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Wiktor Krzysztof Poper

Synteza fluorowanych pochodnych imidazolu typu lepidilinowego

Synthesis of lepidiline-type fluorinated
imidazole derivatives

Praca doktorska wykonana
pod kierunkiem promotora
dr. hab. Marcina Jasińskiego, prof. UŁ
w Katedrze Chemii Organicznej i Stosowanej
Wydziału Chemii Uniwersytetu Łódzkiego

Łódź 2025

„Gratia non tollit naturam, sed perficit.”

- Sanctus Thomas Aquinas, Summa Theologiae

Niniejszą rozprawę doktorską dedykuję
mojej żonie Agnieszce oraz córce Anastazji,
a także wszystkim tym naszym dzieciom,
które dopiero się narodzą.

Pragnę najserdeczniej podziękować
całej mojej rodzinie za bezustanną wiarę,
okazane wsparcie i bezcenną wyrozumiałość.

Poniższa rozprawa nie powstałaby również
gdyby nie wsparcie całego Zespołu:
prof. Marcina Jasińskiego, dr Grety Utecht-Jarzyńskiej,
dr Katarzyny Urbaniak, mgra Kamila Świątka,
Małgorzaty Celedy, mgra Adriana Warcholińskiego;
jak również całej Katedry Chemii Organicznej i Stosowanej.
Za wszystko – z serca dziękuję.
Bóg zapłać.

Monotematyczny cykl publikacji wraz z komentarzem przedstawiony Komisji Uniwersytetu Łódzkiego ds. stopni naukowych w dyscyplinie nauki chemiczne w celu uzyskania stopnia doktora nauk chemicznych.

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Spis publikacji stanowiących podstawę niniejszej rozprawy doktorskiej:

- [**D1**] Poper, W. K.; Jasiński M. **2025** "The introduction of SCF_3 substituents into heterocyclic rings." In *Advances in Heterocyclic Chemistry*, edited by Christopher A. Ramsden, Elsevier. *(pre-proof manuscript)*
- [**D2**] Poper, W. K.; Ma, J.-A.; Jasiński, M. *"*One-Pot Telescoping S-Transfer and Trifluoromethylation for the Synthesis of 2-CF3S-Imidazoles with N-Oxides as Convenient Precursors*"*. *J. Org. Chem.*, **2024**, *89*, 15331.
- [**D3**] Poper, W. K.; Denel-Bobrowska M.; Olejniczak, A. B.; Jasiński, M. "First lepidiline-inspired 1, 3-dibenzyl 2-CF3S-imidazoliums: Design, synthesis and cytotoxic activity study" *Biomed. Pharmacother.*, **2025**, *192*, 118606.
- [**D4**] Poper, W. K.; Świątek, K.; Urbaniak, K.; Olszewska, B.; Jasiński, M. "Lepidiline-Derived Imidazole-2(3H)-Thiones: (3+2)-Cycloadditions vs. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines" *Molecules*, **2025**, *30*, 3851.

Spis treści

1. Streszczenie

Pierścień imidazolu stanowi kluczowy element strukturalny wielu związków organicznych fundamentalnych dla życia, takich jak histydyna, histamina, czy (w formie skondensowanej) guanina lub adenina. Unikatowe właściwości tego heterocykla w kontekście aktywności biologicznej skutkowały znaczącym wzrostem znaczenia pochodnych imidazolu, które od połowy XX wieku zaczęły być coraz szerzej eksplorowane i wykorzystywane m.in. jako farmaceutyki, czy agrochemikalia. Istotną grupę bioaktywnych pochodnych imidazolu stanowią również bardziej złożone związki pochodzenia naturalnego, w tym alkaloidy. Do tej grupy zaliczane są tzw. lepidiliny – sole imidazoliowe, rozpoznane jako związki bioaktywne, cechujące się m.in. wysoką cytotoksycznością wobec wybranych komórek nowotworowych.

Jedna z efektywniejszych metod modulowania właściwości biologicznych związków organicznych polega na wprowadzeniu pojedynczych atomów fluoru lub podstawników fluorowanych takich jak grupy fluoroalkilowe, fluoroalkiloksylowe, czy fluoroalkilotiolowe. W tym kontekście możliwe są dwie podstawowe strategie syntetyczne: (i) wykorzystanie fluorowanych bloków budulcowych do otrzymywania docelowych produktów fluorowanych lub (ii) bezpośrednia funkcjonalizacja niefluorowanego prekursora związku docelowego. I tak, jedną z kluczowych potrzeb stojących przed współczesną syntezą organiczną jest opracowywanie nowych, efektywnych i ekonomicznie uzasadnionych metod otrzymywania związków fluoroorganicznych.

Poprzez realizację zaplanowanych w ramach niniejszego doktoratu badań postanowiłem wyjść tej potrzebie naprzeciw i opracować ogólną metodę otrzymywania nowej klasy trifluorometylotiolowanych pochodnych imidazolu. Mając przy tym na względzie wspomniane wyżej alkaloidy, prowadzone badania ukierunkowane były na uzyskanie serii niejonowych oraz jonowych produktów inspirowanych strukturą lepidilin. Dodatkowym zadaniem zrealizowanym w ramach niniejszego doktoratu,

a zarazem rozwinięciem tematyki skupionej na syntezie fluorowanych pochodnych imidazolu, było zbadanie reaktywności *N*-mono oraz *N*,*N′*-dipodstawionych imidazolo-2-tionów, analogów strukturalnych lepidilin, wobec generowanych *in situ* trifluorometylowanych nitryloimin (CF_3-NI), istotnych bloków budulcowych w syntezie bioaktywnych heterocykli fluorowanych.

Abstract

The imidazole ring is a key structural motif of many organic compounds that are fundamental to life, such as histidine, histamine, or (in condensed form) guanine or adenine. The unique properties of this heterocycle in terms of biological activity have resulted in a significant increase in the importance of imidazole derivatives, which since the mid-20th century have been increasingly explored and utilised, among others, as pharmaceuticals and agrochemicals. The significant group of bioactive imidazole derivatives also includes more complex compounds of natural origin, for instance alkaloids. This group includes the so-called lepidilines – imidazolium salts, recognised as essentially bioactive compounds, characterised, among other things, by high cytotoxicity towards selected cancer cells.

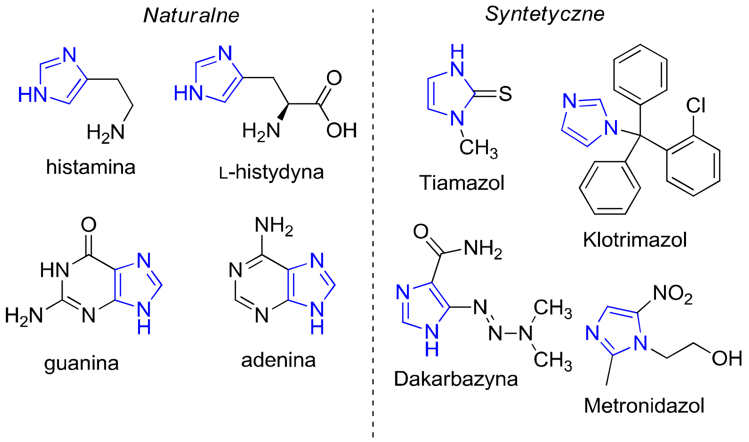
One of the most effective methods of modulating the biological properties of organic compounds is the introduction of fluorinated substituents, such as single fluorine atoms, fluoroalkyl, fluoroalkoxy or fluoroalkylthio groups. In this context, two basic synthetic strategies are possible: (i) the use of fluorinated building blocks to obtain target products with already introduced fluorinated substituents, or (ii) direct functionalisation of a non-fluorinated precursor of the target compound.

Through the research planned as part of this dissertation, I decided to address this need and develop a new method for obtaining trifluoromethylthiolated imidazole derivatives. With the above-mentioned alkaloids in consideration, the research was focused on obtaining a series of non-ionic and ionic derivatives bio-inspired by lepidilines. An additional task carried out as part of this doctoral thesis, and at the same time an extension of the topic focused on the synthesis of fluorinated imidazole derivatives, was to study the reactivity of *N*-mono- and *N*,*N'*-disubstituted imidazole-2-thione structural analogues of lepidilines towards *in situ* generated trifluoromethylated nitrilimines, important building blocks in the synthesis of bioactive fluorinated heterocycles.

2. Wprowadzenie do tematyki badań

2.1. Imidazol a aktywność biologiczna

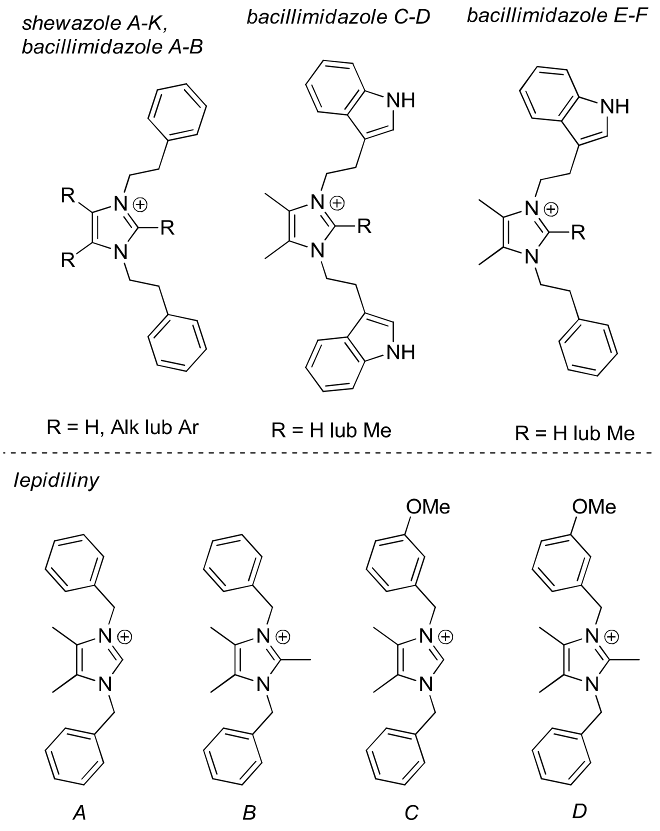
Zgodnie z tytułem niniejszej rozprawy doktorskiej, tematyka podjętych przeze mnie badań skupiona była wokół funkcjonalizacji pochodnych imidazolu (ze szczególnym uwzględnieniem struktur typu lepidilinowego) za pomocą ugrupowań fluorowanych. Wybranie tego motywu strukturalnego jako poddawanego modyfikacjom nie jest bynajmniej przypadkowe, a wynika z istotnej roli, jaką ów heterocykl pełni w wielu związkach bioaktywnych.[1,2] Dość wspomnieć o kluczowych dla życia zasadach azotowych guaninie oraz adeninie zawierających skondensowany pierścień imidazolu, czy histydynie (Rysunek **1.**) – jednym z aminokwasów białkowych. Intensywnie eksplorowane od połowy XX wieku pochodne imidazolu znalazły zastosowanie m.in. jako farmaceutyki, których ważnymi przedstawicielami są Tiamazol, Klotrimazol, Dakarbazyna, czy Metronidazol (Rysunek **1.**).[3,4]



Rysunek 1. Struktury wybranych bioaktywnych pochodnych imidazolu.

Związki te są jedynie przykładami powszechnego zastosowania pierścienia imidazolu w projektowaniu nowych substancji o właściwościach przeciwzapalnych, przeciwgrzybiczych, przeciwnowotworowych i wielu innych niezbędnych w leczeniu współczesnych chorób cywilizacyjnych.[5,6]

2.2. Alkaloidy imidazoliowe



Rysunek 2. Struktury kationów wybranych alkaloidów imidazoliowych.

Moją uwagę jednak przykuły bioaktywne pochodne imidazoliowe pochodzenia naturalnego. Na przestrzeni dekad liczne grupy alkaloidów izolowane były z rozmaitych gatunków bakterii,[7] roślin[8] czy zwierząt.[9] Wśród wspomnianych alkaloidów wyróżniają się sole imidazoliowe, do których zaliczyć można m.in. shewazole,[10] bacillimidazole,[11] czy tytułowe lepidiliny.[12] Owe alkaloidy wyizolowane zostały z korzenia pieprzycy peruwiańskiej (*łac. Lepidium meyenii*), zidentyfikowane jako sole imidazoliowe oparte na pierścieniu 4,5-dimetyloimidazolu, a następnie zbadane pod kątem aktywności biologicznej.[13] Tym samym wykazano ich obiecującą cytotoksyczność wobec kilku nowotworowych linii komórkowych, w tym komórek ludzkich nowotworów trzustki, piersi, czy białaczki.[14] Z tego powodu lepidiliny *per se* stały się inspiracją do prowadzenia badań nad opracowaniem ich metod syntezy *de novo*,[14] jak również ich strukturalnych analogów,[15] kompleksów,[16] głównie w kontekście poszukiwania nowych związków bioaktywnych.

2.3. Struktura i bioaktywność lepidilin

Jak przedstawiono w poprzednim rozdziale, lepidiliny cieszą się uznaniem badaczy głównie dzięki prezentowanej przez te alkaloidy pożądanej aktywności cytotoksycznej. Co warte odnotowania w kontekście samych lepidilin, to wyraźnie wyższą cytotoksycznością cechują się te z grupą metylową w pozycji C(2) pierścienia imidazolu, względem lepidilin C(2)-niepodstawionych. To pozwoliło wysnuć już na początku hipotezę, jakoby obecność niewielkiej grupy lipofilowej mogła istotnie wpływać na cytotoksyczność takich układów.

Tabela 1. Zestawienie aktywności cytotoksycznej lepidilin A-D wobec wybranych ludzkich linii komórkowych nowotworowych oraz odniesienia. PACA2 – rak trzustki; MDA231 – rak piersi; FDIGROV – gruczolakorak jajnika; HL-60 – białaczka; HUVEC – śródbłonek żyły pępowinowej.

	ED_{50}[μg/mL]			**IC_{50}[μg/mL]**	
Lepidilina	**PACA2**	**MDA231**	**FDIGROV**	**HL-60**	**HUVEC**
A	>10	>10	7,39	32,3	>100
B	1,38	1,66	5,26	3,8	>100
C	-	-	-	27,7	>100
D	-	-	-	1,1	>100

W latach 60. XX wieku Hansch ze współpracownikami opracowali parametr lipofilowości π (tzw. parametr Hanscha) pozwalający w sposób liczbowy określić wpływ podstawników wprowadzanych do związków organicznych na ich lipofilowość.[17] Parametr ów jest *ex definitione* różnicą wartości logP współczynnika podziału w układzie oktan-1-ol/woda pomiędzy związkiem zawierającym dany podstawnik, a związkiem referencyjnym:

$$\pi_X = \log P_X - \log P_H$$

$Gdzie$:
$\pi - parametr\ lipofilowości$
$\log P - współczynnik\ podziału\ w\ układzie \frac{oktanol}{woda}$

I tak, dodatnia wartość oznacza wzrost lipofilowości, zaś ujemna wzrost hydrofilowości. Wyliczając w ten sposób wartości parametrów Hanscha dla kilkuset podstawników wykazano, że do relatywnie niewielkich rozmiarowo podstawników zwiększających istotnie lipofilowość związków organicznych należą głównie ugrupowania fluorowane, takie jak $-CF_3$ ($\pi = 0,88$), $-OCF_3$ ($\pi = 1,04$), czy $-SCF_3$ ($\pi = 1,44$).[18]

3. Określenie celów badawczych

Z powyżej omówionych względów za kluczowy motyw strukturalny w zaplanowanych w ramach niniejszego doktoratu badaniach wybrałem ugrupowanie trifluorometylosulfanylowe ($-SCF_3$), zaś za problem badawczy wymagający rozwiązania uznałem opracowanie efektywnej metody syntezy niejonowych oraz jonowych 2-(trifluorometylo)tiolowanych imidazoli typu lepidilinowego. Z tego powodu za podstawowe zagadnienie tematyczne wymagające gruntownego przeanalizowania i omówienia uznałem metody wprowadzania grupy trifluorometylotiolowej do heterocykli. Owo zagadnienie zostało w sposób wyczerpujący przedstawione w pracy przeglądowej [**D1**] wchodzącej w skład niniejszej dysertacji.

Dodatkowym zadaniem uwzględnionym w badaniach realizowanych w ramach niniejszej dysertacji było zbadanie reaktywności generowanych *in situ* trifluorometylowanych nitryloimin wobec imidazolo-2-tionów typu lepidilinowego. W tym kontekście omówienia wymaga dotychczas zgromadzona wiedza na temat reaktywności wspomnianych nitryloimin wobec związków tiokarbonylowych.

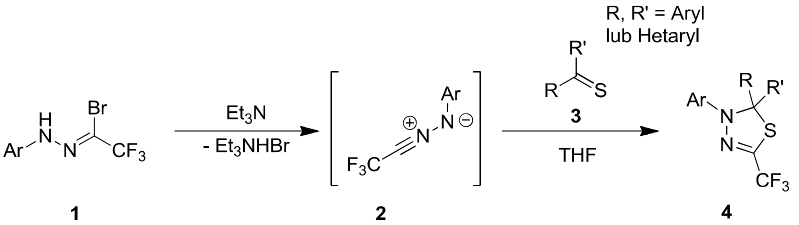
4. Trifluorometylowane nitryloiminy wobec związków tiokarbonylowych

Choć pierwsze przykłady wykorzystania trifluorometylowanych halogenków hydrazonoilowych jako prekursorów trifluorometylowanych nitryloimin stosowanych w reakcjach dipolarnej (3+2)-cykloaddycji sięgają lat 80. ubiegłego wieku,[19] to przez dekady reaktywność tych 1,3-dipoli wobec związków tiokarbonylowych pozostała nierozpoznana. Ponieważ temat ów jest stosunkowo młody i nie został jeszcze dostatecznie szeroko zbadany, nie powstała do tej pory żadna praca przeglądowa poświęcona typowo reaktywności związków tiokarbonylowych ze wspomnianymi nitryloiminami. Tym niemniej fakt, że reakcje te prowadzą do otrzymywania ciekawych układów heterocyklicznych (pochodnych 1,3,4-tiadiazolu), wybrane przykłady zostały przedstawione w pracy poświęconej zagadnieniom w szerszym kontekście.[20]

Poniżej omówione zostaną wszystkie, według mojej najlepszej wiedzy, do tej pory rozpoznane przykłady reakcji trifluorometylowanych nitryloimin ze związkami tiokarbonylowymi.

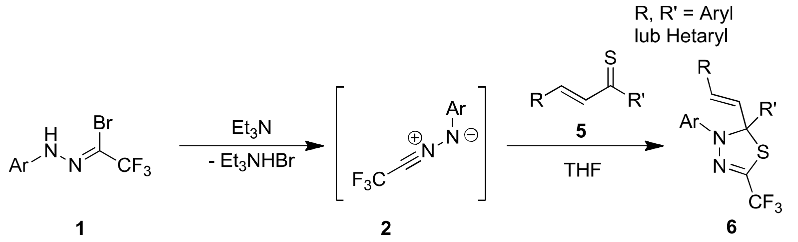
4.1. Tioketony

Historycznie pierwsze doniesienie literaturowe na temat reakcji wspomnianych trifluorometylowanych nitryloimin **2**, generowanych *in situ* z bromków hydrazonoilowych **1** pochodzi z 2016 roku, kiedy to w zespole prof. Jasińskiego zbadano ich reaktywność wobec tioketonów diarylowych, dihetarylowych, jak również arylowo-hetarylowych **3**.[21] W każdym z przypadków reakcja prowadzi do trifluorometylowanych 2,3-dihydro-1,3,4-tiadiazoli **4** (Schemat **1.**). Późniejsze niezależne badania z wykorzystaniem metod obliczeniowych na przykładzie tioketonu arylowo-hetarylowego wykazały, że najkorzystniejszy energetycznie stan przejściowy osiągnięty jest w 3+2-atomowym układzie, co tłumaczy całkowitą regioselektywność reakcji.[22]



Schemat 1. Reakcja trifluorometylowanich nitryloimin z tioketonami arylowymi, hetarylowymi oraz arylo-hetarylowymi.

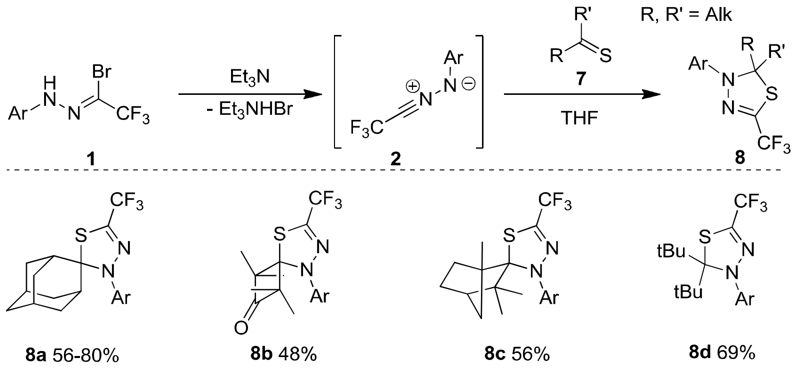
Logicznym rozwinięciem było zbadanie reaktywności trifluorometylowanych nitryloimin wobec tiochalkonów **5** (Schemat **2.**). Choć badane w poprzednich latach bliźniacze układy chalkonowe zachowywały się w reakcjach cykloaddycji jak C=C dipolarofile, to w reakcji z trifluorometylowanymi nitryloiminami zastosowane tiochalkony **5** ulegały addycji do grupy tiokarbonylowej.[23] Uzyskując kolejną serię 2,3-dihydro-1,3,4-tiadiazoli **6** autorzy po raz pierwszy ukazali, że układy tiochalkonowe mogą również reagować jako C=S dipolarofile.



Schemat 2. Reakcja trifluorometylowanich nitryloimin z tiochalkonami.

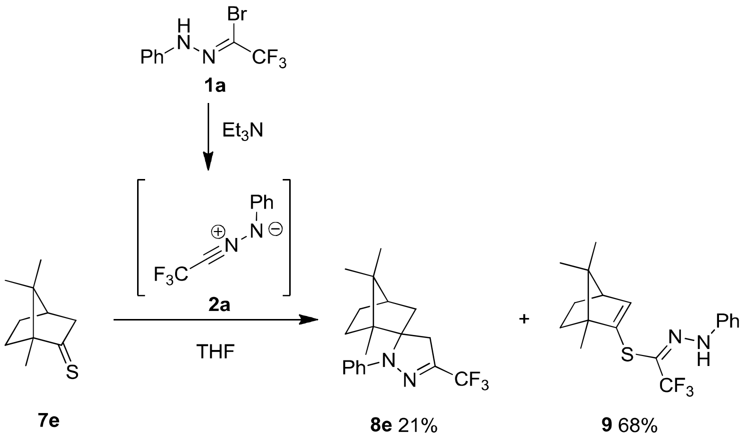
Kontynuując prowadzone w zespole prof. Jasińskiego badania nad reaktywnością fluorowanych nitryloimin wobec związków tiokarbonylowych postanowiono wykorzystać również tioketony alifatyczne oraz cykloalifatyczne **7**.[24] Także te układy, *per analogiam* do wyżej omówionych, ulegają chętnie reakcjom (3+2)-cykloaddycji, prowadząc do trifluorometylowanych 2,3-dihydro-

1,3,4-tiadiazoli **8** (Schemat **3.**). Wątek tej samej reakcji z 2,3-difenylocyklopropentionem, prowadzącej do analogicznych produktów *spiro* został przebadany i opisany osobno w późniejszych latach.[25]



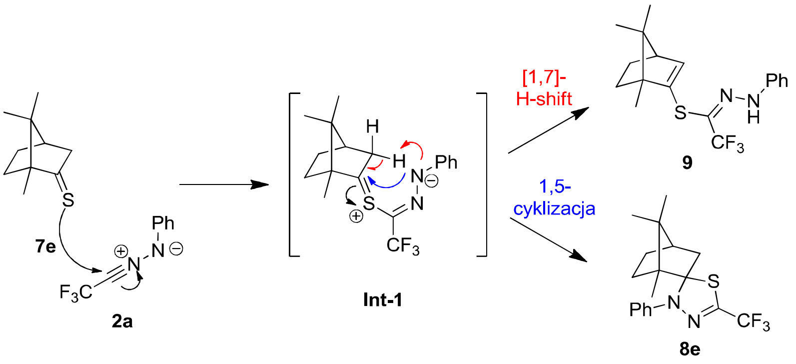
Schemat 3. Reakcja trifluorometylowanich nitryloimin z tioketonami alifatycznymi i cykloalifatycznymi.

Jednakże spośród zbadanych w tej serii pochodnych na szczególną uwagę i osobne omówienie zasługuje reakcja z tiokamforą **7e**, która przebiega w sposób niespodziewany (Schemat **4.**). Skutkiem takiego przebiegu reakcji jest otrzymanie mieszaniny dwóch produktów, gdzie produktem większościowym jest związek acykliczny **9**, zaś oczekiwana pochodna 2,3-dihydro-1,3,4-tiadiazolu **8e** stanowi produkt mniejszościowy.



Schemat 4. Reakcja tiokamfory z trifluorometylowaną nitryloiminą.

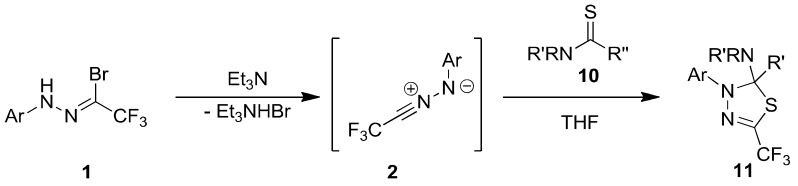
Autorzy pracy podjęli się wyjaśnienia obserwowanego fenomenu. Wskazali oni, że kluczowy może być efekt związany z obecnością elektronoakceptorowej grupy trifluorometylowej, istotnie zwiększającej charakter elektrofilowy 1,3-dipola **2a**. Skutkiem tego jest podatność związku **2a** na atak nukleofilowego atomu siarki z tiokamfory **7e** i wzrost C-H kwasowości sąsiadującej grupy CH_2 (Schemat **5.**). Struktura otrzymanych produktów **8e** oraz **9** sugeruje ponadto, że reakcja przebiega poprzez zwitterjonowy związek pośredni **Int-1**.



Schemat 5. Proponowany mechanizm reakcji tiokamfory z nitryloiminą **2a**.

4.2. Tioamidy

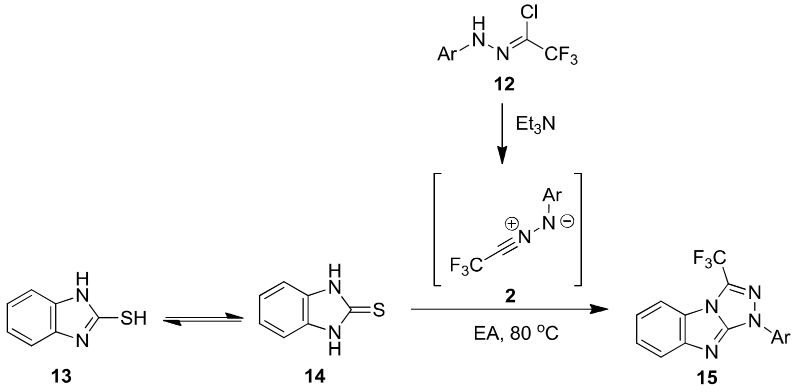
Alternatywną grupą typowych związków tiokarbonylowych, których reaktywność wobec trifluorometylowanych nitryloimin została zbadana, stanowią tioamidy **10**.[26] Zgodnie z oczekiwaniami, również w tym przypadku trifluorometylowane nitryloiminy **2** reagują z ugrupowaniem tiokarbonylowym, prowadząc ponownie do odpowiednich aminowych pochodnych 2,3-dihydro-1,3,4-tiadiazoli **11** (Schemat **6.**).



Schemat 6. Reakcja trifluorometylowanych nitryloimin z tioamidami.

4.3. Benzimidazolo-2-tiole

Za należące do związków tiokarbonylowych uznać można benzimidazolo-2-tiole **13**, choć pozornie mogą na takie nie wyglądać. Owa klasyfikacja znajduje swoją słuszność w tym, że występują one w równowadze tiolowo-tionowej (Schemat **7.**), której obie formy tautomeryczne cechują się swoistą reaktywnością. Należy w tym miejscu również nadmienić, że strukturalnie forma tionowa **14** oparta jest na motywie tiomocznikowym. W kontekście trifluorometylowanych nitryloimin reaktywność ugrupowania tiokarbonylowego **14** została zbadana, jednakże w tym przypadku produktami reakcji nie były spiropochodne 2,3-dihydro-1,3,4-tiadiazolu, lecz skondensowane 1,2,4-triazole **15** (Schemat **7.**). Nawiązując jednocześnie do niniejszej dysertacji należy nadmienić, że przedstawiona reakcja trifluorometylowanych nitryloimin z benzimidazolo-2-tiolami nie była opisana w literaturze w momencie rozpoczęcia badań nad reaktywnością imidazolo-2-tionów.

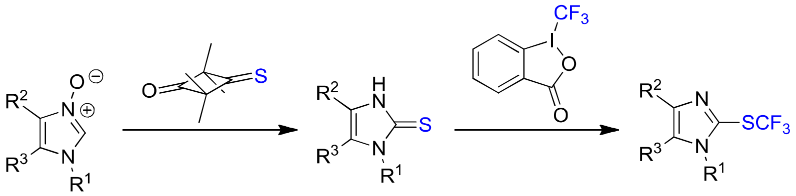


Schemat 7. Reakcja benzimidazolo-2-tioli z trifluorometylowanymi nitryloiminami, z uwzględnieniem tautomerii tiolowo-tionowej.

Podsumowując, reakcje ugrupowań tiokarbonylowych z trifluorometylowanymi nitryloiminami stanowią relatywnie nowy wątek badawczy, zaś przykłady kilku omówionych powyżej reakcji (z tiokamforą oraz benzimidazolo-2-tionami) pokazują, że reakcje te mogą przebiegać w sposób mniej spodziewany, prowadząc do nieoczekiwanych produktów. Z tego powodu w badaniach prowadzonych w ramach niniejszej dysertacji, skupiono uwagę na niezbadanych do tej pory imidazolo-2-tionach typu lepidilinowego (formalnie posiadających układ tiomocznikowy) i podjęto wątek ich reaktywności wobec generowanych *in situ* trifluorometylowanych nitryloimin.

5. Omówienie wyników badań własnych

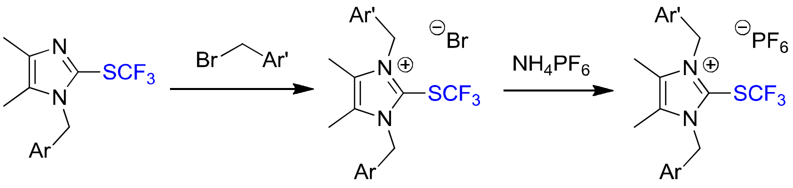
Przedstawione w rozdziale 3. cele badawcze realizowałem chronologicznie, począwszy od opracowania nowej, efektywnej metody syntezy 2-trifluorometylotiolowanych imidazoli. Do tego celu jako dogodne substraty wskazałem *N*-tlenki imidazolu, otrzymywane z odpowiednich formaldimin za pomocą metody opisanej w literaturze.[27] Wybrawszy jako wzorcowy substrat 3-tlenek 1-benzylo-4,5-dimetylo-1*H*-imidazolu przeprowadziłem wstępne testy możliwej C(2)-funkcjonalizacji z wykorzystaniem $AgSCF_3$ jako odczynnika trifluorometylotiolującego. Ze względu na niepowodzenie powyższej metody, wybrałem alternatywną dwuetapową ścieżkę, korzystając z reakcji deoksygenatywnego transferu siarki do pierścienia imidazolu i następczego jej trifluorometylowania. Zbadano trzy odczynniki trifluorometylujące, z czego najefektywniejszy okazał się tzw. odczynnik Togni'ego aktywowany kwasem Brønsteda (HCl). W ten sposób opracowałem nową, efektywną metodę otrzymywania 2-(trifluorometylo)tiolowanych imidazoli **18**, realizując część pierwszego celu badawczego (Schemat **8.**). Reakcja ta wykorzystana została do syntezy 17 nowych związków zawierających zróżnicowane grupy funkcyjne w łańcuchach bocznych pierścienia imidazolu. Pełny proces optymalizacji warunków reakcji, zakres stosowalności opracowanej metody, struktury otrzymanych produktów oraz wszelkie pozostałe istotne szczegóły zostały zebrane i opisane w publikacji stanowiącej podstawę niniejszej dysertacji, oznaczonej numerem **D2**.



16 **17** **18**

Schemat 8. Sekwencja reakcji wykorzystanych w wariancie *one-pot* do syntezy niejonowych 2-(trifluorometylo)tiolowanych imidazoli opisana w publikacji **D2**.

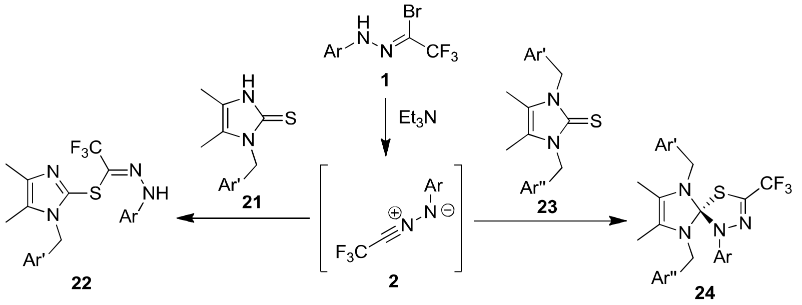
W dalszej części opracowaną uprzednio metodę zastosowałem do syntezy kolejnych niejonowych 2-(trifluorometylo)tiolowanych imidazoli typu lepidilinowego, tj. opartych na motywie 4,5-dimetyloimidazolu z podstawnikiem typu benzylowego w pozycji N(1) układu heterocyklicznego (Schemat **9.**). Otrzymane związki niejonowe typu **18a** następnie przekształciłem do odpowiednich soli imidazoliowych **19** w reakcji *N*-alkilowania pierścienia imidazolu z wykorzystaniem bromków typu benzylowego z następczą wymianą anionu, prowadzącą finalnie do otrzymania serii soli **20** w postaci heksafluorofosforanów (Schemat **9.**). W ten sposób zrealizowałem dalszą część pierwszego celu badawczego niniejszej rozprawy. Wziąwszy jednocześnie pod uwagę omówiony w części literaturowej aspekt potencjalnej bioaktywności otrzymanych soli, związki te (w ramach trwającej współpracy) przekazałem do dalszych badań biologicznych. Jak wykazano, wprowadzenie ugrupowania SCF_3 do soli imidazoliowych typu lepidilinowego w pozycji C(2) istotnie wzmacnia ich aktywność cytotoksyczną, tak wobec komórek nowotworowych, jak i nienowotworowych. Pełny proces optymalizacji warunków reakcji, zakres stosowalności opracowanej metody, struktury otrzymanych produktów oraz wszelkie pozostałe istotne szczegóły zostały zebrane i opisane w publikacji stanowiącej podstawę niniejszej dysertacji, oznaczonej numerem **D3**.



18a **19** **20**

Schemat 9. Synteza 2-(trifluorometylo)tiolowanych soli imidazoliowych opisana w publikacji **D3**.

W trzeciej części pracy badawczej, otrzymywane poprzednio jako istotne substraty imidazolo-2-tiony (formalnie zawierające ugrupowanie tiomocznikowe, tak *N*-monopodstawione **21**, jak i *N,N'*-dipodstawione **23**) wykorzystałem do badań nad ich reaktywnością z wybranymi nitryloiminami typu **2** generowanymi *in situ* z odpowiednich bromków hydrazonoilowych **1** (Schemat **10.**). Wstępne testy wykazały, że jakkolwiek w przypadku *N,N'*-dipodstawionych imidazolo-2-tionów **23** reakcja z generowaną *in situ* nitryloiminą prowadzi do cyklicznych produktów **24** typu *spiro*, to reakcje *N*-monopodstawionych entiolizujących imidazolo-2-tionów **21** z tą samą nitryloiminą **2** prowadzą do acyklicznych produktów typu **22**. Korzystając ze zoptymalizowanych przez mgra Kamila Świątka oraz dr Katarzynę Urbaniak warunków reakcji, otrzymałem serie produktów *spiro* **24** oraz produktów acyklicznych **22**, opartych strukturalnie na pierwotnym motywie imidazolo-2-tionów typu lepidilinowego. Odnosząc się zarazem do reakcji opisanej w podrozdziale **4.3** należy wskazać, że zbadane przeze mnie układy w reakcjach z nitryloiminami prowadzą do produktów typu *spiro* oraz acyklicznych, w przeciwieństwie do zdesulfuryzowanych produktów skondensowanych przedstawionych na Schemacie **7.** Pełny proces optymalizacji warunków reakcji, zakres stosowalności opracowanej metody, struktury otrzymanych produktów oraz wszelkie pozostałe istotne szczegóły zostały zebrane i opisane w publikacji stanowiącej podstawę niniejszej dysertacji, oznaczonej numerem **D4**.



Schemat 10. Badanie reaktywności trifluorometylowanych nitryloimin wobec imidazolo-2-tionów entiolizujących i nieentiolizujących.

Podsumowując, w ramach badań realizowanych do niniejszej dysertacji została opracowana nowa, efektywna metoda otrzymywania 2-(trifluorometylo)tiolowanych pochodnych imidazolu. To podejście zostało z powodzeniem wykorzystane do otrzymania 2-(trifluorometylo)tiolowanych lepidilin oraz ich analogów strukturalnych, które wykazują obiecującą aktywność cytotoksyczną. Ponadto, zbadano reaktywność imidazolo-2-tionów entiolizujących oraz nieentiolizujących wobec trifluorometylotiolowanych nitryloimin, wykazując, że reakcja ta prowadzi do produktów o odmiennej strukturze, w zależności od typu użytego imidazolo-2-tionu.

6. Pozostała działalność naukowa

6.1. Udział w projektach naukowo-badawczych

- **G1** 2022-2025, Kierownik Grantu „Doktoranckie Granty Badawcze 2022” NR 5/ODW/DGB/2022 *„Funkcjonalizacja bioaktywnych pochodnych imidazolu za pomocą grupy trifluorometylotiolowej (SCF3)”*, (opiekun grantu: dr hab. Marcin Jasiński, prof. UŁ).

6.2. Wykaz pozostałych publikacji niewchodzących w skład niniejszej rozprawy doktorskiej

- **P1** Mlostoń, G.; Celeda, M.; Poper, W.; Kowalczyk, M.; Gach-Janczak, K.; Janecka, A.; Jasiński, M. "Synthesis, Selected Transformations and Biological Activity of Alkoxy Analogues of Lepidilines A and C". *Materials* **2020**, *13*, 4190.

6.3. Wykaz zgłoszeń patentowych

- **Z1** Jasiński, M.; Poper, W. K. *Sposób wytwarzania heksafluorofosforanów 2-((trifluorometylo)tio)imidazoliowych typu lepidilinowego*. P.449153 (08.07.2024)

6.4. Odbyte staże naukowe

- **S1** Staż naukowy zrealizowany na Uniwersytecie Strasburskim, COHA, LIMA, finansowany w ramach konkursu SSHN Campus France (01.05.2024-31.07.2024)

6.5. Spis komunikatów konferencyjnych

Komunikaty ustne

- Poper, W. K., Jasiński, M. *N-tlenki imidazolu w syntezie związków bioaktywnych*, Zjazd Wiosenny Sekcji Młodych Polskiego Towarzystwa Chemicznego 2023 (Chęciny, 03-07.05.2023, *nagroda za najlepszy komunikat ustny w kategorii doktoranci*)

- Poper, W. K., Jasiński, M. *Lepidiline-inspired 2-(trifluoromethyl)thiolimidazoliums: synthesis and bioactivity*, Summer School on Organic Synthesis under Non-classical Conditions (Warszawa, 02-06.09.2024)

- Poper, W. K., Jasiński, M. *First lepidiline-inspired trifluoromethylthiolated imidazoliums*, Zjazd Wiosenny Sekcji Młodych Polskiego Towarzystwa Chemicznego 2025 (Bąkowo, 26-30.04.2025, *nagroda za najlepszy komunikat ustny w języku angielskim*)

Komunikaty posterowe

- Poper, W. K.; Jasiński, M. *Pochodne imidazolu sfunkcjonalizowane grupą trifluorometylotiolową (SCF3)*, 64. Zjazd Polskiego Towarzystwa Chemicznego (Lublin, 11-16.09.2022)
- Poper, W. K., Jasiński, M. *Imidazole derivatives functionalized with an SCF_3 group*, XXIII International Symposium "Advances in the Chemistry of Heteroorganic Compounds" (Łódź, 28.10.2022)
- Poper, W. K., Jasiński, M. *Funkcjonalizacja pochodnych imidazolu grupą trifluorometylotiolową*, Zjazd Zimowy Sekcji Młodych Polskiego Towarzystwa Chemicznego 2022 (Opole, 10.12.2022)
- Poper, W. K., Jasiński, M. *Trifluorometylotiolowane analogi alkaloidów lepidilinowych*, X Łódzkie Sympozjum Doktorantów Chemii (Łódź, 18-19.05.2023)
- Poper, W. K., Jasiński, M. *CF_3S-Functionalization of imidazole derivatives*, 23rd Tetrahedron Symposium (Goteborg, 27-30.06.2023)
- Poper, W. K., Jasiński, M. *Nowe podejście do syntezy trifluorometylotiolowanych imidazoli*, 65. Zjazd Polskiego Towarzystwa Chemicznego (Toruń, 18-22.09.2023)
- Poper, W. K., Jasiński, M. *Access to lepidiline-inspired 2-CF_3S-imidazoliums*, 23rd European Symposium on Organic Chemistry (Kopenhaga, 29.06-03.07.2025)

6.6. Organizacja konferencji naukowych

- Członek komitetu organizacyjnego X Łódzkiego Sympozjum Doktorantów Chemii – 2023

- Członek komitetu organizacyjnego XI Łódzkiego Sympozjum Doktorantów Chemii – 2024

6.7. Udział w szkoleniach i warsztatach

- Aktywne uczestnictwo w IV Warsztatach Krajowej Biblioteki Związków Chemicznych POL-OPENSCREEN (Łódź, 03-04.12.2024)

  Poper, W. K.; Jasiński, M.; Olejniczak, A. B.; Denel-Bobrowska, M. *Bioinspirowane trifluorometylotiolowane imidazole – synteza i aktywność biologiczna*

- Szkolenie „Efektywna współpraca w międzynarodowym i międzypokoleniowym zespole projektowym" (Uniwersytet Łódzki, 12-13.05.2025)
- Szkolenie „Succesfully navigating your career in research through collaboration" (Kopenhaga, Beilsteint-Institut, 02.07.2025)

6.8. Pozostałe aktywności naukowe

- Członkostwo w Studenckim Kole Naukowym Chemików „Orbital" UŁ (od 2015)
- Członkostwo w Radzie Samorządu Studenckiego Wydziału Chemii UŁ (2019-2021)
- Czynny udział w organizacji Festynu Naukowe w ramach XIX Festiwalu Nauki, Techniki i Sztuki w Łodzi (2019)
- Czynny udział w organizacji Dnia Chemika Publicznego Liceum Ogólnokształcącego UŁ (2023)
- Czynny udział w organizacji Dnia Otwartego Wydziału Chemii UŁ (2023)
- Czynny udział w organizacji Dnia Otwartego Wydziału Chemii UŁ oraz Wydziału Biologii i Ochrony Środowiska (2024 i 2025)

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Publikacje stanowiące podstawę rozprawy doktorskiej

[D1]
Poper, W. K.; Jasiński M. **2025** “The introduction of SCF_3 substituents into heterocyclic rings.”
In *Advances in Heterocyclic Chemistry*, edited by Christopher A. Ramsden, Elsevier. *(pre-proof manuscript)*

The introduction of SCF_3 substituents into heterocyclic rings

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Contents

Abstract: There is increasing significance of fluoroorganics in the pharmaceutical, agrochemical, and electronic industries, which has stimulated interest in the search for new, reliable, and eco-friendly methods for their preparation using bench-stable and non-toxic chemicals. A particularly significant group of fluorine-containing systems comprises materials based on heterocyclic frameworks. In this chapter, methods for the introduction of the trifluoromethylsulfanyl (SCF_3) group into heterocyclic rings, a substituent of considerable relevance for tuning the physio-chemical properties of organic molecules, are summarized. Two general strategies are presented: (*i*) trifluoromethylation of pre-sulfurized heterocycles such as thiols and disulfides, and (*ii*) direct trifluoromethylthiolation of heterocyclic rings using diverse CF_3S-transferring reagents. Each section provides an overview of developed

methodologies, encompassing the wide range of fluorinated reagents as well as the functionalized heterocyclic substrates, beginning with early reports from the 1970s through to the most recent developments in this area.

Keywords: heterocycles, CF_3S-transfer, trifluoromethylthiolation, thiols, trifluoromethylation, functionalization, synthetic methods.

1. Introduction

Fluorinated substituents have been attracting increasing interest for decades, mainly due to their unique physiochemical properties, enabling the utilization of fluoroorganics in materials chemistry, electronics, and medicinal chemistry. In recent years, the trifluoromethylthiol (SCF_3) group plays a particularly noticeable role within fluorinated substituents, as evidenced by numerous excellent review works devoted to the chemistry of trifluoromethyl thioethers.[1-5] The exceptional nature of the title trifluoromethylthiol unit, resulting — among other factors — from a high lipophilicity (Hansch index of $\pi = 1.44$)[6] and a remarkable electron-withdrawing character (Hammett σ_p parameter of 0.50),[7] has led to the emergence of numerous trifluoromethylthiolated compounds, in which heterocyclic systems occupy an important place.

Of special interest in the context of CF_3S-induced tuning of biological properties are heterocycles considered bioisosteric and/or derivatives functionalized with subunits that resemble the structural motifs present in biological systems. Some of the representative heterocycle-trifluoromethyl thioethers being in the medicinal chemists radar are depicted in Figure 1. For example, the widely used phenylprazole-type pesticide *vaniliprole*[8] (insecticide), and a sulfur analogue of *riluzole*[9] applied in treatment of amyotrophic lateral sclerosis (ALS) are known. Structural analogues of synthetic drugs (*celecoxib* derivative)[10] as well as naturally occurring terpenes (*santonin*[11] and *ambroxide*[12] derivatives) have also been reported. Furthermore, labeling nucleotides with the SCF_3 group leads to sensitive ^{19}F NMR probes employed in the study on structure and function of modified RNA[13] and DNA[14] molecules (a representative 2'-deoxy-2'-trifluoromethylthio-uridine-derived building block for solid-phase synthesis of RNA[15] in shown in Figure 1). Therefore, a major challenge is to develop innovative approaches for introducing the SCF_3 group into heterocyclic frameworks, which could substantially impact the development of new drugs and agrochemicals.

In this chapter, general synthetic methods towards F_3CS-functionalized heterocycles are presented. The mentioned strategies are divided into two categories: (a) *indirect methods* based on trifluoromethylation of sulfur compounds, typically thiols, but also their synthetic equivalents such as disulfides and thiocyanates, upon which the new S−CF_3 bond is formed; (b) *direct approaches* comprising of a one-step late stage introduction of the SCF_3 group into the heterocyclic ring. Despite several disadvantages attributed to indirect methods such as the use of toxic reagents, harsh reaction conditions, moderate efficiency and limited access to appropriate pre-functionalized substrates, notable contributions have been reported in this area. The later direct approach offers a much wider range of possibilities in the synthesis of trifluoromethylthiolated heterocyclic rings. A significant rise in efforts to develop new synthetic procedures that cover selective C−H functionalizations controlled by directing groups (DGs) or mediated by transition-metal- and/or photo-catalysts has been observed. In this context, special attention is paid to shelf-stable CF_3-thiolates (e.g. $AgSCF_3$) along with various O−SCF_3 and N−SCF_3 reagents recognized as convenient sources of key operating intermediates.

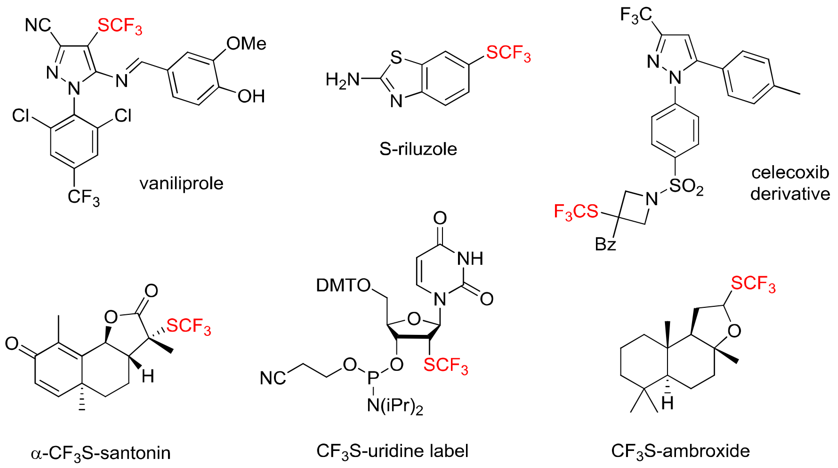


Fig. 1. Structures of selected trifluoromethylthiolated heterocycles.

2. Synthesis of CF_3S-functionalized heterocycles

As mentioned in the introduction, considering the synthetic pathways leading to the target products, two general strategies can be distinguished: the *direct* approach based on a one-step introduction of the SCF_3 group into a heterocyclic ring, and the *indirect* approach, which typically involves a pre-functionalized heterocycle and its subsequent modification resulting in SCF_3 substitution. In section 2.1, our attention will be devoted primarily to the latter strategy, *i.e.*, the utilization of pre-functionalized heterocycles for the synthesis of CF_3S-substituted derivatives.

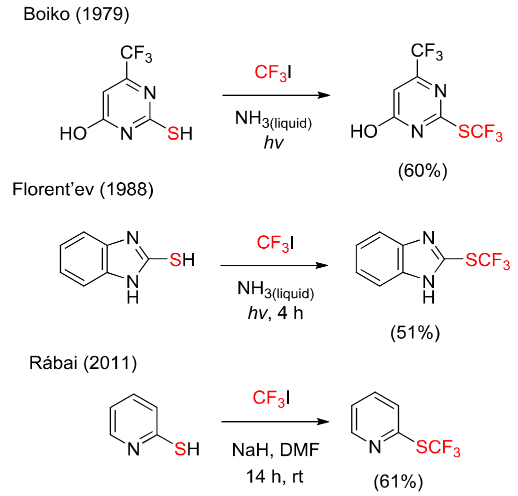
2.1. Indirect approaches (CS−CF_3 bond formations)

When the trifluoromethylthiol group is conceptually disassembled, two constitutive units can be recognized – thiol and trifluoromethyl. Thiols represent convenient and reactive sulfur sources, capable of participating in both radical and ionic processes (the latter due to their soft nucleophilic nature). The second fragment, i.e. the trifluoromethyl moiety, can likewise be generated from numerous precursors either as a radical or as an electrophilic intermediate. Consequently, one of the commonly employed approaches to introduce the SCF_3 group consists of the deliberate combination of these complementary reactivities embedded within the two structural motifs. It is also worth noting that the thiol function attached to heterocyclic system often exist in thione–thiol tautomeric equilibrium with their C=S counterparts. Hence, the thiocarbonyl groups presented in some substrates below should be regarded as precursors of reactive thiol entities.

2.1.1. Radical trifluoromethylations of thiols

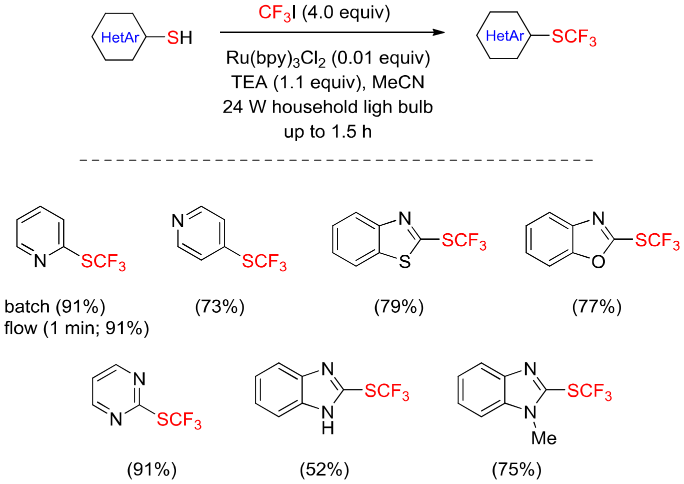
The first reported radical trifluoromethylation approach was presented by Boiko *et al.* in their 1979 publication.[16] The authors demonstrated the photochemically induced trifluoromethylation of pyrimidine-2-thiols using trifluoromethyl iodide, in liquid ammonia, yielding 2-(trifluoromethyl)thiopyrimidine derivatives (Scheme 1). In subsequent studies, the same research group expanded the methodology to reactions of benzimidazole-2-thiol with CF_3I under UV irradiation.[17] The resulting 2-(trifluoromethyl)thiobenzimidazole was further employed in the synthesis of nucleoside analogues, which were evaluated for their antiviral activity, including bioactivity against coronaviruses.

Trifluoroiodomethane was also utilized by Rábai and co-workers,[18] who explored reactivity of this halon toward aromatic thiols, including pyridine-2-thiol, in the presence of sodium hydride as a base (Scheme 1). The authors demonstrated that a radical chain reaction with gaseous CF_3I is also possible without UV activation, although in the case of certain substrates the devised method proved ineffective; for example, inertness of the aforementioned benzimidazole-2-thiol was observed under the applied conditions.



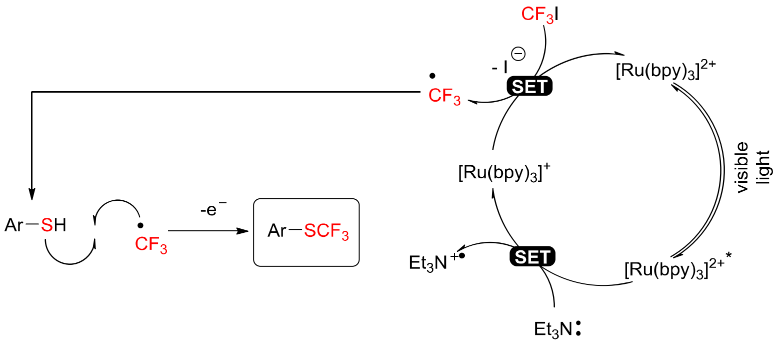
Scheme 1. Early work on radical trifluoromethylation of heterocyclic thiols with CF_3I.

Further exploration of CF_3I as a trifluoromethylating agent in the synthesis of trifluoromethylthiolated heterocycles was undertaken by Noël and co-workers (Scheme 2).[19] In order to enhance the reaction efficiency, they introduced a photocatalytic system, among which *tris*(bipyridine)ruthenium(II) chloride emerged as the most effective catalyst. The optimized conditions enabled the successful trifluoromethylthiolation of a broad range of heterocyclic substrates. Remarkable acceleration of the developed protocol was achieved in a continuous-flow microreactor, which also allowed a reduction of the amount of CF_3I to 1.1 equivalents under the optimized reaction conditions.



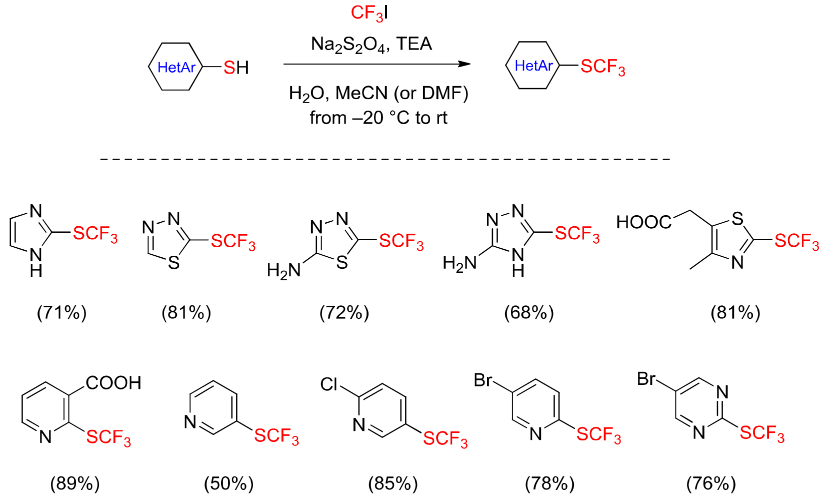
Scheme 2. Photocatalyzed trifluoromethylation of heterocyclic thiols with CF_3I.

The mechanism proposed involves the photoexcitation of the ruthenium(II) catalyst under visible light, followed by the generation of a radical cation that initiates a sequence of single-electron transfer (SET) events, ultimately producing the trifluoromethyl radical (Scheme 3).[19] The latter species subsequently engages in reaction with the thiol to yield the final product.



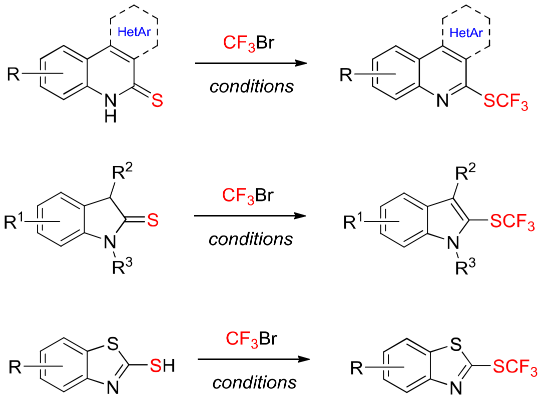
Scheme 3. The proposed mechanism of $[Ru(bpy)_3]Cl_2$-catalyzed trifluoromethylations with CF_3I.

In recent years, Yagupolskii and co-workers have revisited the trifluoromethylation reactions of thiols employing CF_3I.[20] As an electron source they utilized sodium dithionite, capable of generating a sulfite radical anion ($SO_2^{\bullet-}$) that activates the trifluoromethylating agent (Scheme 4). A series of trifluoromethylthiolated imidazole, 1,3,4-thiadiazole, 1,2,4-triazole, 1,3-thiazole, pyridine, and pyrimidine derivatives was prepared in fair yields.



Scheme 4. Dithionite-initiated trifluoromethylations of heteroaryl thiols with CF_3I.

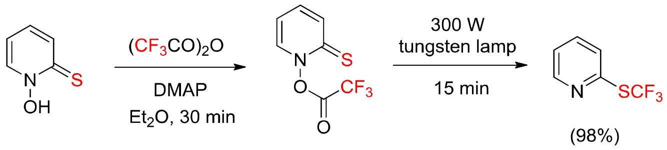
An alternative source of the trifluoromethyl radical was more recently employed by Hu and co-workers (Scheme 5).[21] The authors reported trifluoromethyl bromide as a useful reagent, while the iridium(III) complex served as a convenient electron donor. Although the mechanistic pathway closely mirrors that described by Noël's group (Scheme 3), Hu's investigation focused predominantly on nitrogen-containing heterocycles, encompassing a considerably broader substrate scope. The method afforded series of 6-(trifluoromethylthio)-phenanthridines (23 examples, 48-86%), 2-trifluoromethylthiolated indoles (12 examples, 46-76%) and benzothiazoles (6 examples, 60-68%) derivatives (Scheme 5).



conditions:
fac-Ir^{III}(ppy)$_3$ (1 mol%),
2,6-lutidine (2 equiv),
DMSO, 15 W blue LED

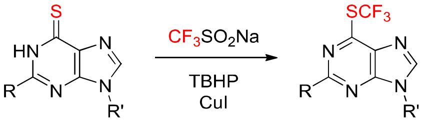
Scheme 5. Blue-LED-induced iridium(III)-catalyzed synthesis of CF$_3$S-functionalized phenanthridines, indoles, and benzothiazoles with CF$_3$Br as a source of trifluoromethyl radical.

Since both of the above mentioned trifluoromethyl sources (CF$_3$I and CF$_3$Br) belong to halons known for their ozone-depleting potential, some efforts have been directed to identify more convenient and environmentally benign reagents capable of generating the trifluoromethyl radical. A seminal contribution in this respect was made by Barton an co-workers,[22] who demonstrated the feasibility of employing *in situ* photodecarboxylation of thiohydroxamate esters (Scheme 6). Under tungsten lamp irradiation, the first formed so-called Barton ester suffered a radical fragmentation, effecting the transfer of the trifluoromethyl group onto the sulfur atom to give 2-(trifluoromethylthio)pyridine quantitatively.



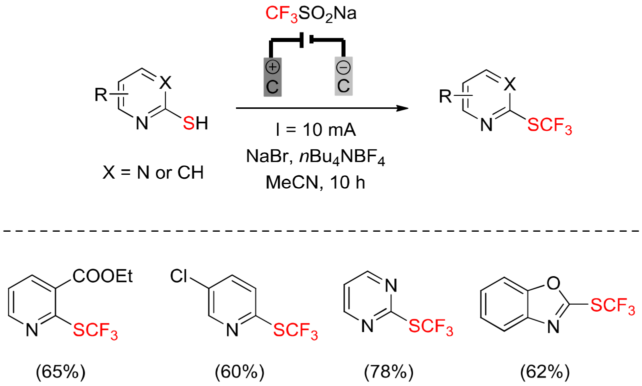
Scheme 6. Photodecarboxylation of TFAA-derived Barton ester leading to 2-CF$_3$S-pyridine.

Inspired by Barton's report, but also by the subsequent work of Langlois on the utilization of sodium trifluoromethanesulfinate (so-called *Langlois' reagent*) for transferring the trifluoromethyl group onto sulfides,[23] Xu and co-workers initiated investigations onto the use of the same reagent for the synthesis of CF$_3$S-substituted nitrogen heterocycles, with particular focus on nucleoside analogues.[24] Their research included reactions of 2-mercaptopurine, a known antineoplastic agent, and its derivatives with the aforementioned reagent in the presence of *tert*-butyl hydroperoxide (TBHP) and copper(I) salts (Scheme 7). Under the optimized conditions, a range of structurally diverse trifluoromethylthiolated N-heterocycles, including analogues of biologically active 2-mercaptopurine and acyclovir, were obtained. Additional trapping experiments confirmed the radical pathway of the studied transformation.



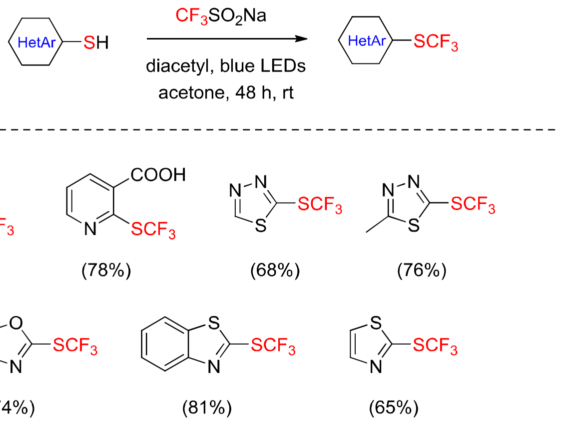
Scheme 7. Cu(I)-Catalyzed synthesis of trifluoromethylated purines with CF_3SO_2Na.

Parallel studies on applications of the Langlois reagent in the synthesis of trifluoromethylated thioethers were undertaken by Dai and Xu.[25] The required trifluoromethyl radical intermediate was efficiently generated under electrocatalytic conditions, which proved particularly effective. Although the scope of the presented investigation focused primarily on thiophenol derivatives, several heterocyclic substrates were also explored, thereby demonstrating the broader applicability of the method. For example, derivatives of nicotinic acid, 3-chloropyridine, pyrimidine, and benzoxazole were accessed (Scheme 8).



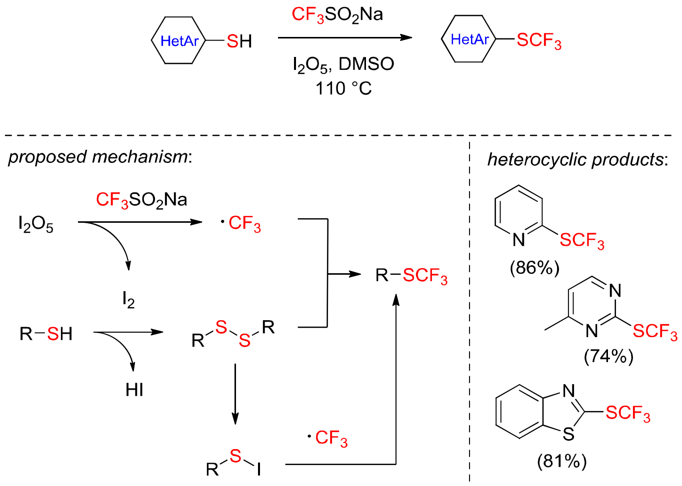
Scheme 8. Electrochemical synthesis of heterocyclic CF_3-thioethers.

An alternative strategy for exploiting sodium trifluoromethanesulfinate in the context of heterocyclic trifluoromethylthiolation involves the use of diacetyl as an organic photocatalyst, under blue- and green-light irradiation.[26] The method developed by Reddy and co-workers proved applicable to a remarkably wide array of heterocyclic systems, encompassing both five- and six-membered rings, available under environmentally friendly conditions (Scheme 9).



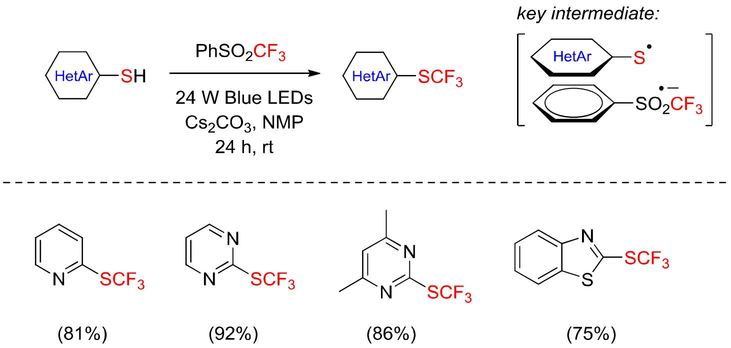
Scheme 9. Blue LED-photocatalyzed trifluoromethylation of heteroaryl thiols with CF_3SO_2Na.

Generation of the trifluoromethyl radical from the Langlois reagent can also be achieved by employing inorganic initiators as demonstrated by the Yi group, who utilized iodine(V) oxide as the initiator.[27] The reaction was shown to proceed efficiently for simple N-heterocyclic substrates (Scheme 10). According to the mechanism proposed, iodine(V) oxide initiates a single-electron transfer (SET) leading to generation of a key trifluoromethyl radical. The iodine species produced in this step oxidizes the thiol to a disulfide, which can subsequently engage in two competing reaction channels: it may react directly with the trifluoromethyl radical to afford the target product, or it may form an iodosulfenyl intermediate that also undergoes trifluoromethyl radical attack, leading to the same final compound.



Scheme 10. Competitive reaction pathways in I_2O_5-mediated trifluoromethylation of thiols.

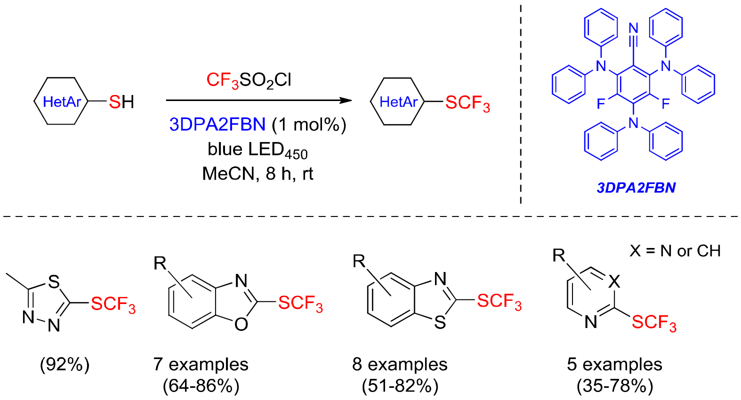
A distinct sulfonyl-based precursor of the trifluoromethyl radical was employed by Hu and co-workers,[28] who in 2022 reported the first radical trifluoromethylation utilizing phenyl trifluoromethyl sulfone. Previously known for its nucleophilic reactivity, this compound was here repurposed as a radical source. The reaction of heteroaromatic thiols with the sulfone under blue-light irradiation afforded a range of CF_3S-functionalized aromatic compounds, including heterocyclic derivatives (Scheme 11).



Scheme 11. Application of $PhSO_2CF_3$ in the synthesis of heteroaryl CF_3-thioethers and the structure of key intermediate.

Based on electrochemical (remarkable decrease of reduction potential of $PhSO_2CF_3$ in the presence of PhSNa) and spectroscopic (UV-vis; strong absorption in the blue region of a DMAc mixture of $PhSO_2CF_3$ and PhSNa) data, the formation of an electron donor-acceptor (EDA) complex followed by Blue-LED excitation and single-electron transfer, leading to a key trifluoromethyl phenyl sulfone radical anion, was proposed for the mentioned model pair of reagents (Scheme 11).

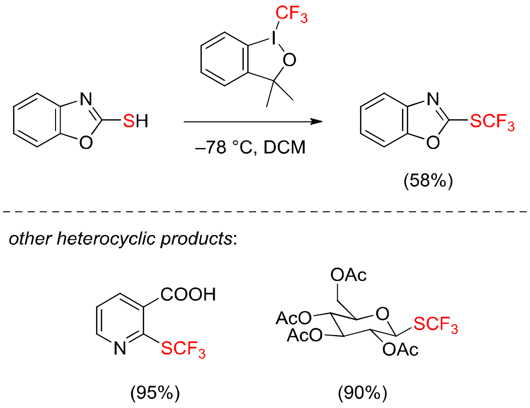
More recently, trifluoromethanesulfonyl chloride (CF_3SO_2Cl) was demonstrated as another convenient and cost-effective source of trifluoromethyl radical ($CF_3^{\bullet}$) in reactions with heteroaryl thiols (Scheme 12).[29] Using highly reducing organo-photocatalyst 3DPA2FBN, under irradiation with visible light (Blue LED, 450 nm), a series of trifluoromethylthiol pyridine, pyrimidine, 1,3,4-thiadiazole, benzo[*d*]thiazole, and benzo[*d*]oxazole derivatives functionalized with halogens (F, Cl, Br), alkyl, alkoxy, fluoroalkyl (Me, *t*Bu, MeO, CF_3) as well as PivNH and 4-ClC_6H_4- groups were prepared, generally in high yields >70%. The authors demonstrated a broad substrate scope of the devised transformation, and based on control experiments employing radical-trapping agents confirmed the radical character of the reaction pathway proceeding through mesolytic decomposition of CF_3SO_2Cl initiated by single-electron transfer from photoexcited catalyst.



Scheme 12. Organo-photocatalytic radical trifluoromethylations with CF_3SO_2Cl.

