RĪGAS TEHNISKĀ UNIVERSITĀTE

Renāte Melngaile

FLUORMETILĒNGRUPAS PĀRNESES REAĢENTU IZSTRĀDE

Promocijas darbs

DEVELOPMENT OF FLUOROMETHYLENE TRANSFER REAGENTS

Doctoral Thesis

RTU Izdevniecība
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RĪGAS TEHNISKĀ UNIVERSITĀTE
Materiālzinātnes un lietišķās ķīmijas fakultāte
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Zinātniskais vadītājs
Docents *Dr. sc. nat.*
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Scientific supervisor
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JĀNIS VELIKS

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OFICIĀLIE RECENZENTI

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Apstiprinu, ka esmu izstrādājusi šo promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē zinātnes doktora (*Ph. D.*) grāda iegūšanai. Promocijas darbs zinātniskā grāda iegūšanai nav iesniegts nevienā citā universitātē.

Renāte Melngaile …….(paraksts)
Datums …….

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa. Tas ietver kopsavilkumu, piecas publikācijas, vienu apskatrakstu, vienu rakstu ķīmisko reaģentu enciklopēdijā. Publikācijas uzrakstītas angļu valodā, to kopējais apjoms, ieskaitot elektroniski pieejamo informāciju, ir 683 lpp.

SATURS/CONTENTS

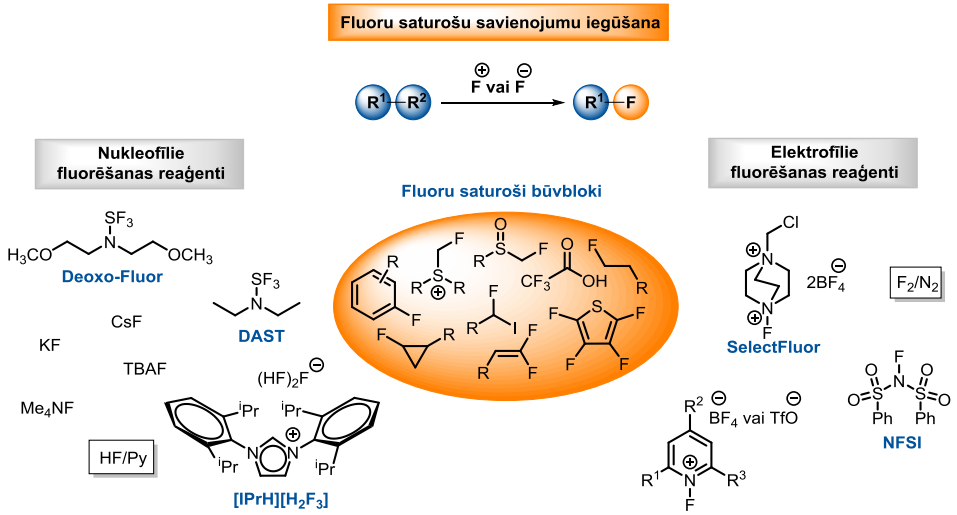
SAĪSINĀJUMI/ABBREVIATION

Ac –acetil-/acetyl
Ar – aril-/aryl
Bn – benzil-/benzyl
cat. – catalyst
COX – ciklooksigenāze/cyclooxygenase
Cy – cikloheksil-/cyclohexyl
d.r. – diastereomēru attiecība/diastereomeric ratio
DAST – dietilaminosēra trifluorīds/diethylaminosulfur trifluoride
DCE – 1,2-dihloretāns/1,2-dichloroethane
DCM – dihlormetāns/dichloromethane
DFT – density functional theory
DMF – *N*,*N*-dimetilformamīds/*N*,*N*-dimethylformamide
EAG – elektronakceptora grupa
ED – electrondonors
ekviv. – ekvivalenti
equiv. – equivalents
Et –etil-/ethyl
EW – electron withdrawing
EWG – electron withdrawing group
HetAr – heteroaril-/(hetero)aryl
IC_{50} – half maximal inhibitory concentration
ist.t. – istabas temperatūra
kat. – katalizators
KMR – kodolu magnētiskā rezonanse
kvant. – kvantitatīvi
LiHMDS – litija heksametildisilizāns/lithium bis(trimethylsilyl)amide
*m*CPBA – *meta*-hloroperoksibenzoskābe/*meta*-chloroperoxybenzoic acid
Me – metil-/methyl
Ms – mezil-/mesyl
MTBE – metil-*terc*-butilēteris/methyl *tert*-butyl ether
NBS – *N*-bromsukcinimīds/*N*-bromosuccinimide
NFSI – *N*-fluorbenzsulfonamīds/*N*-fluorobenzenesulfonimide
NMR – nuclear magnetic resonance
OMe – metoksi-/methoxy
Ph – fenil-/phenyl
RDS – ātrumu noteicošā stadija/rate determining step
rt – room temperature
Tf – triflil-/triflyl
THF – tetrahidrofurāns/tetrahydrofuran

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

Tēmas aktualitāte

Ūdeņraža atoma bioizostērā aizvietošana ar fluora atomu zāļu vielu struktūrā bieži vien uzlabo to fizikāli ķīmiskos rādītājus – matabolisko stabilitāti, biopieejamību, kā arī saistīšanos ar enzīmiem.[1] Saskaņā ar ASV Pārtikas un zāļu pārvaldes datiem vairāk nekā 20% zināmo zāļu vielu satur vismaz vienu fluora atomu, kas liecina par fluora atoma nozīmīgumu bioloģiskās aktivitātes nodrošināšanā.[2] Fluora augstā elektronegativitāte, atoma mazais izmērs, kā arī C–F saites stiprums un spēja veidot spēcīgas ūdeņraža saites atšķir fluoru no pārējiem halogēniem un tiem raksturīgajām pārvērtībām, jo klasiskās halogēnu ievadīšanas metodes fluoru saturošu būvbloku ievadīšanai molekulā bieži vien nav efektīvas.[3]



1. att. C–F saites veidošanai visbiežāk izmantotie reaģenti.

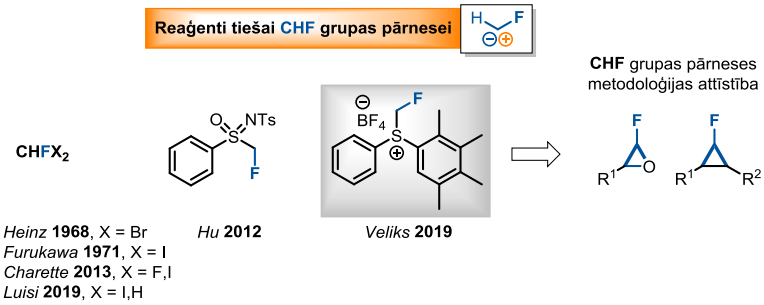
Drošu un videi draudzīgu reaģentu izstrāde fluora ievadīšanai organiskajos savienojumos ir nozīmīgs izaicinājums un aktuāls pētniecības virziens organiskajā ķīmijā.[4]

Gāzveida fluors (F_2), tā agresīvās reģētspējas, zemās selektivitātes, augstās bīstamības, kā arī īpaša laboratorijas aprīkojuma nepieciešamības dēļ netiek plaši pielietots organiskās sintēzes laboratorijas apstākļos.[5] Hidratētam fluorīda jonam novērojama zema nukleofilitāte, taču bezūdens fluorīdjona iegūšana ir apgrūtināta tam piemītošo higroskopisko īpašību dēļ, turpretī, fluorūdeņradim (HF) piemīt augsta toksicitāte. Lai izvairītos no tiešas F_2 vai HF pielietošanas laboratorijas apstākļos, izstrādāti gan nukleofīlie[6], gan elektrofīlie[7] fluorēšanas reaģenti selektīvai C–F saites veidošanai (1. att.).[8]

Zinātniskajā literatūra īpaša uzmanība veltīta tieši monofluorētu būvbloku attīstībai, kas skaidrojams ar viena fluora atoma ievadīšanas metožu un reaģentu iztrūkumu.[9]

Vienkāršākais C–F saturošais fragments ir fluormetilēngrupa,[10] kuras ievadīšanai mērķa molekulā izmanto monofluormetilēngrupas pārneses reaģentus (2. att.), kas galvenokārt ietver viegli virstošu, videi nedraudzīgu freonu tipa savienojumu $CHFX_2$ izmantošanu fluorkarbēnu[11], kā arī fluorkarbenoīdu[12] ģenerēšanai. Viens no veiksmīgākajiem piemēriem

tiešai monofluormetilēngrupas pārnesei ir fluorēts sulfoksimīns, taču tā pielietošanas iespējas ir demonstrētas tikai uz Veinreba amīdiem.[13]



2. att. Literatūrā zināmie fluormetilēngrupas pārneses reaģenti.

Sēra ilīdi[14] kalpo kā karbēna sintētiskie ekvivalenti, ko sekmīgi pielieto organiskajā ķīmijā mazākā karbocikla – ciklopropāna – sintēzei Korija–Čaikovska ciklopropanēšanas reakcijas apstākļos.[15] Sēra ilīda fragmentu saturošiem fluormetilēngrupas pārneses reaģentiem, mūsuprāt, ir liels potenciāls monofluorētu savienojumu iegūšanai. Mūsu grupa pirmo reizi demonstrēja sintētisko pielietojumu sēra fluormetilīdam, ko izdevās ģenerēt no diarilfluormetilsulfonija sāls, lai iegūtu monofluorētus epoksīdus reakcijās ar aldehīdiem un ketoniem.[16] Šādā veidā tika demonstrēts jauns reakcijas virziens diarilfluormetilsulfonija reaģentam – fluormetilēngrupas pārnese, jo līdz šim vienīgais zināmais pielietojums šāda tipa reaģentam bija elektrofīlā fluormetilēšana, ko sākotnēji aprakstīja *Olah* un *Prakash* grupa.[17]

Izpētot literatūru par fluormetilsulfonija sāļu pielietojumu, trūkst informācijas par šī savienojuma *in situ* ģenerēta sēra ilīda potenciālu, kas, mūsuprāt, ir atslēga selektīvām monofluormetilēngrupas pārneses pārvērtībām, iegūstot maz izpētītus fluoru saturošus savienojumus.

Pētījuma mērķis un uzdevumi

Promocijas darba mērķis ir jaunu, efektīvu un praktisku fluormetilēngrupas pārneses reaģentu izstrāde, kā arī minēto reaģentu izmantošana jaunu sintēzes metožu attīstīšanai fluorētu būvbloku sintēzei.

Darba mērķa īstenošanai tika definēti divi uzdevumi:

1) izpētīt fluormetilsulfonija sāļu un to atvasinājumu sintētiskā pielietojuma iespējas monofluorētu savienojumu iegūšanai;

2) sintezēt literatūrā maz pētītus monofluorētus būvblokus/fragmentus, izpētīt to tālāko sintētisko pielietojumu, kā arī potenciāli nozīmīgu zāļu vielu fluorētu analogu iegūšanu.

Zinātniskā novitāte un galvenie rezultāti

Promocijas darba rezultātā izstrādāta:

1) organiskās sintēzes metodoloģija monofluormetilēngrupas pārnesei reakcijās ar aktivētiem alkēniem, diarilfluormetilsulfonija sāls klātbūtnē Korija–Čaikovska ciklopropanēšanas reakcijas apstākļos:
   a) diastereoselektīva vinilsulfonu un vinilsulfonamīdu fluorciklopropanēšana;
   b) dubultaktivētu Maikla akceptoru – arilidēnmalonātu, arilidēncianoesteru, sulfonu – fluorciklopropanēšana, reakcijas limitācijas pētījumi;
   c) fluormetilsulfonija sāls struktūras optimizēšanas pētījumi reakcijās ar nitroalkēniem, kā arī ar citiem Maikla akceptoriem;
2) organiskās sintēzes metodoloģija monofluorciklopropilidēnu iegūšanai no aldehīdiem un ketoniem Džūlija–Kočinska reakcijas apstākļos, pielietojot 5-(1*R**,2*R**)-2-fluorciklopropilsulfonil-1-fenil-1*H*-tetrazolu kā reaģentu;
3) zāļu vielas ibuprofēna fluoru saturoša analoga sintēze, fluorciklopropānam kalpojot kā izopropilgrupas izostēram.

Darba struktūra un apjoms

Promocijas darbs sagatavots kā tematiski vienota zinātnisko publikāciju kopa par fluormetilēngrupas pārneses reaģentu un metodoloģijas izstrādi reakcijās ar dažādiem Maikla akceptoriem, kā arī par iegūto savienojumu – fluorciklopropānu atvasināšanu citu nozīmīgu fluoru saturošu savienojumu iegūšanai.

Darba aprobācija un publikācijas

Promocijas darba galvenie rezultāti apkopoti piecās zinātniskajās oriģinālpublikācijās, vienā apskatrakstā, vienā rakstā ķīmisko reaģentu enciklopēdijā. Pētījuma rezultāti prezentēti sešās zinātniskajās konferencēs.

Zinātniskās publikācijas:

1) **Melngaile, R.**; Sperga, A.; Baldridge, K. K.; Veliks, J. Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts. *Org. Lett*. **2019**, *21* (17), 7174–7178. DOI: 10.1021/acs.orglett.9b02867.

2) Kazia, A.; **Melngaile, R.**; Mishnev, A.; Veliks, J. Johnson–Corey–Chaykovsky Fluorocyclopropanation of Double Activated Alkenes: Scope and Limitations. *Org. Biomol. Chem.* **2020**, *18*, 1384–1388. DOI: 10.1039/C9OB02712B.

3) Sperga, A.; **Melngaile, R.**; Kazia, A.; Belyakov, S.; Veliks, J. Monofluoromethylsulfonium Reagents for Fluoromethylene Transfer Chemistry. *J. Org. Chem.* **2021**, *86* (4), 3196–3212. DOI: 10.1021/acs.joc.0c02561.

4) Muhamadejev, R.; **Melngaile, R.**; Paegle, P.; Zibarte, I.; Petrova, M.; Jaudzems, K.; Veliks J. Residual Solvent Signal of $CDCl_3$ as a *q*NMR Internal Standard for Application in Organic Chemistry Laboratory. *J. Org. Chem.* **2021**, *86* (5), 3890–3896. DOI: 10.1021/acs.joc.0c02744.

5) **Melngaile, R.**; Veliks, J. Synthetic Applications of Monofluoromethylsulfonium Salts. *Synthesis* **2021**, *53* (24), 4549–4558. DOI: 10.1055/a-1548-8240.

6) **Melngaile, R.**; Veliks, J. Sulfonium, (Fluoromethyl)phenyl(2,3,4,5-tetramethylphenyl)-, Tetrafluoroborate(1-) (1:1)[1]. *Encycl. Reagents Org. Synth.* **2021**, 1–4. DOI: 10.1002/047084289X.rn02379.

7) **Melngaile, R.**; Videja, M.; Kuka, J.; Kinens, A.; Zacs, Dz.; Veliks, J. Synthetic Access to Fluorocyclopropylidenes. *Org. Lett.* **2023**, 25 (*13*), 2280–2284.

Zinātniskās konferences, kurās prezentēti darba rezultāti:

1) Melngaile, R. Fluoromethylene Transfer From Diarylfluoromethylsulfonium Salts. *20th Tetrahedron Symposium*, Bangkoka, Taizeme, 18.–21. jūnijs **2019**.

2) Melngaile, R. Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts. 11*th Paul Walden Symposium*, Rīga, Latvija, 19.–20. septembris **2019**.

3) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *12th Paul Walden Symposium.* Tiešsaistē, 28.–29. oktobris **2021**.

4) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *Balticum Organicum Syntheticum*, Viļņa, Lietuva, 3.–6. jūlijs **2022**.

5) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *2nd Drug Discovery Conference* 2022, Rīga, Latvija, 22.–24. septembris **2022**.

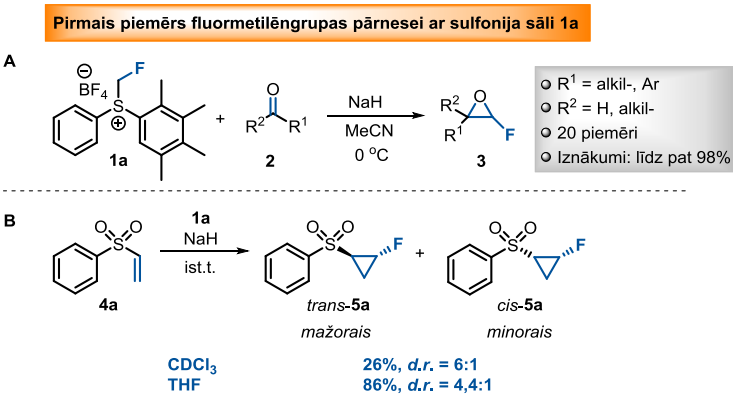
6) Melngaile, R. Recent Advances in Fluoromethylene Transfer. *2nd LIOS conference*, Rīga, Latvija, 29.–30. novembris **2022**.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

1. Diastereoselektīva monofluorciklopropanēšana vinilsulfonu reakcijās ar diarilfluormetilsulfonija sāli

Uzsākot šo pētījumu, literatūrā nebija atrodami piemēri monofluorciklopropānu iegūšanai Korija–Čaikovska ciklopropanēšanas reakcijā. Mūsu grupā veiksmīgi realizētā fluormetilēngrupas pārnese reakcijās ar aldehīdiem un ketoniem **2**, izmantojot diarilfluormetilsulfonija sāli **1a** (3. att., **A**), iedrošināja paplašināt šo pieeju fluorciklopropānu **5** iegūšanai.[16] Bāzes klātienē ģenerētam sēra fluormetilīdam reaģējot ar spēcīgu Maikla akceptoru – vinilsulfonu Korija–Čaikovska reakcijas apstākļos, izdevās parādīt efektīvu pieeju jaunu monofluorētu būvbloku – fluorciklopropilsulfonu iegūšanai.[18]

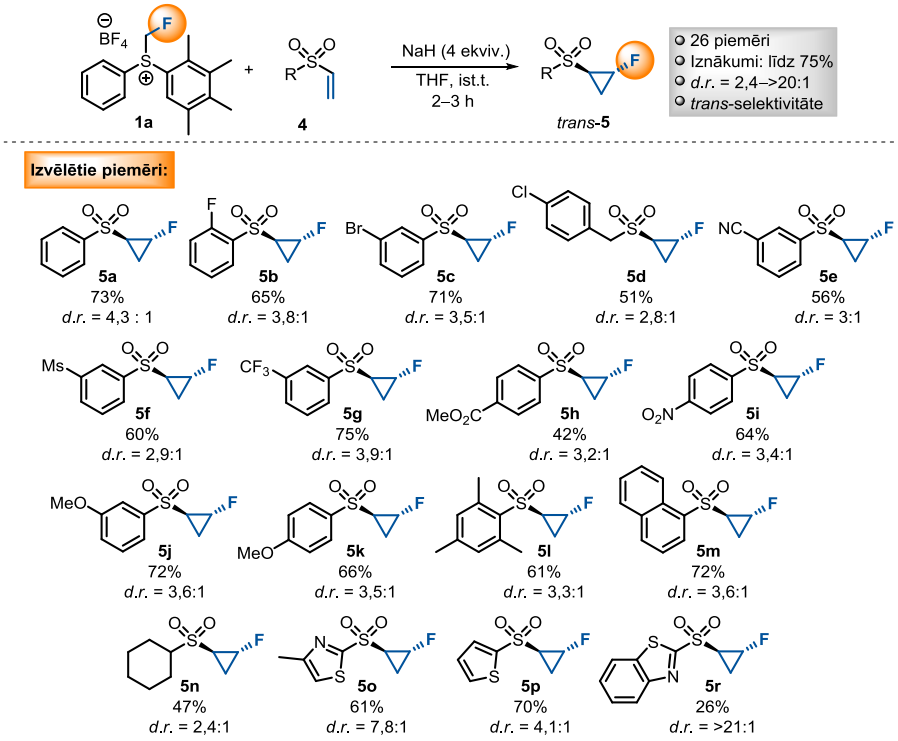
Sākotnēji kā modeļsubstrātu izvēloties fenilvinilsulfonu **4a**, realizējām reakciju deitērētā hloroformā, kas ar KMR analīzi ļāva identificēt vēlamā produkta veidošanos **5a** (3. att., **B**) ar zemu iznākumu (26 %) un apmierinošu diastereoselektivitāti (*d.r.* = 6:1). Reakcijas rezultātā novērojām, ka *trans*-izomērs **5a** veidojās kā pamatprodukts.



3. att. Fluormetilēngrupas pārnese Korija–Čaikovska fluorciklopropanēšanā.

Šķīdinātāju, temperatūras, šķīduma koncentrācijas, kā arī reakcijas komponenšu attiecību optimizēšanas eksperimenti deva iespēju atrast vispiemērotākos apstākļus augstākā kopējā iznākuma iegūšanai (86 %, *d.r.* = 4,4:1), tādēļ substrātu **4** klāsta pētījumus veicām šādos apstākļos: **1a** (2 ekviv.), 60 % NaH (4 ekviv.), THF (0,1 M), argona atmosfērā, ist.t. Jāpiezīmē, ka prakstisku iemeslu dēļ reakcijas diastereoselektivitāti noteicām diastereomēru maisījumam, bet reakcijas iznākumu pēc hromatogrāfiskas attīrīšanas noteicām tikai galvenajam diastereomēram *trans*-**5**.

Substrātu **4** klāsta pētījumu gaitā pārliecinājāmies par dažādu funkcionālo grupu savietojamību ar izstrādātajiem reakcijas apstākļiem (4. att.). Sākotnēji pārbaudījām dažādus aizvietotājus vinilsulfona **4** benzola *orto*, *meta* un *para* pozīcijās. Novērojām, ka labu reaģētspēju uzrādīja ne tikai ar halogēniem (F, Br, Cl) aizvietoti substrāti **4b**–**d**, bet arī ar elektronus akceptorām grupām (CN, Ms, CF_3, CO_2Me, NO_2). Aizvietoti arilvinilsulfoni **4e**–**i** benzola *meta* un *orto* pozīcijās veidoja vēlamos produktus *trans*-**5e**–**i** ar vidējiem līdz labiem iznākumiem (42–75 %) un vidēju diastereoselektivitāti (*d.r.* = 2,9:1–3,9:1).

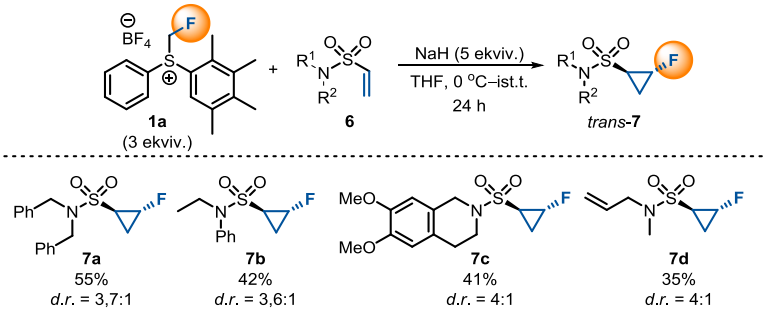


4. att. Fluorciklopropanēšanas reakcijas substrātu **4** klāsta pētījumi.

Reakciju gaitā pārbaudījām arī substrātus ar elektrondonorām grupām (OMe, Me) *meta*, *orto* un *para* pozīcijās (**4j**–**l**), kā arī benzil-, naftil- un cikloheksil- aizvietotus vinilsulfonus (**4d**,**m**,**n**), kā rezultātā ieguvām fluorciklopropilsulfonus **5d**,**m**,**n** ar vidējiem un labiem iznākumiem (47–72 %).

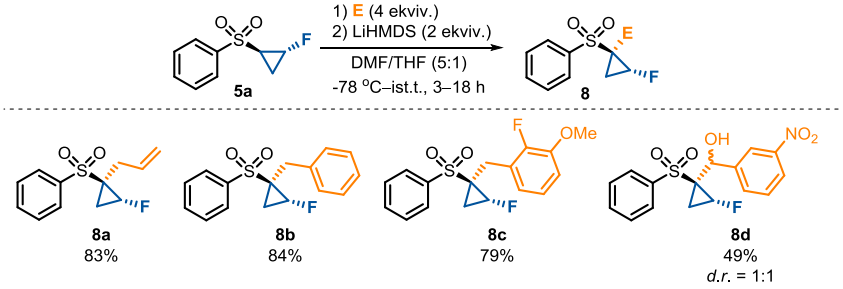
Reakcijas apstākļiem pakļāvām arī heterociklus saturošus vinilsulfonus **4o**–**r**, iegūstot monofluorētus ciklopropānus **5o**–**r** ar zemiem līdz labiem iznākumiem (26–70 %). Interesanti, ka reakcijā ar benztiazola atvasinājumu **4r**, produktu **5r** izdalījām ar zemu iznākumu (26 %), toties augstāko novēroto diastereoselektivitāti (*d. r.* = >21:1). Augstu selektivitāti (*d.r.* = 7,8:1) novērojām arī metiltiazola atvasinājuma **5o** gadījumā. Jāuzsver, ka reakcijas apstākļos zemāko diastereoselektivitāti (*d. r.* = 2,4:1) novērojām tieši reakcijā ar alifātisku substrātu – cikloheksilvinilsulfonu **4n**.

Lai pārliecinātos, vai pēc izstrādātās metodes iespējams iegūt arī fluorciklopropilsulfonamīdus **7**, mēs veicām fluorciklopropanēšanas reakcijas ar *N*-aizvietotiem vinilsulfonamīdiem **6a**–**d** (5. att.). Lai panāktu pilnu izejvielas **6** konversiju, bija nepieciešams palielināt pievienotā diarilfluormetilsulfonija sāls **1a**, kā arī NaH daudzumu. Atbilstošos fluorciklopropilsulfonamīdus ieguvām **7a**–**d** ar zemiem līdz vidējiem iznākumiem (35–55%) un ar vidēju diastereoselektivitāti. Mūsuprāt, zemāki produktu *trans*-**7** iznākumi ir skaidrojami ar vinilsulfonamīdu **6** zemāku reaģētspēju ar sēra ilīdu un izveidojušos produktu **7** daļēju sadalīšanos bāzes pārākumā reakcijas maisījumā.



5. att. Vinilsulfonamīdu **6** klāsta pētījumi monofluorciklopropilsulfonamīdu *trans*–**7** iegūšanai.

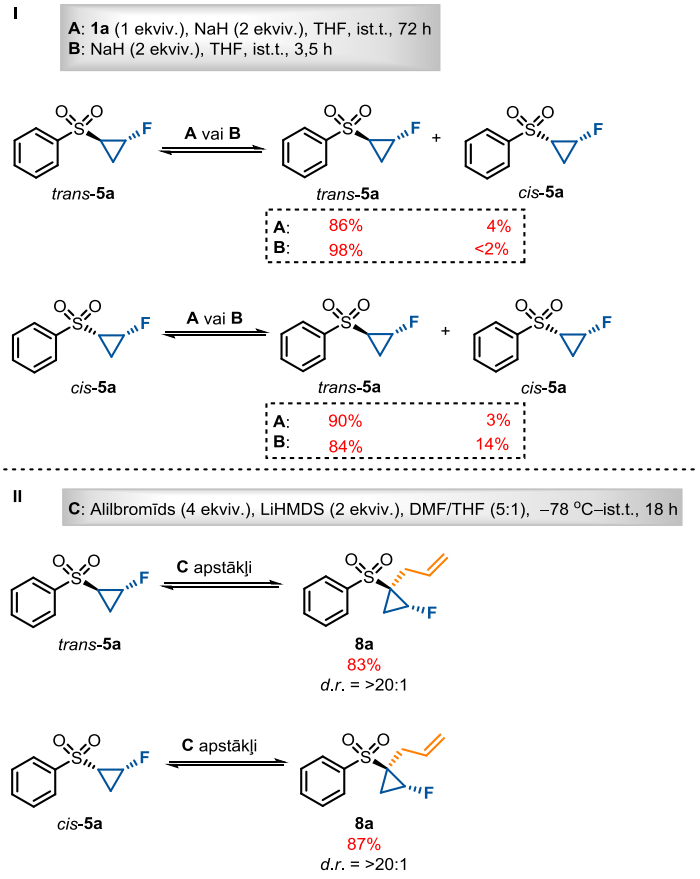
Nākamais pētījuma solis ietvēra fluorciklopropilsulfona *trans*-**5a** tālāku funkcionalizēšanas iespēju izpēti. Šim nolūkam vēlējāmies pārliecināties, vai ir iespējams realizēt alkilēšanas reakciju bāzes klātienē ar tādiem elektrofīliem kā alil- un benzilbromīdiem, kā arī ar benzaldehīda atvasinājumu (6. att.). Reakcijās ar alil- un benzilbromīdiem LiHMDS klātbūtnē ieguvām vēlamos fluorciklopropilsulfona atvasinājumus **8a**–**c** ar ļoti labiem iznākumiem (79–84 %). Jāpiebilst, ka izveidojušies produkti **8a**–**d** saglabāja savu relatīvo konfigurāciju, proti, fluora atoma *trans* novietojumu attiecībā pret sulfonilgrupu, kas liecina par termodinamiski stabilākā karbanjona veidošanos. Savukārt reakcijā ar benzaldehīdu ieguvām spirta grupu saturošu fluorciklopropilsulfona atvasinājumu **8d** kā hromatogrāfiski neatdalāmu divu diastereomēru maisījumu (49 %, *d. r.* = 1:1) teorētiski iespējamo četru vietā.



6. att. Fluorciklopropilsulfona **5a** atvasināšanas reakcijas ar elektrofīliem.

Lai iegūtu padziļinātāku priekšstatu par fluorciklopropanēšanas norises mehānismu un diastereoselektivitātes cēloņiem, realizējām kontroleksperimentus ar izolētiem *cis*-**5a** un *trans*-**5a** produktiem (7. att., **I**). Gan pakļaujot katru no diastereomēriem reakcijas apstākļiem, gan arī tos vienkārši maisot NaH klātienē THF vidē, novērojām pamatdiastereomēra – *trans*-**5a** veidošanos neatkarīgi no izmantotās izejvielas sākotnējās konfigurācijas. Šie rezultāti apliecina termodinamiski stabilākā anjona veidošanos, kas novirza līdzvaru *trans*-**5a** izomēra veidošanās virzienā.

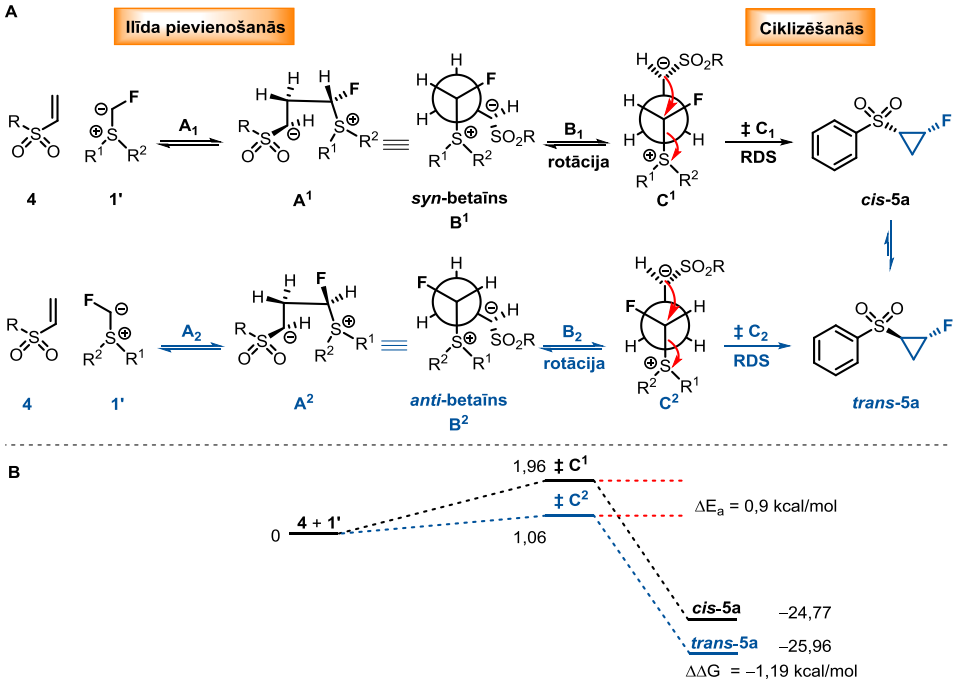
Pakļaujot abus diastereomērus identiskiem alkilēšanas apstākļiem **C** ar alilbromīdu (7. att., **II**), novērojām selektīvu *trans*-produkta **8a** veidošanos (*d. r.* = >20:1) ar augstiem reakcijas iznākumumiem (83–87 %), kas apstiprināja izvirzīto pieņēmumu par termodinamiski stabilākā karbanjona veidošanos sulfona **5a** deprotonēšanas rezultātā.



7. att. Fluorciklopropilsulfonu **5a** kontroleksperimenti.

Lai analizētu fluorciklopropanēšanas mehānismu un labāk izprastu reakcijas diastereoselektivitātes cēloņus, izmantojām datormodelēšanas programatūras kvantu ķīmisko aprēķinu metodes. Saskaņā ar mehānismu (8. att., **A**) *in situ* ģenerētam sēra ilīdam **1'** pievienojoties Maikla akceptoram **4**, veidojas *syn*- un *anti*-betaīni $\mathbf{B^1}$ un $\mathbf{B^2}$, kas pēc C–C saites rotācijas un sulfīda eleminēšanas nākamajā solī, veido attiecīgos ciklizēšanās produktus – fluorciklopropānus *cis*-**5a** un *trans*-**5a**. Reakcijas mehānisma pārejas stāvokļu enerģiju datoraprēķini liecina (R = 3-MePh-, $R^1 = R^2$ = Me-, 8. att., **B**), ka betaīnu $\mathbf{C^1}$ un $\mathbf{C^2}$ ciklizēšanās, kurā sulfīds kalpo par aizejošo grupu, ir šīs pārvērtības ātrumu noteicošā stadija RDS. Aprēķinātā pārejas stāvokļa enerģijas barjera produkta *cis*-**5a** veidošanai ir par 0,9 kcal/mol augstāka nekā *trans*-**5a** gadījumā. Šī enerģijas starpība (ΔEa = 0,9) nosaka sākotnējo kinētisko diastereomēru sadalījumu, kas atbilst diastereomēru attiecībai *d. r.* = 2,56:1, ko iespējams varētu skaidrot ar stēriskiem traucējumiem starp fluora atomu un sulfonilgrupu.

Jāatzīmē, ka galaprodukts *trans*-**5a** ir arī par –1,19 kcal/mol termodinamiski stabilāks nekā *cis*-**5a**, kas reakcijas gaitā bāzes klātbūtnē termodinamiskā līdzsvara ceļā veido *trans*-produktu. Datoraprēķinos iegūtie dati apstiprina kontroleksperimentos novēroto *cis*-**5a** izomerizēšanos par *trans*-**5a** NaH klātbūtnē (7. att., **I**).



8. att. Vinilsulfonu **4** fluorciklopropanēšanas mehānisms.

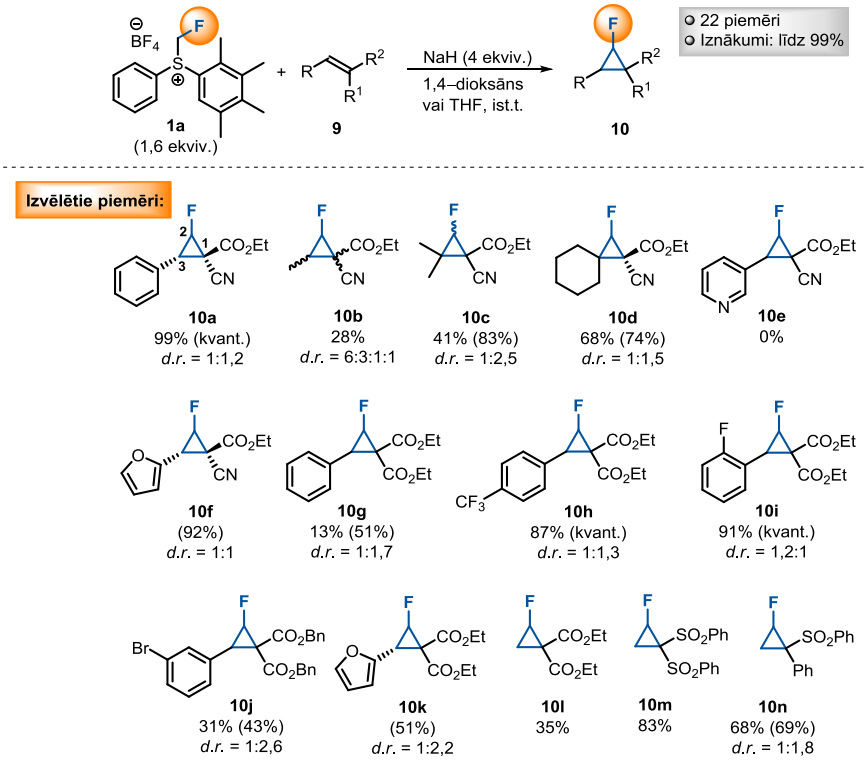
2. Dubultaktivētu alkēnu fluorciklopropanēšana Korija–Čaikovska reakcijas apstākļos

Mūsu grupā iepriekš veiktie pētījumi par fluormetilēngrupas pārnesi Korija–Čaikovska epoksidēšanas reakcijas apstākļos ar aldehīdiem un ketoniem,[16] kā arī izstrādātā metodoloģija reakcijās ar vinilsulfoniem un vinilsulfonamīdiem[18] iedrošināja turpināt pētījumus šajā virzienā. Nākamais uzdevums bija noskaidrot uz sēra ilīdiem balstītas fluormetilēngrupas pārneses potenciālu un ierobežojumus, tādējādi tika pārbaudīts plašāks Maikla akceptoru klāsts fluorciklopropanēšanas reakcijā.[19]

Lai gūtu priekšstatu par piemērotākajiem reakcijas apstākļiem dubultaktivētu alkēnu **9** gadījumā, kā modeļsubstrātu izvēlējāmies etilbenzilidēncianoesteri **9a**. Reakcijas apstākļu optimizēšanas gaitā tika noskaidrots, ka veiksmīgai reakcijas norisei nepieciešams sauss 1,4-dioksāns, 1,6 ekviv. sulfonija sāls **1a**, 4 ekviv. NaH, ist. t., argona atmosfēra.

Uzsākot substrātu **9** klāsta pētījumus (9. att.), sākotnēji pārbaudījām cianoesteru atvasinājumus (**9a**–**f**) un ieguvām atbilstošos fluorciklopropānus **10a**–**f** kā diastereomēru maisījumu ar zemiem līdz izciliem iznākumiem (15–99 %).

Saskaņā ar mūsu novērojumiem arilatvasinātu cianoesteru **9** fluorciklopropanēšana noritēja ar cianogrupas un arilgrupas relatīvās *cis*-konfigurācijas saglabāšanos (C_1, C_3) produktā **10**, kā rezultātā attiecīgi fluorciklopropāns **10a** veidojās kā 2 diastereomēru maisījums no teorētiski četriem iespējamajiem.



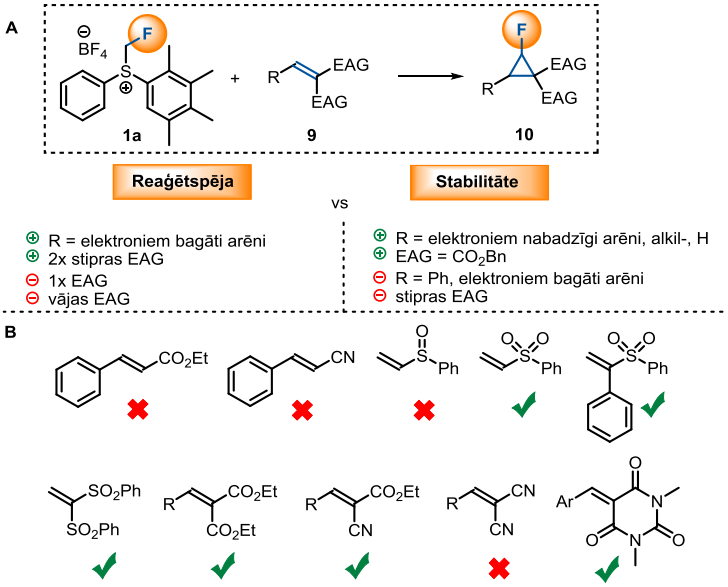
9. att. Dubultaktivētu alkēnu fluorciklopropanēšana.

Piemēram, metilaizvietota fluorciklopropāna **10b** gadījumā novērojām zemu reakcijas iznākumu (28 %), kā arī zemu selektivitāti, veidojoties triju izomēru maisījumam. Savukārt pārvērtībās ar dialkilaizvietota cianoesteru atvasinājumiem **9c**,**d** ieguvām dimetil- un cikloheksilidēnaizvietotus fluorciklopropānus **10c**,**d** ar vidējiem līdz labiem izdalītajiem iznākumiem (41–68 %).

Interesanti, ka, pakļaujot reakcijas apstākļiem piridīn-3-il- aizvietotu substrātu **9e**, vēlamais produkts **10e** neveidojās, bet atguvām izejvielu. Kaut gan furanilcianoestera **9f** gadījumā vēlamais produkts **10f** veidojās ar teicamu KMR iznākumu (92 %), attīrīšanas procesā produkts **10f** pilnībā sadalījās.

Turpmākie substrātu klāsta pētījumi parādīja, ka fluormetilēngrupas pārnesi iespējams realizēt ar arilidēn- un heteroarilidēnmalonāta atvasinājumiem **9**, veidojot vēlamos produktus **10** kā diastereomēru maisījumu ar zemiem līdz ļoti augstiem iznākumiem (13–91 %). Interesanti, ka reakcijā ar benzilidēnmalonāta atvasinājumu **9g** izveidojies produkts **10g** reakcijas apstākļos nebija stabils, kā rezultātā izdalītais iznākums bija zems (13 %), lai gan ievadot alkēna benzola gredzenā elektronus atvelkošas funkcionālās grupas (NO_2, CN, CF_3), kā arī halogēnus (F, Br) produkti veidojās ar vidējiem līdz teicamiem izdalītajiem iznākumiem (31–91 %), toties ar zemu un vidēju diastereoselektivitāti. Furanilgrupu saturošs fluorciklopropāns **10k**, līdzīgi kā furanilcianoestera **9f** gadījumā nebija hromatogrāfiski izdalāms nestabilitātes dēļ. Pētot β-neaizvietotu dubultaktivētu alkēnu **9l**–**n** reaģētspēju, mēs konstatējām stabilu fluorciklopropānu **10l**–**n** veidošanos ar vidējiem līdz ļoti labiem iznākumiem (35–83 %).

Apkopojot eksperimentos gūto informāciju par mono- un diaktivētiem Maikla akceptoriem (10. att.), konstatējām, ka olefīnu reaģētspēja tiešā veidā korelē ar to elektrofilitāti. Tādi monoaktivēti alkēni, piemēram, kanēļskābes etilesteris un kanēļskābes nitrils nav piemēroti substrāti fluormetilēngrupas pārneses reakcijām Korija–Čaikovska apstākļos. Arī vinilsulfoksīds šajos apstākļos vispār nereaģē, toties ar sulfonilgrupu monoaizvietoti alkēni jau ir pietiekami spēcīgi Maikla akceptori veiksmīgai reakcijas norisei.



10. att. Aktivētu olefīnu **9** fluorciklopropanēšanas ierobežojumi.

Runājot par dubultaktivētiem arilidēn- un alkilidēnatvasinājumiem – cianoacetātiem un malonātiem – stipras EA grupas veicina produkta veidošanos, lai gan dažreiz novērojama nestabilu produktu veidošanās. Toties stipras ED grupas arilgredzenā lielākoties veicina fluorciklopropāna atvasinājumu sadalīšanos reakcijas apstākļos, ko varētu skaidrot ar elektrondonējošu grupu veicinātu ciklopropāna cikla atvēršanos.[20]

3. Fluormetilēngrupas pārneses reaģenta optimizēšana

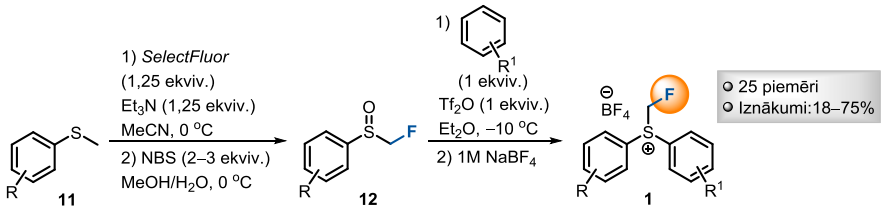
Lai gan 2,3,4,5-tetrametilfenilaizvietotā sulfonija sāls **1a** efektivitāti veiksmīgi demonstrējām reakcijās ar tādiem Maikla akceptoriem kā aldehīdiem, ketoniem, vinilsulfoniem, vinilsulfonamīdiem, kā arī ar dubultaktivētiem alkēniem ar labiem rezultātiem. Jāatzīmē, ka reaģenta **1a** sintēzei raksturīgas augstas izmaksas 1,2,3,4-tetrametilbenzola ierobežotās pieejamības dēļ, kā arī zema atomekonomija.[21]

Līdz šim literatūrā nebija aprakstīta aizvietotāju ietekme uz fluormetilsulfonija sāļu **1** reaģētspēju, stabilitāti, kā arī kristāliskumu. Saskaņā ar esošo literatūru, vairums sulfonija sāļu **1** pastāv kā viskozas eļļas, kas būtiski apgrūtina reaģenta praktisko pielietojumu.[22] Kopsakarības, kas varētu veicināt ērti lietojama, kristāliska reaģenta izstrādi, tajā pašā laikā nezaudējot tā efektivitāti nebija zināmas. Mūsu interesēs bija struktūras optimizēšanas ceļā atklāt efektīvu sulfonija sāls struktūru, samazinot tā sintēzei nepieciešamos resursus un

uzlabojot tā reaģētspēju jau attīstītajās fluormetilēngrupas pārneses reakcijās zemas reaģētspējas substrātiem.

Fluormerilēngrupas pārneses reakcijās ar nitroalkēniem, pielietojot klasisko *S*-monofluormetil-*S*-fenil-2,3,4,5-tetramtilfenilsulfonija tetrafluorborātu (**1a**), mēs novērojām zemu reaģētspēju un niecīgus reakciju iznākumus, tādējādi secinājām, ka sāls **1a** nav piemērotākais reaģents nitrofluorciklopropānu iegūšanai. Mūsu uzdevums bija izpētīt, vai iepējams ar fluormetilsulfonija sāls **1** aizejošās grupas struktūras modifikāciju palīdzību veicināt efektīvāku fluorciklopropanēšanas reakcijas norisi.[23]

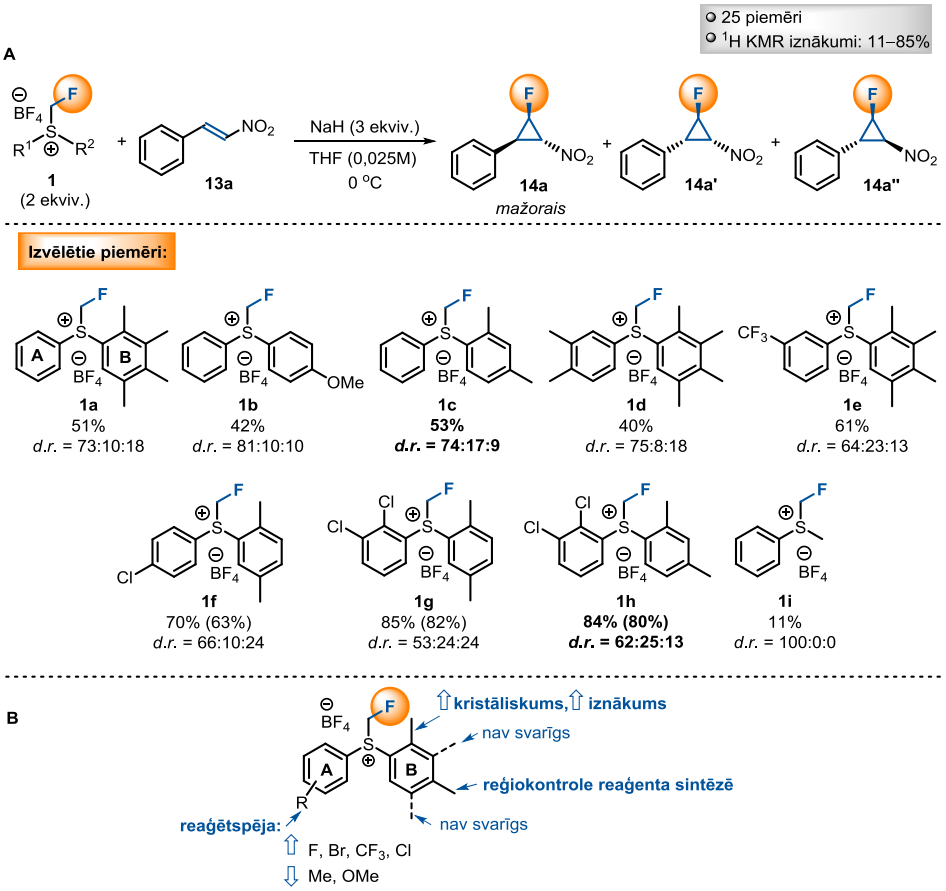
Pētījumu gaitā izdevās izstrādāt efektīvāku fluormetilsulfonija sāls **1** sintēzes ceļu (11. att.), aizvietojot bīstamu un neērti lietojamu fluorēšanas reaģentu DAST[21] ar drošāku un ērtāku elektrofīlo fluorēšans reaģentu *Selectfluor*. Uzlabotā sintēze arī ļāva krietni samazināt reakciju laikus, kā rezultātā ieguvām 25 dažādus fluormetilsulfonija sāļus **1** efektīvā četru stadiju sintēzē, sākot no tioanizola atvasinājumiem **11**.



11. att. Fluormetilsulfonija sāļu **1** sintēzes ceļš.

Kā modeļsubstrātu sulfonija sāļu **1** izpētei sākotnēji izvēlējāmies *β*-nitrostirolu (**13a**). Lai raksturotu aizvietotāju ietekmi, diarilsulfonija sāls **1** fenilgredzenus apzīmējām ar **A** un **B** (12. att., **A**).

Ievadot Me- un MeO- grupas dažādās pozīcijās sulfonija sāls **1** benzola gredzenā **B**, bet gredzenu **A** saglabājot neaizvietotu, ievērojami uzlabojumi reakcijas iznākumos, salīdzinājumā ar sākotnējo reaģentu **1a** netika novēroti. Svarīgi uzsvērt, ka lai gan *m*-ksilolu saturoša sulfonija sāls **1c** izmantošana nedeva būtisku reakcijas iznākuma paaugstināšanos (53 %, *d. r.* = 74:17:9), toties tā sintēzes izmaksas ir ievērojami zemākas nekā **1a** gadījumā. Savukārt Papildus ievadot Me- grupas benzola gredzenā **A** (**1d**), novērojām pat vēlamā produkta **14a** iznākuma samazināšanos (40 %).



12. att. Fluormetilsulfonija sāls **1** iegūšanas shēma.

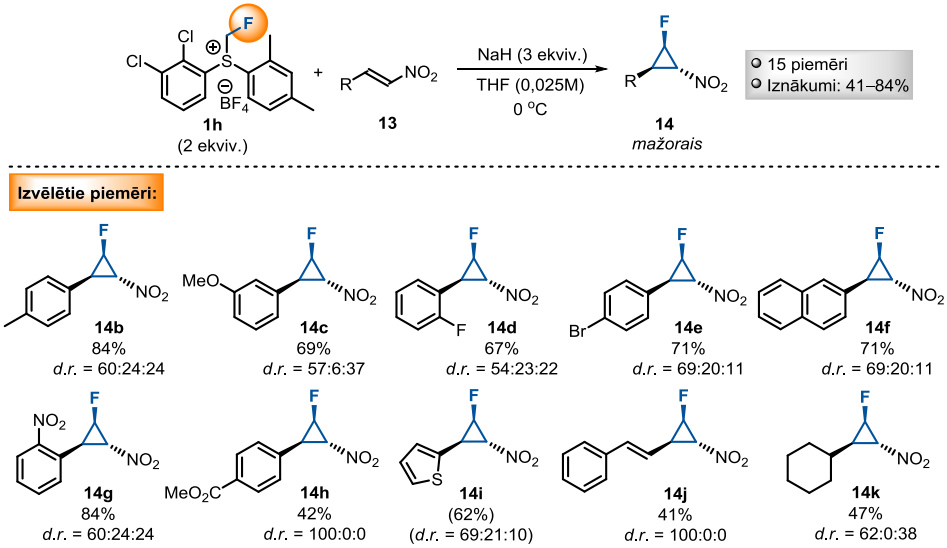
Sulfonija sāls **1** benzola gredzenā **A** ievadot halogēnaizvietotājus (Cl, Br, F) vai trifluormetilgrupu, saglabājot benzola gredzenā **B** ne vairāk kā divas Me- grupas, novērojām iznākuma paaugstināšanos līdz 70 % sulfonija sāls **1f** gadījumā. Turpinājumā, ievadot sāls benzola gredzena **A** *orto* un *meta* pozīcijās divus hlora atomus, bet gredzenā **B** samazinot metilgrupu skaitu līdz divām (**1g**,**h**), izdevās sasniegt šīs pārvērtības augtstāko kopējo iznākumu (84–85 %), bet vidēju diastereoselektivitāti.

Sulfonija sāļu reaģētspējas pētījumos noskaidrojām, ka, sulfonija sāls benzola gredzenā **A** ievadot halogēnus (F, Br, Cl) vai trifluormetilgrupu, novērojami augstāki fluorciklopropānu **14** iznākumi, savukārt ED grupas (Me, OMe) veicina produktu veidošanos ar zemākiem iznākumiem (12. att.). Sulfonija sāls **1** benzola gredzenā **B** metilgrupagrupa *orto* pozīcijā nodrošina sāls kristālisko īpašību saglabāšanos, toties Me grupa *para* pozīcijā veicina reģioselektivitāti fluormetilsulfoksīda **12** elektrofīlās aizvietošanas reakcijā (11. att.).

Interesanti, ka fluorciklopropanēšanas reakcijā ar fluormetilfenilmetilsulfonija sāli **1i** novērojām tikai mažorā diastereomēra **14a** veidošanos ar niecīgu iznākumu (11 %), kas liecina, ka minētās pārvērtības realizēšanai būtiski izmantot diarilaizvietotus fluormetilsulfonija sāļus.

