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RIGA TECHNICAL
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Artūrs Sperga

FLUORĒTU SINTONU PĀRNESES REAKCIJU IZPĒTE

Promocijas darbs

INVESTIGATION OF FLUORINATED SYNTHON TRANSFER REACTIONS

Doctoral Thesis

RTU Izdevniecība
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RĪGAS TEHNISKĀ UNIVERSITĀTE
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Doctoral Thesis

Zinātniskais vadītājs
asociētais profesors *Dr. sc. nat.* JĀNIS VELIKS
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Artūrs Sperga ……………………………. (paraksts)

Datums …………………………….

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa. Tas ietver kopsavilkumu, trīs oriģinālpublikācijas un vienu apskatrakstu. Publikācijas uzrakstītas angļu valodā, to kopējais apjoms ir 34 lpp, ieskaitot elektroniski pieejamo informāciju – 397 lpp.

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SATURS / CONTENT

SAĪSINĀJUMI / ABBREVIATION

Å – angstrēms / angstrom
Ac – acetil- / acetyl
Acac – acetilacetonāts / acetylacetonate
Ar – aril- / aryl
BCP – biciklo[1.1.1]butāns/bicyclo[1.1.1]butane
Boc – *tert*-butiloksikarbonil- / *tert*-butyloxycarbonyl
Bz – benzoil- / benzoyl
d. r. – diastereomēru attiecība / diastereomeric ratio
DCC – *N,N*`-dicikloheksilkarbodiimīds / *N,N*`dicyclohexylcarbodiimide
DCE – 1,2-dihloretāns / 1,2-dichloroethane
DCM – dihlormetāns / dichloromethane
DFT – blīvuma funkcionāļa teorija / density functional theory
DIPEA – *N,N*-diizopropiletilamīns / *N,N*-diisopropylethylamine
DMAP – 4-dimetilaminopiridīns / 4-dimethylaminopyridine
DMSO – dimetilsulfoksīds / dimethyl sulfoxide
EAG – elektronatvelkoša grupa
ekviv. – ekvivalenti
eq – equivalents
Et – etil- / ethyl
eV – elektronvolti / electronvolts
EWG – electron withdrawing group
FG – funkcionālā grupa / functional group
Hal – halogēns / halogen
*i*Pr – izopropil- / isopropyl
IRAK4 – interleikīna-1 receptora saistītā kināze 4 / interleukin-1 receptor-associated kinase 4
ist. t. – istabas temperatūra
kcal – kilokalorija / kilocalories
KMR – kodolu magnētiskā rezonanse
KPhth – kālija ftalimīds / potassium phthalimide
LG – aizejošā grupa / leaving group
LpxC – UDP-3-O-(acil)-*N*-acetilglikozamīna deacetilāze / UDP-3-O-(acyl)-*N*-acetylglucosamine deacetylase
LUMO – zemākā neaizņemtā molekulārā orbitāle / lowest unoccupied molecular orbital
*m*CPBA – *meta*-hlorperoksibenzoskābe / *meta*-chloroperoxybenzoic acid
Me – metil- / methyl
NBS – *N*-bromsukcinimīds / *N*-bromosuccinimide
NCS – *N*-hlorsukcinimīds / *N*-chlorosuccinimide
NHPI – *N*-hidroksiftalimīds / *N*-hydroxyphthalimide
nm – nanometri / nanometers

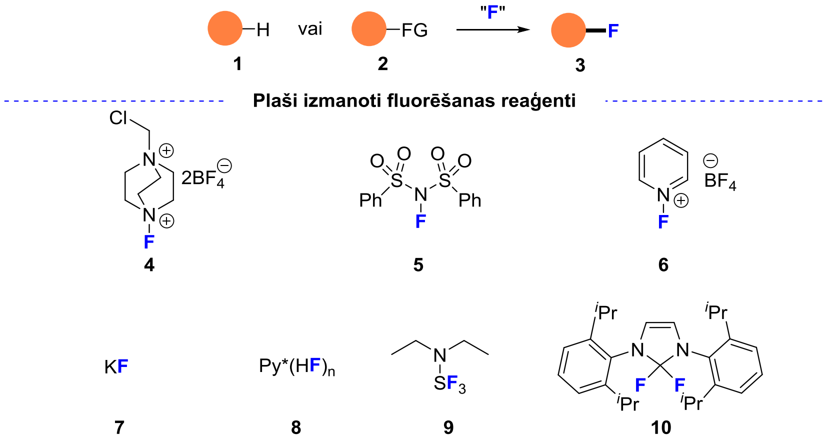
NMR – nuclear magnetic resonance
Nu – nukleofīls / nucleophile
Ph – fenil- / phenyl
PIDA – (diacetoksijod)benzols / (diacetoxyiodo)benzene
Py – piridīns / pyridine
r.r. – reģioizomēru attiecība / regioisomeric ratio
rt – room temperature
TBAI – tetrabutilamonija jodīds / tetrabutylammonium iodide
Tf – trifluormetānsulfonil- / trifluoromethanesulfonyl
THF – tetrahidrofurāns / tetrahydrofuran
TMS – trimetilsilil- / trimethylsilyl
TTP – tetrafenilporfirīns / tetraphenylporphyrin
Trp – triptofāns / tryptophan
Ts – tozil- / tosyl
TS – pārejas stāvoklis / transition state
TTMSS – tris(trimetilsilil)silāns / tris(trimethylsilyl)silane
Tyr – tirozīns / tyrosine
ΔG – Gibsa brīvās enerģijas izmaiņa / Gibbs free energy change
ω – globālā elektrofilitāte / global electrophilicity

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

Tēmas aktualitāte

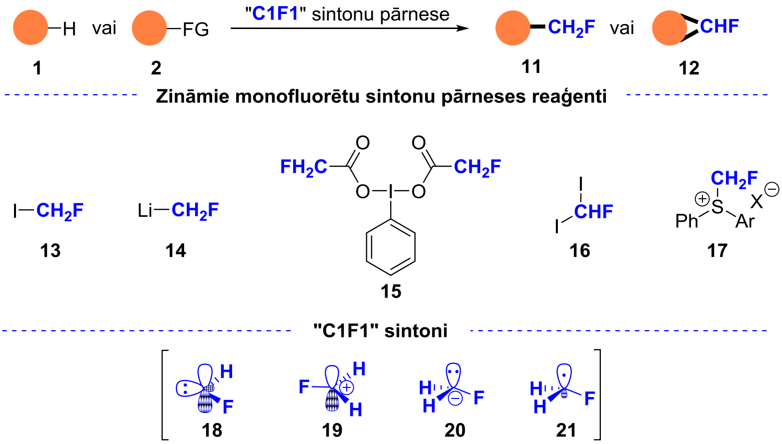
Fluora atoma ievadīšana molekulā ir plaši lietota stratēģija jaunu zāļvielu izstrādē.[1] Funkcionālo grupu vai ūdeņraža atoma aizvietošana ar fluoru spēj būtiski modificēt molekulas farmakoloģiskās īpašības – metabolisko stabilitāti, biopieejamību un mijiedarbību ar mērķa enzīmu. Ņemot vērā plašo fluororganisko savienojumu lietojumu medicīnas ķīmijā, agroķīmijā un materiālzinātnē, nozīmīga ir efektīvu metožu izstrāde fluoru saturošu savienojumu iegūšanai.[2]

Fluorēšanai tiek izmantoti elektrofīlie **4-6** vai nukleofīlie **7-10** fluora avoti oglekļa-ūdeņraža saites **1** vai funkcionālo grupu **2** pārvēršanai par fluorētiem savienojumiem **3** (1. att.).[3]



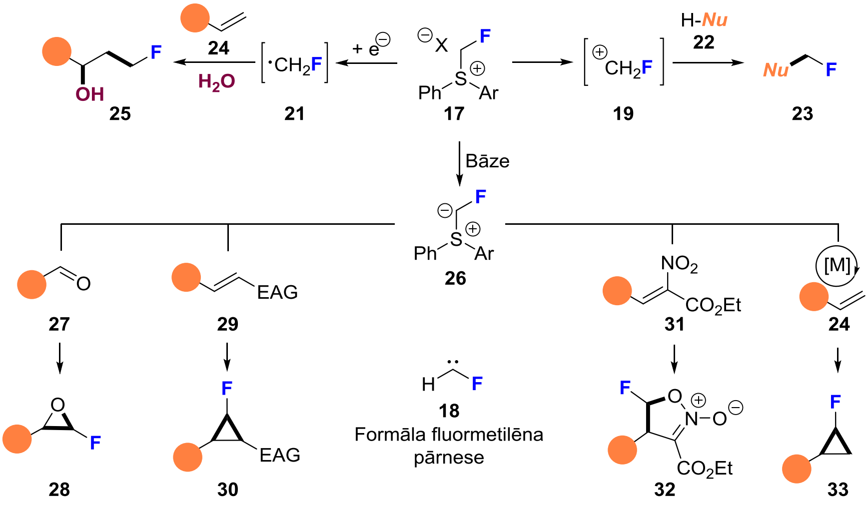
1. att. Reaģenti monofluorētu savienojumu iegūšanai.

Stratēģiski atšķirīga pieeja ir molekulas funkcionalizēšana ar fluorētiem sintoniem, kuros fluors ir tieši saistīts ar reaģētspējīgo oglekļa atomu (2. att.).[4] Lai arī bieži lietota metode trifluormetil-[5–7] un difluormetil-[8] grupu ievadīšanai, monofluorētu sintonu[9] analoģiskas pārvērtības ir retāk pētītas. Tomēr pēdējās desmitgades laikā ir izstrādāti vairāki reaģenti **13-17** efektīvai monofluorētu sintonu pārnesei.[10–13] Ir iespējams veikt fluorkarbēnu **18,** elektrofīlo **19**, nukleofīlo **20** un pat radikāļu **21** monofluormetildaļiņu pārnesi. Izmantojot fluorētu sintonu pieeju, var iegūt produktus **11**, **12**, ko būtu grūti vai pat neiespējami sintezēt ar tiešajām fluorēšanas reakcijām.



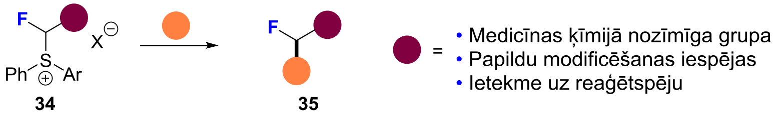
2. att. Monofluorētu sintonu pārnese.

No minētajiem reaģentiem īpaša uzmanība jāpievērš sulfonija sālim **17**, kas var kalpot par multifunkcionālu avotu karbēna **18**, elektrofīla **19** un radikāļa **21** sintoniem (3. att.).[14] Sulfīds ir laba aizejošā grupa, līdz ar to reakcijās ar nukleofīliem **22** tas kalpo par elektrofīlās fluormetilgrupas **19** avotu.[15] Viena elektrona reducēšanā tas fragmentējas par fluormetilradikāli **21**, kas spēj pievienoties alkēniem **24**.[16] Promocijas darba autora un viņa kolēģu grupas līdzšinējos pētījumos ir izstrādātas formālas fluormetilēngrupas **18** pārneses reakcijas. Bāzes klātbūtnē veidojas sēra ilīds **26**, kas stājas reakcijā ar aldehīdiem **27**[17], aktivētiem alkēniem **29**[18], **31**[19], veidojot monofluorētus trīs vai piecločekļu ciklus **28**, **30** un **32**. Savukārt metāla katalizatora klātbūtnē ir iespējams veikt arī neaktivētu alkēnu **24** ciklopropanēšanu un citas reakcijas.[20]



3. att. Fluormetilsulfonija sāls **17** lietojums.

Aizvietoti monofluormetilsulfonija sāļi zinātniskajā literatūrā ir maz aprakstīti.[21–24] Līdz ar to tika nolemts izstrādāt modificētus sulfonija sāļus **34**, ievadot papildu funkcionālās grupas pie reaģētspējīgā oglekļa centra, tādējādi panākot funkcionalizētu monofluorētu sintonu pārneses reakcijas, kuru rezultātā tiktu iegūti produkti **35** (4. att.). Šī pētījuma gaitā bija paredzēts ievadīt funkcionālās grupas, kas ir nozīmīgas medicīnas ķīmijā vai kuras varētu pakļaut tālākām modificēšanas iespējām pēc pirmās sintona pārneses reakcijas. Turklāt mērķis bija noskaidrot, kā papildu aizvietotājs ietekmē sulfonija sāls reaģētspēju.



4. att. Aizvietoti fluormetilsulfonija sāļi **34**.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir izstrādāt jaunus fluormetilsulfonija reaģentus, kas spētu efektīvi veikt funkcionalizētu monofluorētu sintonu pārnesi.

Mērķa sasniegšanai tika definēti divi uzdevumi.

1. Sintezēt funkcionalizētus fluormetilsulfonija sāļus.
2. Izstrādāt jaunas sintēzes metodes fluorētu sintonu pārnesei no sulfonija sāļiem.

Zinātniskā novitāte un galvenie rezultāti

Promocijas darba rezultātā izstrādātas:

1) fluorhalometilsulfonija sāļu sintēzes metodes;
2) alkēnu fluorhalociklopropanēšanas reakcijas, pielietojot sulfonija sāļus;
3) etoksikarbonilaizvietota fluormetilsulfonija sāls sintēze;
4) metālu katalizētas sulfonija sāļa reakcijas ar alkēniem un alilsulfīdiem;
5) biciklopentilaizvietotu fluormetilsulfonija sāļu sintēze;
6) nukleofīlās aizvietošanās reakcijas ar sulfonija sāļiem.

Darba struktūra un apjoms

Promocijas darbs ir tematiski vienota zinātnisko publikāciju kopa par jaunu sulfonija sāļu iegūšanas metodēm un to lietojumu fluorētu sintonu pārneses reakcijās.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti trīs zinātniskajās oriģinālpublikācijās un vienā apskatrakstā. Pētījuma rezultāti prezentēti sešās konferencēs.

Zinātniskās publikācijas

1. Sperga, A.; Veliks, J., Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species. *Chemistry – A European Journal* **2023**, *29* (69), e202301851.
2. Sperga, A.; Pfeifers, T.; Zacs, D.; Veliks, J., Fluorohalomethylsulfonium Salts as a Fluorohalocarbene Source. *Organic Letters* **2024**, *26* (30), 6482–6485.
3. Sperga, A.; Kinens, A.; Veliks, J., Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts. *Organic Letters* **2025**, *27* (21), 5446–5451.
4. Sperga, A.; Pfeifers, T.; Veliks, J., Monofluorinated C1 Synthon Strategy for The Construction of Fluoromethylene-Linked Bicyclo[1.1.1]Pentane Derivatives. *Advanced Synthesis & Catalysis* **2025**, *367*, e70119.

Zinātniskās konferences

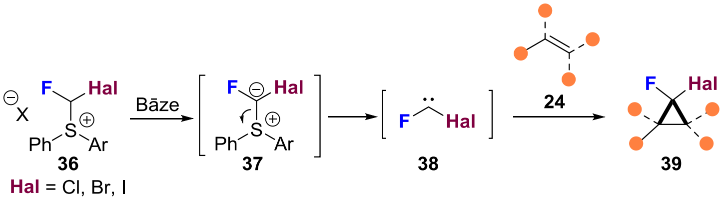
1. Sperga, A.; Veliks, J. Fluorohalomethylsulfonium salts as a novel fluorohalocarbene source. *Latvijas Universitātes 81. zinātniskā konference ķīmijas sekcija*, Rīga, Latvija, 17. marts, **2023**.
2. Sperga, A. Fluorohalomethylsulfonium salts as a novel fluorohalocarbene source. *Paul Walden 13th Symposium on Organic Chemistry,* Rīga, Latvija, 14.–15. septembris, **2023**.
3. Sperga A., Veliks, J. Fluorohalomethylsulfonium salts: novel fluorohalocarbene source. *18th Belgian Organic Synthesis Symposium BOSS 2024,* Ljēža, Beļģija 30. jūnijs–5. jūlijs, **2024**.
4. Sperga, A.; Veliks, J. Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts. *Balticum Organicum Syntheticum*, Rīga, Latvija, 7.–10. jūlijs, **2024**.
5. Sperga, A.; Pfeifers, T.; Veliks, J. Fluoromethyl Bicyclo[1.1.1]pentane Transfer from Sulfonium Salts. *23rd European Symposium on Organic Chemistry*. Kopenhāgena, Dānija 29. jūnijs–3. jūlijs, **2025**.
6. Sperga A. Fluorinated Synthon Transfer from Sulfonium Salts. *14th Paul Walden Symposium*, Rīga, Latvija, 25.–26. septembris, **2025**.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

1. Fluorhalokarbēnu pārnese no fluorhalometilsulfonija sāļiem

Sulfonija sāļi kalpo par efektīvu platformu monofluorētu C1 sintonu pārnesei. Lai ievadītu papildus vektoru tālāku modificēšanu veikšanai, nolēmām izstrādāt reaģentus, kas satur papildu gemināļu halogēna atomu (Hal = Cl, Br, I) fluormetilsulfonija sāļu **36** struktūrās (5. att.).[25] Lai gan difluorometilaizvietotu sulfonija sāļu lietojums ir zināms nukleofīlajās aizvietošanās reakcijās[26–28], kā arī radikāļu[29] un karbēnu ģenerēšanā, citu halogēnu atvasinājumi līdz šim nav bijuši pētīti. Pavisam nesen *Wang* un līdzstrādnieki aprakstīja bromfluorciklopropānu tālāku funkcionalizēšanu[30], tādējādi iegūstot daudzveidīgus monofluorētus savienojumus un parādot šīs stratēģijas potenciālu.

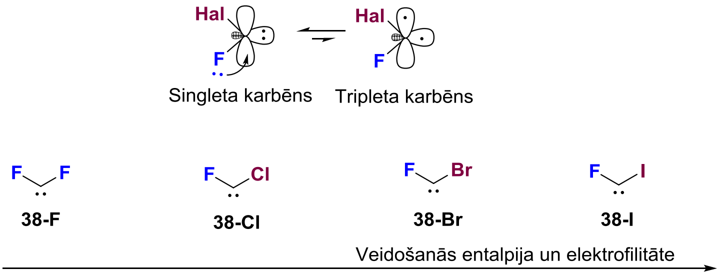
Promocijas darba autors un kolēģi uzskatīja, ka fluorhalometilsulfonija sāļi **36** varētu būtu efektīvi reaģenti karbēnu ģenerēšanai. Nenukleofīlas bāzes klātbūtnē tie tiktu deprotonēti, veidojot sēra ilīdu **37**, kas pēc sulfīda α-eliminēšanas veidotu fluorhalokarbēnu **38**. Dihalokarbēns **38** varētu tālāk reaģēt ar alkēniem **24**, tādējādi iegūstot ciklopropānus **39**.



5. att. Fluorhalokarbēnu ģenerēšana no sulfonija sāļiem.

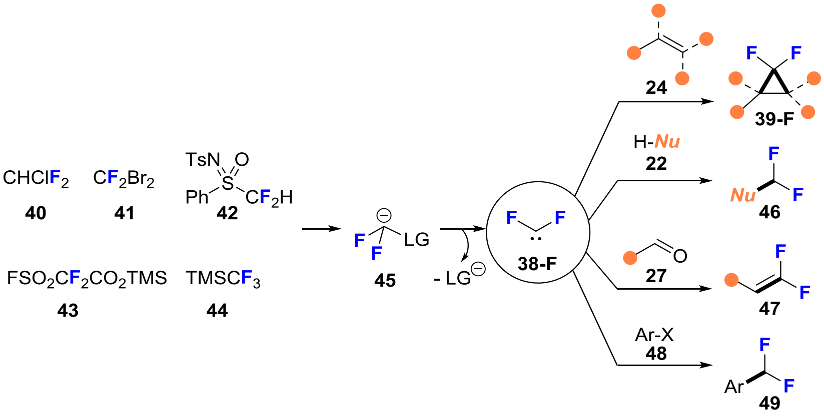
Karbēni ir neitrāli divalenti oglekļa starpsavienojumi, kas satur divus nesapārotus valences elektronus un divus aizvietotājus. Šo daļiņu elektronisko struktūru un reaģētspēju būtiski ietekmē to aizvietotāji. Fluorhalokarbēniem **38** singleta stāvoklis ir enerģētiski izdevīgāks par tripleta stāvokli, jo notiek efektīva fluora nedalīto elektronu pāru pārklāšanās ar karbēna brīvo p-orbitāli (6. att.).[31] Karbēnu reaģētspēja ir atkarīga no spinu multiplicitātes. Singleta karbēnu gadījumā pārsvarā notiek vienlaicīgu saišu veidošana ar substrāta molekulu, savukārt tripleta stāvoklī reakcija noris caur radikāļu starpproduktiem.[32–33]

Fluorhalokarbēnu grupā difluorkarbēnam **38-F** ir viszemākā veidošanās entalpija, un tas ir termodinamiski visstabilākais.[34] Dihalokarbēnu stabilitāte samazinās, fluora atomu aizvietojot ar smagāku halogēna atomu (:CFCl, :CFBr, :CFI), jo p-orbitāles pārklāšanās ar otru halogēna atomu kļūst mazāk efektīva. Šī rezultātā karbēna oglekļa atoms kļūst elektronnabadzīgāks, un līdz ar to tā elektrofilitāte pieaug.[31, 35]



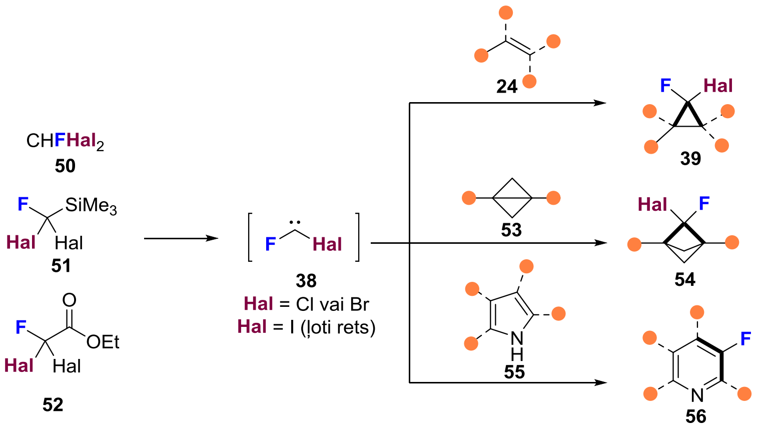
6. att. Fluohalokarbēnu īpašības.

Neskatoties uz aprakstītajiem stabilizēšanas efektiem, fluorhalokarbēni ir ļoti reaģētspējīgi starpsavienojumi. Difluorkarbēnu **38-F** reakcijas ir visbiežāk pētītas, un ir izstrādāti vairāki reaģenti **40-44** tā ģenerēšanai (7. att.).[36–43] Pārsvarā tos iegūst, attiecīgo prekursoru deprotonējot, dekarboksilējot vai desililējot bāzes vai paaugstinātas temperatūras ietekmē, kā rezultātā veidojas karbanjons **45**, kas pēc halogēna vai citas aizejošās grupas α-eliminēšanas veido karbēnu **38-F**. Difluorkarbēniem **38-F** piemīt elektrofīlas īpašības, kas raksturo to ķīmiskās īpašības, kā arī plašo lietojumu sintēzē. Tas piedalās stereospecifiskās [2+1] ciklopievienošanās reakcijās ar alkēniem **24** un alkīniem. Difluorkarbēns pievienojas oglekļa, skābekļa, slāpekļa un sēra nukleofīliem **22**. Izmantojot šo karbēnu, var veikt arī olefinēšanas un pārejas metālu katalizētas šķērssametināšanas reakcijas.



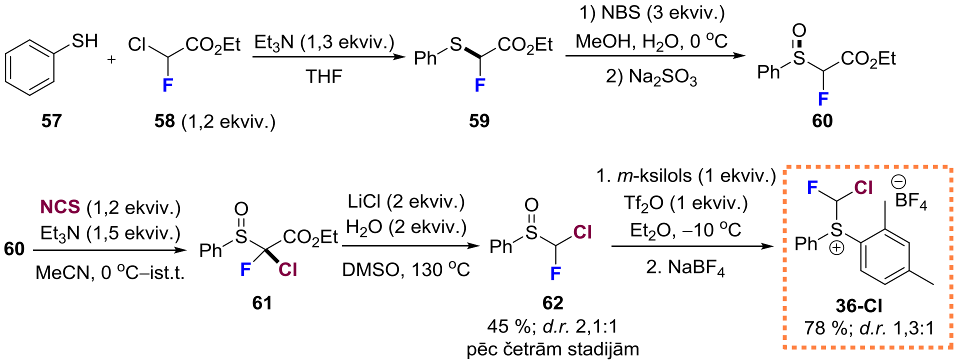
7. att. Difluorkarbēnu ģenerēšana un reaģētspēja.

Savukārt citu fluorhalokarbēnu reakcijas ir ievērojami retāk pētītas. Vēsturiski fluorhalokarbēnu **38** ģenerēšanai ir lietoti fluorhalometāni **50**[31], taču šiem savienojumiem piemīt ozona slāni noārdošas īpašības (8. att.).[44] Pēdējā desmitgadē ir izstrādāti jauni reaģenti – silāni **51**[45] un esteri **52**[46] – efektīvai fluorhalokarbēnu **38** pārnesei.[32, 47] Turklāt ir arī paplašināts lietojuma klāsts, proti, ir iespējams veikt ne tikai alkēnu **24** ciklopropanēšanu, bet arī karbēnu ievietošanos biciklobutāna **53** C-C saitē[48] un pirolu **55** ciklopaplašināšanu.[49] Karbēnu ģenerēšanai dažkārt ir nepieciešami skarbi apstākļi – paaugstināta temperatūra un nukleofīlu bāzu izmantošana. Turklāt fluorjodkarbēna ģenerēšana ir ārkārtīga reta, kā arī šim mērķim lietots tikai viens reaģents – $CHFI_2$.[50] Ņemot vērā minētos trūkumus, tika uzskatīts, ka fluorhalometilsulfonija sāļi **36** spētu sniegt vienotu pieeju fluorhalokarbēnu **38** pārnesei maigos apstākļos.



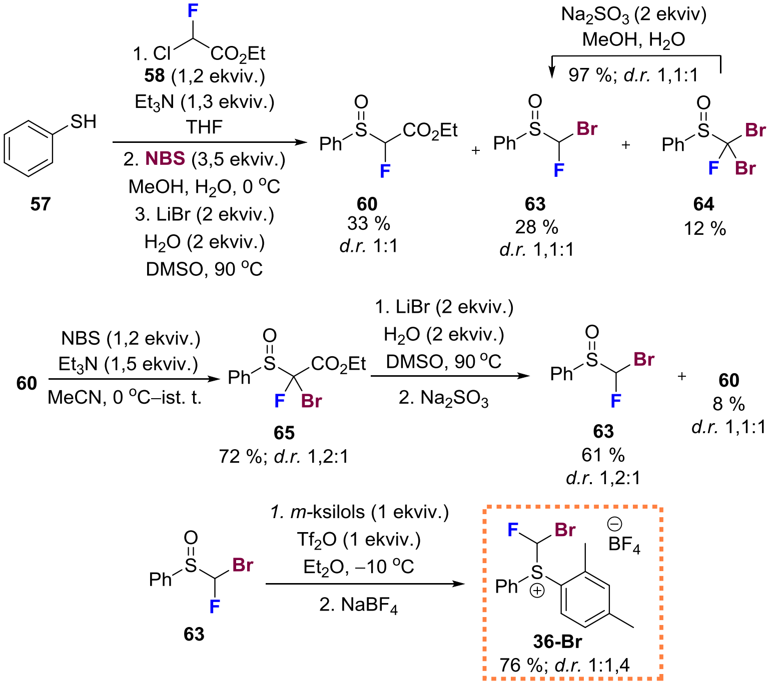
8. att. Fluorhalokarbēnu ģenerēšana un lietojums.

Pētījuma sākumā tika izstrādātas fluorhalometilsulfonija sāļu **36** sintēzes metodes, sākotnēji veicot hloru saturoša savienojuma **36-Cl** sintēzi (9. att.). Pirmajā stadijā bāzes klātbūtnē tika alkilēts tiofenols (**57**) ar etilfluorhloracetātu (**58**), kā rezultātā tika iegūts sulfīds **59**. Savienojums **59** tika oksidēts līdz sulfoksīdam **60** un hlorēts, iegūstot dihaloesteri **61**. Savienojuma **61** Krapčo dekarboksilēšana deva sulfoksīdu **62** ar labu iznākumu četrās stadijās. Noslēdzošajā solī sulfoksīds **62** tika pakļauts Frīdela-Kraftsa tipa arilēšanai ar sekojošu anjonu apmaiņu, veidojot fluorhlormetilsulfonija sāli **36-Cl**.



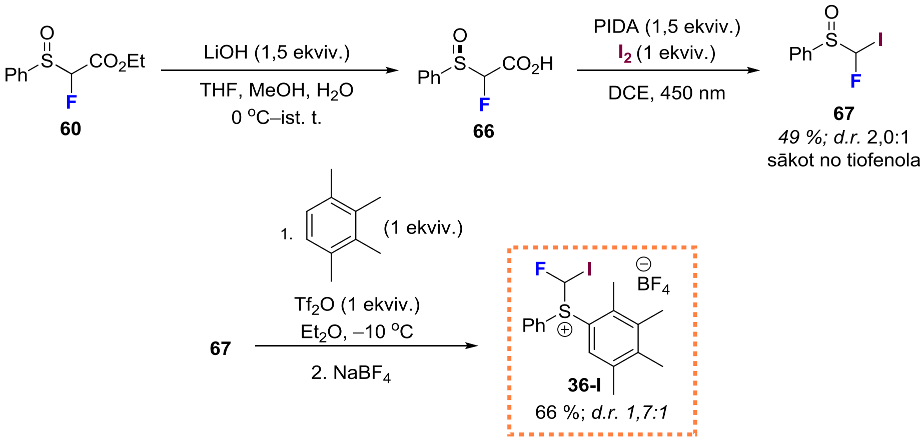
9. att. Ar hloru aizvietota sulfonija sāls **36-Cl** sintēze.

Tālāk tika sintezēts ar bromu aizvietotu sulfonija sāls **36-Br** (10. att.). Sākotnēji tika veikta analoģiska tiofenola (**57**) alkilēšanas reakcija. Tam sekoja oksidēšana un bromēšana vienas kolbas reakcijā. Pēc Krapčo dekarboksilēšanas tika iegūti trīs produkti – **60**, **63** un **64**, mērķa savienojums **63** veidojās ar viduvēju iznākumu trijās stadijās. Abi blakusprodukti – etilesteris **60** un dibromatvasinājums **64** – tika pārvērsti nepieciešamajā sulfoksīdā **63**. Dibromētais savienojums **64** tika reducēts ar nātrija sulfītu. Savukārt esteris **60** tika pakļauts halogenēšanai un atkārtotai Krapčo dekarboksilēšanai. Sulfoksīda **63** arilēšanas reakcijā tika iegūts mērķa savienojums **36-Br** ar labu iznākumu.



10. att. Bromfluormetilsulfonija sāls **36-Br** iegūšana.

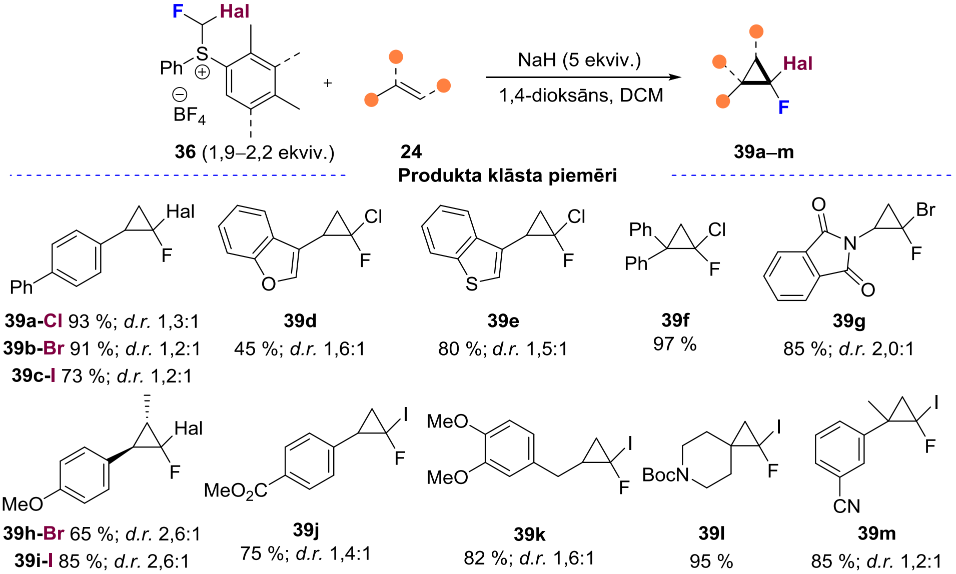
Veiksmīgai jodu saturoša sulfonija sāls **36-I** sintēzei tika īstenota estera **60** hidrolīze un skābes **66** halodekarboksilēšana zilajā gaismā (11. att.). Sulfoksīds **67** tika iegūts ar labu iznākumu četrās stadijās, sākot no tiofenola (**57**). Savukārt arilēšanas reakcijai tika izmantots elektronbagātāks arēns – tetrametilbenzols, kas palīdzēja uzlabot reakcijas iznākumu un produkta **36-I** kristāliskumu.



11. att. Jodēta sulfonija **36-I** sāls iegūšana.

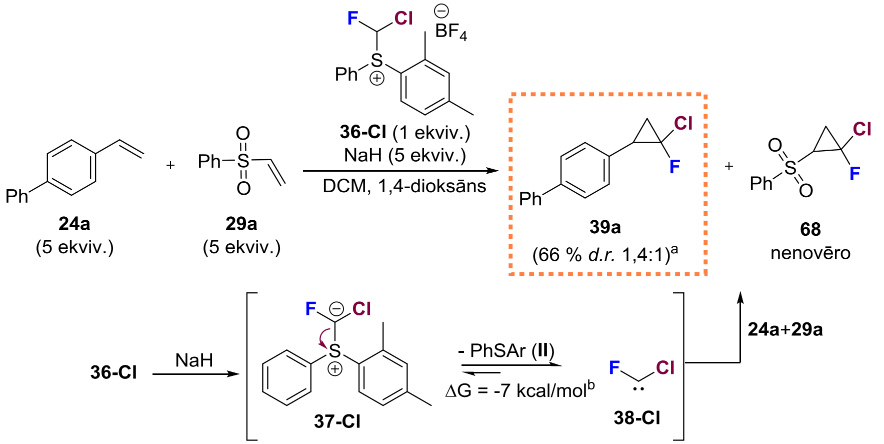
Pētījuma turpinājumā tika noskaidroti optimālie reakcijas apstākļi alkēnu **24** ciklopropanēšanas reakcijai (12. att.). Augstākie produkta **39** iznākumi tika sasniegti, veicot lēnu sulfonija sāls **36** šķīduma pievienošanu alkēna **24** un bāzes maisījumam. Lai sasniegtu pilnu alkēna **24** konversiju, nācās izmantot sulfonija sāls **36** pārākumu. Labākos ciklopropāna **39** iznākumus sniedza bāzes nātrija hidrīda, kā arī šķīdinātāju 1,4-dioksāna un dihlormetāna maisījuma izmantošana.

Optimālos reakcijas apstākļos tika veikta alkēnu **24** substrātu klāsta izpēte (12. att.). Reakcija veiksmīgi noris ar visiem trim (Hal = Cl, Br, I) sulfonija sāļiem **36**. Reakcijas apstākļi tolerē heterocikliskas sistēmas **24d** un **24e**, kā arī 1,1- un 1,2-diaizvietotus alkēnus **24f** un **24h**. Turklāt nekonjugētu dubultsaišu **24k** un **24l** ciklopropanēšana norit ar augstu iznākumu. Tādas funkcionālās grupas kā metoksi- **24h**, metoksikarbonil- **24j**, ciano- **24m**, kā arī *Boc* aizsargāts amīns **24l** ir savietojamas ar ciklopropanēšanas apstākļiem, veidojot produktus **39** ar labiem līdz izciliem iznākumiem kā divu diastereomēru maisījumu.



12. att. Ciklopropānu **39** klāsts.

Lai pārliecinātos par fluorhalokarbēna intermediāta veidošanos, reakcijas apstākļos tika veikti konkurējoši eksperimenti (13. att.), vispirms aplūkojot elektronbagāta alkēna **24a** un eletronnabadzīga alkēna **29a** reaģētspēju ar sulfonija sāli **36-Cl**. Ja reakcijas apstākļos veidotos elektrofīls dihalokarbēns, tad elektronbagāts alkēns **24a** būtu privileģēts substrāts un līdz ar to uzrādītu augstāku produkta **39a** iznākumu. Savukārt, ja ciklopropanēšana noris caur ilīda pievienošanos dubultsaitei un tam sekojošu iekšmolekulāru ciklizēšanu, tad vinilsulfons **29a** būtu labvēlīgs substrāts. Veicot šādu reakciju, tika novērots tikai alkēna **24a** ciklopropanēšanās produkts **39a**, kas liecina par dihalokarbēna **38-Cl** veidošanos reakcijas apstākļos. Turklāt kvantu ķīmiskie aprēķini liecina, ka α-eliminēšana ilīdā **37-Cl** ir termodinamiski labvēlīgs process.

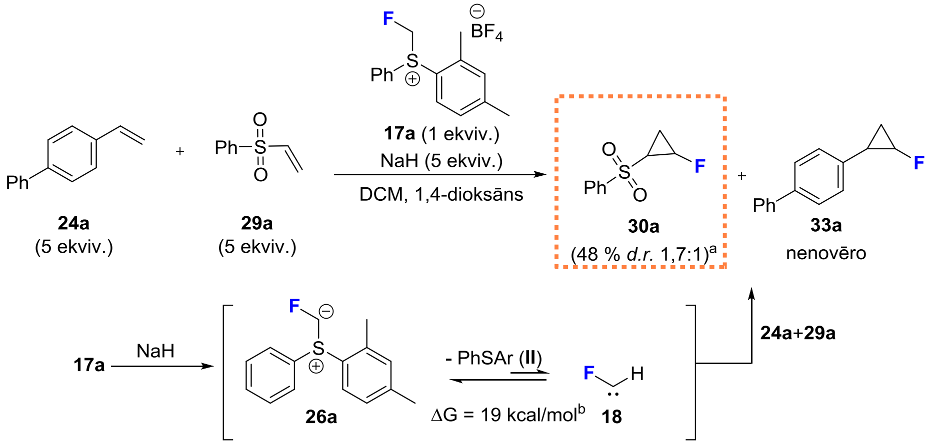


[a] Reakcijas produktu iznākums un *d.r.* noteikts ar ^{1}H KMR no tehniskā reakcijas maisījuma, izmantojot EtOAc par iekšējo standartu.

[b] Gibsa brīvā enerģija karbēna **38-Cl** veidošanai. Optimizēts ar m062x/Def2SVP metodi.

13. att. Sulfonija sāls **36-Cl** reaģētspējas salīdzinājums ar alkēniem **24a** un **29a**.

Tālākā darba izstrādes gaitā tika salīdzināta arī monofluormetilsulfonija sāls **17a** reakcija ar šiem pašiem alkēniem (14. att.). Attiecīgi, ja reakcija norisinātos caur fluorkarbēna **18** starpproduktu, būtu sagaidāma alkēna **24a** ciklopropanēšana. Taču šajā gadījumā tika novērota selektīva elektronnabadzīga alkēna **29a** ciklopropanēšana, kas liecina, ka reakcija noris, visticamāk, caur ilīda **26a** starpproduktu, nevis brīva karbēna **18** iesaisti. Turklāt kvantu ķīmiskie aprēķini liecina, ka monofluorēta karbēna **18** veidošanās ir termodinamiski neizdevīgs process.

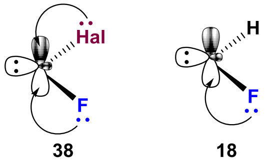


[a] Reakcijas produktu iznākums un *d.r.* noteikts ar ^{1}H KMR no tehniskā reakcijas maisījuma, izmantojot EtOAc par iekšējo standartu.

[b] Gibsa brīvā enerģija karbēna **18** veidošanai. Optimizēts ar m062x/Def2SVP metodi.

14. att. Sulfonija sāls **17a** reaģētspējas salīdzinājums ar alkēniem **24a** un **29a**.

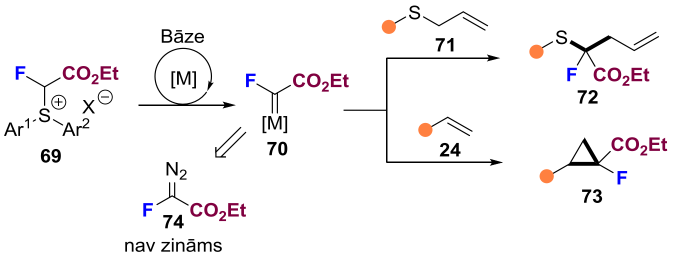
Iegūtos rezultātus var skaidrot, salīdzinot singleta karbēna struktūras (15. att.), kas halokarbēnu gadījumā ir enerģiski izdevīgākas par tripleta stāvokli. Salīdzinot ar monohalokarbēnu **18**, divus halogēna atomus saturošiem karbēniem **38** ir iespējama rezonanses stabilizēšana no abiem halogēna atomiem, kas spēj donēt elektronu blīvumu no nedalītajiem elektronu pāriem tukšajā karbēna p-orbitālē. Līdz ar to dihalokarbēnu **38** veidošanās ir termodinamiski izdevīgāka nekā monohalokarbēnu **18**.



15. att. Halokarbēnu salīdzinājums.

2. Metālu katalizēta fluoracetilkarbēnu pārnese no sulfonija sāļiem

Nākamajā pētījuma posmā tika nolemts pievērsties ar estera grupu funkcionalizētam fluormetilsulfonija sālim **69** (16. att.).[51] Tika izvirzīta hipotēze, ka reaģents **69** bāzes un pārejas metāla katalizatora klātbūtnē būtu spējīgs ģenerēt elektrofīlu metāla karbēna kompleksu **70**. Tas pavērtu iespējas lietot savienojumu **69** metālu karbēnu kompleksiem raksturīgās reakcijās, piemēram, *Doyle-Kirmse* pārgrupēšanās reakcijā ar alilsulfīdiem **71** vai arī alkēnu **24** ciklopropanēšanā. Turklāt estera grupa dotu iespējas turpmākām funkcionalizēšanas reakcijām. Šī stratēģija būtu īpaši lietderīga, jo attiecīgais diazosavienojums **74** nav zināms.