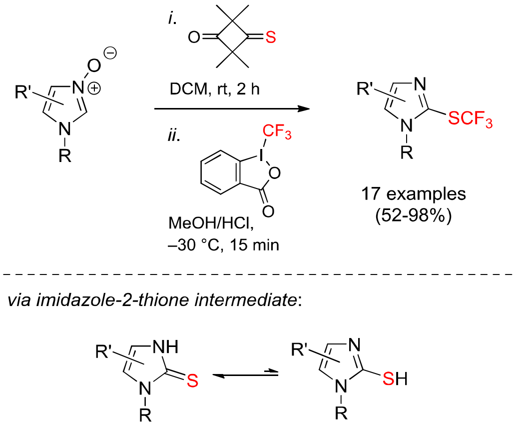
2.1.2. Electrophilic trifluoromethylations of thiols

The coupling of a thiol (or equivalent) group with a trifluoromethyl moiety can also proceed through the use of electrophilic trifluoromethylthio (CF_3^+) sources. In 2007, Togni and co-workers reported the application of trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (commonly known as *Togni reagent I*), a member of the family of hypervalent iodine compounds, in smooth reactions with a variety of heterocyclic thiols.[30] Notably, the formation of by-product disulfide is fully suppressed by running the trifluoromethylation reaction at low temperatures (–78 °C), and the method features remarkable tolerance towards such functional groups as amino, amido, hydroxy, alkyne, carboxylic, and thioacetal. Among the nucleophiles checked in this study were nicotinic acid derivatives, glycosides, and benzo[*d*]xazole-2-thiol (Scheme 13). In the latter case the expected thioether was isolated in fair 58% yield.



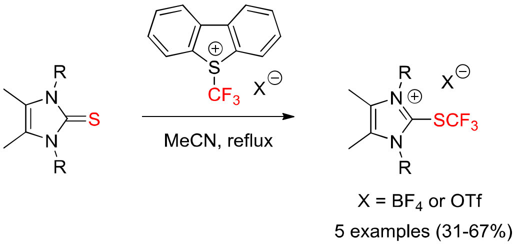
Scheme 13. Electrophilic trifluoromethylations with Togni reagent I.

The use of hypervalent iodine-based trifluoromethylating reagents on heterocyclic systems was later expanded to the preparation of 2-trifluoromethylthioimidazoles (Scheme 14).[31] The devised one-pot procedure involved the initial conversion of starting imidazole *N*-oxides into the corresponding enolisable imidazole-2(3*H*)-thiones, which were trapped with the *Togni reagent II* activated by a Brønsted acid. The obtained 2-CF_3S-imidazoles were further applied in the synthesis of the corresponding lepidiline-type imidazolium salts with promising anticancer activity.[32]



Scheme 14. One-pot synthesis of 2-CF$_3$S-imidazoles through sulfur-transfer and trifluoromethylation of the intermediate imidazole-2-thione with Togni reagent II.

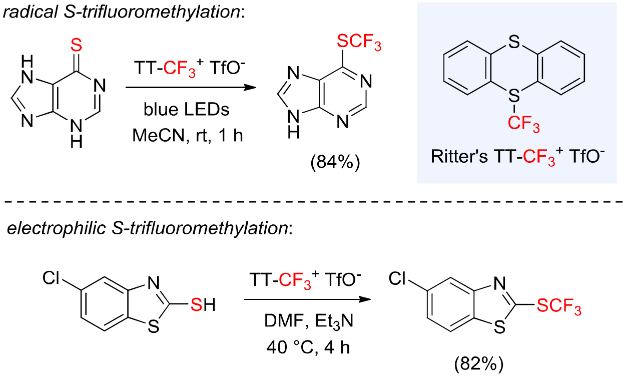
Related investigations on the synthesis of ionic CF$_3$S-imidazoliums had earlier been carried out by Mizuta and co-workers (Scheme 15).[33] The authors examined symmetrically *N*,*N*′-disubstituted imidazole-2-thiones in reactions with electrophilic trifluoromethylating agents based on a dibenzothiophenium core (the so-called Umemoto reagent) to give the respective tetrafluoroborates or triflates, in high yields. One of the resulting materials (R = *i*Pr, X = BF$_4$) was demonstrated as an efficient phase-transfer catalyst (PTC) in alkylation reactions involving active methylene compounds (β-keto esters and β-diesters).



Scheme 15. Preparation of 2-trifluoromethylthiolated imidazolium salts using Umemoto reagent.

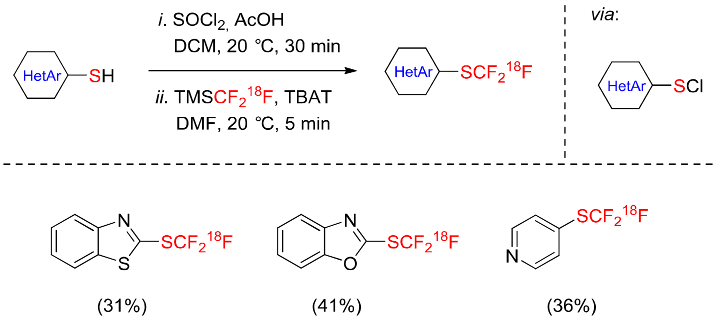
In 2021, the Ritter group reported on new shelf-stable trifluoromethylating reagent, trifluoromethyl thianthrenium triflate (TT-CF$_3^+$TfO$^-$), readily available in a single-step by treatment of thianthrene with trifilic anhydride.[34] Notably, it was demonstrated to be a convenient source of electrophilic (F$_3$C$^+$), radical (F$_3$C$^\cdot$), as well as nucleophilic (F$_3$C$^-$)

intermediates in trifluoromethylation reactions with e.g. enolisable 1,3-dicarbonyls, aza-aromatic heterocycles, and aldehydes, respectively. The developed sulfonium-based reagent proved efficient also in CF_3-transfer onto heterocyclic thiols leading to the respective trifluoromethylsulfanyl products, through either radical or ionic pathways, depending on the reaction conditions. (Scheme 16).



Scheme 16. Radical vs. ionic *S*-trifluoromethylation of heterocyclic thiols with Ritter's reagent.

Notably, the conceptual framework discussed in this subsection can also be extended to the preparation of trifluoromethylthio-labelled compounds incorporating the radioactive isotope fluorine-18. Although the majority of related studies have focused on aromatic systems, several examples of heterocyclic substrates have also been reported. A pioneering work on introducing an isotopically labelled CF_3 group into heterocyclic thiol was reported in 2024 by Veth *et al.*[35] The authors demonstrated that *in situ*-generated sulfenyl chlorides smoothly react with isotopically labelled trimethyl(trifluoromethyl)silane ([^{18}F]Ruppert–Prakash reagent), in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) applied as initiator (Scheme 17). The resulting compounds exhibited promising potential as positron emission tomography (PET) imaging tracers.

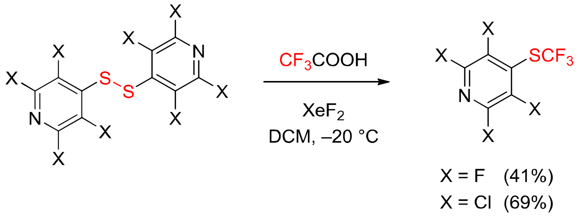


Scheme 17. Application of trimethyl(trifluoromethyl)silane in the synthesis of ^{18}F-labeled CF_3S-heterocycles.

2.1.3. Applications of disulfides

The thiols discussed in the preceding section represent the most often applied class of sulfur-containing organic compounds serving as precursors of the trifluoromethylthiol-functionalized analogues. Nevertheless, they are not the sole representatives of this category, as disulfides may also be employed as viable alternatives. These can be used either as starting materials or as intermediates generated *in situ* from the corresponding thiols.

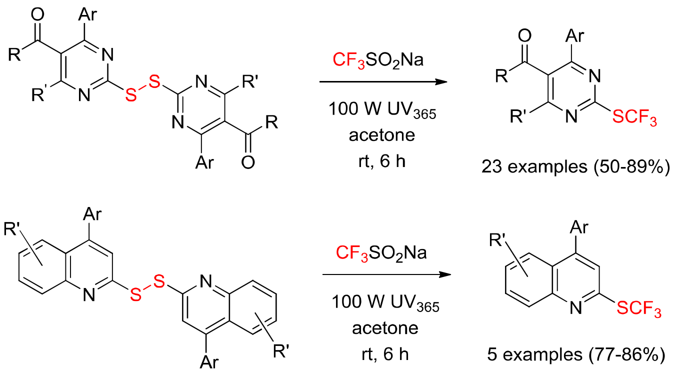
The application of heterocyclic disulfides in the preparation of the respective CF_3S-heterocycles has been reported in a series of works by Sipyagin et al..[36,37] The authors studied the reactions of polyhalogenated pyridine disulfides with trifluoroacetic acid (TFA), in the presence of xenon fluoride (Scheme 18). The disclosed process involves the formation of trifluoromethyl radical through thermal decomposition of the *in situ*-generated xenon bis(trifluoroacetate). The resulting reactive fluoroalkyl radical is then trapped with disulfide to afford the final product and the stabilized perhalophenylthiyl.



Scheme 18. Synthesis of perhalogenated pyridine CF_3-sulfides from disulfides and XeF_2/TFA.

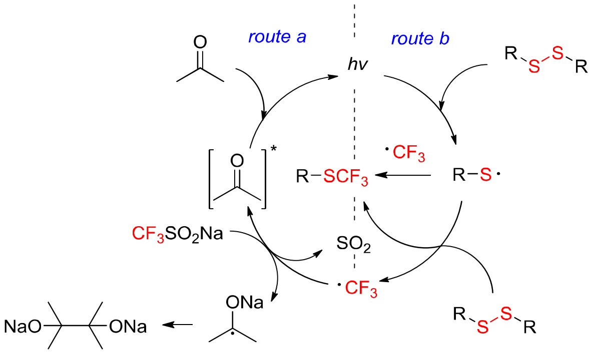
The same group investigated analogous reactions involving thiols as starting materials.[38] However, experimental observations indicated that the studied reaction proceeds via the *in situ* formation of the respective disulfide, which subsequently participates in the trifluoromethylation step.

Studies on the introduction of the CF_3 group into pyrimidine and quinoline frameworks were carried out by Quan and Wang.[39] These authors employed the corresponding diheteroaryl disulfides along with sodium trifluoromethanesulfinate (CF_3SO_2Na). Irradiation of the resulting mixtures with UV light afforded a series of trifluoromethylthiolated products in moderate to high yield (Scheme 19).



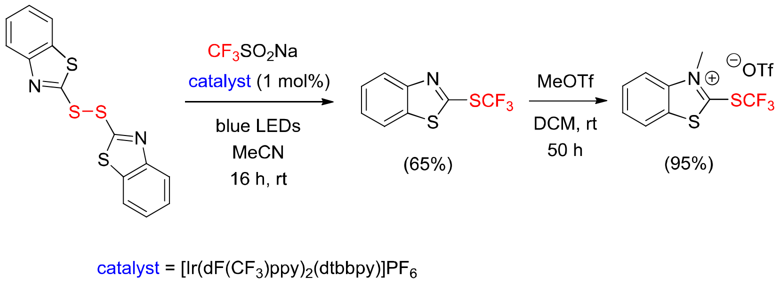
Scheme 19. UV light irradiated *S*-trifluoromethylation of diheteroaryl disulfides with sodium triflinate.

Further control experiments evidenced the crucial role of the applied solvent (acetone) in the devised radical transformation. The mechanism proposed by the authors highlights a potential dual role of the UV irradiation (Scheme 20).[38] On the one hand, it is assumed to excite acetone, which is then reduced by triflinate to give crucial trifluoromethyl radical (*route a*); on the other hand, it promotes the homolytic cleavage of the disulfide bond involving the respective hetarylthiyl radical in *route b*. The open-shell intermediates thus formed subsequently combine to afford the final product.



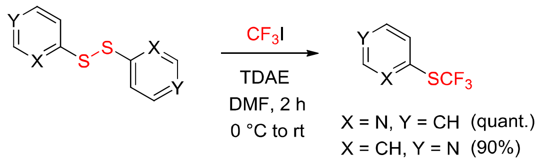
Scheme 20. A plausible mechanism of trifluoromethylation of diheteroaryl disulfides with CF_3SO_2Na involving UV-induced excitation of acetone and homolytic fission of the S–S bond.

Sodium triflinate (CF_3SO_2Na) was also employed by Hopkinson in his studies on dehydroxytrifluoromethylthiolation of alcohols.[39] Treatment of the starting dibenzothiazyl disulfide with the Langlois reagent, in the presence of iridium(III) photocatalyst (1 mol%), activated by blue light, provided the expected 2-trifluoromethylthiolated benzothiazole (Scheme 21).[39] The resulting sulfide was subsequently quaternized with MeOTf to give the corresponding benzo[*d*]thiazolium triflate isolated in 62% overall yield, which was then investigated as a CF_3S^+-source in reactions with a series of primary and secondary aliphatic as well as benzylic and propargylic alcohols.



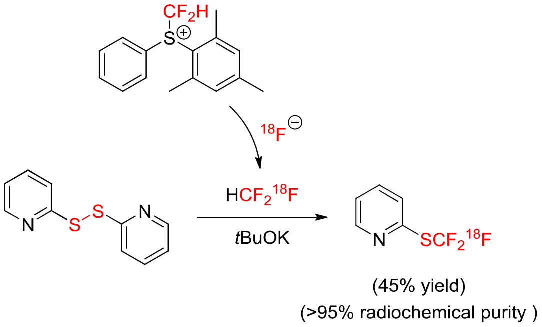
Scheme 21. Ir(III)-Photocatalyzed synthesis of 2-CF_3S-benzothiazole and its *N*-methylation.

Investigations concerning the use of disulfides were also carried out by the Dolbier group, by using the previously discussed trifluoromethyl iodide (Scheme 22).[40] The use of tetrakis(dimethylamino)ethylene (TDAE) as a reducing agent enabled *in situ*-generation of the key trifluoromethyl anion (CF_3^-) – the presence of which was confirmed in a control experiment – initiating the subsequent nucleophilic displacement reactions. Two isomeric pyridine-derived CF_3-sulfides were obtained in excellent yield.



Scheme 22. Access to isomeric pyridine CF_3-sulfides through nucleophilic substitution reactions with trifluoromethyl anion.

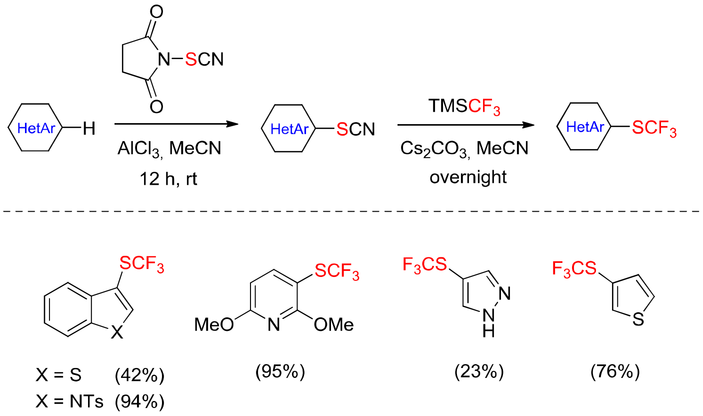
In analogy to applications of thiols in the synthesis of labeled materials, disulfides can likewise serve as reagents for the incorporation of a CF_3S group bearing the ^{18}F atom into heterocyclic frameworks. In this context, a report by Labar and Jubault dealing with the synthesis of the 2-pyridyl derivative through the reaction of the corresponding disulfide with fluoroform containing the ^{18}F isotope, is of note.[41] As shown in Scheme 23, the required radiolabeled fluoroform was delivered from the reaction between (difluoromethyl)(mesityl)-(phenyl) sulfonium salt and $[^{18}F]KF/K_{222}$ used as source of fluoride, and the gaseous product was transferred into the reaction vessel using a flow microreactor system.



Scheme 23. Labar and Jubault synthesis of ^{18}F-labeled 2-trifluoromethylthiolpyridine.

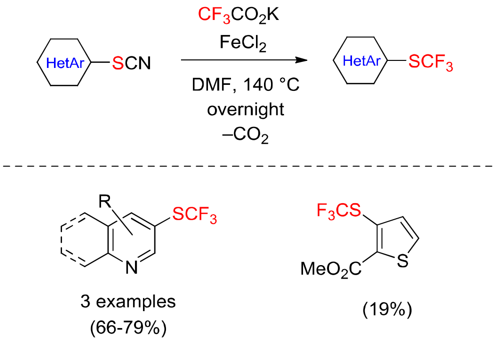
2.1.4. Miscellaneous methods

Beyond the two primary sources of sulfur fragments discussed in the above sections, the work by the Goossen group demonstrated high synthetic potential of *in situ*-generated isothiocyanates in cascade trifluoromethylation reactions leading to CF_3S-heterocycles.[42] As shown in Scheme 24, the *N*-isothiocyanate derived from succinic acid was used as an SCN$^+$ source, and the reaction presumably follows a classical Friedel–Crafts mechanism, necessitating the presence of aluminium chloride as a Lewis acid catalyst. In the second step, the Ruppert–Prakash reagent, activated by caesium carbonate, served as the source of the trifluoromethyl group. Although the discussed protocol was mainly examined on aryl substrates, representative series of heterocycles i.e. indole, pyridine, pyrazole, benzothiophene, and thiophene derivatives, were also involved in the study.



Scheme 24. Telescopic isothiocyanation/trifluoromethylation of (hetero)aryls developed by Goossen group.

An alternative one-step version of the transformation above employs pre-prepared aryl isothiocyanates, and utilizes potassium trifluoroacetate (KTFA) as the trifluoromethylating agent (Scheme 25).[43] The protocol benefits from dual function of the iron(II) chloride, i.e. (i) as a catalyst in the decarboxylation reaction of KTFA leading to nucleophilic trifluoromethyl (CF_3^-), and (ii) as a scavenger for toxic cyanide by-products (KCN) leading to hexacyanoferrate. A limited range of heterocyclic substrates (pyridine, quinoline and thiophene derivatives) has been reported to undergo efficient functionalization under the optimized conditions.



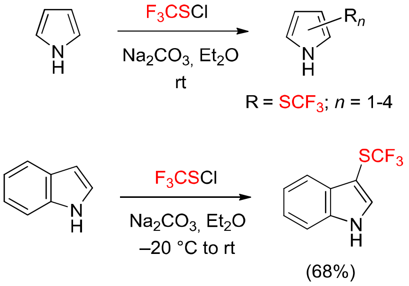
Scheme 25. Fe(II)-catalyzed decarboxylative generation of CF_3 anion in trifluoromethylations of hetaryl isothiocyanates.

2.2. Direct approaches (C−SCF_3 bond formations)

In recent years, much more attention has been paid to the development of straightforward and selective late-stage functionalizations with the trifluoromethylthiol unit through the formation of new C−SCF_3 bonds. The methods reported thus far cover structurally various reagents serving as sources of nucleophilic, electrophilic and/or radical CF_3S intermediates, thus enabling the choice of mechanistic pathway for C−H trifluoromethylthiolation. Among recently reported protocols, transition-metal catalyzed methods and photocatalyzed transition-metal-assisted approaches are of special interest as reflected by the more than twofold higher number of literature reports in comparison to all the other methods. In the following section, modern strategies for direct CF_3S-introductions into heterocyclic scaffolds, employing shelf-stable and easy to handle chemicals such as N−SCF_3 and O−SCF_3 reagents, CF_3SO_n−R derivatives as well as metal trifluoromethylthiolates, are summarized. These are supplemented by less commonly applied but historically important approaches using toxic and volatile trifluoromethylsulphenyl chloride (CF_3SCl) and bis(trifluoromethyl) disulfide (CF_3S−SCF_3).

2.2.1. Trifluoromethylsulfenyl halides

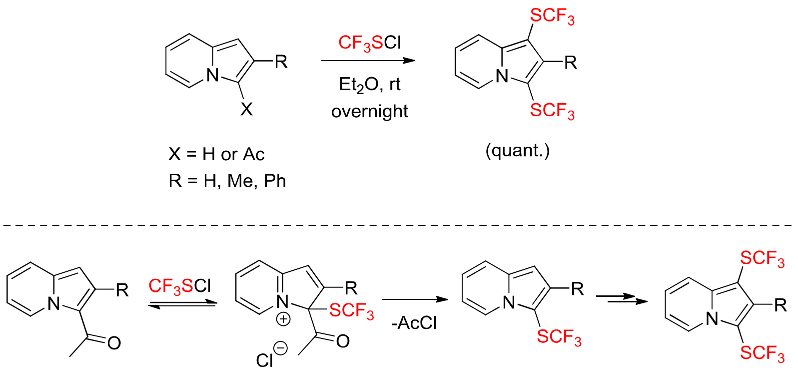
One of the earliest contributions to the synthesis of CF_3S-functionalized heterocycles through direct functionalization with the trifluoromethylthiol group was reported by Haas in the 1970s.[44] In this seminal work, trifluoromethylsulfenyl chloride (CF_3SCl) was employed as a source of CF_3S^+ intermediate for reactions with selected heteroaromatic substrates, with particular attention to five-membered heterocycles such as thiophene, pyrrole, and furan. Among them, pyrrole displayed the highest reactivity and underwent smooth substitution in the absence of catalyst (Scheme 26). The reaction carried out at room temperature, in the presence of excess trifluoromethylthiolating reagent, lead to a mixture of mono-, di-, tri-, and tetra-substituted derivatives, although, some selectivity could be achieved by lowering the temperature. For example, a mixture of 2,4- and 2,5-disubstituted products (1:2 ratio) were obtained at –30 °C. The isolated (poly)functionalized pyrroles were further examined as ligands to form stable coordination complexes with mercury(II) and silver(I) salts, in which the pyrrole nitrogen served as the coordination site exclusively.[45]



Scheme 26. Pioneer work by Haas in trifluoromethylthiolations of N-heterocycles with CF_3SCl.

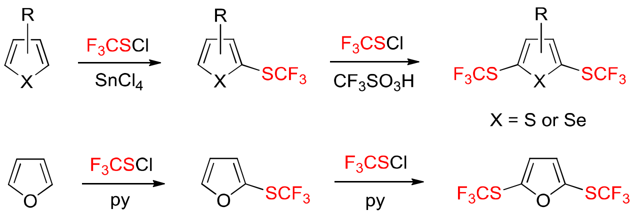
Less reactive indole undergoes trifluoromethylthiolation selectively at the C-3 position, yielding the corresponding monosubstituted product as sole material (Scheme 26). In contrast, carbazole required preliminary activation with a Grignard reagent to afford the respective *N*-trifluoromethylthiol derivative.[44]

The behavior of indolizines toward CF_3SCl proved distinct, as double substitution was generally observed to afford 1,3-bis(trifluoromethylthiolated) products (Scheme 27).[46] Notably, C(3)-acylated analogues also provided 1,3-disubstitution products. As demonstrated, substitution of an acylium group by CF_3S^+ proceeds through the respective zwitterionic intermediate, and proceed as the first step of the studied transformation.



Scheme 27. Synthesis of 1,3-bis(CF_3S)-functionalized indolizines and the mechanistic interpretation of Ac substitution.

In the case of thiophene, the selectivity of trifluoromethylthiolation was observed by using tin(IV) chloride as a catalyst (Scheme 28).[47] Subsequent treatment of the mono-substituted product with an additional portion of F_3CSCl, in the presence of either triflic or nonaflic acid, led to corresponding 2,5-bis(trifluoromethylthiol) analogue. Both mono- and bis-(F_3CS)-thiophenes were also accessible from the corresponding alkyl- and bromo-substituted thiophene precursors. Later investigations extended these protocols to selenophene, which exhibited similar reactivity under analogous reaction conditions.[48]



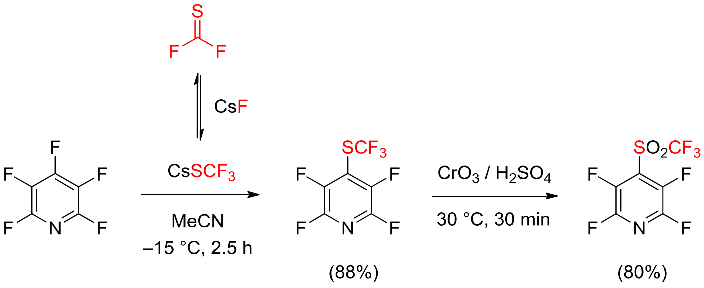
Scheme 28. Stepwise functionalization of furan, thiophene, and selenophene with the SCF_3 group.

Parallel studies on furan derivatives revealed that this heterocyclic ring is also prone to controlled stepwise trifluoromethylthiolation using CF_3SCl (Scheme 28).[46] In this case, addition of pyridine to trap by-product HCl significantly improved the reaction outcome.

Less reactive six-membered N-heterocycles can also be trifluoromethylthiolated with trifluoromethylsulphenyl chloride; however, activation with strong σ-nucleophiles is typically required. For example, functionalization of pyridine proceeded in the presence of $LiAlH_4$ via electrophilic trifluoromethylthiolation of the first formed anionic intermediate complex, to give a mixture of 3-mono- and 3,5-disubstituted products.[49] Despite numerous reports on applications of trifluoromethylsulphenyl chloride, it should be emphasized that CF_3SCl is a volatile and highly toxic, and hence, difficult to handle reagent, that requires special precautions and suitable laboratory equipment. For this reason, numerous more convenient and safe-in-use reagents, presented in the subsequent sections, have been developed and greatly explored in the synthesis of CF_3S-functionalized organic compounds, including heterocyclic systems.

2.2.2. Trifluoromethanethiolates

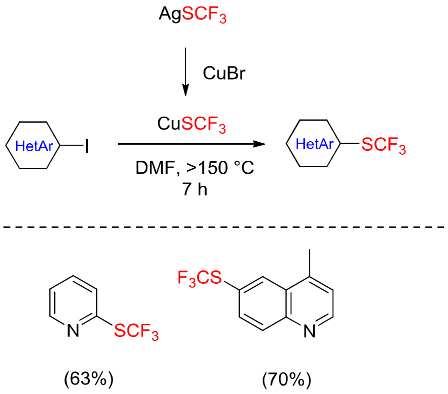
Early studies on the trifluoromethylthiolation of pyridine[46] were subsequently refined by Haas and Dmowski,[50] who utilized a fluorinated thiophosgene analogue as a key reagent. In the presence of a fluoride ion source (among which CsF proved the most effective) this compound generated sufficient stationary concentration of the unstable trifluoromethylthiolate anion (CF_3S^-) as reactive intermediate. Treatment of perfluoropyridine with the *in situ* generated caesium trifluoromethylthiolate ($CsSCF_3$) afforded the 4-trifluoromethylthiolated derivative as the exclusive substitution product (Scheme 29). The latter could be readily oxidized to the corresponding sulfone using Jones reagent.[50]



Scheme 29. Selective trilfuoromethylthiolation of perfluoropyridine with the in situ generated $CsSCF_3$, and subsequent oxidation of the sulfide into the sulfone with Jones reagent.

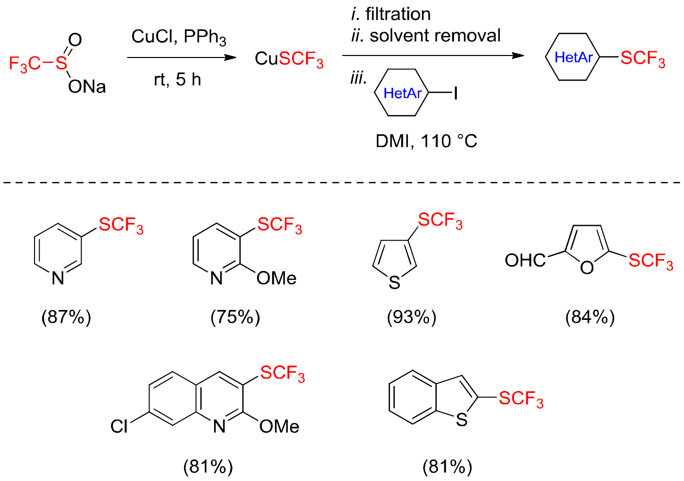
Notably, further attempts to introduce an additional trifluoromethylthiol group into the 4-CF_3S-2,3,5,6-tetrafluoropyridine (Scheme 29) with excess $CsSCF_3$ were unsuccessful.[50] To overcome this limitation, the authors employed a trimeric thiocarbonyl difluoride ($(CF_3S)_2C{=}S$), which upon activation with caesium fluoride, enabled substitution under harsh reaction conditions. Depending on the reaction temperature, either a complex mixture of kinetic bis- and tris-trifluoromethylthiolated products (at 20 °C) or thermodynamically more stable 3,5-bis(CF_3S)-analogue (at 100 °C) was formed solely, indicating the reversible nature of the studied nucleophilic aromatic substitution in perfluorinated pyridine under the applied conditions.

Parallel pioneering studies on the direct introduction of the CF_3S group into heterocyclic frameworks were carried out independently by Yagupolskii.[51] In this case, the authors benefited from a reliable route towards (trifluoromethylthio)copper(I), i.e. accessed by treatment of $AgSCF_3$ with CuBr, in hot acetonitrile, and demonstrated its efficient application in functionalization of iodoarenes, including iodo-substituted N-heterocycles, by heating the mixtures under inert atmosphere (Scheme 30).



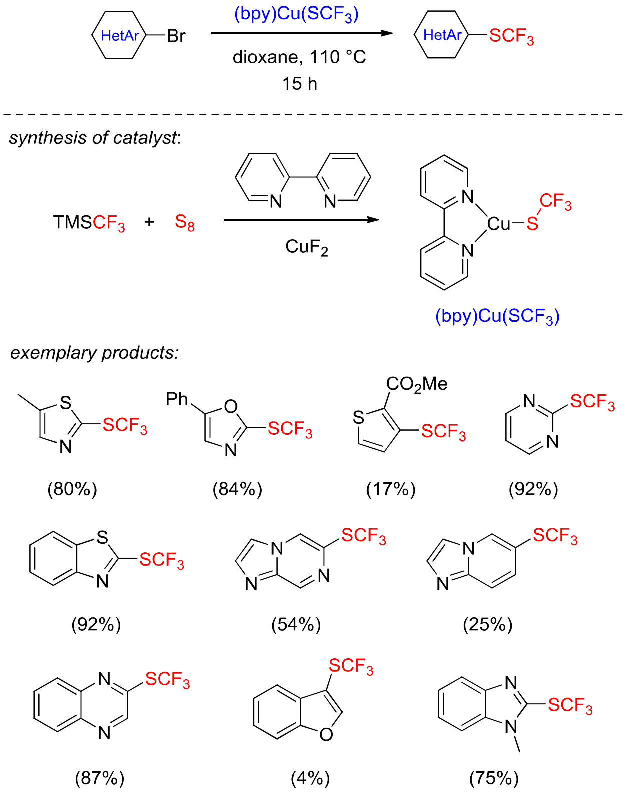
Scheme 30. Alternative route toward key $CsSCF_3$ and its application in reactions with iodohetaryls.

Another approach to $CuSCF_3$ was later proposed by Yang and Vicic, who utilised copper(I) chloride in combination with triphenylphosphine for deoxygenative reduction of Langlois reagent (Scheme 31).[52] The resulting crude salt was demonstrated to efficiently functionalize a range of aryl and heteroaryl iodides in a telescopic manner, by heating in 1,3-dimethyl-2-imidazolidinone (DMI) at 110 °C. Thus, the corresponding trifluoromethylthiolated products derived from pyridine, benzo[*d*]thiophene, thiophene, and furan were prepared in high 75-93% yield.



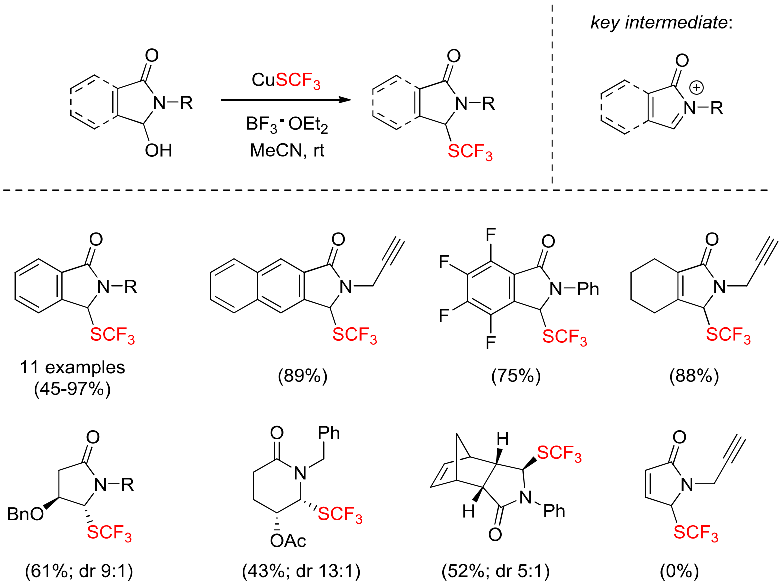
Scheme 31. Telescopic approach towards CF_3S-heteroaryls starting with Langlois' reagent.

In another work by Weng and Huang a family of copper(II) complexes were prepared and utilised for trifluoromethylthiolation coupling reactions with activated aryl and heteroaryl bromides.[53] Although initial attempts proved moderate activity of the designed complexes, systematic optimization identified (bpy)Cu(SCF_3) as an efficient catalyst, which enabled the preparation of numerous CF_3S-substituted derivatives of pyridine, pyrimidine, quinoline, quinazoline, and related nitrogen heterocycles (Scheme 32).[54] The methodology was subsequently extended to selected O- and S-heterocyclic substrates, such as oxazole, thiazole, thiophene, and their fused derivatives, revealing its extraordinary synthetic versatility.



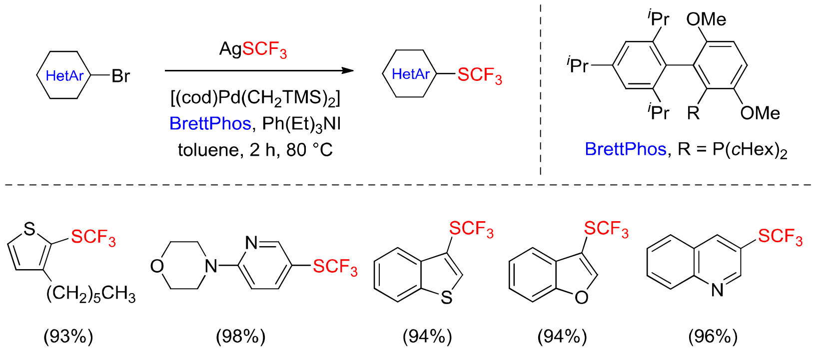
Scheme 32. Synthesis and application of (bpy)Cu(SCF_3) for trifluoromethylthiolation of N-, O-, and S-heteroaryl bromides.

Given the structural importance of indole and isoindole derivatives in medicinal chemistry, Lebœuf and co-workers disclosed an elegant synthesis of 3-CF_3S-isoindolones through boron trifluoride-induced trifluoromethylthiolation of the first formed *N*-acyliminiums with $CuSCF_3$ (Scheme 33).[55] The method employed 3-hydroxyisoindolones as starting materials, which upon treatment with Lewis acid (BF_3 and/or Cu^+) undergo dehydration to give the corresponding iminium cation. Trapping of this intermediate with the CF_3S anion leads to the final product, generally in high yield. The devised protocol was also successfully applied to *N*,*O*-acetal heterocycles such pyrrolidines and piperidines. As to the mechanism of the studied transformation, after exclusion of a radical intermediates, the authors proposed an ionic pathway leading, very likely, via $Cu^{+}(CF_3S)BF_3^{-}$ salt acting as a nucleophilic SCF_3 donor (Scheme 33).



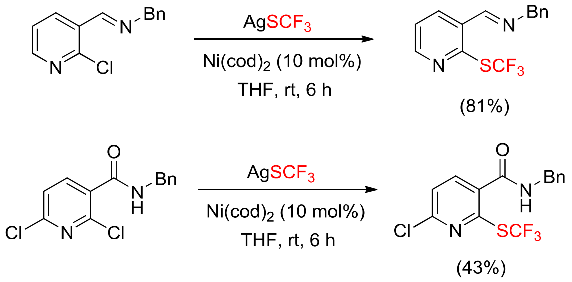
Scheme 33. Synthesis of 3-CF_3S-isoindolones via boron trifluoride-mediated trifluoromethylthiolation of *N*-acyliminium cations with $CuSCF_3$.

Buchwald demonstrated, that in spite of reduced nucleophilicity of the anion in (trifluoromethylthio)silver(I) ($AgSCF_3$), it can also serve as a convenient trifluoromethylthiolating agent in the presence of suitable activating agents.[56] Optimization studies revealed that a Pd/BrettPhos catalytic system combined with a source of iodide anion ($PhEt_3NI$) possibly generating an anionic 'ate' complex with $AgSCF_3$, was particularly efficient for Br/SCF_3 exchange in aryl bromides. It was also proved applicable to a broad range of N-, O-, and S-heterocycles, including pyridine, quinoline, benzofuran, benzothiophene, and thiophene derivatives (Scheme 34).



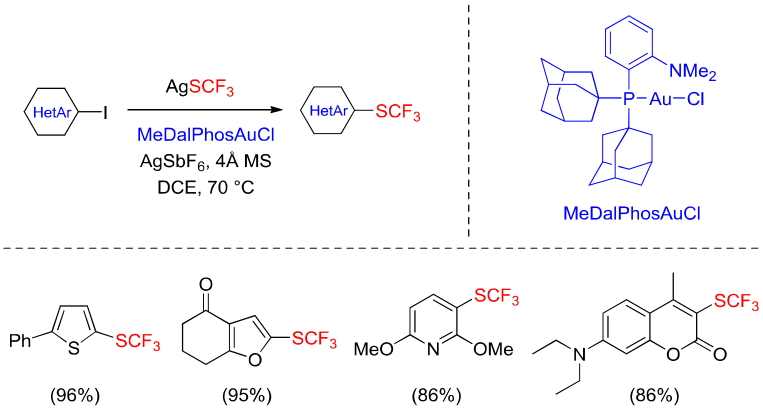
Scheme 34. Activation of $AgSCF_3$ with Pd/BrettPhos/$Ph(Et)_3NI$ in trifluoromethylthiolation of heteroaryl bromides.

Further advances in the use of $AgSCF_3$ for catalytic trifluoromethylthiolation of aryl chlorides and bromides under exceptionally mild conditions were reported by the Love group.[57] In this case, a nickel catalyst bearing cyclooctadiene ligands proved sufficient to mediate transformation without any additives or ligands. Although the study focused mainly on aryl halides including derivatives functionalized with various heterocyclic substituents, two 2-chloropyridine derivatives, bearing either an amide or imine unit as directing group (DG), at the *ortho*-position with respect to the leaving halide, were also reported (Scheme 35).



Scheme 35. Ni-Catalyzed trifluoromethylthiolation of 2-chloropyridines with $AgSCF_3$.

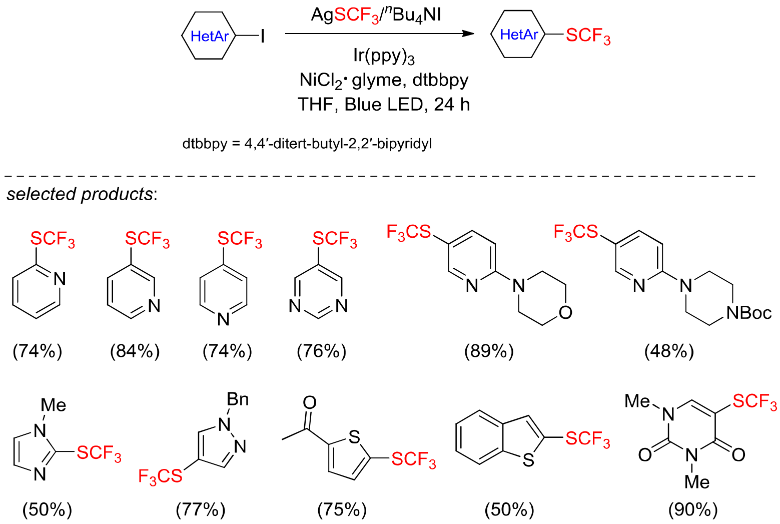
Among a broad range of catalytic systems employing transition metals and metal CF_3S-thiolates developed over the last decade, gold redox catalysts have shown remarkable activity and broad applicability in the synthesis of numerous aryl-, alkenyl-, and alkynyl-trifluoromethyl thioethers.[58] As demonstrated, phosphine–gold complex (MeDalphosAuCl) in combination with silver hexafluoroantimonate(V) applied as activator, efficiently mediated the trifluoromethylthiolation of various (hetero)aryl, vinyl, and acetylene iodides, under mild reaction condition, leading to the cross-coupled products in overall excellent yields. The developed protocol features broad functional group tolerance as demonstrated by the late-stage functionalization of selected bioactive molecules (e.g. Coumarin 1; Scheme 36).



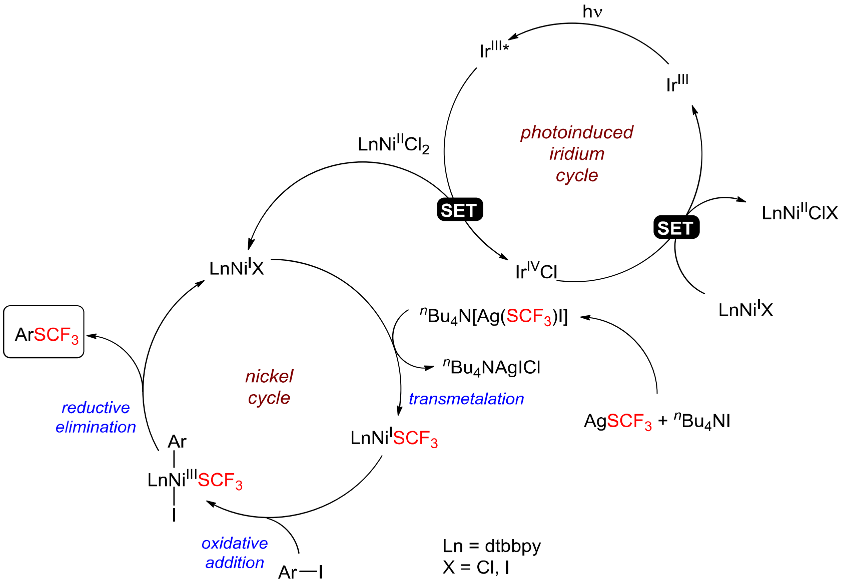
Scheme 36. Au-Catalyzed trifluoromethylthiolation of heteroaryl iodides with $AgSCF_3$.

A particularly efficient catalytic system for carbon–heteroatom coupling involving various aryl and heteroaryl iodides was introduced by Gravatt and Ghosh.[59] This approach is based on a photoredox catalytic system combining iridium(III) and nickel(II) complexes, along with tetrabutylammonium iodide ($^{n}Bu_4NI$) playing a dual role, i.e. as an activator of $AgSCF_3$ and as a redox mediator. The methodology was successfully applied to a variety of medicinally relevant N-, O-, and S-heterocyclic scaffolds (Scheme 37). Thus, pyridine, pyrimidine, pyrazine, pyrrole, pirazole, imidazole, furan, thiophene, 1,3-thiazole, their benzo-fused analogues, and uracil provided the desired CF_3S-functionalized products, generally in high yield >70%.

Based on control experiments supplemented by the literature data, the authors proposed a reaction pathway involving photoexcitation of Ir(III), single-electron reduction of Ni(II), subsequent transmetalation with $AgSCF_3$ to form the dtbbpyNi(I)SCF_3 intermediate, and a sequence of oxidative addition and reductive elimination steps leading to the trifluoromethylthiolated (hetero)aryl product (Scheme 38).

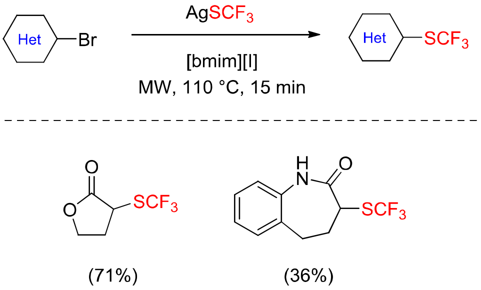


Scheme 37. Photoredox Ir(III)/Ni(II)-catalyzed synthesis of heteroaryl CF$_3$-thioethers with AgSCF$_3$.



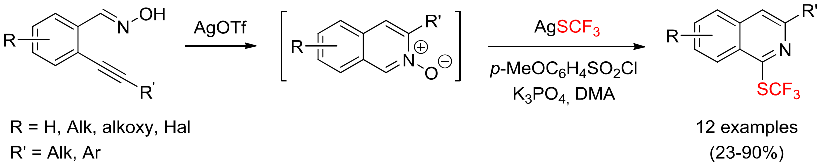
Scheme 38. Proposed catalytic cycles for photoredox Ir(III)/Ni(II)-catalyzed trifluoromethylthiolation of (hetero)aryl iodides developed by Gravatt and Ghosh.

Nucleophilic displacement of a halide with SCF_3 anion in non-aromatic heterocycles can be also performed as demonstrated by Pégot and Magnier.[60] Activation of the silver(I) salt with ionic liquid 1-butyl-3-methylimidazolium iodide ([bmim][I]), under microwave conditions, proved efficient not only for (cyclo)aliphatic halides (Br, Cl, I) but also for certain non-activated primary alcohols. Two CF_3S-heterocyclic products derived from γ-butyrolactone and benzo-fused caprolactam were prepared in this study (Scheme 39).



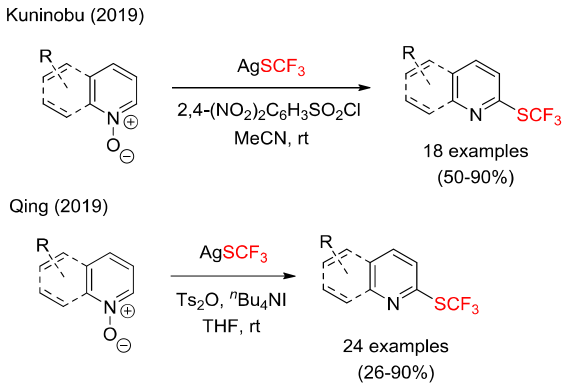
Scheme 39. Ionic liquid-mediated nucleophilic substitution in exemplary non-aromatic bromides.

The application of silver salts in the synthesis of CF_3S-functionalized nitrogen heterocycles was further explored by Ding and Wu, in a tandem AgOTf/$AgSCF_3$-induced cyclisation/trifluoromethylthiolation reaction utilizing *ortho*-alkynyl benzaldehyde oximes as starting materials (Scheme 40).[61] In the presence of silver(I), these substrates undergo intramolecular cyclization to give isoquinoline *N*-oxides, which after subsequent activation via *O*-acylation with *p*-$MeOC_6H_4SO_2Cl$, smoothly trap the SCF_3 anion at the C-2 position of the isoquinoline ring. The final re-aromatization of the heterocycle proceeds through 1,2-elimination of the respective sulfonic acid.



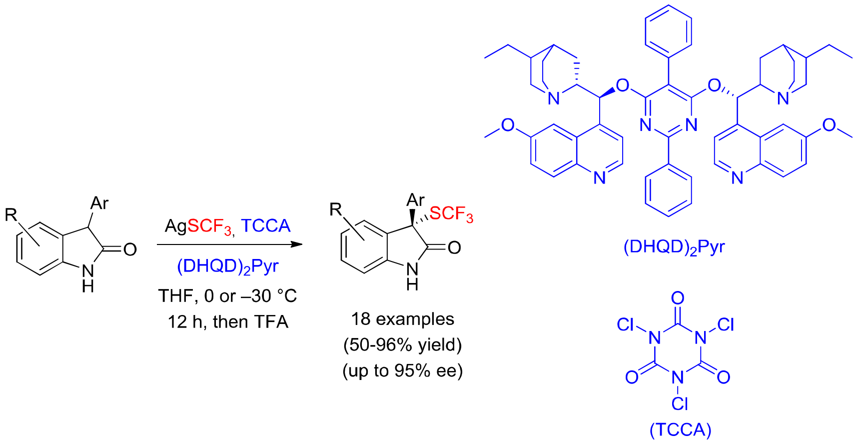
Scheme 40. Silver(I)-mediated domino ring-closure and trifluoromethylthiolation reactions leading to 2-CF_3S-isoquinolines.

The above observation that activated azaaromatic *N*-oxides can serve as suitable reaction partners in trifluoromethylthiol-transfer reactions with $AgSCF_3$ was soon after confirmed in an independent works by the Kuninobu[62] and Qing[63] groups (Scheme 41). In both cases, the addition of reactive sulfonic acid derivatives (by using 2,4-dinitrobenzenesulfonyl chloride or *p*-toluenesulfonic anhydride, respectively) was essential to promote electrophilic activation at the C-2 position of the heterocyclic ring through coordination and stabilization of the *N*-oxide function. In the latter protocol (Quing's variant), the presence of tetrabutylammonium iodide facilitated the generation of a more reactive CF_3S^- species. Both deoxygenative approaches were successfully applied to the trifluoromethylthiolation of various six-membered substrates, especially quinoline but also pyridine, pyrimidine, phenanthridine and isomeric benzo[*f*]quinoline, benzo[*h*]quinoline as well as derivatives of naturally occurring quinidine, yielding the corresponding CF_3S-functionalized products in good yields.



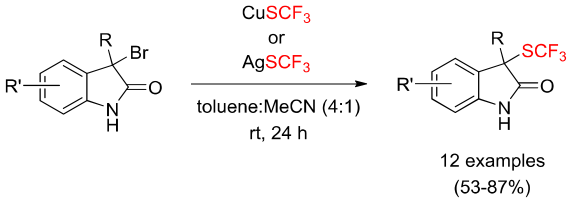
Scheme 41. Deoxygenative C(2)-selective trifluoromethylthiolation of six-membered azaaromatic *N*-oxides with $AgSCF_3$.

In 2014, Liu and Tan disclosed the first enantioselective trifluoromethylthiolation of 2-indolones employing $AgSCF_3$ as a source of electrophilic CF_3S^+ cation (Scheme 42).[64] The required reactive intermediate was generated *in situ* by treating of the starting silver salt with trichloroisocyanuric acid (TCCA), and use of the quinoline-based organocatalysts $(DHQD)_2Pyr$ assured excellent enantiocontrol. A series of 2-oxoindoles bearing a CF_3S-substituted quaternary chirality center located at C-3 of the heterocyclic ring was prepared, generally in high chemical yield and enantiomeric excesses of up to 95%. The absolute configuration (*S*) at the newly generated stereogenic center in the representative product (R = H, Ar = Ph) was unambiguously confirmed by X-ray analysis.



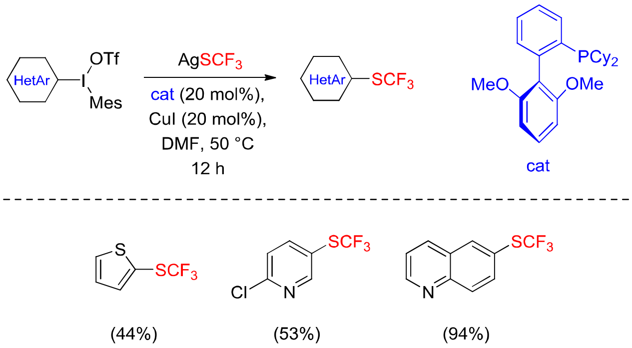
Scheme 42. Organocatalyzed asymmetric trifluoromethylthiolation of 2-oxoindoles with $AgSCF_3$.

The increasing interest in CF_3S-functionalized indole and indolin-2-one derivatives as materials of promising biological properties intensified the search for alternative synthetic methods. For example, Mizuta and co-workers examined the feasibility of introducing the trifluoromethylsulfanyl moiety at the α-position of such sterically demanding carbonyl compounds using the respective halogenated precursors and nucleophilic F_3CS-reagents as reaction partners.[65] The formation of the desired new C_{sp3}–SCF_3 bond was achieved under mild conditions, at room temperature, by simple treatment of the starting bromide with excess (2 equiv.) silver(I) or copper(I) salt, with no additional ligands or oxidants (Scheme 43). A series of the expected racemic products was prepared in fair yields. The presented protocol characterized by a broad functional group tolerance was further adapted to the synthesis of α-CF_3S-functionalized primary and secondary amides.



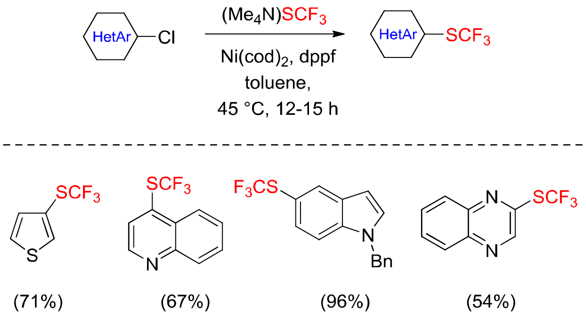
Scheme 43. Synthesis of sterically hindered 3-CF_3S-2-oxindoles using the respective bromides by nucleophilic displacement with $AgSCF_3$ or $CuSCF_3$.

The introduction of the trifluoromethylsulfanyl substituent through carbon–heteroatom coupling was also explored by using hypervalent iodine derivatives as suitable electrophilic partners.[66] Efficient trifluoromethylthiolation was achieved using a copper(I) catalyst in the presence of a phosphine ligand. Although the catalytic protocol was primarily developed for aryl derivatives, its applicability to selected examples of heteroaryl substrates was also demonstrated (Scheme 44).



Scheme 44. Application of di(hetero)aryl-λ^3-iodanes in Cu-catalyzed trifluoromethylthiolation reaction.

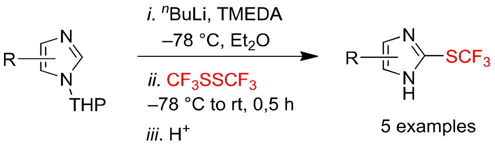
Schoenebeck and co-workers reported a bench-stable, metal-free source of the CF_3S anion in the form of its tetramethylammonium salt.[67] Catalytic trifluoromethylthiolation using this reagent was demonstrated for a variety of aryl and heteroaryl chlorides, in the presence of a nickel(II) catalyst (Ni(cod)2/dppf), to give the corresponding CF_3S-substituted products under mild conditions (Scheme 45).



Scheme 45. Ni-catalyzed CF_3S coupling with (hetero)aryl chlorides.

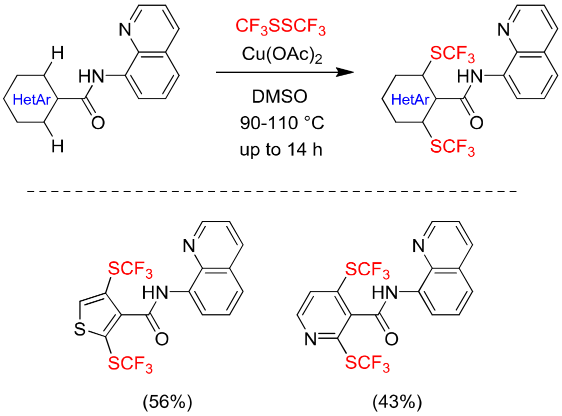
2.2.3. Bis(trifluoromethyl) disulfide ($CF_3S{-}SCF_3$)

In 1985, Haber and co-workers investigated the synthesis and biological activity of a series of perfluoroalkylsulfanyl-functionalized heterocycles, including trifluoromethylthiolated derivatives. The authors reported an approach to 2-(trifluoromethylthio)imidazoles employing disulfide CF_3SSCF_3 as an efficient trifluoromethylthiolating agent in reactions with the *in situ*-generated lithiated *N*-tetrahydropyranyl-protected substrates (Scheme 46).[68] The resulting compounds were examined for their potential anti-arthritic activity.



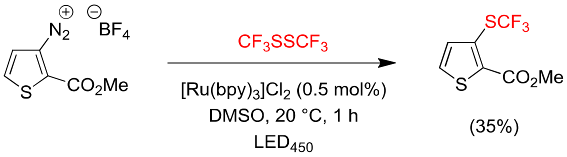
Scheme 46. Trifluoromethylthiolation of lithiated imidazole with CF_3SSCF_3.

An auxiliary-assisted, copper-catalyzed direct trifluoromethylthiolation of *β*-C–H bonds in a series of *N*-(quinolin-8-yl)benzamide derivatives was demonstrated by Daugulis group.[69] The method employs bis(trifluoromethyl) disulfide as a source of trifluoromethyl intermediate; however, the mechanism of this transformation has not been studied in detail. The use of an analogous protocol for representative five- and six-membered heterocycles (thiophene- and pyridine-carboxamides) opened up an access to the respective bis-(CF_3S)-functionalized products (Scheme 47).



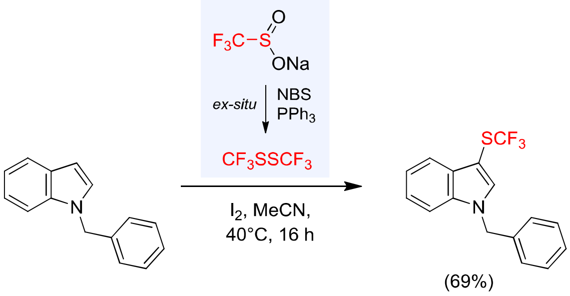
Scheme 47. Double *N*-quinolin-8-yl auxiliary assisted Cu-catalyzed *β*-C-trifluoromethylthiolation of thiophene- and pyridine-carboxamides.

Radical trifluoromethylthiolation of a series of aryldiazonium tetrafluoroborates with bis(trifluoromethyl) disulfide to afford the respective 3-CF_3S-analogues was reported by von Wangelin and co-workers.[70] For the selected thiophene-derived salt involved in the study, the expected product was isolated in low 35% yield (Scheme 48). The developed light-induced (blue LEDs) reaction catalyzed either by eosin Y or $[Ru(bpy)_3]Cl_2$ was compared with the weak base-mediated reaction carried out in dark to demonstrate higher efficiency of the photo-catalyzed approach.



Scheme 48. Photocatalyzed cross-coupling of thiophene-derived diazonium salt with CF_3SSCF_3.

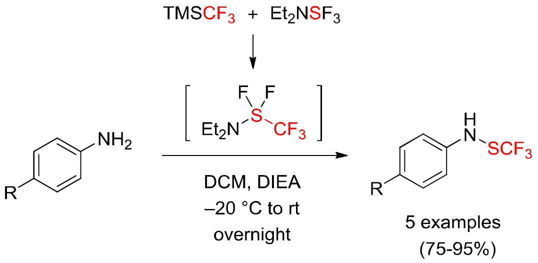
Taking into account the remarkable toxicity of CF_3SSCF_3, Skrydrup *et al.* developed a safer, operationally simple protocol for the *ex-situ* generation of this disulfide in a two chamber system, starting from Langlois reagent, under activation with NBS and PPh_3.[71] The devised protocol was examined in a series of model nucleophilic, electrophilic, and radical transformations, including copper-catalyzed cross-coupling trifluoromethylthiolations with arylboronic acids. In a reaction employing *N*-benzylindole, the expected 3-CF_3S-functionalized product was isolated in 69% yield (Scheme 49).



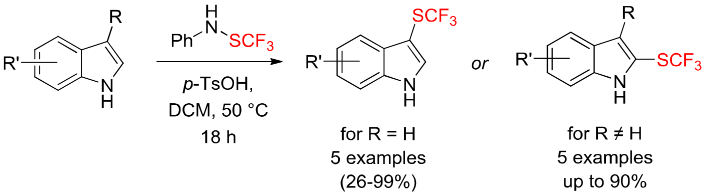
Scheme 49. Application of *ex-situ* generated CF_3SSCF_3 in the synthesis of 1-benzyl-3-CF_3S-inidole.

2.2.4. Applications of N−SCF₃ reagents

A significant advance in the chemistry of electrophilic trifluoromethylthiolating reagents emerged in the early 2010s, when Billard introduced a novel class of compounds – trifluoromethanesulfanylamides.[72] This enabled efficient trifluoromethylthiolation reactions of alkenes and alkynes,[73] aromatic systems,[74] and carbonyl derivatives,[11] which proceed with a CF_3S^+ cation as reactive intermediate. As shown in Scheme 50, the mentioned easy-to-handle $ArNH-SCF_3$ reagents were accessed by treatment of anilines with a mixture of Ruppert-Prakash silane and diethylaminosulfur trifluoride (DAST), under basic conditions. In the realm of direct, late stage C−H functionalization of heterocyclic substrates, the reactivity of trifluoromethanesulfanylamides was explored towards electron-rich indoles, to open up a practical and selective protocol towards C(2)- and C(3)-CF_3S-functionalized products, depending on the substitution pattern in the starting material (Scheme 51).[75] Hence, the reaction of 2,3-unsubstituted indoles furnished 3-trifluoromethylthiolated indoles, whereas 3-alkyl-substituted indoles underwent regioselective functionalization at the C(2)-position.

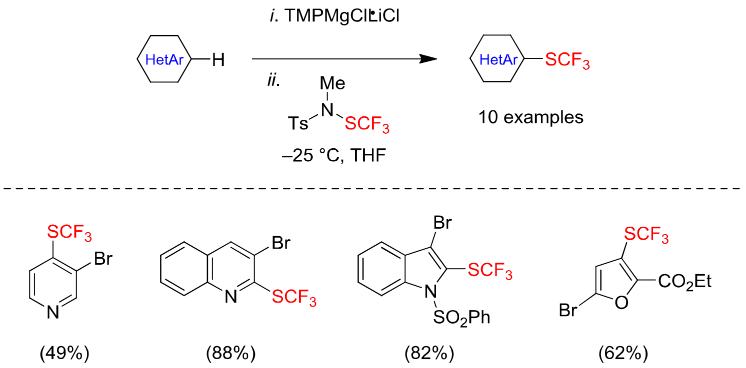


Scheme 50. Synthesis of aryl trifluoromethanesulfanylamides.



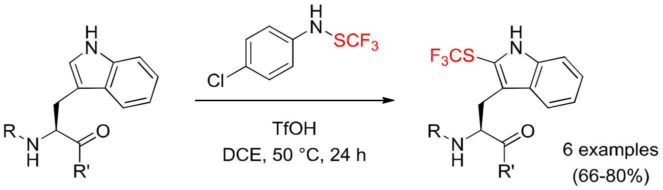
Scheme 51. Application of $ArNH-SCF_3$ reagents in CF_3S^+-transfer into indoles.

Direct transfer of the SCF_3 group to a broad range of heteroaromatic rings including pyridine, quinoline, indole, benzothiophene, thiazole, and furan, using an *N*-methyl *p*-toluene-sulfanylamide derivative (the so-called second-generation CF_3-sulfenamide) was reported in 2015.[76] This enabled a two-step approach comprised of a selective deprotonation of heteroarene with a mixed Mg/Li amide (*Turbo*-Hauser base) followed by trapping of the first formed anion with trifluoromethylthiolating agent (Scheme 52). Notably, in the case of 3-bromopyridine, increasing the reaction temperature to 0 °C enabled a switch of the reaction outcome leading to the respective 3-CF_3-product, formed via an alternative halogen-metal exchange in the first step.



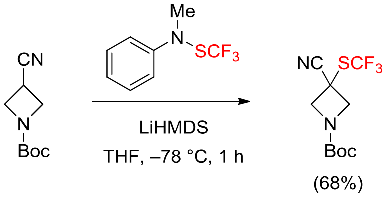
Scheme 52. Trifluromethylthiolation of *in situ*-generated heteroaryl anions with 2nd generation CF_3-sulfenamide.

In subsequent studies, Brigaud and co-workers employed Billard's reagents for the trifluoromethylthiolation of tryptophan derivatives.[77] Inspired by earlier investigations on first-generation sulfenamides,[78] the authors utilized a *p*-chloroaniline-based analogue to access trifluoromethylthiolated tryptophan derivatives on a gram scale (Scheme 53). The designed TfOH-catalyzed transformations proceeded selectively at the C(2) position of the indole ring, even in the case of more complex peptide-bound tryptophan derivatives, significantly affecting local oleophilicity and tuning the p*K*a values of adjacent aryl substituents.



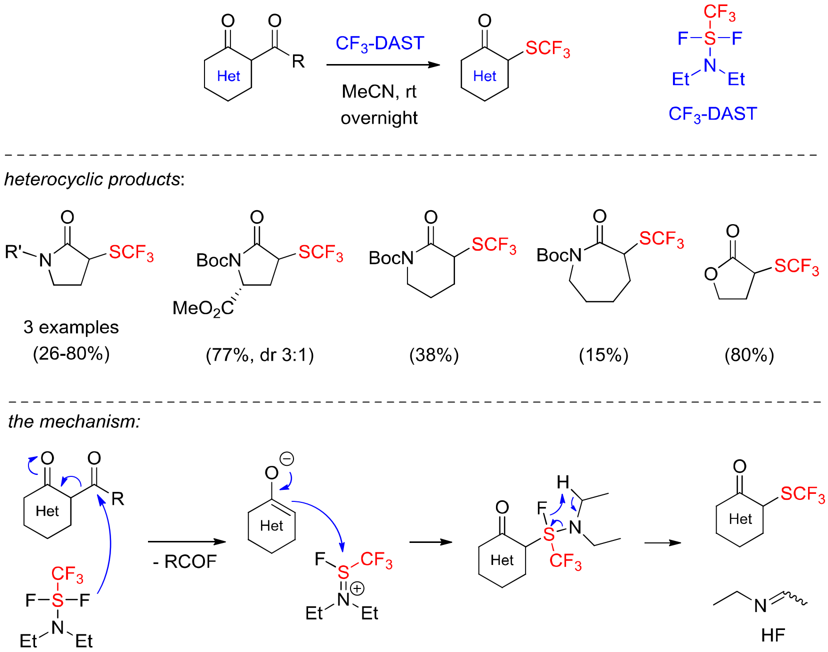
Scheme 53. C(2)-Selective CF_3S-funtionalization of tryptophan-derived peptide substrates.

The second-generation trifluoromethanesulfanylamide derived from *N*-methylaniline was demonstrated to efficiently promote electrophilic trifluoromethylthiolation of an azetidine ring, thus extending the synthetic potential of this class of reagents toward small, strained heterocycles (Scheme 54).[79] Treatment of *N*-Boc-3-cyano-azetidine with strong base (LiHMDS) followed by trapping of the respective anion with CF_3S^+-donor provided the expected 3-CF_3S-functionalized product in high yield of 68%. The structure of the isolated material was proved by X-ray measurements.



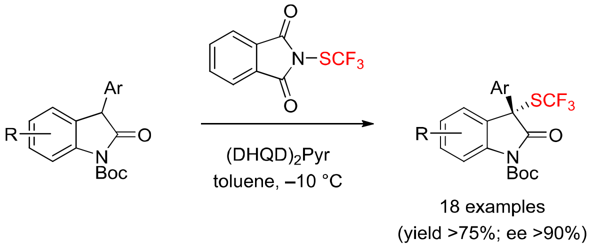
Scheme 54. Trifluoromethylthiolation of azetidine ring.

A distinct mode of reactivity, remarkably different from that reported for classical electrophilic trifluoromethylthiolating reagents, was observed by Shibata and co-workers in trifluoromethylthiolation reactions of 1,3-dicarbonyl compounds using CF_3−DAST reagent.[80] The developed deacylative approach proceeds, very likely, via the initial attack of the CF_3−DAST-generated fluoride anion onto the acyl moiety and subsequent elimination of an acyl fluoride to give the intermediate enolate. The latter is then trifluoromethylthiolated to give the final product. A series of γ-, δ-, and ε-lactams as well as representative lactone CF_3S-derivative were obtained in moderate to good yield (Scheme 55).



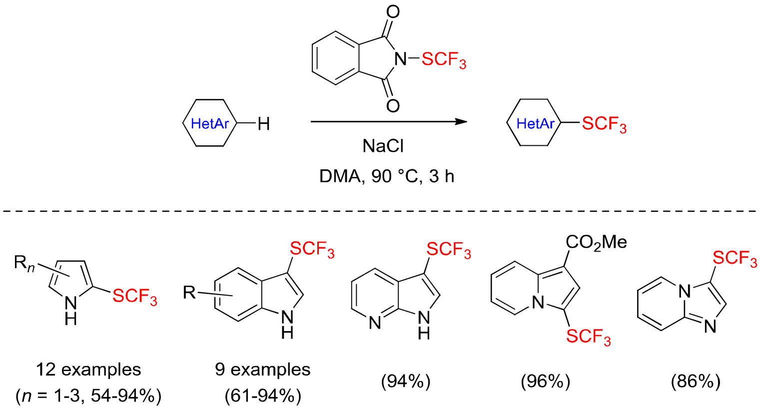
Scheme 55. Deacylative trifluoromethylthiolation of 1,3-dicarbonyl compounds with CF$_3$-DAST; scope of heterocyclic products and the proposed mechanism.

In the search for electrophilic trifluoromethylthiolating CF$_3$S−N-reagents further shelf-stable compounds, i.e. derived from phthalimide, succinimide, and saccharine, have been developed and demonstrated as convenient substrates for functionalization of heterocyclic frameworks. Prompted by pioneer work by Munavalli on the application of CF$_3$S-phthalimide in α-functionalization of masked carbonyls (mainly enamines),[81] the Rueping group developed an efficient protocol for organocatalytic enantioselective trifluoromethylthiolation of sterically hindered 3-aryl-indol-2-ones.[82] Employing *N*-(trifluoromethyl)thiolated phthalimide as the CF$_3$S-source, and the cinchona alkaloid-derived (DHQD)$_2$Pyr catalyst, a series of optically active products with the SCF$_3$ group located at the newly generated quaternary center was obtained in high yields and very high enantioselectivities (ee > 90%) (Scheme 56) (for the structure of the catalyst, see Scheme 42).

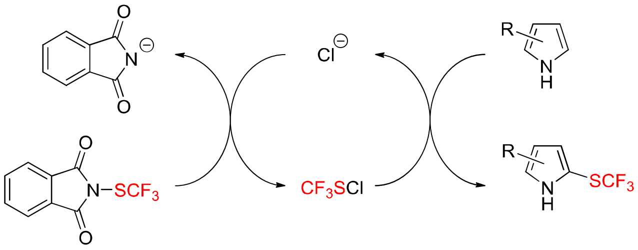


Scheme 56. Organocatalytic enantioselective trifluoromethylthiolation of 3-aryloxindoles using CF_3S-phthalimide.

In parallel, Glorius and co-workers exploited the same phthalimide-based reagent to establish transition metal-free conditions for trifluoromethylthiolation of selected biologically important N-heterocycles.[83] Activation of the reagent with alkali metal halides, most effectively with sodium chloride, enabled the synthesis of 2-trifluoromethylthiolated mono-, di-, and tri-C-substituted pyrroles and indoles, as well as representative azaindoles, indolizines, and imidazopyridines (Scheme 57). As no remarkable influence by radical inhibitor additives on the reaction outcome could be observed, a radical pathway of the studied reaction was ruled out. The proposed mechanism involves chloride anion acting as a Lewis base to *in situ*-generate highly reactive trifluoromethylsulfenyl chloride ($CF_3S{-}Cl$), which subsequently participates in electrophilic aromatic substitution with heteroarene (Scheme 58).