Sulfonija sāls **1** struktūras optimizēšanas gaitā reaģents **1h** uzrādīja augstāko reaģētspēju, tādēļ to izmantojām turpmākajos nitroalkēnu **13** substrātu klāsta pētījumos (13. att.). Alkil-,

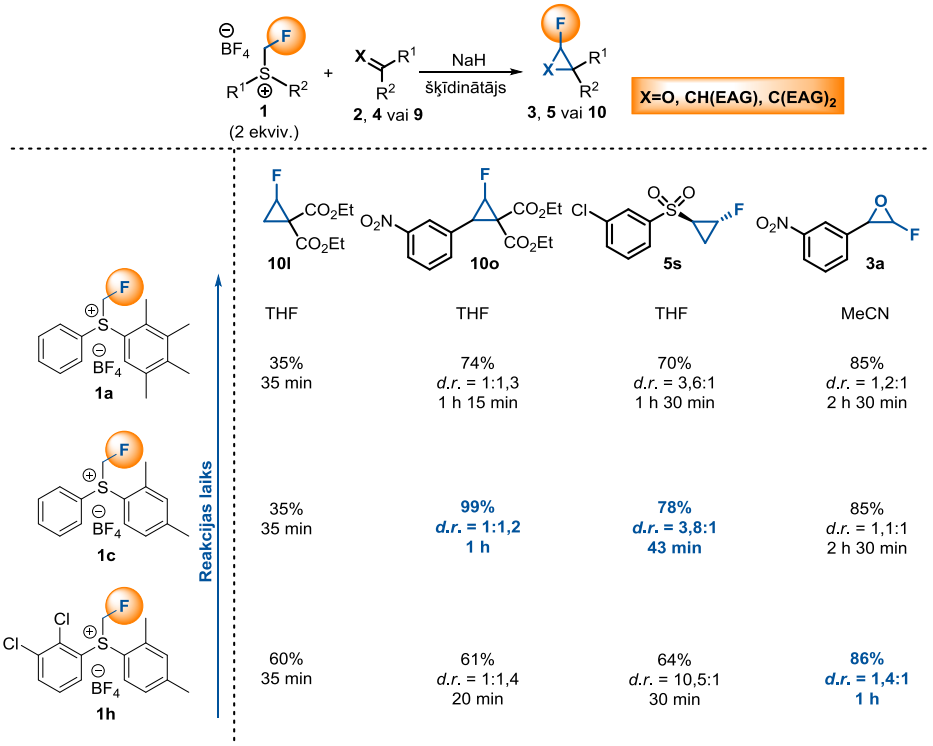
aril-, kā arī heteroarilnitrofluorciklopropānus **14b–i** ieguvām ar vidējiem līdz ļoti labiem iznākumiem (41–84 %), toties ar vidēju diastereoselektivitāti. Izstrādātie reakcijas apstākļi ir savietojami ar plašu funkcionālo grupu klāstu izejvielas **13** benzola gredzenā, piemēram, ED grupas (metil- **13b**, metoksi- **13c**), halogēni (F **13d**, Br **13e**), EA grupas (nitro- **13g**, esteri **13h**, trifluormetilgrupa) benzola gredzenā. Reakcijā ar konjugētu diēnu **13j**, vēlamais produkts **14j** veidojās selektīvi, lai gan ar vidēju iznākumu (41%).



13. att. Nitroalkēnu **13** fluorciklopropanēšanas substrātu klāsts.

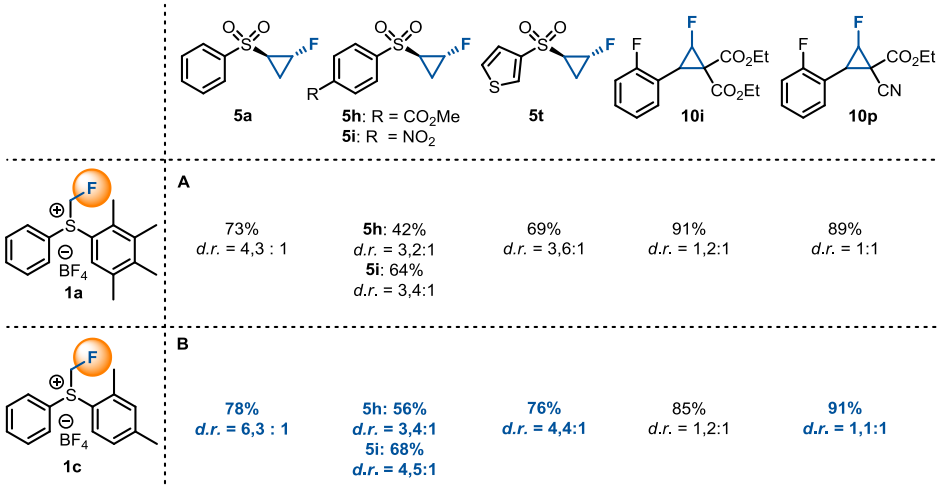
Lai salīdzinātu strukturāli uzlaboto sulfonija sāļu **1c** un **1h** reaģētspēju ar sākotnējo **1a**, mēs demonstrējām fluormetilēngrupas pārneses reakcijas ar malonāta atvasinājumiem **9l**,**o**, vinilsulfonu **4s** un ketonu **2a** (14. att.).

Reakcijā ar sulfonija sāli **1c** bija novērojami produktu **10o** un **5s** iznākumu paaugstināšanās salīdzinājumā ar klasisko sāli **1a**, toties ļoti reaģētspējīgiem substrātiem, piemēram, malonātam **9l** un aldehīdam **2a** piemērotāks izrādījās 2,3-dihlorbenzolu saturošs sulfonija sāls **1h**, kā rezultātā izdevās iegūt produktu **10l** ievērojami augstāku iznākumu (60 %), savukārt fluorepoksīdu **3a** ar nedaudz uzlabotu diastereoselektivitāti īsākā reakcijas laikā. Savukārt substrātiem, kas reaģē lēnāk (**9o**,**4s**), sāls veicināja fluorciklopropanēšanas iznākuma samazināšanos salīdzinājumā ar oriģinālo sulfonija sāli **1a**.



14. att. Sulfonija sāļu **1a**,**c**,**h** salīdzinājums reakcijās ar dažādām substrātu klasēm.

Pētījumu turpinājumā mēs pārbaudījām sulfonija sāls **1c** reaģētspēju fluorciklopropanēšanas reakcijās ar vinilsulfoniem **4a**,**h**,**i**,**t** kā arī ar arilidēnmalonātu atvasinājumiem **9i**,**p**. Šo eksperimentu rezultātā (15. att., **B**) novērojām ne tikai augstākus vēlamo produktu iznākumus (izņemot **10i** gadījumā), bet arī diastereoselektivitātes uzlabojumus.

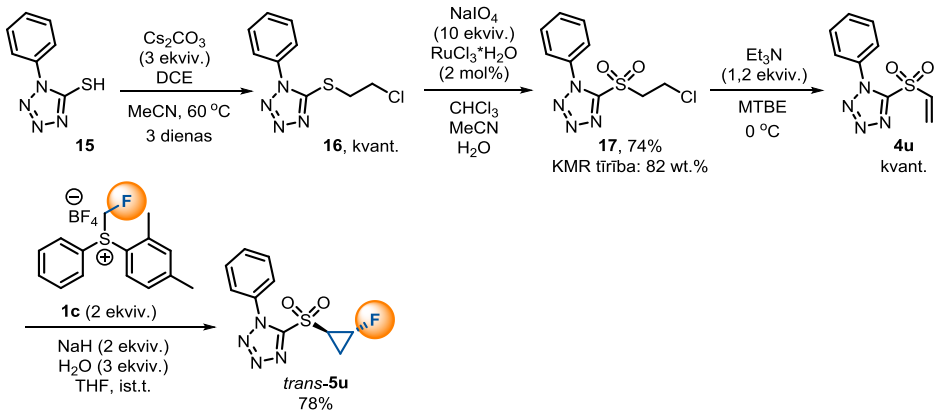


15. att. Sulfonija sāls **1c** reaģētspējas pētījumi.

4. Fluorciklopropilidēnu sintēze, izmantojot 5-(1*R**,2*R**)-2-fluorciklopropilsulfonil-1-fenil-1*H*-tetrazolu

Organiskajā sintēzē ciklopropilidēni jeb metilēnciklopropāni augstā cikla sprieguma[24] un reaģētspējas dēļ zināmi kā stratēģiski būvbloki citu vērtīgu savienojumu iegūšanai ciklopaplašināšanas un, ciklopievienošanas reakciju rezultātā.[25] Demonstrējot fluorciklopropilsulfonu **5** sintēzes metodoloģiju un realizējot to reakcijas ar dažādiem elektrofīliem, mūsu uzmanību piesaistīja sulfona **5a** reakcija ar aldehīdu, veidojoties spirta atvasinājumam **8d** (6. att.). α-Hidroksilaizvietoti sulfoni ir nozīmīgi Džūlija–Kočinska olefinēšanas[26] reakcijas starpprodukti, kas liecināja par šīs pieejas potenciālu fluorciklopropilidēnu sintēzē.

Sākotnēji mūsu uzdevums bija iegūt olefinēšanai nepieciešamo reaģentu **5u**, kas paredzēja četru sintēzes soļu procedūru – 1-fenil-1*H*-tetrazol-5-tiola **15** alkilēšanu ar 1,2-dihloretānu, iegūtā haloalkilsulfīda **16** oksidēšanu ar $NaIO_4$ katalizatora $RuCl_3{\cdot}H_2O$ klātbūtnē, bāzes veicinātu HCl eliminēšanu no sulfona **17**, tā fluorciklopropanēšanu Korija–Čaikovska reakcijas apstākļos (16. att.). Vinilsulfona **4u** iegūšanu realizējām kā vienas kolbas sintēzi, kur radās problēmas HCl eliminēšanas solī.[27] Starpprodukts **17** uzrādīja izteiktu nestabilitāti Et_3N pārākumā, tādēļ bija nepieciešama rūpīga reakcijas apstākļu piemeklēšana.



16. att. Džūlija–Kočinska olefinēšanas reaģenta **5u** sintēze.

Lai noskaidrotu, cik daudz bāzes jāpievieno starpproduktam **17** eliminēšanas stadijā, mēs veicām optimizēšanas eksperimentus ar Et_3N tādos šķīdinātājos kā DCM, Et_2O un MTBE istabas un 0 °C temperatūrā (4.1. tab.). KMR iznākumu produktam **4u** pirms un pēc hromatogrāfiskas attīrīšanas noteicām pēc mūsu izstrādātas analītiskās metodes, izmantojot nedeiterētā $CHCl_3$ atlikuma signālu kā iekšējo standartu.[27]

Par piemērotākajiem apstākļiem vinilsulfona **4u** sintēzei pieņēmām apstākļus Nr. 4, kur HCl eliminēšanas stadiju veicām ar 1,12 ekviv. Et_3N, MTBE, 0 °C 15min laikā ar izcilu iznākumu (99,5 %) un augstu vielas tīrību (97 %) (4.1 tab., Nr. 4).

Pēdējā solī mēs fluorciklopropilsulfonu *trans*-**5u** ieguvām fluorciklopropanēšanas ceļā, pielietojot optimizētas struktūras fluormetilsulfonija sāli **1c**. Rezultātā ieguvām fluorciklopropilsulfonu **5u** kā *trans*-diastereomēru ar labu iznākumu (78 %).

4.1. tabula.

Reakcijas apstākļu optimizēšana, izmantojot qKMR

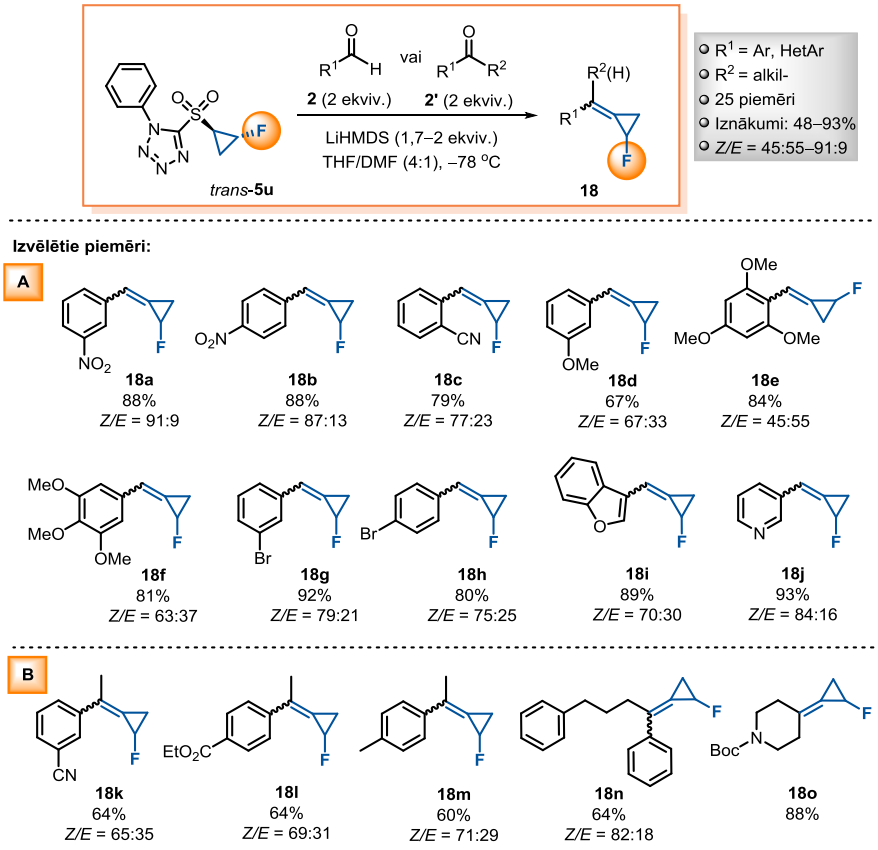
Nr.	Apstākļi	**4u** KMR iznākums, %		Noteikts ar lab. svariem, %	**4u** KMR tīrība, %
		neattīrītam	izolētam		
1	DCM, ist. t., 4 h, Et_3N (2,5 ekviv.)	4,8	–	–	–
2	Et_2O, 0 °C, 15 min, Et_3N (2,27 ekviv.)	87,0	86,4	97	89
3	Et_2O, 0 °C, 15 min, Et_3N (1,12 ekviv.)	100	97,1	103	95
4	MTBE, 0 °C, 15 min, Et_3N (1,12 ekviv.)	100	99,5	103	97

Pētījumu turpinājumā Džūlija–Kočinska olefinēšanas apstākļu optimizēšanai izvēlējāmies 3-nitrofenilbenzaldehīdu **2a** un 4-nitrobenzaldehīdu **2b** kā modeļsubstrātus.[28] Pētījuma gaitā noskaidrojām, ka optimāli reakcijas apstākļi ir: 2 ekviv. aldehīda **2** vai ketona **2'**, 1,7–2 ekviv. LiHMDS (1 M THF), -78 °C, argona atmosfērā, sausā THF/DMF (4:1). Svarīgi atzīmēt, ka reakcijas apstākļos produkti **18** veidojās kā hromatogrāfiski neatdalāms *E*- un *Z*-izomēru maisījums, lai gan kā pamatizomērs veidojās tieši *Z*-fluorciklopropilidēns. Substrātu klāsta pētījumu ietvaros (17. att.) mēs parādījām *orto*-, *meta*-, *para*-aizvietotu benzaldehīdu **2a–j** fluorciklopropilidēšanu, kā rezultātā iegūtie produkti **18a–j** veidojās ar ļoti labiem līdz teicamiem iznākumiem (17. att., **A**).

Z-Selektivitāte ir skaidrojama ar to, ka, visticamāk, reakcija norit caur ciklisku pārejas stāvokli, kurā fluora atoms ir vērsts prom no aldehīda arilaizvietotāja, tādējādi samazinot destabilizējošas fluora un arilgrupas π-sistēmas dipolu-dipolu mijiedarbības.

Interesanti, ka, piemēram, substrāta **2e** gadījumā, *E*/*Z*-selektivitāte krietni pazeminājās, kas, iespējams, liecina par stēriski apjomīga arilaizvietotāja ietekmi uz reakcijas norisi. Iespējams, ka stēriski apjomīgu aizvietotāju gadījumā reakcija noris caur atvērtu pārejas stāvokli, pazeminot selektivitāti.

Reakcijās ar ketoniem **2'** bija novērojami zemāki fluorciklopropilidēnu **18k–o** iznākumi (17. att., **B**), ko varētu skaidrot ar substrātu **2'** karbonilgrupas elektrofilitātes samazināšanos, kā arī ar iespējamām aldolām blakusreakcijām bāzes pārākumā. Arī alfiātisku ketonu **2'** pārvērtības veicām ar augstiem iznākumiem.



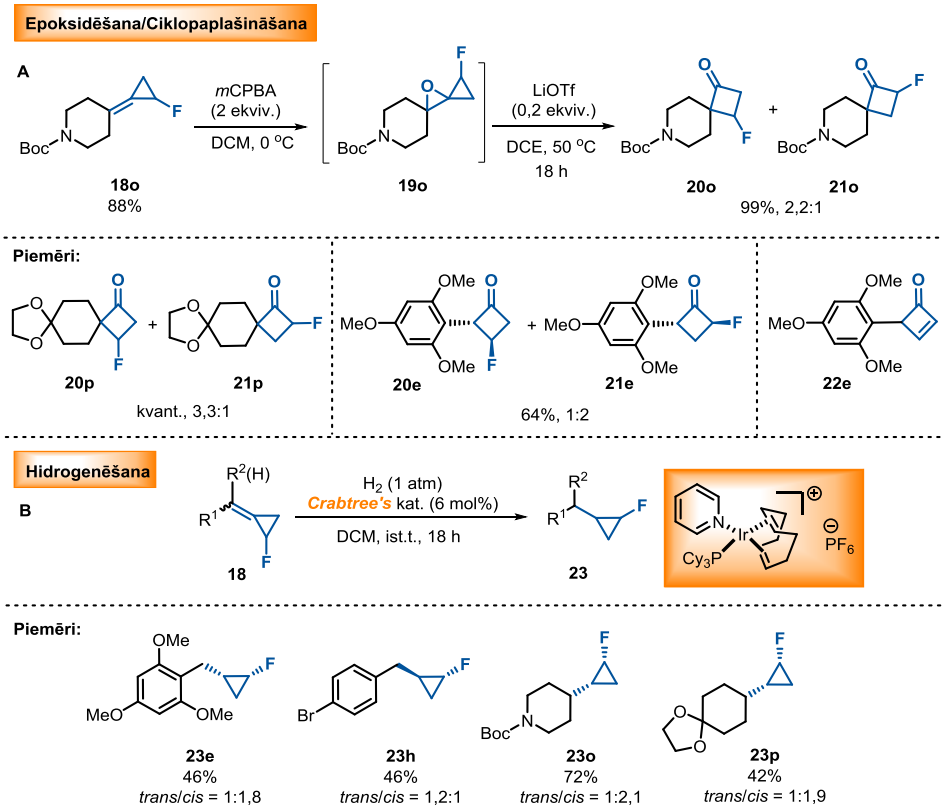
17. att. Džūlija–Kočinska olefinēšanas substrātu klāsts.

Pēc substrātu klāsta pētījumiem vēlējāmies pārbaudīt iegūto fluorciklopropilidēnu reaģētspēju dažādās pārvērtībās (18. att.), tāpēc pētījām fluorciklopropilidēnu **18e**,**o**,**p** epoksidēšanas/ciklopaplašināšanas reakcijas (18. att., **A**).[29]

Substrātu **18o**,**p** divu soļu reakcijā ar *m*CPBA un katalītisku daudzumu Luisa skābes LiOTf, ieguvām α- un β-pozīcijā fluoraizvietotus ciklobutanonus **20o**, **21o** un **20p**, **21p** ar izcilu iznākumu, toties kā neatdalāmu reģioizomēru maisījumu, kur kā mažorais reģioizomērs bija tieši **20o** un **20p**. Produktu hromatogrāfiska attīrīšana šajā gadījumā nebija iespējama, jo savienojumi nebija stabili uz silikagēla. Produktu **20e** un **21e** gadījumā papildus Luisa skābes pievienošana ciklizēšanas ierosināšanai nebija nepieciešama. Fluorciklobutanonus **20e** un **21e** izdalījām ar vidēju iznākumu (64 %), papildus tam novērojams, ka šajā reakcijā ciklobutanons **21e** veidojās kā pamatizomērs, toties otrs reģioizomērs **20e** laikā gaitā sadalījās, eliminējot fluorūdeņradi un veidojot ciklobutēnona blakusproduktu **22e**.

Saskaņā ar literatūru monofluorciklopropilidēnu hidrogenēšana nav pētīta,[30] jo, iespējams, skarbos hidrogenēšanas apstākļos norit cikla atvēršanās un fluora atoma eliminēšana. Savukārt, ciklopropilidēnu hidrogenēšanu visbiežāk veic, izmantojot Pd/C, Reneja-Ni, Ir katalīzi.[31] Lai gan pārbaudījām vairākus hidrogenēšanas apstākļus, kā piemēram, Vilkinsona katalizatoru, Pd/C kā arī citus, novērojām neidentificētu defluorētu produktu veidošanos. Noskaidrojām, ka *Crabtree's* katalizators nodrošina maigu un efektīvu fluorciklopropilidēnu

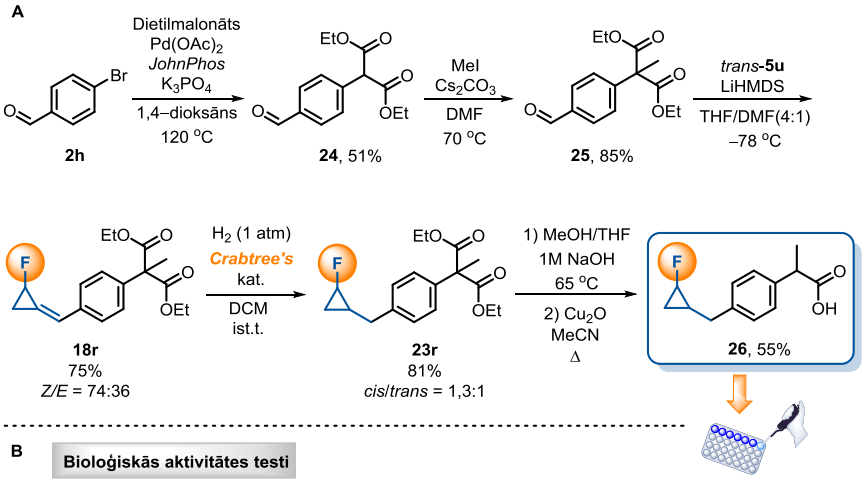
hidrogenēšanu, kā rezultātā ieguvām fluorciklopropānus **23** (19. att., **B**) ar vidējiem un labiem iznākumiem (42–72 %), pamatā veidojoties *cis*-produktam.



18. att. Fluorciklopropilidēnu **18** atvasināšanas iespējas.

Lai parādītu izstrādātās fluorciklopropilidēšanas metodoloģijas izmantošanas potenciālu medicīnas ķīmijā, īstenojām labi zināmas zāļu vielas – ibuprofēna[32] – monofluorciklopropilanaloga **26** sintēzi (19. att., **A**) un veicām bioloģiskās aktivitātes testus uz enzīmiem COX-1 un COX-2 (19. att., **B**). Fluorciklopropilgrupu saturoša ibuprofēna atvasinājuma **26** sintēzi realizējām piecās stadijās, sākot no 4-brombenzaldehīda **2h**. $Pd(OAc)_2$ katalizētā šķērssametināšanas reakcijā savienojums **2h** ar dietilmalonātu veidoja starpproduktu **24**. Malonāta atvasinājuma **24** alkilēšanas reakcijā ar metiljodīdu ieguvām Džūlija–Kočinska olefinēšanai nepieciešamo dietilmalonātu **25**.

Fluorciklopropilidēšanas reakcijā ieguvām nepieciešamo produktu **18r** ar labu iznākumu (75 %) un labu *E*/*Z* attiecību. Hidrogenēšanas rezultātā ieguvām attiecīgo fluorciklopropāna atvasinājumu **23r** produktu – *cis*- un *trans*-izomēru maisījumu – ar ļoti labu iznākumu. Nākamajā solī hidrolizējām malonāta atvasinājumu **23r** un dekarboksilējām starpsavienojumu, lai iegūtu vēlamo zāļu vielas analogu **26** ar vidēju iznākumu (55 %). Hirālās preparatīvās hromatogrāfijas ceļā izdevās attīrīt 3 frakcijas, kurām tika noteikta enzīmu COX-1 un COX-2 inhibīcijas[33] spēju (19. att., **B**).



	Ibuprofen	*(rac)-trans*-**26**	*(+)-cis*-**26***	*(-)-cis*-**26***
COX-1	IC_{50} = 134 μM	**IC_{50} = 25 μM**	**IC_{50} = >500 μM**	**IC_{50} = >500 μM**
COX-2	IC_{50} = 443 μM	**IC_{50} = 1071 μM**	**IC_{50} = 681 μM**	**IC_{50} = >2000 μM**
***S*, c-1/c-2**	0,30	0,023	n/a	n/a

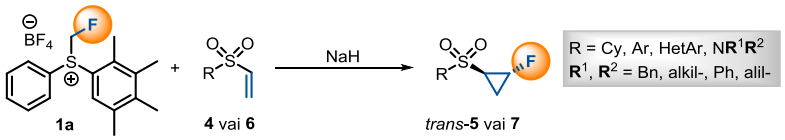
*Relatīvā konfigurācija

19. att. **A** Fluorciklopropilgrupu saturoša ibuprofēna analoga **26** sintēze. **B** Savienojuma **26** bioloģiskās aktivitātes noteikšana.

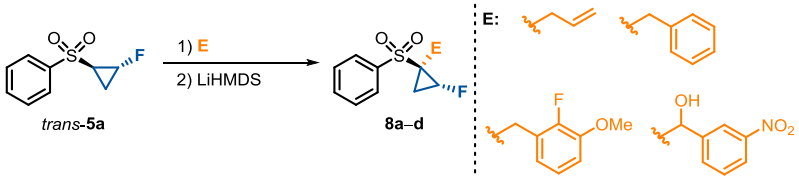
Pārbaudot bioloģisko aktivitāti, (*rac*)-*trans*-**26** uzrādīja augstāku inhibīcijas selektivitāti attiecībā uz COX-1 salīdzinājumā ar ibuprofēnu. Toties (+)-*cis*-**26** gadījumā savienojums uzrādīja zemāku aktivitāti nekā oriģinālā zāļu viela, taču augstāku selektivitāti uz COX-2 nekā uz COX-1, kas ir vēlamais mērķproteīns.

SECINĀJUMI

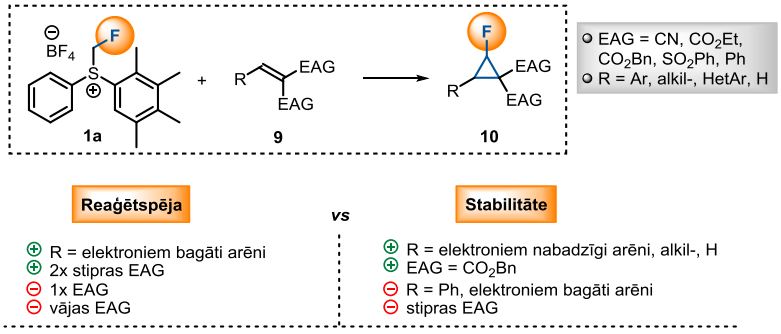
1) Aril-, heteroaril- un cikloheksilaizvietotu vinilsulfonu **4** un *N*-alkil-, fenilaizvietotu vinilsulfonamīdu **6** fluorciklopropanēšanas reakcijā ar diarilfluormetilsulfonija tetrafluorborātu **1a** iespējams iegūt *trans*-fluorciklopropilsulfonus **5** un *trans*-sulfonamīdus **7** ar labiem iznākumiem un vidēju diastereoselektivitāti.



2) Fluorciklopropāna **5a** funkcionalizēšanas reakcijās ar elektrofīliem novērojama *trans*-fluorciklopropānu **8** veidošanās, kas liecina par termodinamiski stabilākā karbanjona veidošanos deprotonēšanas solī neatkarīgi no tā, vai reakciju realizē ar *cis*- vai *trans*-izejvielu.

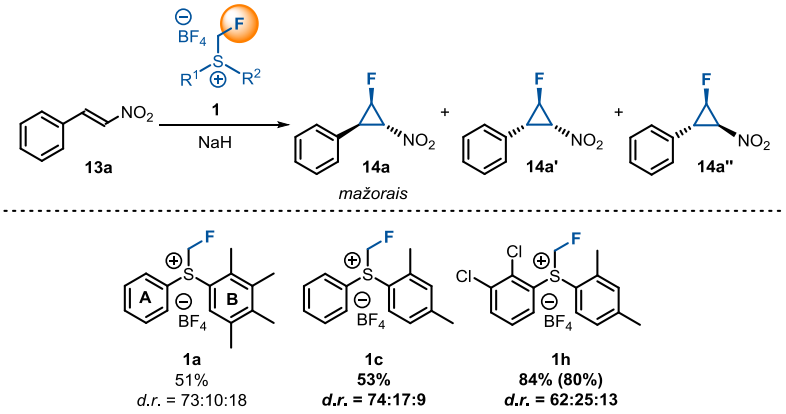


3) Fluormetilēngrupas pārneses reakcijās ar dubultaktivētiem alkēniem **9** novērojami šīs reakcijas ierobežojumi, substrātu reaģētspējai korelējot ar to elektrofilitāti. Elektroniem nabadzīgiem aizvietotājiem un/vai stiprām elektronatvelkošām funkcionālām grupām aizvietoti alkēni veicina reakcijas norisi, toties elektronu donoras grupas un elektroniem bagātas sistēmas samazina iegūto fluorciklopropānu stabilitāti, veicina to sadalīšanos attīrīšanas laikā.



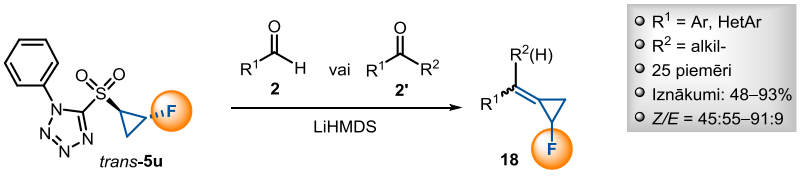
4) Halogēnaizvietotāji fluormetilsulfonija sāls arilgredzenā paaugstina tā reaģētspēju reakcijā ar nitroalkēniem, toties 2,4-dimetilaizvietota arilsistēma nodrošina sāls kristālisku agregātstāvokli. Augstākos reakcijas iznākumus un diastereoselektivitāti nitroalkēnu fluorciklopropanēšanas reakcijā iespējams panākt, izmantojot **1h**. Lai gan iegūto

fluornitrociklopropānu **14** iznākumi bija zemāki, toties sintēzes izmaksu ziņā visizdevīgāk būtu izmantot **1c**.

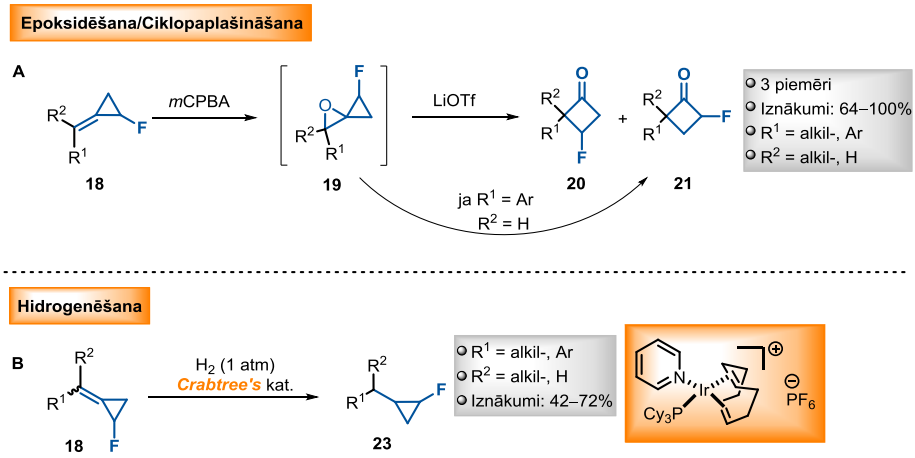


5) Fluormetilēngrupas pārneses reakcijās ar vinilsulfoniem **4** augstākus fluorciklopropānu **5** atvasinājumu iznākumus, kā arī diastereoselektivitāti nodrošināja ar *m*-ksilolu aizvietots fluormetilsulfonija sāls **1c**, savukārt arilidēnmalonātu gadījumā viennozīmīgu tendenci, izmantojot uzlabotas struktūras sulfonija sāļus **1c** vai **1h** nenovērojām. Reakcijā ar 3-nitrobenzaldehīdu **2a** būtiskas priekšrocības, izmantojot modificētas struktūras sulfonija sāļus, nebija novērojamas.

6) Džūlija–Kočinska olefinēšanā, kā reaģentu izmantojot *N*-feniltetrazolu saturošu fluorciklopropilsulfonu **5u**, no aldehīdiem **2** un ketoniem **2'** iespējams iegūt fluorciklopropilidēnus **18** ar labiem iznākumiem, pamatā veidojoties tieši *Z*-izomēram.



7) Fluorciklopropilidēnu **18** hidrogenēšanas reakcijās *Crabtree's* katalizatora klātbūtnē iespējams iegūt attiecīgos fluorciklopropānu **23** ar zemiem līdz vidējiem iznākumiem kā *cis* un *trans*-izomēru maisījumu. Savukārt, fluorciklopropilidēnu **18** reakcijā ar *m*CPBA un kat. daudzumu LiOTf epoksidēšanas/ciklopaplašināšanas rezultātā veidojas fluorciklobutanona atvasinājumi **20** un **21** ar vidējiem līdz izciliem rezultātiem kā divu reģioizomēru maisījums.



8) Fluorciklopropilidēšanas metodoloģiju iespējams ērti izmantot zāļu vielas ibuprofēna fluorciklopropilsaturoša analoga **26** sintēzei. Bioloģiskās aktivitātes testos uz enzīmiem COX-1 un COX-2 iespējams novērot būtiskas fluorētā zāļu vielas analoga **26** stereoizomēru selektivitātes atšķirības salīdzinājumā ar oriģinālo zāļu vielu.

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

To be granted the scientific degree of Doctor of Science (Ph. D.), the present Doctoral Thesis has been submitted for the defence at the open meeting of RTU Promotion Council on May 24, 2023 at the Faculty of Materials Science and Applied Chemistry of Riga Technical University, 3 Paula Valdena Street, Room 272.

OFFICIAL REVIEWERS

Asoc. Professor Dr. chem. Kaspars Traskovskis
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Asist. professor D. Phil. Miriam O'Duill
University of Nottingham, United Kingdom

DECLARATION OF ACADEMIC INTEGRITY

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

Renāte Melngaile …….(signature)
Date …….

The Doctoral Thesis has been prepared as a thematically united collection of scientific publications. It consists of Summary, 5 scientific publications, 1 review, and 1 article in the encyclopedia of chemical reagents. Publications and book chapters have been written in English. The total number of pages is 683, including electronic data.

GENERAL OVERVIEW OF THE THESIS

Introduction

The bioisosteric replacement of a hydrogen atom with a fluorine atom in the molecular structure of drug molecules often improves their physicochemical properties – metabolic stability, bioavailability, as well as binding to enzymes.[1] According to the US Food and Drug Administration data, more than 20 % of registered medicinal substances contain at least one fluorine atom, demonstrating the importance of the fluorine atom in ensuring biological activity.[2] The high electronegativity of fluorine, the small size of the atom, as well as the strength of the C–F bond and the ability to form hydrogen bonds distinguish fluorine from other halogens and their characteristic transformations, hence using classical halogenation methods to introduce fluorine-containing building blocks into a molecule are often not effective.[3]

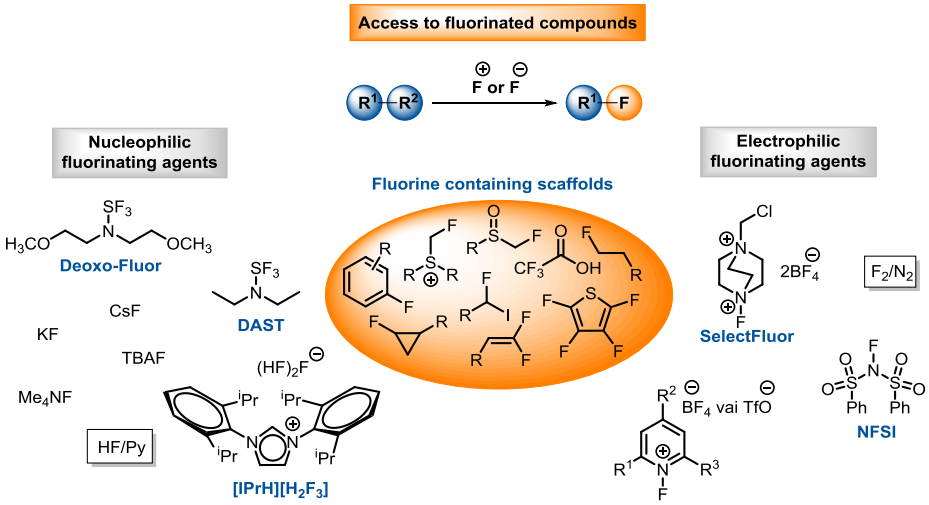


Fig. 1. Most commonly used reagents for C F bond formation.

The development of safe and environmentally friendly reagents for the introduction of fluorine into organic compounds is an important challenge and significant research direction in organic chemistry.[4]

The fluorine gas F_2, due to its aggressive reactivity, low selectivity, significant safety concerns, as well as the need for special laboratory equipment, is not widely used in organic synthesis laboratory conditions.[5] On the other hand, hydrated fluoride ion has low nucleophilicity, and obtaining anhydrous fluoride ion is difficult due to its inherent hygroscopic properties. In contrast, hydrogen fluoride (HF) possesses high toxicity. To avoid direct application of F_2 or HF in laboratory conditions, both nucleophilic[6] and electrophilic[7] fluorination reagents have been developed for selective C-F bond formation (Fig. 1).[8]

In the literature, special attention has been devoted to the development of monofluorinated building blocks, which can be explained by the difficult methods of introducing one fluorine atom and the lack of appropriate reagents.[9]

The simplest C-F-containing fragment is a fluoromethylene group[10] that can be introduced into the target molecule using monofluoromethylene group transfer reagents, which are mainly volatile, environmentally concerning freon-type compounds $CHFX_2$ for the generation of fluorocarbenes[11], as well as for fluorocarbenoids (Figure 2).[12] One of the most successful examples of direct transfer of monofluoromethylene group is fluorinated sulfoximine, but its application possibilities have been demonstrated only on Weinreb amides.[13]

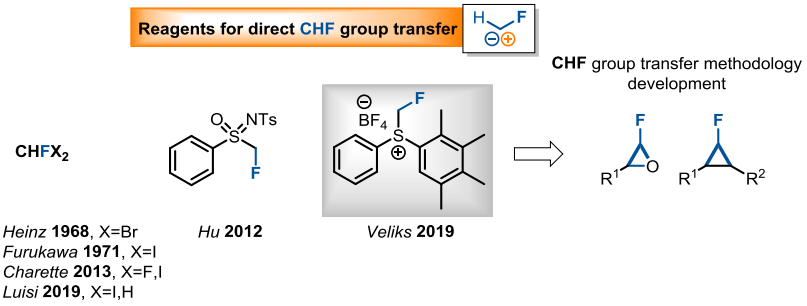


Fig. 2. Fluoromethylene group transfer reagents known in literature.

Sulfur ylides[14] serve as synthetic equivalents of carbene, which are successfully used in organic chemistry for the synthesis of the smallest carbocycle – cyclopropane – under the Corey–Chaykovsky reaction conditions.[15] In our view, fluoromethylene group transfer reagents based on sulfur ylides have great potential for obtaining monofluorinated compounds. Our group demonstrated for the first time the synthetic application of sulfur fluoromethylide, which has been successfully generated from a diarylfluoromethylsulfonium salt. When the ylide intermediate reacted with aldehydes and ketones, monofluorinated epoxides were successfully formed.[16] In this way, a new potential reaction mode was presented for the diarylfluoromethylsulfonium reagent – transfer of the fluoromethylene group. Until now, the only known application of this type of reagent was electrophilic fluoromethylation, which has been originally developed by the Olah and Prakash group.[17]

When examining the literature on the use of fluoromethylsulfonium salts, at the beginning of our study there was a lack of information on the potential of this compound to generate *in situ* sulfur ylide, which we believed to be the key to selective transfer of the monofluoromethylene group, yielding little studied fluorine containing compounds.

Aims and objectives

The aim of the doctoral thesis is the development of new, effective and practical fluoromethylene group transfer reagents, as well as the development of new methods for the synthesis of fluorinated building blocks.

For the implementation of the goal, two tasks were defined:

1) explore synthetic applications of fluoromethylsulfonium based reagents for synthesis of monofluorinated compounds;

2) synthesize poorly known monofluorinated building blocks/fragments, and study their further synthetic application, as well as methodology demonstration for the synthesis of fluorinated analogues of potentially important drug molecules.

Scientific novelty and main results

As a result of the doctoral thesis, the following results were achieved:

1) organic synthesis methodology for the transfer of the monofluoromethylene group to activated alkenes using diarylfluoromethylsulfonium salt under the Corey–Chaykovsky reaction conditions:

a) diastereoselective fluorocyclopropanation of vinylsulfones and vinylsulfonamides;

b) fluorocyclopropanation of double activated Michael acceptors – arylidene malonates, arylidene cyanoesters, sulfones, and the reaction limitation studies;

c) fluoromethylsulfonium reagent structure optimization studies using nitroalkene and other Michael acceptor fluorocyclopropanation as a model reaction.

2) organic synthesis methodology for obtaining monofluorocyclopropylidenes from aldehydes and ketones under the Julia–Kocienski reaction conditions using 5-(*R**,2*R**)-2-fluorocyclopropylsulfonyl-1-phenyl-1*H*-tetrazole as a reagent;

3) demonstration of the synthesis of a fluorine-containing analogue of the drug molecule ibuprofen, with fluorocyclopropane serving as an isostere of the isopropyl group.

Structure of the thesis

The doctoral thesis were prepared as a thematically unified set of scientific publications on the development of fluoromethylene group transfer reagents and methodology in reactions with various Michael acceptors, as well as on the further application of the obtained compounds – fluorocyclopropanes for the discovery of other important fluorine containing compounds.

Publications and approbation of the thesis

The main results of the doctoral thesis were summarized in 5 scientific publications, 1 review and 1 article in the encyclopedia of chemical reagents. Results of the research were presented at 6 scientific conferences.

Scientific publications:

1) **Melngaile, R.**; Sperga, A.; Baldridge, K. K.; Veliks, J. Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts. *Org. Lett*. **2019**, *21* (17), 7174–7178. DOI: 10.1021/acs.orglett.9b02867.

2) Kazia, A.; **Melngaile, R.**; Mishnev, A.; Veliks, J. Johnson–Corey–Chaykovsky Fluorocyclopropanation of Double Activated Alkenes: Scope and Limitations. *Org. Biomol. Chem.* **2020**, *18*, 1384–1388. DOI: 10.1039/C9OB02712B

3) Sperga, A.; **Melngaile, R.**; Kazia, A.; Belyakov, S.; Veliks, J. Monofluoromethylsulfonium Reagents for Fluoromethylene Transfer Chemistry. *J. Org. Chem.* **2021**, *86* (4), 3196–3212. DOI: 10.1021/acs.joc.0c02561.

4) Muhamadejev, R.; **Melngaile, R.**; Paegle, P.; Zibarte, I.; Petrova, M.; Jaudzems, K.; Veliks J. Residual Solvent Signal of $CDCl_3$ as a *q*NMR Internal Standard for Application in Organic Chemistry Laboratory. *J. Org. Chem.* **2021**, *86* (5), 3890–3896. DOI: 10.1021/acs.joc.0c02744.

5) **Melngaile, R.**; Veliks, J. Synthetic Applications of Monofluoromethylsulfonium Salts. *Synthesis* **2021**, *53* (24), 4549–4558. DOI: 10.1055/a-1548-8240.

6) **Melngaile, R.**; Veliks, J. Sulfonium, (Fluoromethyl)phenyl(2,3,4,5-tetramethylphenyl)-, Tetrafluoroborate(1-) (1:1)[1]. *Encycl. Reagents Org. Synth.* **2021**, 1–4. DOI: 10.1002/047084289X.rn02379.

7) **Melngaile, R.**; Videja, M.; Kuka, J.; Kinens, A.; Zacs, Dz.; Veliks, J. Synthetic Access to Fluorocyclopropylidenes. *Org. Lett.* **2023**, 25 (*13*), 2280–2284.

Results of the thesis were presented at the following conferences:

1) Melngaile, R. Fluoromethylene Transfer from Diarylfluoromethylsulfonium Salts. *20th Tetrahedron Symposium*, Bangkok, Thailand, 18–21 June **2019**.

2) Melngaile, R. Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts. *11th Paul Walden Symposium*, Riga, Latvia, 19–20 September **2019**.

3) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *12th Paul Walden Symposium.* Online, 28–29 October **2021**.

4) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *Balticum Organicum Syntheticum*, Vilnius, Lithuania, 3–6 July **2022**.

5) Melngaile, R. Synthesis of Fluorocyclopropylidenes via Julia–Kocienski Olefination. *2nd Drug Discovery Conference* 2022, Riga, Latvia, 22–24 September **2022**.

6) Melngaile, R. Recent Advances in Fluoromethylene Transfer. *2nd LIOS conference*, Riga, Latvia, 29–30 November **2022**.

MAIN RESULTS OF THE THESIS

1. Diastereoselective monofluorocyclopropanation of vinyl sulfones with a fluoromethyldiarylsulfonium salt

At the start of this study, no examples for the synthesis of monofluorocyclopropanes via the Corey–Chaykovsky reaction could be found in the literature. Our group's successfully developed fluoromethylene transfer reaction with aldehydes and ketones **2** exploiting diarylfluoromethylsulfonium salt **1a** (Fig. 3, **A**) encouraged us to extend this approach to access fluorocyclopropanes.[16] We managed to demonstrate an effective approach that afforded new monofluorinated building blocks – fluorocyclopropyl sulfones – under Corey–Chaykovsky reaction conditions in a reaction between a strong Michael acceptor – vinyl sulfone and a base generated sulfur fluoromethylide.[18]

Initially, with phenyl vinyl sulfone **4a** as a model substrate, we carried out the reaction in deuterated chloroform, which allowed us to identify by NMR the formation of the desired product **5a** (Fig. 3, **B**) in a low yield (26 %) and satisfactory diastereoselectivity (*d. r.* = 6:1). *Trans*-isomer **5a** was formed as the major reaction product.

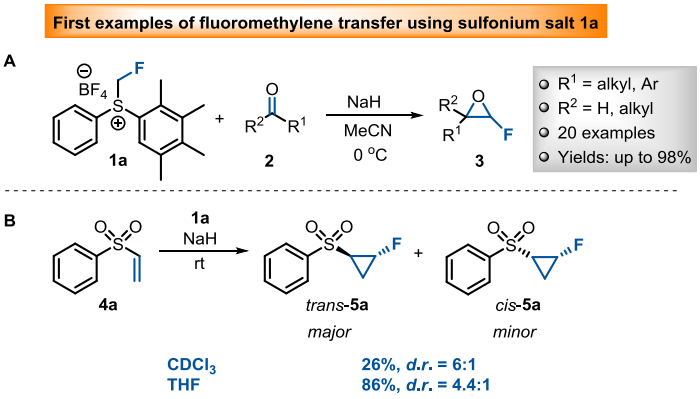


Fig. 3. Fluoromethylene transfer in Corey–Chaykovsky fluorocyclopropanation.

Screening of solvents, temperature, solution concentration, as well as the ratio of the reaction components allowed us to find conditions that gave the highest yield (86 %, *d. r.* = 4.4:1), therefore we further carried out substrate scope studies with vinyl sulfones **4** under the following conditions: **1a** (2 equiv), 60% NaH (4 equiv), THF (0.1 M), argon atmosphere, room temperature. It should be noted that, the reaction diastereoselectivity was determined for a crude reaction mixture, but the yield is shown for chromatographically purified major product *trans*-**5** diastereomer.

While studying the scope of substrate **4**, we verified the compatibility of various functional groups with the developed reaction conditions (Fig. 4). Initially, we tested various aryl substituents at the *ortho*, *meta*, and *para* positions of arylvinylsulfones **4**. We observed that not only halogen (F, Br, Cl) substituents **4b**–**d**, but also substrates containing electron acceptor groups (CN, Ms, CF_3, CO_2Me, NO_2) showed good reactivity. Substituted aryl vinyl sulfones **4e**–**i** at the *meta* and *ortho* positions afforded the desired products *trans*-**5e**–**i** in moderate to good yields (42–75 %) and moderate diastereoselectivities (*d. r.* = 2.9:1–3.9:1).

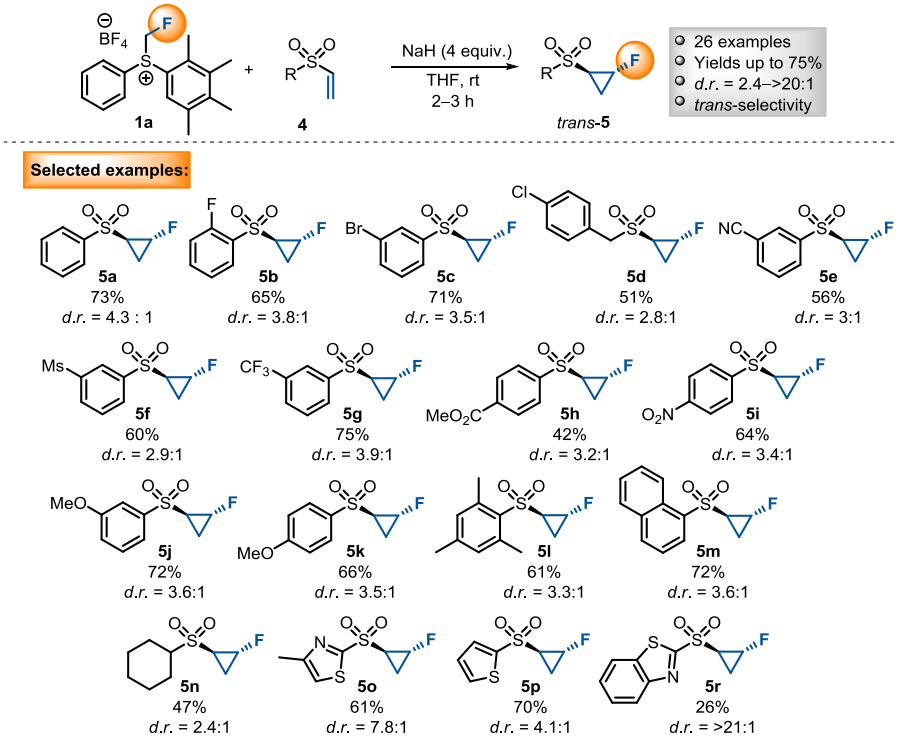


Fig. 4. Substrate **4** scope studies of fluorocyclopropanation reaction.

During the scope studies, we also tested substrates with electron donating groups (OMe, Me) in *meta*, *ortho*, and *para* positions (**4j**–**l**), as well as benzyl-, naphthyl- and cyclohexyl-substituted vinyl sulfones (**4d**,**m**,**n**), as a result of which we obtained fluorocyclopropyl sulfones **5d**,**m**,**n** with moderate to good yields (47–72 %).

We also subjected heterocycle containing vinyl sulfones **4o**–**r** to the reaction conditions and obtained monofluorinated cyclopropanes **5o**–**r** in low to good yields (26–70 %). Interestingly, in the reaction with the benzthiazole derivative **4r**, the product **5r** was isolated with a low yield (26 %), but the highest observed diastereoselectivity (*d. r.* = >21:1). High diastereoselectivity (*d. r.* = 7.8:1) was also observed in the case of methylthiazole derivative **4o**. It should be emphasized that under these reaction conditions, the lowest diastereoselectivity (*d. r.* = 2.4:1) was observed in the reaction with an aliphatic substrate – cyclohexyl vinyl sulfone **4n**.

To verify whether the developed method is also suitable for obtaining fluorocyclopropylsulfonamides **7**, we performed fluorocyclopropanation reactions with *N*-substituted vinyl sulfonamides **6a**–**d** (Fig. 5). To achieve full conversion of starting material **6**, it was necessary to increase the amount of diarylfluoromethyl sulfonium salt **1a** as well as NaH. As a result of the transformations, we obtained monofluorinated cyclopropylsulfonamides **7a**–**d** in low to moderate yields (35–55 %) and with moderate diastereoselectivities. In our opinion, the decreased yields of products *trans*-**7** could be explained by the lower reactivity of vinyl sulfonamides **6** with sulfur ylide and partial degradation of the formed products **7** in presence of excess base in the reaction mixture.

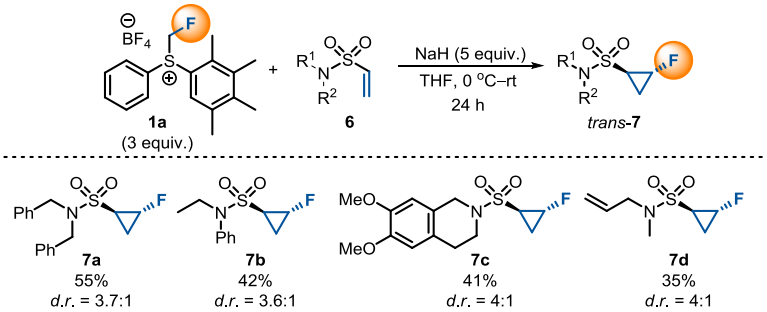


Fig. 5. Vinyl sulfonamide **6** scope studies for the preparation of monofluorocyclopropyl-sulfonamides *trans*-**7**.

The next step in this study involved further functionalization of the fluorocyclopropylsulfone *trans*-**5a**. For this purpose, we opted to verify whether it is possible to carry out alkylation reactions in presence of base with electrophiles such as allyl and benzyl bromides, as well as with a benzaldehyde derivative (Fig. 6). In reactions with allyl and benzyl bromides in the presence of LiHMDS we obtained the desired fluorocyclopropylsulfone derivatives **8a**–**c** in very good yields (79–84 %). It should be noted that the formed products **8a**–**d** kept their relative configuration, namely, the *trans* position of the fluorine atom in relation to the sulfone group, which indicates the formation of the thermodynamically most stable carbanion. However, in the reaction with benzaldehyde **2a**, we obtained hydroxy-containing fluorocyclopropylsulfone derivative **8d** as a chromatographically inseparable mixture of two diastereomers (49 %, *d. r.* = 1:1) instead of the theoretically 4 possible isomers.