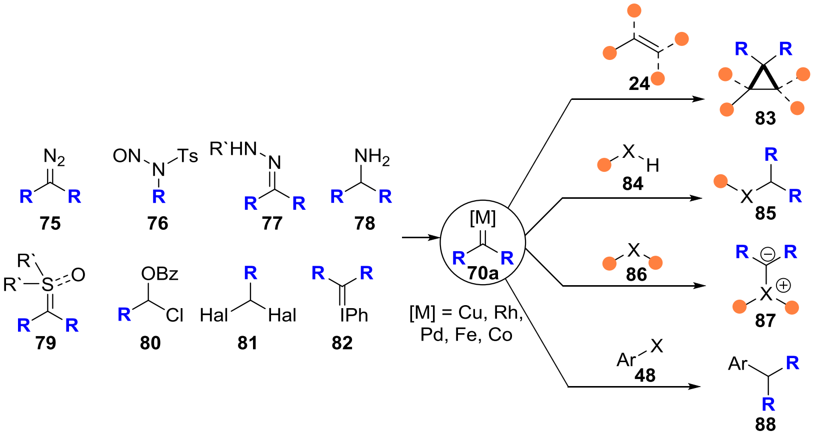


16. att. Sulfonija sāļi kā fluoracetilkarbēnu avots.

Metāla karbēna kompleksiem organiskajā ķīmijā ir plašs lietojums.[52] Metāla karbēna saite ietver karbēna elektronu pāra σ-donēšanu metāla centram un π-atpakaļdonēšanu (*π-backdonation*) no metāla karbēna tukšajā p-orbitālē.[53–54] Elektroniskie efekti metāla karbēna kompleksos ir ļoti atkarīgi no metāla, tā oksidēšanās pakāpes, ligandiem un karbēna aizvietotājiem.[55] Atkarībā no šiem faktoriem karbēna fragments var uzrādīt nukleofīlas vai elektrofīlas īpašības vai arī darboties kā inerts ligands, kas ietekmē paša metāla reaģētspēju.[56] Metāla katalizatoru un tā ligandu modificēšana sniedz iespēju būtiski ietekmēt karbēna centra elektroniskos un stēriskos efektus, tādējādi uzlabojot ķemoselektivitāti, reģioselektivitāti un paverot iespējas asimetriskām transformācijām.[57]

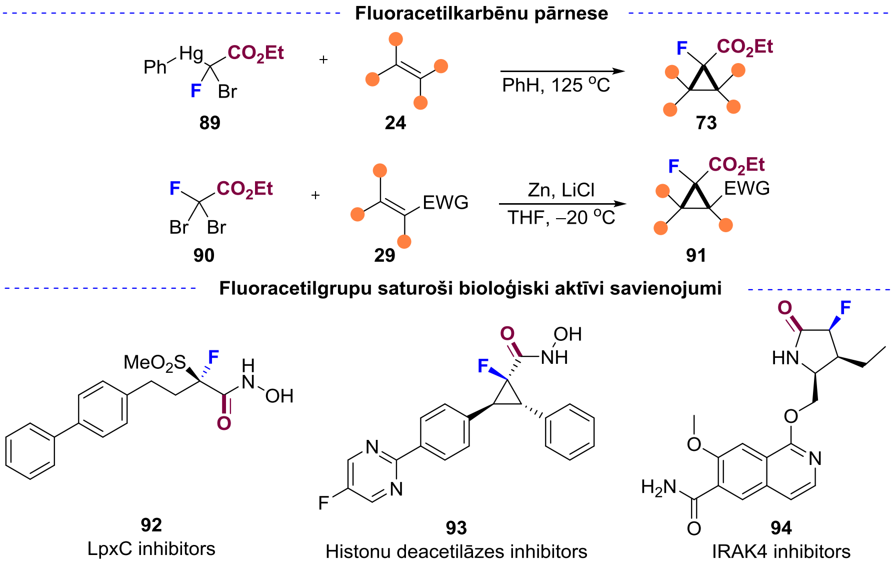
Metāla karbēna kompleksi **70a** parasti ir ļoti reaģētspējīgi starpsavienojumi. Klasiski to ģenerēšanai tiek lietoti diazosavienojumi **75**[58–60] un to prekursori – nirozoamīni **76**, hidrazoni **77** un amīni **78** (17. att.). Tomēr, ņemot vērā diazosavienojumu **75** nestabilitāti[61–62], sprādzienbīstamību un toksicitāti, ir pētīti jauni karbēna avoti. Sulfonija, sulfoksonija ilīdi **79**[63], α-aciloksihalīdi **80**, dihalosavienojumi **81**[64] un jodonija ilīdi **82**[65] sniedz līdzvērtīgu reaģētspēju pārejas metālu katalizētās karbēnu pārneses reakcijās.

Elektrofīlie metāla karbēna kompleksi uzrāda līdzīgu reaģētspēju kā brīvi karbēni. Tie piedalās [2+1] ciklopievienošanās reakcijās ar alkēniem **24** un alkīniem.[66] Ir iespējams veikt karbēna fragmenta pārnesi uz dažādiem nukleofīliem **84**, kā arī veikt ievietošanos C-H saitē.[67] Turklāt tie piedalās ilīdu **87** veidošanā, šķērssametināšanas[68] un citās reakcijās, parādot to daudzveidīgo reaģētspēju.



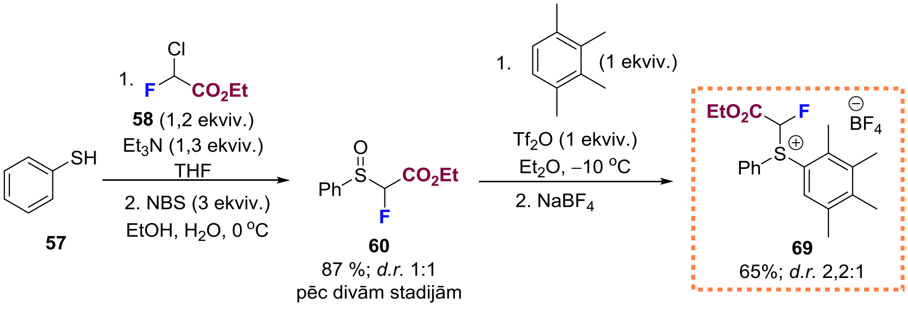
17. att. Metāla karbēnu kompleksu ģenerēšana un lietojums.

Pētījumu iesākot, bija zināms, ka fluoracetilkarbēnu pārnesi var veikt ar organodzīvsudraba reaģentu **89**[69], kas paaugstinātā temperatūrā reaģē ar alkēniem **24**, veidojot ciklopropānus **73**. Turklāt arī dibromofluoracetāts **90**[70] ir piemērots savienojums formālai fluoracetilkarbēna pārnesei reakcijās ar aktivētām dubultsaitēm **29** (18. att.). Tā kā *α*-fluorkarbonilstruktūrelements ir sastopams vairākos bioloģiski aktīvos savienojumos **92-94**[71–73], autoraprāt, sulfonija sāls **69** būtu perspektīvs reaģents, kas spētu funkcionalizēt substrātu, vienlaikus ievadot gan fluora, gan estera grupu.



18. att. Fluoracetilkarbēnu pārnese un α-fluorkarbonilgrupu saturoši bioloģiski aktīvi savienojumi.

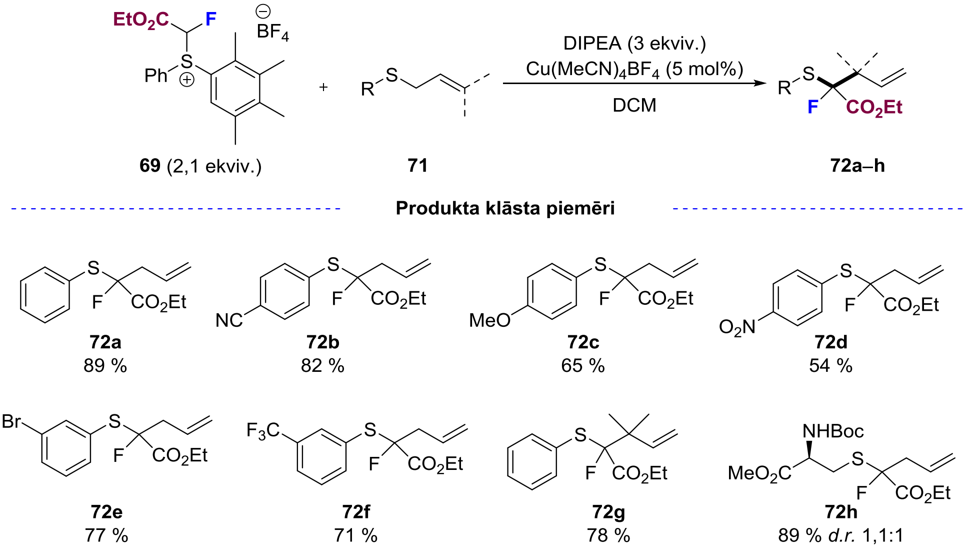
Pētījuma sākumā tika iegūts sulfonija sāls **69** (19. att.). Vispirms tika alkilēts tiofenols (**57**), kam sekoja sulfīda oksidēšana līdz sulfoksīdam **60**. Esteris **60** tika pakļauts Frīdela-Kraftsa arilēšanai un ar labu iznākumu iegūts sulfonija sāls **69** kā divu diastereomēru maisījums.



19. att. Etoksiacetilaizvietota sulfonija sāls **69** sintēze.

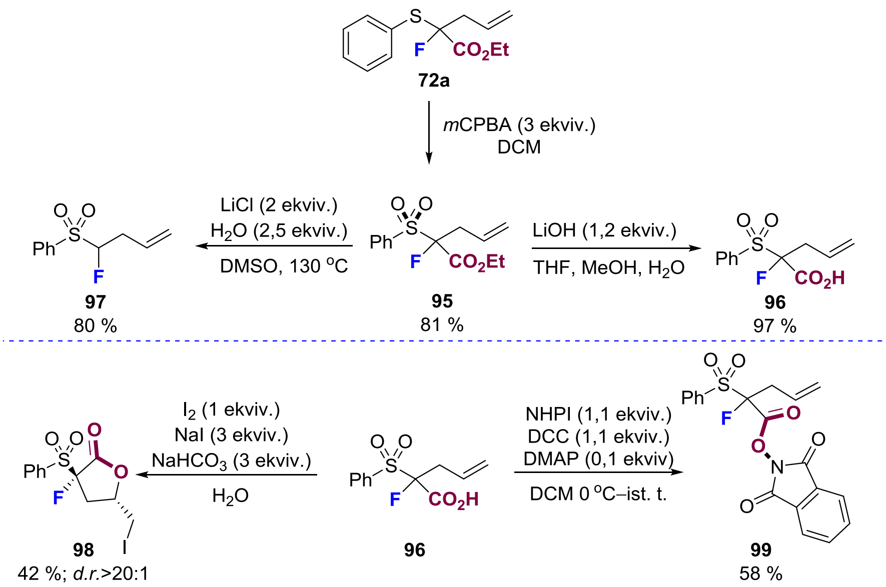
Tika pārbaudīta reaģenta **69** spēja veikt fluoracetilkarbēnu pārnesi uz alilsulfīdu **71a**, kā rezultātā veidotos [2,3]-sigmatropās pārgrupēšanās produkts – fluoru saturošs homoalilsulfīds **72a** (20. att.). Tika atklāts, ka augstāko produkta **72a** iznākumu ir iespējams sasniegt ar vara katalizatoru, par bāzi lietojot diizopropiletilamīnu. Līdzīgi kā dihalokarbēnu reakcijās, bija nepieciešams veikt lēnu sulfonija sāls **69** pievienošanu reakcijas maisījumam.

Optimālos reakcijas apstākļos tika veikta substrātu klāsta izpēte (20. att.). Reakcijas apstākļus var piemērot ciano- **71b**, metoksi- **71c**, nitro- **71d**, brom- **71e** trifluormetil- **71f** funkcionālo grupu saturošiem alilsulfīdiem **71**. Turklāt ar divām metilgrupām aizvietots alilfragments **71g** veiksmīgi viedo attiecīgo pārgrupēšanās produktu **72g**. Izstrādāto metodi var piemērot alilcisteīna atvasinājuma **71h** funkcionalizēšanai.



20. att. [2,3]-Sigmatropās pārgrupēšanās produkti.

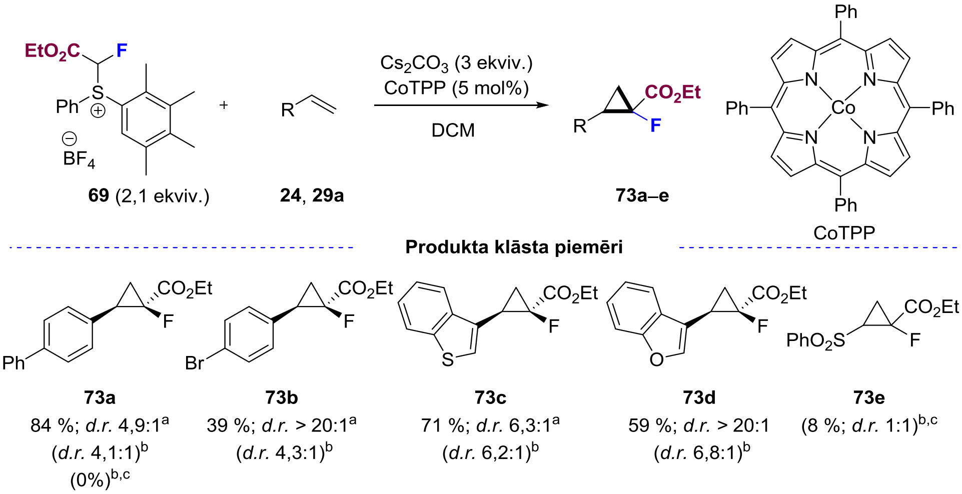
Ar savienojumu **72a** tika veikta funkcionalizēšanu reakciju izpēte (21. att.). Vispirms sulfīds **72a** tika oksidēts līdz sulfonam **95**. Savukārt estera grupu savienojumā **95** var veiksmīgi hidrolizēt, iegūstot skābi **96**. Pakļaujot savienojumu **95** dekarboksilēšanai, tika iegūts homoalilsulfons **97** ar ļoti labu iznākumu. Ar skābi **96** var veikt diastereoselektīvu jodlaktonizēšanu, iegūstot *γ*-laktonu **98**, un sintezēt aktivētu esteri **99**.



21. att. Savienojuma **72a** modificēšanas iespējas.

Darba turpinājumā tika aplūkota stirolu **24** ciklopropanēšanas reakcija ar sulfonija reaģentu **69** (22. att.), atklājot, ka kobalta porfirīns kombinācijā ar cēzija karbonātu kā bāzi dihlormetānā ir piemērotākie reakcijas apstākļi alkēnu **24** ciklopropanēšanai. Turklāt šajā gadījumā nav nepieciešams veikt lēnu sulfonija sāls **69** pievienošanu reakcijas maisījumam. Produkti **73a-d** veidojas ar zemiem līdz labiem iznākumiem kā divu diastereomēru maisījums ar vidēji labu selektivitāti.

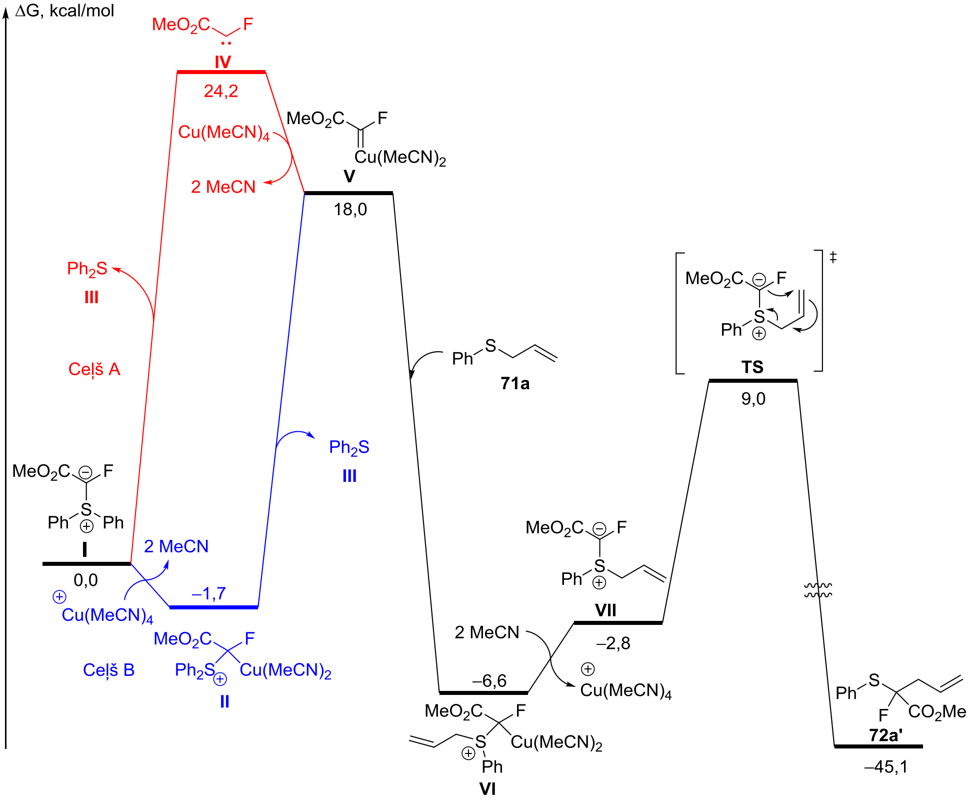
Veicot alkēna **24a** ciklopropanēšanu bez metāla katalizatora, produkta **73a** veidošanās netika novērota. Kā substrātu izmantojot vinilsulfonu **29a**, tika novērota ciklopropāna **73e** veidošanās arī bez metāla katalizatora. Šie novērojumi liecina, ka brīva karbēna veidošanās no sulfonija sāls **69** bāzes klātbūtnē, visticamāk, nenotiek.



[a] Izolētais iznākums. [b] Noteikts no tehniskā reakcijas maisījuma. [c] Bez katalizatora.

22. att. Alkēnu ciklopropanēšanas produkti.

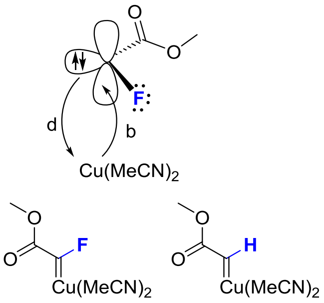
Doyle-Kirmse reakcijas mehānisma izpētei tika veikti DFT aprēķini (23. att.), sākotnēji aplūkojot brīva karbēna **IV** veidošanās iespēju (Ceļš A), taču saskaņā ar aprēķiniem tas ir termodinamiski neizdevīgs process. Tas atbilst iepriekšējiem novērojumiem, kuros alkēna **24a** ciklopropanēšana nenotiek bez katalizatora. Savukārt ilīda **I** koordinēšanās pie metāla (Ceļš B) ir termodinamiski izdevīga. Metāla karbēna kompleksa **V** veidošanās, eliminējot diarilsulfīdu **III**, ir reakcijas limitējošā stadija un enerģētiski neizdevīga, taču joprojām sasniedzama istabas temperatūrā. Nākamajā solī seko alilsulfīda **71a** koordinēšanās pie elektrofīlā karbēna centra, ilīda **VII** veidošanās un metāla katalizatora atgriešana katalītiskajā ciklā. Visbeidzot ilīds **VII** veic [2,3]-sigmatropo pārgrupēšanos, veidojot galaproduktu **72a’**.



23. att. Iespējamais *Doyle-Kirmse* reakcijas mehānisms.

Lai noskaidrotu fluora atoma ietekmi uz metāla karbēna kompleksa īpašībām, tika veikta lādiņu sadalīšanas analīze fluoracetil- **V-F** un acetilkarbēna **V-H** metāla kompleksam (24. att.). Izmantojot šo metodi, tiek aprakstīts karbēna σ elektronu donēšana (d) metāla tukšajās orbitālēs un attiecīgi metāla atpakaļdonēšana (b) (*back donation*) liganda tukšajā orbitālē.[54, 74]

Fluorēta karbēna **V-F** gadījumā tika novērota augstāka donēšanas vērtība (d) metāla centram nekā nefluorēta karbēna **V-H** gadījumā. To varētu skaidrot ar fluora nedalīto elektronu pāru un karbēna elektronu atgrūšanos. Savukārt atpakaļdonēšana fluorēta karbēna **V-F** gadījumā ir mazāka, jo, visticamāk, fluora nedalītie elektronu pāri daļēji aizpilda karbēna tukšo orbitāli. Šie rezultāti liecina, ka fluora atoms darbojas kā elektrondonējošs aizvietotājs. Savukārt LUMO enerģija fluorkarbēna **V-F** gadījumā ir negatīvāka, un tā globālā elektrofilitāte (ω) augstāka, kas liecinātu par **V-F** augstāku reaģētspēju reakcijās ar nukleofīliem.



	V-F	**V-H**
donēšana (d)	0,326	0,287
atpakaļdonēšana (b)	0,035	0,050
ε_{LUMO} (eV)	–7,220	–6,843
ω	11,608	10,203

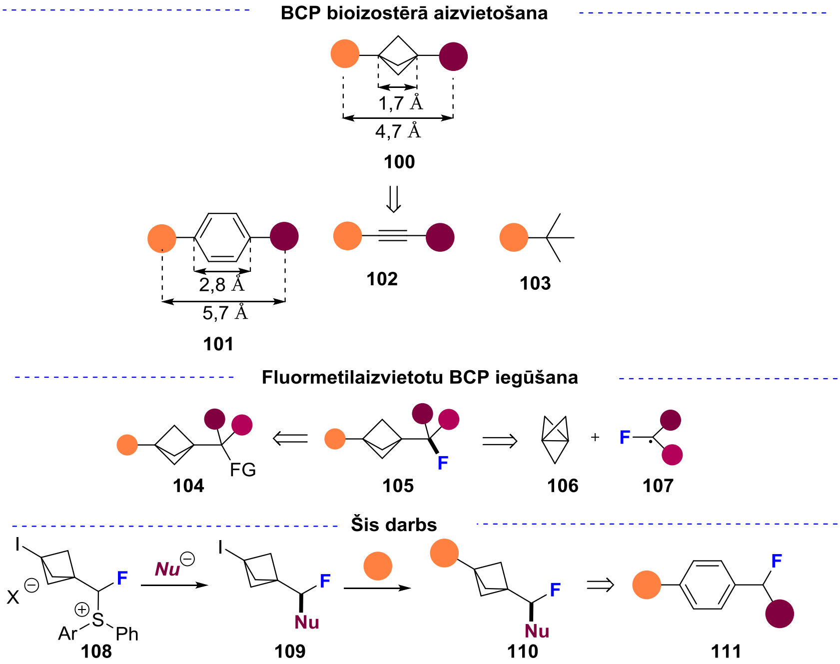
24. att. Fluorēta **V-F** un nefluorēta **V-H** karbēna metāla kompleksa elektroniskie efekti.

3. Fluormetilbicklo[1.1.1]pentāna pārnese no sulfonija sāļiem

Turpinot monofluorētu sintonu pārneses pētījumus no fluormetilsulfonija sāļiem, tika saskatīta iespēja izstrādāt ar bicklo[1.1.1]pentilgrupu (BCP) aizvietotus reaģentus **108** (25. att.).[75] Biciklo[1.1.1]pentāni **100** ir nozīmīgi medicīnas ķīmijā, jo tie var kalpot kā benzola **101**, alkīnu **102** un *t*-butilgrupu **103** bioizostēri.[76–77] Benzola bioizostērā aizvietošana ar BCP var uzlabot metabolisko stabilitāti, jo tiek novērsts oksidējošs arēnu metabolisms, un palielināt šķīdību udenī, jo tiek mazinātas starpmolekulārās π–π mijiedarbības.[76]

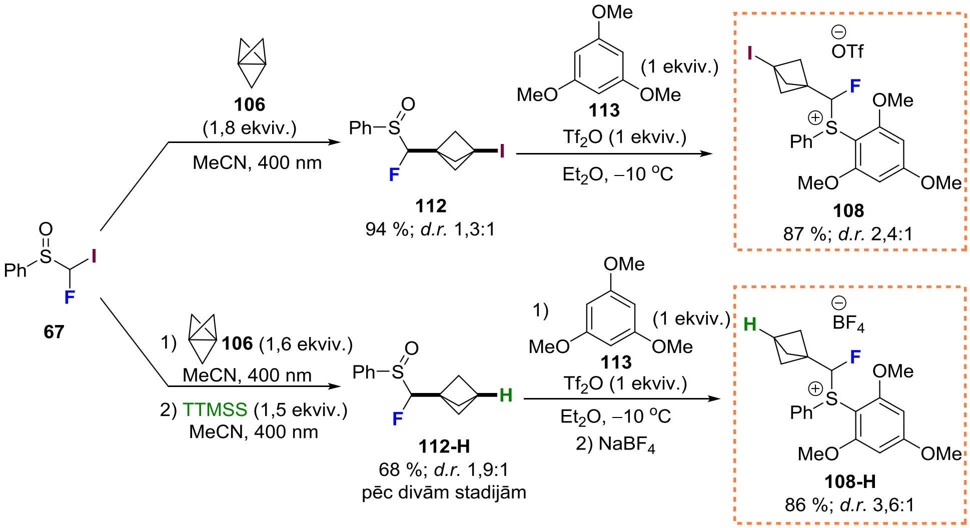
Līdzšinējās metodes monofluormetilaizvietotu BCP **105** iegūšanā balstās funkcionālo grupu pārvērtībās[78] vai fluormetilradikāļu **107**[79–80] pievienošanā [1.1.1]propellānam (**106**).

Līdz ar to tika izvirzīta hipotēze, ka sulfonija sāļi **108** varētu kalpot modulārai ar fluormetilēngrupu saistītu BCP atvasinājumu konstruēšanai. Proti, diarilsulfīda grupa kalpotu kā aizejošā grupa reakcijās ar nukleofīliem[81], turklāt joda aizvietotājs BCP grupā būtu papildu vektors tālākai funkcionalizēšanai, tādējādi iegūstot benzilfluorīda **111** piesātinātus trīsdimensionālus bioizostērus **110**.



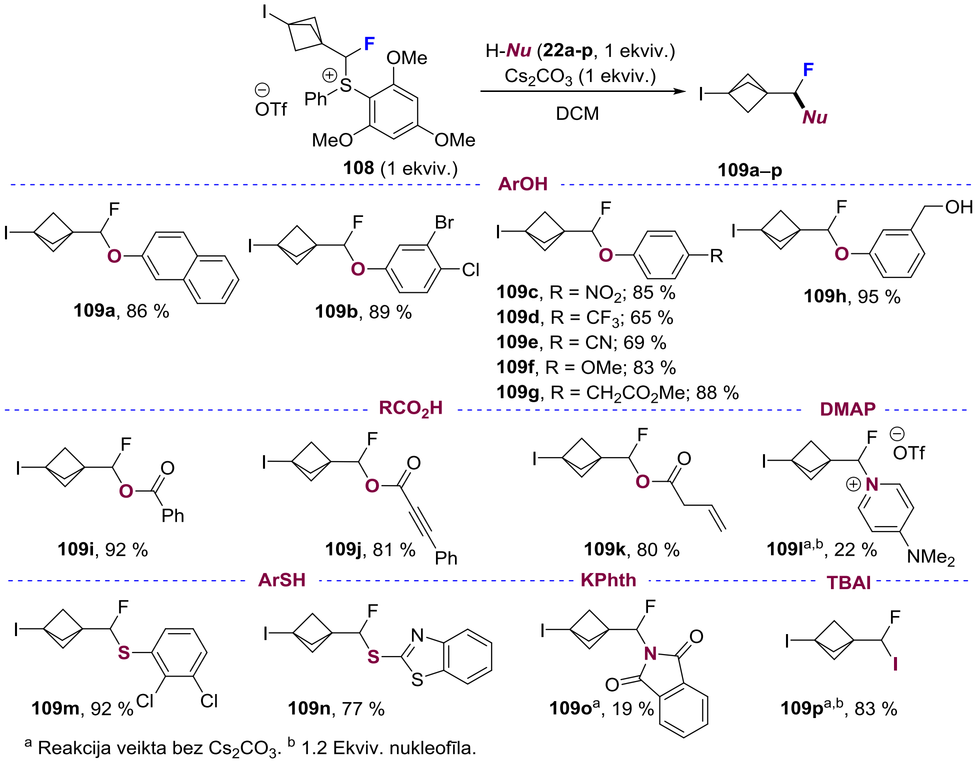
25. att. Biciklopentilgrupas lietojums un iegūšana.

Pētījuma sākumā tika izstrādātas sintēzes metodes BCP fluormetilsulfonija sāļu **108** un **108-H** iegūšanai (26. att.). Sulfoksīds **67** violetajā gaismā ir spējīgs pievienoties propellānam **106**, kā rezultātā tika iegūts biciklopentāns **112** ar izcilu iznākumu. Turklāt joda atomu savienojumā **112** var efektīvi dehalogenēt ar silānu. Šeit vērts izcelt, ka propellāna uzšķelšana noris bez iniciatoru un fotokatalizatoru klātbūtnes. Tālāk attiecīgos sulfoksīdus **112** un **112-H** var pārvērst sulfonija sāļos **108** un **108-H** reakcijā ar trifluormetānsulfonskābes anhidrīdu un trimetoksibenzolu **113**. Šī elektronbagātā arēna **113** izmantošana bija nepieciešama, lai nodrošinātu augstu produkta **108** iznākumu.



26. att. BCP aizvietotu fluormetilsulfonija sāļu **108** iegūšana.

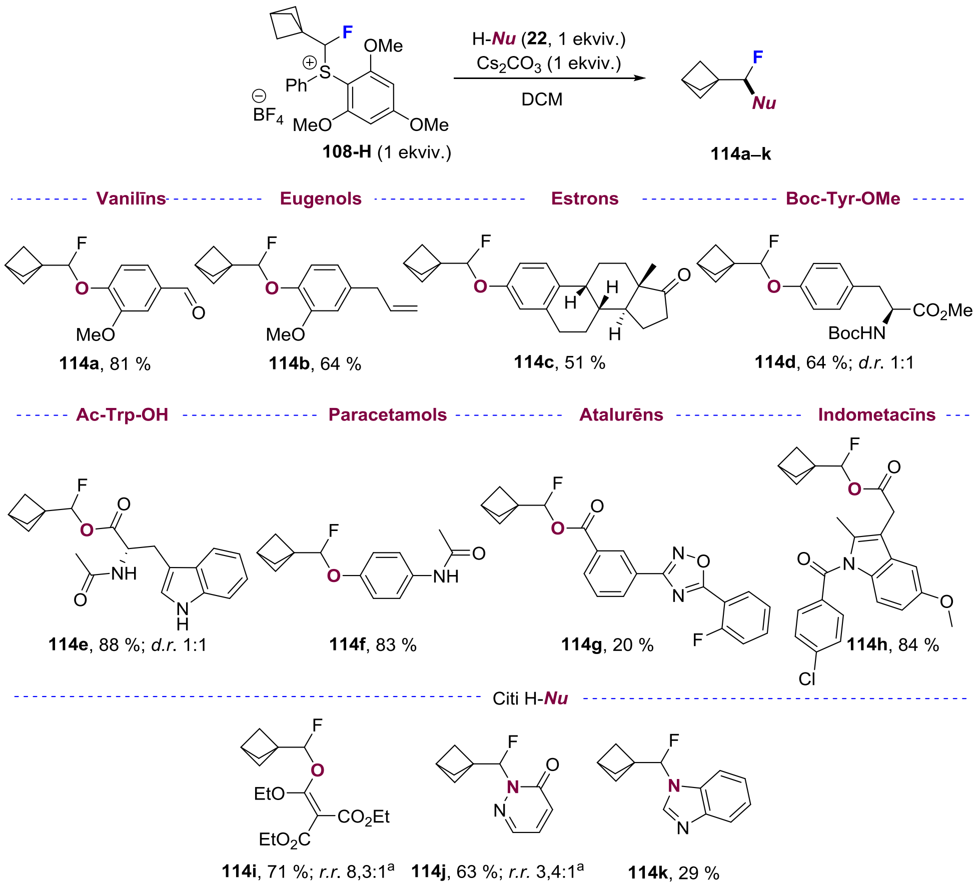
Optimālos reakcijas apstākļos tika veikta substrātu klāsta izpēte (27. att.). Labu līdz izcilu produktu iznākumu novēro reakcijās ar fenoliem **22a-h**, karbonskābēm **22i-k** un tioliem **22m-n**. Šeit jāatzīmē, ka reakcijā selektīvi tiek alkilēts fenola skābekļa atoms, atstājot benzilspirta grupu **22h** neskartu. Tādas funkcionalās grupas kā nitro- **22c**, trifluormetil- **22d**, ciano- **22e**, metoksikarbonil- **22g**, metoksi- **22f**, halogēna atomi **22b**, alkēni **22k** un alkīni **22j** ir saderīgas ar optimizētajiem reakcijas apstākļiem. Heterociklu saturoši nukleofīli **22l**, **22n** un **22o** arī ir saderīgi ar izstrādāto metodi.



[a] Reakcija veikta bez Cs_2CO_3. [b] 1.2 Ekviv. nukleofīla.

27. att. **108** alkilēšanas substrātu klāsts.

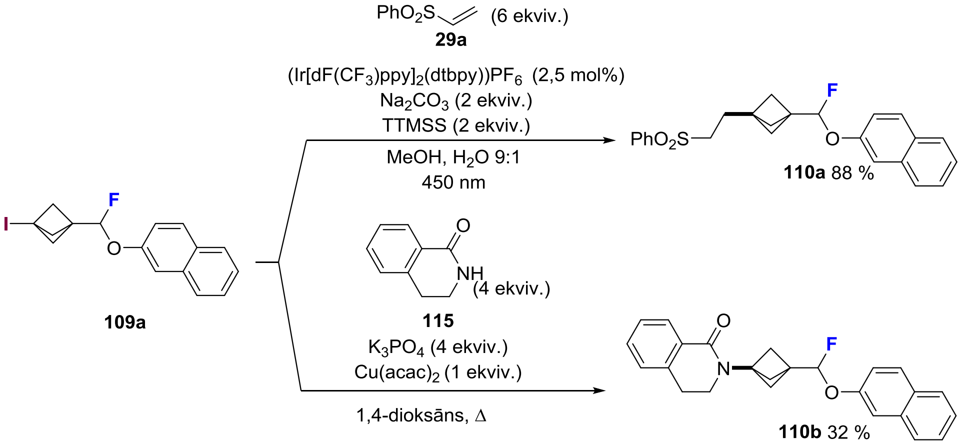
Pētījuma turpinājumā tika aplūkota arī dejodētā sāls **108-H** spēja stāties nukleofīlajās aizvietošanas reakcijās (28. att.). Tādas dabasvielas kā vanilīns, eugenols un estrons tiek veiksmīgi alkilētas, veidojot produktus **114a-c** ar viduvējiem līdz labiem iznākumiem. Metodi var veiksmīgi lietot arī dažādu aminoskābju un zāļvielu funkcionalizēšanai. Reakcijas lietojums tika paplašināts ar trikarboksilāta skābekļa alkilēšanu un *N*-heterociklu funkcionalizēšanu, kā rezultātā iegūti produkti **114i-k**.



[a] Reģioizomēru attiecība noteikta no tehniskā reakcijas masīījuma.

28. att. **108-H** alkilēšanas substrātu klāsts.

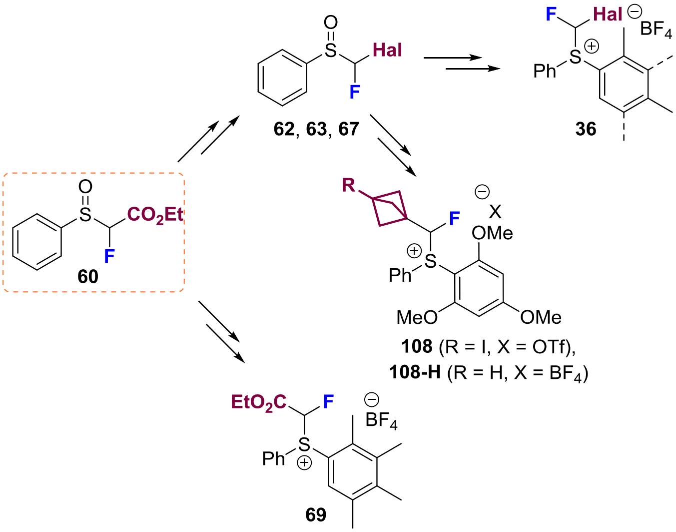
Tālākā darba gaitā tika veiktas joda atoma funkcionalizēšanas reakcijas savienojumam **109a** (29. att). Jodīdu **109a** var veiksmīgi lietot irīdija fotokatalizētai pievienošanai vinilsulfonam **29a**, kā rezultātā tika iegūts 1,3-diaizvietots biciklopentāns **110a** ar teicamu iznākumu.[82] Turklāt savienojumu **109a** var pakļaut vara veicinātai C-N saites veidošanai ar amīdu **115**, iegūstot aminēšanas produktu **110b** ar viduvēju iznākumu.[83]



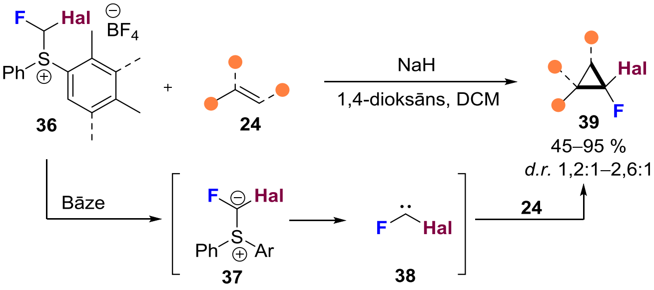
29. att. Jodīda **109a** funkcionalizēšanas reakcijas.

SECINĀJUMI

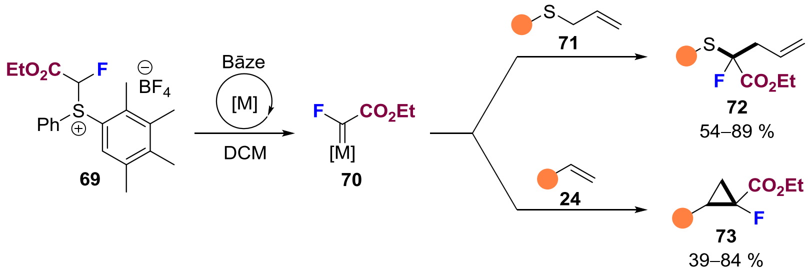
1. Sulfoksīds **60** ir stratēģisks starpsavienojums, lai iegūtu funkcionalizētus fluormetilsulfonija sāļus **36**, **69** un **108**. Estera **60** funkcionālās grupas pārvērtības ir efektīvs paņēmiens, lai ievadītu otru halogēna atomu un iegūtu dihalometilsulfoksīdus **62**, **63** un **67**. Šos sulfoksīdus var pārvērst par dihalometilsulfonija sāļiem **36** vai pievienot propellānam, lai iegūtu biciklopentilaizvietotus fluormetilsulfonija būvblokus **108**.



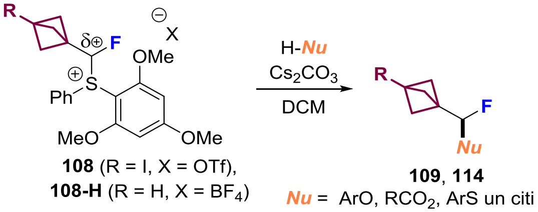
2. Dihalometilsulfonija sāļi **36** bāzes klātbūtnē reaģē ar alkēniem **24**, veidojot dihalociklopropānus **39** ar viduvējiem līdz teicamiem produkta iznākumiem kā divu diastereomēru maisījumu. Konkurējošie eksperimenti un DFT aprēķini liecina par elektrofīla dihalokarbēna **38** ģenerēšanu reakcijas apstākļos.



3. Etoksikarbonilaizvietots fluormetilsulfonija sāls **69** bāzes un metāla katalizatora klātbūtnē reaģē ar alilsulfīdiem **71** un alkēniem **24**, veidojot [2,3]-sigmatropās pārgrupēšanās produktus **72** un ciklopropānus **73**. DFT aprēķini un kontroleksperimenti liecina, ka sulfonija sāls **69** bāzes un metāla katalizatora klātbūtnē veido elektrofīlu metāla karbēna kompleksu **70**.



4. Biciklo[1.1.1]pentilaizvietoti fluormetilsulfonija sāļi **108** kalpo kā elektrofīli fluoralkilgrupas avoti. Fenoli, tioli, karbonskābes un citi nukleofīli tiek efektīvi alkilēti maigos apstākļos, iegūstot fluoralkilaizvietotus produktus.



DOCTORAL THESIS PROPOSED TO RIGA TECHNICAL UNIVERSITY FOR PROMOTION TO THE SCIENTIFIC DEGREE OF DOCTOR OF SCIENCE

To be granted the scientific degree of Doctor of Science (PhD), the present Doctoral Thesis has been submitted for defence at the open meeting of RTU Promotion Council on 12 June 2026 9:00, at the Faculty of Natural Sciences and Technology of Riga Technical University, Paula Valdena iela 3, Room 272.

OFFICIAL REVIEWERS

Professor Dr. chem. Edgars Sūna,
University of Latvia

Principal Researcher Dr. chem. Pāvels Arsenjans,
Latvian Institute of Organic Synthesis, Latvia

Professor PhD Manuel Alcarazo,
Georg-August University of Göttingen, Germany

DECLARATION OF ACADEMIC INTEGRITY

I hereby declare that the Doctoral Thesis submitted for review to Riga Technical University for promotion to the scientific degree of Doctor of Science (PhD) is my own. I confirm that this Doctoral Thesis has not been submitted to any other university for promotion to a scientific degree.

Artūrs Sperga ……………………………. (signature)

Date …………………………….

The Doctoral Thesis has been prepared as a thematically united collection of scientific publications. It consists of a Summary, three scientific publications and one review article. Publications are written in English. The total number of pages is 34, including electronic supporting information – 397 pages.

