and filled with argon three times. The tube was put into glove box and was added activated 4Å molecular sieves (200 mg). After being removed from the glove box, the reaction tube was charged with (Z)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylic acid (*Z*)-**7a** (0.4 mmol, 98.5 mg), PdCl₂ (0.02 mmol, 3.5 mg), dppe (0.04 mmol, 15.9 mg), Cu₂O (0.7 mmol, 100.2

mg). The tube was carefully evacuated and filled with argon three times. Anhydrous DMA (1.3 mL) and DMSO (0.5 mL) were added and the reaction tube was sealed. The reaction mixture was stirred at 140 °C for 15 h and then cooled to room temperature. The reaction mixture was filtered through celite with EtOAc (30 mL), and the resulting organic phase was washed with brine (2 × 10 mL). The organic phase was dried over anhydrous MgSO₄, and the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (Et₂O/*n*-pentane, from 30/1 to 10/1, v/v), affording compound **17a** in 87% yield (*E/Z* = 10/90, 70.5 mg) as a colorless liquid. Since **17a** was volatile, the compound was not dried in vacuo and some Et₂O remained. Besides, (*Z,Z*)-**19a** was separated in 3% yield (5.2 mg) as white solid.

[**17a** (*E/Z* = 10/90)]: ¹H NMR (300 MHz, CDCl₃): δ 7.40 (d, *J* = 8.7 Hz, 2H, *Z* + 2H, *E*), 7.10 (dq, *J* = 16.1, 2.0 Hz, 1H, *E*), 6.90 (d, *J* = 9.0 Hz, 2H, *Z* + 2H, *E*), 6.82 (d, *J* = 12.6 Hz, 1H, *Z*), 6.07 (dq, *J* = 16.1, 6.6 Hz, 1H, *E*), 5.65 (dq, *J* = 12.6, 9.3 Hz, 1H, *Z*), 3.83 (s, 3H, *Z* + 3H, *E*). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.0 (d, *J* = 9.3 Hz, *Z*), -63.3 (dd, *J* = 6.5, 2.0 Hz, *E*). The analytical data of **17a** were in agreement with those reported in the literature.⁵⁷

[(*Z,Z*)-**19a**]: ¹H NMR (300 MHz, CDCl₃): 7.44 (d, *J* = 8.7 Hz, 2 × 2H), 7.00 (s, 2 × 1H), 6.92 (d, *J* = 8.7 Hz, 2 × 2H), 3.85 (s, 2 × 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ -58.1 (s). ¹³C NMR and IR were not tested because of the very low amount of (*Z,Z*)-**19a**. HRMS (AP-TOF): Calcd for C₂₀H₁₆F₆O₂ (*m/z*): 402.1054 [M]⁻, found: 402.1052.



A heating gun-dried reaction tube (20 mL) was evacuated and filled with argon three times. The tube was put into the glove box and was added activated 4Å molecular sieves (200 mg). After being removed from the glove box, the reaction tube was charged with 2-(*p*-tolyl)-1,3,4-oxadiazole **15b** (0.1 mmol, 16.0 mg), PdCl₂ (0.01 mmol, 1.8 mg), dppe (0.02 mmol, 8.0 mg), Cu₂O (0.35 mmol, 50.1 mg). The tube was carefully evacuated and filled with argon three times. Then, 1-methoxy-4-(3,3,3-trifluoropropen-1-yl)benzene **17a** (*E/Z* = 10/90), anhydrous DMA (1.3 mL) and DMSO (0.5 mL) were added and the reaction tube was sealed. The reaction mixture was stirred at 140 °C for 15 h and then cooled to room temperature. ¹⁹F NMR spectrum of the final reaction mixture was tested, and no product of **16b** was observed with **17a** (*E/Z* = 10/90) totally recovered.

X-ray analysis

X-ray analysis for compound **Z-3g** (CCDC 1821471)

Crystal preparation method: In a 2 mL glass vial was added pure **Z-3g** (12 mg), which was completely dissolved in CHCl₃. The solvent was allowed to evaporate slowly at room temperature and the crystal was then formed.

Crystallographic data: The crystal data of **Z-3g** are collected in **Table 56**.