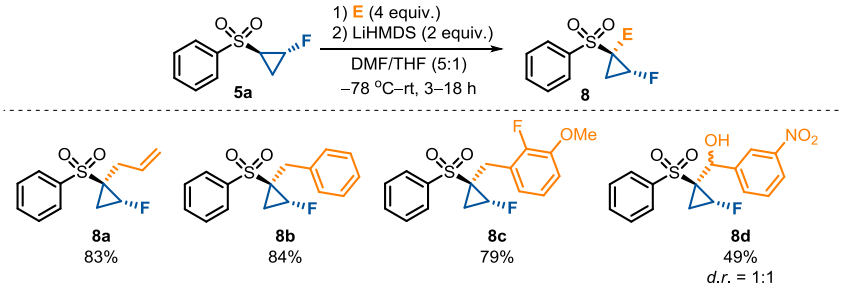


Fig. 6. Functionalization reaction of fluorocyclopropylsulfone **5a** with electrophiles.

In order to gain deeper understanding of the fluorocyclopropanation mechanism and the causes of diastereoselectivity, we performed control experiments with isolated *cis*-**5a** and *trans*-**5a** products (Fig. 7, **I**). By exposing each of the diastereomers to the reaction conditions, and also by simply stirring them in the presence of NaH in THF medium, we observed the formation of the main diastereomer – *trans*-**5a**, regardless of the initial configuration of the substrate used. These results confirm the formation of the thermodynamically most stable anion, which shifts the equilibrium towards the formation of the *trans*-**5a** isomer.

By subjecting both diastereomers to identical alkylation conditions **C** with allyl bromide (Fig. 7, **II**), we observed the selective formation of *trans*-product **8a** (*d. r.* = >20:1) with high

reaction yields (83–87 %), which confirmed the hypothesis of formation of the thermodynamically most stable carbanion as a result of deprotonation of sulfone **5a**.

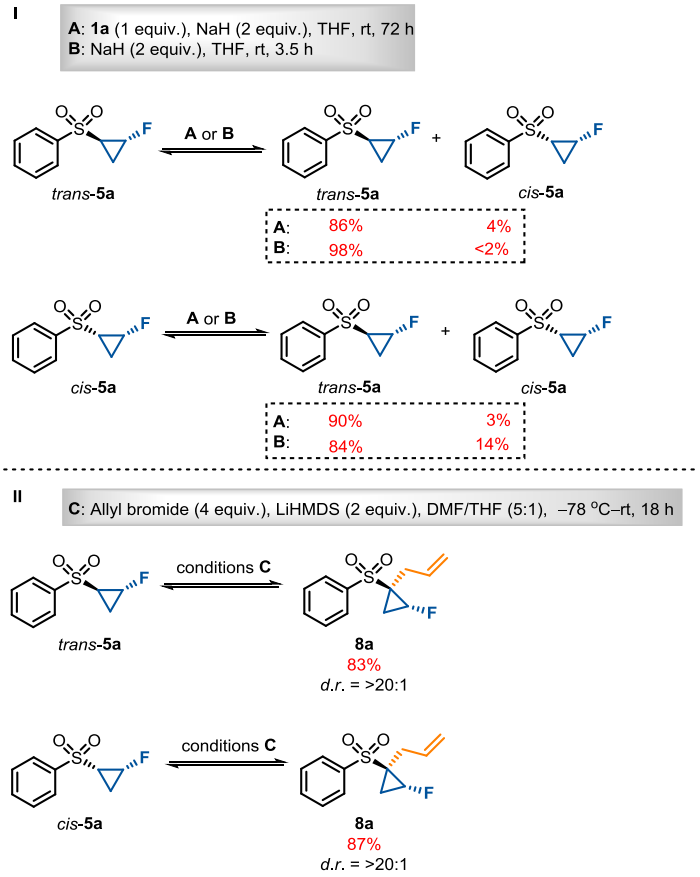


Fig. 7. Control experiments of fluorocyclopropyl sulfones **5a**.

In order to analyze the mechanism of fluorocyclopropanation and to better understand the causes of the reactions diastereoselectivity, we performed quantum chemical calculations. According to the mechanism (Fig. 8, **A**), when in situ generated sulfur ylide **1'** adds to Michael acceptor **4**, *syn*- and *anti*-betaines $\mathbf{B^1}$ and $\mathbf{B^2}$ are formed, which after C–C bond rotation and sulfide elimination in the next step, form the corresponding cyclization products – fluorocyclopropanes *cis*-**5a** and *trans*-**5a**. DFT calculations for the transition state energies of the reaction mechanism (R = 3-MePh, $R^1 = R^2$ = Me, Fig. 8, **B**) show that the $\mathbf{C^1}$ and $\mathbf{C^2}$ cyclization of betaines, in which sulfide serves as the leaving group, is the rate-determining step (RDS) of this transformation. The calculated transition state energy barrier for the formation of the product *cis*-**5a** is 0.9 kcal/mol higher than for *trans*-**5a**. This energy difference ($\Delta E_a = 0.9$) determines the initial kinetic distribution of diastereomers, which corresponds to the ratio of diastereomers *d*. *r* = 2.56:1, that could be explained by the steric hindrance between the fluorine atom and the sulfone group.

It should be noted that the final product *trans*-**5a** is thermodynamically more stable by –1.19 kcal/mol than the *cis*-**5a**, which during the reaction transforms into a *trans*-product in the

presence of a base through thermodynamic equilibrium. The obtained data in computer calculations confirm the isomerization of *cis*-**5a** to *trans*-**5a** in the presence of NaH observed in control experiments (Fig. 7, **I**).

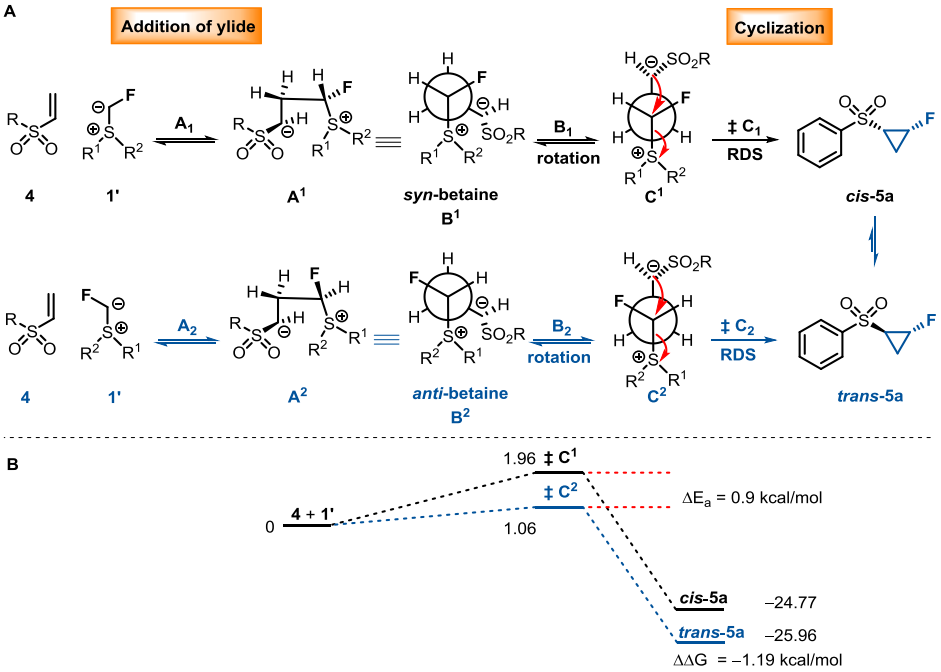


Fig. 8. Mechanism of fluorocyclopropanation of vinyl sulfones **4**.

2. Fluorocyclopropanation of double activated alkenes under Corey–Chaykovsky conditions

Our group's previous studies on the transfer of the fluoromethylene group under Corey–Chaykovsky epoxidation reaction conditions with aldehydes and ketones[16], as well as the developed methodology in reactions with vinyl sulfones, vinyl sulfonamides[18] encouraged further research in this direction. The next task was to clarify the potential and limitations of the developed sulfur ylide based fluoromethylene transfer, thus it was decided to test a wider range of Michael acceptors in the fluorocyclopropanation reaction.[19]

In order to find the most suitable reaction conditions for double activated alkenes **9**, we used ethylbenzylidene cyanoester **9a** as a model substrate. During the optimization of the reaction conditions, it was found that dry 1,4-dioxane, 2 equiv. of sulfonium salt **1a** using 4 equiv of NaH at room temperature under argon atmosphere gave the best results.

Initiating studies of the substrate scope (Fig. 9), we at first screened cyanoester derivatives (**9a**–**f**) and obtained the corresponding fluorocyclopropanes **10** as a diastereomer mixture (**10a**–**f**) in low to excellent yields (15–99 %).

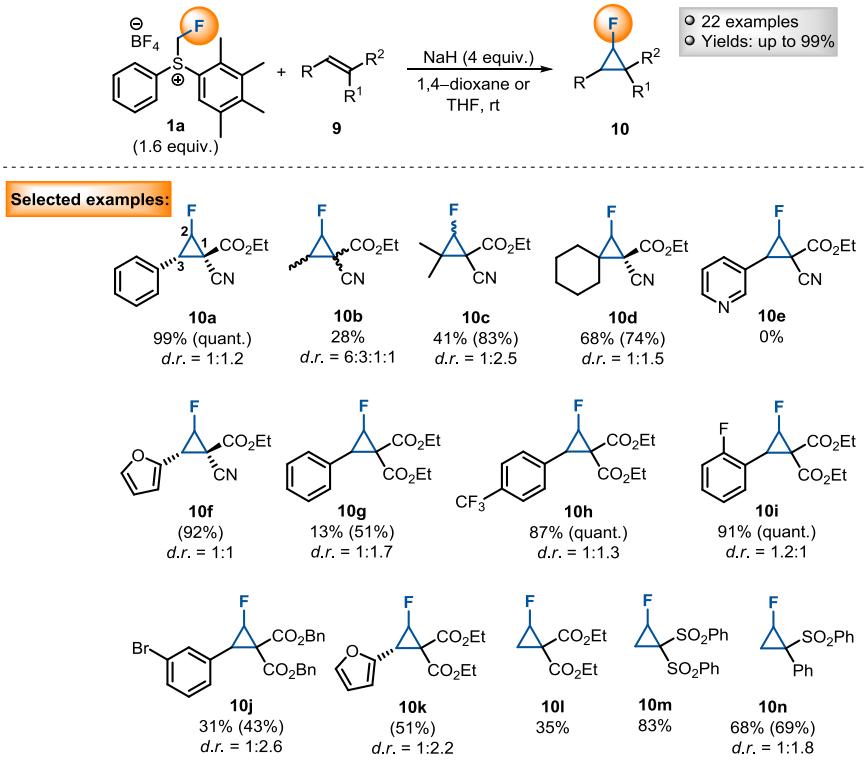


Fig. 9. Fluorocyclopropanation of double activated alkenes.

According to our observations, the fluorocyclopropanation of aryl-derived cyanoesters **9** proceeded with the preservation of the relative *cis*-configuration (C_1, C_3) of the cyano group and the aryl group in product **10**, resulting in the formation of fluorocyclopropane **10a** as a mixture of 2 diastereomers instead of the theoretically 4 possible ones.

For example, in the case of methyl substituted fluorocyclopropane **10b**, we observed a low reaction yield (28 %), as well as low selectivity where a mixture of four isomers was formed. On the other hand, the transformations with dialkyl substituted cyanoester derivatives **9c**,**d**, resulted in dimethyl- and cyclohexylidene substituted fluorocyclopropanes **10c**,**d** with moderate to good isolated yields (41–68 %).

Interestingly, under the reaction conditions 3-pyridinyl-substituted substrate **9e** did not form the desired product **10e**, however the starting material was recovered. Although in the case of furanyl cyanoester **9f** the desired product **10f** was formed in excellent NMR yield (92 %), the product **10f** completely decomposed during the purification process.

Further substrate scope studies revealed that transfer of the fluoromethylene group can be realized with arylidene- and heteroarylidene malonate derivatives **9**, forming the desired products **10** as a mixture of diastereomers in low to very good yields (13–91 %). Furthermore, the product **10g** formed in the reaction with the benzylidene malonate derivative **9g** was not stable under the reaction conditions, as a result of which the isolated yield was low (13 %). Although the introduction of electron withdrawing functional groups (NO_2, CN, CF_3) as well as halogens (F, Br) resulted in products in moderate to excellent isolated yields (31–91%), but with low to moderate diastereoselectivities. When furanyl malonate **9k** was subjected to the

reaction conditions, similarly as in the case of furanyl cyanoester **9f**, the corresponding fluorocyclopropane **10k** turned out to be unstable, consequently, its chromatographic isolation was not successful. Investigating the reactivity of *β*-unsubstituted doubly activated alkenes **9l**–**n**, we observed formation of stable fluorocyclopropanes **10l**–**n** in moderate to very good yields (35–83 %).

Summarizing the results obtained in the experiments with mono- and deactivated Michael acceptors (Fig. 10), we found that the reactivity of olefins is directly correlated with their electrophilicity. Monoactivated alkenes such as cinnamic acid ethyl ester and cinnamic acid nitriles are not suitable substrates for fluoromethylene group transfer reactions under Corey–Chaykovsky conditions. Vinyl sulfoxide does not react at all under these conditions, but alkenes monosubstituted with sulfonyl groups are already strong enough Michael acceptors for a successful reaction.

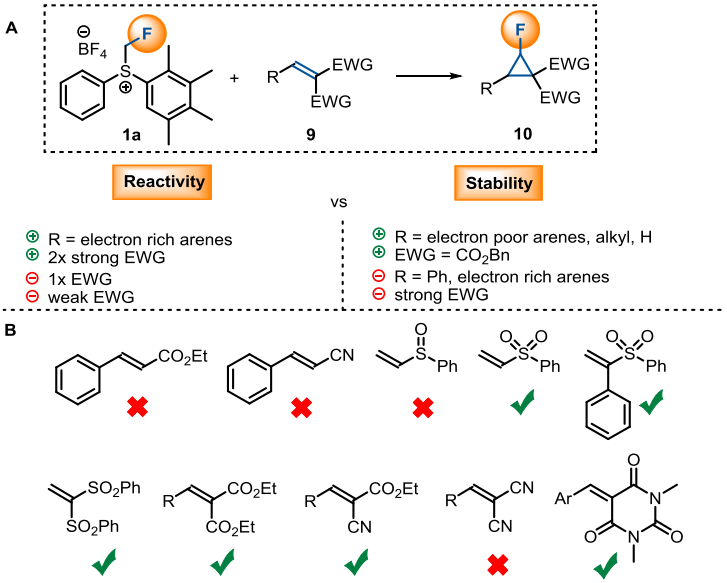


Fig. 10. Limitations of fluorocyclopropanation of activated olefins **9**.

Regarding double activated arylidene- and alkylidene derivatives – cyanoacetates and malonates – strong EW groups favor product formation, although the generation of unstable products sometimes has been observed. However, strong ED groups in the aryl ring mostly contribute to the decomposition of fluorocyclopropane derivatives under reaction conditions, which could be explained by the opening of the cyclopropane ring promoted by electron donating groups.[20]

3. Optimization of the fluoromethylene transfer reagent

Although we successfully demonstrated the effectiveness of 2,3,4,5-tetramethylphenyl substituted sulfonium salt **1a** in reactions with Michael acceptors such as aldehydes, ketones, vinyl sulfones, vinyl sulfonamides, as well as double activated alkenes with good results, it should be noted that the synthesis of reagent **1a** is expensive, due to the limited availability of 1,2,3,4-tetramethylbenzene, furthermore it has as low atomic economy.[21]

Until now, the influence of substituents on the reactivity, stability and crystallinity of fluoromethylsulfonium salts **1** was not known in the literature. According to the literature, most sulfonium salts **1** exist as viscous oils, which significantly complicates the practical application of the reagent.[22] The properties that could contribute to the development of an easy-to-use, crystalline reagent, while maintaining its efficiency, were not known. Our aim was to discover an effective sulfonium reagent through structural optimization, reducing the resources needed for its synthesis, as well as improving its reactivity in the already developed fluoromethylene transfer reactions for low efficiency substrates.

In the fluoromethylene group transfer reactions with nitroalkenes, using the original *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1a**), we observed low reactivity and negligible reaction yields, thus salt **1a** is not the most suitable reagent for obtaining nitrofluorocyclopropanes. Our task was to investigate whether it is possible to promote fluorocyclopropanation more efficiently by modifying the structure of the leaving group of the fluoromethylsulfonium salt **1**.[23]

During the research studies, we developed a synthesis route for fluoromethylsulfonium salt **1** (Fig. 11), replacing the dangerous and inconvenient fluorination reagent DAST[22] with the safer and more convenient electrophilic fluorination reagent *Selectfluor*. The improved synthesis also enabled a significant decrease in reaction times, as a result of which 25 different fluoromethylsulfonium salts **1** were synthesized in an efficient 4 step synthesis starting from thioanisole derivatives **11**.

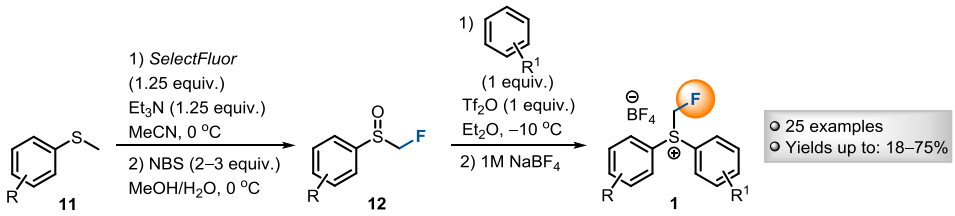


Fig. 11. Synthetic route for fluoromethylsulfonium salts **1**.

We initially chose *β*-nitrostyrene (**13a**) as a model substrate to study performance of sulfonium salts **1**. In order to evaluate the effect of substituents, the phenyl rings of diarylsulfonium salt **1** were labeled as **A** and **B** (Fig. 12).

Introduction of Me- and MeO- groups at different positions in the benzene ring **B** of sulfonium salt **1**, while keeping ring **A** unsubstituted, gave no significant improvements in reaction yields compared to the original reagent **1a**. However, it is important to emphasize that although the use of *m*-xylene containing sulfonium salt **1c** did not result in significant increase in the reaction yield (53 %, *d. r.* = 74:17:9), its synthesis turned out to be more cost efficient in comparison to **1a**. We found out that the methyl substituent in the *ortho* position preserved the crystalline properties of the salt. On the other hand, when additional methyl groups were introduced into the benzene ring **A** (**1d**), we observed a decrease in the yield of the desired product **14a** (40 %).

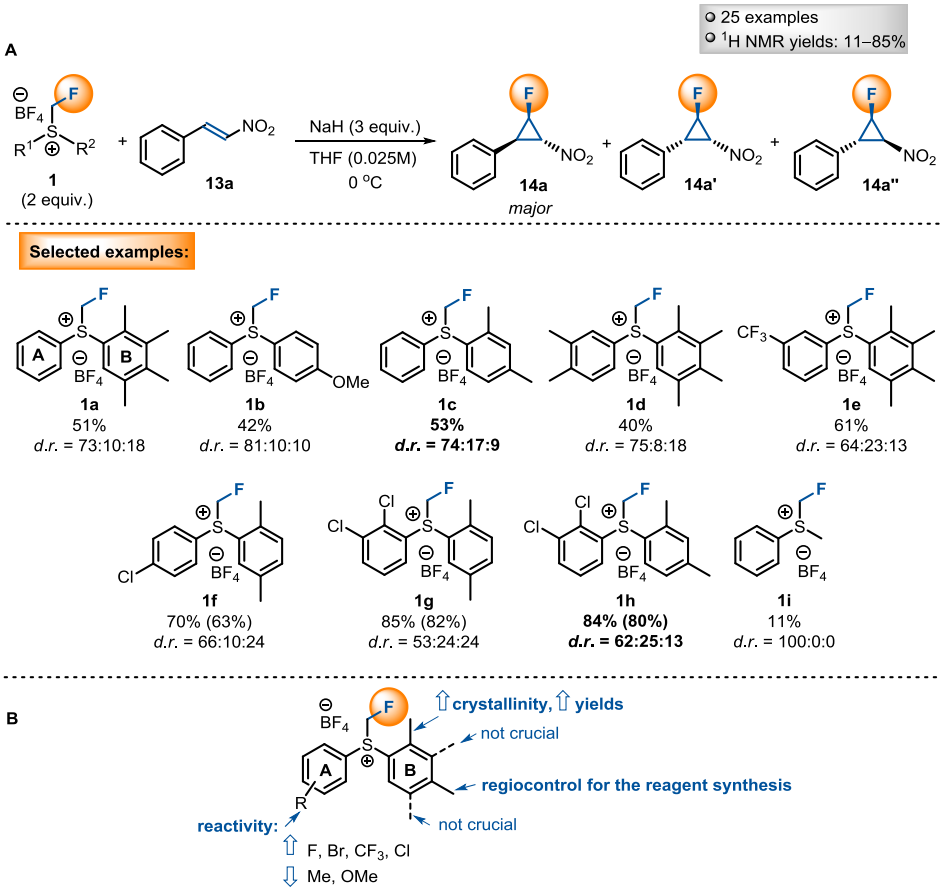


Fig. 12. Preparation of the fluoromethylsulfonium salt **1**.

By introducing halogen substituents (Cl, Br, F) or a trifluoromethyl group into the benzene ring **A** of sulfonium salt **1**, and keeping no more than two methyl groups in benzene ring **B**, we observed an increase in the yield up to 70% in the case of sulfonium salt **1f**. Further, by introducing two chlorine atoms in the *ortho* and *meta* positions of the benzene ring **A**, and reducing the number of methyl groups to two in ring **B** (**1g**,**h**), it was possible to achieve the highest overall yield (84–85 %) for this transformation, but moderate diastereoselectivity.

In the reactivity studies of sulfonium salts **1**, we found that when halogens (F, Br, Cl) or a trifluoromethyl group are introduced into the benzene ring **A**, higher yields of fluorocyclopropanes **14** were observed, while ED groups (Me-, MeO-) resulted in lower yields of the desired product (Fig. 12). In the benzene ring **B** of sulfonium salt **1**, a methyl group in the *ortho* position ensures the crystalline properties of the salt, while a Me group in the *para* position facilitates desired regioselectivity in the electrophilic substitution reaction of fluoromethyl sulfoxide **12** (Fig. 11).

Interestingly, in the fluorocyclopropanation reaction with fluoromethyl phenylmethylsulfonium salt **1i** we observed only the formation of the major diastereomer **14a**, but its yield was negligible (11 %), which indicates that it is essential to use diaryl substituted fluoromethylsulfonium salts for the realization of the mentioned transformation.

During the structure optimization of the sulfonium salt **1**, reagent **1h** showed the highest reactivity, therefore we used it for further studies of the substrates scope of nitroalkenes **13** (Fig. 13). Alkyl-, aryl-, as well as the heteroaryl nitrofluorocyclopropane **14i** were obtained in moderate to very good yields (41–84 %), but with moderate diastereoselectivity. The developed reaction conditions were compatible with a wide range of functional groups, such as ED groups (methyl-**13b**, methoxy-**13c**), halogens (F-**13d**, Br-**13e**), EA groups (nitro-**13g**, ester-**13h**, trifluoromethyl group) in the benzene ring. In addition, the reaction with conjugated diene **13j** selectively formed **14j**, although with an average yield (41 %).

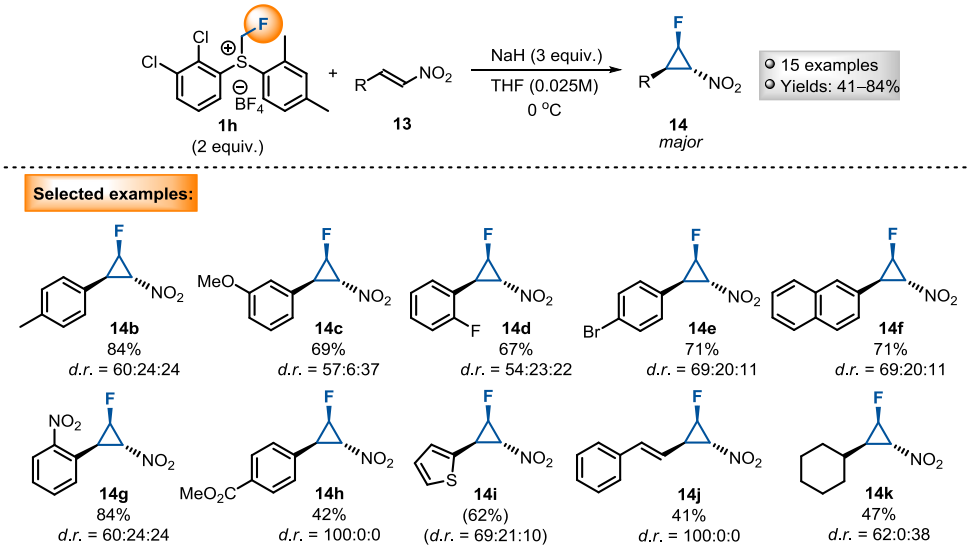


Fig. 13. Substrate scope for the fluorocyclopropanation of nitroalkenes **13**.

To compare the reactivity of the structurally improved sulfonium salts **1c** and **1h** with the original **1a**, we demonstrated fluoromethylene group transfer reactions with malonate derivatives **9l**,**o**, vinyl sulfone **4s**, ketone **2a** (Fig. 14).

We observed that in the reaction with sulfonium salt **1c**, an increase in the yield of products **10o** and **5s** was observed compared to classical salt **1a**. However, in the case of highly reactive substrates, such as malonate **9l** and aldehyde **2a**, 2,3-dichlorobenzene containing sulfonium salt **1h** turned out to be more suitable, as a result we managed to obtain product **10l** with a significantly higher yield (60 %), while fluoroepoxide **3a** was obtained with a slightly improved dastereoselectivity in a shorter reaction time. However, for the slower reacting substrates (**9o**, **4s**), the salt contributed to a decrease in yield compared to the original sulfonium salt **1a**.

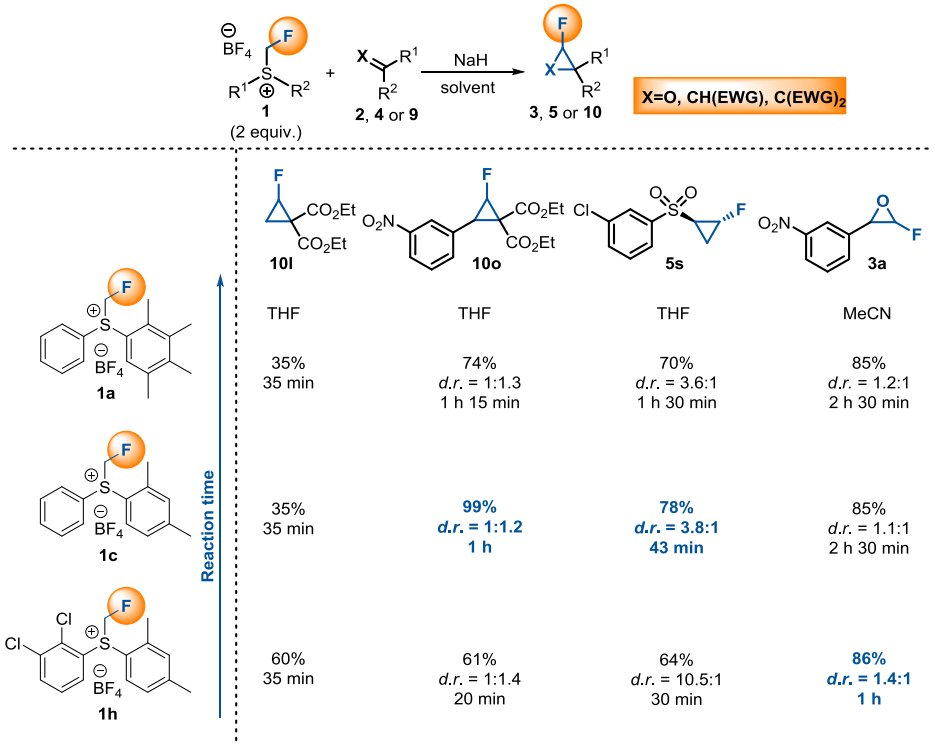


Fig. 14. Comparison of sulfonium salts **1a**,**c**,**h** in reactions with different classes of substrates.

Continuing our research, we tested the reactivity of sulfonium salt **1c** in fluorocyclopropanation reactions with vinyl sulfones **4a**,**h**,**i**,**t** as well as with arylidenemalonate derivatives **9i**,**p**. As a result of these experiments (Fig. 15, **B**), we observed not only higher yields of desired products (except in the case of **10i**), but also improvement in diastereoselectivity.

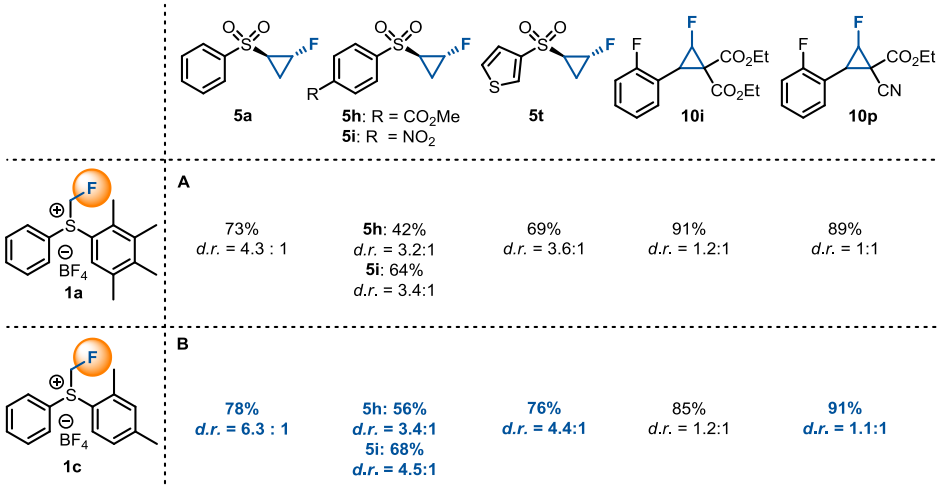


Fig. 15. Reactivity studies of sulfonium salt **1c**.

4. Synthesis of fluorocyclopropylidenes using 5-(1*R**,2*R**)-2-fluorocyclopropylsulfonyl-1-phenyl-1*H*-tetrazole

Cyclopropylidenes or methylenecyclopropanes in organic chemistry are known as strategic building blocks for obtaining other valuable compounds as a result of ring expansion or cycloaddition reactions facilitated by their high ring strain[24] and reactivity.[25] During the development of synthetic methodology towards fluorocyclopropylsulfones **5** and performing their reactions with various electrophiles, our attention was drawn to the reaction of sulfone **5a** with an aldehyde in which the alcohol derivative **8d** (Fig. 6) formed. *α*-Hydroxy substituted sulfones are important intermediates in the Julia–Kocienski olefination[26] reaction, which indicated the potential of this approach in the synthesis of fluorocyclopropylidenes.

Initially, our task was to obtain the olefination reagent **5u** for the transfer of the fluorocyclopropylidene group. The synthesis involved 4 steps – alkylation of 1-phenyl-1*H*-tetrazol-5-thiol **15** with 1,2-dichloroethane, oxidation of the obtained alkyl sulfide **16** with $NaIO_4$ in the presence of catalyst $RuCl_3 \cdot H_2O$, the base promoted elimination of HCl forming **17** and its fluorocycopropanation under Corey–Chaykovsky reaction conditions (Fig. 16).

Performing a one-pot synthesis of vinyl sulfone **4u**, we encountered a problem during the HCl elimination step, in which the intermediate **17** exhibited pronounced instability in excess of Et_3N.[27] Therefore, a careful adjustment of the reaction conditions was necessary.

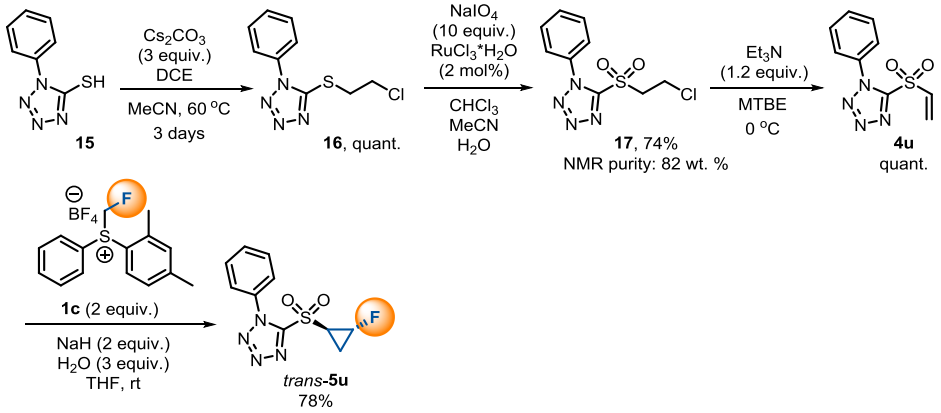


Fig. 16. Preparation of Julia–Kocienski olefination reagent **5u**.

To determine the required quantity of base for the elimination step, we performed optimization experiments with Et_3N in solvents such as DCM, Et_2O and MTBE at rt and at 0 °C (Table 4.1). The qNMR yield for the desired product **4u** before and after chromatographic purification was determined exploiting our developed analytical method – using $CHCl_3$ residue signal as an internal standard.[27]

Table 4.1

Reaction condition screening using qNMR

No.	Conditions	NMR yield of **4u**, %		Determined with laboratory balances, %	NMR purity of **4u**, %
		crude	isolated		
1	DCM, rt, 4 h, Et_3N (2.5 equiv.)	4.8	–	–	–
2	Et_2O, 0 °C, 15 min, Et_3N (2.27 equiv.)	87.0	86.4	97	89
3	Et_2O, 0 °C, 15 min, Et_3N (1.12 equiv.)	100	97.1	103	95
4	MTBE, 0 °C, 15 min, Et_3N (1.12 equiv.)	100	99.5	103	97

The experiments allowed us to develop optimal conditions for the synthesis of vinyl sulfone **4u**. The optimal reaction conditions – 1.12 equiv. of Et_3N, MTBE, 0 °C, 15 min – gave the desired product **4u** with excellent yield (99.5 %) and high purity (97 %) (Table 4.1, No. 4). In the final step using the optimized fluoromethylsulfonium salt **1c** we obtained *trans*-fluorocyclopropyl sulfone **5u** in good yield (78 %).

To optimize the reaction conditions for Julia–Kocienski olefination, we chose 3-nitrophenyl benzaldehyde **2a** and 4-nitro benzaldehyde **2b** as model substrates.[28] In the course of the research, we found out that the optimal reaction conditions are: 2 equiv. of aldehyde **2** or ketone **2'**, 1.7–2 equiv. of LiHMDS (1 M THF), –78 °C, under argon atmosphere, THF/DMF (4:1). It is important to note that under these reaction conditions, products **18** formed as a chromatographically inseparable mixture of *E*- and *Z*-isomers, although *Z*-fluorocyclopropylidene was formed as the major isomer. In substrate studies (Fig 17), we demonstrated the fluorocyclopropylidation of *ortho*, *meta*, *para* substituted benzaldehyde derivatives **2**, leading to products **18a**–**j** in very good to excellent yields (Fig. 17, **A**). The observed *Z*-selectivity could be rationalized due to the most likely cyclic transition state involved in the reaction, in which the fluorine atom is directed away from the aryl substituent of the aldehyde, thus reducing the destabilizing dipole-dipole interactions of the fluorine atom and aryl π-system.

It is interesting that in the case of substrate **2e**, the *E*/*Z*-selectivity decreases significantly, indicating the importance of steric contributions of the bulky substituents. This could be possibly rationalized by the fact that in the case of sterically bulky substituents the reaction proceeds via an open transition state, significantly decreasing the selectivity.

Reactions with ketones **2'** showed lower yields of fluorocyclopropylidenes **18k**–**o** (Fig. 17, **B**), which could be explained by a decrease in the electrophilicity of the carbonyl group of the substrates **2'**, as well as by possible aldol side reactions in the excess of base. We also demonstrated transformations of aliphatic ketones **2'** in high yields.

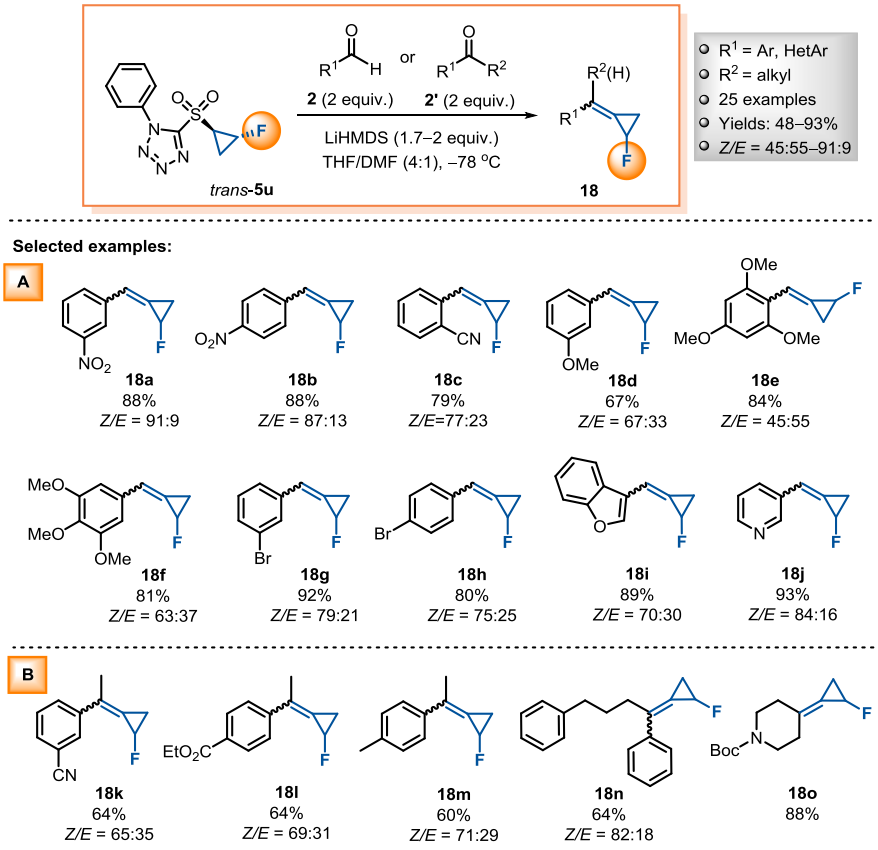


Fig. 17. Substrate scope studies for Julia–Kocienski olefination.

After substrate scope studies, the reactivity of the obtained fluorocyclopropylidenes in various transformations was investigated (Fig. 18), such as, epoxidation/ring expansion reactions of fluorocyclopropylidenes **18e**,**o**,**p** (Fig. 18, **A**).[29]

In the reaction of fluorocyclopropylidenes **18o**,**p** with *m*CPBA and catalytical amount of Lewis acid – LiOTf, *α*- and *β*-fluoro-substituted cyclobutanones **20o**, **21o** and **20p**, **21p** were obtained in excellent yields, however, as an inseparable mixture of regioisomers, where **20o** and **20p** were observed as a major regioisomers.

Chromatographic isolation of the products was not possible in this case, due to the instability of the compounds on silica gel. In the case of products **20e** and **21e**, addition of Lewis acid was not necessary to initiate cyclization. Fluorocyclobutanones **20e** and **21e** were isolated with a moderate yield (64 %) where the cyclobutanone **21e** was formed as the major isomer, but the other regioisomer **20e** decomposed over time due to hydrogen fluoride elimination leading to the formation of cyclobutenone byproduct **22e**.

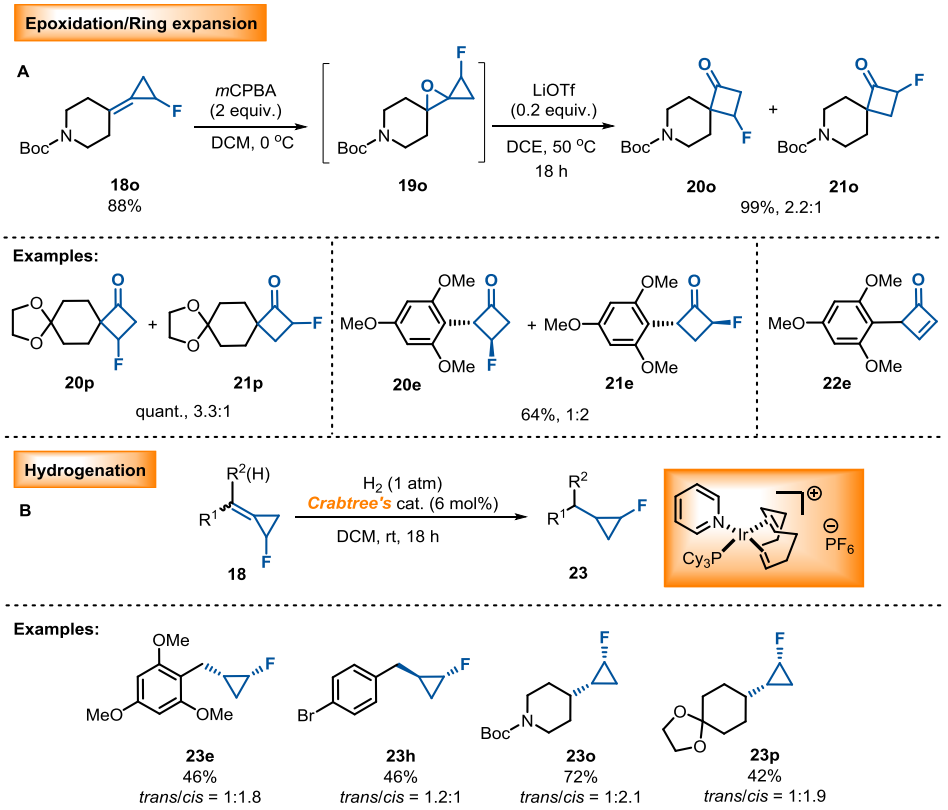
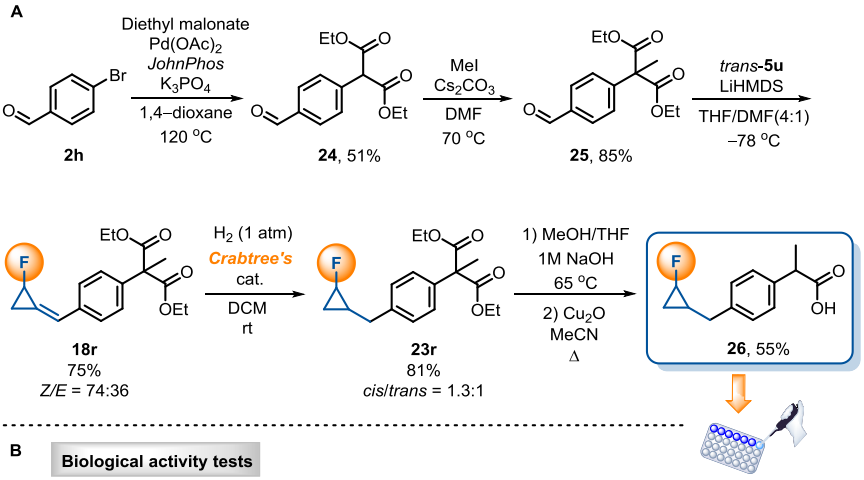


Fig. 18. Derivatisation possibilities of fluorocyclopropylidenes **18**.

According to the literature, the hydrogenation of monofluorocyclopropylidenes has not been studied[30] since ring opening and fluorine elimination can occur under harsh hydrogenation conditions. The hydrogenation of cyclopropylidenes is most often performed using Pd/C, Raney-Ni, Ir catalysis.[31] When we tested several hydrogenation conditions, such as Wilkinson's catalyst, Pd/C as well as others, we observed the formation of unidentified defluorinated products. During the research, we found that Crabtree's catalyst provides a mild and efficient hydrogenation of fluorocycloproylidenes, as a result of which we obtained fluorocyclopropanes **23** (Fig 18, **B**) in moderate to good yields (42–72 %), mainly forming the *cis*-product.

In order to demonstrate the potential of our developed fluorocyclopropylidenation methodology in medicinal chemistry, we carried out the synthesis of a monofluorocyclopropyl-substituted analogue **26** of the well known drug substance – ibuprofen[32] (Fig. 19, **A**) and performed biological activity tests on COX-1 and COX-2 enzymes (Fig. 19, **B**). We have successfully developed the synthesis of ibuprofen derivative **26** in 5 steps (Fig. 19, **A**), starting from 4-bromobenzaldehyde **2h**. The $Pd(OAc)_2$ catalyzed coupling reaction of the compound **2h** with diethyl malonate formed the intermediate **24**. Alkylation of the malonate derivative **24** with methyl iodide yielded the aldehyde component **25** required for Julia–Kocienski olefination. As a result of the fluorocyclopropylidenation reaction, we obtained the desired product **18r** in good yield (75 %) and good *E*/*Z* ratio.



	Ibuprofen	(rac)-trans-26	(+)-cis-26*	(-)-cis-26*
COX-1	IC_{50} = 134 μM	**IC_{50} = 25 μM**	**IC_{50} = >500 μM**	**IC_{50} = >500 μM**
COX-2	IC_{50} = 443 μM	**IC_{50} = 1071 μM**	**IC_{50} = 681 μM**	**IC_{50} = >2000 μM**
S, c-1/c-2	0.30	0.023	n/a	n/a

*Relative configuration

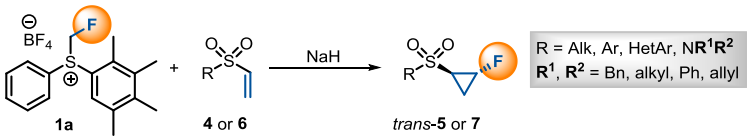
Fig. 19. Synthesis of fluorocyclopropyl-containing ibuprofen analogue **26** (**A**) and its biological activity (**B**).

As a result of hydrogenation, we obtained the corresponding fluorocyclopropane derivative **23r** – a mixture of *cis*- and *trans*-isomers – with a high yield. In the next step, we hydrolyzed the malonate derivative **23r** followed by decarboxylation of intermediate, which yielded the desired analogue of ibuprofen **26** in a moderate yield (55 %). It was possible to purify 3 fractions by chiral preparative chromatography, for which we determined the enzyme inhibition of COX-1 and COX-2[33] (Fig. 19, **B**).

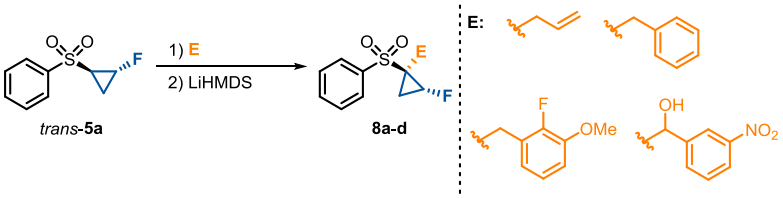
In biological activity tests, (*rac*)-*trans*-**26** showed higher inhibitory selectivity for COX-1 compared to ibuprofen. However, in the case of (+)-*cis*-**26**, the compound showed lower activity than the parent drug but higher selectivity towards the desired target protein COX-2 over the COX-1.

CONCLUSIONS

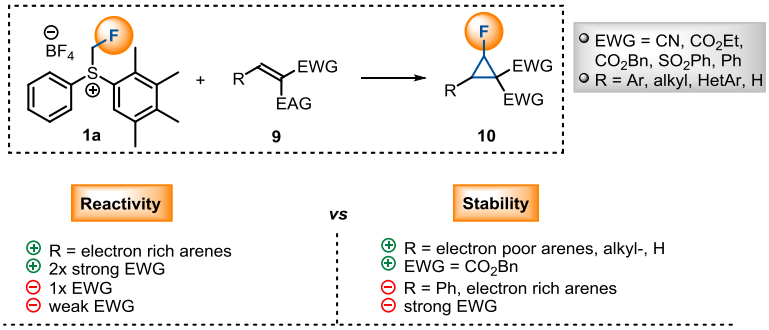
1) The fluorocyclopropanation reaction of aryl-, heteroaryl- and cyclohexyl-substituted vinyl sulfones **4** and *N*-alkyl-, phenyl substituted vinyl sulfonamides **6** with diarylfluoromethylsulfonium tetrafluoroborate **1a** provides access to *trans*-fluorocyclopropyl sulfones **5** and *trans*-sulfonamides **7** in good yields and moderate diastereoselectivity.



2) In further functionalization reactions of fluorocyclopropane **5a** with electrophiles, the formation of *trans*-fluorocyclopropanes **8** is observed, which indicates the formation of a thermodynamically most stable carbanion in the deprotonation step, regardless of whether the reaction is carried out with the *cis*- or *trans*-isomer.

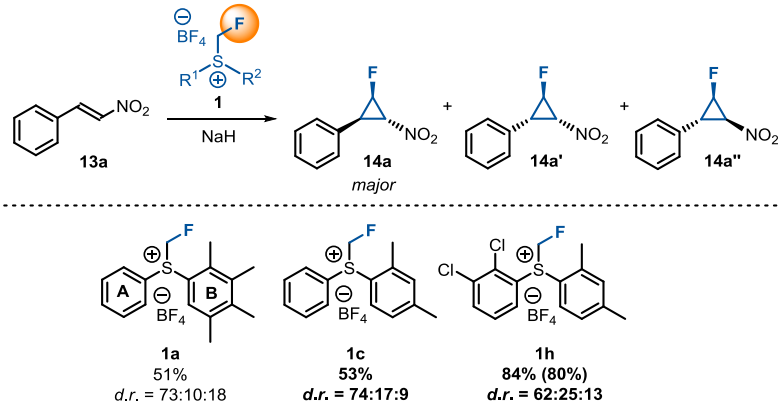


3) The fluoromethylene transfer reaction to double activated alkenes **9** allowed identification of the scope and limitations of this transformation. The reactivity of the substrates correlated with their electrophilicity. Alkenes **9** substituted with electron poor substituents and/or strong electron withdrawing functional groups promote the reaction, whereas electron donating groups and electron rich systems reduce the stability of the formed fluorocyclopropanes **10**, promoting their decomposition complicating their isolation.



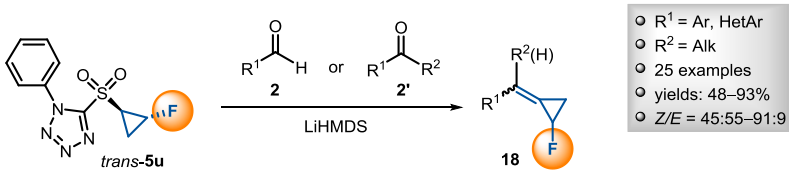
4) Introduction of halogen substituents in the benzene ring of the fluoromethylsulfonium salt improves reactivity of the reaction with nitroalkenes **13**, but a 2,4-dimethyl-substituted aryl system ensures the crystallinity of the salts **1**. The highest reaction yields and diastereoselectivities in the fluorocyclopropanation reaction of nitroalkenes **13** can be

achieved using **1h**. Although the yields of the obtained fluoronitrocyclopropanes **14** were lower, the reagent **1c** is the most affordable from the perspective of availability of starting materials.

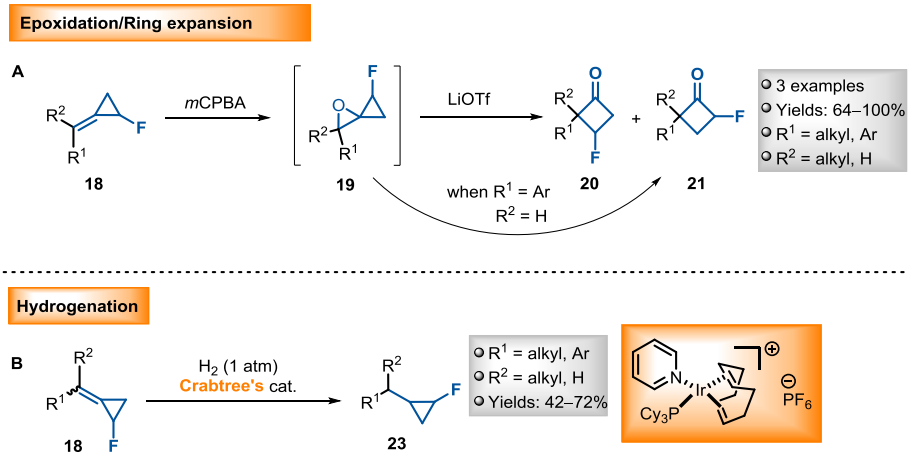


5) In the fluoromethylene transfer reactions with vinylsulfones **4** higher yields of fluorocyclopropane derivatives **5** as well as diastereoselectivity were provided by *m*-xylene substituted fluoromethylsulfonium salt **1c**, while in the case of arylidene malonates, we did not observe significant advantages using sulfonium salts **1c** or **1h**. In the reaction with 3-nitrobenzaldehyde **2a**, optimized sulfonium reagents performed similarly to the original reagent **1a**.

6) Julia–Kocienski olefination, using *N*-phenyltetrazole containing fluorocyclopropylsulfone *trans*-**5u** as a reagent allowed obtaining fluorocyclopropylidenes **18** from aldehydes **2** and ketones **2'** with good yields and the *Z*-selectivity.



7) The hydrogenation of fluorocyclopropylidenes **18** in the presence of Crabtree's catalyst allowed obtaining the corresponding derivatives of fluorocyclopropanes **23** in low to moderate yields as a mixture of *cis*- and *trans*-isomers. On the other hand, epoxidation/ring expansion reactions of fluorocyclopropylidenes **18** with *m*CPBA and catalytical amount of LiOTf leads to fluorocyclobutanone derivatives **20** and **21** in moderate to excellent yields as a mixtures of two regioisomers.



8) The fluorocyclopropylidenation methodology can be conveniently used for the synthesis of a fluorocyclopropyl containing analogue **26** of the drug molecule ibuprofen. In biological activity tests on COX-1 and COX-2 enzymes, it is possible to observe significant differences in stereoisomeric selectivity of the fluorinated analog **26** compared to the original drug.

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Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts

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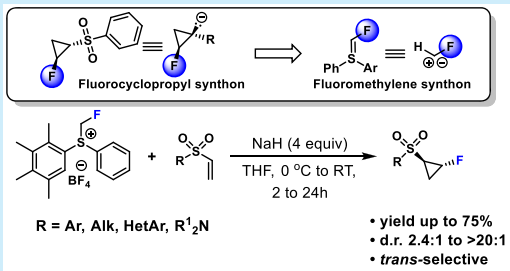
Supporting Information

ABSTRACT: Diarylfluoromethylsulfonium salts, alternatives to freons or advanced fluorinated building blocks, are bench stable and easy-to-use sources of direct fluoromethylene (:CHF) transfer to alkenes. These salts enabled development of a *trans*-selective monofluorinated Johnson−Corey−Chaykovsky reaction with vinyl sulfones or vinyl sulfonamides to access synthetically challenging monofluorocyclopropane scaffolds. The described method offers rapid access to monofluorinated cyclopropane building blocks with further functionalization opportunities to deliver more complex synthetic targets diastereoselectively.