GENERAL OVERVIEW OF THE THESIS

Introduction

The introduction of a fluorine atom into a molecule is a frequently used strategy in the development of new pharmaceuticals.[1] Replacement of a functional group or a hydrogen atom with fluorine can significantly modify pharmacological properties such as metabolic stability, bioavailability, and interaction with the target protein. Regarding the broad applications of organofluorine compounds in medicinal chemistry, agrochemistry, and materials science, the development of efficient strategies for accessing fluorinated compounds is of high interest.[2]

Traditionally, fluorination relies on electrophilic **4-6** or nucleophilic **7-10** fluorine sources to transform carbon-hydrogen bonds **1** or to convert functional groups **2** into fluorinated compounds **3** (Fig. 1).[3]

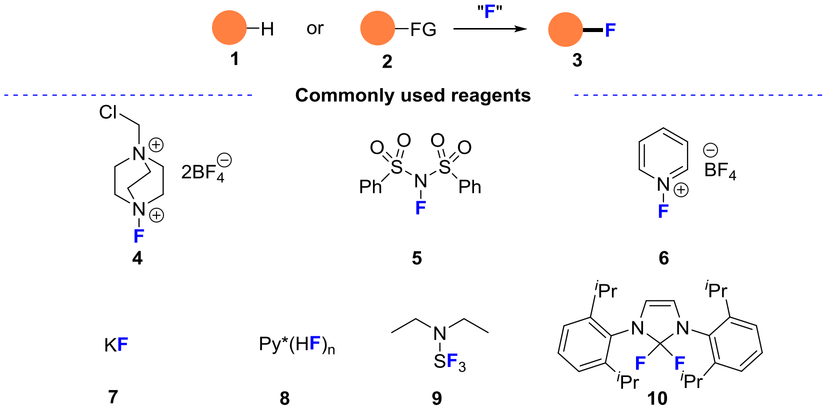


Fig. 1. Reagents for monofluorinated compound synthesis.

An alternative strategy is to functionalize molecules with fluorinated synthons bearing fluorine directly attached to the reactive carbon atom (Fig. 2).[4] While methods for introducing trifluoromethyl-[5–7] and difluoromethyl-[8] groups are well established, analogous transformations of monofluorinated synthons[9] have been less frequently studied. Nevertheless, several reagents **13-17** have been developed over the last decade for the efficient transfer of monofluorinated synthons.[10–13] It is possible to transfer fluorocarbene **18**, electrophilic **19**, nucleophilic **20** and even monofluoromethyl radical **21** species. Using the fluorinated synthon transfer approach, it is possible to access novel structural motifs **11**, **12** that would be challenging to synthesize via direct fluorination reactions.

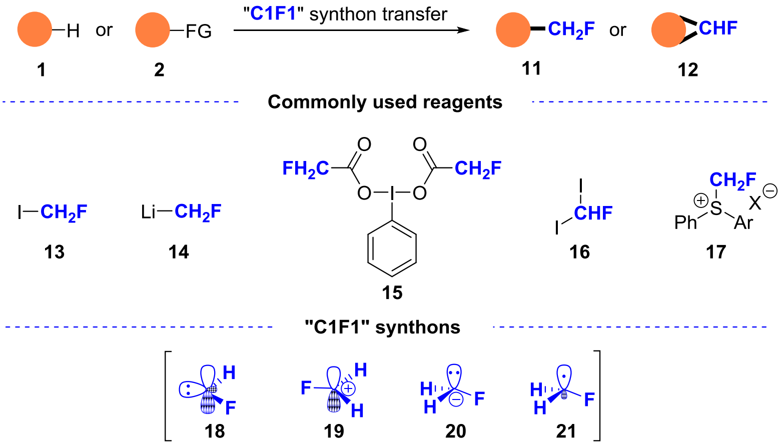


Fig. 2. Monofluorinated synthon transfer.

Among the reagents mentioned, special attention should be drawn to sulfonium salt **17**, which can serve as carbene **18**, electrophilic **19,** and radical **21** synthons (Fig. 3).[14] Sulfides are good leaving group; therefore, in the reactions with nucleophiles **22,** they serve as a source of the electrophilic fluoromethyl **19** group.[15] Upon one electron reduction, they fragment to a fluoromethyl radical **21,** which can add to alkenes **24.**[16] In our group, we have previously developed various formal fluoromethylene transfer reactions. In the presence of a base, they form sulfur ylides **26**, which can react with aldehydes **27**[17] or activated double bonds **29**[18], **31**[19] to give monofluorinated three or five membered cycles **28**, **30** and **32**. Furthermore, in the presence of a metal catalyst, it is possible to cyclopropanate unactivated alkenes **24** among other transformations.[20]

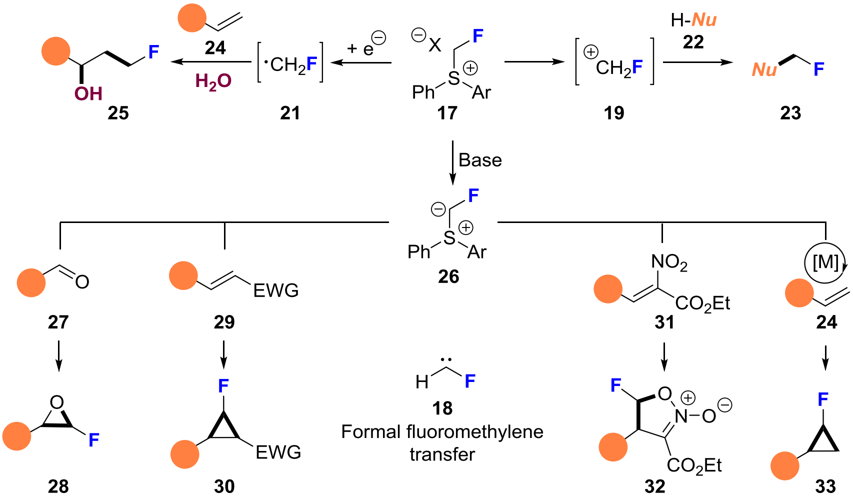


Fig. 3. Synthetic application of fluoromethylsulfonium salt **17**.

Substituted monofluoromethylsulfonium salts **34** have been rarely described in the scientific literature.[21–24] Therefore, we envisioned modifying the sulfonium structure by adding a functional group next to the reactive carbon center, thereby enabling functionalized monofluorinated synthon transfer reactions, which afford product **35** (Fig. 4). In this study, the author aimed to incorporate functional groups that are important in medicinal chemistry or that could provide further modification possibilities after the first reaction. Furthermore, the goal was to determine how these additional groups affect the reactivity of the sulfonium salt.

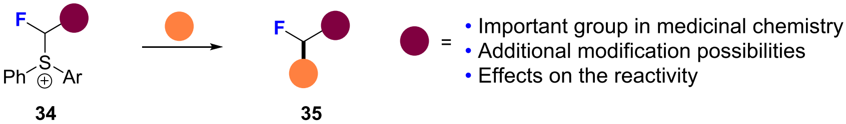


Fig. 4. Substituted fluoromethylsulfonium salts.

Aims and objectives

The doctoral thesis aims to develop novel fluoromethylsulfonium reagents, which could effectively transfer functionalized monofluorinated synthons.

To achieve the goal, the following tasks were defined:

1) synthesis of functionalized fluoromethylsulfonium salts;
2) development of fluorinated synthon transfer reactions from sulfonium salts.

Scientific novelty and main results

As a result of the Doctoral Thesis, the following results were accomplished:

1) synthesis methods of fluorhalomethylsulfonium salts;
2) fluorohalocyclopropanation of alkenes using sulfonium salts;
3) synthesis of ethoxycarbonyl substituted fluoromethylsulfonium salt;
4) metal-catalyzed fluoracetyl carbene transfer to alkenes and allyl sulfides;
5) synthesis of bicyclopentyl substituted fluoromethylsulfonium salts;
6) development of nucleophilic substitution reaction with sulfonium salts.

Structure of the Thesis

The Thesis is a thematically unified set of scientific publications about the synthesis of novel sulfonium salts and their application for fluorinated synthon transfer reactions.

Publications and approbation of the Thesis

The results of the thesis are summarized in three scientific publications and one review article. The results were presented in six conferences.

Scientific publications

1. Sperga, A.; Veliks, J., Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species. *Chemistry – A European Journal* **2023**, *29* (69), e202301851.
2. Sperga, A.; Pfeifers, T.; Zacs, D.; Veliks, J., Fluorohalomethylsulfonium Salts as a Fluorohalocarbene Source. *Organic Letters* **2024**, *26* (30), 6482–6485.
3. Sperga, A.; Kinens, A.; Veliks, J., Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts. *Organic Letters* **2025**, *27* (21), 5446–5451.
4. Sperga, A.; Pfeifers, T.; Veliks, J., Monofluorinated C1 Synthon Strategy for The Construction of Fluoromethylene-Linked Bicyclo[1.1.1]Pentane Derivatives. *Advanced Synthesis & Catalysis* **2025**, *367*, e70119.

Conferences

1. Sperga, A.; Veliks, J. Fluorohalomethylsulfonium salts as a novel fluorohalocarbene source. *81st scientific conference chemistry section*, Riga, Latvia, 17 March **2023**.
2. Sperga, A. Fluorohalomethylsulfonium salts as a novel fluorohalocarbene source. *Paul Walden 13th Symposium on Organic Chemistry*, Riga, Latvia, 14–15 September **2023**.
3. Sperga, A.; Veliks, J. Fluorohalomethylsulfonium salts: novel fluorohalocarbene source. *18th Belgian Organic Synthesis Symposium BOSS 2024*, Liège, Belgium, 30 June–5 July, **2024**.
4. Sperga, A.; Veliks, J. Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts. *Balticum Organicum Syntheticum*, Riga, Latvia, 7–10 July **2024**.
5. Sperga, A.; Pfeifers, T.; Veliks, J. Fluoromethyl Bicyclo[1.1.1]pentane Transfer from Sulfonium Salts. *23rd European Symposium on Organic Chemistry*, Copenhagen, Denmark, 29 June–3 July **2025**.
6. Sperga, A. Fluorinated Synthon Transfer from Sulfonium Salts. *14th Paul Walden Symposium*, Riga, Latvia, 25–26 September **2025**.

MAIN RESULTS OF THE THESIS

1. Fluorohalomethylsulfonium salts as a fluorohalocarbene source

Sulfonium salts can serve as an efficient platform for monofluorinated C1 synthon transfer. In order to insert an additional vector for further functionalization possibilities, the author decided to develop sulfonium reagents **36** bearing additional geminal halogen atom (Hal = Cl, Br, I) (Fig. 5).[25] Although difluoromethylsulfonium salts are known to undergo nucleophilic substitution reactions[26–28] and to generate radicals[29] and carbenes, other halogen derivatives have not been reported. Recently, Wang and co-workers reported the functionalization of bromofluorocyclopropane[30] to access diverse monofluorinated products, highlighting potential of this strategy.

The author hypothesized that reagents **36** could serve as effective fluorohalocarbene sources. Upon deprotonation with a non-nucleophilic base, an ylide **37** could form, which, followed by α-elimination of the sulfide, could generate a dihalocarbene **38** that could be trapped with alkenes **24** to form dihalocyclopropanes **39**.

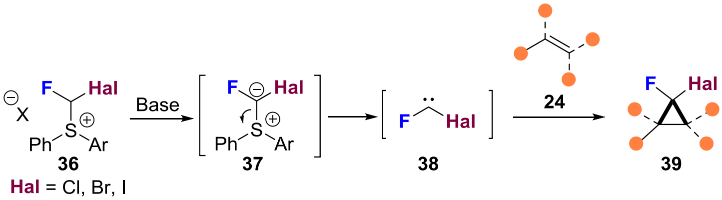


Fig. 5. Fluorohalocarbene generation from sulfonium salts **36**.

Carbenes are neutral divalent carbon intermediates bearing two substituents and two nonbonding valence electrons. Their electronic structure and reactivity are strongly influenced by the nature of substituents. Fluorohalocarbenes **38** preferentially adopt the singlet electronic state, which is energetically more favourable than the triplet state due to effective overlap of the fluorine lone pairs with the empty p-orbital of the carbene (Fig. 6).[31] Carbene reactivity depends on spin multiplicity. Singlet carbenes typically undergo concerted, single step reactions, whereas triplet carbenes react via stepwise pathways involving diradical intermediates.[32–33]

In the series of fluorohalocarbenes, difluorocarbene ($:CF_2$) is the most thermodynamically stable, exhibiting the lowest enthalpy of formation.[34] Stability decreases with substitution by heavier halogens (:CFCl, :CFBr, :CFI) because orbital overlap with second halogen atom becomes less efficient. As a result, the carbene carbon becomes more electron deficient and electrophilicity increases across the series.[31, 35]

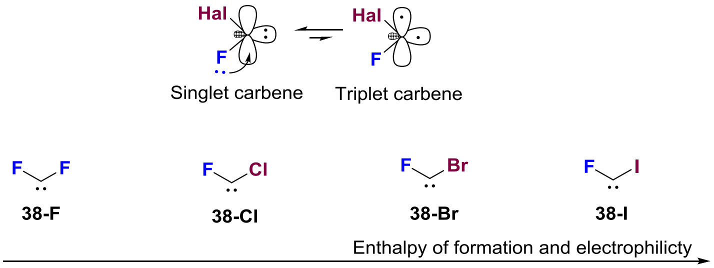


Fig. 6. Fluorocarbene properties.

Despite these stabilization effects, fluorohalocarbenes **38** are highly reactive intermediates. Within the series of fluorohalocarbenes, difluorocarbene **38-F** is the most extensively studied (Fig. 7).[36–43] It can be generated from a variety of reagents **40-44**. Typically, its formation involves the generation of a carbanionic intermediate **45** through deprotonation, decarboxylation or desilylation under basic or thermal conditions. The resulting intermediate subsequently undergoes α-elimination of a halide or other leaving group, leading to carbene **38-F** formation.

The general reactivity of difluorocarbene **38-F** is governed by its electrophilic character. It participates in a wide range of transformations, including stereospecific [2+1] cycloaddition reactions with alkenes **24** and alkynes as well as addition reactions with carbon, oxygen, nitrogen and sulfur nucleophiles **22**. Difluorocarbene is also employed in olefination and transition metal-catalyzed cross-coupling reactions.

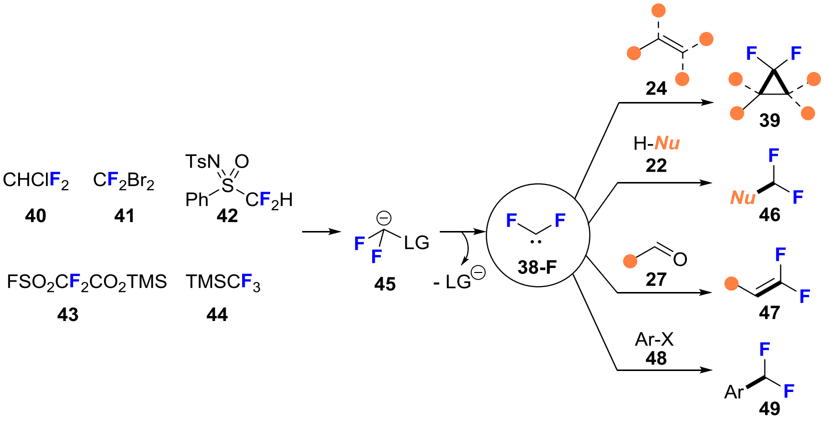


Fig. 7. Difluorocarbene generation and reactivity.

Reactions of other fluorohalocarbenes are far less studied (Fig. 8). Historically, fluorohalocarbenes **38** have been generated using fluorohalomethanes **50**[31] among other reagents. However, fluorhalomethanes possess ozone layer depleting properties.[44] Therefore, over the past decade, novel reagents like silanes **54**[45] and esters **55**[46] have been developed for effective fluorohalocarbene transfer.[32, 47] Furthermore, the recent studies have successfully expanded the substrate scope not only to alkene **24** cyclopropanation, but also to insertion in bicyclobutanes **53** C-C bonds[48] and skeletal editing in pyrroles **55**.[49]

Despite these advances, the reactivity of fluorohalocarbenes remains less developed compared to difluorocarbene. Additionally, harsh conditions, such as elevated temperatures and nucleophilic bases, are often required for fluorohalocarbene generation. In addition, fluoroiodocarbene generation is rare, with only a single reagent reported – $CHFI_2$.[50] Considering these drawbacks, the author thought that fluorohalomethylsulfonium salts **36** could provide a unified approach for fluorohalocarbene **38** transfer under mild conditions.

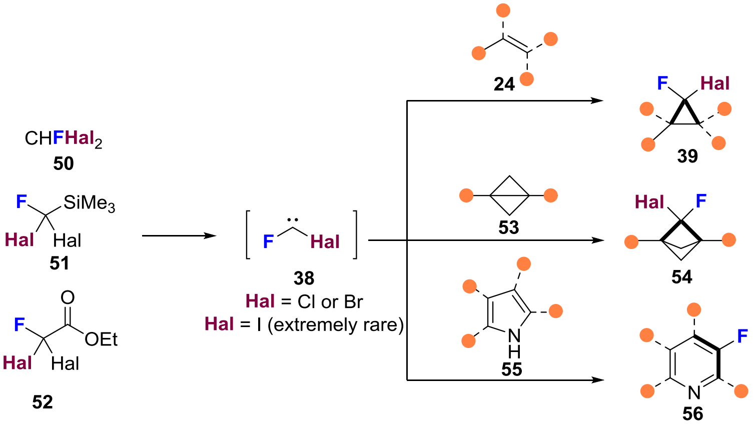


Fig. 8. Fluorohalocarbene generation and application.

The author began the study by developing a synthetic route to fluorohalomethylsulfonium salts **36**. As an initial target, chlorinated salt **36-Cl** was synthesized (Fig. 9). In the first step, thiophenol (**57**) was alkylated with ethyl chlorofluoroacetate (**58**) under basic conditions to obtain a sulfide **59**. Compound **59** was oxidized to sulfoxide **60**, followed by chlorination to afford dihaloester **61**. Krapcho decarboxylation of **61** afforded sulfoxide **62** in good yield over four steps. In the final step, Friedel–Crafts type arylation was performed with the sulfoxide **62**, and after anion exchange chlorofluoromethylsulfonium salt **36-Cl** was obtained.

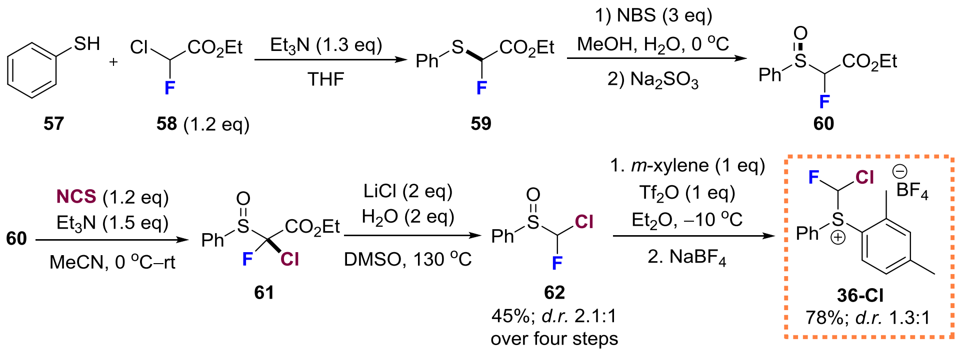


Fig. 9. Chlorine-substituted sulfonium salt **36-Cl** synthesis.

The author continued the study with the synthesis of bromine-substituted sulfonium salt **36-Br** (Fig. 10). As in the previous case, thiophenol (**57**) was alkylated. The sequence was followed by a one-pot oxidation and bromination reaction. After Krapcho decarboxylation, a mixture of three products, **60**, **63** and **64** was obtained, with the target product **63** forming in a mediocre yield over three steps. Luckily, both side products, **60** and **64**, were converted into the necessary intermediate **63**. The dibrominated compound **64** was reduced using sodium sulfite, while the sulfoxide **60** was subjected to a bromination reaction and Krapcho decarboxylation. Finally, arylation of sulfoxide **63** afforded the target compound **36-Br**.

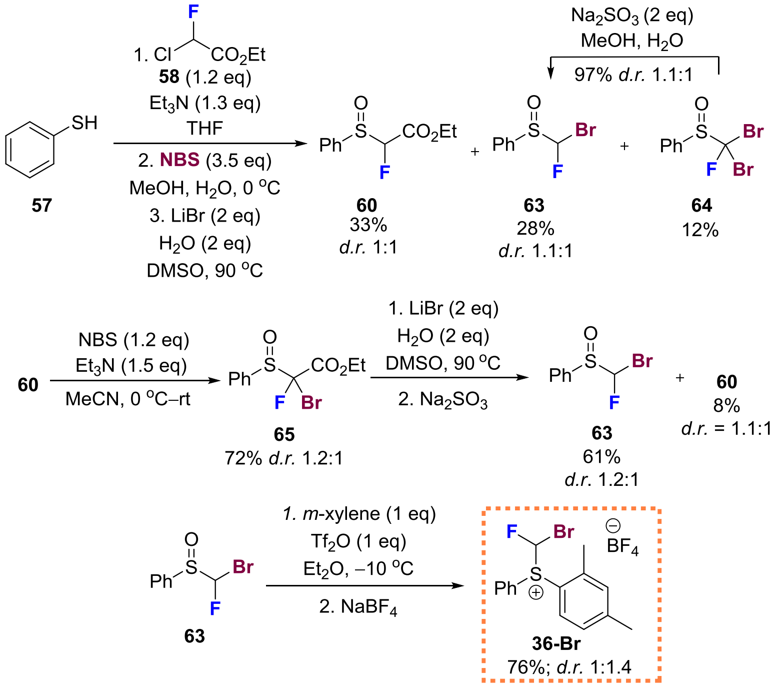


Fig. 10. Bromofluoromethylsulfonium salt **36-Br** synthesis.

For successful iodine-containing sulfonium salt **36-I** synthesis, the ester **60** was hydrolyzed, and the acid **66** was halodecarboxylated under blue light irradiation (Fig. 11). The key intermediate **67** was obtained with good yield over four steps starting from thiophenol (**57**). For the successful arylation reaction, a more electron-rich arene – tetramethylbenzene was selected, which improved the reaction yield and crystallinity of the product **36-I**.

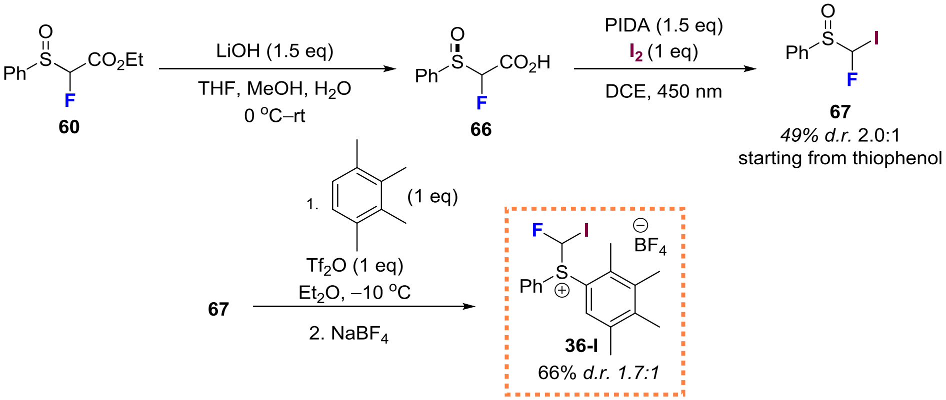


Fig. 11. Iodinated sulfonium salt **36-I** preparation.

The author continued with the determination of the optimal reaction conditions for the alkene **24** cyclopropanation reaction (Fig. 12). The highest product yields were achieved by employing slow addition of the sulfonium salt **36** to the alkene **24** and base mixture. In order to achieve full alkene **24** conversion, an excess of sulfonium salt **36** was needed. The best cyclopropane **39** yields were obtained using sodium hydride as the base with a 1,4-dioxane/dichloromethane solvent mixture.

With the optimized reaction conditions, the author explored the alkene **24** substrate scope (Fig. 12). The reaction proceeded successfully with all three (Hal = Cl, Br, I) sulfonium salts **36**. The reaction conditions tolerated heterocyclic systems **24d** and **24e**, as well as 1,1- and 1,2-disubstituted alkenes **24f** and **24h**. Furthermore, non-conjugated alkenes **24k** and **24l** were cyclopropanated in high yield. Functional groups such as methoxy **24h**, ester **24j**, cyano **24m**, and Boc-protected amine **24l** were well tolerated under the cyclopropanation conditions, forming products **39** in good to excellent yields as a mixture of two diastereomers.

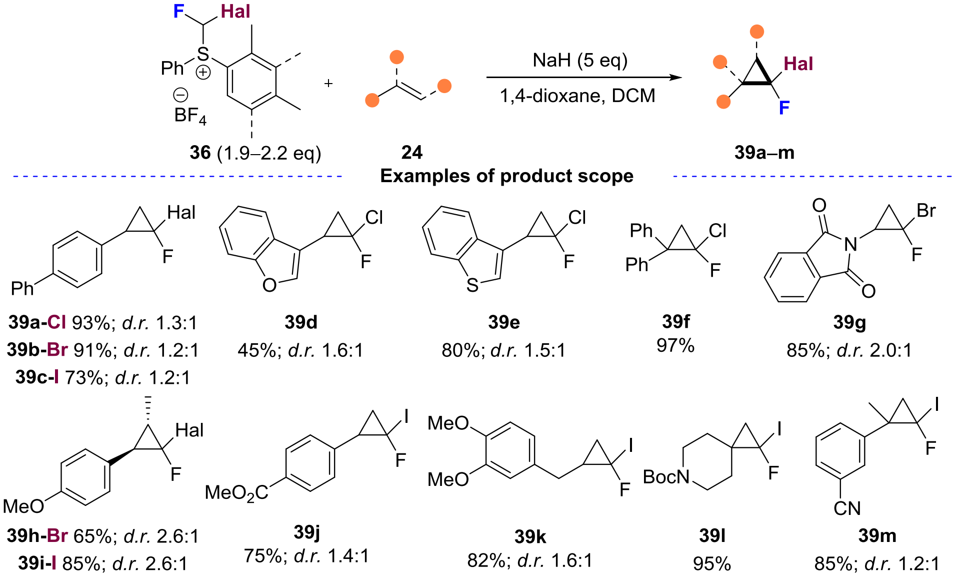
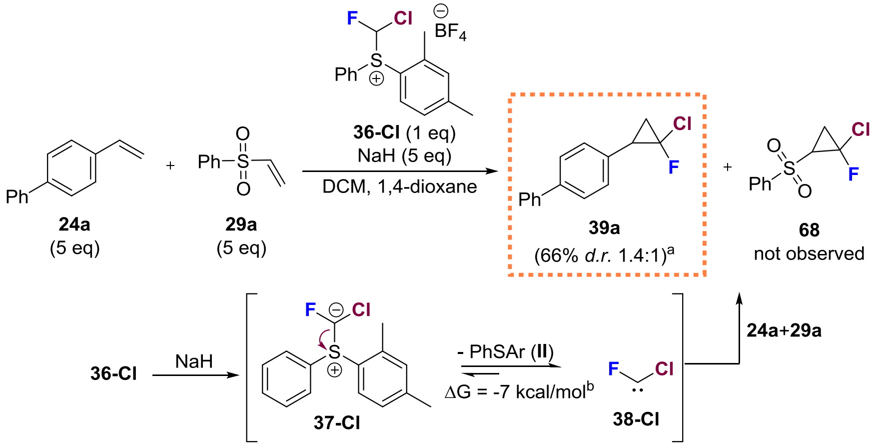


Fig. 12. Cyclopropane **39** scope.

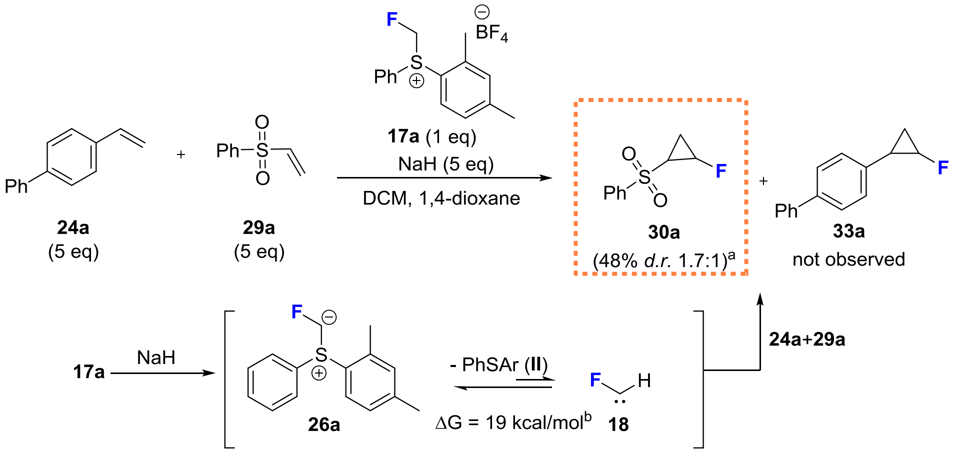
To confirm the formation of the carbene intermediate under the reaction conditions, competition experiments were performed (Fig. 13). Initially, the author compared the reactivity of an electron-rich alkene **24a** and an electron-poor alkene **29a** with the sulfonium salt **36-Cl**. If the reaction proceeded via an electrophilic dihalocarbene, then the electron-rich styrene **24a** would be the preferential substrate, forming the product **39a** in higher yield. Alternatively, if cyclopropanation occurred through ylide addition to the double bond followed by intramolecular cyclization, the vinylsulfone **29a** would be the favoured substrate. The experiment exclusively afforded the styrene **24a**-derived cyclopropane **39a**, strongly supporting fluorohalocarbene **38-Cl** generation under the reaction conditions. In addition, DFT calculations indicated that *α*-elimination from ylide **37-Cl** is a thermodynamically favoured process.



[a] ^{1}H NMR yield and *d.r.* determinded from crude reaction mixture using EtOAc as internal standard.
[b] Gibbs free energies of carbene **38-Cl** formation. Optimization using m062x/Def2SVP method.

Fig. 13. Alkene reactivity comparison with the **36-Cl**.

Next, the reactivity of fluoromethylsulfonium salt **17a** with the same alkenes (Fig. 14) was compared. If the reaction proceeded via a fluorocarbene **18** intermediate, styrene **24a** cyclopropanation would be expected. However, in this case only the vinylsulfone **29a** cyclopropanation was observed, indicating that the reaction proceeds through an ylide **26a** reaction with the activated double bond **29a**, rather than through carbene **18** transfer. Consistently, DFT calculations suggest that monofluorocarbene **18** formation from ylide **26a** is thermodynamically unfavourable.



[a] ^{1}H NMR yield and *d.r.* determinded from the crude reaction mixture using EtOAc as internal standard.
[b] Gibbs free energies of carbene **18** formation. Optimization using m062x/Def2SVP method.

Fig. 14. Alkene reactivity with the sulfonium salt **17a**.

The observed results can be rationalized by comparing structures of carbenes (the singlet state in halocarbenes is more favoured than the triplet state) (Fig. 15). When two halogen atoms are adjacent to the carbene centre **38**, both can provide resonance stabilization by electron density donation from their lone pairs into the empty p-orbital of the carbene. In contrast, a monohalocarbene **18** has only a single halogen atom capable of interacting with the empty orbital. As a result, dihalocarbene **38** formation is thermodynamically more favourable than monohalocarbene **18** formation.

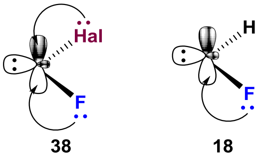


Fig. 15. Halocarbene comparison.

2. Metal-catalyzed fluoroacetyl carbene transfer from sulfonium salts

In the next step of research, the author decided to explore with ester group functionalized fluoromethylsulfonium salt **69** (Fig. 16).[51] The author hypothesized that salt **69**, in basic media and in the presence of a transition metal catalyst, could generate an electrophilic metal carbene complex **70**. Therefore, it could be employed in characteristic metal-catalyzed carbene reactions, such as the Doyle–Kirmse rearrangement with allyl sulfides **71** and alkene **24** cyclopropanation. Furthermore, the ester group can be used as a synthetic handle for additional diversification possibilities. This strategy would be particularly appealing because the corresponding diazocompound **74** is unknown.

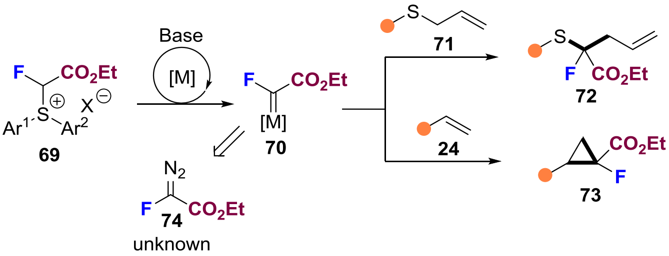


Fig. 16. Fluoroacetyl carbene transfer from sulfonium salt **69**.

Metal carbene complexes are widely used in organic chemistry.[51] Bonding in metal carbene complexes consists of σ-donation from the carbene lone pair to the metal center and π-backdonation from the metal into the empty p orbital of the carbene carbon.[52–53] Therefore, the electronic properties of metal carbenes depend strongly on the nature of the metal, its oxidation state, the ligands, and the carbene substituents.[54] Depending on these factors, the carbene fragment may display nucleophilic or electrophilic character, or even function as an inert ligand that modulates the reactivity of the metal center.[55] Modification of metal catalysts and their ligands enables tuning of the electronic and steric properties of the carbene center, thereby enhancing chemo- and regioselectivity, and enabling asymmetric transformations.[56]

Metal carbene complexes **70a** are typically highly reactive intermediates. Traditionally, they are generated from diazocompounds **75**[57–59] or their precursors, such as nitrosoamines **76**, hydrazones **77**, or amines **78** (Fig. 17). However, due to the instability[60–61], explosiveness and toxicity associated with many diazocompounds, alternative carbene sources have been developed. Sulfonium and sulfoxonium ylides **79**[62], α-acyloxy halides **80**, dihalocompounds **81**[63], and iodonium ylides **82**[64] provide similar reactivity in metal-catalyzed carbene transfer reactions.

Electrophilic metal carbenes exhibit reactivity patterns that parallel those of free carbenes (Fig. 17). They participate in [2+1] cycloaddition reactions with alkenes **24** and alkynes,[65] transfer carbene fragments to nucleophiles **84**, and undergo C-H insertion reactions.[66] Furthermore, they can engage in ylide **86** formation, cross-couplings[67] and other transformations, highlighting their versatility.

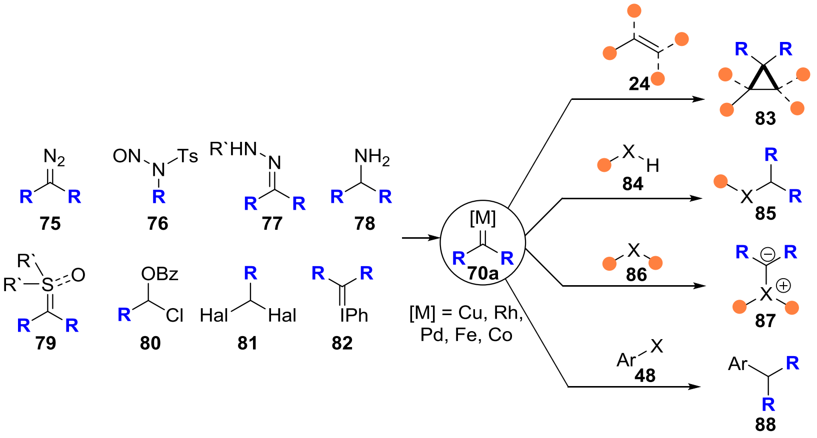


Fig. 17. Metal carbene complex generation and characteristic application.

At the beginning of the study, it was known that fluoroacetyl carbene transfer can be accomplished using the organomercury reagent **89**[69], which, at elevated temperatures, can cyclopropanate alkenes **24** (Fig. 18). Additionally, dibromofluoroacetate **90**[70] is a suitable reagent for formal fluoroacetyl carbene transfer with activated double bonds **29**. Since the *α*-fluorocarbonyl scaffold occurs in various biologically active compounds **92-94**[71–73], the author proposes that sulfonium salt **69** could be a prospective reagent capable of functionalizing substrates through the simultaneous installation of fluorine and an ester group.

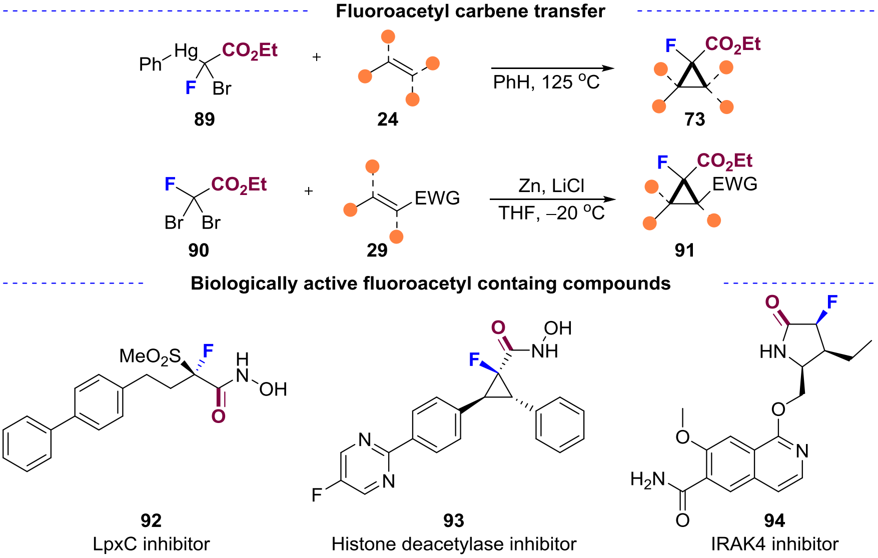


Fig. 18. Fluoroacetyl carbene transfer and *α*-fluorocarbonyl group in biorelevant molecules.

The author began the studies by developing a synthesis of sulfonium salt **69** (Fig. 19). In the first step, thiophenol (**57**) was alkylated and subsequently oxidized to the corresponding sulfoxide **60**. Arylation of ester **60** yielded sulfonium salt **69** in good yield as a mixture of two diastereomers.

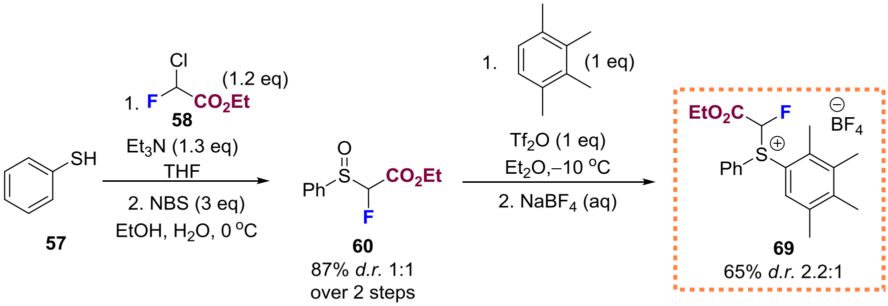


Fig. 19. Ethoxyacetyl substituted sulfonium salt **69** synthesis.

With reagent **69** in hand, the author evaluated its ability to undergo fluoroacetyl carbene transfer to allyl sulfide **71a**, which was expected to yield the [2,3]-sigmatropic rearrangement product – monofluorinated homoallyl sulfide **72a** (Fig. 20). It was found that the highest product yield was achieved using a copper catalyst in combination with diisopropylethylamine as a base. Similar to dihalocarbene transfer, slow addition of sulfonium salt **69** to the reaction mixture was required.

The reaction tolerated substrates bearing cyano- **71b**, methoxy- **71c**, nitro- **71d**, bromo- **71e** and trifluoromethyl- **71f** functional groups. In addition, the dimethyl substituted allyl fragment **71g** successfully rearranged to the product **72g**. Furthermore, this methodology can be applied to an allyl cysteine derivative **71h** functionalization.

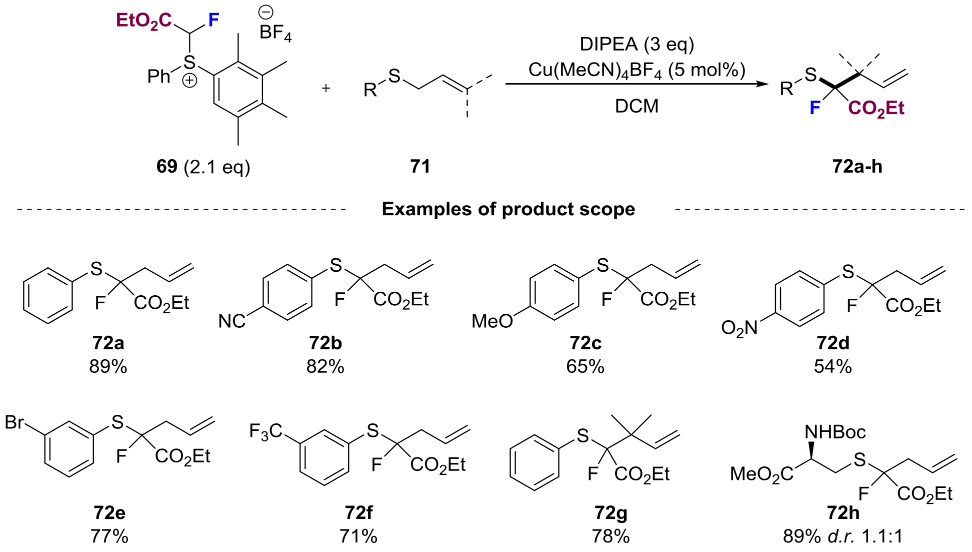


Fig. 20. [2,3]-Sigmatropic rearrangement products.

The author subjected compound **72a** to a series of functionalization reactions (Fig. 21). First, the sulfide **72a** was oxidized to the corresponding sulfone **95**. The ester group in compound **95** can be readily hydrolyzed to afford the carboxylic acid **96**. Decarboxylation of compound **95** furnished homoallyl sulfone **97** in good yield. The acid **96** can be further employed in diastereoselective iodolactonization to yield γ-lactone **98** as well as in the synthesis of activated ester **99**.