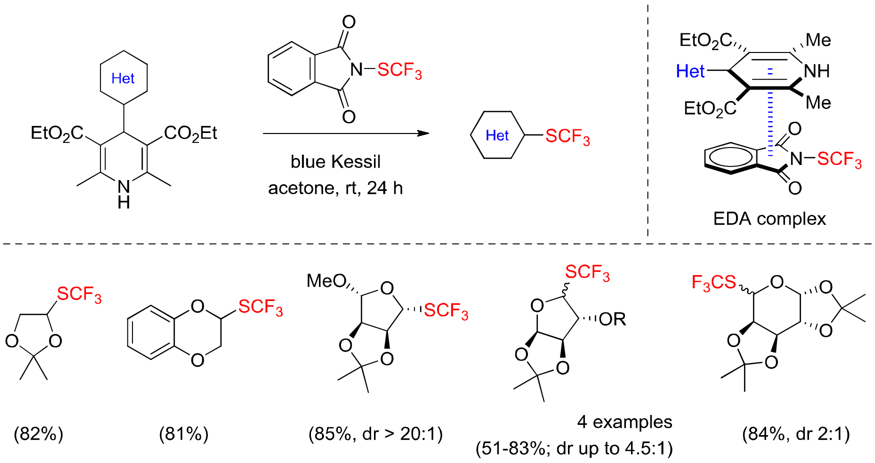


Scheme 57. Halide-activated electrophilic trifluoromethylthiolation of N-heterocycles with Phth-SCF_3.



Scheme 58. The proposed mechanism of [Cl⁻]-activation of Phth-SCF_3.

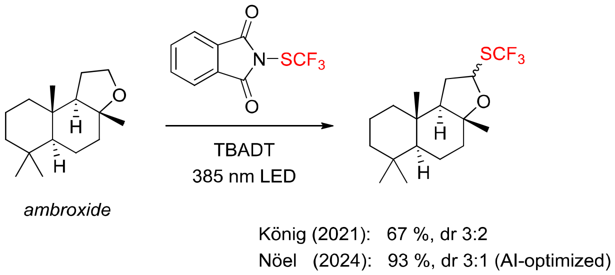
Further contributions on applications of *N*-trifluoromethylsulfanyl-phthalimide were delivered by Gutierrez and Molander, who disclosed a decarbonylative photoinduced C−SCF_3 bond formation protocol for aldehyde surrogates.[84] In the developed catalyst- and additive-free open-to-air protocol starting polysubstituted dihydropyridine derivatives were applied as aldehyde feedstocks (Hantzsch esters), playing the role of a donor for the intermediate electron donor-acceptor (EDA) complex with Phth−SCF_3 (acceptor). The control experiment supplemented by computational analysis revealed that product formation occurs through S_H2 reaction of alkyl radicals with bis(trifluoromethyl)disulfide, generated *in situ* via combination of thiyl radicals. Among the examined substrates, 1,3-dioxolane, benzo-1,4-dioxane, chromane, piperidine, as well as carbohydrate-derived starting materials were checked (Scheme 59).



Scheme 59. Application of Hantzsch esters as aldehyde surrogates in CF_3S-transfer reactions.

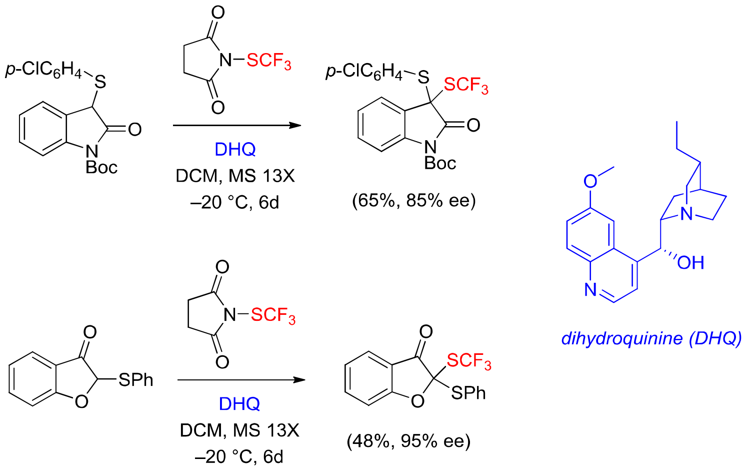
A similar catalyst-free photochemical approach employing Hantzsch esters and succinimide-derived N−SCF_3 reagent was also presented. Upon mild irradiation (LEDs 450 nm, acetone, room temperature, 16 h) the cyclo(hetero)alkyl substituents could be replaced by a SCF_3 group via a radical pathway, to afford piperidines (4 examples, 71-82%) and 4-trifluoromethylsulfanyltetrahydropyran (71%).[85]

Within the analogous methodological context, phthalimide-based CF_3S-reagent was successfully applied to the functionalization of terpenoids, as exemplified by ambroxide. König and co-workers achieved the trifluoromethylthiolation of ambroxide employing earlier developed decatungstate-based photocatalyst (TBADT; $[Bu_4N]_4^+[W_{10}O_{32}]^{4-}$) to provide the corresponding product in 67% yield (Scheme 60).[86] More recently, the Noël group obtained the same product (93%) under analogous photocatalytic conditions but utilizing the so-called *RoboChem*, an AI-driven experimental optimization platform developed in their laboratory.[87] The mentioned AI-system also facilitated the trifluoromethylthiolation of γ-butyrolactone, to give the desired α-CF_3S-analogue in 57% yield (5 mmol scale). Notably, using the *RoboChem* protocol in selected known Giese-type radical additions to alkenes, C_{sp3}−H and C_{sp2}−H trifluoromethylations significantly improved yields relative to conventional optimization approaches.

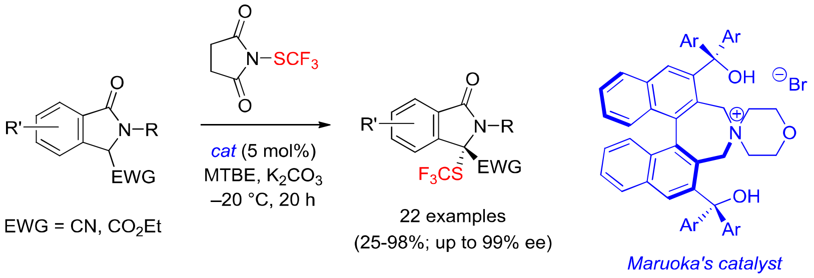


Scheme 60. Trifluoromethylthiolation of ambroxide.

The first examples on organocatalytic enantioselective synthesis of dithioacetals with the *N*-SCF_3 succinimide as the electrophilic SCF_3 donor were reported by Zhou and co-workers.[88] Although the tested reagent proved less reactive than non-fluorinated sources of electrophilic RS^+ intermediates, two exemplary benzo-fused heterocycles were successfully converted into the respective products, using readily available dihydroquinine (DHQ) as catalyst (Scheme 61). The Waser group further explored enantioselective synthesis employing (*N*-(trifluoromethyl)-thio)succinimide towards 3,3-disubstituted isoindolinones bearing a SCF_3 group at newly generated quaternary stereogenic center at the C(3) position.[89] A broad variety of products functionalized with electronically different substituents were obtained, generally in high yields and enantioselectivities, by using bifunctional chiral ammonium salt (Maruoka's catalyst) as a stereo-differentiating agent (Scheme 62).



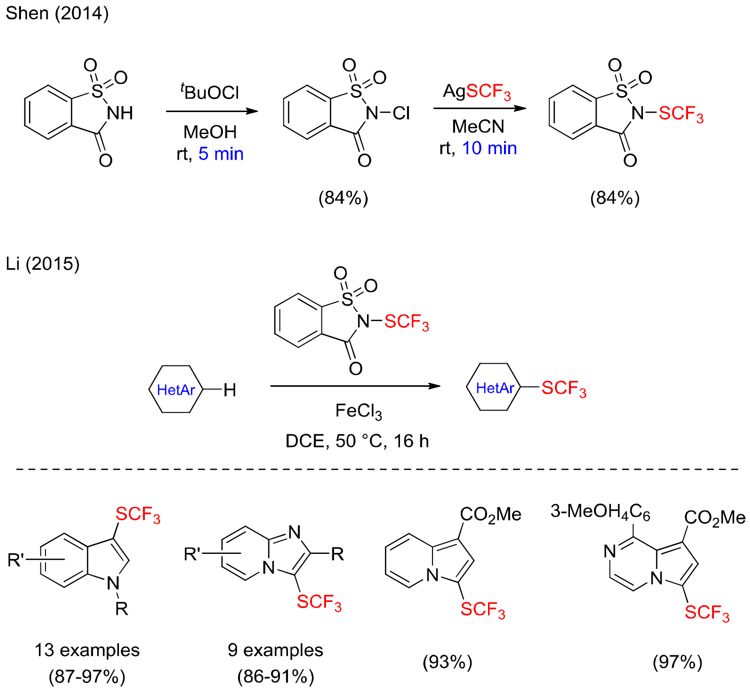
Scheme 61. Organocatalytic asymmetric synthesis of indole- and benzofuran-derived dithioacetals featuring an SCF3 group.



Scheme 62. Asymmetric synthesis of 3-CF3S-isoindolinones.

Another readily available and useful shelf-stable trifluoromethylthiolating reagent, namely *N*-(trifluoromethylthio)saccharin, was reported in 2014 by the Shen group.[90] This reagent allowed smooth functionalization of a variety of nucleophiles such as alcohols, amines, thiols, carbonyl compounds (aldehydes, ketones, and *β*-ketoesters), alkynes, as well as electron-rich arynes. Selected representative heteroarenes (pyrrole and indole derivatives) were also involved in the study to give, under the applied reaction conditions

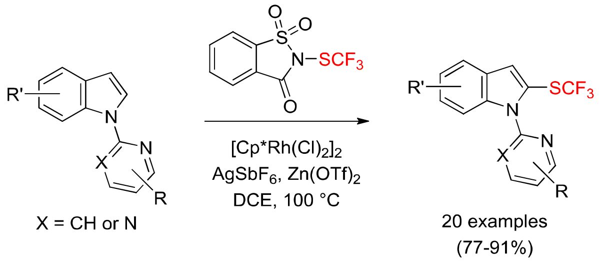
(DCM, rt, 0.5 h), and using TMSCl as an activator, the expected CF_3S-products in excellent yield (>93%). Soon after, a wide range of electron-rich heteroarenes in reactions with *N*-(trifluoromethylthio)saccharin was examined by the Li group.[91] Under Fe(III)-catalysis, a series of trifluoromethylthiol-decorated indoles, imidazo[1,2-*a*]pyridines, indolizines, and pyrrolo[1,2-*a*]pyrazines were obtained in a highly regioselective fashion (Scheme 63). The observed site selectivity closely resembles that of a well-known palladium-catalyzed C–H functionalizations, which is consistent with an electrophilic substitution mechanism.



Scheme 63. Expeditious synthesis of *N*-(trifluoromethylthio)saccharin (Shen, 2014), and its application in direct $FeCl_3$-catalyzed functionalization of heteroarenes (Li, 2015).

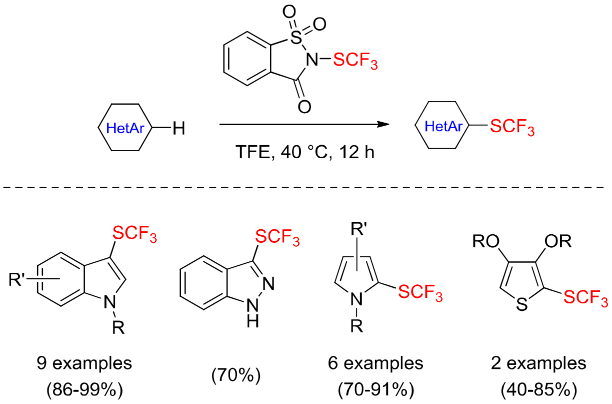
Li and co-workers subsequently extended the *N*-(CF_3S)saccharin-based approach to C−H trifluoromethylthiolation of indoles bearing heterocyclic substituents located at the N(1) position.[92] Employing a rhodium(III) half-sandwich complex activated by silver salts ($AgSbF_6$), in the presence of suitable Lewis acids as an essential additive (best results were noticed with zinc triflate), regioselective 2-trifluoromethylthiolation of indoles was achieved (Scheme

64). The observed switch of selectivity – in comparison with Fe(III)-catalyzed reactions leading to 3-substituted products – is correlated to the N-substituent acting as directing group in a C−H activation pathway, while in the absence of such a group Lewis acid-catalyzed reaction is favored. Application of the same catalytic system to *N*-(pyridin-2-yl)pyrroles afforded the corresponding 2-CF_3S-pyrrole derivatives in high yield (>80%).



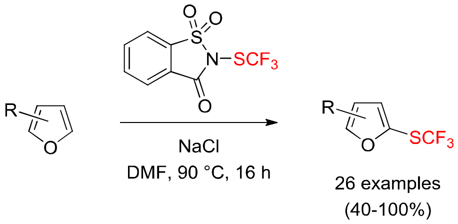
Scheme 64. The role of N-directing groups in C(2)-selective trifluoromethylthiolation of indoles.

Further studies by Shen’s group demonstrated that *N*-(trifluoromethylthio)saccharin can also promote Friedel-Crafts trifluoromethylthiolations under mild metal-free conditions when activated by 2,2,2-trifluoroethanol (Scheme 65).[93] This method displays a broad substrate scope encompassing diverse electron-rich heterocycles and compatibility to a variety of common functional groups such as alkyl, alkoxy, acyl, cyano, ester, nitro, and halides.



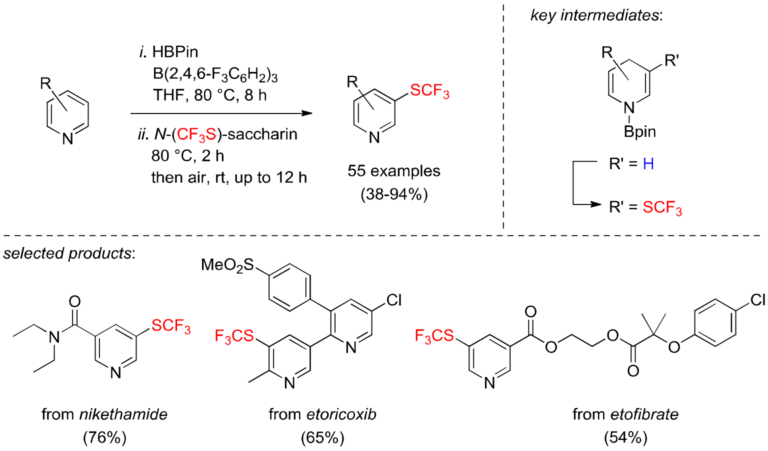
Scheme 65. TFE-induced trifluoromethylthiolation of heteroarenes with *N*-(CF_3S)saccharin.

In 2017, the same reagent was later employed by Glorius and co-workers to explore trifluoromethylthiolation of furans under mild, metal-free conditions.[94] In analogy to earlier reported phthalimide-mediated trifluoromethylthiolations of indoles and pyrroles,[83] sodium chloride was applied as an inexpensive and eco-friendly activator, which facilitates *in situ* formation of highly reactive species (CF_3SCl). The reaction proceeds with excellent regioselectivity and a high functional group tolerance, affording 2-CF_3S-furans as major products (Scheme 66). For example, substrates functionalized with a phenyl group located at C(2) or C(3), bearing such groups as MeO, Cl, F, Br, CF_3, CO_2Et, as well as CN and NO_2, provided the desired products, typically in high yield > 80%.



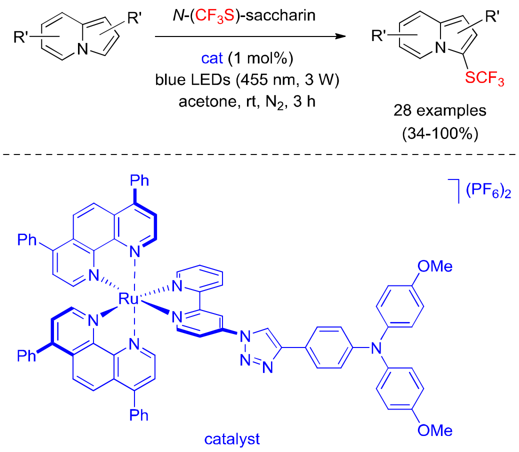
Scheme 66. NaCl-Catalyzed synthesis of 2-CF_3S-furan derivatives.

The synthetic utility of *N*-(trifluoromethylthiol)saccharin in heterocycle functionalization was recently extended to six-membered nitrogen heterocycles by Wang and co-workers.[95] In this study aimed at pyridine functionalization, screening of various trifluoromethylthiolating agents revealed the saccharin-based reagent as the most efficient under the developed cascade reaction conditions. The devised one-pot, three-steps tandem transformation proceeds through initial hydroboration of the pyridine ring to generate a dearomatized dihydropyridine intermediate, which undergoes fully regioselective electrophilic CF_3S-functionalization at the C(3) atom, followed by oxidative re-aromatization of the heterocyclic core (Scheme 67). Late-stage functionalization of twelve drug molecules, including *etoricoxib*, *nikethamide*, *etofibrate*, *metapyron*, *bisacodyl*, *vismodegib*, and *cholesterol nicotinate* demonstrated robustness of the method and its utility for fast access to new drug candidates.



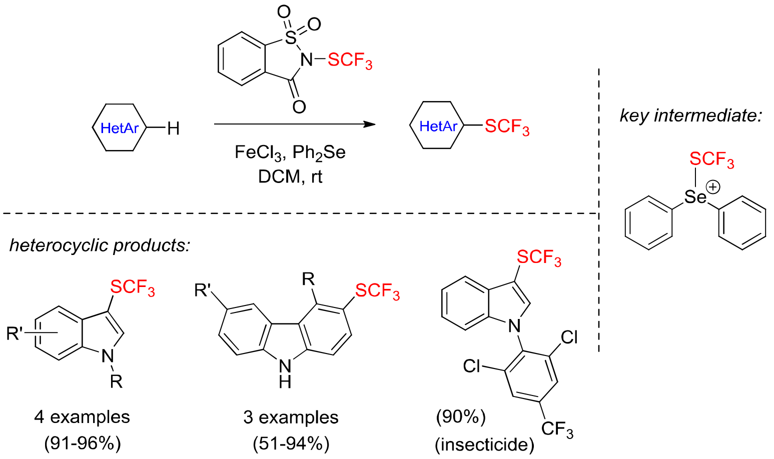
Scheme 67. One-pot three-step 3-trifluoromethylthiolation of pyridines.

A highly chemoselective photocatalytic protocol for the direct functionalization of indolizines with *N*-(CF_3S)saccharin has been developed by Wilhelm.[96] The employed photoredox Ru(II)-catalyst enabled mild, scalable, and fully regioselective radical trifluoromethylthiolation at the C(3) position irrespectively of the substitution pattern of the starting indolizine (Scheme 68). In addition, a 3-CF_3S-analogue of a known histamine H3 receptor antagonist was prepared in excellent yield.



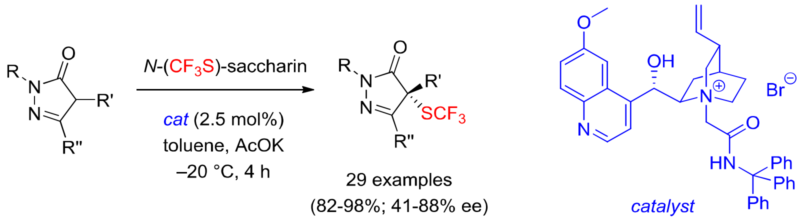
Scheme 68. C(3)-Selective photocatalytic trifluoromethylthiolation of indolizines.

Further catalyzed trifluoromethylthiolations using *N*-(CF_3S)saccharin were reported in 2024. For example, direct C−H functionalization of a wide range of nitrogen heterocycles under dual catalysis using a combination of iron(III) chloride and diphenyl selenide (Ph_2Se) was reported by Sutherland (Scheme 69).[97] Control experiments indicated that the Lewis acid and Lewis base are both required for the activation of trifluoromethylthiolating reagent; initial coordination of Fe(III) with a carbonyl group of *N*-(CF_3S)saccharin enables CF_3S-transfer to give a key trifluoromethylated diphenylselenium cation intermediate. A series of 3-trifluoromethylthiolated indazole and carbazole derivatives were prepared at room temperature, generally in high yield >90%, although highly activated carbazoles bearing competing directing groups led to mixtures of isomeric products. A known biologically active 3-(2,6-dichloro-4-trifluoromethylphenyl)-3-trifluoromthylsulfanylindole, exhibiting potent insecticidal properties against parasitic acarians of mammals, was also obtained by this method in excellent 90% yield.



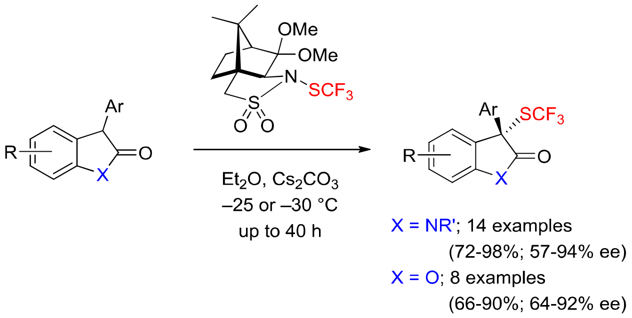
Scheme 69. Trifluoromethylthiolation of indoles and carbazoles under dual Fe(III)/Ph_2Se catalysis.

On the other hand, the Wang group disclosed the first enantioselective protocol for preparation of 4-CF_3S-pyrazolones in excellent yields (41 examples, up to 98%) and high enantiomeric excesses (up to 88%).[98] The enantiocontrol in the studied reaction was assured using a *Cinchona* alkaloid-derived amide-based phase transfer catalyst, through a multiple H-bonding along with the steric pressure exerted by a bulky N-substituent (trityl). The reaction is carried out under exceptionally mild conditions, at –20 °C, in toluene, in the presence of AcOK as a base (Scheme 70). It is noteworthy that the catalyst could be recovered form the mother liquor and reused without observable loss of reactivity or enantioselectivity.



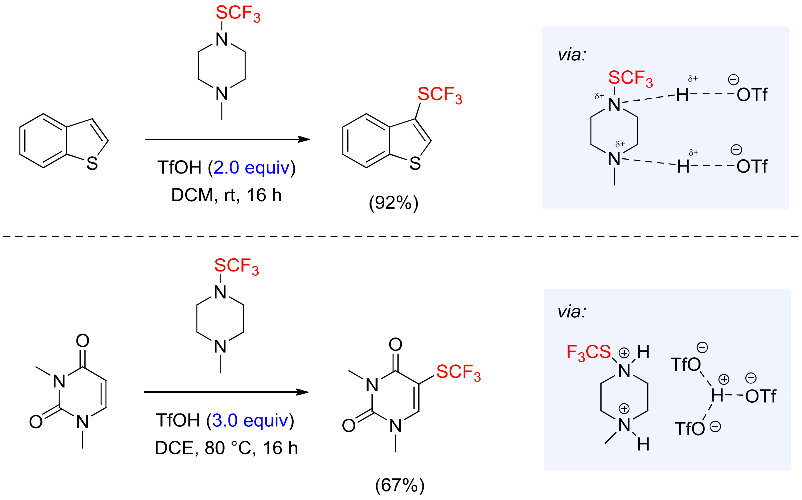
Scheme 70. Cinchona-catalyzed trifluoromethylthiolation of 4-substituted pyrazolones.

In the context of the preparation of enantioenriched heterocyclic molecules, a different approach based on chirality-transfer from optically pure trifluoromethylthiolating agent was demonstrated by the Shen group.[99] These authors developed a family of enantiopure *N*-(CF_3S)-2,10-camphorsultam-derived reagents, of which 7,7-dimethoxy analogue depicted in Scheme 71 was shown to be effective in asymmetric trifluoromethylsulfanylation of prochiral nucleophiles, including heterocyclic derivatives such as oxindoles and benzofuran-2(3*H*)-ones.



Scheme 71. Asymmetric trifluoromethylthiolations of oxindoles and benzofuran-2(3*H*)-ones using chiral 2,10-camphorsultam-derived CF_3S-transfering reagent.

In 2024, Hammond reported on another electrophilic trifluoromethylthiolating reagent, based on an *N*-methylpiperazine framework, featuring sufficient reactivity to enable the CF_3S-functionalization of electron-deficient (hetero)aromatic substrates when activated with excess TfOH.[100] Selected benzo-fused heterocycles were examined to give the respective products under the standard reaction conditions (room temperature, 16h, 2.0 equiv. TfOH), whereas low temperature-controlled reaction (–50 °C) of bithiophene enabled highly selective mono-functionalization (Scheme 72). Notably, the use of a threefold excess of TfOH proved efficient in trifluoromethylthiolation of electron-poor 1,3-dimethyluracil in the reaction involving the postulated more reactive dicationic species.



Scheme 72. Different modes of activation in TfOH-mediated trifluoromethylthiolation of heterocycles with *N*-methyl-*N'*-(CF_3S)-piperazine.

Introduction of two $PhSO_2$ groups onto the N−SCF_3 unit in *N*-trifluoromethylthio-dibenzenesulfonimide by Shen resulted in a remarkable enhancement of the electrophilic character of this CF_3S-transfering agent, which was successfully applied in reactions with variety of nucleophiles, including alkenes.[101] The '***super-electrophilic***' trifluoromethylthiolating ability of the designed molecule, remarkably higher in comparison to other structurally related N−SCF_3 agents (and even to CF_3SCl), was pictured by the theoretical calculation of the Tt^+DA value (trifluoromethylthiol-cation donating ability) of 9.8 kcal mol^{-1} (Figure 2).[102] Indeed, it smoothly reacts with a wide range of electron-rich (hetero)arenes as well as electron-poor activated heteroarenes, under mild conditions, in the absence of any additives (Scheme 73). In certain cases of electron-rich substrates (e.g. 2,6-dimethoxypyridine), a second direct C−H functionalization was also observed to give a mixture of mono- and di-trifluoromethylthiolated products.

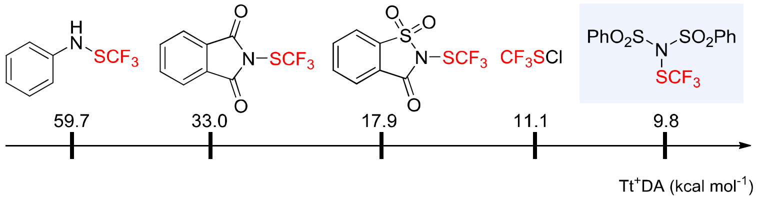
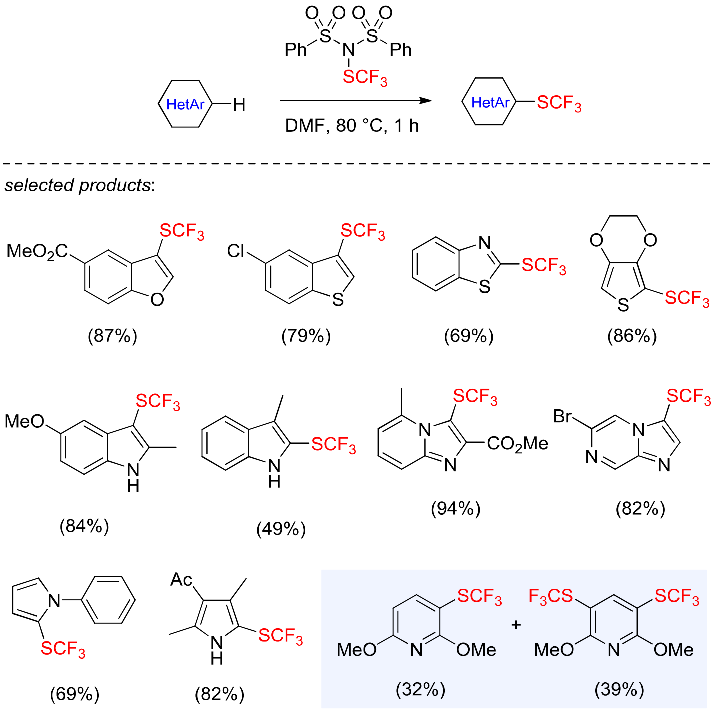


Fig. 2. Tt$^+$DA parameters of selected electrophilic trifluoromethylthiolating agents.



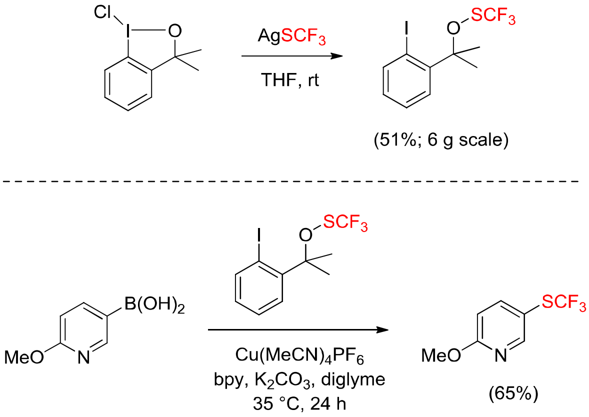
Scheme 73. Additive-free Friedel-Crafts-type trifluoromethylthiolation of heteroaryl substrates with $(PhSO_2)_2NSCF_3$.

Further applications of Shen's *N*-trifluoromethylthio-dibenzenesulfonimide in the chemistry of heterocyclic systems include visible-light-photocatalyzed decarboxylative CF_3S-functionalization,[103] organocatalytic enantioselective trifluoromethylthiolating lactonizations of 4-arylbut-3-enoic acids,[104] Cp*Co(III)-catalyzed directed C−H trifluoromethylthiolations of 2-

phenylpyridines and 6-arylpurines,[105] and highly selective functionalizations of analogues of naturally occurring macrocyclic systems such as bacteriochlorophyll-*c*.[106]

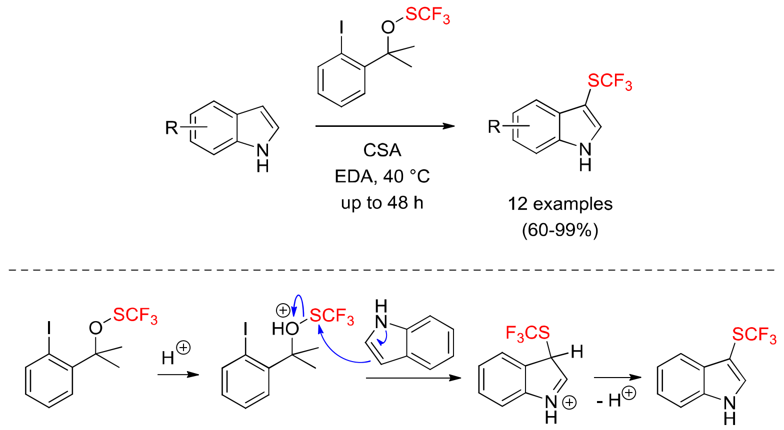
2.2.5. Applications of O−SCF$_3$ reagents

In search for new trifluoromethylthiolating reagents, the Shen group turned attention to the well-established concept of hypervalent iodine compounds in organofluorine chemistry. Inspired by Togni's seminal work on electrophilic trifluoromethylation agents, they reported a structurally analogous CF$_3$S-reagent based on a benziodoxole framework, and demonstrated its high reactivity in C−H functionalizations of terminal acetylenes and β-ketoesters, as well as in cross-couplings with (hetero)arylboronic acids.[107] Two heteroaromatic products, 6-methoxy-3-trifluoromethylsulfanylpyridine (65%; Scheme 74) and 3-trifluoromethylsulfanyl-quinoline (40%), were obtained under Cu(II)-catalyzed conditions. The correct structure of the so-called Lu-Shen reagent as a thioperoxy compound was established in 2015 based on derivatization experiments supplemented by crystalline sponge X-ray analysis.[108]



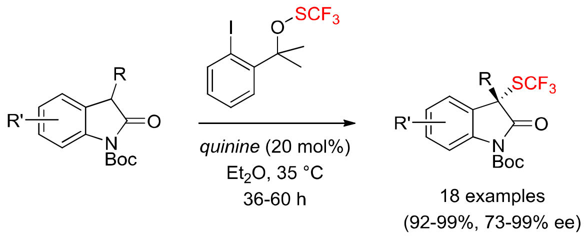
Scheme 74. Synthesis of Lu-Shen reagent and its application in cross-coupling reactions with heteroaryl boronic acids.

Further developments in this group on functionalization of heteroaromatic compounds proved the Lu-Shen reagent effective in C(3)-trifluoromethylthiolation of indoles (Scheme 75).[109] The optimization studies revealed camphorsulfonic acid (CSA) as an optimal Brønsted acid to catalyze the designed transformation, rather than transition-metal catalysts such as Cu(I), Cu(II), and Fe(III) salts. Based on experimental results, protonation of the oxygen atom in the trifluoromethylthiolating agent, thereby generating a reactive oxonium intermediate highly susceptible to nucleophilic attack by the indole nucleus, was proposed. Final deprotonation furnishes the re-aromatized 3-CF_3S-product.



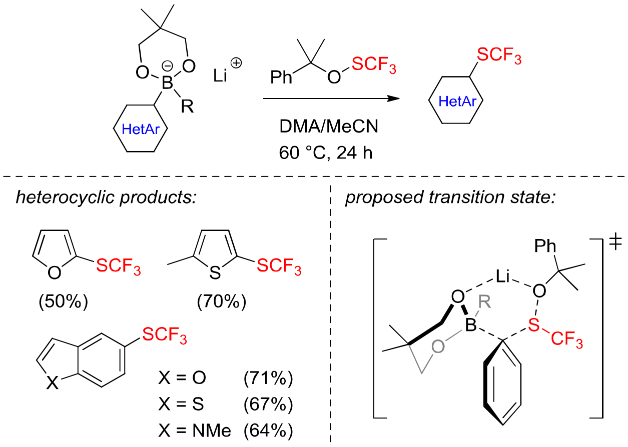
Scheme 75. Application of Lu-Shen reagent in Brønsted acid-mediated synthesis of 3CF_3S-indoles.

The same group reported on enantioselective 3-trifluoromethylthiolation of 3-aryl/alkyl-oxindoles using trifluoromethyl thioperoxide as the electrophilic CF_3S-reagent and quinine as organocatalyst.[110] A series of optically active products bearing the SCF_3 substituent at the newly generated stereogenic quaternary center was obtained in excellent yields and good enantioselectivities of up to 99% ee (Scheme 76). Shortly thereafter, the authors examined a series of structurally related electrophilic trifluoromethanesulfenates (RO−SCF_3 reagents) in selected model reactions including trifluoromethylthiolations of indoles and oxindoles.[111] A structure-reactivity relationship study revealed little impact of the aryl ring substituents on the overall reactivity.



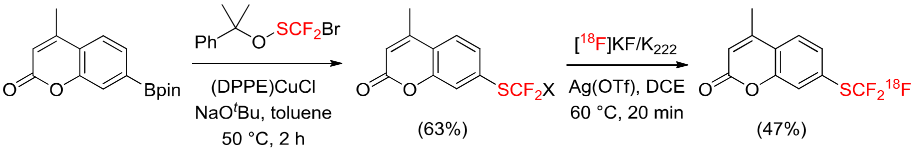
Scheme 76. Quinine-catalyzed asymmetric trifluoromethylthiolation of oxindoles with Lu-Shen reagent.

Despite remarkable interest in the chemistry of RO−SCF_3 reagents in electrophilic trifluoromethylthiolation reactions in recent years,[112] their applications in F_3CS-transfer into heterocyclic scaffolds have been explored to only a limited extent. Single examples of trifluromethylthiolated furan, thiophene, and selected benzo-fused heterocycles prepared through *ipso*-trifluoromethylthiolation of the respective lithium heteroaryl boronates were presented (Scheme 77). Based on DFT calculations, the key role of the Li^+ cation coordinating the oxygen atom of the boronate complex and the oxygen atom of the CF_3S-donor in the transition state, allowing the direct attack of the trifluoromethylthiol group onto the (hetero)aromatic ring, is proposed.[112]



Scheme 77. Trifluoromethylthiolation of lithium (hetero)aryl boronates via *ipso*-substitution and the proposed transition state.

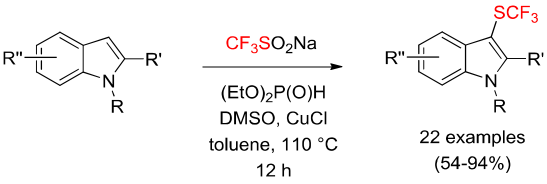
An interesting two-step approach toward ^{18}F-labeled F_3CS-functionalized products comprising copper-catalyzed electrophilic bromodifluoromethylthiolation followed by silver-mediated Br → ^{18}F halogen exchange was developed by Gouverneur and Shen (Scheme 78).[113] Several heterocycles such as quinoline, coumarin, and benzopyran derivatives have been accessed by this method.



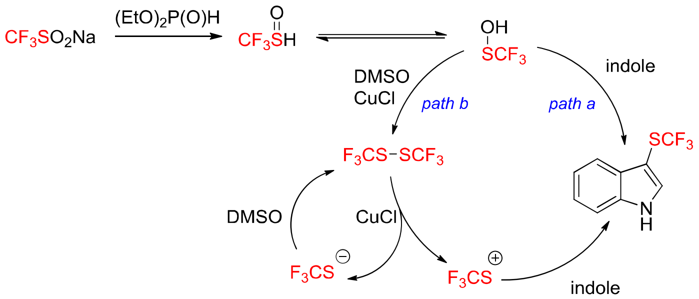
Scheme 78. Two-step synthesis of ^{18}F-labeled 3-methyl-7-trifluoromethylsulfanylcoumarine.

2.2.6. Applications of CF_3SO_n–R derivatives

Sulfonates, previously discussed in the context of trifluoromethylations of heterocyclic thiols (Section 2.1.1.), have also found applications in direct CF_3S-transfer reactions. In this group of chemicals, Langlois' reagent (sodium trifluoromethanesulfinate) remains the most widely applied. For example, Zhang and Yi investigated its application in Cu(I)-mediated trifluoromethylthiolation of indole (22 examples, 54-94%) and pyrrole (3 examples, 84-90%) derivatives, as well as enamines (Scheme 79).[114] The method comprises of the *in situ* generation of bis(trifluoromethyl) disulfide (CF_3SSCF_3) which in the presence of a copper catalyst serves as a source of CF_3S^+ cation intermediate. The reaction is initiated by reduction of CF_3SO_2Na with $(EtO)_2P(O)H$ to give a transient species that tautomerizes to an unstable sulfenol (CF_3S-OH). Reaction then proceeds via two competitive pathways, *i.e.* through less efficient release of the CF_3S^+ from CF_3SOH (*path a*), and through DMSO-assisted reduction of CF_3SOH to give disulfide, which also liberates the CF_3S^+ cation (*path b*) (Scheme 80). The resulting CF_3S^- anion is subsequently oxidized by DMSO to give disulfide. Thus, the CuCl plays the role of both a reducing agent for CF_3SOH, and a catalyst for disulfide activation.

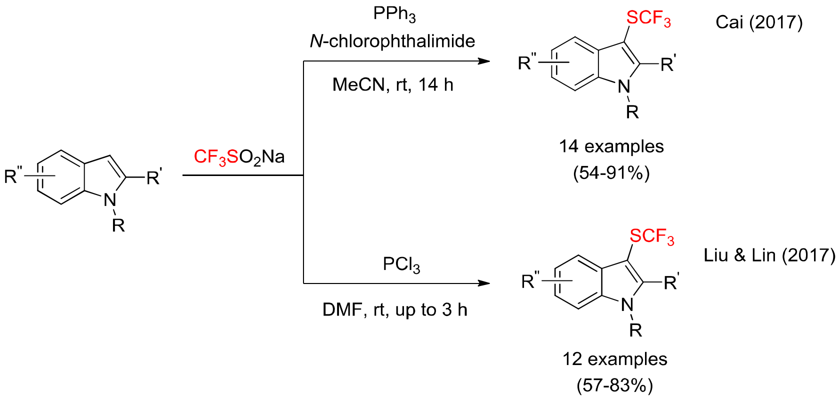


Scheme 79. Cu/DMSO-mediated direct trifluoromethylthiolation of indoles with Langlois' agent.



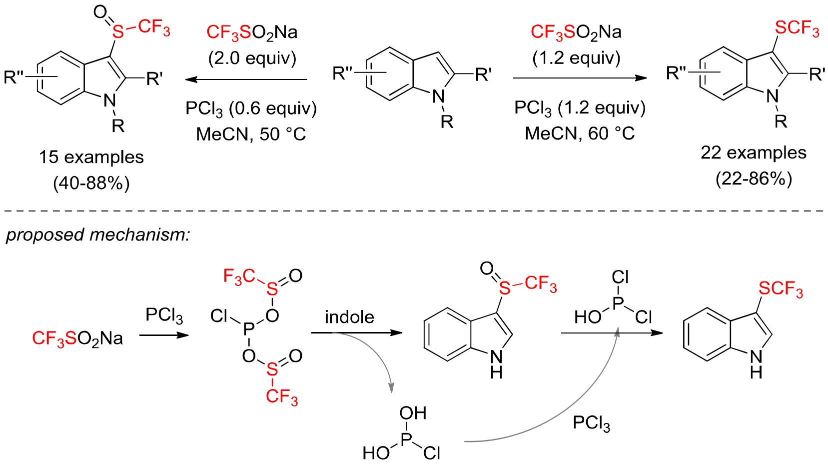
Scheme 80. Proposed mechanism for trifluoromethylthiolation of indole with CF_3SO_2Na.

In the following years, several groups independently extended the scope of Langlois' reagent in transition-metal-free direct trifluoromethylthiolation of indole derivatives. Cai and co-workers developed a metal-free variant employing triphenylphosphine and *N*-chlorophthalimide as a source of chloride anion, very likely generating reactive CF_3SCl *in situ*,[115] whereas Liu and Lin reported a related transformation using PCl_3 (Scheme 81).[116] In the latter approach, ^{19}F NMR analyses confirmed the intermediacy of CF_3SCl and $CF_3S(O)Cl$.



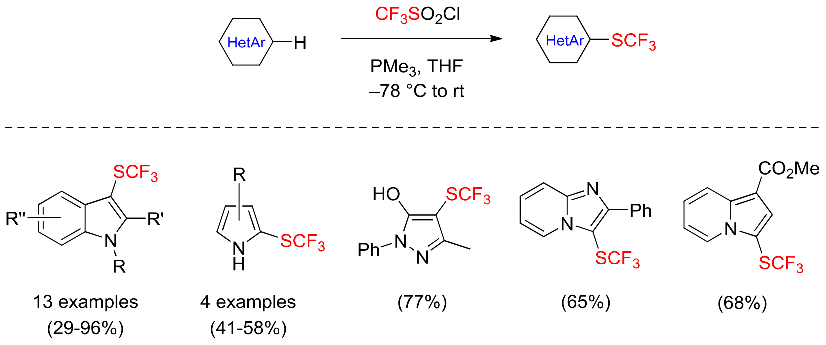
Scheme 81. Trifluoromethylthiolation protocols by the Cai (2017) and Lin (2017) groups.

In a separate study, Lu and Zhao reported on direct trifluoromethylthiolation and trifluoromethylsulfoxidation ($CF_3S(O)$-functionalization) reactions of indole derivatives, under comparable conditions using PCl_3 as both reducing and chlorination reagent.[117] The authors demonstrated that the product distribution, *i.e.* trifluoromethylthiolated compound versus the respective sulfoxide, depends critically on the amounts of reagents (CF_3SO_2Na, phosphorus trichloride), and the reaction temperature. Hence, the introduction of the CF_3S group proceeded efficiently using excess PCl_3 (1.2 equiv.), at slightly elevated temperature (60 °C), while using lesser amounts of PCl_3 (0.6 equiv.) enables stopping the reaction at the initially formed sulfoxide (Scheme 82).



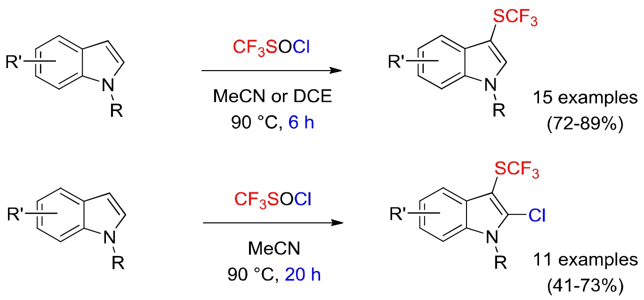
Scheme 82. Trifluoromethylthiolation vs. trifluoromethylsulfoxidation of indoles with CF_3SO_2Na/PCl_3.

As an alternative, more reactive trifluoromethanesulfonyl chloride can also be applied for direct trifluoromethylthiolations of electron-rich heterocycles. Cahard and Shibata utilized this reagent in deoxygenative sulfenylations of indoles, with trimethylphosphine serving as a reducing agent for the *in situ*-generation of CF_3SCl (Scheme 83).[118] Not surprisingly, introduction of an electron-withdrawing group into the indole rings remarkably decelerated the reaction e.g. trifluoromethylthiolation of indole provided the expected 3-CF_3S-product in 85% yield after six hours, whereas the reaction of 5-nitroindole was completed within 96 hours to give the respective product in 65% yield. The developed methodology was also examined in direct functionalization of such nitrogen heterocycles as pyrroles, indolizines, imidazo[1,2-*a*]pyridines, and pyrazoles. Zhao and co-workers adapted a similar approach, using triphenylphosphine as an activator, to broaden the scope to activated (poly)functionalized pyrroles and indolizines bearing at least one electron-withdrawing group such as cyano, acyl or ester.[119]



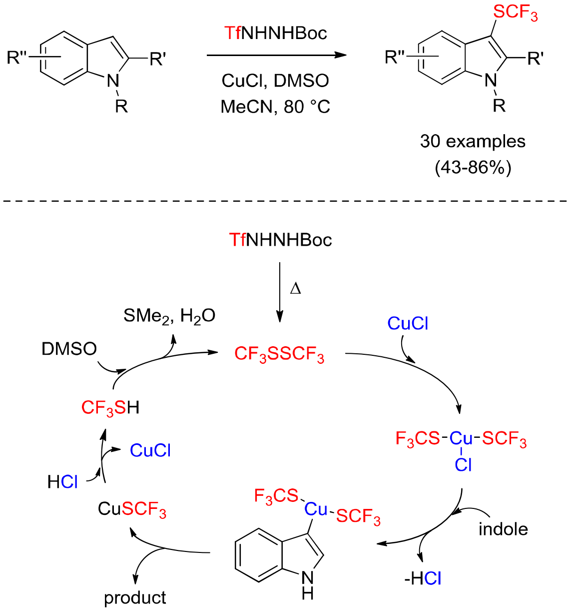
Scheme 83. Trifluoromethylthiolation of indoles with CF_3SO_2Cl/PMe_3.

Similarly, Yi and Zhang demonstrated that sulfinyl chloride (CF_3SOCl) can also act as the source of the electrophilic trifluoromethylthio group in C−H trifluoromethylthiolation of electron-rich N-heterocycles, under catalyst-free conditions and in the absence of reducing agents, by running the reaction at elevated temperatures (Scheme 84).[120] The initial disproportionation of the starting trifluoromethylthiolating reagent to give CF_3SCl and CF_3SO_2Cl is followed by two pathways, i.e. direct Friedel-Crafts-type substitution with CF_3SCl or trifluoromethylsufoxidation and subsequent reduction of the $CF_3S(O)$-group with excess CF_3SOCl. A series of C(3)- and C(2)-trifluoromethylthiolated indoles and thiophenes, respectively, were prepared by this method. Interestingly, by increasing the reaction time from six to twenty hours, 2-chloro-3-trifluoromethylthio-substituted indoles were obtained as major products, indicating CF_3SOCl as a convenient reagent for bifunctionalization (chlorotrifluoromethyl-thiolation) (Scheme 84).



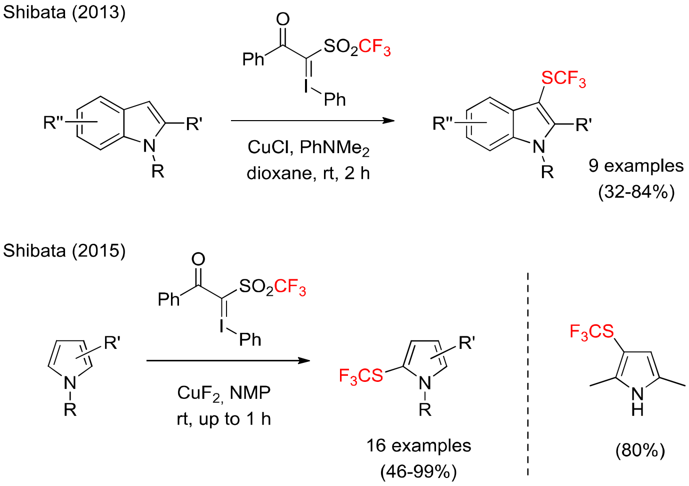
Scheme 84. Reaction-time dependent mono- and bi-functionalization of indoles with CF_3SOCl.

Hydrazides derived from trifluoromethanesulfonic acid have also been employed as effective CF_3S sources in regioselective Cu(I)-catalyzed oxidative trifluoromethylthiolation of structurally diverse indoles (Scheme 85).[121] As the early stage of this reaction, TfNHNHBoc undergoes redox decomposition to *in situ*-generate bistrifluoromethyl disulfide (CF_3SSCF_3). Subsequent oxidative addition of the latter to CuCl leads to a copper(III) intermediate, which is attacked by the nucleophilic indole. Further transformations include reductive elimination leading to product, anion exchange in $CuSCF_3$ and DMSO-mediated oxidation of DMSO regenerate the CuCl catalyst and close the catalytic cycle.



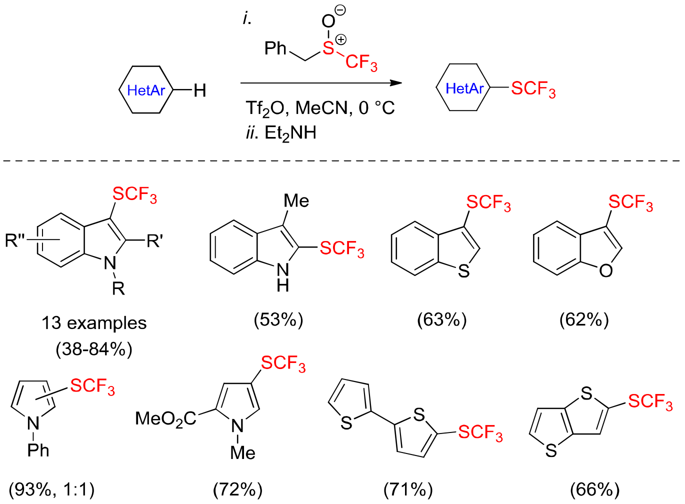
Scheme 85. Proposed mechanism for CF_3S-functionalisation of indoles with TfNHNHBoc under Cu-catalysis, in DMSO.

A different class of electrophilic trifluoromethanesulfonyl reagents incorporating a hypervalent iodine ylide unit, suitable for trifluoromethylthiolation of various nucleophiles under CuCl catalysis, in the presence of *N*,*N*-dimethylaniline, was developed in 2013 by the Shibata group.[122] Beside numerous products derived from enamines and β-keto esters, a series of nine indol-3-yl trifluoromethyl sulfides was prepared in moderate to good yields (Scheme 86). Two potential mechanistic paths involving either copper carbenoid or (more likely) zwitterionic intermediates were discussed by the authors. When CuF_2 and *N*-methylpyrrolidone were employed as a catalyst and solvent, respectively, the same reagent enabled fully regioselective 2-trifluoromethylthiolation of pyrroles.[123] Only in the case of the 2,5-disubstituted substrate (2,5-dimethylpyrrole) was C(3)–H functionalization observed.

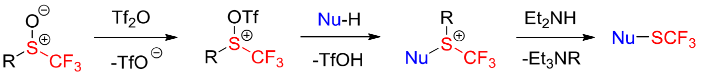


Scheme 86. Application of Shibata's sulfonium hypervalent iodine ylide in mild trifluoromethylthiolation of nitrogen hetarenes.

In 2020, Procter and co-workers reported the use of trifluoromethyl sulfoxides, activated by trifluoromethanesulfonic anhydride, as efficient electrophilic reagents for the trifluoromethylthiolation of a broad range of heterocycles, providing access to structurally diverse CF_3S-substituted frameworks (Scheme 87).[124] A series of CF_3S-functionalized products derived from electron-rich (hetero)arenes were prepared in moderate to high yield, under mild conditions, without any metal-catalyst. In addition, successful CF_3S-functionalization of selected drugs (*dextromethorphan*) and agrochemicals (*pyriproxyfen*) demonstrated robustness and potential practical utility of the developed method in late-stage functionalization of bioactive molecules. In this process, the starting sulfoxide is activated through reaction with Tf_2O to give an electrophilic intermediate, which undergoes the so-called interrupted Pummerer reaction with nucleophiles such as heteroarenes to give a sulfonium salt. Subsequent selective removal of the R substituent by Et_2NH furnish the trifluoromethylthiolated product (Scheme 88).

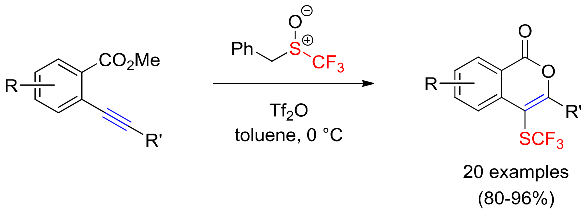


Scheme 87. C–H Trifluoromethylthiolation of heteroaryls with benzyl trifluoromethyl sulfoxide.



Scheme 88. Proposed mechanism for Procter's trifluoromethylthiolations with CF_3-sulfoxide through interrupted Pummerer reaction.

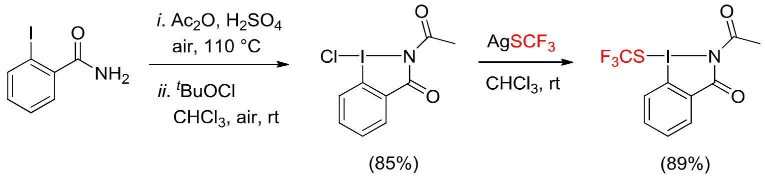
Prompted by Procter's work, Yang and Du developed a synthesis of biologically interesting 4-CF_3S-isocoumarins starting with 2-alkynylbenzoates.[125] The reaction is comprised of *in situ*-generation of electrophilic CF_3S^+ species via interrupted Pummerer reaction, followed by a concerted lactonization and trifluoromethylthiolation process. A series of desired products was obtained in high yields of up to 96% (Scheme 89).



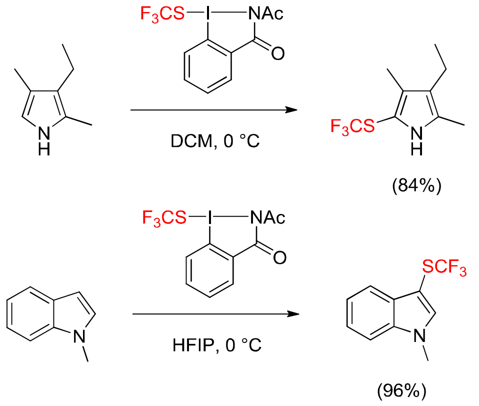
Scheme 89. Access to 4-CF₃S-isocoumarins through tandem trifluoromethylthiolation/lactonization.

2.2.7. Miscellaneous

An exceptional example of a hypervalent iodine-based trifluoromethylthiolating reagent (I–SCF_3) was accessed in a three-step sequence with the final halogen/SCF_3 exchange in a suitable precursor based on the *N*-acetylbenziodazole skeleton (Scheme 90).[126] As demonstrated by DFT analysis, introduction of an acetyl group assured sufficient stability of the product through secondary bonding interactions between the λ³-iodine atom and the C=O group, supplemented by mutual ligand interference. The designed compound exhibits powerful electrophilic trifluoromethylthiolating properties as indicated by computed Tt^+DA value of 10.1 kcal mol^{-1}, which is comparable to Shen's *N*-trifluoromethylthio-dibenzenesulfonimide (Tt^+DA = 9.8 kcal mol^{-1}), and evidenced in a series of direct CF_3S-functionalizations of nucleophiles, including electron-rich arenes, CH-acidic β-dicarbonyl compounds, amines and enamines, thiols and arylselenols, sodium bezenesulfinate, and aryl boronic acids. Trifluoromethylthiolation of two selected heteroarenes, namely 3-ethyl-2,4-dimethylpyrrole and 1-methylindole, provided the expected products in 84% and 96% yield, respectively (Scheme 91). In the latter case, 1,1,1,3,3,3-hexafluro-2-propanol (HFIP) was used as solvent to activate the CF_3S-agent via a hydrogen bonding mode.

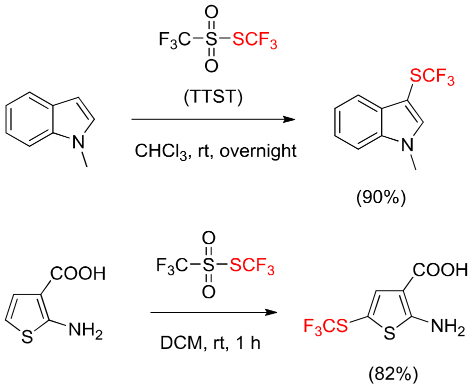


Scheme 90. Synthesis of Zhang's hypervalent trifluoromethylthioiodine(III) reagent.



Scheme 91. Direct functionalization of pyrrole and indole derivatives using Zhang's agent.

In 2023, another atom-economical and bench-stable, yet highly reactive and versatile S-centered trifluoromethylthiolating reagent (S–SCF_3), *S*-trifluoromethyl trifluoromethanesulfonothioate (TTST), was reported by Umemoto and Hammond.[127] This reagent can be readily prepared by simple portion-wise addition of Tf_2O to Langlois' reagent (CF_3SO_2Na), and isolated by direct distillation at atmospheric pressure. In contrast to previously reported CF_3S-donors, depending on the reaction conditions, the devised reagent ($CF_3SO_2SCF_3$) can generate one equivalent of electrophilic CF_3S^+, two equivalents of nucleophilic CF_3S^-, or a mixture of radical species $CF_3S^\bullet$ and $^\bullet CF_3$. As shown in Scheme 92, efficient functionalization of heteroarenes with TTST through direct electrophilic trifluoromethylthiolation, under mild conditions, was demonstrated using 1-methylindole and 2-aminothiophene-3-carboxylic acid.



Scheme 92. Electrophilic CF_3S-functionalization of selected heteroarenes with TTST.

3. Summary

Over the past five decades, methods for introducing CF_3S groups into heterocyclic rings have undergone substantial evolution, although the conceptual foundations have remained largely unchanged. These approaches can generally be divided into two categories. The first is an indirect route, in which sulfur-containing heterocycles such us thiols, but also disulfides and isothiocyanates, serve as substrates and subsequently react with appropriate CF_3-transfering reagent ($CS{-}CF_3$ bond formations). The second involves direct trifluoromethylthiolation of the heterocyclic core ($C{-}SCF_3$ bond formations).

As to the sulfur-containing heterocycles, classification of the methodology depends primarily on the nature of the sulfur substituent. Regardless of the precursor type, the underlying principles of *S*-trifluoromethylations remain fundamentally similar. Historically, the use of trifluoromethyl halides has declined due to their toxicity and environmental impact, particularly ozone depletion. These reagents have been replaced by milder and more practical alternatives, such as Langlois' reagent, Umemoto reagents, and the Togni family of hypervalent iodine reagents.

Direct C−H trifluoromethylthiolation strategies are highly dependent on the choice of the CF_3S-donor. The initially developed toxic and difficult to handle halogen-based trifluoromethylthiolating agents ($CF_3S{-}X$) have been largely replaced by imide-type ($CF_3S{-}N$) chemicals, which offer improved stability and selectivity, yet remarkable reactivity toward nucleophiles, including electron-rich (hetero)arenes.

On the other hand, metal trifluoromethylthiolates, particularly silver and copper salts, continue to serve as convenient nucleophilic sources of the CF_3S anion. In addition, Langlois' reagent has found broad application in direct trifluoromethylthiolation protocols through the *in situ*-generation of electrophilic CF_3S species under mild reaction conditions.

In summary, the synthesis of trifluoromethylthiolated heterocycles has attracted increasing attention over the past two decades, both via indirect and direct methodologies. Despite the extensive repertoire of methods available to date, there is continued interest in developments of heterocyclic trifluoromethylthiolation as a key research area within organofluorine chemistry.

Acknowledgements

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Note

One-Pot Telescoping *S*-Transfer and Trifluoromethylation for the Synthesis of 2-CF_3S-Imidazoles with *N*-Oxides as Convenient Precursors

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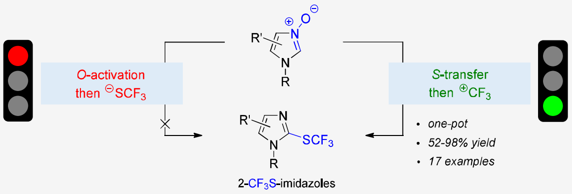
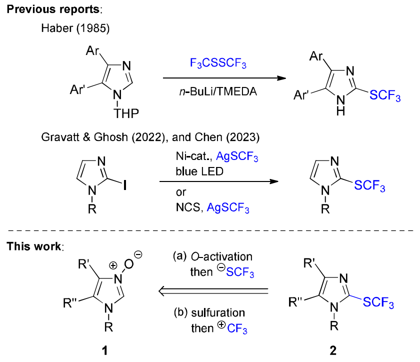


ABSTRACT: Readily available 2-unsubstituted imidazole *N*-oxides were examined as starting materials for the preparation of fully substituted 1,4,5-aryl/alkyl 2-trifluoromethylsulfanyl-imidazoles. Whereas activation of the *N*-oxide function followed by attempted nucleophilic addition of the $^{-}SCF_3$ was in vain, the alternative approach involving "sulfur transfer reaction" and subsequent electrophilic trifluoromethylation with Togni reagent provided target products in high yield via a one-pot procedure. The structure of representative enantiomerically pure imidazol-2-yl trifluoromethyl sulfide was confirmed by X-ray analysis.

Introduction of fluoroalkyl substituent(s) into organic molecules remarkably tunes their physio-chemical and biological behavior.[1] In this context, the SCF_3 group characterized by the highest Hansch parameter (π = 1.44) has attracted special attention due to its extraordinary lipophilicity and highly electron-withdrawing character.[2] Consequently, numerous methods have been developed for the synthesis of compounds functionalized with the trifluoromethylthiol unit,[3] and various heterocyclic systems of significance as new agrochemicals, medicinal targets, and functional materials are known.[4]

Despite enormous interest in manifold *N*-heterocycles decorated with a trifluoromethylthiol group, the title 2-CF_3S-imidazoles are known only to a limited extent (Scheme 1). In early work by Haber, highly toxic bis(trifluoromethyl) disulfide was applied as trifluoromethylthiolating agent in reactions with *N*-(tetrahydropyran-2-yl)-masked 4,5-diaryl-imidazoles, by using organyllithiums as a base.[5] More recently, Gravatt and Ghosh disclosed elegant photoredox Ni-catalyzed trifluoromethylthiolation protocol employing (hetero)aryl iodides and $AgSCF_3$, and the method was successfully applied for the reaction with 2-iodo-1-methylimidazole (R = Me).[6] In a similar NCS-mediated approach, Chen and co-workers accessed 2-CF_3S-1-phenylimidazole (R = Ph), which was further applied as an efficient agent for the dehydroxytrifluoromethylthiolation of alcohols.[7] In addition, synthesis and phase-transfer catalytic properties of some 1,3-dialkylimidazo-

Scheme 1. Reported Syntheses of 2-CF_3S-Imidazoles and the Approaches Examined Herein



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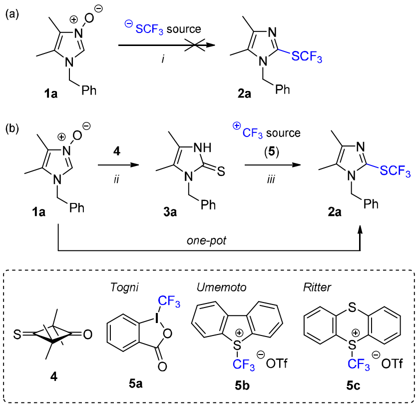
lium salts bearing the CF_3S group have also been documented.[8] Finally, two syntheses of a model 1-methyl-2-CF_3S-benzimidazole through (i) photocatalytic trifluoromethylation of 1-methyl-benzimidazole-2-thiol with CF_3I and (ii) Cu-mediated trifluoromethylthiolation of the respective bromide are known.[9] However, neither of the mentioned works reported on the synthesis of fully substituted imidazole derivatives nor exploited imidazole *N*-oxides as key building blocks.

In continuation of our study aimed at the development of convenient synthetic methods toward fluoroalkylated azoles,[10] we turned our attention to readily available aldonitrone-like imidazole *N*-oxides **1** recognized as superior building blocks for C(2)-functionalization of the imidazole ring.[11] Thus, both nucleophilic trifluoromethylthiolation at the C(2) preceded by *O*-activation of the *N*-oxide function (route a) as well as an indirect pathway comprising the sulfuration/*S*-trifluoromethylation reaction sequence (route b) should be examined (Scheme 1). Here, we report a simple and efficient method for the preparation of fully substituted 2-CF_3S-imidazoles of type **2** via the latter, two-step one-pot protocol.

For the initial experiments, 1-benzyl-4,5-dimethylimidazole *N*-oxide (**1a**), readily available by condensation of diacetyl monoxime and *N*-benzylformaldimine,[12] was selected as the model starting material. Prompted by the seminal work of Kuninobu on direct trifluoromethylthiolation of some six-membered *N*-oxides with $AgSCF_3$,[13] imidazole derivative **1a** was first checked under the analogous reaction conditions, but no desired product **2a** could be detected in the crude mixture (Scheme 2a). Brief screening of the reaction conditions with respect to solvents (DCM, EtOAc, and DMF) and activating agents (TsCl, 2,4-dinitrobenzenesulfonyl chloride, and 1-adamantanecarbonyl chloride) revealed insufficient electrophilic character of the activated imidazole *N*-oxide to trap the SCF_3 anion, and in all of the attempts, unreacted **1a** along with small amounts of the parent heterocycle, that is, 1-benzyl-4,5-dimethylimidazole, were identified in mother liquors.

Scheme 2. Initial Experiments with Imidazole *N*-Oxide 1a[a]



[a]Reagents and conditions: (i) 2,4-$(NO_2)_2C_6H_3SO_2Cl$ (1.1 equiv), $AgSCF_3$ (1.1 equiv), MeCN, rt, overnight; (ii) thione **4** (1.1 equiv), DCM, rt, 2 h, 95% yield; and (iii) **5** (1.5 equiv); for solvent, temperature, and the additives used, see Table 1.

Next, we turned attention to an alternative two-step approach through electrophilic trifluoromethylation of enolizable imidazole-2-thione **3a** as a key intermediate (Scheme 2b). The requisite **3a** was prepared in 95% yield via a known sulfur-transfer method based on sequential (3 + 2)-cycloaddition/cycloreversion reactions of 2-unsubstituted imidazole *N*-oxide **1a** with strained thiocarbonyl agents such as 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**).[12] With a model imidazole-2-thione **3a** in hand, three selected reagents **5a**–**5c**, recommended for electrophilic trifluoromethylations of the thiol group,[14] were checked as reaction partners under mild, neutral conditions (DCM, rt), to provide the target 2-CF_3S-imidazole derivative **2a** in 36% and 25% yields by using Togni (**5a**) and Umemoto (**5b**) reagents, respectively (Table 1, entries 1–2; for the complete optimization table, see the Supporting Information). Taking into account the observed yields and the formation of a rather complex mixture in the latter case, the optimization was continued with Togni reagent.

Table 1. Trifluoromethylation of Imidazole-2-thione 3a[a]

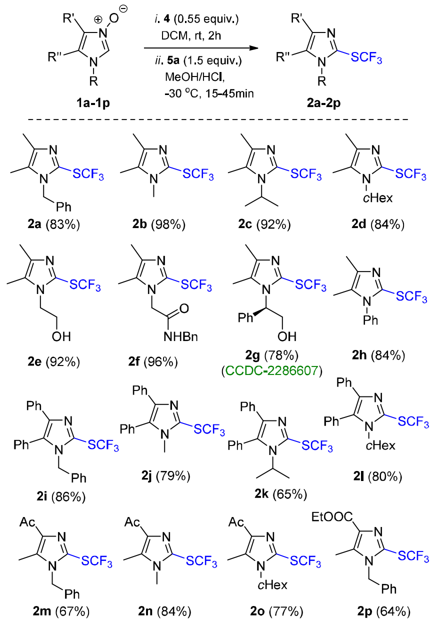
entry	reagent	additive	solvent	temp	yield
1	**5a**		DCM	rt	36
2	**5b**		DCM	rt	25
3	**5c**		DCM	rt	0
4	**5a**		MeCN	rt	28
5	**5a**	TsOH (cat.)	DCM	rt	40
6	**5a**	HCl (cat.)	DCM	rt	44
7	**5a**	HCl (excess)	MeOH	rt	67
8	**5a**	HCl (excess)	MeOH	0 °C	72
9	**5a**	HCl (excess)	MeOH	−30 °C	91
10	**5a**	HCl (excess)	MeOH	−30 °C	83[b]

[a]Reaction conditions: **3a** (0.5 mmol), **5** (0.75 mmol), solvent (5.0 mL), 15 min, inert atmosphere (Ar). Isolated yield of **2a**. [b]One-pot reaction starting from *N*-oxide **1a** (0.5 mmol): thione **4** (0.55 mmol), DCM, rt, 2 h, then **5a** (0.75 mmol), MeOH/HCl, −30 °C, 15 min.

Further analysis of the reaction parameters and the role of additives indicated the beneficial presence of Brønsted acids (entries 5–7),[15] at low temperatures (entries 8–9), and by using dry MeOH saturated with HCl as the reaction medium, at −30 °C, the final product **2a** was obtained in an excellent yield of 91% (entry 9). Furthermore, the one-pot protocol starting with *N*-oxide **1a** was also checked, and, in that case, the first formed crude imidazole-2-thione **3a** was subsequently applied for the optimized trifluoromethylation step to afford **2a** in high 83% overall yield (for two steps; entry 10) after standard chromatographic purification on neutral alumina.

With the optimized conditions in hand, a series of imidazole *N*-oxides **1a**–**1p** was examined to check the scope of the devised one-pot protocol (Scheme 3). In all of the cases, the expected products **2a**–**2p** were obtained in high yield (64–98%) irrespective of the nature of the substituents and functional groups present in the starting material. Thus, (cyclo)alkyl and aryl substituents located at either N(1) or C(4)/C(5) positions of the imidazole ring (**2a**–**2d**, **2h**–**2l**) as well as hydroxy (**2e**), ketone (**2m**–**2o**), ester (**2p**), and amide (**2f**) groups were tolerated, leading to desired products in a fully chemoselective manner. Notably, no epimerization was observed under the applied conditions in reaction with enantiomerically pure imidazole *N*-oxide **1g** bearing a

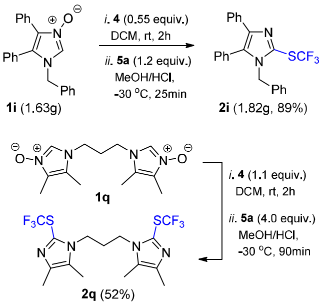
Scheme 3. Scope of Imidazole *N*-Oxides 1 in the One-Pot Synthesis of Imidazol-2-yl Trifluoromethyl Sulfides 2



stereogenic center at the benzylic position. The structure of final products was established based on suitable NMR analyses, supplemented with 2D measurements in certain cases. Particularly, the presence of two diagnostic quartets ($^1J_{C-F} \approx$ 312 Hz and $^3J_{C-F} \approx$ 3.0 Hz) located at δ = 128.0−128.4 and 125.5−129.7, respectively, in the ^{13}C NMR spectra of **2a**−**2p** confirmed the presence of the C(2)SCF$_3$ unit in the obtained series. In addition, in ^{19}F NMR spectra, singlet absorptions were found at the region typical for the trifluoromethylthiol group ($\delta \approx$ −45.0). Finally, single-crystal X-ray analysis of chiral *N*-(2-hydroxy-1-phenylethyl)-functionalized analogue **2g** unambiguously confirmed its molecular structure (see the Supporting Information).