Table 56 Crystal data for **Z-3g**

| | |
|---|---|
| Chemical Formula | C ₁₂ H ₈ F ₃ NO ₂ |
| Molecular Weight / <i>g.mol</i> ⁻¹ | 255.19 |
| Crystal System | Monoclinic |
| Space Group | P 21/n |
| Z, Z' (asymmetric units per unit cell) | 4, 1 |
| a / Å | 7.3847(10) |
| b / Å | 8.4879(12) |
| c / Å | 18.625(3) |
| α / ° | 90 |
| β / ° | 100.016(2) |
| γ / ° | 90 |
| V / Å ³ | 1149.6(3) |
| d _{calc} / <i>g.cm</i> ⁻³ | 1.474 |
| F(000) / e ⁻ | 520 |
| Absorption coefficient μ (MoKα ₁) / <i>mm</i> ⁻¹ | 0.133 |
| Extinction coefficient | 0.323(18) |

Structural description: The asymmetric unit is composed of one molecule of $C_{12}H_8F_3NO_2$ (**Figure 19**). Adjacent molecules along *b* establish $\pi\pi$ interactions ($d \sim 3.6 \text{ \AA}$) leading to chains in this direction (**Figure 20**). The cohesion of the structure is ensured by van der Waals interactions in other directions (**Figure 21**).

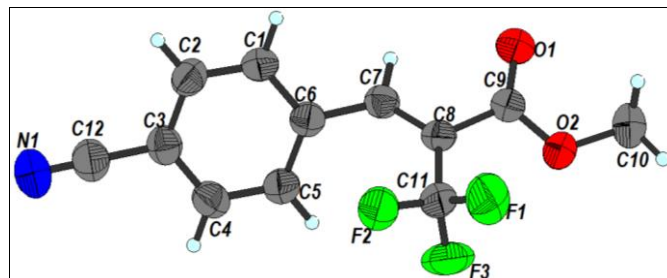


Figure 19 Asymmetric unit in thermal ellipsoidal representation with atom labels

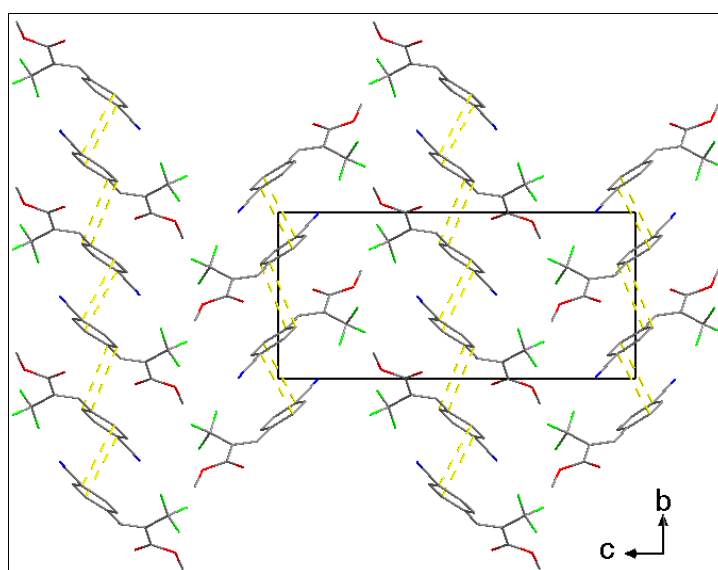


Figure 20 $\pi\pi$ interactions (in dashed yellow lines) established with consecutive molecule in column along *b* direction

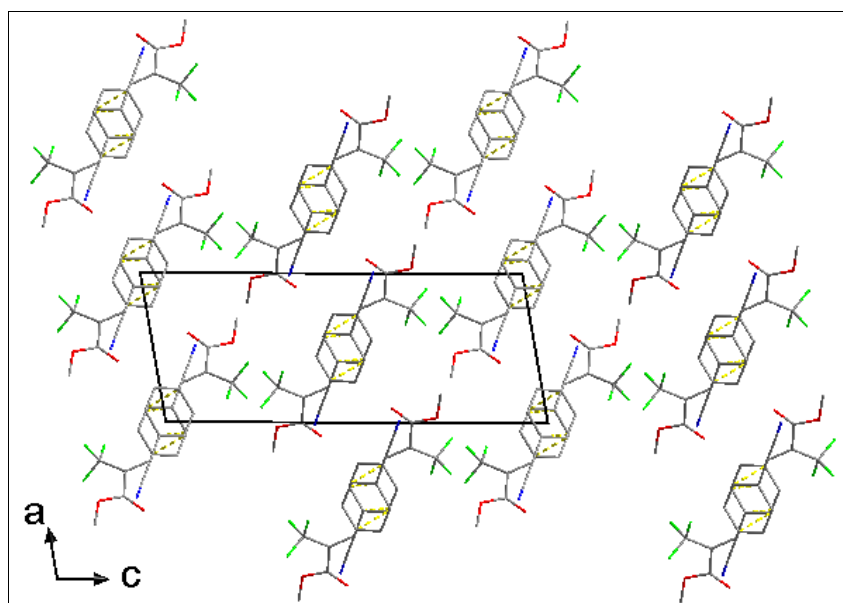


Figure 21 Projection along b

X-ray analysis for compound **Z-7h** (CCDC 1950504)