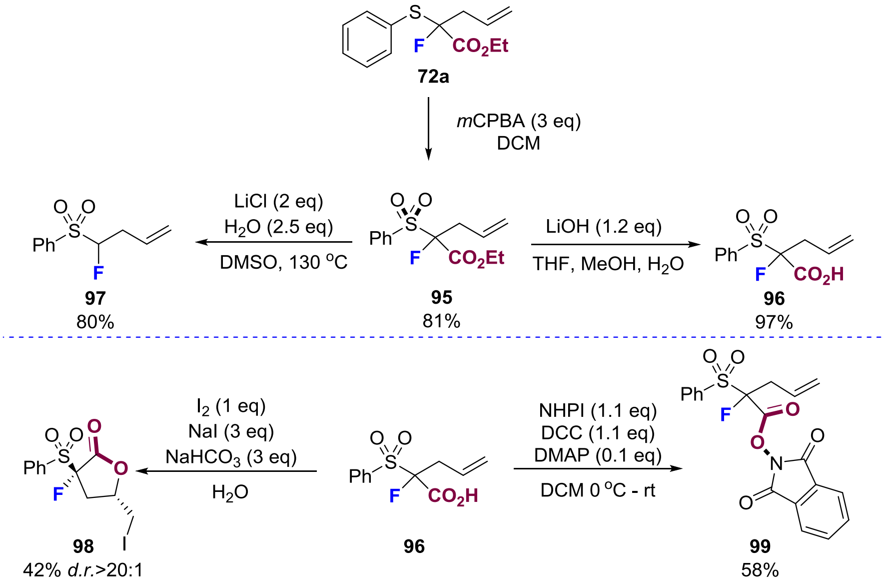
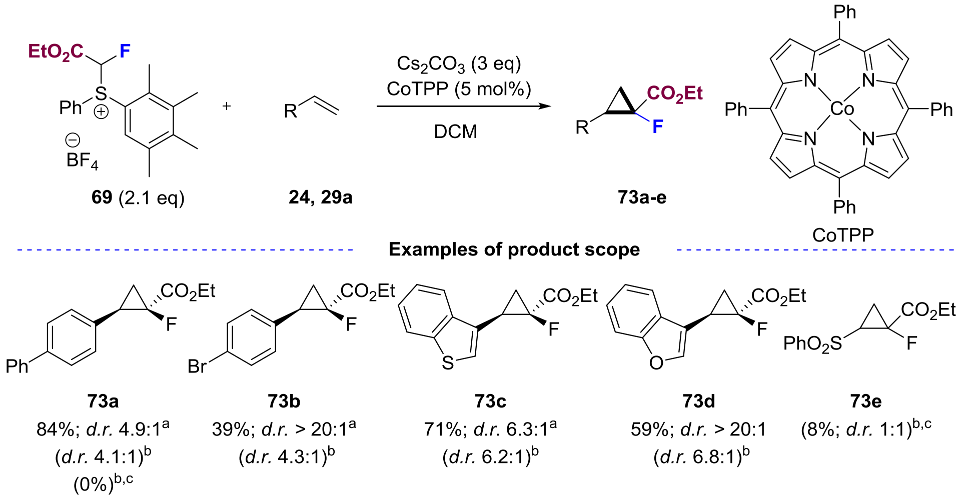


Fig. 21. Modification possibilities of **72a**.

In the continuation of this study, the author explored the cyclopropanation of styrenes **24** using sulfonium reagent **69** (Fig. 22). The author discovered that cobalt porphyrin in combination with cesium carbonate as a base in dichloromethane provided the most suitable conditions for the cyclopropanation of alkenes **24**. Notably, under the developed conditions, slow addition was not required. Products **73a-d** were obtained in moderate to good yields as a mixture of two diastereomers with moderately good selectivity.

In the absence of the catalyst, the author did not observe cyclopropanation of alkene **24a**. However, when employing vinylsulfone **29a** as a substrate, the author observed the formation of cyclopropane **73e** without the catalyst. These observations indicate that the formation of a free carbene from sulfonium salt **69** in the presence of base is unlikely.



[a] Isolated yield and *d.r.* [b] Determined from the crude reaction mixture. [c] In absence of catalyst.

Fig. 22. Cyclopropanation substrate scope.

The Doyle–Kirmse reaction mechanism was investigated using DFT calculations (Fig. 23). First, the possibility of free carbene **IV** generation (path A) was evaluated, which, according to calculations, is a thermodynamically unfavourable process. Cyclopropanation experiments further supported this conclusion, since alkene **24a** did not undergo cyclopropanation in the absence of a catalyst. In contrast, coordination of ylide **I** with the metal centre proved thermodynamically favoured (path B). The rate-limiting step is the formation of the metal carbene complex **V** by elimination of diarylsulfide **III**. Although thermodynamically unfavourable, it remains achievable at room temperature. In the next step, allylsulfide **61a** adds to the electrophilic carbene centre, ylide **VII** is formed, and the metal catalyst is returned in the catalytic cycle. Finally, the ylide **VII** undergoes [2,3]-sigmatropic rearrangement to furnish the desired product **72a’**.

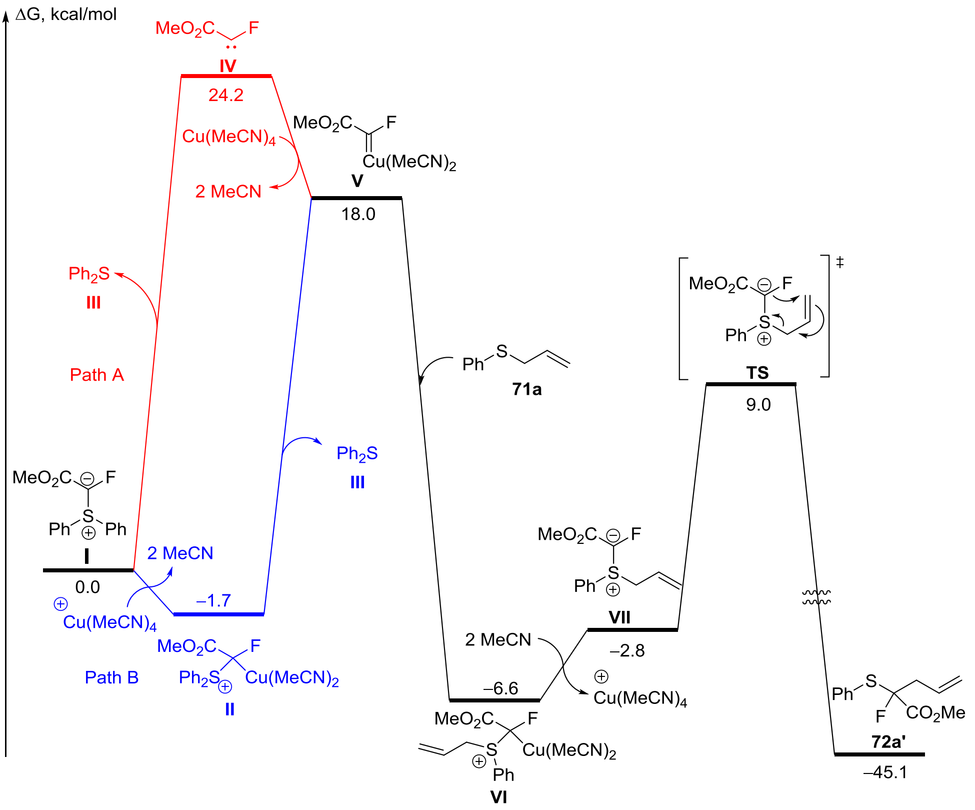
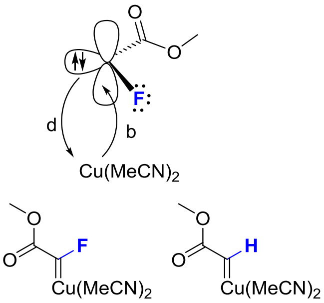


Fig. 23. Possible Doyle–Kirmse reaction mechanism.

In order to determine how fluorine influences the properties of the metal carbene complex, charge decomposition analyses were performed for fluoroacetyl- **V-F** and acetylcarbene **V-H** metal complexes (Fig. 24). This method characterizes the metal complex by measuring carbene`s σ electron density donation (d) to the vacant orbitals of the metal, as well as metal to carbene back donation (b) into the empty carbene orbital.[54, 74]

In the case of the fluorinated carbene **V-F**, we observe an increase in electron donation density (d) compared to the nonfluorinated analogue **V-H**, likely due to repulsion between fluorine`s lone pairs and the carbene`s electron pair. For metal`s back donation to fluorocarbene **V-F**, the value decreases, suggesting that fluorine`s lone pairs partly occupy the carbene`s empty orbital. These results indicate that fluorine acts as an electron-donating substituent. LUMO value of the fluorinated carbene complex **V-F** is more negative, and its global electrophilicity (ω) is higher, which indicates that **V-F** should have higher reactivity towards nucleophiles.



	V-F	**V-H**
donation (d)	0.326	0.287
back-donation (b)	0.035	0.050
ε_{LUMO} (eV)	–7.220	–6.843
ω	11.608	10.203

Fig. 24. Electronic effects of fluorinated **V-F** and defluorinated **V-H** carbene metal complexes.

3. Fluoromethylbicyclo[1.1.1]pentane transfer from sulfonium salts

Building on monofluorinated synthon transfer reactions from sulfonium salts, the author identified an opportunity to design reagents **108** incorporating a bicyclo[1.1.1]pentyl (BCP) group (Fig. 25).[75] BCPs **100** are important bioisosteres in medicinal chemistry, demonstrating potential for benzene **101**, alkyne **102** and *tert*-butyl **103** replacement.[76–77] Bioisosteric substitution of benzene with BCP motifs can increase metabolic stability by limiting oxidative arene metabolism and enhance water solubility through disruption of intermolecular π–π stacking.[74]

Current strategies for the synthesis of monofluorinated BCPs **105** typically involve functional group interconversion[78] or fluoromethyl radical[79–80] **107** addition to [1.1.1]propellane (**106**).

The author envisioned that sulfonium salts **108** could serve for the modular construction of fluoromethylene-linked BCP derivatives. In the reactions with nucleophiles, the diarylsulfide could serve as an efficient leaving group.[79] Furthermore, if an iodine atom were incorporated into the BCP fragment, it could provide additional modification possibilities, thus enabling the synthesis of benzylfluoride **111** saturated three-dimensional bioisosters **110**.

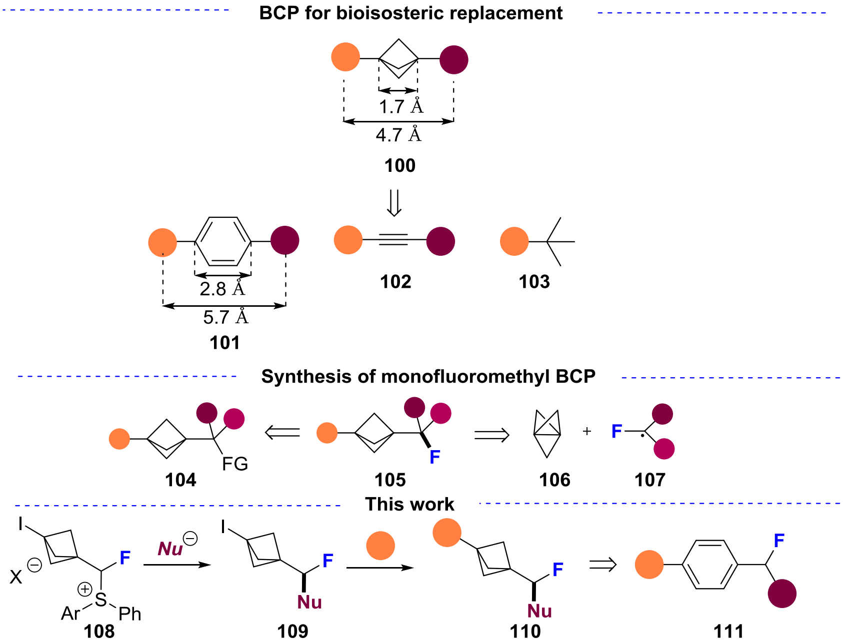


Fig. 25. Overview of BCP group.

The author began the study by developing a synthetic methodology for accessing sulfonium salts **108** and **108-H** (Fig. 26). Under violet light irradiation, sulfoxide **67** underwent addition to propellane **106**, affording bicyclopentane **112** with excellent yield. Furthermore, the iodine atom on BCP **112** can be dehalogenated with a silane. Importantly, the propellane **106** addition proceeds without the need for initiators or photocatalysts. Both sulfoxides **112** and **112-H** can be transformed to sulfonium salts **108** and **108-H** by treatment with 1,3,5-trimethoxybenzene (**113**) in the presence of triflic anhydride. The use of electron-rich arene **113** was crucial for high product yields, as previously employed arenes failed to efficiently deliver sulfonium salt.

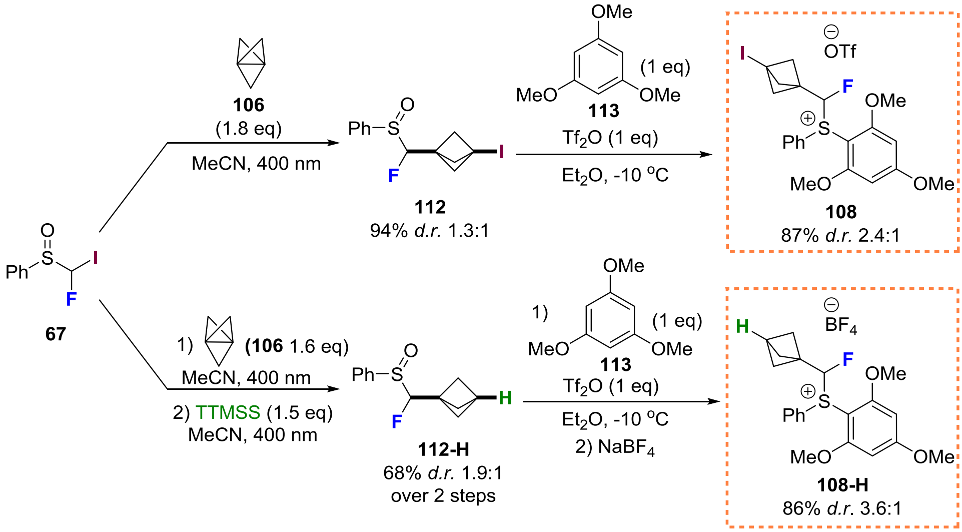
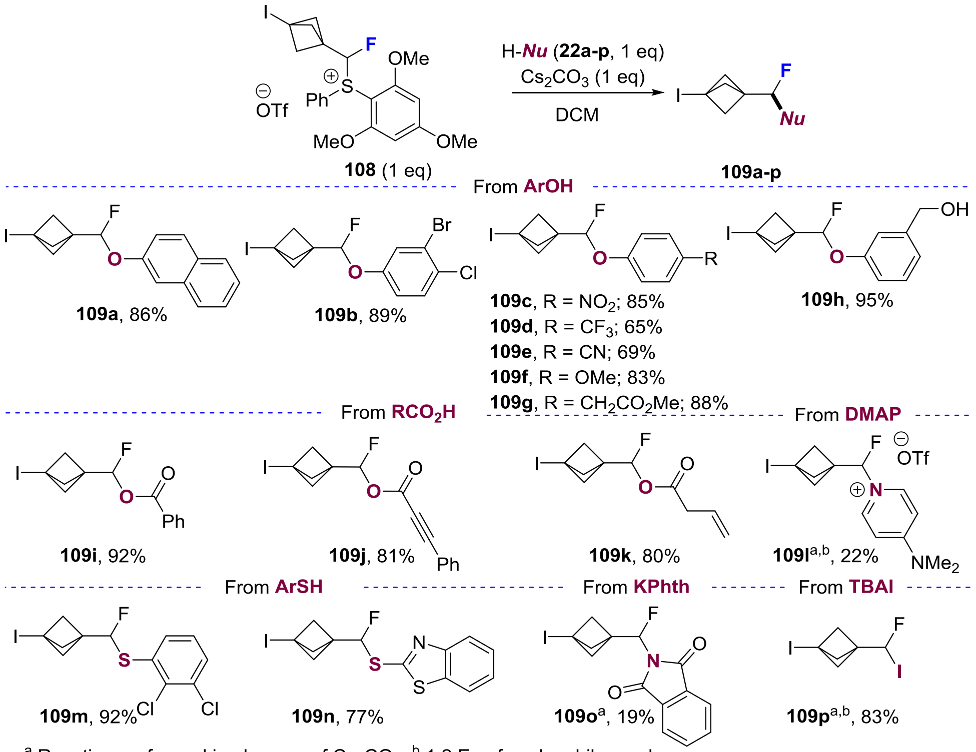


Fig. 26. Fluoromethyl-linked BCP sulfonium salt **108** preparation.

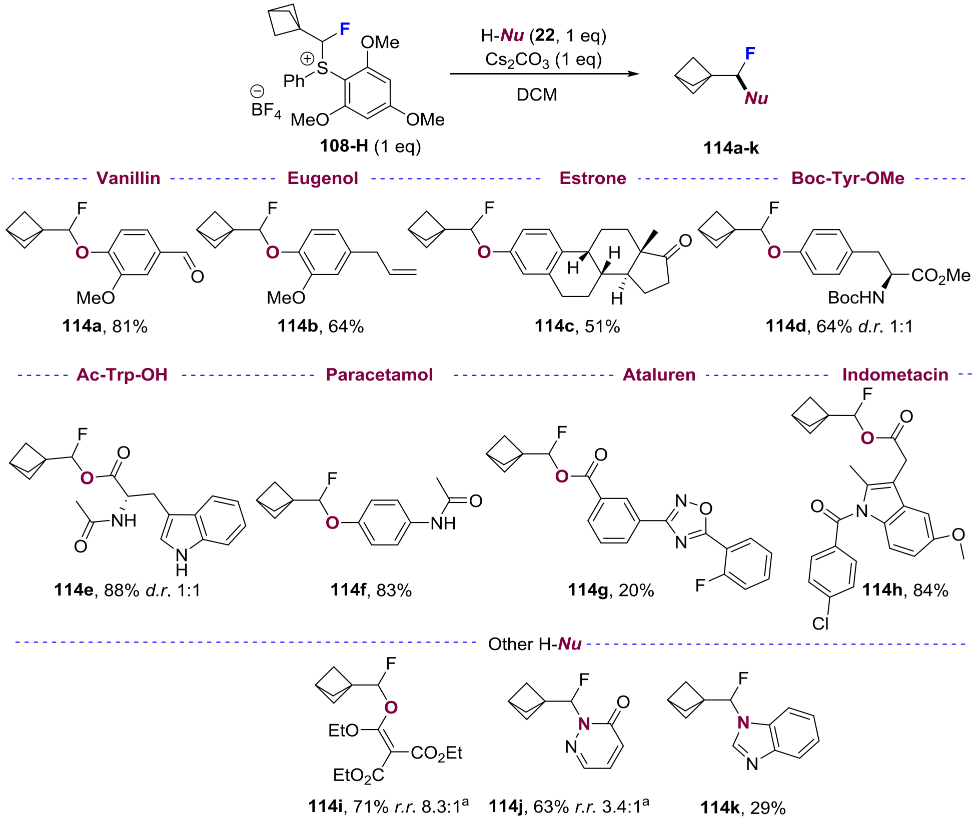
With the optimized reaction conditions, the author explored the substrate scope (Fig. 27). Reaction proceeds in good to excellent yield with phenols **22a-h**, carboxylic acids **22i-k**, and thiophenols **22m-n**. Notably, phenolic oxygen was regioselectively alkylated in the presence of benzylic alcohol **22h**. A broad range of functional groups including nitro- **22c**, trifluoromethyl- **22d**, ciano- **22e**, methoxycarbonyl- **22g**, methoxy- **22f**, halogen atoms **22b**, alkenes **22k** and alkynes **22j** were well tolerated under the reaction conditions. Furthermore, heterocyclic-containing nucleophiles **22n**, **22o**, and **22l** also underwent alkylation.



^{a} Reaction performed in absence of Cs_2CO_3. ^{b} 1.2 Eq of nucleophile used.

Fig. 27. **108** Alkylation substrate scope.

Further, the author explored the potential of deiodinated sulfonium salt **108-H** to undergo nucleophilic displacement reaction (Fig. 28). Natural products such as vanillin, eugenol, and estrone were successfully alkylated, forming products **114a-c** in average to good yields. The methodology was also applied to functionalize various amino acids and drug molecules. Additionally, the substrate scope was extended to oxygen alkylation in tricarboxylate and *N*-heterocycle functionalization.



[a] Regioisomer ratio determined from crude NMR.

Fig. 28. Fluoralkylation substrate scope.

The author further investigated the functionalization of the iodine atom (Fig. 29). Iodide **109a** was successfully employed in iridium photocatalyzed addition to vinylsulfone **29a**, affording 1,3-disubstituted bicyclopentane **110a**.[82] Additionally, compound **109a** underwent copper-mediated in C-N bond formation with amide **115** to yield amination product **110b** with mediocre yield.[83]

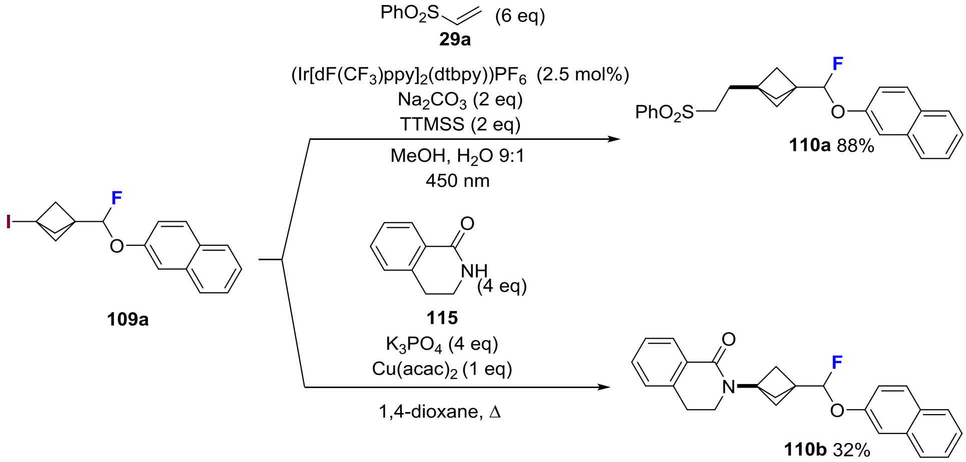
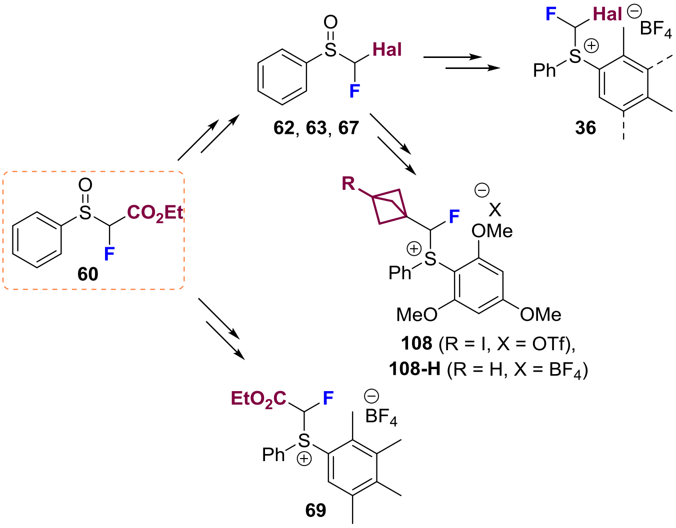


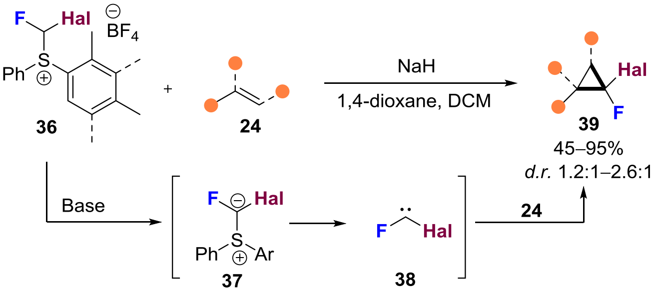
Fig. 29. Iodide **109a** functionalization reactions.

CONCLUSIONS

1. Sulfoxide **60** is a strategic intermediate for functionalized fluoromethylsulfonium salt **36**, **69**, and **108** preparation. Ester **60** functional group interconversion provides an efficient way to introduce additional halogen atoms, affording dihalomethylsulfoxides **62**, **63** and **67**. These sulfoxides can be transformed into dihalomethylsulfonium salts **36** or added to propellane to obtain bicyclopentyl substituted fluoromethylsulfonium salts **108**.

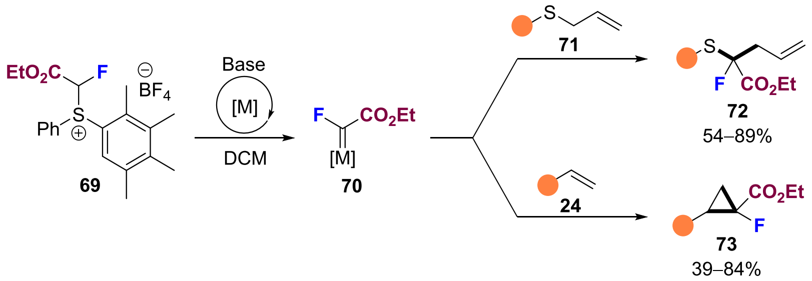


2. Dihalomethylsulfonium salts **36** in the presence of base react with alkenes to form dihalocyclopropanes **39** in moderate to excellent yields as a mixture of two diastereomers. Competition experiments and DFT calculations suggest electrophilic dihalocarbene **38** generation under the reaction conditions.

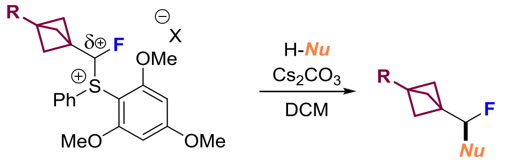


3. Ethoxycarbonyl substituted fluoromethylsulfonium salt **69** in the presence of base and metal catalyst reacts with allyl sulfides **71** and alkenes **24**, forming [2,3]-sigmatropic rearrangement products **72** and cyclopropanes **73**. DFT calculation and control experiments

indicate formation of electrophilic metal carbene complex **70** from sulfonium salt **69** in the presence of base and metal catalyst.



4. Bicyclo[1.1.1]pentyl-substituted sulfonium salts **108** serve as an electrophilic fluoroalkyl group source. Phenols, thiols, carboxylic acids, and other nucleophiles are efficiently alkylated under mild conditions, affording fluoroalkyl-substituted products **109** and **114**.



108 (R = I, X = OTf), **108-H** (R = H, X = BF_4)

109, **114**

Nu = ArO, RCO_2, ArS, and others

ATSAUCES / REFERENCES

1. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *Journal of Medicinal Chemistry* **2015**, *58* (21), 8315–8359.
2. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H., Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chemical Reviews* **2016**, *116* (2), 422–518.
3. Wang, M.; Ruskin, J.; Marques, J.; Garrison, N.; Lectka, T., Selective Fluorination of Complex Molecules: Late-Stage Functionalization. *Chemical Reviews* **2025**, *125* (19), 9382–9428.
4. Liang, T.; Neumann, C. N.; Ritter, T., Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angewandte Chemie International Edition* **2013**, *52* (32), 8214–8264.
5. Barata-Vallejo, S.; Lantaño, B.; Postigo, A., Recent Advances in Trifluoromethylation Reactions with Electrophilic Trifluoromethylating Reagents. *Chemistry – A European Journal* **2014**, *20* (51), 16806–16829.
6. Studer, A., A “Renaissance” in Radical Trifluoromethylation. *Angewandte Chemie International Edition* **2012**, *51* (36), 8950–8958.
7. Liu, X.; Xu, C.; Wang, M.; Liu, Q., Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond. *Chemical Reviews* **2015**, *115* (2), 683–730.
8. Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; am Ende, C. W.; Trabanco, A. A.; Gouverneur, V., Late-stage difluoromethylation: concepts, developments and perspective. *Chemical Society Reviews* **2021**, *50* (14), 8214–8247.
9. Reichel, M.; Karaghiosoff, K., Reagents for Selective Fluoromethylation: A Challenge in Organofluorine Chemistry. *Angewandte Chemie International Edition* **2020**, *59* (30), 12268–12281.
10. Parisi, G.; Colella, M.; Monticelli, S.; Romanazzi, G.; Holzer, W.; Langer, T.; Degennaro, L.; Pace, V.; Luisi, R., Exploiting a “Beast” in Carbenoid Chemistry: Development of a Straightforward Direct Nucleophilic Fluoromethylation Strategy. *Journal of the American Chemical Society* **2017**, *139* (39), 13648–13651.
11. Senatore, R.; Malik, M.; Spreitzer, M.; Holzer, W.; Pace, V., Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (*O*-, *S*-, *N*-, *P*-, *Se*-) with Fluoroiodomethane. *Organic Letters* **2020**, *22* (4), 1345–1349.
12. Ramkumar, N.; Baumane, L.; Zacs, D.; Veliks, J., Merging Copper(I) Photoredox Catalysis and Iodine(III) Chemistry for the Oxy-monofluoromethylation of Alkenes. *Angewandte Chemie International Edition* **2023**, *62* (12), e202219027.
13. Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S., Synthetic studies on the key component of the new generation of quinolonecarboxylic acid, DU-6859. 1. Synthesis of (1*R*,2*S*)-2-fluorocyclopropylamine by the use of optical resolution. *Tetrahedron* **1994**, *50* (13), 3889–3904.
14. Timmann, S.; Feng, Z.; Alcarazo, M., Recent Applications of Sulfonium Salts in Synthesis and Catalysis. *Chemistry – A European Journal* **2024**, *30* (70), e202402768.
15. Prakash, G. K. S.; Ledneczki, I.; Chacko, S.; Olah, G. A., Direct Electrophilic Monofluoromethylation. *Organic Letters* **2008**, *10* (4), 557–560.
16. Noto, N.; Koike, T.; Akita, M., Visible-Light-Triggered Monofluoromethylation of Alkenes by Strongly Reducing 1,4-Bis(diphenylamino)naphthalene Photoredox Catalysis. *ACS Catalysis* **2019**, *9* (5), 4382–4387.

17. Veliks, J.; Kazia, A., Fluoromethylene Transfer from Diarylfluoromethylsulfonium Salts: Synthesis of Fluorinated Epoxides. *Chemistry – A European Journal* **2019**, *25* (15), 3786–3789.
18. Sperga, A.; Melngaile, R.; Kazia, A.; Belyakov, S.; Veliks, J., Optimized Monofluoromethylsulfonium Reagents for Fluoromethylene-Transfer Chemistry. *The Journal of Organic Chemistry* **2021**, *86* (4), 3196–3212.
19. Sperga, A.; Kazia, A.; Veliks, J., Monofluorinated 5-membered rings via fluoromethylene transfer: synthesis of monofluorinated isoxazoline *N*-oxides. *Organic & Biomolecular Chemistry* **2021**, *19* (12), 2688–2691.
20. Sperga, A.; Zacs, D.; Veliks, J., Iron-Catalyzed Fluoromethylene Transfer from a Sulfonium Reagent. *Organic Letters* **2022**, *24* (24), 4474–4478.
21. Gao, F.; Xiao, Y.; Li, Z.; Shen, Q., Sulfonium Ylide Enabled, Copper-Catalyzed Difluoromethylation, Monofluoromethylation, and Monofluoroalkylation of Lithium Aryl ^{n}Butyl Borates. *ACS Catalysis* **2025**, *15* (6), 4644–4653.
22. Feng, Z.; Riemann, L.; Guo, Z.; Herrero, D.; Simon, M.; Golz, C.; Mata, R. A.; Alcarazo, M., Pentafluorocyclopropanation of (Hetero)arenes Using Sulfonium Salts: Applications in Late-Stage Functionalization. *Angewandte Chemie International Edition* **2023**, *62* (35), e202306764.
23. Gupta, R.; Mandal, D.; Jaiswal, A. K.; Young, R. D., FLP-Catalyzed Monoselective C–F Functionalization in Polyfluorocarbons at Geminal or Distal Sites. *Organic Letters* **2021**, *23* (5), 1915–1920.
24. Carbonnel, E.; Pannecoucke, X.; Besset, T.; Jubault, P.; Poisson, T., An electrophilic reagent for the synthesis of OCHFMe-containing molecules. *Chemical Communications* **2018**, *54* (20), 2491–2493.
25. Sperga, A.; Pfeifers, T.; Zacs, D.; Veliks, J., Fluorohalomethylsulfonium Salts as a Fluorohalocarbene Source. *Organic Letters* **2024**, *26* (30), 6482–6485.
26. Liu, G.-K.; Qin, W.-B.; Li, X.; Lin, L.-T.; Wong, H. N. C., Difluoromethylation of Phenols and Thiophenols with the *S*-(Difluo-romethyl)sulfonium Salt: Reaction, Scope, and Mechanistic Study. *The Journal of Organic Chemistry* **2019**, *84* (24), 15948–15957.
27. Gu, Y.-Q.; Long, H.-X.; Zhang, D.-D.; Ruan, M.-F.; Liu, G.-K., Difluoromethyl phenoxathiinium salt: A new general and versatile difluoromethylating reagent with divergent $\cdot CF_2H$, CF_2H+, and $:CF_2$ reactivities. *Science China Chemistry* **2024**, *67* (3), 953–962.
28. Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A., New Electrophilic Difluoromethylating Reagent. *Organic Letters* **2007**, *9* (10), 1863–1866.
29. Noto, N.; Koike, T.; Akita, M., Metal-free di- and tri-fluoromethylation of alkenes realized by visible-light-induced perylene photoredox catalysis. *Chemical Science* **2017**, *8* (9), 6375–6379.
30. Zhang, W.; Huang, Y.-H.; Wu, T.-R.; Yuan, H.-R.; Chen, S.-X.; Wu, B.-B.; Wang, X.-S., Nickel-Catalyzed Reductive Arylation of *gem*-Bromofluorocyclopropanes To Construct Monofluorinated Cyclopropane Derivatives. *Organic Letters* **2025**, *27* (12), 3007–3012.
31. Brahms, D. L. S.; Dailey, W. P., Fluorinated Carbenes. *Chemical Reviews* **1996**, *96* (5), 1585–1632.
32. Sperga, A.; Veliks, J., Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species. *Chemistry – A European Journal* **2023**, *29* (69), e202301851.
33. Born, M.; Ingemann, S.; Nibbering, N. M. M., Heats of Formation of Monohalo Carbenes. Stability and Reactivity of CHX.bul.- (X = F, Cl, Br, and I) Radical Anions. *Journal of the American Chemical Society* **1994**, *116* (16), 7210–7217.
34. Schwartz, M.; Marshall, P., An ab Initio Investigation of Halocarbenes. *The Journal of Physical Chemistry A* **1999**, *103* (39), 7900–7906.

35. Moss, R. A., Dihalodiazirines and the photochemical generation of dihalocarbenes: new light on old problems. *Journal of Physical Organic Chemistry* **2010**, *23* (4), 293–299.
36. Xie, Q.; Hu, J., A Journey of the Development of Privileged Difluorocarbene Reagents $TMSCF_2X$ (X = Br, F, Cl) for Organic Synthesis. *Accounts of Chemical Research* **2024**, *57* (5), 693–713.
37. Ni, C.; Hu, J., Recent Advances in the Synthetic Application of Difluorocarbene. *Synthesis* **2014**, *46* (07), 842–863.
38. Fuchibe, K.; Ichikawa, J., Generation of difluorocarbenes and introduction of fluorinated one-carbon units into carbonyl and related compounds. *Chemical Communications* **2023**, *59* (18), 2532–2540.
39. Dilman, A. D.; Levin, V. V., Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions. *Accounts of Chemical Research* **2018**, *51* (5), 1272–1280.
40. Krishnan, J.; Sahib, K.; Nair, K. G.; Arshad Jouhar, T.; Paul, R. R., Advances in the Synthetic Utility of Difluorocarbene Generated from $TMSCF_3$ (Ruppert-Prakash Reagent) and Its Derivatives. *The Chemical Record* **2025**, *25* (5), e202400243.
41. Zhang, W.; Wang, Y., Recent advances in carbon-difluoroalkylation and –difluoroolefination with difluorocarbene. *Tetrahedron Letters* **2018**, *59* (14), 1301–1308.
42. Wang, X.; Wang, X.; Wang, J., Application of carbene chemistry in the synthesis of organofluorine compounds. *Tetrahedron* **2019**, *75* (8), 949–964.
43. Ma, X.; Su, J.; Song, Q., Unconventional Transformations of Difluorocarbene with Amines and Ethers. *Accounts of Chemical Research* **2023**, *56* (5), 592–607.
44. United Nations Environment Programme. (1987, Annex C: Hydrochlorofluorocarbons and Hydrobromofluorocarbons. United Nations. Retrieved October 7, 2025, from https://ozone.unep.org/treaties/montreal-protocol/articles/annex-controlled-substances.
45. Chen, D.; Fan, Z.; Huang, L.; Gao, K.; Xiao, P.; Ni, C.; Hu, J., $TMSCFX_2$ (X = Cl, Br) as halofluorocarbene sources for the synthesis of halofluorocyclopropanes. *Chemical Communications* **2021**, *57* (3), 319–322.
46. Barrett, C.; Krishnamurti, V.; Ispizua-Rodriguez, X.; Zhu, Z.; Koch, C. J.; Surya Prakash, G. K., *gem*-Halofluorocyclopropanes via [2 + 1] Cycloadditions of In Situ Generated CFX Carbene with Alkenes. *Organic Letters* **2022**, *24* (29), 5417–5421.
47. Thankachan, A. P.; Sindhu, K. S.; Krishnan, K. K.; Anilkumar, G., Recent advances in the syntheses, transformations and applications of 1,1-dihalocyclopropanes. *Organic & Biomolecular Chemistry* **2015**, *13* (33), 8780–8802.
48. Bychek, R.; Mykhailiuk, P. K., A Practical and Scalable Approach to Fluoro-Substituted Bicyclo[1.1.1]pentanes. *Angewandte Chemie International Edition* **2022**, *61* (29), e202205103.
49. Guo, H.; Qiu, S.; Xu, P., One-Carbon Ring Expansion of Indoles and Pyrroles: A Straightforward Access to 3-Fluorinated Quinolines and Pyridines. *Angewandte Chemie International Edition* **2024**, *63* (5), e202317104.
50. Mathias, R.; Weyerstahl, P., Darstellung und Eigenschaften von 1,1-Diiod- und 1-Iod-1-x-cyclopropanen. *Chemische Berichte* **1979**, *112* (9), 3041–3053.
51. Sperga, A.; Kinens, A.; Veliks, J., Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts. *Organic Letters* **2025**, *27* (21), 5446–5451.
52. Gutiérrez, S.; Tomás-Gamasa, M.; Mascareñas, J. L., Organometallic catalysis in aqueous and biological environments: harnessing the power of metal carbenes. *Chemical Science* **2022**, *13* (22), 6478–6495.
53. de Frémont, P.; Marion, N.; Nolan, S. P., Carbenes: Synthesis, properties, and organometallic chemistry. *Coordination Chemistry Reviews* **2009**, *253* (7), 862–892.
54. Frenking, G.; Solà, M.; Vyboishchikov, S. F., Chemical bonding in transition metal carbene complexes. *Journal of Organometallic Chemistry* **2005**, *690* (24), 6178–6204.