In order to check whether the devised protocol can be applied for a larger scale, the synthesis of 2-CF$_3$S-imidazole **2i** was repeated starting with 1.63 g (5.0 mmol) of *N*-oxide **1i** (Scheme 4). Gratifyingly, the desired sulfide was obtained in comparable yield (1.82 g, 89%), despite a smaller excess (1.2 equiv) of trifluoromethylating agent **5a** used in this experiment. Furthermore, bis(imidazole *N*-oxide) **1q** was involved in the study; by using excesses of *S*-transferring agent **4** (0.55 equiv/*N*-oxide group) and **5a** (2.0 equiv/HS-group), the expected bis-trifluoromethylthiolated product **2q** was isolated in fair 52% yield.

Scheme 4. Gram-Scale Synthesis of 2i and Preparation of Bis-sulfide 2q



In summary, fully substituted 1,4,5-aryl/alkyl 2-trifluoromethylsulfanyl imidazoles in overall yields typically exceeding 80% through a two-step one-pot protocol are reported. The devised method based on sulfur-transfer followed by the electrophilic trifluoromethylation reaction sequence exploits readily available and cheap building blocks, that is, imidazole *N*-oxides, cyclobutanethione derivative, and Togni reagent, and it is characterized by excellent chemoselectivity as demonstrated in reactions with hydroxy-, ketone-, ester-, and amide-functionalized starting materials. The presented method can also be recommended for the synthesis of more complex imidazole systems, including chiral and bis-trifluoromethylthiolated analogues.

■ EXPERIMENTAL SECTION

General. All commercially available reagents and solvents were used as received. Products were purified by standard column chromatography (CC) on neutral alumina by using freshly distilled solvents. NMR spectra were taken at 600 MHz (^{1}H) and 151 MHz (^{13}C) and reported relative to the solvent residual peaks [CDCl$_3$: ^{1}H NMR, δ = 7.26; ^{13}C NMR, δ = 77.16] or at 565 MHz (^{19}F) and referenced to CFCl$_3$ (δ = 0.00) used as the external standard. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. IR spectra were taken with an Agilent Cary 630 FTIR spectrometer, in neat. ESI−MS was performed with a Varian 500-MS LC Ion Trap. Combustion analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a MEL-TEMP apparatus (Laboratory Devices), and they are uncorrected.

General Procedure for the Synthesis of Sulfides 2. To a solution of imidazole *N*-oxide **1** (0.5 mmol) in dry DCM (4.0 mL) was added dropwise a solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**, 86 mg, 0.55 mmol, 1.1 equiv) in DCM (3.0 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, the residue was dissolved in MeOH/HCl$_{(sat.)}$ (2.0 mL), cooled to −30 °C, and a solution of **5a** (237 mg, 0.75 mmol, 1.5 equiv) in MeOH/HCl$_{(sat.)}$ (3.0 mL) was added under an inert atmosphere. After the intermediate imidazole-2-thione **3** was fully consumed (TLC monitoring, typically 15−30 min), solvents were removed in vacuo, and the product **2** was purified by column chromatography (CC) on neutral alumina.

1-Benzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1H-imidazole (2a). Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 119 mg (83%); mp 52−54 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.33−7.27 (m, 3H), 6.93−6.92 (m, 2H), 5.30 (s, 2H), 2.23 (s, 3H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 138.3, 136.0, 129.3, 129.1, 128.2 (q, $^1J_{C-F}$ = 312.2 Hz), 128.0, 126.5 (q, $^3J_{C-F}$ = 2.8 Hz), 126.1, 48.6, 13.1, 9.9. ^{19}F NMR (565 MHz, CDCl$_3$): δ −47.2 (s, CF$_3$). IR (neat): ν 3030, 2959, 2929, 1572, 1494, 1453, 1401, 1148, 1092 cm^{-1}. MS (ESI) *m*/*z*: 287.1 (100, [M + H]$^+$). Anal. Calcd for $C_{13}H_{13}F_3N_2S$: C, 54.53; H, 4.58; N, 9.78; S, 11.20. Found: C, 54.48; H, 4.68; N, 9.60; S, 11.23.

■ 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.joc.4c01761.

Synthetic procedures, characterization data, and NMR spectra of all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**−**2q** (ZIP)

Accession Codes

CCDC 2286607 contains 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

The authors declare no competing financial interest.

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Supporting Information

for

One-pot telescoping *S*-transfer and trifluoromethylation for the synthesis of 2-CF_3S-imidazoles with *N*-oxides as convenient precursors

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Content

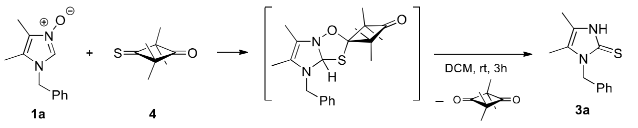
1. General information

Experimental procedures: Commercially available starting materials and solvents (DCM, MeOH) were used as received; if not stated otherwise, reactions were carried out under inert atmosphere of argon, in flame-dried flasks; subsequent manipulations were conducted in air. Products were purified by standard column chromatography (CC) on neutral alumina by using freshly distilled solvents as eluents or by recrystallization from appropriate solvents. Melting points were determined in capillaries with a MEL-TEMP II apparatus (Laboratory Devices), and are uncorrected. Optical rotations were determined with an Anton Paar MCP 500 polarimeter at the temperatures indicated. NMR spectra were measured on a Bruker Avance III or Bruker AvanceNeo instruments (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz); chemical shifts are reported relative to solvent residual peaks [for $CDCl_3$: ^{1}H NMR: $\delta = 7.26$, ^{13}C NMR: $\delta = 77.16$; for DMSO-d_6: ^{1}H NMR: $\delta = 2.50$, ^{13}C NMR: $\delta = 39.52$] or to $CFCl_3$ (^{19}F NMR: $\delta = 0.00$) used as external standard. Assignments and multiplicity of the signals in ^{13}C NMR spectra were deduced based on 2D measurements (HMQC). The IR spectra were taken with an Agilent Cary 630 FTIR spectrometer, in neat. ESI-MS were performed with a Varian 500-MS LC Ion Trap; high resolution MS (ESI-TOF) measurements were performed with a Synapt G2-Si mass spectrometer (Waters). Combustion analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument.

Starting materials: The starting imidazole *N*-oxides **1a**-**1q** were prepared following the literature protocols, through condensation of the corresponding formaldimines with α-hydroxyiminoketones, either using EtOH or glacial acetic acid as a solvent.[1] 2,2,4,4-Tetramethyl-3-thioxocyclobutanone (**4**) was prepared by thionation of the respective ketone with phosphorus pentasulfide.[2]

2. Synthetic procedures and characterization data

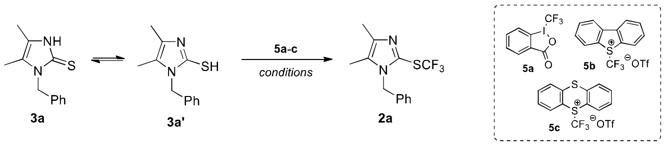
Synthesis of 1-benzyl-4,5-dimethylimidazole-2(3*H*)-thione (3a):[1a] To a solution of imidazole *N*-oxide **1a** (10.0 mmol, 2.00 g) in dry DCM (40 mL) was added dropwise a solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**, 11.0 mmol, 1.72 g, 1.1 equiv.) in DCM (20 mL) and the mixture was stirred at room temperature for 2h. After solvent was removed in vacuo, the resulting material was washed with hexane (4 x 50 mL) and the product was filtered off to give spectroscopically pure imidazole-2-thione **3a** (2.07 g, 95%) as a colorless solid. Mp 225-227 °C (Ref[1a]: Mp 227-228 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.81 (s_{br}, 1H), 7.33-7.30 (m, 2H), 7.28-7.24 (m, 3H), 5.29 (s, 2H), 2.07 (s, 3H), 1.91 (s, 3H).



Scheme S1. Synthesis of model imidazole-2(3*H*)-thione **3a** from the corresponding *N*-oxide **1a** via '*sulfur transfer reaction*' using 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**).

Synthesis of model sulfide 2a – optimization procedure: In round-bottomed flask equipped with a stirring bar a model imidazole-2-thione **3a** (0.5 mmol) was placed and the solvent (2.0 mL) was added. The flask was sealed with a septum under an atmosphere of argon, and cooled or heated, if necessary (see Table S1). Then additive and a solution of trifluoromethylating agent **5** (0.75 mmol, 1.5 equiv.) in a corresponding solvent (3.0 mL) were added to the reaction mixture, and the resulting was stirred for required time. After solvents were removed under reduced pressure the product **2a** was purified by column chromatography on neutral alumina.

Table S1. Synthesis of model trifluoromethyl-sulfide **2a**.



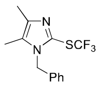
Entry	CF_3-reagent	additive	solvent	temp [°C]	time [min]	yield [%]
1	**5a**	-	DCM	rt	15	36
2	**5a**	-	DCM	rt	120	38
3	**5b**	-	DCM	rt	15	25
4	**5b**	-	DCM	rt	120	24
5	**5c**	-	DCM	rt	15	0
6	**5c**	-	DCM	rt	120	0
7	**5c**	Et_3N	DMF	40	15	0

8	**5a**	-	MeCN	rt	15	28
9	**5a**	TsOH (cat.)	DCM	rt	15	40
10	**5a**	TsOH (cat.)	DCM	0	15	44
11	**5a**	TsOH (cat.)	DCM	–30	15	48
12	**5a**	HCl (cat.)	DCM	rt	15	44
13	**5a**	HCl (cat.)	DCM	–30	15	52
14	**5a**	TsOH (cat.)	MeOH	–30	15	50
15	**5a**	HCl (excess)	MeOH	rt	15	67
16	**5a**	HCl (excess)	MeOH	0	15	72
17	**5a**	HCl (excess)	MeOH	–30	15	91
18	**5a**	HCl (excess)	MeOH	–40	15	90
16	**5a** (*one-pot* starting from **1a**) *	HCl (excess)	MeOH	–30	15	83

* One-pot reaction starting from *N*-oxide **1a** (0.5 mmol): thione **4** (0.55 mmol), DCM, rt, 2h, then **5a** (0.75 mmol), MeOH/HCl, –30 °C, 15 min.

General one-pot procedure for synthesis of 2-CF$_3$S-imidazole derivatives 2a-2q: To a solution of imidazole *N*-oxide **1** (0.5 mmol) in dry DCM (4.0 mL) was added dropwise a solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**, 86 mg, 0.55 mmol, 1.1 equiv.) in DCM (3.0 mL) and the mixture was stirred at room temperature for 2h. The solvent was removed in vacuo, the residue was dissolved in MeOH/HCl$_{(sat.)}$ (2.0 mL), cooled to –30 °C, and a solution of **5a** (237 mg, 0.75 mmol, 1.5 equiv.) in MeOH/HCl$_{(sat.)}$ (3.0 mL) was added under inert atmosphere. After the intermediate imidazole-2-thione **3** was fully consumed (TLC monitoring, typically 15-30 min), solvents were removed in vacuo, and the product **2** was purified by a column chromatography (CC) on neutral alumina.

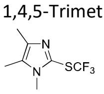
1-Benzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2a**):



2a

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 119 mg (83%); mp 52-54 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.33-7.27 (m, 3H), 6.93-6.92 (m, 2H), 5.30 (s, 2H), 2.23 (s, 3H), 2.04 (s, 3H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 138.3, 136.0, 129.3, 129.1, 128.2 (q, $^1J_{C\text{-}F}$ = 312.2 Hz), 128.0, 126.5 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 126.1, 48.6, 13.1, 9.9. ^{19}F NMR (565 MHz, CDCl$_3$): δ –42.5 (s, CF$_3$). IR (neat) ν 2930, 1573, 1495, 1454, 1402, 1357, 1148, 1092 cm^{-1}. MS (ESI) *m/z*: 287.1 (100, [M+H]$^+$). Anal. Calcd for $C_{13}H_{13}F_3N_2S$: C, 54.53; H, 4.58; N, 9.78; S 11.20. Found: C, 54.48; H, 4.68; N, 9.60; S, 11.23.

1,4,5-Trimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2b**):

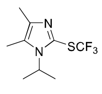


2b

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 103 mg (98%); mp 76-78 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 3.61 (s, 3H), 2.17 (s, 6H). ^{13}C{1H} NMR (151

MHz, CDCl$_3$) δ 137.5, 129.4, 128.3 (q, $^{1}J_{\text{C-F}}$ = 311.9 Hz), 125.8 (q, $^{3}J_{\text{C-F}}$ = 3.3 Hz), 31.9, 12.9, 9.7. ^{19}F NMR (565 MHz, CDCl$_3$): δ –42.7 (s, CF$_3$). IR (neat) ν 1569, 1439, 1394, 1111 cm^{-1}. MS (ESI) *m/z*: 211.2 (100, [M+H]$^+$). Anal. Calcd for $C_7H_9F_3N_2S$: C, 40.00; H, 4.32; N, 13.33; S, 15.25. Found: C, 40.04; H, 4.38; N, 13.41; S, 15.41.

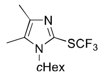
1-Isopropyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2c**):



2c

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 109 mg (92%); mp 32-34 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.02 (sept, *J* = 7.0 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 6H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 138.9, 128.17, 128.15 (q, $^{1}J_{\text{C-F}}$ = 311.9 Hz), 125.5 (q, $^{3}J_{\text{C-F}}$ = 3.3 Hz), 49.6, 21.7, 12.9, 11.0. ^{19}F NMR (565 MHz, CDCl$_3$): δ –41.6 (s, CF$_3$). IR (neat) ν 1502, 1446, 1331, 1170, 1100, 1025 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_9H_{14}F_3N_2S$ 239.0830; Found 239.0827.

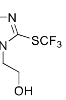
1-Cyclohexyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2d**):



2d

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 117 mg (84%); mp 56-58 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 4.53 (m$_c$, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 1.98-1.90 (m, 4H), 1.84-1.80 (m, 1H), 1.78-1.74 (m, 1H), 1.46-1.38 (m, 2H), 1.26-1.18 (m, 1H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 138.7, 128.3, 128.2 (q, $^{1}J_{\text{C-F}}$ = 311.7 Hz), 125.8 (br, C-2), 58.4, 31.9, 26.3, 25.4, 12.9, 11.3. ^{19}F NMR (565 MHz, CDCl$_3$): δ –43.0 (s, CF$_3$). IR (neat) ν 1566, 1402, 1345, 1323, 1137, 1096 cm^{-1}. MS (ESI) *m/z*: 279.3 (100, [M+H]$^+$). Anal. Calcd for $C_{12}H_{17}F_3N_2S$: C, 51.78; H, 6.16; N, 10.06; S, 11.52. Found: C, 51.74; H, 6.27; N, 10.01; S, 11.73.

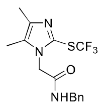
1-(2-Hydroxyethyl)-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2e**):



2e

Reaction time 30 min; CC (alumina, DCM/EtOAc 4:1 gradient 1:1); colorless solid, 110 mg (92%); mp 104-106 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.97 (t, *J* = 5.4 Hz, 1H, OH), 4.10 (t, *J* = 5.8 Hz, 2H), 3.56 (pseudo-q, *J* ≈ 5.6 Hz, 2H), 2.19 (s, 3H), 2.09 (s, 3H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 136.3, 129.3, 128.2 (q, $^{1}J_{\text{C-F}}$ = 311.8 Hz), 124.6 (br, C-2), 59.9, 46.8, 12.6, 9.2. ^{19}F NMR (565 MHz, DMSO-d_6): δ –42.3 (s, CF$_3$). IR (neat) ν 3179, 1588, 1413, 1345, 1111, 1073 cm^{-1}. MS (ESI) *m/z*: 241.2 (100, [M+H]$^+$). Anal. Calcd for $C_8H_{11}F_3N_2OS$: C, 40.00; H, 4.62; N, 11.66; S, 13.34. Found: C, 39.95; H, 4.58; N, 11.55; S, 13.14.

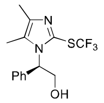
N-benzyl-2-(4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazol-1-yl)acetamide (**2f**):



2f

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 1:1); colorless solid, 165 mg (96%); mp 140-141 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.28 (m, 3H), 7.21-7.26 (m, 2H), 6.03 (t_{br}, $J \approx 5.9$ Hz, 1H, NH), 4.76 (s, 2H), 4.44 (d, $J = 5.9$ Hz, 2H), 2.14 (s, 3H), 2.13 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 165.9, 138.7, 137.5, 129.5, 129.0, 127.99, 127.96 (q, $^1J_{C\text{-}F} = 312.7$ Hz), 127.9, 126.8 (q, $^3J_{C\text{-}F} = 2.9$ Hz), 48.4, 43.9, 12.9, 9.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.2 (s, CF_3). IR (neat) ν 3273, 1659, 1558, 1402, 1297, 1252, 1163, 1141, 1103 cm^{-1}. MS (ESI) *m/z*: 344.2 (100, $[M+H]^+$). Anal. Calcd for $C_{15}H_{16}F_3N_3OS$: C, 52.47; H, 4.70; N, 12.24; S, 9.34. Found: C, 52.50; H, 4.73; N, 12.00; S, 9.34.

(*R*)-2-{4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazol-1-yl}-2-phenylethanol (**2g**):

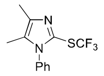


2g

Reaction time 15 min; CC (alumina, DCM gradient DCM/EtOAc 1:1); colorless solid, 123 mg (78%); mp 140-141 °C. $[\alpha]^{20}_D = -39.4°$ (c = 0.185, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.30 (m, 3H), 7.16-7.14 (m, 2H), 6.07 (dd, $J = 5.2$, 8.2 Hz, 1H), 4.56 (dd, $J = 5.2$, 11.6 Hz, 1H), 4.30 (dd, $J = 8.2$, 11.6 Hz, 1H), 3.54 (s_{br}, 1H), 2.08 (s, 3H), 1.80 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 138.5, 136.3, 129.0, 128.7, 128.27 (br, C-2), 128.25, 128.1 (q, $^1J_{C\text{-}F} = 312.3$ Hz), 126.7, 62.8, 61.4, 12.9, 11.0. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.3 (s, CF_3). IR (neat) ν 1502, 1446, 1413, 1371, 1331, 1156, 1100, 1047 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{16}F_3N_2OS$ 317.0935; Found 317.0938.

Crystals of **2g** suitable for X-ray measurements were obtained from dichloromethane/hexane (1:1) mixture by slow evaporation of the solvent.

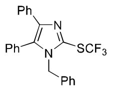
4,5-Dimethyl-1-phenyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2h**):



2h

Reaction time 30 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); colorless solid, 114 mg (84%); mp 64-67 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.51 (m, 3H), 7.17-7.16 (m, 2H), 2.28 (s, 3H), 2.00 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 137.6, 136.2, 130.5, 129.51, 129.47, 128.2, 128.1 (q, $^1J_{C\text{-}F} = 312.0$ Hz), 126.9 (q, $^3J_{C\text{-}F} = 3.4$ Hz), 13.1, 10.1. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.3 (s, CF_3). IR (neat) ν 1595, 1498, 1413, 1163, 1103 cm^{-1}. MS (ESI) *m/z*: 273.2 (100, $[M+H]^+$). Anal. Calcd for $C_{12}H_{11}F_3N_2S$: C, 52.93; H, 4.07; N, 10.29; S, 11.77. Found: C, 53.03; H, 4.08; N, 10.12; S, 11.64.

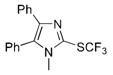
1-Benzyl-4,5-diphenyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2i**):



2i

Reaction time 30 min; CC (alumina, hexanes/DCM 1:4 gradient DCM); colorless solid, 176 mg (86%); mp 128-130 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.51-7.49 (m, 2H), 7.43-7.40 (m, 1H), 7.37-7.34 (m, 2H), 7.26-7.16 (m, 8H), 6.82-6.79 (m, 2H), 5.25 (s, 2H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 141.6, 136.4, 134.1, 133.5, 130.8, 130.3, 129.7 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 129.5, 129.2, 128.9, 128.33, 128.29 (q, $^1J_{C\text{-}F}$ = 312.1 Hz), 127.9, 127.3, 127.1, 126.3, 48.9. ^{19}F NMR (565 MHz, CDCl$_3$): δ –41.5 (s, CF$_3$). IR (neat) ν 1599, 1446, 1402, 1353, 1327, 1133, 1100 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{23}H_{18}F_3N_2S$ 411.1143; Found 411.1142.

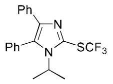
1-Methyl-4,5-diphenyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2j**):



2j

Reaction time 30 min; CC (alumina, DCM); colorless solid, 132 mg (79%); mp 127-128 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.50-7.47 (m, 5H), 7.35-7.34 (m, 2H), 7.22-7.16 (m, 3H), 3.61 (s, 3H). ^{13}C{1H} NMR (151,5 MHz, CDCl$_3$) δ 141.2, 134.3, 133.6, 130.6, 130.4, 129.5, 129.4, 129.3 (q, $^3J_{C\text{-}F}$ = 3.1 Hz), 128.4 (q, $^1J_{C\text{-}F}$ = 312.1 Hz), 128.3, 127.2, 127.1, 33.0. ^{19}F NMR (565 MHz, CDCl$_3$): δ –41.7 (s, CF$_3$). IR (neat) ν 1502, 1443, 1371, 1166, 1141, 1088 cm^{-1}. MS (ESI) *m/z*: 335.2 (100, [M+H]$^+$). Anal. Calcd for $C_{17}H_{13}F_3N_2S$: C, 61.07; H, 3.92; N, 8.38; S, 9.59. Found: C, 60.95; H, 4.00; N, 8.32; S, 9.65.

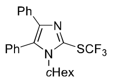
1-Isopropyl-4,5-diphenyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2k**):



2k

Reaction time 30 min; CC (alumina, DCM); colorless solid, 117 mg (65%); mp 94-96 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.52-7.46 (m, 3H), 7.39-7.36 (m, 4H), 7.18-7.12 (m, 3H), 4.77 (sept, *J* = 7.1 Hz, 1H), 1.41 (d, *J* = 7.1 Hz, 6H). ^{13}C{1H} NMR (151 MHz, CDCl$_3$) δ 141.7, 133.7, 133.3, 131.8, 131.2, 129.6, 129.1, 128.3 (q, $^1J_{C\text{-}F}$ = 312.1 Hz), 128.2, 128.1 (br, C-2), 126.98, 126.97, 50.6, 22.9. ^{19}F NMR (565 MHz, CDCl$_3$): δ –41.6 (s, CF$_3$). IR (neat) ν 1502, 1443, 1327, 1163, 1133, 1096 cm^{-1}. MS (ESI) *m/z*: 363.2 (100, [M+H]$^+$). Anal. Calcd for $C_{19}H_{17}F_3N_2S$: C, 62.97; H, 4.73; N, 7.73; S, 8.85. Found: C, 62.86; H, 4.67; N, 7.59; S, 8.73.

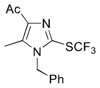
1-Cyclohexyl-4,5-diphenyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2l**):



2l

Reaction time 30 min; CC (alumina, hexanes/DCM 1:4 gradient DCM); colorless solid, 161 mg (80%); mp 161-163 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.46 (m, 3H), 7.39-7.34 (m, 4H), 7.17-7.11 (m, 3H), 4.30 (s_{br}, 1H), 1.85-1.76 (m, 6H), 1.62-1.58 (m, 1H), 1.26-1.21 (m, 2H), 1.03-0.93 (m, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 141.5, 133.7, 133.4, 131.7 (br)*, 131.2 (br, C-2), 129.6, 129.0, 128.3 (q, $^{1}J_{C\text{-}F}$ = 312.3 Hz), 128.2, 126.95, 126.93, 59.3, 33.1, 26.4, 25.2; *overlapped signals. ^{19}F NMR (565 MHz, $CDCl_3$): δ –41.7 (s, CF_3). IR (neat) ν 1443, 1327, 1133, 1100 cm^{-1}. MS (ESI) *m/z*: 403.3 (100, [M+H]$^{+}$). Anal. Calcd for $C_{22}H_{21}F_3N_2S$: C, 65.65; H, 5.26; N, 6.96; S, 7.97. Found: C, 65.70; H, 5.23; N, 6.82; S, 7.79.

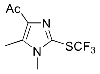
4-Acetyl-1-benzyl-5-methyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2m**):



2m

Reaction time 1 h; CC (alumina, hexanes/DCM 1:4 gradient DCM); colorless solid, 105 mg (67%); mp 71-72 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.29 (m, 3H), 6.94-6.93 (m, 2H), 5.36 (s, 2H), 2.62 (s, 3H), 2.49 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 195.8, 140.2, 139.0, 134.7, 129.3, 129.0 (q, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 128.5, 128.0 (q, $^{1}J_{C\text{-}F}$ = 312.2 Hz), 126.1, 48.4, 27.6, 11.4. ^{19}F NMR (565 MHz, $CDCl_3$): δ –41.5 (s, CF_3). IR (neat) ν 1670, 1543, 1454, 1432, 1398, 1353, 1141, 1096 cm^{-1}. MS (ESI) *m/z*: 315.2 (100, [M+H]$^{+}$). Anal. Calcd for $C_{14}H_{13}F_3N_2OS$: C, 53.50; H, 4.17; N, 8.91; S, 10.20. Found: C, 53.59; H, 4.29; N, 8.72; S, 10.19.

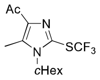
4-Acetyl-1,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2n**):



2n

Reaction time 1 h; CC (alumina, DCM); colorless solid, 99 mg (84%); mp 67-69 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.61 (s, 3H), 2.59 (s, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 195.7, 139.7, 139.1, 128.6 (q, $^{3}J_{C\text{-}F}$ = 3.1 Hz), 128.2 (q, $^{1}J_{C\text{-}F}$ = 311.9 Hz), 31.8, 27.5, 11.3. ^{19}F NMR (565 MHz, $CDCl_3$): δ –41.6 (s, CF_3). IR (neat) ν 1670, 1539, 1372, 1141, 1088 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^{+}$ Calcd for $C_8H_{10}F_3N_2OS$ 239.0466; Found 239.0466.

4-Acetyl-1-cyclohexyl-5-methyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2o**):

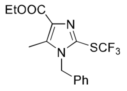


2o

Reaction time 2 h; CC (alumina, DCM); colorless solid, 118 mg (77%); mp 77-78 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.58 (s_{br}, 1H), 2.73 (s, 3H), 2.57 (s, 3H), 2.08-2.01 (m, 2H), 1.97-1.93 (m, 2H), 1.86-1.84 (m, 2H), 1.80-1.77 (m, 1H), 1.47-1.40 (m, 2H), 1.29-1.22 (m, 1H). ^{13}C{1H} NMR (151 MHz,

$CDCl_3$) δ 196.0, 140.2, 138.2, 128.4 (br, C-2), 128.0 (q, $^{1}J_{\text{C-F}}$ = 312.1 Hz), 58.9, 31.5, 27.7, 26.3, 25.2, 12.4. ^{19}F NMR (565 MHz, $CDCl_3$): δ –41.9 (s, CF_3). IR (neat) ν 1674, 1536, 1431, 1364, 1141, 1095 cm^{-1}. MS (ESI) *m/z*: 329.2 (100, [M+Na]$^{+}$). Anal. Calcd for $C_{13}H_{17}F_3N_2OS$: C, 50.97; H, 5.59; N, 9.14; S, 10.47. Found: C, 51.17; H, 5.70; N, 8.93; S, 10.50.

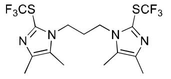
1-Benzyl-4-ethoxycarbonyl-5-methyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**2p**):



2p

Reaction time 90 min; CC (alumina, DCM gradient DCM/EtOAc 4:1); thick colorless oil, 110 mg (64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.29 (m, 3H), 6.93-6.92 (m, 2H), 5.37 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 163.0, 140.6, 134.7, 132.7, 130.2 (q, $^{3}J_{\text{C-F}}$ = 3.3 Hz), 129.3, 128.4, 128.0 (q, $^{1}J_{\text{C-F}}$ = 312.5 Hz), 126.0, 60.9, 48.7, 14.6, 11.3. ^{19}F NMR (565 MHz, $CDCl_3$): δ –41.2 (s, CF_3). IR (neat) ν 1707, 1558, 1454, 1431, 1323, 1201, 1140, 1096 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^{+}$ Calcd for $C_{15}H_{16}F_3N_2O_2S$ 344.0885; Found 345.0891.

1,3-bis{4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazol-1-yl}propane (**2q**):



2q

According to the general protocol imidazole *N*-oxide **1q** (0.5 mmol) was treated with cyclobutanethione **4** (1.1 mmol), followed by Togni reagent (**5a**, 1.5 mmol); reaction time 2 h; CC (alumina, hexanes/DCM 1:4 gradient DCM); colorless solid, 112 mg (52%); mp 104-106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.07 (t, *J* = 7.8 Hz, 4H), 2.19 (s, 3H), 2.17 (s, 3H), 2.03 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 138.6, 128.4, 128.0 (q, $^{1}J_{\text{C-F}}$ = 312.3 Hz), 125.5 (q, $^{3}J_{\text{C-F}}$ = 3.1 Hz), 42.1, 31.4, 13.0, 9.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.3 (s, $2CF_3$). IR (neat) ν 1577, 1402, 1364, 1156, 1096 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^{+}$ Calcd for $C_{15}H_{19}F_6N_4S_2$ 433.0955; Found 433.0962.

Gram-scale synthesis of 2-CF_3S-imidazole 2i: To a solution of imidazole *N*-oxide **1i** (1.63 g, 5.0 mmol) in dry DCM (40 mL) was added dropwise a solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4**, 5.2 mmol, 0.80 g, 1.04 equiv.) in DCM (30 mL) and the mixture was stirred at room temperature for 2h. The solvent was removed in vacuo, the residue was dissolved in MeOH/$HCl_{(sat.)}$ (20 mL), cooled to –30 °C, and a solution of **5a** (6.0 mmol, 1.90 g, 1.2 equiv.) in MeOH/$HCl_{(sat.)}$ (30 mL) was added under inert atmosphere. After the intermediate imidazole-2-thione **3i** was fully consumed (TLC monitoring, 40 min), solvents were removed in vacuo, and the product was purified by a column chromatography (hexanes/DCM 1:4 gradient DCM) on neutral alumina to give **2i** (1.82 g, 89%) as a colorless solid.

3. Copies of NMR spectra

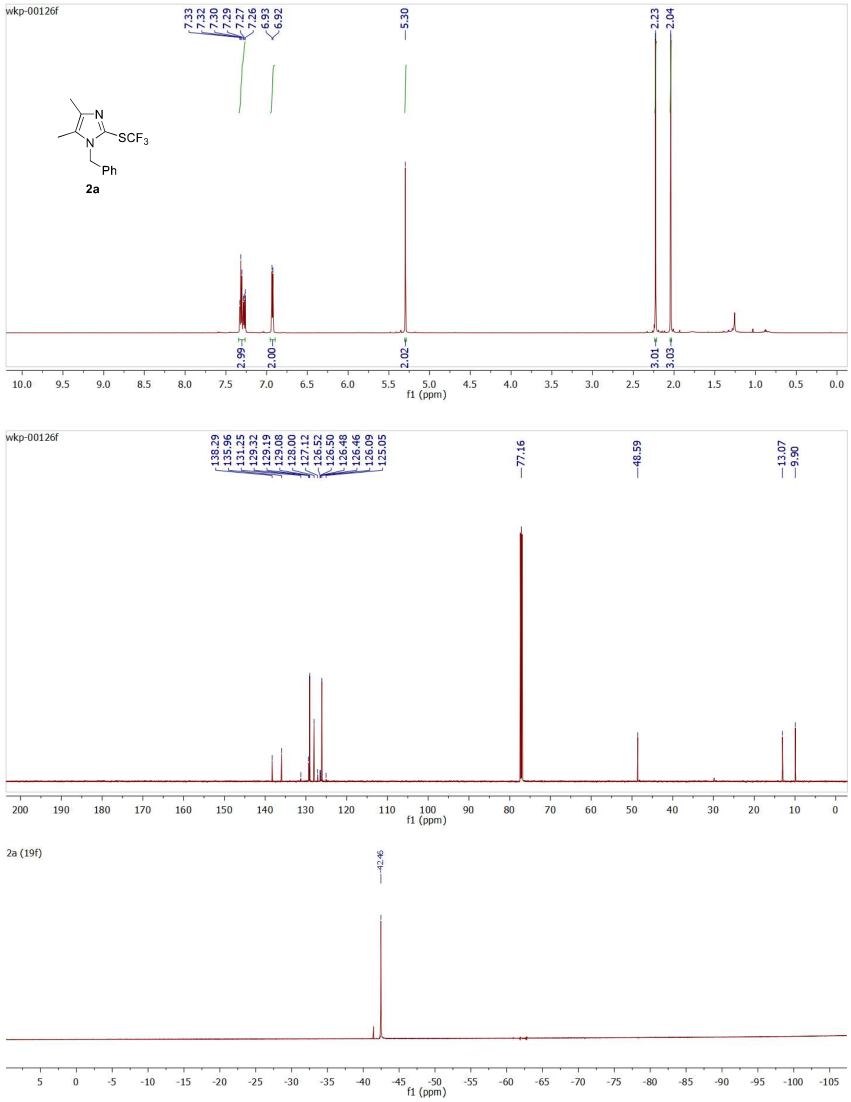


Fig S1. ^{1}H NMR (600 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2a**.

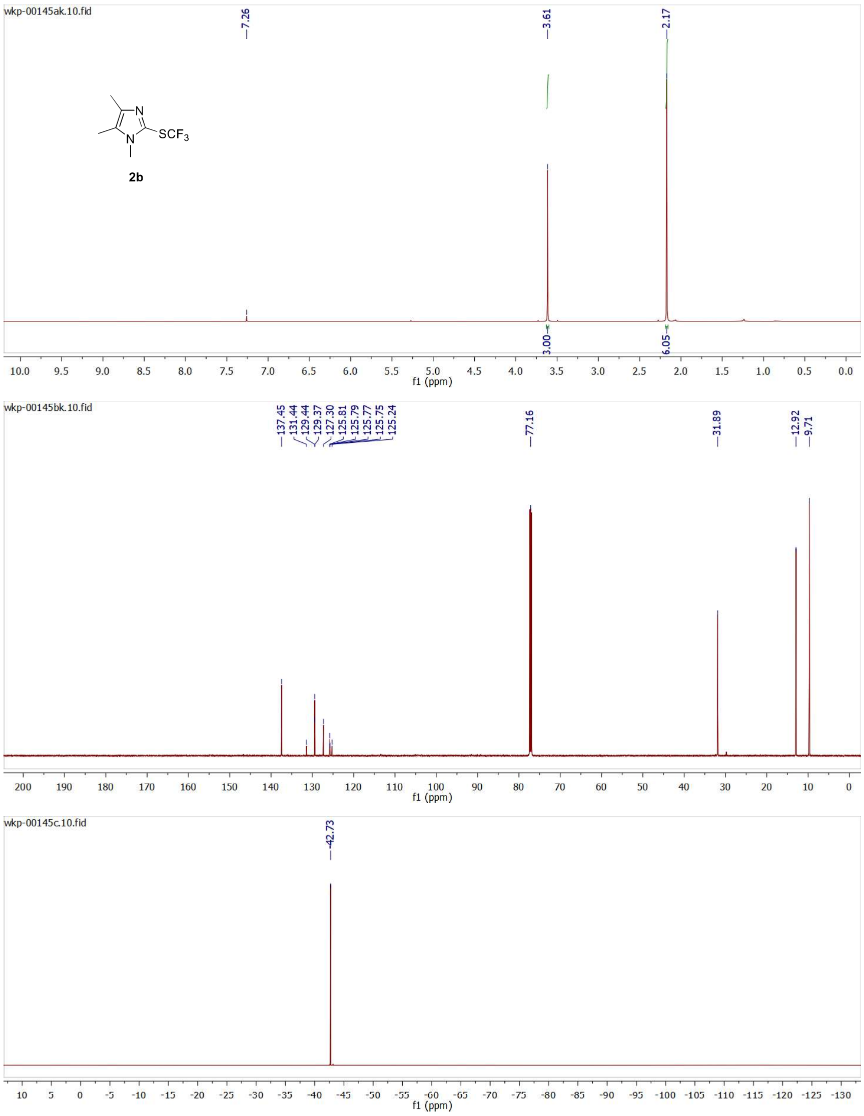


Fig S2. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2b**.

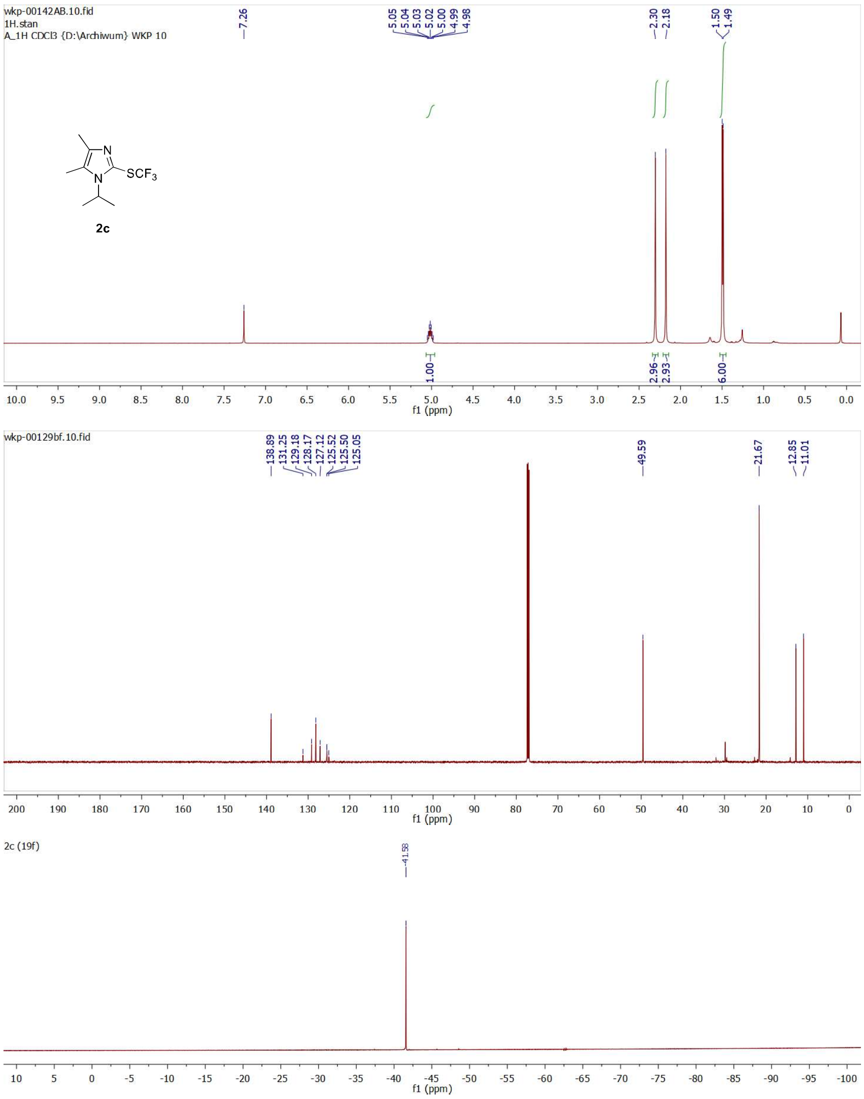


Fig S3. ^1H NMR (600 MHz, $CDCl_3$), $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2c**.

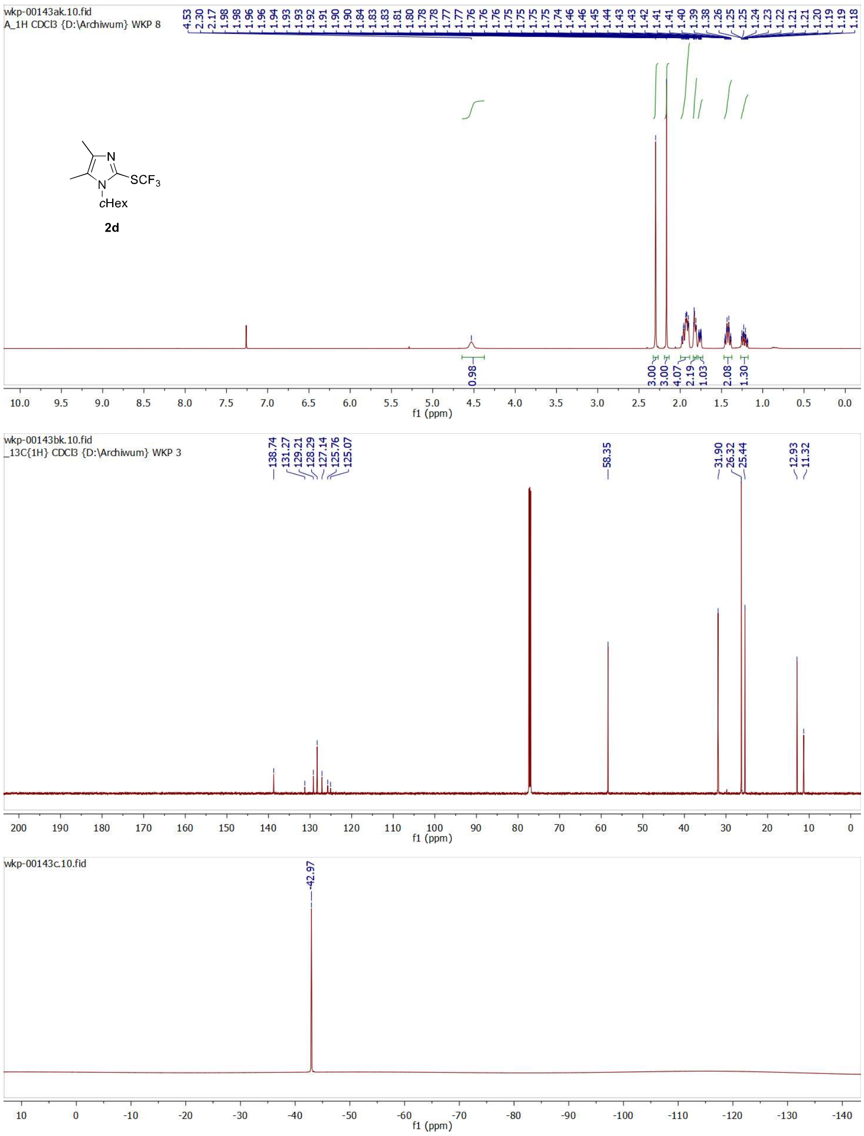


Fig S4. ^{1}H NMR (600 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2d**.

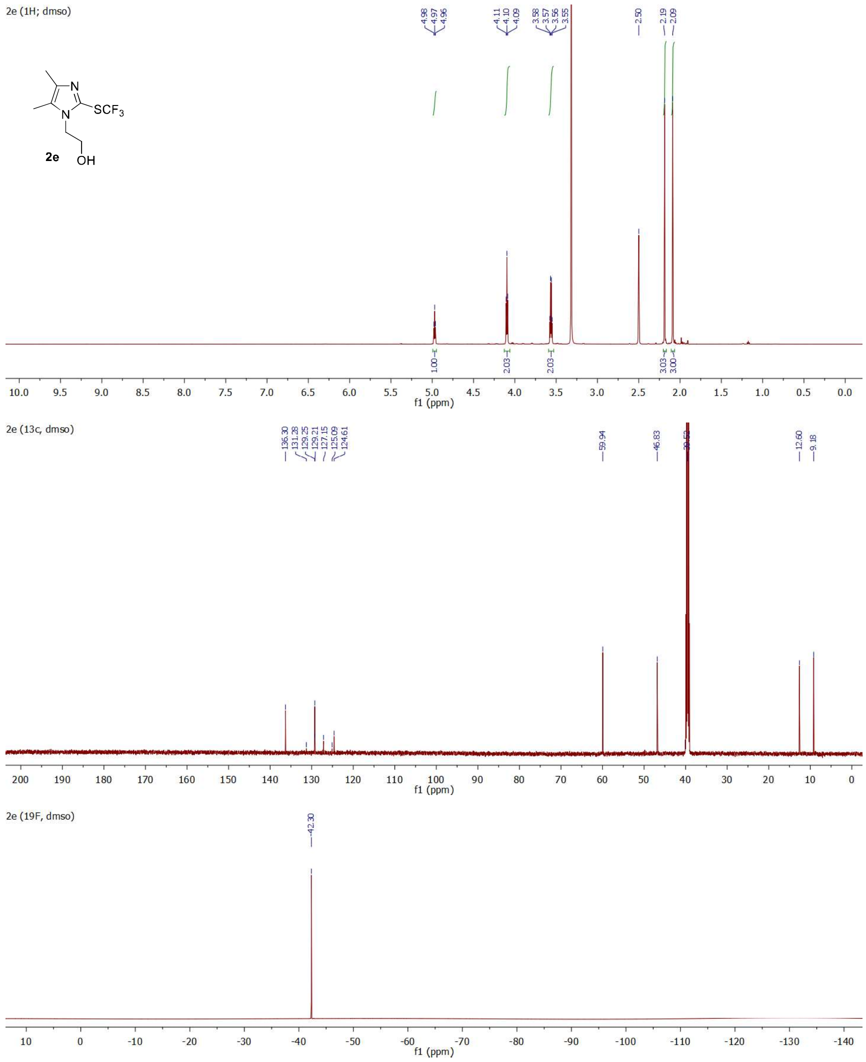


Fig S5. ^{1}H NMR (600 MHz, DMSO-d_6), $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **2e**.

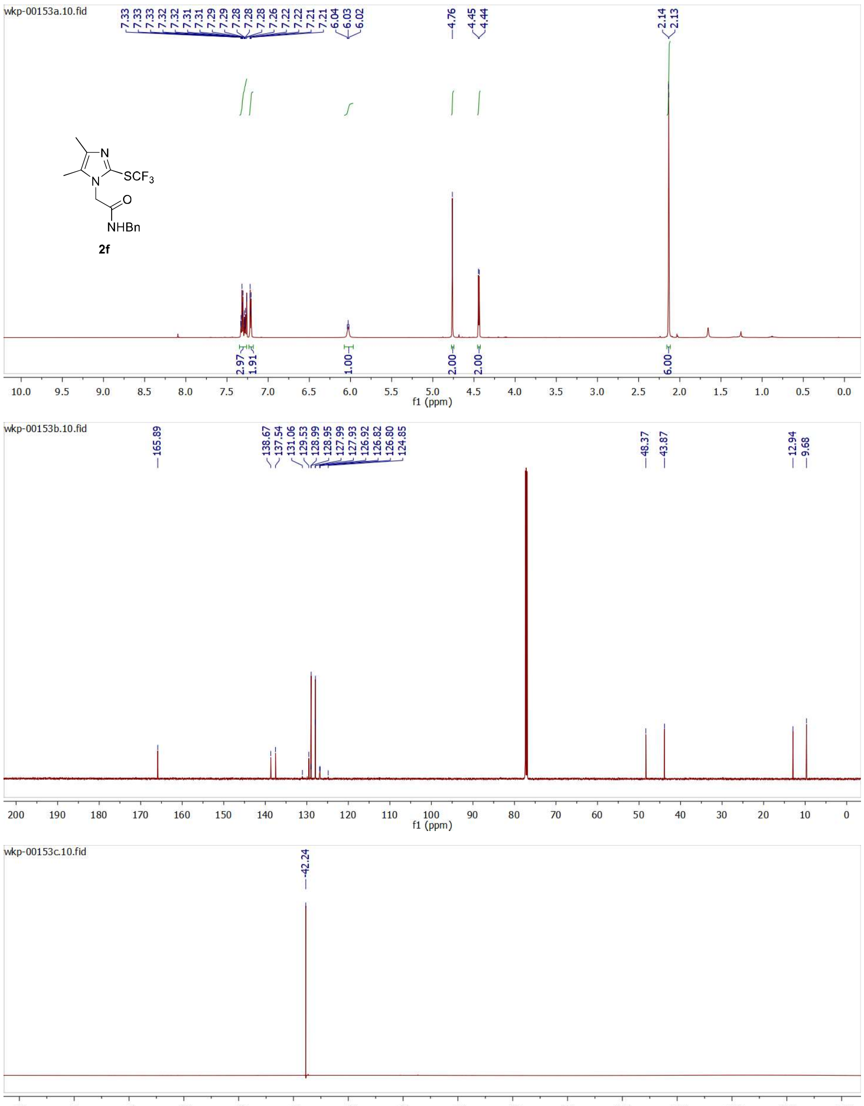


Fig S6. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2f**.

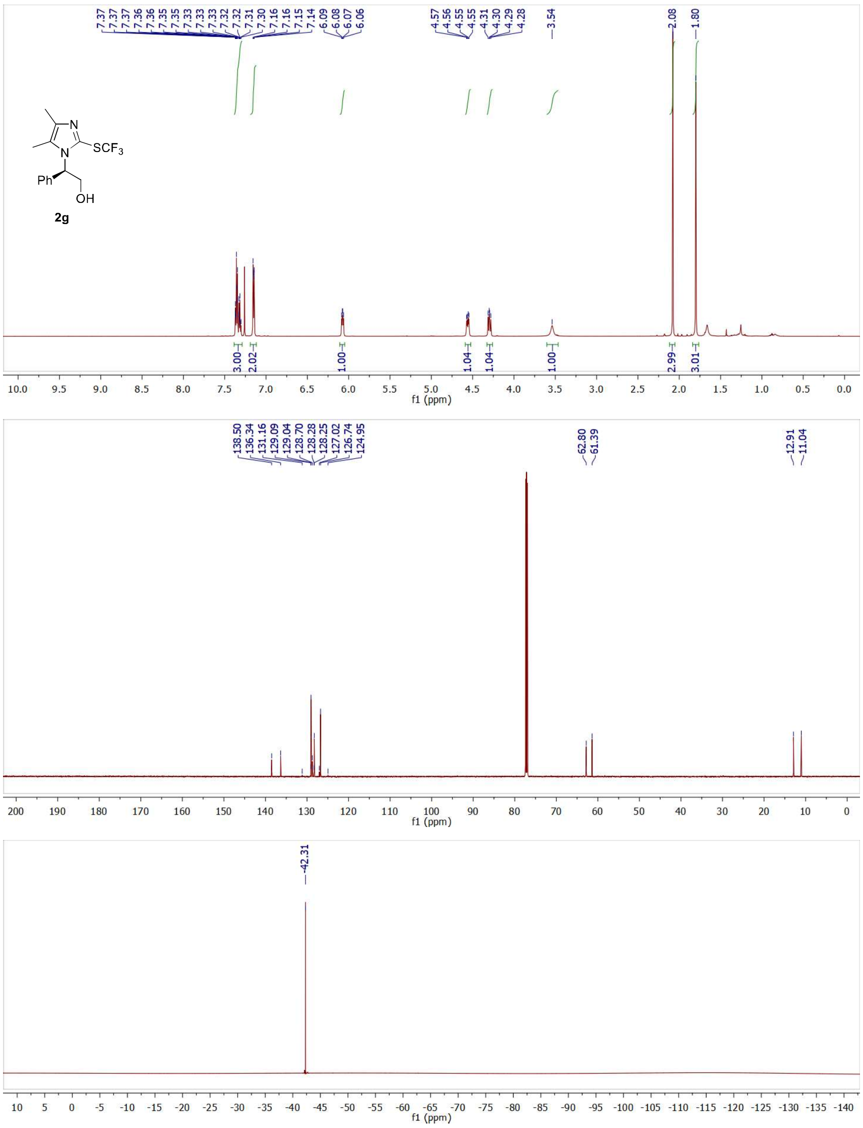


Fig S7. ^{1}H NMR (600 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2g**.

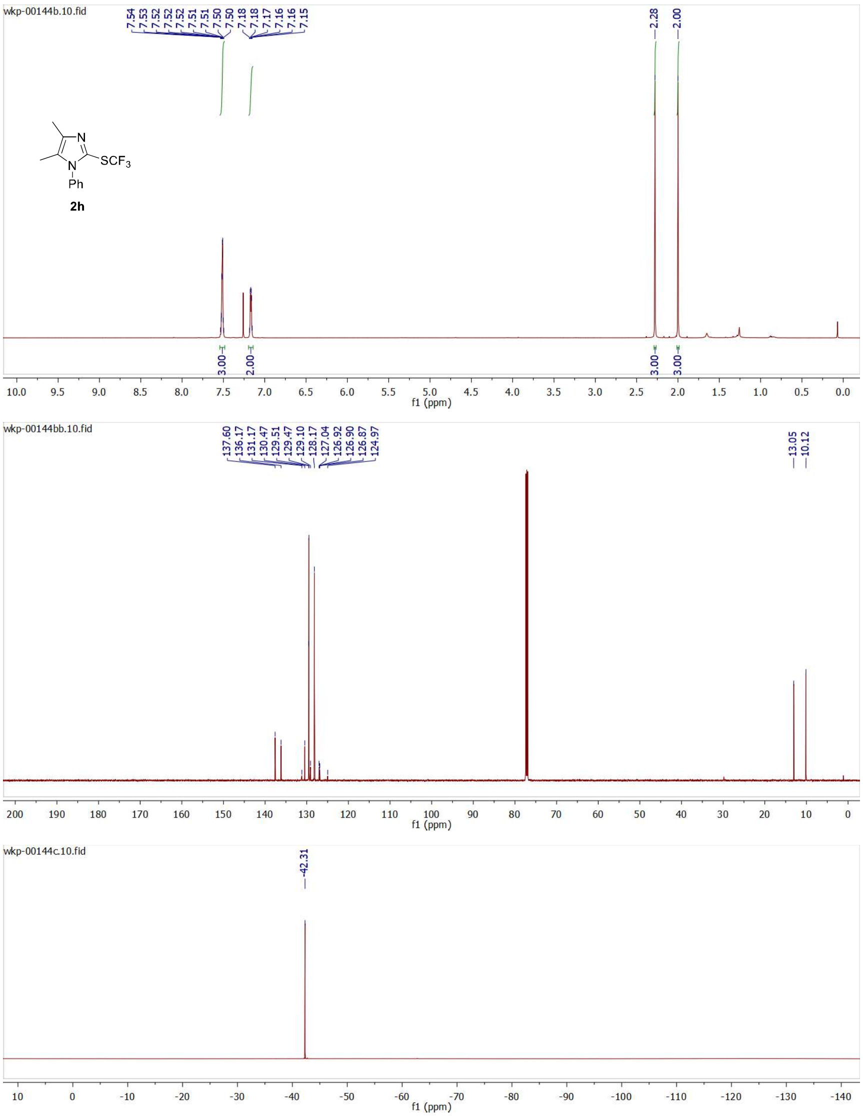


Fig S8. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2h**.

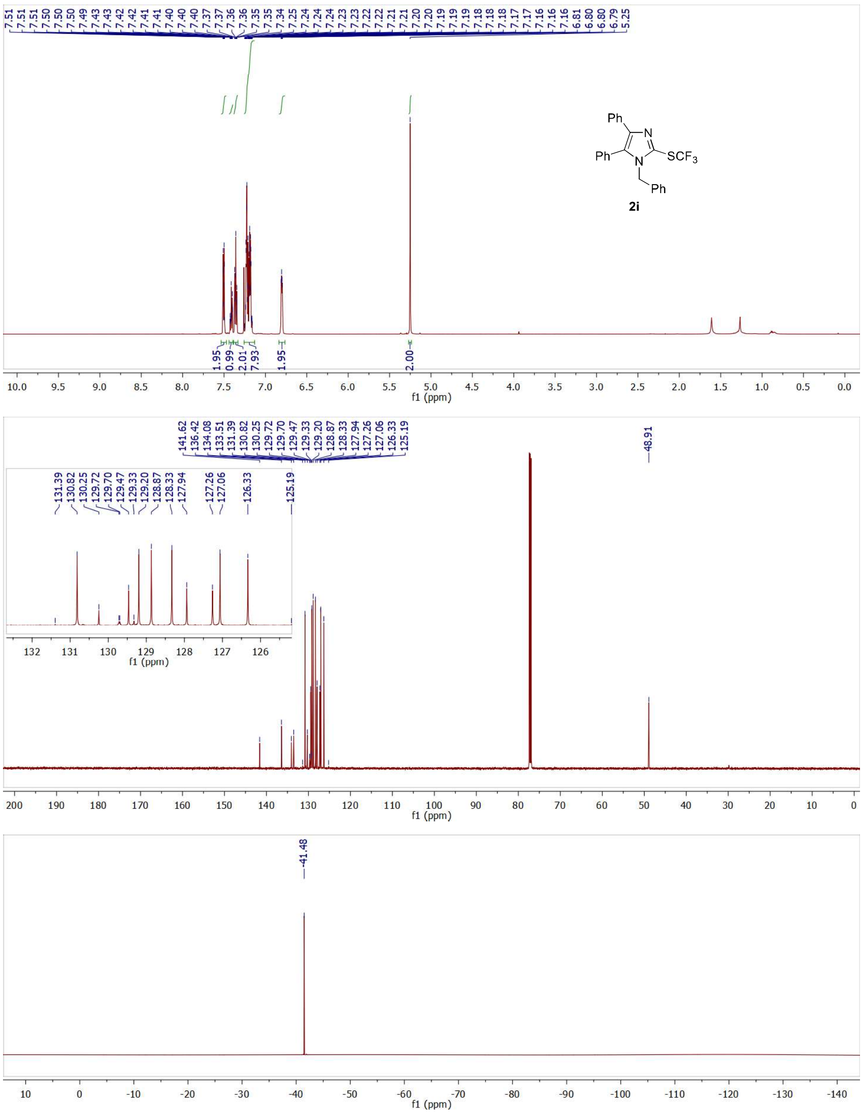


Fig S9. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2i**.

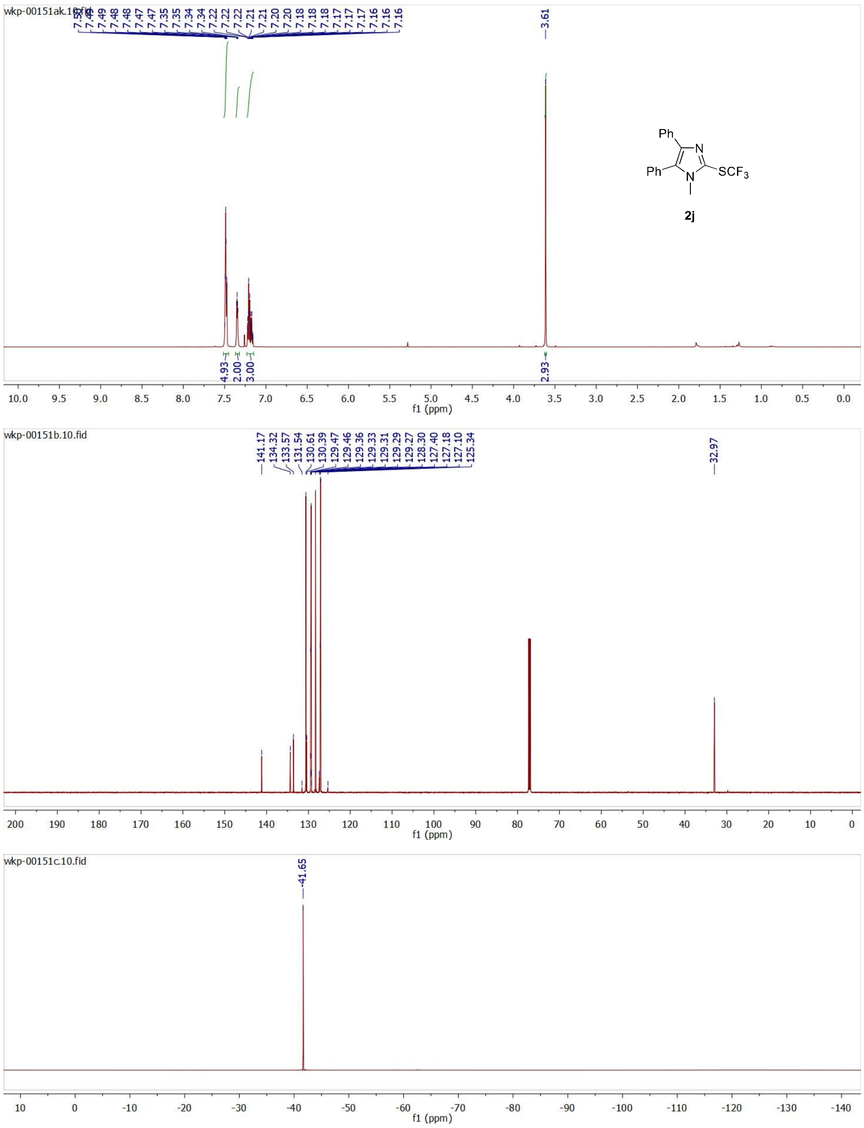


Fig S10. ^1H NMR (600 MHz, $CDCl_3$), $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2j**.

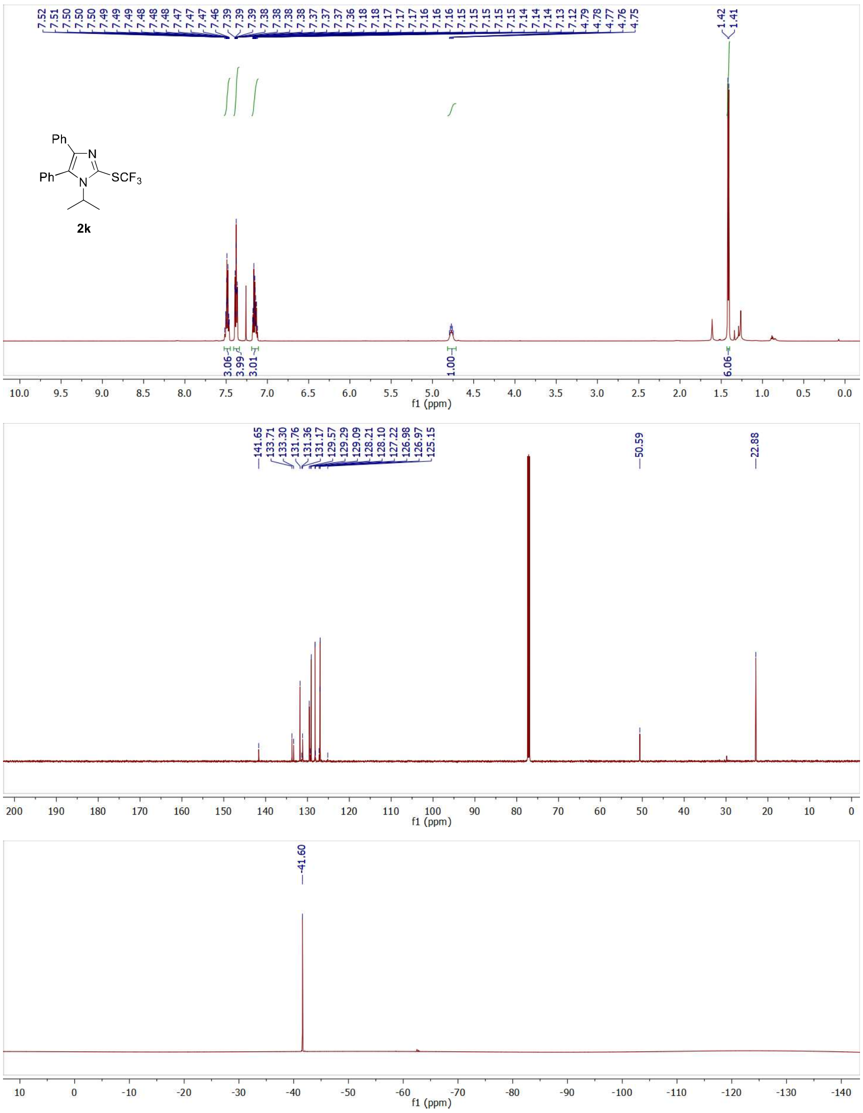


Fig S11. ^1H NMR (600 MHz, $CDCl_3$), $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2k**.

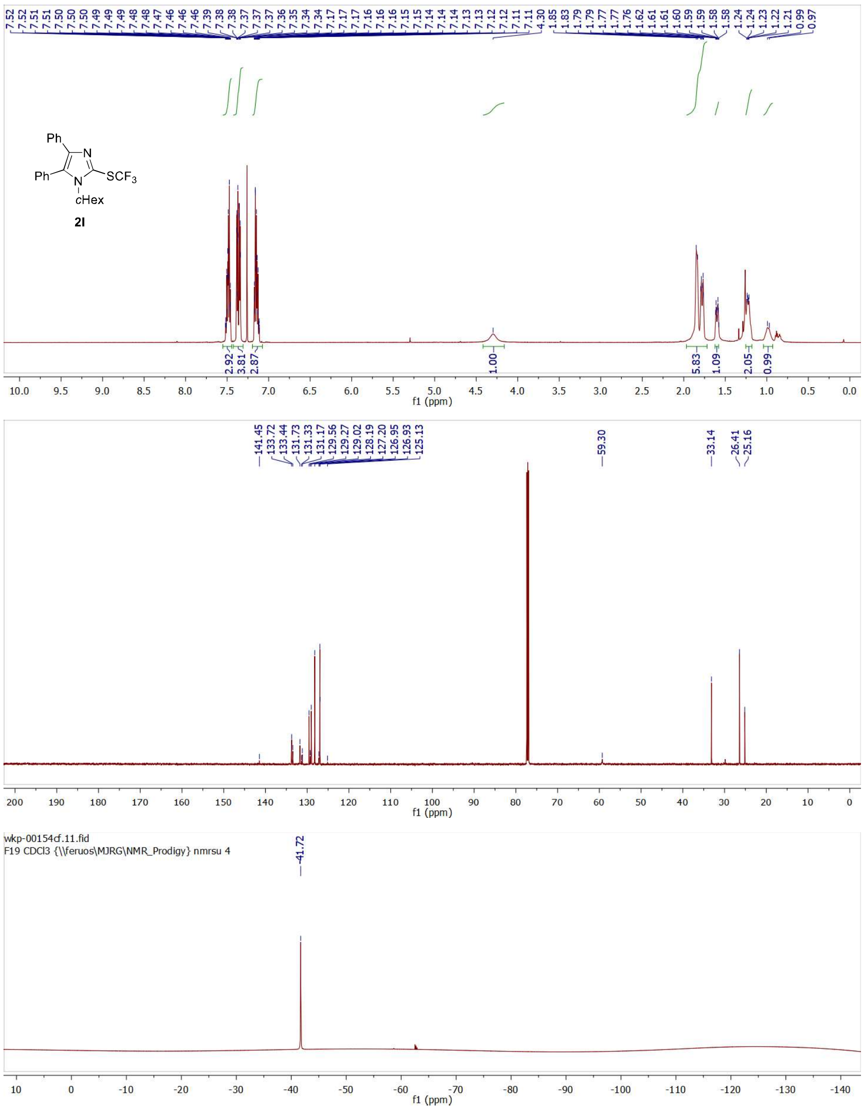


Fig S12. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2l**.

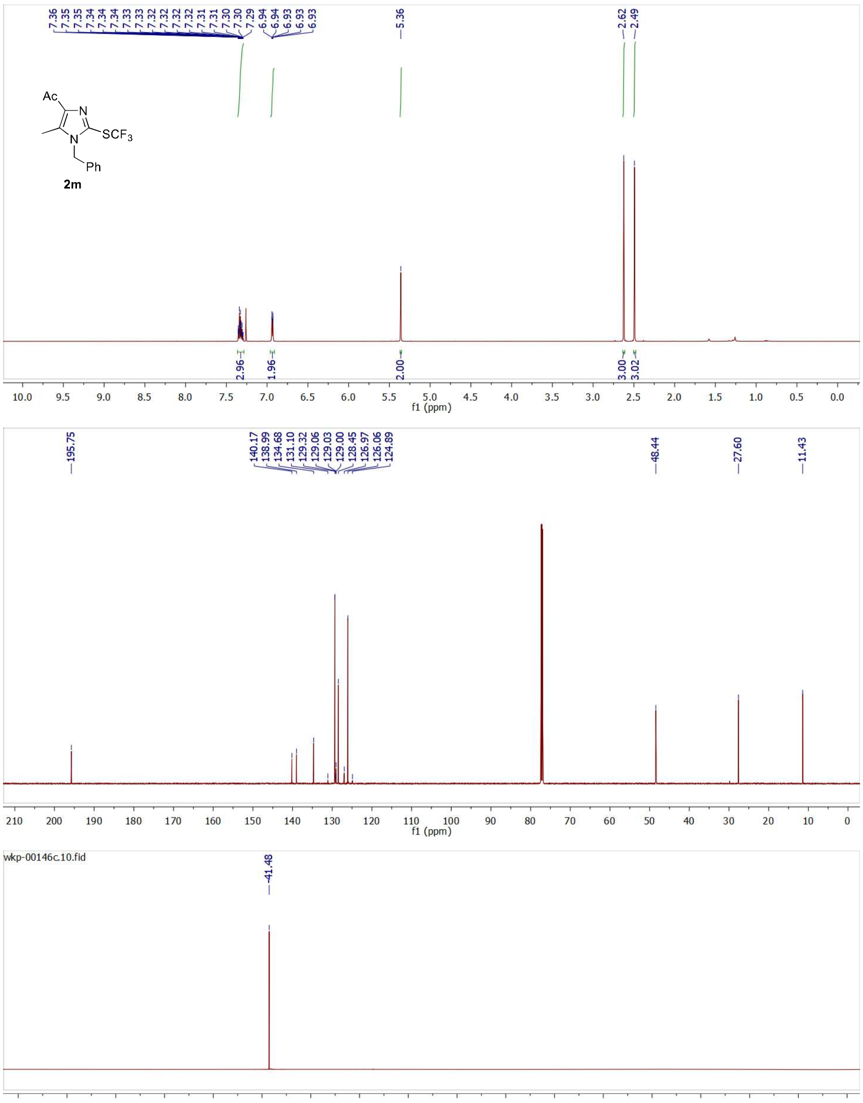


Fig S13. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2m**.