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The cyclopropyl moiety and fluorine atom can be commonly found in drug molecules.[1] Often both of these functionalities add to the physicochemical properties of potential drug molecules in terms of metabolic stability, lipophilicity, and pharmacokinetics.[2] However, the combination of these two moieties into a fluorocyclopropyl moiety is rather rare and much less studied.

A prominent example of a drug molecule containing a fluorocyclopropane motif is the broad spectrum antibiotic Sitafloxacin[3a] (Figure 1A). The recently approved constituent of combination drug to combat hepatitis C virus, Glecaprevir[3b] illustrates that the combination of multiple fluorines and cyclopropanes improves overall profile. In addition, fluorocyclopropyl groups containing Tyk2 JH 2 kinase inhibitors show promising results for the treatment of psoriasis and Crohn's disease.[3c]

Thus, there is a clear need for novel and direct monofluoromethylene (:CHF) transfer methodologies utilizing available substrates and user-friendly reagents. Nevertheless, the intriguing world of small and strained cycles rarely meet together with fluorine due to the limited accessibility of suitable reagents, lack of concise synthetic routes and stability issues of the reactive intermediates.[4] Availability and versatility of various alkenes bearing electron-withdrawing groups would be an ideal platform for the synthesis of monofluorocyclopropanes. Diazofluoromethane would be an atractive source of fluorocarbene, however, it has been predicted to be an unstable species (Figure 1B).[5] Fluorocarbene generated from either low boiling, expensive, or environmentally concerning freons of type $CHFX_2$,[6] gave mixed results in terms of the reactivity and efficiency. To overcome these issues, several indirect methods have been developed to access fluorinated cyclopropanes.[7] Hu's fluorinated sulfoximines have shown to be a direct monofluoromethylenation reagent[8] of alkenes. However, the application of the aforementioned reagent beyond Weinreb amide has not been demonstrated. Other methods accessing monofluorocyclopropanes involve different bond forming approaches, such as, carbenoid addition to vinyl fluorides[9] or fluorination of already existing cyclopropane derivatives.[10] In general, access to α-unsubstituted fluorcyclopropanes suffers from limitation of current synthetic methods. In addition, current methods deliver primarily *cis*-products.[11]

Fluorocarbenoids, generally considered as extremely unstable and difficult to access, have shown recent progress in terms of feasibility and synthetic utility.[12] Our work has demonstrated that bench stable and solid diarylfluoromethyl sulfonium reagents can efficiently transfer the monofluoromethylene group to ketones and aldehydes delivering α-fluoroepoxides under mild conditions.[13] Pursuing research in this direction, we report an efficient protocol for the *trans*-diastereoselective Johnson-Corey-Chaykovsky fluoromethylenation of vinyl sulfones and vinyl sulfonamides using *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1**), now a commercially available reagent,[14] to deliver novel fluorocyclopropane derivatives.

This method delivers monofluorocyclopropane derivatives decorated with functional groups offering an access to the fluorinated building blocks relevant to medicinal chemistry.

We began the investigations with the fluorocyclopropanation of arylvinylsulfones **2** because vinyl sulfones are potent Michael acceptors.[15] Morevoer, fluorocyclopropylsulfones and sulfonamides[16] emerged as new scaffolds in medicinal chemistry. In

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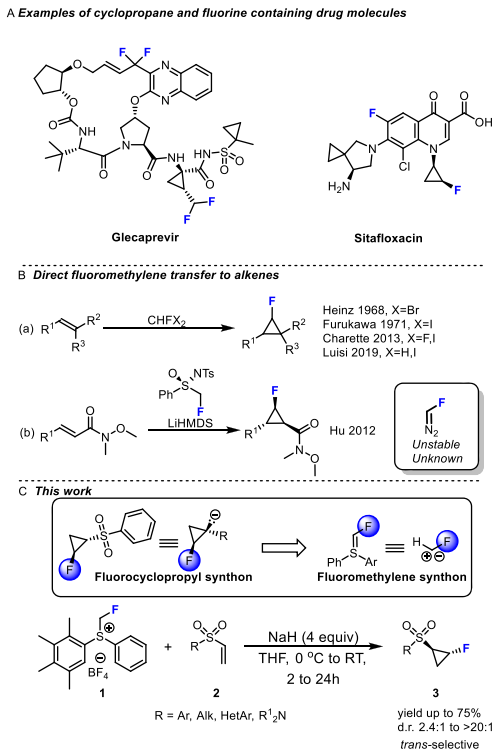


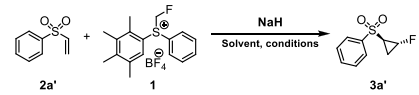
Figure 1. (A) Drug molecules containing both the cyclopropyl moiety and a fluorine atom. (B) Direct methods for monofluoromethylenation of alkenes. (C) Johnson−Corey−Chaykovsky fluorocyclopropanation.

addition, we were attracted to the idea of the potential utility of further functionalization at the α-position of the sulfone group.[17]

Initial attempt to perform the reaction of the fluoromethylsulfonium salt **1** with phenylvinylsulfone **2a′** in chloroform-*d* allowed quick identification of the formation of the desired fluorocyclopropane **3a′** by ^{1}H and ^{19}F NMR albeit in low yield (Table 1, entry 1). Solvent screening identified THF as the optimal solvent (Table 1, entries 2−6). Further dilution or concentration did not give any improvement (entries 7−8). Performing the reaction at lower temperature increased reaction time from 3 to 24 h as well as gave incomplete conversion and lower product **3a′** yield but very high diastereoselectivity (entry 9). Adjusting the amount of sulfonium salt **1** and addition of the base in one portion (entry 10) gave the highest overall yield and the most versatile conditions for the broad spectrum of substrates (vide infra). The final reaction conditions therefore consist of treating **2a′** with **1** (2.0 equiv) and NaH (4.0 equiv) in THF at room temperature giving desired fluorocyclopropylsulfone **3a′** in very good yield with *trans*/*cis* 4.4:1 selectivity.

Adjusting the amount of sulfonium salt **1** and addition of the base in one portion (entry 10) gave the highest overall yield and the most versatile conditions for the broad spectrum of substrates (vide infra). The final reaction conditions therefore consist of treating **2a′** with **1** (2.0 equiv) and NaH (4.0 equiv) in THF at room temperature giving desired fluorocyclopropylsulfone **3a′** in very good yield with *trans*/*cis* 4.4:1 selectivity.

Table 1. Optimization Experiments[a]



no.	**2a′**/**1**/NaH	solvent (c, M)	t (h)	yield **3a′** (%)[b]	d.r. trans/cis
1	1/1/1.5	$CDCl_3$ (0.1)	3	26[c]	6:1
2	1/2/2.2	MeCN (0.05)[f]	18	43	4:1
3	1/1.6/4[d]	$CHCl_3$ (0.1)	20	71	5:1
4	1/1.6/4[d]	1,4-diox (0.1)	20	75	3:1
5	1/1.6/4[d]	CH_2Cl_2 (0.1)	24	76	4:1
6	1/1.6/4[d]	THF (0.1)	3	85	6:1
7	1/1.6/4[d]	THF (0.05)	3	67	9:1
8	1/1.6/4[d]	THF (0.2)	3	78	6:1
9	1/1.6/4[d]	THF (0.1)[f]	24	75	18:1
10	**1/2/4**[e]	**THF (0.1)**	**2.5**	**86**	**4.4:1**

[a]To a mixture of **2a′** (0.1 mmol) and **1** under an Ar atmosphere was added anhydrous solvent followed by 60% NaH in paraffin oil. The reaction mixture was stirred at rt for the indicated time unless otherwise stated. The crude reaction mixture was analyzed by ^{1}H NMR. [b]^{1}H NMR yield determined using EtOAc (1.0 equiv) as an internal reference. [c]67% deuterated product. [d]Stepwise addition of NaH. [e]NaH added in one portion. [f]0 °C to rt.

After identification of optimal reaction conditions, the reaction scope was investigated (Scheme 1). The reaction conditions tolerate a range of substituted arylvinyl sulfones **2** as substrates delivering fluorocyclopropanes **3** with good yields of chromatographically purified *trans*-products. The reaction conditions turned out to be robust giving similar results for large variety of fluorocyclopropylarylsulfones **3**. Such functionalities as ester, nitrile and nitro-groups are tolerated under the reaction conditions. Cycloalkyl **2a** and benzylic **2u** vinylsulfones are tolerated giving the desired fluorocylclopropanes **3a** and **3u** with moderate yields and diastereoselectivities. Heterocyclic substrates **2r**, **2s**, **2v** work well under the reaction conditions. Noteworthy, is that the benzothiazole derivative **3x** forms with excellent diastereoselectivity but low yield. Sulfonamide functionality is abundant in many drug molecules[18] including Glecaprevir (Figure 1, A). To our delight, vinyl sulfonamides **2aa**−**ad** also participate in the reaction with fluoromethyl sulfonium salt **1**. Reaction proceeds with longer reaction time and performs best at lower temperature affording fluorocyclopropyl sulfonamides **3aa**−**ad** in moderate yields. The product **3ad** shows selectivity toward the vinyl sulfone moiety in the presence of another double bond.

The fluorocyclopropanation reaction of vinylsulfones **2** can be easily upscaled to gram scale (Scheme 2). The desired fluorocyclopropyl sulfone **3a′** was obtained with excellent yield and good diastereoselectivity. Both diastereomers can be easily separated chromatographically giving access to both *cis*- and *trans*- diastereomers. This motivated investigating on the use of the compound **3a′** as a nucleophilic fluorocyclopropane building block - a platform for the further functionalization.

An alkylation at the α-position of **3a′** offers an access of more advanced monofluorocyclopropyl- containing products **4** (Scheme 2). The alkylation of fluorocyclopropane **3a′** gave selectively *trans*-products **4** in good yields. We were pleased to see that aldehydes are competent electrophiles as well, to give product **4d′** as a 1:1 mixture of diastereomers while completely retaining *trans*- configuration at α-position. The high diaster-

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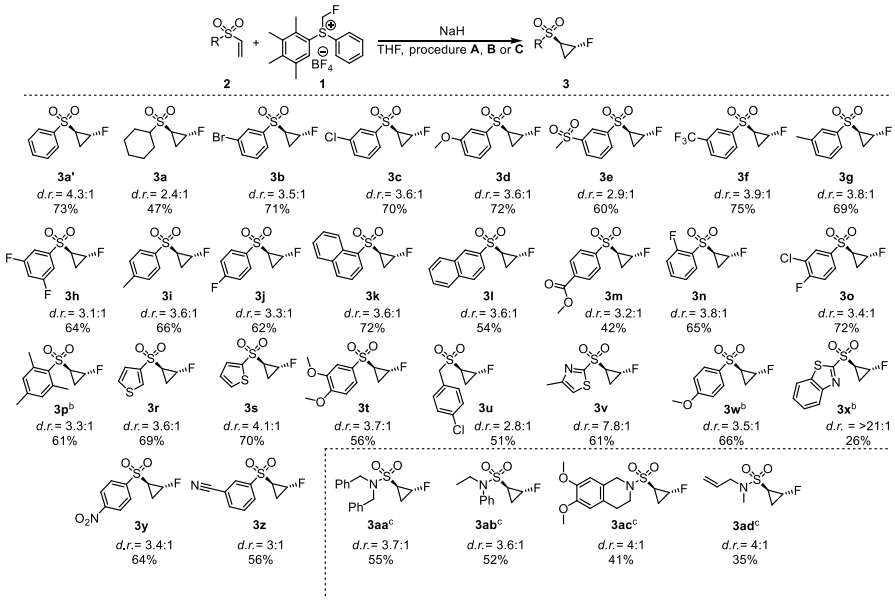
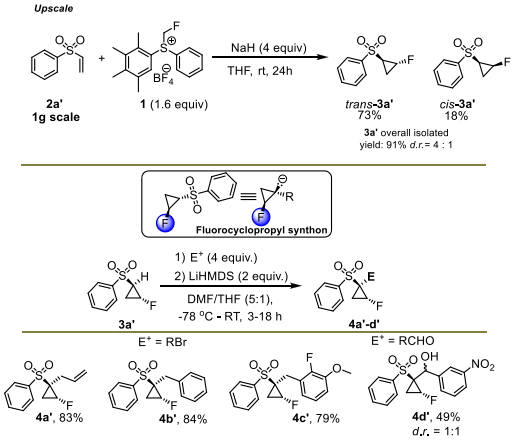
Scheme 1. Reaction Scope of the Fluorocyclopropanation[a]

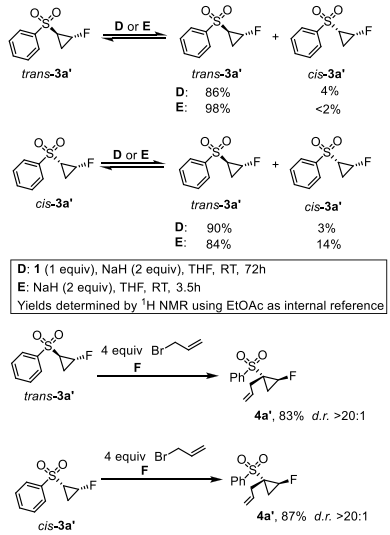


[a]**Procedure A: 2** (0.20 mmol, 1.0 equiv), **1** (2 equiv), 60% NaH (4.0 equiv), dry THF (0.1 M), rt, 2 to 3 h, unless otherwise stated. Isolated yields for *trans*-**3** products; *d.r.* determined by ^{1}H or ^{19}F NMR of the crude reaction mixture. [b]**Procedure B: 2** (0.20 mmol, 1.0 equiv), **1** (3 equiv), 60% NaH (4.0 equiv), dry THF (0.1 M), rt, 24 h [c]**Procedure C: 2** (0.20 mmol, 1.0 equiv), **1** (3 equiv), 60% NaH (5.0 equiv), dry THF (0.2 M), rt, 24 h.

Scheme 2. Upscale and α-Functionalization of Fluorocyclopropyl Sulfone 3a′



Scheme 3. Mechanistic Experiments



eoselectivity affording compounds **4** renders **3a′** a valuable fluorocyclopropylgroup containing building-block.

To gain deeper insight into the origin of the diastereoselectivity observed in the fluorocyclopropanation reaction we pursued mechanistic investigations. Both isolated *cis*-**3a′** or *trans*-**3a′** diastereomers exposed repeatedly to the conditions mimicking the reaction (Scheme 3, conditions **D**) or stirred with the base alone (conditions **E**) in THF afforded *trans*-**3a′** product with *d.r.* ∼ 15:1 without significant decomposition even after 3 days. When both *cis*-**3a′** or *trans*-**3a′** were exposed to the alkylation conditions (conditions **F**) with allylic bromide, both

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diastereomers afforded the same *trans*-**4a**′ product suggesting the involvement of a thermodynamically more stable *trans*-carbanion. The geometry of sulfone stabilized carbanion is known to be nonplanar[19] providing bases for highly stereoselective process.

Computational studies were carried out to identify mechanistic details of the reaction process for the fluorocyclopropanation reaction. Initially, addition of ylide to the activated double bond can afford *syn*- or *anti*- betaines $\mathbf{A^1}$ and $\mathbf{A^2}$, which subsequently undergo rotation, to form $\mathbf{B^1}$ and $\mathbf{B^2}$ (Figure 2, A),

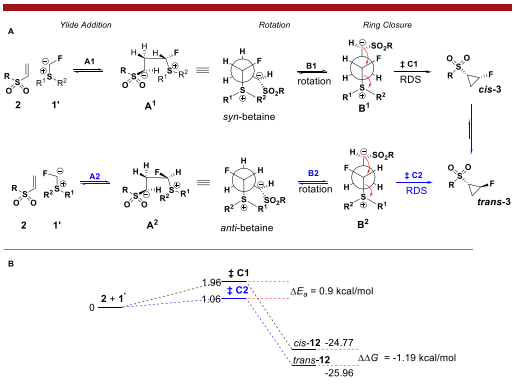

Figure 2. (A) Proposed reaction mechanism. (B) B97D/Def2-TZVPPD (THF)//B97D/Def2-TZVPP (THF) calculated reaction profile for (R = 3-MePh−, $R^1 = R^2$ =Me−). Energetics (including ZPE) in kcal/mol.

respectively.[20] For both pathways, calculations support an attenuated steric model in the transition state, with the ring closing being ‡**C1** and ‡**C2** as the stereoselective steps and formation of *trans* product 0.9 kcal/mol lower in energy than for *cis*-product (Figure 2, B). The calculated thermodynamics also indicates that the *trans*-product is more stable by 1.19 kcal/mol. These results suggest that initially the reaction is kinetically controlled with selectivity consistent with TS energy differentiation, while at longer times thermodynamic equilibration sets in and the energy difference of the products determines the stereoisomeric outcome.

The calculations also show that substituents at the aryl ring have minor influence on the diastereoselectivity of the reaction (see SI, p 41), which is in agreement with experimental results (Scheme 1).

In conclusion we have demonstrated that bench stable and accessible diarylfluoromethyl sulfonium salts are competent fluoromethylene transfer reagents to deliver functionalized monofluorocyclopropanes in Johnson−Corey−Chaykovsky reaction with vinyl sulfones and vinyl sulfonamides. This shows that an active intermediate, sulfur fluoromethylylide, offers an efficient and alternative way to tackle chemistry currently performed mostly by fluorocarbene and fluorocarbenoid chemistry. The synthetic utility of fluorocyclopropylarylsulfones spans from the possibility to introduce the fluorocyclopropane substructure in more complex products to favorable stereoselectivity offering facile access to *trans*-products as opposed to more common *cis*-selective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02867.

Experimental details, computational data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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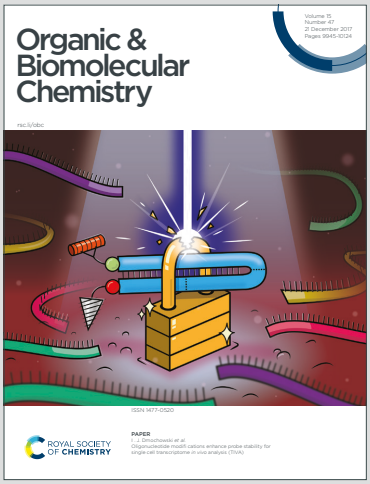

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ARTICLE

Johnson–Corey–Chaykovsky Fluorocyclopropanation of Double Activated Alkenes: Scope and Limitations

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Johnson-Corey-Chaykovsky fluorocyclopropanation of double activated alkenes utilizing *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate is an efficient approach to obtain a range of monofluorocyclopropane derivatives. So far, fluoromethylsulfonium salts display the broadest scope for direct fluoromethylene transfer. In contrast to more commonly used fluorohalomethanes or freon derivatives, diarylfluoromethylsulfonium salts are bench stable, easy-to use reagents useful for the direct transfer of a fluoromethylene group to alkenes giving access to the challanging products - fluorocyclopropane derivatives. An interplay between reactivity of starting materials and stability of formed fluorocyclopropanes determines the outcome of the process.

Introduction

The fluorine atom is commonly found in many pharmaceuticals[1] and agrochemicals[2] due to its unique ability to improve the range of molecular properties. For instance, bioisosteric replacement of hydrogen with fluorine often enhances pharmacophysical properties of drug candidates[3]. On the other hand, a cyclopropane moiety can be found both in natural products and many pharmaceutical drugs[4]. Cyclopropane can act as configurationally stable bioisosteric replacement of a double bond and, in general, it can improve metabolic stability, lipophilicity and solubility of the potential drug candidate. The fluorocyclopropanes[5]– a combination of both chemical entities – cyclopropylgroup and fluorine, is less common, however, is a very interesting substructure to be used in medicinal chemistry for drug discovery. This is exemplified by fluorocyclopropyl-containing pharmaceuticals, such as Sitafloxacin[6], Tyk2 JH 2 kinase inhibitors[7]. Upon lead optimization the fluorine test, where fluorine atom is introduced in various positions of an active molecule is a routine nowadays[8]. However, incorporation of a fluorine atom into a cyclopropane moiety poses many synthetic challenges. Direct fluorination of cyclopropane requires pre-functionalized cyclopropanes[9]. An alternative approach towards these structures is the use of vinylfluorides which are exposed to carbenoid chemistry[10]. Much more perspective from a versatility point of view is direct fluorocarbene or fluorocarbenoid addition to alkenes. For this transformation, freons ($CHFX_2$)[11] or fluoromethylsulfoximine reagents[12] are currently used. These methods, though, used even on a large scale[13], constitute considerable drawbacks, such as the use of low boiling, or environmentally concerning reagents, or suffer from limited substrate scope. Until recently, fluorocarbenoid species were considered a very unstable and difficult to work with species[14a]. However, recent progress has showed feasibility and even remarkable stability of the fluorocarbenoid species to be effectively used in synthesis[14].

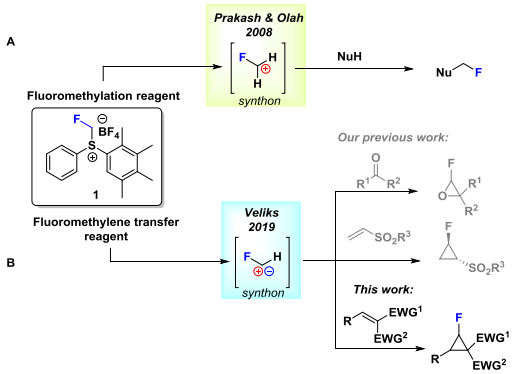

Fig. 1 Fluoromethylsulfonium reagent **1** for: **A** Fluoromethylation; **B** fluoromethylene transfer.

Our recent work has demonstrated that an alternative to halomethane or freon is the solid, bench stable and easy-to-use *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1**) (Fig. 1). This sulfur fluromethylylide precursor, originally developed for electrophilic fluoromethylation[15] (CH_2F-), can be used efficiently as a fluoromethylene transfer (CHF=) reagent to ketones, aldehydes[16a], vinylsulfones and vinylsulfonamides[16b]. Pursuing our research program on fluoromethylene transfer chemistry we aimed to investigated scope and limitation of

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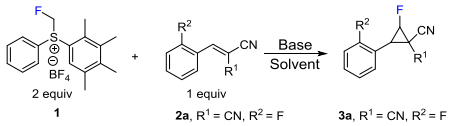
fluoromethylsulfonium reagent **1** for the synthesis of fluorocyclopropane derivatives. Herein, we demonstrate that fluoromethylsulfonium salt **1** is a highly efficient and user friendly reagent for the Jonhnson-Corey-Chaykovsky fluorocyclopropanation of double activated alkenes.

Results and discussion

Initially, for the fluorocyclopropanation reaction arylidene malononitrile **2a** was selected as a model substrate. It was encouraging to observe the formation of the desired fluorocyclopropane **3a** under the initially selected, non-optimized reaction conditions (Table 1, entry 1). After solvent screening (entries 1-4) 1,4-dioxane turned out to be the most efficient reaction media (entry 4) and NaH was identified as an optimal base (entry 4 *vs* 5) affording the fluorocyclopropanated product **3a** with moderate ^{1}H NMR yield. Unfortunately isolation of the dicyano- substituted fluorocyclopropanes **3a** was unsuccessful due to instability of the formed products. In turn, the fluorocyclopropanation of ethyl benzylydenecyanoacetate **4a** was found to be highly efficient (Table 1). The resulting cyanoacetate derived fluorocyclopropane **5a** turned out to be a stable and chromatographically isolable product which was obtained in excellent yield. After adjustment a concentration (entries 6-8) of the optimal reaction conditions are as follows: to a solution of **4a** (1 equiv) and **1** (2 equiv) in dry 1,4-dioxane (0.17 M of **1**) under Ar atmosphere 60% NaH (4 equiv) was added at room temperature. Under the optimized reaction conditions a substrate scope was further investigated (Scheme 1).

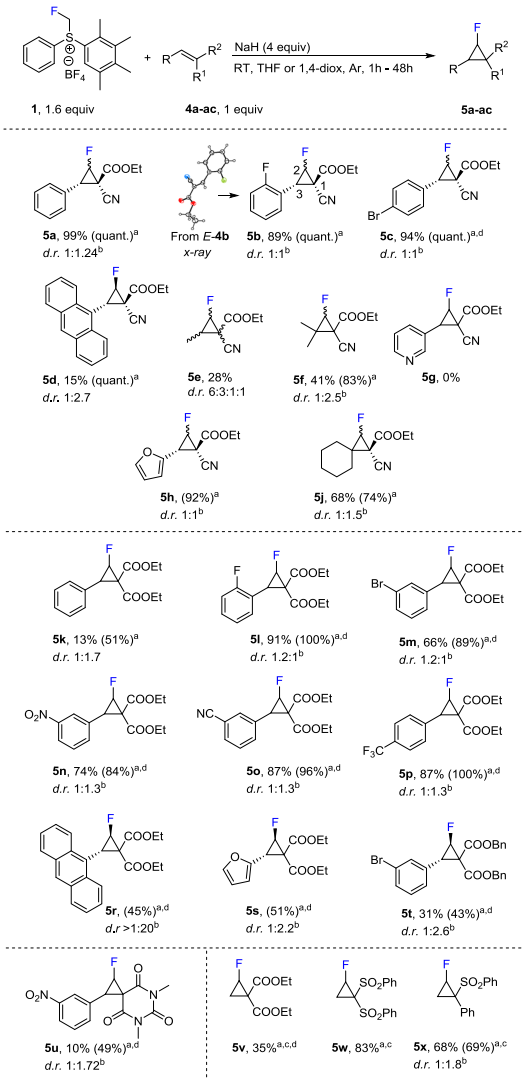
Table 1 Optimization of fluorocycolpropanation reaction of arylidene malononitrile **2a**



Nr.	Base (equiv)	Solvent[d]	SM	Yield **3a,5a**, %[c]	*d.r. cis/trans*
1.	NaH (2.5)[a]	$CDCl_3$	**2a**	15	1/1.28
2.	NaH (2.5)[a]	THF	**2a**	44	1/1.35
3.	NaH (2.5)[a]	MeCN	**2a**	17	1/1.08
4.	NaH (2.5)[a]	1,4-diox	**2a**	55	1/1
5.	*n*-BuLi (2.2)[b]	THF	**2a**	18	1/1.12
6	NaH (4)[a]	1,4-diox	**4a**	85	1/1.7
7	**NaH (4)[a]**	**1,4-diox**[e]	**4a**	**100 (99)**	**1/1.24**
8	NaH (4)[a]	1,4-diox[f]	4a	95	1/1.2

[a] Addition at RT. [b] Addition at -78 °C, then warmed to RT.
[c] ^{1}H NMR yield determined using 1 equiv EtOAc as internal standart (Isolated yield). [d] Sulfonium reagent **1** conc. 0.17 M. [e] 0.11 M. [f] 0.082 M.

The aryl substituted fluorocyclopropyl-cyanoesters **5a-d** were formed with high isolated yields as a mixture of diastereomers.



Scheme 1. Substrate scope for Johnson–Corey–Chaykovsky fluorocyclopropanation reaction. Reaction conditions: To a solution of **4** (0.21 mmol, 1 equiv), **1** (1.6 equiv) in 1,4-dioxane (3 mL) under Ar atmosphere was added NaH (60 % in paraffin

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oil, 4.0 equiv) at RT unless otherwise stated. The reaction mixture was stirred at RT till completion (TLC control). [a] Isolated yields (NMR yields using 1.0 equiv. of EtOAc as an internal reference). [b] d.r. determined for the crude reaction mixture. [c] Reaction performed at 0 °C. [d] THF used as a solvent.

As shown on the example of product **5b**, the original configuration at the positions C-1 and C-3 was transferred from a starting material alkene *E*-**4b** which applies to all aryl-substituted fluorocyclopropanes **5a-d**, **5h** in a cyanoester series. This results in the formation of only two diastereomers instead of 4 possible. Sterically demanding anthracenyl derivative **5b** was formed in excellent NMR yield and increased d.r albeit it could only be isolated with low yield due to its poor stability. This suggests that steric bulk at the position C-1 in the resulting cyclopropane can improve the stereoselectivity at the fluorine bearing center (C-2). The alkyl-substitution of cyanoesters **4e,f,j** is compatible with the fluorocyclopropanation protocol giving products **5e,f,j** in low to good isolated yields. However, the sterically small methyl substitution does not provide transfer of the stereochemistry of the double bond geometry into the product. Methyl- substituted fluorocyclopropane **5e** was obtained as a mixture of all four diastereomers.

Pyridine as a substituent was not compatible with the reaction conditions, despite the full conversion of the starting material **4g** the formation of fluorocyclopropanation product **5g** was not observed. The limitation of the fluorocyclopropanation are substrates containing electron rich aromatic double bond substituents due to obvious instability of the reaction products. The furan derivative **4h** efficiently undergoes fluoromethylene transfer as detected by NMR, however, the product **5h** decomposed upon chromatographic purification.

Arylidene malonate derivatives **4k-t** are well suited substrates for the fluorocyclopropanation reaction giving the products **5k-t** in low to very good yields as a mixture of diastereomers. Electron withdrawing groups (**4n,o,p**) and halogen (**4l,m**) on the aryl moiety of the arylydene malonates **4** furnished good to excellent yields of the fluorocyclopropanes **5**. Olefins with electron rich aryl groups and unsubstituted phenyl substituents (**5k, 5r, 5s**) gave products with moderate NMR yields which were prone to decompose upon isolation. This observation is in line with the stability and kinetics of donor-acceptor (D-A) cyclopropanes where generally electron donating groups increase the cyclopropane cleavage rate[18].. The barbituric acid derivative **4u** involves readily in fluorocyclopropanation reaction affording the fluorocyclopropane **5u** with good NMR yield, however, the isolated yield of the product is rather low.

Further, we investigated cyclopropanation of β-unsubstituted substrates **4v-x**. β-Unsubstituted substrates participate readily in the fluorocyclopropanation process giving stable, isolable products **5v-x** in moderate to high yields.

As a fluorocyclopropane **5k** with unsubstitued phenyl group at cyclopropane was prone to decomposition we opted to alter the ester functionality (Fig. 2 A). This eventually led to the finding that the benzyl esters **5ab** are stable products compared to the other esters **5y,k,z,aa** broadening their potential application.

In order, to summarize the scope and limitations of the current fluorocyclopropanation of activated alkenes using fluoromethylsulfonium salt **1** we compared the reactivity of various monosubstituted Michael acceptors (Fig. 2 B and C) with double activated ones. The reactivity is well correlated with electrophylicities[19] of the corresponding activated Michael acceptors. The phenylvinyl sulfoxide does not react, however, the corresponding sulfone readily involves in the reaction[16a] setting the boundary of the utility of this reaction. Double activated arylidene and methylidene derivatives are a good fit for this reaction. Stronger EWG groups facilitate the fluorocyclopropanation reaction (Fig. 2 C), however, in the case of arylidene derivatives the decreased stability of the formed products can be observed. The EWG groups on the aryl-ring contribute to the improved stability of the fluorocyclopropanes, but those with EDG are of poor stability. The balance between reactivity and stability illustrate the landscape and scope of the process under discussion.

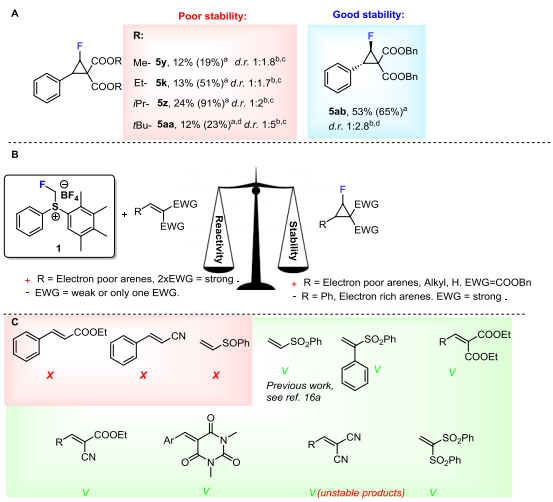

Fig. 2 Scope and limitations of the Johnson-Corey-Chaykovsky fluorocyclopropanation reaction. **A** An ester group influence on the reactivity and stability of phenylsubstituted cyclopropanes **5**. Standard reaction conditions unless otherwise stated. [a] Isolated yields (NMR yields using 1.0 equiv. of EtOAc as an internal reference). [b] d.r. determined for the crude reaction mixture. [c] Solvent – dry MeCN. [d] Solvent – dry THF. **B** The balance of reactivity and stability parameters of the flurocyclopropanation process. **C** The influence of substitutents on the reactivity of Michael acceptors: (x) no reaction; (v) suitable substrates.

In order to get a clearer understanding of the parameters for successful fluorocyclopropanation, we performed several control experiments (Scheme 2). For example, benzylidene barbiturate **4ac** readily participated in fluorocyclopropanation

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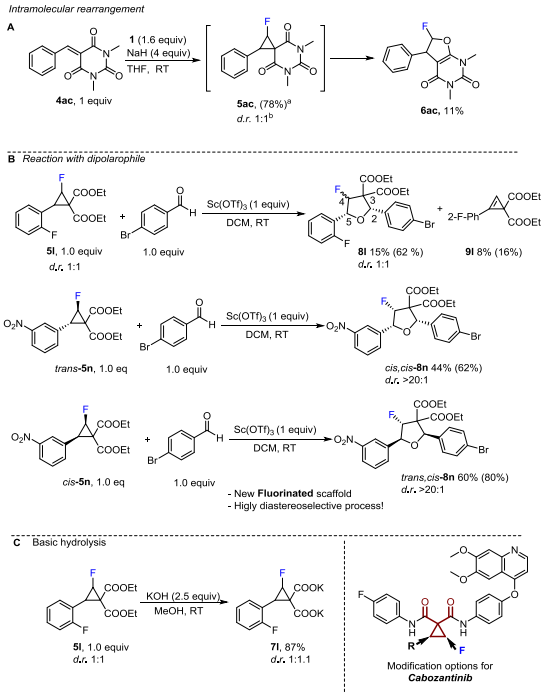
reaction giving good NMR yield of the corresponding cyclopropane **5ac**, however, upon chromatographic isolation only 5-membered rearrangement product **6ac** was obtained (Scheme 2A). Donor-acceptor cyclopropanes are known to involve in various ring-extension reactions[18]. The substrate **5ac** displays an example of intramolecular rearrangement process which is in line with Mayr's[20] observations where arylidene barbiturates in Corey-Chaykovsky reaction give similar 5-membered product. This is explained to proceed via initial formation of a cyclopropane intermediate rather than the *O*-attack to the betaine intermediate of the Corey-Chaykovsky reaction which is in line with our observations. Utilization of D-A cyclopropane[21] properties of fluorocyclopropanes **5** opens perspective for the further synthetic application of these scaffolds. Under unoptimized conditions, fluorocyclopropane **5l** involved in $Sc(OTf)_3$ mediated [3+2] ring-extension reaction with *p*-bromobenzaldehyde as a dipolarophile to give new fluorinated furan scaffold **8l** (Scheme 2 B). The process appeared to be highly diastereoselective with respect to stereocentres at C-2- and C-5 as only 2 diastereomers of **8l** were observed.



Scheme 2 Properties and further functionalization options of fluorocyclopropanes **5**.

Cyclopropene **9l** was detected as the major side product of this transformation. In order to probe the observed stereochemical outcome, isolated *trans*-**5n** and *cis*-**5n** fluorocyclopropanes were exposed to the corresponding ring extension reaction affording only single diastereomers *cis,cis*-**8n** and *trans,cis*-**8n** correspondingly. It is noteworthy that the rotation across the C(4)-C(5) bond takes place resulting in inversion of relative configuration of fluorine and aryl- substituents of fluorofuranes **8** which is in a good agreement with the previously proposed [3+2] cycloaddition reaction mechanism[21a]. Interestingly that fluorocyclopropane **5** scaffold displays remarkable stability under strongly basic conditions. Ester **5l** can be readily hydrolyzed by using KOH (Scheme 2 C) to give salt **7l** in a good isolated yield. This opens an avenue for the potential synthesis of a fluorocyclopropyl analogues of biologically active compounds[22].

Conclusions

We have demonstrated that diarylfluoromethylsulfonium salt **1** can be efficiently used for fluoro-Johnson-Corey-Chaykovsky reaction to afford a range of fluorocyclopropane **5** derivatives. We have investigated scope and limitations of the fluorocyclopropanation reaction which displays the balance between reactivity of substrates and stability of the products. The fluorocyclopropane derivatives **5** are an interesting class of chemical entities with potential application in medicinal chemistry and as well as the intermediates to access new monofluorinated scaffolds by involving them in further reactions.

Conflicts of interest

There are no conflicts to declare.

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Optimized Monofluoromethylsulfonium Reagents for Fluoromethylene-Transfer Chemistry

Arturs Sperga, Renate Melngaile, Armands Kazia, Sergey Belyakov, and Janis Veliks*

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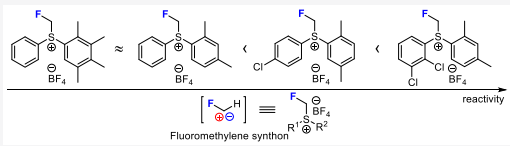
ABSTRACT: An investigation of the properties and reactivity of fluoromethylsulfonium salts resulted in the redesign of the reagents for fluoromethylene transfer chemistry. The model reaction, fluorocyclopropanation of nitrostyrene, turned out to be a suitable platform for the discovery of more streamlined fluoromethylene transfer reagents. The incorporation of halides on one aryl ring increased the reactivity, and 2,4-dimethyl substitution on the other aryl ring provided a balance between the reactivity/crystallinity of the reagent as well as the atom economy. The utility of new reagents was demonstrated by the development of an efficient fluorocyclopropanation protocol to access a range of monofluorinated cyclopropane derivatives.



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INTRODUCTION

Large endeavors in the field of fluorine chemistry have resulted in many efficient new synthetic technologies to incorporate fluorine atoms into a synthetic target.[1] This situation is mainly driven by the fact that a plethora of pharmaceutical drugs,[2] agrochemicals[3] and materials[4] contain fluorine atoms in their chemical structure. One can distinguish two major approaches to accessing monofluorinated organic products: reactions that accommodate the formation of carbon−fluorine bonds or direct fluorination methodologies[5] and the use of preformed fluorinated building blocks.[6] Notably, significantly less investigated is the merger between these two approaches, an application of fluorocarbene precursors, the simplest of the fluoroorganic building blocks, allowing one fluorine and one carbon modification.[7] Fluoromethylation has recently been investigated, offering a single attachment point for the target substrate.[8] However, fluoromethylene group transfer[9−11] formally offers two connection points, giving access to monofluorinated 3-membered rings.[11d] Along this line, we have recently reported on fluoromethylene transfer[12] from *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**2a**) (Figure 1) via ylide intermediate as an alternative to freon ($CHFX_2$) chemistry[7] to access monofluorinated cyclopropane[12b,c] and epoxide[12a] derivatives. Reagent **2a**, originally developed[13] for monofluoromethylation, turned out to be efficient; however, it was not an optimal reagent for fluoromethylene transfer chemistry.[12c]

In the context of global health challenges and threats due to the limited arsenal humanity possesses to combat viral infections,[14] it is notable that multiple cyclopropane rings are present in many known antiviral agents, such as glaveprevir, boceprevir, simeprevir (HCV protease (serine protease) inhibitors), odanacatib (cathepsin and calpain protease (cysteine protease) inhibitors), and others.[15] The bioisosteric

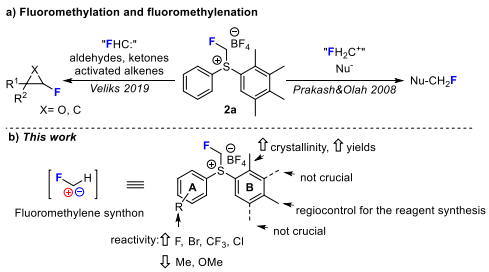

Figure 1. Diarylfluoromethyl sulfonium reagents: (a) fluoromethylation and fluoromethylenation; (b) identification of structural parameters for fluoromethylene-transfer applications.

replacement of hydrogen atoms with fluorine[16] is routine in medicinal chemistry programs; however, access to fluorocyclopropanes[17] is somewhat limited, and fluorocyclopropyl analogues of the aforementioned pharmaceuticals have not been reported.[18] In this endeavor, well-designed reagents as well as handy synthetic methods are of high priority. In our pursuit of developing new fluoromethylene transfer technologies, we have identified several problems of the currently employed fluoromethylsulfonium salts: (i) there is a high cost for the starting material 1,2,3,4-tetramethylbenzene for **2a**

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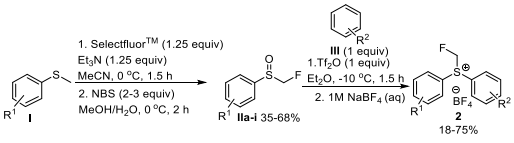
synthesis; (ii) all known monofluoromethylsulfonium salts were reported to be sticky oils, with some exceptions bearing bulky substituents (such as **2a**)[19]—not a favorable property for a practical reagent; (iii) some substrate classes underperformed using **2a**,[12c] for example, nitroalkenes; and (iv) there is a lack of reports of the structure influence on the reagent performance. Therefore, we opted to investigate the properties of sulfonium salts of type **2** to develop a new design of reagents specifically allocated for fluoromethylene transfer purposes.

RESULTS AND DISCUSSION

The synthetic studies initially started with optimization of the synthetic route to obtain fluoromethylene transfer reagents of type **2**. We have modified the existing synthetic routes to obtain sulfonium salts **2**, which typically involve overnight reactions and notorious reagents. We streamlined the process by the replacement of freon chemistry,[13] sluggish nucleophilic substitution[20] with fluoride, or potentially explosive DAST[19] with more user-friendly Selectfluor via a fast fluoro-Pummerer rearrangement process[21] allowing the synthesis of fluoromethylsulfonium reagents **2** within 1 day (Scheme 1). The fast

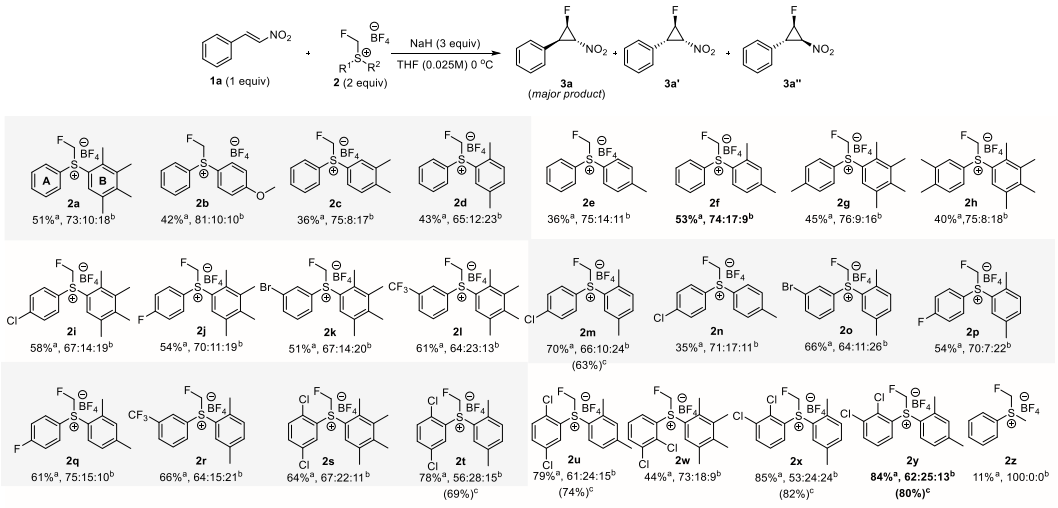
Scheme 1. Synthesis of Diarylfluoromethyl Sulfonium Salts 2



access to the collection of >20 novel reagents **2** allowed the identification of several key structural motifs of the sulfonium salt influencing the reactivity and properties. To investigate the efficiency of the reagents, we selected previously unreported monofluorocyclopropanation of β-nitrostyrene as a model reaction. Nitrostyrenes gave only moderate yields of the corresponding fluorocyclopropanes **3** when using reagent **2a**, a deliberately chosen platform for the detection of changes in reagent performance.

Our model reaction (Scheme 2) allowed us to uncover the reactivity profile of various fluoromethylsulfonium salts. For illustration purposes, we arbitrarily labeled the aryl rings with A and B denotations. The sulfonium salts **2** were arranged according to their substitution pattern in the aryl rings A and B and tested in the fluorocyclopropanation reaction with the aim of improving the F-cyclopropane **3** outcome. Performing the reaction with sulfonium salts **2a**–**f**, ring A remains unsubstituted, but ring B is decorated with methyl or methoxy groups at various positions, giving similar product **3a** yields. However, comparing the prices of the starting materials *m*-xylene (23 eur/mol, Alfa Aesar) and 1,2,3,4-tetramethylbenzene (3382 eur/mol, Alfa Aesar),[22] the comparable performance of the previously unreported reagent **2f** is clearly advantageous over the original tetramethyl-substituted sulfonium salt **2a**. The *o*-methyl group in ring B allows the maintenance of the crystallinity of the corresponding salts, as in our hands, reagents **2** lacking this substitution turned out to be a sticky oil and displayed significantly lower yields of **3a**. The yield of product **3a**, compared to the original reagent **2a**, is slightly decreased if additional methyl groups are introduced in the A ring (compounds **2g**–**h**). However, a slight improvement can be observed when the A ring is decorated with halogen or trifluoromethyl groups (**2i** and **2l**). Furthermore, reagent **2m**, with a decreased number of methyl groups at ring B and a preserved *p*-Cl substituent, gives product **3a** in a good 70% yield. This trend can also be observed for sulfonium salts **2o**, **2q**, and **2r**, but as mentioned above, the removal of *o*-methyl from ring B, as for **2n**, gives a drop in the yield of the desired fluorocyclopropane **3a**. Additional improvements can

Scheme 2. Probing Reagent 2 for Fluorocyclopropanation of Nitrostyrene 1a*



*Reaction conditions: **1a** (0.067 mmol), **2** (0.134 mmol), THF (2.7 mL), and NaH (0.201 mmol). [a]^{1}H NMR yield determined using EtOAc as an internal standard. [b]dr (**3a**/**3a′**/**3a″**) determined by ^{1}H NMR. [c]Isolated yields for the mixture of diastereomers of **3a**.

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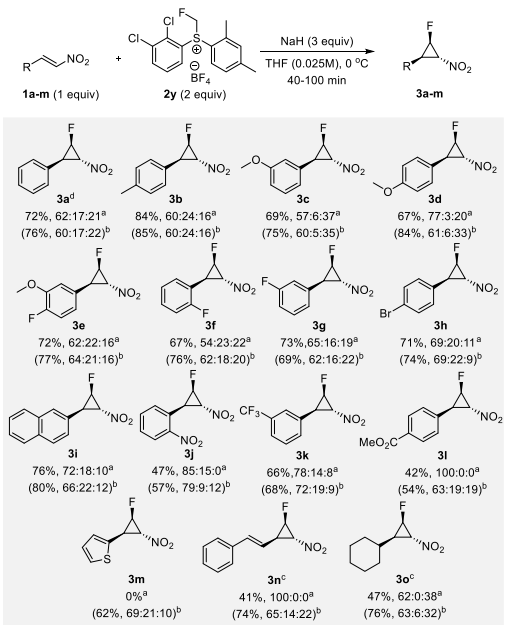
be achieved by the introduction of two halogens in the aryl system (**2t,u**). The modification of halogens at various positions of the benzene ring allowed a significant improvement in the product **3a** yield. The sulfonium salts **2x** and **2y** efficiently afforded **3a** in very good yields and moderate diastereoselectivity. Alkyl-substituted sulfonium salt **2z** performed poorly in the fluorocyclopropanation of nitrostyrene **1a**. Slow diffusion of Et_2O vapor into an acetonitrile solution of sulfonium salts **2a,d,i,p,s,w** resulted in the formation of monocrystals, which allowed us to obtain crystal structures (for more details on the solid structure of **2a**, see the SI). Out of the collection of fluoromethylsulfonium salts **2**, reagent **2f** stands out as the most affordable and **2y** as the most reactive. With improved reagent **2y** in hand, we investigated the substrate scope for the fluorocyclopropanation of nitroalkenes (Scheme 3). The nitrofluorocyclopropanes are formed with

Scheme 3. Fluorocyclopropanation of Nitroalkenes 1*



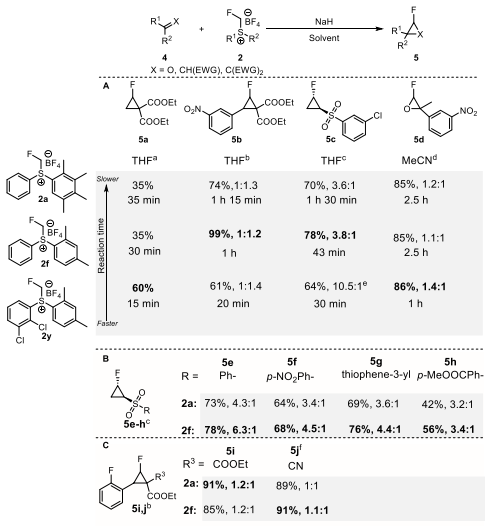
*Reaction conditions: nitroalkene **1** (0.201 mmol, 1 equiv), sulfonium salt **2y** (2 equiv), NaH (3 equiv), THF (0.025 M), 0 °C, 40−100 min. [a]Isolated yield for a mixture of diastereomers **3**/**3′**/**3″**, dr determined by ^{1}H or ^{19}F NMR. [b]Crude product yield determined by ^{1}H NMR using EtOAc as an internal standard, dr determined by ^{1}H or ^{19}F NMR. [c]Three equivalents of **2y** and 4.5 equiv of NaH were used. [d]The reaction was repeated on a 1 mmol scale of **1a**. Isolated yield of **3a** 75%, dr = 68:21:11, ^{1}H NMR yield of crude (72%, dr = 60:21:19).

moderate to very good yields with moderate diastereoselectivities. The aryl- and alkyl-substituted nitroalkenes participate in the reaction, providing a range of fluorocyclopropane **3** derivatives.

Various substituents at the aryl ring are tolerated, such as electron-donating groups (alkyl- **1b**, alkoxy- **1c−e**), halogen **1e−h**, and electron-accepting groups (nitro **1j**, trifluoromethyl- **1k**, and ester **1l**). Nitro- and ester-substituted substrates **1j,l** give fluorocyclopropanes **3j** and **3l** in moderate yield, but the *p*-methyl substituent gives product **3b** in the highest yield. The thiophene **1m**, conjugated diene **1n**, and **1o** alicyclic participate in the fluorocyclopropanation reaction as well, affording corresponding products **3m**, **3n**, and **3o**. The thiophene **3m** forms in rather good yield, as detected by ^{1}H NMR of a crude product; however, the product displayed instability upon chromatographic purification. All other nitrofluorocyclopropanes **3** were obtained as stable, chromatographically isolable products. Conjugated nitroalkene **1n** and cyclohexyl-substituted alkene **1o** gave products in moderate yields. The diastereomers can be readily separated by silica gel chromatography. Most of the nitrofluorocyclopropanes **3** are air-stable oils with naphthyl-substituted product **3i** as an exception, which is a solid. The relative configurations of all three isolated diastereomers of **3a** were assigned by analysis of J_{H-F} and J_{H-H} values in ^{1}H and ^{19}F NMR spectra and additionally supported by NOESY NMR (see the Experimental Section and SI). In order to demonstrate the Johnson−Corey−Chaykovsky[23,12] fluorocyclopropanation of nitroalkenes as a synthetic tool, the upscale of the reaction was performed on a 1 mmol scale, giving comparable results to those of the small-scale reaction.

Furthermore, we probed reagents **2a**, **2f**, and **2y** with other substrate classes (Scheme 4). The 2,4-dimethyl-substituted **2f** reagent performed similarly or slightly better than the original tetramethyl reagent **2a**.[12] For the fast-reacting substrate ethyl methylidene malonate (**4a**), 2,3-dichloro reagent **2y** significantly improved both the reaction time and the yield of product **5a**; however, for the slower reacting substrates **4b** and

Scheme 4. Comparison of Reagents 2a, 2f, and 2y for Different Substrate Classes*



*Isolated yields of **5** reported, dr determined by ^{1}H or ^{19}F NMR of crude product. Reaction conditions: alkene **4** (1 equiv), (a) sulfonium salt **2** (2 equiv), NaH (9.5 equiv), THF (0.0085 M), 0 °C; (b) sulfonium salt **2** (1.6 equiv), NaH (4 equiv), THF (0.07 M), rt; (c) sulfonium salt **2** (2 equiv), NaH (4 equiv), THF (0.1 M), rt; (d) sulfonium salt **2** (1.5 equiv), NaH (1.6 equiv), MeCN (0.05 M), 0 °C; (e) MeCN; (f) 1,4-dioxane used as a solvent.

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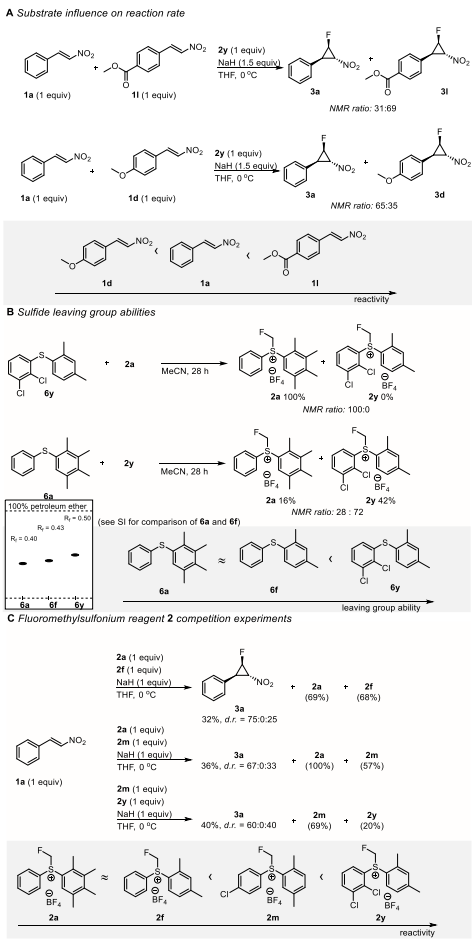
4c, the very reactive reagent **2y** gave lower yields. The prolonged reaction time resulted in competing polymerization of THF,[24] suggesting that **2y** may also act as a strong Lewis acid if not consumed by the substrate. Thus, **2f** is more suitable for Michael acceptors bearing sulfone groups or arylidene malonates. However, the fluoromethylene transfer to ketone **4d**,[12a] which takes 2.5 h with reagent **2a** in MeCN, proceeds in just 1 h when **2y** is used, giving fluoroepoxide **5y** in comparable yield to that of reagents **2a** and **2f**.