55. Dötz, K. H.; Stendel, J., Jr., Fischer Carbene Complexes in Organic Synthesis: Metal-Assisted and Metal-Templated Reactions. *Chemical Reviews* **2009**, *109* (8), 3227–3274.
56. Díez-González, S.; Marion, N.; Nolan, S. P., N-Heterocyclic Carbenes in Late Transition Metal Catalysis. *Chemical Reviews* **2009**, *109* (8), 3612–3676.
57. Davies, H. M. L.; Morton, D., Guiding principles for site-selective and stereoselective intermolecular C–H functionalization by donor/acceptor rhodium carbenes. *Chemical Society Reviews* **2011**, *40* (4), 1857–1869.
58. Mertens, L.; Koenigs, R. M., Fluorinated diazoalkanes – a versatile class of reagents for the synthesis of fluorinated compounds. *Organic & Biomolecular Chemistry* **2016**, *14* (45), 10547–10556.
59. Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A., Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chemical Reviews* **2015**, *115* (18), 9981–10080.
60. Zhang, Z.; Gevorgyan, V., Visible Light-Induced Reactions of Diazo Compounds and Their Precursors. *Chemical Reviews* **2024**, *124* (11), 7214–7261.
61. Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A., Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Organic Process Research & Development* **2020**, *24* (1), 67–84.
62. Fulton, J. R.; Aggarwal, V. K.; de Vicente, J., The Use of Tosylhydrazone Salts as a Safe Alternative for Handling Diazo Compounds and Their Applications in Organic Synthesis. *European Journal of Organic Chemistry* **2005**, *2005* (8), 1479–1492.
63. Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A., Sulfoxonium and Sulfonium Ylides as Diazocarbonyl Equivalents in Metal-Catalyzed Insertion Reactions. *European Journal of Organic Chemistry* **2013**, *2013* (23), 5005–5016.
64. Liu, M.; Uyeda, C., Redox Approaches to Carbene Generation in Catalytic Cyclopropanation Reactions. *Angewandte Chemie International Edition* **2024**, *63* (29), e202406218.
65. Kumar, S.; Borkar, V.; Mujahid, M.; Nunewar, S.; Kanchupalli, V., Iodonium ylides: an emerging and alternative carbene precursor for C–H functionalizations. *Organic & Biomolecular Chemistry* **2023**, *21* (1), 24–38.
66. Kaur, P.; Tyagi, V., Recent Advances in Iron-Catalyzed Chemical and Enzymatic Carbene-Transfer Reactions. *Advanced Synthesis & Catalysis* **2021**, *363* (4), 877–905.
67. Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L., Catalytic Carbene Insertion into C−H Bonds. *Chemical Reviews* **2010**, *110* (2), 704–724.
68. Xia, Y.; Qiu, D.; Wang, J., Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chemical Reviews* **2017**, *117* (23), 13810–13889.
69. Seyferth, D.; Woodruff, R. A., Halomethyl-metal compounds. LXV. Generation of fluorocarboalkoxycarbenes via the organomercury route. *The Journal of Organic Chemistry* **1973**, *38* (23), 4031–4039.
70. David, E.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X., Ethyl dibromofluoroacetate: a versatile reagent for the synthesis of fluorinated molecules. *Tetrahedron* **2013**, *69* (52), 11039–11055.
71. Luckhurst, C. A.; Breccia, P.; Stott, A. J.; Aziz, O.; Birch, H. L.; Bürli, R. W.; Hughes, S. J.; Jarvis, R. E.; Lamers, M.; Leonard, P. M.; Matthews, K. L.; McAllister, G.; Pollack, S.; Saville-Stones, E.; Wishart, G.; Yates, D.; Dominguez, C., Potent, Selective, and CNS-Penetrant Tetrasubstituted Cyclopropane Class IIa Histone Deacetylase (HDAC) Inhibitors. *ACS Medicinal Chemistry Letters* **2016**, *7* (1), 34–39.
72. Lee, K. L.; Ambler, C. M.; Anderson, D. R.; Boscoe, B. P.; Bree, A. G.; Brodfuehrer, J. I.; Chang, J. S.; Choi, C.; Chung, S.; Curran, K. J.; Day, J. E.; Dehnhardt, C. M.; Dower, K.; Drozda, S. E.; Frisbie, R. K.; Gavrin, L. K.; Goldberg, J. A.; Han, S.; Hegen, M.; Hepworth,

D.; Hope, H. R.; Kamtekar, S.; Kilty, I. C.; Lee, A.; Lin, L.-L.; Lovering, F. E.; Lowe, M. D.; Mathias, J. P.; Morgan, H. M.; Murphy, E. A.; Papaioannou, N.; Patny, A.; Pierce, B. S.; Rao, V. R.; Saiah, E.; Samardjiev, I. J.; Samas, B. M.; Shen, M. W. H.; Shin, J. H.; Soutter, H. H.; Strohbach, J. W.; Symanowicz, P. T.; Thomason, J. R.; Trzupek, J. D.; Vargas, R.; Vincent, F.; Yan, J.; Zapf, C. W.; Wright, S. W., Discovery of Clinical Candidate 1-{[(2*S*,3*S*,4*S*)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragment-Based Drug Design. *Journal of Medicinal Chemistry* **2017**, *60* (13), 5521–5542.
73. Rodríguez-Alvarado, M.; Russo, R.; Connell, N. D.; Brenner-Moyer, S. E., Design, organocatalytic synthesis, and bioactivity evaluation of enantiopure fluorinated LpxC inhibitors. *Organic & Biomolecular Chemistry* **2020**, *18* (30), 5867–5878.
74. Dapprich, S.; Frenking, G., Investigation of Donor-Acceptor Interactions: A Charge Decomposition Analysis Using Fragment Molecular Orbitals. *The Journal of Physical Chemistry* **1995**, *99* (23), 9352–9362.
75. Sperga, A.; Pfeifers, T.; Veliks, J., Monofluorinated C1 Synthon Strategy for the Construction of Fluoromethylene-Linked Bicyclo[1.1.1]Pentane Derivatives. *Advanced Synthesis & Catalysis* **2025**, *367* (23), e70119.
76. Shire, B. R.; Anderson, E. A., Conquering the Synthesis and Functionalization of Bicyclo[1.1.1]pentanes. *JACS Au* **2023**, *3* (6), 1539–1553.
77. Baldon, S.; Dell'Amico, L.; Cuadros, S., Synthetic Strategies and Applications of Fluorine-Containing Bridged Bicyclic Compounds. *European Journal of Organic Chemistry* **2024**, *27* (43), e202400604.
78. Wong, M. L. J.; Mousseau, J. J.; Mansfield, S. J.; Anderson, E. A., Synthesis of Enantioenriched α-Chiral Bicyclo[1.1.1]pentanes. *Organic Letters* **2019**, *21* (7), 2408–2411.
79. Huang, W.; Zheng, Y.; Keess, S.; Molander, G. A., A General and Modular Approach to BCP Alkylamines via Multicomponent Difunctionalization of [1.1.1]Propellane. *Journal of the American Chemical Society* **2023**, *145* (9), 5363–5369.
80. Ripenko, V.; Sham, V.; Levchenko, V.; Holovchuk, S.; Vysochyn, D.; Klymov, I.; Kyslyi, D.; Veselovych, S.; Zhersh, S.; Dmytriv, Y.; Tolmachev, A.; Sadkova, I.; Pishel, I.; Horbatok, K.; Kosach, V.; Nikandrova, Y.; Mykhailiuk, P. K., Light-enabled scalable synthesis of bicyclo[1.1.1]pentane halides and their functionalizations. *Nature Synthesis* **2024**, *3* (12), 1538–1549.
81. Bai, Z.; Wang, Z.; Wong, T. H.-F.; Ritter, T., Thianthrenium-enabled modular synthesis of bicyclo[1.1.1]pentanes. *Nature Synthesis* **2025**, *4* (9), 1161–1169.
82. Pickford, H. D.; Nugent, J.; Owen, B.; Mousseau, J. J.; Smith, R. C.; Anderson, E. A., Twofold Radical-Based Synthesis of *N*,*C*-Difunctionalized Bicyclo[1.1.1]pentanes. *Journal of the American Chemical Society* **2021**, *143* (26), 9729–9736.
83. Alonso, M.; Cañellas, S.; Delgado, F.; Serrano, M.; Diéguez-Vázquez, A.; Gómez, J. E., Accelerated Synthesis of Bicyclo[1.1.1]pentylamines: A High-Throughput Approach. *Organic Letters* **2023**, *25* (5), 771–776.

PIELIKUMI / APPENDICES

Sperga, A.; Veliks, J.

Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species

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Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species

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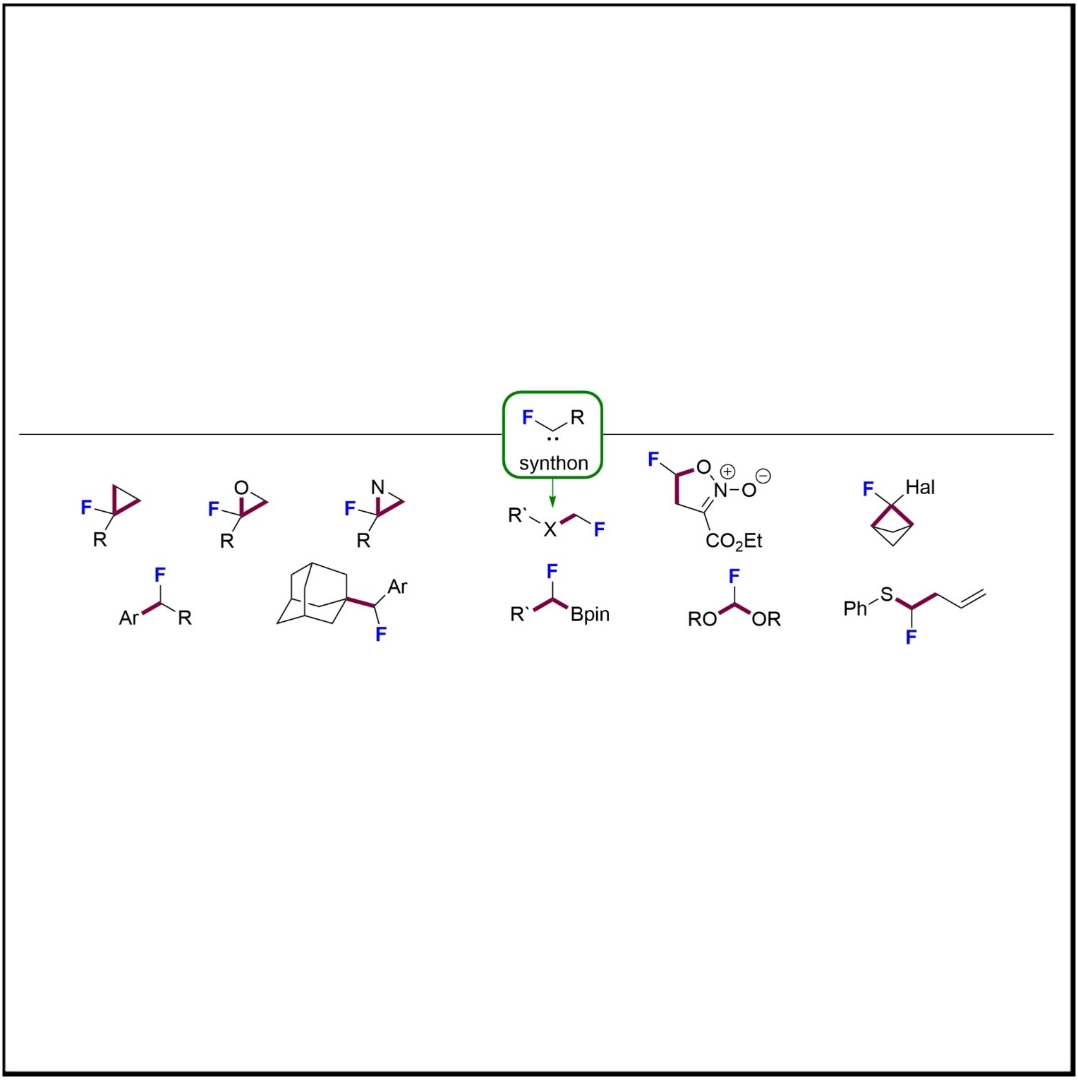


The synthesis of monofluorinated compounds is of great interest because of the vast applications of organofluorine compounds. Recently, the introduction of monofluorocarbene synthons has emerged as an important strategy for the synthesis of fluorine-containing products. In contrast to direct fluorination, in which C–F bonds are formed, the use of monofluorinated carbenes and related reactive species involves C–C or C–X bond formation while delivering valuable fluorine atoms into the target structure. Owing to increased knowledge on carbon-carbon and carbon-heteroatom bond formations, monofluorinated carbenes have enormous potential for the synthesis of organofluorine compounds, which, in our opinion, has not yet been fully exploited. This review summarizes the recent advances in the synthetic applications of monofluorinated carbenes, carbenoids, ylides, and related species.

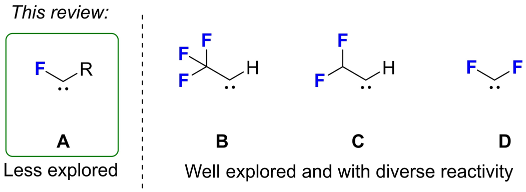
1. Introduction

Fluorine-containing compounds have been broadly employed in materials sciences,[1] medical diagnostics[2] and studies on biochemical mechanisms.[3] The most prominent applications of organofluorine compounds are in the design of pharmaceuticals[4] and agrochemicals.[5] The introduction of a fluorine atom into a molecule can significantly alter its properties, including lipophilicity, metabolic stability, conformation, bioavailability, and interactions with target proteins. Therefore, the replacement of functional groups or hydrogen atoms with fluorine is a common strategy in medicinal chemistry. Therefore, the search for novel methods and reagents to increase access to organofluorine compounds is a flourishing field of research.

Carbenes, carbenoids, metal carbene complexes, ylides, and related species have widespread applications in carbon-carbon and carbon-heteroatom bond formations.[6] The general feature of their reactivity is the formation of two bonds with a central carbon. Fluorinated carbene transfer is an efficient strategy for the synthesis of organofluorine compounds.[7] Trifluoroethylene **B**, difluoroethylene **C**, and difluoromethylene **D** carbene transfers have been widely used for various synthetic applications (Scheme 1) and have been extensively reviewed.[8] However, monofluoromethylene synthon **A** has been far less frequently employed and, to the best of our knowledge, no recent reviews dedicated to monofluoromethylene have been published. Fluoromethylene is likely the smallest member of the family of organofluorine compounds.

The aim of this article is to review the recent applications of monofluoromethylene **A** synthons to access monofluorinated compounds (Scheme 2). The scope of this article includes monofluoromethylene **A** transfers since 1996 when fluorinated carbenes were described in an excellent review by Brahms and Dailey.[9] Other important reviews that include the application of monofluorinated carbenes from various perspectives can be found elsewhere.[10]

This review does not include the synthesis of monofluorolefins; transition-metal-catalyzed cross-couplings; and radical, nucleophilic, and electrophilic monofluoroalkylations.



Scheme 1. Fluorinated carbenes.

2. Monofluorocarbene

Carbene reactivity depends on its spin multiplicity. Triplet carbenes tend to react via two-step radical processes, whereas singlet carbenes generally react via concerted single-step processes.[11] In contrast to methylene carbene, fluorine directly attached to the carbene center stabilizes the singlet state owing to the ability of fluorine to donate a lone pair to the vacant p-orbital (Scheme 3). Another explanation involves fluorine's strong negative inductive effect that increases the p-character of the orbital (Bent's rule) and enhances the s character of the non-bonding lone-pair orbital, thus stabilizing the singlet state.[12] In a series of monohalocarbenes (CHX), fluorine is known to stabilize the carbenes better than other halogens. The stability increases when moving upward in the halogen group ($F > Cl > Br > I$)[13] because of the increased electronegativity and more efficient 2p–2p orbital overlap for fluorine compared to heavier halogens.[14]

Significant efforts were made for determining structural and thermodynamic properties of fluorinated carbenes. Squires et al. determined the monofluoromethylene heat of formation $\Delta H_{f,298}(CHF) = 34.2 \pm 3.0$ kcal/mol.[15] The heat of formation of monohalocarbenes increases as heavier halogens are used.[11] The determined energy gap between the singlet and triplet state was 14.9 ± 0.4 kcal/mol.[16] In a series of monohalomethylenes, the singlet-triplet excitation energies decreased for increasing halogen weights.[11] The monofluorinated singlet state geometry was determined from a laser excitation spectrum with values: C–F = 1.305 Å, C–H = 1.138 Å, and ∠HCF = 104.1°.[17]

The generation of monofluorocarbenes was first reported in 1967. Tang and Rowland reacted an energetic tritium atom with difluoromethane (CH_2F_2).[18] The carbene was subsequently trapped with an alkene in the gas phase to afford monofluorinated cyclopropanes. In the same year, Marolewski and Yang developed an alternative strategy for generating monofluorocarbenes via the photolysis of $CHFBr_2$.[19] In 1968, Schlosser

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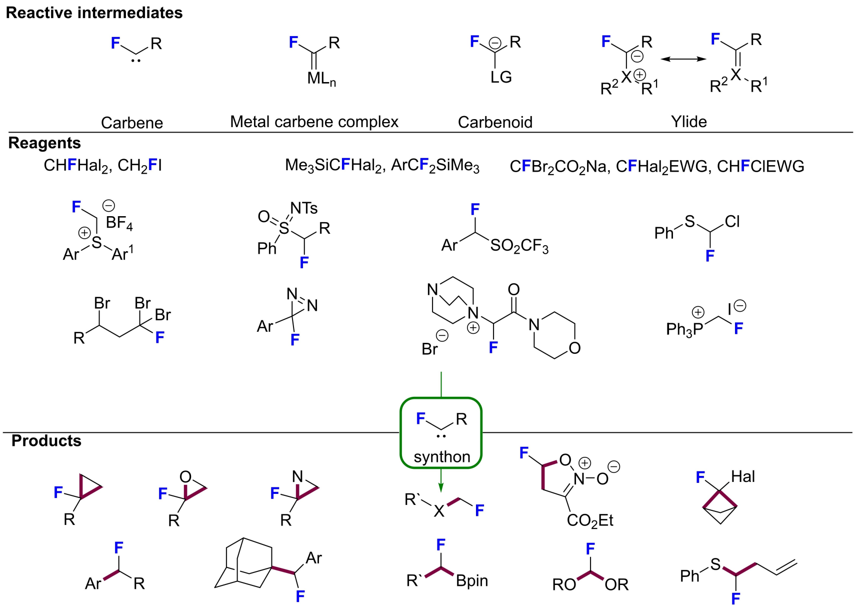
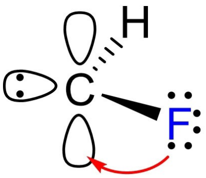


Scheme 2. Overview of monofluorocarbene sources and application.



Scheme 3. Structure of monofluorinated carbene.

and Heinz demonstrated the synthesis of monofluorinated cyclopropanes from dibromofluoromethane ($CHFBr_2$) and *n*-butyllithium in the presence of alkenes. However, they did not differentiate between monofluorocarbenes and carbenoids.[20]

Since then, several other methods for the synthesis of monofluorocarbenes have been developed; however, the these reactions generally have low yields and limited applications, mainly the synthesis of cyclopropanes.[9] Furthermore, fluorohalomethanes are the only source of fluoromethylene carbenes, which often have low boiling points, limited availability, and require nonenvironmentally friendly reagents.

Novel applications of monofluorinated carbenes were achieved in 2005. Khlebnikov et al. demonstrated a novel method for the generation and subsequent application of monofluorocarbenes.[21] Dibromofluoromethane ($CHFBr_2$) undergoes reduction with lead under ultrasound irradiation, forming fluoromethylenecarbene, which adds to imine **1** to form azomethine ylide **2** (Scheme 4). The resulting azomethine ylides **2** undergoes cyclization to afford monofluorinated aziridines **3**. However, if the reaction is carried out in the presence of dipolarophilic dimethyl maleate (**4**), 1,3-dipolar cycloaddition becomes the dominant reaction pathway in the reaction with

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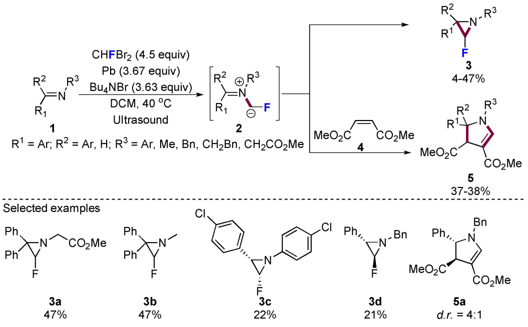
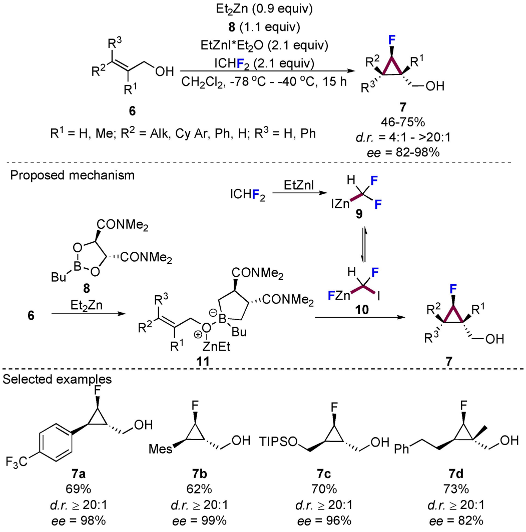
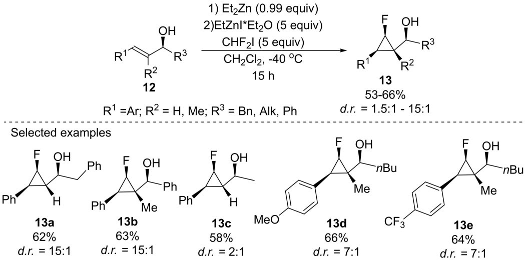


Scheme 4. Fluorocarbene addition to imines.

the *N*-alkylimines of benzaldehydes **1**, and after dehydrofluorination, pyrrolidines **5** are obtained. However, this method suffers from low yields, and the generation of carbenes involves the use of lead. Only one diastereomer was isolated for substrates **3c** and **3d**.



Scheme 5. Fluorocyclopropanation of allyl alcohols.



Scheme 6. Diastereoselective fluorocyclopropanation of allylic alcohols.

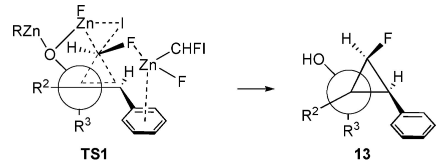
2.1. Monofluorocarbenoids

As a viable alternative to access monofluorinated cyclopropanes, the Simmons–Smith reaction between fluoro(diiodo)methane ($CHFI_2$) and diethylzinc was developed by Nishimura and Furuka in 1971.[22] In contrast to free fluorocarbene reactions, this methodology is highly yielding and has been applied to the synthesis of antibacterials[15,23] functionalized with monofluorinated cyclopropyl amine scaffolds. Furthermore, pyrophoric diethylzinc[24] can be replaced with copper.[25] Unfortunately $CHFI_2$ has limited availability, which limits its broad application.

A novel study on the reactivity and generation of fluoromethylene carbenoids was conducted by Charette et al. in 2013.[26] Researchers developed a method for the diastereo- and enantioselective conversion of allylic alcohols **6** into chiral cyclopropanes **7** (Scheme 5). Difluoroiodomethane initially reacts with ethyl-zinc iodide to form carbenoid **9**, which undergoes halogen scrambling to produce reactive carbenoid **10** which further reacts with chiral alkene intermediate **11** generated from **6** diethylzinc and dioxoborolane **8**. Product **7** was obtained in moderate-to-good yield with excellent diastereo- and enantioselectivity. Furthermore, the reaction tolerated a wide range of allylic alcohols (**6**). The reaction proceeded well with both electron-donating and electron-withdrawing cinnamyl alcohol derivatives, and the alkyl-substituted allylic alcohols were compatible substrates.

In 2015, Navuluri and Charette demonstrated a similar approach based on halogen exchange in the carbenoid, and applied it to the diastereoselective cyclopropanation of various chiral allylic alcohols **12** (Scheme 6).[27] Allylic alcohol **12** was treated with diethylzinc and further reacted with the carbenoids prepared from $EtZnI{*}Et_2O$ and CHF_2I. The following procedure allowed the diastereoselective cyclopropanation of various allylic alcohols **12**. Aryl-conjugated allylic alcohols **12**, bearing electron-withdrawing and electron-donating groups, displayed similar reactivities. However, the sterically smaller groups R^3 or *Z*-alkene geometry in **12** resulted in a drop in *d.r.*

Authors proposed transitions state **TS1** for the observed diastereoselectivity, where it involves fluorine interactions with the zinc carbenoid and coordination of the zinc atom with the π-system (Scheme 7).



Scheme 7. Transition state for diastereoselctive cyclopropanation.

The developed methodology was further employed in the cyclopropanation of chiral styryldioxolanes and the one-pot conversion of cinnamaldehyde to chiral alkoxides, followed by diastereoselective cyclopropanation.

In 2019, Vittorio Pace and Renzo Luisi developed the synthesis of α-fluoroepoxides and aziridines (Scheme 8).[28] This strategy is based on the deprotonation of fluoroiodomethane to give fluoroiodomethyllithium (**14**) and is followed by cyclization with ketone **15** to deliver fluorinated epoxide **16** in low to excellent yields. However, when imine **17** was used, carbenoid **14** addition product **18** formed in high yield. Furthermore, when *N*-sulfonyl-protected ketimine was used as the substrate, the addition-elimination product aziridine **19** was obtained. The authors also demonstrated that products **18** can be cyclized into aziridines under basic conditions.

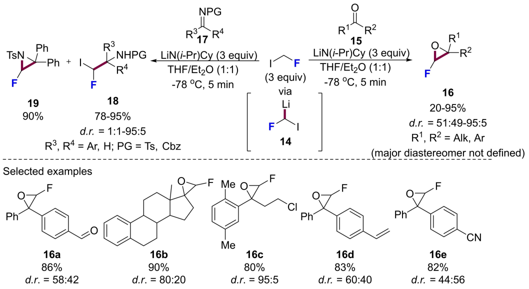
This reaction tolerates a wide range of functional groups, such as halogens, alkenes, alkynes, and nitriles, and shows excellent chemoselectivity towards diarylketones; however, the acetophenone and formyl groups remain unaffected. In another study, the generation of highly reactive intermediate **14** was achieved using flow chemistry.[29]

In 2019, Luisi et al. exploited the electrophilic nature of fluoroiodomethyllithium (**14**) to achieve cyclopropanation of allylic alcohols **20** (Scheme 9).[30] Monofluorinated cyclopropanes **21** were obtained in low to very good yields, and in most cases, with high diastereoselectivity. A wide range of allylic alcohols, including natural products (geraniol and peryllyl alcohol) were tolerated by the reaction conditions. However, if R^1 and R^2 are hydrogen atoms, the reaction would not have occurred. Moreover, substrates bearing electron-accepting groups in the aryl system are unsuitable. Several other alkenes were initially tested for cyclopropanation, including allylic ethers, cynammic acid, homoallylic alcohols, styrene, propargyl alcohols, and preformed allyl lithium alkoxides, which showed no or poor reactivity.

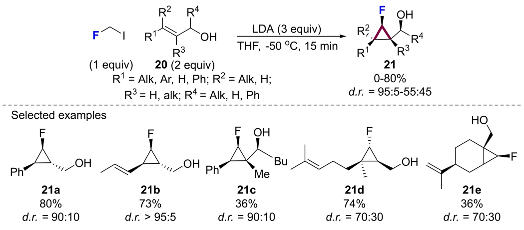
The authors performed DFT calculations, which revealed the enhanced electrophilic properties of fluoroiodomethyllithium carbenoids in THF. The proposed transition state **TS2** involves a carbenoid approach from the less-hindered site and lithium coordination with the alkoxide. (Scheme 10)

In 2020, Aggarwal et al. demonstrated a novel application of fluoroiodomethane.[13] Upon deprotonation, fluoroiodomethyllithium (**14**) is formed, followed by addition to boronate, resulting in -ate complex **I1**. Subsequent 1,2-migration results in formation of α-fluoro-boronic ester **23** (Scheme 11). The key to achieve successful transformation was selection of the carbenoid precursor to ensure: 1) α-elimination does not take place, forming free carbene; 2) a leaving group is sufficient for 1,2-migration; and 3) the leaving group does not stabilize the carbanion to avoid boronate complex dissociation back to the starting materials. DFT calculations suggested that fluoroiodomethyllithium **14** is the optimal candidate.

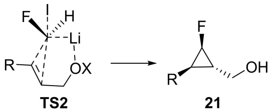
Matteson homologation product **23** can be used further in protodeboronation reactions with 4-*tert*-butylcatechol (TBC) and trifluoroacetic acid (TFA) to afford diverse monofluorinated products **24** in low to moderate yields in a stereospecific manner. Also, α-fluoro-boronic ester **23** can be employed in fluorodeboronation reactions to obtain difluoromethylated compounds **25**. This two-step transformation produced moderate yields and excellent stereocontrol.



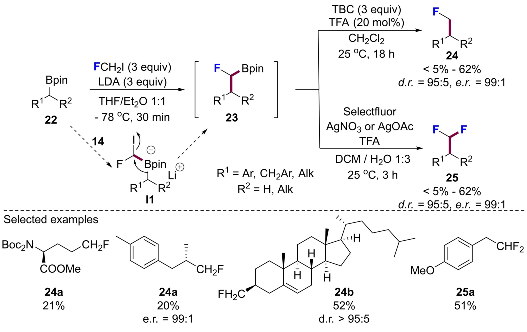
Scheme 8. Fluoroiodomethane application for epoxidation and addition reactions.



Scheme 9. Fluoroiodomethane for cyclopropanation of allylic alcohols.



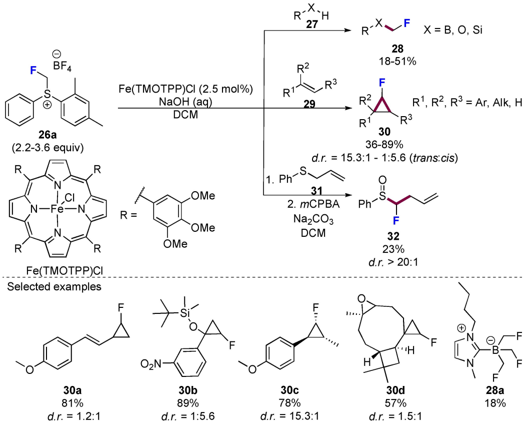
Scheme 10. Proposed transition state for major diastereomer.



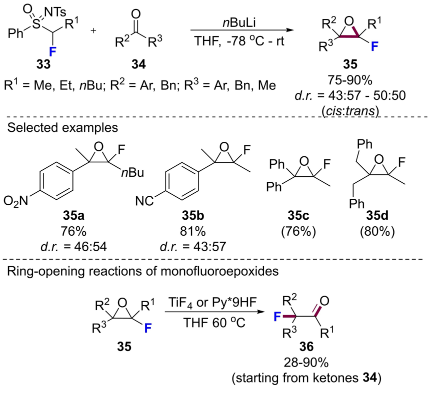
Scheme 11. Lithium carbenoid application in the homologation of boronic esters.

2.2. Monofluorocarbene metal complexes

In 2022, novel fluoromethylene transfer reactions were developed by the Veliks group, employing sulfonium salt **26a** and iron porphyrin catalyst Fe(TMOTPP)Cl (Scheme 12).[31] A porphyrin ligand containing electron-donating groups is the key to successful iron-catalyzed fluoromethylene transfer. In situ generation of carbene metal complexes under basic conditions enabled the fluorocyclopropanation of unactivated alkene **29** to afford monofluorinated cyclopropanes **30** in moderate-to-excellent yields with low-to-moderate diastereoselectivities. Furthermore, the same reaction conditions involving active monofluorocarbene metal intermediates can be applied for X–H insertions in boranes, silanes, and hydroxyl groups in low to moderate yields. Additionally, these reaction conditions were employed in the Doyle–Kirmse or [2,3] – sigmatropic rearrangement with allyl sulfide **31**. This approach obtains diverse highly valuable monofluorinated products **28**, **30**, **32**.



Scheme 12. Iron catalyzed fluoromethylene transfer.



Scheme 13. Sulfoximine **33** application for aldehyde epoxidation.

Monofluorinated carbene-metal complexes have also been utilized in alkene metathesis; however, the synthesis of monofluorinated alkenes has been extensively reviewed[32] and is beyond the scope of this review.

2.3. Formal fluoroalkylene carbene transfer

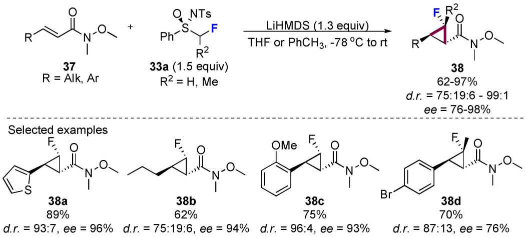
In addition to carbene transfer, several important formal fluoroalkylene transfer reactions have recently been developed.

In 2010, Zhang and Hu applied sulfoximine **33** for the epoxidation of ketone **34** (Scheme 13).[33] This addition-elimination reaction afforded epoxides **35** in good yields but with low diastereoselectivities. The authors observed that the products lacking electron-withdrawing groups in the aryl system decomposed during purification by column chromatography. However, this instability was efficiently exploited to developed acid catalyzed epoxide **35** ring opening/1,2-fluorine shift reaction to obtain various α-fluoro ketones **36**.

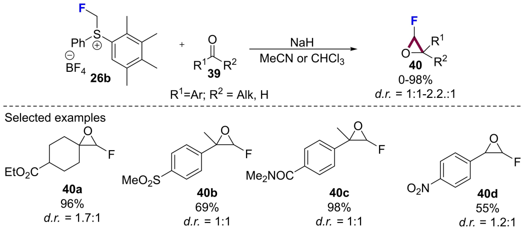
In 2012, Jinbo Hu et al. developed stereoselective cyclopropanation of α,β-unsaturated Weinreb amides **37** using chiral fluorinated sulfoximines **33a** (Scheme 14).[34] Upon deprotonation of sulfoximine **33a** with base it undergoes Michael initiated ring closure with α,β-unsaturated Weinreb amide **37** to form cyclopropanes **38**.

The products were obtained in good-to-excellent yields with high enantio- and diastereoselectivities. This reaction tolerates a wide range of Weinreb amides **37** and can also be applied to construct quaternary fluorine-containing stereogenic centers. Furthermore, Weinreb amides serve as valuable functional groups for producing diverse monofluorinated cyclopropanes. However, the factors governing the stereochemical outcomes remain unclear.

The Veliks group explored the diaryl fluoromethylsulfonium salt **26b**[35] as a fluoromethylene transfer reagent (Scheme 15).[36] They observed that sulfonium salts, upon treatment with a base in deuterated chloroform, underwent H–D exchange, suggesting the formation of sulfur fluoromethylide. This indicates that salt **26b** might be a promising reagent for the Corey–Chaikovsky reaction. Under optimized reaction conditions, a wide variety of ketones and aldehydes **39** underwent epoxide formation with average to excellent yields but low diastereoselectivities. This reaction tolerates a variety of functional groups; however, it is unsuitable for substrates



Scheme 14. Sulfoximine **33a** application for stereoselective cyclopropanation.



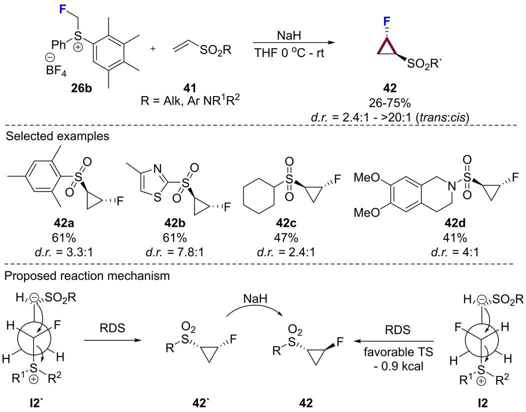
Scheme 15. Sulfonium salt **26 b** in synthesis of monofluoroepoxides **40**.

bearing electron-donating groups in aryl systems because the decomposition of epoxide **40** is observed.

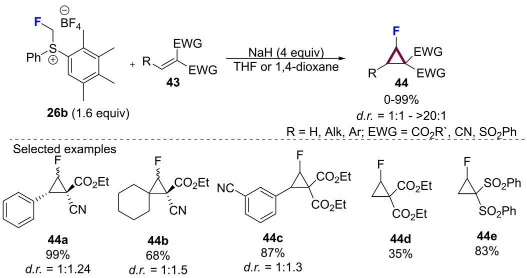
Further, sulfonium salt **26 b** was employed in vinyl sulfone **41** cyclopropanation (Scheme 16).[37] Under basic conditions, various alkenes undergo diastereoselective cyclization to form cyclopropanes **42** in good yields. This reaction tolerates a variety of functional groups and can also be used to obtain cyclopropyl sulfonamides but in diminished yields. The reaction mechanism was investigated using DFT calculations. In the 1st step, ylide addition takes place, followed by rotation, leading to intermediates **I2** and **I2'**. DFT calculations reveal that ring closure is the rate determining step. The transition state leading to the major diastereomer occurs where **42** lacks fluorine and sulfone electrostatic repulsions. Furthermore, the *trans* product **42** is thermodynamically more stable as the *cis* isomer **42'**, but upon treatment with base isomerizes to **42**. The formation of the thermodynamically more stable carbanion product **42** was used in α-functionalization of sulfone in diastereoselective alkylation reactions.

The Veliks group also investigated sulfonium salt **26 b** in the Corey–Chaikovsky cyclopropanation of double-activated alkenes (Scheme 17).[38] Various double activated alkenes **43** are suitable for reactions with sulfonium **26 b** salts in the presence of a base. Arylidene malononitriles and malonates formed cyclopropanes **44** in moderate-to-excellent yields. However, their stability depends on the substituents on the aryl ring-electron-donating group-containing products **44**, which are prone to decomposition during column chromatography. Conversely, electron-withdrawing groups stabilized **44**. For arylidine malonates **43**, the ester group R' considerably affects the reactivity and diastereoselectivity R'$=$Bn displayed the best stability, but R'$=$iPr had the best reactivity. Furthermore, several Michael acceptors were evaluated: the reactivity was dependent on the electrophilicity of the starting materials; arylidine nitriles formed unstable products, cinnamonitrile, ethyl cinnamate, and phenyl vinyl sulfoxide were unreactive.

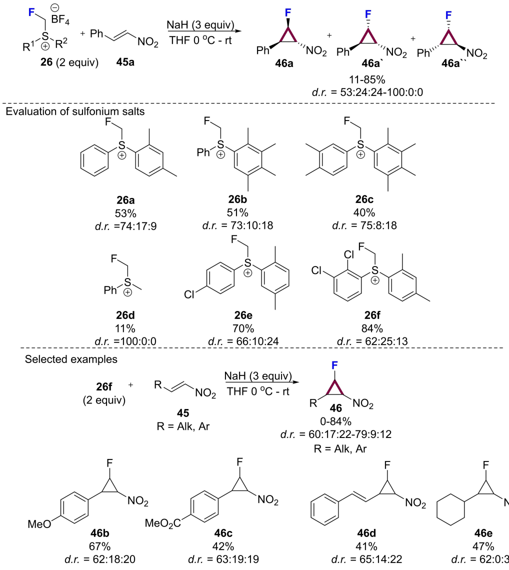
To further explore fluoromethyl sulfonium salt **26 b** reactivity, the Veliks group focused on nitrostyrene **45** cyclopropanation (Scheme 18).[39] However, salt **26 b** gave unsatisfactory results for the cyclopropanation of nitroalkene **45 a**. Therefore, the structure of the sulfonium salt **26** was evaluated to gain insight into the structure-reactivity relationship. Several sulfonium salts **26** were synthesized and tested in the reaction



Scheme 16. Sulfonium salt **26 b** for vinylsulfone cyclopropanation.



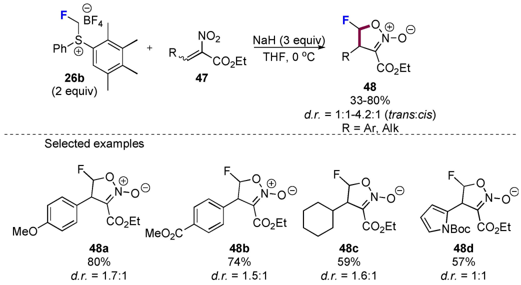
Scheme 17. Double activated alkene cyclopropanation.



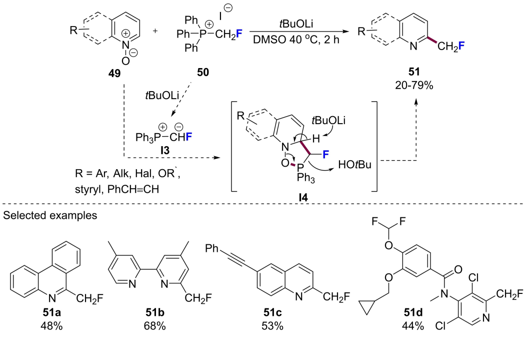
Scheme 18. Evaluation and application of sulfonium salts **26**.

with nitroalkene **45 a**. The electronic properties of the sulfonium salt **26** play a key role in its reactivity. Addition of electron-donating groups to the aryl system decreased the yield of fluorocyclopropane **46 a**. Simplified salt **26 d** showed a considerably lower yield. However, the addition of a halogen atom to the aryl system increased the yield. Therefore, 2,3-dichloro substituted reagent **26 f** was used for the substrate scope investigation. The reaction tolerates both electron-donating and electron-withdrawing groups on the aryl nitrostyrenes **45**. In addition, aliphatic substituents were tolerated in the reaction. The product was obtained in a moderate yield as a mixture of three diastereomers. However, salt **26 a** was a less expensive alternative to the original salt **26 b** because it gave similar results in the cyclopropanation of the previously investigated activated systems.

Another application of sulfonium salt **26 b** for fluoromethylene transfer was demonstrated in [4+1] cyclization with α-nitroacrylates **47** to deliver monofluorinated isoxazoline N-oxides **48** (Scheme 19).[40] Products **48** are formed in average to good yields, and a variety of substrates are suitable for this transformation. Aryl-substituted double bonds with different functional groups, heteroarylidene systems, and cyclohexylidene deliver products in practical yields as a mixture of diastereomers. Furthermore, the use of isoxazoline *N*-oxide **48** application was demonstrated in a deoxygenation and [3+2] cycloaddition to achieve densely functionalized fluorinated heterocycles.



Scheme 19. Fluoromethylene transfer in [4+1] cyclization.



Scheme 20. Deoxygenative fluoromethylation.

For 2021, Qing et al. employed the fluoromethyl phosphonium salt **50** for the deoxygenative C2-fluoromethylation of a variety of pyridine and quinoline *N*-oxide derivatives **49** (Scheme 20).[41] Formal carbene insertion into the C(sp^2)–H bond delivered products **51** in low-to-good yields. Vinyl, alkynyl, and halogen functional groups were well tolerated under optimized reaction conditions. Moreover, this reaction can be applied to the late-stage functionalization of roflumilast *N*-oxide **49 d**. Phosphonium salt **51** in basic media forms ylide **I3** which undergoes addition to *N*-oxide **49** to yield **I4** followed by phosphine oxide elimination and proton transfer to produce **51**.

Similar products can alternatively be obtained by radical fluoromethylation and transition metal-catalyzed cross-coupling reactions,[42] however, this is beyond the scope of this review.

3. Fluorohalocarbenes

The experimentally determined properties of fluorohalocarbenes, such as thermodynamic properties, singlet-triplet energy gaps, and geometry, lack experimental data and sometimes show wide variations in results.[12] The experimentally-determined heat of formation for chlorofluorocarbene is $\Delta H_{f,298}(CFCl) = 7.4 \pm 3.2$. kcal/mol.[15] Ab Initio calculations for fluorohalocarbenes show that enthalpies of formation increases in the following order: $\Delta H_{f,298}(CFCl) = 27.8$, $\Delta H_{f,298}(CFBr) = 86.5$, $\Delta H_{f,298}(CFI) = 154.4$ (kJ/mol), and $\Delta H_{f,298}(CFH) = 145.4$ kJ/mol.[12] These results indicate that chlorofluorocarbene is the most stable fluorohalocarbene.

The geometries of these carbenes and energy gaps between the singlet and triplet states were determined using different calculation methods.[43] The singlet-triplet energy gaps for fluorohalocarbenes increases in following order: $\Delta E_{ST}(CFI) = 109.5$, $\Delta E_{ST}(CFBr) = 132.2$, $\Delta E_{ST}(CFCl) = 147.3$ (kJ/mol), and $\Delta E_{ST}(CFH) = 59.8$ (kJ/mol).[12] The singlet state is more stable in fluorohalocarbenes, where the singlet-triplet energy gap usually increases with more electronegative atoms at the carbene center.