Crystal preparation method: In a 5 mL glass vial was added pure **Z-7h** (17 mg), which was completely dissolved in CHCl_3 . The solvent was allowed to evaporate slowly at room temperature and the crystal was then formed.

Crystallographic data: The crystal data of **Z-7h** are collected in (Table 57).

Table 57 Crystal data for **Z-7h**

| | |
|---|--|
| Chemical Formula | $\text{C}_{11}\text{H}_6\text{F}_3\text{NO}_2$ |
| Molecular Weight / $\text{g}\cdot\text{mol}^{-1}$ | 241.17 |
| Crystal System | Monoclinic |
| Space Group | $P2_1/c$ (n°14) |
| Z, Z' (asymmetric units per unit cell) | 4,1 |
| a / Å | 10.403(3) |
| b / Å | 7.949(2) |
| c / Å | 13.276(4) |
| α / ° | 90 |
| β / ° | 97.448(5) |
| γ / ° | 90 |

| | |
|--|-----------|
| $V / \text{\AA}^3$ | 1088.6(5) |
| $d_{\text{calc}} / \text{g.cm}^{-3}$ | 1.472 |
| $F(000) / e^-$ | 488 |
| Absorption coefficient $\mu (\text{MoK}\alpha_1) / \text{mm}^{-1}$ | 0.136 |

Structural description: The asymmetric unit is composed of one molecule of $\text{C}_{11}\text{H}_6\text{F}_3\text{NO}_2$ (**Figure 22**). The three fluorine atoms are disordered; they exhibit a statistical occupancy factor (sof) of 89% / 11%. Through their carboxylic moieties, molecules establish hydrogen bonds (**Table 58**) that lead to dimers (**Figure 23**). The cohesion of the packing is ensured by weak interactions.

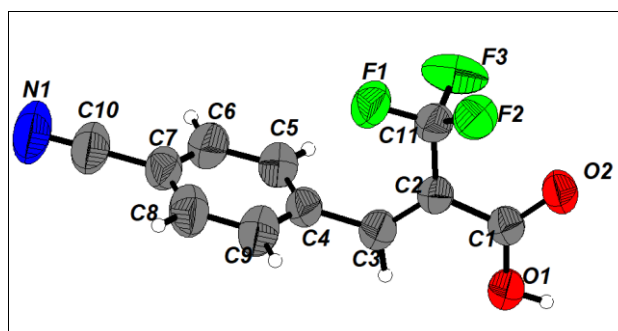


Figure 22 Asymmetric unit in thermal ellipsoidal representation, the fluorine atoms displayed are at 89% of sof

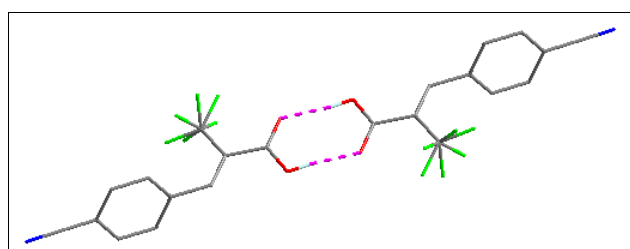


Figure 23 One dimer built from the hydrogen bond interaction

Table 58 Hydrogen bond table

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|------------------------|--------|----------|----------|--------|
| O(1)- H(1)...O(2)#1 | 0.82 | 1.81 | 2.632(2) | 174.5 |