Several control experiments allowed us to draw the landscape of some reaction parameters (Scheme 5). The more electron-deficient substrate **1** (with EWG groups) reacts faster than the one with EDG (Scheme 5A). The leaving group capability of the corresponding diaryl sulfides **6** was probed by substitution reaction experiments with reagent **2** (Scheme 5B). Sulfide **6a** partially replaced **6y** in reagent **2y**; in contrast, **6y** was not capable of outcompeting **6a** from fluoromethylsulfonium salt **2a**. Compounds **6f** and **6a** have comparable leaving group abilities. In this context, it is worth mentioning the chromatographic behavior of diaryl sulfides—**6y** is less polar on silica gel than **6f** and **6a**. This is a favorable property of **6y** for purification purposes, diminishing the possibility of its coelution with products, which typically are more polar than sulfides **6**.

Scheme 5. Control Experiments



The reactivity of sulfonium reagent **2** was investigated by performing several competition experiments, which allowed ranking the selected reagents **2a,f,m,y** (Scheme 5C). The increased number of halogens increases the reactivity of **2**, which correlates well with a higher leaving group capability for halogenated reagents as well as faster reactions (Scheme 4) and improved performance (Scheme 2).

CONCLUSIONS

In conclusion, we have redesigned fluoromethylsulfonium salts for fluoromethylene transfer purposes. To investigate the reactivity of various diaryl fluoromethylsulfonium reagents using fluorocyclopropanation of nitroalkenes as the model reaction, we selected the best reagents for this purpose. (i) 2,4-dimethyl-substituted reagent **2f** offers a cheaper, simpler, and more efficient replacement for the known reagent **2a**; (ii) dichlorinated reagent **2y** turns out to be the most reactive reagent, offering superior performance for previously challenging substrates—nitroalkenes; and (iii) reagent **2f** followed by **2y** would be a rational protocol to search for the best conditions for fluoromethylene transfer chemistry. The reactivity of fluoromethylsulfonium salts increases upon decreasing electron density of the aryl ring. Halogen substituents increase reactivity, but methyl or methoxy substituents decrease reactivity. The *o*-methyl substituent on the aryl ring of reagent **2** provides crystallinity and maintains performance.

EXPERIMENTAL SECTION

General Information. Reagents and starting materials were obtained from commercial sources and used as received. Starting materials and dry solvents (1,4-dioxane, MeCN, DMF, DMSO) were purchased from Fluorochem, SigmaAldrich, Acros, or AlfaAeser and used as received. Anhydrous THF, Et_2O, and DCM were obtained from dry solvent still. Flash column chromatography was carried out using Kieselgel silica gel (35−70 and 60−200 μm). Thin-layer chromatography (TLC) was performed on silica gel using Merck TLC silca gel 60 F254 Aluminum sheets and was visualized by UV lamp, staining with $KMnO_4$. Preparative TLC was carrier out on 20 × 20 cm Merck TLC silca gel 60 F254 aluminum sheets. NMR spectra were recorded on 300 or 400 MHz Bruker spectrometers with chemical shift values (δ) in parts per million using the residual solvent signal as an internal reference. HRMS analyses were performed on a hybrid quadrupole time-of-flight mass spectrometer equipped with an electrospray ion source. Elemental analyses were performed by analytical service of LIOS. X-ray structures were investigated on a Rigaku, XtaLAB Synergy, Dualflex, or HyPix diffractometer. The X-ray structures were deposited with the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The compound names were generated using the ChemDraw structure to name convertor.

General Procedure A for the Synthesis of Sulfoxides IIa-i. Selectfluor (20.00 g, 56.46 mmol, 1.25 equiv) was suspended in anhydrous MeCN (85 mL) under argon atmosphere and cooled to 0 °C. To the suspension was added thioanisole (**Ia**) (5.30 mL, 45.2 mmol, 1 equiv) solution in anhydrous MeCN (10 mL) dropwise over 10 min at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and then to the mixture was slowly added Et_3N (7.87 mL, 56.5 mmol, 1.25 equiv). After 30 min, the reaction mixture was poured on water (500 mL), and the aqueous phase was extracted with petroleum ether (3 × 150 mL). The combined organic phases were

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dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude (fluoromethyl)(phenyl)sulfane intermediate was dissolved in a mixture of MeOH (80 mL) and H_2O (7 mL) and cooled to 0 °C. To the solution was added NBS (16.08 g, 90.33 mmol, 2.00 equiv), and the reaction mixture was stirred at the same temperature until full conversion (TLC control PE/EtOAc 1:1) (~2 h). The reaction mixture was quenched with 10% Na_2SO_3 (~50 mL), and saturated $NaHCO_3$ was added to the mixture until pH = 8. Then MeOH was partly evaporated under reduced pressure, and the suspension was extracted with DCM (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude sulfoxide **IIa** was purified by silica gel column chromatography (eluent gradient PE/EtOAc 5:1 to PE/EtOAc 1:1). The ((fluoromethyl)sulfinyl)benzene **IIa**[13] (2.74 g, 17.3 mmol, 38%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.63 (m, 2H), 7.63−7.52 (m, 3H), 5.10 (dd, J = 48.1, 8.1 Hz, 1H), 5.07 (dd, J = 47.6, 8.2 Hz, 1H).

*1-Chloro-4-((fluoromethyl)sulfinyl)benzene (**IIb**).* The product was obtained following general procedure A using 4-chlorothioanisole (**Ib**) (2.00 g, 12.6 mmol, 1.00 equiv), Selectfluor (5.58 g, 15.8 mmol, 1.25 equiv), Et_3N (2.20 mL, 15.8 mmol, 1.25 equiv), MeCN (24 mL), NBS (4.49 g, 25.2 mmol 2.00 equiv), MeOH (23 mL), and H_2O (2 mL). The product **IIb** (1.36 g, 7.07 mmol, 56%) was obtained as a white solid. Mp: 66−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−7.60 (m, 2H), 7.58−7.53 (m, 2H), 5.11 (dd, J = 47.9, 8.2 Hz, 1H), 5.06 (dd, J = 47.4, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.7, 137.4 (C−F, d, $^3J_{C-F}$ = 6.1 Hz), 130.1, 126.3, 97.8 (C−F, d, $^1J_{C-F}$ = 222.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −212.52 (t, J = 47.7 Hz).HRMS (ESI) m/z: [M + H]$^+$ calcd for C_7H_7OSClF 192.9890, found 192.9898.

*1,2-Dichloro-3-((fluoromethyl)sulfinyl)benzene (**IIc**).* The product was obtained following general procedure A, using 2,3-dichlorothioanisole (**Ic**) (1.000 g, 5.179 mmol, 1.00 equiv), Selectfluor (0.2293 g, 6.474 mmol, 1.25 equiv), Et_3N (0.90 mL, 6.5 mmol, 1.25 equiv), MeCN (26 mL), NBS (1.844 g, 10.36 mmol, 2.00 equiv), MeOH (22 mL), and H_2O (3 mL). The product **IIc** (0.4870 g, 2.145 mmol, 41%) was obtained as a white solid. Mp: 61−63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.81 (m, 1H), 7.68−7.64 (m, 1H), 7.55−7.49 (m, 1H), 5.46 (dd, J = 47.5, 8.5 Hz, 1H), 5.12 (dd, J = 48.1, 8.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.8 (C−F, d, $^3J_{C-F}$ = 8.4 Hz), 134.1, 133.6, 128.9, 128.6, 125.7, 97.2 (C−F, d, $^1J_{C-F}$ = 223.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −214.45 (t, J = 47.7 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_7H_6OSCl_2F$ 226.9500, found 226.9510.

*1-Bromo-3-((fluoromethyl)sulfinyl)benzene (**IId**).* The product was obtained following general procedure A, using 3-bromothioanisole (**Id**) (0.8400 g, 4.136 mmol, 1.00 equiv), Selectfluor (1.832 g, 5.170 mmol, 1.25 equiv), Et_3N (0.72 mL, 5.2 mmol, 1.25 equiv), MeCN (13 mL), NBS (1.472 g, 8.272 mmol, 2.00 equiv), MeOH (11 mL), and H_2O (1 mL). The product **IId** (0.4220 g, 1.780 mmol, 43%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (t, J = 1.8 Hz, 1H), 7.70 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.58 (dt, J = 7.8, 1.1 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 5.12 (dd, J = 47.8, 8.2 Hz, 1H), 5.09 (dd, J = 47.5, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.2 (C−F, d, $^3J_{C-F}$ = 6.1 Hz), 135.3, 131.1, 127.7 (C−F, d, $^4J_{C-F}$ = 0.6 Hz), 124.0, 123.4 (C−F, d, $^4J_{C-F}$ = 0.8 Hz), 98.0 (C−F, d, $^1J_{C-F}$ = 222.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −212.46 (t, J = 47.6 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for C_7H_7OFSBr 236.9385, found 236.9389.

*1-Fluoro-4-((fluoromethyl)sulfinyl)benzene (**IIe**).* The product was obtained following general procedure A, using 4-fluorothioanisole (**Ie**) (2.57 mL, 21.1 mmol, 1.00 equiv), Selectfluor (6.880 g, 26.37 mmol, 1.25 equiv), Et_3N (3.68 mL, 26.4 mmol, 1.25 equiv), MeCN (40 mL), NBS (7.510 g, 42.20 mmol, 2.50 equiv), MeOH (37 mL), and H_2O (3 mL). The product **IIe** (3.717 g, 9.715 mmol, 46%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72−7.66 (m, 2H), 7.30−7.24 (m, 2H), 5.09 (dd, J = 48.0, 8.2 Hz, 1H), 5.04 (dd, J = 47.4, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.2 (C−F, d, $^1J_{C-F}$ = 253.0 Hz), 134.3 (C−F, dd, $^{3,4}J_{C-F}$ = 6.1, 3.1 Hz), 127.3 (C−F, dd, $^{3,4}J_{C-F}$ = 9.2, 0.9 Hz), 117.2 (C−F, d, $^2J_{C-F}$ = 22.7 Hz), 97.8 (C−F, dd, $^{1,6}J_{C-F}$ = 222.3, 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.59 to −106.68 (m), −212.40 (t, J = 47.7 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_7H_7OF_2S$ 177.0186, found 177.0194.

*1-((Fluoromethyl)sulfinyl)-4-methylbenzene (**IIf**).*[19a] The product was obtained following general procedure A, using 4-methylthioanisole (**If**) (2.500 g, 18.09 mmol, 1.00 equiv), Selectfluor (8.009 g, 22.61 mmol, 1.25 equiv), Et_3N (3.15 mL, 22.6 mmol, 1.25 equiv), MeCN (50 mL), NBS (6.438 g, 36.17 mmol, 2.00 equiv), MeOH (60 mL), and H_2O (5 mL). The product **IIf** (1.096 g, 6.364 mmol, 35%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−7.54 (m, 2H), 7.39−7.35 (m, 2H), 5.07 (dd, J = 48.3, 8.2 Hz, 1H), 5.03 (dd, J = 47.5, 8.2 Hz, 1H), 2.43 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −211.47 (t, J = 48.1 Hz).

*1-((Fluoromethyl)sulfinyl)-3-(trifluoromethyl)benzene (**IIg**).* The product was obtained following general procedure A, using 3-trifluoromethylthioanisole (**Ig**) (0.6900 g, 3.590 mmol, 1.00 equiv), Selectfluor (2.226 g, 6.283 mmol, 1.75 equiv), Et_3N (0.88 mL, 6.3 mmol, 1.75 equiv), MeCN (9.8 mL), NBS (1.917 g, 10.770 mmol, 3.00 equiv), MeOH (9 mL), and H_2O (1 mL). The product **IIg** (0.3662 g, 1.619 mmol, 45%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.95 (m, 1H), 7.91−7.81 (m, 2H), 7.73 (tq, J = 7.7, 0.7 Hz, 1H), 5.16 (dd, J = 47.7, 8.2 Hz, 1H), 5.12 (dd, J = 47.4, 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 140.7 (C−F, d, $^3J_{C-F}$ = 6.1 Hz), 132.5 (C−F, q, $^2J_{C-F}$ = 33.5 Hz), 130.3, 129.0 (C−F, q, $^3J_{C-F}$ = 3.6 Hz), 128.2 (C−F, p, $^{4,5}J_{C-F}$ = 1.2 Hz), 123.1 (C−F, q, $^1J_{C-F}$ = 272.9 Hz), 121.9 (C−F, qd, $^{3,4}J_{C-F}$ = 3.8, 1.0 Hz) 97.6 (C−F, d, $^1J_{C-F}$ = 223.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.86, −213.12 (t, J = 47.3 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_8H_7OF_4S$ 227.0154, found 227.0161.

*4-((Fluoromethyl)sulfinyl)-1,2-dimethylbenzene (**IIh**).* The product was obtained following general procedure A, using 3,4-dimethylthioanisole (**Ih**) (1.000 g, 6.568 mmol, 1.00 equiv), Selectfluor (2.908 g, 8.210 mmol, 1.25 equiv), Et_3N (1.14 mL, 8.21 mmol, 1.25 equiv), MeCN (12 mL), NBS (2.338 g, 13.14 mmol, 2.00 equiv), MeOH (10 mL), and H_2O (1 mL). The product **IIh** (0.4600 g, 2.470 mmol, 38%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.38 (dd, J = 7.9, 1.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 5.06 (dd, J = 48.4, 8.2 Hz, 1H), 5.03 (dd, J = 47.5, 8.2 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.7, 138.7, 135.6 (C−F, d, $^3J_{C-F}$ = 6.3 Hz), 130.8, 125.6, 122.4, 98.5 (C−F, d, $^1J_{C-F}$ = 220.4 Hz), 20.0, 20.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −211.15 (t, J = 47.9 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_9H_{12}OFS$ 187.0593, found 187.0600.

*1,4-Dichloro-2-((fluoromethyl)sulfinyl)benzene (**IIi**).* The product was obtained following general procedure A, using 2,5-dichlorothioanisole (**Ii**) (3.000 g, 15.54 mmol, 1.00 equiv), Selectfluor (6.880 g, 19.42 mmol, 1.25 equiv), Et_3N (2.71 mL, 19.4 mmol, 1.25 equiv), MeCN (60 mL), NBS (6.913 g, 38.84 mmol, 2.50 equiv), MeOH (56 mL), and H_2O (6 mL). The product **IIi** (2.930 g, 10.53 mmol, 68%) was obtained as a white solid. Mp: 97−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (t, J = 2.2 Hz, 1H), 7.47 (ddd, J = 8.5, 2.5, 1.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 5.45 (dd, J = 47.5, 8.5 Hz, 1H), 5.14 (dd, J = 48.1, 8.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.2 (C−F, d, $^3J_{C-F}$ = 8.5 Hz), 135.3, 133.3, 131.3, 128.7, 127.5, 97.1 (C−F, d, $^1J_{C-F}$ = 223.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −214.58 (t, J = 47.7 Hz). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_7H_6OFSCl_2$ 226.9500, found 226.9501.

General Procedure B for the Synthesis of Diaryl Fluoromethyl Sulfonium Salts 2a−y.[13,19] ((Fluoromethyl)sulfinyl)-benzene (**IIa**) (2.7400 g, 17.321 mmol, 1 equiv) under argon atmosphere was dissolved in anhydrous Et_2O (80 mL), and to the solution was added 1,2,3,4-tetramethylbenzene (2.77 mL, 17.3 mmol, 1 equiv). To the obtained solution was added trifluoromethanesulfonic anhydride (2.84 mL, 17.3 mmol, 1 equiv) dropwise over 10 min at −10 °C. Upon addition, a solid formed and the resulting suspension was stirred until full conversion of the starting material **IIa** (TLC control PE/EtOAc 1:1) (~2 h). The formed solid was filtered and washed with Et_2O (3 × 20 mL). Then the solid was dissolved in DCM (20 mL) and washed with a 1 M $NaBF_4$ (6 × 30 mL) aqueous

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solution. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was triturated with Et_2O (3 × 40 mL) to afford product **2a**[13] (4.689 g, 12.96 mmol, 75%) as a gray solid. Mp: 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (m, 2H), 7.76−7.69 (m, 1H), 7.66 (m, 2H), 7.43 (s, 1H), 6.55 (dd, J = 46.6, 9.6 Hz, 1H), 6.42 (dd, J = 45.6, 9.5 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.45, −151.51, −207.18 (t, J = 46.4 Hz). Slow Et_2O vapor diffusion into an acetonitrile solution of **2a** gave suitable crystals for a single crystal XRD (CCDC 2032388).

(Fluoromethyl)(4-methoxyphenyl)(phenyl)sulfonium Tetrafluoroborate (2b). The product was obtained following general procedure B, using ((fluoromethyl)sulfinyl)benzene (**IIa**) (750 mg, 4.74 mmol, 1.00 equiv), methoxybenzene (0.52 mL, 4.7 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.78 mL, 3.2 mmol, 1.00 equiv), and Et_2O (25 mL). After addition of trifluoromethanesulfonic anhydride, a triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil was treated with PE, then PE/Et_2O 1:1 and Et_2O. The product **2b** (800 mg, 2.38 mmol, 50%) was obtained as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.79 (m, 4H), 7.77−7.71 (m, 1H), 7.70−7.64 (m, 2H), 7.21−7.15 (m, 2H), 6.54 (dd, J = 46.3, 9.3 Hz, 1H), 6.43 (dd, J = 46.1, 9.3 Hz, 1H), 3.90 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.72, −150.78, −207.88 (t, J = 46.2 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.3, 134.5, 134.4 (C−F, d, $^4J_{C-F}$ = 1.8 Hz), 131.5, 130.7, 122.1 (C−F, d, $^3J_{C-F}$ = 2.1 Hz), 117.3, 109.4 (C−F, d, $^3J_{C-F}$ = 1.7 Hz), 90.5 (C−F, d, $^1J_{C-F}$ = 241.2 Hz), 56.2. HRMS (ESI) m/z: [M]$^+$ calcd for $C_{14}H_{14}FOS^+$ 249.0744, found: 249.0753.

(3,4-Dimethylphenyl)(fluoromethyl)(phenyl)sulfonium Tetrafluoroborate (2c).[19a] The product was obtained following the modified general procedure B, using ((fluoromethyl)sulfinyl)benzene-(**IIa**) (500.0 mg, 3.161 mmol, 1.00 equiv), 1,2-dimethylbenzene (0.38 mL, 3.2 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.52 mL, 3.2 mmol, 1.00 equiv) and Et_2O (6.7 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. The anion exchanged was performed as described in procedure B. The product **2c** (693.0 mg, 2.074 mmol, 66%) was obtained as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.81 (m, 2H), 7.80−7.71 (m, 1H), 7.71−7.67 (m, 2H), 7.67−7.64 (m, 1H), 7.59 (dd, J = 8.1, 2.1 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 6.55 (dd, J = 46.3, 9.3 Hz, 1H), 6.49 (dd, J = 46.2, 9.3 Hz, 1H), 2.36 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.70, −150.75, −207.53 (t, J = 46.2 Hz).

(2,5-Dimethylphenyl)(fluoromethyl)(phenyl)sulfonium Tetrafluoroborate (2d).[19a] The product was obtained following the modified general procedure B, using ((fluoromethyl)sulfinyl)benzene (**IIa**) (500.0 mg, 3.161 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.39 mL, 3.2 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.52 mL, 3.2 mmol, 1.00 equiv) and Et_2O (6.5 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil was crystallized by treatment with PE, then PE/Et_2O 1:1 and Et_2O. The product **2d** (550.0 mg, 1.646 mmol, 52%) was obtained as a yellow solid. Mp: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84−7.75 (m, 2H), 7.78−7.72 (m, 1H), 7.72−7.64 (m, 2H), 7.63 (s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 46.4 Hz, 2H), 2.52 (s, 3H), 2.46 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.99, −151.04, −206.95 (t, J = 46.3 Hz). Slow Et_2O vapor diffusion into acetonitrile solution of **2d** gave suitable crystals for a single crystal XRD[CCDC 2032000].

(Fluoromethyl)(phenyl)(p-tolyl)sulfonium Tetrafluoroborate (2e). The product was obtained following the modified general procedure B, using ((fluoromethyl)sulfinyl)benzene (**IIa**) (500 mg, 3.16 mmol, 1.00 equiv), toulene (0.33 mL, 3.2 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.52 mL, 3.2 mmol, 1.00 equiv) and Et_2O (6.5 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil treated with PE, then PE/Et_2O 1:1 and Et_2O. The product **2e** (340 mg, 1.06 mmol, 34%) was obtained as a dark brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.83 (m, 2H), 7.80−7.72 (m, 3H), 7.70−7.64 (m, 2H), 7.51−7.47 (m, 2H), 6.55 (dd, J = 46.2, 9.4 Hz, 1H), 6.50 (dd, J = 46.1, 9.4 Hz, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.9, 134.8, 132.4, 131.8 (C−F, d, $^4J_{C-F}$ = 1.6 Hz), 131.6, 131.3 (C−F, d, $^4J_{C-F}$ = 1.2 Hz), 121.4 (C−F, d, $^3J_{C-F}$ = 1.9 Hz), 117.1 (C−F, d, $^3J_{C-F}$ = 1.5 Hz), 90.4 (C−F, d, $^1J_{C-F}$ = 242.4 Hz), 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.47, −150.53, −207.79 (t, J = 46.3 Hz). HRMS (ESI) m/z: [M]$^+$ calcd for $C_{14}H_{14}FS^+$ 233.0795, found 233.0811.

(2,4-Dimethylphenyl)(fluoromethyl)(phenyl)sulfonium Tetrafluoroborate (2f). The product was obtained following general procedure B, using ((fluoromethyl)sulfinyl)benzene (**IIa**) (0.2420 g, 1.530 mmol, 1.00 equiv), 1,3-dimethylbenzene (0.19 mL, 1.5 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.25 mL, 1.5 mmol, 1.0 equiv) and Et_2O (6 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange. The product **2f** (0.2928 g, 0.8762 mmol, 57%) was obtained as a beige solid. Mp 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80−7.75 (m, 2H), 7.75−7.70 (m, 2H), 7.68−7.63 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 6.53 (dd, J = 46.5, 9.4 Hz, 1H), 6.50 (dd, J = 45.9, 9.4 Hz, 1H), 2.52 (s, 3H), 2.42 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.01 to −151.16 (m), −207.30 (t, J = 46.2 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.8, 141.9, 134.7, 134.0, 131.6, 131.1, 130.8 (C−F, d, $^4J_{C-F}$ = 4.5 Hz), 130.3, 120.8 (C−F, d, $^3J_{C-F}$ = 2.6 Hz), 116.3, 89.6 (C−F, d, $^1J_{C-F}$ = 241.9 Hz), 21.6, 19.9. HRMS (ESI) m/z: [M]$^+$ calcd for $C_{15}H_{16}FS^+$ 247.0957, found 247.0964.

(Fluoromethyl)(2,3,4,5-tetramethylphenyl)(p-tolyl)sulfonium Tetrafluoroborate (2g).[19a] The product was obtained following general procedure B, using 1-((fluoromethyl)sulfinyl)-4-methylbenzene (**IIf**) (1.096 g, 6.364 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (1.02 mL, 6.36 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (1.04 mL, 0.874 mmol, 1.00 equiv) and Et_2O (40 mL). The product **2g** (1.870 g, 4.970 mmol, 78%) was obtained as a beige amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.64 (m, 2H), 7.48−7.43 (m, 2H), 7.41 (s, 1H), 6.49 (dd, J = 47.1, 9.6 Hz, 1H), 6.43 (dd, J = 46.2, 9.6 Hz, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.67, −151.73, −207.41 (t, J = 46.4 Hz).

(3,4-Dimethylphenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (2h). The product was obtained following general procedure B, using 4-((fluoromethyl)sulfinyl)-1,2-dimethylbenzene (**IIh**) (0.1560 g, 0.8376 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.12 mL, 0.84 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.14 mL, 0.87 mmol, 1.00 equiv) and Et_2O (5 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. After anion exchange the obtained oil was crystallized by treatment with PE, then PE/Et_2O 1:1, and Et_2O. The product **2h** (0.1250 g, 0.3203 mmol, 38%) was obtained as a beige solid. Mp: >110 dec °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.2, 2.3 Hz, 1H), 7.42−7.37 (m, 2H), 6.46 (dd, J = 46.8, 9.4 Hz, 1H), 6.42 (dd, J = 46.0, 9.4 Hz, 1H), 2.48 (s, 3H), 2.37 (s, 3H), 2.34 (s, 6H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.9, 143.8, 141.1, 139.4, 138.2, 137.2, 132.5, 131.5, 128.5, 128.3 (C−F, d, $^4J_{C-F}$ = 4.2 Hz), 117.4 (C−F, d, $^3J_{C-F}$ = 2.4 Hz), 116.8, 89.6 (C−F, d, $^1J_{C-F}$ = 240.7 Hz), 21.2, 20.2, 20.0, 17.7, 17.0, 16.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.61, −151.66, −207.23 (t, J = 46.4 Hz). HRMS (ESI) m/z: [M]$^+$ calcd for $C_{19}H_{24}FS^+$ 303.1583, found 303.1592.

(4-Chlorophenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (2i). The product was obtained following general procedure B, using 1-chloro-4-((fluoromethyl)-sulfinyl)benzene (**IIb**) (0.5000 g, 2.596 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.42 mL, 2.6 mmol, 1.00 equiv), trifluorome-

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thanesulfonic anhydride (0.43 mL, 2.6 mmol, 1.0 equiv), and Et_2O (12 mL). The product **2i** (0.5830 g, 1.470 mmol, 57%) was obtained as a gray solid. Mp: 115−120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79−7.70 (m, 2H), 7.65−7.60 (m, 2H), 6.57 (dd, J = 46.9, 9.5 Hz, 1H), 6.44 (dd, J = 45.9, 9.5 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.98, −151.03, −207.14 (t, J = 46.4 Hz). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.3, 141.7, 139.7, 138.6, 137.6, 132.5 (C−F, d, $^4J_{C-F}$ = 1.0 Hz), 131.8, 128.4 (C−F, d, $^4J_{C-F}$ = 4.7 Hz), 119.6 (C−F, d, $^3J_{C-F}$ = 2.9 Hz), 116.2, 89.8 (C−F, d, $^1J_{C-F}$ = 242.2 Hz), 21.3, 17.9, 17.1, 17.0. HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{19}ClFS^+$ 309.0875, found 309.0886. Slow Et_2O vapor diffusion into acetonitrile solution of **2i** gave suitable crystals for a single crystal XRD (CCDC 2032001).

*(Fluoromethyl)(4-fluorophenyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (**2j**).* The product was obtained following general procedure B, using 1-fluoro-4-((fluoromethyl)-sulfinyl)benzene (**IIe**) (0.3000 g, 1.703 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.28 mL, 1.7 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.28 mL, 1.7 mmol, 1.0 equiv), and Et_2O (7.5 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2j** (0.4995 g, 1.314 mmol, 77%) was obtained as a gray solid. Mp: 80−82 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89−7.83 (m, 2H), 7.46 (s, 1H), 7.39−7.29 (m, 2H), 6.53 (dd, J = 46.6, 9.2 Hz, 1H), 6.48 (dd, J = 45.5, 9.2 Hz, 1H), 2.46 (s, 3H), 2.38 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.3 (C−F, d, $^1J_{C-F}$ = 259.1 Hz), 144.2, 139.6, 138.6, 137.3, 134.1 (C−F, d, $^3J_{C-F}$ = 9.7 Hz), 128.2 (C−F, d, $^3J_{C-F}$ = 4.2 Hz), 119.1 (C−F, d, $^2J_{C-F}$ = 23.2 Hz), 116.5, 116.4 (C−F, t, $^{3,4}J_{C-F}$ = 3.1 Hz), 89.6 (C−F, d, $^1J_{C-F}$ = 241.2 Hz), 21.2, 17.7, 17.0, 16.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −101.04 to −101.13 (m), −150.93, −150.99, −207.12 (t, J = 46.1 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{19}F_2S^+$ 293.1176, found 293.1186.

*(3-Bromophenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (**2k**).* The product was obtained following general procedure B, using 1-bromo-3-((fluoromethyl)-sulfinyl)benzene (**IId**) (0.2000 g, 0.8436 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.14 mL, 0.84 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.14 mL, 0.84 mmol, 1.00 equiv) and Et_2O (5 mL). After anion exchange as described in procedure B the obtained oil was crystallized by treatment with PE, then PE/Et_2O 1:1 and Et_2O. The product **2k** (0.2500 g, 0.5668 mmol, 67%) was obtained as a gray solid. Mp: >130 dec °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88−7.80 (m, 2H), 7.74 (t, J = 1.9 Hz, 1H), 7.58 (t, J = 8.1 Hz, 1H), 7.42 (s, 1H), 6.57 (dd, J = 46.9, 9.5 Hz, 1H), 6.49 (dd, J = 45.7, 9.6 Hz, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.5, 139.7, 138.6, 137.9, 137.7, 133.0, 132.9, 129.8, 128.5 (C−F, d, $^4J_{C-F}$ = 4.9 Hz), 124.9, 123.3 (C−F, d, $^3J_{C-F}$ = 2.9 Hz), 115.7, 89.9 (C−F, d, $^1J_{C-F}$ = 243.2 Hz), 21.3, 17.9, 17.1, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.00, −151.05, −206.63 (t, J = 46.2 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{19}BrFS^+$ 353.0369, found 353.0386.

*(Fluoromethyl)(2,3,4,5-tetramethylphenyl)(3-(trifluoromethyl)-phenyl)sulfonium Tetrafluoroborate (**2l**).* The product was obtained following general procedure B, using 1-((fluoromethyl)sulfinyl)-3-(trifluoromethyl)benzene (**IIg**) (153.0 mg, 0.6764 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.11 mL, 0.68 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.11 mL, 0.68 mmol, 1.0 equiv), and Et_2O (4 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil was crystallized by treatment with PE, then PE/Et_2O 1:1 and Et_2O. The product **2l** (136.0 mg, 0.3161 mmol, 47%) was obtained as a beige solid. Mp: 96−99 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.91−7.85 (m, 2H), 7.43 (s, 1H), 6.63 (dd, J = 46.8, 9.4 Hz, 1H), 6.55 (dd, J = 45.5, 9.4 Hz, 1H), 2.50 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.7, 139.8, 138.8, 138.0, 134.6, 133.6 (C−F, q, $^2J_{C-F}$ = 34.1 Hz), 132.5, 131.1 (C−F, q, $^3J_{C-F}$ = 3.3 Hz), 128.5 (C−F, d, $^4J_{C-F}$ = 4.6 Hz), 127.5 (C−F, d, $^3J_{C-F}$ = 3.8 Hz), 123.3 (C−F, d, $^3J_{C-F}$ = 3.0 Hz), 122.7 (C−F, q, $^1J_{C-F}$ = 273.9 Hz), 115.5, 89.9 (C−F, d, $^1J_{C-F}$ = 242.9 Hz), 21.2, 17.9, 17.1, 17.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.93, −150.71, −150.76, −206.76 (t, J = 46.2 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{18}H_{19}F_4S^+$ 343.1144, found: 343.1143.

*(4-Chlorophenyl)(2,5-dimethylphenyl)(fluoromethyl)sulfonium Tetrafluoroborate (**2m**).* The product was obtained following general procedure B, using 1-chloro-4-((fluoromethyl)sulfinyl)benzene (**IIb**) (0.3000 g, 1.557 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.19 mL, 1.6 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.26 mL, 1.6 mmol, 1.00 equiv), and Et_2O (7.2 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. The anion exchange performed as described in procedure B. The product **2m** (0.1320 g, 0.3581 mmol, 23%) was obtained as a brown solid. Mp: 82−84 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.82−7.74 (m, 2H), 7.66−7.59 (m, 3H), 7.47 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 6.68−6.49 (m, 2H), 2.49 (s, 3H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.0, 140.2, 138.9, 136.3, 133.1, 132.8, 131.9, 130.5 (C−F, d, $^4J_{C-F}$ = 4.4 Hz), 119.6, 118.8 (C−F, d, $^3J_{C-F}$ = 2.8 Hz), 89.5 (C−F, d, $^1J_{C-F}$ = 242.2 Hz), 21.2, 19.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.47, −150.52, −206.88 (t, J = 45.8 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{15}ClFS^+$ 281.0562, found 281.0580.

*(4-Chlorophenyl)(fluoromethyl)(p-tolyl)sulfonium Tetrafluoroborate (**2n**).* The product was obtained following general procedure B, using 1-chloro-4-((fluoromethyl)sulfinyl)benzene (**IIb**) (0.4000 g, 2.076 mmol, 1.00 equiv), toluene (0.22 g, 2.1 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.34 mL, 2.1 mmol, 1.00 equiv), and Et_2O (4.3 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil was treated with PE, then PE/Et_2O 1:1 and Et_2O. The product **2n** (0.1300 g, 0.3666 mmol, 18%) was obtained as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.84−7.80 (m, 2H), 7.79−7.74 (m, 2H), 7.65−7.60 (m, 2H), 7.51−7.46 (m, 2H), 6.57 (dd, J = 46.1, 9.5 Hz, 1H), 6.45 (dd, J = 46.0, 9.3 Hz, 1H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.0, 141.9, 132.7 (C−F, d, $^4J_{C-F}$ = 1.5 Hz), 132.5, 131.8, 131.7 (d, J = 2.0 Hz), 119.8 (C−F, d, $^4J_{C-F}$ = 2.2 Hz), 117.0 (C−F, d, $^3J_{C-F}$ = 1.5 Hz), 90.3 (C−F, d, $^1J_{C-F}$ = 242.5 Hz), 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −149.92, −149.97, −207.97 (t, J = 46.1 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{14}H_{13}ClFS^+$ 267.0405, found 267.0422.

*(3-Bromophenyl)(2,5-dimethylphenyl)(fluoromethyl)sulfonium Tetrafluoroborate (**2o**).* The product was obtained following general procedure B, using 1-bromo-3-((fluoromethyl)sulfinyl)benzene (**IId**) (190 mg, 0.801 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.10 mL, 0.80 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.13 mL, 0.80 mmol, 1.00 equiv), and Et_2O (5 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. After anion exchange the obtained oil was crystallized by treatment with PE, then PE/Et_2O 1:1 and Et_2O. The product **2o** (95.0 mg, 0.230 mmol, 29%) was obtained as a brown solid. Mp: 85−90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89−7.85 (m, 2H), 7.76 (t, J = 1.9 Hz, 1H), 7.62 (s, 1H), 7.59 (t, J = 8.1 Hz, 1H), 7.51 (dd, J = 8.0, 1.7 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 6.62 (dd, J = 45.8, 9.6 Hz, 1H), 6.59 (dd, J = 46.7, 9.6 Hz, 1H), 2.52 (s, 3H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 140.3, 139.2, 138.0, 136.6, 133.3, 133.3, 132.9, 130.7 (C−F, d, $^4J_{C-F}$ = 4.8 Hz), 130.1, 125.0, 122.5 (C−F, d, $^3J_{C-F}$ = 2.9 Hz), 119.2, 89.8 (C−F, d, $^1J_{C-F}$ = 243.5 Hz), 21.3, 19.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.50, −150.55, −206.40 (t, J = 46.3 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{15}BrFS+$ 325.0056, found 325.0074.

*(2,5-Dimethylphenyl)(fluoromethyl)(4-fluorophenyl)sulfonium Tetrafluoroborate (**2p**).* The product was obtained following general

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procedure B, using 1-fluoro-4-((fluoromethyl)sulfinyl)benzene (**IIe**) (0.4000 g, 2.270 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.28 mL, 2.3 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.37 mL, 2.3 mmol, 1.00 equiv), and Et_2O (10 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2p** (0.1850 g, 0.5254 mmol, 23%) was obtained as a gray solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93−7.83 (m, 2H), 7.66 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.41−7.31 (m, 3H), 6.57 (dd, J = 45.5, 9.3 Hz, 1H), 6.54 (dd, J = 46.4, 9.3 Hz, 1H), 2.48 (s, 3H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.5 (C−F, d, $^1J_{C-F}$ = 259.8 Hz), 140.2, 138.6, 136.2, 134.5 (C−F, d, $^3J_{C-F}$ = 9.9 Hz), 133.1, 130.3 (C−F, d, $^4J_{C-F}$ = 4.2 Hz), 119.9, 119.3 (C−F, d, $^2J_{C-F}$ = 23.3 Hz), 115.5 (C−F, t, $^{3,4}J_{C-F}$ = 3.1 Hz), 89.4 (C−F, d, $^1J_{C-F}$ = 241.5 Hz), 21.2, 19.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −100.42 to −100.55 (m), −150.50, −150.56, −207.02 (t, J = 45.8 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{15}F_2S^+$ 265.0863, found 265.0871. Slow Et_2O vapor diffusion in **2p** acetonitrile solution gave suitable crystals for a single crystal XRD (CCDC 2032003).

*(2,4-Dimethylphenyl)(fluoromethyl)(4-fluorophenyl)sulfonium Tetrafluoroborate (**2q**).* The product was obtained following general procedure B, using 1-fluoro-4-((fluoromethyl)sulfinyl)benzene (**IIe**) (0.4000 g, 2.270 mmol, 1.00 equiv), 1,3-dimethylbenzene (0.28 mL, 2.3 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.37 mL, 2.3 mmol, 1.00 equiv), and Et_2O (10 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2q** (0.4640 g, 1.318 mmol, 58%) was obtained as a gray solid. Mp: 53−55 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (m, 2H), 7.77 (d, J = 8.3 Hz, 1H), 7.40−7.32 (m, 3H), 7.29 (s, 1H), 6.52 (d, J = 46.0 Hz, 2H), 2.51 (s, 3H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.4 (C−F, d, $^1J_{C-F}$ = 259.6 Hz), 146.9, 141.7, 134.3 (C−F, d, $^3J_{C-F}$ = 9.9 Hz), 134.0, 130.5 (C−F, d, $^4J_{C-F}$ = 4.4 Hz), 130.4, 119.2 (C−F, d, $^2J_{C-F}$ = 23.3 Hz), 116.6, 115.9 (C−F, d, $^{3,4}J_{C-F}$ = 3.2 Hz), 89.7 (C−F, d, $^1J_{C-F}$ = 241.6 Hz), 21.6, 19.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −100.71 to −100.79 (m), −150.68, −150.73, −207.33 (t, J = 45.9 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{15}F_2S^+$ 265.0863, found 265.0870.

*(2,5-Dimethylphenyl)(fluoromethyl)(3-(trifluoromethyl)phenyl)-sulfonium Tetrafluoroborate (**2r**).* The product was obtained following general procedure B, using 1-((fluoromethyl)sulfinyl)-3-(trifluoromethyl)benzene (**IIg**) (0.1800 g, 0.7958 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.11 mL, 0.68 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.10 mL, 0.80 mmol, 1.0 equiv), and Et_2O (5 mL). After addition of trifluoromethanesulfonic anhydride, triflate salt formed as an oil. Upon completion of the reaction the formed Et_2O layer was decanted from the product. After anion exchange as described in procedure B the obtained oil was treated with PE, then PE/Et_2O 1:1 and Et_2O. The product **2r** (65.0 mg, 0.161 mmol, 20%) was obtained as a brown amorphous solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.1 Hz, 1H), 8.05−7.96 (m, 1H), 7.92−7.84 (m, 2H), 7.63 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 46.7, 9.7 Hz, 1H), 6.64 (dd, J = 45.9, 9.7 Hz, 1H), 2.54 (s, 3H), 2.48 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 140.4, 139.4, 136.8, 135.0, 133.0 (C−F, q, $^2J_{C-F}$ = 34.3 Hz), 133.4, 132.5, 131.5 (C−F, q, $^3J_{C-F}$ = 3.2 Hz), 130.7 (C−F, d, $^4J_{C-F}$ = 5.0 Hz), 127.8 (C−F, d, $^3J_{C-F}$ = 3.7 Hz), 122.6 (C−F, q, $^1J_{C-F}$ = 273.7 Hz), 122.5 (C−F, d, $^3J_{C-F}$ = 2.9 Hz), 119.0, 90.0 (C−F, d, $^1J_{C-F}$ = 243.8 Hz), 21.3, 19.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.99, −150.09, −150.15, −206.44 (t, J = 46.4 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{16}H_{15}SF_4^+$ 315.0831, found 315.0835.

*(2,5-Dichlorophenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (**2s**).* The product was obtained following general procedure B, using 1,4-dichloro-2-((fluoromethyl)-sulfinyl)benzene (**IIi**) (0.3000 g, 1.321 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.21 mL, 1.3 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.22 mL, 1.3 mmol, 1.00 equiv), and Et_2O (24 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2s** (0.2109 g, 0.4892 mmol, 37%) was obtained as a beige solid. Product decomposition is observed in deuterated chloroform and deuterated acetonitrile solvent system. Mp: 178−182 °C. ^1H NMR (400 MHz, $CDCl_3$+ 10% MeCN - d_3): δ 7.64 (dd, J = 8.6, 2.2 Hz, 1H), 7.58 (s, 1H), 7.57−7.53 (m, 1H), 7.06 (s, 1H), 6.49 (dd, J = 45.9, 9.3 Hz, 1H), 6.32 (dd, J = 45.1, 9.3 Hz, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$+ 10% MeCN - d_3): δ 144.6, 139.4, 138.4, 137.5, 135.9, 135.4, 133.5, 132.8, 130.9 (C−F, d, $^4J_{C-F}$ = 3.1 Hz), 128.4 (C−F, d, $^4J_{C-F}$ = 3.0 Hz), 122.1 (C−F, d, $^3J_{C-F}$ = 2.0 Hz), 113.9, 88.0 (C−F, d, $^1J_{C-F}$ = 243.2 Hz), 20.5, 17.3, 16.6, 16.5. ^{19}F NMR (376 MHz, $CDCl_3$+ 10% MeCN-d_3): δ −146.76, −146.82, −200.62 (t, J = 45.7 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{18}FSCl_2^+$ 343.0490, found 343.0496. Slow Et_2O vapor diffusion into acetonitrile solution of **2s** gave suitable crystals for a single crystal XRD (CCDC 2031999).

*(2,5-Dichlorophenyl)(2,5-dimethylphenyl)(fluoromethyl)-sulfonium Tetrafluoroborate (**2t**).* The product was obtained following general procedure B, using 1,4-dichloro-2-((fluoromethyl)-sulfinyl)benzene (**IIi**) (0.5000 g, 2.202 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.27 mL, 2.2 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.36 mL, 2.2 mmol, 1.00 equiv), and Et_2O (40 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2t** (0.2533 g, 0.6285 mmol, 29%) was obtained as a brown solid. Product decomposition was observed in chloroform-*d*. Mp: >95 °C dec. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J = 8.6, 2.2 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.35 (s, 1H), 6.74 (dd, J = 46.9, 9.8 Hz, 1H), 6.61 (dd, J = 45.9, 9.8 Hz, 1H), 2.65 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR spectra was not obtained due to the product instability. ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.34, −204.96 (t, J = 46.3 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{14}FSCl_2$ + 315.0177, found 315.0190.

*(2,5-Dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)-sulfonium Tetrafluoroborate (**2u**).* The product was obtained following general procedure B, using 1,4-dichloro-2-((fluoromethyl)-sulfinyl)benzene (**IIi**) (0.5000 g, 2.202 mmol, 1.00 equiv), 1,3-dimethylbenzene (0.27 mL, 2.2 mmol, 1.0 equiv), trifluoromethanesulfonic anhydride (0.36 mL, 2.2 mmol, 1.0 equiv), and Et_2O (40 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2u** (0.3277 g, 0.8131 mmol, 37%) was obtained as a gray solid. Product decomposition is observed in chloroform-*d*. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 8.6, 2.2 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.38−7.30 (m, 2H), 6.70 (dd, J = 46.6, 9.6 Hz, 1H), 6.56 (dd, J = 45.9, 9.7 Hz, 1H), 2.65 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 147.5, 142.7, 136.1, 136.0, 134.2, 134.0, 133.2, 131.4 (C−F, d, $^4J_{C-F}$ = 3.5 Hz), 131.3 (C−F, d, $^4J_{C-F}$ = 3.3 Hz), 130.6, 122.4 (C−F, d, $^3J_{C-F}$ = 2.0 Hz), 114.8, 88.8 (C−F, d, $^1J_{C-F}$ = 243.8 Hz), 21.8, 19.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.31, −205.63 (t, J = 46.2 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{14}FSCl_2^+$ 315.0177, found 315.0189.

*(2,3-Dichlorophenyl)(fluoromethyl)(2,3,4,5-tetramethylphenyl)-sulfonium Tetrafluoroborate (**2w**).* The product was obtained following general procedure B, using 1,2-dichloro-3-((fluoromethyl)-sulfinyl)benzene (**IIc**) (0.2000 g, 0.8807 mmol, 1.00 equiv), 1,2,3,4-tetramethylbenzene (0.14 mL, 0.88 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.14 mL, 0.88 mmol, 1.00 equiv), and Et_2O (5 mL). The product **2w** (0.2560 g, 0.5938 mmol, 67%) was obtained as a brown solid. Mp: 114−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86−7.82 (m, 2H), 7.67 (t, J = 8.1 Hz, 1H), 7.14 (s, 1H), 6.67 (dd, J = 45.9, 9.2 Hz, 1H), 6.55 (dd, J = 45.7, 9.2 Hz, 1H), 2.63 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.7, 139.6, 138.8, 138.2, 136.3, 136.2, 133.6, 130.6, 130.5 (C−F, d, $^4J_{C-F}$ = 3.1 Hz), 128.9 (C−F, d, $^4J_{C-F}$ = 2.7 Hz), 123.5 (C−F, d, $^3J_{C-F}$ = 1.2 Hz), 115.0, 88.8 (C−F, d, $^1J_{C-F}$ = 241.8

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Hz), 21.1, 17.8, 17.1, 17.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.41, −151.46, −205.56 (t, J = 45.8 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{18}SCl_2F$+ 343.0490, found 343.0500. Slow Et_2O vapor diffusion in **2w** acetonitrile solution gave suitable crystals for a single crystal XRD (CCDC 2032002).

*(2,3-Dichlorophenyl)(2,5-dimethylphenyl)(fluoromethyl)-sulfonium Tetrafluoroborate (**2x**).* The product was obtained following general procedure B, using 1,2-dichloro-3-((fluoromethyl)-sulfinyl)benzene (**IIc**) (0.3000 g, 1.321 mmol, 1.00 equiv), 1,4-dimethylbenzene (0.16 mL, 1.3 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.22 mL, 1.3 mmol, 1.00 equiv), and Et_2O (10 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2x** (0.3140 g, 0.7791 mmol, 59%) was obtained as a white solid. Product decomposition is observed in chloroform-*d*. Mp: 84−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.81 (m, 2H), 7.73−7.63 (m, 1H), 7.47 (dd, J = 7.9, 1.7 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 6.71 (dd, J = 45.6, 9.2 Hz, 1H), 6.57 (dd, J = 45.5, 9.2 Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 140.4, 139.7, 136.7, 136.5, 136.4, 133.7, 133.0, 131.2 (C−F, d, $^4J_{C-F}$ = 2.6 Hz), 130.8, 130.6 (C−F, d, $^4J_{C-F}$ = 3.1 Hz), 122.8, 118.3, 88.6 (C−F, d, $^1J_{C-F}$ = 242.7 Hz), 21.1, 19.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.88, −205.72 (t, J = 45.4 Hz). HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{14}FSCl_2^+$ 315.0177, found 315.0188.

*(2,3-Dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)-sulfonium Tetrafluoroborate (**2y**).* The product was obtained following general procedure B, using 1,2-dichloro-3-((fluoromethyl)-sulfinyl)benzene (**IIc**) (0.3000 g, 1.321 mmol, 1.00 equiv), 1,3-dimethylbenzene (0.16 mL, 1.3 mmol, 1.00 equiv), trifluoromethanesulfonic anhydride (0.22 mL, 1.3 mmol, 1.00 equiv), and Et_2O (10 mL). The formed sulfonium triflate was washed with 0.5 M $NaBF_4$ aqueous solution for anion exchange as described in procedure B. The product **2y** (0.3630 g, 0.9006 mmol, 68%) was obtained as a white solid. Product decomposition is observed in deuterated chloroform. Mp: 111−112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.78 (m, 2H), 7.66 (t, J = 8.2 Hz, 1H), 7.44−7.37 (m, 1H), 7.34−7.32 (m, 1H), 7.30 (dd, J = 8.3, 2.0 Hz, 1H), 6.70 (dd, J = 45.8, 9.3 Hz, 1H), 6.53 (dd, J = 45.6, 9.3 Hz, 1H), 2.68 (s, 3H), 2.41 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.05, −206.04 (t, J = 45.8 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 147.4, 142.6, 136.4, 136.3, 133.9, 133.6, 131.5 (C−F, d, $^4J_{C-F}$ = 2.7 Hz), 130.6, 130.6, 130.5 (C−F, d, $^4J_{C-F}$ = 3.3 Hz), 123.1 (C−F, d, $^3J_{C-F}$ = 1.4 Hz), 115.0, 88.7 (C−F, d, $^1J_{C-F}$ = 242.8 Hz), 21.7, 19.9. HRMS (ESI) m/z: $[M]^+$ calcd for $C_{15}H_{14}FSCl_2^+$ 315.0177, found 315.0184.

*(Fluoromethyl)(methyl)(phenyl)sulfonium Tetrafluoroborate (**2z**).* (Fluoromethyl)(phenyl)(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate (**2b**) (200.0 mg, 0.5522 mmol) was added to thioanisole (2 mL) under argon atmosphere. The resulting suspension was stirred for 3 days at room temperature. To the reaction mixture petroleum ether (2 mL) was added, and the obtained suspension was carefully decanted from precipitate; addition of petroleum ether and decantation were repeated two more times. Precipitate was then washed with Et_2O (3 mL x 5). The product **2z** (118.6 mg, 0.4860 mmol, 88%) was obtained as a brown solid. Mp: 88−91 °C. ^{1}H NMR (300 MHz, MeCN- d_3): δ 7.92 (d, J = 7.6 Hz, 2H), 7.89−7.80 (m, 1H), 7.80−7.69 (m, 2H), 6.04 (dd, J = 46.0, 8.8 Hz, 1H), 5.97 (dd, J = 45.3, 8.4 Hz, 1H), 3.29 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$+ MeCN-d_3): δ 135.5, 131.4, 131.3, 120.2, 89.4 (C−F, d, $^1J_{C-F}$ = 238.9 Hz), 21.1 (C−F, d, $^3J_{C-F}$ = 5.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$ + MeCN-d_3): δ −145.87, −145.92, −209.15 (t, J = 46.1 Hz). HRMS: $[M]^+$ calcd for $C_8H_{10}FS^+$ 157.0487, found 157.0493.

Synthesis of α,β-Unsaturated Nitroalkenes 1a−o. The compounds **1a**−**l**,[25] **1m**,[26] **1n**,[27] and **1o**[28] were prepared following the literature procedures.

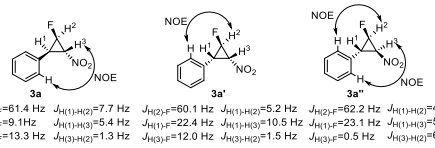
General Procedure for the Reagent 2 Performance Assessment in Fluorocyclopropanation of Nitrostyrene 1a. A mixture of nitrostyrene **1a** (0.067 mmol) and sulfonium salt **2** (0.1341 mmol) in anhydrous THF (2.7 mL) under Ar atmosphere was cooled to 0 °C. To the mixture was added NaH (0.2013 mmol). The reaction mixture was stirred at the same temperature until full conversion (determined by TLC using eluent PE/EtOAc) or for 6 h if full conversion was not achieved. To the reaction mixture was added Et_2O (5 mL), and the resulting suspension was filtered and the solid on the filter was washed with Et_2O (3 × 2 mL). The filtrate was evaporated under reduced pressure. To the residue were added $CDCl_3$ (0.6 mL) and an internal standard EtOAc (1 equiv). For the ^{1}H or ^{19}F NMR analysis the solution was transferred to an NMR tube.

General Procedure C for the Synthesis of Monofluorinated Nitrocyclopropanes 3a−m. (*E*)-(2-Nitrovinyl)benzene (**1a**) (30.0 mg, 0.201 mmol, 1 equiv) was dissolved in anhydrous THF (8 mL), and the formed solution was cooled to 0 °C. Then (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv) was added to the solution followed by immediate addition of NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv). The reaction mixture was stirred at 0 °C until full conversion of nitroalkene **1a** (TLC control, PE/EtOAc 10:1) (∼60 min). Et_2O (12 mL) was added to the reaction mixture, and after stirring for 10 min the resulting suspension was filtered. The filtrate was evaporated under reduced pressure to give a crude product **3a** (76%, dr = 60:17:22, determined by ^{1}H NMR, using EtOAc as an internal standard). The crude product was purified by silica gel column chromatography (eluent gradient PE/EtOAc 100:0 to PE/EtOAc 10:1). The product **3a** (26.2 mg, 0.145 mmol, 72%, dr = 62:17:21) was obtained as a yellow oil. The diastereomers can be separated using preparative TLC (PE/Et_2O 7:1). Three separate diastereomers were obtained.

((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)benzene (**3a**).* First fraction (14.2 mg, 0.0784 mmol, 39%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.35 (m, 3H), 7.31−7.27 (m, 2H), 5.47 (ddd, J = 61.4, 7.7, 1.3 Hz, 1H), 4.87 (ddd, J = 13.3, 5.4, 1.3 Hz, 1H), 3.47 (ddd, J = 9.1, 7.7, 5.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 129.9 (C−F, d, $^3J_{C-F}$ = 2.6 Hz), 129.0, 128.8 (C−F, d, $^4J_{C-F}$ = 1.1 Hz), 128.5, 75.8 (C−F, d, $^1J_{C-F}$ = 242.2 Hz), 63.5 (C−F, d, $^2J_{C-F}$ = 13.3 Hz), 35.3 (C−F, d, $^2J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.48 (ddd, J = 61.3, 13.3, 9.1 Hz). Anal. Calcd for $C_9H_8FNO_2$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.59; H, 4.45; N 7.73.

((1S,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)benzene (**3a′**).* Second fraction (3.2 mg, 0.018 mmol, 9%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.32 (m, 3H), 7.29−7.26 (m, 2H), 5.73 (ddd, J = 60.0, 5.2, 1.5 Hz, 1H), 4.97 (ddd, J = 12.0, 10.4, 1.5 Hz, 1H), 3.48 (ddd, J = 22.3, 10.5, 5.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 129.1, 129.0 (C−F, d, $^4J_{C-F}$ = 1.2 Hz), 128.9, 128.9 (C−F, d, $^3J_{C-F}$ = 2.4 Hz), 75.0 (C−F, d, $^1J_{C-F}$ = 238.7 Hz), 63.8 (C−F, d, $^2J_{C-F}$ = 13.5 Hz), 36.7 (C−F, d, $^2J_{C-F}$ = 10.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −206.65 (ddd, J = 60.1, 22.4, 12.0 Hz).