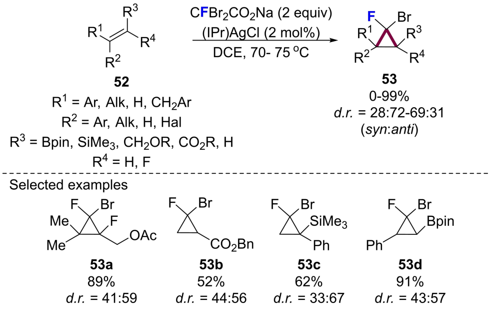
For several fluorinated carbenes, the experimental activation parameters were determined for reactions with alkenes.[44] Fluorohalocarbenes are electrophilic. Increasing the number of fluorine atoms at the carbene center increased the stability of $CF_2 > CFCl > CCl_2$ but decreased the reaction rate with alkenes.[14]

Historically, fluorohalocarbenes were generated using halofluoromethanes^9. However, these are not environmentally friendly reagents because of their potential ozone-depleting properties and limited accessibility, which have facilitated the development of various alternative reagents. This review focuses on novel fluorohalocarbene generation methods and applications since 2015, as previous studies on the synthesis of dihalocyclopropanes have been reviewed.[10b,45]

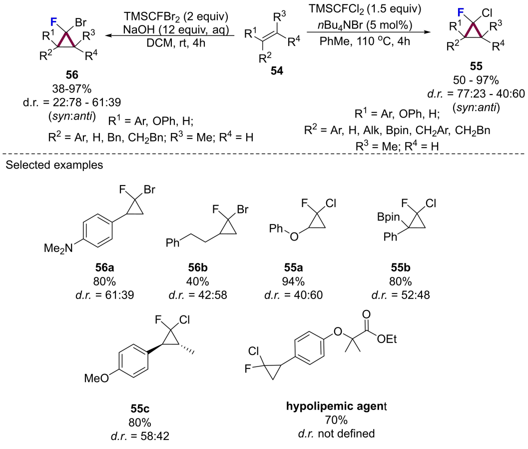
In 2018, Semenov developed a method for generating bromofluorocarbenes.[46] Dibromofluoroacetate undergoes Ag-catalyzed decomposition to form bromofluorocarbenes, which are subsequently trapped by alkenes **52** to form various cyclopropanes **53** in low to excellent yields (Scheme 21) as a mixture of diastereomers.

The reaction conditions were compatible with a wide range of alkenes containing various functional groups such as esters, silanes, and boronates. Interestingly, using this method, cyclopropanation can also be applied to electron-poor double bonds, which are usually unsuitable substrates for carbene transfer.[47] However, a large excess of the carbene source (8 equiv) is required for this reaction.

In 2021, Hu et al. investigated $TMSCFX_2$ (X = Cl, Br) as an alternative precursor for fluorohalocarbene generation (Scheme 22).[48] The nucleophile attacks the silane reagents $TMSCFHal_2$ to produce CFX_2^- followed by α-elimination to afford carbenes CFX. Chlorofluoro cyclopropanation of alkene **54** was achieved under a catalytic amount of $n\text{Bu}_4\text{NBr}$ at an elevated temperature. In this reaction, diverse aryl- and heteroaryl-conjugated alkenes **54** were cyclopropanated to afford products **55** in good-to-excellent yields but with low diastereoselectivities. The authors noted that bromofluoro cyclopropanation afforded lower yields owing to the formation of ring-opening side products.



Scheme 21. Silver-catalyzed synthesis of dihalocyclopropanes.



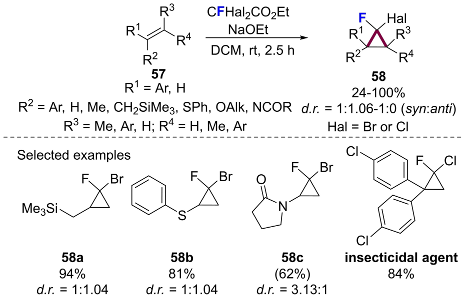
Scheme 22. $TMSCFHal_2$ as a fluorohalocarbene source.

To overcome this problem, bromofluorocyclopropanation was performed using aqueous NaOH at room temperature. Under the optimized reaction conditions, diverse bromofluorocyclopropanes **56** were obtained in good to excellent yields, but mostly with low diastereoselectivity.

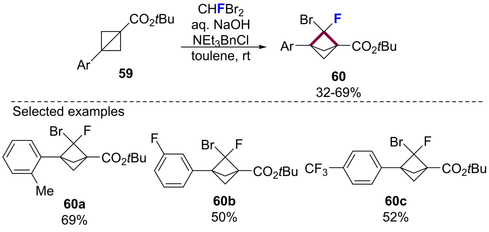
In 2022, Prakash et al. developed a new freon-free fluorohalocyclopropanation method based on carbene generation from commercially available ethyl dihalofluoroacetate using sodium ethoxide under mild conditions at room temperature (Scheme 23).[49] The carbene generated in situ undergoes [2+1] cycloaddition with alkenes **57** forming fluorohalocyclopropanes **58** in medium to quantitative yields as a mixture of diastereomers.

In 2022, Mykhailiuk and Bychek extended the reactivity of bromofluorocarbenes.[50] Fluorobromocarbene was generated from $CHFBr_2$ using an aqueous base and phase-transfer catalysis, which was further reacted with bicyclo[1.1.0]butanes **59** to deliver ring expansion products **60** in moderate yields (Scheme 24). This reaction tolerates both electron-withdrawing and electron-donating substituents on the aryl ring. Substrates lacking aryl systems were not compatible with the reaction conditions. Furthermore, **60** can be debrominated and functionalized to access the fluoro-bicyclo[1.1.1]pentane building blocks, which are highly relevant in medicinal chemistry.[51]

In 2021, Recsei and Barda developed an interesting methodology to access bis(aryloxy)fluoromethanes.[52] The proposed mechanism involved bromofluoro carbene generation from dibromofluoromethane (Br_2FCH), K_3PO_4, or KOH. In this reaction, aryloxide **I5** undergoes addition to carbene **I6**, followed by bromide elimination to form the second carbene **I9**, which is



Scheme 23. Halogenated esters as source of fluorohalocarbene.

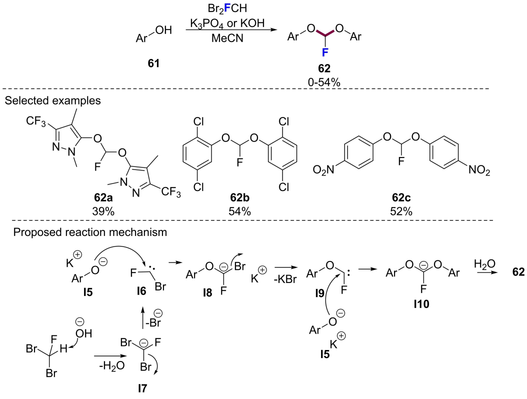


Scheme 24. Dihalocarbene applications for ring expansion.

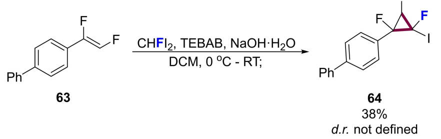
further trapped by another molecule of aryloxide **I5**. After protonation, fluoroacetals **62** were obtained (Scheme 25). The reactions with **61** containing phenols were not successful, but those with starting material **61** containing electron-withdrawing groups formed product **62** in reasonable yields. Dibromofluoromethane (Br_2FCH) also undergoes monoinsertion into thiols.[53]

In comparison to other halofluorocarbenes, fluoroiodocarbenes have rarely been applied in synthesis.[54]

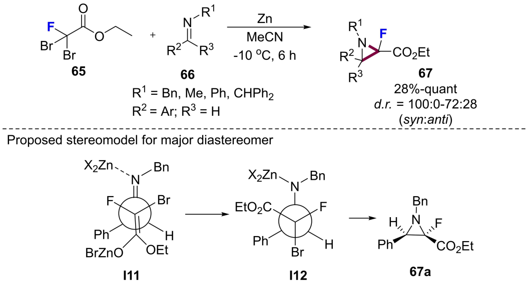
David O'Hagan et al. in 2019 applied fluorodiiodomethane ($CHFI_2$) to the generation of fluoroiodocarbene and subsequently trapped it with alkene **63** to afford 1,2,3-trifluorocylopropanes **64** (Scheme 26).[55]



Scheme 25. Synthesis of monofluorinated acetals via bromofluorocarbene.



Scheme 26. Fluoroiodocarbene transfer.



Scheme 27. Application of **65** for aziridine synthesis.

4. Fluoroacetyl Carbene Transfer

Fluoroacetylcarbene transfer is widely used in various applications. Usually, ethyl dibromofluoroacetate (**65**) is employed as a precursor to formal α-fluoroester carbene transfer. Several review articles have been published on the reactivity and applications of ethyl dibromofluoroacetate.[56] In addition to olefination reactions, reagent **65** has also been used for [2+1] cycloaddition reactions.

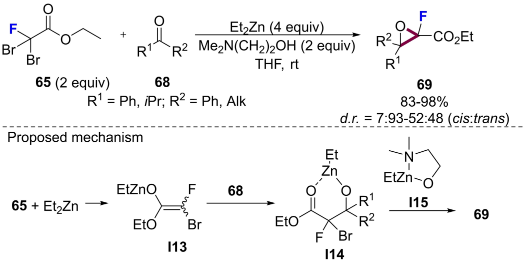
Akira Ando et al. applied ethyl dibromofluoroacetate (**65**) in a Reformatsky-type aza-Darzen reaction with imine **66** using zinc (Scheme 27).[57] High chemoselectivity for the formation of 3-membered ring **67** versus azetidine was achieved using acetonitrile as a coordinating solvent.

The reaction proceeded under mild conditions without zinc activation. The yields of **67** ranged from good to excellent, and good diastereoselectivity was achieved. However, aliphatic aldimines and ketimines did not form their corresponding products. To rationalize the observed stereochemical outcome, the authors provided a tentative stereomodel for the reaction, in which minimized steric repulsions in the enolate addition step **I11** play a key role in diastereoselectivity.

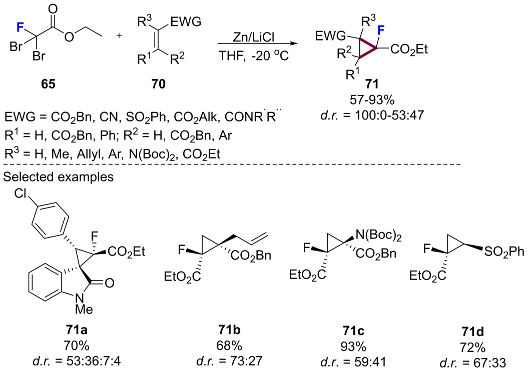
In 2010, Jubault et al. synthesized fluorinated glycidic ester **69** from ketone **68** using ethyl dibromofluoroacetate (**65**), diethylzinc, and *N*,*N*-dimethylethanolamine (Scheme 28).[58] The reaction proceeds under mild conditions and delivers product **69** in excellent yield. Liquid–liquid extraction was sufficient to obtain product **69** with reasonable purity. The addition of *N*,*N*-dimethylethanolamine is crucial for the epoxidation step, which increases the nucleophilicity of the intermediate alkoxide **I14**.

Philippe Jubault et al. further explored the reactivity of ethyl dibromofluoro acetate (**65**) in the cyclopropanation reaction with electron-deficient alkenes **70** (Scheme 29).[59] Under the optimized reaction conditions, a wide variety of Michael acceptors **70** participated in the reaction to deliver highly functionalized monofluorinated cyclopropanes **71** in moderate to excellent yields. Furthermore, the synthetic utility of this reaction was demonstrated on a 30 g scale with alkenes **70**.

Jubault et al. applied a similar methodology to the asymmetric synthesis of monofluorinated cyclopropanes (Scheme 30).[60] Amides **72** underwent cycloaddition with electron-deficient alkenes **73** to afford cyclopropanes **74**. Cyclopropanes **74** were obtained in good yield as an enriched



Scheme 28. Application of **65** for epoxide synthesis.



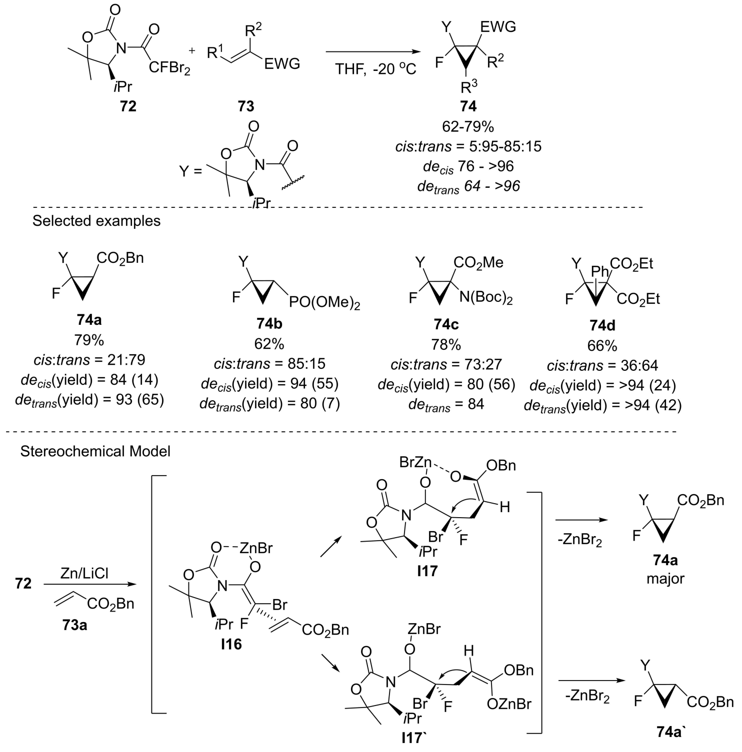
Scheme 29. Synthesis of cyclopropanes via fluoroacetyl carbene transfer.

mixture of *cis* or *trans* isomers, with good to excellent diastereomeric excess. Various Michael acceptors **73** undergo transformations, and the *cis*:*trans* ratio depends on the electron-withdrawing groups. Phosphonates and sulfones display reverse selectivity to acrylates. The authors reported that the stereomodels for acrylate **73a** cyclopropanation exhibited high stereocontrol of the fluorine quaternary center achieved by stereoselective 1,4-addition, where the *Z*-configuration of the enolate is favored because of steric effects. The cyclopropanation step is less selective, but *trans* isomer **74a** is favored with acrylates because of zinc atom chelation in intermediate **I17**. However, this stereochemical model does not explain the reversed *cis*:*trans* ratio of substrates bearing phosphonate and sulfone electron-withdrawing groups.

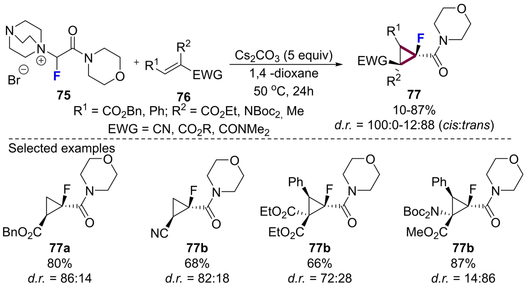
These reactions have been employed for synthesis of biologically active molecules.[61]

In 2013, Jubault et al. studied a novel synthetic strategy to access densely functionalized monofluorinated cyclopropanes **77** via Michael-initiated ring closures.[62] Quaternary ammonium salt **75** undergoes an addition-elimination reaction with electron-poor double bonds **76** to deliver cyclopropanes **77** in high yields and diastereoselectivities (Scheme 31). Morpholine-substituted amide **75** showed the highest reactivity towards alkene **76**.

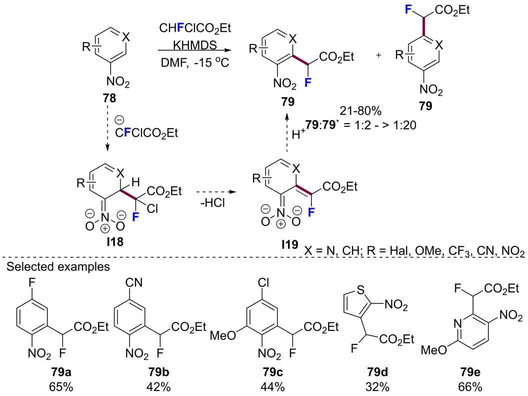
In 2016, Mąkosza et al. succeeded in formal fluoroacetyl carbene C(sp^2)–H insertion to access α-fluoro-α-nitroarylacetates **79**.[63] Upon treatment with a base, ethyl chlorofluoroacetate forms a carbanion, which adds to nitroarene **78** at the *ortho* or *para* position to form **I18**. Following HCl elimination and proton transfer, intermediate **I19** afforded **79** (Scheme 32). This nucleophilic substitution tolerates a wide range of functional groups, including fluorinated nitrobenzenes, which are



Scheme 30. Asymmetric synthesis of cyclopropanes via fluoracetamide transfer.



Scheme 31. Ammonium salt **75** for cyclopropanation of activated alkenes.



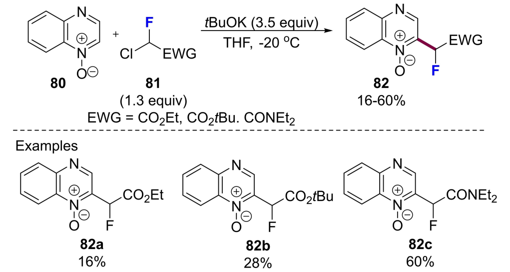
Scheme 32. Ethyl chlorofluoroacetate addition to aromatic systems.

prone to S_NAr. Product **79** was obtained in low-to-good yield, mostly with high regioselectivity towards the *para* insertion product. Furthermore, the application of **79** in base-mediated alkylation reactions was demonstrated.

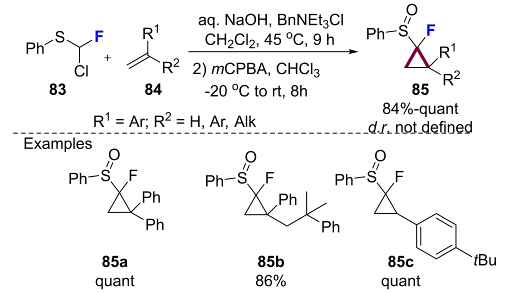
In 2022, Mieczysław et al. explored vicarious nucleophilic substitutions to functionalize quinoxaline *N*-oxides **80** with carbon nucleophiles. Three examples of fluoroacetyl transfers have been reported. In the reaction between chlorofluoroacetyl derivatives **81** and quinoxaline N-oxides **80** under basic conditions, vicarious nucleophilic substitution takes place to access monofluorinated derivatives **82** (Scheme 33).[64]

5. Fluorothiocarbene Transfer

In 2013, Masayuki Kirihara et al. reported chlorofluoromethyl phenyl sulfide (**83**) as a carbene source for the cyclopropanation of unactivated alkenes **84** to access functionalized cyclopropanes **85** (Scheme 34).[65] Fluorothiocarbenes generated under basic conditions from **83** undergo [2+1] cycloaddition with alkenes **84**. Fluorocyclopropyl sulfides were further oxidized to achieve successful isolation. Product **85** was obtained in excellent yield as a mixture of diastereomers and was further applied in desulfurization to synthesize monofluorinated cyclopropanes; however, only a limited substrate scope was demonstrated for this transformation.

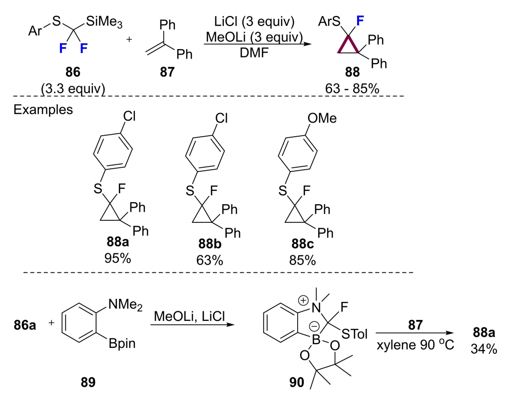


Scheme 33. Ethyl chlorofluoroacetate addition to aromatic systems.



Scheme 34. Fluorothiocarbene generation and application.

In 2022, Dilman et al. developed novel silane reagents **86** for fluorothiocarbene generation (Scheme 35)[66] which were activated in the presence of lithium methoxide and lithium chloride additives. Fluorothiocarbene further undergoes cyclopropanation of 1,1′-diphenylethylene (**87**), to obtain products **88** in very good yields. The authors also demonstrated the trapping of fluorothiocarbene with dimethylaminophenylborane **89** forming a zwitterionic adduct **90** which, upon heating,



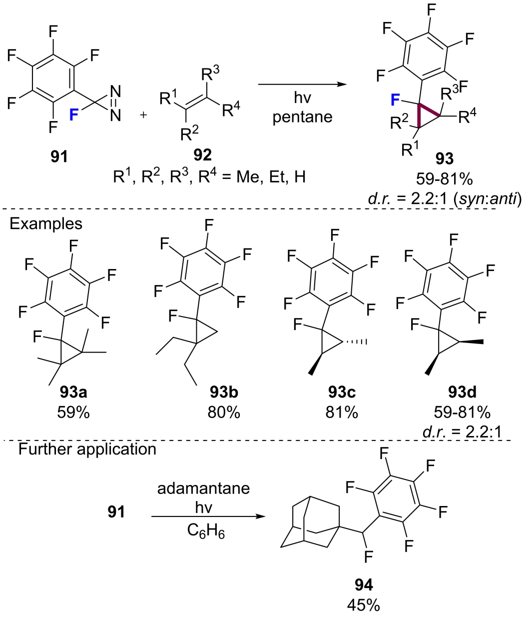
Scheme 35. Fluorothiocarbene generation from silane **86**.

releases carbene and forms the corresponding product **88a** with 1,1-diphenylethylene (**87**) in lower yields.

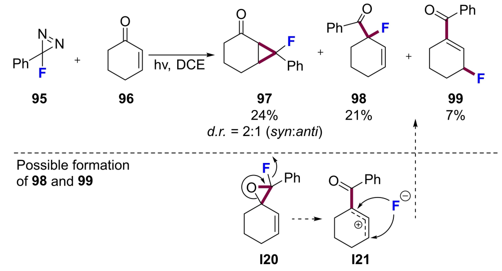
6. Arylflurocarbenes

In 2011, Krogh-Jespersen et al. investigated perfluorinated diazirine **91** as the carbene source.[67] Upon laser flash photolysis of diazirine **91** in the presence of alkene **92**, cyclopropanation occurred, affording cyclopropanes **93** (Scheme 36). Product **93** was formed in average to good yields, where the configuration of alkene **92** was transferred to the formed product **93**. In this study, a single example of C(sp^3)–H insertion in adamantane was demonstrated.

In 2007, Sauers et al. showed that the reaction of diazirine **95** with cyclohexenone **96** under laser flash photolysis delivered a mixture of products (Scheme 37).[68] Cyclopropane **97** was obtained, and products **98** and **99** most likely arose from the epoxidation of the ketone group, followed by epoxide **I20** ring opening, forming allylic cation **I21**, which reacts with the eliminated fluoride to deliver a mixture of isomers **98** and **99**.



Scheme 36. Diazirine **91** as a carbene source.



Scheme 37. Fluorophenyl carbene addition to the unsaturated ketone.

Rigby and Aasmul employed diazirine **100** in cyclopropanation of vinyl isocyanates **101** to obtain functionalized cyclopropane **102** after methanolysis in average yield (Scheme 38).[69]

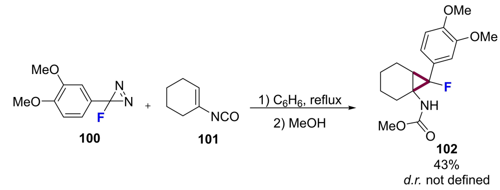
6.1. Formal arylfluorocarbene transfer

In 2022, Xu et al. applied triflone **103** in Michael addition-elimination reactions with activated double bond-containing substrates **104** to synthesize monofluorinated α-arylsubstituted cyclopropanes **105** (Scheme 39).[70] Product **105** was obtained in good yield and generally with good diastereomeric ratios.

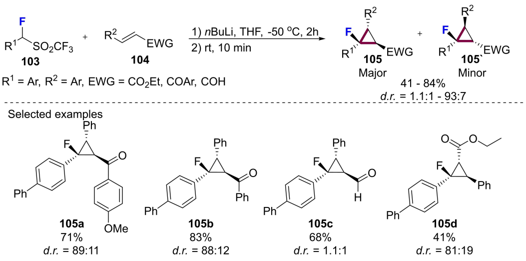
In 2022, Szymczak et al. developed a novel reagent for the arylfluoromethylene transfer (Scheme 40).[71] Borazine **107** undergoes addition to ketone **106** followed by fluoride elimination to deliver epoxide **108**. The reaction could also be applied to activated carbonyls **106** to obtain bis-addition products **109**.

7. Alkynylcarbene

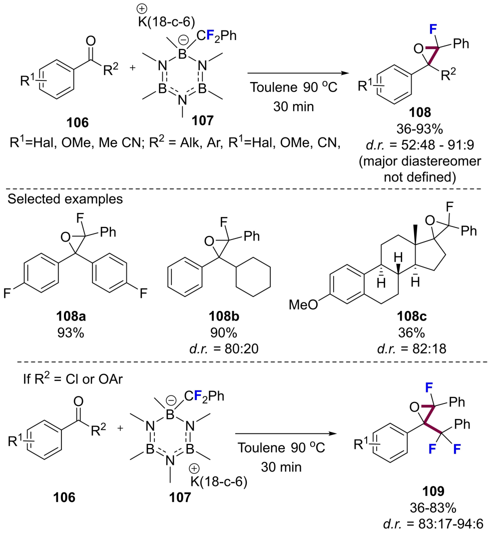
In 2002, Nefedov et al. developed a strategy for generating propargylic carbenes **I27** from halogenated alkenes **110** via elimination cascade reactions in basic conditions (Scheme 41).[72] Carbenes **I27** were utilized in olefin **111** cyclization to afford the corresponding cyclopropanes **112** in low to good yields as a mixture of diastereomers.



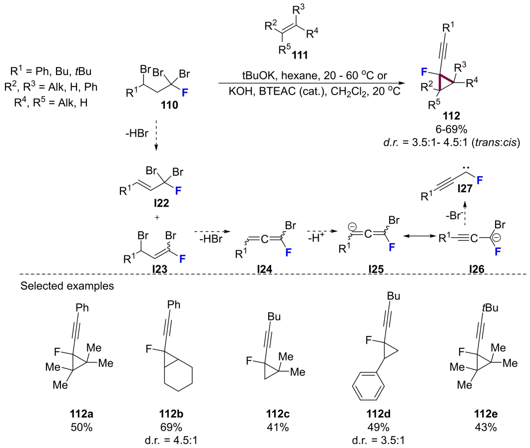
Scheme 38. Diazirine **100** application in cyclopropanation.



Scheme 39. Synthesis of cyclopropanes using triflone **103**.



Scheme 40. Synthesis of fluoroepoxides with borazines **107**.



Scheme 41. Alkynyl carbene generation and application in cyclopropanation.

8. Applications for Synthesis of Biologically Relevant Molecules

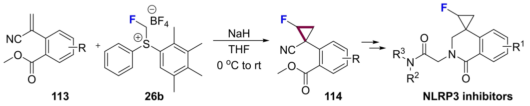
The synthetic methodologies and reagents described in this section can be used to synthesize biologically active compounds. Fluorine atoms and cyclopropyl groups are important functionalities in medicinal chemistry. However, the additive effect of both groups should be evaluated and better understood. There are several examples of the successful use of the fluorocycloproyl group because it alters biological activity and selectivity.

Denali Therapeutics employed sulfonium salt **26b** in the cyclopropanation of activated alkenes **113** to obtain monofluorinated cyclopropanes **114** which were subsequently used for the synthesis of NLRP3 inhibitors (Scheme 42).[73]

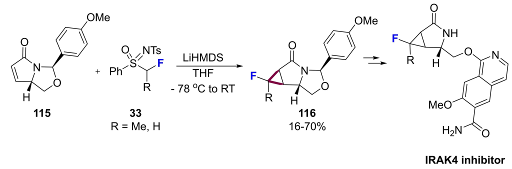
Another monofluorocyclopropanation reaction was used by Pfizer for the synthesis of IRAK4 inhibitors (Scheme 43).[74] Unsaturated amide **115** was cyclopropanated with sulfoximines **33** to obtain diastereoselective cyclopropanes. Precursor **116** was used to prepare IRAK4 inhibitors.

In 2020, Veliks et al. developed the diastereoselective synthesis of fluorocyclopropyl cabozantinib analogues.[75] The synthesis started from methylidene malonate **117** cyclopropanation with sulfonium salt **26b** to afford cyclopropane **118** (Scheme 44). Fluorinated cabozantinib analogs were prepared via diastereoselective ester hydrolysis and amide bond formation. The *trans* diastereomer of F-cabozantinib displayed higher activity against c-Met Kinase than the non-fluorinated analog. After chiral preparative HPLC separation of *trans* enantiomers (+)-F-Cabozantinib displayed more than 10 times higher selectivity towards cancer Hep G2 cells than non-cancerous HEK293 cells compared to the parent drug cabozantinib.

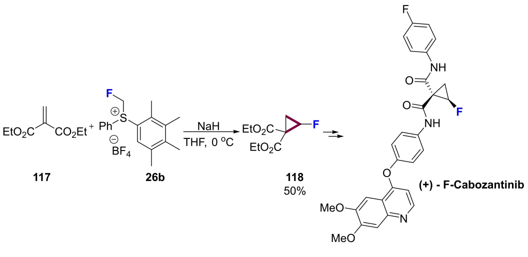
In 2015, Jubault et al. developed a fluorinated Simeprevir analog (HCV NS3/4 A protease inhibitor, a therapeutic agent against the hepatitis C virus).[76] This synthesis relied on the cyclopropanation of alkene **119** with ethyl dibromofluoroacetate **65** to afford cyclopropane **120** (Scheme 45). Biological



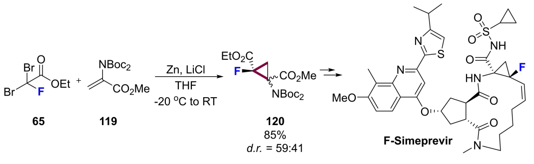
Scheme 42. Sulfonium salt **26b** application for the synthesis of NLRP3 inhibitors.



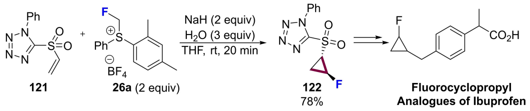
Scheme 43. Diastereoselective cyclopropanation for the synthesis of IRAK4 inhibitors.



Scheme 44. Fluorinated cabozantinib synthesis using **26b**.



Scheme 45. Synthesis of the fluorinated Simeprevir analogue.



Scheme 46. Synthesis of the fluorocyclopropyl analogue of ibuprofen.

analyses of F-Simeprevir revealed decreased antiviral activity compared with that of the original Simeprevir.

In 2023, Melngaile et al. applied fluoromethyl sulfonium salt **26a** to the diastereoselective cyclopropanation of sulfone **121** to afford cyclopropane **122** (Scheme 46).[77] Intermediate **122** was further used to synthesize the fluorocyclopropyl analog of ibuprofen via the Julia–Kocinski reaction as a key step. After chiral preparative HPLC separation of isomers biological evaluation of the synthesized analogues revealed that the incorporation of monofluorinated cyclopropanes can alter the selectivity toward COX-1 vs. COX-2.

9. Conclusions and Outlook

In recent years, monofluoromethylene (CHF) transfer has gained significant attention in the research community as an approach for the formation of otherwise difficult fluorinated products. Novel monofluorinated synthon transfer reagents and reactions were developed, facilitating the synthesis of monofluorinated compounds and providing access to novel fluorinated scaffolds. Some of these transformations were achieved with excellent diastereo- and enantioselectivities. However, these reactions are usually limited to 3-membered ring syntheses. In addition, asymmetric transformations have limited applications to allylic alcohols and Weinreb amide cyclopropanations.

For dihalocarbene (CFHal) transfer, a few new reagents that allow dihalocarbene transfer have emerged. However, apart from few exceptions, their reactivity is limited to cyclopropane synthesis, which typically proceeds with poor stereoselectivity. The current state-of-the-art fluorohalocarbene transfer reactions lag considerably behind the rich chemistry of difluorocarbene, and in our opinion, the potential of these reactive species has not been fully realized.

For formal fluoroacetyl carbene transfers, new reactions have been developed for the synthesis of 3-membered rings and formal insertion reactions of the Csp^2–H bond. Some of these transformations have been achieved in a stereoselective manner to deliver highly functionalized products. However, the reactivity again fell behind that of the non-fluorinated acetyl carbene transfer ($CHCO_2Et$).

Recently, several other fluorinated carbene synthon transfer reagents have been developed, including arylfluorocarbenes, fluorothiocarbenes, and alkynyl carbenes. The diversity of these novel carbenes is very low and their main application is in cyclopropanation.

Some of these reactions have attracted interest in medicinal chemistry from both industry and academia for obtaining biologically active monofluorinated compounds that would otherwise be almost unreachable. Therefore, novel monofluorinated carbene transfer reactions are of great interest. Future research should focus on the introduction of novel fluorinated carbene synthons and development of innovative reactions leading to new fluorinated motifs. Furthermore, there is a need for novel catalytic asymmetric transformations and research on reaction mechanisms to gain deeper insights into the effect of fluorine on the reactivity and observed selectivities.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: carbenes · carbenoids · fluorine · monofluorocarbene · ylides

[1] R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496–3508.
[2] a) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545–4553; b) I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo, G. Resnati, *Chem. Rev.* **2015**, *115*, 1106–1129; c) C. Zhang, K. Yan, C. Fu, H. Peng, C. J. Hawker, A. K. Whittaker, *Chem. Rev.* **2022**, *122*, 167–208.
[3] a) M. Cheng, C. Guo, M. L. Gross, *Angew. Chem. Int. Ed.* **2020**, *59*, 5880–5889; b) H. Chen, S. Viel, F. Ziarelli, L. Peng, *Chem. Soc. Rev.* **2013**, *42*, 7971–7982.
[4] a) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359; 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; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; d) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**,

5, 637–643; e) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319.

[5] a) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29; b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; c) Q. Wang, H. Song, Q. Wang, *Chin. Chem. Lett.* **2022**, *33*, 626–642.

[6] a) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365–1377; b) D. Zhu, L. Chen, H. Fan, Q. Yao, S. Zhu, *Chem. Soc. Rev.* **2020**, *49*, 908–950; c) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; d) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904; e) B. Wang, D. Qiu, Y. Zhang, J. Wang, *Beilstein J. Org. Chem.* **2016**, *12*, 796–804; f) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724; g) X. Zhao, G. Wang, A. S. K. Hashmi, *ChemCatChem* **2021**, *13*, 4299–4312; h) H. Keipour, V. Carreras, T. Ollevier, *Org. Biomol. Chem.* **2017**, *15*, 5441–5456; i) C. Damiano, P. Sonzini, E. Gallo, *Chem. Soc. Rev.* **2020**, *49*, 4867–4905; j) M.-Y. Huang, S.-F. Zhu, *Chem. Sci.* **2021**, *12*, 15790–15801; k) V. Carreras, N. Tanbouza, T. Ollevier, *Synthesis* **2020**, *53*, 79–94; l) Z. Liu, J. Wang, *J. Org. Chem.* **2013**, *78*, 10024–10030; m) Y. He, Z. Huang, K. Wu, J. Ma, Y.-G. Zhou, Z. Yu, *Chem. Soc. Rev.* **2022**, *51*, 2759–2852; n) Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810–13889.

[7] a) X. Wang, X. Wang, J. Wang, *Tetrahedron* **2019**, *75*, 949–964; b) J.-H. Lin, J.-C. Xiao, *Acc. Chem. Res.* **2020**, *53*, 1498–1510; c) L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547–10556; d) K. Fuchibe, J. Ichikawa, *Chem. Commun.* **2023**, *59*, 2532–2540.

[8] a) W. Zhou, W.-J. Pan, J. Chen, M. Zhang, J.-H. Lin, W. Cao, J.-C. Xiao, *Chem. Commun.* **2021**, *57*, 9316–9329; b) A. D. Dilman, V. V. Levin, *Acc. Chem. Res.* **2018**, *51*, 1272–1280; c) C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842–863; d) X. Ma, J. Su, Q. Song, *Acc. Chem. Res.* **2023**, *56*, 592–607; e) P. K. Mykhailiuk, R. M. Koenigs, *Chem. Eur. J.* **2019**, *25*, 6053–6063.

[9] D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585–1632.

[10] a) J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson, P. Jubault, *Chem. Eur. J.* **2021**, *27*, 2935–2962; b) M. Fedoryński, *Chem. Rev.* **2003**, *103*, 1099–1132; c) A. Pons, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Synthesis* **2016**, *48*, 4060–4071; d) L. Ielo, V. Pillari, M. Miele, D. Castiglione, V. Pace, *Synlett* **2021**, *32*, 551–560; e) M. Colella, P. Musci, M. Andresini, M. Spennacchio, L. Degennaro, R. Luisi, *Org. Biomol. Chem.* **2022**, *20*, 4669–4680; f) A. Pons, L. Delion, T. Poisson, A. B. Charette, P. Jubault, *Acc. Chem. Res.* **2021**, *54*, 2969–2990.

[11] M. Born, S. Ingemann, N. M. M. Nibbering, *J. Am. Chem. Soc.* **1994**, *116*, 7210–7217.

[12] M. Schwartz, P. Marshall, *J. Phys. Chem. A* **1999**, *103*, 7900–7906.

[13] V. Fasano, N. Winter, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2020**, *59*, 8502–8506.

[14] R. A. Moss, *J. Phys. Org. Chem.* **2010**, *23*, 293–299.

[15] J. C. Poutsma, J. A. Paulino, R. R. Squires, *J. Phys. Chem. A* **1997**, *101*, 5327–5336.

[16] M. K. Gilles, K. M. Ervin, J. Ho, W. C. Lineberger, *J. Phys. Chem.* **1992**, *96*, 1130–1141.

[17] T. Suzuki, S. Saito, E. Hirota, *J. Mol. Spectrosc.* **1981**, *90*, 447–459.

[18] Y.-N. Tang, F. S. Rowland, *J. Am. Chem. Soc.* **1967**, *89*, 6420–6427.

[19] T. Marolewski, N. C. Yang, *Chem. Commun. (London)* **1967**, 1225–1226, https://doi.org/10.1039/C19670001225.

[20] M. Schlosser, G. Heinz, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 820–821.

[21] A. S. Konev, M. S. Novikov, A. F. Khlebnikov, *Tetrahedron Lett.* **2005**, *46*, 8337–8340.

[22] J. Nishimura, J. Furukawa, *J. Chem. Soc. D* **1971**, 1375–1376, https://doi.org/10.1039/C29710001375.

[23] O. Tamura, M. Hashimoto, Y. Kobayashi, T. Katoh, K. Nakatani, M. Kamada, I. Hayakawa, T. Akiba, S. Terashima, *Tetrahedron Lett.* **1992**, *33*, 3483–3486.

[24] P. Knochel, in *Encyclopedia of Reagents for Organic Synthesis (EROS)*, **2001**.

[25] N. Kawabata, M. Tanimoto, S. Fujiwara, *Tetrahedron* **1979**, *35*, 1919–1923.

[26] L.-P. B. Beaulieu, J. F. Schneider, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 7819–7822.

[27] C. Navuluri, A. B. Charette, *Org. Lett.* **2015**, *17*, 4288–4291.

[28] S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi, V. Pace, *Org. Lett.* **2019**, *21*, 584–588.

[29] M. Colella, A. Tota, Y. Takahashi, R. Higuma, S. Ishikawa, L. Degennaro, R. Luisi, A. Nagaki, *Angew. Chem. Int. Ed.* **2020**, *59*, 10924–10928.

[30] M. Colella, A. Tota, A. Großjohann, C. Carlucci, A. Aramini, N. S. Sheikh, L. Degennaro, R. Luisi, *Chem. Commun.* **2019**, *55*, 8430–8433.

[31] A. Sperga, D. Zacs, J. Veliks, *Org. Lett.* **2022**, *24*, 4474–4478.

[32] a) A. Nouaille, J. Lorkowski, X. Pannecoucke, M. Mauduit, T. Poisson, S. Couve-Bonnaire, *ACS Catal.* **2021**, *11*, 12307–12323; b) G. Landelle, M. Bergeron, M.-O. Turcotte-Savard, J.-F. Paquin, *Chem. Soc. Rev.* **2011**, *40*, 2867–2908; c) B. Zajc, R. Kumar, *Synthesis* **2010**, *2010*, 1822–1836; d) Q. Luo, X. Wang, J. Hu, *Tetrahedron* **2022**, *113*, 132694; e) H. Yanai, T. Taguchi, *Eur. J. Org. Chem.* **2011**, *2011*, 5939–5954.

[33] W. Zhang, J. Hu, *Adv. Synth. Catal.* **2010**, *352*, 2799–2804.

[34] X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 6966–6970.

[35] a) R. Melngaile, J. Veliks, *Synthesis* **2021**, *53*, 4549–4558; b) R. Melngaile, J. Veliks, in *Encyclopedia of Reagents for Organic Synthesis (EROS)*, pp. 1–4.

[36] J. Veliks, A. Kazia, *Chem. Eur. J.* **2019**, *25*, 3786–3789.

[37] R. Melngaile, A. Sperga, K. K. Baldridge, J. Veliks, *Org. Lett.* **2019**, *21*, 7174–7178.

[38] A. Kazia, R. Melngaile, A. Mishnev, J. Veliks, *Org. Biomol. Chem.* **2020**, *18*, 1384–1388.

[39] A. Sperga, R. Melngaile, A. Kazia, S. Belyakov, J. Veliks, *J. Org. Chem.* **2021**, *86*, 3196–3212.

[40] A. Sperga, A. Kazia, J. Veliks, *Org. Biomol. Chem.* **2021**, *19*, 2688–2691.

[41] C.-C. Hu, W.-Q. Hu, X.-H. Xu, F.-L. Qing, *J. Fluorine Chem.* **2021**, *242*, 109695.

[42] M. Reichel, K. Karaghiosoff, *Angew. Chem. Int. Ed.* **2020**, *59*, 12268–12281.

[43] a) E. Sun, R. Li, Q. Sun, C. Wei, H. Xu, B. Yan, *J. Phys. Chem. A* **2012**, *116*, 10435–10440; b) G. B. Bacskay, *Mol. Phys.* **2015**, *113*, 1608–1617; c) E. Sun, J. Zhang, R. Li, Q. Sun, C. Wei, H. Xu, B. Yan, *Int. J. Quantum Chem.* **2014**, *114*, 66–73; d) K. K. Irikura, W. A. Goddard, III, J. L. Beauchamp, *J. Am. Chem. Soc.* **1992**, *114*, 48–51.

[44] a) R. A. Moss, M. Zhang, K. Krogh-Jespersen, *Org. Lett.* **2010**, *12*, 3476–3479; b) M. Zhang, R. A. Moss, J. Thompson, K. Krogh-Jespersen, *J. Org. Chem.* **2012**, *77*, 843–850.