Symmetry transformation used to generate equivalent atoms :#1 -x+2,-y,-z

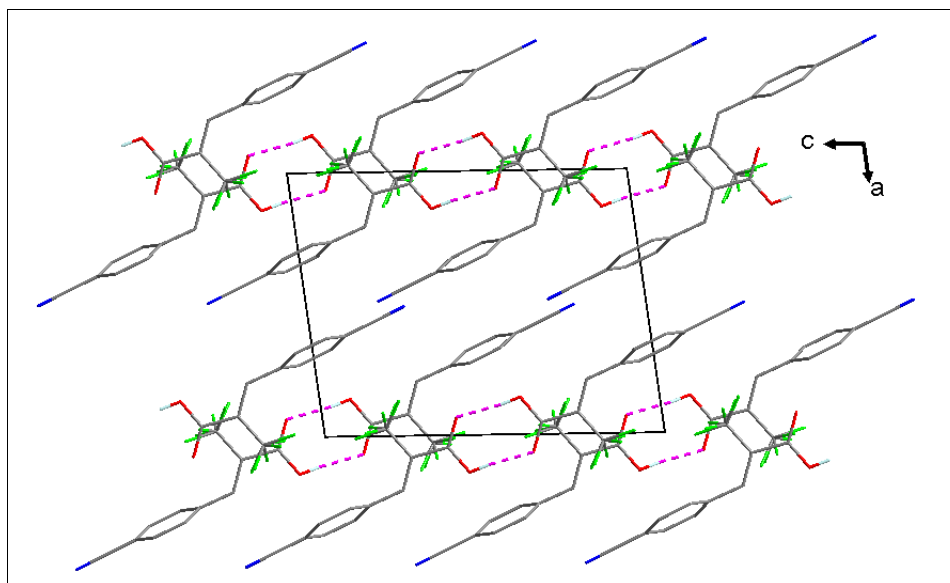


Figure 24 Projection along b

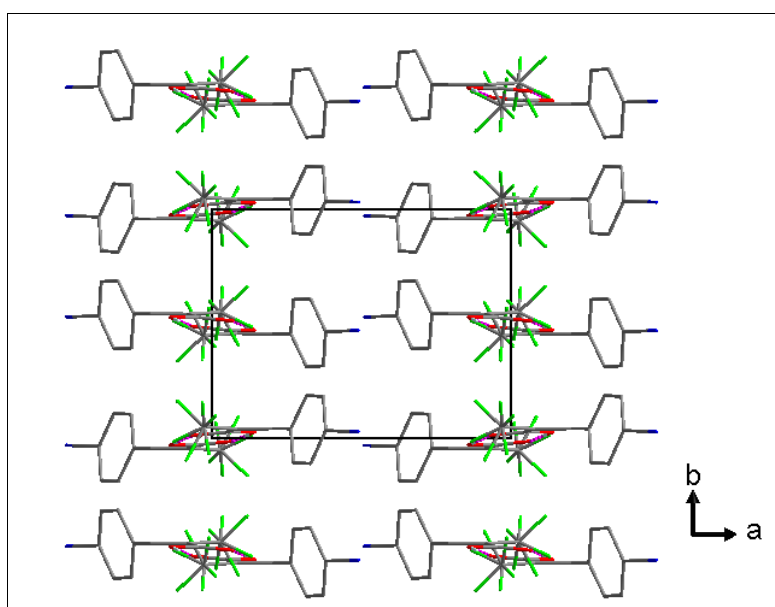


Figure 25 Projection along c

X-ray analysis for compound *E-16g*

Crystal preparation method: In a 2 mL glass vial was added pure *E-16g* (8 mg), which was completely dissolved in CHCl_3 . Then *n*-hexane (similar volume as CHCl_3) was carefully added to form two phases. Afterwards, the solvents were allowed to evaporate slowly at room temperature and the crystal was then formed.

Crystallographic data: The crystal data of *E-16g* are collected in (Table 59).

Table 59 Crystal data for *E-16g*

| | |
|------------------|--|
| Chemical Formula | $\text{C}_{19}\text{H}_{12}\text{F}_6\text{N}_2\text{O}$ |
|------------------|--|

| | |
|--|------------|
| Molecular Weight / $g.mol^{-1}$ | 398.31 |
| Crystal System | Monoclinic |
| Space Group | $P2_1/n$ |
| Z, Z' (asymmetric units per unit cell) | 4,1 |
| a / Å | 9.5774(19) |
| b / Å | 13.958(3) |
| c / Å | 13.331(3) |
| α / ° | 90 |
| β / ° | 98.506(4) |
| γ / ° | 90 |
| V / Å ³ | 1762.5(6) |
| d_{calc} / $g.cm^{-3}$ | 1.501 |
| F(000) / e^{-} | 808 |
| Absorption coefficient μ (MoK α_1) / mm^{-1} | 0.138 |

Structural description: The asymmetric unit is composed of one molecule of C₁₉H₁₂F₆N₂O (**Figure 26**, **Figure 27**). The fluorine atoms {F1, F2, and F3} are delocalised on {F1B, F2B, and F3B} with statistical occupancy factors of 64/36%. Some packing representations are given in **Figure 28-Figure 30**.