((1S,2R*,3S*)-2-Fluoro-3-nitrocyclopropyl)benzene (**3a″**).* Third fraction (4.3 mg, 0.024 mmol, 12%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.32 (m, 3H), 7.16−7.12 (m, 2H), 4.95 (ddd, J = 61.8, 6.3, 4.4 Hz, 1H), 4.58 (ddd, J = 6.2, 5.3, 0.5 Hz, 1H), 3.95 (dt, J = 23.1, 4.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 132.5 (C−F, d, $^3J_{C-F}$ = 1.2 Hz), 129.3, 128.5, 127.3, 74.8 (C−F, d, $^1J_{C-F}$ = 247.3 Hz), 63.8 (C−F, d, $^2J_{C-F}$ = 10.5 Hz), 32.2 (C−F, d, $^2J_{C-F}$ = 10.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −215.54 (dd, J = 62.2, 23.1 Hz).



Upscale Reaction for the Synthesis of 2-Fluoro-3-nitrocyclopropyl)benzene (3a). The reaction was performed following general procedure C on a 1 mmol scale of (*E*)-(2-nitrovinyl)benzene **1a**. Crude **3a** (72%, *d.r.* = 60:21:19, determined by ^{1}H NMR, using EtOAc as an internal standard). Isolated yield of **3a** (75%, 0.7524 mmol, dr = 68:21:11).

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*1-(2-Fluoro-3-nitrocyclopropyl)-4-methylbenzene (**3b**).* The product was obtained following general procedure C, using (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**1b**) (32.8 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.6036 mmol, 3 equiv), and THF (8 mL) to give the crude product **3b** (85%, dr = 60:24:16, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3b** (32.8 mg, 0.168 mmol, 84%, dr = 60:24:16) was obtained as a yellow oil. For separation of diastereomers a preparative TLC was used, eluting with PE/Et$_2$O 7:1. Three separate diastereomers were obtained.

1-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-4-methylbenzene (**3b**).* First fraction (17.5 mg, 0.0897 mmol, 45%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21−7.15 (m, 4H), 5.44 (ddd, J = 61.4, 7.7, 1.2 Hz, 1H), 4.83 (ddd, J = 13.3, 5.3, 1.3 Hz, 1H), 3.43 (ddd, J = 8.7, 7.8, 5.4 Hz, 1H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 138.4, 129.7, 128.7 (C−F, d, $^4J_{C-F}$ = 1.4 Hz), 126.8 (C−F, d, $^3J_{C-F}$ = 2.7 Hz), 75.8 (C−F, d, $^1J_{C-F}$ = 241.9 Hz), 63.6 (C−F, d, $^2J_{C-F}$ = 13.5 Hz), 35.2 (C−F, d, $^2J_{C-F}$ = 9.3 Hz), 21.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −216.50 (ddd, J = 61.3, 13.1, 9.0 Hz). Anal. Calcd for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; N, 7.18. Found: C, 62.37; H, 5.49; N 6.75.

1-((1S,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-4-methylbenzene (**3b′**).* Second fraction (7.2 mg, 0.037 mmol, 18%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.15 (m, 4H), 5.70 (ddd, J = 60.0, 5.2, 1.5 Hz, 1H), 4.94 (ddd, J = 12.0, 10.4, 1.5 Hz, 1H), 3.44 (ddd, J = 22.5, 10.4, 5.2 Hz, 1H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 138.8, 129.8, 128.8 (C−F, d, $^4J_{C-F}$ = 1.0 Hz), 125.7, 75.1 (C−F, d, $^1J_{C-F}$ = 238.2 Hz), 63.8 (C−F, d, $^2J_{C-F}$ = 13.9 Hz), 36.6 (C−F, d, $^2J_{C-F}$ = 10.7 Hz), 21.3. ^{19}F NMR (376 MHz, CDCl$_3$): δ −206.61 (ddd, J = 60.1, 22.4, 12.1 Hz).

1-((1S,2R*,3S*)-2-Fluoro-3-nitrocyclopropyl)-4-methylbenzene (**3b′′**).* Third fraction (5.1 mg, 0.026 mmol, 13%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18−7.14 (m, 2H), 7.06−7.01 (m, 2H), 4.92 (ddd, J = 61.9, 6.3, 4.4 Hz, 1H), 4.54 (ddd, J = 6.3, 5.3, 0.6 Hz, 1H), 3.91 (dt, J = 23.1, 4.8 Hz, 1H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 138.4, 130.0, 129.4 (C−F, d, $^3J_{C-F}$ = 1.1 Hz), 127.1, 74.9 (C−F, d, $^1J_{C-F}$ = 247.1 Hz), 63.8 (C−F, d, $^2J_{C-F}$ = 10.7 Hz), 32.0 (C−F, d, $^2J_{C-F}$ = 9.9 Hz), 21.2. ^{19}F NMR (376 MHz, CDCl$_3$): δ −215.67 (dd, J = 61.5, 22.9 Hz).

*1-(2-Fluoro-3-nitrocyclopropyl)-3-methoxybenzene (**3c**).* The product was obtained following general procedure C, using (*E*)-1-methoxy-3-(2-nitrovinyl)benzene (**3c**) (36.0 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)-sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3c** (75%, dr = 60:5:35, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3c** (29.2 mg, 0.138 mmol, 69%, dr = 57:6:37) was obtained as a yellow oil. For separation of diastereomers a preparative TLC was used, eluting with PE/Et$_2$O 7:1. Two separate diastereomers were obtained.

1-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-3-methoxybenzene (**3c**).* First fraction (13.9 mg, 0.0658 mmol, 33%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29 (t, J = 8.0 Hz, 1H), 6.92−6.83 (m, 2H), 6.81 (m, 1H), 5.45 (ddd, J = 61.4, 7.7, 1.3 Hz, 1H), 4.85 (ddd, J = 13.4, 5.4, 1.3 Hz, 1H), 3.81 (s, 3H), 3.44 (ddd, J = 9.1, 7.7, 5.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 160.0, 131.3 (C−F, d, $^3J_{C-F}$ = 2.6 Hz), 130.1, 121.1 (C−F, d, $^2J_{C-F}$ = 1.3 Hz), 114.8 (C−F, d, $^2J_{C-F}$ = 1.2 Hz), 113.8, 75.8 (C−F, d, $^1J_{C-F}$ = 242.5 Hz), 63.5 (C−F, d, $^2J_{C-F}$ = 13.5 Hz), 55.5, 35.2 (C−F, d, $^2J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −216.37 (ddd, J = 61.4, 13.7, 9.1 Hz). HRMS calcd for [M + H]$^+$: $C_{10}H_{11}NO_3F$ 212.0723, found 212.0719.

1-((1S,2R*,3S*)-2-Fluoro-3-nitrocyclopropyl)-3-methoxybenzene (**3c′′**).* Third fraction (8.6 mg, 0.041 mmol, 20%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.27 (t, J = 7.9 Hz, 1H), 6.86 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 6.71−6.66 (m, 2H), 4.94 (ddd, J = 61.8, 6.3, 4.4 Hz, 1H), 4.57 (td, J = 6.0, 5.4, 0.6 Hz, 1H), 3.92 (dt, J = 23.0, 4.8 Hz, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 160.3, 133.9 (C−F, d, $^3J_{C-F}$ = 1.2 Hz), 130.4, 119.2, 113.7, 113.3, 74.7 (C−F, d, $^1J_{C-F}$ = 247.3 Hz), 63.8 (C−F, d, $^2J_{C-F}$ = 11.0 Hz), 55.5, 32.2 (C−F, d, $^2J_{C-F}$ = 10.1 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −215.45 (dd, J = 61.8, 23.0 Hz).

*1-(2-Fluoro-3-nitrocyclopropyl)-4-methoxybenzene (**3d**).* The product was obtained following general procedure C, using (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (**1d**) (36.0 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)-sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3d** (84%, dr = 61:6:33, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3d** (28.6 mg, 0.135 mmol, 67%, dr = 77:3:20) was obtained as a yellow oil. For separation of the major diastereomer a preparative TLC was used, eluting with PE/Et$_2$O 7:1.

1-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-4-methoxybenzene (**3d**).* First fraction (17.7 mg, 0.0838 mmol, 42%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23−7.18 (m, 2H), 6.93−6.88 (m, 2H), 5.44 (ddd, J = 61.4, 7.7, 1.3 Hz, 1H), 4.79 (ddd, J = 13.3, 5.3, 1.3 Hz, 1H), 3.81 (s, 3H), 3.41 (ddd, J = 9.0, 7.7, 5.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 159.7, 130.0 (C−F, d, $^4J_{C-F}$ = 1.2 Hz), 121.8 (C−F, d, $^3J_{C-F}$ = 2.9 Hz), 114.5, 75.9 (C−F, d, $^1J_{C-F}$ = 241.6 Hz), 63.7 (C−F, d, $^2J_{C-F}$ = 13.4 Hz), 55.5, 34.9 (C−F, d, $^2J_{C-F}$ = 9.4 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −216.56 (ddd, J = 61.4, 13.3, 8.9 Hz). HRMS calcd for [M + H]$^+$: $C_{10}H_{11}NO_3F$ 212.0723, found 212.0726.

*1-Fluoro-4-(2-fluoro-3-nitrocyclopropyl)-2-methoxybenzene (**3e**).* The product was obtained following general procedure C, using (*E*)-1-fluoro-2-methoxy-4-(2-nitrovinyl)benzene (**1e**) (39.7 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)-(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.402 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.6036 mmol, 3 equiv) and THF (8 mL) to give the crude product **3e** (77%, dr = 64:21:16, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3e** (38.6 mg, 0.168 mmol, 72%, dr = 62:22:16) was obtained as a yellow oil. For separation of the major diastereomer a preparative TLC was used, eluting with PE/Et$_2$O 5:1.

1-Fluoro-4-((1R,2R*,3R*)-2-fluoro-3-nitrocyclopropyl)-2-methoxybenzene (**3e**).* First fraction (12.2 mg, 0.0532 mmol, 27%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.07 (dd, J = 11.0, 8.3 Hz, 1H), 6.87 (dd, J = 7.8, 2.2 Hz, 1H), 6.87−6.79 (m, 1H), 5.45 (ddd, J = 61.3, 7.7, 1.3 Hz, 1H), 4.81 (ddd, J = 13.4, 5.4, 1.3 Hz, 1H), 3.90 (s, 3H), 3.43 (ddd, J = 8.8, 7.8, 5.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 152.5 (C−F, d, $^1J_{C-F}$ = 247.9 Hz), 148.1 (C−F, d, $^2J_{C-F}$ = 11.0 Hz), 126.1 (C−F, dd, $^{3,4}J_{C-F}$ = 3.8, 2.7 Hz), 121.4 (C−F, dd, $^{3,4}J_{C-F}$ = 7.0, 1.5 Hz), 116.6 (C−F, d, $^2J_{C-F}$ = 18.8 Hz), 114.2, 74.5, 63.6 (C−F, d, $^2J_{C-F}$ = 13.5 Hz), 56.5, 34.7 (d, J = 9.2 Hz). ^{19}F NMR (376 MHz, CDCl$_3$): δ −134.70 (ddd, J = 11.1, 7.6, 4.0 Hz), −216.39 (ddd, J = 61.2, 13.1, 8.8 Hz). HRMS calcd for [M + H]$^+$: $C_{10}H_{10}NO_3F_2$ 230.0629, found 230.0624.

*1-Fluoro-2-(2-fluoro-3-nitrocyclopropyl)benzene (**3f**).* The product was obtained following general procedure C, using (*E*)-1-fluoro-2-(2-nitrovinyl)benzene (**1f**) (33.6 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3f** (76%, dr = 62:18:20, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3f** (26.7 mg, 0.134 mmol, 67%, dr = 54:23:22) was obtained as a yellow oil. For separation of diastereomers a preparative TLC was used, eluting with PE/Et$_2$O 7:1. Three separate diastereomers were obtained.

1-Fluoro-2-((1R,2R*,3R*)-2-fluoro-3-nitrocyclopropyl)benzene (**3f**).* First fraction (12.9 mg, 0.0648 mmol, 32%) a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40−7.30 (m, 1H), 7.29−7.21 (m, 1H), 7.19−7.08 (m, 2H), 5.50 (ddd, J = 61.3, 7.8, 1.4 Hz, 1H), 4.86 (ddd, J = 13.3, 5.5, 1.3 Hz, 1H), 3.52 (ddd, J = 8.8, 7.7, 5.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 161.9 (C−F, d, $^1J_{C-F}$ = 248.7 Hz), 130.4 (C−F, d, $^3J_{C-F}$ = 8.3 Hz), 129.9 (C−F, t, $^3J_{C-F}$ = 2.5 Hz), 124.5 (C−F, d, $^4J_{C-F}$ = 3.7 Hz), 117.3 (C−F, dd, $^{2,3}J_{C-F}$ = 14.3, 3.0 Hz), 116.0

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(C−F, d, $^{2}J_{C-F}$ = 21.2 Hz), 75.2 (C−F, d, $^{1}J_{C-F}$ = 242.5 Hz), 62.6 (C−F, d, $^{2}J_{C-F}$ = 13.7 Hz), 29.2 (C−F, dd, $^{2,3}J_{C-F}$ = 9.2, 4.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.52 to −115.64 (m), −216.02 (dddd, J = 61.1, 13.3, 8.8, 2.6 Hz). Anal. Calcd for $C_9H_7F_2NO_2$: C, 54.28; H, 3.54; N, 7.03. Found: C, 55.26; H, 3.77; N 6.60.

1-Fluoro-2-((1S,2R*,3R*)-2-fluoro-3-nitrocyclopropyl)benzene (**3f′**).* Second fraction (5.5 mg, 0.028 mmol, 14%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.27 (m, 2H), 7.16 (td, J = 7.6, 1.3 Hz, 1H), 7.07 (ddd, J = 9.5, 8.4, 1.1 Hz, 1H), 5.69 (ddd, J = 59.6, 5.2, 1.4, 0.5 Hz, 2H), 5.03 (ddd, J = 11.9, 10.2, 1.5 Hz, 1H), 3.40 (ddd, J = 21.8, 10.2, 5.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.9 (C−F, dd, $^{1,4}J_{C-F}$ = 248.4, 1.6 Hz), 130.7 (C−F, d, $^{3}J_{C-F}$ = 8.2 Hz), 130.5 (C−F, d, $^{3}J_{C-F}$ = 2.8 Hz), 124.6 (C−F, d, $^{4}J_{C-F}$ = 3.8 Hz), 116.5 (C−F, d, $^{2}J_{C-F}$ = 14.4 Hz), 116.0 (C−F, d, $^{2}J_{C-F}$ = 21.0 Hz), 74.8 (C−F, dd, $^{1,4}J_{C-F}$ = 239.8, 2.5 Hz), 63.1−62.9 (C−F, m), 31.2 (C−F, dd, $^{2,3}J_{C-F}$ = 11.6, 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −115.64 to −115.72 (m), −205.91 (ddd, J = 60.1, 21.8, 12.1 Hz).

1-Fluoro-2-((1S,2R*,3S*)-2-fluoro-3-nitrocyclopropyl)benzene (**3f′′**).* Third fraction (4.6 mg, 0.023 mmol, 12%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.28 (m, 1H), 7.18−7.06 (m, 3H), 5.09 (ddd, J = 61.7, 6.2, 4.5 Hz, 1H), 4.69 (ddd, J = 6.2, 5.5, 0.6 Hz, 1H), 3.93 (ddd, J = 23.1, 5.5, 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 161.3 (C−F, d, $^{1}J_{C-F}$ = 247.5 Hz), 130.3 (C−F, d, $^{3}J_{C-F}$ = 8.3 Hz), 129.2 (C−F, d, $^{3}J_{C-F}$ = 3.4 Hz), 124.8 (C−F, d, $^{4}J_{C-F}$ = 3.8 Hz), 119.9 (C−F, dd, $^{2,3}J_{C-F}$ = 13.8, 1.1 Hz), 116.3 (C−F, d, $^{2}J_{C-F}$ = 21.1 Hz), 74.1 (C−F, dd, $^{1,4}J_{C-F}$ = 247.0, 4.0 Hz), 63.2 (C−F, d, $^{2}J_{C-F}$ = 6.1 Hz), 27.7 (C−F, dd, $^{2,3}J_{C-F}$ = 11.5, 2.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.21 to −117.31 (m), −215.82 (ddd, J = 62.2, 23.1, 1.5 Hz).

*1-Fluoro-3-(2-fluoro-3-nitrocyclopropyl)benzene (**3g**).* The product was obtained following general procedure C, using (*E*)-1-fluoro-3-(2-nitrovinyl)benzene (**1g**) (33.6 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv) and THF (8 mL) to give the crude product **3g** (69%, dr = 62:16:22, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3g** (29.3 mg, 0.147 mmol, 73%, dr = 65:16:19) was obtained as a slightly yellow oil. For separation of diastereomers a preparative TLC was used, eluting with PE/Et_2O 7:1. Three separate diastereomers were obtained.

1-Fluoro-3-((1R,2R*,3*)-2-fluoro-3-nitrocyclopropyl)benzene (**3g**).* First fraction (16.7 mg, 0.0838 mmol, 42%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (td, J = 8.0, 6.0 Hz, 1H), 7.12−7.05 (m, 1H), 7.08−7.01 (m, 1H), 7.02−6.98 (m, 1H), 5.46 (ddd, J = 61.1, 7.7, 1.3 Hz, 1H), 4.84 (ddd, J = 13.4, 5.4, 1.3 Hz, 1H), 3.45 (td, J = 8.8, 7.7, 5.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 162.9 (C−F, d, $^{1}J_{C-F}$ = 247.5 Hz), 132.2 (C−F, dd, $^{3,3}J_{C-F}$ = 8.2, 2.8 Hz), 130.6 (C−F, d, $^{3}J_{C-F}$ = 8.4 Hz), 124.7 (C−F, dd, $^{4,4}J_{C-F}$ = 3.1, 1.4 Hz), 116.0 (C−F, dd, $^{2,4}J_{C-F}$ = 22.8, 1.7 Hz), 115.6 (C−F, d, $^{2}J_{C-F}$ = 21.0 Hz), 75.5 (C−F, d, $^{1}J_{C-F}$ = 242.8 Hz), 63.4 (C−F, d, $^{2}J_{C-F}$ = 13.5 Hz), 34.6 (C−F, d, $^{2,4}J_{C-F}$ = 9.2, 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −111.81 (td, J = 9.0, 6.0 Hz), −216.63 (ddd, J = 61.2, 13.1, 8.9 Hz). HRMS calcd for $[M + H]^+$: $C_9H_8NO_2F_2$ 200.0523, found 200.0511.

1-Fluoro-3-((1S,2R*,3R*)-2-fluoro-3-nitrocyclopropyl)benzene (**3g′**).* Second fraction (4.4 mg, 0.0221 mmol, 11%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (td, J = 8.0, 5.9 Hz, 1H), 7.08−7.04 (m, 1H), 7.04−6.98 (m, 2H), 5.70 (ddd, J = 59.8, 5.2, 1.5 Hz, 1H), 4.97 (ddd, J = 11.9, 10.4, 1.5 Hz, 1H), 3.45 (ddd, J = 21.9, 10.4, 5.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.0 (C−F, d, $^{1}J_{C-F}$ = 247.7 Hz), 131.2 (C−F, d, $^{3}J_{C-F}$ = 8.0 Hz), 130.7 (C−F, d, $^{3}J_{C-F}$ = 8.4 Hz), 124.7 (C−F, dd, $^{4,4}J_{C-F}$ = 3.0, 1.2 Hz), 116.2 (C−F, dd, $^{2,4}J_{C-F}$ = 22.5, 1.0 Hz), 116.1 (C−F, d, $^{2}J_{C-F}$ = 21.0 Hz), 74.7 (C−F, d, $^{1}J_{C-F}$ = 239.4 Hz), 63.7 (C−F, d, $^{2}J_{C-F}$ = 13.7 Hz), 36.0 (C−F, d, $^{2,4}J_{C-F}$ = 11.1, 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −111.73 to −111.84 (m), −206.67 (ddd, J = 59.9, 21.9, 12.0 Hz).

1-Fluoro-3-((1S,2R*,3S*)-2-fluoro-3-nitrocyclopropyl)benzene (**3g′′**).* Third fraction (5.8 mg, 0.029 mmol, 15%) a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (td, J = 8.1, 5.9 Hz, 1H), 7.03 (tdd, J = 8.4, 2.6, 0.9 Hz, 1H), 6.93 (ddt, J = 7.7, 1.7, 0.8 Hz, 1H), 6.86 (dt, J = 9.3, 2.2 Hz, 1H), 4.94 (ddd, J = 61.5, 6.4, 4.4 Hz, 1H), 4.58 (ddd, J = 6.2, 5.3, 0.7 Hz, 1H), 3.94 (dt, J = 22.7, 4.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 163.2 (C−F, d, $^{1}J_{C-F}$ = 248.3 Hz), 134.8 (C−F, dd, $^{3,3}J_{C-F}$ = 7.7, 1.1 Hz), 131.1 (C−F, d, $^{3}J_{C-F}$ = 8.4 Hz), 123.0 (C−F, d, $^{4}J_{C-F}$ = 3.1 Hz), 115.6 (C−F, d, $^{2}J_{C-F}$ = 21.0 Hz), 114.5 (C−F, d, $^{2}J_{C-F}$ = 22.5 Hz), 74.4 (C−F, d, $^{1}J_{C-F}$ = 247.9 Hz), 63.7 (C−F, d, $^{2}J_{C-F}$ = 10.7 Hz), 31.7 (C−F, dd, $^{2,4}J_{C-F}$ = 10.4, 2.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −111.26 (td, J = 8.9, 6.0 Hz), −215.38 (dd, J = 61.5, 22.8 Hz).

*1-Bromo-4-(2-fluoro-3-nitrocyclopropyl)benzene (**3h**).* The product was obtained following general procedure C, using (*E*)-1-bromo-4-(2-nitrovinyl)benzene(**1h**) (45.9 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3h** (74%, dr = 69:22:9, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3h** (36.9 mg, 0.142 mmol, 71%, dr = 69:20:11) was obtained as a yellow oil. For separation of diastereomers a preparative TLC was used, eluting with PE/Et_2O 7:1.

1-Bromo-4-((1R,2R*,3R*)-2-fluoro-3-nitrocyclopropyl)benzene (**3h**).* First fraction (24.5 mg, 0.0942 mmol, 47%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.49 (m, 2H), 7.18−7.14 (m, 2H), 5.46 (ddd, J = 61.2, 7.7, 1.3 Hz, 1H), 4.82 (ddd, J = 13.3, 5.4, 1.3 Hz, 1H), 3.41 (ddd, J = 8.8, 7.6, 5.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 132.2, 130.5 (C−F, d, $^{4}J_{C-F}$ = 1.5 Hz), 128.9 (C−F, d, $^{3}J_{C-F}$ = 2.7 Hz), 122.7, 75.5 (C−F, d, $^{1}J_{C-F}$ = 242.5 Hz), 63.3 (C−F, d, $^{2}J_{C-F}$ = 13.4 Hz), 34.5 (C−F, d, $^{2}J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.55 (ddd, J = 61.2, 13.2, 9.0 Hz). Anal. Calcd for $C_9H_7BrFNO_2$: C, 41.57; H, 2.71; N, 5.39. Found: C, 42.97; H, 3.08; N 4.87.

1-Bromo-4-((1S,2R*)-2-fluoro-3-nitrocyclopropyl)benzene (**3h′+3h′′**).* Second fraction (10.7 mg, 0.0411 mmol, 21%, dr = 67:33) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.45 (m, 4H), 7.18−7.13 (m, 2H), 7.06−6.99 (m, 2H), 5.68 (ddd, J = 59.8, 5.2, 1.5 Hz, 1H), 4.96 (ddd, J = 11.9, 10.4, 1.5 Hz, 1H), 4.92 (ddd, J = 61.5, 6.3, 4.4 Hz, 1H), 4.55 (ddd, J = 6.2, 5.3, 0.5 Hz, 1H), 3.90 (dt, J = 22.7, 4.8 Hz, 1H), 3.40 (ddd, J = 22.0, 10.4, 5.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 132.5, 132.3, 131.4 (C−F, d, $^{3}J_{C-F}$ = 1.0 Hz), 130.6 (C−F, d, $^{4}J_{C-F}$ = 1.3 Hz), 129.0 (C−F, d, $^{4}J_{C-F}$ = 0.6 Hz), 127.9, 123.1, 122.6, 74.7 (C−F, d, $^{1}J_{C-F}$ = 239.4 Hz), 74.4 (C−F, d, $^{1}J_{C-F}$ = 247.9 Hz), 63.9−63.4 (C−F, m), 36.0 (C−F, d, $^{2}J_{C-F}$ = 11.1 Hz), 31.6 (C−F, d, $^{2}J_{C-F}$ = 10.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −206.60 (ddd, J = 59.9, 22.0, 12.2 Hz), −215.45 (dd, J = 61.5, 22.4 Hz).

*2-(2-Fluoro-3-nitrocyclopropyl)naphthalene (**3i**).* The product was obtained following general procedure C, using (*E*)-2-(2-nitrovinyl)naphthalene (**1i**) (40.1 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3i** (80%, dr = 66:22:12, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3i** (35.5 mg, 0.154 mmol, 76%, dr = 72:18:10) was obtained as a slightly yellow oil. For separation of the major diastereomer a silica gel column chromatography was used, eluting with PE/EtOAc 10:1.

2-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)naphthalene (**3i**).* First fraction (12.8 mg, 0.0554 mmol, 28%) white solid. Mp: 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.81 (m, 3H), 7.78 (s, 1H), 7.57−7.47 (m, 2H), 7.36 (dd, J = 8.5, 1.9 Hz, 1H), 5.54 (ddd, J = 61.3, 7.7, 1.3 Hz, 1H), 4.98 (ddd, J = 13.3, 5.4, 1.3 Hz, 1H), 3.63 (ddd, J = 9.0, 7.6, 5.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 133.3, 133.0, 128.9, 128.2 (C−F, d, $^{4}J_{C-F}$ = 1.5 Hz), 127.9, 127.9, 127.2 (C−F, d, $^{3}J_{C-F}$ = 2.6 Hz), 126.9, 126.8, 126.2 (C−F, d, $^{4}J_{C-F}$ = 1.2 Hz), 75.9 (C−F, d, $^{1}J_{C-F}$ = 242.5 Hz), 63.6 (C−F, d, $^{2}J_{C-F}$ = 13.5 Hz), 35.5 (C−F, d, $^{2}J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.14 (ddd, J = 61.3, 13.1, 9.0 Hz). HRMS calcd for $[M + H]^+$: $C_{13}H_{11}NO_2F$ 232.0778, found 232.0774.

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1-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-2-nitrobenzene (**3j**).* The product was obtained following general procedure C, using (*E*)-1-nitro-2-(2-nitrovinyl)benzene (**1j**) (32.2 mg, 0.166 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)-sulfonium tetrafluoroborate (**2y**) (133.7 mg, 0.3317 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 19.9 mg, 0.604 mmol, 3 equiv), and THF (6.6 mL) to give the crude product **3j** (57%, *dr* = 79:9:12, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3j** (17.6 mg, 0.0778 mmol, 47%, dr = 85:15:0) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 8.15 (dd, J = 8.4, 1.4 Hz, 1H), 7.71−7.66 (m, 1H), 7.61−7.54 (m, 2H), 5.55 (ddd, J = 60.6, 7.6, 1.2 Hz, 1H), 4.77 (ddd, J = 13.7, 5.8, 1.2 Hz, 1H), 3.93 (ddd, J = 8.7, 7.7, 5.5 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ (major diastereomer) 149.8, 134.0, 132.0 (C−F, d, $^4J_{C-F}$ = 1.8 Hz), 130.0, 125.7, 125.2 (C−F, d, $^3J_{C-F}$ = 3.3 Hz), 75.4 (C−F, d, $^1J_{C-F}$ = 241.8 Hz), 63.5 (C−F, d, $^2J_{C-F}$ = 13.7 Hz), 33.1 (C−F, d, $^2J_{C-F}$ = 8.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ (major diastereomer) −213.54 (ddd, J = 60.3, 13.3, 8.2 Hz). Anal. Calcd for $C_9H_7FN_2O_4$: C, 47.80; H, 3.12; N, 12.39. Found: C, 48.40; H, 3.28; N, 11.86.

*1-(2-Fluoro-3-nitrocyclopropyl)-3-(trifluoromethyl)benzene (**3k**).* The product was obtained following general procedure C, using (*E*)-1-(2-nitrovinyl)-3-(trifluoromethyl)benzene (**1k**) (43.7 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)-(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv) and THF (8 mL) to give the crude product **3k** (68%, *dr* = 72:19:9, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, **3k** (32.8 mg, 0.132 mmol, 66%, dr = 78:14:8 obtained as a yellow oil. For separation of the major diastereomer a preparative TLC was used, eluting with PE/Et_2O 7:1.

1-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)-3-(trifluoromethyl)benzene (**3k**).* First fraction (22.9 mg, 0.0919 mmol, 46%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.60 (m, 1H), 7.57−7.46 (m, 3H), 5.50 (ddd, J = 61.1, 7.7, 1.3 Hz, 1H), 4.89 (ddd, J = 13.4, 5.4, 1.3 Hz, 1H), 3.52 (ddd, J = 8.8, 7.7, 5.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 132.2 (C−F, p, $^{4,5}J_{C-F}$ = 1.2 Hz), 131.6 (C−F, d, $^2J_{C-F}$ = 32.6 Hz), 131.0 (C−F, d, $^3J_{C-F}$ = 2.7 Hz), 129.6, 125.8 (C−F, d, $^{3,4}J_{C-F}$ = 3.8, 1.3 Hz), 125.4 (C−F, d, $^3J_{C-F}$ = 3.7 Hz), 123.8 (C−F, d, $^1J_{C-F}$ = 272.5 Hz), 75.4 (C−F, d, $^1J_{C-F}$ = 242.7 Hz), 63.2 (C−F, d, $^2J_{C-F}$ = 13.6 Hz), 34.4 (C−F, d, $^2J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.83, −216.49 (ddd, J = 61.0, 13.5, 8.8 Hz). Unstable under HRMS conditions.

Methyl 4-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)benzoate (**3l**).* The product was obtained following general procedure C, using methyl (*E*)-4-(2-nitrovinyl)benzoate (**1l**) (41.6 mg, 0.201 mmol, 1 equiv), (2,3-dichlorophenyl)(2,4-dimethylphenyl)-(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (162.1 mg, 0.4023 mmol, 2 equiv), NaH (60% dispersion in mineral oil, 24.1 mg, 0.604 mmol, 3 equiv), and THF (8 mL) to give the crude product **3l** (54%, dr = 63:19:19, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification, with silica gel column chromatography and preparative TLC (PE/Et_2O 5:1) main diastereomer **3l** (20.2 mg, 0.0844 mmol, 42%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−8.00 (m, 2H), 7.39−7.32 (m, 2H), 5.49 (ddd, J = 61.2, 7.7, 1.4 Hz, 1H), 4.90 (ddd, J = 13.4, 5.4, 1.4 Hz, 1H), 3.92 (s, 3H), 3.49 (ddd, J = 8.8, 7.7, 5.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.5, 134.9 (C−F, d, $^3J_{C-F}$ = 2.4 Hz), 130.3, 130.2, 128.9 (C−F, d, $^4J_{C-F}$ = 1.3 Hz), 75.6 (C−F, d, $^1J_{C-F}$ = 242.9 Hz), 63.4 (C−F, d, $^2J_{C-F}$ = 13.4 Hz), 52.4, 34.8 (C−F, d, $^2J_{C-F}$ = 9.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.47 (ddd, J = 61.2, 13.1, 9.0 Hz). HRMS calcd for $[M + H]^+$: $C_{11}H_{11}NO_4F$ 240.0672, found: 240.0671.

((E)-2-((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)vinyl)benzene (**3n**).* The product was obtained following a modified general procedure C, where ((1*E*,3*E*)-4-nitrobuta-1,3-dien-1-yl)benzene (**1n**) (38.0 mg, 0.217 mmol, 1 equiv) was dissolved in THF (8.7 mL) and at 0 °C (2,3-dichlorophenyl)(2,4-dimethylphenyl)-(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (174.9 mg, 0.4339 mmol, 2 equiv) and NaH (60% dispersion in mineral oil, 26.0 mg, 0.651 mmol, 3 equiv) were added. After 1 h, an additional portion of (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (87.5 mg, 0.217 mmol, 1 equiv) and NaH (60% dispersion in mineral oil, 13.0 mg, 0.325 mmol, 1.5 equiv) was added, and the mixture was stirred for another 60 min to give the crude product **3n** (74%, dr = 65:14:22, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification by silica gel column chromatography and preparative TLC (PE/Et_2O 7:1) main diastereomer **3n** (18.3 mg, 0.0883 mmol, 41%) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.26 (m, 5H), 6.80 (d, J = 15.9 Hz, 1H), 5.94 (dd, J = 15.9, 8.9 Hz, 1H), 5.40 (ddd, J = 60.4, 7.4, 1.2 Hz, 1H), 4.62 (ddd, J = 13.7, 4.7, 1.3 Hz, 1H), 3.09 (dddd, J = 9.0, 8.2, 4.7, 0.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 136.7, 135.9, 128.9, 128.6, 126.5, 117.3 (C−F, d, $^3J_{C-F}$ = 7.4 Hz), 75.8 (C−F, d, $^1J_{C-F}$ = 240.3 Hz), 63.4 (C−F, d, $^2J_{C-F}$ = 14.2 Hz), 34.9 (C−F, d, $^2J_{C-F}$ = 9.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.47 (ddd, J = 60.3, 13.7, 8.2 Hz). HRMS calcd for $[M + H]^+$: $C_{11}H_{11}FNO_2$ 208.0774, found: 208.0772.

*(2-Fluoro-3-nitrocyclopropyl)cyclohexane (**3o**).* The product was obtained following a modified general procedure C, where (*E*)-(2-nitrovinyl)cyclohexane (**1o**) (26.2 mg, 0.169 mmol, 1 equiv) was dissolved in THF (8.7 mL) and at 0 °C (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (136.1 mg, 0.3377 mmol, 2 equiv) and NaH (60% dispersion in mineral oil, 20.3 mg, 0.507 mmol, 3 equiv) were added. After 1 h, an additional portion of (2,3-dichlorophenyl)(2,4-dimethylphenyl)-(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (68 mg, 0.17 mmol, 1 equiv) and NaH (60% dispersion in mineral oil, 10.1 mg, 0.253 mmol, 1.5 equiv) was added and the mixture was stirred for another 40 min to give the crude product **3o** (76% dr = 63:6:32, determined by ^{1}H NMR, using EtOAc as an internal standard). After purification with silica gel column chromatography and preparative TLC (PE/EtOAc 30:1) two diastereomers were obtained.

((1R,2R*,3R*)-2-Fluoro-3-nitrocyclopropyl)cyclohexane (**3o**).* First fraction (9.1 mg, 0.049 mmol, 29%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.27 (ddd, J = 61.8, 7.5, 0.9 Hz, 1H), 4.31 (ddd, J = 13.4, 4.9, 0.9 Hz, 1H), 2.09 (dddd, J = 10.4, 9.2, 7.5, 5.0 Hz, 1H), 1.90−1.63 (m, 6H), 1.28−1.20 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 76.5 (C−F, d, $^1J_{C-F}$ = 238.2 Hz), 62.1 (C−F, d, $^2J_{C-F}$ = 13.4 Hz), 38.1 (C−F, d, $^2J_{C-F}$ = 9.4 Hz), 33.9 (C−F, d, $^3J_{C-F}$ = 4.4 Hz), 32.5, 32.4, 26.0, 25.9, 25.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −219.16 (ddd, J = 62.0, 13.4, 9.2 Hz).

((1S,2R*,3S*)-2-Fluoro-3-nitrocyclopropyl)cyclohexane (**3o′′**).* Third fraction (5.8 mg, 0.031 mmol, 18%) a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (ddd, J = 62.7, 6.3, 4.4 Hz, 1H), 4.14 (dd, J = 6.3, 5.1 Hz, 1H), 2.62 (ddd, J = 24.0, 9.5, 4.8 Hz, 1H), 1.85−1.62 (m, 5H), 1.31−1.02 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 74.2 (C−F, d, $^1J_{C-F}$ = 243.7 Hz), 61.6 (C−F, d, $^2J_{C-F}$ = 11.2 Hz), 36.4, 34.4 (C−F, d, $^2J_{C-F}$ = 6.8 Hz), 31.5, 31.0, 26.0, 25.7, 25.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −216.35 (dd, J = 63.0, 24.0 Hz). HRMS calcd for $[M + H]^+$: $C_9H_{15}NO_2F$ 188.1087, found: 188.1081.

Synthesis of other Fluorocyclopropanes 5a−j. *Diethyl 2-Fluorocyclopropane-1,1-dicarboxylate (**5a**).*[12c] To a solution of diethyl 2-methylenemalonate (**4a**) (30 mg, 0.17 mmol, 1.0 equiv) in anhydrous THF (20 mL) cooled in ice bath under Ar atmosphere was added sulfonium salt **2y** (140.5 mg, 0.349 mmol, 2.0 equiv) followed by NaH (60% dispersion in mineral oil, 66 mg, 1.7 mmol, 9.5 equiv). The reaction mixture was stirred for 15 min at 0 °C. The color of the reaction mixture changed from pale gray turbid to light brown. A TLC control (PE/Et_2O 3:1) indicated full conversion of the starting material **4a** (R_f 0.25, staining with $KMnO_4$ TLC stain, color appears without heating) after 10 min. While still cold, the solvent was evaporated under reduced pressure (do not immerse the flask in a heating bath!). The resulting brown residue was suspended in petroleum ether (PE) (∼2 mL), and directly transferred to a Pasteur pipet equipped with a cotton plug and silica gel (H 45 mm, W 6 mm). The residue was eluted with 100% PE until all (2,3-dichlorophenyl)-(2,4-dimethylphenyl)sulfane (**6y**) was collected (R_f 0.64 PE/Et_2O 3:1), and then the eluent was switched to PE/Et_2O 3:1 (fraction volume ∼0.6 mL) to collect the desired fluorocyclopropane **5a** (R_f

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0.35 PE/Et_2O 3:1). After solvent evaporation (do not immerse in the heating bath! Product could be volatile) the desired product **5a** (21.4 mg, 60%) was obtained as a colorless oil.

Under the same conditions, the reagents **2a** and **2f** showed full conversion of the starting material **4a** in 35 and 30 min correspondingly. The corresponding isolated yields of **5a** (12.5 mg, 35%) for the reagent **2a** and **5a** (12.5 mg, 35%) for the reagent **2f**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.06 (ddd, J = 64.4, 6.1, 4.2 Hz, 1H), 4.37−4.09 (m, 4H), 2.21−2.09 (m, 1H), 1.63−1.53 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.0, 164.7 (C−F, d, $^3J_{C-F}$ = 3.3 Hz), 75.0 (C−F, d, $^1J_{C-F}$ = 234.6 Hz), 62.2, 62.0, 34.6 (C−F, d, $^2J_{C-F}$ = 12.3 Hz), 20.1 (C−F, d, $^2J_{C-F}$ = 9.1 Hz), 14.2, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −212.50 (ddd, J = 64.3, 22.2, 14.2 Hz).

General Procedure for the Synthesis of Vinyl Sulfones 4c,e−h. The vinylsulfones **4c,e−h** were synthesized following the literature procedure.[12b]

General Procedure E for the Synthesis of Fluorocyclopropyl Sulfones 5c,e−h. To a solution of 1-chloro-3-(vinylsulfonyl)-benzene (**4c**) (21.1 mg, 0.10 mmol, 1 equiv) in anhydrous THF (1 mL) under argon atmosphere was added (2,4-dimethylphenyl)-(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (69.6 mg, 0.21 mmol, 2 equiv) at room temperature. To the reaction mixture was added NaH (60% dispersion in mineral oil, 16.7 mg, 0.42 mmol, 4 equiv). The reaction mixture was stirred at room temperature until completion (30−40 min) (TLC control). The reaction mixture was filtered through a cotton plug, and the collected precipitate on the plug was washed with THF (3 × 2 mL). The filtrate was evaporated under reduced pressure (*trans*/*cis* dr = 3.8:1 of crude by ^{19}F NMR). The crude product was purified by prep. TLC (eluent: PE, PE/EtOAc, 3/1). After chromatography the *trans* product **5c** 19.0 mg (78%) was obtained as a yellowish oil.

Under the same conditions using sulfonium salt **2a** the reaction time was 1 h 30 min and the product yield 70% (for crude *trans*:*cis* dr = 3.6:1).[12b]

General Procedure F for the Synthesis of Fluorocyclopropyl Sulfone 5c in THF. To a solution of 1-chloro-3-(vinylsulfonyl)-benzene (**4c**) (20.7 mg, 0.10 mmol, 1 equiv) in anhydrous THF (1 mL) under argon atmosphere was added (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (82.3 mg, 0.20 mmol, 2 equiv) at 0 °C. To the reaction mixture was added NaH (60% dispersion in mineral oil, 16.34 mg, 0.41 mmol, 4 equiv). The reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was filtered through a cotton plug and the collected precipitate on the plug was washed with THF (3 × 2 mL). The filtrate was evaporated under reduced pressure (*trans*:*cis* dr = 2.8:1 of crude by ^{19}F NMR). The crude product was purified by prep. TLC (eluent: PE, PE/EtOAc, 4/1, 3/1). After chromatography the *trans* product **5c** 11.4 mg (48%) was obtained as a yellowish oil.

General Procedure G for the Synthesis of Fluorocyclopropylsulfone 5c in MeCN. To a solution of 1-chloro-3-(vinylsulfonyl)-benzene (**4c**) (22.0 mg, 0.11 mmol, 1 equiv) in anhydrous MeCN (1 mL) under argon atmosphere was added (2,3-dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (87.5 mg, 0.22 mmol, 2 equiv) at room temperature. To the reaction mixture was added NaH (60% dispersion in mineral oil, 17.4 mg, 0.43 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 30 min. Then the reaction mixture was filtered through a cotton plug, and the collected precipitate on the plug was washed with MeCN (3 × 2 mL). The filtrate was evaporated under reduced pressure. The crude product was purified by preparative TLC (eluent: PE, PE/EtOAc, 3/1). (^{19}F NMR of crude *trans*:*cis* dr = 10.5:1). After chromatography, the *trans* product **5c** 16.4 mg (64%) was obtained as a yellowish oil.

*trans-1-Chloro-3-((2-fluorocyclopropyl)sulfonyl)benzene (**5c**).*[12b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (t, J = 1.8 Hz, 1H), 7.82−7.76 (m, 1H), 7.65 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 5.03 (dddd, J = 62.9, 6.3, 4.3, 1.8 Hz, 1H), 2.95−2.85 (m, 1H), 1.77−1.64 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.8, 136.2, 134.6, 131.3, 128.2, 126.2, 71.2 (C−F, d, $^1J_{C-F}$ = 234.6 Hz), 38.3 (C−F, d, $^2J_{C-F}$ = 11.2 Hz), 13.9 (C−F, d, $^2J_{C-F}$ = 10.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −209.69 (dq, J = 63.0, 16.4 Hz).

*trans-1-((2-Fluorocyclopropyl)sulfonyl)benzene (**5e**).*[12b] The product was obtained following general procedure E from phenyl vinyl sulfone (**4e**) (17.4 mg, 0.10 mmol, 1 equiv) using (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (68.3 mg, 0.20 mmol, 2 equiv) and NaH (60% dispersion in mineral oil, 16.3 mg, 0.41 mmol, 4 equiv). (^{19}F NMR of crude *trans*:*cis* dr = 6.3:1). After chromatography the *trans* product **3m** 16.1 mg (78%) was obtained as a colorless oil. Under the same conditions using sulfonium salt **2a** product yield was 73% (for crude *trans*:*cis* dr = 4.3:1).[12b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.88 (m, 2H), 7.71−7.66 (m, 1H), 7.62−7.56 (m, 2H), 5.03 (dddd, J = 63.1, 6.7, 3.9, 1.7 Hz, 1H), 2.89 (dddd, J = 15.5, 10.4, 7.1, 1.8 Hz, 1H), 1.76−1.60 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 139.9, 134.1, 129.6, 127.8, 71.0 (C−F, d, $^1J_{C-F}$ = 233.8 Hz), 38.1 (C−F, d, $^2J_{C-F}$ = 10.9 Hz), 13.4 (C−F, d, $^2J_{C-F}$ = 10.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −209.99 (dddd, J = 63.2, 19.1, 15.5, 12.1 Hz).

*trans-1-((2-Fluorocyclopropyl)sulfonyl)-4-nitrobenzene (**5f**).*[12b] The product was obtained following general procedure E from 1-nitro-4-(vinylsulfonyl)benzene (**4f**) (21.5 mg, 0.10 mmol, 1 equiv) using (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (67.4 mg, 0.20 mmol, 2 equiv) and NaH (60% dispersion in mineral oil, 16.1 mg, 0.40 mmol, 4 equiv). (^{19}F NMR of crude *trans*:*cis* dr = 4.5:1). After chromatography the *trans* product **5f** 16.7 mg (68%) was obtained as a yellow oil. Under the same conditions using sulfonium salt **2a**[12b] product yield was 64% (for crude *trans*:*cis* dr = 3.4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47−8.40 (m, 2H), 8.15−8.07 (m, 2H), 5.17−4.95 (m, 1H), 2.99−2.87 (m, 1H), 1.83−1.69 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 151.1, 145.3, 129.3, 124.9, 70.8 (C−F, d, $^1J_{C-F}$ = 235.4 Hz), 37.9 (C−F, d, $^2J_{C-F}$ = 11.5 Hz), 13.8 (C−F, d, $^2J_{C-F}$ = 10.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −209.5 (dm, J = 62.7 Hz).

*trans-3-((2-Fluorocyclopropyl)sulfonyl)thiophene (**5g**).*[12b] The product was obtained following general procedure E from 3-(vinylsulfonyl)thiophene (**4g**) (17.8 mg, 0.10 mmol, 1 equiv) using (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (68.3 mg, 0.20 mmol, 2 equiv) and NaH (60% dispersion in mineral oil, 16.3 mg, 0.41 mmol, 4 equiv). (^{19}F NMR of crude *trans*:*cis* dr = 4.4:1). After chromatography the *trans* product **5g** 15.9 mg (76%) was obtained as a yellowish oil. Under the same conditions using sulfonium salt **2a** product yield was 69% (for crude *trans*:*cis* dr = 3.6:1).[12b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J = 3.1, 1.3 Hz, 1H), 7.50 (dd, J = 5.1, 3.1 Hz, 1H), 7.41 (dd, J = 5.2, 1.3 Hz, 1H), 5.13−4.92 (m, 1H), 3.00−2.88 (m, 1H), 1.76−1.63 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 140.0, 132.3, 128.7, 125.6, 70.8 (C−F, d, $^1J_{C-F}$ = 234.0 Hz), 38.1 (C−F, d, $^2J_{C-F}$ = 11.1 Hz), 13.3 (C−F, d, $^2J_{C-F}$ = 10.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −209.90 (dq, J = 63.2, 15.9 Hz).

*Methyl trans-4-((2-Fluorocyclopropyl)sulfonyl)benzoate (**5h**).*[12b] The product was obtained following general procedure E from methyl 4-(vinylsulfonyl)benzoate (**4h**) (23.8 mg, 0.11 mmol, 1 equiv) using (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (84.8 mg, 0.25 mmol, 2.4 equiv) and NaH (60% dispersion in mineral oil, 16.8 mg, 0.42 mmol, 4 equiv). (^{19}F NMR of crude *trans*:*cis* dr = 3.4:1). After chromatography the *trans* product **5h** 15.2 mg (56%) was obtained as a yellowish oil. Under the same conditions using sulfonium salt **2a** product yield was 42% (for crude *trans*:*cis* dr = 3.2:1).[12b] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28−8.20 (m, 2H), 8.02−7.94 (m, 2H), 5.16−4.92 (m, 1H), 3.97 (s, 3H), 2.97−2.84 (m, 1H), 1.78−1.63 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 165.5, 143.6, 135.2, 130.8, 127.8, 70.9 (C−F, d, $^1J_{C-F}$ = 234.6 Hz), 52.9, 37.9 (C−F, d, $^2J_{C-F}$ = 11.4 Hz), 13.6 (C−F, d, $^2J_{C-F}$ = 10.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −209.77 (dddd, J = 63.0, 18.9, 15.7, 13.4 Hz).

General Procedure H for Fluorocyclopropanation of Double-Activated Alkenes. *Diethyl 2-Fluoro-3-(2-fluorophenyl)-cyclopropane-1,1-dicarboxylate (**5i**).*[12c] Diethyl 2-(2-fluorobenzylidene)malonate (**4i**) (130 mg, 0.488 mmol, 1 equiv) and (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetra-

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fluoroborate (**2f**) (261 mg, 0.781 mmol, 1.6 equiv) were suspended in anhydrous THF (7 mL) under argon atmosphere. To the suspension was added NaH (60% dispersion in mineral oil, 78 mg, 1.95 mmol, 4 equiv), and the mixture was stirred at room temperature until completion (TLC control). Afterwards, the solvent was evaporated under reduced pressure (*the flask kept above the heating bath). The crude material was suspended in PE/Et_2O (40:7) and filtered through a cotton plug. The filtrate was concentrated under reduced pressure (*). The crude product was dissolved in $CDCl_3$ (1 mL) and an internal standard (EtOAc 1 equiv) was added. NMR yield 94%, dr 1:0.85. The crude product was purified by silica gel column chromatography (PE/EtOAc 100:0 to 80:20). Product **5i** was obtained as a light yellow oil as a mixture of (2*R**,3*R**)- and (2*S**,3*R**)-diastereomers (124 mg, 85%, dr 1:1). ^{1}H NMR corresponds to the reported spectra in literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.22 (m, 1H), 7.41−7.10 (m, 1H), 7.11−7.00 (m, 2H), 5.56 (dd, J = 63.2, 4.7 Hz, 1H)^{2R*,3R*}, 5.25 (dd, J = 63.4, 6.4 Hz, 1H)^{2S*,3R*}, 4.40−4.22 (m, 4H), 4.09−3.99 (m, 2H), 3.94 (q, J = 7.1 Hz, 2H), 3.85 (dd, J = 22.0, 4.7 Hz, 1H)^{2R*,3R*}, 3.03 (dd, J = 11.2, 6.4 Hz, 1H)^{2S*,3R*}, 1.33 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H).

*Diethyl 2-Fluoro-3-(3-nitrophenyl)cyclopropane-1,1-dicarboxylate (**5b**).*[12c] The product was obtained following general procedure H, using diethyl 2-(3-nitrobenzylidene)malonate (**4b**) (60 mg, 0.20 mmol, 1 equiv), (2,4-dimethylphenyl)(fluoromethyl)(phenyl)-sulfonium tetrafluoroborate (**2f**) (109 mg, 0.327 mmol, 1.6 equiv), and NaH (60% dispersion in mineral oil, 33 mg, 0.82 mmol, 4 equiv). The reaction mixture was stirred in anhydrous THF (4.3 mL) for 1 h. NMR yield 99%, dr 1:1.2. Product was purified by silica gel column chromatography (PE/EtOAc 100:0 to 80:20). Product **5b** was obtained as a yellow oil as a mixture of (2*R**,3*R**)- and (2*S**,3*R**)-diastereomers (66 mg, 99%, dr = 1:1.29).

General Procedure I for Cyclopropanation of Double-Activated Alkenes. *Diethyl 2-Fluoro-3-(3-nitrophenyl)-cyclopropane-1,1-dicarboxylate (**5b**).*[12c] Diethyl 2-(3-nitrobenzylidene)malonate (**4b**) (41 mg, 0.17 mmol, 1 equiv) was dissolved in anhydrous THF (2.8 mL) and cooled to 0 °C. (2,3-Dichlorophenyl)(2,4-dimethylphenyl)(fluoromethyl)sulfonium tetrafluoroborate (**2y**) (113 mg, 0.280, 2 equiv) and NaH (60% dispersion in mineral oil, 17 mg, 0.42 mmol, 3 equiv) were subsequently added. The reaction mixture was stirred at the same temperature for 20 min (TLC control). Then the solvent was evaporated under reduced pressure. The crude material was suspended in ether and filtered through a cotton plug. The obtained filtrate was concentrated under reduced pressure. The crude product was dissolved in $CHCl_3$ (1 mL) and an internal standard (1 equiv EtOAc) was added. NMR yield 76%, dr 1:1.4. The crude product was purified via column chromatography (PE/EtOAc 100:0 to 80:20). Product **5b** was obtained as a light yellow oil (27.8 mg, 61%, dr 1:1.2). ^{1}H NMR corresponds to the reported spectra in literature.[12c] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27−8.22 (m, 1H), 8.18−8.08 (m, 3H), 7.72−7.67 (m, 1H), 7.60−7.54 (m, 1H), 7.52−7.45 (m, 2H), 5.58 (dd, J = 62.2, 4.6 Hz, 1H)^{2R*,3S*}, 5.20 (dd, J = 63.4, 6.4 Hz, 1H)^{2S*,3S*}, 4.43−4.23 (m, 4H), 4.09 (q, J = 7.1 Hz, 2H), 4.01−3.86 (m, 3H), 3.08 (dd, J = 10.6, 6.0 Hz, 1H)^{2S*,3S*}, 1.33 (t, J = 6.92, 3H), 1.31 (t, J = 7.24 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −213.19 (dd, J = 62.2, 21.2 Hz), −219.40 (dd, J = 63.6, 10.6 Hz). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.5, 164.3, 163.8 (C−F, d, $^3J_{C-F}$ = 3.3 Hz), 162.6 (C−F, d, $^3J_{C-F}$ = 2.1 Hz), 148.3, 148.0, 136.2 (C−F, d, $^4J_{C-F}$ = 3.5 Hz), 134.8, 133.9, 133.1 (C−F, d, $^3J_{C-F}$ = 1.9 Hz), 129.6, 129.3, 129.0, 125.7, 125.3 (C−F, d, $^4J_{C-F}$ = 3.3 Hz), 123.7, 123.0, 122.6, 76.7 (C−F, d, $^1J_{C-F}$ = 238.9 Hz), 76.1 (C−F, d, $^1J_{C-F}$ = 225.8 Hz), 62.8, 62.7, 62.0, 61.9, 43.6 (C−F, d, $^2J_{C-F}$ = 12.7 Hz), 38.3 (C−F, d, $^2J_{C-F}$ = 9.7 Hz), 35.1 (C−F, d, $^2J_{C-F}$ = 11.6 Hz), 32.3 (C−F, d, $^2J_{C-F}$ = 6.8 Hz), 14.1, 14.0, 13.8, 13.8.