[45] A. P. Thankachan, K. S. Sindhu, K. K. Krishnan, G. Anilkumar, *Org. Biomol. Chem.* **2015**, *13*, 8780–8802.

[46] A. A. Andrianova, Y. D. Maslova, M. A. Novikov, S. E. Semenov, O. M. Nefedov, *J. Fluorine Chem.* **2018**, *209*, 49–55.

[47] a) M. Goswami, B. de Bruin, W. I. Dzik, *Chem. Commun.* **2017**, *53*, 4382–4385; b) P. S. Nosik, S. V. Ryabukhin, O. O. Grygorenko, D. M. Volochnyuk, *Adv. Synth. Catal.* **2018**, *360*, 4104–4114.

[48] D. Chen, Z. Fan, L. Huang, K. Gao, P. Xiao, C. Ni, J. Hu, *Chem. Commun.* **2021**, *57*, 319–322.

[49] a) C. Barrett, V. Krishnamurti, X. Ispizua-Rodriguez, Z. Zhu, C. J. Koch, G. K. Surya Prakash, *Org. Lett.* **2022**, *24*, 5417–5421; b) C. Aouf, M. Santelli, *Tetrahedron Lett.* **2011**, *52*, 688–691.

[50] R. Bychek, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205103.

[51] a) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849; b) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 4590–4647.

[52] C. Recsei, Y. Barda, *Beilstein J. Org. Chem.* **2021**, *17*, 813–818.

[53] L. Trump, A. Lemos, B. Lallemand, P. Pasau, J. Mercier, C. Lemaire, A. Luxen, C. Genicot, *Angew. Chem. Int. Ed.* **2019**, *58*, 13149–13154.

[54] a) R. Mathias, P. Weyerstahl, *Chem. Ber.* **1979**, *112*, 3041–3053; b) P. Weyerstahl, R. Mathias, G. Blume, *Tetrahedron Lett.* **1973**, *14*, 611–612.

[55] Z. Fang, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Chem. Commun.* **2019**, *55*, 10539–10542.

[56] a) E. David, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Tetrahedron* **2013**, *69*, 11039–11055; b) A. Tarui, K. Sato, M. Omote, I. Kumadaki, A. Ando, *Adv. Synth. Catal.* **2010**, *352*, 2733–2744.

[57] A. Tarui, N. Kawashima, K. Sato, M. Omote, A. Ando, *Tetrahedron Lett.* **2010**, *51*, 4246–4249.

[58] G. Lemonnier, L. Zoute, J.-C. Quirion, P. Jubault, *Org. Lett.* **2010**, *12*, 844–846.

[59] P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 2270–2273.

[60] P. Ivashkin, S. Couve-Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 5130–5133.

[61] a) G. Lemonnier, C. Lion, J.-C. Quirion, J.-P. Pin, C. Goudet, P. Jubault, *Bioorg. Med. Chem.* **2012**, *20*, 4716–4726; b) G. Milanole, S. Couve-Bonnaire, J.-F. Bonfanti, P. Jubault, X. Pannecoucke, *J. Org. Chem.* **2013**, *78*, 212–223.

[62] T. Ferrary, E. David, G. Milanole, T. Besset, P. Jubault, X. Pannecoucke, *Org. Lett.* **2013**, *15*, 5598–5601.

[63] J. Czaban-Jóźwiak, R. Loska, M. Mąkosza, *J. Org. Chem.* **2016**, *81*, 11751–11757.

[64] A. Zasada, J. Brześkiewicz, D. Antoniak, M. Bechcicka, R. Loska, M. Mąkosza, *Org. Biomol. Chem.* **2023**, *21*, 994–999.

[65] M. Kirihara, T. Ogata, A. Itou, S. Naito, M. Kishida, K. Yamazaki, H. Tabata, H. Takahashi, *Chem. Lett.* **2013**, *42*, 1377–1379.

[66] E. A. Ilin, V. O. Smirnov, A. D. Dilman, *J. Fluorine Chem.* **2022**, *261–262*, 110025.

[67] R. A. Moss, Y. Shen, L. Wang, K. Krogh-Jespersen, *Org. Lett.* **2011**, *13*, 4752–4754.

[68] R. A. Moss, L. Wang, R. R. Sauers, *Tetrahedron Lett.* **2007**, *48*, 5551–5554.

[69] J. H. Rigby, M. Aasmul, *Heterocycles* **2004**, *62*, 143–147.

[70] H. Wang, R.-Y. Yang, B. Xu, *Chem. Eur. J.* **2022**, *28*, e202104364.

[71] S. Guo, W. Sun, J. W. Tucker, K. D. Hesp, N. K. Szymczak, *Chem. Eur. J.* **2023**, *29*, e202203578.

[72] K. N. Shavrin, V. D. Gvozdev, O. M. Nefedov, *Russ. Chem. Bull.* **2002**, *51*, 1237–1253.

[73] C. B. A. L. Bagdasarian, R. A. Craig II, J. De Vicente Fidalgo, A. A. Estrada, B. M. Fox, C. Hu, B. J. Huffman, K. W. Lexa, L. G. Nilewski, M. Osipov, A. Thottumkara (Denali Therapeutics inc.), WO2022232632, 2022.

[74] M. E. B. D. R. Anderson, K. J. Curran, C. M. Dehnhardt, L. K. Gavrin, J. A. Goldberg, S. Han, D. Hepworth, H.-C. Huang, A. Lee, K. L. Lee, F. E. Lovering, M. D. Lowe, J. P. Mathias, N. Papaioannou, A. Patny, B. S. Pierce, E. Saiah, J. W. Strohbach, J. D. Trzupek, R. Vargas, X. Wang, S. W. Wright, C. W. Zapf (Pfizer inc.), WO2015150995, 2015.

[75] J. Veliks, M. Videja, A. Kinens, R. Bobrovs, M. Priede, J. Kuka, *ACS Med. Chem. Lett.* **2020**, *11*, 2146–2150.

[76] G. Milanole, F. Andriessen, G. Lemonnier, M. Sebban, G. Coadou, S. Couve-Bonnaire, J.-F. Bonfanti, P. Jubault, X. Pannecoucke, *Org. Lett.* **2015**, *17*, 2968–2971.

[77] R. Melngaile, M. Videja, J. Kuka, A. Kinens, D. Zacs, J. Veliks, *Org. Lett.* **2023**, *25*, 2280–2284.

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2. pielikums / Appendix 2

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Fluorohalomethylsulfonium Salts as a Fluorohalocarbene Source

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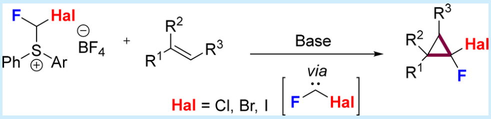
ABSTRACT: Synthesis of fluoroorganic compounds is of great importance due to their extensive application in medicinal chemistry, agrochemicals, and materials. Herein, we report efficient synthesis of novel diaryl fluorohalomethyl sulfonium salts. The application showcased proficient reagents for Freon-free fluorochloro-, fluorobromo-, and fluoroiodocarbene transfer to alkenes. The developed mild, room temperature conditions for the cyclopropanation do not require any metal catalysts and allow synthetic access to diverse cyclopropanes.



The vast application of organofluorine compounds demands innovative strategies for the construction of fluorine containing products,[1−4] especially in high yielding, user-friendly, and environmentally friendly fashion. Fluorinated carbene transfer reactions are an elegant synthetic strategy to functionalize molecules by creating new carbon−carbon or carbon−heteroatom bonds and at the same to deliver the valuable fluorine atom to the target structure.[5,6] Various fluorinated carbene transfer reactions have been extensively employed to access fluoroorganic compounds. However, fluorohalocarbene transfer reactions are far less employed in the synthesis.[7]

The current strategy for fluorohalocarbene transfer involves the use of fluorohalomethanes,[8] which are environmentally concerning reagents due to their ozone depleting properties. Alternatively, organomercury reagents and halogenated ketones can be used. Recently, halogenated esters ($CFHal_2CO_2Et$),[9] carboxylates ($CFHal_2COONa$),[10] and fluorohalomethyl silanes ($TMSCFHal_2$)[11] have emerged as an alternative for fluorohalocarbene transfer. These carbenes are efficient reactive species for the synthesis of fluorohalocyclopropanes. The generation of reactive species often involves hazardous reagents, precious metals, and elevated temperature, thus limiting the use of various functional groups and transformations. Furthermore, fluoroiodocarbene transfer is extremely rare, with only one reagent known to date - fluorodiiodomethane ($CHFI_2$),[12,13] which has limited availability. In contrast to difluorocarbene transfer,[14−17] fluorohalocarbene transfer reagents and reactions are far less developed (Figure 1).[18−20]

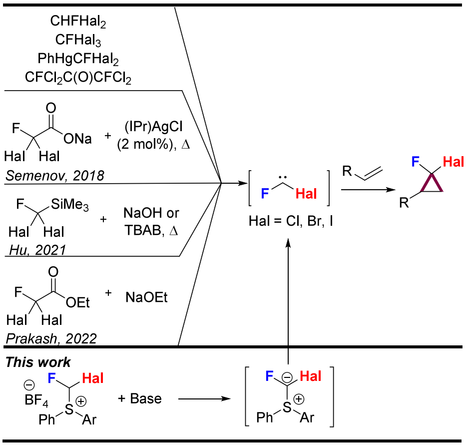


Figure 1. Reagents for fluorohalocarbene transfer.

To overcome the aforementioned drawbacks, we envisioned that dihalosulfonium salts may serve as a superior alternative, where carbene generation could be achieved via deprotonation and subsequent α-elimination to deliver a fluorohalocarbene, which, if trapped with an alkene, will produce *gem*-dihalocyclopropanes.

It emerges that fluorohalomethyl sulfonium salts are efficient carbene transfer reagents. We started our research by developing syntheses toward all three fluorohalomethyl sulfonium salts **ClFS**, **BrFS**, and **IFS** (Scheme 1).

Thiophenol **1** was alkylated with ethyl chlorofluoroacetate under basic conditions, followed by sulfide oxidation, which was further chlorinated, and after a Krapcho decarboxylation sulfoxide, **2** was obtained in good yield over 4 steps (Scheme

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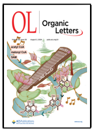
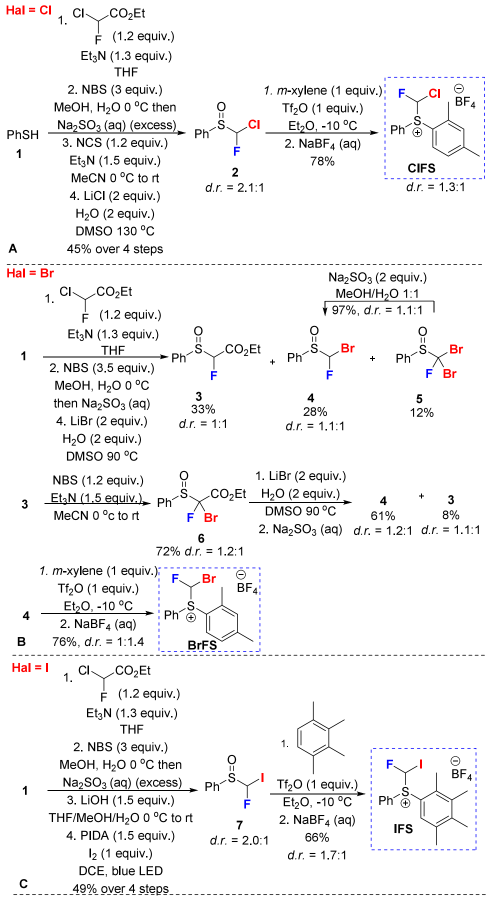


https://doi.org/10.1021/acs.orglett.4c02327
Org. Lett. 2024, 26, 6482−6485

Scheme 1. Synthetic Access to Fluorohalomethyl Sulfonium Salts



1A). Deoxygenative arylation of **2** with *m*-xylene afforded **ClFS** in a high yield.

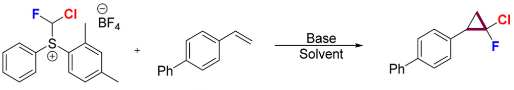
Synthesis of bromofluoromethyl sulfonium salt **BrFS** was achieved by alkylation of thiopenol, followed by a one pot oxidation and bromination (Scheme 1B). Krapcho decarboxylation afforded a mixture of three products. Fortunately, both side products can be transformed to the necessary sulfoxide **4**. Side product **5** undergoes smooth reduction with sulfite. Sulfoxide **3** can be brominated with NBS under basic conditions, and subsequent decarboxylation of **6** yields target precursor **4**. After a Friedel−Crafts-type arylation of sulfoxide, **4** target compound **BrFS** was obtained.

The fluoroiodomethyl sulfonium salt **IFS** synthesis was achieved by the same alkylation and oxidation sequence as described above, followed by ester hydrolysis and iododecarboxylation as the key step (Scheme 1C). Coupling with 1,2,3,4-tetramethylbenzene was crucial for higher product yield and improved properties such as purity and solidity.

For each reaction sequence, most of the intermediates were telescoped, involving only one column chromatography step for the synthesis of **ClFS** and **IFS**. These syntheses were achieved without the use of Freons and with a cheap fluorine source and where the ester group played a key role in halogen introduction.

With the three sulfonium salts in hand, we examined dihalocarbene generation in the presence of styrene **8a** (Table 1). Pleasingly, when **ClFS** was treated with base in the presence of alkene **8a**, cyclopropane **9a** formation was observed as a mixture of two diastereomers (entry 1). Changing the addition time of the **ClFS** solution to the reaction mixture or performing reactions at lower temperatures did not offer any improvement (entries 2−4). However, the use of more concentrated **ClFS** 1,4-dioxane:DCM solution (5:1 v:v) resulted in almost full conversion and in excellent product yield (entry 4). The use of other bases decreased the conversion and product yield (entries 9−12). Attempts to increase the reaction diastereoselectivity using carbene transfer catalysts gave no improvement (see SI for more details).

Table 1. Opimization of Reaction Conditions



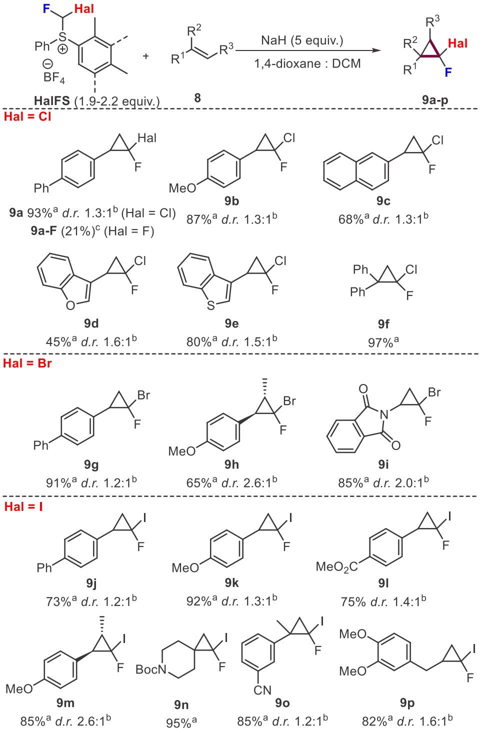
ClFS (2 equiv) **8a** **9a**

Entry[a]	Solvent (M)	Addition time	Base (equiv)	Yield **9a**[b] (*d.r.*)	**8a**[b]
1	DCM (0.32)	2 h 15 min	NaH (5)	61% (1.3:1)	28%
2[c]	DCM (0.32)	2 h 15 min	NaH (5)	59% (1.3:1)	33%
3	DCM (0.32)	3 h 30 min	NaH (5)	59% (1.3:1)	33%
4	DCM (0.32)	1 h 10 min	NaH (5)	64% (1.3:1)	29%
5	DCM (0.20)	4 h	NaH (5)	62% (1.3:1)	37%
6	DCM (0.55)	1 h 20 min	NaH (5)	70% (1.3:1)	20%
7	THF (0.32)	2 h 20 min	NaH (5)	61% (1.4:1)	26%
8	**1,4-dioxane:DCM (0.61)**	**1 h 12 min**	**NaH (5)**	**93%** (1.3:1)	**3%**
9	DCM (0.32)	2 h 15 min	LiOH[d]	42% (1.6:1)	47%
10	DCM (0.32)	2 h 15 min	K_2CO_3[d]	36% (1.6:1)	60%
11	DCM (0.32)	2 h 15 min	KOH[d]	43% (1.7:1)	48%
12	DCM (0.32)	2 h 15 min	NaOH[d]	44% (1.3:1)	51%

[a] To alkene **8a** (0.11 mmol) and base, solution of **ClFS** was slowly added under Ar atm. at RT. [b] Yield and *d.r.* determined for crude reaction mixture using ^{1}H NMR and EtOAc as internal standard. [c] At 0 °C [d] Saturated aqueous solution (0.2 mL).

With optimized reaction conditions in hand, we evaluated the substrate scope (Scheme 2). All three fluorohalomethyl sulfonium salts are compatible with reaction conditions and tolerate a wide variety of alkenes. Alkenes in conjugation with heterocyclic systems (**8d**, **8e**) and disubstituted alkenes (**8f**, **8h**, **8m−o**) form product **9** in average to excellent yields. Functional groups such as methoxy- (**8b**), phthalimide (**8i**), methoxycarbonyl- (**8l**), cyano (**8o**), and Boc protected amine (**8n**) furnish cylopropanes **9** with good yields. Furthermore nonconjugated alkene (**8p**) also shows reasonable reactivity. However, similar difluoromethylsulfonium salt[21] under stand-

Scheme 2. Substrate Scope Reactivity



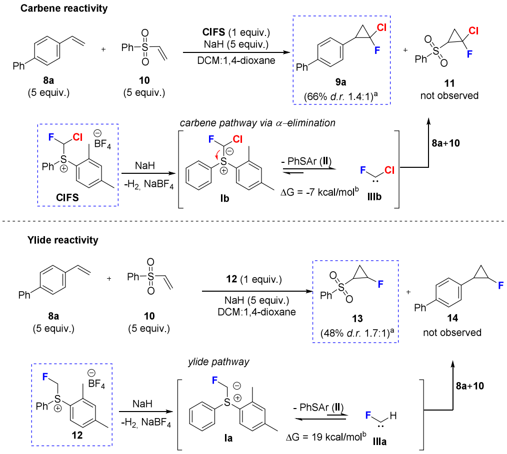
[a]Isolated yield. [b]d.r. determined from crude ^{1}H or ^{19}F NMR. [c]NMR yield determined using EtOAc as internal standard.

ard reaction conditions was less efficient and gave a lower yield of difluorocarbene transfer product **9a-F**.[21b]

The developed mild conditions: room temperature reaction and use of non-nucleophilic base as a promoter for carbene generation, allowing access to diverse cyclopropanes, which would be inaccessible using previous methods.

In order to support the proposed carbene pathway, competition experiments were performed (Scheme 3) where electron rich **8a** and deficient **10** alkenes were reacted in the presence of dihalosulfonium salt **ClFS**. Only unactivated alkene **8a** reacted leaving electron poor alkene–vinylsulfone (**10**) completely unaffected. This strongly supports dihalocarbene reactivity due to its electrophilic nature.[22] On the contrary, monofluoromethyl sulfonium salt **12**[23] gave only fluorinated cyclopropane **13**[23c] originating from the electron poor sulfone **10**. Due to the nucleophilic character of the ylide species, the preferred reaction partner was a good Michael acceptor **10** leaving vinylbiphenyl (**8a**) completely unreacted. This striking difference in reactivity is in agreement with the favorable α-elimination when leading to stabilized dihalocarbenes[24] and marks a clear distinction between monfluoromethyl and fluorohalomethyl sulfonium salt reactivities. Additionally, DFT calculations support this observation as the formation of fluorochlorocarbene (**IIIb**) from ylide (**Ib**) is thermodynamically favorable, in contrast to fluorocarbene (**IIIa**), where α-elimination is an uphill process.

Scheme 3. Control Experiments



[a]^{1}H NMR yield and d.r. determinded from crude reaction mixture using EtOAc as internal standard. [b]Gibbs free energies of carbene **III** formation. Optimization using m062x/Def2SVP method.

In conclusion, we have successfully developed three novel fluorohalomethyl sulfonium salts for the transfer of fluorohalocarbenes in reactions with alkenes. The mild conditions employed for carbene generation allowed for the synthesis of diverse cyclopropanes. The obtained fluorohalomethyl reagents display pronounced carbene reactivity contrary to the monofluoromethylsulfonium salts, which prefer the ylide pathway.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c02327.

Experimental procedures and characterization of products, including NMR spectra, DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011**, *40* (7), 3496−3508.

(2) Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Bombelli, F. B.; Metrangolo, P.; Resnati, G. 19F Magnetic Resonance Imaging (MRI): From Design of Materials to Clinical Applications. *Chem. Rev.* **2015**, *115* (2), 1106−1129.

(3) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58* (21), 8315−8359.

(4) Fujiwara, T.; O'Hagan, D. Successful fluorine-containing herbicide agrochemicals. *J. Fluorine Chem.* **2014**, *167*, 16−29.

(5) Wang, X.; Wang, X.; Wang, J. Application of carbene chemistry in the synthesis of organofluorine compounds. *Tetrahedron* **2019**, *75* (8), 949−964.

(6) Fuchibe, K.; Ichikawa, J. Generation of difluorocarbenes and introduction of fluorinated one carbon units into carbonyl and related compounds. *Chem. Commun.* **2023**, *59* (18), 2532−2540.

(7) Sperga, A.; Veliks, J. Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species. *Chem. Eur. J.* **2023**, *29*, No. e202301851.

(8) Brahms, D. L. S.; Dailey, W. P. Fluorinated Carbenes. *Chem. Rev.* **1996**, *96* (5), 1585−1632.

(9) Barrett, C.; Krishnamurti, V.; Ispizua-Rodriguez, X.; Zhu, Z.; Koch, C. J.; Surya Prakash, G. K. gem-Halofluorocyclopropanes via [2 + 1] Cycloadditions of In Situ Generated CFX Carbene with Alkenes. *Org. Lett.* **2022**, *24* (29), 5417−5421.

(10) Andrianova, A. A.; Maslova, Y. D.; Novikov, M. A.; Semenov, S. E.; Nefedov, O. M. (NHC)AgCl catalyzed bromofluorocyclopropanation of alkenes with CFBr2CO2Na. *J. Fluorine Chem.* **2018**, *209*, 49−55.

(11) Chen, D.; Fan, Z.; Huang, L.; Gao, K.; Xiao, P.; Ni, C.; Hu, J. TMSCFX2 (X = Cl, Br) as halofluorocarbene sources for the synthesis of halofluorocyclopropanes. *Chem. Commun.* **2021**, *57* (3), 319−322.

(12) Mathias, R.; Weyerstahl, P. Darstellung und Eigenschaften von 1,1-Diiod- und 1-Iod-1-x-cyclopropanen. *Chem. Ber.* **1979**, *112* (9), 3041−3053.

(13) Fang, Z.; Cordes, D. B.; Slawin, A. M. Z.; O'Hagan, D. Fluorine containing cyclopropanes: synthesis of aryl substituted all-cis 1,2,3-trifluorocyclopropanes, a facially polar motif. *Chem. Commun.* **2019**, *55* (71), 10539−10542.

(14) Zhou, W.; Pan, W.-J.; Chen, J.; Zhang, M.; Lin, J.-H.; Cao, W.; Xiao, J.-C. Transition-metal difluorocarbene complexes. *Chem. Commun.* **2021**, *57* (74), 9316−9329.

(15) Dilman, A. D.; Levin, V. V. Difluorocarbene as a Building Block for Consecutive Bond-Forming Reactions. *Acc. Chem. Res.* **2018**, *51* (5), 1272−1280.

(16) Ni, C.; Hu, J. Recent Advances in the Synthetic Application of Difluorocarbene. *Synthesis* **2014**, *46* (07), 842−863.

(17) Ma, X.; Su, J.; Song, Q. Unconventional Transformations of Difluorocarbene with Amines and Ethers. *Acc. Chem. Res.* **2023**, *56* (5), 592−607.

(18) Bychek, R.; Mykhailiuk, P. K. A Practical and Scalable Approach to Fluoro-Substituted Bicyclo[1.1.1]pentanes. *Angew. Chem., Int. Ed.* **2022**, *61* (29), No. e202205103.

(19) Recsei, C.; Barda, Y. Synthesis of bis(aryloxy)fluoromethanes using a heterodihalocarbene strategy. *Beilstein J. Org. Chem.* **2021**, *17*, 813−818.

(20) Trump, L.; Lemos, A.; Lallemand, B.; Pasau, P.; Mercier, J.; Lemaire, C.; Luxen, A.; Genicot, C. Late-Stage 18F-Difluoromethyl Labeling of N-Heteroaromatics with High Molar Activity for PET Imaging. *Angew. Chem., Int. Ed.* **2019**, *58* (37), 13149−13154.

(21) (a) Yue, C.-B.; Lin, J.-H.; Cai, J.; Zhang, C.-P.; Zhao, G.; Xiao, J.-C.; Li, H. O-Difluoromethylation of 1,3-diones with S-difluoromethyl sulfonium salt. *RSC Adv.* **2016**, *6* (42), 35705−35708. (b) Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Olah, G. A. Synthesis of gem-Difluorinated Cyclopropanes and Cyclopropenes: Trifluoromethyltrimethylsilane as a Difluorocarbene Source. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153−7157.

(22) Moss, R. A. Dihalodiazirines and the photochemical generation of dihalocarbenes: new light on old problems. *J. Phys. Org. Chem.* **2010**, *23*, 293−299.

(23) (a) Sperga, A.; Melngaile, R.; Kazia, A.; Belyakov, S.; Veliks, J. Optimized Monofluoromethylsulfonium Reagents for Fluoromethylene-Transfer Chemistry. *J. Org. Chem.* **2021**, *86*, 3196−3212. (b) Sperga, A.; Zacs, D.; Veliks, J. Iron-Catalyzed Fluoromethylene Transfer from a Sulfonium Reagent. *Org. Lett.* **2022**, *24*, 4474−4478. (c) Melngaile, R.; Sperga, A.; Baldridge, K. K.; Veliks, J. Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts. *Org. Lett.* **2019**, *21*, 7174−7178.

(24) Gronert, S.; Keeffe, J. R.; More O'Ferrall, R. A. *Contemporary Carbene Chemistry* **2013**, 1−39.

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Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts

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Metal-Catalyzed Fluoroacetyl Carbene Transfer from Sulfonium Salts

Arturs Sperga, Artis Kinens, and Janis Veliks*

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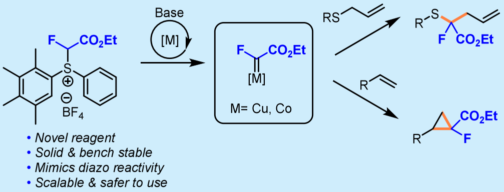
ABSTRACT: The synthesis of organofluorine compounds is pivotal in developing innovative pharmaceuticals, materials, and agrochemicals. Fluorinated carbene transfer offers a promising strategy for forming new carbon−carbon and carbon−heteroatom bonds, facilitating one-carbon editing by simultaneously introducing fluorine into target structures. In this study, we introduce a novel fluoroacetyl sulfonium reagent, (2-ethoxy-1-fluoro-2-oxoethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (**1**), serving as an effective alternative to the currently unknown 2-diazo-2-fluoroacetate for ethyl fluoroacetyl carbene transfer. This reagent is applied in Doyle−Kirmse and cyclopropanation reactions operating under mild conditions with the use of earth-abundant metal catalysts. This approach enables the efficient synthesis of valuable monofluorinated products.



The development of novel retrosynthetic strategies to access monofluorinated compounds is highly regarded as they constitute a significant fraction of newly approved small molecule drugs; 39% in 2023 contain this smallest member of the halogen family in their molecular structures.[1−4] Carbenes are prominent species for one-carbon editing purposes,[5] especially if they can simultaneously deliver a fluorine atom. The carboxylate moiety is one of the most important functionalities in biology and medicinal chemistry;[6,7] additionally, its rich synthetic application allows it to be used as a functional handle for further synthetic modifications.[8−10]

The fluoroacetyl moiety can be found in various biologically active compounds (Figure 1A).[11−13] Incorporation of fluorine at the α position into carbonyl compounds usually involves deprotonation followed by electrophilic fluorination using N−F reagents,[14−18] thus requiring an additional synthetic step and limiting the use of base sensitive substrates. Another strategy involves using α-fluoroacetyl-containing building blocks in order to obtain target compounds.[19,20]

Formal fluoroacetyl carbene transfer has been previously developed for [2+1] cyclization with activated alkenes[21] (Figure 1B), carbonyls,[22] and imines[23] using ethyl dibromofluoroacetate.[24,25] The reaction proceeds via a zinc enolate intermediate utilizing its nucleophilic properties.

Regarding the plethora of synthetically useful applications for metal-catalyzed acetyl carbene reactions,[26−31] fluoroacetyl carbene transfer remains largely unexplored (Figure 1C). We hypothesized that a fluorinated analogue might exhibit a similar reactivity profile and enable simultaneous delivery of fluorine and the acetyl group into the target structure. However, to the best of our knowledge, the corresponding ethyl diazofluoroacetate, which could serve as a carbene precursor, is unknown and may also pose safety concerns in terms of toxicity and stability.[32−34]

To overcome these limitations, we thought that sulfonium salt **1** might serve as a safe and easy-to-handle carbene source.[35−38] After ylide formation, complexation with a metal center, and sulfide elimination, it would give rise to a metal carbene complex, allowing us to exploit the characteristic electrophilic properties of the carbene. It is particularly noteworthy that for an archetypical carbene transfer process such as the Doyle−Kirmse reaction,[39−42] sulfonium salts were generally not used as reagents, except in rare instances. Sulfonium salts could be especially relevant for this purpose when the corresponding diazo compounds are nonexistent, unstable, or problematic to scale up due to safety reasons. We have verified our hypothesis and performed fluoroacetyl carbene transfer from sulfonium reagent **1** by developing efficient protocols for the Doyle−Kirmse reaction and cyclopropanation[43−47] of styrenes using our novel reagent (Figure 1D).

We started our studies by developing an efficient synthesis of (2-ethoxy-1-fluoro-2-oxoethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium·BF$_4$ (**1**) (Scheme 1), which was prepared in three steps starting from inexpensive, commercially available starting materials. The alkylation of thiophenol (**6**) with ethyl

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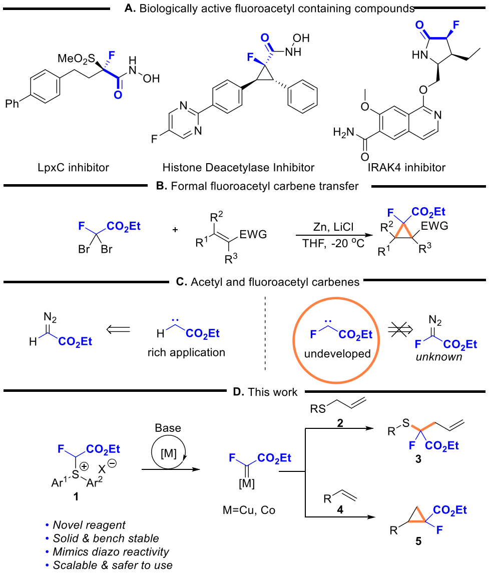
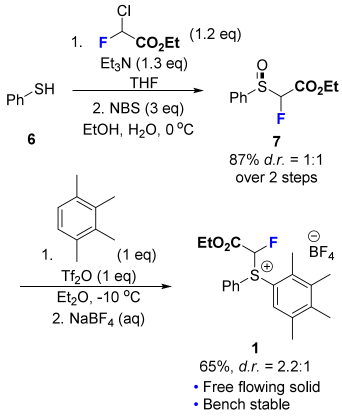


Figure 1. (A) Biologically active molecules containing the fluoroacetyl moiety. (B) Representative example of formal fluoroacetyl carbene transfer. (C) Comparison of acetyl and fluoroacetyl carbene. (D) This work.

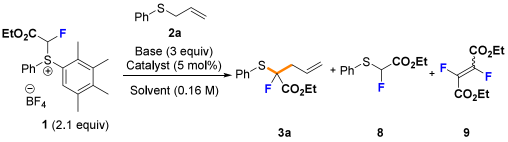
Scheme 1. Synthesis of Sulfonium Salt 1



chlorofluoroacetate, followed by NBS-mediated oxidation, afforded sulfoxide **7**, which was further subjected to aryl coupling with 1,2,3,4-tetramethylbenzene in the presence of triflic anhydride. Upon anion metathesis, this sequence afforded sulfonium reagent **1** in good yield as a free-flowing, bench-stable solid. The obtained reagent exists as a 2.2:1 mixture of diastereomers.

With reagent **1** in hand, its ability to undergo fluoroacetyl carbene transfer was investigated. As a model reaction, the Doyle–Kirmse reaction was selected using allyl phenyl sulfide (**2a**) as a substrate (Table 1). Initially, tetraphenylporphyrin iron(III) chloride (Fe(TPP)Cl) was used as the catalyst in the presence of Cs_2CO_3 as a base in 1,4-dioxane as the entry conditions. We were pleased to observe the formation of rearrangement product **3a** (Table 1, entry 1), albeit in a minute yield. This motivated us to further screen solvents (entries 2–4); DCM turned out to be most promising giving a moderate yield of the product. The reaction was accompanied by the formation of deallylated sulfide **8** and formal carbene dimerization product diethyl 2,3-difluorobut-2-enedioate (**9**). Further screening of metal catalysts revealed that $Cu(MeCN)_4BF_4$ is the most efficient catalyst. Adjusting the base (entry 13) and using a syringe pump for the slow addition of sulfonium salt **1** improved the reaction yield. Interestingly, the reaction without a metal catalyst also formed product **3a** (entry 14), albeit in minor yield, possibly through a simple substitution reaction in which allyl sulfide acts as a nucleophile, replacing diaryl sulfide as the better leaving group, followed by ylide generation and [2,3]-sigmatropic rearrangement.[48] Alternatively, the uncatalyzed free carbene transfer pathway cannot be excluded; however, it is less likely.

Table 1. Optimization of the Doyle–Kirmse Reaction



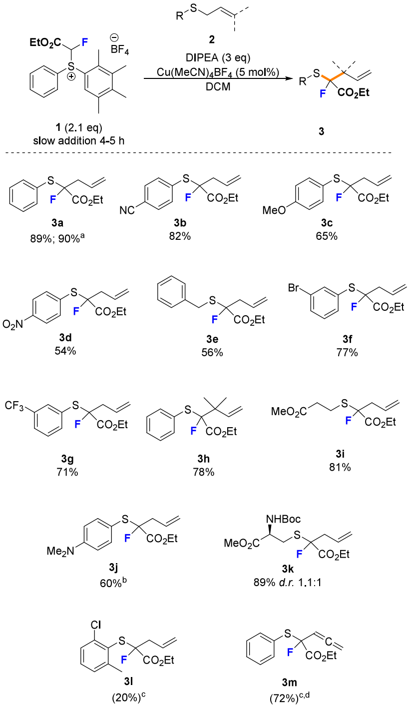
entry[a]	solvent	catalyst	base	yield (3a/8/9[e]) (%)
1	1,4-dioxane	Fe(TPP)Cl	Cs_2CO_3	5/1/32
2	THF	Fe(TPP)Cl	Cs_2CO_3	10/1/38
3	MeCN	Fe(TPP)Cl	Cs_2CO_3	2/2/59
4	DCM	Fe(TPP)Cl	Cs_2CO_3	46/5/17
5	DCM	CuI	Cs_2CO_3	58/21/15
6	DCM	IMesCuCl	Cs_2CO_3	20/24/30
7	DCM	$Rh_2(OAc)_4$	Cs_2CO_3	29/41/trace
8	DCM	$Cu(MeCN)_4BF_4$	Cs_2CO_3	74/8/18
9	DCM	CoTPP	Cs_2CO_3	45/10/13
10	DCM	$Cu(MeCN)_4BF_4$	DIPEA	67/13/12
11[b]	DCM	$Cu(MeCN)_4BF_4$	DIPEA	43/4/17
12[c]	DCM	$Cu(MeCN)_4BF_4$	DIPEA	43/14/15
13[d]	DCM	$Cu(MeCN)_4BF_4$	DIPEA	88/1/14
14	DCM	–	Cs_2CO_3	7/2/34

[a] Allyl sulfide **2a** (0.115 mmol), sulfonium salt **1**, a catalyst, and a base were stirred for 4–5 h in a solvent under an Ar atmosphere at room temperature. After completion of the reaction, the mixture was evaporated (for entries 1–3), suspended in DCM, and filtered through a short pad of silica gel eluting with DCM. For entries 4–14, the reaction mixture was directly filtered through a short pad of silica gel eluting with DCM. The reaction yield was determined from the ^{19}F NMR crude mixture using $PhCF_3$ as the internal standard. [b] At 0.082 M. [c] At 0 °C. [d] A solution of sulfonium salt **1** in DCM (0.72 mL) was added over 4 h to a mixture of allyl sulfide, a base, and a catalyst. [e] Yield for **9** calculated assuming **2a** as the limiting reagent.

With the optimized reaction conditions in hand, we investigated the substrate scope (Scheme 2). Various allyl aryl sulfides **2**, bearing a broad spectrum of functional groups, were tolerated under the reaction conditions.

Electron-withdrawing groups such as cyano, nitro, and trifluoromethyl (**2b**, **2d**, and **2g**, respectively) afforded rearrangement products **3** in moderate to good yields. An electron-donating group such as methoxy (**2c**) gave good yields. Pleasingly, arylbromide **3f** is well tolerated under the optimized reaction conditions. The substrate scope was

Scheme 2. Substrate Scope for the Doyle−Kirmse Reaction[e]



[a]On a 1.15 mmol scale of **2**. [b]Fe(TPP)Cl (5 mol %) instead of $Cu(MeCN)_4BF_4$. [c]Crude NMR yield determined from ^{19}F NMR using $PhCF_3$ as an internal standard. [d]Phenyl propargyl sulfide used. [e]For the reactions, to **2** (0.115 mmol), $Cu(MeCN)_4BF_4$ (5 mol %), and DIPEA (3 equiv) is added mixture **1** (2.1 equiv in 0.72 mL of DCM) over 4−5 h under an Ar atmosphere at room temperature.

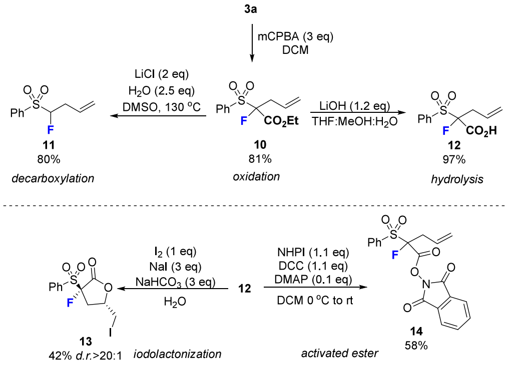
successfully expanded to include nonconjugated sulfides (**3e** and **3i**). Furthermore, *gem*-dimethyl-substituted alkene **2h** proved to be an efficient reactant.

However, for the dimethylamino group containing substrate **2j**, the iron porphyrin catalyst showed a superior result, which might be attributed to electrophilic copper catalyst inhibition by amine coordination. Fortunately, protected *S*-allyl cysteine **2k** showed outstanding reactivity under the optimized conditions. *Ortho*-disubstituted substrate **2l** showed a diminished product yield, probably due to steric hindrance around the sulfide. Propargylic sulfide **3m** gave a product with a moderate yield, but its decomposition was observed during purification.

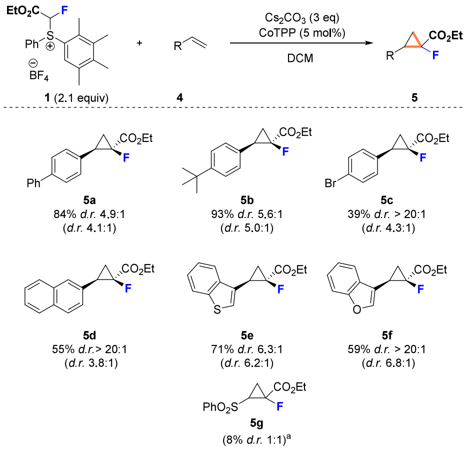
Product **3a** was further subjected to various functionalization reactions (Scheme 3). Oxidation using *m*CPBA gave sulfone **10** in a good yield. Krapcho decarboxylation of **10** afforded monofluorinated homoallyl sulfone **11**. Ester **10** is readily hydrolyzed using LiOH, forming carboxylic acid **12** in excellent yield. Acid **12** undergoes highly diastereoselective iodolactonization to form *γ*-lactone **13**. Furthermore, it is possible to access activated ester **14** by coupling with *N*-hydroxyphthalimide.

To further expand the application of sulfonium reagent **1** and demonstrate its application as a diazo surrogate, we turned our attention to cyclopropanation of alkenes **4** (Scheme 4). The use of a cobalt porphyrin catalyst and Cs_2CO_3 furnished cyclopropanes **5** in low to excellent yields and moderate diastereoselectivity without the need for the slow addition of sulfonium **1** (for reaction optimization, see the Supporting Information). Pleasingly, heterocyclic systems **4e** and **4f** are well tolerated under the reaction conditions. Activated alkene (vinylsulfonyl)benzene (**4g**) under metal free conditions provided product **5g** in low yield. However, internal alkenes were unreactive.

Scheme 3. Product Functionalization



Scheme 4. Cyclopropanation Reaction Scope[b]



[a]Metal free reaction; ^{19}F NMR yield determined from the crude reaction mixture using $PhCF_3$ as an internal standard. [b]For the reactions, alkene **4** (0.115 mmol), sulfonium salt **1**, CoTPP (5 mol %), and Cs_2CO_3 are stirred for 3−4 h under an Ar atmosphere at room temperature. dr in parentheses determined from crude ^1H or ^{19}F NMR.

Further investigations were conducted to gain additional insight into whether the carbene transfer from sulfonium salt **1** occurs via ylide *α*-eliminative decomposition to free carbene or through a stepwise reaction with a copper catalyst to form metal-stabilized carbene. Our previous studies revealed that although structurally similar, monofluorinated sulfonium salts bearing different α-substituents might exhibit either ylide[36] or free carbene reactivities.[35] According to density functional theory (DFT) calculations, α-elimination to form free carbene **IV** is less favored thermodynamically (Figure 2, path B) compared to the formation of copper-stabilized carbene **V**, which is energetically more accessible (Figure 2, path A). Once carbene **V** reacts with allyl sulfide **2a**, it affords metal-bound ylide[49] **VI**, which may then undergo free ylide **VII** formation followed by a 1,3-sigmatropic rearrangement[48] to give the desired product **3a′**. Additionally, experimental validation excludes the free carbene pathway, as no cyclopropanation product was observed for an uncatalyzed process using unactivated alkene (see Table S1, entry 10); however, small quantities of Corey−Chaykovsky product **5g** were formed with activated alkene (vinylsulfonyl)benzene (**4g**), supporting the involvement of ylide in the initial steps of the process (see the Supporting Information for details).