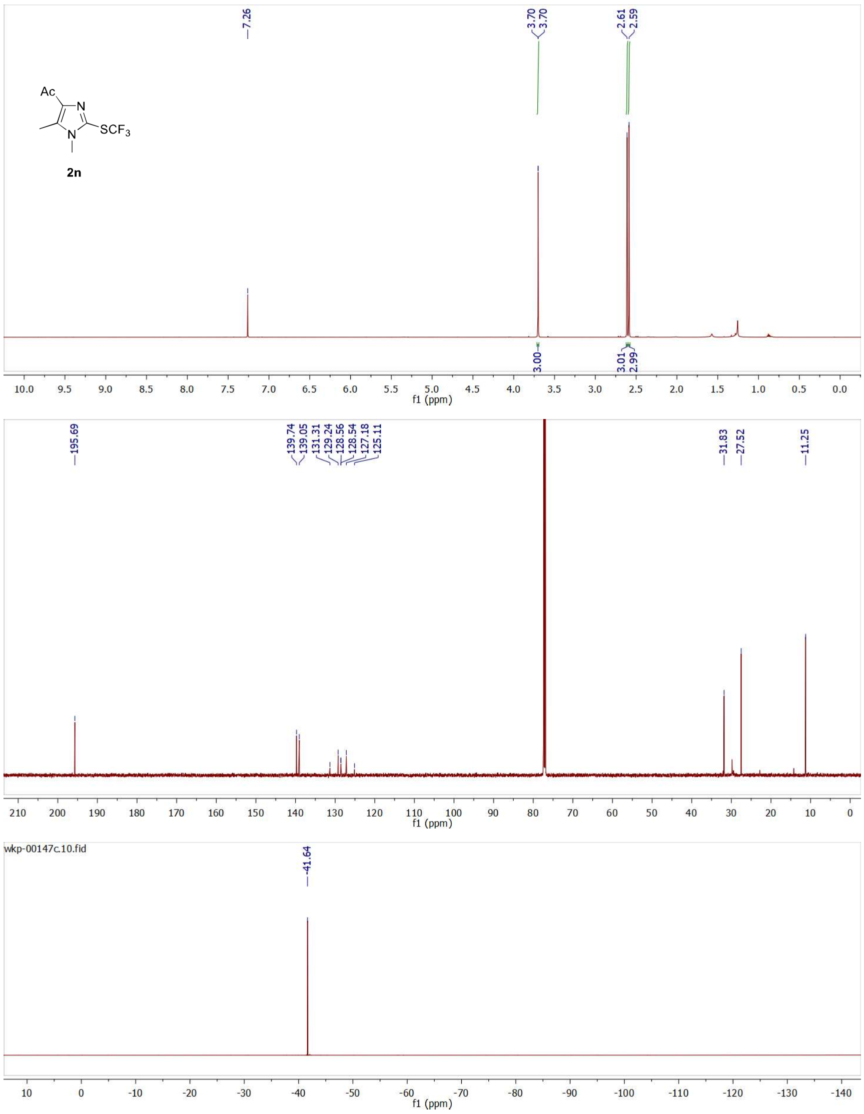


Fig S14. ^{1}H NMR (600 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2n**.

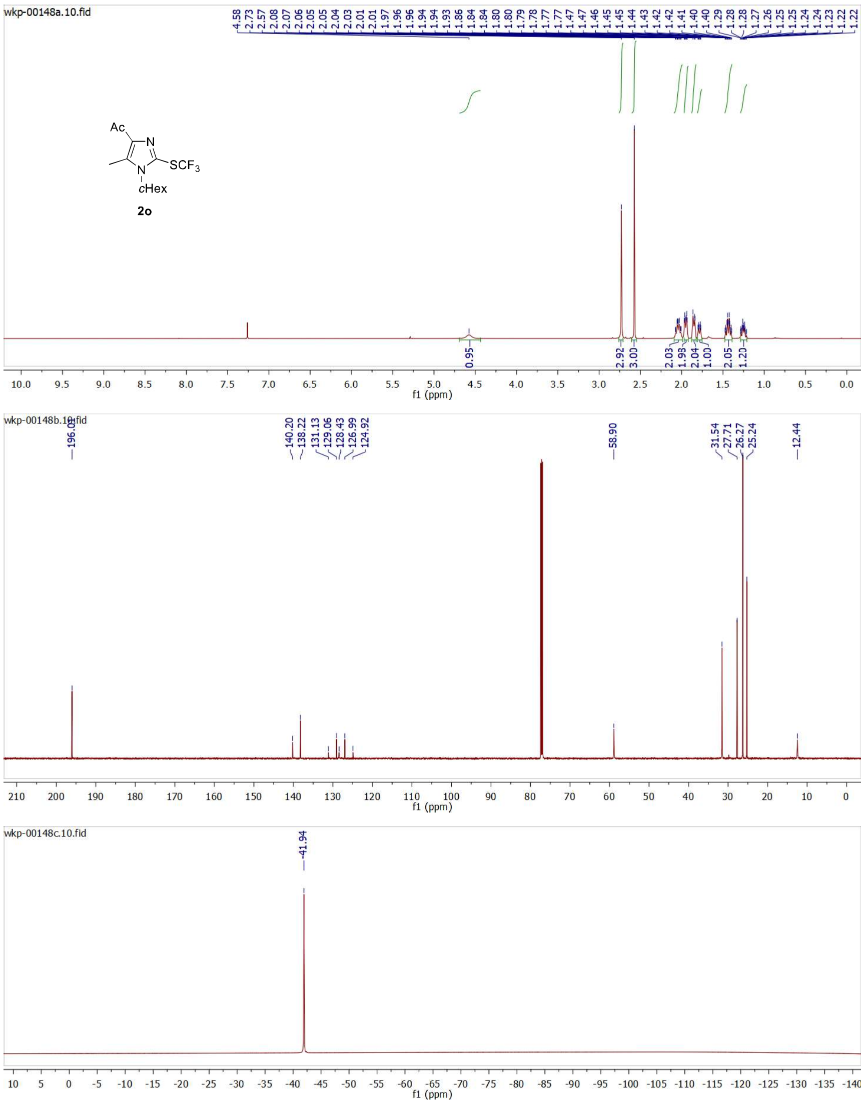


Fig S15. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2o**.

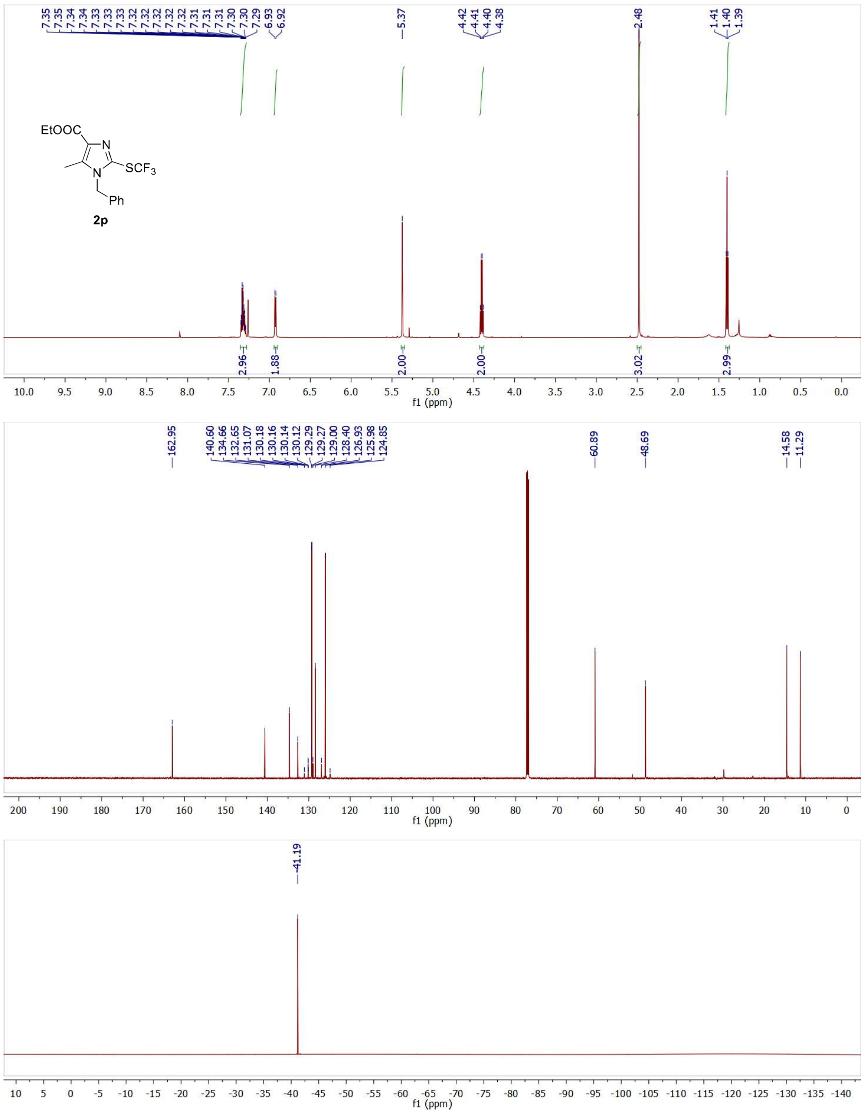


Fig S16. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **2p**.

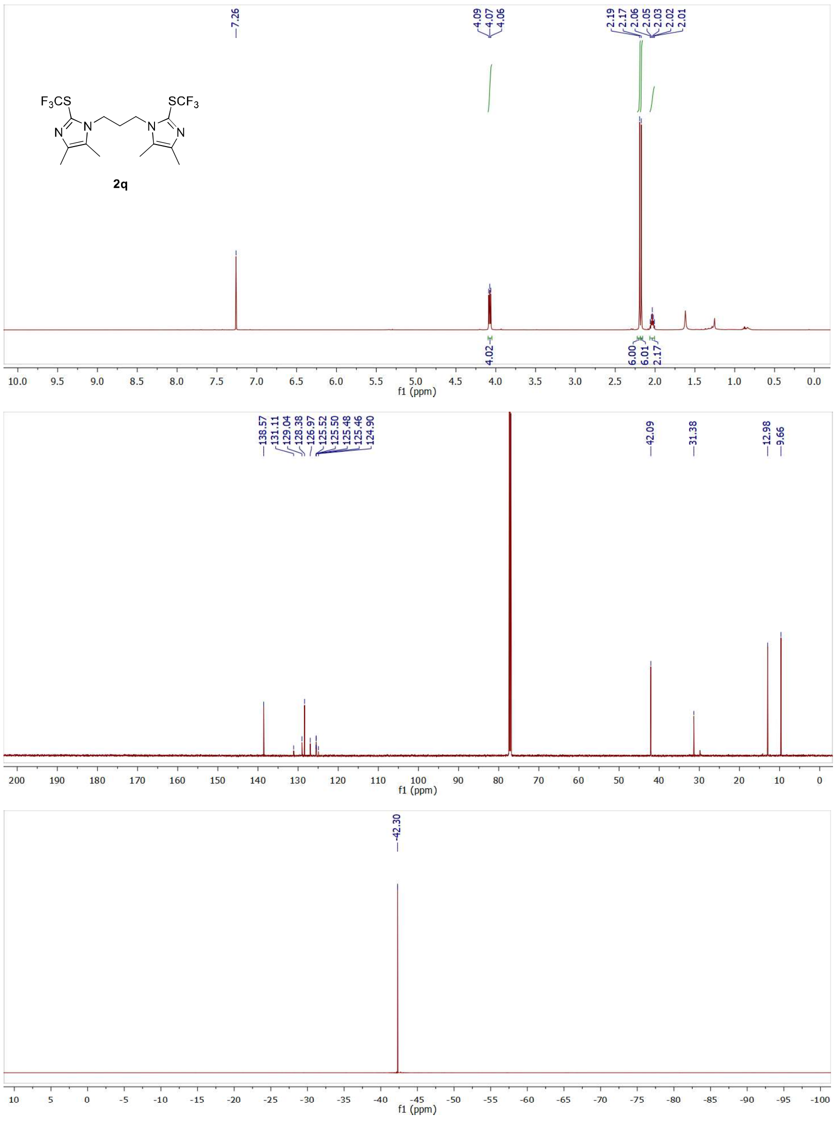


Fig S17. ^{1}H NMR (600 MHz, $CDCl_3$), $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **2q**.

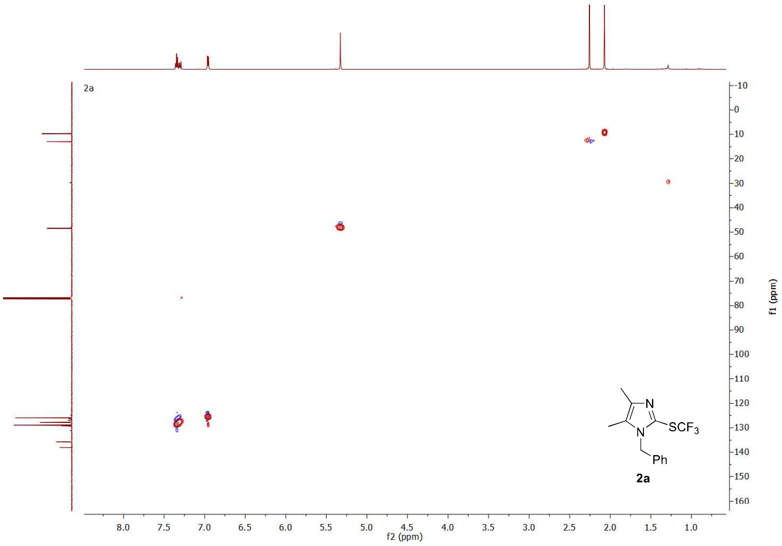
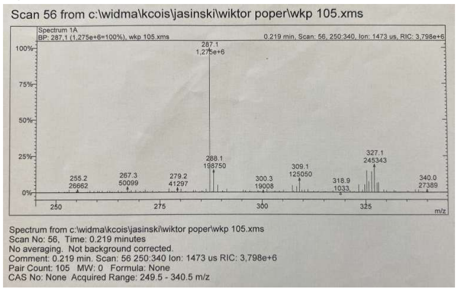
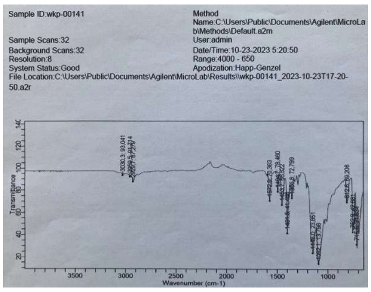


Fig S18. HMQC ($CDCl_3$) for **2a**.



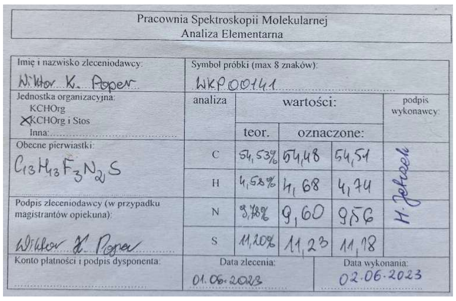
Scan 56 from c:\widma\kcois\jasinski\wiktor poper\wkp 105.xms

Spectrum from c:\widma\kcois\jasinski\wiktor poper\wkp 105.xms
Scan No: 56, Time: 0.219 minutes
No averaging. Not background corrected.
Comment: 0.219 min. Scan: 56 250:340 Ion: 1473 us RIC: 3,798e+6
Pair Count: 105 MW: 0 Formula: None
CAS No: None Acquired Range: 249.5 - 340.5 m/z



Sample ID:wkp-00141
Sample Scans:32
Background Scans:32
Resolution:8
System Status:Good
File Location:C:\Users\Public\Documents\Agilent\MicroLab\Results\\wkp-00141_2023-10-23T17-20-50.a2r

Method
Name:C:\Users\Public\Documents\Agilent\MicroLab\Methods\Default.a2m
User:admin
Date/Time:10-23-2023 5:20:50
Range:4000 - 650
Apodization:Happ-Genzel



Pracownia Spektroskopii Molekularnej
Analiza Elementarna

Imię i nazwisko zleceniodawcy: Wiktor K. Poper	Symbol próbki (max 8 znaków): WKP00141				
Jednostka organizacyjna: KCHOrg ☒ KCHOrg i Stos Inna:	analiza	wartości:			podpis wykonawcy:
		teor.	oznaczone:		
Obecne pierwiastki: $C_{13}H_{13}F_3N_2S$	C	54,53%	54,48	54,51	H. Jeżowek
	H	4,58%	4,68	4,74	
Podpis zleceniodawcy (w przypadku magistrantów opiekuna): Wiktor K. Poper	N	9,78%	9,60	9,56	
	S	11,20%	11,23	11,18	
Konto płatności i podpis dysponenta:	Data zlecenia: 01.06.2023		Data wykonania: 02.06.2023		

Fig S19. (+)-ESI-MS, IR, and EA analyses for **2a**.

4. Crystallographic analysis

Crystallographic analysis of 2g: Single crystals of **2g** ($C_{14}H_{15}F_3N_2OS$) were measured. A suitable crystal was selected and measured on a XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer. The crystal was kept at 100 K during data collection. Using Olex2,[3a] the structure was solved with the SHELXT[3b] structure solution program using Intrinsic Phasing and refined with the XL[3c] refinement package using Least Squares minimization. Crystallographic data have been deposited at the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC-2286607. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/

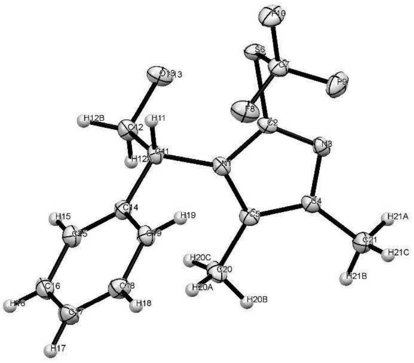


Fig S20. A view of the molecular structure of compound **2g**. Displacement ellipsoids are drawn at the 50% probability level. X-ray data collected at the ambient temperature 100 K.

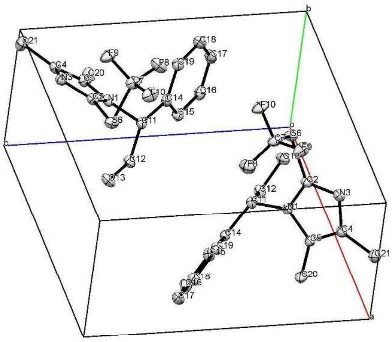


Fig S21. A view of the molecular packing in the structure of compound **2g**.

Crystal structure determination of 2g: Crystal Data for $C_{14}H_{15}F_3N_2OS$ (*M* =316.34 g/mol): monoclinic, space group $P2_1$ (no. 4), *a* = 8.02196(5) Å, *b* = 9.17291(7) Å, *c* = 10.23087(6) Å, *β* = 104.7965(6)°, *V* = 727.870(9) Å^3, *Z* = 2, *T* = 100 K, μ(Cu Kα) = 2.303 mm^{-1}, *Dcalc* = 1.443 g/cm^3, 47326 reflections measured (8.94° ≤ 2Θ ≤ 159.76°), 2995 unique (R_{int} = 0.0328, R_{sigma} = 0.0111) which were used in all calculations. The final R_1 was 0.0192 (I > 2σ(I)) and wR_2 was 0.0512 (all data).

Refinement model description
Number of restraints - 1, number of constraints - unknown.

Details:
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups, All O(H) groups
2.a Ternary CH refined with riding coordinates:
 C11(H11)
2.b Secondary CH2 refined with riding coordinates:
 C12(H12A,H12B)
2.c Aromatic/amide H refined with riding coordinates:
 C19(H19), C15(H15), C17(H17), C18(H18), C16(H16)
2.d Idealised Me refined as rotating group:
 C20(H20A,H20B,H20C), C21(H21A,H21B,H21C)
2.e Idealised tetrahedral OH refined as rotating group:
 O13(H13)

Table S2. Crystal data and structure refinement for **2g**.

Identification code	158_2
Empirical formula	$C_{14}H_{15}F_3N_2OS$
Formula weight	316.34
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.02196(5)
b/Å	9.17291(7)
c/Å	10.23087(6)
α/°	90
β/°	104.7965(6)
γ/°	90
Volume/Å^3	727.870(9)
Z	2
ρ_{calc}g/cm^3	1.443
μ/mm^{-1}	2.303
F(000)	328.0
Crystal size/mm^3	0.88 × 0.14 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.94 to 159.76

Index ranges	-9 ≤ h ≤ 10, -11 ≤ k ≤ 10, -13 ≤ l ≤ 12
Reflections collected	47326
Independent reflections	2995 [R_{int} = 0.0328, R_{sigma} = 0.0111]
Data/restraints/parameters	2995/1/194
Goodness-of-fit on F^2	1.080
Final R indexes [I>=2σ (I)]	R_1 = 0.0192, wR_2 = 0.0512
Final R indexes [all data]	R_1 = 0.0193, wR_2 = 0.0512
Largest diff. peak/hole / e Å^{-3}	0.17/-0.14
Flack parameter	0.009(4)

Table S3. Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters (Å$^2\times10^3$) for **2g**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S6	4163.9(5)	6352.2(5)	1496.0(4)	18.75(11)
F8	6250.8(14)	7507.2(13)	3662.0(11)	29.4(3)
F9	6236.2(14)	8640.2(12)	1826.4(12)	29.0(3)
F10	4034.7(13)	8791.0(11)	2666.9(11)	27.8(2)
O13	3277.6(15)	2895.3(14)	1328.7(12)	21.6(3)
N3	6926.8(17)	5657.4(16)	537.6(13)	17.2(3)
N1	6577.2(18)	4160.2(16)	2158.7(13)	15.5(3)
C5	7981(2)	3652.0(19)	1731.0(16)	16.9(3)
C7	5239(2)	7886.5(19)	2449.7(18)	20.8(3)
C14	7064(2)	3012.6(19)	4411.8(16)	16.6(3)
C4	8177(2)	4595.5(19)	742.0(17)	17.4(3)
C19	8269(2)	4031.8(19)	5088.6(16)	19.1(3)
C2	5992(2)	5363.9(17)	1393.8(16)	15.9(3)
C15	7138(2)	1592.9(19)	4907.8(17)	20.2(4)
C17	9620(2)	2210(2)	6716.2(17)	23.5(4)
C12	4503(2)	2287.7(19)	2442.3(16)	19.4(3)
C20	8998(2)	2314(2)	2248.0(18)	23.9(4)
C11	5734(2)	3486.3(18)	3136.9(15)	15.9(3)
C18	9544(2)	3627(2)	6224.6(17)	22.6(4)
C21	9509(2)	4590(2)	-46.5(19)	25.7(4)
C16	8410(2)	1202(2)	6060.7(16)	22.9(3)

Table S4. Anisotropic Displacement Parameters (Å$^2\times10^3$) for **2g**. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U11	U22	U33	U23	U13	U12
S6	15.63(18)	15.76(18)	23.30(19)	-0.40(17)	2.13(13)	2.06(15)
F8	29.2(5)	27.3(6)	27.2(5)	-5.2(4)	-0.9(4)	1.8(5)
F9	28.8(5)	19.2(5)	43.7(6)	-0.7(5)	18.1(5)	-3.8(4)

F10	27.2(5)	17.2(5)	42.2(6)	-3.7(5)	14.8(5)	3.8(4)
O13	22.6(6)	19.7(6)	18.5(6)	-4.7(5)	-1.9(4)	1.6(5)
N3	18.3(7)	16.7(7)	15.2(6)	0.7(5)	1.8(5)	-0.8(5)
N1	19.0(7)	13.4(7)	13.6(6)	-0.6(5)	3.3(5)	1.3(5)
C5	19.2(7)	15.6(8)	15.9(7)	-1.6(6)	4.6(6)	2.5(6)
C7	20.7(8)	14.9(8)	27.5(9)	-0.1(7)	7.3(7)	2.5(7)
C14	18.7(7)	17.8(8)	14.2(7)	-0.5(6)	5.9(6)	1.1(6)
C4	18.7(8)	16.9(8)	15.6(7)	-0.1(6)	2.8(6)	1.1(6)
C19	22.5(8)	16.8(8)	18.4(7)	0.0(6)	6.0(6)	-0.1(7)
C2	16.9(7)	13.8(8)	15.3(7)	-0.9(6)	1.2(6)	1.5(6)
C15	23.3(8)	18.3(10)	19.3(7)	-0.7(6)	6.1(6)	-1.4(6)
C17	21.3(8)	30.9(10)	17.1(8)	3.5(7)	2.5(6)	3.8(7)
C12	22.1(8)	17.0(8)	17.6(7)	-0.2(6)	2.4(6)	-1.2(6)
C20	30.3(9)	20.4(9)	23.8(8)	4.4(7)	12.0(7)	9.1(7)
C11	20.0(8)	14.1(8)	14.0(7)	-0.1(6)	4.8(6)	-0.5(6)
C18	21.0(8)	25.1(9)	20.5(8)	-2.3(7)	3.0(6)	-2.2(7)
C21	25.3(9)	29.0(10)	24.8(8)	6.4(8)	10.2(8)	4.8(7)
C16	27.6(8)	21.3(9)	21.1(8)	5.3(7)	8.4(6)	3.2(8)

Table S5. Bond Lengths for **2g**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S6	C7	1.8019(18)	C5	C4	1.371(2)
S6	C2	1.7499(16)	C5	C20	1.494(2)
F8	C7	1.343(2)	C14	C19	1.395(2)
F9	C7	1.336(2)	C14	C15	1.393(2)
F10	C7	1.335(2)	C14	C11	1.522(2)
O13	C12	1.415(2)	C4	C21	1.495(2)
N3	C4	1.375(2)	C19	C18	1.388(2)
N3	C2	1.318(2)	C15	C16	1.395(2)
N1	C5	1.389(2)	C17	C18	1.390(3)
N1	C2	1.365(2)	C17	C16	1.384(3)
N1	C11	1.479(2)	C12	C11	1.526(2)

Table S6. Bond Angles for **2g**.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C2	S6	C7	98.30(8)	C15	C14	C11	122.29(15)
C2	N3	C4	105.70(14)	N3	C4	C21	120.98(15)
C5	N1	C11	128.37(14)	C5	C4	N3	110.07(15)
C2	N1	C5	106.17(13)	C5	C4	C21	128.94(16)
C2	N1	C11	125.18(14)	C18	C19	C14	120.36(16)
N1	C5	C20	125.28(14)	N3	C2	S6	124.17(12)
C4	C5	N1	105.99(14)	N3	C2	N1	112.05(14)

C4	C5	C20	128.70(15)	N1	C2	S6	123.73(12)
F8	C7	S6	112.98(12)	C14	C15	C16	120.14(16)
F9	C7	S6	114.07(12)	C16	C17	C18	119.29(16)
F9	C7	F8	106.30(14)	O13	C12	C11	108.95(13)
F10	C7	S6	107.99(11)	N1	C11	C14	110.95(13)
F10	C7	F8	107.44(14)	N1	C11	C12	109.83(12)
F10	C7	F9	107.75(14)	C14	C11	C12	114.94(14)
C19	C14	C11	118.63(15)	C19	C18	C17	120.52(17)
C15	C14	C19	119.07(15)	C17	C16	C15	120.61(19)

Table S7. Torsion Angles for **2g**.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O13	C12	C11	N1	-57.68(17)	C2	N3	C4	C5	0.21(18)
O13	C12	C11	C14	176.39(13)	C2	N3	C4	C21	-179.02(16)
N1	C5	C4	N3	-0.67(18)	C2	N1	C5	C4	0.84(17)
N1	C5	C4	C21	178.48(17)	C2	N1	C5	C20	-177.51(16)
C5	N1	C2	S6	176.83(12)	C2	N1	C11	C14	-139.34(15)
C5	N1	C2	N3	-0.76(18)	C2	N1	C11	C12	92.49(18)
C5	N1	C11	C14	47.5(2)	C15	C14	C19	C18	1.2(2)
C5	N1	C11	C12	-80.71(19)	C15	C14	C11	N1	-125.80(16)
C7	S6	C2	N3	-79.04(15)	C15	C14	C11	C12	-0.4(2)
C7	S6	C2	N1	103.65(14)	C20	C5	C4	N3	177.61(16)
C14	C19	C18	C17	-1.1(3)	C20	C5	C4	C21	-3.2(3)
C14	C15	C16	C17	-0.6(2)	C11	N1	C5	C4	175.06(15)
C4	N3	C2	S6	-177.24(12)	C11	N1	C5	C20	-3.3(3)
C4	N3	C2	N1	0.35(18)	C11	N1	C2	S6	2.4(2)
C19	C14	C15	C16	-0.4(2)	C11	N1	C2	N3	-175.22(14)
C19	C14	C11	N1	52.89(19)	C11	C14	C19	C18	-177.49(15)
C19	C14	C11	C12	178.25(14)	C11	C14	C15	C16	178.28(15)
C2	S6	C7	F8	-60.16(13)	C18	C17	C16	C15	0.8(3)
C2	S6	C7	F9	61.41(13)	C16	C17	C18	C19	0.0(3)
C2	S6	C7	F10	-178.84(12)					

Table S8. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for **2g**.

Atom	*x*	*y*	*z*	U(eq)
H13	3146.03	2337.36	659.05	32
H19	8217.65	5007.87	4770.18	23
H15	6319.94	889.8	4460.14	24
H17	10493.77	1935.59	7493.97	28
H12A	5156.91	1505.35	2127.32	23
H12B	3909.15	1858.02	3088.3	23
H20A	9445.12	2384.22	3231.22	36

H20B	9961.88	2225.53	1827.03	36
H20C	8253.41	1454.77	2025.03	36
H11	5013.27	4260.12	3411.63	19
H18	10371	4324.96	6669.52	27
H21A	8941.62	4643.83	-1014.59	39
H21B	10186.58	3689.62	142.51	39
H21C	10273.78	5431.59	215.51	39
H16	8446.13	234.43	6398.57	28

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First lepidiline-inspired 1,3-dibenzyl 2-CF_3S-imidazoliums: Design, synthesis and cytotoxic activity study

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ABSTRACT

A series of lepidiline-type 4,5-dimethylimidazolium hexafluorophosphates, functionalized with F atom(s) as well as the CF_3, OCF_3, OCH_3 and SCF_3 groups located either in the central core or placed at benzyl-type *N*-substituents, was prepared, and the cytotoxicity against selected cancer cell lines was examined. The applied four-step protocol based on condensation of diacetyl monoxime with formaldimines (hexahydro-1,3,5-triazines), one-pot telescopic sulfur-transfer followed by electrophilic trifluoromethylation, and subsequent *N*-alkylation of the central imidazole ring, enabled access to symmetrical and unsymmetrical products. The counterion metathesis provided crystalline hexafluorophosphates, which were isolated in high overall yield. Analysis of biological activity of the intermediate CF_3S-imidazoles and the corresponding imidazoliums against HeLa, HepG2, and A549 cancer cell lines revealed amplified cytotoxicity of the final salts in comparison to natural lepidiline alkaloids, which is promising in the context of drug discovery.

1. Introduction

The imidazole ring is a key structural motif in many bioactive compounds, including numerous naturally occurring alkaloids of various substitution patterns [1]. The mentioned heterocyclic unit is also incorporated in synthetic drugs and agrochemicals, of which fluorinated imidazoles and benzimidazoles are of special interest [2]. In this group, imidazolium salts represent a pivotal class of ionic compounds, renowned for their extensive applications in organic synthesis, catalysis, pharmacology, and agrochemistry [3]. Distinctive physio-chemical properties of imidazoliums, such as high thermal stability, low volatility and the ability to form room-temperature ionic liquids (RTILs), have rendered them subjects of considerable scientific inquiry. In this context, remarkable attention has been paid to naturally occurring lepidilines and related 4,5-dimethylimidazolium salts identified as a readily available platform of notable biological activities, which position them as promising candidates for structural manipulations towards new bioactive compounds and other materials of special properties [4–6].

The lepidiline alkaloids based on 1,3-dibenzylated 4,5-dimethylimidazolium chlorides (lepidilines A-D, Fig. 1) have been known for over two decades as the components of the roots of *Lepidium meyenii*, so-called Maca, an edible plant native to South America [5]. Three further imidazolium alkaloids functionalized with a single benzyl group were also identified as secondary metabolites in Maca only recently. They were named as lepidilines E, F and G [6]. Notably, dried roots of this 'Peruvian ginseng' are a common food additive available worldwide with several claimed biological activities such as anti-bacterial, anti-oxidative, and anti-hypertensive properties [7]; improvement of the fecundity by Maca extracts was also reported [8]. For this reason, an in-depth study on phenotype-related nutrition content and potential clinical applications of Maca components has been undertaken [7–9].

The first isolated imidazolium alkaloids in the series, i.e. lepidiline A (**1a**, 1,3-dibenzyl-4,5-dimethylimidazolium chloride) and lepidiline B (**1b**, 1,3-dibenzyl-2,4,5-trimethylimidazolium chloride), exhibit promising cytotoxicity [10], and for this reason, manipulation of their structures can be of interest in searching for effective anticancer agents. In a series of independent works by Kerr, Tacke, and Tóth groups, lepidiline A was demonstrated as a suitable precursor for *N*-heterocyclic carbene (NHC) ligand in complexes of iridium(I), copper(I), silver(I), and gold(I), respectively [11]. Noteworthy, binding of silver and gold metal ions onto lepidiline-derived carbene resulted in significantly

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enhanced cytotoxicity of the formed complexes against ovarian, gastrointestinal, breast and uterine cancer cells [11c]. On the other hand, our group demonstrated that introduction of fluorine atom or fluoroalkylated substituents into the peripheral benzyl units of lepidiline scaffold amplifies cytotoxic activity of the modified alkaloid, possibly due to increase of its lipophilic character [12].

Among small fluorinated substituents, the trifluoromethylthiol (SCF_3) group is known for its ability to remarkably increase lipophilicity, metabolic stability and bioavailability of the parent compound, which is essential for the effective design of new pharmaceuticals [13]. Of the key parameters that highlight the uniqueness of the SCF_3 unit, the physicochemical Hansch parameter of 1.44, i.e. much higher than that of the CF_3 group (0.88), is of special importance [14]. Introduction of the trifluoromethylsulfanyl group into an organic molecule enhances the oleophilicity of the modified compound to a great extent, and in turn, often leads to increased permeability and bioavailability [15]. Thus, in continuation of our study aimed at *de novo* synthesis of lepidilines and their structural analogs [10,16], we turned attention to new derivatives functionalized with the SCF_3 group located at C(2) of the imidazole core. Here we report on the synthesis of the title 2-trifluoromethylthiolimidazolium hexafluorophosphates and the results on initial screening of their cytotoxic properties against HeLa (cervix), HepG2 (liver), and A549 (lung) cell lines.

2. Results and discussion

2-Trifluoromethylthiol-imidazolium salts are very little known in the literature, and to the best of our knowledge, there are only two synthetic methods reported thus far [17]. Historically, the first approach published in 2016 by Mizuta was based on the reaction of *N,N'*-dialkylimidazole-2-thiones with Umemoto-type electrophilic trifluoromethylating reagents applied as sources of the "CF_3^+ " [17a]. The target 2-CF_3S-imidazoliums were further examined in the context of the phase-transfer catalysis. In 2023, an alternative approach utilizing the $AgSCF_3$ as a source of the "SCF_3^-" intermediate in trifluoromethylthiolation of 1-phenylimidazole was presented [17b]. The first formed imidazole was subsequently quaternized with TfOMe to afford the desired imidazolium salt, which was applied as a dehydroxytrifluoro-methylthiolating agent in reactions with benzyl-type alcohols.

In order to identify the most efficient protocol towards the designed materials of type **4**, we began our synthetic study with testing three conceivable routes, namely (*i*) the electrophilic trifluoromethylthiolation of the in situ generated NHC-carbene derived from lepidiline A (**1a**) with a suitable "SCF_3^+" source, (*ii*) electrophilic trifluoromethylation of the respective imidazole-2(3*H*)-thione **5a** with a convenient "CF_3^+"-transferring reagent, and (*iii*) *N*-alkylation of the corresponding imidazole **6a** pre-functionalized with the SCF_3 group (Scheme 1).

As to the first approach, we have tested the possibility to directly trifluoromethylthiolate the in situ generated NHC-type carbene derived from the model lepidiline A (**1a**). Prompted by the literature reports [18], easily available *N*-(trifluoromethylthio)-saccharin was examined under various reactions conditions, using either Et_3N or pyridine as a base (in MeCN or THF, rt or reflux), however, in all the attempts no consumption of **1a** could be observed.

In contrast, the expected smooth CF_3^+-transfer onto imidazole-2-thione **5a** by using *S*-(trifluoromethyl)dibenzothiophenium triflate (Umemoto reagent I) was observed upon heating MeCN solution [17a]. In that case, the expected product was formed in moderate yield (ca. 25–30 %, based on ^{1}H NMR). Unfortunately, the target salt was contaminated with a reasonable amounts of unidentified polar by-products, and the isolation of the analytically pure sample of **4a** was troublesome. Gratifyingly, treatment of CF_3S-functionalized imidazole

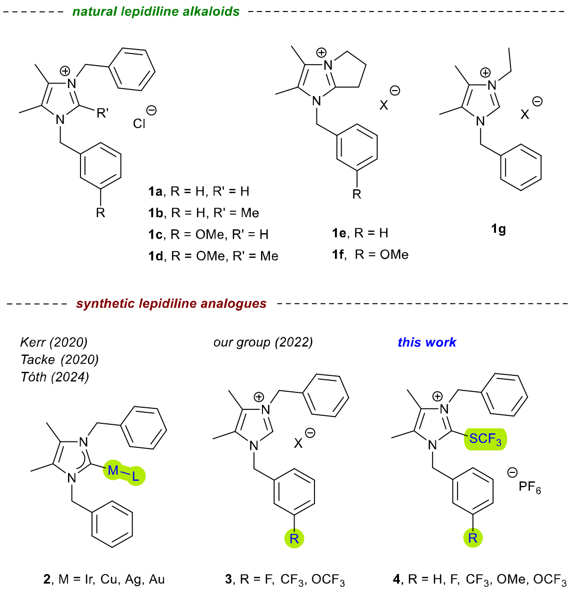
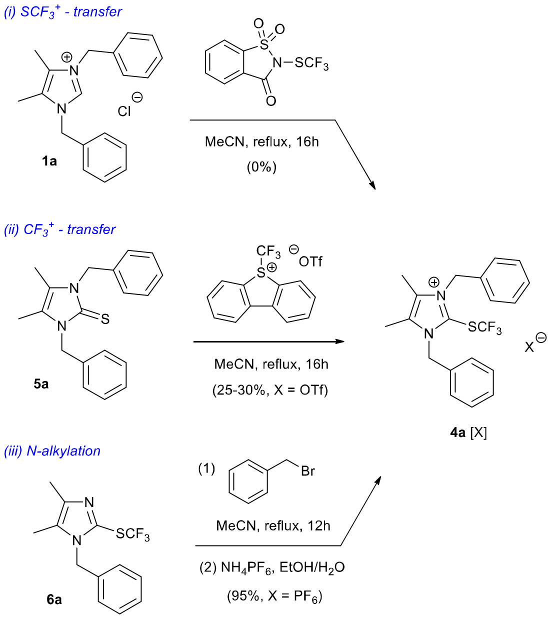
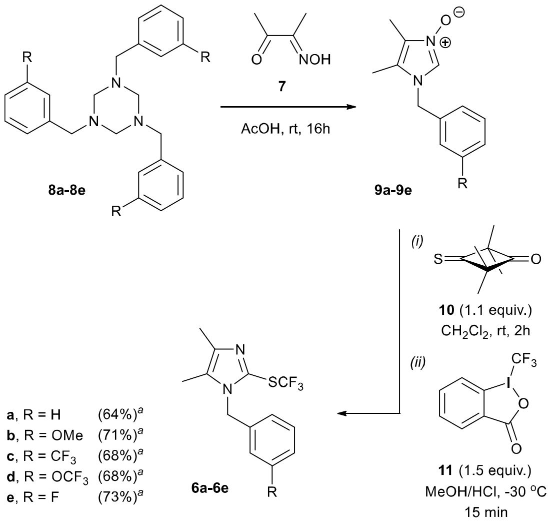


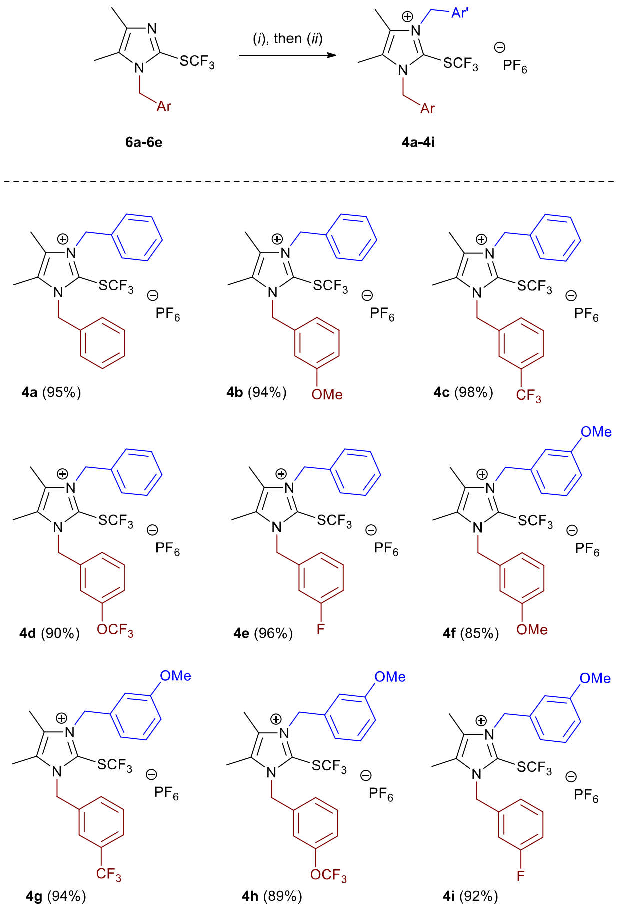
Fig. 1. Structures of natural lepidilines A-G (**1a-1g**) and synthetic analogs of lepidiline A: Metal-NHC complexes 2, ionic derivatives with a partially fluorinated benzyl substituents 3, and the CF_3S-fonctonalized salts 4 reported herein.



Scheme 1. Initial attempts in the synthesis of **4a**.



Scheme 2. Synthesis of 2-CF$_3$S-imidazoles **6a-6e:** ^{a} overall yield (for three steps).



Scheme 3. Scope of target 2-CF_3S-imidazolium hexafluorophosphates **4** prepared through *N*-alkylation of imidazoles **6** and subsequent ion exchange: (*i*) BnBr or 3-$MeOC_6H_4CH_2Br$, MeCN, reflux 12 h; (*ii*) NH_4PF_6, EtOH/H_2O.

6a with slight excess benzyl bromide, in hot MeCN, provided the expected salt **4a** [X = Br] identified as the exclusive product (>98 %). Attempts to get the analytically pure sample through recrystallization or by trituration (with Et_2O) revealed a highly hygroscopic character of the obtained bromide, and for this reason, the ion metathesis with NH_4PF_4 was carried out to give an easy-to-handle crystalline salt **4a** [X = PF_6] in excellent 91 % overall yield.

To briefly check whether the reaction time can be shortened, the *N*-benzylation of **6a** was repeated under microwave activation to provide the expected product **4a** in 1 h of heating (110 °C) only, both in solution (MeCN) and in neat, but lower overall yields of 71 % and 60 %, respectively, were achieved after the subsequent ion exchange step. On the other hand, U-sonication of the MeCN solution of benzyl bromide and **6a** showed trace conversion (<5 %) after 1 h at room temperature. Thus, the synthesis of the designed salts of type **4** was continued under classical manner, by refluxing MeCN solution overnight.

Taking into account the planned biological activity studies, the synthetic method reported by Chen et al. towards key trifluoromethylthiolated imidazoles, comprising metal-based reagents ($AgSCF_3$), was ruled out [17b]. Hence, we turned attention to our recent protocol employing imidazole *N*-oxides demonstrated as useful intermediates for the synthesis of 2-CF_3S-functionalized imidazoles **6** [19]. As outlined in Scheme 2, the synthesis follows condensation of diacetyl monoxime (**7**) with 1,3,5-trisubstituted hexahydro-1,3,5-triazines **8** (trimers of the corresponding reactive formaldimines) to give imidazole *N*-oxides of type **9** [12]. Subsequent one-pot telescoping sulfur-transfer carried out by treatment of **9** with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**10**) and trifluoromethylation of the first formed imidazole-2 (3*H*)-thiones with Togni reagent (**11**) led to desired materials **6a-6e**, which were isolated in fair overall yields 64–73 % (after 3 steps).[1]

With key precursors **6a-6e** in hand, a series of target symmetric (**4a**,**4 f**) and unsymmetric (**4b-4e**, **4 g-4i**) trifluoromethylthiolated imidazolium salts were prepared by *N*-alkylation using either benzyl bromide or 3-methoxybenzyl bromide as an electrophile. Subsequent counterion metathesis in the first-formed bromides with NH_4PF_6, in aqueous ethanol, provided the final hexafluorophosphates **4** isolated as spectroscopically pure, colorless precipitate, in excellent yield > 90 % (Scheme 3).[2] The structure of all products was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR analysis, IR and high resolution MS measurements. For example, in ^{1}H NMR spectrum of **4a**, a set of diagnostic singlet absorptions found at $\delta = 2.20$ (6 H) and $\delta = 5.68$ (4 H), attributed to two equivalent Me and two CH_2 groups, respectively, indicated the C_2-symmetry of the obtained product. Next, the presence of the C(2)SCF_3 unit in **4a** was evidenced by two quartets at $\delta = 126.3$ ($^1J_{C\text{-}F} = 316.6$ Hz) and $\delta = 127.9$ ($^3J_{C\text{-}F} = 2.8$ Hz) in ^{13}C{1 H} NMR, and supplemented by a singlet absorption at $\delta = -38.6$ in ^{19}F NMR. In the latter spectrum, additional doublet located at $\delta = -73.9$, characterized by a remarkable coupling constant ($J_{P\text{-}F}$) of 712.3 Hz, clearly confirmed the presence of the $[PF_6]^-$ anion, while HRMS analysis validated molecular formula of the imidazolium cation as $[C_{20}H_{20}F_3N_2S]^+$.

Results on cytotoxicity of all new synthetic 2-CF_3-lepidilines **4a-4i** and of non-ionic precursors **6a-6e**, supplemented by previously reported activity of structurally similar 1-benzyl-3-(3-fluorobenzyl)-4,5-dimethylimidazolium hexafluorophosphate (**3a**, R = F, X = PF_6 [12]; for general structure of previously studied laterally fluorinated imidazoliums **3**, see Fig. 1) checked against the same normal and cancer cell lines, are collected in Table 1.

Lepidiline A itself has a moderate to low in vitro anticancer effect when tested against a panel of cancer cell lines of various origins. It was found that it exerts only low or no toxicity up to approximately 60 μM [11c]. Therefore, the cytotoxic effects observed in cell line studies are mainly due to the presence of substituents in modified lepidilines.

Lepidiline A is also a convenient *N*-heterocyclic carbene precursor, therefore a suitable ligand source for metal complexes. Thus, its copper (I), gold(I), and silver(I) complexes were synthesized and tested against various types of cancer cells as well as bone marrow-derived and adipose-derived mesenchymal stem cells. Authors demonstrated that the binding of metal ions to lepidiline A results in enhanced cytotoxicity, likely due to the induction of intracellular reactive oxygen species (ROS) by the copper complex, particularly given the increased electron-withdrawing properties of the ligand. Notably, the silver and gold complexes showed their potential to overcome multidrug resistance effect [11c].

It is well known that introducing a fluorine-containing substituent into the heterocyclic core of an organic compound substantially increases its bioactivity [20]. Recently, we have demonstrated that functionalization of the lateral benzylic 'arm' in lepidiline A with a single fluorine atom or fluoromethyl groups such as CF_3 and OCF_3, enhances cytotoxicity of the parent alkaloid [12]. For example, 1-benzyl-3-(3-fluorobenzyl)-4,5-dimethylimidazolium hexafluoro-phosphate (**3a**) was highly active on HeLa cell lines, and less cytotoxic against non-cancer cell lines (Table 1). It can be hypothesized that this modification enhances the cytotoxic activity of the modified alkaloid; this may be due to an increase in its lipophilic character [20b].

The incorporation of the CF_3S group has been demonstrated to enhance both lipophilicity and electron-withdrawing characteristics, thereby increasing the bioavailability of therapeutic compounds. Consequently, the incorporation of CF_3S units into drug-like molecules has emerged as a significant strategy in contemporary organic chemistry [20c]. In light of the findings, a new series of derivatives were synthesized and functionalized with the SCF_3 group located at C(2) of the imidazole core. It was observed that the obtained products exhibited amplified toxicity, with the results depending on the specific cell line utilized in the studies.

For comparison purposes, the in vitro cytotoxic activity study of the designed CF_3S-functionalized compounds of type **4** and **6**, were also carried out with non-cancer cell lines MRC-5, Vero, LLCMK2, and NCTC clone 929, as well as three cancer cell lines HepG2 (human hepatocellular carcinoma cells), A549 (human lung carcinoma cells), and HeLa (human cervix adenocarcinoma cells). The cytotoxicity of the investigated materials was established by the measurement of 50 % inhibition of cell growth by the MTT assay and expressed as the CC_{50} parameter [21], and the results are collected in Table 1 (selectivity index values were also calculated for selected cell lines, see Supporting Information). As expected, introduction of the SCF_3 group into the imidazole ring further amplified cytotoxic character of the obtained imidazole derivatives.

In general, A549 and HeLa cell lines were found most sensitive towards imidazolium salts **4**. In contrast, non-cancer cell lines MRC-5, Vero and LLCMK2 were affected by **4** to a lesser extent (except for the highly cytotoxic model analog of lepidiline A, i.e., salt **4a**). In contrast, non-ionic precursors **6** exhibited higher cytotoxicity against normal cells (especially on Vero and NCTC clone 929), rather than on cancer cell lines, of which HepG2 and HeLa showed similar, moderate sensitivities.

Analysis of the structure-activity relationship revealed that imidazolium salts **4** bearing additional fluoromethyl groups showed promising selectivity as exemplified by CF_3-benzyl-functionalized derivative **4c**, for which the CC_{50} values on HepG2 and A549 cell lines (5.0 μM and 2.8 μM) were at least an order of magnitude lower than those measured

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[1] *General Procedure A for synthesis of 2-CF_3S-imidazoles* ***6a-6e***: A solution of diacetyl monoxime (**7**, 1.0 mmol, 101 mg) and hexahydro-1,3,5-triazine **8** (0.35 mmol) in glacial acetic acid (6 mL) was stirred at room temperature for 16 h. After excess conc. HCl was added dropwise (0.5 mL), the solvents were removed in vacuo, the residue was dissolved in MeOH (5 mL), solid $NaHCO_3$ (1.0 g) was added, and the stirring was continued until the evolution of CO_2 ceased (30 min). The solvent was evaporated, CH_2Cl_2 (10 mL) was added, and the precipitates were removed by filtration through a short plug of Celite®. After solvent was removed from the filtrate, the resulting material was triturated with Et_2O (10 mL), the crude imidazole *N*-oxide **9** was filtered off and dried under vacuum. The obtained material was dissolved in dry CH_2Cl_2 (8 mL). A solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**10**, 172 mg, 1.1 mmol) in DCM (6.0 mL) was then added dropwise, and the mixture was stirred at room temperature (rt) for 2 h. The solvent was removed in vacuo, the resulting material was dissolved in $MeOH/HCl_{(sat.)}$ (4.0 mL), cooled to −30 °C, and a solution of **11** (475 mg, 1.5 mmol) in $MeOH/HCl_{(sat.)}$ (6.0 mL) was added under inert atmosphere. After 15 min, solvents were removed in vacuo, and the product **6** was purified by column chromatography (CC) on neutral alumina. 1-Benzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6a**): CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 183 mg (64 %); mp 53–54 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 2.22 (s, 3 H), 5.29 (s, 2 H), 6.91–6.93 (m, 2 H), 7.26–7.33 (m, 3 H). ^{13}C{1 H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.0, 48.6, 126.1, 126.4 (q, $^3J_{C\text{-}F} \approx 3.1$ Hz), 128.0, 128.1 (q, $^1J_{C\text{-}F} = 312.3$ Hz), 129.1, 129.4, 135.9, 138.2. ^{19}F NMR (565 MHz, $CDCl_3$): δ −42.5 (s, CF_3). ESI-MS *m/z*: 287.2 (100, $[M+H]^+$). NMR spectra are in full accordance with those reported in the literature [19]

[2] *General Procedure B for synthesis of 1,3-dibenzylated 2-CF_3S-imidazolium hexafluorophosphates* ***4a-4i***: To a solution of 2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole **6** (0.5 mmol) in MeCN (5 mL), benzyl bromide or 3-methoxybenzyl bromide (1.5 mmol) was added, and the resulting mixture was refluxed for 12 h. After the solvent was removed in vacuo, the resulting crude bromide was dissolved in $EtOH/H_2O$ (1 mL, v/v 1:1), and the solid NH_4PF_6 (0.53 mmol, 87 mg) was added. The obtained precipitate was filtered off, washed with $EtOH/H_2O$ (3 × 1 mL, v/v 1:1), then with distilled water (3 × 1 mL), and the product was air dried. 1,3-Dibenzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluo-rophosphate (**4a**): colorless solid, 248 mg (95 %); mp 150–152 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.20 (s, 6 H), 5.68 (s, 4 H), 7.08–7.11 (m, 4 H), 7.35–7.38 (m, 2 H), 7.40–7.44 (m, 4 H). ^{13}C{1 H} NMR (151 MHz, DMSO-d_6) δ 10.1, 51.9, 126.27, 126.31 (q, $^1J_{C\text{-}F} = 316.6$ Hz), 127.9 (q, $^3J_{C\text{-}F} = 2.8$ Hz), 129.1, 129.7, 132.1, 134.6. ^{19}F NMR (565 MHz, DMSO-d_6): δ −38.6 (s, CF_3), −73.9 (d, $J_{P\text{-}F} = 712.3$ Hz, PF_6). IR (neat) ν 1480, 1457, 1353, 1170, 1096, 831 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M-PF_6]^+$ calcd for $C_{20}H_{20}F_3N_2S$ 377.1299, found 377.1298.

Table 1
Cytotoxicity assay results in concentrations of compounds ranging from 0.1 to 1000 μM on A549, HepG2, HeLa, Vero, LLCMK2, NCTC clone 929 and MRC-5 cells. Selectivity index values are shown in Supplementary Information.

cmpd	CC_{50} [μM]						
	Non-cancer cell lines				Cancer cell lines		
	MRC-5	Vero	LLCMK2	NCTC clone 929	HepG2	A549	HeLa
3a[a]	149.7 ± 4.2	56.3 ± 3.2	150.3 ± 2.50	148.3 ± 11.5	316.7 ± 5.80	38.0 ± 3.5	0.080 ± 0.001
4a	12.5 ± 4.6	< 0.01	< 0.01	< 0.01	10.1 ± 1.6	< 0.01	< 0.01
4b	30.0 ± 7.9	32.0 ± 3.8	158.0 ± 20.2	8.8 ± 1.4	12.3 ± 2.2	13.0 ± 2.0	48.4 ± 4.8
4c	28.0 ± 5.3	24.3 ± 3.2	242.4 ± 13.7	7.5 ± 0.8	5.0 ± 0.7	2.8 ± 0.4	11.1 ± 2.2
4d	19.0 ± 3.3	19.2 ± 3.3	44.6 ± 3.1	3.6 ± 0.5	6.0 ± 0.8	1.5 ± 0.3	9.5 ± 2.4
4e	58.6 ± 17.0	28.8 ± 2.9	207.0 ± 36.6	0.15 ± 0.04	18.6 ± 2.7	7.1 ± 2.1	19.8 ± 4.5
4 f	46.5 ± 15.6	16.2 ± 2.6	332.7 ± 38.8	3.3 ± 0.7	18.0 ± 3.2	2.1 ± 0.5	0.10 ± 0.02
4 g	37.6 ± 11.7	14.0 ± 2.8	86.8 ± 8.5	3.3 ± 1.4	10.2 ± 2.0	< 0.01	0.06 ± 0.01
4 h	11.1 ± 2.7	0.5 ± 0.1	0.80 ± 0.03	< 0.01	3.5 ± 1.2	< 0.01	< 0.01
4i	12.6 ± 2.4	< 0.01	0.9 ± 0.2	< 0.01	17.0 ± 2.3	< 0.01	< 0.01
6a	310.9 ± 63.6	6.0 ± 1.5	21.8 ± 4.3	0.5 ± 0.1	99.1 ± 16.8	371.4 ± 51.1	56.7 ± 6.8
6b	116.8 ± 17.5	13.7 ± 1.9	30.8 ± 6.6	0.24 ± 0.19	92.8 ± 6.8	188.5 ± 21.6	47.6 ± 7.1
6c	97.1 ± 11.3	3.8 ± 0.9	9.3 ± 3.1	0.5 ± 0.1	35.3 ± 4.7	72.0 ± 10.8	42.3 ± 8.8
6d	40.8 ± 4.5	6.8 ± 1.2	20.7 ± 4.5	13.3 ± 3.6	27.7 ± 5.3	88.3 ± 17.8	67.1 ± 10.6
6e	39.0 ± 11.8	13.8 ± 3.6	31.0 ± 8.1	0.03 ± 0.01	92.0 ± 11.0	190.9 ± 46.4	35.2 ± 5.5

[a] results from ref. [12]

for non-cancer MRC-5, Vero, and LLCMK2 cells (28.0 μM, 24.3 μM, and 242.4 μM, respectively). Furthermore, introduction of the OMe group in unsymmetrical imidazoliums **4g-4i** bearing substituents located at *meta* positions of both benzyl groups, provided materials active against A549 and HeLa cell lines at nanomolar concentrations (up to 10 nM), however, enhanced activity on non-cancer cells was also observed in these cases. The mentioned results on bi/tri-functionalized fluorinated lepidilines encourage further study in search of cytotoxic analogs with a larger safety margin.

3. Conclusions

Trifluoromethylsulfanyl-imidazolium salts inspired by naturally occurring lepidiline alkaloids were prepared, and their cytotoxic activity on selected four non-cancer and three cancer cell lines was checked. The synthesis of the designed materials comprised two telescopic one-pot procedures, i.e. (*i*) acid-catalyzed condensation of formaldimines with diacetyl monoxime, sulfur transfer towards the intermediate imidazole *N*-oxide, and electrophilic *S*-trifluoromethylation of the first formed imidazole-2-thione with Togni reagent, followed by (*ii*) fully chemoselective *N*-alkylation of the obtained 2-CF_3S-imidazole and the final Br → PF_6 anion exchange. In comparison to biological activity of previously reported natural lepidilines and their synthetic analogs, the obtained products exhibited amplified cytotoxicity, especially on HeLa, but also on A549 cell lines. Among the tested compounds the most active was simple 2-SCF_3-derivative of the natural lepidiline A (i.e. salt **4a**), along with two other imidazoliums **4 h** and **4i**, bearing additional OMe group and either OCF_3 or F atom located at the lateral benzyl units. The presented results demonstrated that introduction of the SCF_3 group into the imidazolium ring, remarkably enhances the biological activity, and nicely supplement previous results on the synthesis and bioactivity studies on fluorinated natural products [22].

CRediT authorship contribution statement

Marta Denel-Bobrowska: Investigation. **Poper Wiktor Krzysztof:** Investigation. **Olejniczak Agnieszka:** Writing – review & editing, Supervision, Conceptualization. **Marcin Jasiński:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Marcin Jasinski reports financial support was provided by University of Lodz. Wiktor K. Poper reports financial support was provided by University of Lodz. Agnieszka B. Olejniczak and Marta Denel-Bobrowska reports financial support was provided by Polish Academy of Sciences. Agnieszka B. Olejniczak and Marta Denel-Bobrowska reports financial support was provided by Republic of Poland Ministry of Science and Higher Education. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

MJ and ABO designed chemical and biological experiments, respectively; WKP prepared and characterized all intermediates and target compounds; MDB examined cytotoxicity of the final compounds; MJ drafted the manuscript; all authors contributed to the final version of the paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2025.118606.

Data availability

Data will be made available on request.

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Supporting Information for

First lepidiline-inspired 1,3-dibenzyl 2-CF$_3$S-imidazoliums: Design, synthesis and cytotoxic activity study

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Content:

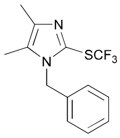
1. General information

Solvents and common starting materials were purchased and used as received. If not stated otherwise, reactions in solutions were carried out under an inert atmosphere of argon, in flame-dried flasks; subsequent manipulations were conducted in air. Microwave heating was performed with CEM Discover SP 909155; reactions were carried out in Fixed Power (continuous irradiation) mode with Activent® assistance, with a set power of 150 MW. Sonication experiments were carried out with Omni Ruptor 4000 at a 20 kHz frequency. Products of type **6** were purified by standard column chromatography (CC) on neutral alumina, using freshly distilled solvents as eluents; the final solid materials of type **4** were recrystallized from EtOH/H_2O (v/v 1:1) mixtures. Melting points were determined in capillaries with a Stuart SMP30 apparatus with automatic temperature monitoring, and are uncorrected. NMR experiments were performed with a Bruker Avance III or with a Bruker AvanceNeo instruments (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz); chemical shifts are given relative to solvent residual peaks [for $CDCl_3$: ^{1}H NMR: δ = 7.26, ^{13}C NMR: δ = 77.16; for DMSO-*d*$_6$: ^{1}H NMR: δ = 2.50, ^{13}C NMR: δ = 39.52; for CD_3CN: ^{1}H NMR: δ = 1.94, ^{13}C NMR: δ = 1.32, 118.26][1] or to $CFCl_3$ (^{19}F NMR: δ = 0.00) used as external standard. The IR spectra were measured with an Agilent Cary 630 FTIR spectrometer, in neat. ESI-MS were performed with a Varian 500-MS LC Ion Trap; high-resolution MS (ESI-TOF) measurements were taken with a Waters Synapt G2-Si mass spectrometer. Diacetyl monoxime (**7**) was prepared from butanone using isoamyl nitrite in analogy to the procedure reported by Semon and Damerell.[2] Hexahydro-1,3,5-triazines **8** were prepared by condensation of the respective benzylamines with paraformaldehyde, in methanol, at room temperature, and the resulting crude products were used in the next step without purification.[3]

2. Synthetic procedures and characterization data

General Procedure A for synthesis of 2-CF_3S-imidazoles **6a**-**6e**: A solution of diacetyl monoxime (**7**, 1.0 mmol, 101 mg) and hexahydro-1,3,5-triazine **8** (0.35 mmol) in glacial acetic acid (6 mL) was stirred at room temperature for 16 h. After excess conc. HCl was added dropwise (0.5 mL), the solvents were removed in vacuo, the residue was dissolved in MeOH (5 mL), solid $NaHCO_3$ (1.0 g) was added, and the stirring was continued until the evolution of CO_2 ceased (30 min). The solvent was evaporated, CH_2Cl_2 (10 mL) was added, and the precipitates were removed by filtration through a short plug of Celite®. After the solvent was removed from the filtrate, the resulting material was triturated with Et_2O (10 mL), the crude imidazole *N*-oxide **9** was filtered off and dried under vacuum. The obtained material was dissolved in dry CH_2Cl_2 (8 mL), a solution of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**10**, 172 mg, 1.1 mmol) in DCM (6.0 mL) was added dropwise, and the mixture was stirred at rt for 2h. The solvent was removed in vacuo, the resulting material was dissolved in MeOH/$HCl_{(sat.)}$ (4.0 mL), cooled to –30 °C, and a solution of **11** (475 mg, 1.5 mmol) in MeOH/$HCl_{(sat.)}$ (6.0 mL) was added under inert atmosphere. After 15 min, solvents were removed in vacuo, and the product **6** was purified by column chromatography (CC) on neutral alumina.

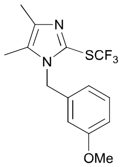
1-Benzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6a**):



6a

CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 183 mg (64%); mp 53-54 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.22 (s, 3H), 5.29 (s, 2H), 6.91-6.93 (m, 2H), 7.26-7.33 (m, 3H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.0, 48.6, 126.1, 126.4 (q, $^{3}J_{\text{C-F}} \approx 3.1$ Hz), 128.0, 128.1 (q, $^{1}J_{\text{C-F}} = 312.3$ Hz), 129.1, 129.4, 135.9, 138.2. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.5 (s, CF_3). ESI-MS *m/z*: 287.2 (100, $[M+H]^+$). NMR spectra are in full accordance with those reported in the literature.[4]

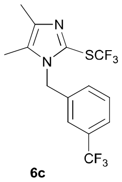
4,5-Dimethyl-1-(3-methoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6b**):



6b

CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 225 mg (71%); mp 69-71 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.22 (s, 3H), 3.76 (s, 3H), 5.26 (s, 2H), 6.46 (m_c, 1H), 6.50-6.52 (m, 1H), 6.80-6.82 (m, 1H), 7.22-7.24 (m, 2H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.0, 48.4, 55.3, 112.1, 113.0, 118.3, 126.4 (q, $^{3}J_{\text{C-F}} \approx 3.0$ Hz), 128.1 (q, $^{1}J_{\text{C-F}} = 312.1$ Hz), 129.4, 130.1, 137.5, 138.2, 160.2. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.5 (s, CF_3). IR (neat) ν 1614, 1588, 1457, 1405, 1293, 1238, 1167, 1133, 1096, 1051, cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{16}F_3N_2OS$ 317.0935, found 317.0935.

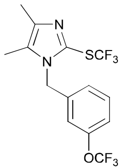
4,5-Dimethyl-1-(3-trifluoromethylbenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6c**):



6c

CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 241 mg (68%); mp 65-66 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.24 (s, 3H), 5.35 (s, 2H), 7.02-7.05 (m, 1H), 7.27-7.28 (m, 1H), 7.44-7.7.47 (m, 1H), 7.55-7.57 (m, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.1, 48.1, 123.0 (q, $^{3}J_{\text{C-F}} \approx 3.7$ Hz), 123.9 (q, $^{1}J_{\text{C-F}} = 273.3$ Hz), 125.0 (q, $^{3}J_{\text{C-F}} \approx 3.7$ Hz), 126.6 (q, $^{3}J_{\text{C-F}} \approx 3.1$ Hz), 128.0 (q, $^{1}J_{\text{C-F}} = 312.2$ Hz), 129.1, 129.3 (br), 129.8, 131.6 (q, $^{2}J_{\text{C-F}} = 32.6$ Hz), 137.0, 138.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.3 (s, CF_3), –62.8 (s, CF_3). IR (neat) ν 1577, 1435, 1409, 1327, 1096, 1074, 1014 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{13}F_6N_2S$ 355.0704, found 355.0703.

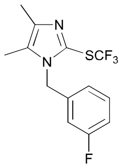
4,5-Dimethyl-1-(3-trifluoromethoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6d**):



6d

CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 252 mg (68%); mp 49-51 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.24 (s, 3H), 5.31 (s, 2H), 6.81-6.85 (m, 2H), 7.14-7.17 (m, 1H), 7.35-7.37 (m, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.1, 48.0, 118.8, 120.4, 120.5 (q, $^{1}J_{\text{C-F}} \approx 257.6$ Hz), 124.3, 126.6 (q, $^{3}J_{\text{C-F}} = 3.0$ Hz), 128.0 (q, $^{1}J_{\text{C-F}} \approx 312.3$ Hz), 129.2, 130.6, 138.3, 138.6, 149.9 (q, $^{3}J_{\text{C-F}} = 1.6$ Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.4 (s, CF_3), –57.9 (s, CF_3). IR (neat) ν 1439, 1409, 1264, 1223, 1137, 1100, 1014 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^{+}$ calcd for $C_{14}H_{13}F_6N_2OS$ 371.0653, found 371.0649.

4,5-Dimethyl-1-(3-fluorobenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole (**6e**):

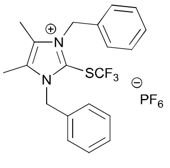


6e

CC (neutral Al_2O_3, DCM gradient DCM/EtOAc 4:1); colorless solid, 222 mg (73%); mp 50-52 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.23 (s, 3H), 5.29 (s, 2H), 6.61-6.63 (m, 1H), 6.70-6.72 (m, 1H), 6.96-6.99 (m, 1H), 7.27-7.31 (m, 1H). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 9.9, 13.1, 48.0 (d, $^{4}J_{\text{C-F}} \approx 1.4$ Hz), 113.2 (d, $^{2}J_{\text{C-F}} \approx 22.7$ Hz), 115.1 (d, $^{2}J_{\text{C-F}} \approx 21.0$ Hz), 121.6 (d, $^{4}J_{\text{C-F}} \approx 3.2$ Hz), 126.5 (q, $^{3}J_{\text{C-F}} \approx 3.1$ Hz), 128.1 (q, $^{1}J_{\text{C-F}} = 312.3$ Hz), 129.2, 130.8 (d, $^{3}J_{\text{C-F}} \approx 8.2$ Hz), 138.51, 138.52 (d, $^{3}J_{\text{C-F}} \approx 7.0$ Hz), 163.3 (d, $^{1}J_{\text{C-F}} \approx 247.5$ Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ –42.4 (s, CF_3), –111.9 (m$_c$, Ar-F). IR (neat) ν 1618, 1592, 1491, 1439, 1405, 1252, 1159, 1133, 1096 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^{+}$ calcd for $C_{13}H_{13}F_4N_2S$ 305.0736, found 305.0734.

<u>General Procedure B</u> for synthesis of 2-CF_3S-imidazolium hexafluorophosphates **4a-4i**: To a solution of 2-[(trifluoromethyl)sulfanyl]-1*H*-imidazole **6** (0.5 mmol) in MeCN (5 mL), benzyl bromide or 3-methoxybenzyl bromide (1.5 mmol) was added, and the resulting mixture was refluxed for 12h. After the solvent was removed in vacuo, the resulting crude bromide was dissolved in EtOH/H_2O (1 mL, v/v 1:1), and the solid NH_4PF_6 (0.53 mmol, 87 mg) was added. The obtained precipitate was filtered off, washed with EtOH/H_2O (3 × 1 mL, v/v 1:1), then with distilled water (3 × 1 mL), and the product was air dried.

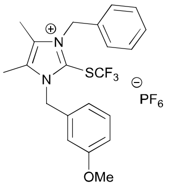
1,3-Dibenzyl-4,5-dimethyl-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4a**):



4a

colorless solid, 248 mg (95%); mp 150-152 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.20 (s, 6H), 5.68 (s, 4H), 7.08-7.11 (m, 4H), 7.35-7.38 (m, 2H), 7.40-7.44 (m, 4H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 10.1, 51.9, 126.27, 126.31 (q, $^1J_{C\text{-}F}$ = 316.6 Hz), 127.9 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 129.1, 129.7, 132.1, 134.6. ^{19}F NMR (565 MHz, DMSO-d_6): δ –38.6 (s, CF_3), –73.9 (d, $J_{P\text{-}F}$ = 712.3 Hz, PF_6). IR (neat) ν 1480, 1457, 1353, 1170, 1096, 831 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M–PF_6]$^+$ calcd for $C_{20}H_{20}F_3N_2S$ 377.1299, found 377.1298.

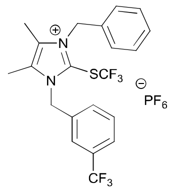
1-Benzyl-4,5-dimethyl-3-(3-methoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4b**):



4b

colorless solid, 259 mg (94%), mp 103-105 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.20 (s, 6H, 2Me), 3.76 (s, 3H, OMe), 5.72 (s, 2H), 5.76 (s, 2H), 6.78-6.85 (m, 2H), 6.95-6.96 (m, 1H), 7.26-7.27 (m, 2H), 7.33-7.44 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.53 (br, 2Me), 50.5, 50.7, 55.2, 112.9, 113.3, 118.7, 126.4 (q, $^1J_{C\text{-}F}$ = 315.8 Hz), 126.8, 128.3, 128.6 (br, C-2), 128.9, 130.1, 133.16, 133.20, 133.4, 134.9, 159.6. ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.2 (s, CF_3), –70.2 (d, $J_{P\text{-}F}$ = 711.5 Hz, PF_6). IR (neat) υ 1607, 1469, 1424, 1349, 1260, 1156, 1103, 828 cm^{-1}. HRMS (ESI-TOF) m/z: [M–PF_6]$^+$ calcd for $C_{21}H_{22}F_3N_2OS$ 407.1405, found 407.1400.