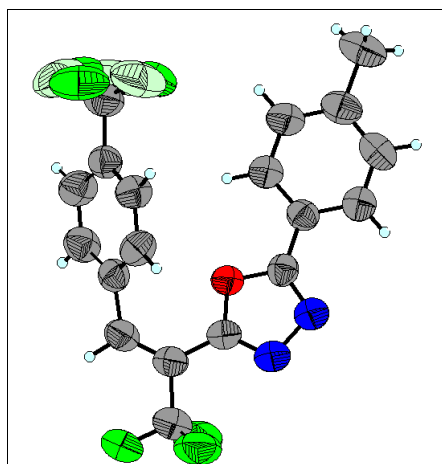


Figure 26 Asymmetric unit in thermal ellipsoidal representation (the delocalised fluorine atoms are displayed in light (64%) and lighter green (36%) according to their occupancy factor)

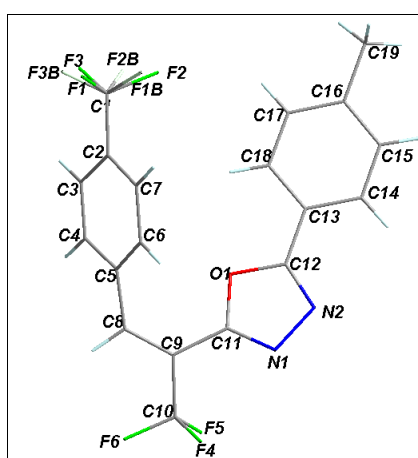


Figure 27 Asymmetric unit with atom labels

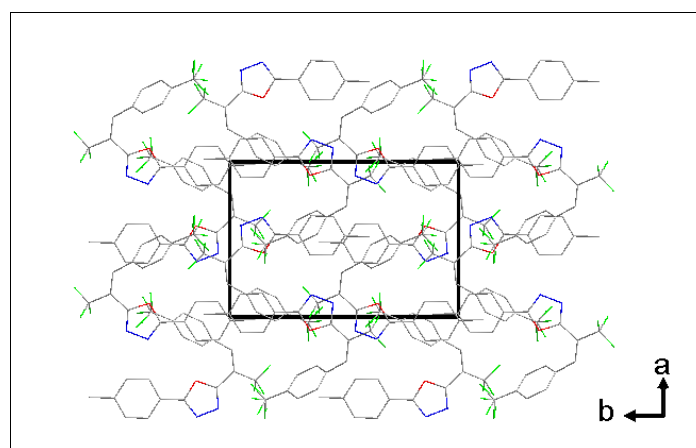


Figure 28 Projection along c

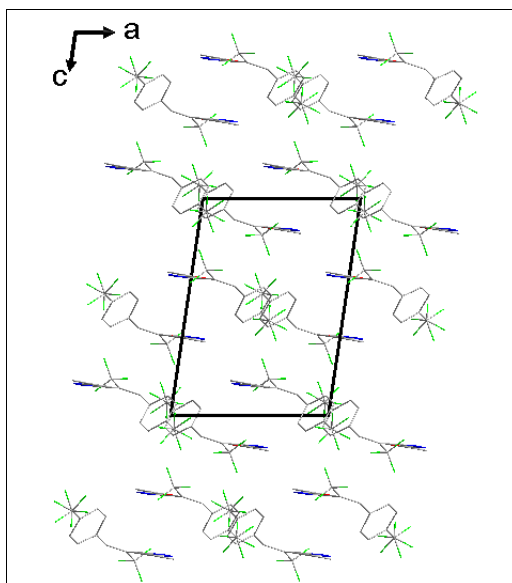


Figure 29 Projection along b

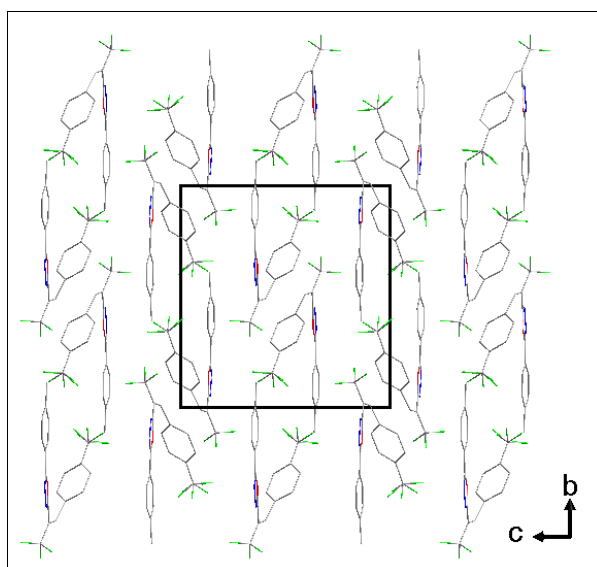


Figure 30 Projection along a

Curriculum Vitae

XIAO Pan

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Education

- 2017.10–present:** INSA Rouen Normandie, France. Major in Organic Chemistry, **Ph.D.** candidate
- 2014.09–2017.07:** Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, Shanghai, P. R. China. Major in Organic Chemistry, **M.S.**
- 2010.09–2014.07:** Hubei University, Wuhan, P. R. China. Major in Chemical Biology, **B.S.**

Professional Experiences

- 2017.10–present:** Study on transition metal-catalyzed fluoroalkenylation reactions in Group “Synthesis of Fluorinated Biomolecules” in COBRA, under supervision of Prof. Jean-Philippe Bouillon and Dr. Samuel Couve-Bonnaire. INSA Rouen Normandie, France
- 2014.09–2017.07:** Study on radical fluoroalkylation reactions in “Key Laboratory of Organofluorine Chemistry”, under supervision of Prof. Jinbo Hu. SIOC, Shanghai, P. R. China
- 2014.02–2014.05:** Study on the synthesis of N(2)-L-alanyl-L-glutamine in “College of Chemistry and Chemical Engineering”, under supervision of Prof. Yan Li. Hubei University, Wuhan, P. R. China

Conferences

- 2019.10:** Journées de Chimie Organique 2019 (JCO 2019), Palaiseau, France (Poster communication)