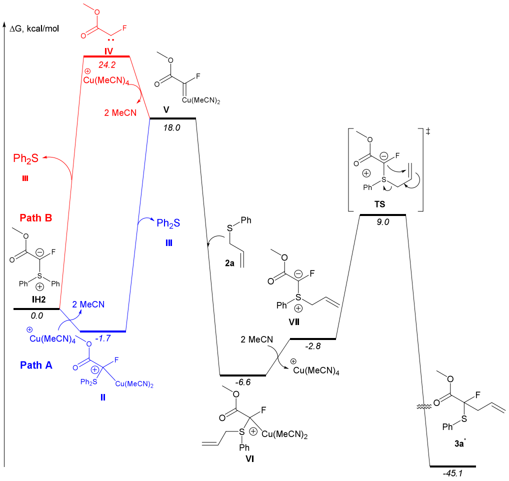
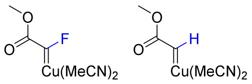


Figure 2. Thermodynamic analysis of potential intermediates of the reaction mechanism using DFT calculations (m06-2x/Def2TZVP using DCM as the solvent).

In order to improve our understanding of the properties of the fluoroacetyl carbene, we performed charge distribution analysis for carbene−copper complexes **V** and **V-H** (Table 2; see the Supporting Information for additional computational details). The analysis revealed that fluoroacetyl carbene−copper complex **V** showed more σ donation (0.326) and less back-donation (0.035) compared to acetyl carbene **V-H**. This indicates that the fluorinated carbene transfers more electron density (0.291) to the copper core than the ligand bearing hydrogen. Additionally, the energy of the lowest unoccupied molecular orbital (LUMO) for fluoroacetyl carbene complex **V** is more negative than that of nonfluorinated carbene complex **V-H**. This results in the higher electrophilicity of complex **V**, as indicated by increased electrophilicity index ω (11.608) in comparison to that of simple acetyl carbene−copper complex **V-H** (10.203).

Table 2. Calculated Orbital Energies and Global Electrophilicities of Carbene−Copper Complexes V and V-H



	V	**V-H**
donation (d)	0.326	0.287
back-donation (b)	0.035	0.050
$d - b$	0.291	0.237
$\varepsilon_{\text{LUMO}}$ (eV)	−7.220	−6.843
ω	11.608	10.203

We have developed novel highly efficient fluoroacetyl carbene transfer reactions utilizing a stable and easy-to-handle sulfonium salt. The application was showcased in the Doyle−Kirmse and cyclopropanation reactions. Metal-stabilized carbene generation takes place under mild conditions using weak and non-nucleophilic bases such as DIPEA and Cs_2CO_3. Furthermore, the employed metal catalysts for carbene transfer are earth abundant. To the best of our knowledge, these are the first fluoroacetyl carbene transfer reactions indicating similar reactivity to nonfluorinated ethyl-acetylcarbene. Our findings open the door for the further exploration of reactivity to access medicinal chemistry relevant α-fluoroacetyl groups in one step.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01416.

General methods, procedures, characterization data, copies of NMR spectra, and six additional references (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359.

(2) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633−10640.

(3) Wang, Q.; Bian, Y.; Dhawan, G.; Zhang, W.; Sorochinsky, A. E.; Makarem, A.; Soloshonok, V. A.; Han, J. FDA approved fluorine-containing drugs in 2023. *Chin. Chem. Lett.* **2024**, *35*, 109780.

(4) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.

(5) Yuan, T.; Shi, L. Recent advances in carbon atom addition for ring-expanding single-atom skeletal editing. *Organic Chemistry Frontiers* **2024**, *11*, 7318−7332.

(6) Maag, H. Prodrugs of Carboxylic Acids. In *Prodrugs: Challenges and Rewards Part 1*; Stella, V. J., Borchardt, R. T., Hageman, M. J., Oliyai, R., Maag, H., Tilley, J. W., Eds.; Springer: New York, 2007; pp 703−729.

(7) Bredael, K.; Geurs, S.; Clarisse, D.; De Bosscher, K.; D'hooghe, M. Carboxylic Acid Bioisosteres in Medicinal Chemistry: Synthesis and Properties. *J. Chem.* **2022**, *2022*, 2164558.

(8) Li, L.; Yao, Y.; Fu, N. Free Carboxylic Acids: The Trend of Radical Decarboxylative Functionalization. *Eur. J. Org. Chem.* **2023**, *26*, No. e202300166.

(9) Xiao, P.; Pannecoucke, X.; Bouillon, J.-P.; Couve-Bonnaire, S. Wonderful fusion of organofluorine chemistry and decarboxylation strategy. *Chem. Soc. Rev.* **2021**, *50*, 6094−6151.

(10) Kitcatt, D. M.; Nicolle, S.; Lee, A.-L. Direct decarboxylative Giese reactions. *Chem. Soc. Rev.* **2022**, *51*, 1415−1453.

(11) Rodríguez-Alvarado, M.; Russo, R.; Connell, N. D.; Brenner-Moyer, S. E. Design, organocatalytic synthesis, and bioactivity evaluation of enantiopure fluorinated LpxC inhibitors. *Organic & Biomolecular Chemistry* **2020**, *18*, 5867−5878.

(12) Lee, K. L.; Ambler, C. M.; Anderson, D. R.; Boscoe, B. P.; Bree, A. G.; Brodfuehrer, J. I.; Chang, J. S.; Choi, C.; Chung, S.; Curran, K. J.; Day, J. E.; Dehnhardt, C. M.; Dower, K.; Drozda, S. E.; Frisbie, R. K.; Gavrin, L. K.; Goldberg, J. A.; Han, S.; Hegen, M.; Hepworth, D.; Hope, H. R.; Kamtekar, S.; Kilty, I. C.; Lee, A.; Lin, L.-L.; Lovering, F. E.; Lowe, M. D.; Mathias, J. P.; Morgan, H. M.; Murphy, E. A.; Papaioannou, N.; Patny, A.; Pierce, B. S.; Rao, V. R.; Saiah, E.; Samardjiev, I. J.; Samas, B. M.; Shen, M. W. H.; Shin, J. H.; Soutter, H. H.; Strohbach, J. W.; Symanowicz, P. T.; Thomason, J. R.; Trzupek, J. D.; Vargas, R.; Vincent, F.; Yan, J.; Zapf, C. W.; Wright, S. W. Discovery of Clinical Candidate 1-{[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragment-Based Drug Design. *J. Med. Chem.* **2017**, *60*, 5521−5542.

(13) Luckhurst, C. A.; Breccia, P.; Stott, A. J.; Aziz, O.; Birch, H. L.; Bürli, R. W.; Hughes, S. J.; Jarvis, R. E.; Lamers, M.; Leonard, P. M.; Matthews, K. L.; McAllister, G.; Pollack, S.; Saville-Stones, E.; Wishart, G.; Yates, D.; Dominguez, C. Potent, Selective, and CNS-Penetrant Tetrasubstituted Cyclopropane Class IIa Histone Deacetylase (HDAC) Inhibitors. *ACS Med. Chem. Lett.* **2016**, *7*, 34−39.

(14) Wilkinson, J. A. Recent advances in the selective formation of the carbon-fluorine bond. *Chem. Rev.* **1992**, *92*, 505−519.

(15) Lal, G. S.; Pez, G. P.; Syvret, R. G. Electrophilic NF Fluorinating Agents. *Chem. Rev.* **1996**, *96*, 1737−1756.

(16) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264.

(17) Rozatian, N.; Hodgson, D. R. W. Reactivities of electrophilic N−F fluorinating reagents. *Chem. Commun.* **2021**, *57*, 683−712.

(18) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174.

(19) Grygorenko, O. O.; Melnykov, K. P.; Holovach, S.; Demchuk, O. Fluorinated Cycloalkyl Building Blocks for Drug Discovery. *ChemMedChem* **2022**, *17*, No. e202200365.

(20) Grygorenko, O. O.; Melnykov, K. P. Fluorinated building blocks in drug design: new pathways and targets. *Future Medicinal Chemistry* **2024**, *16*, 1375−1378.

(21) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. One-Step Synthesis of Highly Functionalized Monofluorinated Cyclopropanes from Electron-Deficient Alkenes. *Org. Lett.* **2012**, *14*, 2270−2273.

(22) Lemonnier, G.; Zoute, L.; Quirion, J.-C.; Jubault, P. First Efficient Synthesis of Fluorinated Glycidic Esters from Ketones. *Org. Lett.* **2010**, *12*, 844−846.

(23) Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Ando, A. Diastereoselective synthesis of 2-fluoroaziridine-2-carboxylates by Reformatsky-type aza-Darzens reaction. *Tetrahedron Lett.* **2010**, *51*, 4246−4249.

(24) David, E.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. Ethyl dibromofluoroacetate: a versatile reagent for the synthesis of fluorinated molecules. *Tetrahedron* **2013**, *69*, 11039−11055.

(25) Sperga, A.; Veliks, J. Recent Advances in Monofluorinated Carbenes, Carbenoids, Ylides, and Related Species. *Chem. - Eur. J.* **2023**, *29*, No. e202301851.

(26) Ye, T.; McKervey, M. A. Organic Synthesis with.alpha.-Diazo Carbonyl Compounds. *Chem. Rev.* **1994**, *94*, 1091−1160.

(27) Doyle, M. P.; Forbes, D. C. Recent Advances in Asymmetric Catalytic Metal Carbene Transformations. *Chem. Rev.* **1998**, *98*, 911−936.

(28) Huang, M.-Y.; Zhu, S.-F. Uncommon carbene insertion reactions. *Chemical Science* **2021**, *12*, 15790−15801.

(29) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Catalytic Carbene Insertion into C−H Bonds. *Chem. Rev.* **2010**, *110*, 704−724.

(30) He, Y.; Huang, Z.; Wu, K.; Ma, J.; Zhou, Y.-G.; Yu, Z. Recent advances in transition-metal-catalyzed carbene insertion to C−H bonds. *Chem. Soc. Rev.* **2022**, *51*, 2759−2852.

(31) Bera, S.; Jana, S.; Samanta, R. Recent Progress on Copper-Catalyzed C−C Bond Formation via C(sp2)−H Insertions Using Diazo and Related Compounds. *Synthesis* **2024**, *56*, 29−46.

(32) Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Process Res. Dev.* **2020**, *24*, 67−84.

(33) Clark, J. D.; Shah, A. S.; Peterson, J. C. Understanding the large-scale chemistry of ethyl diazoacetate via reaction calorimetry. *Thermochim. Acta* **2002**, *392−393*, 177−186.

(34) Maurya, R. A.; Min, K.-I.; Kim, D.-P. Continuous flow synthesis of toxic ethyl diazoacetate for utilization in an integrated microfluidic system. *Green Chem.* **2014**, *16*, 116−120.

(35) Sperga, A.; Pfeifers, T.; Zacs, D.; Veliks, J. Fluorohalomethylsulfonium Salts as a Fluorohalocarbene Source. *Org. Lett.* **2024**, *26*, 6482−6485.

(36) Sperga, A.; Zacs, D.; Veliks, J. Iron-Catalyzed Fluoromethylene Transfer from a Sulfonium Reagent. *Org. Lett.* **2022**, *24*, 4474−4478.

(37) Timmann, S.; Feng, Z.; Alcarazo, M. Recent Applications of Sulfonium Salts in Synthesis and Catalysis. *Chem. - Eur. J.* **2024**, *30*, No. e202402768.

(38) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. Sulfoxonium and Sulfonium Ylides as Diazocarbonyl Equivalents in

Metal-Catalyzed Insertion Reactions. *Eur. J. Org. Chem.* **2013**, *2013*, 5005−5016.

(39) Shi, C.-Y.; Zhou, B.; Teng, M.-Y.; Ye, L.-W. Recent Advances in the Asymmetric Doyle−Kirmse Reaction. *Synthesis* **2023**, *55*, 3895−3905.

(40) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. Highly effective catalytic methods for ylide generation from diazo compounds. Mechanism of the rhodium- and copper-catalyzed reactions with allylic compounds. *Journal of Organic Chemistry* **1981**, *46*, 5094−5102.

(41) Kirmse, W.; Kapps, M. Reaktionen des Diazomethans mit Diallylsulfid und Allyläthern unter Kupfersalz-Katalyse. *Chem. Ber.* **1968**, *101*, 994−1003.

(42) Jana, S.; Guo, Y.; Koenigs, R. M. Recent Perspectives on Rearrangement Reactions of Ylides via Carbene Transfer Reactions. *Chem. - Eur. J.* **2021**, *27*, 1270−1281.

(43) Lu, H.; Dzik, W. I.; Xu, X.; Wojtas, L.; de Bruin, B.; Zhang, X. P. Experimental Evidence for Cobalt(III)-Carbene Radicals: Key Intermediates in Cobalt(II)-Based Metalloradical Cyclopropanation. *J. Am. Chem. Soc.* **2011**, *133*, 8518−8521.

(44) Pellissier, H. Recent developments in asymmetric cyclopropanation. *Tetrahedron* **2008**, *64*, 7041−7095.

(45) Liu, M.; Uyeda, C. Redox Approaches to Carbene Generation in Catalytic Cyclopropanation Reactions. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202406218.

(46) Tan, L.; Wu, K.; Li, G. Rapid Olefin Cyclopropanation Catalyzed by a Bioinspired Cobalt Complex. *Chem. - Asian J.* **2023**, *18*, No. e202300873.

(47) Ebner, C.; Carreira, E. M. Cyclopropanation Strategies in Recent Total Syntheses. *Chem. Rev.* **2017**, *117*, 11651−11679.

(48) Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. Blue-Light-Induced Carbene-Transfer Reactions of Diazoalkanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1203−1207.

(49) Laconsay, C. J.; Tantillo, D. J. Metal Bound or Free Ylides as Reaction Intermediates in Metal-Catalyzed [2,3]-Sigmatropic Rearrangements? It Depends. *ACS Catal.* **2021**, *11*, 829−839.

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RESEARCH ARTICLE doi.org/10.1002/adsc.70119 ADVANCED SYNTHESIS & CATALYSIS

Monofluorinated C1 Synthon Strategy for the Construction of Fluoromethylene-Linked Bicyclo[1.1.1]Pentane Derivatives

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Abstract: Fluoroalkyl-substituted bicyclo[1.1.1]pentanes (BCPs) have emerged as an attractive scaffold in drug discovery. Herein, the modular construction of fluoromethyl-linked BCPs is reported. Fluoroiodomethyl phenyl sulfoxide is found to be a synthetic equivalent of a formal fluoromethylene radical cation synthon, which, under metal-free conditions and violet light irradiation (400 nm), enables an atom-transfer radical addition reaction to [1.1.1]propellane. This straightforward approach provides access to novel bicyclo[1.1.1]pentane-substituted fluoromethyl sulfonium reagents. The electrophilic properties of these sulfonium salts allow nucleophilic displacement under mild conditions, enabling the introduction of the fluoromethyl bicyclopentyl group into diverse natural products and drug molecules with good functional group tolerance.

Keywords: bicyclo[1.1.1]pentanes, fluoromethylation, late stage functionalization, nucleophilic substitution, photochemistry, sulfonium salts

1. Introduction

Bicyclo [1.1.1]pentanes (BCPs) have appeared as efficient bioisosteres of benzene, as well as alkynyl and *t*Bu groups (**Figure 1**A).[1–5] Replacement of the phenyl group with this 3D sp^3-rich scaffold can enhance physicochemical and pharmacokinetic properties, such as lipophilicity and metabolic stability, while maintaining similar sterics and biological activity. Fluorine incorporation is a crucial strategy in medicinal chemistry to enhance the properties of a compound.[6–8] Therefore, merging both of these fragments is of high importance.[9]

In recent years, much effort has been devoted to the synthesis of difluoromethyl ($–CF_2R$)[10–19] or trifluoromethyl ($–CF_3$)[20–24] substituted BCPs. However, the synthesis of monofluoromethyl ($–CFR_2$) BCP compounds has been far less reported, despite the fact that the monofluoromethyl BCP fragment is present in various biologically active compounds (Figure 1B).[25–27]

One strategy for fluorine incorporation relies on functional group interconversion in BCP-containing molecules, namely, deoxyfluorination of alcohols[27] or electrophilic fluorination of acidic CH bonds under basic conditions[28] (Figure 1C).

Another approach relies on using [1.1.1]propellane in strain release reactions with monofluoromethyl radicals (Figure 1D).[29–31] These methods allow 1,3-difunctionalization of propellane, forming various monofluoromethylated BCPs in a single step.

However, the substrate scope for these monofluoromethylation reactions remains limited compared to di- or trifluoromethylation methods. Furthermore, the necessity to use expensive transition metal catalysts or harsh reaction conditions for radical generation limits the applicability. Another limitation is the synthesis of monofluorinated radical precursors, which might be problematic for highly functionalized substrates.

Therefore, to overcome these limitations, we envisioned a novel approach (Figure 1E). Fluoroiodomethyl phenyl sulfoxide[32] can serve as a C1F1 precursor, enabling access to a formal fluoromethylene radical cation synthon. It can undergo an atom-transfer radical addition (ATRA) reaction with propellane and, after sulfonium formation, participate in further nucleophilic displacement reactions. Functionalization of the fluoromethylene-BCP-substituted sulfonium salt with nucleophiles would yield structurally diverse products that are inaccessible using

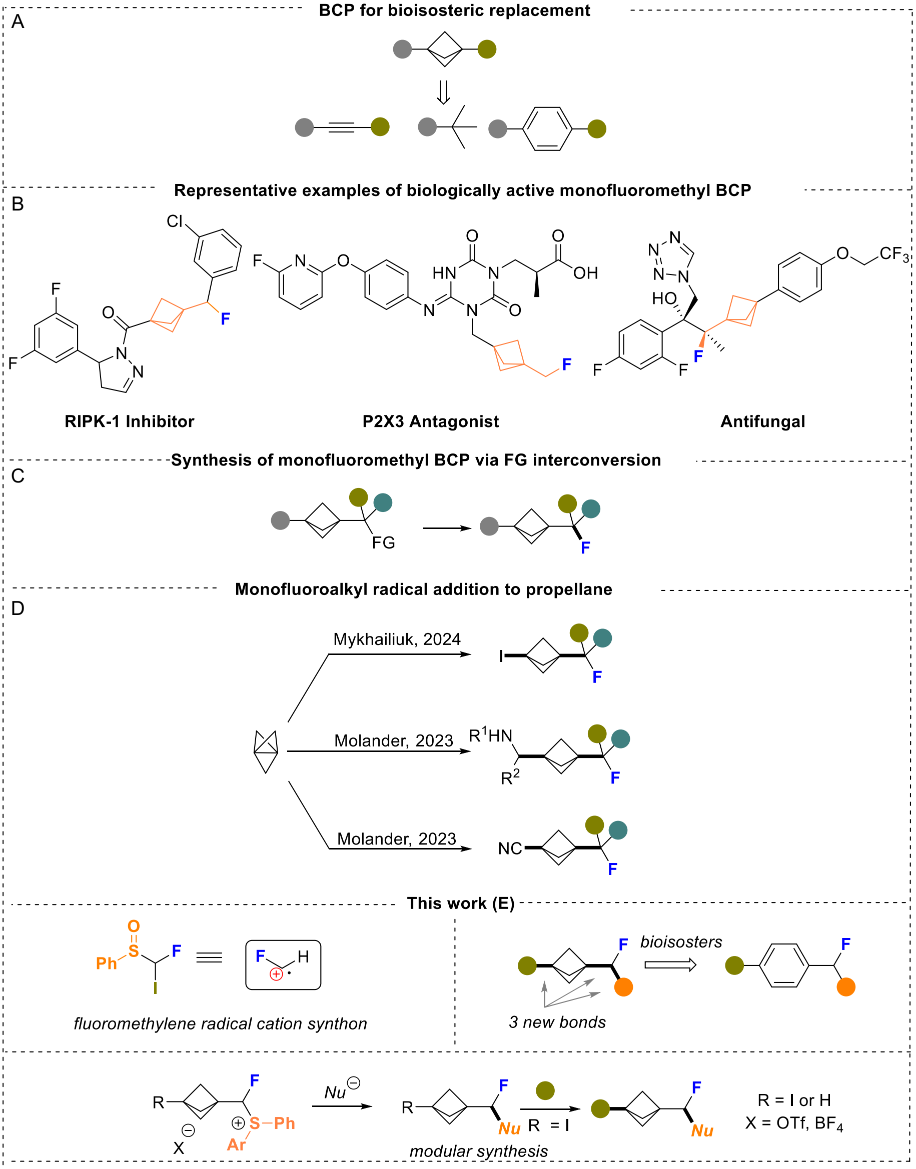
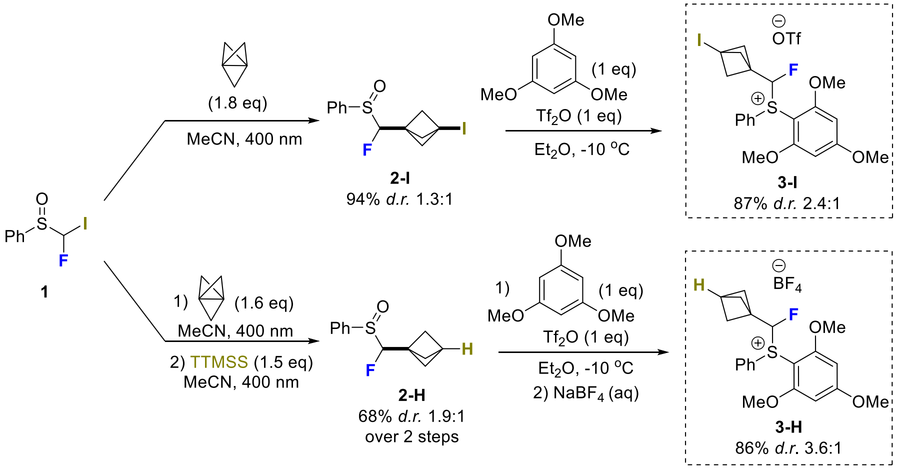


Figure 1. A) Application of BCPs for bioisosteric replacement. B) Fluoromethyl-BCP application in medicinal chemistry. C) Fluorine introduction via functional group conversion. D) Synthesis of fluoromethyl-BCP via radical addition. E) This work.

previous strategies. Furthermore, incorporation of an iodine atom into the BCP fragment would provide a handle for additional modification possibilities.[29,33–39] During the preparation of this article, Ritter's group reported an elegant strategy relying on orthogonally difunctionalized BCPs.[40]

2. Results and Discussion

We began our research by developing an efficient protocol for the synthesis of fluoromethyl-BCP-substituted sulfonium salt **3** (**Scheme 1**). We were pleased to find that fluoroiodomethyl sulfoxide **1**[32] adds to [1.1.1]

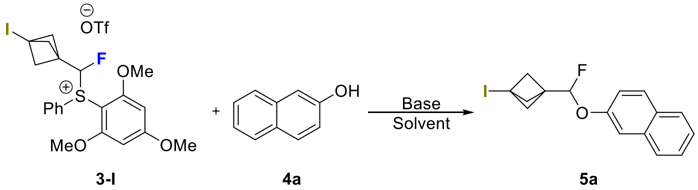


Scheme 1. Synthesis of sulfonium salts.

propellane in high yield, solely using purple light irradiation, without the need for any activators (for details, see SI). Furthermore, **2-I** can be deiodinated by treatment with tris(trimethyl)silane, again without any additives, to afford **2-H** in good yield in a one-pot, two-step procedure. For sulfonium **3-I** formation, it was crucial to use electron-rich 1,3,5-trimethoxybenzene to suppress side product formation. In the case of **3-H**, anion metathesis was necessary to obtain the reagent in solid form.

With reagent **3-I** in hand, we optimized the nucleophilic substitution reaction (**Table 1**). This approach demonstrates modular construction opportunities, in which the fluoromethylene (–CHF–) group serves as a linker. Pleasingly, naphthol **4a** smoothly underwent nucleophilic displacement in acetonitrile (MeCN) using

Table 1. Optimization of fluoromethyl-BCP transfer.



Entry[a]	Base [eq]	3-I [eq]	4a [eq]	Solvent	Yield 5a
1	Cs_2CO_3 (1)	**(1)**	**(1)**	MeCN	81%
2[b]	DIPEA (1)				22%
3[c]	–				0%
4	**Cs_2CO_3 (1)**			1,4-dioxane	61%
5				Acetone	75%
6				DMF	62%
7				**DCM**	**85%**
8	Cs_2CO_3 (1.2)		(1.2)		83%
9	Cs_2CO_3 (1)	(1.2)	(1)		84%

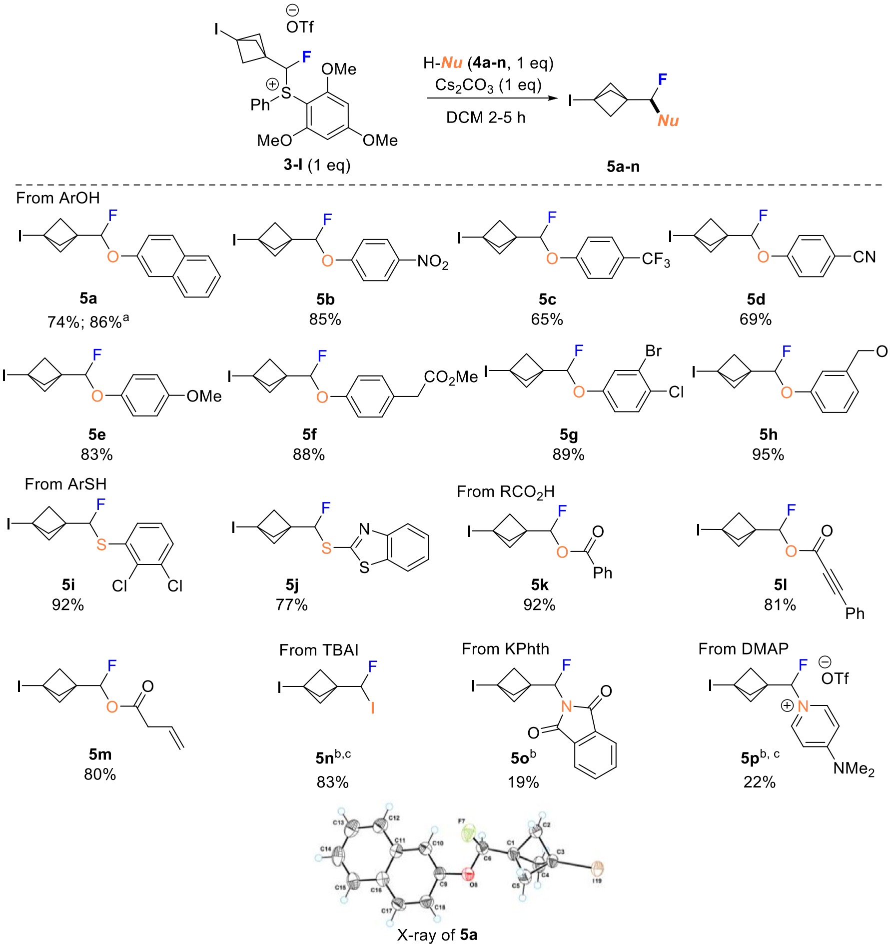
[a] To sulfonium **3-I** (0.05 mmol), **4a** and base were added solvent (0.5 ml) under Ar atm. The reaction was stirred for 4h. After completion, the reaction mixture was evaporated. The reaction yield was determined from the ^{19}F NMR crude mixture using $PhCF_3$ as the internal standard.

[b] 70% of **3-I** was remaining.

[c] 89% of **3-I** was remaining.

Cs_2CO_3 as a base, yielding product **5a** in high yield (entry 1). However, the reaction proceeded sluggishly with *N,N*-diisopropylethylamine (DIPEA) (entry 2), and no product was observed in the absence of a base (entry 3). Solvent screening revealed that in dichloromethane (DCM), product **5a** was formed slightly better. Nevertheless, other solvents (entries 1, 4–6) also gave decent product yields. Changing the equivalents of reactants did not lead to further improvement (entries 8–9).

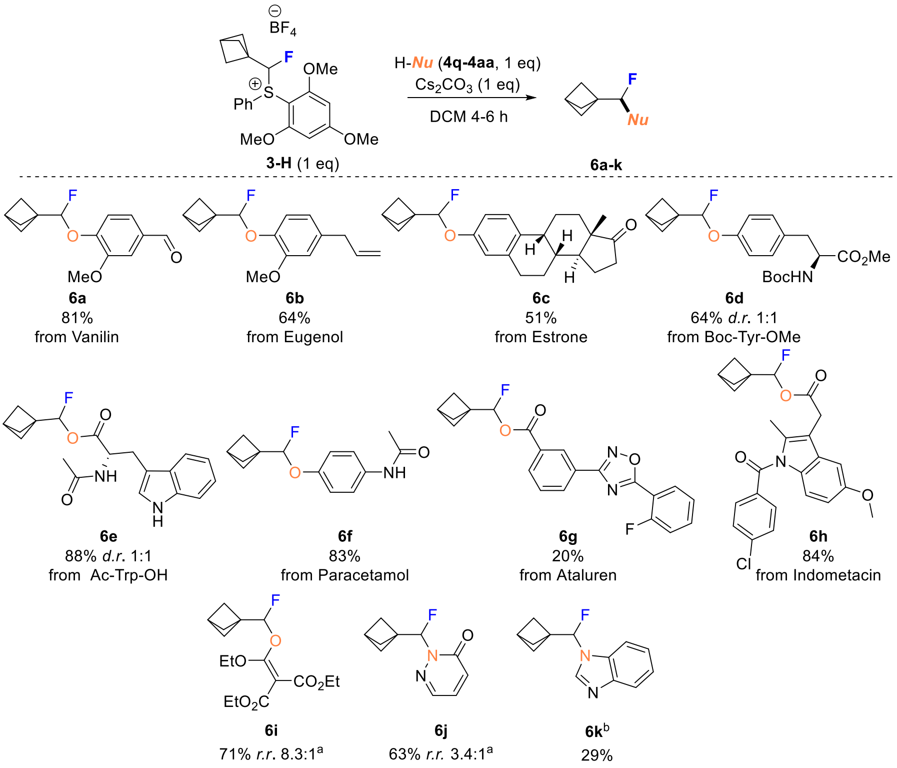
With the optimized conditions in hand, we investigated the substrate scope. Various phenols were alkylated with the sulfonium salt under mild conditions (**Scheme 2**). The reaction conditions tolerate a wide variety of functional groups. Electron-withdrawing groups such as nitro **4b**, trifluoromethyl **4c**, cyano **4d**, as well as electron-donating methoxy group **4e** provided products in moderate to good yields. Furthermore, the ester group **4f** and halogen atoms **4g** were well-tolerated. Importantly, the phenolic oxygen is regioselectively alkylated in substrate **4h**, while the aliphatic alcohol remains intact. The substrate scope was extended to thiophenols **4i, 4j**, and various carboxylic acids (**4k–4m**). The application of our methodology was further demonstrated for substitution with iodide **4n**, phthalimide **4o**, and DMAP (**4p**), albeit in low product yields.



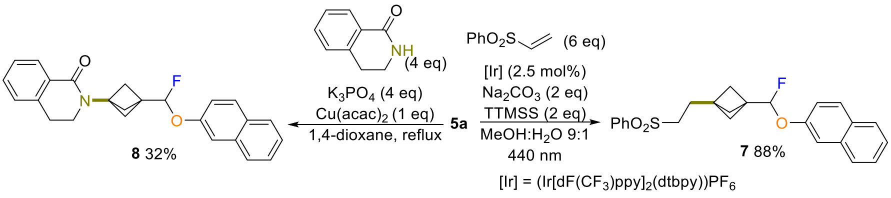
Scheme 2. Substrate scope for I-BCP-fluoromethyl transfer. Reaction conditions: To sulfonium **3-I** (0.1 mmol), nucleophile (1 eq.), and Cs_2CO_3 (1 eq.) were added DCM (1.0 ml) under Ar atm. The reactions were stirred for 2–6 h. a) 1 mmol scale; b) reaction performed in absence of Cs_2CO_3, and c) 1.2 eq. of nucleophile used.

To our delight, the deiodinated sulfonium salt **3-H** also proved to be highly effective in nucleophilic displacement reactions (**Scheme 3**). Various natural products **6a–c** and amino acids **6d**, **6f** smoothly underwent alkylation. Late-stage functionalization of drug molecules was also possible, as demonstrated by phenol **6e** or carboxylic acid **6g**, **6h** alkylation. The BCP fluoromethyl transfer was further extended to *O*-alkylation in methanetricarboxylate **6i** and for *N*-alkylation reactions in heterocycles **6j**, **6k**. These findings highlight the broad application, diverse functional group tolerance, and late-stage functionalization potential of our developed strategy.

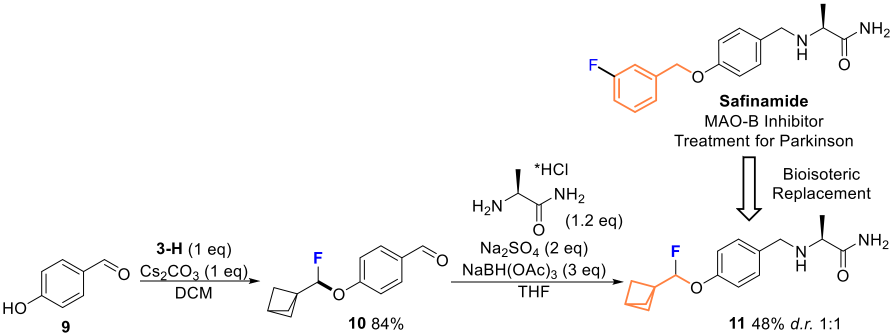
To demonstrate the orthogonal functionalization potential of the sulfonium salt **3-I**, we carried out valorization reactions using iodo-bicyclobutane **5a** (**Scheme 4**). We were able to perform Giese-type addition[39] to vinylsulfone using iridium photocatalysis.



Scheme 3. Substrate scope for alkylation reactions with **3-H**. Reaction conditions: To sulfonium **3-H** (0.1 mmol), nucleophile (1 eq.), and Cs_2CO_3 (1 eq.) were added DCM (1.0 ml) under Ar atm. The reactions were stirred for 4–6 hr. a) determined from crude ^{19}F NMR; and b) 0.12 mmol scale.



Scheme 4. Iodo-BCP **5a** functionalization possibilities.



Scheme 5. Synthesis of safinamide analog.

Furthermore, **5a** was suitable for copper-mediated cross-coupling with an amide[35], affording 1,3-difunctionalized bicyclobutane **8**.

Additionally, we were interested to employ the reagent **3-H** for the synthesis of a biologically relevant drug analog, thereby demonstrating its potential for bioisosteric replacement possibilities (**Scheme 5**). A Safinamide analog was obtained starting from 4-hydroxybenzaldehyde (**9**). Alkylation of **9** under the optimized conditions afforded **10** in high yield. Aldehyde **10** was further subjected to reductive amination with alanine amide, forming Safinamide analog **11**, in which the benzyl group was replaced with a monofluoromethyl-BCP group.

3. Conclusions

We have developed a modular approach, in which a formal fluoromethylene radical cation synthon serves as a linker to combine BCP with diverse functionalities. The successful ATRA reaction of phenyl fluoroiodomethyl sulfoxide with [1.1.1]propellane enabled the synthesis of novel fluoromethyl-BCP sulfonium salts. These are excellent reactants for nucleophilic substitution with phenols, carboxylic acids, and other nucleophiles under mild conditions. The iodinated sulfonium salt can be further employed in orthogonal functionalization reactions to obtain highly complex monofluoromethyl BCP products. Finally, a synthetic application was demonstrated for late-stage functionalization and drug analog synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

References

[1] P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839.
[2] I. Sánchez-Sordo, S. Barbeira-Arán, M. Fañanás-Mastral, *Org. Biomol. Chem.* **2024**, *11*, 916.
[3] M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046.
[4] J. Tsien, C. Hu, R. R. Merchant, T. Qin, *Nat. Rev. Chem.* **2024**, *8*, 605.
[5] B. R. Shire, E. A. Anderson, *JACS Au.* **2023**, *3*, 1539.
[6] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315.
[7] 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.
[8] Y. Du, Y. Bian, D. Baecker, G. Dhawan, A. Semghouli, L. Kiss, W. Zhang, A. E. Sorochinsky, V. A. Soloshonok, J. Han, *Chem.—A Eur. J.* **2025**, *31*, e202500662.
[9] S. Baldon, L. Dell'Amico, S. Cuadros, *Eur. J. Org. Chem.* **2024**, *27*, e202400604.
[10] Y. Guo, J. Zhu, Y. Wang, Y. Li, H. Hu, P. Zhang, J. Xu, W. Li, *ACS Catal.* **2024**, *14*, 619.
[11] Y. Zhu, F. Yi, N. Zhou, Y. Zhang, Y. Zhang, X. Zhao, K. Lu, *Org. Biomol. Chem.* **2024**, *22*, 7024.

[12] M.-D. Zhang, H.-Y. Zhao, X. Zhang, *Eur. J. Org. Chem.* **2024**, *27*, e202400572.
[13] M. Chen, Y. Cui, X. Chen, R. Shang, X. Zhang, *Nat. Commun.* **2024**, *15*, 419.
[14] X.-T. Feng, Q.-Q. Min, X. Zeng, H.-Y. Zhao, X. Zhang, *ACS Catal.* **2024**, *14*, 5879.
[15] W. Huang, S. Keess, G. A. Molander, *Angew. Chem., Int. Ed.* **2023**, *62*, e202302223.
[16] S. Cuadros, G. Goti, G. Barison, A. Raulli, T. Bortolato, G. Pelosi, P. Costa, L. Dell'Amico, *Angew. Chem., Int. Ed.* **2023**, *62*, e202303585.
[17] S. Baldon, J. Paut, E. Anselmi, G. Dagousset, B. Tuccio, G. Pelosi, S. Cuadros, E. Magnier, L. Dell'Amico, *Chem. Sci.* **2025**, *16*, 6957.
[18] J. Shen, L.-F. Yang, K. Ge, H. Xu, C. Shen, *Org. Lett.* **2025**, *27*, 6179.
[19] R. Xu, B. Cao, Y. Wang, J. Zhang, Y. Huang, W. Li, *Green Chem.* **2025**, *27*, 9223.
[20] S. Pandit, T. Ritter, *Angew. Chem., Int. Ed.* **2025**, *64*, e202506785.
[21] G. Zhang, Z. Luo, G. Mei, H. Wang, C. Ding, *Eur. J. Org. Chem.* **2024**, *27*, e202400386.
[22] Z. Bai, B. Lansbergen, T. Ritter, *J. Am. Chem. Soc.* **2023**, *145*, 25954.
[23] V. Srinivasu, D. Das, P. Chandu, K. G. Ghosh, D. Sureshkumar, *Org. Lett.* **2023**, *25*, 5308.
[24] E. M. Alvarez, Z. Bai, S. Pandit, N. Frank, L. Torkowski, T. Ritter, *Nat. Synth.* **2023**, *2*, 548.
[25] G. Deng, Y. Yao, X. Liu, Z. Li, M. Dai, R. Huan, R. Tang, D. Huang, Q. Zhang, Y. Wang, Y. Ye, J. Peng, *WO2022206862*, **2022**.
[26] Y. Wang, H. Liao, H. Chen, Z. Lin, S. Hu, *WO2023184482*, **2023**.
[27] N. Richards, R. Lewis, M. Hamilton, W. Ray, F. Alvarez, D. Pfaffinger, N. Reyna, J. Cross, S. K. V. Ramaswamy, J. Bardenhagen, Y. L. Lightfoot, P. Acton, S. Goodwani, *WO2021062199*, **2021**.
[28] M. L. J. Wong, J. J. Mousseau, S. J. Mansfield, E. A. Anderson, *Org. Lett.* **2019**, *21*, 2408.
[29] V. Ripenko, V. Sham, V. Levchenko, S. Holovchuk, D. Vysochyn, I. Klymov, D. Kyslyi, S. Veselovych, S. Zhersh, Y. Dmytriv, A. Tolmachev, I. Sadkova, I. Pishel, K. Horbatok, V. Kosach, Y. Nikandrova, P. K. Mykhailiuk, *Nat. Synth.* **2024**, *3*, 1538.
[30] W. Huang, Y. Zheng, S. Keess, G. A. Molander, *J. Am. Chem. Soc.* **2023**, *145*, 5363.
[31] W. Dong, S. Keess, G. A. Molander, *Chem. Catal.* **2023**, *3*, 100608.
[32] A. Sperga, T. Pfeifers, D. Zacs, J. Veliks, *Org. Lett.* **2024**, *26*, 6482.
[33] Y. Zhao, J. Zhang, Z.-J. Zhan, Q. Fan, X.-Q. Xiao, Y. Bai, S.-F. Ni, X. Shao, *Org. Lett.* **2024**, *26*, 4406.
[34] X. Zhao, J.-Y. Shou, F.-L. Qing, *Sci. China Chem.* **2023**, *66*, 2871.
[35] M. Alonso, S. Cañellas, F. Delgado, M. Serrano, A. Diéguez-Vázquez, J. E. Gómez, *Org. Lett.* **2023**, *25*, 771.
[36] E. Yen-Pon, L. Li, G. Levitre, J. Majhi, E. J. McClain, E. A. Voight, E. A. Crane, G. A. Molander, *J. Am. Chem. Soc.* **2022**, *144*, 12184.
[37] J. Nugent, B. R. Shire, D. F. J. Caputo, H. D. Pickford, F. Nightingale, I. T. T. Houlsby, J. J. Mousseau, E. A. Anderson, *Angew. Chem., Int. Ed.* **2020**, *59*, 11866.
[38] N. T. Thirumoorthi, C. Jia Shen, V. A. Adsool, *Chem. Commun.* **2015**, *51*, 3139.
[39] H. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, *J. Am. Chem. Soc.* **2021**, *143*, 9729.
[40] Z. Bai, Z. Wang, T. H.-F. Wong, T. Ritter, *Nat. Synth.* **2025**, *4*, 1161.

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