*Ethyl 1-Cyano-2-fluoro-3-(2-fluorophenyl)cyclopropane-1-carboxylate (**5j**).*[12c] The product was obtained following general procedure H using ethyl 2-cyano-2-((2-fluorophenyl)methylidene)-acetate (**4j**) (48 mg, 0.22 mmol, 1 equiv), (2,4-dimethylphenyl)-(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (117 mg, 0.350 mmol, 1.6 equiv), and NaH (60% dispersion in mineral oil, 35 mg, 0.88 mmol, 4 equiv), and anhydrous 1,4-dioxane (3.2 mL) was used as a solvent. The reaction mixture was stirred for 40 min. NMR yield −97%,dr 1.07:1. Product **5j** was obtained as a colorless oil as a mixture of 2*R**,3*R** and 2*S**,3*R** diastereomers (50 mg, 91%, dr 1.14:1). ^{1}H NMR corresponds to the reported spectra in literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.42 (m, 1H), 7.42−7.33 (m, 1H), 7.28−7.10 (m, 2H), 5.38 (dd, J = 61.0, 5.3 Hz, 1H)^{2R*,3R*}, 5.34 (dd, J = 61.8, 6.2 Hz, 1H)^{2S*,3R*}, 4.38 (q, J = 7.23 Hz, 2H), 4.34 (q, J = 7.18 Hz, 2H) 3.97 (dd, J = 21.06, 5.38 Hz 1H), 3.29 (dd, J = 11.8, 5.8 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H).

General Procedure J for Synthesis of Monofluorinated Epoxides.[12a] To *m*-nitroacetophenone (**4d**) (22.8 mg, 1.0 equiv, 0.138 mmol) in anhydrous MeCN (2.8 mL) under argon atmosphere was added (2,4-dimethylphenyl)(fluoromethyl)(phenyl)sulfonium tetrafluoroborate (**2f**) (69.2 mg, 1.5 equiv, 0.207 mmol) immediately followed by NaH (60% dispersion in mineral oil, 8.84 mg, 1.60 equiv, 0.221 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 2 h 30 min. After completion (TLC control), the reaction mixture was evaporated. The solid residue was suspended in Et_2O (2 × 2 mL) and filtered through a cotton plug. The solvent was evaporated. The ^{1}H NMR yield for the crude product was determined using EtOAc (1 equiv) as an internal standard (100%, dr 1:1.). The crude product was purified by silica gel (pretreated with 2% Et_3N in PE) column chromatography (Pasteur pipet) eluting with PE then switched to PE/EtOAc 10:1 to give the desired product **5d** (23.2 mg, 85%, dr 1.1:1) as a colorless oil.

Under the same conditions, the reagent **2a** (75.0 mg, 0.207 mmol, 1.5 equiv) gave full conversion in 2.5 h and the desired product **5d** (23.2 mg, 86%, dr 1.2:1) was obtained as a colorless oil.

Under the same conditions, the reagent **2y** (83.4 mg, 1.5 equiv, 0.207 mmol) gave full conversion in 1 h and the desired product **5d** (23.5 mg, 86%, dr 1.4:1) was obtained as a colorless oil.

*3-Fluoro-2-methyl-2-(3-nitrophenyl)oxirane (**5d**).*[12a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (ddt, J = 2.2, 1.7, 0.5 Hz, 1H), 8.22−8.16 (m, 3H)^{trans,cis}, 7.79−7.74 (m, 1H), 7.66−7.61 (m, 1H), 7.60−7.53 (m, 2H)$^{trans,\ cis}$, 5.60 (d, J = 87.5 Hz, 1H)^{cis}, 5.38 (dq, J = 87.4, 0.5 Hz, 1H)^{trans}, 1.87 (dd, J = 1.2, 0.5 Hz, 3H)^{trans}, 1.70 (d, J = 2.8 Hz, 3H)^{cis}. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 148.6, 148.4, 140.1 (C−F, d, $^3J_{C-F}$ = 3.9 Hz), 138.2 (C−F, d, $^3J_{C-F}$ = 4.4 Hz), 133.0, 131.6, 129.9, 129.5, 123.5, 123.4, 122.2, 120.9, 93.3 (C−F, d, $^1J_{C-F}$ = 276.9 Hz), 93.2 (C−F, d, $^1J_{C-F}$ = 271.4 Hz), 62.0 (C−F, d, $^2J_{C-F}$ = 17.1 Hz), 60.8 (C−F, d, $^2J_{C-F}$ = 17.0 Hz), 20.2 (C−F, d, $^3J_{C-F}$ = 4.4 Hz), 16.2 (C−F, d, $^3J_{C-F}$ = 3.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −150.71 (d, J = 87.4 Hz)^{trans}, −154.44 (dq, J = 87.8, 2.7 Hz)^{cis}.

Procedure for Obtaining Diaryl Sulfides 6. *Phenyl(2,3,4,5-tetramethylphenyl)sulfane (**6a**).* The side product **6a** was isolated from the reactions using the reagent **2a**. Isolation by silica gel column chromatography, eluted with 100% petroleum ether (R_f 0.40). **6a** obtained as a white solid. Mp: 64−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.19 (m, 3H), 7.15−7.04 (m, 3H), 2.38 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 138.5, 137.3, 136.5, 136.3, 134.8, 134.1, 129.0, 128.8, 127.7, 125.4, 20.7, 17.9, 17.1, 2. Due to poor ionization under HRMS conditions a molecular ion cannot be detected.

*(2,4-Dimethylphenyl)(phenyl)sulfane (**6f**).* The side product **6f** was isolated from the reactions using the reagent **2f**. Isolation by silica gel column chromatography, eluted with 100% petroleum ether (R_f 0.43). **6f** obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 7.9 Hz, 1H), 7.17−7.12 (m, 2H), 7.09−7.01 (m, 4H), 6.93−6.89 (m, 1H), 2.26 (s, 4H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.0, 138.7, 137.5, 134.6, 131.7, 129.4, 129.1, 128.4, 127.7, 125.9, 21.2, 20.7. Due to poor ionization under HRMS conditions a molecular ion cannot be detected.

*(2,3-Dichlorophenyl)(2,4-dimethylphenyl)sulfane (**6y**).* The side-product **6y** was isolated from the reactions using the reagent **2y**. Isolation by silica gel column chromatography, eluted with 100% petroleum ether (R_f 0.50). **6y** obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.8 Hz, 1H), 7.20−7.16 (m, 2H), 7.08 (ddt, J = 7.9, 2.2, 0.8 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.42 (dd,

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J = 8.1, 1.4 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.9, 140.7, 140.6, 136.8, 133.5, 132.2, 128.9, 128.3, 127.3, 126.5, 126.5, 124.6, 21.4, 20.6. Due to poor ionization under HRMS conditions a molecular ion cannot be detected.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02561.

Experimental procedures for control experiments, X-ray crystallography data, and NMR spectra (PDF)

Accession Codes

CCDC 2031999−2032003 and 2032388 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Residual Solvent Signal of $CDCl_3$ as a qNMR Internal Standard for Application in Organic Chemistry Laboratory

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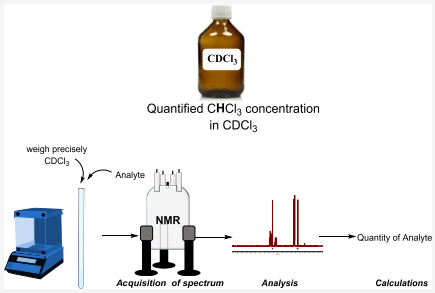
ABSTRACT: A nuclear magnetic resonance (NMR) spectrometer is a key instrument in the organic synthesis laboratory for structure determination, reaction control, and compound purity analysis. In addition to qualitative analysis, the application of NMR for quantitative analysis (qNMR) is gaining popularity. qNMR allows for simple quantification of crude product mixtures, determination of reaction yields, and purity of organic compounds. The determination of NMR yield requires the addition of an internal standard to each sample. Herein, we report a method where $CDCl_3$ residual solvent signal is used as an internal standard for qNMR after quantification in the solvent batch. This method significantly simplifies sample preparation and allows straightforward recovery of the analyte by the simple evaporation of the NMR solvent. The accuracy of the method is comparable to qNMR with 1,3,5-trimethoxybenzene as an internal standard if the herein described guidelines are followed.



INTRODUCTION

A nuclear magnetic resonance (NMR) spectrometer is the most commonly used instrument for structure elucidation in organic chemistry.[1] An access to an NMR spectrometer is a requirement for a modern organic synthesis lab. For example, a research group working in the area of synthetic organic chemistry usually runs hundreds of samples per month.[2] Besides "making sure one made the right compound", chemists use it for determination of purity of a sample, mechanistic experiments, and determination of reaction (NMR) yields by qNMR[3] which requires the addition of an internal standard to the sample. This approach is also used for the quality control of pharmaceutical ingredients[4] and in other areas where quantification of organic compounds is important.[5]

$CDCl_3$ is one of the most commonly used NMR solvents in the organic synthesis lab. It is the preferred solvent due to its affordable price, good solubilizing properties of many organic compounds, and straightforward recovery of the sample after analysis by simple evaporation. The recovery of a sample after qNMR analysis is, however, often problematic even from volatile solvents if the internal standard applied is nonvolatile.[2]

A signal due to incompletely deuterated NMR solvent residue is always present in the NMR spectrum. An experienced chemist would quickly recognize a singlet at 7.26 ppm and might use it to adjust the ppm scale.[6] Here, we propose to take full advantage of this mostly ignored signal in the NMR spectrum as it carries extra valuable information, i.e., a defined concentration of protons in a deuterated NMR solvent batch. Determination of the concentration of the $CHCl_3$ residue for each batch of $CDCl_3$ used in the lab does not require much effort in comparison with the expected value of quantitative information on compound concentrations in all measured samples. We show that the residual solvent signal of $CDCl_3$ can be used as an internal standard for qNMR and that its concentration remains constant for the batch if it is stored properly. Figure 1 shows our approach in comparison with the conventional qNMR method.

There are numerous reports on qNMR[3] including two where residual protons in D_2O and dimethyl sulfoxide (DMSO)-d_6 are considered as potential internal standards for the quantification of natural products.[7,8] However, it is not a common practice in organic synthesis labs to use residual solvent as a qNMR standard. To gain maximum accuracy of this approach, the best practices of the qNMR sample preparation and sample acquisition[3,9] should be taken into consideration. The purpose of this study is to demonstrate the practicality of this approach in an organic synthesis laboratory setting for daily use with simple sample preparation efforts and easy recovery of the analyte.

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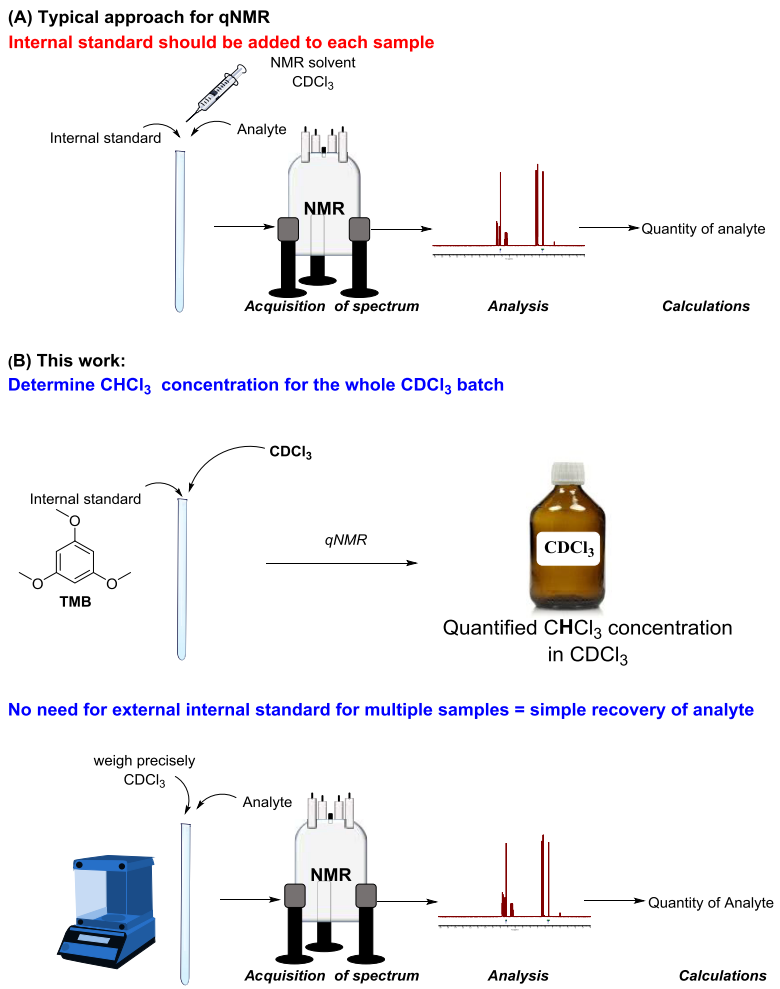

Figure 1. (A) NMR internal standard should be added to each sample. (B) No need for the addition of extra internal standard after the determination of residual $CHCl_3$ concentration in $CDCl_3$.

Table 1. T_1 Relaxation Time for $CHCl_3$ and TMB (400 MHz)

	T_1, s		
	$CHCl_3$	TMB 2,4,6-C**H**	TMB 1,3,5-OCH_3
average (n = 3 measurements)	6.314 ± 0.004	3.688 ± 0.004	1.760 ± 0.002

RESULTS AND DISCUSSION

We started our study with the determination of the concentration of nondeuterated $CHCl_3$ residual solvent in a $CDCl_3$ batch using the internal standard 1,3,5-trimethoxybenzene (TMB).[2] Since $CHCl_3$ is a smaller molecule than the usual internal standards, its relaxation is expected to be slower and care must be taken to use appropriate experimental parameters (pulse length and recycle delay) for the qNMR experiments. Therefore, we determined the T_1 relaxation time for $CHCl_3$ and TMB as a primary internal standard (Table 1).

Based on the measured T_1 values, we chose the qNMR acquisition parameters as follows: 14° pulse, recycle delay 30 s, and 32−128 scans yielding experiment times of 21−75 min (on a 400 and 300 MHz instrument, respectively). The theoretical recovery of the $CHCl_3$ magnetization during the recycle delay is 99.97% and practically 100% for TMB protons as well as other compounds of similar or larger size. Reduction of the recycle delay to 7 s would yield an experiment time of 8−26 min and still ensure >99% recovery of the $CHCl_3$ magnetization. As expected, on both instruments, we observed a good linear correlation (linearity) between the concentration

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of the internal standard $c_{(TMB)}$ and its corresponding integral value $I_{(TMB)}$, when the integral value $I_{(CHCl3)}$ of the $CHCl_3$ signal was set to 100 (for 400 MHz data see Figure 2, for 300 MHz data see the Supporting Information).

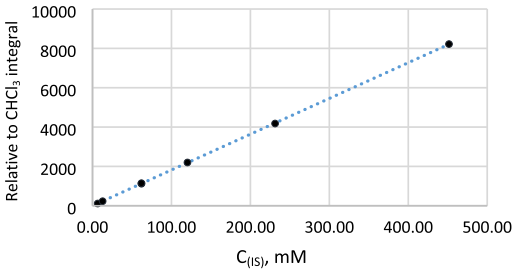

Figure 2. Integral value of internal standard 1,3,5-trimethoxybenzene (TMB) as a function of its concentration, when residual $CHCl_3$ integral value is set to 100 (400 MHz).

To determine the $CHCl_3$ concentration in our $CDCl_3$ batch, we prepared three independent samples and performed three measurements for each sample. The obtained $c_{(CHCl3)}$ was 16.231 ± 0.138 mM (standard deviation of 0.85%). To test the stability of the $CHCl_3$ content in $CDCl_3$, we repeated the determination of $CHCl_3$ concentration after 1 month and obtained 16.144 ± 0.037 mM (standard deviation of 0.23%). The difference of −0.087 mM or −0.54% is within the standard deviation of the first measurement, which indicates that the $CHCl_3$ concentration remains constant for at least 1 month.

Once the precise $CHCl_3$ concentration in a $CDCl_3$ batch has been determined, the residual solvent signal can be used as an internal standard for qNMR. To assess the accuracy of this approach, we used it to determine the weight $m_{(qNMR\ CHCl3)}$ of nine compounds and compared the obtained values with the balance weight $m_{(balance)}$ as well as cross-checked the results with those from qNMR using the accepted internal standard TMB (Table 2). All measurements were repeated three times and the standard deviation was calculated to determine the precision of the measurement. The accuracy of the method was evaluated by calculating the percentage errors of the determined qNMR weight $m_{(qNMR)}$ with respect to the balance weight $m_{(balance)}$ using both $CHCl_3$ and TMB as internal standards. The sample purity provided by the suppliers was taken into account. All samples were measured on both 400 MHz and 300 MHz instruments and the results were compared.

The selected test compounds include common solvents (Table 2, **1**−**3**), reagents in different states of matter (solid **4**, **5**; oil **7**), a pharmaceutical drug (**6**), and a compound with limited solubility in $CDCl_3$ (**8**, with MeCN additive as a solubilizing cosolvent). On average, the obtained $m_{(qNMR\ CHCl3)}$ values differ by 3.0% from the balance weight $m_{(balance)}$ and by 2.5% from the weight determined using TMB as internal standard $m_{(qNMR\ TMB)}$. At the same time, the $m_{(qNMR\ TMB)}$ values differ by about 2.5% from the balance weight $m_{(balance)}$. The difference between the results obtained from two different $CDCl_3$ solvent batches is similarly in a range of 2−3% (Table 2, 1). The maximum qNMR error between the measurements with $CHCl_3$ as internal standard is 6.2 and 8.8% using 400 and 300 MHz instruments, respectively. Among the measurements using TMB, the corresponding maximum errors are 5.2 and 8.6%. These results indicate that the accuracy of our proposed method is comparable to the conventional approach using TMB as an internal standard.

The precision expressed as a standard deviation for repeated measurements using $CHCl_3$ as an internal standard was in the range of 0.06−1.66% with one exception. The results for the aldehyde **4** displayed lower repeatability (standard deviation of 4.36%) at 300 MHz, which could be explained by the instability of the sample during a longer measurement time, as was required for this instrument. The standard deviation of the measurements using TMB was between 0.02 and 0.86%. This indicates that the precision is notably higher than the accuracy using both approaches.

As with qNMR in general, the present method requires good solubility of the tested compounds in the NMR solvent. The compound **8** displayed only partial solubility in $CDCl_3$; therefore, cosolvent was added to improve solubility. The obtained results for this compound show some of the largest errors with respect to balance weight; however, also, in this case, the results using $CHCl_3$ or TMB as an internal standard are comparable. Another limitation of the method is the potential overlap of the analyte signals with $CHCl_3$ signal, which limits its applicability to compounds that do not show signals around 7.26 ppm. With regard to the detection limit and useful $CHCl_3$ concentration, the number of scans may need to be adjusted to reach the desirable S/N ratio for the signals under analysis taking into consideration the best practices of qNMR.[2] Additionally, the analyte concentration may need to be adjusted by dilution using an appropriate volume of $CDCl_3$ to obtain both $CHCl_3$ and analyte signal intensities at the desired signal-to-noise ratio as well as in the working range of the spectrometer's analog-to-digital converter. For this purpose, the sample can be prepared in appropriate size vials (equipped with a screwing cap to avoid evaporation losses), which would allow us to use a higher volume of $CDCl_3$. For the best result, a precise determination of $CDCl_3$ weight is crucial. Therefore, we recommend using a balance for measuring the $CDCl_3$ weight, as this is very easy to do and guarantees the best accuracy. We do not recommend using simple hypodermic syringes for this purpose, as this will add extra uncertainty to the measurement (see the Supporting Information). The concentration of $CHCl_3$ should be determined for each bottle regardless if it has the same or different LOT number. This will remove any uncertainties that might arise due to varying manufacturing, packing, storage, and shipment conditions. For example, two different $CDCl_3$ batches with D 99.8% content used for the experiments in Table 2 (batch A and B) have approximately a 3% difference in the $CHCl_3$ concentration.

To exemplify the utility of the current technique in the organic synthesis laboratory, we present its application in the synthesis of vinyl sulfone **9**. The compound **9** can be prepared in three steps (Scheme 1 and Table 3) starting from 1-phenyl-1*H*-tetrazole-5-thiol (**10**), which is alkylated with 1,2-dichloromethane to yield 5-((2-chloroethyl)thio)-1-phenyl-1H-tetrazole (**11**). Further, oxidation of sulfide **11** to a corresponding sulfone **12** can be accomplished using $NaIO_4$ in the presence of catalyst $RuCl_3{\cdot}H_2O$.[10] Purity of the crude intermediate **12** was determined using the herein described qNMR method, which helped to adjust the quantity of the required base in the next step (Table 3). The desired product, vinyl sulfone **9**, turned out to be unstable in dichloromethane when using

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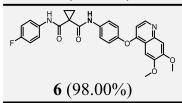
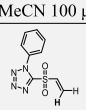
Table 2. Compound Weight Determined by qNMR $m_{(qNMR)}$ Using $CHCl_3$ or 1,3,5-Trimethoxybenzene and Balance $m_{(balance)}$

compound (purity)[c]	$m_{(balance)}$[d], mg	NMR spectrometer	Error of $m_{(qNMR)}\% = (m_{(balance)} \times purity - m_{(qNMR)}) \times 100\%/(m_{(balance)} \times purity)$[e]			
			$CHCl_3$ method		1,3,5-trimethoxybenzene	
			Error, %	Stdev.S, % (3 repeats)[f]	Error, %	Stdev.S, % (3 repeats)[f]
 **1** (99.99%)	14.87 *batch A*[a]	400 MHz	4.08	*0.25*	2.14	*0.04*
		300 MHz	4.24	*1.66*	2.77	*0.04*
	12.16 *batch B*[b]	400 MHz	2.22	*0.06*	-1.09	*0.08*
		300 MHz	0.67	*0.34*	-0.88	*0.13*
 **2** (96.30%)	16.37	400 MHz	3.72	*0.12*	4.18	*0.07*
		300 MHz	7.17	*1.54*	3.94	*0.14*
 **3** (99.90%)	16.86	400 MHz	-1.08	*0.46*	-0.98	*0.02*
		300 MHz	-0.15	*0.99*	0.18	*0.11*
 **4** (97.00%)	11.16	400 MHz	0.81	*0.38*	-3.22	*0.13*
		300 MHz[g]	8.78	*4.36*	-4.28	*0.62*
 **5** (98.00%)	11.69	400 MHz	-0.78	*0.38*	-0.92	*0.11*
		300 MHz	0.20	*0.75*	0.55	*0.20*
 **6** (98.00%)	13.43	400 MHz	2.32	*0.37*	1.10	*0.31*
		300 MHz	-0.39	*0.60*	4.80	*0.64*
 **7** (99.00%)	22.30	400 MHz	-1.01	*0.06*	-0.04	*0.10*
		300 MHz	-3.14	*1.32*	-0.42	*0.27*
 **8** (98.00%) +MeCN 100 µL	11.54	400 MHz	6.15	*0.49*	5.15	*0.13*
		300 MHz	7.67	*1.46*	8.64	*0.86*
 **9** (99.0%)	12.32	400 MHz	-0.27	*0.35*	-2.22	*0.25*
		300 MHz	-5.24	*0.55*	-1.65	*0.38*
Average of absolute values of errors, %			**3.00**		**2.46**	

[a]All calculations were performed using $CDCl_3$ batch A (Eurisotop, chloroform D, 99.80% D, Lot: S1541) $c_{(CHCl3)}$ = 16.231 mmol/L unless otherwise stated. [b]$CDCl_3$ batch B (Aldrich, chloroform-*d*, 99.80% D, Lot # STBJ5818) $c_{(CHCl3)}$ = 16.700 mmol/L. Signals of protons highlighted in bold were used for integration. [c]As indicated in the certificate of analysis provided by the supplier. [d]Sample weight measured on analytical balance *d* = 0.01 mg. [e]Error calculated as the difference between the balance weight and qNMR weight taking into consideration the compound purity. [f]Three independent measurements for each sample. [g]Due to compound **4** instability in solution, lowered accuracy was observed on 300 MHz instrument (acquisition time 1 h 15 min).

excess Et_3N as a base (Table 3, entry 1). Therefore, a careful adjustment of the reaction conditions (entries 2−4) was performed to find an optimal reaction solvent and stoichiometry of base. Using the $CDCl_3$ qNMR method, both, ^1H NMR yields and the purity of product **9** was easily evaluated for the crude and the isolated product **9**, thereby allowing rapid identification of optimal reaction conditions (entry 4). The elimination reaction from **12** to product **9**

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Scheme 1. Synthesis of Sulfone 12

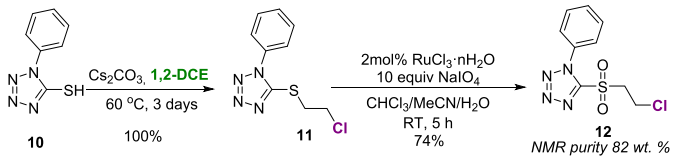
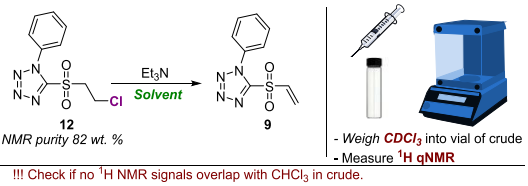


Table 3. Reaction Optimization Using $CDCl_3$ qNMR Technique



!!! Check if no ^{1}H NMR signals overlap with $CHCl_3$ in crude.
!!! Check if the compound is completely soluble in $CDCl_3$.
!!! Tare a vial with a cap, weigh $CDCl_3$ in a sealed vial with cap.
!!! Make sure the $CDCl_3$ does not react with analyte.

		NMR yield of **9**, %[b]			
entry	conditions[a]	crude[c]	isolated[d]	balance yield of **9**, %	NMR purity of **9**, %[b,e]
1	DCM, RT, 4 h, 2.5 equiv TEA	4.8			
2	Et_2O, 0 °C, 15 min, 2.27 equiv TEA	87.0	86.4	97	89
3	Et_2O, 0 °C, 15 min, 1.12 equiv TEA	100	97.1	103	95
4	MTBE, 0 °C, 15 min, 1.12 equiv TEA	100	99.5	103	97

[a]All reactions were performed on 0.301 mmol scale of **12**. [b]qNMR performed on a 400 MHz instrument using residual $CHCl_3$ as an internal standard. [c]The crude **9** used for analysis. [d]Product isolated using silica gel column chromatography (PE/EtOAc 5:1 to 1:1). Balance yield, NMR yield, and purity determined for the same sample. [e]NMR purity calculated following eq 5, see Experimental Section.

under the optimized conditions turned out to be a quantitative process. The balance yield of isolated **9** includes the weight of impurities, whereas the qNMR yield is calculated for a pure substance in a sample, thereby allowing us to estimate the sample purities (entries 2–4). Application of the residual $CHCl_3$ as an internal standard made possible the complete recovery of the analyzed samples by simple solvent evaporation.

We advise chemists who routinely use NMR in their work to quantify the $CHCl_3$ concentration of the particular solvent batch and label the bottle with the determined concentration, which is a simple task to do. This needs to be done once for each batch of $CDCl_3$ and, if properly stored, the value should be constant for at least 1 month. Our results show that the present method is sufficiently accurate and precise for qNMR applications in routine organic chemistry. This method offers a simple alternative to an external standard or the ERETIC qNMR methods.[12] According to the literature, ERETIC gives approximately 3% of error,[12a] which is comparable to the average error of using $CHCl_3$ (3.00%) and TMB (2.46%) as internal standards (Table 2). To adopt it as an analytical chemistry tool or evaluate its suitability for other purposes, we suggest to validate this method for the compound of interest using an established internal standard on your own instrument and determine the uncertainties of the measurement.

CONCLUSIONS

We have proposed a very simple approach for the fast determination of NMR yield in the organic synthesis lab by the determination of residual solvent concentration in each $CDCl_3$ batch and using the residual solvent signal as an internal standard. The valuable quantitative information carried by the residual solvent adds an extra dimension besides the usual qualitative interpretation of the ^{1}H NMR data. Our results indicate that the residual $CHCl_3$ gives comparable accuracy with 1,3,5-trimethoxybenzene as an internal standard. In addition, the use of NMR solvent residue as an internal standard simplifies qNMR sample preparation and provides an opportunity for very straightforward sample recovery by simple NMR solvent evaporation. This approach has a huge potential in reaction optimization and fast purity assessment of the reaction intermediates and common lab chemicals without the necessity to add any foreign materials to the sample.

EXPERIMENTAL SECTION

General Experimental Details. The weights of the internal standard 1,3,5-trimethoxybenzene (TMB), $CDCl_3$, and compounds **1**–**9** were measured using analytical balance BOECO d = 0.01 mg placed on a stone table. All of the prepared samples were measured within 24 h to avoid errors from solvent evaporation losses. Spectra were recorded on (1) a 400 MHz Bruker Avance Neo spectrometer equipped with 5 mm double-resonance broadband CryoProbe Prodigy using the parameters: 14° pulse (90° pulse = 12 μs), d_1 = 30 s, ns = 32, acquisition time = 4.19 s (32k points), spectral width 19.5333 ppm centered at 6.175 ppm and (2) a 300 MHz Bruker Fourier spectrometer equipped with 5 mm dual-channel EasyProbe using the parameters: 14° pulse (90° pulse = 14.5 μs), d_1 = 30 s, ns = 128, acquisition time = 5.37 s (32k points), spectral width 20.3339 ppm centered at 6.175 ppm. The chosen interscan (pulse) delay d_1 was based on the measured T_1 relaxation times of the standard and analyte to ensure a near-complete (>99.97%) relaxation of $CHCl_3$.[3] However, in most cases, the interscan delay can be reduced to approximately 10 s (which ensures 99.4% relaxation using 14° pulse tip angle) without deteriorating the accuracy of the method (as

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demonstrated in the Supporting Information). Each qNMR spectrum was taken three times (two for only $CDCl_3$). 1,3,5-Trimethoxybenzene TraceCERT, purity = 99.96% (Lot# BCBW3670) and 99.82 (Lot# BCC9688) was purchased from Sigma-Aldrich. $CDCl_3$ batch A: Eurisotop, chloroform D, 99.80% D, (Lot: S1541). $CDCl_3$ batch B: Aldrich, chloroform-*d*, 99.80% D, (Lot # STBJ5818). ^1H NMR spectra were transformed and analyzed with Mestrenova software (Mestrelab Research). All spectra before integration were transformed with the baseline correction (Whittaker Smoother).

General Procedure A for the $CHCl_3$ Concentration Determination in $CDCl_3$. In a 4 mL vial equipped with a screwing cap internal standard 1,3,5-trimethyoxybenzole (TMB) (>∼11 mg) was precisely weighed. The capped vial with TMB was placed on an analytical balance and tare was measured. To the vial, $CDCl_3$ (∼1 mL) was added, the vial immediately sealed with a screwing cap, and the precise weight of $CDCl_3$ was measured by analytical balance. The sample was shaken till all TMB dissolved. The clear TMB solution was transferred to an NMR tube and ^1H NMR spectrum was recorded using the above-described parameters. The signals of $CHCl_3$ at 7.26 ppm and those of 1,3,5-trimethyoxybenzole at 6.09 and 3.77 ppm were integrated. Average $c_{(CHCl3)}$ was calculated from three independent measurements (three repeats for each) using eq 1

$$c_{(CHCl_3)} = \frac{I_{(CHCl_3)} \times c_{(TMB)} \times N_{(TMB)}}{I_{(TMB)}} \quad (1)$$

where $c_{(CHCl3)}$ is the concentration of the $CHCl_3$ residue in $CDCl_3$, $c_{(TMB)}$ is the concentration of internal standard, and $N_{(TMB)}$ is the ratio of the number of protons of the signal used for integration in internal standard (TMB) and the number of protons in solvent residue ($CHCl_3$). $I_{(CHCl3)}$ is the integral of solvent residue (at 7.26 ppm) and $I_{(TMB)}$ is the integral of the internal standard signal (for TMB, the aromatic CH signal at 6.09 ppm was used).

General Procedure B for the Analyte Weight Determination by ^1H NMR Using $CDCl_3$ Solvent Residue or TMB as an Internal Standard. The analyte (>∼11 mg) was weighed in a 4 mL vial equipped with a screwing cap. To crosscheck the results, TMB (∼11 mg) was also added to the reference samples listed in Table 2. The capped vial with a sample was placed on an analytical balance and tare was measured. To the vial, $CDCl_3$ (∼1 mL) was added, the vial was immediately sealed with a screwing cap, and the precise weight of $CDCl_3$ was measured by an analytical balance. The sample was shaken till all of the analyte dissolved. The sample solution was transferred to the NMR tube and ^1H NMR spectrum was recorded. The signal of $CHCl_3$ at 7.26 ppm and a signal of choice from the analyte were integrated. The analyte weight was calculated using the previously determined $C_{(CHCl3)}$ concentration following eq 2

$$m_{(qNMR\ CHCl_3)} = \frac{c_{(CHCl_3)} \times I_{(X)} \times M_{(X)} \times m_{(CDCl_3)}}{I_{(CHCl_3)} \times N_{(X)} \times \rho_{(CDCl_3)}} \quad (2)$$

For comparison, the compound weight $m_{(qNMR\ IS)}$ using 1,3,5-trimethoxybenzene (TMB) as the internal standard was calculated following eq 3

$$m_{(qNMR\ TMB)} = \frac{I_{(X)} \times N_{(TMB)} \times M_{(X)} \times m_{(TMB)}}{I_{(TMB)} \times N_{(X)} \times M_{(TMB)}} \times \text{TMB purity} \quad (3)$$

where $c_{(CHCl3)}$ is the calculated protonated chloroform concentration [mM/L], $I_{(X)}$ is the integral intensity of the studied compound, $I_{(CHCl3)}$ is the integral intensity of protonated chloroform [100], $M_{(X)}$ is the molecular weight test item [g/mol], $m_{(CDCl3)}$ is the sample weight of chloroform [g], $N_{(X)}$ is the number of protons for the integrated signal in the molecule of an analyte, $\rho_{(CDCl3)}$ is the density of chloroform [1500 mg/mL], $N_{(TMB)}$ is the number of protons for the integrated signal in the molecule of standard, $m_{(TMB)}$ is the sample weight of standard [mg], and $M_{(TMB)}$ is the molecular weight standard [g/mol].

The errors were calculated using the equation error% = $(m_{(balance)} \times \text{purity} - m_{(qNMR)})/(m_{(balance)} \times \text{purity}) \times 100\%$.

Application of qNMR $CDCl_3$ Technique in the Reaction Optimization Experiments.[10] *5-((2-Chloroethyl)sulfonyl)-1-phenyl-1H-tetrazole (**12**).*[10] To a mixture of 1-phenyl-1H-tetrazole-5-thiol (**10**) (3.178 g, 17.83 mmol, 1.00 equiv) and Cs_2CO_3 (17.4 g, 53.5 mmol, 3.0 equiv) was added 1,2-dichloroethane (116 mL, 1480 mmol, 93 equiv) and MeCN (4 mL) at RT. The reaction mixture was stirred at 60 °C for 3 days. TLC (PE/EtOAc 5:1) showed full conversion. The reaction mixture was diluted with water (150 mL) and extracted with DCM (3 × 200 mL). The combined organic phases were dried over anh. $NaSO_4$, filtered, and evaporated to give the intermediate product 5-((2-chloroethyl)thio)-1-phenyl-1H-tetrazole (**11**) (4.30 g, 100%) as an off-white solid, which was subjected to the next step without additional purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.44 (m, 3H), 3.91−3.86 (m, 2H), 3.72−3.62 (m, 2H).[10,11] To a mixture of crude sulfide from previous step (4.212 g, 17.50 mmol, 1.0 equiv) in $CHCl_3$ (12 mL) and MeCN (12 mL) was added $NaIO_4$ (37.4 g, 175 mmol, 10 equiv). To the mixture, a solution of $RuCl_3$ hydrate (83 mg, 0.37 mmol, 0.02 equiv) in water (42 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred for 5 h at room temperature. The reaction progress was monitored by TLC (PE/EtOAc 5:1). After the completion, 100 mL of water was added to the mixture. The reaction mixture was extracted with MTBE (3 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ and filtered through a plug of silica gel covered with anh. Na_2SO_4. The plug was washed with MTBE till no more product was detected by TLC in the filtrate. The filtrate was evaporated under reduced pressure to give the desired product (3.549 g, 74%, $NMR_{(qNMR\ CDCl3)}$ purity = 82%) as an off-white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.48 (m, 5H), 4.23−4.07 (m, 2H), 4.10−3.96 (m, 2H).[10,11]

*Reaction Optimization for the Synthesis of 1-Phenyl-5-(vinylsulfonyl)-1H-tetrazole (**9**).* To a chloride **12** (100 mg, 82% purity, 0.301 mmol, 1.0 equiv) in a solvent (4 mL) (see Table 3) at 0 °C was added triethylamine (46.9 μL, 0.337, 1.12 equiv). A white precipitate formed. The reaction mixture was stirred for 15 min at 0 °C. The white precipitate was filtered off, filter-cake washed with solvent (1 mL), and the filtrate was evaporated under reduced pressure. To the crude product, ∼3 g of precisely weighted $CDCl_3$ with previously determined $CHCl_3$ concentration was added (following general procedure **B**). After the measurement of ^1H NMR under qNMR conditions, the product weight in the sample was determined according to eq 2. The NMR yield for the crude was calculated by eq 4

$$\text{yield}_{(qNMR)} = \frac{m_{(qNMR\ CDCl_3)}}{m_{(theoretical)}} \times 100\% \quad (4)$$

The NMR sample was completely recovered by solvent evaporation under reduced pressure and the obtained residue was purified by silica gel column chromatography (PE/EtOAc 5:1 to 1:1) to give product **2**. The qNMR yield for the isolated product was obtained as previously mentioned using eq 4. The product qNMR purity was calculated by eq 5

$$\text{purity}_{(qNMR)} = \frac{m_{(qNMR\ CDCl_3)}}{m_{(balance)}} \times 100\% \quad (5)$$

^1H NMR (400 MHz, chloroform-*d*) δ 7.71−7.56 (m, 5H), 7.13 (dd, J = 16.5, 9.8 Hz, 1H), 6.71−6.62 (m, 1H), 6.49 (dd, J = 9.9, 1.1 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02744.

The tables with data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Synthetic Access to Fluorocyclopropylidenes

Renate Melngaile, Melita Videja, Janis Kuka, Artis Kinens, Dzintars Zacs, and Janis Veliks*

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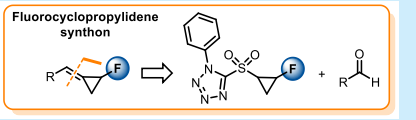
ABSTRACT: Herein we report an approach for the straightforward preparation of fluorocyclopropylidene group from aldehydes and ketones via Julia–Kocienski olefination using the newly developed reagent 5-((2-fluorocyclopropyl)sulfonyl)-1-phenyl-1*H*-tetrazole. Derivatization of monofluorocyclopropylidene compounds includes hydrogenation to deliver fluorocyclopropylmethyl compounds and fluorinated cyclobutanones. The utility of the described method is demonstrated by the synthesis of a fluorocyclopropyl-containing analogue of ibuprofen. Bioisosteric replacement of isobutyl with the fluorocyclopropyl group may be used for tuning biological properties of drug molecules.



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The cyclopropyl fragment and the fluorine atom are increasingly prevalent in drug discovery efforts because of their ability to modify activity and bioavailability.[1] However, the combination of these two moieties as in the fluorocyclopropyl group is less studied,[2] even though such functional groups are promising structural motifs from the perspective of medicinal chemistry.[3] Additionally, synthetic access to fluorinated derivatives such as fluorocyclopropylidene and fluorinated methylenecyclopropane (F-MCP) moieties[4] is limited. Despite this, potential applications of compounds with these functional groups have been reported.[5,6] Methylenecyclopropane (MCP) is a highly strained (~40 kcal/mol) structure containing an exocyclic double bond[7] and thus possesses unique chemical properties and broad and valuable synthetic applications.[8] Facile access to strategic fluorinated intermediates could potentially benefit medicinal chemistry studies, as many useful transformations can be achieved under mild conditions that exploit the reactivity of MCP derivatives (Figure 1).

Herein we report a new reagent, 5-((2-fluorocyclopropyl)-sulfonyl)-1-phenyl-1*H*-tetrazole (**6**), for the straightforward preparation of the fluorocyclopropylidene or F-MCP group from aldehydes and ketones. Synthesis of rare[4−6] monofluorocyclopropylidene derivatives **8** and **10** via Julia–Kocienski olefination[9] using **6** offers further modification options. The unique character of reagent **6** is its remarkable stability, given the fact that, generally, reagents containing *β*-leaving groups are not suitable for Julia–Kocienski olefination due to instability via elimination. We started our studies by the preparation of **6** in four steps using a fluorocyclopropanation strategy developed in our group, using fluoromethyl sulfonium **5** (see the Supporting Information (SI) for more details).[10] Reagent **6** is a solid bench-stable compound that can be readily used for synthesis. Reagent **6** was prepared following the sequence shown in Scheme 1.

Lability of the phenyltetrazole functionality is known to cleave the C–S bond and to release SO_2 under basic conditions.[11] Achieving fluorocyclopropanation of the corresponding vinyl sulfone **4** was particularly challenging, as the conventional approach[10] would lead to decomposition of the starting material under basic conditions.[12] After careful tuning of the reaction conditions, we were able to perform fluorocyclopropanation of vinyl sulfone **4** using our improved sulfonium reagent **5**.[13] With reagent **6** in hand, optimization of

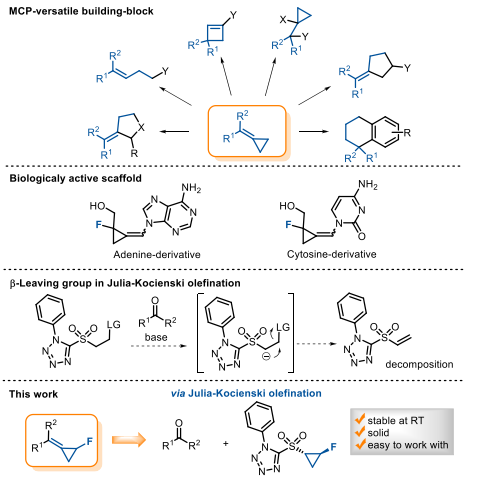

Figure 1. Applications of alkylidenecyclopropanes

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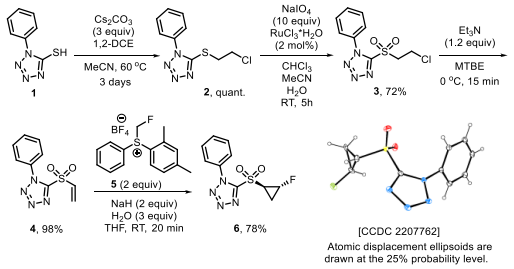
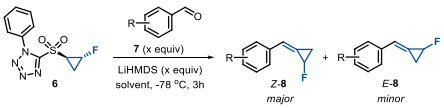
Scheme 1. Synthesis of Reagent 6



the reaction conditions (Table 1) for fluorocyclopropylidene synthesis from aldehydes was performed. Initial attempts to

Table 1. Optimization of Fluorocyclopropylidene 8 Synthesis



entry	6/7/base	solvent (c, mmol/mL)	yield of 8 (%)[a]	Z/E[b]
1	1/4/1.5	THF (0.1)	44[c]	67:33
2	1/4/1.5	Et_2O (0.1)	26[c]	72:28
3	1/4/1.5	DMF (0.1)	62[c]	89:11
4[f]	1/4/1.5	DMF (0.1)	48[c]	88:12
5	1/4/1.5	DMF (0.05)	84[c]	85:15
6	1/2/1.5	DMF (0.05)	78[c]	86:14
7	1/2/1.5[e]	DMF (0.05)	86[c]	86:14
8	1/2/1.7	4:1 THF/DMF (0.1)	97[d]	89:11
9	1/2/1.7	4:1 THF/DMF (0.1)	85[c]	91:9
10	1/1.5/1.7	4:1 THF/DMF (0.1)	78[d]	78:22

[a]^{1}H NMR yields determined using EtOAc (1.0 equiv) as an internal reference. [b]Z/E ratios determined by ^{19}F NMR analysis of the crude samples; for structure determination of Z/E isomers, see the SI. [c]**8a**, R = 3-NO_2. [d]**8b**, R = 4-NO_2. [e]NaHMDS was used as the base. [f]The reaction was performed at −20 °C.

generate the carbanion first from reagent **6** followed by addition of aldehyde **7a** were unsuccessful.

We approached the synthesis of fluorocyclopropylidenes by employing Barbier conditions.[14] We were pleased to see that monofluorocyclopropylidene **8a** formed when LiHMDS was used as the base in THF, albeit in moderate yield (Table 1, entry 1). After screening various solvents and temperatures (entries 2−7), it was established that the optimal conditions (entries 8 and 9) were achieved using LiHMDS as the base in a 4:1 THF/DMF mixture at −78 °C, providing **8a** and **8b** formation in excellent yield with good Z/E selectivity.

Having the optimal reaction conditions in hand, we continued with a substrate scope investigation (Scheme 2). The determined reaction conditions tolerated a wide range of aromatic aldehydes **7**. Aldehydes containing electron-withdrawing groups, such as nitro (**7a−c**), cyano (**7n**), and halogens (**7d**, **7e**) as well as electron-donating groups (**7f−j**) gave good to excellent yields of the corresponding fluorocyclopropylidenes **8** with Z/E selectivities up to 90:10. The Z isomer turned out to be the main product, which, based on our DFT calculations (Figure 2; see Figure S3 for other isomeric TSs of higher energy), is a likely result of the reaction proceeding via a closed transition state, where TS **A** is more favorable than TS **B** due to diminished dipole−dipole interactions where fluorine atom is pointing away from the aryl substituent of aldehyde **7**. However, in the case of the bulky substrates **7i**, **7m**, and *ortho*- substituted **7p** the selectivity was significantly decreased, which could likely arise from these reactions proceeding via an open transition state due to increased steric demand. The stereochemistry of the fluorocyclopropylidene products was determined by NOESY experiments (see the SI). Additionally, ketones **9** turned out to be good substrates for this reaction. A wide range of ketones, including ones bearing electron-withdrawing and -donating groups or functionalities such as ester (**9e**), sulfone (**9d**), or an alkyl chain (**9g**), a piperidine-derived ketone, (**9h**) and alicyclic ketones (**9i**, **9j**), successfully gave the desired disubstituted cyclopropylidenes **10**, albeit with moderate Z/E selectivity. Notably, the diastereomeric product **10i** was obtained in good yield and diastereoselectivity (93%, 9:1 dr). Fluorocyclopropylidenes **8** and **10** are compounds of moderate stability at room temperature but can be stored in a freezer (−20 °C) for several months without noticeable decomposition. However, the described products are unstable in $CDCl_3$, and therefore, benzene-d_6 was used as the solvent for NMR analysis. The remarkable ability of reagent **6** to participate in the Julia−Kocienski reaction without notable eliminative decomposition could be attributed to the formation of the thermodynamically more stable *trans* carbanion,[10] preventing a potential fluoride leaving group from an *anti*-periplanar arrangement representing unique example in a class.

To further demonstrate the utility of fluorinated MCP derivatives **8** and **10**, an epoxidation/ring expansion reaction[15] was investigated (Scheme 3). After testing various Lewis acids (see Table S1), almost quantitative conversion of the piperidine-derived F-MCP **10h** to the corresponding fluorocyclobutanone derivatives **12h** and **13h** was achieved using lithium triflate. Fluorinated cyclobutanone derivatives **12i** and **13i** were formed spontaneously upon treatment of **8i** with *m*CPBA, as a stabilized benzylic carbocation can form for the substrate **8i**. The regiochemistry and stereochemistry of **12** and **13** were determined by using ^{1}H−^{19}F HOESY NMR (see the SI), and the structure of **13i** was further confirmed unambiguously by X-ray crystallography (Figure 3).

Hydrogenation of the cyclopropane derivatives, especially for fluorinated substrates, proved to be challenging. Standard hydrogenation conditions using Pd/C, Wilkinson's catalyst, or Li/NH_3 resulted in decomposition products with loss of fluorine and/or ring opening. We were pleased to find that Crabree's catalyst[16] turned out to be a mild hydrogenation catalyst that provided the desired fluorocyclopropylmethyl derivatives **14**, demonstrating the potential value of the fluorinated building blocks **8** and **10**.

In order to probe the current methodology for its suitability for the synthesis of medicinally relevant targets, we developed a synthetic route to **20** (Scheme 4), a fluorocyclopropyl analogue of ibuprofen, one of the most commonly used nonsteroidal anti-inflammatory drugs.[17] The Pd-catalyzed arylation of 4-bromobenzaldehyde **15** with diethyl malonate afforded intermediate **16**, which was further methylated with MeI. Our developed methodology was successfully applied to the synthesis of cyclopropylidene derivative **18**, which was hydrogenated and finally decarboxylated to afford fluoroibu-

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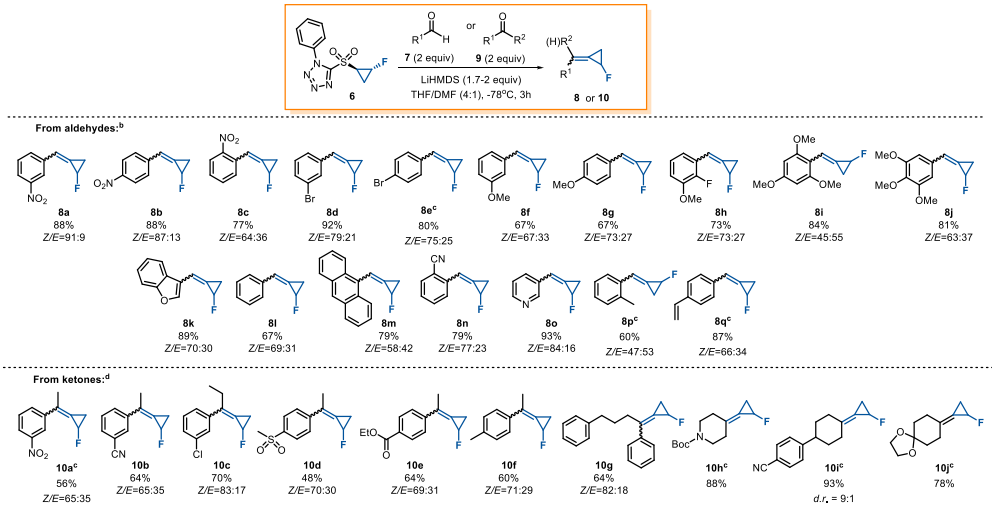
Scheme 2. Substrate Scope of Julia–Kocienski Olefination[a]



[a]*Z*/*E* ratios were determined by ^{19}F NMR analyses of purified samples. [b]Conditions: **6** (0.07–0.08 mmol, 1.0 equiv), **7** (2.0 equiv), LiHMDS (1 M in THF; 1.7 equiv), dry THF/DMF (4:1; 0.1 M), Ar atmosphere, −78 °C, 3 h. [c]See the SI for the reaction scale. [d]Conditions: **6** (0.11–0.12 mmol, 1.0 equiv), **9** (2.0 equiv), LiHMDS (1 M in THF; 2 equiv), dry THF/DMF (4:1; 0.1 M), Ar atmosphere, −78 °C, 3 h.

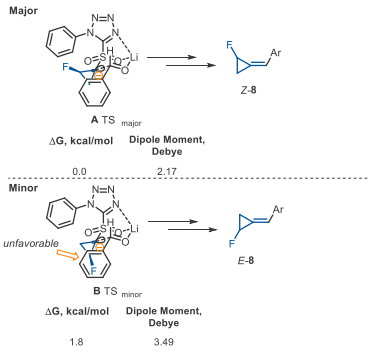
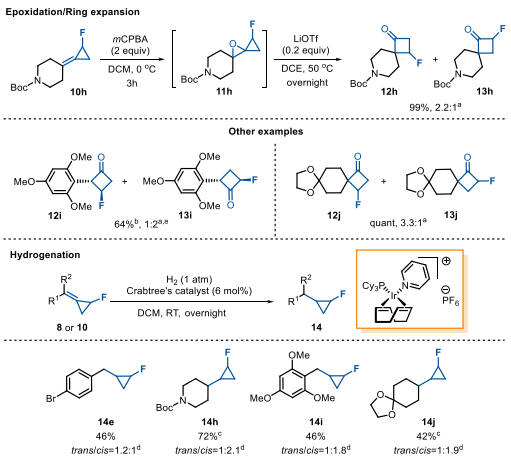


Figure 2. Energy comparison of transition states calculated using the ωB97XD/6-311++G(2df,p) method.

profen derivative **20** as a mixture of stereoisomers. Chiral preparative HPLC allowed separation of the stereoisomers, which were subjected to an enzymatic assay to determine inhibition of COX-1 and COX-2 enzymes. It was found that (*rac*)-*trans*-**20** displayed 5-fold-higher activity toward COX-1 but lower inhibitory potency toward COX-2 than the reference compound ibuprofen. The stereoisomer (+)-*cis*-**20** resulted in a moderate loss of inhibitory potency, while the stereoisomer (−)-*cis*-**20** can be considered inactive toward COX-2. Both *cis*-**20** stereoisomers are inactive toward COX-1. These results demonstrate that incorporation of the fluorocyclopropyl moiety can significantly modify biological response to the parent compound and highlight that the fluorocyclopropylmethyl group goes beyond bioisosteric replacement of the isobutyl group, giving a new handle to medicinal chemists for fine-tuning of biological activity in SAR studies.

Scheme 3. Examples of Synthetic Application of F-MCPs



[a]**12**/**13** ratio determined by ^{19}F NMR analysis. [b]In the presence of *m*CPBA (1.1 equiv, 2 h), spontaneous cyclization of **8i** into **12i** and **13i** takes place. [c]^{1}H NMR yield determined using 1,2-DCE as an internal reference. [d]**14** *cis*/*trans* ratio determined by ^{19}F NMR analysis. [e]Major diastereomers for **12i** and **13i** are shown. **12i** is an unstable compound.

In conclusion, we have developed a synthetically useful approach to access rare but potentially attractive fluorocyclopropylidenes or monofluorinated methylenecyclopropanes (F-MCPs). This class of compounds could be potentially used as strategic intermediates to access valuable fluorinated products. The synthesis of a fluorinated ibuprofen analogue reveals that

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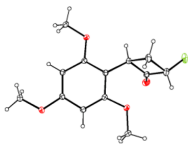
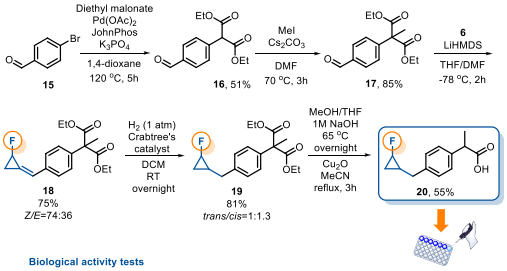


Figure 3. Solid-state structure [CCDC 2207752] of cyclobutanone **13i**. Atomic displacement ellipsoids are drawn at the 25% probability level.