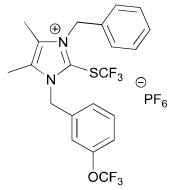
1-Benzyl-4,5-dimethyl-3-(3-trifluoromethylbenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4c**):



4c

colorless solid, 289 mg (98%), mp 127-128 °C. ^{1}H NMR (600 MHz, CD_3CN) δ 2.20 (s, 3H), 2.21 (s, 3H), 5.69 (s, 2H), 5.75 (s, 2H), 7.18-7.20 (m, 2H), 7.39-7.45 (m, 4H), 7.51 (m$_c$, 1H), 7.61-7.64 (m, 1H), 7.72-7.74 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, CD_3CN) δ 10.41, 10.44, 51.5, 52.2, 124.4 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.0 (q, $^1J_{C\text{-}F}$ = 271.4 Hz), 126.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 127.4 (q, $^1J_{C\text{-}F}$ = 315.5 Hz), 127.6, 128.3 (br, C-2), 129.7, 130.1, 131.0, 131.5 (br), 131.7 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 133.7, 135.2, 135.5, 135.7. ^{19}F NMR (565 MHz, CD_3CN) δ –40.1 (s, SCF_3), –63.1(s, CF_3), –72.9 (d, $J_{P\text{-}F}$ = 706.5 Hz, PF_6). IR (neat) υ 1484, 1431, 1331, 1163, 1096, 828 cm^{-1}. HRMS (ESI-TOF) m/z: $[M–PF_6]^+$ calcd for $C_{21}H_{19}F_6N_2S$ 445.1173, found 445.1172.

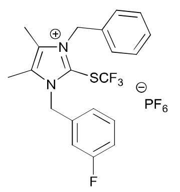
1-Benzyl-4,5-dimethyl-3-(3-trifluoromethoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4d**):



4d

colorless solid, 273 mg (90%), mp 134-135 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.197 (s, 3H), 2.204 (s, 3H), 5.77 (s, 2H), 5.83 (s, 2H), 7.26-7.28 (m, 2H), 7.31-7.33 (m, 1H), 7.35 (m$_c$, 1H), 7.37-7.44 (m, 4H), 7.56-7.59 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.5, 9.6, 50.0, 50.7, 119.7, 120.0 (q, $^1J_{C\text{-}F}$ = 256.6 Hz), 120.8, 126.0, 126.3 (q, $^1J_{C\text{-}F}$ = 315.8 Hz), 126.8, 128.3, 128.8 (q, $^3J_{C\text{-}F}$ = 3.0 Hz), 128.9, 130.9, 133.2, 133.28, 133.31, 136.2, 148.7 (q, $^3J_{C\text{-}F}$ = 1.6 Hz). ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.3 (s, SCF_3), –56.8 (s, OCF_3), –70.2 (d, $J_{P\text{-}F}$ = 711.6 Hz, PF_6). IR (neat) υ 1484, 1454, 1252, 1215, 1170, 1100, 828 cm^{-1}. HRMS (ESI-TOF) m/z: $[M–PF_6]^+$ calcd for $C_{21}H_{19}F_6N_2OS$ 461.1122, found 461.1123.

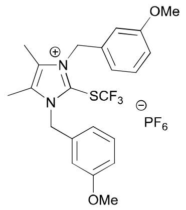
1-Benzyl-4,5-dimethyl-3-(3-fluorobenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4e**):



4e

colorless solid, 260 mg (96%), mp 127-129 °C. ^{1}H NMR (600 MHz, CD$_3$CN) δ 2.21 (s, 6H, 2Me), 5.68 (s, 4H, 2CH$_2$), 6.62-6.64 (m, 1H), 7.02-7.03 (m, 1H), 7.14-7.19 (m, 3H), 7.39-7.48 (m, 4H). ^{13}C{^{1}H} NMR (151 MHz, CD$_3$CN) δ 10.37, 10.42, 51.5 (br), 52.2, 114.5 (d, $^2J_{\text{C-F}}$ = 23.4 Hz), 116.4 (d, $^2J_{\text{C-F}}$ = 21.2 Hz), 123.6 (d, $^4J_{\text{C-F}}$ = 2.9 Hz), 127.4 (q, $^1J_{\text{C-F}}$ = 315.0 Hz), 127.6, 128.2 (br, C-2), 129.7, 130.1, 132.1 (d, $^3J_{\text{C-F}}$ = 8.6 Hz), 133.7, 135.6, 135.7, 136.4 (d, $^3J_{\text{C-F}}$ = 7.7 Hz), 164.0 (d, $^1J_{\text{C-F}}$ = 245.3 Hz). ^{19}F NMR (565 MHz, CD$_3$CN) δ –40.2 (s, CF$_3$), –72.9 (d, $J_{\text{P-F}}$ = 706.7 Hz, PF$_6$), –113.6 (m$_c$, Ar-F). IR (neat) υ 1454, 1398, 1349, 1260, 1193, 1159, 1088, 828 cm^{-1}. HRMS (ESI-TOF) m/z: [M–PF$_6$]$^+$ calcd for C$_{20}$H$_{19}$F$_4$N$_2$S 395.1205, found 395.1202.

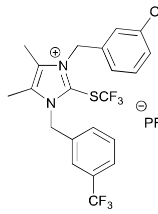
4,5-Dimethyl-1,3-di(3-methoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4f**):



4f

colorless solid, 247 mg (85%), mp 120-122 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.19 (s, 6H), 3.76 (s, 6H), 5.72 (s, 4H), 6.78-6.85 (m, 4H), 6.94-6.97 (m, 2H), 7.32-7.36 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.5, 50.5, 55.2, 112.9, 113.3, 118.7, 126.4 (q, $^1J_{\text{C-F}}$ = 316.0 Hz), 128.6 (q, $^3J_{\text{C-F}}$ = 3.2 Hz), 130.1, 133.2, 134.9, 159.6. ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.2 (s, CF$_3$), –70.2 (d, $J_{\text{P-F}}$ = 711.2 Hz, PF$_6$). IR (neat) υ 1603, 1465, 1424, 1341, 1293, 1260, 1156, 1103, 1036, 824 cm^{-1}. HRMS (ESI-TOF) m/z: [M–PF$_6$]$^+$ calcd for C$_{22}$H$_{24}$F$_3$N$_2$O$_2$S 437.1511, found 437.1508.

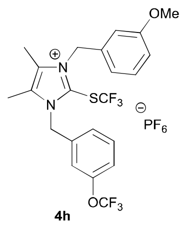
4,5-Dimethyl-1-(3-methoxybenzyl)-3-(3-trifluoromethylbenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4g**):



4g

colorless solid, 291 mg (94%), mp 145-147 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.19 (s, 3H), 2.20 (s, 3H), 3.76 (s, 3H), 5.73 (s, 2H), 5.88 (s, 2H), 6.79-6.87 (m, 2H), 6.94-6.97 (m, 1H), 7.32-7.35 (m, 1H), 7.51-7.54 (m, 1H), 7.65-7.68 (m, 1H), 7.74-7.77 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.55, 9.57, 50.1, 50.6, 55.2, 112.9, 113.3, 118.7, 123.8 (q, $^3J_{\text{C-F}}$ = 3.6 Hz), 124.0 (q, $^1J_{\text{C-F}}$ = 272.2 Hz), 125.1 (q, $^3J_{\text{C-F}}$ = 4.0 Hz), 126.4 (q, $^1J_{\text{C-F}}$ = 315.9 Hz), 129.0 (q, $^3J_{\text{C-F}}$ = 3.2 Hz), 129.6 (q, $^2J_{\text{C-F}}$ = 31.9 Hz), 130.0, 130.1, 130.9, 133.1, 133.3, 134.8, 135.0, 159.6. ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.3 (s, SCF$_3$), –61.1 (s, CF$_3$), –70.2 (d, $J_{\text{P-F}}$ = 711.0 Hz, PF$_6$). IR (neat) υ 1607, 1484, 1428, 1331, 1256, 1156, 1096, 828 cm^{-1}. HRMS (ESI-TOF) m/z: [M–PF$_6$]$^+$ calcd for $C_{22}H_{21}F_6N_2OS$ 475.1279, found 475.1280.

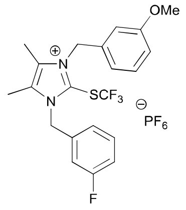
4,5-Dimethyl-1-(3-methoxybenzyl)-3-(3-trifluoromethoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4h**):



4h

colorless solid, 280 mg (88%); mp 127-129 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.20 (s, 3H), 2.21 (s, 3H), 3.76 (s, 3H), 5.72 (s, 2H), 5.82 (s, 2H), 6.78-6.80 (m, 1H), 6.85 (m$_c$, 1H), 6.94-6.97 (m, 1H), 7.30-7.40 (m, 4H), 7.55-7.59 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.5, 9.6, 50.1, 50.6, 55.2, 112.9, 113.4, 118.8, 119.8, 120.0 (q, $^1J_{\text{C-F}}$ = 256.7 Hz), 120.9, 126.1, 126.3 (q, $^1J_{\text{C-F}}$ = 316.2 Hz), 129.1 (q, $^3J_{\text{C-F}}$ = 2.8 Hz), 130.0, 130.9, 133.1, 133.2, 134.8, 136.2, 148.6 (br, *C*OCF$_3$), 159.6. ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.4 (s, SCF$_3$), –56.8 (s, OCF$_3$), –70.2 (d, $J_{\text{P-F}}$ = 711.0 Hz, PF$_6$). IR (neat) υ 1610, 1495, 1428, 1256, 1219, 1156, 1100, 828 cm^{-1}. HRMS (ESI-TOF) m/z: [M–PF$_6$]$^+$ calcd for $C_{22}H_{21}F_6N_2O_2S$ 491.1228, found 491.1230.

4,5-Dimethyl-1-(3-fluorobenzyl)-3-(3-methoxybenzyl)-2-[(trifluoromethyl)sulfanyl]-1*H*-imidazolium hexafluorophosphate (**4i**):



4i

colorless solid, 262 mg (92%), mp 112-114 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.19 (s, 3H), 2.20 (s, 3H), 3.76 (s, 3H), 5.72 (s, 2H), 5.78 (s, 2H), 6.80-6.83 (m, 2H), 6.94-6.98 (m, 1H), 7.12-7.24 (m, 3H), 7.32-7.37 (m, 1H), 7.45-7.50 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 9.5, 9.6, 50.1, 50.6, 55.2, 113.0, 113.3, 113.8 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 118.7, 123.0 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 126.4 (q, $^1J_{C\text{-}F}$ = 316.0), 128.7 (q, $^3J_{C\text{-}F}$ = 2.9 Hz), 130.1, 131.0 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 133.1, 133.3, 134.8, 136.2 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 159.6, 162.4 (d, $^1J_{C\text{-}F}$ = 244.4 Hz). ^{19}F NMR (565 MHz, DMSO-d_6) δ –39.3 (s, CF_3), –70.2 (d, $J_{P\text{-}F}$ = 711.5 Hz, PF_6), –112.3 (m_c, Ar-F). IR (neat) υ 1603, 1454, 1424, 1356, 1260, 1156, 1103, 1036, 828 cm^{-1}. HRMS (ESI-TOF) m/z: $[M–PF_6]^+$ calcd for $C_{21}H_{21}F_4N_2OS$ 425.1311, found 425.1306.

3. Copies of NMR spectra

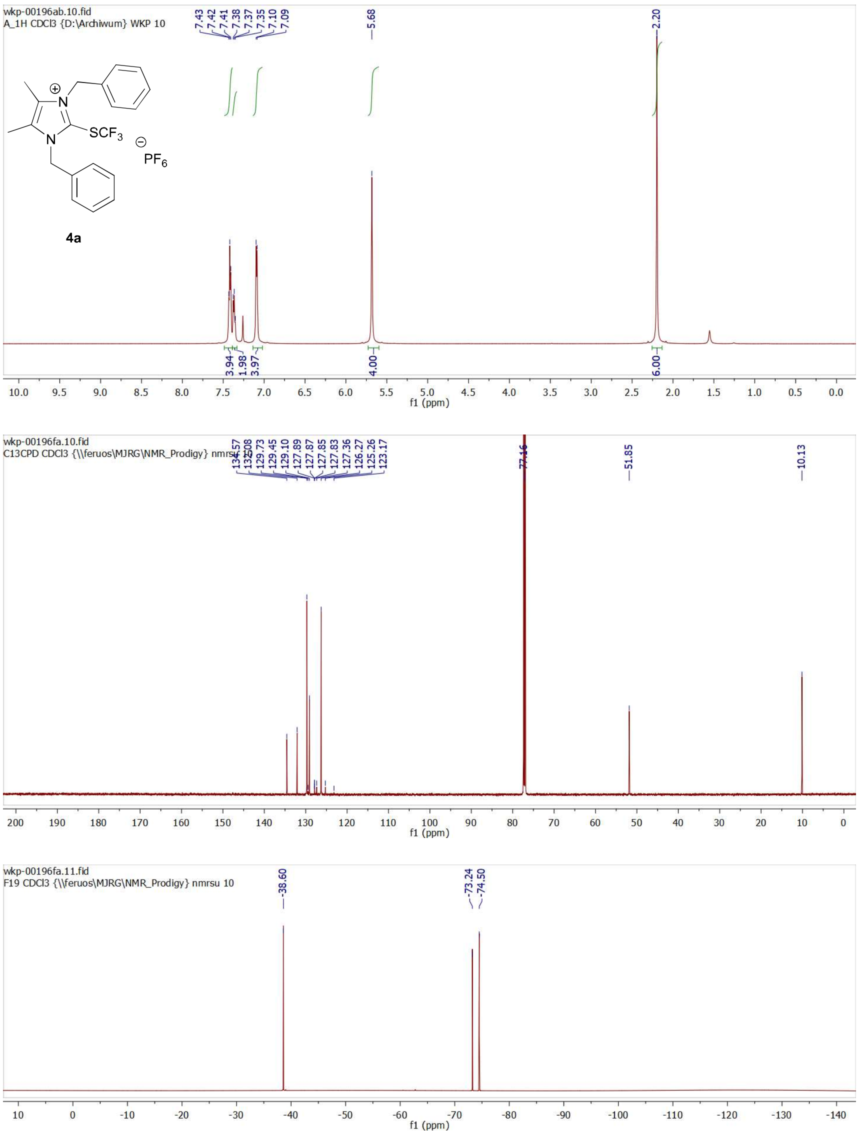


Fig S1. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **4a**.

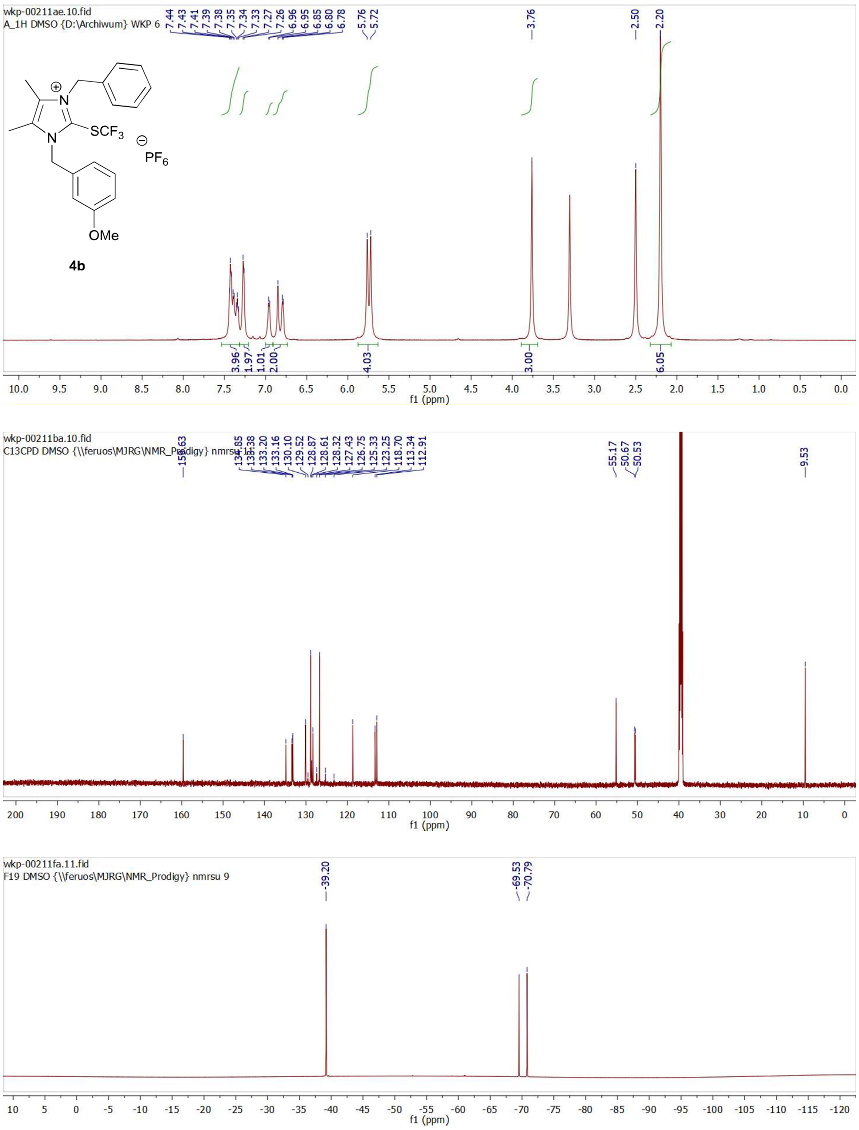


Fig S2. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4b**.

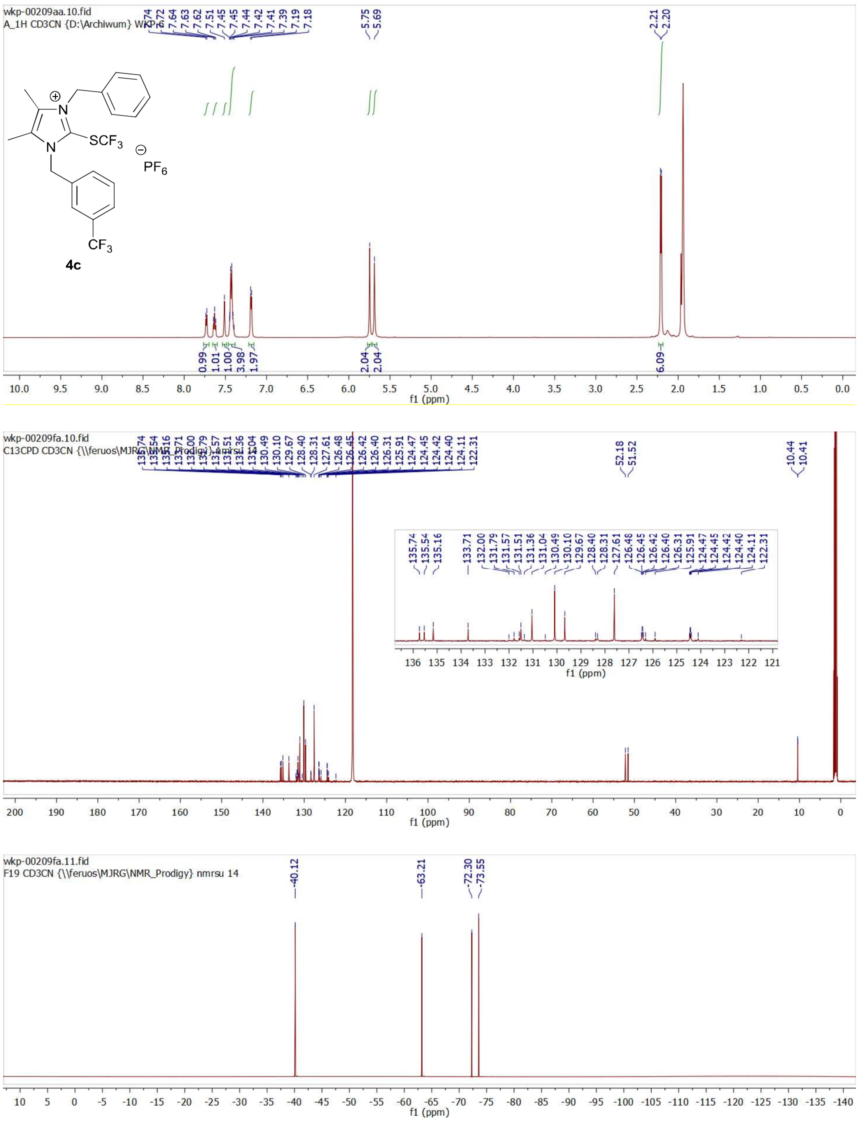


Fig S3. ^{1}H NMR (600 MHz, CD_3CN), ^{13}C NMR (151 MHz, CD_3CN) and ^{19}F NMR (565 MHz, CD_3CN) spectra for compound **4c**.

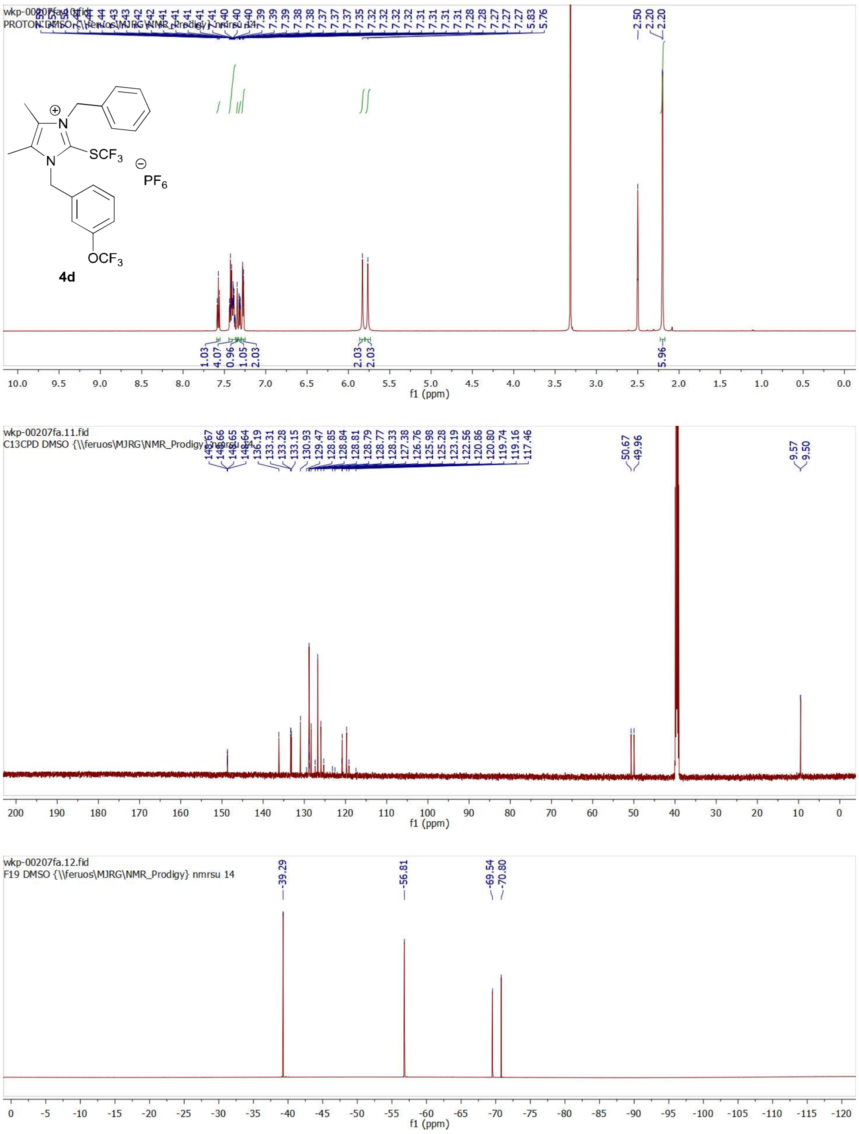
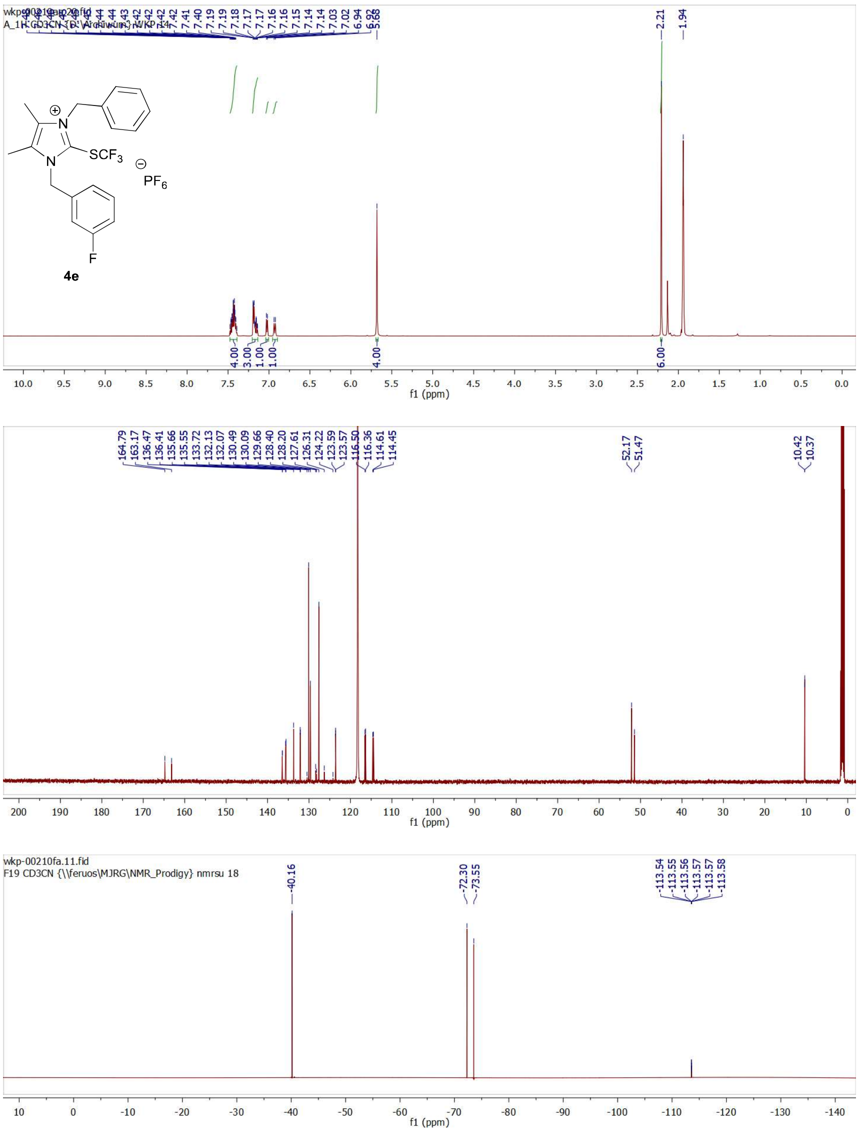


Fig S4. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4d**.



4e

Fig S5. ^{1}H NMR (600 MHz, CD_3CN), ^{13}C NMR (151 MHz, CD_3CN) and ^{19}F NMR (565 MHz, CD_3CN) spectra for compound **4e**.

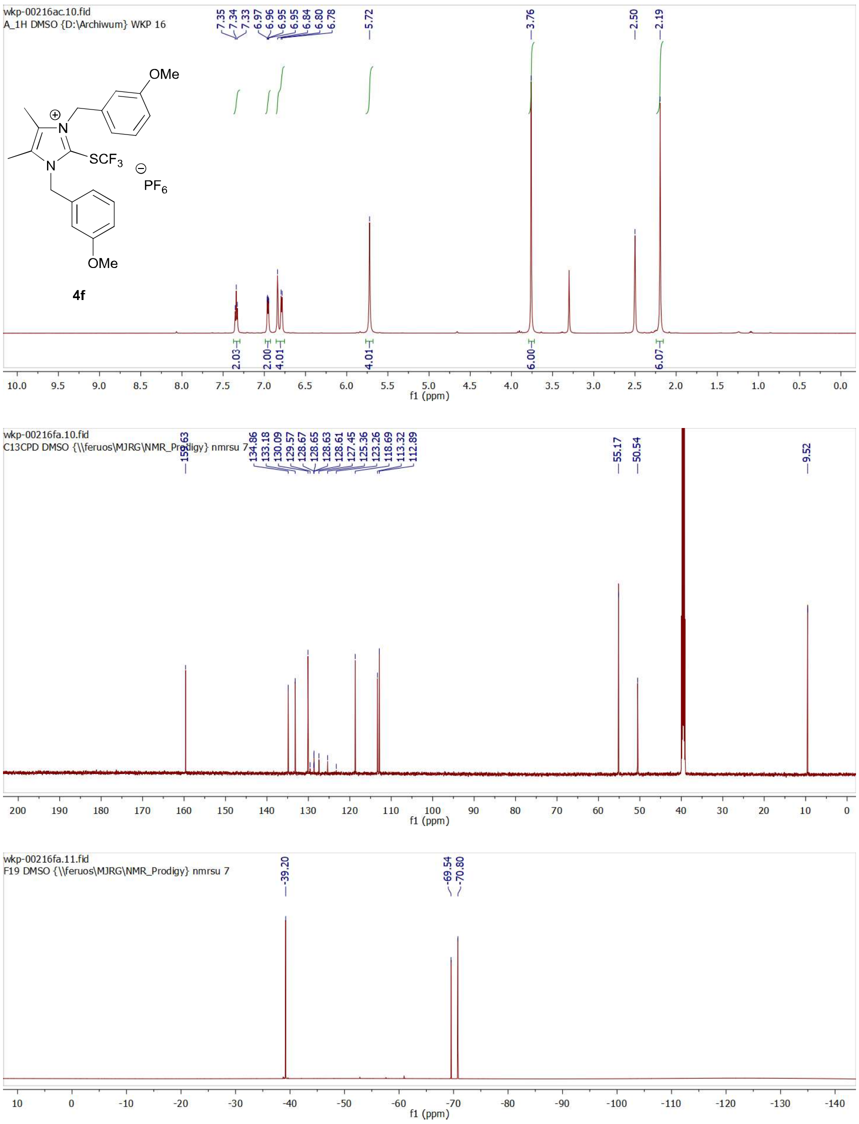


Fig S6. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4f**.

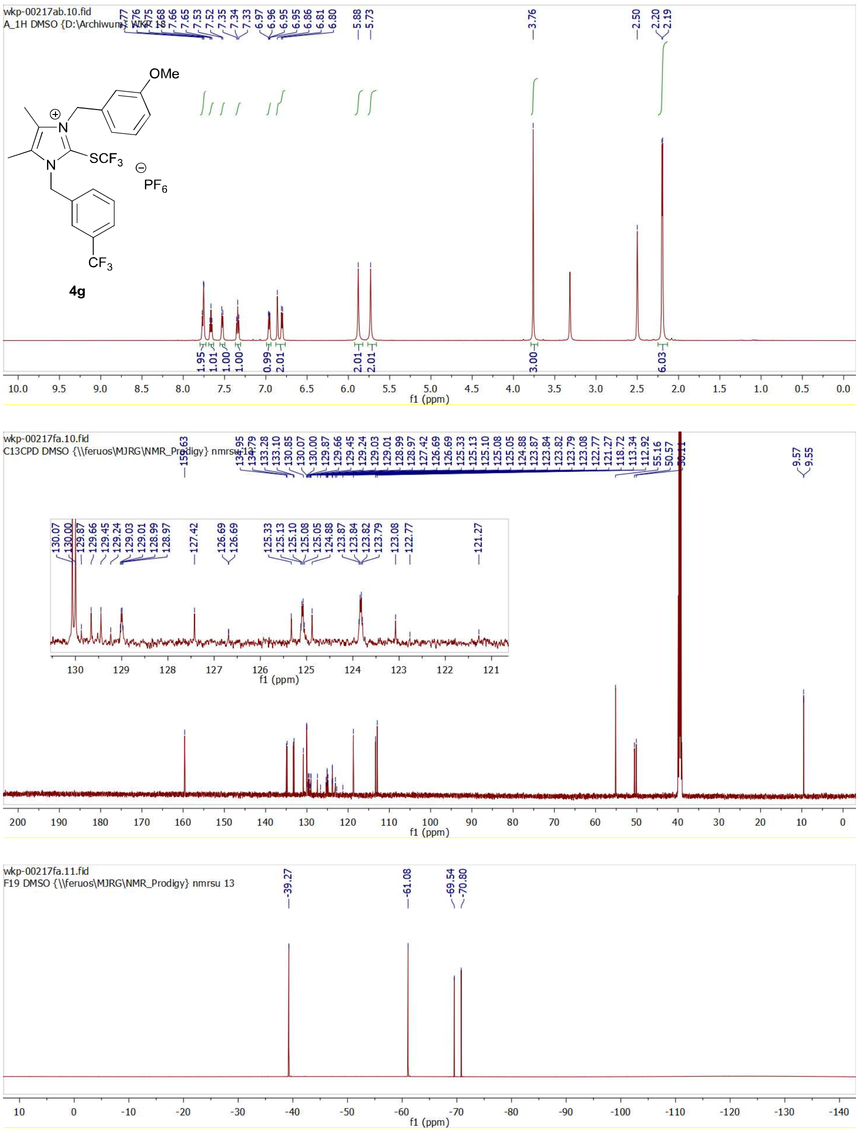


Fig S7. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4g**.

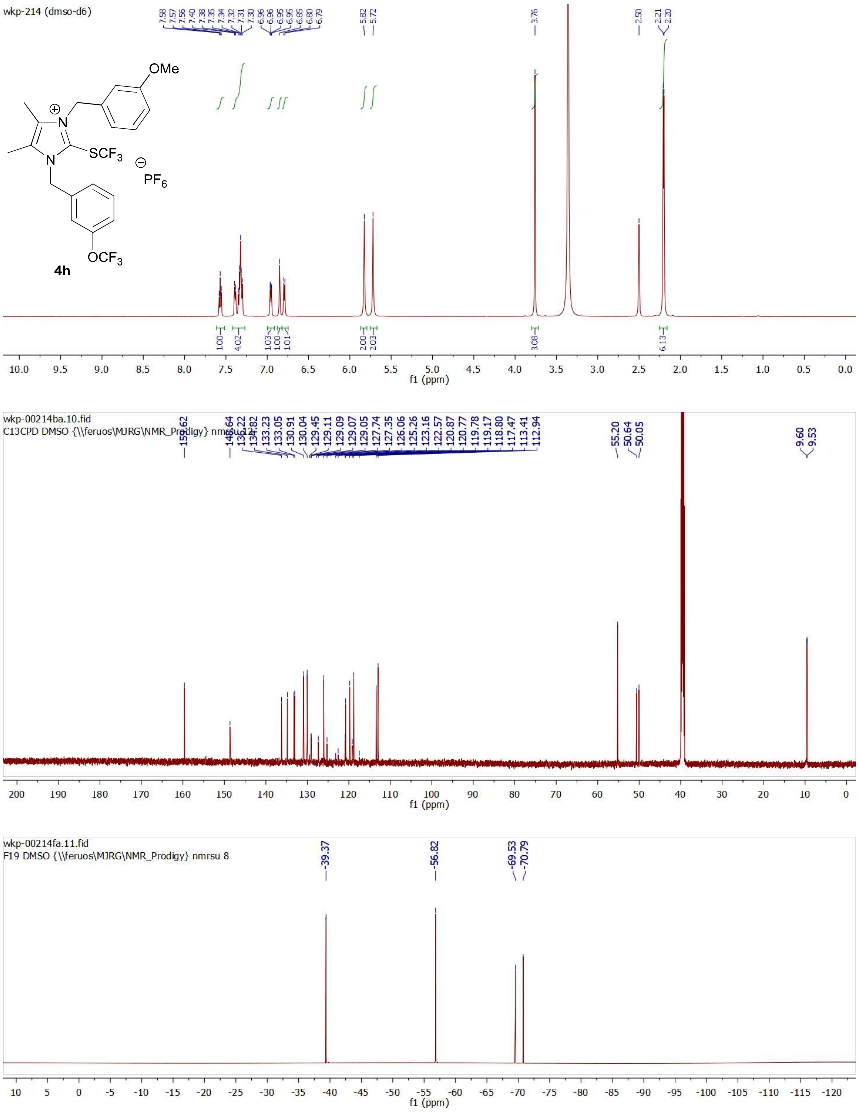


Fig S8. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4h**.

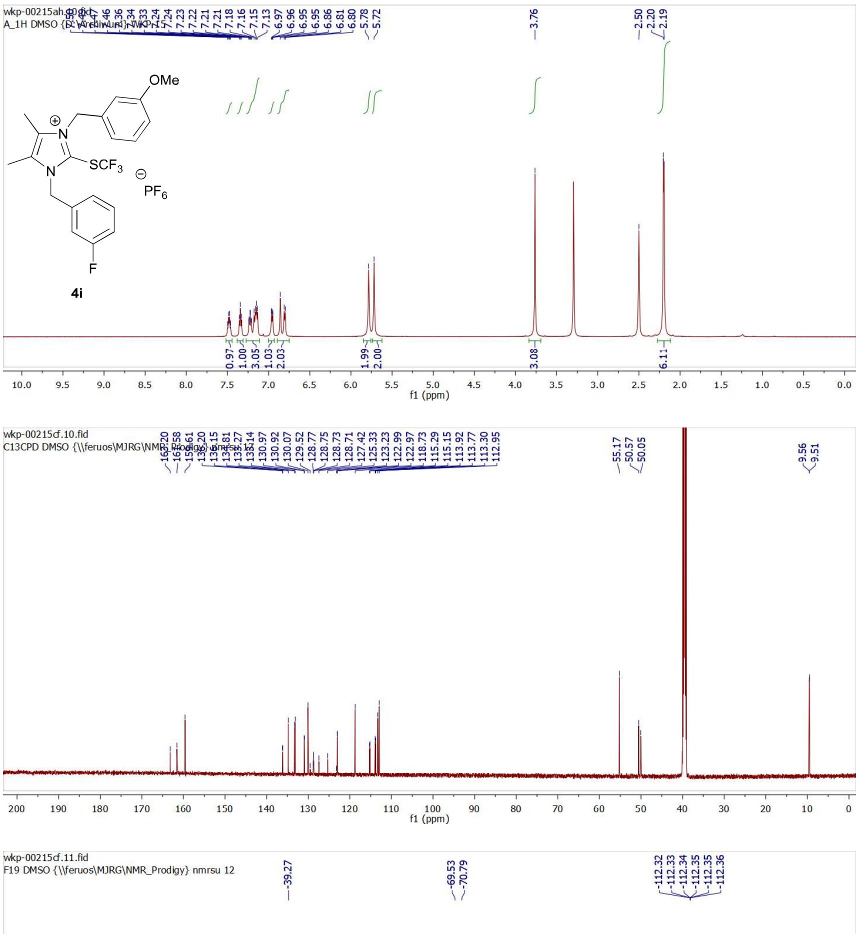


Fig S9. ^{1}H NMR (600 MHz, DMSO-d_6), ^{13}C NMR (151 MHz, DMSO-d_6) and ^{19}F NMR (565 MHz, DMSO-d_6) spectra for compound **4i**.

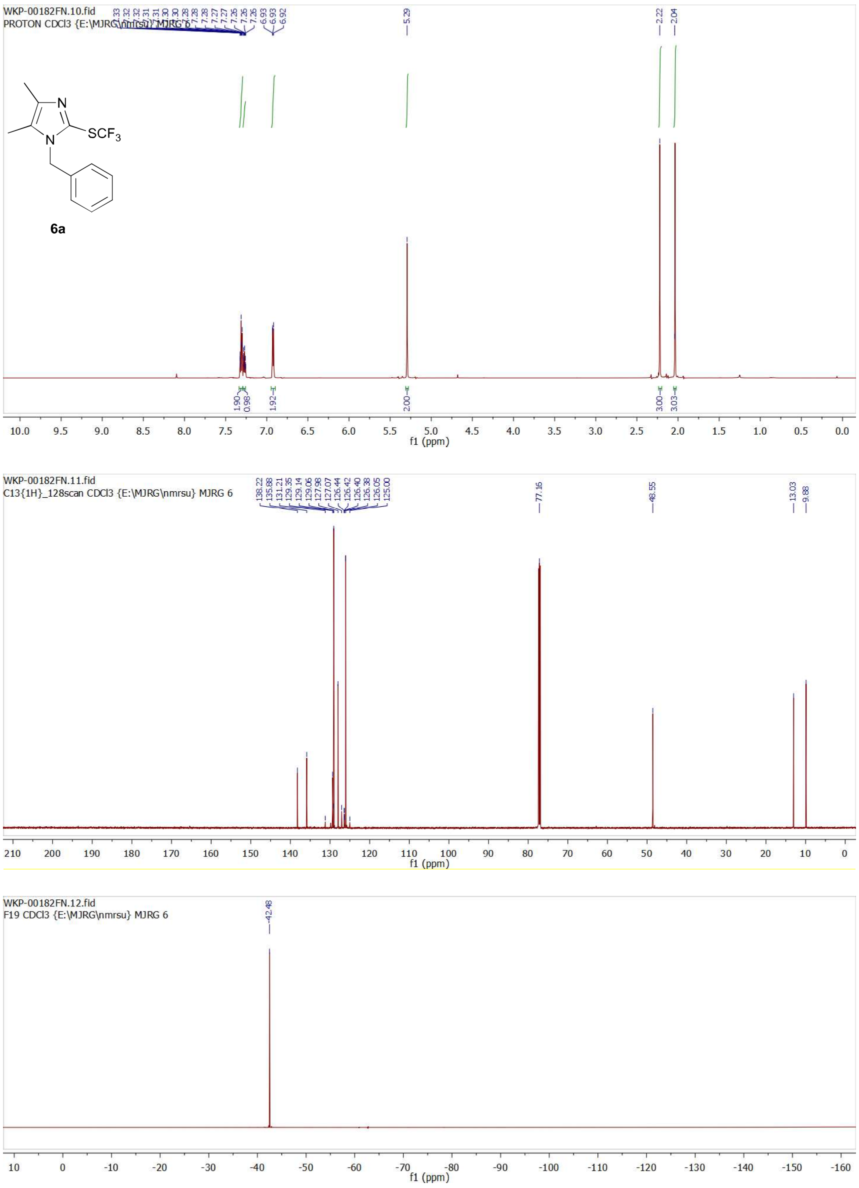


Fig S10. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **6a**.

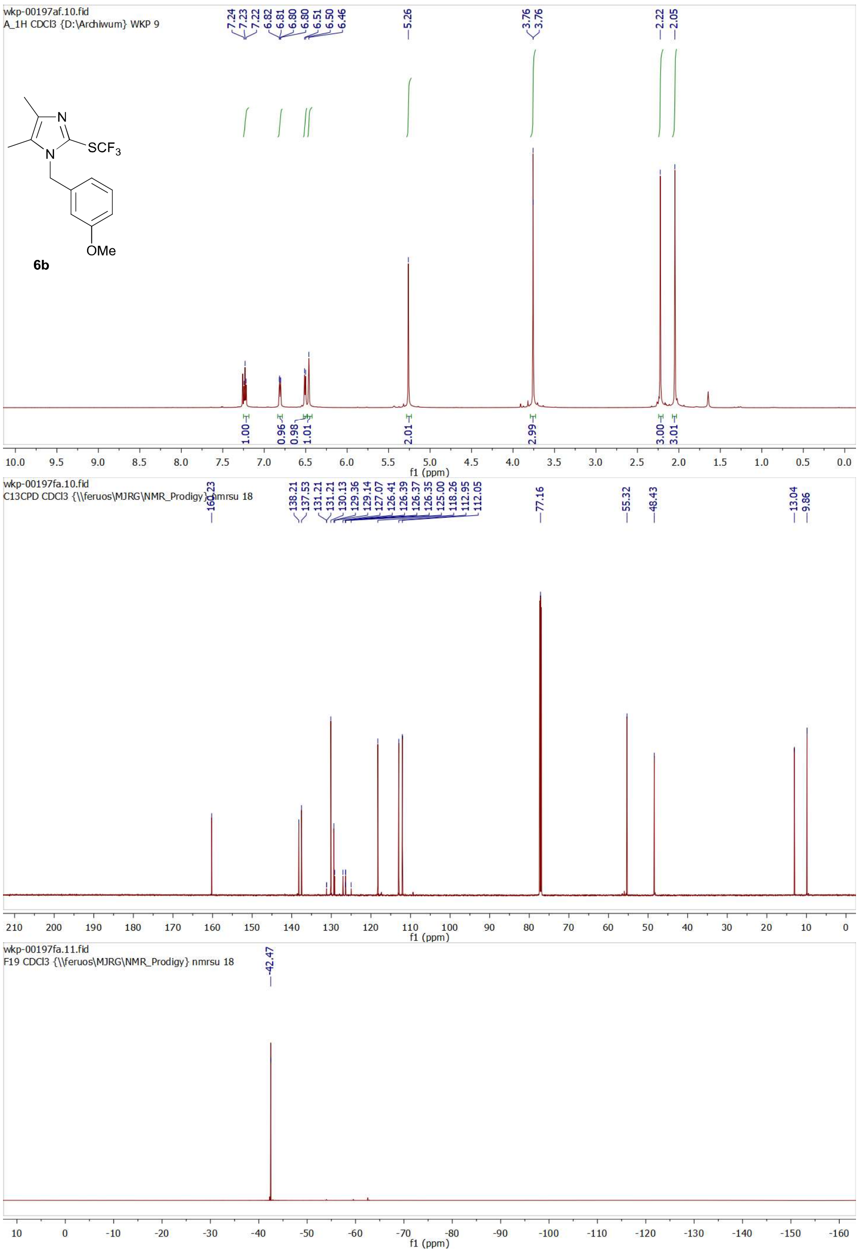


Fig S11. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **6b**.

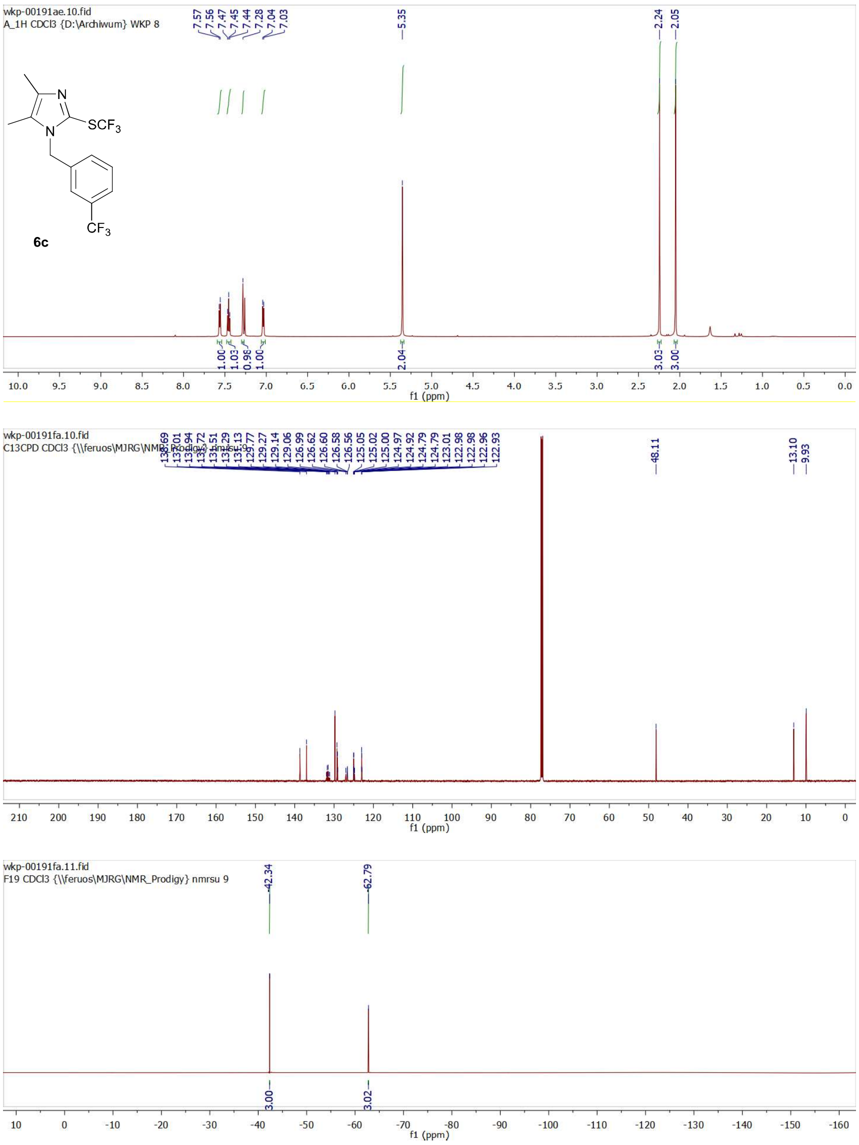


Fig S12. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **6c**.

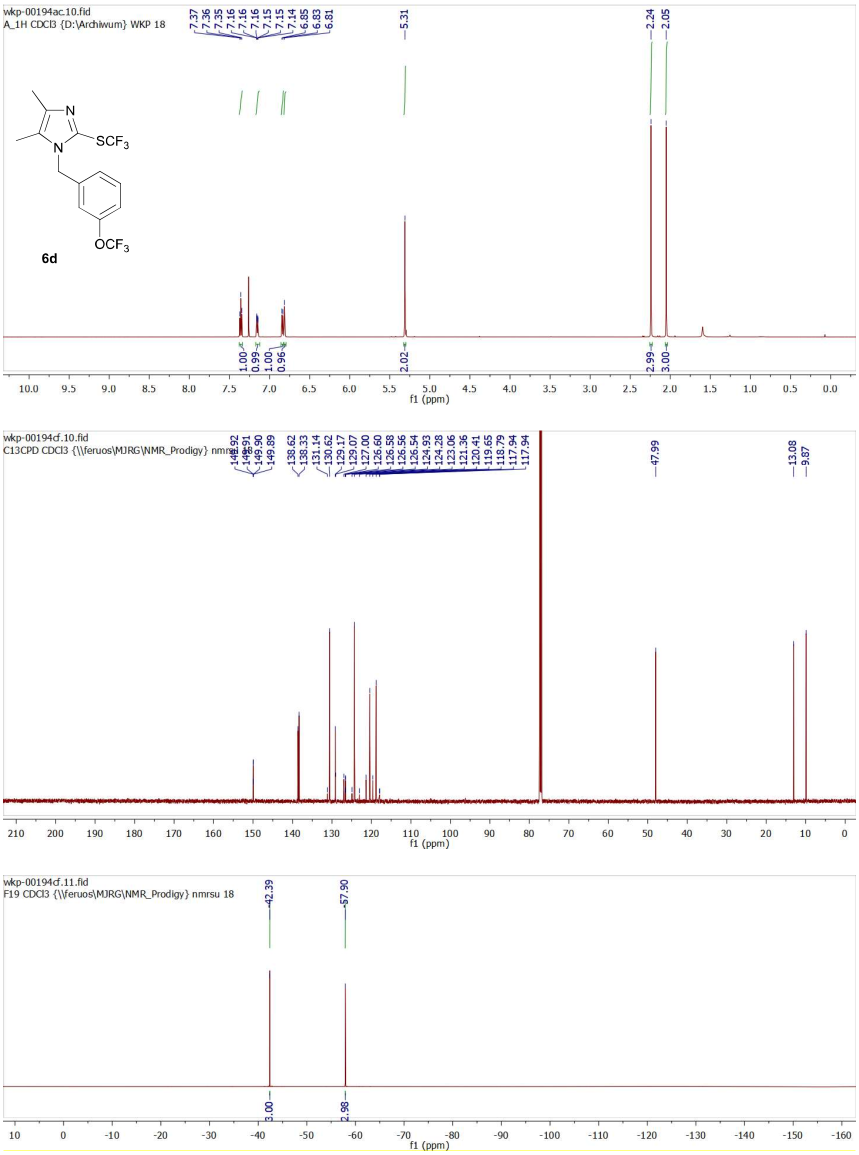


Fig S13. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **6d**.

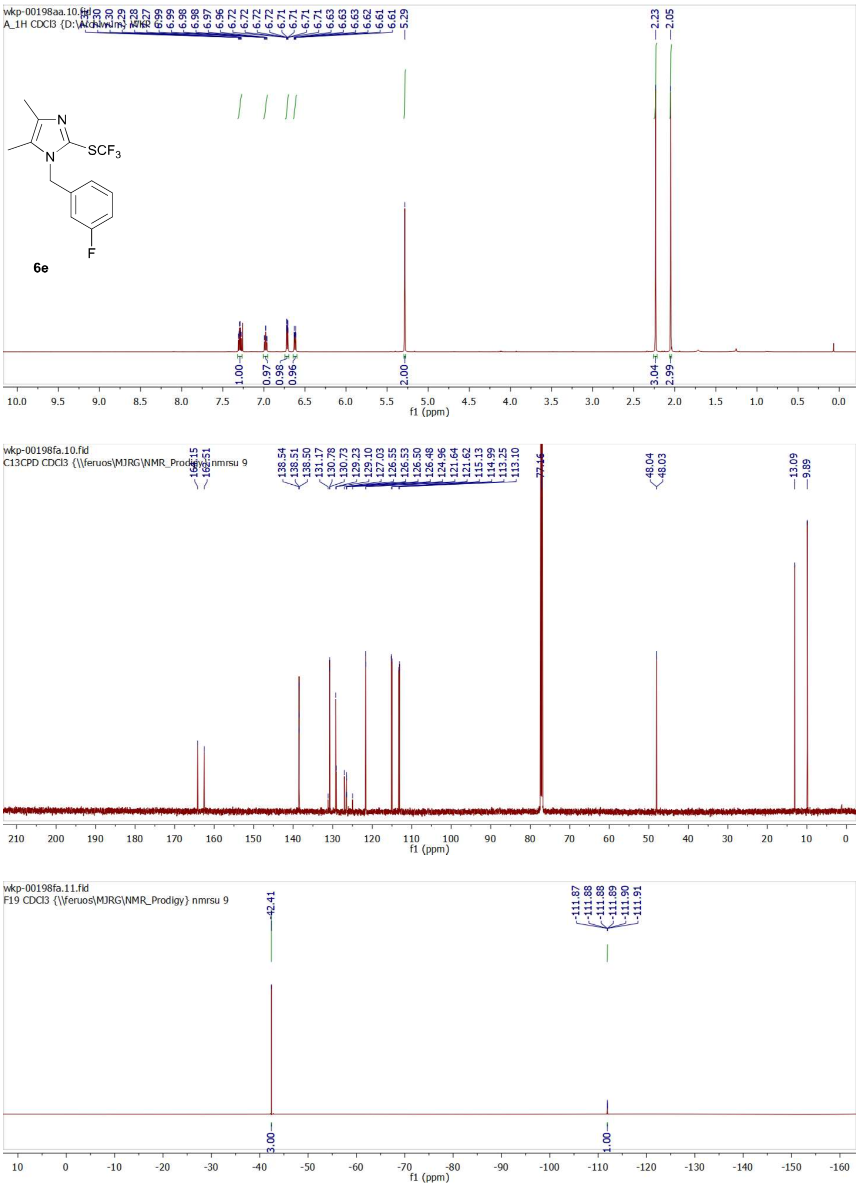


Fig S14. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **6e**.

4. Cytotoxicity analyses

Stock solution of each compound (**4a**-**4i**, **6a**-**6e**) was prepared in DMSO at 100 mM and diluted with medium supplemented with 10% FBS. The final content of DMSO in solutions did not exceed 0.1%.

Cancer cell lines: A549 (ATCC CCL-185, Human lung carcinoma cells), HepG2 (ATCC HB-8065, Human hepatocellular carcinoma), HeLa (ATCC CCL-2, Human cervix adenocarcinoma cells).

Non-cancer cell lines: Vero (ATTC CCL-81, Cercopithecus aethiops normal kidney cells), LLCMK2 (ATTC CCL-7, Macaca mulatta normal kidney cells), NCTC clone 929 (ATCC CCL-1, Mus musculus normal subcutaneous connective tissue cells), MRC-5 (ATCC CCL-171, Human lung normal fibroblasts).

Chemicals: Minimum Essential Medium Eagle (MEM, Sigma-Aldrich), Fetal bovine serum (FBS, Sigma-Aldrich), antibiotics (Sigma-Aldrich), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma-Aldrich), dimethylformamide (DMF, Sigma-Aldrich), sodium dodecylsulfate (SDS, Sigma-Aldrich).

Methods

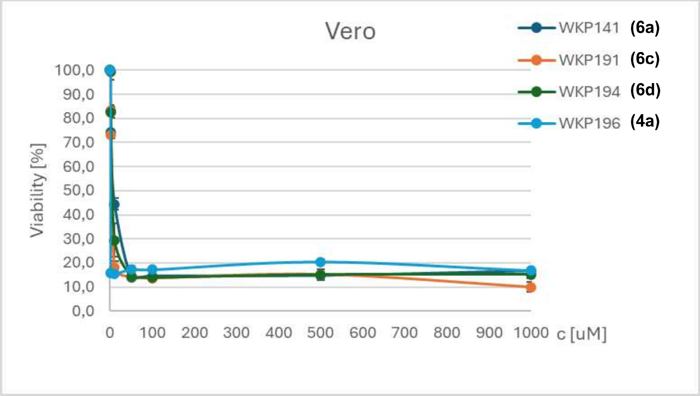
Cytotoxicity assay

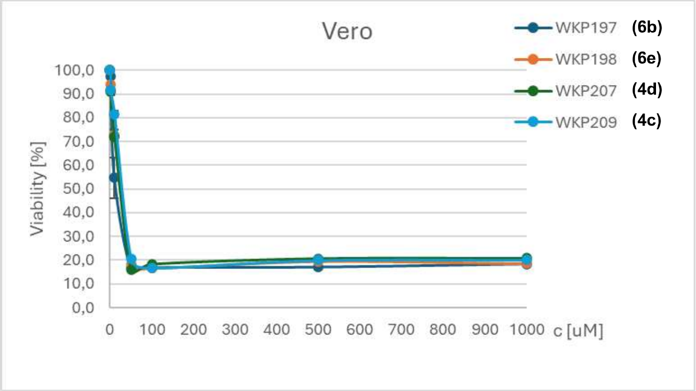
A549, HepG2, HeLa, Vero, LLCMK2, NCTC clone 929 and MRC-5 cells were propagated in Minimum Essential Medium supplemented with 10% heat-inactivated fetal bovine serum and 1% penicillin/streptomycin mixture (10 000 units/mL penicillin G with 10 mg/mL streptomycin). Upon reaching 80–90% confluency, cells were harvested with 0.25% trypsin in 1 mM EDTA and seeded into 96-well microplates at $2x10^4$ cells/well. After overnight incubation of cells at 37˚C in a humidified atmosphere containing 5% CO_2, the culture medium was removed and replaced with a 100 µL of freshly prepared solution of compounds diluted with the growth medium supplemented with 10% FBS, 1% penicillin/streptomycin mixture, for obtaining concentrations ranging from 0.1 to 1000 µM. All experiments were carried out in triplicate, in two independent experiments. Compounds treated and untreated cells were incubated at 37˚C for 48 h in humidified atmosphere containing 5% CO_2. After that the cytotoxicity of investigated compounds was observed microscopically and cell viability was determined with MTT assay.

Cell viability determination

The cytotoxicity was evaluated by the MTT assay. After incubation with drugs the cells were treated with 25 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye solution (5 mg/mL) for 2 h and lysed with 100 µL of solvent solution containing: 45 mL of dimethylformamide (DMF), 13,5 g of sodium dodecylsulfate (SDS), and 55 mL distilled water. After overnight incubation in 37˚C optical density at 550 nm and with a reference wavelength of 670 nm was measured in ELISA reader (VarioskanLux, Thermo Scientific) and CC_{50} (50% cytotoxic concentration) was calculated.

Graphs


Vero
WKP141 (6a)
WKP191 (6c)
WKP194 (6d)
WKP196 (4a)
Viability [%]
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
0
100
200
300
400
500
600
700
800
900
1000
c [uM]


Vero
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WKP198 (6e)
WKP207 (4d)
WKP209 (4c)
Viability [%]
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80,0
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60,0
50,0
40,0
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10,0
0,0
0
100
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500
600
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900
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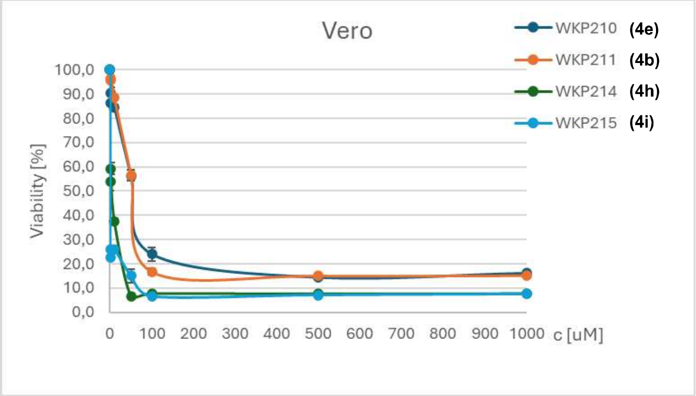
c [uM]


Vero
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WKP211 (4b)
WKP214 (4h)
WKP215 (4i)
Viability [%]
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60,0
50,0
40,0
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10,0
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0
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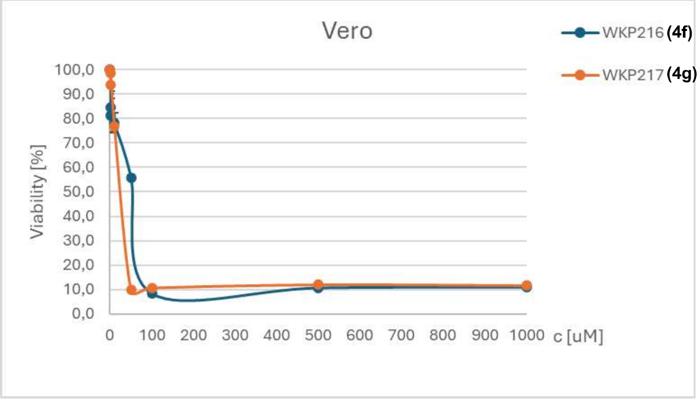
c [uM]


Vero
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WKP217 (4g)
Viability [%]
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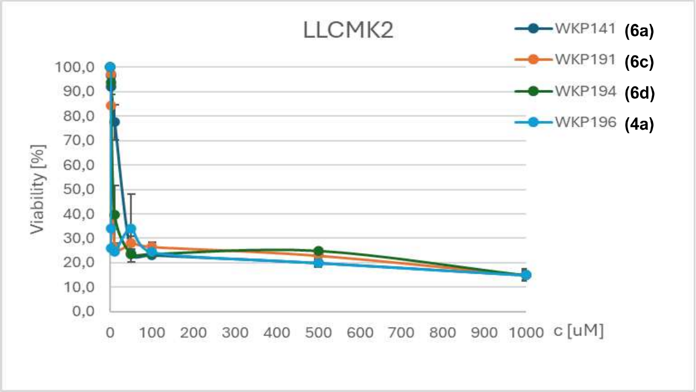
c [uM]


LLCMK2
WKP141 (6a)
WKP191 (6c)
WKP194 (6d)
WKP196 (4a)
Viability [%]
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70,0
60,0
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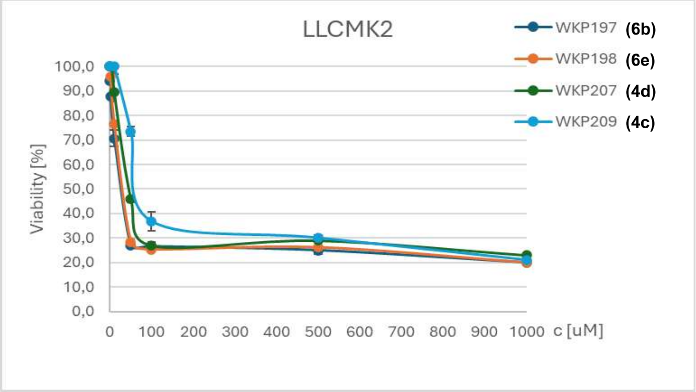
c [uM]


LLCMK2
WKP197 (6b)
WKP198 (6e)
WKP207 (4d)
WKP209 (4c)
Viability [%]
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80,0
70,0
60,0
50,0
40,0
30,0
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10,0
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200
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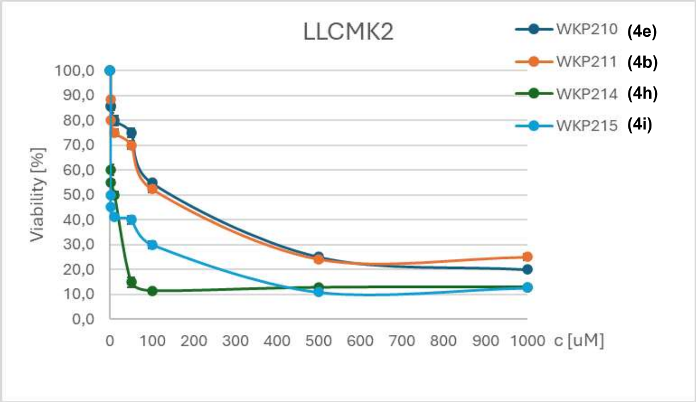
1000
c [uM]


LLCMK2
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WKP211 (4b)
WKP214 (4h)
WKP215 (4i)
Viability [%]
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70,0
60,0
50,0
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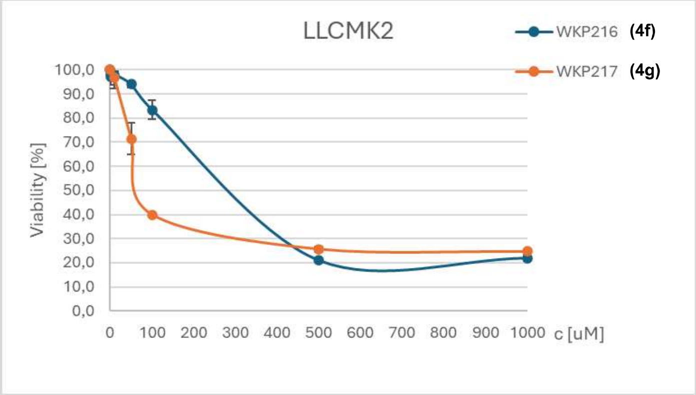
LLCMK2
WKP216 (4f)
WKP217 (4g)
Viability [%]
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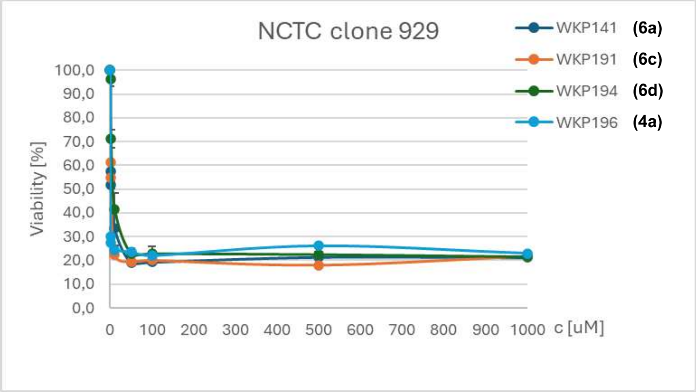
0,0
0
100
200
300
400
500
600
700
800
900
1000
c [uM]


NCTC clone 929
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WKP191 (6c)
WKP194 (6d)
WKP196 (4a)
Viability [%]
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80,0
70,0
60,0
50,0
40,0
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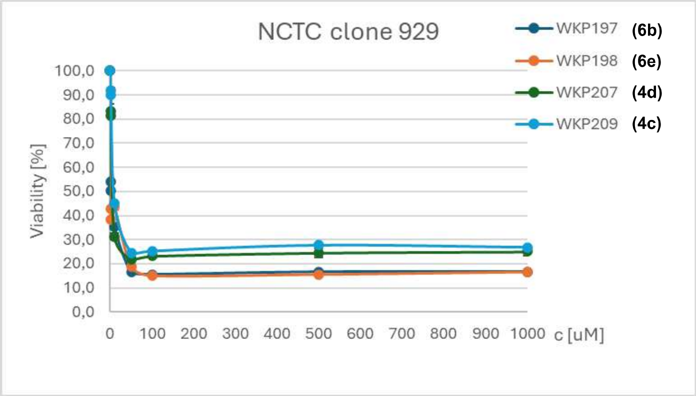
c [uM]


NCTC clone 929
WKP197 (6b)
WKP198 (6e)
WKP207 (4d)
WKP209 (4c)
Viability [%]
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90,0
80,0
70,0
60,0
50,0
40,0
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500
600
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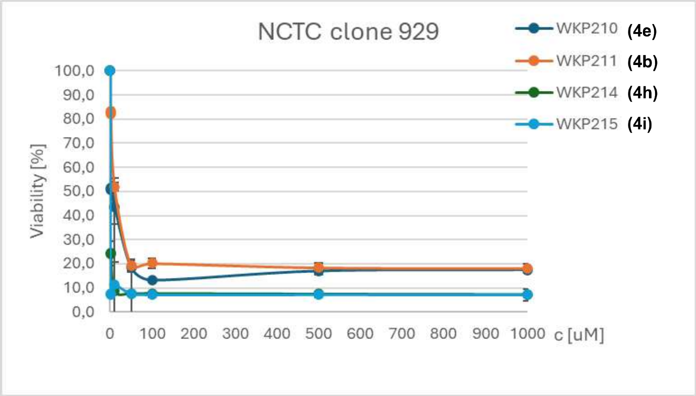
800
900
1000
c [uM]


NCTC clone 929
WKP210 (4e)
WKP211 (4b)
WKP214 (4h)
WKP215 (4i)
Viability [%]
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
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100
200
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500
600
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800
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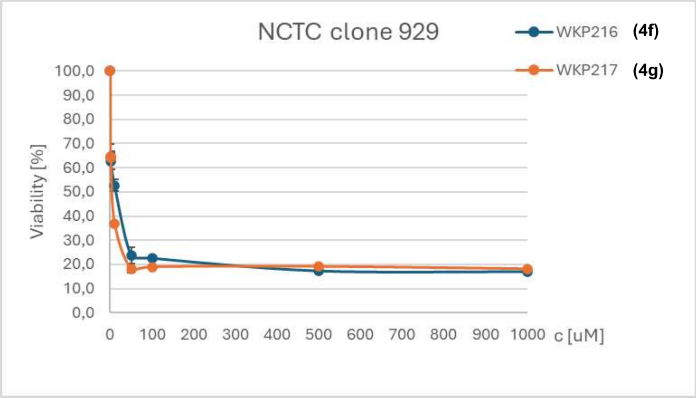
1000
c [uM]


NCTC clone 929
WKP216 (4f)
WKP217 (4g)
Viability [%]
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90,0
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60,0
50,0
40,0
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10,0
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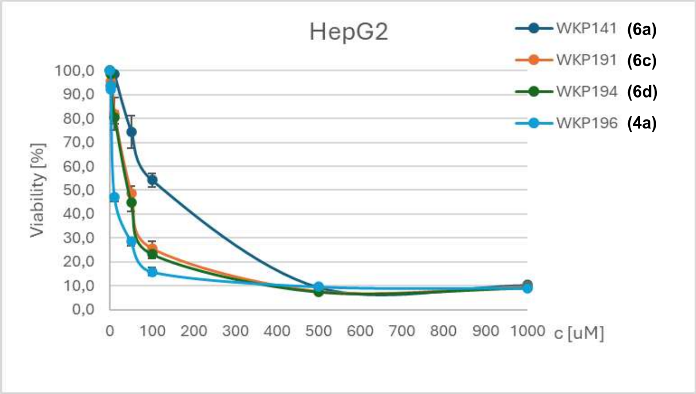
0
100
200
300
400
500
600
700
800
900
1000
c [uM]