- 2019.06:** Journées Nord-Ouest Européennes des Jeunes Chercheurs 2019 (JNOEJC 2019), Mont Saint Aignan, France (Oral presentation)
- 2018.06:** Journées Nord-Ouest Européennes des Jeunes Chercheurs 2018 (JNOEJC 2018), Lille, France (Oral presentation)
- 2016.11:** The 14th National Conference on Fluorine Chemistry of the Chinese Chemical Society, Fuzhou, P. R. China (Participant)

Publications

- PhD:** (1) **P. Xiao**, C. Schlinquer, X. Pannecoucke, S. Couve-Bonnaire, J.-P. Bouillon, Ligand-Free Palladium-Catalyzed Mizoroki-Heck Reaction to Synthesize Valuable α -Trifluoromethylacrylates,

J. Fluorine Chem. **2020**, *233*, 109483, DOI: <https://doi.org/10.1016/j.jfluchem.2020.109483>

- (2) **P. Xiao**, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, Ligand Free Palladium-Catalyzed Synthesis of α -Trifluoromethylacrylic acids and Related Acrylates by Three-Component Reaction, *Adv. Synth. Catal.* **2020**, *362*, 945-954, DOI: 10.1002/adsc.201901446
- (3) **P. Xiao**, C. Schlinquer, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, Synthesis of α -Trifluoromethylacrylates by Ligand-Free Palladium-Catalyzed Mizoroki-Heck Reaction, *J. Org. Chem.* **2019**, *84*, 2072-2082, DOI: 10.1021/acs.joc.8b03085
- Master:**
- (4) **P. Xiao**, C. Ni, W. Miao, M. Zhou, J. Hu, D. Chen, J. Hu, Fluoroalkylation of Various Nucleophiles with Fluoroalkyl Sulfones Through a Single Electron Transfer Process, *J. Org. Chem.* **2019**, *84*, 8345-8359, DOI: 10.1021/acs.joc.9b00419
- (5) **P. Xiao**, J. Rong, C. Ni, J. Guo, X. Li, D. Chen, J. Hu, Radical (Phenylsulfonyl)difluoromethylation of Isocyanides with PhSO₂CF₂H under Transition-Metal-Free Conditions, *Org. Lett.* **2016**, *18*, 5912-5915, DOI: 10.1021/acs.orglett.6b03013