Scheme 4. Synthesis and Biological Evaluation of a Fluorocyclopropyl Analogue of Ibuprofen



Biological activity tests

	Ibuprofen	*(rac)-trans-***20***	*(+)-cis-***20***	*(-)-cis-***20***
COX-1	IC_{50}= 134 μM	IC_{50}= 25 μM	IC_{50}= >500 μM	IC_{50}= >500 μM
COX-2	IC_{50}= 443 μM	IC_{50}= 1071 μM	IC_{50}= 681 μM	IC_{50}= >2000 μM
S, c-1/c-2	0.30	0.023	n/a	n/a

*Relative configuration shown

the fluorocyclopropylmethyl moiety can be used to fine-tune the biological activity of the compounds under investigation.

■ 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.3c00579.

Synthetic procedures, analytical data, DFT calculations, and NMR spectra (PDF)

Accession Codes

CCDC 2207752 and 2207762 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Synthetic Applications of Monofluoromethylsulfonium Salts

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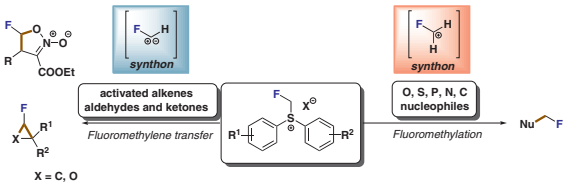

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Abstract Monofluoromethylsulfonium salts are emerging reagents for the fluoromethylation and fluoromethylenation or fluoromethylene transfer. Using this type of reagent is a simple approach for the introduction of the fluoromethyl group into a wide range of nucleophiles using mild basic conditions. Recently, fluoromethylsulfonium salts have been demonstrated to act as a synthetic equivalent for the challenging fluoromethylene synthon. For instance, these reagents can be used for the direct synthesis of monofluoroepoxides and fluorocyclopropanes from activated alkenes via a sulfur fluoromethylide intermediate. Sulfonium salts are an alternative, easy-to-handle option to volatile and environmentally concerning freons for achieving monofluorinated compounds. This review focuses on synthetic application of these reagents known to date.

Key words fluoromethylation, fluoromethylenation, sulfur fluoromethylide, sulfonium salts, fluorocarbene, fluoromethylene transfer

Renate Melngaile was born in Riga, Latvia, and received her Master's degree in chemistry and chemical technology from Riga Technical University in 2019. Currently, she is working on her Ph.D. thesis under the supervision of Dr. Janis Veliks at the Latvian Institute of Organic Synthesis. Her current research interests include development of novel fluoromethylene group transfer reagents.

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1 Introduction

The incorporation of a fluorine atom into a molecule has an impact on its physical and chemical properties which often results in improved pharmacological properties of the biologically active scaffold.[1] Thus, compounds containing a fluorine moiety have a prominent place in the pharmaceutical and agrochemical industries.[2] Therefore, the strategic introduction of a fluorine atom or a fluoroalkyl group at different stages of drug development has become routine practice.[3] The high demand in these fields has encouraged organic chemists to develop general and efficient reagents and methods for the preparation of fluorinated compounds.[4] A plethora of convenient methods for the effective installation of trifluoromethyl[5] or difluoromethyl[6] groups into target molecules are known in the literature. In contrast, methodologies for the direct introduction of monofluoromethyl (CH_2F)[7,8] or fluoromethylene (CHF) groups[9] are far less explored.

Within electrophilic monofluoromethylation reagents,[7a] fluoromethylsulfonium salts[10] have a prominent place as they fulfill the requirements of solid, shelf-stable, easy-to-use reagents.[11] Prior to 2008, the synthetic application of monofluoromethylsulfonium salts was unexplored.[12,13] This review will cover two currently known reaction modes for this type of reagent: the originally designated fluoromethylation (CH_2F)[13] and more recently discovered fluoromethylene transfer (CHF)[14] that enables access to monofluorinated 3- and also 5-membered rings. Fluoromethylene transfer has remained underdeveloped for a long time, due to the previously reported extreme instability of fluorocarbenoid

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species.[15] However, recent progress in this area indicates the huge synthetic potential of such reactive species.[16a] Until recent, there were only two *direct* approaches to fluoromethylene group transfer: the use of low boiling and environmentally concerning freons of type $CHFX_2$[16] or the utilization of Hu's fluorinated sulfoximines, although, for this reagent substrate scope was limited exclusively to Weinreb amides.[17] A limited range of reagents and challenging monofluorocarbene chemistry have often justified adding extra synthetic steps for indirect incorporation of the fluoromethylene synthon into a substrate.[18] So, the use of fluoromethylsulfonium salts as sulfur fluoromethylide precursors and competent *direct* fluoromethylene transfer reagents has resulted in a new avenue of research in this area.[19]

The fluoromethylsulfonium salts **1** can be prepared in 4 to 5 steps starting from sodium benzenethiolate,[13] phenyl sulfoxides,[11] chloromethyl phenyl sulfide,[20] or thioanisole[19c,] using such reagents as CsF, DAST, CH_2ClF, or Selectfluor. For example, fluorination of thioanisole (**I**) with Selectfluor[19c] via fluoro-Pummerer process and the following oxidation affords fluoromethyl sulfoxides **II**, which can be further reacted with trifluoromethanesulfonic anhydride which participate in an electrophilic aromatic substitution reaction with arenes **III** (Figure 1); this affords fluoromethylsulfonium salts **1** in low to good yields.

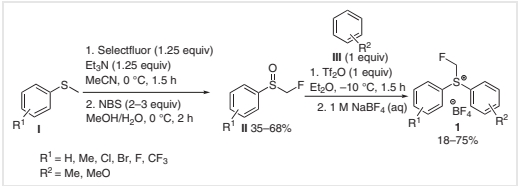
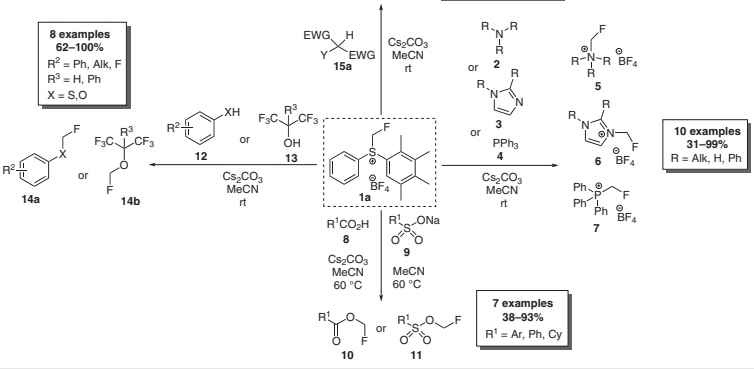


Figure 1 Synthesis of fluoromethylsulfonium salts

2 Fluoromethylation of O-, N-, S-, P-, and C-Nucleophiles

In 2008, Prakash, Olah, and co-workers demonstrated for the first time that diaryl(fluoromethyl)sulfonium tetrafluoroborate **1a** acts as an electrophilic monofluoromethylating reagent for direct CFH_2 group transfer to nucleophiles.[13] The fluoromethylsulfonium salt **1a** is a solid, user-friendly reagent, which is insensitive to moisture with a remarkable stability. The reagent **1a** (Scheme 1) is efficient for the electrophilic introduction of the monofluoromethyl group into C-, S-, O-, N-, and P-nucleophiles under mild conditions using Cs_2CO_3 as a base. The efficiency of sulfonium salt **1a** was investigated in reactions with various primary, secondary, and tertiary amines, indole, pyridine, and 4-(dimethylamino)pyridine, also substituted imidazoles and several triarylphosphines (Scheme 1).

The fluoromethylation of amines proved to be successful only for tertiary amines **2** and imidazoles **3** which formed monofluoromethylated tetrafluoroborate salts **5** and **6**, respectively, in high yields. Among the tested phosphines, only triphenylphosphine (**4**) gave the desired monofluoromethyl tetrafluoroborate salt **7** in low yield (31%). Generally, fluoromethylation reactions with **1a** proceeded at room temperature, however, the carboxylic acids **8** and sulfonate **9** required heating to 60 °C to access the corresponding fluoromethyl esters **10** or **11**; in the case of sodium sulfonate **9**, no extra base was required for the reaction. Moreover, fluoromethylsulfonium salt **1a** performed



Scheme 1 Fluoromethylation of various nucleophiles with (fluoromethyl)phenyl(2,3,4,5-tetramethylphenyl)sulfonium tetrafluoroborate

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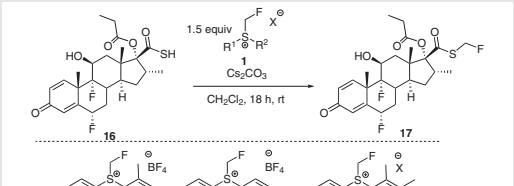
efficiently in reactions with naphthols, phenols, perfluorophenol, and thiophenol **12** and fluorinated alcohols **13** forming the corresponding monofluoromethyl thioethers or ethers **14a** and **14b** in high yields. Unfortunately, the reagent **1a** was unable to monofluoromethylate simple aliphatic alcohols. The C-nucleophiles **15a**, stabilized with two electron-withdrawing groups, for example, esters and sulfones, were also suitable substrates for monofluoromethylation, affording the corresponding fluoromethylated products **15b** in a moderate to good yields.

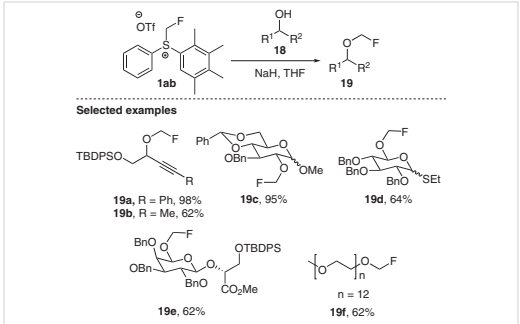
This methodology was applied in the synthesis of various biologically relevant products: monofluorinated derivatives of γ-butyrobetaine and trimethyllysine[20] and steroids and their derivatives.[21] Leitão showed that fluticasone 17-propionate (**17**) was efficiently prepared by fluoromethylation of the corresponding sulfide precursor **16**[11] with related fluoromethylsulfonium salt analogues **1** in DCM using Cs_2CO_3 as a base (Scheme 2). All the fluoromethylsulfonium salts utilized were oily solids with the only exception being 2,3,4,5-tetramethylphenyl-substituted analogues **1da** and **1db**. Of the various fluoromethylsulfonium salts examined, the triflate salt **1db** gave the highest yield of **17**.



Scheme 2 Fluoromethylation of fluticasone 17-propionate

In comparison to the results of Prakash, Olah, and co-workers,[13] Maycock and co-workers showed that fluoromethylation reactions with O-nucleophiles can be performed successfully with various alcohols when (fluoromethyl)phenyl(2,3,4,5-tetramethylphenyl)sulfonium triflate (**1ab**) was used in the presence of sodium hydride as base.[22] Complex starting materials like acetylenic alcohols, glucosides, and PEG550 monomethyl ether (Scheme 3) were compatible with the reaction conditions.

In 2017, Lu, Shen, and co-workers developed improved electrophilic monofluoromethylating sulfonium ylide based reagents, (fluoromethyl)phenylsulfonium bis(methoxycarbonyl)methylide (**20a**) and (fluoromethyl)4-nitrophenylsulfonium bis(methoxycarbonyl)methylide (**20b**).[23] Reagent **20a** reacted under mild reaction conditions not only with a wide range of phenols **21**, but also with primary, secondary, allylic, propargylic, and tertiary alcohols **23**, which could contain a heteroaryl moiety, furnishing the corresponding



Scheme 3 Fluoromethylation of a range of O-nucleophiles

monofluoromethyl ethers **22** and **24** in good to high yields (Scheme 4).

4-Nitro-substituted reagent **20b** was best suited to C-nucleophiles **25** using Cs_2CO_3 as a base in NMP at room temperature. The transformation was efficient with different malonate derivatives delivering products **26** in high yields (Scheme 4).[23] Likewise, as O-nucleophiles both aryl- and alkyl-substituted carboxylic acids **27** showed high reactivity providing monofluoromethyl esters **28** in high yields, although benzoic acids with strong electron-withdrawing groups displayed decreased yields. Notably, sulfonic acids **29** were transformed into fluoromethyl esters **30** smoothly without any additive or base.

N-Nucleophiles **31**, including amides or heteroarenes, such as indazole, pyrazole, imidazole, pyrrolo[2,3-*d*]pyrimidine, and benzotriazole, were suitable substrates in monofluoromethylation reactions in good yields (Scheme 4).[23]

Mechanistic studies with deuterated reagents suggested that the formation of the monofluoromethyl ether proceeds through a nucleophilic substitution pathway rather than a monofluorocarbene pathway.[23]

In 2020, Lu, Shen, and co-workers reported two newly developed reagents, sulfonium ylide basd compounds bearing either a strongly electron-withdrawing 1,1,1,5,5,5-hexafluoropentane-2,4-dione backbone (Scheme 5) or a cyclic malonate unit (Scheme 6), which both were reported to possess even better reactivity towards a variety of primary, secondary, and tertiary alcohols and heteroatom nucleophiles, also including soft C-nucleophiles such as malonate derivatives.[24] The structure-activity relationships of these reagents was investigated and it was found that the electrophilicity and thereby reactivity of fluoromethylation reagent can be improved by decreasing the electron density on the sulfur atom.

The C-selective monofluoromethylation of β-keto esters **34a**,**b** can be performed by exploiting 1,1,1,5,5,5-hexafluoropentane-2,4-dione reagent **33a** containing an electron-withdrawing nitro group on the benzene ring

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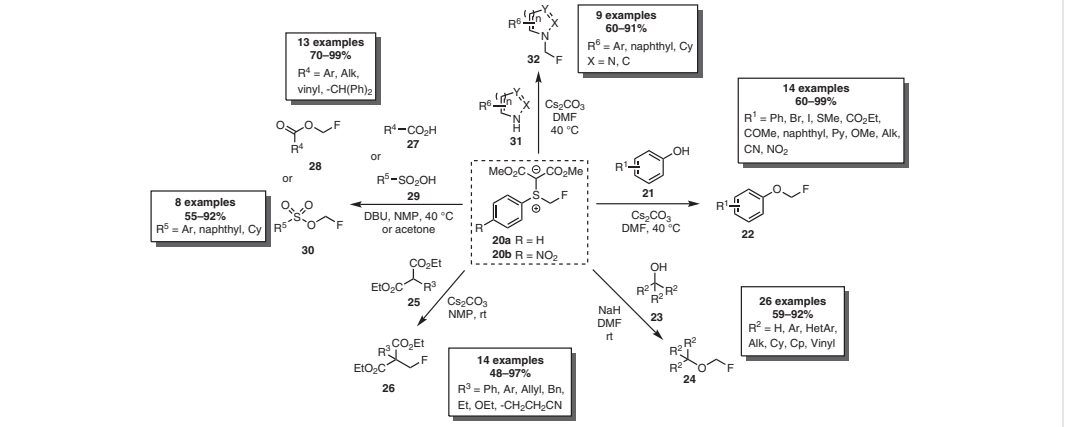
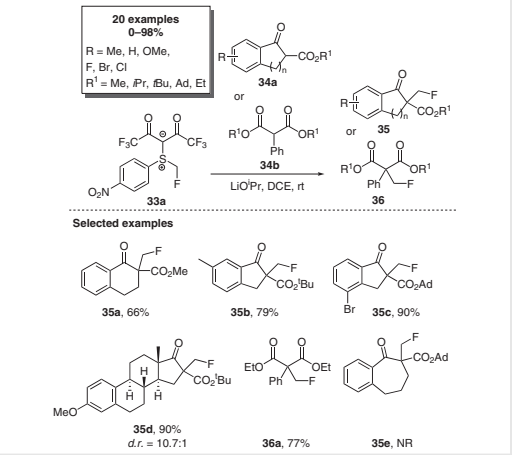


Scheme 4 Reactions of sulfonium salts with various O-, N-, and C-nucleophiles under basic conditions

(Scheme 5).[24] The substrate scope of this transformation included both electron-donating and -withdrawing groups in different positions on the arene moiety of **34a**, providing C-selective products **35a–e** and **36a** with up to 98% yield; the yield was generally influenced by steric hindrance of the corresponding substrate ester group.



Scheme 5 C-Selective fluoromethylation of β-keto esters

Further studies revealed that C- or O-selectivity of β-keto esters monofluorination can be controlled by choosing an appropriate sulfonium salt and a strong organic base, *tert*-butyliminotri(pyrrolidino)phosphorane (BTPP). O-Selective monofluoromethylation reactions of β-keto esters **34** with sulfonium ylide reagent **33b** provided monofluoromethyl vinyl ethers **37** containing electron-donating and electron-withdrawing groups (Scheme 6).[24]

Furthermore, the use of such nucleophiles as electron-rich or -poor phenols **38** and heterophenols **39** was examined under these reaction conditions with reagent **33b** and the formation **40** and **41**, respectively, was observed in moderate to high yields (Scheme 6).[24]

To generalize the application of reagent **33b**, the reaction was performed also with carboxylic acids **42** to give acid esters **43** bearing both electron-donating or electron-withdrawing groups including halogens, free hydroxy, amino, or amide groups and an enolizable ketone moiety. Under the standard conditions, an investigation of the substrate scope gave products **43** of benzoic, vinyl, and aliphatic carboxylic esters in good to excellent yields (Scheme 6).[24]

For the monofluoromethylation of thiophenols **44** and heteroaryl N-nucleophiles **45**, NaH was a more appropriate base and afforded **46** and **47**, respectively, in high yields with short reaction times (Scheme 6).[24]

A similar approach was also exploited by Besset, Jubault, Poisson, and co-workers, who designed advanced sulfonium salt **48** to introduce the CHFMe group into O- and S-nucleophiles **49** and **50** under mild basic conditions (Scheme 7).[25] The developed methodology was efficient for phenols **49** (X = O) and thiophenols **49** (X = S) bearing several functional groups to afford the corresponding OCFHMe-containing derivatives **51** and **52** in up to 94% yield, though reaction with benzylic and homobenzylic alcohols **50** resulted in lower yields.

In 2020, Liu and co-workers developed bench-stable, solid fluoromethylsulfonium salts, **54a** (PF_6^-) (Scheme 8) and **54b** (BF_4^-) (Scheme 9), which showed efficient reactivi-

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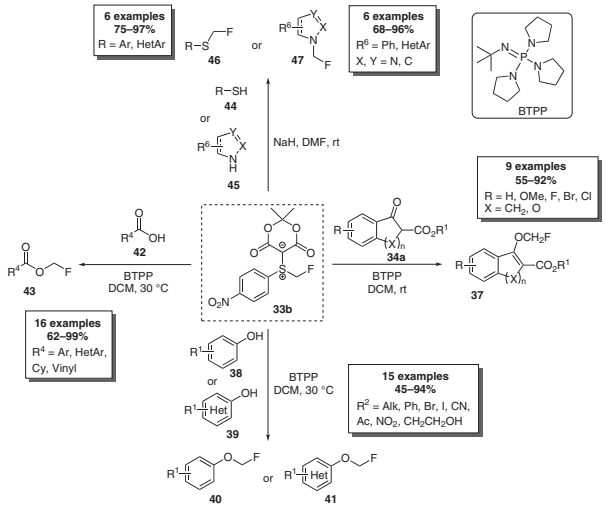
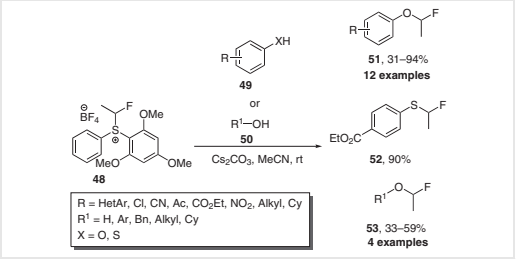


Scheme 6 Reactions of a sulfonium salt with various O-, N-, and C-nucleophiles under basic conditions

ty and regioselective in the C- or O-fluoromethylation of 1,3-dicarbonyl compounds, malonates **55** and β-keto esters **57**.[26]

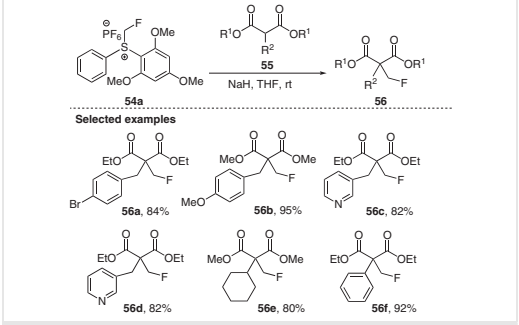
Substrate scope studies on 2-alkyl-, 2-aryl-, and 2-heteroaryl-substituted malonic esters **55** in reaction with (fluoromethyl)phenyl(2,4,6-trimethoxyphenyl)sulfonium hexafluorophosphate (**54a**) indicated that the mild reaction conditions tolerate diverse functional groups such as ester, nitro, halogen, and also heteroarenes, to give C-monofluoromethylated products **56** in good to excellent yields (Scheme 8).[26]

Interestingly, in the case of the monofluoromethylation of β-keto esters **57** the corresponding O-monofluoromethylated products **58** formed as major products (Scheme 9).[26]



Scheme 7 Introduction of the OCHFMe group into O- and S-nucleophiles via using (fluoromethyl)phenyl(2,4,6-trimethoxyphenyl)sulfonium tetrafluoroborate

Higher yields of products **58** were achieved by using sulfonium tetrafluoroborate **54b** instead of hexafluorophosphate **54a**. Under the optimized reaction conditions a substrate scope that included tetralone carboxylates, cyclohexanone carboxylate, and indanone carboxylates **57** was examined (Scheme 9).[26] For benzo-fused carbo- and heterocyclic β-keto esters **57**, products **58** were obtained in high yields regardless of the electronic effects and position of substituents in the benzene ring.



Scheme 8 Fluoromethylation of malonic esters

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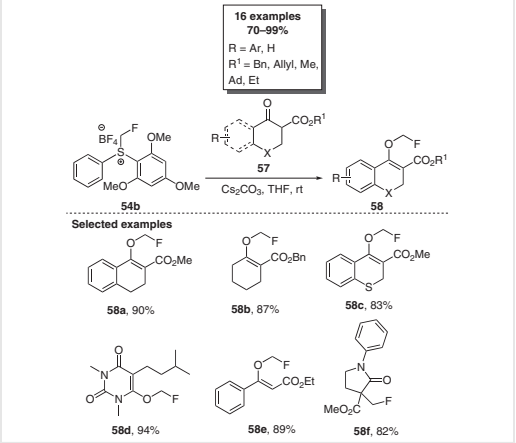
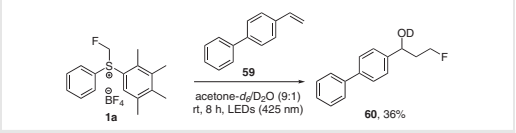


Scheme 9 Fluoromethylation of β-keto esters

3 Sulfonium Salts for Radical Monofluoromethylation of Alkenes

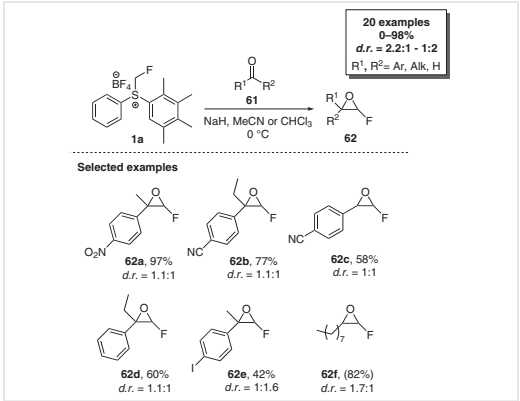
In 2019, Koike, Akita, and co-worker reported a single example of visible-light metal-free photoredox-catalyzed hydroxymonofluoromethylation of 4-vinylbiphenyl (**59**) in the presence of fluoromethylsulfonium salt **1a** by generating a monofluoromethyl ($^{\bullet}CH_2F$) radical (Scheme 10).[27] The sulfonium salt **1a** was not the optimal reagent for this reaction and in further studies it was replaced by a sulfoximine-based precursor [CH_2F–S(=O)(=NTs)-Ph], however, this example shows that sulfonium salts can be applied for photoredox-catalyzed monofluoromethyl radical generation.



Scheme 10 Monofluoromethylation of alkenes via photoredox-catalyzed reactions

4 Sulfonium Salts for Fluoromethylene Transfer

In 2019, the Veliks group demonstrated first example of fluoromethylsulfonium salt **1a** as a direct fluoromethylene (CHF) transfer reagent in the synthesis of fluoroepoxides.[14] Moreover, this approach was the first evidence for the feasibility of a sulfur fluoromethylide as a synthetic equivalent to the otherwise challenging fluoromethylene synthon. Diaryl(fluoromethyl)sulfonium salt **1a** as bench-stable, user friendly reagent[10,13] was used to develop an efficient method for the formation of the uncommon[16i,28] 2-unsubstituted fluoroepoxides **62** in a monofluorinated version of the Johnson–Corey–Chaykovsky reaction (Scheme 11).



Scheme 11 Fluoromethylene transfer to aldehydes and ketones; isolated yields are given, with NMR yields in parentheses

The reaction conditions accommodated a variety of aryl, aliphatic, and alicyclic substituted ketones and aldehydes **61**. Notably, the reaction tolerated a range of functional groups on the aryl ring, such as nitro, cyano, ester, amide, trifluoromethyl, and sulfone, affording products **62a–f** in moderate to high yields. Electron-withdrawing groups were found to increase the stability of fluoroepoxides **62**, by contrast, substrates bearing electron-donating groups on the aryl ring did not afford the desired products due to the instability of the corresponding epoxides **62**. The scope of obtained products was restricted by the stability of the resulting product, and not by fluoromethylenation.

Based on this strategy, the Veliks group then reported the Johnson–Corey–Chaykovsky fluorocyclopropanation using sulfonium reagent **1a**[19a] with vinyl sulfones or vinyl sulfonamides to access synthetically challenging monofluorocyclopropanes,[29] which were previously generally obtained via fluorocarbene and fluorocarbenoid chemistry.[16] The best conditions (Scheme 12), which involved sodium hydride as base and THF as an appropriate solvent, exhibited broad scope of functionalized aryl, heteroaryl, and cyclohexyl vinyl sulfones **63** to give fluorocyclopropanes **64a–f** with good yields of the major *trans*-product.

Notably, also vinyl sulfonamides participated in the fluorocyclopropanation with reagent **1a** delivering fluorocyclopropyl-substituted sulfonamide derivatives, such as **64f** (Scheme 12).[19a] Although, lower electrophilicity of vinyl

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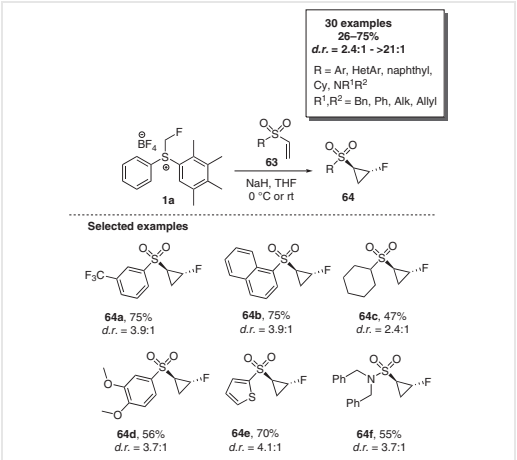
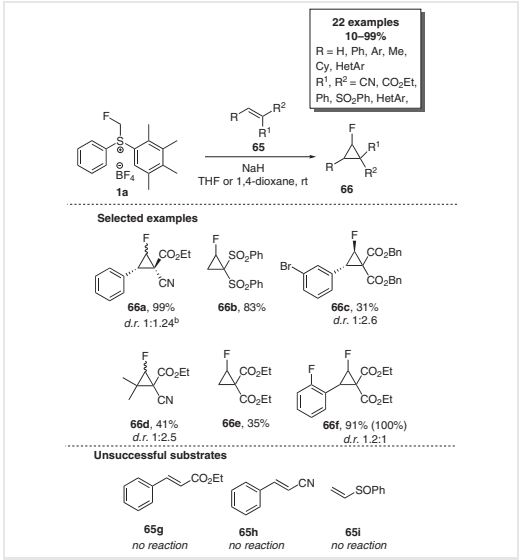


Scheme 12 Fluorocyclopropanation of vinyl sulfones and amides

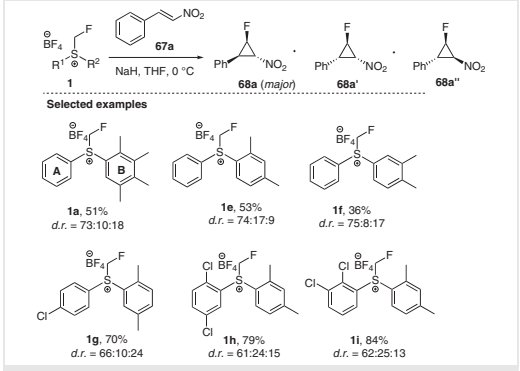


Scheme 13 Successful fluorocyclopropanation of double activated alkenes

sulfonamides compared to sulfones resulted in longer reaction times and moderate product yields. Interestingly, the substrate scope demonstrated similar ratios of diastereomers for a large variety of fluorocyclopropanes despite the different nature of the functionalities present. Experimental and computational studies were carried out to explore mechanistic details of the fluorocyclopropanation reaction. According to the calculations the ring closing is the stereoselectivity determining step for the formation of product **64**. Results showed that the transition state for the *trans*-product was 0.9 kcal/mol lower in energy than for the corresponding *cis*-product. Moreover, the calculated data on the thermodynamic stability also indicates that the *trans*-product is more stable by 1.19 kcal/mol. These results mean that initially the transformation is kinetically controlled with selectivity consistent with TS energy differentiation, but in the course of the reaction thermodynamic equilibration takes effect and the energy difference of the products defines the final stereoisomeric ratio.

Moreover, the fluorocyclopropanation of double activated alkenes **65** proceeds well using fluoromethylsulfonium salt **1a** (Scheme 13).[19b] Substituted arylidenemalononitrile, arylidenemalonate, disulfone, and arylidenebarbiturate derivatives were demonstrated to be compatible reaction partners.

The scope and limitations of the fluorocyclopropanation of activated alkenes **65** using fluoromethylsulfonium salt **1a** was investigated, where the reactivity of various monosubstituted Michael acceptors with double activated ones was compared. The reactivity is well correlated with electrophilicities of the corresponding activated Michael acceptors. For example, several substrates (**65g–i**) bearing only a single electron-withdrawing group were not reactive towards the sulfonium reagent **1a**. The phenyl vinyl sulfoxide (**65i**) does not react, however, the more electron-withdrawing phenyl vinyl sulfone **63** (see Scheme 12) readily takes part in this reaction and this sets the boundary of the utility of this reaction. Double activated arylidene and methylidene derivatives are a good fit for this reaction. Stronger electron-withdrawing groups facilitate the fluorocyclopropanation reaction, however, in the case of arylidene derivatives decreased stability of the formed products can be observed. The electron-withdrawing groups on the aryl



Scheme 14 Study of various reagents for fluorocyclopropanation via reaction with β-nitrostyrene

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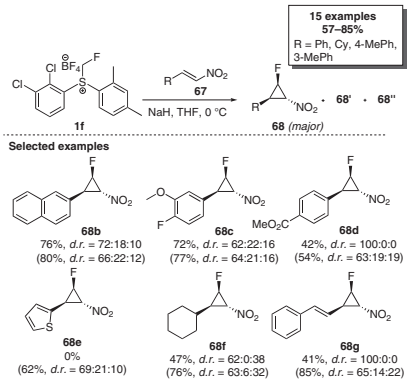


Scheme 15 Fluorocyclopropanation of nitroalkenes; isolated yields are given, with NMR yields in parentheses

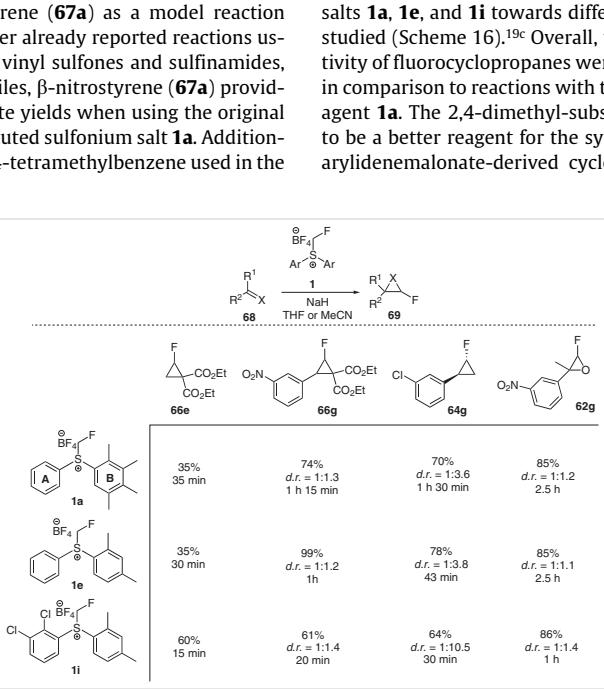
ring contribute to the improved stability of the fluorocyclopropanes **66**, but those with electron-donating groups are of poor stability.

In 2021 the Veliks group investigated efficiency of various sulfonium salts **1** by employing the monofluorocyclopropanation of β-nitrostyrene (**67a**) as a model reaction (Scheme 14).[19c] Unlike other already reported reactions using as substrates ketones, vinyl sulfones and sulfinamides, malonate, and malononitriles, β-nitrostyrene (**67a**) provided product **68a** in moderate yields when using the original tetramethylphenyl-substituted sulfonium salt **1a**. Additionally, the high cost of 1,2,3,4-tetramethylbenzene used in the synthesis of **1a** prompted the search for a more affordable and similarly effective reagent. The *ortho*-methyl group as a substituent on the phenyl ring B in **1a** and **1e** ensured their crystallinity and higher yields in comparison to reagents lacking this substitution, such as **1f**.

It was concluded that reagents based on *o*,*p*-dimethyl-substituted reagent **1e** were a potentially efficient but more affordable replacement to the original tetramethyl-substituted reagent **1a** due to the significantly lower price of starting material *m*-xylene used for the preparation of the sulfonium salt **1e**. Furthermore, the introduction of halogens (F, Cl, or Br) or a CF_3 group on phenyl ring A in most cases increased the reaction yield. But the highest yield and diastereoselectivity in the model fluorocyclopropanation reaction was achieved in the reaction of sulfonium salt **1i** containing *o*,*m*-chloro groups on phenyl ring A.

With most reactive sulfonium salt **1i** in hand, the substrate scope of aryl- and alkyl-substituted nitroalkenes **67** was studied (Scheme 15).[19c] Under these reaction conditions fluorocyclopropane derivatives **68b–g** bearing electron-donating groups (alkyl, alkoxy) and electron-accepting groups (halogens, CF_3, NO_2, ester) on the aryl ring were obtained in moderate to very good yields with moderate diastereoselectivities.

Furthermore, the efficiency of developed sulfonium salts **1a**, **1e**, and **1i** towards different substrate classes was studied (Scheme 16).[19c] Overall, the yields and stereoselectivity of fluorocyclopropanes were similar or slightly higher in comparison to reactions with the original tetramethyl reagent **1a**. The 2,4-dimethyl-substituted reagent **1e** proved to be a better reagent for the synthesis of sulfone **64g** and arylidenemalonate-derived cyclopropane **66g**, but in the



Scheme 16 Reactivity study of sulfonium salts via reactions with various Michael acceptors

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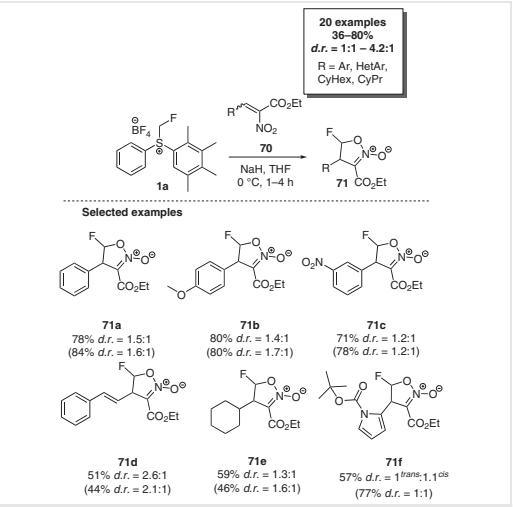
case of fluorocyclopropyl diester **66e** and fluoroepoxide **62g** better results were achieved using 2,3-dichloro reagent **1i**.

In 2021, the Veliks group showed that fluoromethylene transfer from diaryl(fluoromethyl)sulfonium salts can be also applied to the synthesis of monofluorinated 5-membered rings in a formal [4+1] cyclization (Scheme 17).[30] The synthetic methodology was developed to access monofluorinated isoxazoline *N*-oxides **71** in one step starting from substituted 2-nitroacrylates **70** using fluoromethylsulfonium reagent **1a** (Scheme 17). The reaction conditions tolerate various substituents on the aryl ring, such as, conjugated alkenes and alicyclic and heterocyclic substituents. The transformation can alternatively be performed using more affordable and atom economical reagent **1e** providing comparable yields of product **71**. The formed monofluorinated isoxazoline *N*-oxides **71** represent a rare class of monofluorinated heterocycles that can be further used for the synthesis of complex polycyclic heterocycles in a dipolar cycloaddition reactions.



Scheme 17 Synthesis of monofluorinated isoxazoline *N*-oxides; isolated yields are given, with NMR yields in parentheses

5 Conclusions

In conclusion, monofluoromethylsulfonium salts are an emerging class of stable and non-volatile reagents capable donating fluoromethyl or fluoromethylene groups. The currently known reaction modes for this type of reagents include electrophilic fluoromethylation as well as fluoromethylene transfer, which proceeds via fluoromethylide as an active intermediate. Application of fluoromethylsulfonium reagents as a source of fluoromethyl radical is an underexplored area. Yet this approach potentially might offer valuable synthetic utility in future. The fluoromethylsulfonium salts provide direct and attractive methods for monofluoromethylation or monofluoromethylenation reactions, as alternative reagents to the more commonly used freons or halofluoromethanes (CH_2FX) .

Conflict of Interest

The authors declare no conflict of interest.

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Melngaile, R.; Veliks, J. Sulfonium, (Fluoromethyl)phenyl(2,3,4,5-tetramethylphenyl)-, Tetrafluoroborate(1-) (1:1)[1]. *Encycl. Reagents Org. Synth.* **2021**, 1–4.

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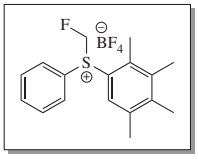
https://doi.org/10.1002/047084289X.rn02379.

Sulfonium, (Fluoromethyl)phenyl (2,3,4,5-tetramethylphenyl)-, Tetrafluoroborate(1-) (1:1)[1]



[1009088-40-7] $C_{17}H_{20}BF_5S$ (MW 362.22)

InChI = 1S/C17H20FS.BF4/c1-12-10-17(15(4)14(3)13(12)2)19(11-18)16-8-6-5-7-9-16;2-1(3,4)5/h5-10H,11H2,1-4H3;/q+1;-1

InChIKey = SDWOHFZFPMIYRL-UHFFFAOYSA-N

Alternative Name(s): *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate, $STBF_4$.

Physical Data: mp 118–121 °C.

Solubility: soluble in dichloromethane, chloroform, dimethylformamide, and acetonitrile; partially soluble in THF (upon standing solvent polymerization observed); and insoluble in water, diethyl ether, and petroleum ether.

Form Obtained in: white or light brown solid; commercially available.

Analysis of Reagent Purity: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.76–7.69 (m, 1H), 7.66 (m, 2H), 7.43 (s, 1H), 6.55 (dd, J = 46.6, 9.6 Hz, 1H), 6.42 (dd, J = 45.6, 9.5 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 139.4, 138.2, 137.4, 134.3, 131.4, 130.8, 128.4 (d, J = 4.6 Hz), 121.2 (d, J = 2.7 Hz), 116.2, 89.6 (d, J = 241.7 Hz), 21.1, 17.7, 16.9, 16.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.45, −151.51, −207.18 (t, J = 46.4 Hz).

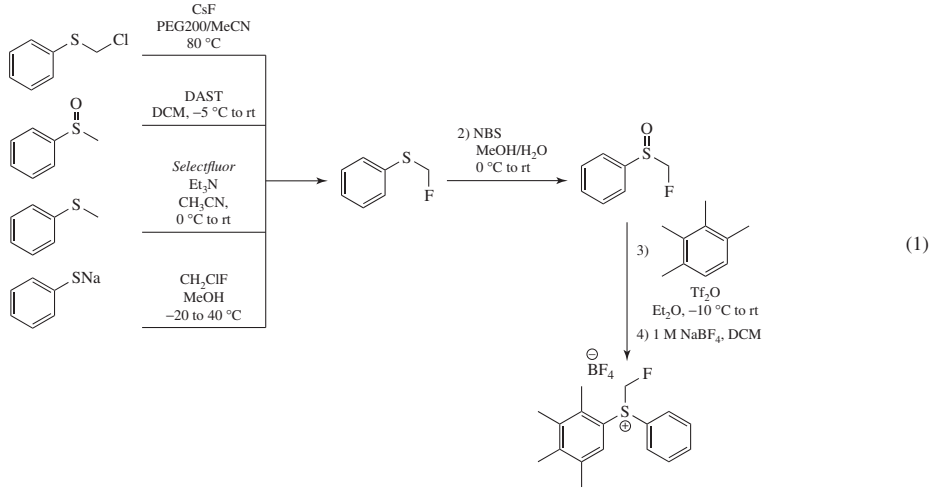
Preparative Method: prepared in a four-step process starting from sodium phenyl thiolate, phenyl sulfoxide, or thioanisole.

Purification: extraction between dichloromethane and water, silica gel chromatography (eluent gradient CH_2Cl_2, then CH_2Cl_2/MeCN 1:1), or/and washing precipitate with petroleum ether/diethyl ether.

Handling, Storage, and Precautions: bench stable and can be stored more than one year at room temperature. No information is currently available in terms of the reagent's effect on health.

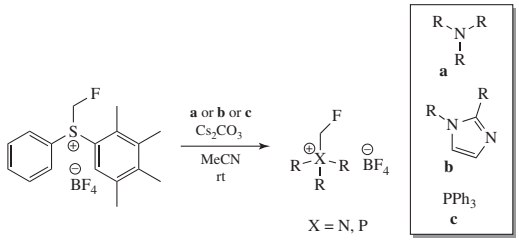
Introduction. The *S*-(monofluoromethyl)diarylsulfonium tetrafluoroborate ($STBF_4$) is a reagent used for fluoromethylation (CH_2F–transfer) or fluoromethylenation (CHF=transfer) reactions. In 2008, Prakash et al. demonstrated that $STBF_4$ can be used as an electrophilic monofluoromethylating reagent for the direct electrophilic monofluoromethyl group transfer or fluoromethylation in reactions with C-, S-, O-, N-, and P-nucleophiles under basic conditions.[1] Recently, Veliks and coworkers reported its application as a fluoromethylene transfer or fluoromethylenation reagent. A method was developed to access substituted fluorocyclopropanes and fluoroepoxides under the Johnson–Corey–Chaykovsky reaction conditions.[2–4]

Preparation Methods. The fluoromethyl sulfonium salt $STBF_4$ can be obtained in a four-step sequence (eq 1). In the first step, fluorination of chloromethyl phenyl sulfide,[5,6] methyl phenyl sulfoxide,[5] thioanisole,[3] or fluoromethylation of thiolate[1] takes place by exploiting different fluorination or fluoromethylation reagents such as CsF, *Selectfluor* or DAST, and CH_2ClF. Further, oxidation of the corresponding fluoromethyl phenyl sulfide with NBS results in fluoromethyl phenyl sulfoxide. Electrophilic aromatic substitution with 1,2,3,4-tetramethyl benzene yields fluoromethyl sulfonium triflate, which consequently is converted to fluoromethyl sulfonium tetrafluoroborate ($STBF_4$) after anion exchange using $NaBF_4$ (aq).[1–6]



(1)

Fluoromethylation of Tertiary Amines, Imidazoles, and Triphenylphosphine. The electrophilic monofluoromethylation (CFH_2–) reagent $STBF_4$ was used for the synthesis of monofluoromethylated salts of nitrogen and phosphorus nucleophiles (eq 2).[1] The ability of $STBF_4$ to fluoromethylate primary, secondary, and tertiary amines was investigated using indole, pyridine, and 4-dimethylaminopyridine, with substituted imidazoles and triarylphosphines as substrates. Among the tested nitrogen nucleophiles, only the tertiary amines and imidazoles provided the expected monofluoromethylated tetrafluoroborate salts; only triphenylphosphine was reported to give the corresponding monofluoromethyl tetrafluoroborate salt, albeit in low yield.



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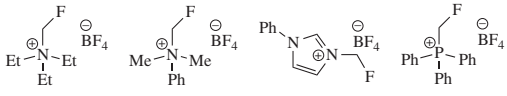
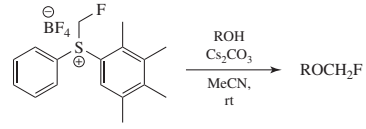


86% 83% 92% 31%

(2)

Fluoromethylation of Carboxylic and Sulfonic Acids. The reagent $STBF_4$ was used for fluoromethylation of carboxylic acids and sulfonic acids (eq 3) to access the corresponding fluoromethyl esters.[1] The fluoromethylation of carboxylic acids proceeded in the presence of Cs_2CO_3 as a base, whereas sodium salts of the sulfonic acids were reacted directly without using a base. The ester formation takes place at elevated temperature.

Fluoromethylation of Phenols, Naphthols, and Fluorinated Alcohols. The same authors also demonstrated sulfonium salt reactivity toward naphthols, phenols, perfluorophenol, thiophenol, and fluorinated alcohols (eq 4).[1] In the case of oxygen nucleophiles, the pK_a of the substrates should not exceed 10 for a monofluoromethylation reaction to proceed in high yields. Thus, monofluoromethylation of simple aliphatic alcohols could not be performed using $STBF_4$.



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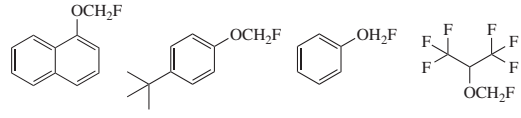
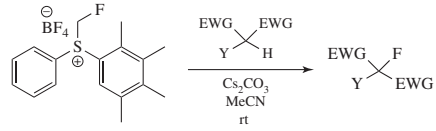


94% 100% 88% 83%

(4)

Among various carbon nucleophiles containing an acidic hydrogen atom, only those substrates, activated with at least two electron-withdrawing groups, proved to react with $STBF_4$ (eq 5), affording corresponding fluoromethylated derivatives in moderate to good yields.



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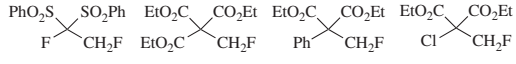
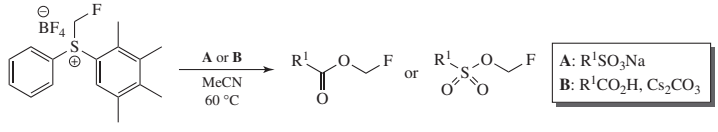


72% 75% 32% 71%

(5)



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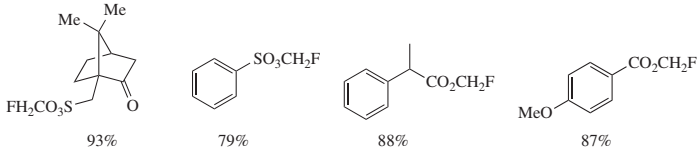


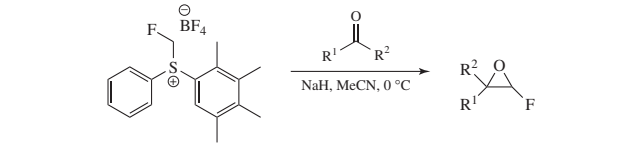
93% 79% 88% 87%

(3)

Fluoromethylenation of Aldehydes and Ketones. The fluoromethylsulfonium salt $STBF_4$ may also act as a fluoromethylene (CHF=) transfer reagent. This was demonstrated on aldehydes and ketones (eq 6) by the synthesis of uncommon 2-unsubsituted fluoroepoxides in moderate to high yields in a monofluoro version of Johnson–Corey–Chaykovsky reaction.[2] The reaction conditions tolerate a number of aryl, aliphatic, and alicyclic-substituted ketones and aldehydes. Most common functional groups on the aryl ring, such as nitro, cyano, ester, amide, trifluoromethyl, and sulfone, were accommodated. Notably, electron-withdrawing groups on aryl substituents were observed to increase the stability of the fluoroepoxide products; however, substrates containing electron-donating groups on the aromatic ring did not result in the desired products due to instability of the corresponding fluoroepoxides.

The authors also observed that the same strategy can be exploited similarly in Johnson–Corey–Chaykovsky fluorocyclopropanation of activated alkenes in the presence of a base.

Fluorocyclopropanation of Activated Alkenes. The fluoromethylsulfonium reagent $STBF_4$ was efficiently used for the synthesis of monofluorocyclopropanes from vinyl sulfones and vinyl sulfonamides (eq 7).[3] The reaction proceeds in high yield with moderate to good *trans*-selectivity, and the major *trans*-diastereomer can be easily isolated by chromatography in moderate to good yields. The reaction conditions tolerate a broad scope of substituted aryl-, heteroaryl-, and cyclohexylvinyl sulfones, involving a variety of functional groups such as halogens, cyano, methoxy, nitro, ester, and methyl groups. The reactions with vinyl sulfonamides required longer reaction times and resulted in fluorocyclopropane products in moderate yields.



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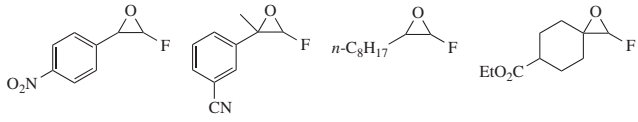
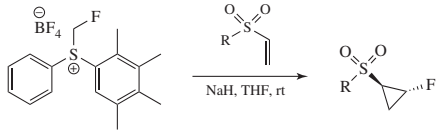


dr = 1:1, 58% | dr = 1:1, 98% | dr = 1.7:1 (82% NMR yield) | dr = 1.7:1, 96%

(6)



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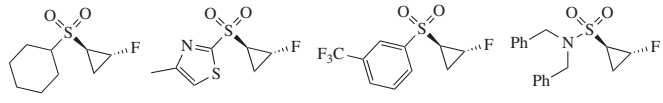
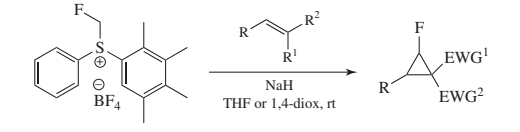


dr = 2.4:1, 47% | dr = 7.8:1, 61% | dr = 3.9:1, 75% | dr = 3.7:1, 55%

(7)

The fluoromethylsulfonium salt $STBF_4$ was also employed in Johnson–Corey–Chaykovsky fluorocyclopropanation of double-activated alkenes including arylidene malononitrile, arylidene malonate, arylidene disulfone, and arylidene barbiturate derivatives (eq 8).[4] The corresponding fluorocyclopropanes were obtained in low to excellent yields with low diastereoselectivity. Generally, two EWG groups at the double bond are beneficial for the fluorocyclopropanation to proceed smoothly. Alkenes bearing a single EWG such as sulfoxide, ester, or cyano group did not participate in this reaction (exception sulfones vide supra). The overall fluorocyclopropane yield strongly depends on the stability of the formed products. The fluorocyclopropanes bearing two geminal electron-withdrawing groups and electron-poor aromatic substituent were stable and chromatographically isolable products; however, electron-rich aromatic substituents render the products unstable. The donor–acceptor properties of such fluorocyclopropanes allowed their application in the synthesis of fluorinated furane derivatives.



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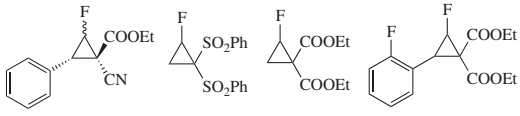
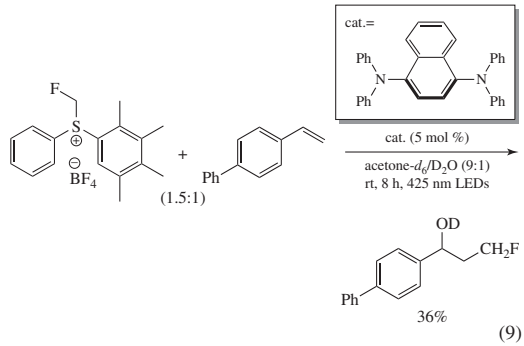


dr = 1:1.24[b] 99% | 83% | 35% | dr = 1.2:1 91%

(8)

Monofluoromethylation of Alkenes in Photoredox-catalyzed Reactions. In addition to the conventional application of the fluoromethyl sulfonium salt as a fluoromethyl or a fluoromethylene group transfer reagent, in 2019 Akita and coworkers presented a single example (eq 9) of hydroxy-monofluoromethylation of *p*-vinylbiphenyl by generating a monofluoromethyl ($\cdot CH_2F$) radical from fluoromethyl sulfonium salt via visible-light metal-free photoredox catalysis using 1,4-bis-(diphenylamino)naphthalene.[7]



(9)

Related Reagents. Fluoroiodomethane; Fluorodiiodomethane; Phenylsulfonylfluoromethylphosphonate; Benzene, 1,1′-[(Fluoromethylene)bis(sulfonyl)]bis-.

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R. Melngaile strādā Latvijas Organiskās sintēzes institūta Organiskās sintēzes laboratorijā, un viņas zinātniskās intereses saistītas ar jaunu fluormetilēngrupas pārneses reaģentu izpēti. Viņa ir piecu oriģinālpublikāciju, viena apskatraksta starptautiski citējamos žurnālos, kā arī raksta ķīmisko reaģentu enciklopēdijā līdzautore.

Renate Melngaile was born in 1994 in Riga. In 2017, she obtained a Bachelor's degree in Chemical Technology from Riga Technical University (RTU) on the topic "Investigation of intramolecular iodosulfenylation of olefins" (supervisors: Dr. chem. Anna Nikitjuka, Professor Dr. chem. Aigars Jirgensons). In 2019, she obtained a Master's degree in Chemical Technology from RTU on the topic "Fluorocyclopropanation of vinylsulfones in the Corey-Chaykovsky reaction" (supervisor: Dr. sc. nat. Jānis Veliks) for which she received Mārtiņš Straumanis and Alfrēds Ieviņš Award in Chemistry of Latvian Academy of Sciences. She is also a co-author of the study "New reagent for organic synthesis with high application potential in medicinal chemistry", which the Latvian Academy of Sciences named one of the ten best scientific achievements of Latvia in 2019.
R. Melngaile is currently a research associate in the Latvian Institute of Organic Synthesis (Laboratory of organic synthesis) and her research interests are focused on studies of new fluoromethylene group transfer reagents.
She is a co-author of five original publications, one review article in international scientific journal, as well as an article in encyclopedia of chemical reagents.