HepG2
WKP141 (6a)
WKP191 (6c)
WKP194 (6d)
WKP196 (4a)
Viability [%]
100,0
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80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
0
100
200
300
400
500
600
700
800
900
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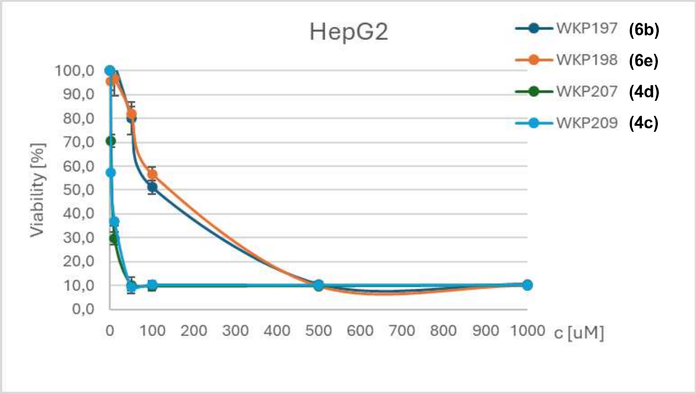
c [uM]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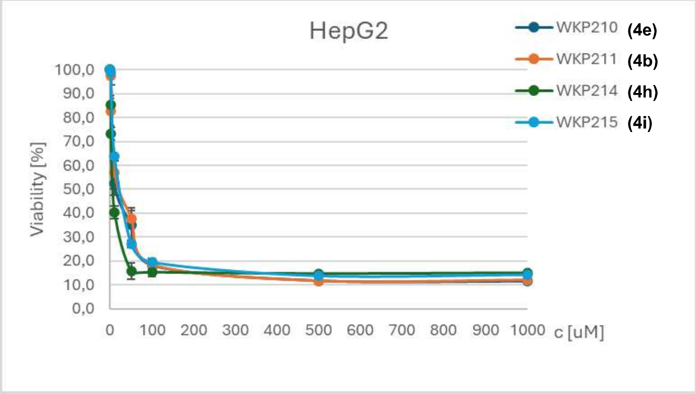
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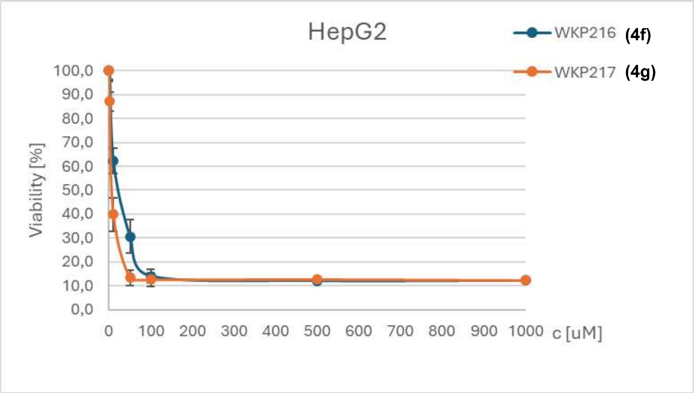
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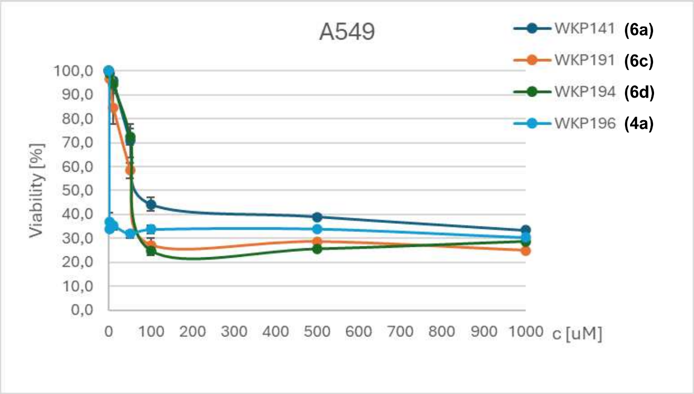
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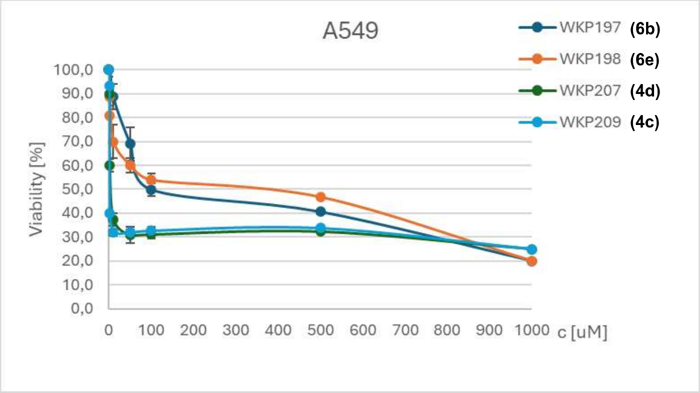
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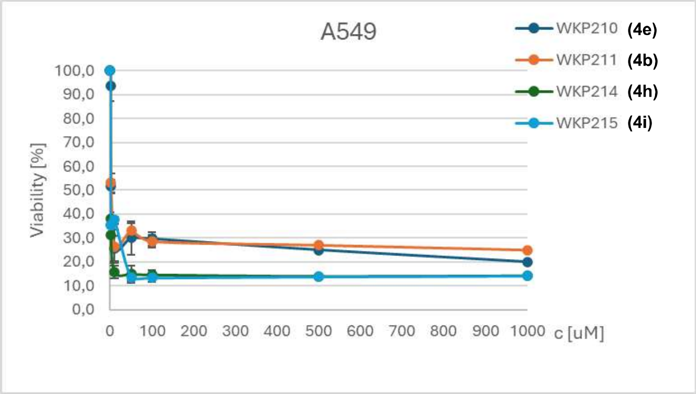
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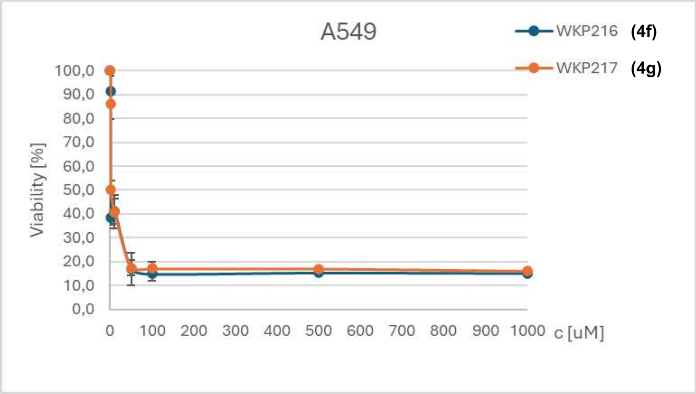
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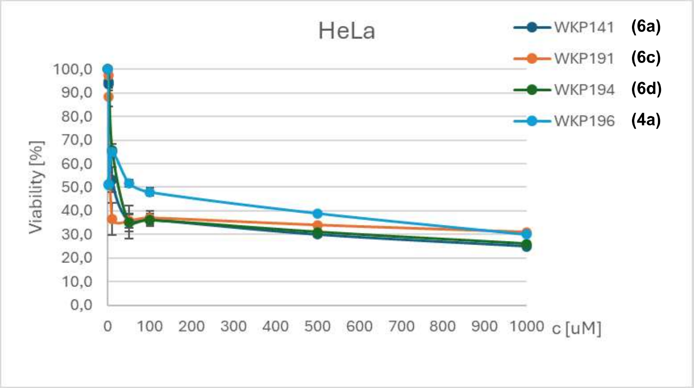
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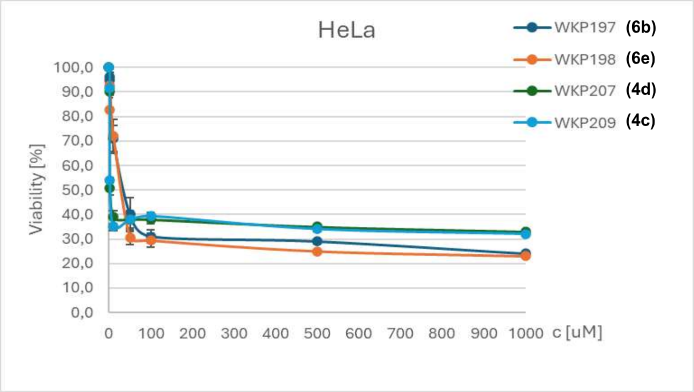
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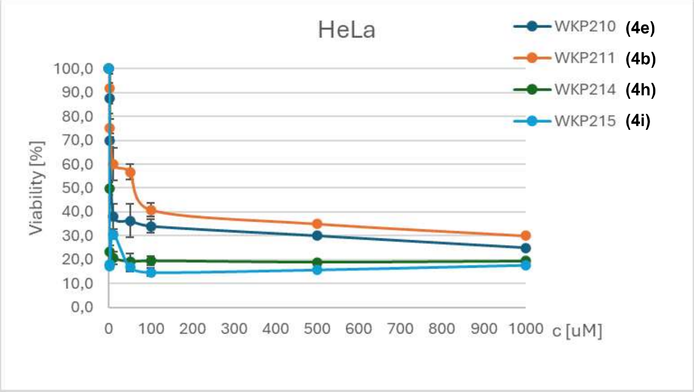
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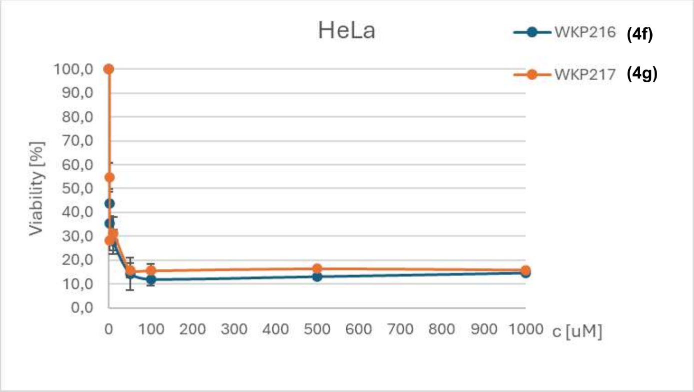
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Viability [%]
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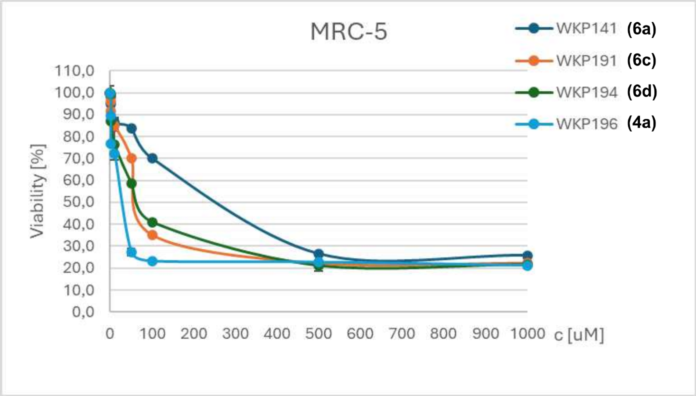
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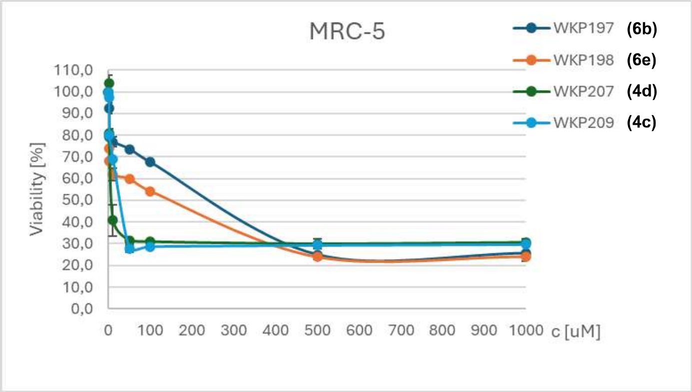
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WKP207 (4d)
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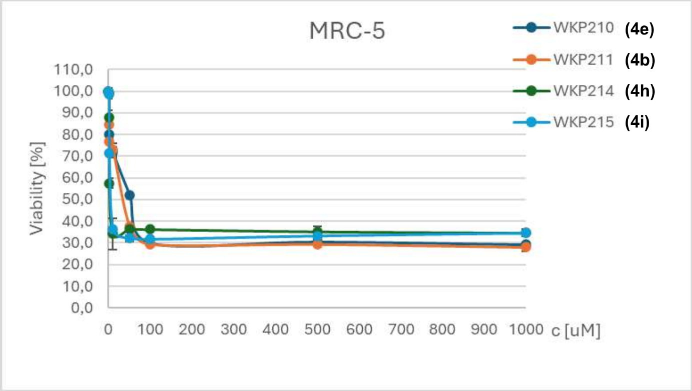
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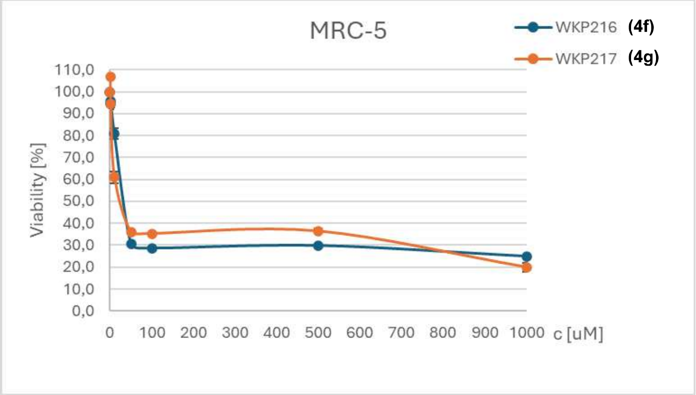

Selectivity Index

Table S1. Selectivity Index (SI) values calculated for selected cell lines.

cmpd	Selectivity Index		
	MRC-5/A549	Vero/HeLa	MRC-5/HepG2
3a	3.94	703.75	0.47
4a	1250.00	1.00	1.24
4b	2.31	0.66	2.44
4c	10.00	2.19	5.60
4d	12.67	2.02	3.17
4e	8.25	1.45	3.15
4f	22.14	162.00	2.58
4g	3760.00	233.33	3.69
4h	1110.00	50.00	3.17
4i	1260.00	1.00	0.74
6a	0.84	0.11	3.14
6b	0.62	0.29	1.26
6c	1.35	0.09	2.75
6d	0.46	0.10	1.47
6e	0.20	0.39	0.42

5. References

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3. G. Mlostoń, M. Kowalczyk, M. Celeda, M. Jasiński, M. Denel-Bobrowska, A. B. Olejniczak, *Molecules* **2022**, *27*, 3524.
4. W. K. Poper, J.-A. Ma, M. Jasiński, *J. Org. Chem.* **2024**, *89*, 15331.

[D4]

Poper, W. K.; Świątek, K.; Urbaniak, K.;
Olszewska, B.; Jasiński, M.
Molecules, **2025**, *30*, 3851.

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Article

Lepidiline-Derived Imidazole-2(3*H*)-Thiones: (3+2)-Cycloadditions vs. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines

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* Correspondence: mjasinski@uni.lodz.pl; Tel.: +48-42-635-5766

Abstract

Two series of imidazole-2(3*H*)-thiones inspired by naturally occurring lepidiline alkaloids, bearing either one or two benzyl-type substituents located at the N(1)/N(3) atoms, respectively, were prepared and examined in reactions with in situ generated *C*-trifluoromethyl-*N*-aryl nitrile imines. *N*,*N*-Dibenzylated imidazole-2-thiones served exclusively as C=S dipolarophiles to afford hitherto unknown CF_3-functionalized spiro [1,3,4-thiadiazole-5,2′-imidazole] derivatives formed through the (3+2)-cycloaddition pathway. In contrast, the enolizable *N*-monobenzylated imidazole-2-thiones provided acyclic products, i.e., hydrazonothioates, resulting from nucleophilic addition of the respective en(thio)late onto the *C*-termini of the 1,3-dipole. The presented results extend the scope of both fluorinated products available via trapping of the in situ generated CF_3-nitrile imines as well as synthetic analogues of lepidilines. In addition, spectroscopic analysis of the obtained products and the known related systems revealed ^{13}C NMR chemical shifts attributed to the *C*-(CF_3) atom as useful probes to differentiate the open-chain hydrazonothioates (δ = 112–120), 2,2-diaryl/dialkyl-2,3-dihydro-1,3,4-thiadiazoles (δ = 130–145), and more strained spiro-1,3,4-thiadiazole derivatives (δ = 166–170) reported herein.

Keywords: spiro-heterocycles; nitrile imines; imidazoles; (3+2)-cycloadditions; lepidilines; fluorinated products; alkaloids

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1. Introduction

There is increasing interest in the chemistry of imidazole alkaloids recognized as compounds of various structures and numerous roles in biological processes, and in certain cases, they are applied for medicinal needs [1–4]. Although the majority of known imidazole alkaloids originate from marine organisms, terrestrial flora also offer a variety of imidazole-based materials. For example, a lactone-functionalized imidazole alkaloid pilocarpine (**1**), first isolated from north Brazilian plant Maranham Jaborandi (*Pilocarpus microphyllus*), is an effective agent for treatment of so-called 'dry mouth' (xerostomia) as well as medication to treat glaucoma in order to reduce intraocular pressure (pressure inside the eye) (Figure 1) [5]. *Lepidium* genome, widely distributed in South America, is considered another valuable source of imidazole-based alkaloids. Thus, non-ionic dimeric structures such as lepidine (**2**) as well as monomeric lepidinoside A (**3a**, R = H) and lepidinoside B (**3b**, R = OMe) functionalized with β-D-galactopyranose moiety were identified as secondary metabolites in annual herb called garden cress (*Lepidium sativum*) [6,7]. On the other hand, several ionic *N*,*N*-dibenzylated imidazolium alkaloids such as lepidiline A and lepidiline C (**4a**,**b**; R = H or OMe, respectively) were identified in Maca root (*Lepidium meyenii*) [8–10], a known nutrient food rich in vitamins, minerals, and proteins [11,12].

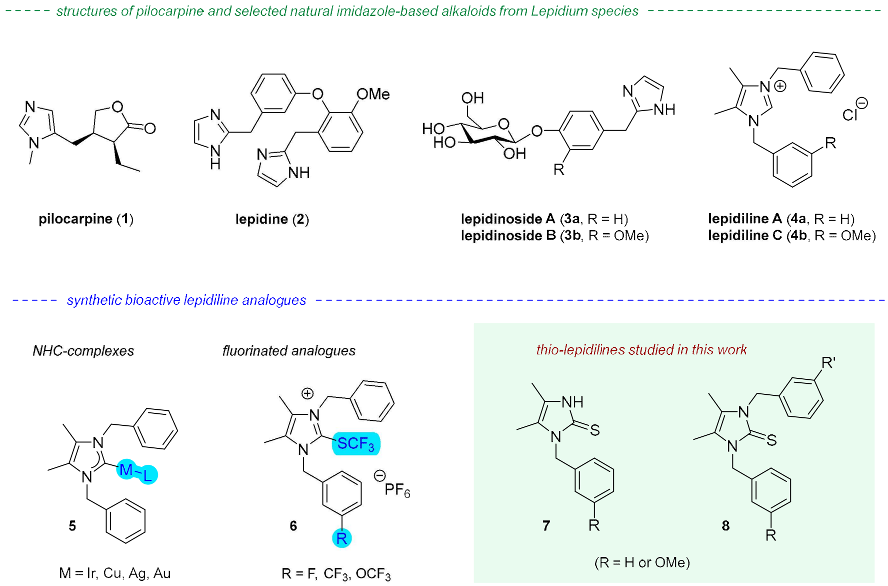
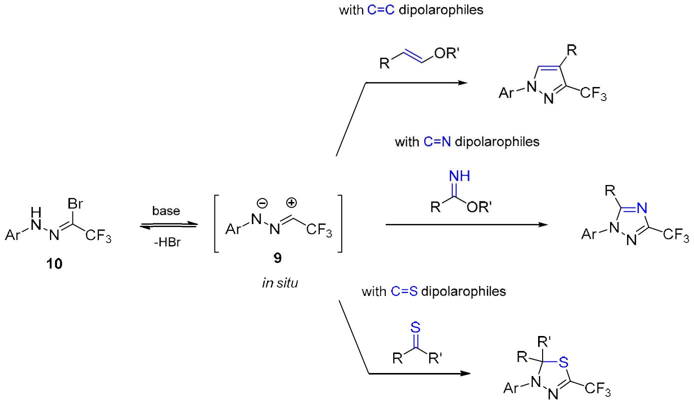


Figure 1. Structures of pilocarpine (**1**) and selected imidazole-based alkaloids **2**–**4** found in *Lepidium* species, synthetic bioactive lepidiline analogues **5** and **6**, and the enolizable and non-enolizable thio-lepidilines **7** and **8**, respectively, studied herein.

Notably, natural lepidilines exhibit promising anticancer properties [8], and for this reason, modification of their structures is considered an attractive strategy for the preparation of new bioactive compounds with desired bioactivity profiles. For example, in a series of independent work by Tacke, Kerr, and Tóth groups, lepidiline A demonstrated a suitable starting material for preparation of *N*-heterocyclic carbene (NHC) complexes with several metal ions, of which silver(I) and gold(I) complexes were demonstrated to be remarkably cytotoxic against ovarian and uterine, as well as breast cancer cells (Figure 1) [13–15]. Furthermore, our work demonstrated that introduction of the fluorine atom or fluorinated groups such as CF_3 and OCF_3 at *meta* position of the peripheral benzylic substituents in lepidiline [16], as well as functionalization of the central imidazole ring with the SCF_3 moiety [17], remarkably amplifies anticancer activity of the parent alkaloid. Hence, further study towards fluorinated lepidilines of various substitution patterns is of general interest.

In a series of recent work, the CF_3-functionalized nitrile imines of type **9**, formally derived from trifluoroacetonitrile, were demonstrated to be highly useful building blocks to access various fluorinated heterocyclic systems of general importance for pharmaceutical and agrochemical applications (Scheme 1) [18–22]. The mentioned 1,3-dipoles **9** can be easily generated in situ through base-mediated dehydrohalogenation of the respective hydrazonoyl precursors such as bromides **10** [23], and in the presence of suitable dipolarophile, they smoothly undergo Huisgen cycloaddition reactions to give five-membered products. For instance, highly chemo- and regioselective (3+2)-cycloadditions using the

C=C (or C≡C), C=N, and the C=S dipolarophilic reaction partners were developed to afford valuable CF_3-functionalized pyrazoles [24–27], 1,2,4-triazoles [28–30], and 1,3,4-thiadiazole derivatives [31–33], respectively.



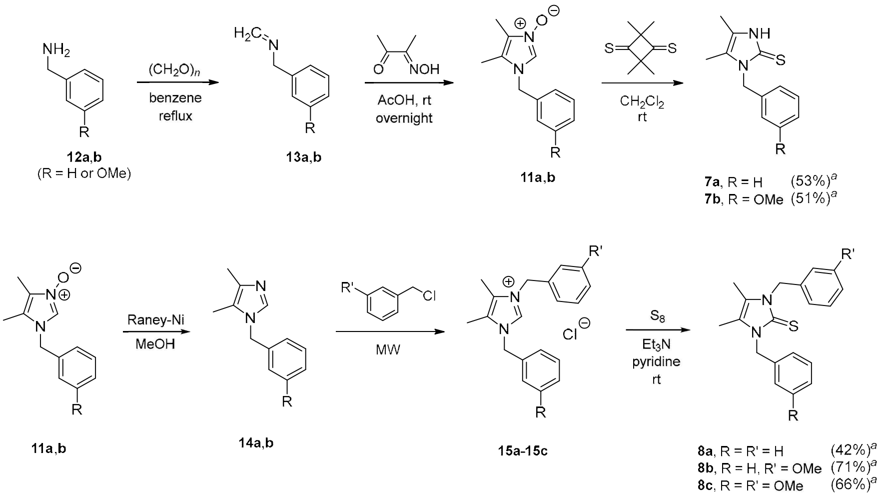
Scheme 1. Generation of CF_3-nitrile imines **9** through base-induced dehydrohalogenation of hydrazonoyl bromides **10**, and exemplary 1,3-dipolar cycloadditions of **9** with selected C=C, C=N, and C=S dipolarophiles leading to pyrazoles, 1,2,4-triazoles, and 1,3,4-thiadiazoles, respectively.

Taking into account the unusually high reactivity of the C=S group in 1,3-dipolar cycloaddition reactions (for this reason, thiocarbonyls are often called as *superdipolarophiles* [34,35]), in continuation of our quest towards fluorinated lepidilines and related imidazole derivatives [36–38], the thioxo-functionalized analogues, i.e., enolizable and non-enolizable imidazole-2(3*H*)-thiones **7** and **8** (Figure 1), respectively, were prepared and examined in reactions with in situ-generated CF_3-nitrile imines **9**. Here we report different reaction outcomes observed for reactions of the selected imidazole-2-thiones; whereas enolizable substrates of type **7** provided exclusively acyclic products (i.e., hydrazonothioates) formed by nucleophilic addition of the respective thiolates onto the *C*-termini of the 1,3-dipole, the non-enolizable 1,3-dibenzyl-imidazole-2-thiones **8** afforded solely the expected spiro [1,3,4-thiadiazole-5,2′-imidazole] derivatives resulting from the (3+2)-cycloaddition of the 1,3-dipole and the C=S group of dipolarophile **8**. The scope and limitations of both developed reactions was also checked.

2. Results and Discussion

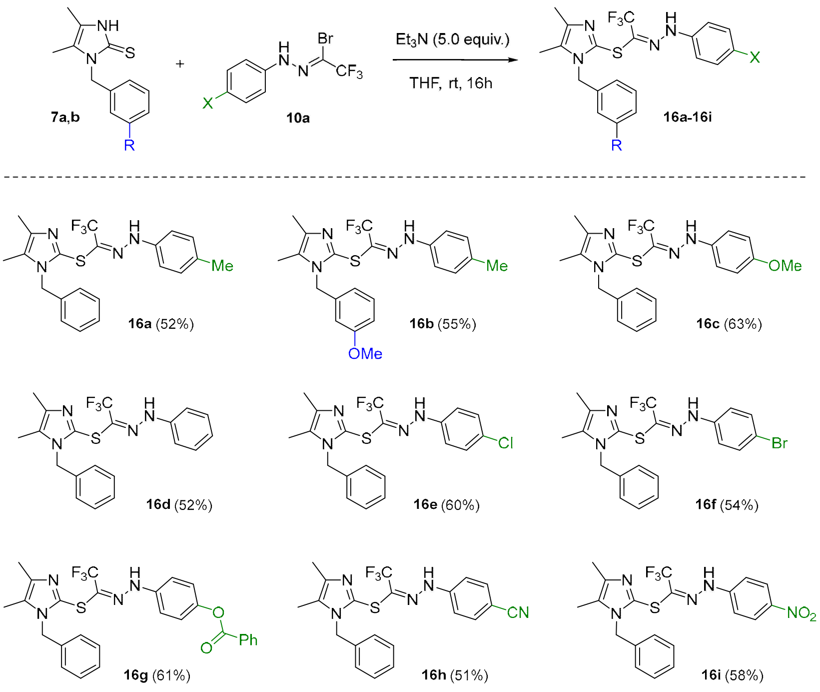
The required imidazole-2-thiones **7** and **8** are readily available building blocks that can be prepared using the corresponding nitrone-like 2-unsubstitutied imidazole *N*-oxides **11** recognized as convenient precursors for various imidazole-based systems [39–41]. Following the general protocol depicted in Scheme 2, two selected enolizable imidazole derivatives bearing benzyl (**7a**) or 3-methoxybenzyl (**7b**) substituent located at the N(1) of the imidazole ring were prepared through the one-pot telescopic approach starting from the respective benzylamines **12** (see, Supporting Information in Supplementary File S1), by treatment of **12** with solid paraformaldehyde under reflux, followed by acid-induced (in glacial AcOH [36]) condensation of the first formed formaldimines **13** with diacetyl monoxime to give *N*-oxides **11a** and **11b**. Sulfur-transfer with 2,2,4,4-tetramethylcyclobutane-1,3-dithione [42] provided the desired enolizable imidazole-2-thiones **7a** and **7b**, which were isolated in fair overall yield of 53% and 51% (for 3 steps), respectively. With two intermediate imidazole *N*-oxides

11a and **11b** in hand, the non-enolizable series of imidazole-2-thiones **8a–8c** was synthesized in a one-pot manner starting with deoxygenation of **11** with Raney-nickel, in MeOH, at room temperature, followed by microwave-activated *N*-benzylation of the imidazole ring with selected benzyl chlorides (R′ = H or OMe) to give the corresponding imidazolium chlorides **15**. Subsequent sulphuration of the in situ-generated *N*-heterocyclic carbenes derived from salts **15** with elemental sulfur in pyridine afforded desired products of type **8**. Also, in this case the overall yield of isolated products **8a**, **8b**, and **8c** was satisfactory (42%, 71%, and 66%, respectively; for three steps from imidazole *N*-oxides **11**).



Scheme 2. Synthesis of imidazole-2-thiones **7a**,**b** and **8a–8c** employing imidazole *N*-oxides **11** as key intermediates: [a] overall yield for 3 steps.

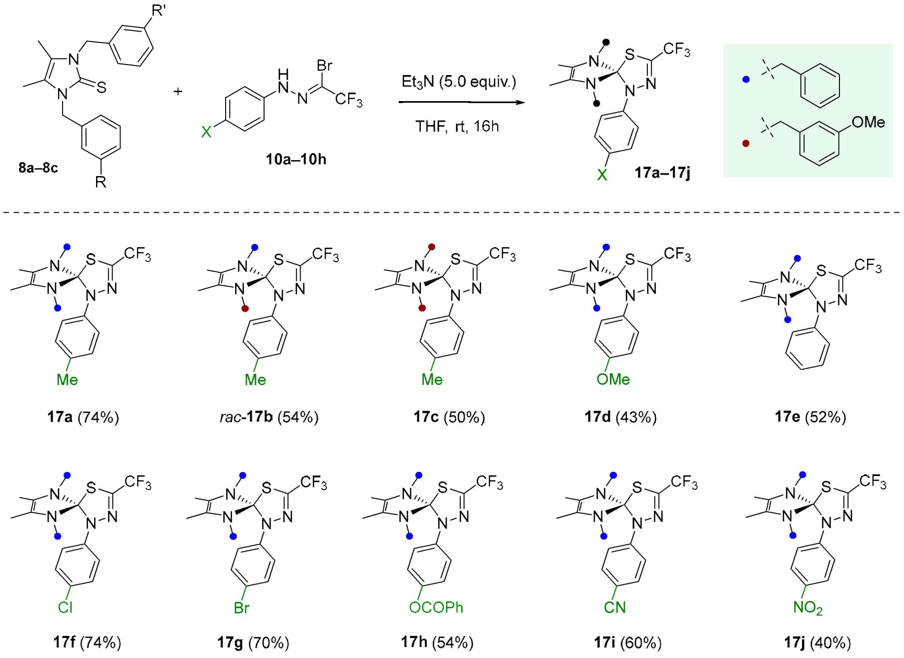
A series of CF_3-nitrile imine precursors, i.e., hydrazonoyl bromides **10**, was prepared following the general literature protocols by NBS-mediated bromination [31] of the azomethine group in trifluoroacetaldehyde arylhydrazones [43]. Based on our experience in base-induced in situ generation of nitrile imines **9** and their trapping with dipolarophiles [24–26,44,45] as well as other bifunctional reagents in solution [46,47], but also under solvent-free mechanochemical conditions [48,49], the initial experiments were carried out using slight excess imidazole-2-thione **7a** (1.2 equiv.), and *N*-tolyl-functionalized bromide **10a** (1.0 mmol) selected as a model precursor, in dry THF solution, in the presence of three-fold excess Et_3N (Scheme 3). To our delight, slow consumption of the starting imidazole-2-thione was observed at room temperature, and after overnight stirring, the reaction was complete. Whereas increasing excess of triethylamine to 5 equiv. slightly accelerated the studied transformation, replacement of THF by toluene or by dichloromethane showed no positive effects on the reaction progress. Also, increase in the reaction temperature (THF, up to 65 °C) provided more complex reaction mixtures, presumably due to decomposition of the first formed product. Removal of the solid triethylammonium bromide by filtration followed by purification of the crude products on chromatography column provided solid material, which was recrystallized from petroleum ether/dichloromethane mixture to give colorless crystalline **16a** in 52% yield. Whereas the ESI-MS measurements supplemented by combustion analysis confirmed the expected molecular formula as $C_{21}H_{21}F_3N_4S$, analysis of spectroscopic data of the isolated material suggested the open-chain structure of **16a** (i.e., the respective hydrazonothioate resulting from nucleophilic addition) rather than the isomeric (3+2)-cycloaddition product formed by the attack onto the C=S bond. In particular, in the ^{13}C NMR spectrum of **16a** the diagnostic quartet ($^2J_{C\text{-}F}$ = 37.6 Hz) attributed to the *C*-(CF$_3$) atom was found at a remarkably higher field of δ = 113.2 in comparison to absorptions observed for typical 2,2-(hetero)diaryl- and 2,2-dialkyl-2,3-dihydro-1,3,4-thiadiazole derivatives, usually between δ = 130–145 [31–33].



Scheme 3. Synthesis of hydrazonothioates **16a–16i** derived from enolizable imidazole-2-thiones **7a** and **7b**: scope of hydrazonoyl bromides **10**.

An analogous result was observed for the reaction of *m*-methoxybenzyl-functionalized derivative **7b** with the model CF$_3$-nitrile imine **9a**; also in that case, the corresponding hydrazonothioate **16b** was formed as a single product, which was isolated as an analytically pure oil in comparable yield of 55% (Scheme 3). Next, a series of hydrazonoyl bromides **10b–10h** was involved into the study and examined in reactions with imidazole-2-thione **7a** under standard reaction conditions. In all the experiments, the exclusive thiophilic addition of **7a** onto positively charged C atom of the nitrile imine **9** was observed to afford hydrazonothioates **10c–10i** in moderate yield (51–63%), irrespectively of the electronic nature of the substituent located at the *para* position of the *N*-phenyl group in hydrazonoyl bromide **10**.

In continuation of the study, 1,3-dibenzyl-4,5-dimethylimidazole-2-thione (**8a**) was examined in reaction with model CF$_3$-nitrile imine **9a** under the analogous reaction conditions. The consumption of starting materials along with the formation of a single product was observed within 6 h (by TLC monitoring), and after removal of the solvents followed by standard column chromatography, the expected (3+2)-cycloadduct **17a** (74%) was isolated as a colorless solid (Scheme 4). The structure of **17a** was confirmed on the basis of spectroscopic analysis; for example, in the ^{1}H NMR spectrum, a set of characteristic signals attributed to the C_2-symmetric imidazole unit was located at δ = 2.06 (6H, 2 Me) and δ = 5.08 (4H, 2 CH_2Ph), while absorptions found at δ = 2.16 (3H, Me) and between δ = 6.55–7.11 (14H) revealed the presence of all three aromatic substituents. More importantly, in the ^{13}C NMR spectrum the diagnostic absorption attributed to the C(2) atom of the 1,3,4-thadiazole ring was found at δ = 167.2 ($^2J_{C\text{-}F}$ = 33.3 Hz), indicating the formation of a strained system, while absorption at $\delta = -66.5$ in the ^{19}F NMR spectrum denoted the presence of a single CF_3 group. Further tests including ESI-MS measurements and combustion analysis confirmed the molecular formula of **17a** as $C_{28}H_{27}F_3N_4S$ and the analytical purity of the sample.



Scheme 4. Synthesis of spiro [1,3,4-thiadiazole-5,2′-imidazole] derivatives **17a–16j** derived from non-enolizable imidazole-2-thiones **8a–8c**: scope of hydrazonoyl bromides **10**.

Imidazole-2-thiones bearing one (**8b**) or two *m*-methoxybenzyl (**8c**) groups were also reacted with CF_3-nitrile imine **9a** to afford (3+2)-cycloadducts *rac*-**17b** and **17c**, albeit partial decomposition of these products was observed during purification on column, and the spectroscopically pure samples were isolated in lower yield (54% and 50%, respectively). Finally, a series of variously substituted nitrile imines were examined, and in all of the cases the expected spiro products were formed. Notably, the presence of such synthetically useful substituents and functional groups as methoxy, halogens (Cl and Br), ester (OCOPh), as well as strongly electron-withdrawing cyano and nitro moieties were tolerated, and the desired materials **17d–17j** were isolated in fair 50–74% yield (Scheme 4).

Some time ago, a series of thiocarbonyl compounds was examined in reactions with CF_3-nitrile imines of type **9**. Thus, (cyclo)aliphatic [31] and (hetero)aromatic thioketones [32], monomeric thiochalcones [33] as well as perfluorinated secondary thioamides [50] provided the expected 5-membered products, namely 2,2-disubstituted 2,3-dihydro-1,3,4-thiadiazoles, which were fully characterized by spectroscopic methods. In all of these cases, in the ^{13}C NMR spectra the diagnostic absorption attributed to the C(5) atom (q, $^{2}J_{\text{C-F}} \approx 37$–$43$ Hz) linked with the CF_3 group was found between $\delta = 130$–145 (Figure 2).

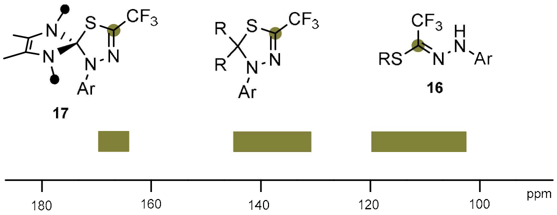
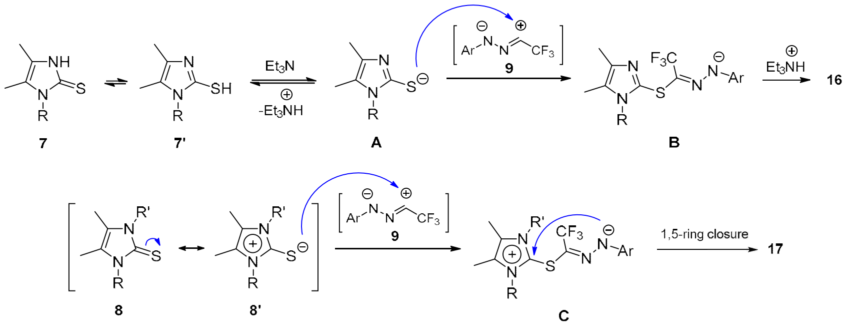


Figure 2. The diagnostic ^{13}C NMR chemical shifts attributed to the *C*-(CF_3) atom in known CF_3-functionalized 2,2-dialkyl/diaryl-2,3-dihydro-1,3,4-thiadiazoles [31–33,50], lepidiline-derived hydrazonothioates **16** and spiro-1,3,4-thiadiazole derivatives **17** reported in this work.

In the present work, the thiourea-type lepidiline analogues **7** and **8** provided different products depending on the substitution pattern; whereas enolizable substrates afforded hydrazonothioates **16**, the non-enolizable starting materials yielded solely the corresponding *spiro* products **17**. These structural differences can be observed in the ^{13}C NMR spectra as the analogous quartet signal is either remarkably high-field (unhindered adducts) or down-field shifted (more strained spiro[imidazo-1,3,4-thiadiazoles]), respectively (Figure 2). Thus the ^{13}C NMR absorption of the *C*(CF_3) atom can be considered a useful probe to easily differentiate the type of products formed in reactions between thiocarbonyl compounds and the CF_3-nitrile imines.

The formation of hydrazonothioates **16** and spiro (3+2)-cycloadducts **17** also deserve a brief comment; in the former case, the starting enolizable imidazole-2-thione **7** presumably suffer deprotonation under the applied reaction conditions to give highly nucleophilic en(thio)late intermediate **A** (Scheme 5). The formed anion smoothly adds to the *C*-termini of the nitrile imine **9** to give **B**. Subsequent protonation of the negatively charged N atom in nicely stabilized **B** leads to sterically unhindered product **16**. In the case of non-enolizable imidazole-2-thiones **8**, no corresponding thiolate anion operates; taking into account known remarkable polarization of the carbon–sulfur bond in imidazole-2-thiones [51], we tentatively propose that the reaction initiates thiophilic addition of nitrile imine onto **8′**, leading to zwitterionic intermediate of type **C**. This first formed adduct undergoes 1,5-ring closure to afford final sterically demanding (3+2)-cycloadduct **17** in a fully regioselective manner.



Scheme 5. The proposed mechanisms for the formation of hydrazonothioates **16** and (3+2)-cycloadducts **17**.

3. Materials and Methods

3.1. Chemical Synthesis General Methods

Experimental procedures: Solvents and chemicals were purchased and used as received. Products were purified by standard column chromatography (CC) on silica gel (230–400 mesh). Melting points were determined in capillaries with a MEL-TEMP II apparatus (Laboratory Devices, Holliston, MA, USA) or with a Stuart SMP30 apparatus (Bibby Scientific Ltd., Stone, Staffordshire, UK) with automatic temperature monitoring, and are uncorrected. The NMR spectra were taken on a Bruker AVIII instrument (^{1}H at 600 MHz, ^{13}C at 151 MHz, and ^{19}F at 565 MHz) (Bruker BioSpin AG, Fällanden, Switzerland). Chemical shifts are reported relative to solvent residual peaks; for $CDCl_3$: ^{1}H NMR: $\delta = 7.26$, ^{13}C NMR: $\delta = 77.16$ or to $CFCl_3$ (^{19}F NMR: $\delta = 0.00$) used as external standard. The IR spectra were measured with an Agilent Cary 630 FTIR spectrometer (Agilent Technologies, Santa Clara, CA, USA), in neat. MS (ESI) were taken with a Varian 500-MS LC Ion Trap (Varian, Inc., Walnut Creek, CA, USA), and high resolution MS (ESI-TOF) measurements were taken with a Waters Synapt G2-Si mass spectrometer (Waters Corporation, Milford, MA, USA). Combustion analyses were performed with a Vario EL III (Elementar Analysensysteme GmbH, Langenselbold, Germany) instrument.

Starting materials: Hydrazonoyl bromides **10** were prepared by reaction of the corresponding trifluoroacetaldehyde arylhydrazones with NBS, according to general protocol [31], while the required fluoral hydrazones were obtained by condensation of aqueous fluoral hydrate (~75% in H_2O) with commercial arylhydrazines [43]. The intermediate imidazole *N*-oxides **11** were prepared by AcOH-catalyzed condensation of formaldimines with diacetyl monoxime, as described [36]. Sulphuration of the latter imidazole *N*-oxides was carried out using cyclobutane-derived thioketone according to general report [42].

3.2. General Procedure for Synthesis of Cycloadducts **16** and **17**

In a round-bottomed flask equipped with a stirring bar, an imidazole-2-thione **7** or **8** (1.2 mmol) was dissolved in dry THF (5 mL), the hydrazonoyl bromide **10** (1.0 mmol) was added followed by triethylamine (505 mg, 0.7 mL, 5.0 mmol), the flask was covered with a stopper, and the solution was stirred at ambient temperature until the starting hydrazonoyl bromide was fully consumed (TLC monitoring; typically 6 h for reactions of imidazole-thiones **7**, and 4 h for symmetric analogues **8**). The solvents were removed in vacuo, and the product was isolated via a standard column chromatography (CC) on silica gel (gradient petroleum ether to petroleum ether/CH_2Cl_2 1:3 for hydrazonothioates

16; gradient hexane to hexane/AcOEt 2:3 for spiro-products **17**), and recrystallized from a petroleum ether/dichloromethane mixture (in the case of products **16**).

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-tolyl)-ethanehydrazonothioate (**16a**): colorless crystals, 218 mg (52%), mp 105–106 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.98, 2.19, 2.32 (3s, 3H each), 5.29 (s, 2H), 6.93–6.95 (m, 2H), 7.12–7.17 (m, 4H), 7.27–7.33 (m, 3H), 11.37 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.6, 12.8, 20.9, 48.4, 113.2 (q, $^{2}J_{\text{C-F}}$ = 37.6 Hz), 114.2, 121.2 (q, $^{1}J_{\text{C-F}}$ = 271.5 Hz, CF$_3$), 126.2, 127.5, 127.9, 129.0, 129.90, 129.92, 132.1, 136.00, 136.01, 140.6. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.32 (s, CF$_3$). ESI-MS (*m*/*z*) 419.5 (100, $[M+H]^+$). IR (neat) v 1569, 1513, 1349, 1256, 1156, 1081 cm^{-1}. Anal. Calcd for $C_{21}H_{21}F_3N_4S$ (418.5): C 60.27, H 5.06, N 13.39, S 7.66; found: C 60.11, H 5.19, N 13.34, S 7.69.

1-(3-Methoxybenzyl)-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-tolyl)-ethanehydrazonothioate (**16b**): thick yellow oil, 247 mg (55%). ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.99, 2.19, 2.32, 3.74 (4s, 3H each), 5.26 (s, 2H), 6.47 (m$_{\text{c}}$, 1H), 6.52–6.54 (m, 1H), 6.81–6.83 (m, 1H), 7.12–7.17 (m, 4H), 7.22–7.25 (m, 1H), 11.36 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.6, 12.8, 20.8, 48.3, 55.3, 111.9, 113.19 (q, $^{2}J_{\text{C-F}}$ = 37.6 Hz), 113.21, 114.2, 118.4, 121.1 (q, $^{1}J_{\text{C-F}}$ = 271.6 Hz, CF$_3$), 127.5, 129.8, 129.89, 130.08, 132.1, 136.0, 137.6, 140.6, 160.2. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.27 (s, CF$_3$). ESI-MS (*m*/*z*) 449.4 (100, $[M+H]^+$). IR (neat) v 1599, 1566, 1506, 1446, 1264, 1174, 1122, 1029 cm^{-1}. Anal. Calcd for $C_{22}H_{23}F_3N_4SO$ (448.5): C 58.92, H 5.17, N 12.49, S 7.15; found: C 58.95, H 5.17, N 12.41, S 7.34.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-metoxyphenyl)-ethanehydrazonothioate (**16c**): beige crystals, 274 mg (63%), mp 90–92 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.98, 2.18, 3.79 (3s, 3H each), 5.28 (s, 2H), 6.87–6.89 (m, 2H), 6.93–6.95 (m, 2H), 7.17–7.19 (m, 2H), 7.26–7.33 (m, 3H), 11.33 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.7, 12.9, 48.4, 55.8, 112.6 (q, $^{2}J_{\text{C-F}}$ = 37.7 Hz), 114.8, 115.4, 121.2 (q, $^{1}J_{\text{C-F}}$ = 271.4 Hz, CF$_3$), 126.2, 127.4, 128.0, 129.0, 130.0, 135.9, 136.0, 136.8, 155.6. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.19 (s, CF$_3$). ESI-MS (*m*/*z*) 435.3 (100, $[M+H]^+$). IR (neat) v 1562, 1506, 1407, 1331, 1234, 1141, 1096, 1036, 969 cm^{-1}. Anal. Calcd for $C_{21}H_{21}F_3N_4SO$ (434.5): C 58.05, H 4.87, N 12.90, S 7.38; found: C 58.00, H 4.79, N 12.77, S 7.57.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-phenyl-ethanehydrazonothioate (**16d**): cream solid, 210 mg (52%), mp 89-91 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.99, 2.20 (2s, 3H each), 5.29 (s, 2H), 6.93–6.95 (m, 2H), 7.00–7.02 (m, 1H), 7.24–7.27 (m, 2H), 7.28–7.34 (m, 5H), 11.45 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.7, 12.9, 48.4, 114.1 (q, $^{2}J_{\text{C-F}}$ = 37.6 Hz), 114.3, 121.1 (q, $^{1}J_{\text{C-F}}$ = 271.8 Hz, CF$_3$), 122.6, 126.2, 127.6, 128.0, 129.1, 129.4, 129.8, 136.0, 136.1, 142.9. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.53 (s, CF$_3$). ESI-MS (*m*/*z*) 405.3 (100, $[M+H]^+$). IR (neat) v 1621, 1547, 1491, 1457, 1402, 1338, 1252, 1148, 1096, 1077 cm^{-1}. Anal. Calcd for $C_{20}H_{19}F_3N_4S$ (404.5): C 59.39, H 4.74, N 13.85, S 7.93; found: C 59.38, H 4.74, N 13.79, S 8.01.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-chlorophenyl)-ethanehydrazonothioate (**16e**): colorless solid, 264 mg (60%), mp 114–116 °C (decomp.). ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.99, 2.18 (2s, 3H each), 5.27 (s, 2H), 6.92–6.94 (m, 2H), 7.16–7.19 (m, 2H), 7.27–7.33 (m, 5H), 11.57 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.7, 12.9, 48.5, 115.0 (q, $^{2}J_{\text{C-F}}$ = 37.7 Hz), 115.5, 120.9 (q, $^{1}J_{\text{C-F}}$ = 271.9 Hz, CF$_3$), 126.2, 127.5, 127.6, 128.0, 129.1, 129.4, 129.6, 135.9, 136.1, 141.6. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.76 (s, CF$_3$). (−)-ESI-MS (*m*/*z*) 438.9 (35, $[M\{^{37}Cl\}-H]^-$), 437.0 (100, $[M\{^{35}Cl\}-H]^-$). IR (neat) v 1558, 1487, 1405, 1327, 1159, 1107, 973 cm^{-1}. Anal. Calcd for $C_{20}H_{18}ClF_3N_4S$ (438.9): C 54.73, H 4.13, N 12.77, S 7.30; found: C 54.72, H 4.08, N 12.80, S 7.44.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-bromophenyl)-ethanehydrazonothioate (**16f**): beige solid, 261 mg (54%), mp 108–110 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 1.99, 2.17 (2s, 3H each), 5.27 (s, 2H), 6.92–6.94 (m, 2H), 7.11–7.13 (m, 2H), 7.26–7.33 (m, 3H), 7.40–7.43 (m, 2H), 11.58 (s$_{\text{br}}$, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.7, 12.9, 48.5, 114.9, 115.2 (q, $^{2}J_{\text{C-F}}$ = 37.8 Hz), 115.9, 120.9 (q, $^{1}J_{\text{C-F}}$ = 271.8 Hz, CF$_3$), 126.2, 127.7, 128.0, 129.1, 129.6, 132.3, 135.9, 136.1, 142.1. ^{19}F NMR (565 MHz, CDCl$_3$) δ −65.80 (s, CF$_3$). (−)-ESI-MS (*m*/*z*) 483.1 (97, $[M\{^{81}Br\}-H]^-$), 482.1 (100, [M{^{79}Br}-H]$^-$). IR (neat) *v* 1558, 1484, 1406, 1327, 1141, 1159, 1100, 973 cm^{-1}. Anal. Calcd for $C_{20}H_{18}BrF_3N_4S$ (483.4): C 49.70, H 3.75, N 11.59, S 6.63; found: C 49.78, H 3.85, N 11.65, S 6.86.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-benzoyloxyphenyl)-ethanehydrazonothioate (**16g**): beige crystals, 319 mg (61%), mp 125–128 °C (decomp.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99, 2.19 (2s, 3H each), 5.29 (s, 2H), 6.93–6.94 (m, 2H), 7.17–7.19 (m, 2H), 7.27–7.33 (m, 5H), 7.50–7.53 (m, 2H), 7.62–7.65 (m, 1H), 8.20–8.22 (m, 2H), 11.53 (s_{br}, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.7, 12.9, 48.5, 114.5 (q, $^2J_{C\text{-}F}$ = 37.4 Hz), 115.0, 121.0 (q, $^1J_{C\text{-}F}$ = 271.9 Hz, CF_3), 122.7, 126.2, 127.7, 128.0, 128.7, 129.1, 129.7, 129.8, 130.3, 133.7, 135.9, 136.1, 140.8, 146.2, 165.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ −65.62 (s, CF_3). ESI-MS (*m/z*) 525.3 (100, [M+H]$^+$). IR (neat) *v* 1737, 1558, 1502, 1331, 1245, 1193, 1144, 1111, 1062, 1025, 977 cm^{-1}. Anal. Calcd for $C_{27}H_{23}F_3N_4SO_2$ (524.6): C 61.82, H 4.42, N 10.68, S 6.11; found: C 61.60, H 4.27, N 10.41, S 6.09.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-cyanophenyl)-ethanehydrazonothioate (**16h**): beige crystals, 218 mg (51%), mp 118–120 °C (decomp.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.00, 2.18 (2s, 3H each), 5.27 (s, 2H), 6.92–6.93 (m, 2H), 7.28–7.34 (m, 5H), 7.58–7.61 (m, 2H), 12.02 (s_{br}, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.7, 12.9, 48.5, 105.1, 114.5, 118.4 (q, $^2J_{C\text{-}F}$ = 37.8 Hz), 119.5, 120.5 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, CF_3), 126.1, 127.9, 128.1, 129.08, 129.13, 133.8, 135.7, 136.2, 146.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ −66.39 (s, CF_3). (−)-ESI-MS (*m/z*) 428.0 (100, [M-H]$^-$). IR (neat) *v* 2215, 1602, 1551, 1502, 1413, 1338, 1297, 1249, 1129, 977 cm^{-1}. Anal. Calcd for $C_{21}H_{18}F_3N_5S$ (429.5): C 58.73, H 4.22, N 16.31, S 7.47; found: C 58.71, H 4.27, N 16.27, S 7.62.

1-Benzyl-4,5-dimethylimidazol-2-yl 2,2,2-trifluoro-N′-(4-nitrophenyl)-ethanehydrazonothioate (**16i**): yellow crystals, 260 mg (58%), mp 108–111 °C (decomp.). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.01, 2.19 (2s, 3H each), 5.28 (s, 2H), 6.93–6.94 (m, 2H), 7.28–7.34 (m, 5H), 8.20–8.24 (m, 2H), 12.22 (s_{br}, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.7, 12.9, 48.5, 113.8, 119.4 (q, $^2J_{C\text{-}F}$ = 37.9 Hz), 120.5 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 125.9, 126.1, 128.0, 128.2, 129.9, 129.2, 135.6, 136.2, 142.6, 148.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ −66.53 (s, CF_3). ESI-MS (*m/z*) 450.3 (100, [M+H]$^+$). IR (neat) *v* 1580, 1551, 1495, 1331, 1252, 1148, 1107 cm^{-1}. Anal. Calcd for $C_{20}H_{18}F_3N_5O_2S$ (449.5): C 53.45, H 4.04, N 15.58, S 7.13; found: C 53.37, H 4.10, N 15.43, S 7.21.

1′,3′-Dibenzyl-4′,5′-dimethyl-4-(4-tolyl)-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17a**): colorless solid, 376 mg (74%), mp 143–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.06 (s, 6H), 2.16 (s, 3H), 5.08 (s, 4H), 6.55–6.57 (m, 2H), 6.80–6.82 (m, 2H), 7.11–7.14 (m, 4H), 7.19–7.21 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.9, 20.6, 50.3, 117.5, 121.0 (q, $^1J_{C\text{-}F}$ = 277.0 Hz, CF_3), 124.6, 127.9, 128.3, 128.9, 129.4, 133.0, 133.1, 142.5, 142.9, 167.2 (q, $^2J_{C\text{-}F}$ = 33.3 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ −66.46 (s, CF_3). ESI-MS (*m/z*) 509.3 (100, [M+H]$^+$). IR (neat) *v* 1498, 1450, 1297, 1238, 1156, 1111, 1077, 991 cm^{-1}. Anal. Calcd for $C_{28}H_{27}F_3N_4S$ (508.6): C 66.12, H 5.35, N 11.02, S 6.30; found: C 66.21, H 5.32, N 10.88, S 6.43.

1′-Benzyl-3′-(3-methoxybenzyl)-4′,5′-dimethyl-4-(4-tolyl)-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17b**): colorless solid, 290 mg (54%), mp 137–139 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08, 2.09, 2.18, 3.67 (4s, 3H each), 5.06, 5.10 (2s, 2H each), 6.56–6.59 (m, 2H), 6.71–6.76 (m, 3H), 6.81–6.84 (m, 2H), 7.13–7.15 (m, 3H), 7.20–7.23 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.96, 9.97, 20.7, 50.44, 50.47, 55.5, 113.6, 114.3, 117.6, 120.2, 121.0 (q, $^1J_{C\text{-}F}$ = 276.9 Hz, CF_3), 124.6, 124.7, 128.0, 128.4, 129.0, 129.5, 129.9, 133.1, 133.2, 134.7, 142.7, 143.1, 160.1, 167.3 (q, $^2J_{C\text{-}F}$ = 33.2 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ −66.56 (s, CF_3). IR (neat) *v* 1498, 1439, 1298, 1286, 1238, 1166, 1111, 1077 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{29}H_{30}F_3N_4OS$ 539.2092, found 539.2098.

1′,3′-Bis(3-methoxybenzyl)-4′,5′-dimethyl-4-(4-tolyl)-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17c**): colorless solid, 284 mg (50%), mp 124–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09 (s, 6H), 2.18 (s, 3H), 3.66 (s, 6H), 5.05 (s, 4H), 6.56–6.58 (m, 2H), 6.71–6.75 (m, 6H), 6.82–6.84 (m, 2H), 7.12–7.15 (m, 2H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.9, 20.7, 50.4, 55.5, 113.6, 114.4, 117.5, 120.1, 121.1 (q, $^1J_{\text{C-F}}$ = 276.9 Hz, CF$_3$), 124.7, 129.5, 129.9, 133.0, 134.6, 142.7, 143.0, 160.1, 167.1 (q, $^2J_{\text{C-F}}$ = 32.1 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.54 (s, CF$_3$). IR (neat) v 1603, 1491, 1439, 1260, 1159, 1115, 980 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{30}H_{32}F_3N_4O_2S$ 569.2198, found 569.2198.

1′,3′-Dibenzyl-4′,5′-dimethyl-4-(4-methoxyphenyl)-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17d**): pale yellow solid, 225 mg (43%), mp 49–51 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.10 (s, 6H), 3.66 (s, 3H), 5.09 (s, 4H), 6.52–6.57 (m, 4H), 7.10–7.13 (m, 4H), 7.20–7.23 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 9.9, 50.3, 56.7, 114.3, 119.7, 121.0 (q, $^1J_{\text{C-F}}$ = 276.9 Hz, CF$_3$), 124.4, 127.9, 128.4, 129.0, 133.3, 138.3, 143.3, 156.3, 167.8 (q, $^2J_{\text{C-F}}$ = 32.5 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.46 (s, CF$_3$). IR (neat) v 1498, 1443, 1290, 1230, 1167, 1115, 1073, 1028, 991 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{28}H_{28}F_3N_4OS$ 525.1936, found 525.1938.

1′,3′-Dibenzyl-4′,5′-dimethyl-4-phenyl-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17e**): pale yellow solid, 257 mg (52%), mp 57–59 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.10 (s, 6H), 5.11 (s, 4H), 6.65–6.67 (m, 2H), 6.84–6.86 (m, 1H), 7.00–7.03 (m, 2H), 7.12–7.15 (m, 4H), 7.19–7.21 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 10.0, 50.5, 117.2, 121.0 (q, $^1J_{\text{C-F}}$ = 277.0 Hz, CF$_3$), 123.3, 124.9, 127.1, 128.0, 128.5, 128.9, 129.0, 133.0, 142.8, 144.9, 167.4 (q, $^2J_{\text{C-F}}$ = 32.4 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.57 (s, CF$_3$). IR (neat) v 1595, 1491, 1454, 1290, 1230, 1167, 1118, 1059, 988 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{27}H_{26}F_3N_4S$ 495.1830, found 495.1835.

4-(4-Chlorophenyl)-1′,3′-dibenzyl-4′,5′-dimethyl-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17f**): colorless solid, 391 mg (74%), mp 63–65 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.17 (s, 6H), 5.10 (s, 4H), 6.46–6.48 (m, 2H), 6.86–6.88 (m, 2H), 7.09–7.10 (m, 4H), 7.18–7.24 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 10.0, 50.4, 118.2, 120.9 (q, $^1J_{\text{C-F}}$ = 277.2 Hz, CF$_3$), 124.9, 128.0, 128.2, 128.56, 128.64, 129.0, 132.8, 142.3, 143.4, 168.2 (q, $^2J_{\text{C-F}}$ = 32.4 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.58 (s, CF$_3$). IR (neat) v 1484, 1454,1286, 1234, 1170, 1118,1006, 988 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{27}H_{25}ClF_3N_4S$ 529.1441, found 529.1447.

4-(4-Bromophenyl)-1′,3′-dibenzyl-4′,5′-dimethyl-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17g**): colorless solid, 400 mg (70%), mp 69–71 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.17 (s, 6H), 5.09 (s, 4H), 6.40–6.42 (m, 2H), 7.00–7.02 (m, 2H), 7.08–7.10 (m, 4H), 7.18–7.24 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 10.0, 50.4, 115.8, 118.5, 120.9 (q, $^1J_{\text{C-F}}$ = 277.1 Hz, CF$_3$), 125.0, 128.0, 128.6, 129.0, 131.5, 132.7, 142.1, 143.9, 168.2 (q, $^2J_{\text{C-F}}$ = 32.5 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.57 (s, CF$_3$). IR (neat) v 1484, 1454, 1286, 1234, 1170, 1118, 1066, 1006, 987 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{27}H_{25}BrF_3N_4S$ 573.0935, found 573.0941.

4-(4-Benzoyloxyphenyl)-1′,3′-dibenzyl-4′,5′-dimethyl-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17h**): colorless solid, 331 mg (54%), mp 149–150 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.15 (s, 6H), 5.14 (s, 4H), 6.64–6.67 (m, 2H), 6.86–6.89 (m, 2H), 7.14–7.17 (m, 4H), 7.23–7.25 (m, 6H), 7.49–7.51 (m, 2H), 7.61–7.64 (m, 1H), 8.15–8.17 (m, 2H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 10.0, 50.6, 117.9, 121.0 (q, $^1J_{\text{C-F}}$ = 277.1 Hz, CF$_3$), 122.0, 124.9, 128.1, 128.67, 128.70, 129.1, 129.7, 130.2, 132.9, 133.7, 142.7, 142.8, 146.7, 165.0, 167.5 (q, $^2J_{\text{C-F}}$ = 32.6 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.61 (s, CF$_3$). IR (neat) v 1737, 1498, 1454, 1356, 1282, 1200, 1192, 1107, 1059, 1006, 988 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{34}H_{30}F_3N_4O_2S$ 615.2042, found 615.2037.

4-(4-Cyanophenyl)-1′,3′-dibenzyl-4′,5′-dimethyl-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17i**): pale yellow solid, 312 mg (60%), mp 67–69 °C. ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.27 (s, 6H), 5.08, 5.14 (2s$_{\text{br}}$, 2H each), 6.45–6.48 (m, 2H), 7.05–7.09 (m, 6H), 7.13–7.20 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 10.0, 50.5, 105.1, 116.1, 119.1, 120.8 (q, $^1J_{\text{C-F}}$ = 277.4 Hz, CF$_3$), 125.5, 128.1, 128.8, 129.1, 132.3, 132.5, 141.1, 148.1, 168.9 (q, $^2J_{\text{C-F}}$ = 32.5 Hz). ^{19}F NMR (565 MHz, CDCl$_3$) δ −66.67 (s, CF$_3$). IR (neat) v 2222, 1603, 1498, 1454, 1238, 1170, 1170, 1118, 1080, 1010, 988 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{25}F_3N_5S$ 520.1783, found 520.1787.

1′,3′-Dibenzyl-4′,5′-dimethyl-4-(4-nitrophenyl)-2-trifluoromethylspiro [1,3,4-thiadiazole-5,2′-imidazole] (**17j**): light red solid, 216 mg (40%), mp 53–55 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (s, 6H), 5.08, 5.16 (2s$_{br}$, 2H each), 6.44–6.48 (m, 2H), 7.06–7.09 (m, 4H), 7.11–7.16 (m, 6H), 7.66–7.68 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 10.0, 50.6, 115.3, 120.8 (q, $^1J_{C\text{-}F}$ = 277.5 Hz, CF_3), 124.4, 125.6, 128.0, 128.8, 129.1, 132.2, 140.9, 142.1, 149.7, 169.3 (q, $^2J_{C\text{-}F}$ = 32.6 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ −66.67 (s, CF_3). IR (neat) v 1592, 1495, 1454, 1334, 1271, 1238, 1170, 1107 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{25}F_3N_5O_2S$ 540.1681, found 540.1691.

4. Conclusions

In summary, two series of lepidiline-inspired imidazole-2(3*H*)-thiones were examined in reactions with in situ-generated trifluoromethylated nitrile imines. Enolizable imidazole-2-thiones solely provided the respective hydrazonothioates formed through nucleophilic *S*-addition onto the 1,3-dipole, whereas the *N*,*N*-disubstituted non-enolizable analogues afforded the corresponding (3+2)-cycloadducts in high yield. The latter products belong to a hitherto very little-known spiro [1,3,4-thiadiazole-5,2′-imidazole] family [52] and are the first examples of non-ionic spiro-analogues of naturally occurring lepidiline alkaloids as well as new fluorinated imidazole-thiadiazole hybrids of potential interest in medicine, agrochemistry, and material sciences [53–55]. The present work further expands the scope of products available by trapping of CF_3-nitrile imines with thiocarbonyl substrates and reveals absorptions of the *C*-(CF_3) atom in the ^{13}C NMR spectrum as a useful probe for the differentiation of the open-chain, monocyclic, and spiro-cyclic products in the series. Furthermore, the presented results nicely supplement a more recent study on (chemo)selectivity problems in reactions of enolizable azaheterocyclic thiones [56,57].

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/molecules30193851/s1: Supplementary File S1. Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of all new compounds.

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Supporting Information
for

Lepidiline-Derived Imidazole-2(3*H*)-thiones: (3+2)-Cycloadditions *vs*. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines

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Content:

Synthesis of imidazole-2-thiones 7 and 8

Synthesis of imidazole-2-thiones **7a**-**7b**: A mixture of benzylamine **12a** or **12b** (10.0 mmol) and aqueous formaldehyde (37%, 0.98 g, 12.0 mmol) in benzene (15 mL) was refluxed in a Dean−Stark apparatus for 2 h. The solvent was removed under reduced pressure to give trimer of formaldimine **13** (> 95% purity). To a solution of this crude trimeric formaldimine **13** in glacial acetic acid (20 mL) was added diacetyl monoxime (10.0 mmol), and the resulting mixture was stirred at room temperature overnight. Then, excess concentrated HCl was added (4 mL), the solvents were removed under reduced pressure, and the resulting product was dissolved in MeOH. After excess solid $NaHCO_3$ was added the stirring was continued for 2 h until the evolution of CO_2 ceased. The solvent was removed in vacuo, the residue was triturated with CH_2Cl_2, the precipitate salts were filtered off, the solvent was removed, and the residue was washed with a few portions of Et_2O to give crude imidazole *N*-oxide **11**. To a solution of this crude imidazole *N*-oxide in dry DCM (30.0 mL) was added dropwise a solution of 2,2,4,4-tetramethyl-3-thioxocyclo-butanone (1.9 g, 11.0 mmol) in DCM (15.0 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, the resulting was triturated with E_2O to give product **7**.

1-Benzyl-4,5-dimethylimidazole-2-thione (**7a**):[1] Colorless solid, 1.16 g (53%). ^1H NMR (600 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.08 (s, 3H), 5.29 (s, 2H), 7.24-7.27 (m, 3H), 7.30-7.33 (m, 2H), 11.07 (s_{br}, 1H).

1-(3-Methoxybenzyl)-4,5-dimethylimidazole-2-thione (**7b**): Colorless solid, 1.27 g (51%); mp 202-204 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.07 (s 3H), 3.78 (s, 3H), 5.26 (s, 2H), 6.78-6.84 (m, 3H), 7.20-7.24 (m, 1H), 11.24 (s_{br}, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.2, 9.3, 48.0, 55.4, 112.9, 113.1, 119.4, 120.1, 121.9, 129.9, 138.1, 159.6, 160.1. IR (neat) ν 3071, 2919, 1610, 1584, 1487, 1398, 1286, 1226, 1148, 1051 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}N_2OS$ 249.1062, found 249.1064.

Synthesis of imidazole-2-thiones **8a**-**8c**: To a solution of imidazole *N*-oxide **11** (2.0 mmol) in MeOH (5.0 mL) was added portion-wise an excess of freshly prepared suspension of Raney-nickel in MeOH. The resulting mixture was stirred at room temperature until the starting *N*-oxide was fully consumed (TLC monitoring; ca. 1.5 h). The solids were filtered off and the solvent was removed in vacuo to give spectroscopically pure imidazole **14**. To a deoxygenated solution of this imidazole **14** in MeCN (20 mL) was added benzyl chloride (380 mg, 3.0 mmol) or 3-methoxybenzyl chloride (470 mg, 3.0 mmol), and the resulting mixture was MW-irradiated at 110 °C until the starting imidazole was fully consumed (TLC monitoring; ca. 1 h). The solvent was removed under reduced pressure, and the crude product **15** was washed with several portions of dry Et_2O, dissolved in CH_2Cl_2 and precipitated by portion-wise addition of hexanes. The resulting imidazolium chloride **15** and elemental sulfur (4.0 mmol) in a pyridine/Et_3N mixture (1:1, 20.0 mL) were stirred at room temperature overnight. The solvents were removed in vacuo, and the obtained residue was purified by short chromatography column (using CH_2Cl_2 as an eluent) to give products **8a**-**8c**.

1,3-Dibenzyl-4,5-dimethylimidazole-2-thione (**8a**).[2] Colorless solid, 259 mg (42%). ^1H NMR (600 MHz, $CDCl_3$) δ 1.95 (s, 6H), 5.44 (s, 4H), 7.25-7.34 (m, 10H).

1-(3-Methoxybenzyl)-3-benzyl-4,5-dimethylimidazole-2-thione (**8b**).[2] Waxy solid, 480 mg (71%). ^1H NMR (600 MHz, $CDCl_3$) δ 1.95 (s, 3H), 1.96 (s, 3H), 3.78 (s, 3H), 5.41 (s, 2H), 5.44 (s, 2H), 6.79-6.81 (m, 1H), 6.83−6.87 (m, 2H), 7.22-7.25 (m, 1H), 7.26−7.33 (m, 5H).

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[1] G. Mlostoń et al., *Helv. Chim. Acta* **1998**, 81, 1585–1595.

[2] G. Mlostoń et al., *J. Nat. Prod.* **2021**, *84*, 3071–3079.

1-(3-Methoxybenzyl)-3-benzyl-4,5-dimethylimidazole-2-thione (**8c**). Thick colorless oil, 486 mg (66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96 (s, 6H), 3.78 (s, 6H), 5.41 (s, 4H), 6.79-6.81 (m, 2H), 6.83-6.86 (m, 4H), 7.21-7.24 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 9.4, 48.9, 55.3, 112.7, 113.1, 119.3, 121.5, 129.8, 138.3, 160.0, 163.0. IR (neat) ν 1599, 1584, 1491, 1454, 1398, 1341, 1260, 1226, 1148, 1040 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}N_2O_2S$ 369.1637, found 369.1642.

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for compounds 16 and 17

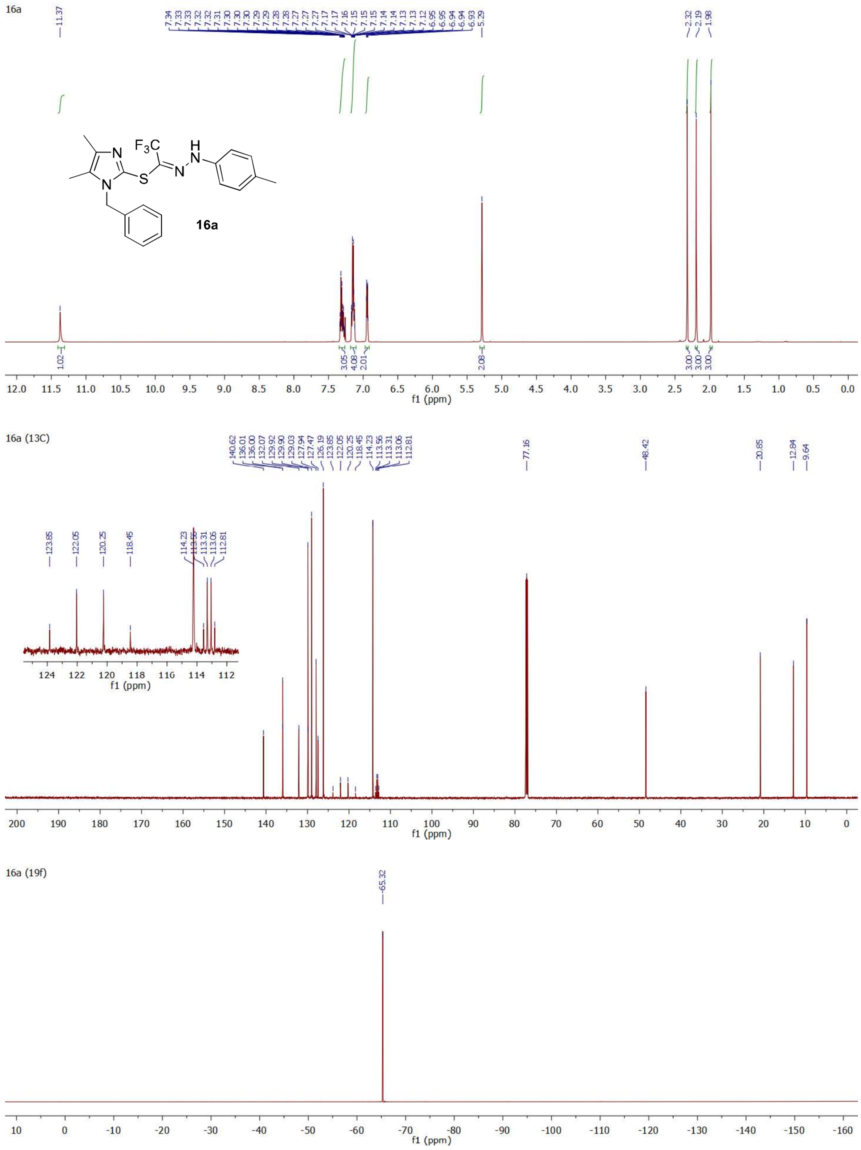
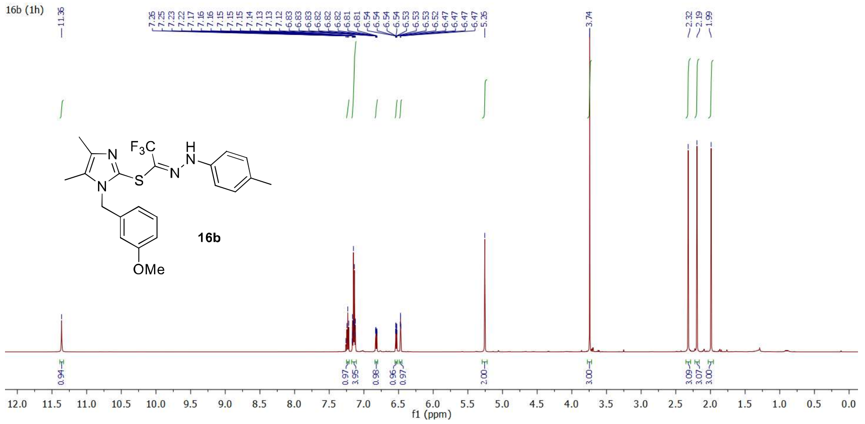
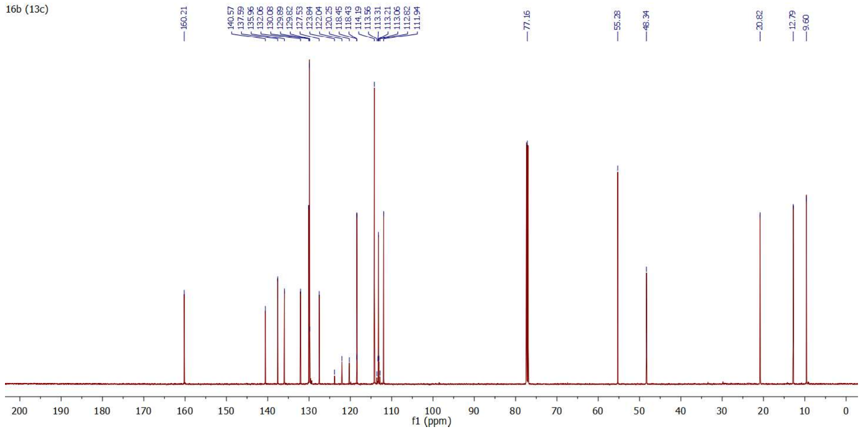


Figure S1. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16a**.





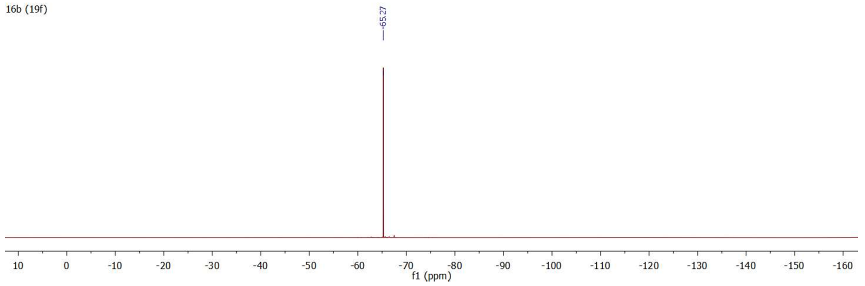


Figure S2. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16b**.

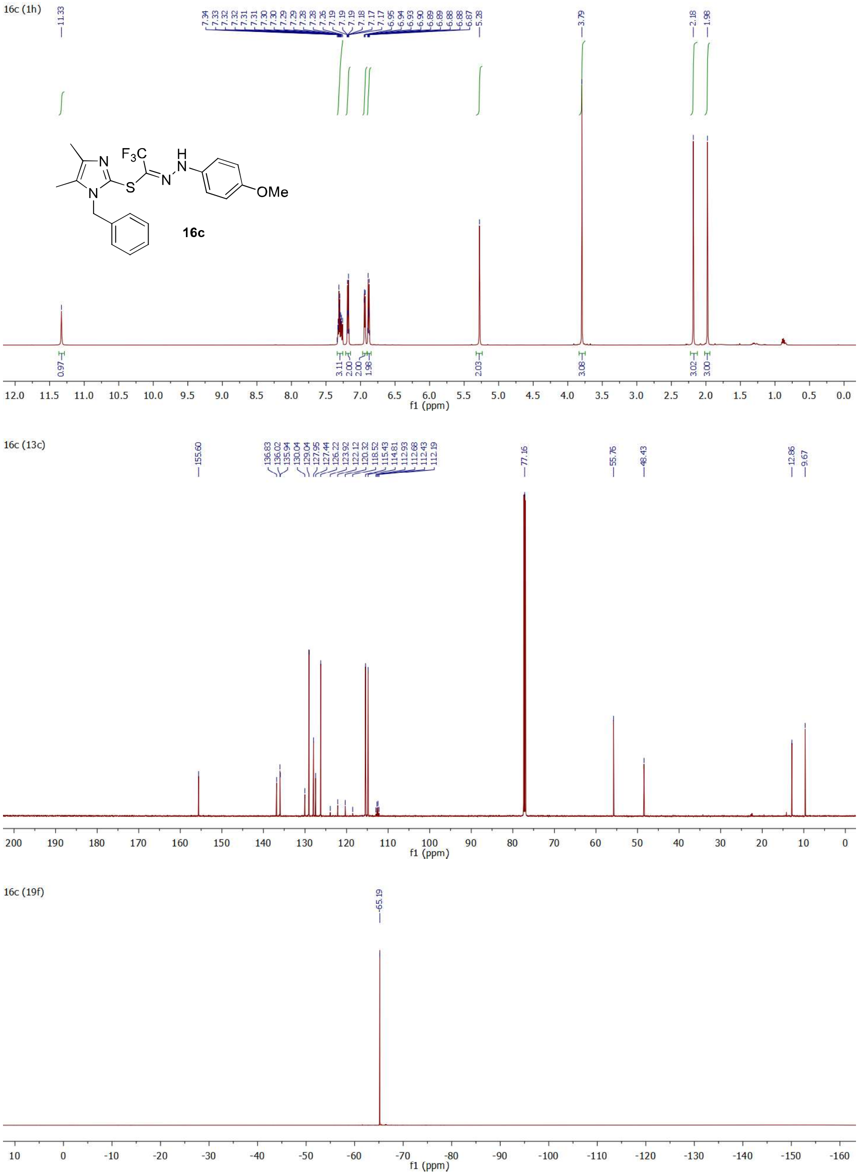


Figure S3. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16c**.

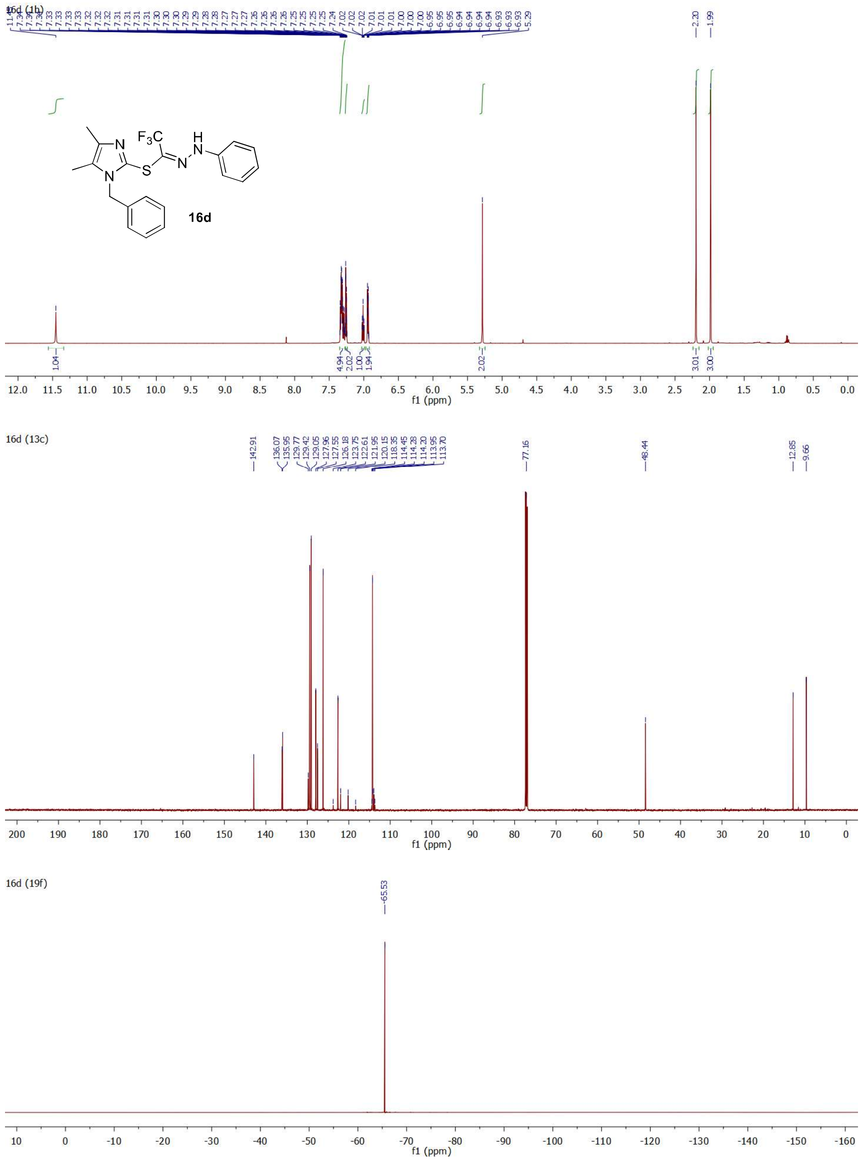
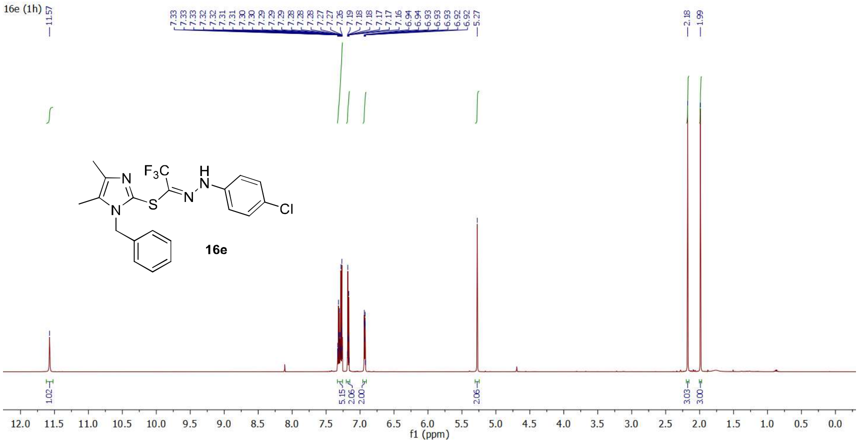
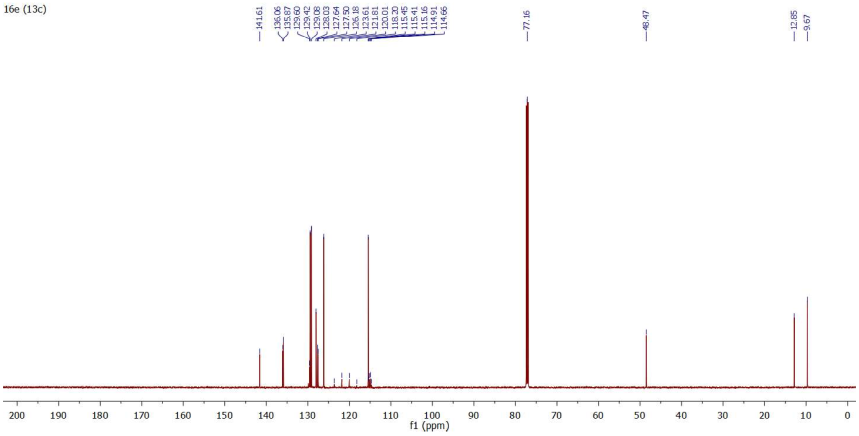


Figure S4. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16d**.

16e (1h)



16e (13c)



16e (19f)

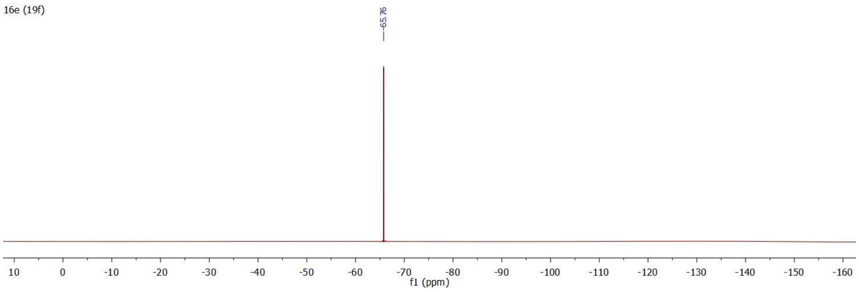


Figure S5. ^1H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **16e**.

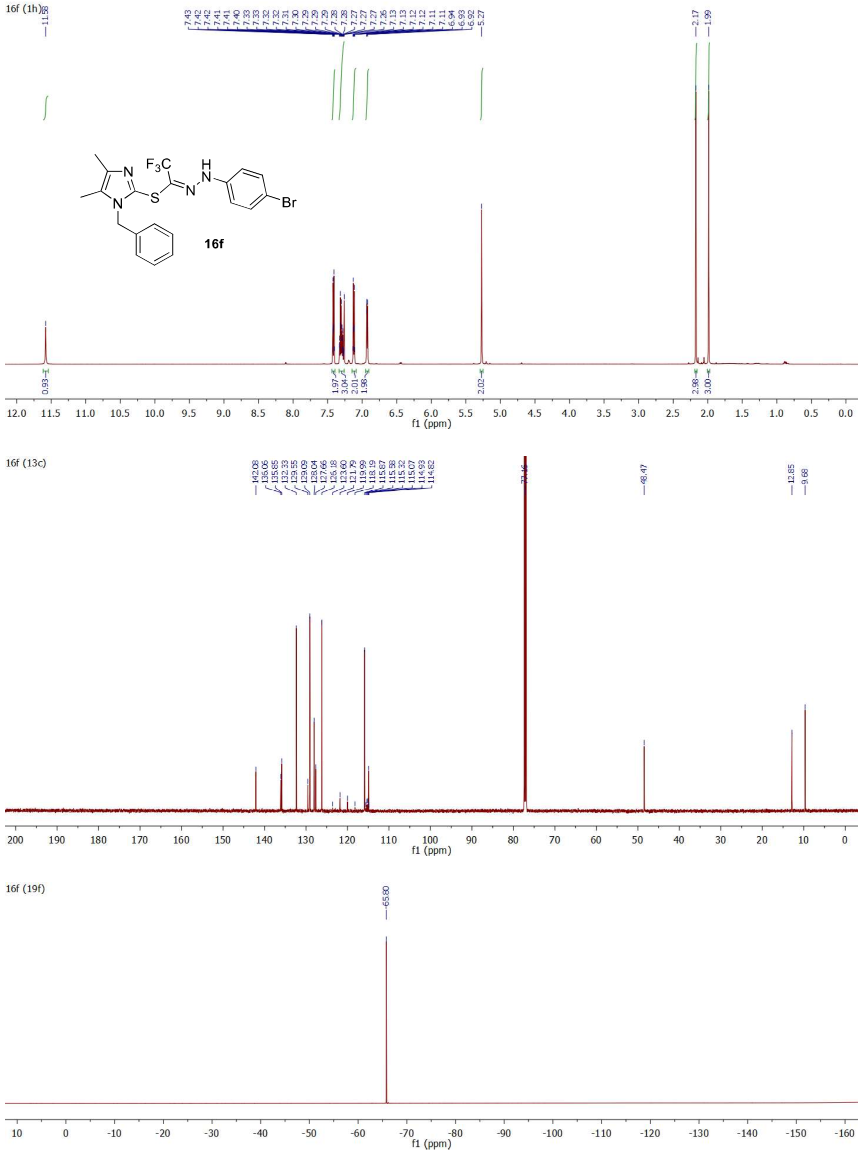


Figure S6. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **16f**.

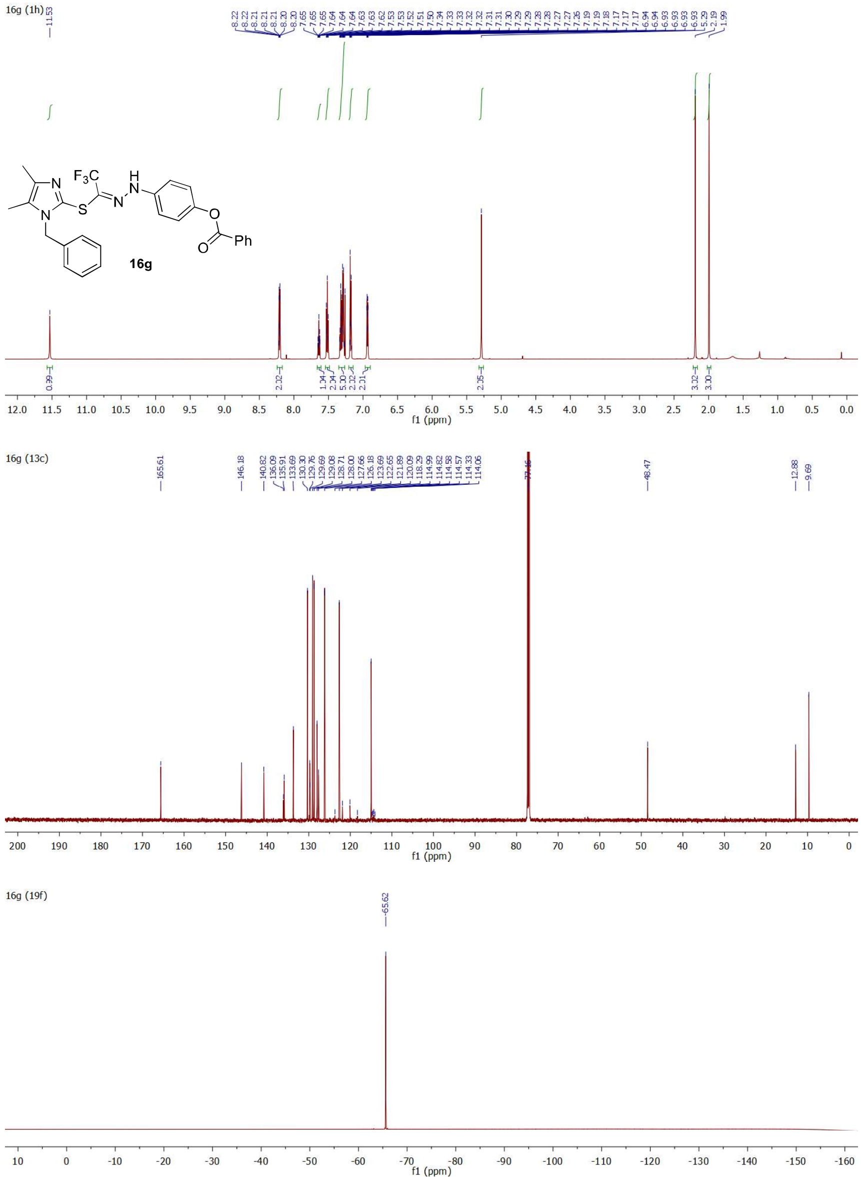


Figure S7. ^1H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16g**.

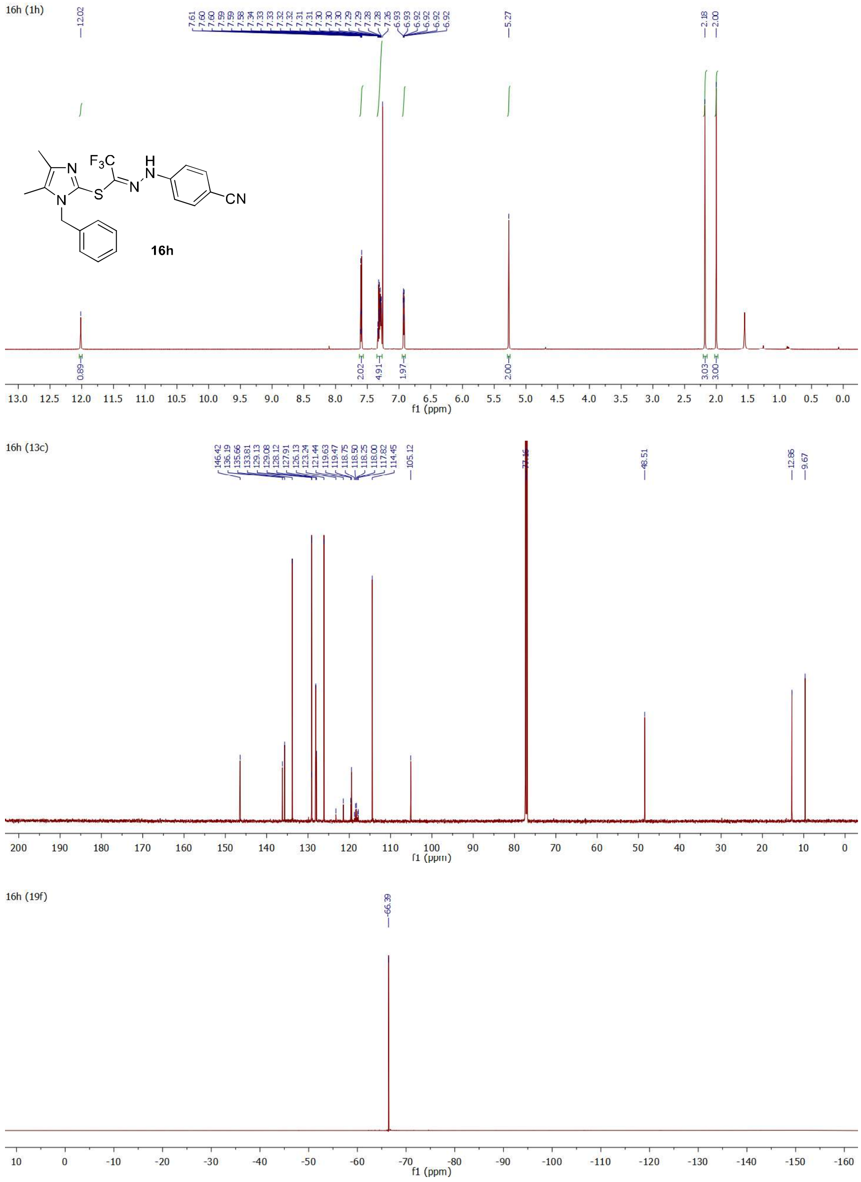


Figure S8. ^1H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **16h**.

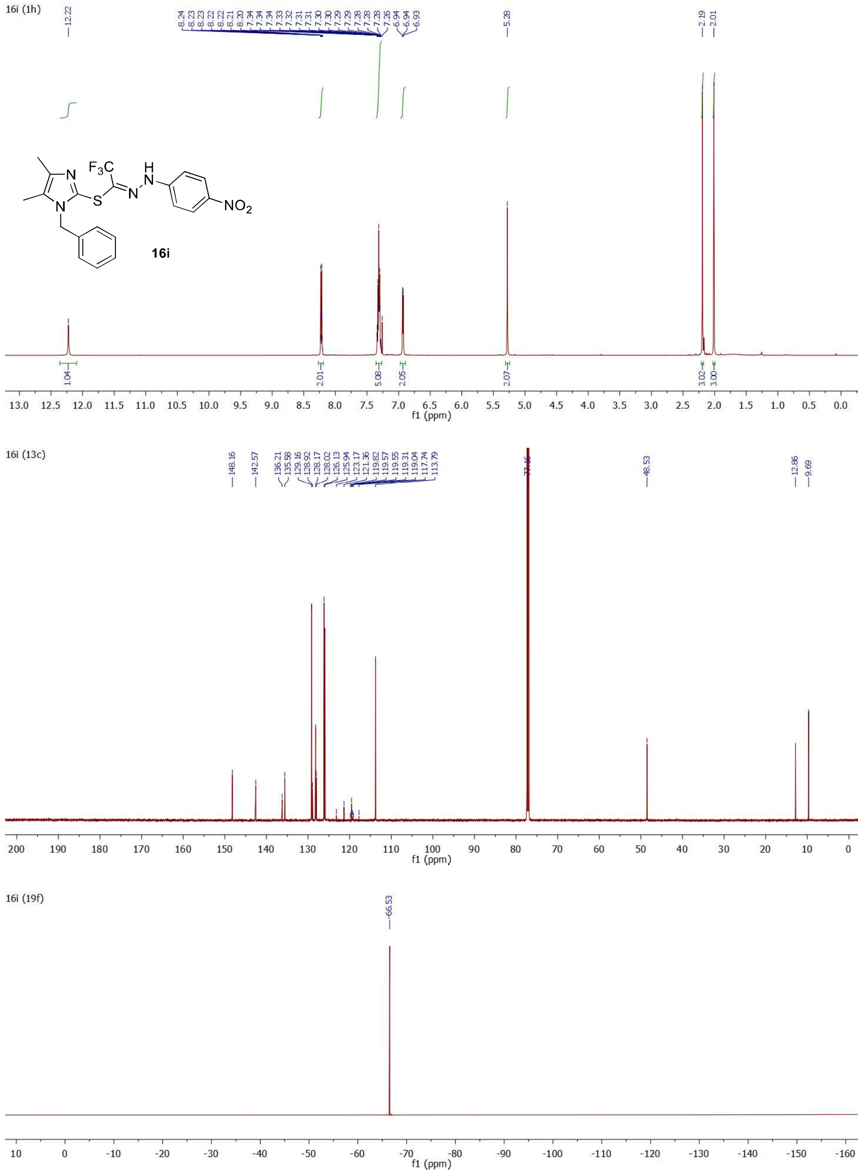


Figure S9. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **16i**.

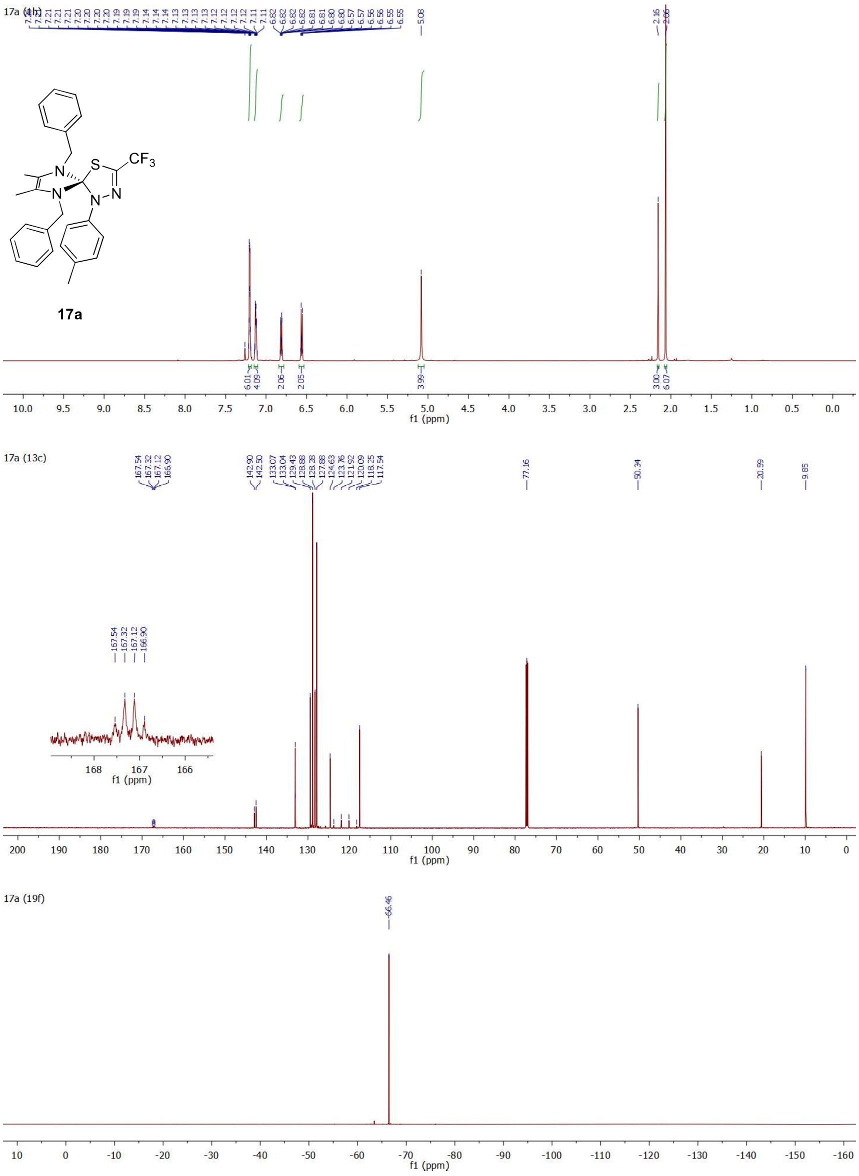


Figure S10. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **17a**.

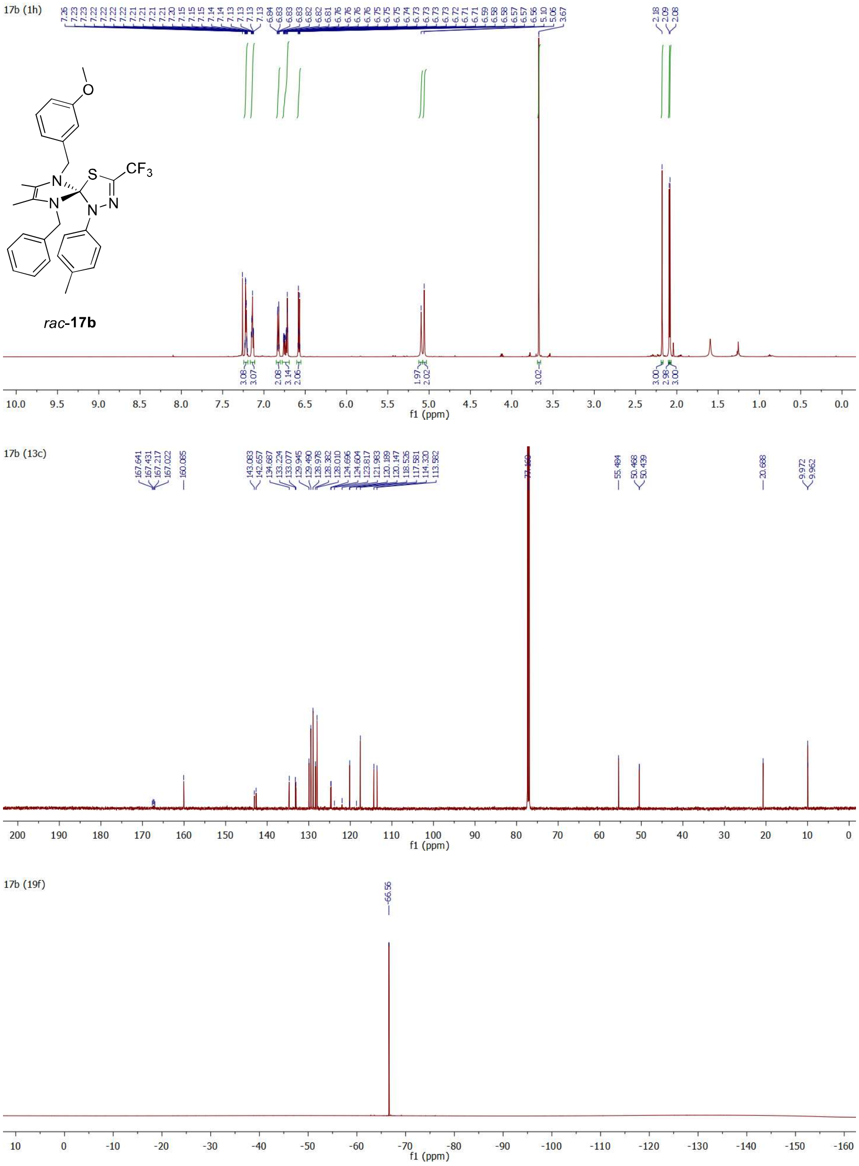


Figure S11. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **17b**.

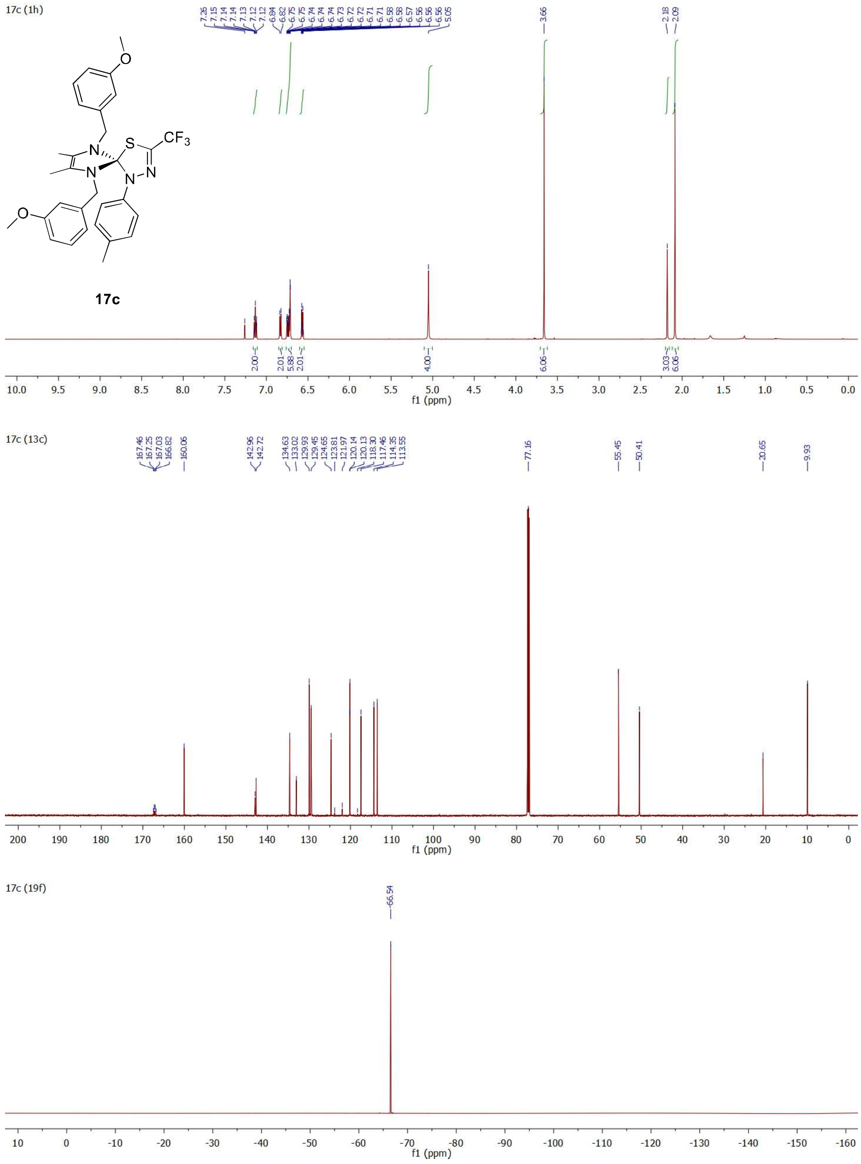
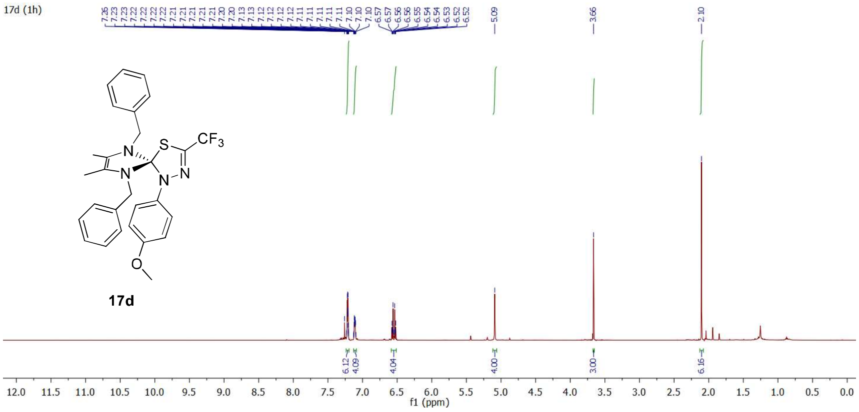
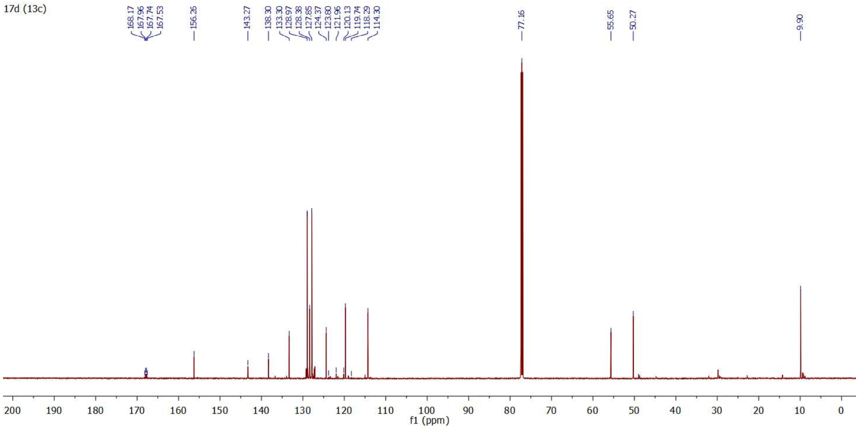


Figure S12. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17c**.





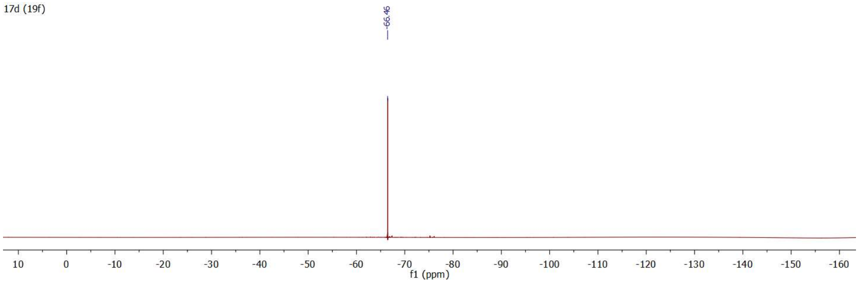


Figure S13. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17d**.

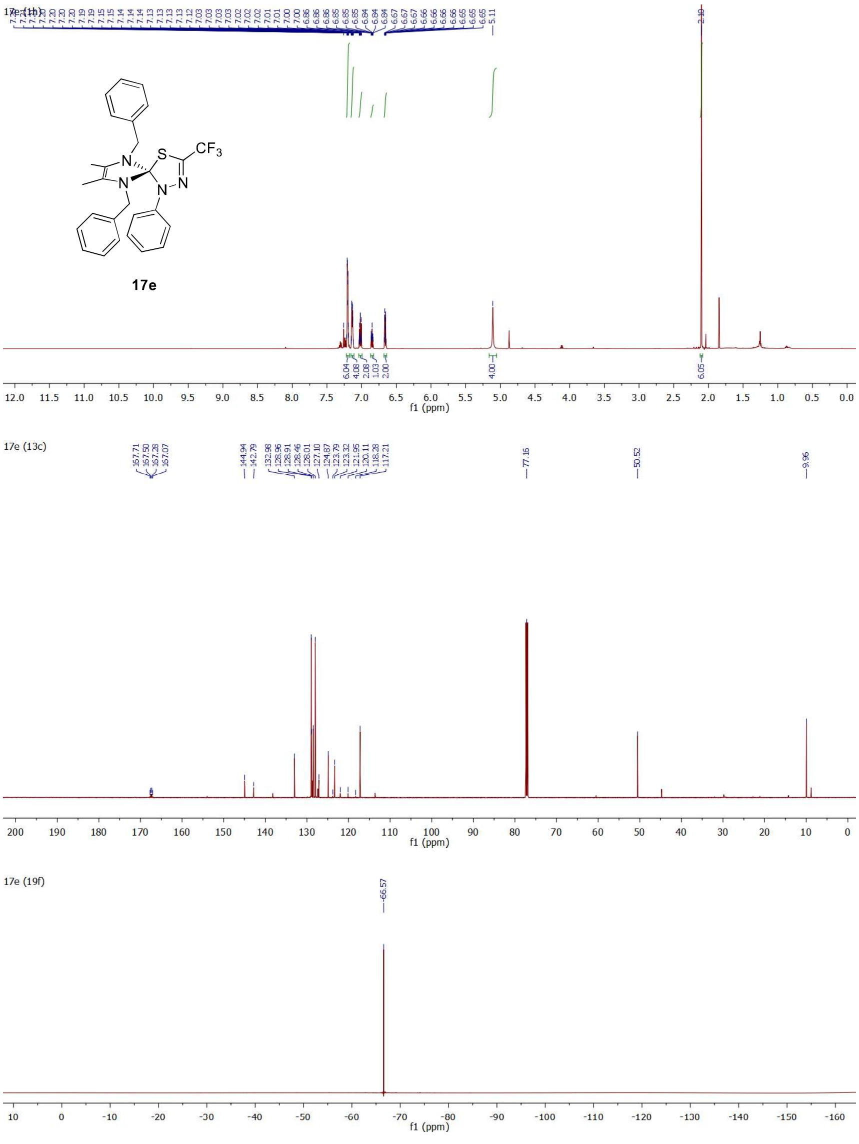
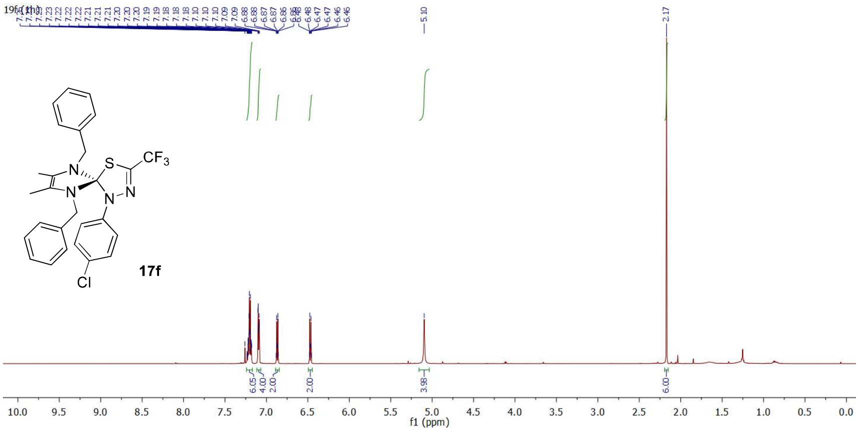
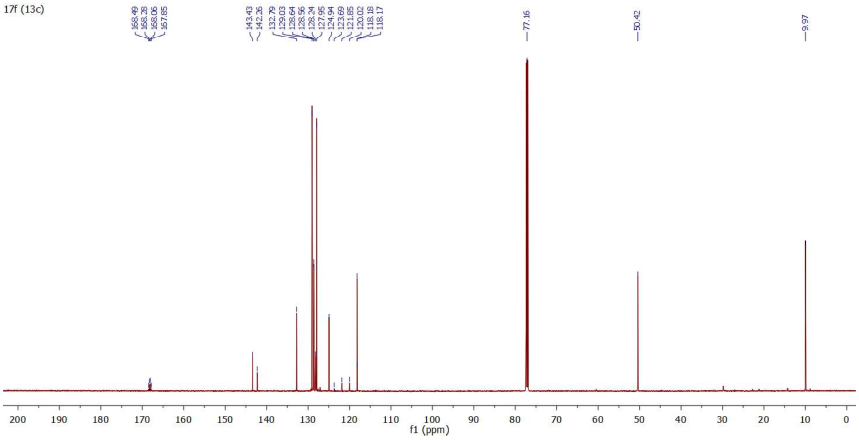


Figure S14. ^1H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17e**.





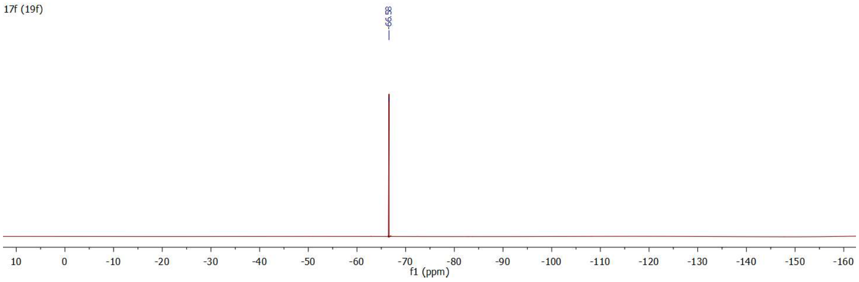
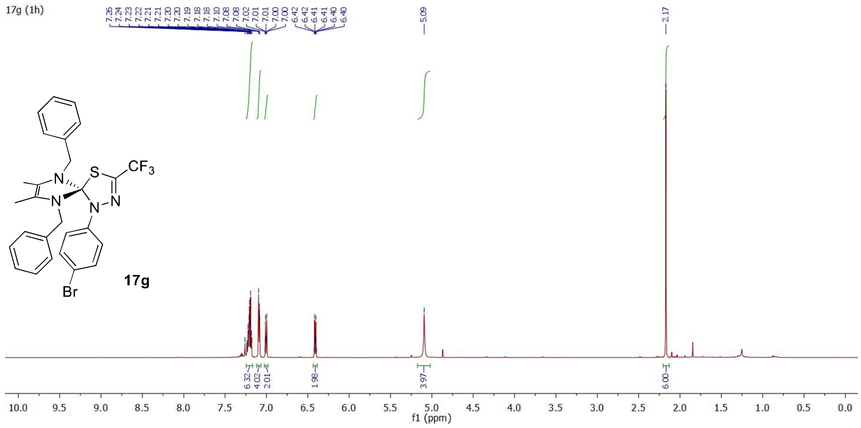
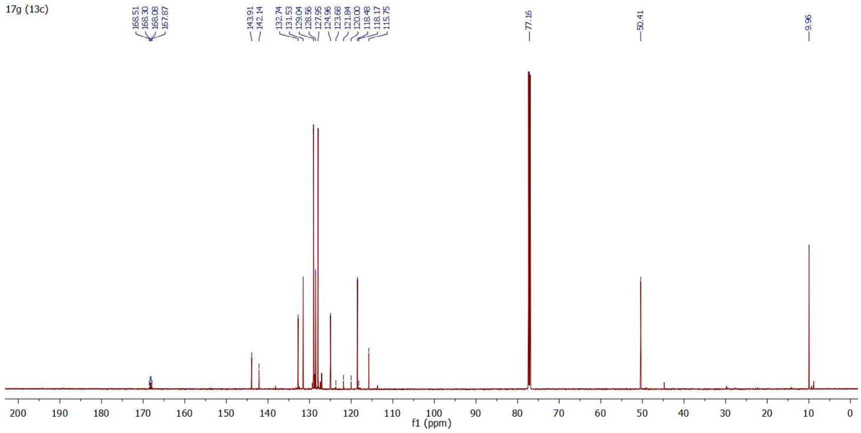


Figure S15. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **17f**.





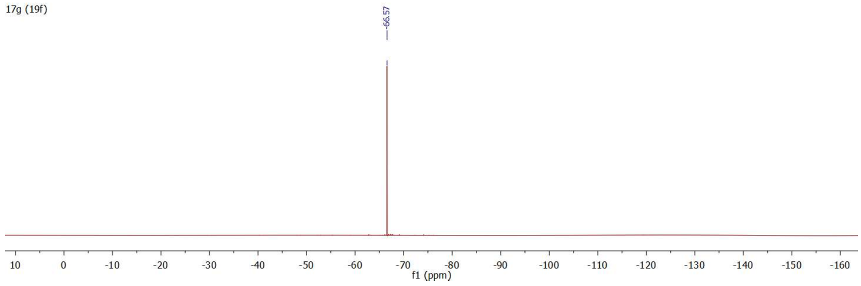


Figure S16. ^{1}H NMR (600 MHz, CDCl$_3$), ^{13}C NMR (151 MHz, CDCl$_3$) and ^{19}F NMR (565 MHz, CDCl$_3$) spectra for compound **17g**.

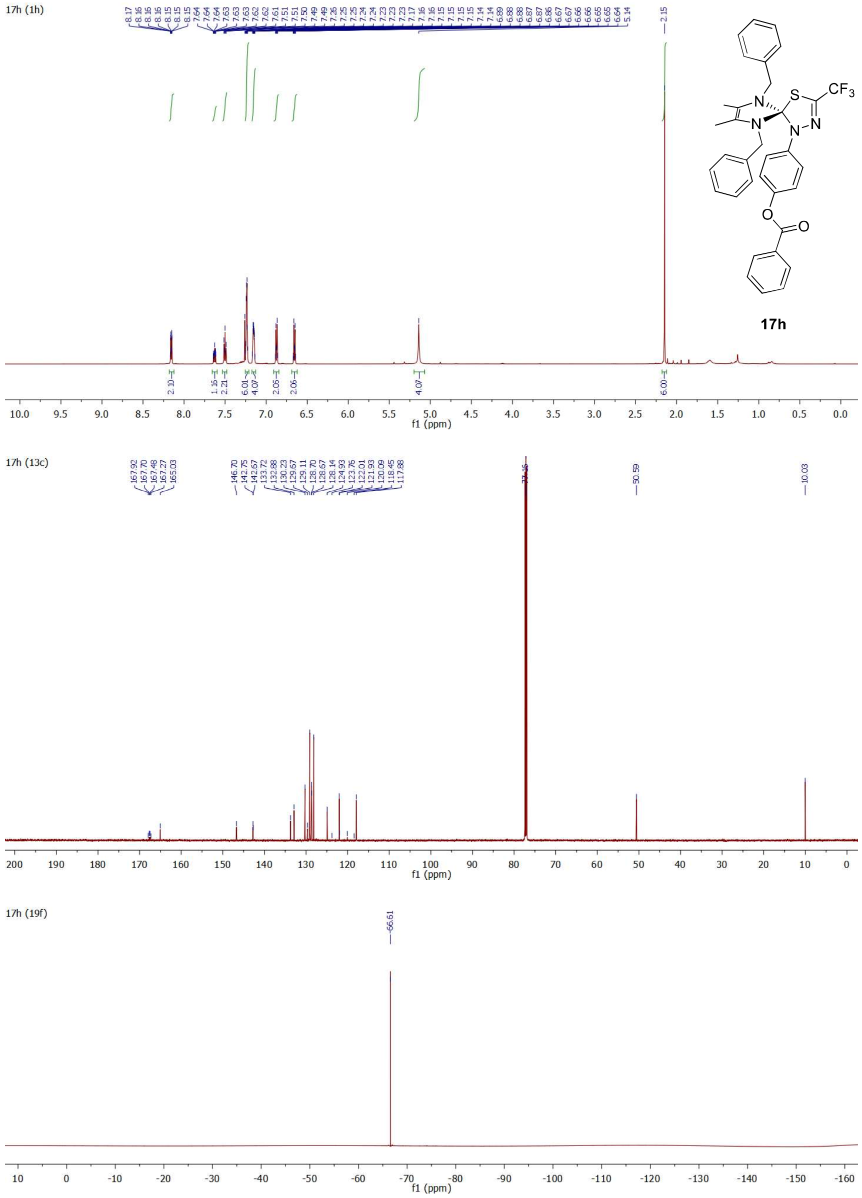


Figure S17. ^{1}H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17h**.

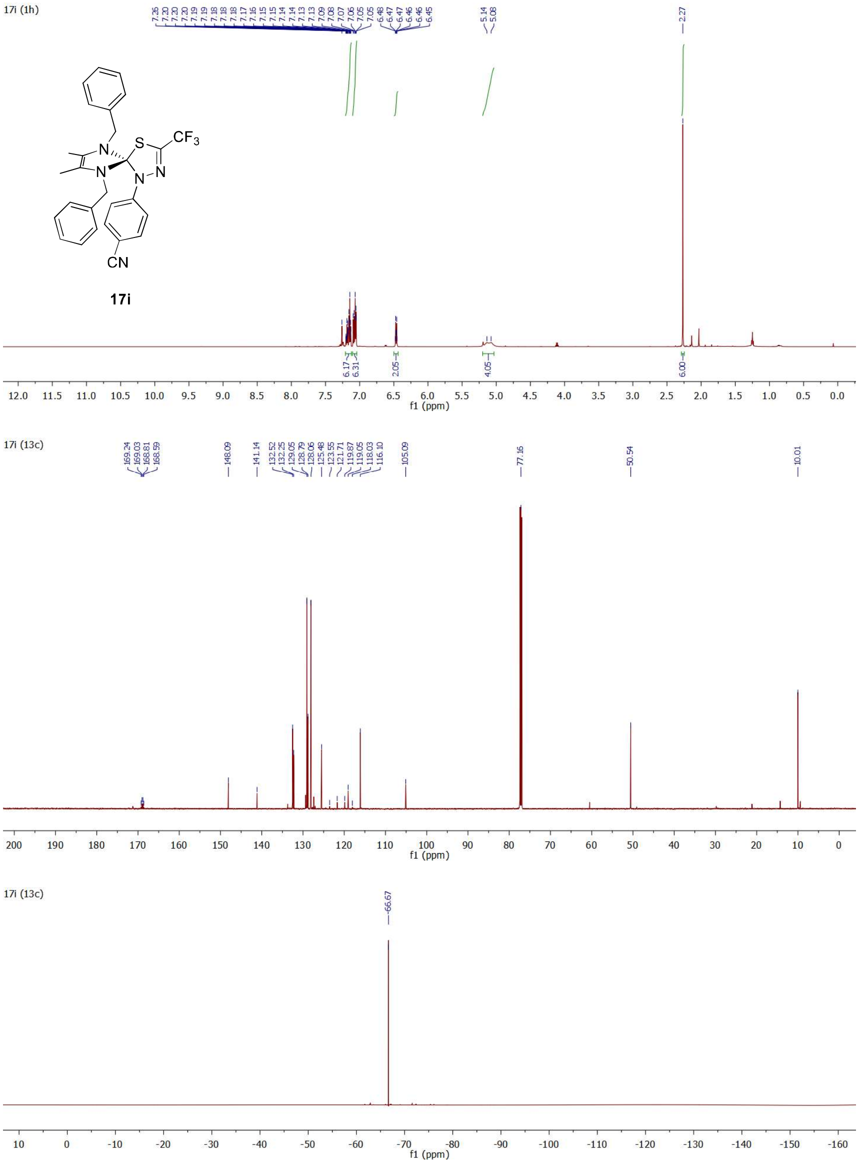


Figure S18. ^1H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17i**.

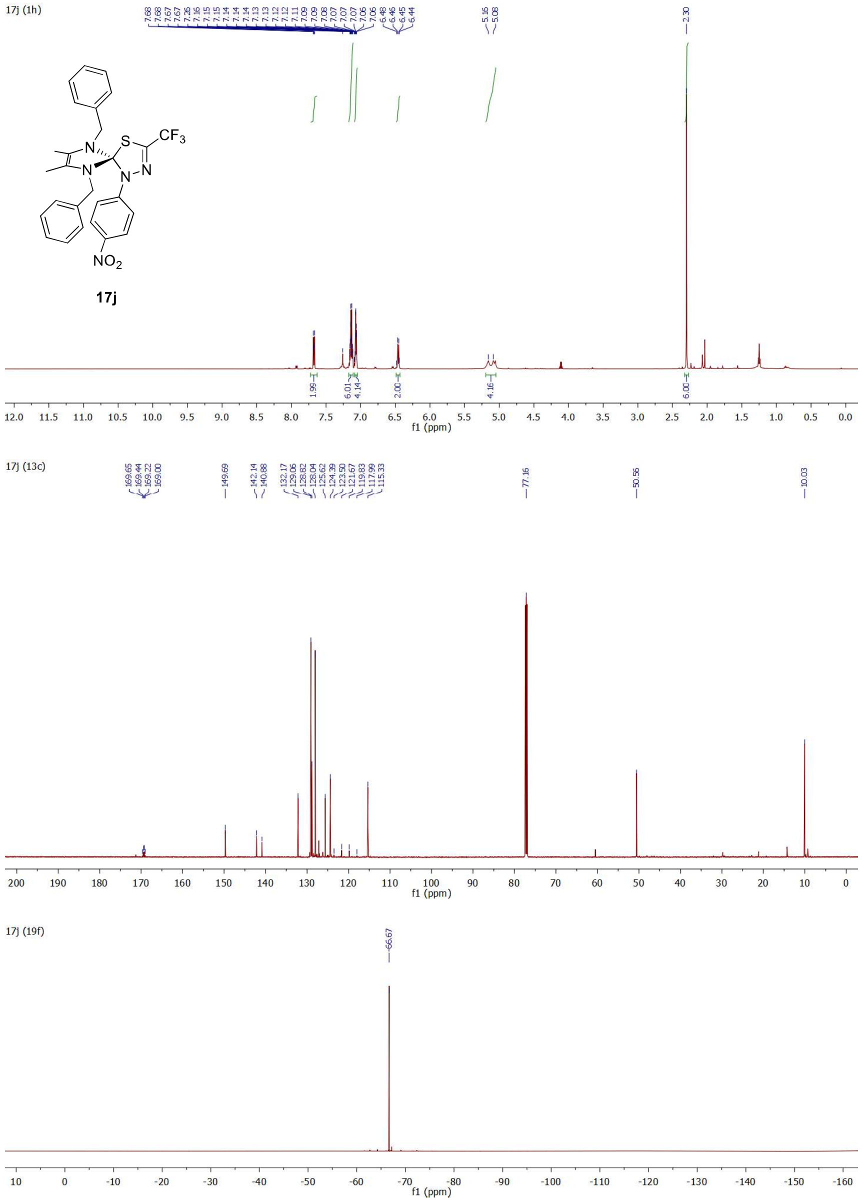


Figure S19. ^1H NMR (600 MHz, $CDCl_3$), ^{13}C NMR (151 MHz, $CDCl_3$) and ^{19}F NMR (565 MHz, $CDCl_3$) spectra for compound **17j**.

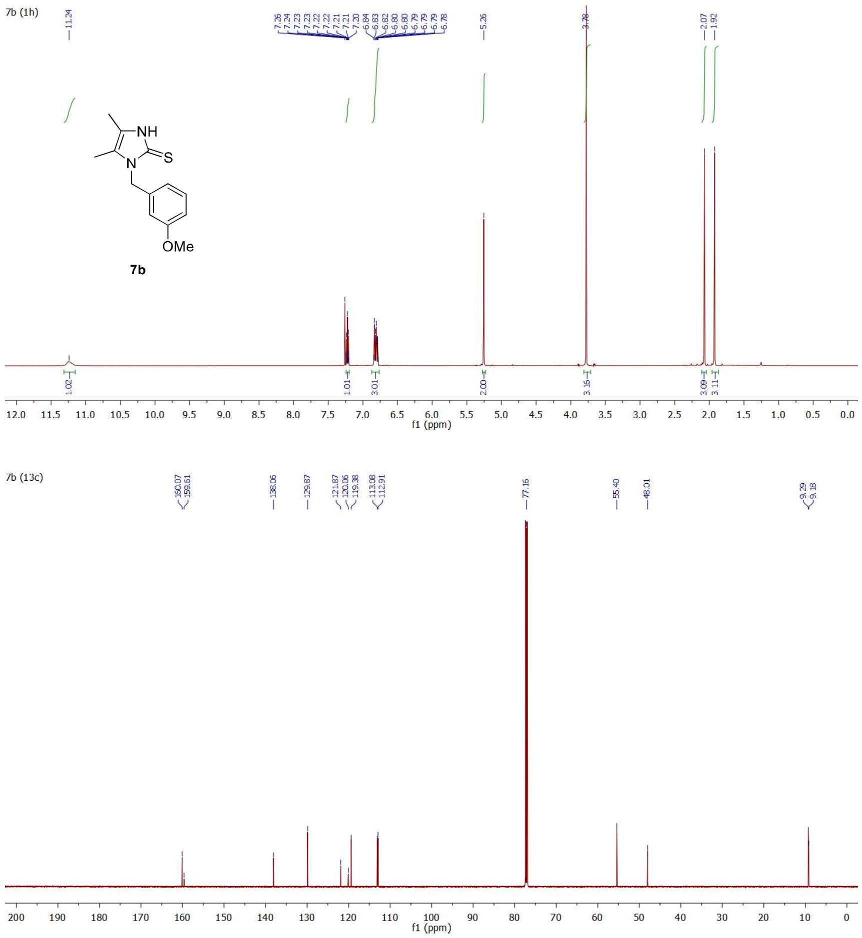


Figure S20. ^{1}H NMR (600 MHz, CDCl$_3$) and ^{13}C NMR (151 MHz, CDCl$_3$) spectra for compound **7b**.

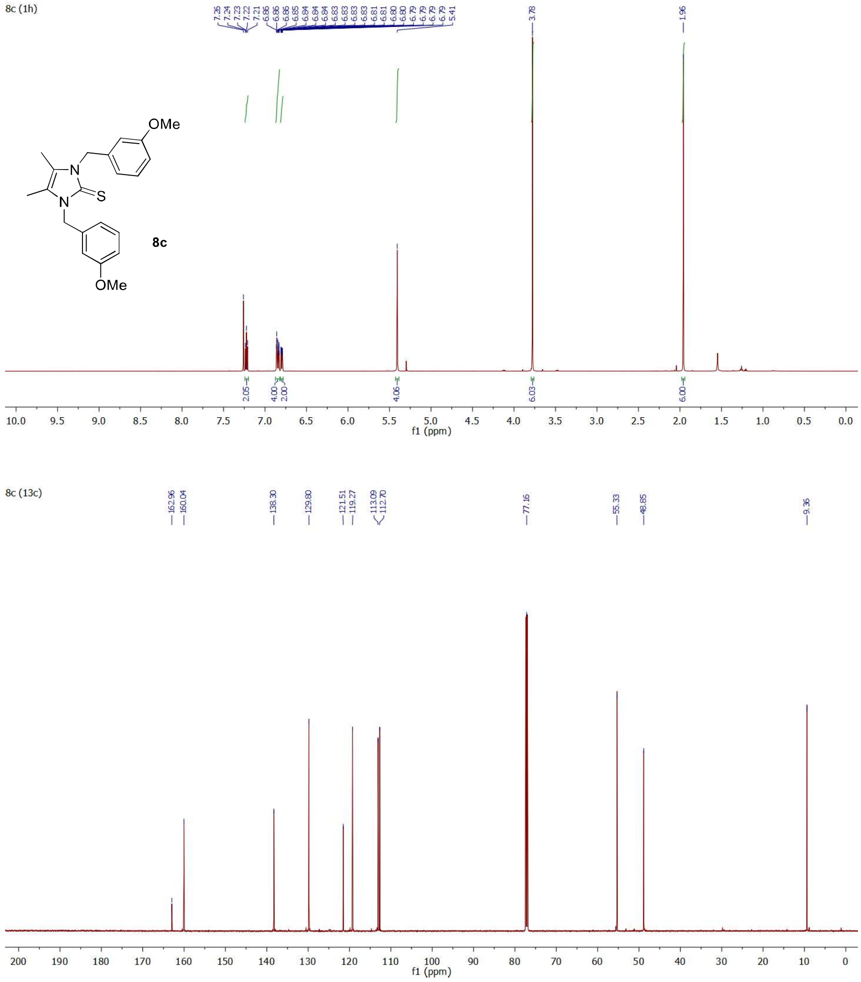


Figure S21. ^{1}H NMR (600 MHz, $CDCl_3$) and ^{13}C NMR (151 MHz, $CDCl_3$) spectra for compound **8c**.

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OŚWIADCZENIE

Oświadczam, że mój wkład w powstanie poniższych publikacji polegał na:

- **[D1]** Poper, W. K.; Jasiński M. **2025** "The introduction of SCF$_3$ substituents into heterocyclic rings." In *Advances in Heterocyclic Chemistry*, edited by Christopher A. Ramsden, Elsevier. (pre-proof manuscript)
- **[D2]** Poper, W. K.; Ma, J.-A.; Jasiński, M. "One-Pot Telescoping *S*-Transfer and Trifluoromethylation for the Synthesis of 2-CF$_{3S}$-Imidazoles with *N*-Oxides as Convenient Precursors". *J. Org. Chem.*, **2024**, *89*, 15331.
- **[D3]** Poper, W. K.; Denel-Bobrowska M.; Olejniczak, A. B.; Jasiński, M. "First lepidiline-inspired 1, 3-dibenzyl 2-CF$_3$S-imidazoliums: Design, synthesis and cytotoxic activity study" *Biomed. Pharmacother.*, **2025**, *192*, 118606.
- **[D4]** Poper, W. K.; Świątek, K.; Urbaniak, K.; Olszewska, B.; Jasiński, M. "Lepidiline-Derived Imidazole-2(3*H*)-Thiones: (3+2)-Cycloadditions vs. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines" *Molecules*, **2025**, *30*, 3851.

- w przypadku rozdziału do monografii *Adv. Heterocycl Chem.*, Volume 149 (praca **D1**) - zaproponowaniu ogólnej tematyki i zakresu materiału, częściowym opracowaniu manuskryptu oraz korespondencji z Edytorem (Christopher A. Ramsden)

- w pozostałych przypadkach (prace **D2**-**D4**), na stworzeniu ogólnej koncepcji i planu badań, zapewnieniu finansowania na realizację części prac eksperymentalnych, udziału w analizie danych, współpracy w przygotowaniu manuskryptów publikacji, jak również prowadzeniu korespondencji z edytorami czasopism oraz opracowaniu finalnych wersji prac.

KIEROWNIK
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Tianjin, December 13th, 2025

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DECLARATION

To whom it may concern, herein I would like to declare, that my contribution to the below work pertains to:

- [**D2**] Poper, W. K.; Ma, J.-A.; Jasiński, M. *"*One-Pot Telescoping *S*-Transfer and Trifluoromethylation for the Synthesis of 2-CF_3S-Imidazoles with *N*-Oxides as Convenient Precursors*". J. Org. Chem.*, **2024**, *89*, 15331.

Conceptual cooperation and cooperation in the preparation of the manuscript.

Sincerely,

Jun-An Ma

………………………………………….

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oznaczeniu aktywności cytotoksycznej badanych związków wobec panelu 7 linii komórkowych.

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Planowanie badan związanych z oznaczeniem cytotoksyczności związków chemicznych będących przedmiotem publikacji; analiza i interpretacja wyników cytotoksyczności, przegląd draftu publikacji.

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OŚWIADCZENIE

Oświadczam, że mój wkład w powstanie poniższej publikacji polegał na:

- **[D4]** Poper, W. K.; Świątek, K.; Urbaniak, K.; Olszewska, B.; Jasiński, M. "Lepidiline-Derived Imidazole-2(3H)-Thiones: (3+2)-Cycloadditions vs. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines" *Molecules*, **2025**, *30*, 3851.

współpracy w zakresie optymalizacji warunków reakcji *N*-monopodstawionych imidazolo-2-tionów typu lepidilinowego z trifluorowanymi nitryloiminami oraz współpracy nad analizą wyników.

K. Urbaniak
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- **[D4]** Poper, W. K.; Świątek, K.; Urbaniak, K.; Olszewska, B.; Jasiński, M. "Lepidiline-Derived Imidazole-2(3*H*)-Thiones: (3+2)-Cycloadditions vs. Nucleophilic Additions in Reactions with Fluorinated Nitrile Imines" *Molecules*, **2025**, *30*, 3851.

syntezie bromków hydrazonoilowych **10a-h** oraz wykonaniu optymalizacji warunków reakcji bromku hydrazonoilowego **10a** z imidazolo-2-tionem **8a**.

Świątek Kamil

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współpracy w zakresie syntezy i oczyszczania wyjściowych substratów **7a**, **7b**, **8a** – **8c**, oraz współpracy w zakresie syntezy i oczyszczania związków **17a**, **17b** i **17c**.

Barbara Olszewska
(podpis)